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Maternal serum concentrations of perfluoroalkyl substances during pregnancy and gestational weight gain: The Avon Longitudinal Study of Parents and Children

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Abstract

Perfluoroalkyl substances (PFAS) are chemicals used in the manufacture of consumer products. PFAS may act as endocrine disruptors, influencing metabolic pathways and weight-related outcomes. Previous studies observed an association between perfluorooctane sulfonic acid (PFOS) and higher gestational weight gain among under-/normal weight mothers. We analyzed associations of maternal serum pregnancy concentrations of PFAS with gestational weight gain (GWG) using data from 905 women in a subsample of the Avon Longitudinal Study of Parents and Children. Women were routinely weighed in antenatal check-ups; absolute GWG was determined by subtracting the first weight measurement from the last. Linear regression was used to explore associations of maternal PFAS concentrations with absolute GWG, stratified by prepregnancy body mass index. Associations of maternal PFOS, perfluorooctanoic acid (PFOA), and perfluorohexane sulfonic acid (PFHxS) concentrations with absolute GWG were null; 10% higher PFOS was associated with GWG of -0.03 kg (95% CI: -0.11, 0.06) among under-/normal weight mothers. Ten percent higher perfluorononanoic acid (PFNA) was associated with a higher GWG of 0.09 kg (95% CI: 0.02, 0.16) among under-/normal weight mothers. Overall, findings suggest no association between maternal PFOA, PFOS, and PFHxS concentrations and GWG, and a weak positive association between maternal PFNA and GWG.

Keywords

ALSPAC; endocrine disruptors; perfluoroalkyl substances; gestational weight gain; perfluorooctanoic acid (PFOA); perfluorooctane sulfonic acid (PFOS); perfluorohexane sulfonic acid (PFHxS); perfluorononanoic acid (PFNA)

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are a group of synthetic chemicals used to make fluoropolymer coatings and products that resist heat, oil, stains, grease, and water. Fluoropolymer coatings are used in products such as clothing, furniture, adhesives, food packaging, non-stick cookware, and the insulation of electrical wire. Exposure to PFAS is ubiquitous and occurs through water, food, and indoor air [1]. PFAS can be found in circulating blood, breastmilk, cord blood, and can be transferred to the fetus through the placenta during pregnancy [2-6]. Frequently studied PFAS include perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA).

PFAS are a public health concern due to their environmental persistence and the ability of some PFAS to bioaccumulate in body tissue [7-10]. Half-lives in human serum are approximately 2-4 years for PFOA, 3-6 years for PFOS, and 5-16 years for PFHxS [11-14]. Data on the human half-life of PFNA are limited, though findings to date suggest that PFNA is more persistent in humans than PFOA [15], which is consistent with toxicokinetic data from rodents [16-20]. The prevalence, persistence, and bioaccumulative nature of PFAS in humans, wildlife, and the environment led to an industry phase out and replacement of some of these chemicals in the United States and Europe [7, 21, 22].

Studies suggest that PFAS exposure can have growth- and weight-related effects. For example, early life PFOA exposure is associated with an increased risk of childhood adiposity [23]. Data from humans and animals suggest that PFAS exposure may disrupt endocrine signaling [24, 25], and alter adipocyte profiles [26] and the expression of adipocyte genes [27]. Because pregnancy is a period of increased susceptibility to the potential adverse effects of environmental contaminants due to physiological and behavioral changes [28], gestational weight gain (GWG) is of particular interest. GWG is an important predictor of a number of neonatal and maternal outcomes, such as those related to birth size and future obesity risk. Inadequate GWG is associated with risk of low birth weight, while

excess GWG is associated with macrosomia (excessive birth weight) [29]. Excess GWG is also associated with gestational diabetes, increased weight retention, and obesity in mothers [30, 31], and an increased risk of obesity in children [32]. Therefore, the identification of predictors of excess GWG is an opportunity to address the growing global obesity epidemic [33].

To date, few studies have examined the effects of endocrine disrupting chemicals on GWG. One study of American women (n=218) found that some persistent organic pollutants (POPs), namely p,p'-dichlorodiphenyl trichloroethane (p,p'-DDT) and PFOS, were moderately positively associated with GWG [34]. Another study of Canadian women (n=1,609) examined the association of PFAS with GWG, finding that maternal PFOS concentrations were positively associated with GWG among women who began their pregnancy as underweight or normal weight [35].

The current study aimed to explore whether maternal serum concentrations of PFOA, PFOS, PFHxS, and PFNA during pregnancy were associated with absolute gestational weight gain and IOM recommendations for GWG, taking into account pre-pregnancy BMI.

2. Study design and methods

2.1 Study population

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a prospective birth cohort of 14,541 pregnancies. ALSPAC enrolled pregnant women with an expected delivery date between 1 April 1991 and 31 December 1992 from three health districts in the former county of Avon, Great Britain. Information was collected on these parents and children through interviews, mailed questionnaires, and clinic visits. Details on ALSPAC recruitment and study methods have been described elsewhere [36, 37].

Selection criteria for this subsample of ALSPAC differed for mothers of daughters and mothers of sons. A nested case-control study was conducted within the ALSPAC cohort to explore associations of prenatal maternal concentrations of various suspected endocrine disrupting chemicals and age at

menarche among the daughters. Details of the nested case-control study are described elsewhere [38]. Cases were girls that obtained early menarche, defined as menarche prior to 11.5 years of age. To account for the nested case-control study design, the sample was weighted to adjust for under-representation of the true number of girls without early menarche (weight for cases was 1 and for controls was 15.1). Additional samples from mothers of sons were selected to maximize data on puberty and dual energy X ray absorptiometry (DXA) scans. At the time maternal serum samples were selected to be analyzed for PFAS concentrations, there were 457 mother-son dyads who had maternal serum samples collected during pregnancy as well as two or more completed puberty questionnaires before the age of 13 and two or more DXA scans for sons. Because of the differences in sampling schemes, data from mothers of daughters and mothers of sons were analyzed separately.

The study website contains details of all the data that are available through a fully searchable data dictionary and variable search tool (<http://www.bris.ac.uk/alspac/researchers/our-data/>). We obtained ethical approval for the study from the ALSPAC Ethics and Law Committee, the Local Research Ethics Committees, and the Centers for Disease Control and Prevention (CDC) Institutional Review Board. Mothers provided written informed consent for participation in the study. Consent for biological samples has been collected in accordance with the Human Tissue Act (2004). Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time.

2.2 Exposure assessment

The following PFAS were included in this analysis: PFOA, PFOS, PFHxS, and PFNA. Maternal serum samples were collected from mothers during pregnancy at median 18 weeks gestation (interquartile range (IQR): 11, 32). Serum concentrations of PFAS are considered to be relatively stable throughout pregnancy [39], therefore the earliest available serum sample was chosen in the event that multiple samples were available. Maternal serum samples were held in storage facilities at the

University of Bristol until they were transferred under controlled conditions to the National Center for Environmental Health of the CDC in the United States for analysis. Samples were analyzed by on-line solid-phase extraction coupled to isotope dilution high-performance liquid chromatography-tandem mass spectrometry [40, 41]. Limits of detection (LODs) were 0.10 ng/mL (PFOA, PFHxS), 0.20 ng/mL (PFOS), and 0.082 ng/mL (PFNA) among the mothers of daughters, while LODs were 0.10 ng/mL for all four PFAS among the mothers of sons. We detected the four PFAS in all samples analyzed.

2.3 Outcome assessment

Women were routinely weighed in antenatal check-ups and six trained research midwives abstracted data from obstetric medical records. Data abstractions included every measurement of weight entered into the medical records and the corresponding gestational age and date (median number of repeat measurements per woman: 10; IQR: 9, 11). The first weight measurement (kg) was subtracted from the last to determine absolute weight gain, which was calculated for all women who had at least one weight measurement prior to 18 weeks and one weight measurement after 28 weeks gestation. The first weight measurement was collected at median 10 weeks (IQR: 8, 11) and the last weight measurement was collected at median 39 weeks (IQR: 38, 40). The time between the last weight measurement and delivery was brief (median: 0 weeks; IQR: 0, 1). The 2009 Institute of Medicine (IOM) definitions of recommended GWG [29] were used to allocate mothers into categories of below recommended, recommended, and above recommended GWG, based on weight measurements from the obstetric records.

Pre-pregnancy BMI was based on model-predicted pre-pregnancy weight (0 weeks gestation) determined through a previously described random effects model that included splines [42] and maternal report of height. Self-reported and predicted pre-pregnancy weight were highly correlated in ALSPAC mothers (Pearson's $r = 0.93$).

2.4 Covariates

Potential confounders were identified *a priori* based on previously published literature and biological plausibility. We considered the following as covariates: maternal race (white/non-white), maternal education (classified as <O-level (ordinary level: required, completed at age 16), O-level, or >O-level), predicted pre-pregnancy BMI (kg/m²), maternal smoking during pregnancy (any/none), maternal age at delivery (years), parity (nulliparous/multiparous), gestational age at delivery (weeks), and gestational age at sample collection (weeks).

2.5 Statistical analysis

Descriptive analyses were conducted for each PFAS. Kruskal-Wallis and Wilcoxon Rank Sum tests were utilized to compare median PFAS for each level of the covariates and to test for differences in PFAS serum concentrations between levels of recommended GWG.

The exposures studied were PFOA, PFOS, PFHxS, and PFNA, which were modeled as log-transformed continuous variables. Linear regression models were used to examine the association of maternal PFAS with absolute GWG. Because associations between maternal health and GWG often differ by pre-pregnancy BMI, the simplest strategy is to conduct analyses stratified by pre-pregnancy BMI category [29]. This approach produces results in a format similar to IOM guidelines, which are BMI category-specific [43]. Pre-pregnancy BMI, which was calculated using the mother's self-reported height and predicted weight at 0 weeks gestation, was categorized as underweight (BMI<18.5 kg/m²), normal weight (18.5≤BMI<25 kg/m²), overweight (25≤BMI<30 kg/m²), or obese (>30 kg/m²), and further collapsed as under-/normal weight and overweight/obese. Polytomous logistic regression models were used to examine the association of maternal PFAS with category of IOM recommended GWG. Residual analyses were conducted as part of evaluating model fit and assumptions. Multiple imputation using the fully conditional specification method was performed to address missing covariate and outcome data [44]; approximately 20% of observations had one or more variables with a missing value

for which values were imputed. Given the exploratory nature of this study, we did not adjust for multiple comparisons.

Because the sampling schemes of mother-child dyads in the subsamples differed by sex, we combined results using meta-analytic techniques. We pooled the effect estimates from mothers of sons and mothers of daughters using fixed effects models. Statistical heterogeneity among the subsamples was assessed using the chi-square test (results were defined as heterogeneous for a p value <0.10) [45]. The potential heterogeneity between groups was quantified using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. The I^2 statistic is calculated using $100\% \times (Q - \text{degrees of freedom}) / Q$, where Q is the Cochran's heterogeneity statistic, which is chi-square distributed [46]. Usually, values of the I^2 statistic <25% are indicative of low heterogeneity, those ranging between 25% and 75% of moderate heterogeneity, and those >75% of high heterogeneity [46].

Data analysis was performed using SAS 9.4 (Cary, NC) with the exception of the meta-analytic procedures, which were performed using Stata 15 (College Station, TX).

3. Results

The study sample comprised predominantly white mothers (98.7%) who attained ordinary levels of education or higher (78.9%) (percentages are among mothers with non-missing data for each characteristic) (**Table 1**). Most mothers entered pregnancy at a normal BMI (67.6%) and were 25 years or older at delivery (83.7%). Nearly all mothers delivered at term (95.2%) and slightly less than half of mothers were nulliparous (48.9%). Few mothers smoked during pregnancy (14.2%).

Among mothers of sons and mothers of daughters, median maternal concentrations of all four PFAS under study were higher among nulliparous women (**Table 1**). Among mothers of daughters, median maternal PFOA and PFOS concentrations were higher among white mothers than non-white mothers (PFOA: 3.8 versus 2.3 ng/mL; PFOS: 19.9 versus 14.6 ng/mL) and median maternal PFOS

concentrations were lower among mothers who smoked during pregnancy (PFOS: 17.2 versus 20.5 ng/mL).

Of the 391 mothers of sons with data on weight gain, 44% gained adequate weight, 29% gained too little weight, and 27% gained too much weight according to IOM guidelines (**Table 1**). Of the 379 mothers of daughters with data on weight gain, 37% gained adequate weight, 32% gained too little weight, and 31% gained too much weight according to IOM guidelines. Median maternal PFOA, PFOS, PFHxS, and PFNA concentrations did not differ by category of IOM recommended GWG.

In models considering absolute GWG as the outcome, there was little evidence of associations of PFAS with GWG among mothers who began their pregnancies as under- or normal weight (**Table 2**). For under- and normal weight mothers of daughters, 10% higher PFNA was associated with a higher GWG of 0.16 kg (95% CI: 0.06, 0.26), though it should be noted that the concentration range for PFNA is rather narrow (median: 0.5, IQR: 0.4, 0.7) (**Supplemental Table 1**). When the mothers of sons and mothers of daughters were combined through meta-analytic techniques, the positive association remained: 10% higher PFNA was associated with a higher GWG of 0.09 kg (95% CI: 0.02, 0.16), though there was considerable heterogeneity present (I^2 : 75.3%) (**Table 2**).

Associations among overweight/obese mothers were null. A weak negative association was observed between PFOA and absolute GWG among overweight/obese weight mothers of daughters (**Table 2; Supplemental Table 1**). For every 10% higher PFOA, GWG was -0.28 kg (95% CI: -0.57, 0.01) lower among overweight/obese mothers of daughters. When the mothers of sons and mothers of daughters were combined through meta-analytic techniques, the weak negative association remained: 10% higher PFOA was associated with a lower GWG of -0.20 kg (95% CI: -0.41, 0.02) (I^2 : 0.0%).

We conducted multiple sensitivity analyses of the categorization of pre-pregnancy BMI in analyses of absolute GWG. In **Table 3**, we examined four categories of BMI: underweight ($BMI < 18.5$ kg/m²), normal weight ($18.5 \leq BMI < 25$ kg/m²), overweight ($25 \leq BMI < 30$ kg/m²), and obese (> 30 kg/m²).

When BMI was split into four categories, associations and direction were comparable to when BMI was dichotomized (under-/normal weight versus overweight/obese). For example, the weak association of PFNA and absolute gestational weight among under-/normal weight mothers (0.09 kg (95% CI: 0.02, 0.16)) persisted when examining under- and normal weight mothers separately (0.24 kg (95% CI: 0.00, 0.48) and 0.07 (95% CI: 0.00, 0.15), respectively). Results stratified by infant sex are presented in **Supplemental Table 2**.

Associations of maternal PFAS with IOM recommended GWG were largely null in adjusted models (**Table 4**), with the exception of PFOS and GWG below the recommendations among mothers of daughters. For 10% higher PFOS, mothers of daughters were 5% more likely (OR: 1.05, 95% CI: 1.01, 1.09) to gain below the recommended amount of weight, compared to mothers with adequate weight gain (**Supplemental Table 3**). When the mothers of sons and mothers of daughters were combined through meta-analytic techniques, this association remained: for 10% higher PFOS, mothers were 3% more likely to gain below the recommended amount of weight (95% CI: 1.00, 1.07), though there was moderate heterogeneity present (I^2 : 50.6%) (**Table 4**).

4. Discussion

We hypothesized that high maternal concentrations of PFAS in pregnancy would increase risk of gaining excessive weight throughout pregnancy since it has previously been shown that PFAS can alter the cell signaling involved in weight homeostasis, particularly as it relates to peroxisome proliferator-activated receptors involved in adipogenesis [47, 48]. However, results from the present study were largely null. While we observed a suggestion that under- and normal weight women may gain slightly more weight with higher maternal PFNA concentrations, this may be due to noise as the association was weak and must be interpreted with caution as the concentration range for PFNA is quite narrow (median: 0.5, IQR: 0.4, 0.7).

To put these findings in the context of previous studies of PFAS and GWG, two studies have found a significant association of PFOS with GWG, but no other PFAS. One study (n=1,609) reported that higher maternal PFOS concentrations in the first trimester were associated with modestly higher GWG among Canadian women with underweight or normal weight pre-pregnancy BMI (<25 kg/m²), but not among women with overweight or obese pre-pregnancy BMI (≥25 kg/m²). This study did not examine PFNA, and maternal PFOA, PFOS, and PFHxS concentrations were notably lower in this modern Canadian study population than ALSPAC [35]. The second study (n=218), which used self-reported GWG, also found that PFOS (collected pre-pregnancy) was moderately associated with GWG among women starting pregnancy with an underweight or normal weight BMI [34]. The maternal PFAS concentrations in this contemporary U.S. population were similar to ALSPAC concentrations, with the exception of PFNA, which was substantially lower among ALSPAC mothers [49]. Lastly, mothers from the U.S. and Canada were more prone to gaining above the IOM recommended GWG (40.8% (U.S.) and 56.5% (Canada) versus 29.0% in ALSPAC) [34, 35].

Among women with underweight or normal weight pre-pregnancy BMI (<25 kg/m²) in our study, PFNA, not PFOS, was associated with modestly higher GWG. That said, the remainder of our results are in line with previous studies: there appears to be no association of PFOA and PFHxS with GWG, regardless of pre-pregnancy BMI. While we were not able to replicate previous findings of an association of PFOS with GWG among mothers with underweight or normal weight pre-pregnancy BMI in our study of British mothers, we did observe a similar direction of association among women with underweight or normal weight pre-pregnancy BMI, but with a different PFAS (PFNA instead of PFOS). There were notable differences in measurement that could account for the varying results observed, such as different timing of PFAS measurement (pre-pregnancy versus during pregnancy), different methods of collecting GWG data (self-reported versus medical record abstraction), different outcomes of GWG

(absolute weight gain, rate of weight gain, adherence to IOM guidelines, etc.) and control for more confounding factors.

Previous ALSPAC studies of maternal PFAS concentrations during pregnancy have found growth and weight-related effects among offspring. Prenatal PFAS exposure, namely PFOS, was associated with smaller size at birth (weight, crown to heel length, and head circumference) [50, 51], but larger size at 20 months (for PFOS) [50]. Additionally, prenatal exposure to PFOA and PFOS was associated with girls' percent total body fat at age nine within some strata of maternal education status [52]. While the previous studies have focused on prenatal exposure to PFAS and observed subtle disruptions to endocrine signaling and altered adipocyte profiles, the present study does not show the same effect with GWG among mothers.

Our study has several strengths, including the substantial covariate data available, prospective timing, and repeat weight measurements during pregnancy collected as part of routine care. Limitations include potential confounding by gestational transfer of PFAS to the fetus or maternal changes in serum volume [53], the inability to identify maternal and fetal contributions to GWG, the potential for dietary patterns to confound the association of PFAS with GWG, not examining the synergy between or cumulative effect of the PFAS under study, and the unclear temporal relationship between PFAS measurements and GWG. Additionally, it is possible that there was limited power in the overweight and obese group. Lastly, the concentration range for PFNA in this study was rather narrow, so caution should be taken in interpreting those results.

Another notable limitation is that the subsamples of mothers of sons and mothers of daughters used in this study differed from the overall ALSPAC cohort on some factors (data not shown). For example, mothers in our subsample were more likely to be highly educated and older than mothers in the overall cohort. These differences are unsurprising given that to be selected for our subsamples, children had to still be engaged with the study during puberty (completing two or more puberty questionnaires),

and sons were required to also have two or more DXA scans, which required a clinic visit.

Nonparticipation and loss to follow-up tends to be more pronounced among the less advantaged and less healthy [54-61].

Another limitation of studies of PFAS and other endocrine disrupting chemicals measured in blood is the concern about reverse causality and confounding because the outcome of interest may affect the measured biomarker level and there may be shared biological determinants of the exposure measure and outcome (e.g., hemodynamics), respectively [62]. Much of the work addressing this issue has been situated in studies of PFAS and birth size [63-68]. These previous studies have shown that reverse causality and confounding are less of a concern when there is a wide range of exposure and when blood samples are collected early in pregnancy [66, 67]. We were able to address such concerns through design and analysis in our study. The majority of samples were collected early in pregnancy: one-third of mothers had blood sampled in the first 12 weeks and the median age of sample collection was 18 weeks gestation, and we adjusted for gestational age (in weeks) of sample collection in our analyses.

Our exploratory examination of the relationship of maternal PFAS concentrations during pregnancy with GWG suggests that PFAS is not associated with absolute or recommended GWG. While we observed that under- and normal weight women may gain slightly more weight with higher maternal PFNA concentrations, it is possible that these findings are driven by chance. Complex pathways between maternal chemical burdens and GWG may exist, and further research in diverse populations is warranted to better understand this relationship and its potential implications for maternal and childhood obesity.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Table 1. Characteristics of the mothers of Avon Longitudinal Study of Parents and Children (ALSPAC) (1991-1992) sub-study population (N=905) by maternal serum concentrations of perfluoroalkyl substance (ng/mL).

Characteristic ^a	Frequency n (%)	PFOA Median (IQR)	PFOS Median (IQR)	PFHxS Median (IQR)	PFNA Median (IQR)
Mothers of sons (N=457)					
Overall	457 (100)	3.0 (2.3-3.8)	13.8 (11.0-17.7)	1.9 (1.4-2.5)	0.4 (0.3-0.5)
Maternal race	n= ^b				
White	441 ^b	3.0 (2.3-3.8)	13.9 (11.0-17.9)	1.9 (1.4-2.5)	0.4 (0.3-0.5)
Non-white	<5 ^b	2.1 (2.0-6.3)	12.7 (9.1-15.6)	1.3 (1.0-4.1)	0.2 (0.2-0.3)
Maternal education ^c	n=446				
< O-level	96 (21.5)	2.8 (2.4-3.6)	13.9 (11.0-17.3)	1.9 (1.5-2.3)	0.4 (0.3-0.5)
O-level	154 (34.5)	3.1 (2.3-3.8)	14.8 (11.9-18.9)	1.8 (1.3-2.3)	0.4 (0.3-0.4)
>O-level	196 (43.9)	3.0 (2.3-3.9)	13.6 (10.7-17.2)	1.9 (1.4-2.5)	0.3 (0.3-0.4)
Pre-pregnancy BMI, kg/m ²	n=413				
<18.5 (underweight)	46 (11.1)	3.0 (2.2-3.7)	13.8 (10.1-18.4)	1.9 (1.5-2.3)	0.3 (0.2-0.4)
18.5-24.99 (normal weight)	282 (68.3)	3.0 (2.3-3.8)	14.2 (11.2-18.6)	1.9 (1.4-2.5)	0.4 (0.3-0.5)
25-29.99 (overweight)	63 (15.3)	2.8 (2.4-3.6)	13.5 (10.6-17.1)	2.0 (1.5-2.5)	0.3 (0.3-0.4)
≥30 (obese)	22 (5.3)	2.8 (2.4-3.9)	12.0 (10.1-15.6)	1.7 (1.1-1.9)	0.3 (0.3-0.4)
Prenatal smoking	n=441				
Any	44 (10.0)	3.0 (2.4-3.6)	13.2 (11.0-17.2)	2.0 (1.7-2.6)	0.4 (0.3-0.5)
None	397 (90.0)	3.0 (2.3-3.8)	14.0 (11.1-17.9)	1.9 (1.4-2.4)	0.4 (0.3-0.5)
Maternal age at delivery, years	n=453				
<25	54 (11.9)	3.0 (2.3-3.7)	12.6 (10.6-16.9)	1.6 (1.1-1.9)*	0.4 (0.3-0.4)
25-29	188 (41.5)	3.2 (2.5-4.0)	14.1 (11.9-18.8)	1.8 (1.4-2.5)*	0.4 (0.3-0.5)
≥30	211 (46.6)	2.9 (2.2-3.7)	13.9 (10.8-17.3)	1.9 (1.4-2.5)*	0.4 (0.3-0.5)
Gestational age, weeks	n=457				
<37 weeks	26 (5.7)	3.4 (2.4-3.9)	13.8 (12.8-17.0)	1.8 (1.5-2.7)	0.4 (0.3-0.5)
≥37 weeks	431 (94.3)	2.9 (2.3-3.8)	13.8 (10.9-17.9)	1.9 (1.4-2.5)	0.4 (0.3-0.5)
Parity	n=442				
Nulliparous	213 (48.2)	3.4 (2.7-4.2)*	14.3 (11.8-18.0)*	2.0 (1.5-2.6)*	0.4 (0.3-0.5)*
Multiparous	229 (51.8)	2.6 (2.2-3.3)*	13.6 (10.6-17.0)*	1.8 (1.3-2.3)*	0.3 (0.2-0.4)*
Gestational Weight Gain ^d	n=391				
Below	115 (29.4)	2.8 (2.3-3.7)	13.9 (11.2-17.6)	1.9 (1.4-2.5)	0.4 (0.3-0.5)
Within	171 (43.7)	3.0 (2.3-3.8)	13.8 (11.0-17.7)	1.9 (1.4-2.5)	0.4 (0.3-0.5)
Above	105 (26.9)	3.1 (2.5-3.8)	13.6 (11.0-17.6)	1.9 (1.4-2.5)	0.4 (0.4-0.6)
Mothers of daughters (N=448)					
Overall	448 (100)	3.7 (2.8-4.8)	19.8 (15.1-24.9)	1.6 (1.2-2.2)	0.5 (0.4-0.7)
Maternal race	n=431				
White	423 (98.1)	3.8 (2.9-4.8)*	19.9 (15.2-25.3)*	1.6 (1.2-2.2)	0.5 (0.4-0.7)
Non-white	8 (1.9)	2.3 (1.6-2.9)*	14.6 (8.1-18.4)*	1.4 (0.9-1.7)	0.5 (0.2-0.7)
Maternal education ^c	n=429				
< O-level	89 (20.7)	3.6 (2.8-4.4)	18.2 (14.9-23.3)	1.6 (1.3-2.2)	0.5 (0.4-0.7)
O-level	140 (32.6)	3.7 (2.9-5.0)	19.6 (15.1-26.0)	1.6 (1.2-2.3)	0.6 (0.4-0.7)
>O-level	200 (46.6)	3.9 (2.8-4.8)	20.4 (15.2-25.3)	1.7 (1.2-2.2)	0.5 (0.4-0.7)
Pre-pregnancy BMI, kg/m ²	n=401				
<18.5 (underweight)	43 (10.7)	3.1 (2.4-4.7)	17.0 (14.0-24.7)	1.6 (1.0-2.7)	0.5 (0.3-0.6)
18.5-24.99 (normal weight)	268 (66.8)	3.8 (2.8-4.8)	20.2 (15.3-25.2)	1.6 (1.2-2.2)	0.5 (0.4-0.7)
25-29.99 (overweight)	63 (15.7)	3.5 (2.9-4.4)	19.2 (15.2-24.8)	1.7 (1.3-2.3)	0.5 (0.4-0.7)
≥30 (obese)	27 (6.7)	4.1 (3.3-5.0)	20.4 (17.0-27.9)	1.5 (1.3-2.2)	0.7 (0.4-0.7)
Prenatal smoking	n=427				

Any	79 (18.5)	3.4 (2.9-4.4)	17.2 (13.4-21.4)*	1.7 (1.3-2.4)	0.5 (0.3-0.7)*
None	348 (81.5)	3.8 (2.8-4.9)	20.5 (15.4-25.6)*	1.6 (1.2-2.2)	0.6 (0.4-0.7)*
Maternal age at delivery, years	n=445				
<25	92 (20.7)	3.9 (3.0-4.8)	18.5 (14.1-23.1)	1.6 (1.2-2.1)	0.5 (0.4-0.6)
25–29	164 (36.9)	3.8 (3.0-4.9)	20.7 (15.4-25.4)	1.6 (1.2-2.1)	0.6 (0.4-0.7)
≥30	189 (42.5)	3.6 (2.5-4.6)	19.7 (15.1-25.5)	1.7 (1.2-2.4)	0.5 (0.4-0.7)
Gestational age, weeks	n=448				
<37 weeks	17 (3.8)	4.4 (2.8-5.3)	22.7 (15.3-27.5)	1.7 (1.2-1.9)	0.6 (0.4-0.7)
≥37 weeks	431 (96.2)	3.7 (2.8-4.8)	19.6 (15.0-24.8)	1.6 (1.2-2.3)	0.5 (0.4-0.7)
Parity	n=419				
Nulliparous	208 (49.6)	4.4 (3.4-5.4)*	21.5 (17.0-26.4)*	1.8 (1.4-2.4)*	0.6 (0.4-0.7)*
Multiparous	211 (50.4)	3.1 (2.4-4.0)*	18.2 (14.2-23.7)*	1.5 (1.1-2.2)*	0.5 (0.3-0.7)*
Gestational Weight Gain ^d	n=379				
Below	120 (31.7)	3.6 (2.8-4.6)	21.4 (15.7-25.6)	1.6 (1.2-2.4)	0.5 (0.4-0.7)
Within	141 (37.2)	3.9 (2.8-4.8)	20.4 (15.2-24.8)	1.6 (1.2-2.2)	0.5 (0.4-0.7)
Above	118 (31.3)	3.9 (2.9-4.9)	20.0 (15.5-25.6)	1.7 (1.3-2.3)	0.6 (0.4-0.7)

Abbreviations: n, number; g, grams; kg, kilograms; kg/m², kilograms per meter-squared; IQR, interquartile range

^a Compared using Kruskal-Wallis or Wilcoxon Rank Sum tests

^b Counts and percents suppressed due to small cell sizes

^c <O-level=none, Certificate of Secondary Education, and vocational education, which are equivalent to no diploma or a GED in the United States. O-levels (ordinary levels) are required and completed at the age of 16. >O-level=A-levels (advanced levels) completed at 18, which are optional, but required to get into university; and a university degree.

^d Refers to below, within, or above IOM recommended total gestational weight gain. For underweight women (BMI <18.5), recommendations are 12.5-18 kg total weight gain; for normal weight women (BMI 18.5-24.9): 11.5-16 kg; for overweight women (BMI 25.0-29.9): 7-11.5 kg; and for obese women (BMI ≥30.0): 5-9 kg [29].

* Indicates p<0.05

Table 2. Adjusted^a models of maternal perfluoroalkyl substance serum concentrations (ng/mL) and absolute gestational weight gain, stratified by under-/normal weight pre-pregnancy BMI and overweight/obese pre-pregnancy BMI, in the Avon Longitudinal Study of Parents and Children sub-study population (N=905).

	Model	Coefficient ^b	95% CI	Heterogeneity p-value	I ² statistic ^c
PFOA	Under-/ Normal Weight	0.01	-0.08, 0.09	0.67	0.0%
	Overweight/ Obese	-0.20	-0.41, 0.02	0.40	0.0%
PFOS	Under-/ Normal Weight	-0.03	-0.11, 0.06	0.85	0.0%
	Overweight/ Obese	-0.12	-0.30, 0.06	0.99	0.0%
PFHxS	Under-/ Normal Weight	0.00	-0.05, 0.05	0.26	19.8%
	Overweight/ Obese	0.02	-0.08, 0.11	0.66	0.0%
PFNA	Under-/ Normal Weight	0.09	0.02, 0.16	0.04	75.3 %
	Overweight/ Obese	-0.12	-0.31, 0.07	0.98	0.0%

Abbreviations: N, number; CI, confidence interval

^a Adjusted for maternal education, prenatal smoking, maternal age at delivery, parity, pre-pregnancy BMI, gestational age at delivery, and gestational age at sample

^b Coefficient representing a 10% increase in the PFAS of interest

^c The I² statistic indicates the percentage of variance in a meta-analysis that is attributable to study heterogeneity rather than chance. It is calculated using $100\% \times (Q - df) / Q$ where Q is the Cochran's heterogeneity statistic, which is chi-square distributed [46]

Table 3. Adjusted^a models of maternal perfluoroalkyl substance serum concentrations (ng/mL) and absolute gestational weight gain, stratified by pre-pregnancy BMI, in the Avon Longitudinal Study of Parents and Children sub-study population (N=905).

	Model	Coefficient^b	95% CI	Heterogeneity p-value	I² statistic^c
PFOA	Underweight	0.06	-0.14, 0.26	0.32	0.0%
	Normal Weight	-0.01	-0.11, 0.08	0.49	0.0%
	Overweight	-0.03	-0.33, 0.26	0.69	0.0%
	Obese	-0.29	-0.65, 0.08	0.40	0.0%
PFOS	Underweight	0.02	-0.24, 0.28	0.78	0.0%
	Normal Weight	-0.03	-0.13, 0.06	0.89	0.0%
	Overweight	-0.04	-0.29, 0.21	0.10	62.4%
	Obese	-0.07	-0.36, 0.22	0.29	12.1%
PFHxS	Underweight	0.01	-0.12, 0.13	0.42	0.0%
	Normal Weight	0.01	-0.05, 0.07	0.34	0.0%
	Overweight	0.11	-0.03, 0.25	0.96	0.0%
	Obese	0.02	-0.15, 0.19	0.38	0.0%
PFNA	Underweight	0.24	0.00, 0.48	0.80	0.0%
	Normal Weight	0.07	0.00, 0.15	0.04	76.0%
	Overweight	-0.07	-0.28, 0.13	0.17	48.1%
	Obese	-0.34	-0.99, 0.30	0.60	0.0%

Abbreviations: N, number; CI, confidence interval

^a Adjusted for maternal education, prenatal smoking, maternal age at delivery, parity, pre-pregnancy BMI, gestational age at delivery, and gestational age at sample

^b Coefficient representing a 10% increase in the PFAS of interest

^c The I² statistic indicates the percentage of variance in a meta-analysis that is attributable to study heterogeneity rather than chance. It is calculated using $100\% \times (Q - df) / Q$ where Q is the Cochran's heterogeneity statistic, which is chi-square distributed [46]

Table 4. Adjusted^a models of maternal perfluoroalkyl substance serum concentrations (ng/mL) and category of IOM recommended gestational weight gain (below or above recommendations versus reference group: adequate weight gain) in the Avon Longitudinal Study of Parents and Children sub-study population (N=905).

	Model	OR ^b	95% CI	Heterogeneity p-value	I ² statistic ^c
PFOA	Below ^d	1.00	0.97, 1.04	0.31	1.3%
	Above ^e	1.00	0.96, 1.04	0.82	0.0%
PFOS	Below	1.03	1.00, 1.07	0.16	50.6%
	Above	0.99	0.95, 1.03	0.89	0.0%
PFHxS	Below	1.00	0.99, 1.02	0.60	0.0%
	Above	1.01	0.98, 1.03	0.38	0.0%
PFNA	Below	1.01	0.98, 1.05	0.75	0.0%
	Above	1.02	0.99, 1.06	0.66	0.0%

Abbreviations: N, number; OR, odds ratio; CI, confidence interval; IOM, Institute of Medicine

^a Adjusted for maternal education, prenatal smoking, maternal age at delivery, parity, pre-pregnancy BMI, gestational age at delivery, and gestational age at sample

^b Represents a 10% increase in the PFAS of interest

^c The I² statistic indicates the percentage of variance in a meta-analysis that is attributable to study heterogeneity rather than chance. It is calculated using $100\% \times (Q - df) / Q$ where Q is the Cochran's heterogeneity statistic, which is chi-square distributed [46]

^d Below recommendations for IOM recommended gestational weight gain

^e Above recommendations for IOM recommended gestational weight gain

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Supplemental Table 1. Adjusted^a models of maternal perfluoroalkyl substance serum concentrations (ng/mL) and absolute gestational weight gain, stratified by under-/normal weight pre-pregnancy BMI and overweight/obese pre-pregnancy BMI, in the Avon Longitudinal Study of Parents and Children sub-study population (N=905).

Model	Mothers of Sons (N=457)			Mothers of Daughters (N=448)		
	Coefficient ^b	95% CI	p-value	Coefficient ^b	95% CI	p-value
PFOA	<i>Interaction by pre-pregnancy BMI</i>					
Under-/ Normal Weight	-0.01	-0.12, 0.10	0.86	0.03	-0.09, 0.14	0.67
Overweight/ Obese	-0.09	-0.42, 0.25	0.61	-0.28	-0.57, 0.01	0.06
PFOS	<i>Interaction by pre-pregnancy BMI</i>					
Under-/ Normal Weight	-0.04	-0.15, 0.08	0.54	-0.02	-0.14, 0.11	0.77
Overweight/ Obese	-0.12	-0.40, 0.16	0.41	-0.12	-0.36, 0.12	0.32
PFHxS	<i>Interaction by pre-pregnancy BMI</i>					
Under-/ Normal Weight	-0.03	-0.11, 0.05	0.44	0.03	-0.04, 0.09	0.42
Overweight/ Obese	-0.01	-0.15, 0.14	0.91	0.04	-0.10, 0.17	0.60
PFNA	<i>Interaction by pre-pregnancy BMI</i>					
Under-/ Normal Weight	0.01	-0.09, 0.12	0.82	0.16	0.06, 0.26	0.002
Overweight/ Obese	-0.11	-0.40, 0.17	0.43	-0.12	-0.37, 0.13	0.36

Abbreviations: N, number; CI, confidence interval

^a Adjusted for maternal education, prenatal smoking, maternal age at delivery, parity, pre-pregnancy BMI, gestational age at delivery, and gestational age at sample

^b Coefficient representing a 10% increase in the PFAS of interest

Supplemental Table 2. Adjusted^a models of maternal perfluoroalkyl substance serum concentrations (ng/mL) and absolute gestational weight gain, stratified by pre-pregnancy BMI, in the Avon Longitudinal Study of Parents and Children sub-study population (N=905).

Model		Mothers of Sons (N=457)			Mothers of Daughters (N=448)		
		Coefficient ^b	95% CI	p-value	Coefficient ^b	95% CI	p-value
PFOA	Underweight	0.23	-0.16, 0.61	0.24	0.00	-0.23, 0.24	0.99
	Normal Weight	-0.04	-0.17, 0.08	0.49	0.02	-0.12, 0.17	0.75
	Overweight	0.00	-0.35, 0.36	0.98	-0.13	-0.70, 0.45	0.65
	Obese	0.01	-0.79, 0.81	0.98	-0.37	-0.78, 0.04	0.08
PFOS	Underweight	-0.04	-0.53, 0.45	0.87	0.04	-0.28, 0.36	0.80
	Normal Weight	-0.04	-0.17, 0.09	0.55	-0.03	-0.17, 0.11	0.71
	Overweight	0.13	-0.20, 0.46	0.43	-0.29	-0.68, 0.11	0.15
	Obese	-0.27	-0.75, 0.21	0.27	0.06	-0.32, 0.43	0.76
PFHxS	Underweight	-0.12	-0.47, 0.22	0.48	0.03	-0.11, 0.17	0.70
	Normal Weight	-0.03	-0.12, 0.07	0.58	0.03	-0.05, 0.11	0.40
	Overweight	0.11	-0.06, 0.28	0.19	0.10	-0.14, 0.35	0.40
	Obese	-0.06	-0.32, 0.19	0.62	0.09	-0.14, 0.31	0.45
PFNA	Underweight	0.20	-0.20, 0.61	0.32	0.27	-0.04, 0.57	0.08
	Normal Weight	-0.01	-0.12, 0.10	0.86	0.15	0.04, 0.26	0.01
	Overweight	0.06	-0.22, 0.35	0.66	-0.23	-0.53, 0.07	0.14
	Obese	-0.16	-1.13, 0.81	0.74	-0.51	-1.42, 0.39	0.27

Abbreviations: N, number; CI, confidence interval

^a Adjusted for maternal education, prenatal smoking, maternal age at delivery, parity, pre-pregnancy BMI, gestational age at delivery, and gestational age at sample

^b Coefficient representing a 10% increase in the PFAS of interest

Supplemental Table 3. Adjusted^a models of maternal perfluoroalkyl substance serum concentrations (ng/mL) and category of IOM recommended gestational weight gain (below or above recommendations versus reference group: adequate weight gain) in the Avon Longitudinal Study of Parents and Children sub-study population (N=905).

Model		Mothers of Sons (N=457)			Mothers of Daughters (N=448)		
		OR ^b	95% CI	p-value	OR ^b	95% CI	p-value
PFOA	Below ^c	0.98	0.92, 1.04	0.47	1.02	0.97, 1.07	0.44
	Above ^d	0.99	0.92, 1.06	0.77	1.00	0.96, 1.04	0.97
PFOS	Below	0.99	0.93, 1.06	0.80	1.05	1.01, 1.09	0.02
	Above	0.99	0.91, 1.07	0.72	0.99	0.95, 1.04	0.74
PFHxS	Below	0.99	0.95, 1.04	0.71	1.00	0.99, 1.02	0.61
	Above	0.99	0.95, 1.04	0.69	1.02	0.99, 1.05	0.28
PFNA	Below	1.02	0.97, 1.08	0.48	1.01	0.96, 1.06	0.75
	Above	1.01	0.95, 1.07	0.72	1.03	0.99, 1.07	0.14

Abbreviations: N, number; OR, odds ratio; CI, confidence interval; IOM, Institute of Medicine

^a Adjusted for maternal education, prenatal smoking, maternal age at delivery, parity, pre-pregnancy BMI, gestational age at delivery, and gestational age at sample

^b Represents a 10% increase in the PFAS of interest

^c Below recommendations for IOM recommended gestational weight gain

^d Above recommendations for IOM recommended gestational weight gain