Maternal serum concentrations of perfluoroalkyl substances and birth size in British boys

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Abstract

Per- and polyfluoroalkyl substances (PFAS) have been widely used in commercial and industrial manufacturing processes since the 1950s. Inverse associations between prenatal exposure to PFAS and birth size have been found in populations around the globe. This study examined the association of prenatal maternal serum concentrations of perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA) and birth size in British boys. The study included 457 mother-son dyads participating in the Avon Longitudinal Study of Parents and Children (ALSPAC). Birth weight (g), crown to heel length (cm), and head circumference (cm) were collected at delivery. PFAS were detected in all maternal serum samples during pregnancy (median: 30 weeks gestation (interquartile range: 12–33)). Median concentrations (interquartile range) were 13.8 ng/mL (11.0, 17.7), 3.0 ng/mL (2.3, 3.8), 1.9 ng/mL (1.4, 2.5), and 0.4 ng/mL (0.3, 0.5) for PFOS, PFOA, PFHxS, and PFNA, respectively. In multivariable linear regression models, inverse associations were detected between PFOS (continuous) and birth weight ($\beta = -8.50$ g, 95% CI = -15.93, -1.07 g), crown to heel length ($\beta = -0.04$ cm, 95% CI = -0.08, -0.01 cm), and head circumference ($\beta = -0.02$ cm, 95% CI = -0.04, -0.002 cm). In conclusion, prenatal exposure to high levels of PFOS may be associated with reduced birth size in male infants.

Keywords

ALSPAC; Endocrine disruptors; Perfluoroalkyl substances; Birth size; Birth weight

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1. Introduction

Perfluorinated compounds are organic substances characterized by a long chain of carbon-fluorine bonds with unique stability and extremely low surface tension (Giesy and Kannan, 2001; Paul et al., 2009; Wang et al., 2009). Per- and polyfluoroalkyl substances (PFAS) are highly stable in the environment. The low surface tension allows PFAS to repel dirt, water, and oil. As a result, they are commonly used as surfactants in textiles, footwear, furniture, carpets, lubricants, waxes, fire-fighting foam, and nonstick coatings (Giesy and Kannan, 2001; Paul et al., 2009; Wang et al., 2009). PFAS have been found in water, sediment, soil, and wildlife across the globe (Jensen and Leffers, 2008). The long fluorinated chain does not degrade in the environment or in humans (Lau et al., 2007).

Exposure to PFAS is ubiquitous and occurs through water, food, and indoor air (Agency for Toxic Substances Disease Registry, 2009). Common perfluoroalkyl acids include perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA), though a number of forms have been phased out. PFAS are lipophilic and hydrophobic (DeWitt, 2015), thus readily bind to proteins in blood. As a result, they accumulate in the blood, kidneys, liver, and spleen over long periods of exposure (Olsen et al., 2007). Half-lives in human serum are approximately 2–4 years for PFOA, 3–6 years for PFOS, and 8–16 years for PFHxS (Bartell et al., 2010; Olsen et al., 2007; Worley et al., 2017; Zhang et al., 2013b). Data on the half-life of PFNA are limited, though findings to date suggest that PFNA is more persistent in humans than PFOA (Zhang et al., 2013a). PFAS are readily transferred to the fetus through the placenta (Apelberg et al., 2007a).

Several animal studies have suggested that prenatal PFAS exposure can influence fetal growth; specifically, prenatal PFOS and PFOA exposure can reduce birth weight and gestational age at delivery among rodents (Lau et al., 2004, 2006; Luebker et al., 2005). A number of potential mechanisms have been posited, including a disturbance of lipid and glucose homeostasis, suppression of primary antibody responses, altered glucocorticoids and reproductive hormone levels, or effects on cell proliferation and differentiation (DeWitt et al., 2012; Goudarzi et al., 2017; Yang et al., 2002).

The epidemiological literature on prenatal PFAS exposure and birth size (birth weight, birth length, and head circumference) has been mixed, with some studies finding that higher concentrations are associated with reduced birth size (Apelberg et al., 2007b; Chen et al., 2012; Fei et al., 2007; Maisonet et al., 2012; Meng et al., 2018; Minatoya et al., 2017; Sagiv et al., 2018; Starling et al., 2017), while others observe largely null associations (Ashley-Martin et al., 2017; Hamm et al., 2010; Manzano-Salgado et al., 2017; Shoaff et al., 2018; Whitworth et al., 2012; Woods et al., 2017), with inconsistent results across PFAS chemicals. To date, studies of PFAS exposure and birth size have been conducted in American, Canadian, Danish, Norwegian, Spanish, Japanese, and Taiwanese populations. While the aforementioned are examples of relevant studies, there are also published systematic reviews/meta-analyses on the topic (Bach et al., 2015; Johnson et al., 2014; Steenland et al., 2018). In particular, an updated meta-analysis with bias analysis of serum

PFOA and birth weight concluded that human evidence provides only modest support for lower birth weight with higher maternal PFOA concentrations (Steenland et al., 2018).

The Avon Longitudinal Study of Parents and Children (ALSPAC) is an ongoing prospective birth cohort of British children. Previous research has shown that maternal serum concentrations of PFOS, PFOA, and PFHxS during pregnancy are inversely associated with birth size in ALSPAC girls (Maisonet et al., 2012). Studies have found that exposure to PFAS can affect the functioning of both androgen and estrogen receptors *in utero* (Kjeldsen and Bonefeld-Jørgensen, 2013). Because sex hormones have differential roles by gender on fetal development, PFAS may therefore have differential effects on fetal development. Thus, this study aimed to assess the association between maternal serum concentrations of PFOS, PFOA, PFHxS, and PFNA with birth weight, crown to heel length, and head circumference in infant males, in mother-son dyads from the ALSPAC cohort.

2. Methods

2.1. Study population

ALSPAC recruited pregnant women with expected delivery dates between April 1st, 1991 and December 31st, 1992. The study enrolled 14,541 pregnant women and their children from three health districts of the former Avon region in South West England. Recruitment methods have been described elsewhere (Boyd et al., 2013; Fraser et al., 2013). Enrolled mothers and children provided biological samples, completed questionnaires, and participated in clinical assessments.

The present study uses a subset of data to study the association between prenatal endocrine disrupting chemical exposure and growth and development in boys. The subset was selected to maximize data on puberty and dual energy X ray absorptiometry (DXA) scans. At the time maternal serum samples were 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 (five questionnaires possible, starting at age 8) and two or more DXA scans for sons (five DXA scans possible, starting at age 9).

Please note that the study website contains details of all the data that is 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.

2.2. Exposure assessment

The following PFAS were included in this analysis: PFOA, PFOS, PFHxS, and PFNA. Maternal serum samples were collected at median 30 weeks gestation (interquartile range (IQR): 12–33 weeks). 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 (NCEH) of the Centers for Disease Control and Prevention

(CDC) in the United States for analysis in 2015. Samples were analyzed by on-line solid-phase extraction coupled to isotope dilution high-performance liquid chromatography-tandem mass spectrometry (Kato et al., 2011a). The limit of detection was 0.10 ng/mL for all PFAS under study. There were no samples below the limit of detection. Serum concentrations of PFAS are considered to be relatively stable throughout pregnancy (Fei et al., 2007), therefore the earliest available serum sample was chosen in the event that multiple samples were available.

2.3. Outcome assessment

Birth weight (g) was abstracted from infant medical records. Trained ALSPAC staff measured crown to heel length (cm) using a Harpenden neonatometer (Holtain Ltd.) and head circumference (cm) using a lasso tape measure within 24 h of birth (median 1 day, range: 1–14 days). Additional details on birth size measurement and quality control are described elsewhere (Dunger et al., 1998; Taylor et al., 2016).

2.4. Covariates

Potential confounders were identified *a priori* based on previously published literature and biological plausibility. Potential confounders were factors known to be associated with birth size as well as PFAS body burden, but not on the causal pathway between PFAS and birth size. We considered the following as covariates: maternal weight gain during pregnancy (kg), maternal age at delivery (years), maternal pre-pregnancy BMI (kg/m^2), maternal education (classified as < O-level [ordinary level: required, completed at age 16], O-level, or > O-level), vitamin use or folic acid use during pregnancy (yes/no), smoking during pregnancy (yes/no), alcohol use during pregnancy (yes/no), parity (nulliparous/multiparous), and gestational age at sample collection (weeks). Clinical staff documented maternal age and gestational age at sample collection, while the remainder of the covariates were self-reported on questionnaires completed by the mother during or immediately after pregnancy.

2.5. Statistical analyses

All analyses were conducted in SAS 9.4 (Cary, NC, USA). Descriptive analyses were conducted for each PFAS. Kruskal-Wallis and Wilcoxon Rank Sum tests were utilized to test for differences in PFAS concentrations between tertiles of birth size measures (birth weight, crown to heel length, head circumference) and to compare median PFAS values for each level of the covariates.

A set of potential confounding variables was identified *a priori* for consideration in multivariable linear regression models used to separately estimate the association between prenatal PFAS concentrations and birth weight, head circumference, and crown to heel length. Full multivariate models assessed confounding by maternal weight gain, maternal age, maternal pre-pregnancy BMI, maternal education, vitamin use, folic acid use, smoking during pregnancy, alcohol use during pregnancy, parity, and gestational age at sample collection, as well as interaction terms between PFAS and maternal BMI, parity, and education. There were no significant interaction terms. The final model was selected after removing covariates from the full model that did not satisfy our *a priori* change-in-estimate criterion of 10%.

Two sensitivity analyses were conducted. First, given the range of PFAS concentrations, PFAS were analyzed as quintiles (in addition to tertiles) to better detect nonlinear associations. Second, analyses were repeated in a subset of mother-son dyads with blood sampled during the first trimester (12 weeks).

3. Results

In this subset of the ALSPAC cohort, boys were predominantly born to normal weight (18.5 BMI < 25) (72.7%) mothers under the age of 35 (88.1%) who had attained at least ordinary levels (O-levels) of education (78.5%) (Table 1). A slight majority of mothers was multiparous (52.0%) and the vast majority did not smoke (90.0%) or drink alcohol (85.7%) during pregnancy. Maternal serum PFAS concentrations were strongly correlated with one another; PFOA and PFOS (r = 0.63) and PFOS and PFNA (r = 0.60) were most strongly correlated (Table S1). Of the four PFAS assessed, PFOS was present at the highest concentrations in serum (median: 13.8 ng/mL, IQR: 11.0, 17.7 ng/mL) (Table 1). Concentrations of all four PFAS under study were higher among nulliparous women and among women with serum samples taken in the first 20 weeks of pregnancy, but there were no other strong associations between PFAS and maternal characteristics. There was some evidence that mothers who reported taking folic acid had higher PFAS concentrations than those who did not. Univariate results generally showed an inverse association between tertiles of birth size and PFAS, although this was only significant for PFOS and birth weight. Maternal PFOS concentrations were highest for infants with the lowest birth weight (14.4 ng/mL for those < 3290 g versus 13.2 ng/mL for those > 3720 g).

In adjusted models, results were attenuated but PFOS remained inversely associated with birth weight (Table 2). A 1-ng/mL higher PFOS level was associated with a −8.50 g (95% confidence interval (CI): −15.93, −1.07 g) lower birth weight. In adjusted models where PFAS concentrations were categorized into tertiles of exposure, there were weak inverse associations between PFNA with birth weight. Infants in the highest tertile (tertile 3) of PFNA exposure weighed −133.02 g less than those in the lowest tertile of PFNA exposure (95% CI: −265.41, −0.64 g; p-trend: 0.06). Similar results were observed when quintiles of PFAS exposure were used as opposed to tertiles in sensitivity analyses (Table S2).

In multivariable models, PFOS was inversely associated with crown to heel length and marginally associated with head circumference (Table 2). A 1-ng/mL higher PFOS was associated with a −0.04 cm (95% CI: −0.08, −0.01 cm) lower crown to heel length. A 1-ng/mL higher PFOS was associated with a mean difference in head circumference of −0.02 cm (95% CI: −0.04, −0.002 cm). There was some evidence of similar inverse associations between PFHxS and PFNA and crown to heel length and head circumference. In adjusted models where PFAS concentrations were categorized into tertiles of exposure, there were suggestions of inverse associations between PFOS and head circumference. Compared to those in the lowest tertile of PFOS exposure, the mean difference in head circumference was −0.25 cm (95% CI: −0.58, 0.07 cm) for infants in the highest tertile of exposure.

In our sensitivity analysis, we examined those (n = 115) with blood sampled in the first trimester (12 weeks). The associations between all PFAS and birth weight were null but in

the same direction as was observed for the entire study sample across all four PFAS of interest. Among those with blood sampled in the first trimester, a 1-ng/mL higher PFOS level was associated with a -8.95 g (95% CI = -25.53, 7.63 g) lower birth weight (data not shown).

4. Discussion

Evidence from animal and human studies suggests that prenatal exposure to PFAS may have adverse effects on fetal growth. We explored associations of maternal serum concentrations of PFOS, PFOA, PFHxS, and PFNA during pregnancy with birth size (birth weight, crown to heel length, and head circumference) in a sample of British boys. We found that higher prenatal PFOS concentrations were associated with lower birth weight, shorter crown to heel length, and smaller head circumference. While differences may not be considered large at the individual or clinical level, it is important to consider implications at the population level. A relatively modest and subclinical effect size may be associated with substantial population burden if the exposure is prevalent (Bellinger, 2012; Johnson et al., 2014), like PFAS.

Inverse associations of prenatal PFOS concentrations with birth size were found in both the present study and among girls in the same cohort (Maisonet et al., 2012). PFOS was associated with lower birth weight and shorter crown to heel length for both sexes of infants. PFOA and PFHxS were associated with reduced birth weight among the ALSPAC girls cohort, but not among boys, though the direction of the association is consistent, suggesting considerable interaction by sex is unlikely. Previous studies have examined the association of PFAS and birth size by infant sex, and most did not report differences by infant sex. Three studies found no interaction (Sagiv et al., 2018; Shoaff et al., 2018; Starling et al., 2017), while another study found interaction by sex only when examining dichotomous outcomes like low birth weight (Manzano-Salgado et al., 2017). Overall, the literature to date suggests PFAS may have little differential effect on fetal development by sex.

Outside of the ALSPAC cohort, our weakly inverse or null results are consistent with those reported in other epidemiologic studies of PFAS and birth size. The PFAS concentrations in this study are generally similar to levels reported in previous studies (Apelberg et al., 2007b; Ashley-Martin et al., 2017; Chen et al., 2012; Fei et al., 2007; Hamm et al., 2010; Manzano-Salgado et al., 2017; Meng et al., 2018; Minatoya et al., 2017; Sagiv et al., 2018; Shoaff et al., 2018; Starling et al., 2017; Whitworth et al., 2012; Woods et al., 2017), though PFNA is lowest in the present study. Studies from Japan (n = 168) (Minatoya et al., 2017), the United States (Maryland) (n = 299) (Apelberg et al., 2007b), Denmark (n = 1,400) (Fei et al., 2007), and Taiwan (n = 429) (Chen et al., 2012) have found evidence of inverse associations of PFOA and PFOS with birth size. An American study (Massachusetts) (n = 1,645) found a weakly inverse association of maternal PFNA with birth weight (Sagiv et al., 2018). A third American study (Ohio) (n = 272) analyzed PFAS as a class using Bayesian Hierarchical Linear Models and found that for a 10-fold increase in chemical concentration, the mean difference in birth weight was -11 g for PFAS (Woods et al., 2017). Finally, as we observed in our study for PFOA, PFHxS, and PFNA, other studies have found some evidence of modestly inverse or null associations between PFAS and birth weight (Ashley-Martin et al.,

2017; Hamm et al., 2010; Manzano-Salgado et al., 2017; Shoaff et al., 2018; Whitworth et al., 2012).

A 2014 meta-analysis by Johnson et al. examined PFOA and birth size and estimated a 19-g reduction in birth weight with each 1 ng/mL increase in maternal serum PFOA concentrations (Johnson et al., 2014). Estimates for length (−0.06 cm per 1 ng/mL increase) and head circumference (−0.03 cm per 1 ng/mL increase) were also reported. While our null or slightly positive estimates of PFOA as a continuous variable are not similar in effect size to the values reported in this meta-analysis, our effect estimates for the third tertile of PFOA exposure suggest that higher PFOA exposure is associated with smaller birth size outcomes. When quintile of PFOA exposure was examined in relation to birth weight, estimates for all quintiles except the fourth quintile were null but slightly positive. Infants in the fourth quintile of PFOA exposure weighed −56.63 g less than those in the lowest quintile of PFOA exposure (95% CI: (−215.17, 101.92 g). These findings may suggest that the association between PFOA and birth size outcomes is not linear in our population. The shape of the association (linear or nonlinear) of PFAS and birth size is unresolved and leads to questions about the use of meta-analyses, particularly with higher concentrations of PFAS (Food Standards Australia New Zealand (FSANZ), 2017).

Of the four PFAS under study, PFOS is typically found in the highest concentration in humans, but it has declined over the last two decades (Kato et al., 2011b). In contrast, PFNA levels have been on the rise, which is thought to be related to the degradation of volatile fluorotelomer alcohols, which are used in stain repellents (Kato et al., 2011b). While PFOS had a stronger association with birth size than PFNA in the ALSPAC cohort from the early 1990s, it is possible that the higher PFNA levels found today would imitate the effect of PFOS in the 1990s. The latter was seen in the Massachusetts study, which took place a decade later and found a weakly inverse association of maternal PFOS and PFNA with birth weight (Sagiv et al., 2018).

We compared PFAS concentrations in ALSPAC to levels in adult females of the National Health and Nutrition Examination Survey (NHANES) in the United States in the late 1990s (closest NHANES measurements to ALSPAC collection) and into the mid-2010s (most recent NHANES measurements) (Table S3) (Centers for Disease Control and Prevention, 2017). Concentrations in ALSPAC mothers were similar though slightly lower than NHANES 1999–2000 levels. As expected given the temporal trends of PFAS exposure, PFAS concentrations in ALSPAC mothers were higher than 2015–2016 NHANES concentrations, with the exception of PFNA. For additional context, a comparison of maternal serum concentrations of PFAS in European and Asian cohorts has been published previously (Bjerregaard-Olesen et al., 2017). ALSPAC PFOA and PFOS geometric mean concentrations were within the range of concentrations observed in these Scandinavian and Chinese cohorts (which took place between 1996 and 2015) (Table S3). ALSPAC PFHxS concentrations were higher while PFNA concentrations were lower than concentrations observed in European and Asian cohorts (Bjerregaard-Olesen et al., 2017).

This study benefitted from a large sample size, prospective design, and reliable biological measure of four PFAS. However, we note a few limitations. Self-reported smoking and

alcohol use during pregnancy are often unreliable, and these measures may suffer from social desirability bias. Education was the only proxy for socioeconomic status used in this analysis because many women did not report income. Environmental factors linked to income, including housing, water contamination, occupational exposure, and diet can increase both the likelihood of PFAS exposure and decreased birth size. Therefore, it is possible that there is residual confounding by income.

Another limitation is that the sub-sample used in this study differed from the overall ALSPAC cohort on some factors. For example, mothers in our sample were more likely to be white, highly educated, older, and nonsmokers than mothers in the overall ALSPAC cohort (data not shown). These differences are unsurprising given that to be selected for this sub-sample, children still had to be engaged with the study during puberty (completing two or more puberty questionnaires) and to have completed two or more DXA scans, which required a clinic visit. Generally, nonparticipation and loss to follow-up tends to be more pronounced among the less advantaged and less healthy (Barchielli and Balzi, 2002; Goldberg et al., 2001; Heilbrun et al., 1982; Knudsen et al., 2010; Reilly and Kelly, 2011; Strandberg et al., 1995; Strandhagen et al., 2010; Wilhelmsen et al., 1976).

Lastly, there is some 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 pregnancy outcome (e.g., hemodynamics), respectively (Savitz, 2014). 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 (Sagiv et al., 2018; Steenland et al., 2018). To address such concerns in our study, we adjusted for gestational age (in weeks) of sample collection. We also conducted a sensitivity analysis examining only those (n = 115) with blood sampled in the first trimester (12 weeks). In our sensitivity analysis, the associations between all PFAS and birth weight were null (potentially due to a lack of power), but in the same direction as was observed for the entire study sample across all four PFAS of interest. Specifically, the association of PFOS with birth weight was strikingly similar, although less precise, among those with blood collected in the first trimester (β = −8.95, 95% CI = −25.53, 7.63g) compared to the entire study sample (β = −8.50, 95% CI = −15.93, −1.07 g). This sensitivity analysis suggests that reverse causality and confounding may not be a substantial concern in our study.

In conclusion, British boys born to mothers with higher serum concentrations of PFOS during pregnancy appear to weigh less, have a shorter crown to heel length, and a smaller head circumference at birth. Other PFAS under study also showed some evidence of inverse associations with birth size outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Frequency distribution and maternal serum PFAS concentrations (in ng/mL) for select characteristics [a] (n = 457).

	Frequency [n(%)]	PFOS Median (IQR)	PFOA Median (IQR)	PFHxS Median (IQR)	PFNA Median (IQR)
Overall	457 (100)	13.8 (11.0, 17.7)	3.0 (2.3, 3.8)	1.9 (1.4, 2.5)	0.4 (0.3, 0.5)
Birth weight (g)	447				
<3290	148 (32.4)	14.4 (12.0, 18.3)*	3.2 (2.4, 3.8)	1.9 (1.5, 2.4)	0.4 (0.3, 0.5)
3290–3720	142 (31.1)	13.8 (11.5, 18.6)*	2.9 (2.2, 3.8)	1.8 (1.3, 2.5)	0.4 (0.3, 0.4)
>3720	157 (34.3)	13.2 (10.1, 16.7)*	2.8 (2.3, 3.7)	1.9 (1.3, 2.3)	0.3 (0.2, 0.4)
Crown to heel length (cm)	412				
<50.3	137 (33.3)	14.3 (11.2, 17.4)	3.1 (2.3, 3.7)	1.9 (1.4, 2.4)	0.3 (0.3, 0.5)
50.3–52	133 (32.3)	14.0 (10.9, 19.5)	3.0 (2.4, 4.2)	1.9 (1.5, 2.5)	0.4 (0.3, 0.5)
>52	142 (34.5)	13.6 (10.6, 16.5)	2.9 (2.3, 3.6)	1.8 (1.3, 2.2)	0.3 (0.3, 0.4)
Head circumference (cm)	416				
<34.5	137 (32.9)	14.1 (11.5, 18.2)	3.0 (2.3, 3.7)	1.9 (1.5, 2.4)	0.4 (0.3, 0.5)
34.5–35.7	134 (32.2)	14.4 (10.9, 18.0)	2.9 (2.2, 3.7)	1.7 (1.3, 2.5)	0.4 (0.3, 0.4)
>35.7	135 (32.5)	13.4 (10.5, 16.7)	2.9 (2.4, 3.8)	1.9 (1.3, 2.3)	0.3 (0.3, 0.5)
Maternal weight gain (kg)	363				
<2.25	121 (33.3)	13.8 (11.2, 17.1)	3.0 (2.3, 3.8)	1.8 (1.3, 2.4)	0.6 (0.4, 0.9)
2.25–5.40	122 (33.6)	13.9 (10.7, 18.2)	3.0 (2.2, 3.7)	1.9 (1.5, 2.6)	0.6 (0.4, 0.9)
>5.40	120 (33.1)	13.9 (10.3, 17.9)	3.0 (2.3, 3.8)	1.9 (1.4, 2.5)	0.6 (0.4, 0.8)
Maternal age	453				
<35	399 (88.1)	13.9 (11.2, 17.7)	3.0 (2.3, 3.7)	1.8 (1.4, 2.4)	0.4 (0.3, 0.5)
35	54 (11.9)	13.7 (10.6, 17.2)	3.0 (2.2, 4.1)	2.1 (1.3, 2.5)	0.4 (0.3, 0.5)
Maternal BMI (kg/m³)	429				
<18.5	8 (1.9)	11.7 (9.4, 19.2)	2.6 (1.5, 3.7)	1.8 (1.1, 2.5)	0.4 (0.2, 0.5)
18.5–25	312 (72.7)	14.1 (11.2, 18.3)	3.1 (2.3, 3.8)	1.9 (1.4, 2.5)	0.4 (0.3, 0.5)
25–30	82 (19.1)	13.6 (11.3, 17.1)	2.9 (2.3, 3.8)	1.8 (1.4, 2.2)	0.4 (0.3, 0.5)
>30	27 (6.3)	12.4 (10.9, 16.3)	2.9 (2.6, 3.5)	1.8 (1.3, 2.1)	0.3 (0.3, 0.4)
Maternal education [b]	446				
< O-level	96 (21.5)	13.9 (11.0, 17.3)	2.8 (2.4, 3.6)	1.9 (1.5, 2.3)	0.4 (0.3, 0.5)

	Frequency [n(%)]	PFOS Median (IQR)	PFOA Median (IQR)	PFHxS Median (IQR)	PFNA Median (IQR)
O-level	154 (34.5)	14.8 (11.9, 18.9)	3.1 (2.3, 3.8)	1.8 (1.3, 2.3)	0.4 (0.3, 0.4)
> O-level	196 (43.9)	13.6 (10.7, 17.2)	3.0 (2.3, 3.9)	1.9 (1.4, 2.5)	0.3 (0.3, 0.4)
Vitamin use	436				
Yes	373 (85.6)	14.0 (11.1, 17.9)	3.0 (2.3, 3.8)	1.8 (1.4, 2.4)	0.4 (0.3, 0.5)
No	63 (14.4)	13.8 (10.1, 18.0)	3.1 (2.2, 3.7)	2.0 (1.5, 2.6)	0.3 (0.2, 0.4)
Folic Acid Use	436				
Yes	77 (17.7)	14.1 (11.3, 18.0)	3.1 (2.4, 3.8)	1.9 (1.4, 2.5)	0.4 (0.3, 0.5)
No	359 (82.3)	13.1 (10.0, 17.4)	2.7 (2.1, 3.8)	1.8 (1.3, 2.4)	0.3 (0.2, 0.4)
Smoking during pregnancy	442				
No	398 (90.0)	14.0 (11.1, 17.9)	3.0 (2.3, 3.8)	1.9 (1.4, 2.4)	0.4 (0.3, 0.5)
Yes	44 (10.0)	13.2 (11.0, 17.2)	3.0 (2.4, 3.6)	2.0 (1.7, 2.6)	0.4 (0.3, 0.5)
Alcohol during pregnancy	449				
No	385 (85.7)	14.0 (11.2, 17.7)	3.0 (2.3, 3.8)	1.8 (1.4, 2.4)	0.4 (0.3, 0.5)
Yes	64 (14.3)	12.6 (10.3, 16.7)	2.7 (2.4, 3.5)	2.0 (1.4, 2.6)	0.4 (0.3, 0.4)
Parity	446				
0	214 (48.0)	14.3 (11.8, 18.0)*	3.4 (2.7, 4.2)*	2.0 (1.5, 2.6)*	0.4 (0.3, 0.5)*
1	232 (52.0)	13.6 (10.6, 17.1)*	2.6 (2.2, 3.4)*	1.8 (1.3, 2.3)*	0.3 (0.2, 0.4)*
Gestational age at sample (wk)	457				
20	174 (38.1)	14.6 (11.6, 18.6)*	3.1 (2.4, 3.9)*	2.0 (1.5, 2.6)*	0.4 (0.3, 0.5)*
>20	283 (61.9)	13.6 (10.8, 16.9)*	2.8 (2.2, 3.6)*	1.8 (1.3, 2.4)*	0.3 (0.3, 0.4)*

Abbreviations: PFOS perfluorooctane sulfonic acid; PFOA perfluorooctanoic acid; PFHxS perfluorohexane sulfonic acid; PFNA perfluorononanoic acid; IQR interquartile range.

*
Indicates p < 0.05.

[a]
Compared using Kruskal-Wallis or Wilcoxon Rank Sum tests.

[b]
O-levels (ordinary levels) are required and completed at the age of 16.

Table 2

Regression coefficients (β) and 95% confidence intervals for the association between maternal serum PFAS concentrations (ng/mL) and birth weight (g), crown to heel length (cm), and head circumference (cm).

Tertile Range (ng/mL)	Birth Weight[a]		Crown to Heel Length[b]		Head Circumference[b]	
	n = 447		n = 412		n = 416	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
PFOS						
Cont.	−10.92 (−18.79, −3.05)*	−8.50 (−15.93, −1.07)*	−0.04 (−0.08, −0.01)*	−0.04 (−0.08, −0.01)*	−0.02 (−0.04, −0.003)*	−0.02 (−0.04, −0.002)*
T1[c] 4.7–12.1	Reference		Reference		Reference	
T2 12.2–16.0	−124.14 (−244.67, −3.60)*	−26.57 (−147.31, 94.17)	−0.03 (−0.56, 0.51)	0.15 (−0.38, 0.69)	−0.13 (−0.45, 0.19)	−0.03 (−0.36, 0.30)
T3 16.1–49.1	−154.75 (−274.68, −34.81)*	−83.88 (−201.43, 33.68)	−0.57 (−1.10, −0.03)*	−0.52 (−1.05, 0.01)	−0.31 (−0.62, 0.01)	−0.25 (−0.58, 0.07)
p-trend	0.01	0.16	0.04	0.05	0.06	0.12
PFOA						
Cont.	−10.73 (−48.61, 27.13)	13.58 (−23.87, 51.03)	−0.04 (−0.20, 0.13)	0.00 (−0.16, 0.17)	0.00 (−0.09, 0.10)	0.03 (−0.07, 0.13)
T1 1.2–2.4	Reference		Reference		Reference	
T2 2.5–3.4	−18.84 (−141.36, 103.67)	−52.79 (−175.59, 70.01)	0.01 (−0.53, 0.56)	0.12 (−0.43, 0.67)	−0.09 (−0.42, 0.23)	−0.03 (−0.37, 0.30)
T3 3.5–12.4	−93.25 (−215.77, 29.26)	−45.96 (−170.84, 78.92)	−0.27 (−0.81, 0.28)	−0.16 (−0.72, 0.41)	−0.08 (−0.41, 0.24)	−0.05 (−0.39, 0.29)
p-trend	0.13	0.49	0.32	0.56	0.63	0.79
PFHxS						
Cont.	−0.98 (−10.91, 8.95)	−5.23 (−14.37, 3.90)	−0.01 (−0.05, 0.03)	−0.02 (−0.06, 0.02)	−0.01 (−0.03, 0.02)	−0.01 (−0.04, 0.01)
T1 0.5–1.5	Reference		Reference		Reference	
T2 1.6–2.1	−71.25 (−193.36, 50.86)	−72.86 (−192.99, 47.26)	−0.37 (−0.91, 0.16)	−0.25 (−0.78, 0.29)	−0.26 (−0.58, 0.06)	−0.22 (−0.55, 0.10)
T3 2.2–74.2	−80.73 (−201.88, 40.41)	−53.87 (−173.65, 65.91)	−0.52 (−1.06, 0.02)	−0.39 (−0.93, 0.15)	−0.15 (−0.48, 0.17)	−0.05 (−0.37, 0.28)
p-trend	0.20	0.40	0.06	0.16	0.35	0.82
PFNA						
Cont.	−307.94 (−595.01, −20.87)*	−169.58 (−448.32, 109.16)	−0.79 (−2.06, 0.47)	−0.79 (−2.02, 0.45)	−0.40 (−1.15, 0.35)	−0.51 (−1.26, 0.25)
T1 0.1–0.2	Reference		Reference		Reference	
T2 0.3	−135.60 (−277.61, 6.41)	−95.46 (−238.00, 47.09)	−0.39 (−1.03, 0.25)	−0.27 (−0.91, 0.38)	−0.15 (−0.53, 0.23)	−0.11 (−0.50, 0.28)

Tertile Range (ng/mL)	Birth Weight[a]		Crown to Heel Length[b]		Head Circumference[b]	
	n = 447		n = 412		n = 416	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
T3 0.4–1.6	−203.69 (−331.22, −76.16)*	−133.02 (−265.41, −0.64)*	−0.36 (−0.93, 0.21)	−0.30 (−0.90, 0.30)	−0.16 (−0.51, 0.18)	−0.24 (−0.60, 0.13)
p-trend	0.002	0.06	0.29	0.36	0.38	0.18

Abbreviations: PFOS perfluorooctane sulfonic acid; PFOA perfluorooctanoic acid; PFHxS perfluorohexane sulfonic acid; PFNA perfluorononanoic acid; 95% CI 95% confidence interval; Cont. Continuous; T1 tertile 1; T2 tertile 2; T3 tertile 3.

*
Indicates p < 0.05.

[a]In adjusted models, controlling for maternal age, maternal pre-pregnancy BMI, folic acid use, smoking during pregnancy, alcohol use during pregnancy, parity, and gestational age at sample collection.

[b]In adjusted models, controlling for maternal pre-pregnancy BMI, folic acid use, smoking during pregnancy, parity, and gestational age at sample collection.

[c]T2 and T3 represent tertiles 2 and 3, where T3 is the highest category of exposure. Tertile 1 (lowest category of exposure) is the reference group.