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Prenatal Concentrations of Perfluoroalkyl Substances and Bone Health in British Girls at Age 17

Zuha Jeddy[a,b], **Jonathan H. Tobias**[c], **Ethel V. Taylor**[a], **Kate Northstone**[d], **W. Dana Flanders**[a,e], and **Terryl J. Hartman**[a,e]

[a]Emergency Management, Radiation, and Chemical Branch, Division of Environmental Health Science and Practice, National Center for Environmental Health (NCEH), Centers for Disease Control and Prevention, 4770 Buford Hwy NE, Atlanta, GA, USA

[b]Oak Ridge Institute for Science and Education, Oak Ridge, Tennessee, USA

[c]Musculoskeletal Research Unit, Translational Health Science, Bristol Medical School, Bristol, UK

[d]Population Health Science, Bristol Medical School, Bristol, UK

[e]Rollins School of Public Health, Emory University, 1518 Clifton Rd, Atlanta, GA, USA

Abstract

Purpose.—Perfluoroalkyl substances (PFAS) are used to make protective coatings on common household products. Prenatal exposures have been associated with developmental outcomes in offspring. Using data from the Avon Longitudinal Study of Parents and Children (ALSPAC), we investigated the association between prenatal concentrations of PFAS and bone health in girls at 17 years of age and whether body composition can explain any associations.

Methods.—We measured concentrations of perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), perfluorohexane sulfonate (PFHxS), and perfluorononanoate (PFNA) in maternal serum samples collected during pregnancy. We obtained bone health outcomes in the girls, such as bone mineral density, bone mineral content, bone area, and area adjusted bone mineral content from whole body dual-energy x-ray absorptiometry (DXA) scans. We used multivariable linear regression to explore associations between each PFAS and each bone health outcome with adjustment for important confounders such as girl's age at clinic visit, maternal education, and gestational age at sample collection. We also controlled for girl's height and lean mass to explore the role body composition had on observed associations.

Results.—Prenatal PFOS, PFOA, PFHxS and PFNA concentrations were associated with inverse effects on bone size and mass after adjusting for important confounders. Conversely, PFNA was positively associated with area-adjusted bone mineral content. However, most significant associations attenuated after additional controlling for height and lean mass.

Corresponding author: Zuha Jeddy, MPH, CDC/NCEH/HSB, 4770 Buford Hwy, NE, MS F-60, Chamblee, GA 30341, (770) 488-3425, Ykl3@cdc.gov.

Conflict of Interest

Zuha Jeddy, Jonathan H. Tobias, Ethel V. Taylor, Kate Northstone, W. Dana Flanders, Terryl J. Hartman declare that they have no conflict of interest.

Conclusions.—Prenatal concentrations of some PFAS may be associated with reduced bone mass and size in adolescent girls, although it is not clear whether these associations are driven by body size.

Mini-abstract

Prenatal exposures to perfluoroalkyl substances (PFAS) have been associated with developmental outcomes in offspring. We found that prenatal concentrations of some PFAS may be associated with reduced bone mass and size in 17-year-old British girls, although it is not clear whether these associations are driven by body size.

Keywords

PFAS; ALSPAC; bone development; body composition; adolescent

Introduction

Perfluoroalkyl substances (PFAS) are endocrine disrupting chemicals (EDCs) that can interrupt signaling pathways during fetal development through alteration of hormonal functions [1]. The chemical properties of PFAS can help create protective coatings on many household consumer products, such as food packaging, nonstick cookware, and textiles. PFAS are also used in the production of industrial products. While Europe and the U.S. have phased out production of some PFAS due to potential adverse health effects associated with exposure, they remain a public health concern because of their long half-lives and persistent ability to accumulate in human tissues [2–5]. Common PFAS include perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), perfluorohexane sulfonate (PFHxS), and perfluorononanoic acid (PFNA). During critical periods of development, the developing fetus is particularly vulnerable to chemicals like EDCs that alter hormonal pathways [6]. PFAS are found in circulating blood and cord blood and are transferred to a fetus through the placenta during pregnancy. [6–8]. Toxicological studies indicate that certain PFAS accumulate in bone tissue in the fetus and could cause altered bone development [9].

Several epidemiological studies have suggested a possible inverse relationship between various EDC exposures and bone health [10–13]. Specifically, two cross sectional studies using samples from the U.S. National Health and Nutrition Examination Survey (NHANES) have found lower bone mineral density with increased exposure to certain PFAS [13,12]. However, no studies to date have examined the relationship between in utero exposure to PFAS and bone health in offspring in adolescence.

Our primary objective was to examine associations between maternal exposure to PFAS during pregnancy and their daughters' bone health at 17 years of age using data from mothers and daughters in the Avon Longitudinal Study of Parents and Children (ALSPAC). Given the close dependency of bone mass acquisition on growth and body composition [14], we were also keen to establish whether any observed associations between prenatal PFAS and measures of bone health could be explained by height, fat or lean mass.

Methods

Study Design and Population

ALSPAC is a birth cohort that recruited pregnant women with expected delivery dates between April 1991 and December 1992. The study enrolled 14,541 pregnant women and their children at birth from three health districts of the former Avon region in South West England. Previous papers have described recruitment methods [15,16]. Enrolled mothers and children provided biological samples, completed questionnaires and participated in clinical assessments. The study website contains additional details for all available data through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/).

The current analysis uses data from an ancillary nested case-control study originally designed to study the association between prenatal EDC exposure and timing of menarche [17]. We selected data for our study from the original sample where we defined case subjects as girls who had early menarche (before 11.5 years of age) and control subjects were a random sample of remaining girls. Among the 448 mother-daughter dyads from the original nested case-control study, 257 have measured maternal gestational blood concentrations for all studied PFAS and a complete whole body dual energy X-ray absorptiometry (DXA) scan done during the daughters'17 year-old clinic visit. We obtained 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.

Laboratory Analysis

Researchers at ALSPAC transferred blood samples under controlled conditions to the National Center for Environmental Health laboratories of the CDC for analysis. The lab measured serum levels of PFOS, PFOA, PFHxS, and PFNA in maternal blood collected at a median gestational age of 15 weeks. Laboratory methods have been described previously [18]. Limits of detection for the assays were 0.2 ng/mL for PFOS, 0.1 ng/mL for PFOA, 0.1 ng/mL for PFHxS, and 0.08 ng/mL for PFNA. Quality control measures were implemented using standards, reagent blanks, and study samples. Precision of measurements for the analytes, as relative standard deviation, ranged from 8 to 13%.

Data collection

All of the daughters included in our study (n=257) completed a DXA scan at 17 years of age. A Lunar prodigy narrow fan beam densitometer (GE Medical Systems Lunar, Madison, WI, USA) was used to perform a whole body DXA scan, from which total body less head bone mineral content (BMC), bone mineral density (BMD), bone area (BA), fat mass, and lean mass were obtained, as was area-adjusted BMC (ABMC). A DXA scan of the left hip, from which total and femoral neck BMD were obtained, was performed at the same time. Height was measured using a Harpenden Stadiometer (Holtain, Crymych, Pembs, UK). Some daughters (n=230) also completed tibial peripheral quantitative computerized topography (pQCT) using the Statex XCT2000L (Stratec, Pforzheim, Germany) at 17 years of age. pQCT measures the parameters of the tibia in detail and provides a more

comprehensive assessment of bone than DXA scans during developmental ages [19]. Cortical BMC (BMCc), cortical BMD (BMDc), and cortical BA (BAc) were measured from the pQCT scan with XCT custom software version 6.00B. A circular ring model was used to derive periosteal circumference (PC) and cortical thickness (CT). A threshold above 650 mg/cm^3 was used to define cortical bone [20].

Plasma was separated from sample and frozen at −80 degrees Celsius within 4 hours from collection. Plasma concentrations of β-C-telopeptides of type I collagen (CTX), a marker for bone turnover, were measured using electrochemiluminescence immunoassays (Roche Diagnostics, Lewes, UK) in fasting samples collected around 15 years of age (n=120).

ALSPAC researchers collected covariate data on mothers and daughters through medical records and questionnaires. We characterized low birth weight as less than 2,500 g at delivery. Researchers collected information on maternal pre-pregnancy body mass index (BMI), education, ethnicity, age at delivery, and smoking status during pregnancy. We collected data on whether the child was ever breastfed by questionnaire at 15 months of age. Age at menarche was determined from questionnaires obtained throughout childhood and early menarche was defined as younger than 11.5 years of age [21].

Statistical Analysis

We measured associations between maternal PFAS concentrations and bone health outcomes using weighted linear regression models, with weights inversely proportional to selection probabilities. To account for the original nested case-control study design, we weighted the sample 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). All prenatal PFAS concentration variables and bone health variables were continuous. Potential confounding variables were selected *a priori* for consideration in model selection and backwards elimination was used to determine which confounders were important contributors (Model 1) [22]. We evaluated associations by examining beta coefficients of the exposure, representing the estimated change in bone measure with a one unit (ng/mL) higher PFAS concentration, and their 95% confidence intervals. A negative beta coefficient represents a lower bone measure associated with a one unit (ng/mL) higher PFAS concentration. We then first evaluated the associations between PFAS and bone measures in models that adjusted for the following confounders: maternal education, gestational age at maternal serum sample collection, and daughter's age at clinic visit. Breastfeeding status and maternal smoking status during pregnancy were not found to be significant confounders. To explore the possible role of growth and body composition in the observed associations, we then examined other models adjusted for height and body composition, guided by results of univariate regression analysis. We used complete cases for all analyses. SAS version 9.2 (SAS Institute Inc., Cary, NC) was used to conduct all analyses.

Results

Table 1 describes demographic characteristics of our sample of 257 mother daughter dyads. Overall, mean (SD) maternal PFOS, PFOA, PFHxS, and PFNA concentrations were 21.92

(10.72) ng/mL, 4.08 (1.83) ng/mL, 2.59 (5.36) ng/mL, and 0.56 (0.22) ng/mL, respectively. Table 2 presents means of the bone health outcomes examined in the study.

After adjusting for confounders (age at clinic visit, maternal education, and gestational age at sample collection), several of the PFAS studied showed weak associations with parameters obtained from whole body DXA scans. ABMC was positively associated with each of the PFAS. A one ng/mL higher PFOS was associated with a −0.0008 g/cm^2 (95% CI: −0.002, 0.000) lower BMD, −5.94 g (95% CI: −10.96, −0.92) lower BMC, −4.07 cm^2 (95% CI: −7.38, −0.76) lower BA and 0.76g (95% CI: −0.78, 2.31) higher ABMC (Table 3). Similarly, a one ng/mL higher PFNA was associated with a −0.0152 g/cm^2 (95% CI: −0.055, 0.025) lower BMD, −254.44 g (95% CI: −457.08, −51.80) lower BMC,−207.03 cm^2 (95% CI: −339.82, −74.25) lower BA, but an 86.33 g (95% CI: 24.61, 148.05) higher ABMC. We also found weak evidence of inverse association between PFOA and bone area, but little or no association with PFHxS concentration.

To explore any effects of body size on these associations, we examined the association between maternal PFAS serum concentrations and fat mass, lean mass, and height of the daughter individually using linear regression to help design regression models looking at effects on bone health. We found moderate associations between certain PFAS and total lean mass and height, however weaker or no associations with fat mass (Supplemental Table 1). Based on these preliminary results, we adjusted for height and lean mass individually and together with important confounders to examine whether associations seen between PFAS and bone health were direct effects independent of body composition.

Following adjustment for height alone, associations with PFOS, PFOA and PFNA and bone parameters were all attenuated. Adjustment for lean mass alone, or height plus lean mass, led to similar attenuation of associations between PFOS and BMC and BA to that seen for height adjustment. Associations between PFOA and BA, and between PFNA and BMC, BA and ABMC, were unaffected by lean mass adjustment.

Associations with additional bone measures at 15 and 17 years of age available for a subset of the population can be found in supplemental material. Mean and standard deviation of plasma CTX levels, pQCT, and hip DXA measures can be found in Supplemental Table 2. After adjusting for important confounders, weak or no associations were found between maternal PFAS concentrations and CTX levels at 15 years of age (Supplemental Table 3), tibial pQCT outcomes at 17 years of age (Supplemental Table 4), or total hip or femoral neck BMD measured with hip DXA at 17 years of age (Supplemental Table 5).

Discussion

In our study of the potential association between prenatal PFAS concentrations and several markers of bone health in girls during adolescence, we found moderate inverse associations with bone size and mass in confounder-adjusted analyses. These associations attenuated after additional adjustment for body composition variables, height and lean mass. Conversely, we found PFNA to be directly related to ABMC.

Measures of body size including fat mass, lean mass, and height, have been found to be associated with bone mineral density [23,14]. Our results suggest that the effect of prenatal PFAS exposure on body size may influence the effect of PFAS exposure on bone health measures, given the attenuation of the associations we observed by height adjustment. However, the precise mechanisms appeared to differ since associations with PFOS were attenuated to a similar extent by height and lean mass adjustment, whereas those for PFOA and PFNA were only attenuated by height adjustment.

The mechanism through which body size influences the association between maternal PFAS concentrations on bone health remains unclear. In a previous ALSPAC study of 447 mother daughter dyads, maternal PFAS concentrations were associated with fetal and postnatal growth. While a negative association was seen between PFAS exposure and birthweight, a positive association was seen between PFOS and weight at 20 months [17]. Addition of birthweight to the models presented in this analysis did not change the results (data not shown). An ancillary study (n=359) found no association between prenatal PFAS exposure and percent body fatness in ALSPAC girls at 9 years of age overall [24].

However, previous studies have reported positive associations between PFAS and body size, such as body fatness, lean mass, and height, which is highly related to bone measures. A Danish cohort study with similar PFAS exposure reported an association between maternal serum PFOA concentrations during pregnancy and adiposity in female offspring at 20 years of age (n=345) [25]. The direct association seen in other cohort studies between body size and BMD would suggest that maternal PFAS concentrations would also be positively association with BMD. In the present study, after controlling for body size, such as height and lean mass, most of the associations between maternal PFAS exposure and BMD, BMC, and BA remain negative. However, positive associations were seen between maternal PFAS concentrations and AMBC, a bone measure less dependent on body size, possibly reflecting a reciprocal relationship between bone size and volumetric bone mineral density as previously reported in this cohort on pQCT scan [26]

There are many risk factors for fractures and discussing early life factors in relation to fracture risk later in life is particularly important when discussing implications of our findings on future skeletal health. Bone size is an important determinant of fracture risk in biomechanical terms, however, it is unclear how total body measures used in our study relate to fracture risk in childhood and later in life [27]. A previous ALSPAC study found total body BMD to be associated with fracture risk in childhood; however, the actual parameters used in the previous study, such as BMD adjusted for body size, were not significantly associated with prenatal PFAS concentrations in the current study [28]. Additionally, while hip BMD is known to predict subsequent fracture risk, we did not observe a significant association with prenatal PFAS exposure. Toxicological studies have reported that maternal exposure can result in PFAS accumulation in bone tissues and causes decreases in bone mineral density, particularly with PFOA [9].

To our knowledge, no previous epidemiologic studies have examined the association between *in utero* PFAS exposure and bone health later in life. However, using cross sectional data from NHANES, two studies reported inverse associations between PFAS exposure and

bone health in women, results of which are consistent with those reported here. The first study used data on 2,339 adults from the 2005–2006 and 2007–2008 cycles of NHANES to examine the association between serum concentrations of PFOA and PFOS and total lumbar spine and total hip BMD in adults. This study found inverse associations between serum PFOS concentrations and total lumbar spine BMD in premenopausal women [12]. A second study using samples from the 2009–2010 NHANES population found similar results. This study found among adult women overall, higher serum PFOS and PFHxS concentrations were associated with lower BMD and higher prevalence of osteoporosis [13]. Although these studies suggest a relationship between PFAS exposure and bone health in adults through the possible disruption of hormonal functioning, they do not examine the potential prenatal effects of PFAS *in utero* exposure on subsequent bone development through adolescence.

There are potential limitations to the current analyses. We weighted linear regression models to account for study design; however, bias may be introduced by analyzing data from a sample population originally selected for a nested case-control study for another outcome. When comparing the sample used for the current analysis (n=257) to the original sample 448 mother daughter dyads, the current sample included more mothers in the higher education categories. Blood samples for maternal PFAS concentrations were only collected once during pregnancy and were assumed to be both indicators of exposure throughout pregnancy and a proxy for fetal exposure. We controlled for gestational age at sample collection to account for variability in the timing of sample collection across pregnancies.

In conclusion, prenatal PFAS exposure may be associated with bone mass and size in adolescent girls; however, it is unclear whether these associations are mostly explained by the effects of PFAS on body size. Additional research about the implications of these results for skeletal health, including fracture risk, can help further explain the relationship between prenatal exposures to environmental exposures, such as PFAS, and bone health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of study population (n=257) for mothers and daughters enrolled in ALSPAC with maternal serum concentrations and DXA measures at 17 years of age.

	Frequency [n (%)]	PFOS (ng/mL) [Median (IQR[a])]	PFOA (ng/mL) [Median (IQR[a])	PFHxS (ng/mL) [Median (IQR[a])	PFNA (ng/mL) [Median (IQR[a]))]
Overall	257 (100)	20.2 (15.6, 25.5)	3.8 (2.9, 4.9)	1.7 (1.3, 2.3)	0.6 (0.4, 0.7)
Maternal Prepregnancy BMI					
Underweight (<18.5 kg/m^2)	13 (5.1)	17.0 (14.0, 22.6)	3.4 (2.8, 4.7)	1.5 (1.3, 2.0)	0.5 (0.3, 0.6)
Normal (18.5–24.9 kg/m^2)	169 (65.8)	20.5 (15.5, 25.5)	3.9 (2.9, 5.1)	1.8 (1.2, 2.4)	0.6 (0.4, 0.7)
Overweight (25.0–29.9 kg/m^2)	40 (15.6)	21.2 (18.6, 25.9)	3.4 (3.3, 5.1)	1.9 (1.6, 3.1)	0.6 (0.5, 0.7)
Obese (≥30.0 kg/m^2)	15 (5.8)	17.4 (13.1, 21.2)	3.0 (2.6, 4.3)	1.3 (1.1, 1.7)	0.5 (0.3, 0.7)
Maternal Education[b]					
Less than O level	31 (12.1)	19.3 (17.0, 22.5)	3.8 (2.9, 4.9)	1.7 (1.4, 2.4)	0.6 (0.4, 0.7)
O level	90 (35.0)	19.9 (14.9, 25.6)	3.8 (2.9, 4.9)	1.6 (1.2, 2.3)	0.6 (0.4, 0.7)
Greater than O level	128 (49.8)	20.8 (15.8, 25.4)	4.0 (2.9, 5.0)	1.8 (1.3, 2.3)	0.5 (0.4, 0.7)
Maternal Race					
White	248 (96.5)	20.4 (15.7, 25.5)	3.9 (2.9, 5.0)	1.7 (1.3, 2.3)	0.6 (0.4, 0.7)
Nonwhite	4 (1.6)	18.4 (14.7, 22.4)	2.9 (2.4, 3.2)	1.6 (1.2, 1.7)	0.7 (0.5, 0.7)
Maternal Age at Delivery (years)					
<25	45 (17.5)	21.7 (15.6, 25.5)	4.4 (3.3, 5.1)	1.7 (1.3, 2.4)	0.6 (0.4, 0.7)
25–29	92 (35.8)	20.1 (15.9, 25.1)	3.8 (3.0, 4.9)	1.6 (1.2, 2.1)	0.6 (0.4, 0.7)
≥29	119 (46.3)	20.1 (15.5, 25.6)	3.7 (2.7, 4.8)	1.9 (1.3, 2.5)	0.5 (0.4, 0.7)
Maternal Smoking Status during first 3 months of pregnancy					
Yes	56 (21.8)	19.0 (13.6, 23.5)	3.4 (2.8, 4.7)	1.7 (1.3, 2.5)	0.5 (0.3, 0.7)
No	197 (76.7)	21.1 (16.4, 25.5)	3.9 (2.9, 5.0)	1.7 (1.3, 2.2)	0.6 (0.4, 0.7)
Low Birth Weight (<2,500g at delivery)					
Yes	11 (4.3)	28.5 (18.9, 38.2)	4.2 (3.3, 5.6)	1.6 (1.4, 2.7)	0.7 (0.6, 0.7)
No	246 (95.7)	20.2 (15.5, 25.1)	3.8 (2.9, 4.9)	1.7(1.3, 2.3)	0.6 (0.4, 0.7)
Preterm Delivery (<37 weeks gestation)					
Yes	8 (3.1)	27.5 (23.1, 40.6)	4.8 (4.0, 6.1)	1.8 (1.4, 2.5)	0.7 (0.6, 0.8)
No	248 (96.5)	20.2 (15.6, 25.2)	3.8 (2.9, 4.9)_	1.7 (1.3, 2.3)	0.6 (0.4, 0.7)
Ever Breastfed					
Yes	209 (81.3)	20.4 (15.6, 25.5)	3.8 (2.9, 4.9)	1.7 (1.3, 2.4)	0.6 (0.4, 0.7)
No	35 (13.6)	18.3 (16.7, 23.4)	3.8 (3.1, 4.9)	1.7 (1.4, 2.3)	0.5 (0.4, 0.6)
Early Menarche					
Yes	131 (51.0)	19.7 (16.2, 25.2)	3.9 (2.9, 5.3)	1.8 (1.3, 2.3)	0.6 (0.4, 0.7)
No	126 (49.0)	21.2 (15.2, 25.5)	3.8 (2.7, 4.7)	1.7 (1.2, 2.3)	0.5 (0.4, 0.7)

[a] Interquartile range

[b] O-level= ordinary level; <O-level=none, Certificate of Secondary Education, or Vocational education; >O-level= Advanced level

Table 2.

Mean and standard deviation of total body less head bone variables measured by dual energy X-ray absorptiometry (DXA) scans at 17 years of age

	N	Mean	SD
Bone Mineral Density (g/cm^2)	257	1.05	0.07
Bone Mineral Content (g)	257	2070.02	363.31
Bone Area (cm^2)	257	1964.63	236.79
Area Adjusted Bone Mineral Content (g)	257	2253.85	113.74

Table 3.

Regression coefficients (β) for the association between maternal PFAS concentrations (ng/mL) and total body less head bone variables measured by dual energy X-ray absorptiometry (DXA) scans at 17 years of age (n=248)

	Bone Mineral Density (g/cm^2)		Bone Mineral Content (g)		Bone Area (cm^2)		Area Adjusted Bone Mineral Content (g)	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
PFOS								
Model 1[a]	−0.0008	(−0.002, 0.000)	−5.94	(−10.96, −0.92)	−4.07	(−7.38, −0.76)	0.76	(−0.78, 2.31)
Model 2[b]	−0.0003	(−0.001, 0.001)	−2.08	(−6.20, 2.04)	−1.23	(−3.75, 1.30)	−0.06	(−1.49, 1.37)
Model 3[c]	0.0000	(−0.001, 0.001)	−2.02	(−5.98, 1.94)	−1.63	(−4.33, 1.07)	0.66	(−0.91, 2.23)
Model 4[d]	0.0000	(−0.001, 0.001)	−0.98	(−4.69, 2.72)	−0.69	(−3.05, 1.68)	0.14	(−1.26, 1.54)
PFOA								
Model 1[a]	−0.0020	(−0.007, 0.003)	−21.95	(−48.52, 4.63)	−16.98	(−34.47, 0.52)	6.00	(−2.13, 14.12)
Model 2[b]	0.0012	(−0.004, 0.006)	3.50	(−18.36, 25.35)	1.70	(−11.70, 15.10)	0.70	(−6.90, 8.30)
Model 3[c]	−0.0015	(−0.006, 0.003)	−19.55	(−40.03, 0.93)	−15.48	(−29.40, −1.55)	5.92	(−2.21, 14.05)
Model 4[d]	−0.0011	(−0.005, 0.003)	−5.94	(−25.68, 13.79)	−2.99	(−15.60, 9.62)	−1.02	(−8.48, 6.44)
PFHxS								
Model 1[a]	−0.0002	(−0.002, 0.002)	−2.24	(−11.12, 6.63)	−1.61	(−7.46, 4.25)	0.40	(−2.31, 3.11)
Model 2[b]	0.0001	(−0.002, 0.002)	−0.08	(−7.21, 7.05)	−0.01	(−4.38, 4.35)	−0.06	(−2.53, 2.42)
Model 3[c]	0.0006	(−0.001, 0.002)	2.48	(−4.40, 9.37)	1.35	(−3.34, 6.05)	0.26	(−2.47, 2.99)
Model 4[d]	0.0006	(−0.001, 0.002)	2.26	(−4.16, 8.67)	1.15	(−2.95, 5.24)	0.37	(−2.05, 2.79)
PFNA								
Model 1[a]	−0.0152	(−0.055, 0.025)	−254.44	(−457.08, −51.80)	−207.03	(−339.82, −74.25)	86.33	(24.61, 148.05)
Model 2[b]	0.0102	(−0.028, 0.049)	−52.55	(−220.64, 115.54)	−59.49	(−162.33, 43.34)	45.37	(−12.85, 103.58)
Model 3[c]	0.0009	(−0.032, 0.034)	−164.58	(−322.21, −6.96)	−151.14	(−257.81, −44.47)	84.19	(22.18, 146.20)
Model 4[d]	0.0044	(−0.029, 0.038)	−77.08	(−227.76, 73.60)	−71.73	(−167.72, 24.27)	40.98	(−15.82, 97.78)

[a]Adjusted for age at clinic visit, maternal education, and gestational age at sample collection

[b]Adjusted for age at clinic visit, maternal education, gestational age at sample collection, and height

[c]Adjusted for age at clinic visit, maternal education, gestational age at sample collection, and lean mass

[d]Adjusted for age at clinic visit, maternal education, gestational age at sample collection, height, and lean mass