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ARTICLE

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Gestational perfluoroalkyl substance exposure and body mass index trajectories over the first 12 years of life

Joseph M. Braun[1] · Melissa Eliot[1] · George D. Papandonatos[2] · Jessie P. Buckley[3] · Kim M. Cecil[4] · Heidi J. Kalkwarf[5] · Aimin Chen[6] · Charles B. Eaton[1,7] · Karl Kelsey[1] · Bruce P. Lanphear[8] · Kimberly Yolton[5]

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Abstract

Background/objectives Gestational exposure to perfluoroalkyl substances (PFAS), a ubiquitous class of persistent endocrine disrupting chemicals, is associated with increased risk of obesity and cardiometabolic disease. However, it is unclear if gestational PFAS exposure is associated with adiposity trajectories related to adult obesity and cardiometabolic health.

Subjects/methods We measured perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), perfluorononaoic acid, and perfluorohexanesulfonic acid (PFHxS) concentrations in maternal serum collected between 16 weeks gestation and delivery in a cohort of 345 mother–child pairs in Cincinnati, OH (enrolled 2003-06). From age 4 weeks to 12 years, we measured weight and length or height up to eight times and calculated child body mass index (BMI) (1865 repeated measures). Using covariate-adjusted linear mixed models and splines to account for repeated BMI measures and nonlinear BMI patterns, respectively, we estimated the age/magnitude of infancy BMI zenith (~1 year) and childhood BMI nadir (~5 years), BMI accrual from 8 to 12 years, and BMI at age 12 years by PFAS terciles.

Results BMI trajectories varied by PFOA concentrations (age × PFOA interaction p value = 0.03). Children born to women with higher PFOA concentrations had lower infancy and early childhood BMI, earlier BMI nadir, accelerating BMI gains in mid-childhood and adolescence, and higher BMI at age 12 years. Some of these associations were non-monotonic. PFOS and PFHxS were not associated with alterations in BMI trajectories, but were monotonically associated with lower BMI across infancy, childhood, and adolescence. Compared to children in the first PFOS tercile, those in the second (β: −0.83; 95% confidence interval (CI): −2.11, 0.51 kg/m^2), and third (β: −1.41; 95% CI: −2.65, −0.14 kg/m^2) had lower BMI at age 12 years.

Conclusions These results suggest that gestational PFOA exposure may be associated with BMI trajectories related to adult obesity and cardiometabolic disease, while PFOS and PFHxS exposure is associated with lower BMI in the first 12 years of life.

Introduction

In the United States (USA), a staggering 32% of children are obese or overweight [1]. Obesity during childhood or

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✉ Joseph M. Braun
joseph_braun_1@brown.edu

[1] Department of Epidemiology, Brown University, Providence, RI, USA

[2] Department of Biostatistics, Brown University, Providence, RI, USA

[3] Department of Environmental Health and Engineering, Johns Hopkins University, Baltimore, MD, USA

[4] Department of Radiology, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA

[5] Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA

[6] Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania, Philadelphia, PA, USA

[7] Department of Family Medicine, Warren Alpert Medical School of Brown University, Providence, RI, USA

[8] Faculty of Health Sciences, Simon Fraser University, Vancouver, BC, Canada

adolescence increases the risk of atherosclerosis, cardiovascular disease, type 2 diabetes, hypertension, some cancers, and obesity in adulthood [2–5]. Early life adiposity patterns are strong risk factors for adolescent and adult obesity and cardiometabolic disease [6–16]. Later age and higher magnitude of infancy body mass index (BMI) zenith has been associated with excess adiposity and increased risk of obesity in adolescents and adults [8, 14, 15]. Moreover, earlier age of adiposity rebound is associated with increased risk of obesity and cardiometabolic disease in adolescence and adulthood [8, 14–16]. In one study, a 1.9 years earlier BMI rebound was associated with 3.9 times the odds of metabolic syndrome at age 31 years [14].

Gestational exposure to obesogenic chemicals has been associated with early life adiposity patterns, suggesting that the risk of adulthood obesity and cardiometabolic disease may be preventable [17, 18]. Perfluoroalkyl substances (PFAS), a class of environmentally persistent anthropogenic chemicals, are suspected obesogens. PFAS are used in oil/water repellant textiles, food packaging, cleaning products, and firefighting foams or as processing aids for fluoropolymer manufacturing [19]. Nearly all adults in the USA and internationally, including pregnant women, have detectable levels of PFAS in their serum and many PFAS have biological half-lives on the order of years in humans [20–25]. Gestational PFAS exposure may perturb early life adiposity patterns and increase adipose tissue accrual by reprogramming biological pathways regulating growth, adipocyte differentiation or proliferation, neuroendocrine regulation, or energy metabolism [26–31].

Epidemiological studies suggest that gestational PFAS exposure is associated with decreased fetal growth [32, 33], alterations in infant or childhood growth [34, 35], and increased adiposity during infancy, childhood, and adulthood [35–40]. However, we are unaware of studies examining whether gestational PFAS exposure is associated with childhood adiposity patterns related to later life obesity or cardiometabolic disease, namely higher infancy BMI zenith, earlier BMI nadir, or accelerations in BMI accrual during childhood and adolescence [7–13]. Thus, we used a prospective cohort study to investigate whether maternal serum concentrations of four PFAS were associated with features of BMI patterns from age 4 weeks to 12 years in 345 children from Cincinnati, Ohio.

Methods

Study participants

Between March 2003 and January 2006, we recruited pregnant women into a longitudinal pregnancy and birth cohort study, the Health Outcomes and Measures of the Environment Study (The HOME Study) [41, 42]. We identified women living in the Cincinnati, OH region who attended one of nine prenatal practices affiliated with three hospitals. Eligibility criteria included: 16 ± 3 weeks gestation, ≥18 years old, residing in a residence built in or before 1978, not living in a mobile/trailer home, HIV-negative, not taking medications for seizures or thyroid disorders, planning to continue prenatal care and deliver at the collaborating clinics and hospitals, planning to live in the greater Cincinnati area for the next year, English fluency, and no diagnosis of diabetes, bipolar disorder, schizophrenia, or cancer resulting in radiation treatment or chemotherapy. The present analysis includes 345 mothers who gave birth to a singleton child and had gestational serum PFAS measurements, covariate data, and at least one child anthropometry assessment between ages 4 weeks and 12 years.

The Institutional Review Boards of Cincinnati Children's Hospital Medical Center (CCHMC) and all delivery hospitals approved the study protocol. The Centers for Disease Control and Prevention (CDC) deferred to the CCHMC IRB as the IRB of record since the role of the CDC was primarily technical oversight of the PFAS assays. Women provided written informed consent for themselves and their children. Children provided written informed assent at the 12-year visit.

Gestational PFAS exposure assessment

We measured serum PFAS concentrations in maternal venous blood samples collected at ~16 weeks gestation, 26 weeks gestation, or within 24 h of delivery. After separating serum from clotted blood, we stored samples at −80 °C until they were shipped on dry ice to the CDC laboratories. While most women had a sufficient volume of serum for quantification of PFASs in their 16-week sample ($n = 294$, 85.2%), some women did not and we quantified PFAS concentrations in samples collected at 26 weeks ($n = 34$, 9.9%) or within 24 h of delivery ($n = 17$, 4.2%). Staff at the CDC laboratory quantified perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), perfluorononaoic acid (PFNA), and perfluorohexanesulfonic acid (PFHxS) concentrations using on-line solid phase extraction coupled with high performance liquid chromatography-isotope dilution tandem mass spectrometry [43]. We detected all four PFASs in every sample, with limits of detection ranging between 0.082 and 0.2 ng/mL. Quality control materials and reagent blanks were included in each analytic batch with coefficients of variation in repeated quality control materials of ~6%.

Infant and child anthropometry

We measured children's weight and length or height during home or clinic visits at ages 4 weeks and 1–5, 8, and 12

years of age. At each visit, we measured weight to the nearest 0.01 kg with the child dressed in undergarments or a dry diaper using a digital scale. At the 4-week and 1-year visit, we measured infant length with a length board to the nearest 0.1 cm. We measured height at later study visits to the nearest 0.1 cm with the child standing straight without shoes or head coverings and heels positioned against the wall using a wall-mounted stadiometer. Each weight, length, and height measure was taken in triplicate and averaged for analysis. We calculated BMI in kg/m^2. Examiners were blinded to mother and children's PFAS concentrations.

Potential confounders

Trained research assistants collected sociodemographic covariates including maternal race, age, marital status, and household income using standardized computer-assisted interviews. We assessed perinatal variables including maternal prepregnancy weight, height, and parity via standardized chart abstraction forms. We calculated prepregnancy BMI using self-reported weight/height for ~66% of women and imputed missing values for the remainder using Super Learner (Supplementary Methods) [44]. Finally, we averaged serum cotinine (a biomarker of tobacco smoke exposure) concentrations measured at 16 or 26 weeks gestation or within 48 h of birth to assess secondhand or active tobacco smoke exposure [45].

We selected potential confounders that might be associated with both gestational PFAS concentrations and child growth using a directed acyclic graph (Supplementary Fig. 1). We did not adjust for potential causal intermediates (e.g., birth weight and breastfeeding) in our primary analyses, as prenatal PFAS concentrations have previously been associated with reduced fetal growth and decreased breastfeeding duration [32, 46]. We derived a minimum sufficient set of variables that included maternal race, maternal age, maternal BMI, parity, household income, and gestational tobacco smoke exposure. We included child sex and child age at BMI measurement as precision variables.

Statistical analyses

First, we calculated univariate statistics of gestational PFAS concentrations, repeated BMI measures, and covariates. We also computed the Pearson correlation coefficient between $\log_2$-transformed PFOA, PFOS, PFNA, and PFHxS concentrations.

Next, we examined the shape of the relation between age and infant/child BMI (kg/m^2) using spaghetti plots. Then, we fit a linear mixed model with fixed effects given by a truncated cubic polynomial spline for age with child-specific random intercepts and linear age slopes to account for the nonlinear shape of the age–BMI relation and repeated measures on each child, respectively [47]. We began by using a cubic polynomial spline to characterize the shape of this relation; we then chose the number and position of the knots based on the distribution of the anthropometry measurements (Supplementary Table 1). A forward selection approach was based on adding knots one at a time and choosing their location via profile likelihood estimation, while keeping the location of previously selected knots fixed. Non-nested model comparison using the Akaike Information Criterion resulted in the single-knot model $\mathrm{BMI}(t_{ij}) = (\beta_0 + b_{0\mathrm{i}}) + (\beta_1 + b_{1\mathrm{i}}) \times t_{ij} + \beta_{2*} t_{ij}^2 + \beta_3 \times t_{ij}^3 + \gamma_3 \times (t_{ij} - \mathrm{t}_0)^3 \times I(t_{ij} > t_0) + \varepsilon_{ij}$. Here $(b_{0\mathrm{i}}, b_{1\mathrm{i}})$ is a vector of normally distributed random effects with mean 0 and unstructured covariance matrix, ε_{ij} denotes a normally distributed residual of 0 mean and homoscedastic variance, and $I(s)$ is an indicator function taking the value 0 for $s \le 0$ and 1 for $s > 0$. As study visit did not occur on the same date for all children, the jth visit time for the ith child given by t_{ij} is allowed to vary across children. The fixed effects part of this model has a first derivative $\mathrm{BMI}^{(1)}(t_{ij}) = \beta_1 + 2 \times \beta_{2*} t_{ij} + 3 \times \beta_3 \times t_{ij}^2 + 3 \times \gamma_3 \times (t_{ij} - t_0)^2 \times I(t_{ij} > t_0)$, a truncated quadratic spline whose roots closest to the knot t_0 can also be obtained in closed form and give the zenith and nadir of early childhood BMI.

With adjustment for covariates, we examined several aspects of children's longitudinal BMI measurements by fitting the linear mixed model above using R package lme4 (https://cran.r-project.org/web/packages/lme4). First, we determined whether the overall BMI trajectory varied according to PFAS tercile using the age × PFAS interaction term p value; we considered BMI trajectories to vary if this p value was <0.05. Then, we estimated five features of average BMI trajectories according to terciles of gestational PFAS concentrations that have been associated with increased risk of later life obesity and cardiometabolic disease [6–13]. These features included [1]: the age (years) of the infancy BMI zenith [2], the magnitude (kg/m^2) of infancy BMI zenith [3], the age (years) of early childhood BMI nadir [4], the magnitude (kg/m^2) of early childhood BMI nadir, and [5] the rate (kg/m^2/year) of adolescent BMI change (age 8–12 years). These features can be expressed as functions of the fixed effects parameters of the truncated basis spline model given above, when PFAS exposure is coded so that the tercile of interest is the reference group. In addition to PFAS exposure, our model adjusted for potential confounding by maternal race, age, BMI, parity, household income, gestational tobacco smoke exposure, and child sex. All potential confounders were centered at the sample mean, including categorical ones resulting in average BMI trajectories at a particular PFAS tercile for a theoretical sample whose maternal race and child sex composition reflects that of the HOME Study. We used percentile

bootstrap approaches to estimate 95% confidence intervals (CIs) for all quantities of interest based on parametric bootstrapping with $B = 10{,}000$ iterations in a parallel processing environment.

Secondary and sensitivity analyses

We conducted a secondary analysis by modeling the age–BMI relation separately for boys and girls given that prior studies suggest potential sex-specific associations [38]. Then, we conducted sensitivity analyses to test the robustness of our results to various adjustments and assumptions. First, we examined whether plasma volume expansion during pregnancy, hypertensive disorders during pregnancy, or maternal diet during pregnancy confounded the association between PFAS and BMI trajectories by limiting our analyses to women with serum PFAS measures at 16 weeks gestation, excluding women with pregnancy-induced hypertensive disorders, and adjusting for maternal intake of fish, respectively. We examined hypertensive disorders since reduced renal function during pregnancy may be associated with both higher serum PFAS levels and lower birth weight, with the latter being a predictor of subsequent BMI (Supplementary Fig. 2). Using standardized chart abstraction, we characterized gestational hypertension, preeclampsia, eclampsia, and hemolysis, elevated liver enzymes, low platelet count syndrome as pregnancy-induced hypertensive diseases [48]. We assessed the frequency of finfish or shellfish intake during the first half of pregnancy with a standardized question. Finally, we restricted our analyses to children who had three or more BMI measures between ages 4 weeks and 12 years to determine if our results were sensitive to including children with fewer repeated BMI measures.

Results

At baseline, women included in this analysis were predominately non-Hispanic White (62.0%), college educated (50.1%), nulliparous (42.9%), and nonsmokers (89.6%) (Table 1). On average, they were 29.9 years old at delivery and had a median household income of $55,000/year during pregnancy. Baseline characteristics of women included in this analysis were similar to the full cohort [42].

Median serum PFAS concentrations ranged from 0.9 (PFNA) to 13.8 (PFOS) ng/mL (Supplementary Table 2). Pearson correlations coefficients between $\log_2$-transformed PFAS concentrations ranged from 0.38 (PFNA-PFHxS) to 0.64 (PFOS-PFHxS) (Supplementary Fig. 3). Among women with two or more serum PFAS measures at 16 weeks, 26 weeks, and birth, the intraclass correlation coefficients (ICC) between repeated PFOA (ICC = 0.76), PFOS (ICC = 0.76), PFNA (ICC = 0.68), and PFHxS (ICC = 0.78) indicated very good to excellent reproducibility [49].

Three-hundred and forty-five children (53.3% girls) had 1865 repeated BMI measures and 83.1% of children ($n = 287$) had at least three BMI measurements (Supplementary Table 3). Fifty-eight percent ($n = 200$) of children had at least one BMI measurement during the early childhood, middle childhood, and adolescence periods (Supplementary Table 4). Those with one BMI measurement ($n =$

Table 1 Baseline sociodemographic and perinatal characteristics of HOME Study women and their infants ($n = 345$).

Characteristic	*n* (%)
Maternal race	
Non-Hispanic White	214 (62.0)
Non-Hispanic Black	109 (31.6)
Other	22 (6.4)
Maternal age at delivery (years)	
18 to <25	81 (23.5)
25 to <30 years	95 (27.5)
30 to <35 years	114 (33.0)
≥35 years	55 (15.9)
Household income ($ per year)	
<20,000	76 (22.0)
20,000 to <40,000	62 (18.0)
40,000 to <80,000	111 (32.2)
≥80,000	96 (27.8)
Maternal education	
<High school	4 (1.2)
Some high school or high school	79 (22.9)
Some college or technical school	89 (25.8)
≥Bachelor's degree	173 (50.1)
Parity	
Nulliparous (0)	148 (42.9)
Parous: 1	108 (31.3)
Parous: 2+	89 (25.8)
Tobacco smoke exposure[a]	
None	109 (31.6)
Secondhand	200 (58.0)
Active	36 (10.4)
Prepregnancy BMI	
Underweight/Lean (<25 kg/m^2)	147 (42.6)
Overweight (25 to <30 kg/m^2)	115 (33.3)
Obese (>30 kg/m^2)	83 (4.1)
Infant sex	
Female	184 (53.3)
Male	161 (46.7)

[a]Characterized by maternal serum cotinine concentrations during pregnancy. None: <0.015 ng/mL, secondhand: 0.015 to <3 ng/mL, and active: ≥3 ng/mL.

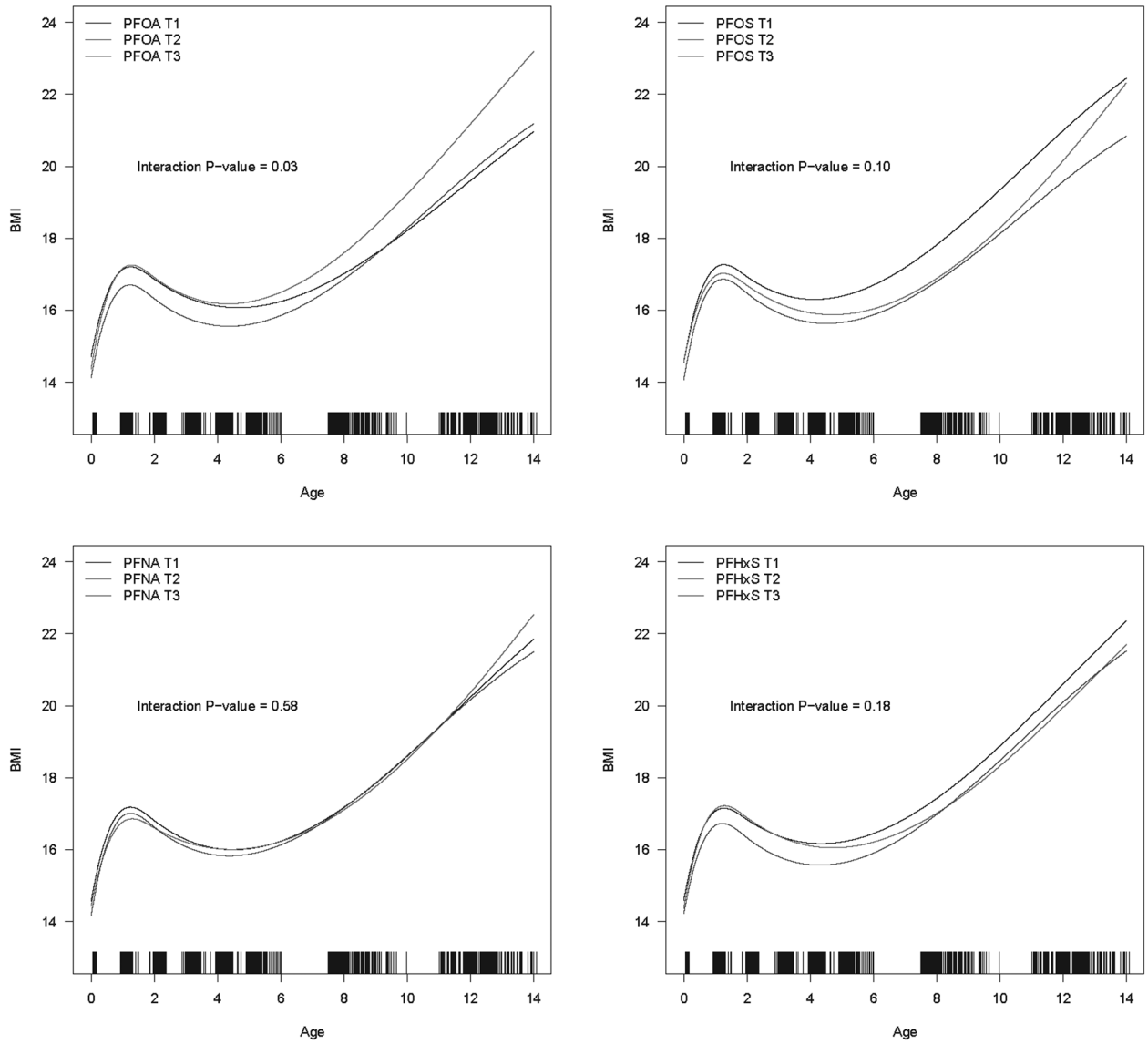

Fig. 1 Adjusted mean child BMI as a function of age according to terciles of maternal PFOA (panel A), PFOS (panel B), PFNA (panel C), and PFHxS (panel D) concentrations during pregnancy among HOME Study mother–child dyads: derived using linear mixed models with a spline for the age–BMI relation ($n = 345$, 1865 repeated BMI measures)[a]. [a]Adjusted for maternal race (non-Hispanic White, non-Hispanic Black, and other), maternal age (continuous, years), maternal BMI (continuous, kg/m^2), parity (nulliparous, parous: 1, and parous: 2+), household income (continuous, US$/year), gestational tobacco smoke exposure ($\log_{10}$-transformed serum cotinine concentrations), and child sex. *: Ranges of first, second, and third PFOA concentration terciles were 0.5–4.2, 4.3–6.5, and 6.7–26 ng/mL, respectively. Ranges of first, second, and third PFOS concentration terciles were 0.4–10, 11–16, and 16–57 ng/mL, respectively. Ranges of first, second, and third PFNA concentration terciles were 0.1–0.8, 0.9–1.0, and 1.1–2.9 ng/mL, respectively. Ranges of first, second, and third PFHxS concentration terciles were 0.1–1.0, 1.1–2.0, and 2.1–33 ng/mL, respectively. **: Fringes along x-axis of each plot indicate age and number of observations. ***: PFOA × age interaction p value = 0.03, PFOS × age interaction p value = 0.10, PFNA × age interaction p value = 0.58, and PFHxS × age interaction p value = 0.18.

63, $n = 18.3\%$) during these three periods had them almost exclusively during early childhood ($n = 57$, 90%), while 50% of those with two measures had them during either middle childhood or adolescence. The average BMI rose in the 1st year of life, declined to a nadir between 4 and 5 years of age, and rose linearly from age 5 to 12 years (Supplementary Table 1).

Using a covariate-adjusted linear mixed model with a spline to flexibly estimate the relation between child age and BMI, BMI trajectories varied non-monotonically according to PFOA terciles (PFOA × age interaction p value = 0.03) (Fig. 1, Panel a and Supplementary Fig. 4). Notably, children in the second PFOA tercile had similar magnitude and age of BMI zenith (Table 2), an earlier nadir

Table 2 Adjusted magnitude and age of infancy BMI zenith according to maternal PFAS concentration terciles during pregnancy among HOME Study mother–child dyads: derived using linear mixed models with a spline for the age–BMI relation ($n = 345$, 1865 repeated BMI measures)[a].

PFAS and tercile (range, ng/mL)	Mean BMI (kg/m^2)	BMI difference (95% CI)	Mean age (years)	Age difference (95% CI)
PFOA-T1 (0.5–4.2)	17.2	Ref	1.25	Ref
PFOA-T2 (4.3–6.5)	17.3	0.05 (−0.31, 0.40)	1.27	0.02 (−0.10, 0.07)
PFOA-T3 (6.7–26)	16.7	−0.50 (−0.87, −0.15)	1.23	−0.02 (−0.11, 0.06)
PFOS-T1 (0.4–10)	17.3	Ref	1.27	Ref
PFOS-T2 (11–16)	17.0	−0.24 (−0.60, 0.10)	1.25	−0.02 (−0.06, 0.12)
PFOS-T3 (16–57)	16.9	−0.40 (−0.76, −0.06)	1.25	−0.02 (−0.10, 0.06)
PFNA-T1 (0.1–0.8)	17.2	Ref	1.24	Ref
PFNA-T2 (0.9–1.0)	16.9	−0.32 (−0.48, 0.21)	1.30	0.06 (−0.04, 0.18)
PFNA-T3 (1.1–2.9)	17.0	−0.16 (−0.48, 0.16)	1.25	0.01 (−0.07, 0.08)
PFHxS-T1 (0.1–1.0)	17.2	Ref	1.27	Ref
PFHxS-T2 (1.1–2.0)	17.2	0.06 (−0.29, 0.43)	1.28	0.01 (−0.07, 0.10)
PFHxS-T3 (2.1–33)	16.7	−0.42 (−0.80, −0.06)	1.22	−0.05 (−0.14, 0.03)

[a]Adjusted for maternal race (non-Hispanic White, non-Hispanic Black, and other), maternal age (continuous, years), maternal BMI (continuous, kg/m^2), parity (nulliparous, parous: 1, and parous: 2+), household income (continuous, US$/year), gestational tobacco smoke exposure ($\log_{10}$-transformed serum cotinine concentrations), and child sex (male and female).

Table 3 Adjusted magnitude and age of early childhood BMI nadir according to maternal PFAS concentration terciles during pregnancy among HOME Study mother–child dyads: derived using linear mixed models with a spline for the age–BMI relation ($n = 345$, 1865 repeated BMI measures)[a].

PFAS and tercile (range, ng/mL)	Mean BMI (kg/m^2)	BMI difference (95% CI)	Mean age (years)	Age difference (95% CI)
PFOA-T1 (0.5–4.2)	16.1	Ref	4.65	Ref
PFOA-T2 (4.3–6.5)	16.2	0.11 (−0.40, 0.61)	4.33	−0.32 (−0.96, 0.27)
PFOA-T3 (6.7–26)	15.6	−0.52 (−1.04, 0.00)	4.36	−0.29 (−0.94, 0.32)
PFOS-T1 (0.4–10)	16.3	Ref	4.13	Ref
PFOS-T2 (11–16)	15.9	−0.43 (−0.92, 0.07)	4.71	0.58 (0.00, 1.20)
PFOS-T3 (16–57)	15.6	−0.67 (−1.02, −0.19)	4.51	0.38 (−0.17, 0.95)
PFNA-T1 (0.1–0.8)	16.0	Ref	4.51	Ref
PFNA-T2 (0.9–1.0)	16.0	0.00 (−0.54, 0.52)	4.44	−0.07 (−0.77, 0.62)
PFNA-T3 (1.1–2.9)	15.8	−0.17 (−0.64, 0.29)	4.37	−0.14 (−0.65, 0.38)
PFHxS-T1 (0.1–1.0)	16.2	Ref	4.35	Ref
PFHxS-T2 (1.1–2.0)	16.0	−0.12 (−0.64, 0.40)	4.72	0.37 (−0.28, 1.02)
PFHxS-T3 (2.1–33)	15.6	−0.60 (−1.09, −0.09)	4.31	−0.04 (−0.59, 0.51)

[a]Adjusted for maternal race (non-Hispanic White, non-Hispanic Black, and other), maternal age (continuous, years), maternal BMI (continuous, kg/m^2), parity (nulliparous, parous: 1, and parous: 2+), household income (continuous, US$/year), gestational tobacco smoke exposure ($\log_{10}$-transformed serum cotinine concentrations), and child sex (male and female).

(−0.32 years; 95% CI: −0.96, 0.27) (Table 3), a more rapid increase in BMI from age 8 to 12 years (0.35 kg/m^2/y; 95% CI: 0.11, 0.39) (Table 4), and higher absolute BMI at age 12 years (1.57 kg/m^2; 95% CI: 0.34, 2.83) (Table 5) compared to children in the first PFOA tercile. Relative to children in the first PFOA tercile, those in the third tercile had lower magnitude of BMI zenith (−0.5 kg/m^2; 95% CI: −0.87, −0.15) (Table 2), lower magnitude (−0.52 kg/m^2; 95% CI: −1.04, 0), and earlier age (−0.29 years; 95% CI: −0.94, 0.32) of BMI nadir (Table 3), but similar rate of BMI change from age 8 to 12 years and BMI at age 12 years (Tables 4 and 5).

While children's BMI trajectories did not vary according to maternal PFOS (PFOS × age interaction p value = 0.10) or PFHxS terciles (PFHxS × age interaction p value = 0.18) (Fig. 1 panels c–d and Supplementary Fig. 4), PFOS and PFHxS were associated with reduced BMI from 4 weeks to 12 years of age. Compared to children in the first tercile, children born to women in the third terciles of PFOS and PFHxS had lower magnitude of infancy BMI zenith (PFOS: −0.40 kg/m^2; 95% CI: −0.75, −0.06 and PFHxS: −0.42 kg/m^2; 95% CI: −0.80, −0.06), lower magnitude of BMI nadir (PFOS: −0.67 kg/m^2; 95% CI: −1.02, −0.19 and PFHxS: −0.60 kg/m^2; 95% CI: −1.09, −0.09), and

Table 4 Adjusted rate of BMI change from age 8 to 12 years according to maternal PFAS concentration terciles during pregnancy among HOME Study mother–child dyads: derived using linear mixed models with a spline for the age–BMI relation ($n = 345$, 1865 repeated BMI measures)[a].

PFAS and tercile (range, ng/mL)	Mean rate of BMI change (kg/m^2/year)	Difference in BMI rate (95% CI)
PFOA-T1 (0.5–4.2)	0.65	Ref
PFOA-T2 (4.3–6.5)	0.90	0.35 (0.11, 0.39)
PFOA-T3 (6.7–26)	0.74	0.09 (−0.05, 0.24)
PFOS-T1 (0.4–10)	0.79	Ref
PFOS-T2 (11–16)	0.82	0.03 (−0.12, 0.17)
PFOS-T3 (16–57)	0.70	−0.09 (−0.24, 0.04)
PFNA-T1 (0.1–0.8)	0.76	Ref
PFNA-T2 (0.9–1.0)	0.82	0.06 (−0.11, 0.22)
PFNA-T3 (1.1–2.9)	0.75	−0.01 (−0.15, 0.12)
PFHxS-T1 (0.1–1.0)	0.79	Ref
PFHxS-T2 (1.1–2.0)	0.73	−0.06 (−0.20, 0.09)
PFHxS-T3 (2.1–33)	0.78	−0.01 (−0.15, 0.13)

[a]Adjusted for maternal race (non-Hispanic White, non-Hispanic Black, and other), maternal age (continuous, years), maternal BMI (continuous, kg/m^2), parity (nulliparous, parous: 1, and parous: 2+), household income (continuous, US$/year), gestational tobacco smoke exposure ($\log_{10}$-transformed serum cotinine concentrations), and child sex (male and female).

lower BMI at age 12 years (PFOS: −1.41 kg/m^2; 95% CI: −2.65, −0.14 and PFHxS: −0.50 kg/m^2; 95% CI: −1.78, 0.76) (Tables 2, 3, and 5). These associations were monotonic for PFOS. PFOS and PFHxS levels were also associated with later age at adiposity nadir (~0.4–0.6 years), but in a non-monotonic manner (Table 4).

Children's BMI trajectories did not vary according to maternal PFNA terciles (PFNA × age interaction p value = 0.48) (Fig. 1 and Supplementary Fig. 4). Moreover, PFNA levels were not associated with the childhood BMI features we examined (Tables 2–5).

Secondary and sensitivity analyses

There was evidence that the association of PFOA with children's BMI trajectories was modified by child sex (PFOA × sex × age interaction p value = 0.013) (Supplementary Fig. 4). BMI at the time of early childhood BMI nadir was monotonically lower among boys in the second and third PFOA terciles, whereas the age of early childhood BMI nadir was non-monotonically earlier among girls in the top two terciles (Supplementary Tables 4–6). In both sexes, the association of PFOA with other BMI trajectories features was similar. Child sex did not modify the association of PFOS, PFNA, and PFHxS with BMI trajectories (PFAS × sex × age interaction p values ≥ 0.19) (Supplementary Fig. 4).

The pattern of associations was not markedly different when we limited our analysis to women with serum PFAS measures at 16 weeks, excluded women with pregnancy-induced hypertensive disorders, adjusted for fish intake during pregnancy, or excluded children with <3 BMI measurements (Supplementary Tables 7–10). However, when restricting to 16-week PFAS measurements or adjusting for fish intake during pregnancy, some associations were attenuated toward the null for PFOA (rate of BMI change from age 8 to 12 years for the second vs. first tercile) and PFOS (magnitude of BMI zenith and nadir and BMI nadir timing) (Supplementary Tables 7 and 9).

Discussion

In this cohort, maternal serum PFOA, PFOS, and PFHxS concentrations were associated with features of BMI trajectories from birth to age 12 years. The dose–response and direction of these associations varied by the specific PFAS and childhood BMI trajectory feature. We observed non-monotonic associations of PFOA with age at adiposity nadir, BMI change from age 8 to 12 years, and BMI at age 12 years. Children in the second PFOA tercile had an earlier age at adiposity nadir, greater increases in BMI between age 8 and 12 years, and higher BMI at age 12 years. The magnitude and age of early childhood BMI nadir across PFOA terciles differed for boys and girls, but patterns were similar for infancy BMI zenith and rate of BMI gain from age 8 to 12 years. In contrast to our findings for PFOA, PFOS and PFHxS were associated had lower BMI in the first 12 years of life, and associations were monotonic for PFOS. PFNA was not associated with the BMI features we examined.

In multiple studies, higher serum PFOA concentrations during pregnancy have been associated with lower birth weight and reduced early childhood BMI [32, 33, 50], altered growth and excess adiposity during childhood and adolescence [35, 37, 38, 51], and excess adiposity in adulthood [36]. Experimental studies suggest that PFOA exposure can increase adipocyte differentiation and cause elevated body weight and adipocyte lipid accumulation in rodents [29, 52–55]. In a pilot study of HOME Study neonates, we observed that prenatal serum PFOA concentrations were associated with hypomethylation of genes related to fetal programming, growth, and obesity in leukocytes [56].

We speculate that prenatal exposure to chemicals that restrict fetal growth, like PFOA, may set off a cascade of maladaptive processes that reprogram systems involved in growth, energy metabolism, appetite, or adipogenesis

Table 5 Adjusted mean BMI (kg/m^2) and difference in BMI (kg/m^2) from ages 4 weeks to 12 years according to maternal PFAS tercile during pregnancy among HOME Study mother–child dyads: derived using linear mixed models with a spline for the age–BMI relation ($n = 345$, 1865 repeated BMI measures)[a].

Age (years)	Tercile[b,c]	PFOA (95% CI)	PFOS (95% CI)	PFNA (95% CI)	PFHxS (95% CI)
0.07	T1	15.0 (14.8, 15.3)	14.9 (14.6, 15.2)	14.9 (14.7, 15.1)	14.9 (14.7, 15.2)
0.07	T2-T1	−0.30 (−0.66, 0.08)	−0.01 (−0.39, 0.38)	−0.17 (−0.56, −0.24)	−0.19 (−0.57, 0.18)
0.07	T3-T1	−0.58 (−0.95, −0.19)	−0.47 (−0.85, −0.08)	−0.37 (−0.72, −0.01)	−0.37 (−0.77, 0.02)
1	T1	17.1 (16.9, 17.4)	17.2 (16.9, 17.4)	17.1 (16.9, 17.3)	17.1 (16.8, 17.3)
1	T2-T1	0.03 (−0.34, 0.38)	−0.23 (−0.59, 0.12)	−0.34 (−0.71, 0.02)	−0.05 (−0.30, 0.41)
1	T3-T1	−0.50 (−0.85, −0.14)	−0.40 (−0.76, −0.04)	−0.17 (−0.50, 0.15)	−0.40 (−0.77, 0.04)
2	T1	16.9 (16.6, 17.1)	16.9 (16.7, 17.2)	16.8 (16.6, 17.0)	16.8 (16.6, 17.1)
2	T2-T1	0.05 (−0.30, 0.38)	−0.24 (−0.58, 0.10)	−0.20 (−0.55, 0.15)	0.05 (−0.29, 0.40)
2	T3-T1	−0.55 (−0.89, −0.20)	−0.46 (−0.80, −0.13)	−0.18 (−0.49, 0.13)	−0.51 (−0.86, −0.16)
3	T1	16.4 (16.1, 16.7)	16.5 (16.2, 16.7)	16.3 (16.0, 16.5)	16.4 (16.1, 16.7)
3	T2-T1	0.04 (−0.35, 0.42)	−0.28 (−0.67, 0.11)	−0.07 (−0.47, 0.34)	−0.01 (−0.40, 0.40)
3	T3-T1	−0.57 (−0.98, −0.18)	−0.55 (−0.93, −0.17)	−0.20 (−0.56, 0.16)	−0.58 (−0.98, −0.18)
4	T1	16.1 (15.8, 16.5)	16.3 (16.0, 16.6)	16.0 (15.7, 16.3)	16.2 (15.8, 16.5)
4	T2-T1	0.07 (−0.39, 0.53)	−0.37 (−0.84, 0.09)	0.00 (−0.49, 0.49)	−0.08 (−0.54, 0.40)
4	T3-T1	−0.55 (−1.03,−0.07)	−0.64 (−1.10, −0.19)	−0.18 (−0.62, 0.25)	−0.60 (−1.07, −0.12)
5	T1	16.1 (15.7, 16.5)	16.4 (16.0, 16.8)	16.0 (15.7, 16.4)	16.2 (15.8, 16.6)
5	T2-T1	0.15 (−0.40, 0.69)	−0.51 (−1.05, 0.03)	0.01 (−0.57, 0.58)	−0.16 (−0.70, 0.40)
5	T3-T1	−0.48 (−1.05, 0.07)	−0.73 (−1.27–0.20)	−0.15 (−0.66, 0.36)	−0.58 (−1.14, −0.03)
8	T1	17.0 (16.4, 17.6)	17.8 (17.2, 18.4)	17.2 (16.6, 17.7)	17.4 (16.8, 18.0)
8	T2-T1	0.57 (−0.27, 1.43)	−0.94 (−1.80, −0.09)	−0.08 (−0.98, 0.84)	−0.41 (−1.26, 0.46)
8	T3-T1	−0.16 (−1.03, 0.70)	−1.02 (−1.87, −0.17)	−0.02 (−0.82, 0.78)	−0.45 (−1.32, 0.43)
12	T1	19.6 (18.7, 20.5)	21.0 (20.1, 21.9)	20.2 (19.4, 21.0)	20.6 (19.7, 21.5)
12	T2-T1	1.57 (0.34, 2.83)	−0.83 (−2.11, 0.41)	0.13 (−1.23, 1.50)	−0.65 (−1.90, 0.65)
12	T3-T1	0.23 (−1.06, 1.53)	−1.41 (−2.65, −0.14)	−0.07 (−1.26, 1.09)	−0.50 (−1.78, 0.76)

[a]Adjusted for maternal race (non-Hispanic White, non-Hispanic Black, and other), maternal age (continuous, years), maternal BMI (continuous, kg/m^2), parity (nulliparous, parous: 1, and parous: 2+), household income (continuous, US$/year), gestational tobacco smoke exposure (log_{10}-transformed serum cotinine concentrations), and child sex (male and female).

[b]Adjusted mean BMI is displayed for first tercile children with the average covariate pattern, otherwise difference in second vs. first and third vs. first tercile is shown.

[c]Ranges of first, second, and third PFOA concentration terciles were 0.5–4.2, 4.3–6.5, and 6.7–26 ng/mL, respectively. Ranges of first, second, and third PFOS concentration terciles were 0.4–10, 11–16, and 16–57 ng/mL, respectively. Ranges of first, second, and third PFNA concentration terciles were 0.1–0.8, 0.9–1.0, and 1.1–2.9 ng/mL, respectively. Ranges of first, second, and third PFHxS concentration terciles were 0.1–1.0, 1.1–2.0, and 2.1–33 ng/mL, respectively.

[57, 58]. Earlier BMI nadir and BMI accelerations from childhood to adolescence are risk factors for subsequent obesity, cardiometabolic disease, cardiovascular disease, ischemic stroke, and type 2 diabetes [7–13]. Given this, future studies could examine prenatal PFOA concentrations in relation to adolescent or adulthood cardiometabolic or cardiovascular risk factors or disease.

Prenatal PFOS and PFHxS concentrations have not been consistently associated with BMI features across infancy and childhood. In two studies, prenatal PFOS concentrations were associated with lower adiposity in 415 US girls at age 5 months [40] and lower BMI and waist circumference in 811 Danish children at age 7 years [59]. In contrast, prenatal PFOS concentrations were associated with higher childhood adiposity in 811 8-year-old girls from the USA [38], higher BMI in 381 Swedish children at ages 3–5 years [51], and higher waist-to-hip ratio in 1022 5–9-year-old children from Greenland and Ukraine [37].

The pattern of associations for individual PFAS from this and other studies do not conclusively indicate that a given PFAS is obesogenic or associated with infancy, childhood, or adolescent BMI trajectories related to later life obesity. Indeed, some studies did not observe an association of prenatal PFAS exposure with excess child or adult adiposity or higher risk of being overweight or obese [60–62]. However, there is consistent evidence in both epidemiological studies and experimental studies of animals that prenatal PFOA exposure is associated with reduced fetal

growth [32, 63]. The discrepant findings across cohorts might be due to different levels of maternal serum PFAS concentrations, as well as the method and timing of child adiposity assessment. The timing of assessment could be critical if PFAS exposures are associated with alterations in changes in weight or length/height because these studies have assessed childhood adiposity at times ranging from 1 month of age to adulthood. Finally, it is not clear why we observed that PFOS and PFHxS were associated with lower BMI, and PFOA with a more "obesogenic" BMI profile, but prior studies report that the biological mechanisms of PFOA and PFOS exposure differ, despite subtle differences in chemical structures [64, 65].

Adolescence may be a period of life to mitigate the potential impact of PFAS exposure on later life risk of adverse cardiometabolic outcomes. Notably, in a study of over 62,000 Danish men, those who went from being overweight to normal weight between age 7 and 13 years or 13 years and early adulthood had reduced risk for type 2 diabetes relative to men who were persistently overweight [13]. Moreover, in over 2700 participants from the Bogalusa Heart Study, greater rates of BMI change in adolescence were associated with increased risk of adult obesity and the rates of change were stronger predictors than absolute BMI during adolescence [9].

This study has several strengths and limitations. First, we applied appropriate growth modeling techniques in over 1800 repeated BMI measurements between infancy and adolescence to determine if PFAS concentrations were associated with features of BMI trajectories related to later life risk of obesity and cardiometabolic disease. Despite having eight repeated BMI measurements, we had a greater density of measurements in early childhood. Thus, caution is warranted in interpreting features at later ages. Relatedly, there was loss to follow-up, particularly at ages 4 and 5 years. Reassuringly, participants who remained in the study were generally similar to the full cohort and the presented results were not substantially different when we limited to participants with three or more repeated BMI measurements [41, 42]. Second, while we controlled for variables associated with maternal PFAS concentrations that are also potentially important determinants of childhood growth patterns [66], there may be residual confounding. Notably, we had a relatively crude measure of maternal diet during pregnancy and we were not able to control for maternal renal function during pregnancy (i.e., glomerular filtration rate (GFR)). Higher GFR has been associated with both higher birth weight and lower serum PFAS concentrations [67]. Thus, not controlling for GFR could bias our results. While our results were similar when we restricted to women with PFAS measures at 16 weeks gestation, the rate of BMI change from age 8 to 12 years for the second PFOA tercile was attenuated with this restriction. Interestingly, a prior study examining prenatal serum PFAS and childhood adiposity did not report substantially different results when controlling for maternal GFR during pregnancy [38]. Finally, we did not estimate the potential aggregate effect of PFAS mixtures on childhood growth patterns. Maternal serum PFAS concentrations were positively correlated, indicating joint exposure to multiple PFAS, although we identified different dose–response patterns between PFOA and PFOS exposures. Future studies could use novel and evolving methods to examine the impact of PFAS mixtures on BMI trajectories and also examine the impact of postnatal PFAS exposures on child BMI trajectories [68].

In this cohort, maternal serum PFOA concentrations were non-monotonically associated with features of childhood BMI trajectories related to adolescent and adulthood obesity and cardiometabolic disease. PFOS concentrations, and to a lesser extent, PFHxS concentrations, were associated with lower BMI during the first 12 years of life. These results highlight the importance of quantifying the potential effects of chemical obesogens on both absolute levels of adiposity, as well as adiposity trajectories. Future studies should determine if adiposity trajectory features mediate previously observed associations of prenatal PFAS exposure with later life obesity and cardiometabolic disease.

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Compliance with ethical standards

Conflict of interest Brown University was compensated for JMB's services as an expert witness for plaintiffs in litigation related to PFAS-contaminated drinking water; these funds were not paid to JMB directly. JMB received a honorarium for serving on an advisory board to Quest Diagnostics. CBE was compensated as an expert witness for plaintiffs in litigation related to PFAS-contaminated drinking water. BPL served as an expert witness in cases related to childhood lead poisoning, but he has not personally received any compensation for these services. The other authors report no conflict of interest.

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