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Associations of pre- and postnatal per- and polyfluoroalkyl substance exposure with adolescents' eating behaviors

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Background: Per- and polyfluoroalkyl substances (PFAS), persistent environmental chemicals, may act as obesogens by interacting with neuroendocrine pathways regulating energy homeostasis and satiety signals influencing adolescent eating behaviors.

Methods: In 211 HOME Study adolescents (Cincinnati, OH; recruited 2003–2006), we measured PFAS concentrations in serum collected during pregnancy, at delivery, and at ages 3, 8, and 12 years. Caregivers completed the Child Eating Behavior Questionnaire (CEBQ) at age 12, and we calculated food approach and food avoidance scores. Using quantile-based g-computation, we estimated covariate-adjusted associations between a mixture of four gestational PFAS and CEBQ scores. We identified high (n = 76, 36%) and low (n = 135, 64%) longitudinal PFAS mixture exposure profiles between delivery and age 12 years using latent profile analysis and related these to CEBQ scores. We examined whether child sex or physical activity modified these associations.

Results: We observed no association of gestational PFAS mixture with food approach or food avoidance scores. Children in the higher longitudinal PFAS mixture profile had slightly higher food approach scores (β: 0.47, 95% CI: –0.27, 1.23) and similar food avoidance scores (β: –0.15, 95% CI: –0.75, 0.46) compared with children in the lower profile. We found some evidence that higher physical activity favorably modified the association between longitudinal PFAS mixture profiles and emotional overeating (interaction *P* value = 0.13). Child sex did not consistently modify any associations.

Conclusions: Serum PFAS concentrations were not consistently linked to adolescent eating behaviors in this study, suggesting alternative pathways, such as metabolic rate, may underlie previously observed associations between PFAS exposure and childhood obesity.

Keywords: Adolescents; Childhood eating behaviors; Chemical mixture; Polyfluoroalkyl substances

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Data are available upon reasonable request. The HOME Study Principal Investigators welcome new collaborations with other investigators and have actively engaged in collaborative data-sharing projects. Interested investigators should visit https://homestudy.research.cchmc.org/contact or contact Drs. Joseph M. Braun (joseph_braun_1@brown.edu) and Kimberly Yolton (kimberly.yolton@cchmc.org) to obtain additional information about The HOME Study, discuss collaborative opportunities, and request a project proposal form. The HOME Study Protocol Review Committee reviews proposed research projects to ensure that they do not overlap with extant projects and are an efficient use of scarce resources (e.g., biospecimens).

Code available upon request. Interested investigators should contact Taylor-Marie Vasil (taylor-marie_vasil@alumni.brown.edu).

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Introduction

Per- and polyfluoroalkyl substances (PFAS) are endocrine-disrupting chemicals (EDCs) that have been used in industry and consumer products worldwide.[1,2] PFAS are resistant to biological, chemical, and thermal degradation, making them valued in applications such as nonstick cookware, oil- and water-repellent textiles, firefighting foams, food packaging, cosmetics, and more.[2,3] Due to their widespread production and use, most adults and children in the United States have been exposed to PFAS.[4]

PFAS are considered obesogens due to their ability to influence growth, adiposity, and metabolism.[5] Gestational PFAS exposure in adolescents has been associated with reduced fetal growth, excess adiposity, risk of being overweight or obese, and related cardiometabolic disease.[5–9] Longitudinal PFAS exposure in adolescents has also been associated with metabolic syndrome, diabetes, overweight/obesity, and cardiometabolic disease.[6,10,11] However, the biological pathways underlying these associations are unclear.

One potential pathway by which PFAS could exert its broad effects on growth and metabolism is by influencing eating

What this study adds:
We investigated the association of both gestational and postnatal exposure to PFAS with eating behaviors in adolescence. We found that serum PFAS concentrations were not associated with adolescent eating behaviors in this cohort. However, we found evidence that PFAS exposures may be linked to more obesogenic eating behaviors in children with lower levels of physical activity.

behaviors. The hypothalamic circuits related to appetite and food intake regulation begin forming during embryonic development and can be influenced by environmental factors.[12] These circuits regulate food intake and appetite, integrating inputs from emotion and reward centers.[12,13] Leptin, a crucial hormone in this process, promotes the formation of hypothalamic pathways and regulates eating behaviors later in life.[14–17] Indeed, PFAS can disrupt hypothalamic neuropeptides that regulate food intake.[12,13,18,19] Perturbations in the hypothalamic appetite regulatory systems due to environmental factors during pregnancy, including EDCs like PFAS, may affect a child's risk of altered growth or metabolic disease.[20–22] EDC-induced hormonal activity on leptin, ghrelin, and insulin may impact eating behavior to increase or decrease food intake.[17,23] Despite their potential interaction with neuroendocrine circuits involved in eating behaviors, few studies have explored the impact of PFAS on eating behaviors.[17]

Previous studies show that obese children have obesogenic eating behaviors.[24–27] Food approach behaviors, measured by the Childhood Eating Behavior Questionnaire (CEBQ), such as food responsiveness, enjoyment of food, and emotional overeating are positively associated with adiposity, whereas food avoidance behaviors are negatively associated.[25,26] However, the directionality of these associations remains unclear; some studies showed that higher body mass index (BMI) at earlier ages predicted more food approach behaviors at 10 years of age.[24,28] Additionally, prior studies have found correlations between appetitive hormones and CEBQ scores.[29] Some human studies have shown that certain food approach behaviors are associated with obesity and related cardiometabolic traits, representing a biological pathway through which obesogens exert their effects.[30,31] Thus, food approach behaviors, which develop early in a child's life, may be a modifiable factor to help prevent childhood obesity.[20,32]

The premise of this study was in part based on prior studies reporting that early-life PFAS exposure is associated with excess adiposity and increased cardiometabolic risk.[10,11] However, we are unaware of studies evaluating gestational and longitudinal PFAS exposure in relation to eating behaviors. Thus, we examined the association of developmental PFAS exposure with subsequent eating behaviors in adolescence. We hypothesized that higher serum PFAS concentrations during gestation and adolescence would be associated with obesogenic parent-reported eating behaviors in adolescence.

Methods

Study participants

The data used for the study come from the Health Outcomes and Measures of the Environment (HOME) Study, a pregnancy and birth cohort that recruited pregnant women of ages 18–45 years in the greater Cincinnati area in their 2nd trimester between the years of 2003 and 2006. Inclusion criteria included: ≥18 years of age, 16 ± 3 weeks gestation, and living in a home built before 1978 in the Cincinnati, OH area. Exclusion criteria were: a history of HIV infection; previous diagnosis of diabetes, schizophrenia, bipolar disorder, or cancer; or taking medications for thyroid disorders or seizures. The study recruited 468 mothers; clinic and home follow-up visits were conducted when children were aged 4 weeks and 1, 2, 3, 4, 5, 8, and 12 years.[33] At these home or clinic visits, trained staff collected biospecimens to assess environmental chemical exposures and conducted health assessments.[33]

A total of 256 caregiver–child pairs completed the 12-year visit.[34] We excluded twins (n = 14) and those with missing data for serum PFAS biomarkers (n = 14) and other relevant covariates (n = 17). The final study sample size included in the analysis was 211 adolescents (Supplemental Figure 1; http://links.lww.com/EE/A305); serum PFAS data were available for 196 adolescents during gestation (maternal or cord serum), 133 adolescents at the 3-year visit, 160 adolescents at the 8-year visit, and 180 adolescents at the 12-year visit.

The study obtained approval from the Institutional Review Boards of Cincinnati Children's Hospital Medical Center and cooperating delivery hospitals.[34] At all study visits, the mothers or primary caregivers of the participants gave written informed consent. Additionally, at the 12-year study visit, adolescents provided written informed assent.

Per- and polyfluoroalkyl substances exposure assessment

Trained laboratory staff quantified serum PFAS concentrations in maternal serum samples collected at 16 or 26 weeks' gestation or delivery and children's serum samples at delivery (cord serum), and ages 3, 8, and 12 years.[33] Gestational serum PFAS concentrations were measured at 16 weeks of pregnancy for 86% of women; when 16-week serum samples were unavailable, 26-week (9.5%) or maternal delivery samples (4.5%) were used. Laboratory staff quantified concentrations of perfluorooctanoic acid (PFOA), perfluorohexanesulphonic acid (PFHxS), perfluorooctane sulfonic acid (PFOS), and perfluorononanoic acid (PFNA) using online solid phase extraction coupled to high-performance liquid chromatography-isotope dilution with tandem mass spectrometry.[35,36] The limits of detection (LOD) were ~0.1 ng/mL and interassay coefficients of variation were ~6%.[35,36] For any values below the LOD, we substituted the LOD/√2. Each analytic batch included reagent blanks and low- and high-concentration QC samples.

Adolescent eating behavior assessment

During the 12-year visit, caregivers completed the CEBQ to assess their child's eating behaviors.[37,38] The CEBQ, a valid and reliable parent-reported instrument that evaluates eight dimensions of eating behaviors, is composed of 35 questions rated on a five-point Likert scale. A higher score reflects an increased presence of the eating behavior as perceived by the parent. The eight subscales assess food approach behaviors (food responsiveness, enjoyment of food, emotional overeating, and desire for drinks) and food avoidance behaviors (satiety responsiveness, slowness in eating, food fussiness, and emotional undereating). Previous studies have reported good internal consistency of the CEBQ (Cronbach's α: 0.79–0.91).[37] The CEBQ showed similar internal consistency in this study (Cronbach's α: 0.70–0.90).[39] Construct validity has been confirmed in prior studies based on the CEBQ's correlation with direct measures of eating behavior (i.e., eating without hunger, caloric compensation, eating rate, and energy intake).[37,38]

Covariate assessment

We collected covariates using maternal interviews, medical record abstraction, valid and reliable questionnaires, or physical examinations. Researchers collected maternal sociodemographic information at baseline, including maternal age,

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Table 1.

Descriptive statistics of adolescent food approach behavior and food avoidance behavior scores by covariates in HOME Study mothers and their adolescents

		Food approach behavior		Food avoidance behavior	
	n	Mean ± SD	*P* value	Mean ± SD	*P* value
Overall	211	10.8 (2.5)		10.0 (2.0)	
Adolescent sex			0.02[a]		0.22
Female	115	11.1 (2.5)		10.2 (1.9)	
Male	96	10.3 (2.5)		9.9 (1.9)	
Adolescent race			0.01[a]		0.20
Non-Hispanic White	123	10.5 (2.3)		10.2 (2.0)	
Non-Hispanic Black	76	11.8 (2.7)		9.8 (2.1)	
Other	12	9.2 (2.3)		9.5 (2.2)	
Adolescent pubic hair stage			0.01[a]		0.02[a]
Stage 1	22	9.6 (2.0)		10.0 (1.8)	
Stage 2	54	10.4 (2.3)		10.8 (2.1)	
Stage 3	64	10.7 (2.6)		9.8 (2.0)	
Stage 4	44	11.0 (2.5)		10.0 (1.9)	
Stage 5	27	12.1 (2.8)		9.2 (2.1)	
Maternal age at delivery			0.56		0.14
18–25 years	50	11.1 (2.8)		9.8 (2.3)	
>25–35 years	129	10.6 (2.5)		10.0 (2.0)	
>35 years	32	10.7 (2.4)		10.7 (1.7)	
Annual household income ($)			0.02[a]		0.53
<45,000	67	11.4 (2.8)		9.9 (2.1)	
45,000–75,000	86	10.3 (2.0)		10.1 (2.1)	
>75,000	58	10.4 (2.5)		10.2 (1.9)	
Child depression inventory scores			0.17		0.27
<65	191	10.7 (2.4)		10.0 (2.0)	
≥65	20	11.5 (3.2)		10.5 (1.9)	
Gestational serum cotinine (ng/mL)			0.09[a]		0.38
<0.015 (unexposed)	62	10.2 (2.3)		10.1 (2.1)	
0.015–3 (secondhand)	129	11.0 (2.6)		10.1 (1.9)	
≥3 (active smoker)	20	11.4 (2.6)		9.4 (2.4)	
Child physical activity scores			0.03[a]		0.36
0–2.5	101	11.1 (2.6)		10.2 (1.9)	
>2.5	110	10.4 (2.4)		9.9 (2.1)	
Prepregnancy BMI (kg/m^2)			0.19		0.56
<25	68	10.7 (2.7)		10.1 (2.1)	
25–30	90	10.4 (2.5)		10.2 (1.7)	
≥30	53	11.2 (2.2)		9.8 (2.2)	

Food approach summary score was the sum of scores on food responsiveness, emotional overeating, enjoyment of food, and desire to drink subscales from the Child Eating Behavior Questionnaire (CEBQ). Food avoidance summary score was the sum of scores on satiety responsiveness, slowness in eating, emotional undereating, and food fussiness CEBQ subscales.

[a]$P \leq 0.05$.

income, and education. Prepregnancy BMI was derived from self-reported weight and height. We assessed active smoking and secondhand tobacco smoke exposure using maternal serum cotinine concentrations at 16 weeks of gestation.[11] To characterize gestational tobacco smoke exposure, we created a three-category variable in Table 1 to represent unexposed (gestational serum cotinine concentrations <0.015 ng/mL), exposed to secondhand tobacco smoke (0.015–3 ng/mL), and active smokers (>3 ng/mL).[11] Mothers reported the race of their child during the postpartum visit, and we abstracted child sex from hospital medical charts. Duration of breastfeeding was collected during interviews during the first 3 years of the adolescent's life.

Trained nutrition research assistants administered three 24-hour recalls (2 weekdays and 1 weekend day) at the 12-year visit.[34] These were used to calculate macronutrient, micronutrient, and total daily energy intake with the Nutrition Data System for Research software, as well as Healthy Eating Index scores (HEI-2010), a measure of diet quality used to evaluate dietary patterns and conformity with United States Department of Agriculture dietary recommendations.[40,41]

Adolescents self-assessed their pubertal stage (Tanner Stages 1–5) using diagrams of breast and pubic hair for girls and pubic hair only for boys during the 12-year visit.[42] They also completed the Physical Activity Questionnaire for Older Children (PAQ-C) and Children's Depression Inventory-II (CDI-II) at this visit.[43,44] The PAQ-C is a valid assessment of physical activity levels and consists of a series of questions that ask about different aspects of a child's physical activity habits.[43] The CDI-II is a valid and reliable measure of depressive symptoms in children.[44]

We created a directed acyclic graph using prior literature to determine potential confounders associated with gestational or longitudinal PFAS concentrations and adolescent eating behaviors and to verify that adjustments were not made for mediators or colliders (Supplemental Figure 2; http://links.lww.com/EE/A305).[45,46]

Statistical analysis

After exploratory data analysis, we calculated univariate statistics of individual CEBQ scale scores, as well as food approach (sum of food responsiveness, emotional overeating, enjoyment of food, and desire to drink) and food avoidance (sum of satiety responsiveness, slowness in eating, emotional undereating, and food fussiness) summary scores. Next, we calculated univariate statistics of the food approach summary score, food avoidance summary score, and gestational serum PFOS concentrations across strata of potential confounders. We chose PFOS because it had the highest correlation coefficients with the other PFAS chemicals (Spearman's $r = 0.31–0.60$) (Supplemental Tables 1–4; http://links.lww.com/EE/A305). These correlation

coefficients were similar at all periods (gestation, 3, 8, and 12 years) (Supplemental Tables 1–4; http://links.lww.com/EE/A305). We additionally calculated univariate statistics of all four serum PFAS concentrations at each period. Finally, the distributions of all four serum PFAS concentrations $\log_2$-transformed to reduce the influence of outliers.

We used two different approaches to estimate the impact of gestational or longitudinal PFAS mixtures on eating behaviors. First, we used quantile-based g-computation (QGComp) to estimate covariate-adjusted associations between gestational concentrations of the mixture of PFOA, PFHxS, PFOS, and PFNA with each CEBQ outcome scale summary score. QGComp calculates the parameters of a marginal structural model to estimate the effect on the outcome of a simultaneous, one-quantile increase of all PFAS in the mixture.[47] This allowed us to estimate the total effect of the mixture (ψ), the positive and negative associations contributing to the total effect, and the relative contribution of each PFAS to the positive and negative associations.[47] PFOA, PFHxS, PFOS, and PFNA were categorized into quartiles for this analysis.

We previously used latent profile analysis (LPA) to identify profiles of longitudinal PFAS mixture exposure from gestation through childhood and adolescence.[48] Briefly, we applied LPA to repeated PFAS measures to find participant subgroups that share comparable serum concentrations of the four PFAS over time (birth to age 12 years). Therefore, LPA offers a means to detect complex interactions among various PFAS compounds, revealing how they combine to create distinct profiles that could show varying associations with predictors and outcomes.[49,50] Two profiles were identified and used in this analysis: high exposure (n = 76, 36%) and low exposure (n = 135, 64%). We calculated the proportion of high and low PFAS exposure profiles according to covariates among study participants (Table 1).

We used multivariable linear regression for two sets of analyses. First, we estimated differences in food approach summary scores and food avoidance summary scores among children in the high exposure profile compared to the low exposure profile. Next, we examined associations of $\log_2$-transformed serum PFAS (PFOA, PFHxS, PFOS, and PFNA) at each period (gestation, cord, 3, 8, and 12 years) separately with the CEBQ food approach summary and food avoidance summary scores. In our primary analyses, we adjusted for adolescent sex, adolescent race, adolescent pubic hair staging, maternal age at delivery (years), maternal income (dollars), CDI-II scores, gestational serum cotinine concentrations (ng/mL), PAQ-C scores, and prepregnancy BMI (kg/m^2). Duration of any breastfeeding (weeks) was adjusted for in the longitudinal (3-year, 8-year, and 12-year visits) analyses.

Secondary and sensitivity analyses

In sensitivity analyses, we adjusted for dietary quality (HEI-2010, continuous) and adolescent BMI (age- and sex-standardized *z*-scores at 12 years, continuous) to determine if these adjustments changed our results. Importantly, these were not included as covariates in the primary analyses because they are potentially causal intermediates on the path from PFAS exposure to CEBQ or may not be causes of earlier life PFAS exposure. Finally, we conducted three sets of secondary analyses. First, we examined the associations of $\log_2$-transformed serum PFAS concentration at each time separately with each CEBQ outcome scale and with the food approach and food avoidance summary scores. Next, we examined whether child sex or physical activity modified the associations of individual PFAS or their mixture with the CEBQ food approach and food avoidance summary scores because sex and physical activity have been found to alter the relationship between gestational PFOA concentrations and cardiometabolic risk in adolescents.[17] The critical level of significance for interaction terms was $\alpha = 0.20$. We performed the statistical analyses for the multivariable linear regression models using SAS version 9.4 (SAS Institute, Cary, NC) and created the figures using RStudio version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).[51,52]

Results

At the 12-year study visit, adolescents were on average aged 12.4 years (range: 11.0–14.1 years). Fifty-four percent of adolescents were female, 58% were non-Hispanic White, and 9% had elevated depression scores on the CDI-II (Table 1). Sixty-one percent of the mothers were exposed to secondhand tobacco smoke during their pregnancy, and 9% were active smokers based on gestational serum cotinine concentrations. Compared with participants excluded from the analysis, those included were more likely to be non-Hispanic Black, have a higher CDI-II score, be exposed to secondhand smoke, and have a higher PAQ-C score (Supplemental Table 5; http://links.lww.com/EE/A305).

PFAS concentrations were >LOD in at least 98% of samples at all ages (Supplemental Table 6; http://links.lww.com/EE/A305). For all four PFAS concentrations, median serum PFAS concentrations rose between delivery and age 3 years and then declined thereafter (Supplemental Table 6; http://links.lww.com/EE/A305).

Compared with other groups, median gestational serum PFOS concentrations tended to be higher among those who were in the non-Hispanic White and other race category, had a higher income, and had a prepregnancy BMI of 21–34 kg/m^2 ($P < 0.05$) (Supplemental Table 7; http://links.lww.com/EE/A305).

Thirty-six percent (n = 76) of adolescents were assigned to the high PFAS exposure LPA profile (Supplemental Table 7; http://links.lww.com/EE/A305). Compared with the low exposure profile, participants in the high PFAS exposure profile tended to be non-Hispanic White, pubic hair stage 1–3, have mothers >age 25 years at delivery, with income of <$45,000 or >$75,000, and prepregnancy BMI of <25 or 25–30 kg/m^2 ($P < 0.05$) (Supplemental Table 7; http://links.lww.com/EE/A305).

Mean food avoidance behavior summary scores were similar across covariates (Table 1 and Supplemental Table 8; http://links.lww.com/EE/A305). In contrast, food approach behavior summary scores were 1–2 points higher among adolescents who were female, non-Hispanic Black, exposed to tobacco smoke in utero, had higher public hair stage, lower household income, lower PAQ-C scores, and had mothers with higher prepregnancy BMI, compared to respective reference groups ($P < 0.05$) (Table 1).

Overall, we did not find consistent associations of PFAS exposure during gestation, childhood, or adolescence with adolescent eating behaviors in this cohort. Using QGComp, the gestational PFAS mixture was not associated with food approach summary scores or food avoidance summary scores, nor any individual CEBQ subscale (Tables 2 and 3). Additionally, individual gestational PFAS concentrations were not associated with CEBQ scores (Tables 2 and 3).

Notably, the high longitudinal PFAS exposure profile average food approach behavior scores were modestly higher (β: 0.47, 95% CI: −0.27, 1.23) compared to the low exposure profile (Table 4). However, average food avoidance behavior scores were more similar across the two profiles (β: −0.15, 95% CI: −0.75, 0.46), although in the opposite direction of the food approach association (Table 4). Among childhood serum PFAS concentrations, PFHxS concentrations at 3 and 8 years of age were associated with −0.39 (95% CI: −0.79, 0.00) and −0.37 (95% CI: −0.81, 0.06) point lower food avoidance scores, respectively (Table 5). However, no associations of other gestational or childhood serum PFAS concentrations were observed with food avoidance or approach behaviors during adolescence (Table 5).

Table 2.

Adjusted differences in CEBQ food approach summary scores for a simultaneous one quartile increase in all four gestational serum PFAS concentrations (ng/mL) during pregnancy and the relative contribution of each PFAS to the positive and negative associations using quantile-based g-computation: The HOME Study (n = 196)

PFAS/CEBQ subscale	β (95% CI)	Positive scaled effect size	Negative scaled effect size
Food approach			
Scaled effect size	0.03 (–0.40, 0.45)	0.12	–0.10
PFOA weight		-	0.99
PFHxS weight		0.16	-
PFOS weight		0.84	-
PFNA weight		-	0.01
Food responsiveness			
Scaled effect size	–0.05 (–0.20, 0.10)	0.06	–0.11
PFOA weight		-	0.50
PFHxS weight		-	0.44
PFOS weight		1	-
PFNA weight		-	0.06
Emotional overeating			
Scaled effect size	0.07 (–0.05, 0.19)	0.09	–0.02
PFOA weight		0.07	-
PFHxS weight		0.59	-
PFOS weight		-	1
PFNA weight		0.33	-
Enjoyment of food			
Scaled effect size	–0.04 (–0.17, 0.08)	0.01	–0.05
PFOA weight		-	0.48
PFHxS weight		0.62	-
PFOS weight		0.38	-
PFNA weight		-	0.52
Desire to drink			
Scaled effect size	0.05 (–0.12, 0.21)	0.07	–0.02
PFOA weight		-	1
PFHxS weight		0.09	-
PFOS weight		0.87	-
PFNA weight		0.04	-

Coefficients and 95% CI are from quantile g-computation linear regression models that included each CEBQ scale as the independent variable and each PFAS at the gestation period as the dependent variable. Models adjusted for adolescent sex (female, male), adolescent race (non-Hispanic Black, non-Hispanic White, and other), adolescent pubic hair staging (ordinal), maternal age at delivery (continuous), maternal income (continuous), CDI-II scores (continuous), gestational serum cotinine concentrations (continuous), PAQ-C scores (continuous), and prepregnancy BMI (continuous). The scaled effect size represents the effect size of each PFAS toward either the positive or negative direction for their effect on the entire mixture.

Secondary and sensitivity analyses

No appreciable change in the associations between the gestational PFAS mixture and food approach behaviors was observed after adjusting for adolescent BMI or dietary intake (Supplemental Table 9; http://links.lww.com/EE/A305), but some attenuation of associations between the gestational PFAS mixture and food avoidance scale summary score was noted after adjusting for these covariates (Supplemental Table 9; http://links.lww.com/EE/A305).

Adjusting for adolescent BMI *z*-scores (age- and sex-standardized) strengthened the association between high longitudinal PFAS exposure profile and food approach summary scores (β: 0.66, 95% CI: –0.06, 1.38) (Supplemental Table 10; http://links.lww.com/EE/A305). However, associations were similar when adjusting for HEI scores and food avoidance scores when adjusting for BMI and HEI scores (Supplemental Table 10; http://links.lww.com/EE/A305).

We did not find consistent evidence that child sex-modified associations between PFAS concentrations, individually or as a mixture, and CEBQ scores (Supplemental Tables 11–13; http://links.lww.com/EE/A305).

In contrast, we found some suggestion that physical activity modified the associations between PFAS and CEBQ scores such that higher physical activity favorably modified some associations (Supplemental Tables 14 and 15; http://links.lww.com/EE/A305). Notably, each quartile increase in the gestational PFAS mixture was associated with higher emotional overeating scores among children with low physical activity (β: 0.21; 95% CI: 0.04, 0.40), but the association was protective among those with high physical activity (β: –0.26; 95% CI: –0.49, –0.03) (PFAS × activity interaction *P* value = 0.03) (Supplemental Table 14; http://links.lww.com/EE/A305). Additionally, the association between the longitudinal PFAS exposure profile and CEBQ food approach scores was unfavorable among children in the low physical activity group (β: 1.14; 95% CI: 0.07, 2.21) compared to the high physical activity group (β: 0.10; 95% CI: –0.84, 1.03) (PFAS × activity interaction *P* value = 0.13) (Supplemental Table 15; http://links.lww.com/EE/A305). This appeared to be driven by emotional overeating scores (PFAS × activity interaction *P* value = 0.08) (Supplemental Table 15; http://links.lww.com/EE/A305). We did not find consistent evidence that physical activity scores modified the association of each individual PFAS at each period with food approach or food avoidance behaviors (Supplemental Table 16; http://links.lww.com/EE/A305).

Discussion

We found no consistent evidence that PFAS exposure during gestation, childhood, or adolescence was associated with adolescent eating behaviors in this cohort, but higher longitudinal PFAS mixture exposure was modestly associated with higher food approach behavior scores. We also found some evidence that greater physical activity may attenuate the association of PFAS exposures during both gestation and childhood with more obesogenic eating behaviors. Collectively, these results suggest that mechanisms or factors other than eating behaviors underlie previously observed associations of early-life PFAS exposure with later-life obesity risk and cardiometabolic dysregulation.

Table 3.

Adjusted differences in CEBQ food avoidance summary scores for a simultaneous one quartile increase in all four gestational serum PFAS concentrations (ng/mL) during pregnancy and the relative contribution of each PFAS to the positive and negative associations using quantile-based g-computation: The HOME Study (n = 196)

PFAS/CEBQ subscale	β (95% CI)	Positive scaled effect size	Negative scaled effect size
Food avoidance			
Scaled effect size	0.19 (–0.17, 0.54)	0.18	–0.03
PFOA weight		-	1
PFHxS weight		0.05	-
PFOS weight		0.89	-
PFNA weight		0.06	-
Satiety responsiveness			
Scaled effect size	0.02 (–0.09, 0.13)	0.02	–0.02
PFOA weight		0.35	-
PFHxS weight		0.22	-
PFOS weight		-	1
PFNA weight		0.42	-
Slowness in eating			
Scaled effect size	0.07 (–0.05, 0.20)	0.14	–0.08
PFOA weight		-	0.79
PFHxS weight		-	0.21
PFOS weight		0.67	-
PFNA weight		0.33	-
Emotional undereating			
Scaled effect size	0.07 (–0.08, 0.23)	0.15	–0.08
PFOA weight		-	0.98
PFHxS weight		-	0.02
PFOS weight		0.56	-
PFNA weight		0.44	-
Food fussiness			
Scaled effect size	0.02 (–0.14, 0.18)	0.15	–0.13
PFOA weight		0.79	-
PFHxS weight		0.21	-
PFOS weight		-	0.26
PFNA weight		-	0.74

Coefficients and 95% CI are from quantile g-computation linear regression models that included each CEBQ scale as the independent variable and each PFAS at the gestation period as the dependent variable. Models adjusted for adolescent sex (female, male), adolescent race (non-Hispanic Black, non-Hispanic White, other), adolescent pubic hair staging (ordinal), maternal age at delivery (continuous), maternal income (continuous), CDI-II scores (continuous), gestational serum cotinine concentrations (continuous), PAQ-C scores (continuous), and prepregnancy BMI (continuous). The scaled effect size represents the effect size of each PFAS toward either the positive or negative direction for their effect on the entire mixture.

Table 4.

Adjusted differences in CEBQ scores in the high longitudinal PFAS exposure profile versus the low longitudinal PFAS exposure profile: The HOME Study (N = 211)

CEBQ scale	β (95% CI)
Food approach	0.47 (–0.27, 1.23)
Food responsiveness	0.07 (–0.28, 1.23)
Emotional overeating	0.11 (–0.11, 0.33)
Enjoyment of food	0.04 (–0.18, 0.25)
Desire to drink	0.26 (–0.03, 0.55)
Food avoidance	–0.15 (–0.75, 0.46)
Satiety responsiveness	0.05 (–0.13, 0.24)
Slowness in eating	0.01 (–0.21, 0.23)
Emotional undereating	0.03 (–0.24, 0.31)
Food fussiness	–0.24 (–0.52, 0.04)

Coefficients and 95% CI are from multivariable linear regression models that included the CEBQ food approach subscales and food avoidance subscales as the independent variable and the high PFAS exposure profile as the dependent variable. Models adjusted for adolescent sex (female, male), adolescent race (non-Hispanic Black, non-Hispanic White, other), adolescent pubic hair staging (ordinal), maternal age at delivery (continuous), maternal income (continuous), CDI-II scores (continuous), gestational serum cotinine concentrations (continuous), PAQ-C scores (continuous), prepregnancy BMI (continuous), and duration of any breastfeeding (continuous).
Food approach summary score was the sum of scores on food responsiveness, emotional overeating, enjoyment of food, and desire to drink subscales from the Child Eating Behavior Questionnaire (CEBQ). Food avoidance summary score was the sum of scores on satiety responsiveness, slowness in eating, emotional undereating, and food fussiness CEBQ subscales.

A previous study from this cohort provides evidence of the biological pathways that may underlie associations between postnatal PFAS and eating behaviors.[53,54] Liu et al[53] previously found that the high versus low PFAS profile was associated with four differentially methylated positions in peripheral leukocytes annotating to gene regions related to cancers, cognition, and cardiometabolic health. In a cross-sectional study of 8-year-old children from the HOME Study, serum concentrations of PFOA, PFHxS, PFOS, and PFNA were associated with metabolic features related to amino acid and butanoate metabolism. We speculate that postnatal PFAS exposures may alter the expression of genes related to energy metabolism, which in turn affect satiety and hunger cues.[53,54]

Few studies have examined whether PFAS exposure affects eating behaviors in adolescence, but phthalates have been associated with eating behaviors.[17] Leader et al[17] found that higher maternal and paternal preconception urinary concentrations of certain phthalate biomarkers were linked to increased food approach behaviors and decreased food avoidance behaviors in children. While preconception levels of some phthalates were related to CEBQ scores, maternal pregnancy concentrations of these chemicals were not consistently associated with CEBQ scores.[17] We speculate that the absence of an association between early-life PFAS exposure and eating behaviors could be due to a waning effect of the association as eating behaviors change in response to development and social, cultural, and family factors. Moreover, early adiposity in adolescence may impact subsequent eating behaviors, making it challenging to

Table 5.

Adjusted differences in CEBQ summary scores per doubling in serum PFAS concentrations (ng/mL) during pregnancy and at ages 3, 8, and 12 years: The HOME Study

		β (95% CI)	
Period	n	Food approach	Food avoidance
PFOA			
Gestation	196	−0.26 (−0.93, 0.42)	0.15 (−0.40, 0.69)
Cord	122	−0.37 (−1.16, 0.37)	0.15 (−0.48, 0.79)
3-year visit	133	−0.63 (−1.78, 0.52)	0.44 (−0.53, 1.41)
8-year visit	160	−0.15 (−1.35, 1.04)	0.34 (−0.61, 1.29)
12-year visit	180	0.11 (−0.93, 1.15)	0.49 (−0.29, 1.18)
PFHxS			
Gestation	196	0.15 (−0.33, 0.63)	0.08 (−0.30, 0.47)
Cord	122	0.08 (−0.55, 0.71)	0.28 (−0.26, 0.82)
3-year visit	133	−0.05 (−0.52, 0.43)	−0.39 (−0.79, 0.00)
8-year visit	160	0.39 (−0.15, 0.94)	−0.37 (−0.81, 0.06)
12-year visit	180	0.29 (−0.22, 0.79)	−0.11 (−0.49, 0.28)
PFOS			
Gestation	196	0.20 (−0.42, 0.83)	0.23 (−0.27, 0.73)
Cord	122	−0.07 (−0.07, 0.56)	0.35 (−0.19, 0.89)
3-year visit	133	−0.01 (−0.82, 0.80)	0.09 (−0.59, 0.78)
8-year visit	160	−0.11 (−0.93, 0.71)	0.06 (−0.59, 0.72)
12-year visit	180	0.03 (−0.71, 0.77)	−0.16 (−0.72, 0.39)
PFNA			
Gestation	196	−0.01 (−0.80, 0.78)	0.36 (−0.27, 0.98)
Cord	122	−0.30 (−1.18, 0.59)	0.21 (−0.54, 0.97)
3-year visit	133	−0.06 (−1.23, 0.09)	0.08 (−0.49, 0.65)
8-year visit	160	0.06 (−0.59, 0.70)	−0.02 (−0.54, 0.49)
12-year visit	180	−0.05 (−0.78, 0.68)	0.09 (−0.45, 0.65)

Coefficients and 95% CI are from multivariable linear regression models that included the CEBQ food approach summary score and food avoidance summary score as the independent variable and each PFAS at each period as the dependent variable. Models adjusted for adolescent sex (female, male), adolescent race (non-Hispanic Black, non-Hispanic White, other), adolescent pubic hair staging (ordinal), maternal age at delivery (continuous), maternal income (continuous), CDI-II scores (continuous), gestational serum cotinine concentrations (continuous), PAQ-C scores (continuous), and prepregnancy BMI (continuous). Duration of any breastfeeding was adjusted for in the longitudinal (3-year, 8-year, and 12-year visits) analyses. Each PFAS was $\log_2$ transformed in the models.

Food approach summary score was the sum of scores on food responsiveness, emotional overeating, enjoyment of food, and desire to drink subscales from the Child Eating Behavior Questionnaire (CEBQ). Food avoidance summary score was the sum of scores on satiety responsiveness, slowness in eating, emotional undereating, and food fussiness CEBQ subscales.

establish links between early-life PFAS exposure, eating behaviors, adiposity, and related cardiometabolic biomarkers.[24,55,56]

Our finding that physical activity attenuated the adverse associations of PFAS exposure with CEBQ scores is consistent with prior studies. Braun et al[57] found that physical activity attenuated the associations between gestational PFOA concentrations and cardiometabolic risk scores in children at age 12 years, specifically insulin resistance, leptin to adiponectin ratio, and central adiposity, within the same cohort as this study. At least two other studies found similar associations in adults. Cardenas et al[58] observed attenuation of the association between PFOA concentrations and diabetes incidence among those who were randomized to an intervention to increase physical activity and improve diet. Borghese et al[59] found that higher levels of physical activity dampened the association of PFOA concentrations with gamma-glutamyltransferase concentrations. The findings from these studies emphasize the need to identify solution-oriented approaches to mitigate the adverse effects of PFAS exposure.[60]

This study had some limitations and strengths. First, the sample size of the study was modest with moderate statistical power to detect subtle associations, particularly for effect measure modification. Second, we did not examine whether food approach or food avoidance behaviors earlier in life were related to PFAS exposures; however, prior studies show that CEBQ scores have good to excellent reproducibility between ages 7 and 13 years.[61] Moreover, the CEBQ relies on caregivers' perceptions, which may introduce measurement error, particularly because parents may not fully know their child's behavior outside of the home, such as in school. However, the CEBQ has good internal consistency, reliability, and criterion-related validity against objective eating behavior measures.[37,38] Third, the participants of this study resided in housing constructed before 1978, and the majority were non-Hispanic White, highly educated, and had household incomes around the regional median, where the results may not be generalizable to more heterogeneous populations.[62] However, except for PFOA, the maternal serum concentrations of other PFAS (PFHxS: 1.4 ng/mL; PFOS: 13.3 ng/mL; PFNA: 0.9 ng/mL) in HOME Study participants resembled those found in pregnant women in the United States at the same time.[62–64] Fourth, the HOME Study's comprehensive collection of covariates allowed us to control for several potential confounding factors. Finally, we were able to leverage repeated measures of serum PFAS and apply sophisticated biostatistical approaches to estimate the impact of PFAS mixtures during two distinct life stages of gestation and childhood on eating behavior among adolescents.

Conclusions

Collectively, we found no associations of PFAS exposure during gestation, childhood, or adolescence with adolescent eating behaviors in this cohort. However, greater physical activity favorably modified the potential adverse association of gestational and postnatal PFAS mixtures with obesogenic eating behaviors. Overall, this suggests that other mechanisms or factors underlie previously observed associations of early-life PFAS exposure with later-life obesity risk and cardiometabolic dysregulation. Future studies could consider examining reward mechanisms, food choices, sensory preferences, or resting metabolic rate in relation to EDCs like PFAS since these are other eating behavior adjacent features that impact obesity risk and metabolic dysregulation.[65]

Conflicts of interest statement

Joseph Braun was financially compensated for his service as an expert witness for plaintiffs in litigation related to PFAS-contaminated drinking water. The other authors declare that they have no conflicts of interest with regard to the content of this report.

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