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Birth Outcomes in Relation to Prenatal Exposure to Per- and Polyfluoroalkyl Substances and Stress in the Environmental Influences on Child Health Outcomes (ECHO) Program

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Background: Per- and polyfluoroalkyl substances (PFAS) are persistent and ubiquitous chemicals associated with risk of adverse birth outcomes. Results of previous studies have been inconsistent. Associations between PFAS and birth outcomes may be affected by psychosocial stress.

Objectives: We estimated risk of adverse birth outcomes in relation to prenatal PFAS concentrations and evaluate whether maternal stress modifies those relationships.

Methods: We included 3,339 participants from 11 prospective prenatal cohorts in the Environmental influences on the Child Health Outcomes (ECHO) program to estimate the associations of five PFAS and birth outcomes. We stratified by perceived stress scale scores to examine effect modification and used Bayesian Weighted Sums to estimate mixtures of PFAS.

Results: We observed reduced birth size with increased concentrations of all PFAS. For a 1-unit higher log-normalized exposure to perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), perfluorononanoic acid (PFNA), and perfluorohexane sulfonic acid (PFHxS), we observed lower birthweight-for-gestational-age z-scores of $\beta = -0.15$ [95% confidence interval (CI): −0.27, −0.03], $\beta = -0.14$ (95% CI: −0.28, −0.002), $\beta = -0.22$ (95% CI: −0.23, −0.10), $\beta = -0.06$ (95% CI: −0.18, 0.06), and $\beta = -0.25$ (95% CI: −0.37, −0.14), respectively. We observed a lower odds ratio (OR) for large-for-gestational-age: $OR_{PFNA} = 0.56$ (95% CI: 0.38, 0.83), $OR_{PFDA} = 0.52$ (95% CI: 0.35, 0.77). For a 1-unit increase in log-normalized concentration of summed PFAS, we observed a lower birthweight-for-gestational-age z-score [−0.28; 95% highest posterior density (HPD): −0.44, −0.14] and decreased odds of large-for-gestational-age (OR = 0.49; 95% HPD: 0.29, 0.82). Perfluorodecanoic acid (PFDA) explained the highest percentage (40%) of the summed effect in both models. Associations were not modified by maternal perceived stress.

Discussion: Our large, multi-cohort study of PFAS and adverse birth outcomes found a negative association between prenatal PFAS and birthweight-for-gestational-age, and the associations were not different in groups with high vs. low perceived stress. This study can help inform policy to reduce exposures in the environment and humans. https://doi.org/10.1289/EHP10723

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Introduction

Per- and polyfluoroalkyl substances (PFAS) are a group of synthetic chemicals used in nonstick and stain- and water-resistant consumer products, as well as in industrial processes. PFAS are persistent in the environment and in the human body.[1] Pathways of human exposure include ingestion of contaminated drinking water and food, and inhalation.[2,3] As a result, PFAS are widely detectable in human biomonitoring studies, including studies showing that nearly 100% of pregnant women studied have measurable levels of PFAS in their bodies.[4] Reported human health associations include carcinogenicity (kidney and testicular cancers),[5] cardiovascular effects (dyslipidemia[6]), pregnancy-induced hypertension,[7] impaired renal function,[8,9] endocrine disruption (thyroid disease and altered age at menarche),[10,11] obesity,[12] and immune effects (immunotoxicity and decreased antibody production).[13–15]

PFAS have been associated with adverse effects on fetal development in both animal and human studies.[16,17] Reductions in birthweight have been reported with higher exposure to perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA), and perfluorononanoic acid (PFNA).[18–31] A systematic review and meta-analysis of animal and human research found sufficient evidence for an inverse association between PFOA and birthweight.[16] Fewer studies have examined PFAS in relation to preterm birth; however, a recent review and meta-analysis found maternal PFOS was associated with increased risk of preterm birth.[32] Only one study examined PFAS in relation to large-for-gestational-age, and it reported no association.[33]

Psychosocial stressors and responses to stress during pregnancy are associated with perinatal outcomes and may also contribute to the persistence of disparities in adverse birth outcomes by socioeconomic status and racial and ethnic groups.[31,34] Experiences of psychosocial stress during pregnancy may be more prevalent among women of lower socioeconomic status as indicated by lower education or income level.[35] Perceived stress may also be higher among women of color because of racial and gender-based discrimination.[36–38] Environmental chemical exposures can co-occur with chronic psychosocial risk factors during pregnancy.[39,40] This combination may have a greater impact than each individual factor alone and result in amplified risk of adverse pregnancy outcomes.[40–42] Furthermore, these environmental and psychosocial stressors may operate via similar biological systems and mechanisms (i.e., endocrine or metabolic disruption, inflammation, and epigenetic changes).[41]

The Environmental influences on Child Health Outcomes (ECHO) program is a National Institutes of Health initiative to address pediatric outcomes with high public health impact.[43] ECHO comprises 69 cohorts from across the United States and includes over 57,000 mother–child dyads.[44] The program is well powered to analyze environmental exposures in a demographically and geographically diverse study population including 56 cohorts with chemical biomonitoring data for mothers and children.[45] The present study estimates associations using ECHO data from 11 pregnancy cohorts to examine the extent to which prenatal exposure to PFAS is associated with increased risk of adverse birth outcomes and whether these associations are modified by stress.

Methods

Overview

ECHO cohorts were invited to participate based on consent for data sharing with ECHO of the mother–child pairs[46] and were harmonized and pooled for analysis. Mothers were required to have either extant prenatal PFAS data or at least one serum or plasma biospecimen collected during pregnancy that was available for assessment of PFAS concentration. Data on child birthweight or gestational age at birth were required for participation, and the study population was restricted to singleton births and included 3,339 mother–child pairs from 11 cohorts between 1999 and 2019 (Figure S1). Cohorts submitted data to the ECHO Data Analysis Center for analysis. Cohort was not considered when determining inclusion for this analytic data set. All cohorts had institutional review board approvals from their local institutions. Written consent to participate in the ECHO study was obtained for all participants. Participants received various stipends for their time according to the individual cohort.

PFAS

Laboratory methods varied by cohort (Table S1). PFAS were measured (in nanograms per milliliter) in plasma or serum at three laboratories: the California Department of Toxic Substances Control,[34] the Centers for Disease Control and Prevention (CDC),[30,47,48] and the Wadsworth Human Health Exposure Analysis Resource Laboratory.[49] All laboratories participated in the CDC's quality assurance program to test interlaboratory comparisons. The number of PFAS measured in each cohort varied from 8 to 14 (Table S2). PFAS were included in the present analysis if more than 60% of values were above the method limit of detection (LOD) and no cohort had <40% below the LOD (Table S2). Five PFAS met these criteria: PFOA, PFOS, PFNA, perfluorohexane sulfonic acid (PFHxS), and perfluorodecanoic acid (PFDA). If a cohort had separate sums of branched and linear chain isomers for PFOA or PFOS, the two were summed as total PFOA or PFOS.[50] Distributions of PFAS were examined by cohort, year, and perceived stress scale (PSS; Table S3). LOD varied between labs and within cohorts owing to batches performed years apart (Table S3). For those observations that were below the LOD, we imputed exposure values as the LOD divided by the square root of 2. PFAS measures were nonnormally distributed, and, thus, were natural log transformed (Figure S2). Most cohorts collected prenatal biospecimens during the second trimester (9 cohorts, $n = 2{,}531$, Table S1). For three cohorts ($n = 565$) with PFAS measured at multiple time points, concentrations above the LOD were averaged. We tested the correlations between the different PFAS and each PFAS across different trimesters of exposure. Spearman correlations of PFAS concentrations measured multiple times during pregnancy were strong ($\rho > 0.8$), with one exception, which was moderately correlated [PFDA in the first and third trimesters ($\rho = 0.53$)] (Table S4). We compared PFAS concentrations to those measured by the National Health and Nutrition Examination Surveys (NHANES) during the study period (Table S5).

Prenatal Stress

We examined maternal stress as an effect modifier of the relationship between PFAS and birth outcomes. For a subset of cohorts (8 of 11, $N = 2{,}032$), maternal stress was assessed using the PSS administered in the prenatal period; the PSS measures perceptions of life as uncontrollable, unpredictable, and overwhelming.[51] The PSS is a widely used self-report instrument for measuring stress perception and is available in three versions, with 4, 10, or 14 items [PSS-4 (1 cohort, $n = 402$), PSS-10 (5 cohorts, $n = 1{,}148$), and PSS-14 (2 cohorts, $n = 459$), respectively], each containing items rated on a five-point Likert scale. Psychometric data support reliability and validity of the PSS-10 in comparison with the PSS-14 and perceived helplessness ($r = 0.85$) and perceived self-efficacy ($r = 0.82$) scales, respectively.[52] In addition, the PSS-4 has been validated in pregnant women and correlated strongly ($\rho = 0.71$)

with the Assessment of Stress portion of the Prenatal Psychosocial Profile and was valid in predicting maternal depression (Edinburgh Postnatal Depression Scale, $r = 0.67$), and quality of life (mental health component of the Short-Form-12, $r = -0.62$).[53] Cohorts were administered one version of the PSS (Table S1), and item response theory was used to harmonize PSS to a t-score metric by the ECHO Patient-Reported Outcomes Core [ECHO PRO Core Data Harmonization Group, ECHO-wide Cohort Protocol (version 2.0), Harmonization Technical Report (version 5.2, 24 March 2021)].[54] PSS scores were unavailable for participants in three cohorts (the Project Viva cohort, the Kaiser Permanente Research Bank Pregnancy Cohort, and the New Hampshire Birth Cohort) and partially missing in other cohorts except for Illinois Kids Development Studies, which had complete data on PSS [$N = 2{,}009$ (60%) of 3,339].

Birth Outcomes

Outcomes included gestational age at birth (completed weeks), preterm birth (birth <37 vs. ≥37 wk gestation), term low birthweight (birthweight <2,500 vs. ≥2,500 g among births at ≥37 wk gestation), birthweight-for-gestational-age and sex-specific z-scores, and both small- and large-for-gestational-age (<10th percentile and >90th percentile, respectively) using a 2017 referent population in the United States.[55] Birth outcomes and covariates were obtained according to the protocol for each cohort (from medical records or self-report).

Statistical Analysis

We analyzed two continuous and four dichotomous birth outcomes using linear and logistic regression, respectively, in relation to single PFAS exposures. Covariates selected as potential confounders *a priori* based on a directed acyclic graph (Figure S3) included cohort (base model), maternal age at delivery (<25, 25–29, 30–34, ≥35 y), parity (0, ≥1), maternal educational attainment [<high school; high school degree, General Educational Development (GED), or equivalent; some college, no degree; bachelor's degree and above], and maternal race/ethnicity (non-Hispanic White, non-Hispanic Black, non-Hispanic Asian/Pacific Islander, non-Hispanic other, and Hispanic). Race/ethnicity was included as a social construct and proxy for racism and discrimination. The non-Hispanic other category included Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, multiple race, or any other race group not included in a more specific category. We examined race/ethnicity in relation to PSS scores because we hypothesized racism and discrimination might be associated with perceived stress. Our study was restricted to participants with non-missing data on these covariates. Factors related to the outcome and to stress but not PFAS (e.g., maternal tobacco use, prenatal secondhand smoke exposure) were considered in sensitivity analyses. Additional covariates were considered potential mediators [e.g., maternal body mass index (BMI), gestational diabetes, gestational hypertension, and preeclampsia] and were not considered confounders and not included in analytic models. We performed stratified analyses by PSS scores, which were dichotomized at the median of the t-scores and examined the p-value of the interaction term to determine potential effect modification (results with $p < 0.1$ were noted).

We estimated the effect of summed concentrations of five PFAS (PFOA, PFOS, PFNA, PFHxS, and PFDA) using Bayesian Weighted Sums, a recent Bayesian approach that provides the effect of the mixture of PFAS, as well as the percentage contribution of each of the PFAS. This approach allows the data and model to estimate the weights[56] and uses a Dirichlet prior that restricts values of the weights to sum to 1 and restricts individual values to a 0–1 range.[57] These analyses were similarly adjusted for the covariates and stratified by PSS. We provide 95% highest posterior density (HPD) intervals as opposed to 95% credible intervals.

We performed several sensitivity analyses to assess the robustness of our results and explore additional effect modifiers and confounders. We performed a stratified analysis by infant sex to identify potential sex-specific associations of PFAS and birth outcomes and examined the p-value of the interaction term to determine potential effect modification (results with $p < 0.1$ were noted). We conducted a trimester-stratified analysis to compare results by timing of PFAS measurements during pregnancy. Because results may be sensitive to inclusion of specific cohorts, we conducted leave-one-out analyses, excluding each cohort from calculation of the main effects of PFAS. We examined quartiles of exposure in relation to the outcomes to assess the linearity of the exposure–response relationship. We performed the birthweight-for-gestational-age z-score analysis with cohort as a random effect in mixed effects models to determine if our main findings were impacted by cohort heterogeneity. We adjusted for prenatal tobacco smoke exposure (indicators of either any maternal smoking or secondhand smoke during pregnancy) as an additional potential confounder for birthweight-for-gestational-age z-score and large-for-gestational-age. Last, we provided estimates of the association between non–log-transformed PFAS and continuous birth weight (adjusted for gestational age) given the difficulty of interpreting log-transformed values of PFAS in relation to z-scores of birthweight-for-gestational-age and the potential that log transformation may bias the results. We chose not to correct for multiple comparisons given the few *a priori* tests and our preference to present actual observations.[58] Primary statistical analyses were conducted using Stata (version 17.0; StataCorp), and correlation maps and Bayesian mixtures analyses were conducted in R (version 4.1.0; R Development Core Team) using the JAGS software program (version 4.3.1). Software code to recreate results of this work is maintained by the ECHO Data Analysis Center (https://dcricollab.dcri.duke.edu/sites/echomaterials/SitePages/Home.aspx).

Results

This study included 3,339 mother–child pairs from 11 cohorts in ECHO. Mothers were demographically and racially/ethnically diverse, with about half non-Hispanic White (53.8%) and having a bachelor's degree or higher educational attainment level (53.0%) (Table 1). The mean age of mothers at delivery was 30.9 ± 5.8 y. The years of birth for all cohorts ranged from 1999 through 2019 (Table S1).

Four PFAS were detected in 96%–100% of participants (PFOS, PFOA, PFNA, and PFHxS) and concentrations were lower than those measured in NHANES (Table S5). Most PFAS were moderately positively correlated with Spearman correlations between $\rho = 0.14$ (PFDA and PFHxS) and $\rho = 0.83$ (PFOA and PFOS) (Figure S4). PFAS concentrations were highest among participants from older cohorts, although not monotonically, and PFAS decreased across years except for PFHxS, which increased between 2015 and 2019, although levels were not as high as earlier (1999–2003) (Table S3).

As compared with participants who were white, a higher proportion of participants who were Asian and other race/ethnicity had above-median levels of PSS. A lower proportion of participants who were Hispanic or unknown race/ethnicity had above-median levels of PSS, and levels of PSS were similar among participants who were Black (Table S6).

We estimated the associations between each PFAS and birth outcome with adjusted linear and logistic regression models (Table 2). We observed lower birthweight-for-gestational-age z-scores with

Table 1. Characteristics of the study population among selected ECHO cohorts ($N = 3,339$).

Characteristic	N (%) or mean ± SD
Maternal race/ethnicity	
Hispanic/Latina	653 (20.8)
Non-Hispanic White	1,687 (53.8)
Non-Hispanic Black	509 (16.2)
Non-Hispanic Asian	193 (6.2)
Non-Hispanic other	96 (3.1)
Unknown	201
Maternal educational attainment	
<High school	312 (9.5)
High school degree, GED, or equivalent	530 (16.1)
Some college, no degree	702 (21.4)
Bachelor's degree and above	1,742 (53.0)
Unknown	53
Maternal age at delivery (y)	
<25	497 (15.7)
25–29	672 (21.3)
30–34	1,124 (35.6)
≥35	867 (27.4)
Unknown	179
PSS scale	
PSS t-score category	49.8 ± 9.9[a]
<Median (50.6)	1,003 (49.9)
≥Median (50.6)	1,006 (50.1)
Unknown	1,330
Gestational age (wk)	38.9 ± 1.9
Preterm birth (<37 wk)	
Yes	252 (7.5)
No	3,087 (92.5)
Birthweight (g)	3,337.4 ± 563.3
Low birthweight (<2,500 g)	
Yes	182 (5.5)
No	3,157 (94.5)
Size for gestational age[b]	
Small-for-gestational-age	357 (10.7)
Appropriate-for-gestational-age	2,623 (78.6)
Large-for-gestational-age	359 (10.8)
Child sex	
Male	1,643 (49.2)
Female	1,696 (50.8)
Parity prior to indexed birth	
0	1,783 (53.4)
≥1	1,556 (46.6)
Prenatal tobacco use	
Yes	200 (7.2)
No	2,573 (92.8)
Unknown	165
Prenatal secondhand smoke	
Yes	1,386 (64.0)
No	781 (36.0)
Unknown	1,172
Prepregnancy BMI (kg/m^2)	26.1 ± 6.3[c]
Gestational diabetes	
Yes	321 (10.5)
No	2,722 (89.5)
Unknown	296
Gestational hypertension	
Yes	154 (8.5)
No	1,667 (91.5)
Unknown	1,518
Preeclampsia	
Yes	104 (5.6)
No	1,751 (94.4)
Unknown	1,484
Year of birth	
1999	28 (0.8)
2000	330 (9.9)
2001	310 (9.3)
2002	170 (5.1)
2003	4 (0.1)
2009	9 (0.3)
2010	122 (3.7)
2011	225 (6.7)
2012	283 (8.5)
2013	243 (7.3)
2014	204 (6.1)
2015	278 (8.3)
2016	287 (8.6)
2017	283 (8.5)
2018	286 (8.6)
2019	98 (2.9)
Cohort	
Chemicals in Our Bodies (CiOB)	402 (12.0)
Illinois Kids Development Studies (IKIDS)	184 (5.5)
Project Viva	842 (25.2)
Healthy Start	652 (19.5)
New Hampshire Birth Cohort Study (NHBCS)	324 (9.7)
Markers of Autism Risk in Babies Learning Early Signs (MARBLES)	39 (1.2)
Emory (Atlanta)	424 (12.7)
Maternal And Developmental Risks from Environmental and Social Stressors (MADRES)	347 (10.4)
Pregnancy and EnvironmenT And Lifestyle Study (PETALS)	124 (3.7)
Rochester	35 (1.0)
Kaiser Permanente Research Bank Pregnancy Cohort (KPRB-PC)	13 (0.4)

Note: BMI, body mass index; ECHO, Environmental influences on Child Health Outcomes; GED, General Educational Development; PSS, perceived stress scale; SD, standard deviation.
[a]$n = 2,009$.
[b]Small-, appropriate-, and large-for-gestational-age were defined, respectively, as singleton infants with weight <10th percentile, 10th–90th percentile, and >90th percentile of birthweight-for-gestational-age and sex using a 2017 U.S. reference population.
[c]$n = 3,219$.

increasing concentrations of all PFAS. For a 1-unit higher log-normalized exposure to PFOA, PFOS, PFNA, PFHxS, and PFDA, we observed a lower birthweight-for-gestational-age z-score of $\beta = -0.15$ [95% confidence interval (CI): −0.27, −0.03], $\beta = -0.14$ (95% CI: −0.28, −0.002), $\beta = -0.22$ (95% CI: −0.33, −0.10), $\beta = -0.06$ (95% CI: −0.18, 0.06), and $\beta = -0.25$ (95% CI: −0.37, −0.14), respectively. Positive point estimates for PFAS and risk of small-for-gestational-age were consistent for all PFAS, with ORs ranging from 1.06 to 1.29, although 95% CIs for all estimates included the null. We observed lower odds ratios (ORs) of large-for-gestational-age, with estimates for PFNA and PFDA excluding the null: $OR_{PFNA} = 0.56$ (95% CI: 0.38, 0.83), and $OR_{PFDA} = 0.52$ (95% CI: 0.35, 0.77). Point estimates for all PFAS showed increased risk of term low birth weight, with ORs ranging from 1.13 to 2.24, although 95% CIs included the null. All PFAS showed increased risk of preterm birth and decreased gestational age at birth, although all but one estimate included the null in fully adjusted models ($\beta_{PFOA} = -0.22$; 95% CI: −0.43, −0.01) with the exception of PFHxS (Table 2).

When stratified by PSS, associations between some PFAS and birthweight-for-gestatonal-age z-scores were stronger (i.e., larger decreases) among those who reported below-median levels of perceived stress, although tests did not show evidence of statistical interaction (Table 3). Similar results were observed for large-for-gestational-age with stronger decreased risk among those with lower perceived stress (Table 3). Three estimates had interaction terms with $p < 0.1$, although not in a consistent direction; PFOS was associated with increased risk of small-for-gestational-age among those with lower perceived stress (OR = 1.57; 95% CI: 0.73, 3.38), PFHxS with increased risk of large-for-gestational-age among those with higher perceived stress (OR = 1.13; 95% CI: 0.51, 2.49),

Table 2. Associations of continuous measures of prenatal natural log-transformed PFAS (ng/mL) concentrations and risk of adverse birth outcomes in selected ECHO cohorts.

	Birthweight-for-gestational-age z-scores		Small-for-gestational-age[a]		Large-for-gestational-age[a]		Term low birth weight		Preterm birth		Gestational age at birth (wk)	
PFAS	*N*	β (95% CI)	*N*	OR (95% CI)	*N*	OR (95% CI)	*N*	OR (95% CI)	*N*	OR (95% CI)	*N*	β (95% CI)
PFOA												
Model 1	3,099	−0.27 (−0.38, −0.15)	2,752	1.20 (0.83, 1.74)	2,791	0.55 (0.38, 0.79)	2,815	1.29 (0.53, 3.16)	3,063	1.27 (0.86, 1.87)	3,102	0.03 (−0.16, 0.23)
Model 2	3,099	−0.15 (−0.27, −0.03)	2,752	1.07 (0.72, 1.59)	2,791	0.75 (0.51, 1.12)	2,815	1.43 (0.54, 3.80)	3,063	1.41 (0.93, 2.14)	3,102	−0.22 (−0.43, −0.01)
PFOS												
Model 1	3,099	−0.27 (−0.41, −0.14)	2,752	1.23 (0.80, 1.89)	2,791	0.61 (0.40, 0.94)	2,815	1.40 (0.50, 3.92)	3,063	1.18 (0.71, 1.96)	3,102	0.06 (−0.18, 0.29)
Model 2	3,099	−0.14 (−0.28, −0.00)	2,752	1.06 (0.68, 1.65)	2,791	0.87 (0.55, 1.39)	2,815	1.21 (0.43, 3.39)	3,063	1.29 (0.76, 2.18)	3,102	−0.16 (−0.40, 0.09)
PFNA												
Model 1	3,099	−0.29 (−0.41, −0.18)	2,752	1.18 (0.81, 1.71)	2,791	0.46 (0.32, 0.67)	2,815	1.42 (0.58, 3.49)	3,063	1.31 (0.87, 1.97)	3,102	0.01 (−0.20, 0.21)
Model 2	3,099	−0.22 (−0.33, −0.10)	2,752	1.09 (0.74, 1.60)	2,791	0.56 (0.38, 0.83)	2,815	1.67 (0.64, 4.35)	3,063	1.43 (0.93, 2.19)	3,102	−0.17 (−0.38, 0.04)
PFHxS												
Model 1	3,099	−0.12 (−0.23, 0.00)	2,752	1.29 (0.89, 1.89)	2,791	0.73 (0.51, 1.04)	2,815	1.13 (0.47, 2.71)	3,063	0.86 (0.55, 1.34)	3,102	0.24 (0.04, 0.44)
Model 2	3,099	−0.06 (−0.18, 0.06)	2,752	1.25 (0.84, 1.87)	2,791	0.86 (0.59, 1.25)	2,815	1.14 (0.46, 2.84)	3,063	0.97 (0.61, 1.55)	3,102	0.02 (−0.19, 0.23)
PFDA												
Model 1	3,047	−0.30 (−0.41, −0.18)	2,701	1.22 (0.85, 1.76)	2,744	0.47 (0.32, 0.69)	2,770	1.93 (0.86, 4.34)	3,011	1.16 (0.77, 1.75)	3,050	−0.01 (−0.22, 0.19)
Model 2	3,047	−0.25 (−0.37, −0.14)	2,701	1.18 (0.81, 1.73)	2,744	0.52 (0.35, 0.77)	2,770	2.24 (0.96, 5.24)	3,011	1.22 (0.80, 1.86)	3,050	−0.11 (−0.32, 0.09)

Note: Beta coefficients (βs) and ORs represent 1 log-unit increase in PFAS concentration (ng/mL) and are presented with 95% CI. Model 1 was adjusted for cohort (dummy variables). Model 2 was additionally adjusted for maternal race/ethnicity (Hispanic, non-Hispanic White, Black, Asian, other), for maternal educational attainment (<high school, high school degree/GED, some college, bachelor's degree or higher), maternal age at delivery (<25, 25–29, 30–34, ≥35 y), parity (0, ≥1). CI, confidence interval; ECHO, Environmental influences on Child Health Outcomes; GED, General Educational Development; OR, odds ratio; PFAS, per- and polyfluoroalkyl substances; PFDA, perfluorodecanoic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid.
[a]Appropriate-for-gestational-age is the referent from both small- and large-for-gestational age estimates.

and PFDA with increased risk of term low birth weight among those with higher perceived stress (OR = 5.25; 95% CI: 1.08, 25.64) (Table 3). Some associations were stronger in the subsample with PSS scores, including increased PFHxS and lower birthweight-for-gestational-age, increased PFOA and lower risk of large-for-gestational-age, and increased PFOA and PFNA and increased risk of preterm birth (Table 3).

Bayesian Weighted Sums results were largely consistent with the main findings (Table 4). The change in birthweight-for-gestational-age z-scores for a 1-unit increase in the sum of logged PFAS was −0.28 (95% HPD: −0.44, −0.14). The odds of small- and large-for-gestational-age associated with summed PFAS were 1.13 (95% HPD: 0.68, 1.83) and 0.49 (95% HPD: 0.29, 0.82), respectively. The percentages of the summed effect for birthweight-for-gestational-age z-scores and large-for-gestational-age explained by PFDA were 40%. The percentages of the summed effect explained by each PFAS for small-for-gestational-age were approximately equal to one another (Table 5). Odds of preterm birth and term low birth weight were both elevated for the summed effect of PFAS: 1.45 (95% HPD: 0.82, 2.55) and 1.04 (95% HPD: 1.00, 1.07), respectively. Among those with low PSS, associations between PFAS and each birth outcome were consistent and stronger than for those with high PSS, although all 95% HPD included the null (Table 4).

Associations between most PFAS and birth outcomes were stronger among female compared with male infants. Eight of 30 interaction terms had $p < 0.1$, and three of those with $p < 0.05$ are noted here. Among female infants, PFOA, PFOS, and PFNA were associated with decreased birthweight-for-gestational-age ($\beta_{PFNA} = -0.29$; 95% CI: −0.46, −0.12). Decreased odds of large-for-gestational-age were also stronger in females for several PFAS ($OR_{PFOA} = 0.54$; 95% CI: 0.31, 0.93; $OR_{PFNA} = 0.38$; 95% CI: 0.22, 0.66; $OR_{PFDA} = 0.39$; 95% CI: 0.22, 0.69) (Table 6).

When stratified by trimester of exposure, some results were stronger in the first trimester for PFNA and PFDA and birthweight-for-gestational-age (Table S7). The estimates were less precise, and study populations differed between trimesters, with fewer participants in the third trimester.

When each cohort was removed from the pooled analysis at a time, most of the results were similar (Figure S5). In some cases, excluding the Project Viva, Atlanta, or Maternal And Developmental Risks from Environmental and Social Stressors cohorts influenced the results in various directions, but the results were overall consistent.

In general, associations of PFAS quartiles were consistent with the continuous main results for birthweight-for-gestational-age z-scores and risk of large-for-gestational-age. Quartile analyses showed associations with increased odds of preterm birth when exposed to the highest quartile of PFOA (OR = 2.87; 95% CI: 1.28, 6.44) and PFNA (OR = 1.74; 95% CI: 1.05, 2.89) (Figure S6, Table S8), where continuous associations were in the same direction with 95% CIs that included the null (Table 3). When using a mixed effects model, allowing for random effects by cohort, we not see notable changes in either point estimates or CIs (Table S9). Results did not differ when adjusted for prenatal exposure to tobacco smoke, which included maternal smoking and secondhand smoke during pregnancy (Table S10). Estimates of changes in birthweight (in grams) associated with an interquartile increase in PFAS (not log transformed) showed consistent results in terms of directionality of the association (Table S11). The largest decrements in birthweight were associated with increases in PFNA (β = −15.99; 95% CI: −29.77, −2.22) and PFDA (β = −15.76; 95% CI: −26.81, −4.71) (Table S11).

Discussion

This is the largest study, to the best of our knowledge, in the United States of pregnancy exposures to PFAS and adverse birth

Table 3. Associations of prenatal natural log-transformed PFAS (ng/mL) and birth outcomes stratified by perceived stress study population among selected ECHO cohorts.

	Birthweight-for-gestational-age z-scores		Small-for-gestational-age[a]		Large-for-gestational-age[a]		Term low birth weight		Preterm birth		Gestational age at birth (wk)	
PFAS	*N*	β (95% CI)	*N*	OR (95% CI)	*N*	OR (95% CI)	*N*	OR (95% CI)	*N*	OR (95% CI)	*N*	β (95% CI)
PFOA												
Pooled	1,830	−0.18 (−0.32, −0.05)	1,658	1.04 (0.66, 1.64)	1,620	0.54 (0.33, 0.88)	1,628	1.30 (0.40, 4.19)	1,766	1.72 (1.05, 2.82)	1,831	−0.21 (−0.44, 0.02)
Low PSS	900	−0.19 (−0.37, −0.00)	804	0.97 (0.53, 1.79)	797	0.53 (0.28, 1.01)	673	0.98 (0.20, 4.71)	839	1.56 (0.82, 2.98)	901	−0.14 (−0.44, 0.15)
High PSS	930	−0.18 (−0.38, 0.03)	842	1.16 (0.57, 2.38)	813	0.66 (0.31, 1.41)	599	3.56 (0.41, 30.66)	904	1.94 (0.88, 4.24)	930	−0.32 (−0.67, 0.04)
p-Value[b]		0.95		0.41		0.80		0.13		0.18		0.22
PFOS												
Pooled	1,830	−0.08 (−0.25, 0.09)	1,658	0.92 (0.55, 1.54)	1,620	0.88 (0.48, 1.61)	1,628	0.96 (0.29, 3.14)	1,766	1.50 (0.79, 2.85)	1,831	−0.11 (−0.39, 0.16)
Low PSS	900	−0.14 (−0.39, 0.11)	804	1.57 (0.73, 3.38)	797	0.83 (0.35, 1.97)	673	0.62 (0.13, 2.98)	839	1.98 (0.74, 5.29)	901	−0.14 (−0.54, 0.26)
High PSS	930	−0.01 (−0.24, 0.22)	842	0.52 (0.26, 1.04)	813	1.12 (0.46, 2.73)	599	1.70 (0.28, 10.20)	904	1.24 (0.53, 2.93)	930	−0.12 (−0.51, 0.27)
p-Value[b]		0.37		0.06		0.70		0.19		0.94		0.58
PFNA												
Pooled	1,830	−0.22 (−0.35, −0.08)	1,658	1.11 (0.71, 1.73)	1,620	0.54 (0.33, 0.88)	1,628	1.83 (0.57, 5.90)	1,766	1.71 (1.03, 2.85)	1,831	−0.16 (−0.39, 0.07)
Low PSS	900	−0.33 (−0.53, −0.14)	804	1.76 (0.94, 3.30)	797	0.49 (0.25, 0.98)	673	1.71 (0.38, 7.60)	839	1.92 (0.95, 3.88)	901	−0.23 (−0.54, 0.08)
High PSS	930	−0.08 (−0.28, 0.12)	842	0.67 (0.35, 1.30)	813	0.69 (0.33, 1.46)	599	2.44 (0.39, 15.17)	904	1.59 (0.74, 3.42)	930	−0.11 (−0.45, 0.23)
p-Value[b]		0.23		0.23		0.70		0.23		0.63		0.85
PFHxS												
Pooled	1,830	−0.17 (−0.33, −0.01)	1,658	1.54 (0.91, 2.59)	1,620	0.66 (0.38, 1.14)	1,628	0.78 (0.24, 2.50)	1,766	0.98 (0.52, 1.81)	1,831	0.06 (−0.21, 0.32)
Low PSS	900	−0.16 (−0.40, 0.07)	804	1.27 (0.59, 2.75)	797	0.47 (0.22, 1.03)	673	0.28 (0.05, 1.44)	839	1.87 (0.73, 4.81)	901	−0.03 (−0.41, 0.35)
High PSS	930	−0.15 (−0.37, 0.07)	842	1.87 (0.89, 3.91)	813	1.13 (0.51, 2.49)	599	1.94 (0.33, 11.54)	904	0.53 (0.23, 1.23)	930	0.16 (−0.22, 0.54)
p-Value[b]		0.41		0.86		0.09		0.15		0.11		0.87
PFDA												
Pooled	1,781	−0.23 (−0.38, −0.08)	1,610	1.08 (0.68, 1.74)	1,576	0.57 (0.32, 1.00)	1,586	2.23 (0.74, 6.68)	1,717	1.38 (0.81, 2.34)	1,782	−0.09 (−0.34, 0.16)
Low PSS	874	−0.32 (−0.53, −0.11)	778	1.28 (0.67, 2.46)	775	0.44 (0.20, 0.96)	648	1.00 (0.19, 5.34)	813	1.27 (0.61, 2.63)	875	−0.28 (−0.61, 0.06)
High PSS	907	−0.12 (−0.34, 0.10)	820	0.86 (0.43, 1.73)	791	0.83 (0.36, 1.93)	582	5.25 (1.08, 25.64)	881	1.42 (0.65, 3.13)	907	0.15 (−0.22, 0.53)
p-Value[b]		0.42		0.56		0.38		0.07		0.79		0.06

Note: Pooled rows represent the combined high and low PSS groups for comparison. Beta coefficients (βs) and ORs represent 1 log-unit increase in PFAS concentration (ng/mL) and are presented with 95% CIs. Low PSS, below-median PSS t-scores. High PSS, above-median PSS t-scores. Models were adjusted for cohort, maternal race/ethnicity (Hispanic, non-Hispanic White, Black, Asian, other), for maternal educational attainment (<high school, high school degree/GED, some college, bachelor's degree or higher), maternal age at delivery (<25, 25–29, 30–34, ≥35 y), parity (0, ≥1). CI, confidence interval; ECHO, Environmental influences on Child Health Outcomes; GED, General Educational Development; OR, odds ratio; PFAS, per- and polyfluoroalkyl substances; PFDA, perfluorodecanoic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; PSS, perceived stress scale.

[a]Appropriate-for-gestational-age is the referent from both small- and large-for-gestational age estimates.

[b]*p*-Value of interaction term (PSS × PFAS).

Table 4. Estimates of the Risk Difference (RD) from Bayesian Weighted Sums analysis of selected prenatal natural log-transformed PFAS (ng/mL) and risk of adverse birth outcomes in 11 selected ECHO cohorts.

	Birthweight-for-gestational-age *z*-scores			Small-for-gestational-age[a]			Large-for-gestational-age[a]			Preterm birth			Term low birth weight			Gestational age at birth (weeks)		
Categories	RD	95% HPD	*N*	OR	95% HPD	*N*	OR	95% HPD	*N*	OR	95% HPD	*N*	OR	95% HPD	*N*	RD	95% HPD	*N*
Summed effect	−0.28	(−0.44, −0.14)	3,083	1.13	(0.68, 1.83)	2,734	0.49	(0.29, 0.82)	2,776	1.45	(0.82, 2.55)	3,086	1.04	(1.00, 1.07)	3,086	−0.23	(−0.51, 0.05)	3,086
Low PSS	−0.41	(−0.68, −0.14)	878	1.39	(0.52, 3.48)	782	0.31	(0.11, 0.79)	788	2.03	(0.73, 5.54)	879	1.03	(0.97, 1.09)	879	−0.24	(−0.69, 0.20)	879
High PSS	−0.15	(−0.43, 0.12)	911	0.80	(0.31, 2.17)	836	0.67	(0.24, 1.81)	805	1.56	(0.53, 4.93)	911	1.06	(1.00, 1.12)	911	−0.08	(−0.58, 0.42)	911

Note: Model was adjusted for cohort, maternal race/ethnicity (Hispanic, non-Hispanic White, Black, Asian, other), for maternal educational attainment (<high school, high school degree/GED, some college, Bachelor's degree or higher), maternal age at delivery (<25, 25–29, 30–34, ≥35 years), parity (0, 1+). RDs and ORs represent 1 log unit increase in PFAS concentrations (ng/mL) and are presented with 95% HDP. ECHO, Environmental influences on Child Health Outcomes; GED, General Educational Development, HDP, highest posterior density; OR, odds ratio; PFAS, per-and polyfluoroalkyl substances; PFDA, perfluorodecanoic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; RD, risk difference.
[a]Appropriate-for-gestational-age is the referent from both small- and large-for-gestational age estimates.

Table 5. Weights of each PFAS in Bayesian Weighted Sums analysis of selected prenatal natural log-transformed PFAS (ng/mL) and risk of adverse birth outcomes in 11 selected ECHO cohorts.

	Birthweight-for-gestational-age *z*-scores		Small-for-gestational-age[a]		Large-for-gestational-age[a]		Preterm birth		Term low birth weight		Gestational age at birth (weeks)	
Categories	Weights	95% HPD	Weights	95% HPD	Weights	95% HPD	Weights	95% HPD	Weights	95% HPD	Weights	95% HPD
Summed effect												
PFOA	0.15	(0.00, 0.38)	0.20	(0.00, 0.51)	0.13	(0.00, 0.35)	0.22	(0.00, 0.57)	0.24	(0.00, 0.58)	0.26	(0.00, 0.61)
PFOS	0.12	(0.00, 0.34)	0.21	(0.00, 0.55)	0.11	(0.00, 0.30)	0.19	(0.00, 0.49)	0.16	(0.00, 0.42)	0.20	(0.00, 0.51)
PFNA	0.22	(0.00, 0.52)	0.20	(0.00, 0.53)	0.23	(0.00, 0.55)	0.22	(0.00, 0.55)	0.18	(0.00, 0.46)	0.20	(0.00, 0.53)
PFHxS	0.10	(0.00, 0.27)	0.20	(0.00, 0.53)	0.14	(0.00, 0.37)	0.16	(0.00, 0.45)	0.13	(0.00, 0.37)	0.14	(0.00, 0.40)
PFDA	0.40	(0.02, 0.71)	0.20	(0.00, 0.52)	0.40	(0.03, 0.74)	0.20	(0.00, 0.50)	0.29	(0.00, 0.62)	0.20	(0.00, 0.51)
Low PSS												
PFOA	0.14	(0.00, 0.39)	0.17	(0.00, 0.47)	0.18	(0.00, 0.46)	0.19	(0.00, 0.50)	0.20	(0.00, 0.52)	0.19	(0.00, 0.49)
PFOS	0.13	(0.00, 0.36)	0.21	(0.00, 0.56)	0.13	(0.00, 0.37)	0.19	(0.00, 0.51)	0.18	(0.00, 0.47)	0.18	(0.00, 0.49)
PFNA	0.30	(0.00, 0.63)	0.22	(0.00, 0.57)	0.19	(0.00, 0.47)	0.24	(0.00, 0.57)	0.22	(0.00, 0.54)	0.22	(0.00, 0.55)
PFHxS	0.18	(0.00, 0.44)	0.20	(0.00, 0.52)	0.27	(0.00, 0.58)	0.20	(0.00, 0.51)	0.19	(0.00, 0.49)	0.17	(0.00, 0.47)
PFDA	0.24	(0.00, 0.54)	0.19	(0.00, 0.50)	0.22	(0.00, 0.53)	0.18	(0.00, 0.47)	0.21	(0.00, 0.52)	0.24	(0.00, 0.58)
High PSS												
PFOA	0.22	(0.00, 0.56)	0.17	(0.00, 0.49)	0.21	(0.00, 0.53)	0.24	(0.00, 0.57)	0.22	(0.00, 0.54)	0.23	(0.00, 0.60)
PFOS	0.17	(0.00, 0.47)	0.24	(0.00, 0.60)	0.18	(0.00, 0.49)	0.19	(0.00, 0.50)	0.16	(0.00, 0.44)	0.20	(0.00, 0.53)
PFNA	0.19	(0.00, 0.50)	0.20	(0.00, 0.52)	0.22	(0.00, 0.56)	0.21	(0.00, 0.53)	0.17	(0.00, 0.46)	0.19	(0.00, 0.51)
PFHxS	0.22	(0.00, 0.54)	0.19	(0.00, 0.54)	0.19	(0.00, 0.50)	0.17	(0.00, 0.48)	0.14	(0.00, 0.38)	0.19	(0.00, 0.52)
PFDA	0.21	(0.00, 0.53)	0.20	(0.00, 0.53)	0.20	(0.00, 0.51)	0.20	(0.00, 0.51)	0.31	(0.00, 0.67)	0.19	(0.00, 0.51)

Note: Model was adjusted for cohort, maternal race/ethnicity (Hispanic, non-Hispanic White, Black, Asian, other), for maternal educational attainment (<high school, high school degree/GED, some college, Bachelor's degree or higher), maternal age at delivery (<25, 25–29, 30–34, ≥35 years), parity (0, 1+). RDs and ORs represent 1 log unit increase in PFAS concentrations (ng/mL) and are presented with 95% HDP. ECHO, Environmental influences on Child Health Outcomes; GED, General Educational Development; HDP, highest posterior density; OR, odds ratio; PFAS, per-and polyfluoroalkyl substances; PFDA, perfluorodecanoic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; RD, risk difference.
[a]Appropriate-for-gestational-age is the referent from both small- and large-for-gestational age estimates.

Table 6. Associations of prenatal natural log-transformed PFAS concentrations (ng/mL) and risk of adverse birth outcomes stratified by infant sex in selected ECHO cohorts.

	Birthweight-for-gestational-age z-scores		Small-for-gestational-age[a]		Large-for-gestational-age[a]		Term low birth weight		Preterm birth		Gestational age at birth (wk)	
PFAS	*N*	β (95% CI)	*N*	OR (95% CI)	*N*	OR (95% CI)	*N*	OR (95% CI)	*N*	OR (95% CI)	*N*	β (95% CI)
PFOA												
Male	1,525	−0.12 (−0.29, 0.05)	1,344	1.23 (0.67, 2.24)	1,378	1.11 (0.62, 1.98)	1,028	1.78 (0.29, 11.05)	1,487	1.69 (0.95, 3.03)	1,526	−0.19 (−0.49, 0.11)
Female	1,574	−0.18 (−0.35, −0.02)	1,407	0.93 (0.55, 1.58)	1,398	0.54 (0.31, 0.93)	1,441	1.25 (0.37, 4.23)	1,556	1.04 (0.56, 1.91)	1,576	−0.22 (−0.52, 0.08)
p-Value[b]		0.06		0.66		0.03		0.26		0.54		0.24
PFOS												
Male	1,525	−0.06 (−0.27, 0.14)	1,344	0.92 (0.47, 1.78)	1,378	1.30 (0.67, 2.53)	1,028	0.56 (0.08, 3.80)	1,487	1.36 (0.64, 2.88)	1,526	−0.20 (−0.56, 0.15)
Female	1,574	−0.21 (−0.39, −0.02)	1,407	1.14 (0.62, 2.10)	1,398	0.60 (0.31, 1.16)	1,441	1.41 (0.41, 4.92)	1,556	1.05 (0.49, 2.25)	1,576	−0.08 (−0.42, 0.26)
p-Value[b]		0.04		0.07		0.16		0.28		0.16		0.21
PFNA												
Male	1,525	−0.14 (−0.31, 0.03)	1,344	1.09 (0.61, 1.95)	1,378	0.84 (0.47, 1.51)	1,028	1.16 (0.22, 6.24)	1,487	1.74 (0.96, 3.13)	1,526	−0.27 (−0.57, 0.03)
Female	1,574	−0.29 (−0.46, −0.12)	1,407	1.05 (0.62, 1.79)	1,398	0.38 (0.22, 0.66)	1,441	1.81 (0.53, 6.24)	1,556	1.02 (0.54, 1.90)	1,576	−0.04 (−0.34, 0.26)
p-Value[b]		0.04		0.92		<0.01		0.12		0.92		0.89
PFHxS												
Male	1,525	−0.05 (−0.23, 0.13)	1,344	1.17 (0.62, 2.19)	1,378	0.91 (0.53, 1.56)	1,028	0.19 (0.03, 1.18)	1,487	0.96 (0.49, 1.90)	1,526	0.11 (−0.19, 0.42)
Female	1,574	−0.05 (−0.22, 0.11)	1,407	1.30 (0.77, 2.21)	1,398	0.85 (0.50, 1.46)	1,441	1.98 (0.70, 5.64)	1,556	0.92 (0.47, 1.80)	1,576	−0.04 (−0.33, 0.25)
p-Value[b]		0.35		0.13		0.87		0.04		0.61		0.21
PFDA												
Male	1,496	−0.20 (−0.37, −0.03)	1,316	1.19 (0.67, 2.13)	1,353	0.69 (0.40, 1.21)	1,005	1.68 (0.32, 8.93)	1,458	1.32 (0.73, 2.38)	1,497	−0.20 (−0.50, 0.09)
Female	1,551	−0.31 (−0.47, −0.14)	1,384	1.12 (0.67, 1.87)	1,376	0.39 (0.22, 0.69)	1,419	2.23 (0.80, 6.26)	1,533	1.09 (0.59, 2.00)	1,553	−0.04 (−0.33, 0.26)
p-Value[b]		0.34		0.87		0.08		0.36		0.86		0.64

Note: Models were adjusted for cohort (dummy variables), maternal race/ethnicity (Hispanic, non-Hispanic White, Black, Asian, other), for maternal educational attainment (<high school, high school degree/GED, some college, bachelor's degree or higher), maternal age at delivery (<25, 25–29, 30–34, ≥35 y), parity (0, ≥1). CI, confidence interval; ECHO, Environmental influences on Child Health Outcomes; GED, General Educational Development; OR, odds ratio; PFAS, per- and polyfluoroalkyl substances; PFDA, perfluorodecanoic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid.

[a]Appropriate-for-gestational-age is the referent from both small- and large-for-gestational age estimates.

[b]*p*-Value of interaction term (infant sex × PFAS).

outcomes. We found that higher levels of several PFAS were associated with lower birthweight-for-gestational-age z-scores and lower risk of being large-for-gestational-age. Associations between PFAS and preterm birth and term low birth weight were also observed, although results were less robust.

Associations between PFAS and birth outcomes were not modified by perceived stress. These findings were unexpected because of our hypothesis that exposure to chemical and social stressors would result in stronger associations; however, given the known associations between stress and birthweight, the additional effect of PFAS may be minimal.[59]

The ECHO study population for this analysis included pregnancies from 11 cohorts in seven states across the United States. This unique and demographically diverse study population enabled us to examine five PFAS measured prenatally and their association with continuous and categorical birth outcomes related to gestational age and birthweight. Statistical power allowed for stratified analyses to explore potential effect modifiers and sensitivity analyses to explore potential bias stemming from timing during pregnancy, assumptions of linearity or threshold effects, additional confounders, and influence by different cohorts spanning time and place.

In our study, birth years of the children spanned 21 years (1999–2019), during which time there was an overall decrease in exposures to PFAS owing to the phase-out of some PFAS. Correlations were generally high across trimesters, providing evidence that PFAS levels remain relatively consistent across pregnancy. Our analysis removing one cohort at a time showed that a few cohorts deviated from the pattern, but overall they were notably consistent. Their results were published previously,[30] as were results for several other individual cohorts, including Chemicals in Our Bodies, Illinois Kids Development Studies, and Healthy Start.[31,60–62]

Our findings of lower birthweight-for-gestational-age z-scores confirm previous studies wherein PFAS were associated with lower birthweight-for-gestational-age, intrauterine growth restriction, and small-for-gestational-age, and reduced fetal growth.[16,27,32,60] Our findings overall support a shift in the distribution of birthweight toward decreased birth size measured continuously (i.e., birthweight-for-gestational-age z-scores) and categorically (i.e., large-for-gestational-age) and are suggestive of increased risk of preterm birth.

Despite some inconsistencies in previous studies and meta-analyses, our findings confirm the recent report from the National Academy of Science (NAS) stating there is sufficient evidence of an association between PFAS and decreased infant and fetal growth, which weighted evidence based on low risk of bias.[63] For example, two meta-analyses of birthweight in relation to PFOA[64] and PFOS[65] found decreases in birthweight, which is consistent with our results; notably, when restricted to studies earlier in pregnancy, associations in these meta-analyses were null. In contrast, results of our study show stronger associations between increased PFOA in the first trimester and lower birthweight-for-gestational-age z-scores and increased risk of term low birth weight and small-for-gestational-age. There are several possibilities as to why these meta-analyses may differ, such as the inclusion of studies that did not adjust for gestational age and/or parity, were cross-sectional in design, were conducted in study populations outside of the United States, or were driven by a single study.[64,65] Among samples with PFAS exposures at multiple times in pregnancy in our study, concentrations were strongly correlated across trimesters (Table S4). Glomerular filtration rate (GFR) has been suggested as a confounder of trimester-specific associations of PFAS with birth outcomes; however, a recent systematic analysis of the PFAS literature by the NAS found that the available evidence of

PFAS on GFR were insufficient to determine a relationship.[63] Further, the Project Viva cohort included in this study previously found that GFR did not confound the relationship between PFAS and birth outcomes.[30] GFR levels were not available for other cohorts; however, if GFR were to confound the PFAS-birthweight relationship, it would be expected to do so later in pregnancy. Our trimester-specific analysis did not support this potential confounding or reverse causality. Finally, effects on birthweight have been found in multiple animal species including mouse, rat, zebrafish, and fruit flies.[66]

Our study found an association between PFOS and preterm birth consistent with prior work,[30,67,68] including a recent review and meta-analysis showing a linear positive association between PFOS and risk of preterm birth[32]; however, our results were not as precisely estimated. Given that preterm birth is a multifactorial outcome and PFAS may contribute to a small risk increase, large studies (and/or highly exposed participants) are needed to find such effects.

Our findings are consistent with a previous study in which associations between PFAS and birthweight-for-gestational-age z-scores were stronger among females,[27] but they contradict another study that found stronger associations among males.[69] Biological mechanisms by which PFAS may affect birth outcomes are largely unknown, but research has investigated potential pathways including endocrine disruption,[70] systemic inflammation,[71] metabolic dysfunction,[72] placental function,[73] and epigenetic changes.[74]

Despite our large sample size, uncertainties in our estimates remain. Our study was limited to participants with nonmissing data on key variables. In addition, some PFAS were not able to be examined because levels were below the LOD. As legacy PFAS are phased out and replaced with alternative PFAS, our studies must be updated with changing levels to be examined in relation to multifactorial health outcomes. Methodologically, there is no agreed-upon approach to evaluate the effects of PFAS, or other chemicals, as a mixture. Our Bayesian Weighted Sums approach assumes linearity of the summed effect of PFAS, which appeared defensible based on the results exploring effects of PFAS by exposure quartiles (Table S8, Figure S6).

Future studies can address some of these limitations. A large study such as ECHO may be able to better investigate mediation effects of prepregnancy BMI and maternal conditions, such as gestational diabetes and hypertensive disorders in pregnancy, that may be on the causal pathway between PFAS and fetal growth once more of those data become available. Similarly, future studies can examine interaction with other environmental chemicals. Furthermore, birthweight is a single measurement in time, and further studies are needed to investigate the potential impact of PFAS on infant and child health outcomes.

In conclusion, we found that maternal PFAS concentrations during pregnancy are associated with lower birthweight-for-gestational-age z-scores and suggestive of an association with preterm birth. These associations are consistent with previous studies showing decreased birth weight/fetal growth. Associations were stronger among females, although fewer previous studies were able to confirm these findings. We did not find these associations to differ between mothers with high vs. low perceived stress. Given the persistence of PFAS in the environment and human bodies, ubiquitous exposure, and the transfer of maternal PFAS *in utero* and during breastfeeding, disruption of fetal growth remains a health threat in offspring and needs to be addressed as part of efforts evaluating interventions and prevention.

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G.B.H, X.N., and S.B. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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