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Detected prenatal perfluorooctanoic acid (PFOA) exposure is associated with decreased fetal head biometric parameters in participants experiencing higher perceived stress during pregnancy in the MADRES cohort

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Abstract

Background: Perfluoroalkyl substances (PFAS) are ubiquitous synthetic chemicals with long half-lives and are known to cross the placenta during pregnancy. We examined the influence of

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CRediT authorship contribution statement

Alicia K. Peterson: Conceptualization, Data curation, Formal analysis, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Sandrah P. Eckel:** Methodology, Writing – review & editing. **Rima Habre:** Methodology, Writing – review & editing. **Tingyu Yang:** Data curation, Software, Writing – review & editing. **Dema Faham:** Data curation, Writing – review & editing. **Monica Amin:** Data curation, Writing – review & editing. **Brendan H. Grubbs:** Methodology, Writing – review & editing. **Shohreh F. Farzan:** Methodology, Writing – review & editing. **Kurunthachalam Kannan:** Data curation, Writing – review & editing. **Morgan Robinson:** Data curation, Writing – review & editing. **Deborah Lerner:** Methodology, Writing – review & editing. **Laila A. Al-Marayati:** Methodology, Writing – review & editing. **Daphne K. Walker:** Methodology, Writing – review & editing. **Edward G. Grant:** Methodology, Writing – review & editing. **Carrie V. Breton:** Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing – review & editing. **Theresa M. Bastain:** Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing – review & editing.

Supplementary materials

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Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Potential conflict of interest exists:

maternal PFAS levels on *in utero* fetal growth trajectories and assessed whether maternal stress modified these associations.

Methods: Blood serum concentrations of five PFAS (PFOS, PFHxS, PFNA, PFOA, PFDA) were measured in 335 prenatal specimens (mean gestational age (GA): 21±9 weeks) in the MADRES cohort. Fetal growth outcomes (head circumference (HC), abdominal circumference (AC), biparietal diameter (BPD), femur length (FL), and estimated fetal weight (EFW)) were abstracted from ultrasound medical records and measured at the 3rd trimester study visit (N = 833 scans, GA range 10–42 weeks, mean 2.4 scans/participant). Adjusted linear mixed models with a GA quadratic growth curve were used for each PFAS exposure and growth outcome. PFOS and PFHxS were modeled continuously (100% sample detection), while PFOA, PFNA, and PFDA were modeled categorically (57–70% sample detection). Scores on the Perceived Stress Scale (PSS) measured in pregnancy were dichotomized at the median (<13 vs. ≥ 13) in stratified models.

Results: Participants were on average 29±6 years old and predominately Hispanic (76%). Median serum concentrations of PFOS, PFHxS, PFNA, PFOA and PFDA were 1.34, 1.10, 0.07, 0.12, and 0.04 ng/mL, respectively. Participants with detected PFOA concentrations had fetuses with −2.5 mm (95% CI −4.2, −0.8) smaller HC and−0.7 mm (95% CI −1.3, −0.2) smaller BPD on average for a fixed GA than those without detected PFOA concentrations. In models stratified by PSS level, the effects of PFOA on fetal growth parameters were stronger and only significant in participants with higher stress levels (HC: β= −3.5, 95% CI −5.8, −1.4; BPD: β = −0.8, 95% CI −1.6, −1.1).

Conclusions: Prenatal PFOA exposure adversely impacted fetal head biometric parameters in participants experiencing higher stress during pregnancy.

Keywords

PFAS; PFOA; Fetal growth; Health disparities; Stress; Pregnancy

1. Introduction

Per –and polyfluoroalkyl substances (PFAS) are a class of synthetic chemicals that consists of over 4,700 separate compounds (Sinclair et al., 2020). Due to their oil and water resistant qualities, they have been commonly used in a wide range of items including non-stick cookware, shampoos, waterproof clothing, fire-fighting foam and fast food packaging (Sinclair et al., 2020; Dauchy et al., 2017; Schaider et al., 2017). The strong and stable bond created between carbon and fluorine (Ding and Peijnenburg, 2013) make these compounds persistent in the environment and the most common exposure route to humans is through ingestion (i.e. dietary fish intake and drinking water) (De Silva et al., 2021). Given their association with numerous health problems (Bassler et al., 2019; Chen et al., 2018; Chou et al., 2017; Zeng et al., 2019) perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) were phased out of production in the United States in the early 2000s (EPA, 2010). However, due to the long half-lives of PFAS (Olsen et al., 2007), these compounds as well as other PFAS have been found in >99% of blood samples from American adults and children within the National Health and Nutrition Examination Survey (NHANES) study population in recent years (Calafat et al., 2007; Ye et al., 2018).

A particularly susceptible period of exposure to PFAS may be during pregnancy due to the biological changes occurring in the mother (Varshavsky et al., 2020) as well as the ability for PFAS to cross the placental barrier to reach the fetus and bioaccumulate in the placenta (Blake and Fenton, 2020; Mamsen et al., 2019). Implications of PFAS exposure for fetal growth are important to understand, as fetal development may predict health outcomes across the life course. Low birthweight (<2500 g) increases risk for metabolic health conditions later in life (Barker et al., 1993, 2005; Gluckman et al., 2008) and *in utero* growth parameters including head circumference and abdominal circumference are significantly associated with childhood cognitive outcomes and obesity risk (Bartels et al., 2020; Rückinger et al., 2010; Von Ehrenstein et al., 2009). Substantial literature reflected through meta-analyses have indicated that exposure to PFAS, particularly PFOA and PFOS, during pregnancy is associated with lower infant birthweight (Bach et al., 2015; Dzierlenga et al., 2020; Negri et al., 2017; Steenland et al., 2018), however, there are few studies that have explored the influence on growth *in utero* by standard ultrasound biometry measurements of fetal head circumference, biparietal diameter, abdominal circumference, femur length, and estimated fetal weight (Costa et al., 2019; Ouidir et al., 2020).

Pregnant persons of non-Hispanic Black and Hispanic populations have higher rates of low birthweight infants compared to their non-Hispanic white counterparts (Osterman et al., 2021). In some studies, PFAS levels have also differed by racial and ethnic groups. A study conducted within NHANES found that PFOS levels were highest in non-Hispanic Black persons, followed by non-Hispanic white persons, and lowest in Mexican-American individuals (Calafat et al., 2007). In contrast, a small cohort of middle aged women (N = 178) found levels of PFOA and perfluorohexanesulfonic acid (PFHxS) to be higher in non-Hispanic white women compared to Black women. A United States cohort comprised of 12 clinical sites assessed a panel of 11 PFAS analytes and found that pregnant persons who were non-Hispanic white or Asian tended to have higher levels for most analytes compared to Black and Hispanic pregnant persons (Ouidir et al., 2020). However, studies assessing PFAS exposure on fetal growth within health disparities populations and those specifically in Hispanic/Latina populations are currently limited.

Health disparity populations face unique stressors related to structural inequities based on race and ethnicity, discrimination, low-income levels, and negative stereotypes (Williams, 2018). It is well documented that psychological distress such as perceived stress experienced prior to pregnancy and during pregnancy influences adverse pregnancy outcomes including low infant birthweight (Lima et al., 2018; Staneva et al., 2015). Previous research has suggested that multiple exposures to chemicals and psychosocial stress may exhibit a cumulative effect on fetal growth (Vesterinen et al., 2017).

The objective of this study was to assess the influence of five PFAS analytes including PFOS, PFOA, PFHxS, perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA) from a panel of fourteen PFAS analytes quantified during pregnancy on longitudinal fetal growth trajectories of fetal head circumference, biparietal diameter, abdominal circumference, femur length, and estimated fetal weight within a structurally marginalized population. Additionally, this study explored whether perceived stress experienced during pregnancy modified these associations. We hypothesized that participants with higher

prenatal PFAS exposure would have infants with decreased fetal growth trajectories and that pregnant persons with higher stress would be more vulnerable to the health effects of PFAS.

2. Methods

2.1. Study sample

This study included a subset of participants from the ongoing Maternal And Developmental Risks from Environmental and Social Stressors (MADRES) pregnancy cohort. Details related to the study design, protocol, and demographics of the cohort have previously been described (Bastain et al., 2019). Briefly, participants were eligible if they were less than 30 weeks pregnant, at least 18 years of age, and a fluent speaker of English or Spanish. Exclusion criteria for the study included multiple gestation, the inability to participate and provide consent due to a physical, mental or cognitive disability, current incarceration, or human immunodeficiency virus (HIV) positive status. Recruitment occurred during pregnancy from four prenatal clinic sites including two community health centers, one county hospital prenatal clinic, and one private obstetrics and gynecology practice. At time of study enrollment, informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization to access medical records were obtained from each participant and the University of Southern California's Institutional Review Board (IRB) approved all aspects of the study.

Participants from the larger MADRES cohort were included in the current study if the following criteria were met: (1) data were available for PFAS concentrations measured in blood serum, (2) at least one prenatal ultrasound scan with fetal biometry measurements was available, and (3) data on maternal race/ethnicity and fetal sex were present. PFAS concentrations were measured in Spring 2019 in blood serum samples that were collected from 359 participants from December 2015 until February 2019. Of these 359 participants, 344 had at least one prenatal ultrasound (859 total scans). We removed five participants with missing information on race/ethnicity and four participants with missing data on fetal sex resulting in a final sample size of 335 unique participants with a total of 833 ultrasound scans. The consort diagram illustrating those included is shown in Fig. 1.

2.2. Serum PFAS analysis

Maternal blood samples were collected at an in-person study visit (median gestational age 19.0 weeks, range 5.7–38.3 weeks) using red top 10 mL serum tubes. The blood samples were processed and serum was aliquoted and then stored at −80°C until shipment to the Wadsworth Center's Human Health Exposure Assessment Resource (WC-HHEAR) laboratory at NYU Langone Medical Center (Dr. Kannan's laboratory). Fourteen PFAS namely, PFHxS, PFOS, PFOA, PFNA, PFDA, perfluorobutanesulfonic acid (PFBS), perfluoroheptanoic acid (PFHPA), perfluroundecanoic acid (PFUNDA), perfluorododecanoic acid (PFDODA), perfluorooctanesulfonamide (PFOSA), n-ethyl perfluorooctane sulfonamido acetic acid (NETFOSAA), n-methyl perfluorooctane sulfonamido acetic acid (NMFOSAA), perfluoro-n-pentanoic acid (PFPEA), and perfluorohexanoic acid (PFHxA) were analyzed. The method for the analysis of 14 PFAS

in serum has been previously described (Honda et al., 2018) as well as the full methods specifically used in the MADRES cohort for PFAS serum assessment (Peterson et al., 2022).

The limit of detection (LOD) of target analytes ranged from 0.02 to 0.05 ng/mL. Five of the fourteen PFAS had at least 50% of samples above the LOD and were included in subsequent data analysis approaches. The analytes included were PFOS (100% detected), PFHxS (100% detected), PFNA (70% detected), PFOA (65% detected) and PFDA (57% detected).

2.3. Fetal growth assessment

Fetal growth was assessed by transabdominal ultrasound and included five fetal biometry outcomes. Outcomes comprised of two head measurements: (1) head circumference (mm) defined as the length along the skull bone and (2) biparietal diameter (mm) defined as the maximum diameter of a transverse section of the skull. Additionally, we measured femur bone length (mm) and abdominal circumference (mm). These fetal biometry measurements were used to estimate fetal weight (g) using the Hadlock et al. (1985) formula.

Ultrasound data were obtained from two sources. Licensed, certified sonographers conducted study-measured ultrasound scans at the third trimester study visit (≥ 28 weeks gestation) either in the MADRES study clinic by a single technician (86 scans) or at Keck Hospital by two technicians (61 scans). We also abstracted prenatal electronic medical records (EMR) (686 scans). Scans were conducted throughout pregnancy ranging from 9.6 weeks gestation to 41.6 weeks gestation with the majority in the second and third trimesters. Data were from 10 scans taken in the first trimester (<14 weeks gestation), 400 scans in the second trimester (≥14 weeks to <28 weeks gestation) and 423 scans in the third trimester (≥ 28 weeks gestation). The number of scans per participant ranged from 1–8 with a mean of 2.5±1.3. All scans were conducted between December 2015 and August 2019.

2.4. Perceived stress scale

The 10-item Perceived Stress Scale (PSS) (Cohen, 1988) was collected at each trimester study visit via interviewer-administered questionnaire in either Spanish or English. The 10 item PSS scale has been validated and utilized in countless studies worldwide to assess perceived stress (Andreou et al., 2011; Anwer et al., 2020; Bastianon et al., 2020; Dao-Tran et al., 2017; Ezzati et al., 2014; González-Ramírez et al., 2013; Huang et al., 2020; Makhubela, 2020; Manzar et al., 2019; Mondo et al., 2021; Reis et al., 2019; Roberti et al., 2006; Ruisoto et al., 2020; Smith et al., 2014; Soria-Reyes et al., 2022), has been shown to be superior in psychometric properties compared to the 4-item or 14-item PSS scale (Lee, 2012), and has been validated for use within Hispanic populations (Baik et al., 2019). The scale measures the amount of perceived stress experienced by the participant with questions to capture how uncontrollable, unpredictable, and over-loading one's life was within the last month (30 days). Each question was answered with a Likert scale ranging from never (score of 0) to very often (score of 4). The individual answers were then totaled for an overall PSS score ranging from 0 to 40, with higher numbers indicating more perceived stress. The interviewer-administered questionnaire either occurred over the phone (second trimester) or in person in a private study suite (first and third trimester) and we then selected the

trimester-specific PSS score that aligned with the blood collection time point that measured PFAS levels.

2.5. Covariates

Covariates to be included in multivariable models were selected based on current literature. The variables included demographic characteristics, pregnancy related variables, and aspects related to study design.

Demographic variables were race/ethnicity, nativity, level of attained education, annual household income, participant's age at recruitment, pre-pregnancy body mass index (BMI), and any reported personal smoking during pregnancy. All variables were self-reported via interviewer-administered questionnaires in either English or Spanish with the exception of pre-pregnancy BMI in kg/m^2, which was calculated using self-reported pre-pregnancy weight and study measured height with a stadiometer (Perspectives enterprises model PE-AIM-101). Pregnancy related variables included birth order, which was self-reported via interviewer administered questionnaire, fetal sex, which was abstracted from electronic medical records for the majority of participants (96%) or self-reported from the mother (4%) and fish consumption during pregnancy. Dietary fish intake was captured through an interviewer-administered questionnaire collected at the third trimester visit which accessed the frequency of consuming seafood during pregnancy, including fish sticks, fresh oily fish, other fresh fish, canned tuna, and shellfish. A summary variable was created for all fish intake with the following categories: never (62%), monthly (16%), at least weekly (12%), or unknown (10%).

Lastly, variables related to the study design included site of recruitment, ultrasound scan location/technician, gestational age at time of ultrasound scan, and gestational age at time of blood sample for PFAS concentration analysis. Gestational ages at time of blood sample collection and ultrasound scan were calculated by subtracting the number of weeks between the infant's date of birth and the date of the ultrasound or blood sample from the gestational age in weeks at time of birth. Gestational age at birth was calculated and standardized using a hierarchy of methods (Committee on Obstetric Practice, t.A.I.o.U.i.M. and t.S.f.M.-F. Medicine, 2017). A first trimester (<14 weeks gestation) ultrasound measurement of crown-rump length was deemed ideal if available (60%) and if missing, a second trimester (<28 weeks gestation) ultrasound measurement of fetal biparietal diameter was used (27%). If no measurements from an early ultrasound were available, gestational age at birth was established from a physician's best clinical estimate from the EMR (13%).

Covariates were visualized through a directed acyclic graph (DAG) using Dagitty (Textor et al., 2016) and minimal sufficient adjustment sets for estimating the total effect of prenatal PFAS exposure on *in utero* fetal growth consisted of fetal sex, fish consumption, gestational age at blood sample, gestational age at ultrasound, household income, maternal education, nativity, parity, pre-pregnancy BMI and race/-ethnicity (Supplemental Fig. 1).

2.6. Statistical analysis

Distributions of participant demographic and pregnancy characteristics were summarized using means and standard deviations for continuous variables (age, pre-pregnancy BMI,

gestational age at blood sample, gestational age at ultrasound scan) and frequencies and percentages for categorical variables (income, education, race/ethnicity, fetal sex, parity, fish consumption, nativity). The relationships between participant demographics and PFAS levels within the MADRES cohort have previously been reported (Peterson et al., 2022), we additionally assessed participant demographics and PSS level through Pearson's Chi Square tests for categorical variables or two-sample t-tests for continuous variables. Each fetal growth outcome was visualized through spaghetti plots and smoothed scatterplots across gestational weeks to assess growth trends over time.

Linear mixed models were used to evaluate the relationship between PFAS concentrations and each fetal growth outcome. For PFOS and PFHxS, which were detected in 100% of samples, both exposures were modeled continuously with the natural log transformation due to right skewness and to compare results across previous studies. For PFOA, PFNA and PFDA, which had detection percentages ranging from 57 to 70%, exposures were dichotomized and modeled categorically as detected (>LOD) or non-detected (≤LOD). Likelihood ratio tests of nested models were used to determine whether a random slope of gestational age at ultrasound scan was needed in addition to the random intercept for each participant. There was strong evidence to include both random intercepts and slopes ($p < 0.001$) and to allow correlation between them ($p < 0.001$). Additionally, due to the non-linearity of fetal growth outcomes over gestation, gestational age at scan also included a quadratic term, which was significant when comparing nested models ($p < 0.001$). We found no evidence for a statistical interaction between PFAS analytes and gestational age at time of ultrasound scan ($p > 0.05$).

Final models allowed for a quadratic growth curve in gestational age at time of scan, with participant-level random effects, a main fixed effect of PFAS and adjustment for key covariates. Covariates were modeled as follows: gestational age at scan (weeks, centered at 20 weeks), participant age (years), pre-pregnancy BMI (kg/m^2), gestational age at blood sample (weeks), fetal sex (male, female), parity (first born, second or more, missing indicator), race/ethnicity (Hispanic, non-Hispanic Black, non-Hispanic white, non-Hispanic other), annual household income (<$50,000, $50,000–$99,999, ≥$100,000, reported "Do not Know"), education (high school diploma or less, some or completed college, some graduate training), nativity (US born, non-US born, missing indicator), fish consumption during pregnancy (never, monthly, at least weekly, missing indicator), recruitment site indicator and ultrasound source indicator. Personal smoking during gestation was not included as a covariate due to very few participants reporting any smoking (<2%); however, we evaluated the influence of personal smoking by removing these participants in a sensitivity analysis.

To determine if the association of prenatal PFAS exposure on fetal growth trajectories was modified by perceived stress, an interaction term was added to fully adjusted models and we stratified by higher and lower perceived stress. PSS scores were dichotomized at the median score (PSS Median = 13, Range = 0–33); 166 participants (totaling 418 scans) were classified as having "lower perceived stress", and 169 participants (totaling 415 scans) were classified as having "higher perceived stress". Additionally, to further explore potential relationships between PSS and PFAS, Pearson's Chi Square tests (PFOA, PFNA, PFDA) and Wilcoxon Rank Sum tests (PFHxS, PFOS) were implemented.

Several sensitivity analyses were conducted to further evaluate the robustness of results. We first removed scans that were taken prior to the blood sample that measured PFAS (46 participants, 212 scans removed) to assess whether PFAS concentrations measured after the ultrasound scans influenced our results. Additionally, we wanted to determine whether maternal pregnancy complications influenced our results. We first additionally adjusted for existing or gestational hypertension/pre-eclampsia and existing or gestational diabetes that were abstracted from the EMR. Within the sample, 45.3% of participants had either existing or gestational diabetes (33.4%), had either existing or gestational hypertensive disorders (20.3%), or both (8.4%). We then additionally removed participants who had more than five ultrasound scans, which may indicate a higher risk pregnancy (9 participants, 60 scans removed). Lastly, to ensure participants who smoked were not driving our results, participants who reported any smoking during gestation were removed from our models (6 participants, 9 scans removed).

Data management was conducted in SAS Version 9.4 and linear mixed models were estimated using the nlme R package (Pinheiro et al., 2012). All models met assumptions, multi-collinearity assessed from the variance inflation factor (VIF) indicated no concerns, and all tests used two-sided hypotheses with $\alpha = 0.05$.

3. Results

3.1. Participant characteristics

Participants were on average 29±6 years of age at study recruitment, Hispanic (76%), had a high school diploma or less of education (53%), US born (51%) and overweight prior to pregnancy (mean pre-pregnancy BMI: 28±6). The majority of fetuses were male (52%) and were the second or greater child of the participant (62%). Demographic and participant characteristics are shown in Table 1. The only demographic characteristic shown to be associated with PSS level within this study was country of birth, with more participants reporting higher perceived stress for participants born outside of the United States (53%) than those born within the United States (47%) ($p = 0.04$).

3.2. Prenatal serum PFAS concentrations

Five of the fourteen analytes, PFOS, PFHxS, PFNA, PFOA, and PFDA, had at least 50% of samples above the LOD. Of the remaining analytes, the highest percentage of detected samples was 17%. Median concentrations of PFOS, PFHxS, PFNA, PFOA and PFDA were 1.34, 1.10, 0.07, 0.12, 0.04 ng/mL, respectively. The distributions of all measured PFAS concentrations are shown in Table 2.

3.3. Prenatal serum PFAS and fetal growth outcomes

We found that participants who had detectible levels of prenatal PFOA exposure had fetuses with −2.5 mm (95% CI −4.2, −0.8) smaller head circumference on average compared to fetuses of participants without detected prenatal PFOA levels for a fixed gestational age at time of ultrasound. Additionally, participants who had detected levels of prenatal PFOA exposure had fetuses with −0.7 mm (95% CI −1.3, −0.2) smaller biparietal diameter compared to fetuses of participants without detected prenatal PFOA levels for a fixed

gestational age at time of ultrasound. We did not find significant associations with other PFAS and fetal growth outcomes.

We evaluated whether participants experiencing higher compared to lower levels of perceived stress were more vulnerable to the effects of PFOA. When assessing PFOA detection status and PSS level in a Pearson Chi Square test, there was not a significant association between the two variables ($p = 0.13$). However, out of all participants that reported higher stress, there was a higher proportion of those with PFOA detected (Supplemental Table 1). In stratified linear mixed models by perceived stress level, we found that the association between PFOA and biparietal diameter or head circumference was stronger and only significant in participants experiencing higher levels of stress (Head Circumference: $\beta = -3.5$ mm, 95% CI −5.8, −1.3; Biparietal Diameter $\beta = -0.8$ mm, 95% CI −1.6, −0.03) compared to those experiencing lower levels of stress (Figs. 2 and 3) for a fixed gestational age at time of ultrasound. A formal test of interaction was not statistically significant ($p > 0.05$). Supplemental Figs. 2–4 show the remaining non-significant results for prenatal PFAS exposures and other fetal growth outcomes.

Lastly, we assessed the robustness of our results of PFOA on fetal head circumference and fetal biparietal diameter through sensitivity analyses and our conclusions remained consistent. Models that (1) additionally adjusted for hypertension/diabetes, (2) removed participants who had more than five ultrasound scans, (3) removed participants with any reported personal gestational smoking, and (4) removed scans that had been conducted before the blood sample was collected are shown in Supplemental Fig. 5.

4. Discussion

This study found that participants with detected levels of PFOA measured during gestation had fetuses with reduced growth trajectories for both head circumference and biparietal diameter when compared to participants who did not have PFOA detected within their blood serum for a fixed gestational age at time of ultrasound. Additionally, associations were modified by maternal perceived stress during pregnancy with significant inverse associations only observed in mothers reporting higher levels of perceived stress. We also found that many PFAS compounds analyzed within the MADRES sample had limited to no detection and were lower than levels in other pregnancy cohorts with the exception of PFHxS, which was typically higher (Costa et al., 2019; Ouidir et al., 2020; Woodruff et al., 2011).

Reaching adequate fetal growth milestones across gestation is a critical component of a healthy pregnancy and reduced fetal growth has been shown to predict later life adverse outcomes. Several studies have shown larger *in utero* fetal head circumference, still in normal ranges, to be associated with positive childhood neurodevelopment reflected through cognitive, language and visual skills, as well as intelligence quotient (IQ) (Von Ehrenstein et al., 2009; Gale et al., 2006; Villar et al., 2021). Research has suggested that environmental exposures in pregnancy could disrupt fetal growth, potentially leading to negative downstream effects (Zheng et al., 2016).

Our results are consistent with other studies that have quantified the association of prenatal PFOA exposure on head circumference at birth (Apelberg et al., 2007; Xiao et al., 2020). Two studies have explored the association of prenatal PFAS exposure on fetal growth measured *in utero* and the results have been conflicting (Costa et al., 2019; Ouidir et al., 2020). A multi-site US based cohort among higher education and higher income women with low-risk pregnancies assessed 11 PFAS analytes and found prenatal PFAS exposure to be significantly associated with femur length, although depending on the analyte, both positive (NMeFOSAA, PFDA, PFHpA, PFHxS, PFNA, PFOA) and negative associations (PFOSA, PFDS) were observed (Ouidir et al., 2020). No significant associations were observed with biparietal diameter or fetal head circumference (Ouidir et al., 2020). A study in Spain among higher education and higher income women found no significant main effects between PFAS exposure and fetal growth outcomes, but showed evidence for effect modification by maternal smoking status with smoking mothers having significantly decreased fetal femur length and estimated fetal weight with PFOA and PFNA exposure (Costa et al., 2019). No significant associations were observed with fetal biparietal diameter, and head circumference was not included within the study (Costa et al., 2019).

Although there is evidence that psychosocial stress and chemical exposures during pregnancy may produce joint effects on fetal growth (Vesterinen et al., 2017), no studies to date have assessed whether maternal perceived stress modifies the influence of prenatal PFAS exposure on fetal growth measured *in utero*. One study used a mixture approach of prenatal PFAS exposure and maternal stressors (perceived stress and depression) through quantile g-computation and observed an inverse association with the PFAS and stress mixture and birthweight z-scores, although it did not reach statistical significance (Eick et al., 2022). Two studies have shown that prenatal PFAS exposure influences corticotrophin-releasing hormone and cortisone levels in pregnancy (Dreyer et al., 2020; Eick et al., 2022), suggesting that stress may be an important effect modifier for PFAS exposure effects. Future studies should further investigate how maternal stress and PFAS interact to impact fetal growth, particularly in populations experiencing greater health disparities who also tend to have higher exposures to environmental contaminants and may face a unique constellation of stressors (Williams, 2018; Nguyen et al., 2020).

The current study has several strengths. First, the study population is comprised of an underrepresented group in the literature of predominately low-income Hispanic participants who traditionally have been excluded from previous research. Additionally, several PFAS were assessed, including PFNA, PFDA, and PFHxS, which have not been as comprehensively studied as PFOA and PFOS. This study also examined the relationship of these analytes on longitudinal fetal growth trajectories measured across pregnancy, rather than on birth outcomes. Lastly, this is one of the first studies to explore how perceived stress experienced in pregnancy modifies the association with PFAS on fetal growth and suggests that women with higher stress and higher PFOA levels face larger adverse impacts on fetal development.

Limitations also exist within this study. First, PFAS concentrations were measured only once within pregnancy, which limited our ability to assess how these levels changed across gestation and samples were not limited to a single trimester for blood serum collection.

This study assumed that PFAS levels were relatively stable across pregnancy due to their long half-lives. A previous study with PFOA and PFOS levels measured from blood serum in both the first and second trimester found a high degree of correlation between the two time points (Fei et al., 2007). An additional study with blood samples taken at all three trimesters of pregnancy found PFOA, PFOS, PFNA, and PFDA to slightly decrease over pregnancy while PFHxS remained stable (Chen et al., 2021). Additionally, we were limited in our modeling approaches as several analytes measured in the panel were not detected or had very low detection. Nine of the fourteen measured analytes were excluded completely and three of the five included ranged between 57–70% detected. For these reasons, mixture methods approaches were not conducted and PFOA, PFNA, and PFDA were only assessed dichotomously, which additionally limited the ability to test for dose response relationships. Lastly, although several sensitivity analyses were performed to assess the robustness of our results and we included covariates determined to be associated with both PFAS exposure and fetal growth in multivariable models including pregnancy complications and diet (i.e. fish intake), we acknowledge that residual confounding remains possible to explain the associations seen with decreased fetal growth.

5. Conclusions

Maternal serum PFOA concentrations were associated with lower fetal head circumference and biparietal diameter growth trajectories across pregnancy and these associations were stronger among participants reporting higher levels of perceived stress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The datasets generated and/or analyzed are not publicly available due to containing information that could compromise the privacy of research participants but are available from the corresponding author on reasonable request.

Abbreviations:

PFAS	per and polyfluoroalkyl substances

PFOA	perfluorooctanoic acid
PFOS	perfluorooctanesulfonic acid
PFHxS	perfluorohexanesulfonic acid
PFNA	perfluorononanoic acid
PFDA	perfluorodecanoic acid

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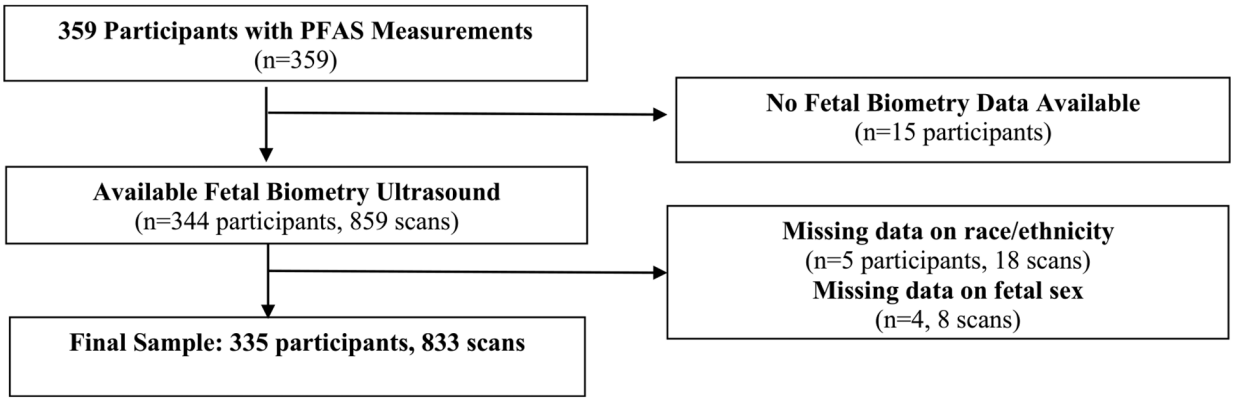

Fig. 1.
Consort diagram of included participants.

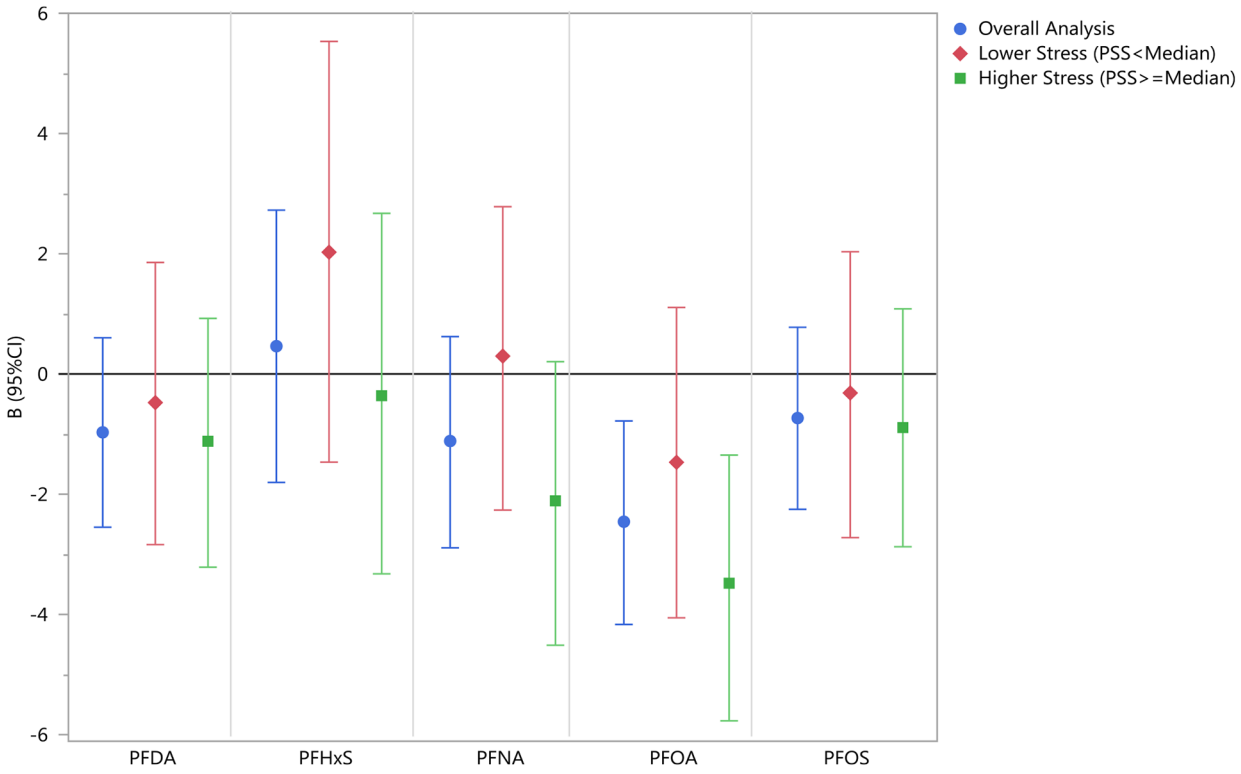

Fig. 2.

Prenatal Serum PFAS Concentrations and Fetal Head Circumference (*N* = 799 scans).All models adjusted for gestational age at ultrasound scan, gestational age squared, fetal sex, parity, education, household income, gestational age at time of blood sample, maternal race/ethnicity, recruitment site, age at recruitment, pre-pregnancy BMI, source of ultrasound, fish consumption, nativity. Note: PFDA, PFNA and PFOA modeled as >LOD referenced to ≤LOD; PFHxS and PFOS modeled continuously and are log transformed.

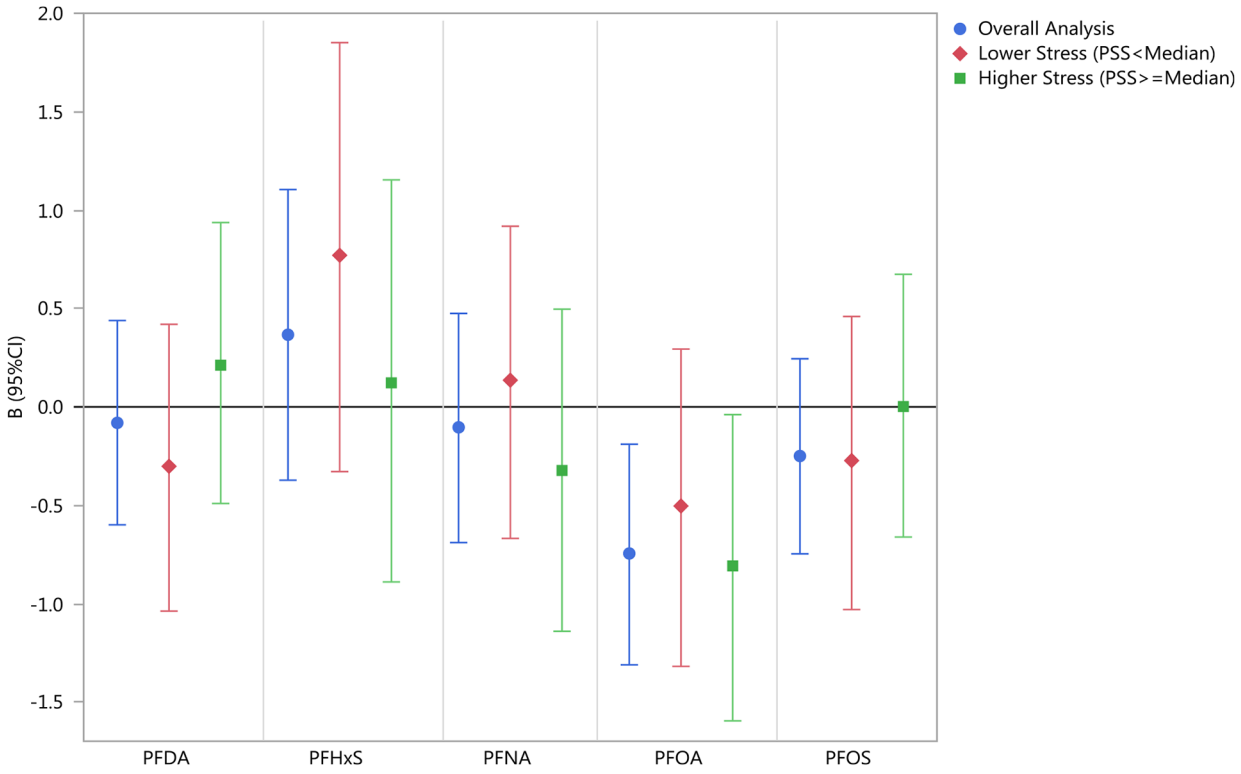

Fig. 3.

Prenatal Serum PFAS Concentrations and Fetal Biparietal Diameter (*N* = 806 scans).All models adjusted for gestational age at ultrasound scan, gestational age squared, fetal sex, parity, education, household income, gestational age at time of blood sample, maternal race/ethnicity, recruitment site, age at recruitment, pre-pregnancy BMI, source of ultrasound, fish consumption, nativity. Note: PFDA, PFNA and PFOA modeled as >LOD referenced to ≤LOD; PFHxS and PFOS modeled continuously and are log transformed.

Table 1

Participant characteristics ($N = 335$).

Characteristic	N (%) or Mean (SD)
Maternal	
Age (years)	29.4 (6.0)
Race/Ethnicity	
Hispanic	254 (75.8%)
Non-Hispanic Black	35 (10.5%)
Non-Hispanic White	31 (9.2%)
Non-Hispanic Other	15 (4.5%)
Household Income	
<$50,000	159 (47.5%)
$50,000–$99,999	63 (18.8%)
>$100,000	29 (8.6%)
Reported “Don’t Know”	84 (25.1%)
Education	
Completed high school or less	177 (52.8%)
Some college or completed college	129 (38.5%)
Some graduate training	29 (8.7%)
Country of Birth	
US Born	170 (50.7%)
Non-US Born	155 (46.3%)
Unknown	10 (3.0%)
Pre-Pregnancy BMI (kg/m^2)	28.1 (6.2)
Any Personal Smoking During Pregnancy	6 (1.8%)
Fetus	
Male	173 (51.6%)
Birth Order	
First	116 (34.6%)
Second or more	208 (62.1%)
Unknown	11 (3.3%)

Table 2

Distribution of PFAS (ng/mL) concentrations in maternal blood serum (N = 335).

Analyte	Abbreviation	LOD (ng/mL)	% Above LOD	Min	Q 1	Q2	Q 3	Max
Perfluorooctanesulfonic acid	PFOS	0.02	100%	0.09	0.96	1.34	1.89	10.36
Perfluorohexanesulfonic acid	PFHxS	0.02	100%	0.36	0.79	1.10	1.50	4.10
Perfluorononanoic acid	PFNA	0.02	70%	ND	ND	0.07	0.19	1.10
Perfluorooctanoic acid	PFOA	0.035	65%	ND	ND	0.12	0.39	3.43
Perfluorodecanoic acid	PFDA	0.035	57%	ND	ND	0.04	0.09	2.32
Perfluoro-n-pentanoic acid	PFPEA	0.05	17%	ND	ND	ND	ND	1.19
Ethyl Perfluorooctane sulfonamido acetic acid	NETFOSAA	0.02	12%	ND	ND	ND	ND	0.12
N-methyl Perfluorooctane sulfonamido acetic acid	NMFOSAA	0.02	10%	ND	ND	ND	ND	0.38
Perfluroundecanoic acid	PFUNDA	0.02	9%	ND	ND	ND	ND	0.72
Perfluorohexanoic acid	PFHXA	0.05	1%	ND	ND	ND	ND	0.11
Perfluorobutanesulfonic acid	PFBS	0.02	1%	ND	ND	ND	ND	0.08
Perfluorododecanoic acid	PFDODA	0.035	1%	ND	ND	ND	ND	0.94
Perfluorooctanesulfonamide	PFOSA	0.02	0%	ND	ND	ND	ND	ND
Perfluoroheptanoic acid	PFHPA	0.05	0%	ND	ND	ND	ND	ND

ND=Not Detected; Q1= Quartile 1 (25th percentile), Q2= Quartile 2 (50th percentile), Q3= Quartile 3 (75th percentile)