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Endocrine disruptors and neonatal anthropometry, NICHD Fetal Growth Studies - Singletons

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Abstract

Background: Intrauterine exposure to endocrine disrupting chemicals (EDCs) has been equivocally associated with birth weight, length and head circumference with limited attention to anthropometric endpoints such as umbilical circumference and limb lengths.

Objective: To explore 76 prenatal maternal plasma EDC concentrations in a healthy obstetric cohort and 7 neonatal anthropometric endpoints by maternal race/ethnicity.

Methods: The study cohort comprised 2106 (564 White, 549 Black, 590 Hispanic, 403 Asian) healthy pregnant women recruited from 12 U.S. clinical sites between 2009 and 2012 who were followed through delivery. Neonates underwent standardized anthropometric assessment (weight, length, head and umbilical circumference, and mid- upper arm and thigh length). Plasma EDC

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Dataset

The analytic file prepared for this work along with its code and supporting documentation is readily available upon request from Dr. Jagteshwar Grewal (grewalja@mail.nih.gov) consistent with the NIH Intramural Research Program's data sharing policy.

concentrations were quantified using high resolution gas chromatography-high resolution mass spectrometry and liquid chromatography-tandem mass spectrometry. EDCs were log-transformed and rescaled by their deviations (SD) when modeled relative to neonatal endpoints using linear regression adjusting for age, education, pre-pregnancy body mass index (BMI), serum cotinine, serum lipids for lipophilic chemicals, and a race/ethnicity interaction term; p-values had false discovery rate correction (< 0.05).

Results: The cohort comprised women aged 28 (SD = 5) years with normal BMIs (23.6 kg/m^2, SD = 3). Maternal EDC concentrations varied by self-identified race/ethnicity and neonatal outcomes, though no specific EDC was consistently associated with neonatal anthropometric outcomes across racial/ethnic groups. For the overall cohort, perfluorooctanoic acid was negatively associated with birth length per SD increase in concentration (β = −0.23 cm; 95% CI −0.35, −0.10), while perfluorohexanesulfonic acid was negatively associated with umbilical circumference (β = −0.26 cm; 95% CI −0.40, −0.13), perfluorodecanoic acid with arm length (−0.09 cm; 95% CI −0.14, −0.04), and PCBs congeners 118/106 (−0.12 cm; 95% CI −0.20, −0.04) and 146/161 (− 0.14 cm; 95% CI −0.23, −0.05) with thigh length, as were 7 other poly-and-perfluorinated alkyl substances (PFASs).

Conclusions: Among healthy pregnant women with low risk antenatal profiles and relatively low EDC concentrations, reductions in umbilical circumference and bone lengths may be a sensitive marker of intrauterine EDC exposure, particularly for PFAS.

Keywords

Anthropometry; Endocrine disrupting chemicals; Fetal growth; Neonate; Pregnancy

1. Introduction

A healthy intrauterine environment is fundamental for optimal fetal growth given the rapidity of cellular proliferation, epigenetic programming and numerous other developmental processes that characterize pregnancy. During this sensitive window, exposures can adversely affect embryonic and fetal development, as evident from notable historical exposures such as clinically administered diethylstilbestrol (Reed and Fenton, 2013) and thalidomide (Vargesson, 2015), as recently reviewed, to war induced population famine which is reported to have a profound effect on health across the lifespan (El Hajj et al., 2014). In the past few decades, evidence has arisen in support of other environmental exposures that alter fetal growth and development including endocrine disrupting chemicals (EDCs), which are defined as exogenous chemicals capable of interfering with hormone action (Zoeller et al., 2012). EDCs remain of concern given their ubiquitous exposure for contemporary pregnant women (Woodruff et al., 2011) via a multitude of pathways such as ingestion, inhalation or dermal absorption. Fetuses become exposed to EDCs via placental transfer in varying degrees depending on the chemical and molecular structure of the compound among other toxicokinetic properties, such as being lipophilic (i.e., organochlorine pesticides, polybrominated and chlorinated biphenyls, polybrominated diphenyl ethers) or not (i.e., poly-and-perfluorinated alkyl substances) (Negri et al., 2017).

Various classes of EDCs have been both positively and negatively associated with infants' birth size typically measured by weight, length and head circumference, possibly given the essential role of hormones for developmental homeostasis and the unique properties of individual chemicals (Caserta et al., 2013). Recent meta analyses focusing on environmental exposures including EDCs have found evidence in support of perfluorooctanoic acid (PFOA) and reduced birth weight (Johnson et al., 2014; Negri et al., 2017) and similarly for polychlorinated biphenyl (PCB) congener #153 (Govarts et al., 2012; Nieuwenhuijsen et al., 2013). Another review focusing on preterm birth concluded that strong evidence existed for high concentrations of DDE, suggestive evidence for lower DDE concentrations and inconclusive evidence for other persistent EDCs (Ferguson et al., 2013). Cohort studies with preconception measurement of persistent EDCs are important given that they reflect exposure in the periconception window, or before the reported decline in concentrations over gestation (Bloom et al., 2007). Findings from the few preconception cohort studies have reported reduced birth weights (84–195 g) for girls relative to maternal preconception serum concentrations of dichlorodiphenyltri-chloroethane (DDT), polybrominated diphenyl ether (PBDE) congeners #28 and #183, and also paternal concentrations of PBDE #183 and PCB #167 (Robledo et al., 2015). Specific parental PCB congeners and maternal perfluorooctane sulfonamide (PFOSA) concentrations were associated with reduced (98–170 g) birth weight in boys (Robledo et al., 2015). In addition, decrements in birth length and head circumference were reported for specific organochlorine pesticides, PBDE and PCB congeners. Even larger (471 g) reductions were found in another preconception study for anti-estrogenic PCBs (Murphy et al., 2010). In a pregnancy cohort, perfluorononanoic (PFNA) and PFOA concentrations were negatively (≈ 50g) associated with birth weight (Starling et al., 2017).

A lingering question is whether associations observed for EDCs and infant birth size remain when focusing on healthy women with low risk antenatal profiled and uncomplicated pregnancies that may foster optimal fetal growth. Moreover, it is important to determine whether EDCs are associated with neonatal anthropometry, since it provides greater insight about adiposity and body composition in light of evidence suggesting that some EDCs may be obesogens (Grüm and Blumberg, 2009). Typically, however, anthropometric assessments are not routinely performed on neonates prompting greater reliance on more traditional measures of birth size such as weight, length and head circumference as captured in medical records and birth certificates.

In response to data gaps about EDCs and neonatal anthropometry moving beyond traditional measures of birth size, our research aims were to examine the relation between maternal plasma concentrations of persistent EDCs and neonates' anthropometry with further attention to maternal race/ethnicity in a pregnancy cohort. The cohort was explicitly recruited for their low risk prenatal profiles that are important for optimal growth irrespective of maternal race/ethnicity. We assessed 76 individual EDCs and their potential additivity with regard to neonatal anthropology, and also effect modification with maternal race/ ethnicity in relation to 6 measured neonatal anthropometry outcomes. Standardized neonatal anthropometric assessments provide additional data on extremity bone lengths not typically captured in medical records or birth certificates. In light of the diversity of this pregnancy cohort and an expanded assessment of neonatal size, we designed this work as an

exploratory study to assess individual chemicals looking for signals rather than making assumptions about mixtures.

2. Methods

2.1. Design and study cohort

The study cohort comprises 2106 (90% of original cohort, n = 2334) women with singleton pregnancies who participated in the NICHD Fetal Growth Studies and who delivered a live born infant and had plasma samples available for the quantification of EDCs. Women were recruited from 12 U.S. clinical sites (i.e., Christiana Care Health System, Columbia University Medical Center, Fountain Valley Regional Hospital and Medical Center, Medical University of South Carolina, Miller Children's Hospital Long Beach Memorial Medical Center, New York Hospital Queens, Northwestern University Feinberg School of Medicine, St. Peter's University Hospital, Tufts Medical Center, University of Alabama at Birmingham, University of California at Irvine, and Women and Infants Hospital of Rhode Island) between July 2009 and January 2013. The Study's primary goal was to determine whether fetal growth under optimal maternal conditions (i.e., low risk antenatal profile) varied by self-identified maternal race/ethnicity (i.e., non-Hispanic White, non-Hispanic Black, Hispanic, and Asian/Pacific Islander) necessitating the use of race/ethnic specific standards for monitoring pregnant women (Buck Louis et al., 2015). To achieve this goal, the Study recruited healthy women with low risk pregnancies who met eligibility criteria: **aged 18–40 years; not obese (pre-pregnancy body mass index** (BMI) 19.0–29.9 weight in kg/height in m^2); **healthy lifestyle** (i.e., no alcohol consumption, cigarette smoking or illicit drug usage); **uneventful reproductive history** (i.e., spontaneous conception; no history of fetal or neonatal deaths, preterm or low birth weight infants, congenital malformations or macrocosmia); **no prior adverse medical history** (i.e., asthma requiring weekly medication, autoimmune disorders, cancer, diabetes mellitus, epilepsy or seizures requiring medication, hematologic disorders, hypertension, psychiatric disorders, renal disease, thyroid disease); and **healthy gravid history** (i.e., no history of gestational diabetes, severe preeclampsia/eclampsia, or hemolysis, elevated liver enzymes, low platelet count (HELLP Syndrome). Eligible women were enrolled at 10 weeks 0 days to 13 weeks 6 days after obstetrical ultrasound screening to ensure accurate gestational dating. Overall, 564 non-Hispanic White, 549 non-Hispanic Black, 590 Hispanic, and 403 Asian/Pacific Islander women fully completed the study protocol. Full human subjects' approval was obtained from all participating clinical and data coordinating centers and the NICHD's institutional review boards; women did not participate until giving informed consent. Complete study details are presented elsewhere (Grewal et al., 2018).

2.2. Data collection and neonatal measurement

Upon enrollment, women completed in-person interviews and prepregnancy BMI was estimated using self-reported height and weight prior to becoming pregnant. Women were followed through delivery, and newborns underwent standardized neonatal anthropometric assessments at a mean age of 1.7 ± 3 days depending upon the infant's conditions or other factors such as early discharge precluding assessment. Specifically, trained research nurses completed the neonatal anthropometric assessment along with a second person who helped

hold the neonate's position for measurement of weight and length, midupper arm and thigh lengths, and head and umbilical circumferences. All measurements were performed with the infant in a dry diaper with a light blanket with correction for their combined weight relative to the newborn's weight. **Weight** was measured using an electronic infant scale or beam balance scale and recorded in grams (g) (Lohman et al., 1988). **Length** in centimeters (cm) represented the distance between the infant's soles of the feet to the top of the head and was measured using a seca 416 Infantometer (SECA, Hamburg, Germany), with the infant in a supine position (Doull et al., 1995; Shinwell and Shlomo, 2003; Pereira-Da-Silva et al., 2006). **Upper-arm length** was taken on the right side of the body, with the infant held or seated on the assistant's lap in a forward-facing position (Catalano et al., 1995; National Health and Nutrition Examination Study, 2007–2008). The mid-point of the upper arm was located by flexing the elbow to 90° with palm facing superiorly. The tape was placed perpendicular to the long axis over the triceps muscle between two landmarks, with the mid-point marked with a cosmetic pencil and kept snug over the skin without tissue compression. **Upper-thigh length** was taken on the right side of the body with the infant held on the assistant's lap or in a supine position (Catalano et al., 1995; National Health and Nutrition Examination Study, 2007–2008). The tape measure was placed perpendicular to the long axis of the quadriceps muscle between the crural fold and large semilunar crease above the patella and was placed snugly against the skin without tissue compression. For **head circumference**, the tape measure was placed anteriorly on the forehead above the eyebrows and posteriorly to the maximum protrusion of the occiput (Catalano et al., 1995; National Health and Nutrition Examination Study, 2007–2008). The **umbilical circumference**, or waist circumference, was measured by placing the tape on the abdomen just above the (cephalward) umbilicus, while being perpendicular to the long mid-axis of the trunk (Williams and Brain, 2001; Stetzer et al., 2002; Fok et al., 2005; Rodriguez et al., 2008). All measurements were made to the nearest 0.1 cm and taken twice, or a third time if any differed by the expected technical errors of measurement (de Onis et al., 2004; Johnson et al., 1997; Ulijaszek and Kerr, 1999). The distribution of missing neonatal measurements was (in descending order): length (n = 341), umbilical circumference (n = 337), upper arm length (n = 331), upper thigh length (n = 331), weight (n = 320), and head circumference (n = 320). Assessments were not conducted for 316 (15%) neonates.

2.3. Blood collection and analysis

At the enrollment visit, ≈ 20 ml of blood was obtained from women, centrifuged and aliquoted per 1-ml of plasma for banking following standardized protocol. After being stored at − 80 °C, plasma samples were shipped on dry ice to the Wadsworth Center for the quantification of specific persistent EDCs, as described below. Before implementing chemical analysis, the clinical phlebotomy and collection equipment were tested for target analytes and none was found allowing for quantification of plasma samples, which were in ≈ 3 ml aliquots. Specifically, measurement included: 11 **organochlorine pesticides** (OCPs: beta-hexachlorocyclohexane (β-HCH), gamma-hexachlorocyclohexane (γ-HCH), hexachlorobenzene (HCB), trans-chlordane, trans-nonachlor, *p,p′*-dichlorodiphenyldichloroethylene (*p,p′*- DDE), *o,p′*-dichlorodiphenyldichloroethane (*o,p′*-DDD), *p,p′*-dichlorodiphenyldichloroethane (*p,p′*-DDD),*p,p′*-dichlorodiphenyltrichloroethane (*p,p′*-DDT), mirex); 1 **polybrominated biphenyl** (PBB 153), 9

polybrominated diphenyl ethers (PBDE congeners 28, 47, 85, 99, 100, 153, 154, 183, 209); 44 polychlorinated biphenyls (PCBs), including tri-through deca-chlorobiphenyls, and 11 **poly-and-per-fluorinated alkyl substances** (PFASs: *N*-methylperfluoro-1-octane-sulfonamidoacetic acid (N-MeFOSAA), perfluorodecanoic acid (PFDA), perfluorododecanoic acid (PFDoDA), perfluorodecane sulfonate (PFDS), perfluoroheptanoic acid (PFHpA), perfluorohexanesulfonic acid (PFHxS), perfluorononanoic acid (PFNA), perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), perfluorooctane sulfonamide (PFOSA), perfluoroundecanoic acid (PFUnDA)).

For the analysis of PCBs, PBDEs, PBB and OCPs, 1 ml of plasma was spiked with ^{13}C-labelled internal standard mixture (250 pg each for OCPS, PBB, PBDEs, PCBs), vortexed and placed in a refrigerator overnight. Then, 1 ml of 88% formic acid was added and sonicated for 15 min, which was followed by the addition of 2 ml of milli-Q water. The samples were then passed through solid phase extraction (SPE) cartridges packed with 1.3 g of Sepra C18-E (Rapid Trace SPE Workstation) and eluted with dichloromethane, which was concentrated to 1 ml. Extracts were then passed through SPE cartridges packed with 0.2 g of silica gel/1.1 g of sulfuric acid silica gel and eluted with 30% dichloromethane in hexane, which was concentrated to a final volume of 50 μl under a gentle stream of nitrogen. PBDEs were analyzed using a (Agilent Technologies, Atlanta, GA) gas chromatograph (GC 7890A) coupled with a mass spectrometer (MSD 5975). Analyte separation was accomplished using a Zebron 5MS (15 m, 0.25-mm i.d., and 0.10-μm film thickness; Phenomenex) capillary column. OCPs were analyzed using a Thermo Finnigan (Bremen, Germany) Trace GC Ultra coupled with a double focusing sector mass spectrometer (DFS). Analyte separation was carried out by a DB-5MS (30 m, 0.25-mm i.d., and 0.25-μm film thickness; Agilent Technologies) capillary column. PCBs were analyzed by a JEOL (Tokyo, Japan) UltraFocus high resolution mass spectrometer (JMS-800D). Analyte separation was by a HP-5MS (30 m, 0.25-mm i.d., and 0.25-μm film thickness; Agilent Technologies) capillary column. Quantification of PBDEs, OCPs and PCBs was based on an isotope dilution method with ^{13}C-labelled internal standards. Two procedural blanks and SRM1958 were analyzed for every 27 samples.

For PFAS quantification, the sample extraction was similar to that reported earlier (Asimakopoulos and Thomaidis, 2015) with some modifications (Honda et al., 2018). In brief, 200 μl of plasma was transferred into a polypropylene (PP) tube and spiked with ^{13}C-labelled internal standards. To this mixture, 100 μl of 10% ammonia solution (v/v) was added. After 30 min, 780 μl of 1% ammonium formate in methanol (w/v) was added and vortexed. The sample was centrifuged and supernatant was loaded on to Hybrid-SPE cartridge (Supleco, Bellefonte, PA). The elute was concentrated 3 times under a gentle stream of nitrogen. The target analytes in eluate were quantified by an ultraperformance liquid chromatography (Acquity I Class; Waters, Milford, MA, US) coupled with an electrospray triple quadrupole tandem mass spectrometry (API 5500; AB SCIEX, Framingham, MA, US). The separation of target analytes was carried out by an Acquity UPLC BEH C18 column (1.7 μm, 50 × 2.1 mm, Waters). Serum cotinine was measured using an ultra-performance liquid chromatography coupled with an electrospray triple quadrupole tandem mass spectrometry, and concentrations were reported as ng/ml.

All chemicals were reported as ng/ml for analysis without substituting concentrations below laboratory limits of quantification (LOQ) to minimize bias when estimating human health outcomes (Richardson and Ciampi, 2003; Schisterman et al., 2006). In keeping with our exploratory design, we assessed all EDCs relative to neonatal anthropometry irrespective of the percentage of measurements above the LOQs for two key reasons: 1) LOQs are not fixed cut points and they often vary across labs and batches; and 2) to avoid assuming the absence of meaningful EDC signals relative to neonatal size for less prevalent chemicals or those with a sizable percentage of observations below laboratory detection limits.

2.4. Statistical analysis

We assessed the completeness of exposure and outcome data and summarized the distributional properties as medians (Md) and interquartile ranges (IQRs) for the overall cohort and by maternal race/ethnicity. Wilcoxon nonparametric tests were used to assess significance ($p < 0.05$; two-sided). Given the availability of measurements for all women, imputation was not required.

In the multivariable phase, we assessed each EDC after log transformation and rescaling by its standard deviation (SD) in relation to each neonatal anthropometry outcome using linear regression techniques. Rescaling was done to aid in the interpretation of findings, as the units for EDCs are quite small (ng/ml) and not as commonly understood as are SDs. Beta coefficients were estimated along with 95% confidence interval (CIs). Log (1 + x) transformations were done for most EDCs. However, slightly different log (10 + x) transformations were used for 11 (14%) EDCs (i.e., HCB, oxychlordane, trans-chlordane, trans-nonachlor, PBDEs 47 and 99, PCBs 18_17, 31_28, 90_101_89, 138_158, 153) whose minimum reported values were between − 10 and − 1 stemming from blank-corrected negative laboratory values. In light of the lengthy exclusion criteria aimed at the selection of healthy low risk women, covariates a priori were chosen to include maternal age (years), prepregnancy BMI (kg/m^2), race (White, Black, Hispanic, Asian), education (< high school, high school or equivalent, some college/associate degree, master's degree or higher), infant gender (male, female), and log(1 + x) transformed serum cotinine concentration (ng/ml). Delivery mode was included in head circumference models and categorized as spontaneous vaginal, outlet/low forceps or outlet vacuum, mid-forceps or rotation with forceps or vacuum, Cesarean section without labor, Cesarean section with trial of labor, and unknown). Total plasma lipids (ng/ml) were included for all lipophilic EDCs except PFASs, which are not lipophilic. We did not adjust for gestational age at birth as it is a study outcome and given that it is an intermediate in the relation with neonatal anthropometry. Such adjustment has been empirically demonstrated to introduce bias in causal inference (Ananth and Schisterman, 2017). We also did not adjust for parity in light of the inclusion/exclusion criteria to minimize introducing over-adjustment bias. We also formally tested for a chemical-race/ethnic interaction and included it in models, as empirically supported by the data. To adjust for the many comparisons made, we used false discovery rate (FDR) correction of < 0.05 for estimating q-values (Storey and Tibshrani, 2003) for assessing statistical significance. Descriptive analyses were performed using R (version 3.2.3), and models with SAS software (version 9.4; SAS Institute Inc., Cary, NC). The analytic file and

its supporting code and documentation are available upon request (Jagteshwar Grewal; grewalja@mail.nih.gov).

3. Results

There were 2106 (92% of original cohort) women with an observed live birth and measured EDC concentrations; 20 (1%) women experience a pregnancy loss after enrollment and pregnancy outcomes were unknown for 175 (8%) women who did not complete the protocol. Neither pregnancy loss (≈ 1%) nor completion rates (93% non-Hispanic White, 91% non-Hispanic Black, 92% Hispanic, and 90% Asian) varied by maternal race/ethnicity. Overall, the study cohort had a mean age of 30, 25, 27, and 31 years, and pre-pregnancy BMIs of 23.2, 24.1, 24.3, and 22.2, for non-Hispanic White, non-Hispanic Black, Hispanic, and Asian women, respectively (Table 1). Also, the cohort comprised married college educated women with health insurance and a comparable percentage of (null)parous women. The secondary sex ratio was 1.08 and comparable across racial/ethnic groups with the exception of a reversal (0.98) for non-Hispanic Black women.

Several significant differences were observed in median EDC concentrations across the four racial/ethnic groups (Table 2). In general, there was evidence that Asian women had higher total lipid adjusted OCP (Md 227.1, IQR 128.8, 685.7 ng/g) and PCB (Md 43.8, IQR 23.1,78.3 ng/g) concentrations in comparison to other women, whereas non-Hispanic Black women had the highest comparative total lipid adjusted PBDE concentrations (Md 28.5; IQR 14.8, 51.2 ng/g).

We observed significant racial/ethnic differences in neonatal weight, length, upper arm length, and head and umbilical circumference despite comparable gestational ages of approximately 39.4 weeks (Table 3). Neonates born to non-Hispanic Black mothers had lower birth weights, lengths and head circumferences than neonates born to other maternal groups.

In multivariable regression models with a race/ethnicity interaction term, we found no consistent pattern between any EDC and length of gestational age after FDR correction (see Supplemental Table 1). We also were unable to identify consistent patterns between EDCs and traditional measures of birth size (Table 4). None of the EDCs were significantly associated with birth weight or head circumference after FDR correction despite many beta coefficients being negative. Four signals were observed for birth weight and all were indicative of a reduction, though findings varied by maternal race/ethnicity. These findings included two PBDE congeners and two PFAS compounds. Specifically, PBDE #28 was negatively associated with length (cm) ($\beta = -0.22$ (− 0.39, −0.05) but only among Hispanic women, as was PBDE #153 ($\beta = -0.37$; −0.56, −0.18) but only among Black women. PFOA and PFOSA were associated with length in Black (P = −0.47; −0.73, −0.21) and White (β = 0.49; 0.24, 0.74) women, respectively, though in opposing directions.

Notably more associations were observed when assessing EDCs beyond traditional birth size measures (Table 5). Specific EDCs were negatively associated with umbilical circumference, upper arm and upper thigh lengths for the overall study cohort, though other associations

emerged for particular maternal race/ethnic groups depending upon the EDC. Specifically, PFHxS was the only EDC associated with umbilical circumference (β = −10.26cm; −0.40, −0.13) in the study cohort, while PFDA was the sole EDC associated with upper arm length ((β = −0.09cm; −0.14, −0.04). No significant positive associations were observed for EDCs in the overall cohort, though some racial/ethnic subgroup differences were noted.

Another key observation was a rather persistent pattern of PFASs being negatively associated with bone lengths, viz., 7/10 (70%) PFASs were found to be associated with reductions (cm) in upper thigh length for the study cohort (Table 5). These included: N-MeFOSA (β = −0.09; −0.16, −0.03); PFDA (β = −0.14; −0.21, −0.07); PFHpA (β = −0.13; −0.20, −0.06); PFHxS (β = −0.12; −0.19, −0.05); PFNA (β = −0.16; −0.22, −0.10); PFOA (β = −0.19; −0.26, − 0.12); and PFUnDA (β = −0.15; −0.23, −0.07). The findings for arm and thigh length reductions seemed to be most predominate among White versus other race/ethnic neonates.

4. Discussion

In this racially/ethnically diverse contemporary pregnancy cohort comprising healthy women with low risk antenatal profiles at enrollment, we observed some evidence that specific EDCs, in particular PFASs, were associated with reduced neonatal bone lengths, i.e., upper arm and thigh and overall newborn length. These findings were based upon standardized neonatal anthropometric assessments and are robust to FDR correction, given the number of EDCs under study and comparisons made. The peak velocity for fetal length is during the second trimester, and our findings may suggest that this may is a sensitive window for fetal PFAS exposure (Grantz et al., 2018). These observations need to be interpreted in the context of our carefully screened cohort for the inclusion of pregnant women with low risk antenatal profiles, which were posited to foster optimal fetal growth irrespective of maternal race/ethnicity. Had we not completed neonatal anthropometric assessments, we would have missed important findings that emerged for specific EDCs and reductions in upper arm and thigh lengths, and a negative association between maternal prenatal PFHxS concentration and umbilical circumference in the overall cohort. This finding may have important implications for health as it approximates newborn waist circumference and recognizing that adult waist circumference is associated with morbidity and mortality (e.g., polycystic ovarian syndrome, cardiovascular disease, total and cause-specific mortality). However suggestive, it remains to be established whether PFHxS is an obesogen for neonates and one with implications for childhood obesity (Braun, 2017). We are unaware of any previously published work that assessed PFAS concentrations and neonatal anthropometry, thereby, precluding a more complete interpretation of our findings. However, our findings are consistent with the conclusion of a recent review of environmental exposures on fetal and child growth that noted the absence of published research on measured fetal growth relative to PFAS exposure (Zheng et al., 2016).

Other important study observations include differences in EDC concentrations by maternal race/ethnicity in contemporary populations of pregnant women. This finding is important as the heterogeneity of natality increases in U.S. populations with recent data reflecting that minority newborns now surpass those of non-Hispanic whites (www.census.gov/newsroom/

releases/archives/population/cb12-90.html). Specifically, we observed that Asian women, who are often underrepresented in U.S. pregnancy cohorts, had higher concentrations of many OCPs, PCBs and PFASs relative to other women, whereas non- Hispanic Black women had the highest PBDE concentrations.

While our models included interaction terms for maternal race/ethnicity, the lack of consistent findings is perplexing but may reflect biologic differences in fetal growth irrespective of EDCs at environmentally relevant concentrations, or varying routes of exposure that are unique to specific subgroups of pregnant women (Axelrad et al., 2009; James-Todd et al., 2016; Nelson et al., 2012; Zota et al., 2010). We previously reported racial/ethnic differences in fetal growth for this cohort (Buck Louis et al., 2015), and our findings have recently been corroborated in other low risk obstetric study populations outside the U.S. (Kiserud et al., 2017; Sletner et al., 2017). Collectively these findings suggest that despite minimizing medical and lifestyle exposures that impact fetal growth, racial/ethnic differences may exist and underscore the need for customized monitoring of diverse populations to maximize children's health. This finding also may have implications for the assessment of environmental influences on fetal growth and neonatal size.

While previous authors have provided insight about specific EDCs and traditional measures of infant size such as birth weight, length and head circumference, our data offer new insight on the relation between environmentally relevant concentrations of persistent EDCs in healthy low risk women and other anthropometric endpoints such as umbilical circumference and upper- arm and thigh lengths. Our findings suggest that bone length may be a sensitive endpoint when assessing the impact of EDCs on fetal growth, particularly PFAS exposure in pregnant women with low risk antenatal profiles. Given the error in measuring birth length, care should be taken to use standardized assessments such as those incorporated into this work. Also of note are findings that report an association between PFAS exposure and reduction in bone density in the non-pregnant U.S. population (Khalil et al., 2016). Moreover, continued reliance on traditional birth size measures such as birth weight and head circumference may preclude the identification of other signals such as bone length and umbilical circumference, the latter outcome being a potential marker of health across the (Zhang et al., 2008).

Our findings need to be interpreted within important study limitations despite our unique cohort, individually measured EDCs in women and standardized assessments of neonates. We cannot rule out error associated with reliance on self-identified maternal race/ethnicity, though it is the same construct used in clinical practice, survey research and in enumerating U.S. (census) populations. Despite FDR correction, we explored many EDCs in light of few available data and future initiatives aimed at the assessment of mixtures also may be informative. Also, our findings may not be relevant for pregnant women with unique residential or occupational exposures.

Model specification is another important consideration in weighing our findings in the context of the existing literature. In thinking about our specific findings that select PFASs may be associated with reduced neonatal size, we cannot rule out residual confounding particularly as related to parity. While parity may be associated with differences in neonatal

anthropometry (Gaillard et al., 2014) especially between the first two births (Hinkle et al., 2014), purported reasons for such differences are largely unknown but may reflect changes in maternal physiology, behaviors, or weight gain along with changes in paternity (Khong et al., 2003; Villamor and Cnattingius, 2006; Trogstad et al., 2001; Miranda et al., 2011). Some of these factors and also reproductive history, gravid disease and risky lifestyles were controlled for in the study design phase in light of our lengthy exclusion criteria aimed at identifying pregnant women for optimal fetal growth (Grewal et al., 2018). Moreover, PFASs bind to albumin and not lipids resulting in a lower placental transfer than lipophilic EDCs (Fromme et al., 2010; Kim et al., 2011). Even in the context of some transfer across pregnancy, it is also important to keep in mind that mean daily uptake of specific PFAS such as PFOS and PFOA is estimated to be approximately 2–3 ng/kg and largely from dietary sources (Fromme et al., 2009). Collectively, these findings have prompted some investigators to characterize changes in PFAS concentrations in pregnant women as being transitory (Tao et al., 2008). While parity is reported to be associated with body burden of PFASs via lactation history (Whitworth et al., 2012), neonatal assessments were performed at approximately 1.7 days following delivery and before the establishment of breastfeeding.

We recognize that there are many possible reasons why our findings do not corroborate earlier studies suggestive of diminished birth size beyond cohort heterogeneity. Exposure profiles for our cohort were generally lower than those reported for 268 pregnant women participating in the 2003–2004 NHANES cross-sectional study (Woodruff et al., 2011), which may reflect our selection of healthy women with low risk prenatal profiles or time periods (2009–2013) corresponding to declining environmental exposure routes. It remains possible that women with a prior history of pregnancy complications or gravid diseases as well as women with risky contemporary lifestyles may have higher EDC concentrations than women with low risk prenatal profiles, though the former were not captured in our study due to our strict inclusion criteria needed for maximizing optimal fetal growth. Unfortunately, we have no data on ineligible women's chemical profiles. Other possible explanations reflect our observational design, and varying laboratory protocols and analytic modeling techniques used across studies. We also appreciate the possibility that fetuses not growing optimally may influence maternal EDC concentrations, possibly through a reduction in plasma volume expansion and reduced glomerular filtration rate. However, a recent Navigation Guide systematic review based upon 31 studies focusing on glomerular filtration rate and fetal growth concluded there is insufficient evidence to support such reverse causality (Vesterinen et al., 2015).

5. Conclusions

We found PFASs were the class of EDC chemicals most consistently associated with measured neonatal anthropometry and, particularly, bone lengths. Reductions included overall birth length but also reduction in upper arm and thigh lengths.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations:

β-HCH beta	Hexachlorocyclohexane
BMI	Body mass index
CI	Confidence interval
EDCs	Endocrine disrupting chemicals
γ-HCH	gamma-Hexachlorocyclohexane
HCB	Hexachlorobenzene
N-MeFOSAA	*N*-methylperfluoro-1-octanesulfonamidoacetic acid
***o,p′*-DDD**	*o,p′*-Dichlorodiphenyldichloroethane
OCPs	Organochlorine pesticides
PFDA	Perfluorodecanoic acid
PFDoDA	Perfluorododecanoic acid
PFDS	Perfluorodecane sulfonate
PFHpA	Perfluoroheptanoic acid
PFHxS	Perfluorohexanesulfonic acid
PFNA	Perfluorononanoic acid
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctanesulfonic acid
PFOSA	Perfluorooctane sulfonamide
PFUnDA	Perfluoroundecanoic acid
PBB	Polybrominated biphenyl
PBDEs	Polybrominated diphenyl ethers
PCBs	Polychlorinated biphenyls
PFASs	Poly-and-perfluorinated alkyl substances

***p,p′*-DDE**	Dichlorodiphenyldichloroethylene
***p,p′*-DDD**	*p,p′*-Dichlorodiphenyldichloroethane
***p,p′*-DDT**	*p,p′*-Dichlorodiphenyltrichloroethane
SD	Standard deviation
Trans-chlordane	trans-nonachlor

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Table 1

Description of cohort by self-identified maternal racial/ethnic identity, NICHD Fetal Growth Studies- singletons, 2009–2013.

Characteristic	Cohort n = 2106		Non-Hispanic White n = 564	Non-Hispanic Black n = 549	Hispanic n = 590	Asian/Pacific Islander n = 403
Mean (± standard deviation)						
Age (years)	28 ± 5	n = 2106	30 ± 4	25 ± 5	27 ± 5	31 ± 5
Pre-pregnancy BMI (kg/m^2)[a]	23.6 ± 3.0	n = 2101	23.2 ± 2.8	24.1 ± 3.1	24.3 ± 2.8	22.2 ± 2.6
Prenatal BMI (kg/m^2)[b]	24.4 ± 3.5	n = 2087	24.1 ± 3.1	24.9 ± 3.7	25.2 ± 3.4	23.1 ± 3.2
Number (percent)						
Parous						
Previous live birth	1073 (51)	n = 2106	256 (45)	272 (50)	358 (61)	187 (46)
No previous live birth	1033 (49)	n = 2106	308 (55)	277 (51)	232 (39)	216 (54)
Education						
College or more	1522 (72)	n = 2106	534 (95)	340 (62)	311 (53)	337 (84)
Less than college	584 (28)	n = 2106	30 (5)	209 (38)	279 (47)	66 (16)
Marital status						
Married/living as married	1595 (76)	n = 2104	530 (94)	266 (49)	430 (73)	369 (92)
Not married	509 (24)	n = 2104	33 (6)	282 (52)	160 (27)	34 (8)
Health insurance						
Private/Managed care	1361 (65)	n = 2106	534 (95)	263 (48)	226 (38)	338 (84)
Other	745 (35)	n = 2106	30 (5)	286 (52)	364 (62)	65 (16)
Sex index birth						
Male	1088 (52)	n = 2096	306 (54)	270 (50)	306 (52)	206 (51)
Female	1008 (48)	n = 2096	257 (46)	276 (51)	280 (48)	195 (49)
Secondary sex ratio	1.08		1.19	0.98	1.09	1.06

NOTE: Missing data were minimal, < 1% for marital status and 1% for prenatal BMI and infant sex.

[a]Self-reported height and weight prior to pregnancy, body mass index (BMI, kg/m^2).

[b]Measured height and weight upon enrollment into cohort, body mass index (BMI, kg/m^2).

Table 2

Distribution of chemical concentrations by self-identified maternal race, NICHD Fetal Growth Studies – singletons. 2009–2013.

Chemical class	% < LOQ	Cohort (n = 2106) Median (IQR)	Non-Hispanic White (n = 564) Median (IQR)	Non-Hispanic Black (n = 549) Median (IQR)	Hispanic (n = 590) Median (IQR)	Asian or Pacific Islander (n = 403) Median (IQR)	p-Value
OCPs (ng/g):							
β-HCH	51.6	0 (0, 4.388)	0 (0, 1.794)	0 (0, 1.367)	0.927 (0, 4.706)	12.26 (3.237, 70.557)	< 0.001
γ-HCH	93.4	0	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.17
HCB	10	7.062 (4.052, 10.589)	6.583 (4.236, 9.385)	7.204 (3.601, 10.907)	6.428 (3.702, 9.899)	8.687 (5.131, 15.602)	< 0.001
Oxychlordane	26	2.566 (0.729, 4.436)	4.016 (2.345, 5.769)	2.343 (0.457, 4.094)	1.748 (0, 3.199)	2.053 (0.174, 4.211)	< 0.001
Trans-chlordane	71	0 (−0.853, 1.23)	−0.121 (−0.827, 0.509)	0.151 (−0.972, 2.472)	0 (−0.818, 1.368)	0 (−0.721, 0.986)	< 0.001
Trans-nonachlor	9.7	4.615 (2.503, 7.894)	5.896 (3.609, 9.755)	4.78 (2.947, 7.814)	3.424 (1.624, 5.624)	4.75 (2.502, 8.546)	< 0.001
p,p′-DDE	0.2	82.566 (52.236, 168.992)	65.915 (47.867, 93.569)	58.774 (42.379, 88.259)	125.007 (64.895, 257.952)	175.973 (91.33, 457.065)	< 0.001
o,p′-DDD	96.9	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.05
p,p′-DDD	72.2	0 (0, 0.493)	0 (0, 0)	0 (0, 0.451)	0 (0, 0.519)	0.437 (0, 1.207)	< 0.001
p,p′-DDT	35.2	1.273 (0, 2.645)	0.568 (0, 1.781)	0.834 (0, 1.614)	1.318 (0, 2.741)	4.081 (1.905, 10.792)	< 0.001
Mirex	68.2	0 (0, 0.771)	0 (0, 0.729)	0 (0, 0.718)	0 (0, 0.384)	0 (0, 1.5)	< 0.001
Total OCPs	–	109.959 (72.034, 205.484)	90.734 (68.404, 120.819)	81.588 (59.679, 123.597)	156.281 (84.106, 298.475)	227.144 (128.759, 685.652)	< 0.001
PBBs (ng/g):							
PBB 153	98.8	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0. 0)	0.67
PBDEs (ng/g):							
BDE28	63.1	0 (0, 1.081)	0 (0, 0.588)	0 (0, 1.271)	0 (0, 1.27)	0 (0, 0.944)	< 0.001
BDE47	7.4	8.776 (3.944, 17.786)	6.812 (3.347, 13.059)	12.558 (6.873, 24.837)	9.889 (4.628, 19.592)	6.651 (2.3, 13.206)	< 0.001
BDE85	97.1	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0. 0)	0.11
BDE99	38.1	2.169 (0, 5.441)	1.356 (0, 3.88)	3.23 (0, 8.925)	2.484 (0, 5.927)	1.556 (0, 4.293)	< 0.001
BDE100	28.2	2.169 (0, 4.392)	1.638 (0, 3.531)	3.151 (1.282, 6.526)	2.302 (0.58, 4.726)	1.343 (0, 3.165)	< 0.001
BDE153	58	0 (0, 7.149)	0 (0, 11.411)	3.179 (0, 12.206)	0 (0, 4.113)	0 (0, 3.352)	< 0.001
BDE154	61.7	0.46 (0, 2.86)	0 (0, 3.085)	1.069 (0, 2.884)	0 (0, 2.779)	1.128 (0, 2.675)	0.12
BDE183	99.8	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0. 0)	0.31
BDE209	99.9	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0. 0)	0.28
Total PBDEs	–	20.006 (8.982, 42.587)	17.877 (7.29, 36.492)	28.534 (14.785, 59.199)	19.905 (9.238, 41.016)	13.893 (5.452, 31.657)	< 0.001
PCBs (ng/g):							

Chemical class	% < LOQ	Cohort (n = 2106) Median (IQR)	Non-Hispanic White (n = 564) Median (IQR)	Non-Hispanic Black (n = 549) Median (IQR)	Hispanic (n = 590) Median (IQR)	Asian or Pacific Islander (n = 403) Median (IQR)	p-Value
Di-CB							
5/8	83.9	−0.00048 (−0.598, 0.533)	−0.065 (−0.483, 0.333)	0.004 (−0.772, 0.658)	0.047 (−0.595, 0.535)	0.041 (−0.656, 0.622)	0.13
Tri-CB							
18/17	76.6	−0.095 (−0.962, 0.747)	−0.178 (−0.804, 0.405)	−0.148 (−1.34, 0.901)	−0.061 (−0.934, 0.84)	0.054 (−0.949, 0.926)	0.04
22	98.4	−0.043 (−0.228, 0.112)	−0.043 (−0.164, 0.081)	−0.055 (−0.286, 0.144)	−0.048 (−0.241, 0.112)	−0.03 (−0.225, 0.135)	0.83
31/28	59.6	0.435 (−0.803, 1.557)	0.447 (−0.41, 1.332)	0.38 (−1.189, 1.69)	0.333 (−0.946, 1.396)	0.69 (−0.641, 1.977)	0.02
33/20	93.7	−0.097 (−0.443, 0.192)	−0.085 (−0.33, 0.129)	−0.116 (−0.6, 0.247)	−0.105 (−0.469, 0.198)	−0.1 (−0.457, 0.221)	0.91
37	99.0	−0.035 (−0.157, 0.084)	−0.042 (−0.139, 0.055)	−0.039 (−0.184, 0.103)	−0.028 (−0.159, 0.097)	−0.021 (−0.16, 0.091)	0.77
Tetra-CB							
41/64	90.9	−0.133 (−0.569, 0.272)	−0.102 (−0.456, 0.223)	−0.188 (−0.778, 0.351)	−0.172 (−0.624, 0.256)	−0.117 (−0.498, 0.281)	0.44
44	90.9	−0.194 (−0.646, 0.204)	−0.198 (−0.562, 0.102)	−0.211 (−0.803, 0.296)	−0.186 (−0.691, 0.203)	−0.15 (−0.565, 0.256)	0.56
47/48/75	94.7	0.032 (−0.243, 0.259)	0.023 (−0.212, 0.203)	0.04 (−0.306, 0.273)	−0.007 (−0.283, 0.225)	0.108 (−0.156, 0.356)	< 0.001
49/43	93.3	−0.123 (−0.469, 0.154)	−0.122 (−0.389, 0.094)	−0.163 (−0.593, 0.204)	−0.122 (−0.483, 0.149)	−0.105 (−0.434, 0.19)	0.62
52/73	77.6	−0.366 (−1.526, 0.656)	−0.413 (−1.219, 0.374)	−0.535 (−2.136, 0.898)	−0.357 (−1.492, 0.687)	−0.235 (−1.281, 0.919)	0.1
66/80	84.1	0.248 (−0.062, 0.6)	0.294 (0.028, 0.556)	0.174 (−0.198, 0.574)	0.17 (−0.133, 0.49)	0.411 (0.077, 0.844)	< 0.001
70/76	87.4	−0.249 (−0.83, 0.325)	−0.187 (−0.632, 0.237)	−0.323 (−1.069, 0.384)	−0.266 (−0.842, 0.329)	−0.231 (−0.827, 0.362)	0.24
74/61	37.9	1.116 (0.519, 1.943)	1.639 (0.999, 2.66)	0.858 (0.38, 1.469)	0.735 (0.275, 1.274)	1.516 (0.807, 2.436)	< 0.001
Penta-CB							
90/101/89	80.1	−0.42 (−1.488, 0.529)	−0.414 (−1.279, 0.37)	−0.581 (−1.806, 0.62)	−0.486 (−1.521, 0.47)	−0.215 (−1.322, 0.824)	0.03
93/95	81.4	−0.422 (−1.426, 0.475)	−0.371 (−1.173, 0.316)	−0.507 (−1.743, 0.608)	−0.478 (−1.501, 0.411)	−0.343 (−1.372, 0.563)	0.34
99	41	1.061 (0.466, 1.89)	1.26 (0.7, 2.112)	0.999 (0.358, 1.707)	0.701 (0.249, 1.299)	1.44 (0.783, 2.701)	< 0.001
85/120	99.5	0.017 (−0.078, 0.1)	0.02 (−0.059, 0.094)	0.009 (−0.096, 0.102)	0.012 (−0.085, 0.095)	0.024 (−0.074, 0.11)	0.25
110	90.3	−0.236 (−0.755, 0.22)	−0.225 (−0.603, 0.162)	−0.33 (−0.979, 0.31)	−0.231 (−0.753, 0.224)	−0.2 (−0.742, 0.254)	0.6
118/106	20.9	1.944 (1.016, 3.268)	2.476 (1.494, 3.841)	1.516 (0.714, 2.661)	1.443 (0.687, 2.476)	2.752 (1.686, 4.644)	< 0.001
105/127	64.5	0.606 (0.291, 1.054)	0.695 (0.417, 1.161)	0.494 (0.168, 0.844)	0.466 (0.211, 0.818)	0.946 (0.524, 1.565)	< 0.001
114/122	98.5	0.126 (0.06, 0.206)	0.195 (0.115, 0.309)	0.107 (0.044, 0.172)	0.087 (0.029, 0.136)	0.152 (0.097, 0.235)	< 0.001
Hexa-CB							
128	98.3	0.105 (0, 0.208)	0.064 (0, 0.181)	0.107 (0, 0.196)	0.097 (0, 0.179)	0.166 (0.038, 0.317)	< 0.001
137	93.1	0.246 (0.118, 0.431)	0.363 (0.194, 0.57)	0.218 (0.097, 0.345)	0.15 (0.05, 0.28)	0.337 (0.192, 0.571)	< 0.001
138/158	5.5	4.991 (2.85, 8.343)	6.35 (4.071, 9.702)	4.082 (2.338, 6.72)	3.565 (2.098, 5.597)	7.51 (4.394, 12.691)	< 0.001

Chemical class	% < LOQ	Cohort (n = 2106) Median (IQR)	Non-Hispanic White (n = 564) Median (IQR)	Non-Hispanic Black (n = 549) Median (IQR)	Hispanic (n = 590) Median (IQR)	Asian or Pacific Islander (n = 403) Median (IQR)	p-Value
146/161	62.5	0.582 (0.269, 1.17)	0.696 (0.353, 1.287)	0.468 (0.192, 0.914)	0.4 (0.157, 0.768)	1.184 (0.582, 2.23)	< 0.001
153	5.9	5.826 (3.21, 10.371)	7.579 (4.734, 11.904)	4.92 (2.697, 8.167)	4.082 (2.164, 6.604)	9.39 (5.249, 15.848)	< 0.001
156	65.8	0.596 (0.346, 1.058)	0.939 (0.558, 1.534)	0.465 (0.286, 0.795)	0.388 (0.237, 0.655)	0.759 (0.502, 1.308)	< 0.001
157	97.9	0.133 (0.068, 0.25)	0.205 (0.107, 0.35)	0.111 (0.055, 0.194)	0.093 (0.045, 0.154)	0.189 (0.106, 0.32)	< 0.001
167	95	0.207 (0.115, 0.356)	0.272 (0.157, 0.409)	0.165 (0.09, 0.272)	0.157 (0.09, 0.258)	0.338 (0.186, 0.557)	< 0.001
Hepta-CB							
170	26.9	1.374 (0.811, 2.288)	1.862 (1.2, 2.793)	1.03 (0.648, 1.743)	0.988 (0.644, 1.551)	2.006 (1.317, 3.448)	< 0.001
172/192	94.9	0.147 (0.045, 0.311)	0.191 (0.063, 0.374)	0.1 (0.021, 0.203)	0.097 (0.026, 0.199)	0.282 (0.145, 0.584)	< 0.001
177	90.5	0.235 (0.103, 0.437)	0.27 (0.133, 0.44)	0.176 (0.062, 0.35)	0.168 (0.069, 0.305)	0.447 (0.225, 0.881)	< 0.001
180	5.2	3.372 (1.934, 5.842)	4.796 (3.104, 6.923)	2.438 (1.509, 4.403)	2.418 (1.506, 3.771)	5.207 (3.241, 9.503)	< 0.001
182/187	35.5	1.244 (0.574, 2.341)	1.468 (0.846, 2.396)	1.023 (0.352, 1.898)	0.88 (0.348, 1.547)	2.325 (1.136, 4.462)	< 0.001
183	74.1	0.504 (0.273, 0.842)	0.591 (0.367, 0.917)	0.418 (0.184, 0.697)	0.397 (0.194, 0.629)	0.788 (0.452, 1.275)	< 0.001
Octa-CB							
194	62.4	0.628 (0.354, 1.075)	0.906 (0.574, 1.318)	0.496 (0.303, 0.878)	0.442 (0.265, 0.708)	0.872 (0.51, 1.555)	< 0.001
195	97.3	0.172 (0.092, 0.282)	0.224 (0.145, 0.321)	0.141 (0.069, 0.234)	0.128 (0.069, 0.207)	0.239 (0.129, 0.426)	< 0.001
196/203	56.2	0.743 (0.403, 1.234)	0.949 (0.618, 1.463)	0.631 (0.345, 1.068)	0.519 (0.287, 0.845)	1.021 (0.578, 1.926)	< 0.001
199	62	0.631 (0.32, 1.157)	0.823 (0.505, 1.379)	0.526 (0.246, 0.991)	0.409 (0.218, 0.703)	0.994 (0.514, 1.963)	< 0.001
202	94.4	0.183 (0.07, 0.345)	0.236 (0.113, 0.372)	0.165 (0.046, 0.305)	0.113 (0.023, 0.21)	0.31 (0.13, 0.629)	< 0.001
Nona-CB							
206	82.9	0.386 (0.208, 0.66)	0.48 (0.306, 0.735)	0.371 (0.206, 0.641)	0.262 (0.14, 0.445)	0.484 (0.24, 0.96)	< 0.001
208	96.2	0.149 (0.059, 0.279)	0.182 (0.098, 0.298)	0.148 (0.059, 0.274)	0.086 (0.029, 0.187)	0.221 (0.087, 0.459)	< 0.001
Deca-CB							
209	91.9	0.28 (0.167, 0.462)	0.297 (0.191, 0.462)	0.263 (0.164, 0.421)	0.215 (0.126, 0.352)	0.412 (0.242, 0.713)	< 0.001
Total PCBs	–	27.281 (13.149, 48.952)	35.256 (19.803, 55.147)	21.765 (9.84, 40.738)	17.318 (8.479, 33.274)	43.809 (23.05, 78.261)	< 0.001
PFASs (ng/ml):							
N-MeFOSAA	20.1	0.058 (0.028, 0.116)	0.064 (0.039, 0.116)	0.093 (0.048, 0.168)	0.039 (0.019, 0.077)	0.041 (0.019, 0.086)	< 0.001
PFDA	1	0.248 (0.159, 0.416)	0.296 (0.188, 0.467)	0.208 (0.133, 0.376)	0.198 (0.142, 0.287)	0.363 (0.23, 0.602)	< 0.001
PFDoDA	49.1	0.026 (0.013, 0.053)	0.028 (0.014, 0.047)	0.026 (0.013, 0.06)	0.018 (0.01, 0.029)	0.053 (0.023, 0.103)	< 0.001
PFDS	91.9	0.013 (0.004, 0.029)	0.016 (0.006, 0.027)	0.019 (0.008, 0.038)	0.006 (0.0003309, 0.015)	0.017 (0.007, 0.041)	< 0.001
PFHpA	58.3	0.023 (0.008, 0.056)	0.027 (0.009, 0.073)	0.021 (0.007, 0.047)	0.022 (0.007, 0.057)	0.027 (0.009, 0.051)	< 0.001

Chemical class	% < LOQ	Cohort (n = 2106) Median (IQR)	Non-Hispanic White (n = 564) Median (IQR)	Non-Hispanic Black (n = 549) Median (IQR)	Hispanic (n = 590) Median (IQR)	Asian or Pacific Islander (n = 403) Median (IQR)	p-Value
PFHxS	0	0.707 (0.444, 1.229)	1.153 (0.742, 1.833)	0.738 (0.443, 1.26)	0.512 (0.34, 0.801)	0.593 (0.418, 0.905)	< 0.001
PFNA	0	0.763 (0.531, 1.155)	0.926 (0.641, 1.349)	0.654 (0.469, 1.021)	0.671 (0.48, 0.94)	0.933 (0.635, 1.293)	< 0.001
PFOA	0	1.985 (1.297, 3.001)	2.883 (1.961, 4.285)	1.699 (1.076, 2.519)	1.709 (1.152, 2.517)	1.92 (1.386, 2.696)	< 0.001
PFOS	0	5.133 (3.39, 7.981)	6.856 (4.633, 10.119)	5.435 (3.57, 8.33)	3.61 (2.475, 5.086)	5.689 (3.696, 8.476)	< 0.001
PFOSA	99.5	0 (−0.002, 0)	0 (−0.003, 0)	0 (−0.002, 0)	0 (−0.002, 0)	0 (0, 0)	< 0.001
PFUnDA	1.7	0.184 (0.094, 0.349)	0.209 (0.126, 0.324)	0.155 (0.089, 0.341)	0.127 (0.076, 0.199)	0.415 (0.177, 0.785)	< 0.001

NOTE: Analysis restricted to women with live births. Plasma OCP, PBB, PBDE, and PCB concentrations were adjusted for total serum lipids. Non-zero concentrations were rounded to 3 decimal places. Valid n's for EDCs are: OCPs (n = 2079), PBB (n = 2078), PCBs (n = 2076), PFASs (n = 2101). p-Values obtained from Kruskal-Wallis nonparametric test comparing medians chemical concentrations by race/ethnicity. HCB, hexachlorobenzene; LOQ, laboratory limits of quantification with percent below reported; IQR, interquartile range; N-MeFOSAA, *N*-methylperfluoro-1-octanesulfonamidoacetic acid; OCPs, organochlorine pesticides; *o,P*-dichlorodiphenyldichloroethane (*o,P′*-DDD); PBDEs, polybrominated diphenyl ethers; PCBs, polychlorinated biphenyls; PFASs, poly- and per-fluorinated alkyl substances; PFDS, perfluorodecane sulfonate; PFHpA, perfluoroheptanoic acid; PFHxS, perfluorohexanesulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOSA, perfluorooctane sulfonamide; PFUnDA, perfluoroundecanoic acid; *p,p′*-DDE, *p,p′*-dichlorodiphenyldichloroethylene; *p,p′*-DDT, *p,p′*- dichlorodiphenyltrichloroethane.

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Table 3

Neonatal anthropometry by self-identified maternal race/ethnicity, NICHD Fetal Growth Studies – singletons, 2009–2013.

Anthropometric measurement	Cohort Md (IQR)	Non-Hispanic White Md (IQR)	Non-Hispanic Black Md (IQR)	Hispanic Md (IQR)	Asian Md (IQR)	p-Value
Gestational age	39.4 (38.7, 40.3)	39.4 (38.9, 40.3)	39.4 (38.4, 40.3)	39.4 (38.7, 40.3)	39.3 (38.6, 40.1)	0.07
Birth weight (g)						
Weight	3280 (3005, 3590)	3402 (3090, 3685)	3185 (2912, 3459)	3300 (3008, 3600)	3210 (3005, 3546)	< 0.001
Lengths (cm)						
Birth length	50.0 (48.5, 51.8)	50.8 (49.0, 52.2)	49.8 (48.0, 51.0)	50.0 (48.5, 51.5)	50.0 (48.6, 51.7)	< 0.001
Upper arm	10.0 (9.5, 11.0)	10.2 (10.0, 11.0)	10.0 (9.0, 11.0)	10.0 (9.5, 10.9)	10.0 (9.5, 10.5)	< 0.001
Upper thigh	10.2 (9.8, 11.0)	10.0 (9.5, 11.1)	10.0 (10.0, 11.0)	10.2 (9.5, 11.0)	10.4 (9.7, 11.0)	0.77
Circumferences (cm)						
Head	34.0 (33.0, 35.0)	34.4 (33.5, 35.3)	33.5 (32.5, 34.5)	34.0 (33.0, 35.0)	34.0 (33.1, 35.0)	< 0.001
Umbilical	31.1 (29.5, 33.0)	31.5 (29.6, 33.0)	30.2 (29.0, 32.0)	31.8 (30.0, 33.0)	31.5 (29.9, 33.1)	< 0.001

NOTE: Restricted to live births born to 564 White, 549 Black, 590 Hispanic, and 403 Asian mothers participating in the study. All data were rounded to nearest decimal place. Missing data for anthropometric measurements were: < 1% (gestational age, birth weight), 6% (weight, head circumference) and 7% (birth length, upper arm and thigh lengths). p-Values were obtained from the Kruskal-Wallis nonparametric test comparing median concentrations by race/ethnicity. Md, median; IQR interquartile range.

Table 4

Significant associations robust to false discovery rate correction between plasma chemical concentrations and neonatal anthropometry, NICHD Fetal Growth Studies - singletons, 2009–2013.

EDC (ng/ml)	Birth weight (g) β (95% CI)					Birth length (cm) β (95% CI)					Head circumference (cm) β (95% CI)				
	Cohort	White	Black	Hispanic	Asian	Cohort	White	Black	Hispanic	Asian	Cohort	White	Black	Hispanic	Asian
PBDEs:															
28	−18.99(−60.17,22.19)	−33.64(−133.3,66.01)	−9.68(−34.89,15.54)	−9.78(−41.20,21.64)	−22.90(−146.71,100.97)	−0.16(−0.38,0.06)	0.00(−0.56,0.52)	−0.12(−0.25,0.02)	−0.22 †(−0.39,−0.05)	−0.29(−0.96,0.38)	−0.13(−0.26,0.01)	−0.29(−0.61,0.04)	−0.05(−0.13,0.04)	0.01(−0.09,0.11)	−0.19(−0.59,0.21)
153	−2.69(−30.55,25.18)	−12.80(−40.90,16.15)	−1.11(−36.59,34.37)	15.39(−53.90,85.77)	−13.20(−86.51,60.14)	−0.18 *(−0.33,−0.03)	0.00(−0.17,0.13)	−0.37 ††(−0.56,−0.18)	0.01(−0.37,0.38)	−0.32(−0.72,0.08)	−0.04(−0.13,0.05)	−0.04(−0.13,0.05)	−0.06(−0.18,0.05)	0.01(−0.22,0.24)	−0.05(−0.29,0.18)
PFSAs:															
PFOA	−5.90(−28.75,16.94)	−8.91(−45.14,27.31)	−28.30(−76.22,19.52)	11.43(−34.99,57.85)	2.21(−48.10,52.52)	−0.23 †(−0.35,−0.10)	−0.05(−0.25,0.15)	−0.47 ††(−0.73,−0.21)	−0.20(−0.45,0.06)	−0.20(−0.47,0.08)	−0.04(−0.12,0.03)	−0.05(−0.17,0.07)	−0.14(−0.29,0.02)	0.03(−0.12,0.18)	−0.01(−0.18,0.15)
PFOSA	−2.54(−23.81,18.74)	21.10(−24.53,66.74)	−28.20(−68.68,12.35)	−13.78(−60.29,32.74)	10.69(−25.83,47.21)	0.16 **(0.04, 0.27)	0.49 ††(0.24,0.74)	−0.03(−0.25,0.19)	0.20(−0.05,0.45)	−0.03(−0.23,0.16)	0.00(−0.07,0.07)	−0.06(−0.21,0.09)	−0.04(−0.17,0.09)	−0.05(−0.20,0.10)	0.17 **(0.05, 0.29)

NOTE: Findings restricted to significant findings robust to false discovery rate (FDR) adjustment; however, all significant findings are presented in Supplemental Table 2. Separate models were run for each chemical and racial/ethnic group adjusting maternal age, education, pre-pregnant body mass index, serum lipids (except PFASs), serum cotinine, infant sex, and a chemical-maternal race/ethnic interaction term. Head circumference models also were adjusted for mode of delivery. Chemicals were log-transformed and scaled by SD. Mode of delivery was additionally adjusted for head circumference. CI, confidence interval; PBDEs, polybrominated diphenyl ethers; PFOA, perfluorooctanoic acid; PFOSA, perfluorooctane sulfonamide.

*p < 0.05.

**p ≤0.01.

†False discovery rate (FDR) correction p < 0.05.

††FDR p ≤ 0.01

Table 5

Significant associations robust to false discovery rate correction between plasma chemical concentrations and neonatal umbilical circumference and upper arm and thigh lengths, NICHD Fetal Growth Studies - singletons, 2009–2013.

Chemical	Umbilical circumference (cm) β (95% CI)					Upper arm length (cm) β (95% CI)					Upper thigh length (cm) β (95% CI)				
(ng/ml)	Cohort	White	Black	Hispanic	Asian	Cohort	White	Black	Hispanic	Asian	Cohort	White	Black	Hispanic	Asian
OCPs:															
HCB	1.01 ** (0.31, 1.71)	**4.71 †† (2.46, 6.95)**	−0.61 (−1.94, 0.72)	−0.06 (−1.03, 0.91)	0.003 (−0.10, 0.11)	0.11 (−0.18, 0.40)	0.46 (−0.48, 1.40)	−0.13 (−0.69, 0.42)	0.10 (−0.31, 0.50)	0.02 (−0.03, 0.06)	0.32 (−0.06, 0.69)	1.43 * (−0.21, 2.65)	−0.30 (−1.02, 0.42)	0.13 (−0.40, 0.65)	0.005 (−0.05, 0.06)
p,p′-DDE	0.09 (−0.11, 0.29)	−0.20 (−0.76, 0.36)	0.61 * (0.14, 1.07)	−0.13 (−0.31, 0.05)	0.10 (−0.12, 0.31)	−0.04 (−0.12, 0.05)	−0.01 (−0.24, 0.22)	−0.14 (−0.33, 0.06)	−0.03 (−0.10, 0.05)	0.02 (−0.07, 0.11)	0.11 (0.01, 0.22)	0.51 † (0.21, 0.81)	0.02 (−0.23, 0.27)	0.01 (−0.09, 0.11)	−0.09 (−0.20, 0.03)
PCBs:															
118/106	0.00 (−0.15, 0.14)	0.01 (−0.22, 0.24)	0.05 (−0.26, 0.35)	−0.04 (−0.46, 0.38)	−0.03 (−0.19, 0.12)	0.03 (−0.04, 0.09)	−0.02 (−0.11, 0.08)	0.04 (−0.09, 0.17)	0.07 (−0.11, 0.24)	0.01 (−0.05, 0.08)	−0.12 † (−0.20, −0.04)	−0.10 (−0.22, 0.02)	−0.15 (−0.31, 0.02)	−0.29 * (−0.51, −0.06)	0.04 (−0.04, 0.12)
146/161	0.07 (−0.09, 0.23)	−0.07 (−0.41, 0.27)	0.31 (−0.03, 0.65)	0.02 (−0.36, 0.39)	0.03 (−0.12, 0.18)	−0.04 (−0.11, 0.03)	0.00 (−0.14, 0.14)	−0.03 (−0.17, 0.11)	−0.13 (−0.28, 0.03)	−0.01 (−0.07, 0.06)	−0.14 † (−0.23, −0.05)	−0.03 (−0.22, 0.15)	−0.27 ** (−0.45, −0.08)	−0.30 ** (−0.49, −0.09)	0.02 (−0.06, 0.11)
PFASs:															
N-MeFOSAA	−0.06 (−0.18, 0.06)	0.15 (−0.11, 0.41)	−0.14 (−0.36, 0.07)	−0.28 * (−0.52, −0.05)	0.03 (−0.24, 0.3)	−0.06 * (−0.11, −0.01)	−0.14 ** (−0.25, −0.04)	−0.03 (−0.11, 0.06)	−0.01 (−0.11, 0.08)	−0.05 (−0.17, 0.06)	−0.09 † (−0.16, −0.03)	−0.16 * (−0.3, −0.02)	−0.01 (−0.12, 0.11)	−0.12 (−0.25, 0.01)	−0.08 (−0.23, 0.07)
PFDA	0.07 (−0.05, 0.20)	0.43 † (0.19, 0.68)	−0.39 †† (−0.6, −0.17)	−0.11 (−0.39, 0.18)	0.36 ** (0.12, 0.6)	−0.09 † (−0.14, −0.04)	−0.21 †† (−0.31, −0.11)	−0.06 (−0.15, 0.03)	0.07 (−0.05, 0.18)	−0.15 ** (−0.25, −0.05)	−0.14 †† (−0.21, −0.07)	−0.32 †† (−0.45, −0.19)	−0.18 ** (−0.3, −0.06)	−0.02 (−0.17, 0.14)	−0.07 (−0.17, 0.09)
PFDoDA	0.15 * (0.02, 0.29)	0.41 * (0.06, 0.77)	−0.34 ** (−0.59, −0.11)	0.03 (−0.13, 0.19)	0.52 † (0.22, 0.83)	−0.06 * (−0.12, 0.00)	−0.10 (−0.24, 0.05)	0.03 (−0.07, 0.13)	0.04 (−0.03, 0.11)	−0.22 † (−0.35, −0.1)	−0.10 ** (−0.18, −0.03)	−0.17 (−0.36, 0.02)	−0.13 * (−0.26, 0)	0.00 (−0.09, 0.09)	−0.10 (−0.27, 0.06)
PFDS	−0.11 (−0.26, 0.05)	−0.14 (−0.5, 0.21)	−0.38 †† (−0.59, −0.17)	−0.10 (−0.52, 0.32)	0.20 * (0.02, 0.38)	−0.07 * (−0.13, 0.00)	−0.05 (−0.2, 0.1)	−0.09 * (−0.18, 0)	−0.04 (−0.22, 0.13)	−0.11 * (−0.16, −0.01)	−0.11 ** (−0.20, −0.03)	−0.29 † (−0.49, −0.1)	−0.06 (−0.17, 0.06)	−0.08 (−0.3, 0.15)	−0.02 (−0.12, 0.08)
PFHpA	−0.13 * (−0.25, −0.01)	0.20 * (0.02, 0.38)	−0.27 (−0.55, 0.02)	−0.07 (−0.29, 0.15)	−0.38 ** (−0.65, −0.11)	0.03 (−0.03, 0.08)	−0.07 (−0.15, 0)	0.08 (−0.04, 0.2)	0.04 (−0.05, 0.14)	0.05 (−0.06, 0.16)	−0.13 †† (−0.20, −0.06)	−0.18 †† (−0.28, −0.08)	−0.14 (−0.29, 0.01)	0.03 (−0.09, 0.15)	−0.24 ** (−0.38, −0.09)
PFHxS	−0.26 †† (−0.40, −0.13)	0.08 (−0.12, 0.27)	−0.34 ** (−0.56, −0.12)	−0.36 * (−0.64, −0.08)	−0.43 * (−0.76, −0.1)	0.03 (−0.02, 0.09)	0.01 (−0.09, 0.07)	0.05 (−0.04, 0.15)	0.11 (−0.01, 0.22)	−0.01 (−0.15, 0.12)	−0.12 † (−0.19, −0.05)	−0.09 (−0.19, 0.01)	−0.14 * (−0.26, −0.02)	−0.02 (−0.18, 0.13)	−0.22 * (−0.40, −0.04)
PFNA	0.06 (−0.06, 0.18)	0.25 * (0.01, 0.49)	−0.20 (−0.42, 0.02)	−0.14 (−0.38, 0.09)	0.33 ** (0.08, 0.58)	−0.04 (−0.09, 0.01)	−0.15 ** (−0.25, −0.05)	0.06 (−0.03, 0.15)	0.04 (−0.05, 0.14)	−0.12 ** (−0.23, −0.02)	−0.16 †† (−0.22, −0.10)	−0.32 †† (−0.45, −0.19)	−0.19 ** (−0.31, −0.08)	−0.06 (−0.19, 0.06)	−0.06 (−0.2, 0.07)
PFOA	−0.06 (−0.19, 0.07)	0.15 (−0.05, 0.35)	−0.26 (−0.52, 0.01)	−0.19 (−0.45, 0.06)	0.07 (−0.21, 0.35)	−0.02 (−0.07, 0.03)	−0.11 * (−0.19, −0.02)	0.05 (−0.06, 0.16)	0.07 (−0.03, 0.18)	−0.09 (−0.21, 0.02)	−0.19 †† (−0.26, −0.12)	−0.26 †† (−0.37, −0.15)	−0.22 ** (−0.36, −0.08)	−0.10 (−0.24, 0.04)	−0.18 * (−0.33, −0.03)
PFOS	0.04 (−0.09, 0.16)	0.17 (−0.07, 0.41)	−0.26 * (−0.49, −0.03)	−0.17 (−0.45, 0.11)	0.40 † (0.16, 0.65)	−0.04 (−0.1, 0.01)	−0.08 (−0.18, 0.02)	−0.04 (−0.13, 0.06)	0.05 (−0.07, 0.17)	−0.10 ** (−0.21, 0)	−0.03 (−0.10, 0.04)	−0.20 † (−0.33, −0.07)	−0.11 (−0.23, 0.02)	0.11 (−0.05, 0.26)	0.08 (−0.05, 0.22)
PFUnDA	0.09 (−0.05,0.23)	0.09 (−0.27,0.44)	− 0.27 * (−0.48,− 0.06)	0.06 (−0.28,0.40)	**0.49 †† (0.28, 0.70)**	−0.02 (−0.08,0.04)	−0.08 (−0.22,0.07)	0.05 (−0.03,0.14)	0.14 * (0, 0.29)	**−0.19 †† (−0.28,−0.10)**	**−0.15 †† (−0.23,−0.07)**	**−0.32 †† (−0.51,−0.13)**	−0.14 * (−0.25,−0.02)	−0.07 (−0.25,0.12)	−0.07 (−0.19,0.04)

NOTE: Restricted to significant findings robust to false rate discovery (FDR) correction shown in boldface; however, all significant findings are presented in Supplemental Table 3. Models were adjusted for maternal age, education, pre-pregnant body mass index, serum cotinine, serum lipids (except PFASs), infant sex, and a chemical-maternal race/ethnic interaction term. Chemicals were log-transformed and scaled by their standard deviations for analysis. Mode of delivery was additionally adjusted for in head circumference models. CI, confidence interval; HCB, hexachlorobenzene; N-MeFOSAA, *N*-methylperfluoro-1-octanesulfonamidoacetic acid; OCPs, organochlorine pesticides; PCBs, polychlorinated biphenyls; PFASs, poly- and per-fluorinated alkyl substances; PFDS, perfluorodecane sulfonate; PFHpA, perfluoroheptanoic acid; PFHxS, perfluorohexanesulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFUnDA, perfluoroundecanoic acid; *p,p′-DDE*, *p,p′*-dichlorodiphenyldichloroethylene; *p,p′*-DDT, *p,p′*-dichlorodiphenyltrichloroethane.

* p < 0.05.

** p≤ 0.01.

† FDR p < 0.05.

$^{\dagger\dagger}_{\text{FDR p} \leq 0.01}$.