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Examining endocrine disruptors measured in newborn dried blood spots and early childhood growth in a prospective cohort

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Abstract

Objective: To determine whether newborn concentrations of perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), and bisphenol A (BPA) are associated with early childhood growth.

Methods: We included 1954 singletons and 966 twins from the Upstate KIDS Study (born 2008–2010) with newborn dried blood spot concentrations of PFOS, PFOA and BPA quantified by liquid chromatography tandem mass spectrometry. Children's weight and height were reported from birth through 3 years of age. Repeated measures were modelled using generalized linear mixed models.

Results: PFOS and PFOA were associated with lower BMI (-0.078 kg/m^2 ; -0.12 , -0.038 and -0.076 kg/m^2 ; -0.17 , -0.051 per 1 SD increase in log PFOS and PFOA, respectively) and not with

early obesity among singletons. Inconsistent associations were observed for twins. BPA levels were higher among neonates with NICU stay ($p<0.001$), making associations difficult to interpret.

Conclusion: Perfluorinated alkyl substances did not exhibit obesogenic associations with early measures of childhood growth. Blood-based BPA measures are limited by the non-persistent nature of the chemical and unknown sources from hospital settings may present only transient exposures.

Keywords

BPA; PFOS; PFOA; body mass index; children

Introduction

The evidence for endocrine-disrupting chemicals (EDC) being a contributor to the worldwide obesity epidemic remains speculative but include observations that laboratory animals have also grown larger over time. As such animals are well controlled by genetics and nutrition, it pointed to another source of exposure for the observed obesogenic effects (1, 2). Targeted studies have shown that prenatal exposures to EDCs may promote adipocyte differentiation, among other mechanisms (3). EDCs that have a particular impact on metabolic pathways and promote obesity have been termed “obesogens” (4).

Perfluorinated alkyl substances (PFASs), used in coatings or repellants such as Teflon or stain resistant clothing, are persistent chemicals and suspected obesogens (4). Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) are two commonly measured PFASs. Prenatal exposure to endocrine disruptors has unfortunately become ubiquitous (5). Half-lives of PFOS and PFOA among adults living in a community with high exposure due to water contamination, was observed to be 3–4 years (6). Hence, cross-sectional data from the NHANES Survey 2003–2004 showed that almost all pregnant women in the U.S. had quantifiable levels of these EDCs (5), raising concerns over their long-term impact on early childhood growth. The evidence of associations between prenatal exposures to PFASs and offspring obesity from ten prospective investigations has also been equivocal (7, 8, 9, 10, 11, 12, 13, 14, 15, 16). Four studies included over 1000 participants (7, 12, 14, 16). Both positive and negative associations have been identified along with some suggestion of greater impact in girls.

Bisphenol A (BPA) is used in the production of polycarbonate plastics and resins for a range of products including toys, cans and food containers (17), and may have obesogenic effects through multiple mechanisms including its ability to weakly bind to the estrogen receptor. Alternatively, hormonal imbalances may affect hypothalamic or other neuronal areas controlling appetite (18). BPA is rapidly metabolized and has a very short half-life of approximately 6 hours in adults, with almost complete excretion by 24 hours observed after oral consumption of its radiolabeled form (19). Even with rapid metabolism, frequent repeated exposure in BPA leaching materials has caused concern for early life exposure. Longitudinal studies have examined prenatal BPA, as measured using 1–2 maternal spot urine samples, and early childhood growth (20), with the majority finding no associations (21, 22, 23, 24, 25). Postnatal exposure from medical equipment used in hospitals may be an

important route of exposure that previous studies did not capture using maternal urine samples during pregnancy. In particular, babies requiring a neonatal intensive care unit (NICU) stay have high BPA levels due to exposure from medical devices (26).

Prompted by the equivocal literature in the context of ubiquitous exposure for contemporary birth cohorts, we sought to determine the associations between 3 EDCs – PFOS, PFOA and BPA – and longitudinally capture early childhood growth, infant rapid weight gain and obesity in a population-based birth cohort. A unique feature of this cohort is the measurement of EDCs in newborn dried blood spots (DBS) to capture neonatal exposure in lieu of proxy prenatal exposures (27). PFOS and PFOA have previously been measured in blood spots with similar concentrations as found in whole blood (27, 28). Given the potential ease of background contamination of BPA on filter papers especially in paper products, we previously performed methodologic work to validate DBS (27). Under several quality assurance procedures, including field blanks from unspotted sections of the blood spot card, we were able to measure levels of BPA in the blood (27). Although not all sources of contamination arising from sampling may be removed (e.g. use of capillary tubes at point of blood contact), we hypothesized that any unaccounted-for contamination would only induce random measurement error rather than systematic error and that DBS measures could remain good indicators of early life exposure of these ubiquitous chemicals. We also suspect that BPA levels most likely reflect postnatal exposure rather than prenatal exposure due to BPA's short half-life and non-persistent nature. Whereas previous studies were conducted solely among singletons, we also evaluated associations among twins, given their susceptibility to preterm delivery. In addition, we evaluated sex specific effects due to the suspected differences in endocrine interactions of these chemicals.

Methods

Study population

The Upstate KIDS study enrolled infants at approximately 4 months in New York State (excluding New York City) to study the impact of infertility treatment on child growth and development through 3 years of age (29). The study recruited (2008–2010) all infants conceived by infertility treatment at 4 months postpartum. For every singleton conceived by treatment, three who were not were also recruited, frequency matched on region of delivery. All twins and higher order multiples were also recruited. We previously observed that children conceived by infertility treatment (n=1408 (32%), oversampled by design) grew similarly to children not conceived with treatment (n=3023) after accounting for plurality (30). The New York State Department of Health and the University at Albany Institutional Review Boards approved the study. Parents provided written informed consent.

Growth measures

At enrollment, mothers received child health journals to record clinically measured values of weight and length from pediatric wellness visits (30). Mothers reported the measures, date and/or child's age at each visit in standardized questionnaires. Multiple entries on each questionnaire allowed mothers to report measures from multiple visits at each questionnaire (sent at 4, 8, 12, 18, 24, 30 and 36 months). Children had on average seven measurements as

reported by mothers over the first three years of age. Birth length values were from maternal report. Birth weight came from birth certificates. Data were fully inspected with editing for outliers as previously described (30) and z-scores were calculated using the World Health Organization Child Growth Standards.

Laboratory methods

We asked parents at 8 months following delivery for permission to use their child's residual DBS from Newborn Screening to measure EDCs. Sixty-two percent of contacted parents agreed and details of the retrieval process and the validity of using DBS can be found elsewhere (27, 31). Chemical concentrations of PFOS, PFOA, and BPA were measured from whole blood eluted from one 16mm diameter DBS, using liquid chromatography tandem mass spectrometry per previously validated methods accounting for potential contamination from storage and handling (27). Limits of detection were 0.3, 0.03, and 0.05 ng/ml, for PFOS, PFOA, and BPA, respectively (27). Background contamination was taken into account by using unspotted sections of the filter paper as field blanks to account for any contamination that arise from hospital settings and subtracting these background levels from measured concentrations. The percentage of concentrations below the LOD were 0.1% for PFOS, 0.5% for PFOA, and 10% for BPA, reflecting ubiquitous exposure in newborns. Instrument derived concentrations were used without substituting concentrations below the LOD to avoid bias when estimating human health effects (32).

Covariates

Mothers reported on race/ethnicity, alcohol, smoking, marital/cohabitation status and paternal anthropometrics at enrollment. Parental ages, insurance status, parity, infant gender, and gestational age came from birth certificates. Prepregnancy weight and height information to derive body mass index (BMI) was from birth certificates and relied on maternal report if missing (n=53; <1%).

Statistical analysis

Of the children with chemical measurements (n=3111), 191 (6%) singletons/twins were missing information on all weight measurements after birth prompting exclusion from growth analyses. For length analyses, 342 were excluded (11% infants). Chemical concentrations were log-transformed and scaled by standard deviation. Non-linear associations were examined by quartiles of chemical concentrations.

Linear mixed models with a random slope and cubic splines for age and age-sex interactions were used to estimate mean differences in infant growth per log standard deviation (SD) increase in chemical concentrations from birth to 36 months. Nodes for the splines were picked at the points where data centered, namely 8, 16, 20, 24, and 28 months, in keeping with the American Academy of Pediatrics' guidelines that suggest more frequent assessment at younger ages. These models assumed any shifts in the whole trajectory of weight/height/BMI by chemical concentrations were the same over time. Rate of change was separately investigated by rapid weight gain analyses (defined below based on the difference between infant and birth weight). Plurality interactions were found to be significant. As previous literature had detected sex differences, singleton analyses were further stratified by

sex although twin analyses were not due to smaller sample size. Any analyses which included twins were clustered on family to account for correlations between sibling pairs. Logistic regression with generalized estimating equations was used to estimate odds ratios (95% CI) for rapid infant weight gain and risk of childhood overweight. As there were no significant differences previously observed for infertility treatment and growth trajectories after accounting for plurality, (30) we did not further stratify analyses by treatment exposure.

Rapid infant weight gain is an assessment of whether babies grew more rapidly than expected with regards to their weight gain after delivery. To examine rapid infant weight gain, a two-step approach to the analysis was implemented. First, weight gain since birth was calculated at 4, 9 and 12 months using weights predicted from linear mixed models with cubic splines accounting for sex and sex*time interactions (30). Predicted weights were used for standardization as children did not always visit the pediatrician at exactly the same point in time. All weight information before and after those time points (e.g., 3, 5, 11 months, etc.) informed the predictive models for estimating weight at those time points. Then, as a second step, weight gain was calculated by taking the difference between predicted weights and birthweight. Standard deviation scores (SDS) were calculated for each child at each time point by taking the difference between the child's weight gain and average weight gain among singletons in our sample, divided by their standard deviations (33). A child was classified as having experienced rapid weight gain if his/her SD was above 0.5 for 4 or 9 months or above 0.67 for 12 months (33). These cutoffs have been previously associated with risk of non-alcoholic liver steatosis in children and represent a clinically meaningful definition for whether the weight gain was considered too rapid or not (33). Childhood obesity (95th percentile for BMI) was evaluated among participants with both weight and height reported at the same pediatric visit past 24 months of age (n=1074 singletons and 476 twins). Children older than 2 years of age at or above the 95th percentile for BMI were identified using the z-scores calculated using the WHO standards as described above. Analyses were adjusted for maternal age (continuous), pre-pregnancy body mass index (BMI, kg/m²), education (less than high school, high school, some college, college, graduate studies), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), private insurance status (yes/no), and infant sex. Other covariates such as neonatal intensive care unit stay (yes/no), breastfeeding at discharge (yes/no), gestational diabetes (yes/no), and maternal smoking (never, before pregnancy, during pregnancy) did not meaningfully change the estimates of associations and for parsimony were not retained. Gestational age (weeks) and birth weight (grams) were added separately to evaluate the impact of those covariates. As missing covariate data were <5% of the sample, we did not apply multiple imputations on trajectory or rapid weight gain analyses but performed analyses on participants with complete information. To evaluate the impact of missing data on obesity analyses, we used multiple imputations to create 50 datasets deriving missing BMI information for all children. The imputation model included maternal age, maternal race, pre-pregnancy BMI, paternal BMI, private insurance, married/living as married, maternal education, infertility treatment, pre-gestational and gestational diabetes, pregnancy smoking, pregnancy hypertension, plurality, infant sex, NICU stay, gestational age, breast feeding at delivery, chemical concentrations, and last recorded weight z-score. All analyses were conducted in SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

There were 3111 children (from 2,636 families) with EDCs quantified, including 966 twins (440 twin-pairs from the same family and 86 twins without measures from their cotwin). Correlations between related twins (n=440 pairs) were high for PFOS and PFOA concentrations ($r=0.83$ and 0.75 , respectively) but lower for BPA ($r=0.23$). Median (interquartile range; IQR) concentrations of PFOS in one set of twins was 1.61 (1.07, 2.24) and their cotwins was 1.61 (1.08, 2.30) ng/ml. For PFOA these were 0.98 (0.62, 1.46) and 1.04 (0.63, 1.64), respectively.

Family characteristic comparisons among children with longitudinal growth data are shown in Table 1. On average, seven measures of weight and length/height were reported per child. Most mothers were white, married, college educated, and had private health insurance. A quarter of women were obese, 34% conceived with infertility treatment and 66% never smoked. The median (IQR) concentrations of PFOS, PFOA and BPA were 7.8 (3.4, 14.6) ng/ml, 1.7 (1.1, 2.4) ng/ml, and 1.1 (0.7, 1.6) ng/ml, respectively. The correlation between PFOS and PFOA was 0.32, and -0.01 between BPA and either PFAS. BPA concentrations were higher among neonates who were in the intensive care unit (NICU) (median [IQR] 8.4; 4.4, 15.2) ng/ml) as well as among babies who were delivered by c-section even after removing those who went to the NICU (8.3; 3.5, 15.4 ng/ml). Otherwise, no differences were found by socio-demographics, infertility treatment or by breastfeeding at hospital discharge (data not shown).

Significant ($p<0.05$) interactions were observed for PFAS and plurality prompting stratification by plurality, and infant sex for singletons (Table 2). PFOS and PFOA were inversely associated with weight-for-length and BMI. For each SD increase in log unit of PFOS, BMI was lower in girls by -0.16 (95% CI: -0.24 , -0.08) kg/m^2 and to a lesser extent in boys by -0.06 (95% CI: -0.15 , 0.02) kg/m^2 . For PFOA, this decrease in BMI seemed to be tied to increased length of 0.13 cm (95% CI: 0.02, 0.25 cm) per SD increase but was imprecise when sex stratified. BPA was positively associated with weight and BMI among singletons, with stronger associations observed for boys in comparison to girls. For each SD increase in log unit of BPA, BMI increased by 0.11 kg/m^2 (95% CI: 0.04, 0.19) among boys but not for girls (0.01; -0.06 , 0.09). These observations held true even after further adjusting for NICU stay, infertility treatment, or other pregnancy factors (data not shown).

We further evaluated non-linear associations with BMI z-score by quartiles of EDCs. (Table 3) PFOA exhibited a dose-response among singletons with lower BMI z-scores observed for each increasing quartile. Singleton girls exhibited a clearer dose-response while a lower BMI was found of similar magnitude for the second and third quartiles as compared to the first quartile among singleton boys. Conversely, twins with higher PFOA levels had higher BMI with concentrations above the first quartile being associated with higher BMI. When further adjusted for birthweight and gestational age, estimates for PFOA quartiles among singleton girls remained similar (data not shown). Lastly, PFOS was associated with lower BMI z-score among singletons in the highest quartile as compared to the lowest quartile, but adjustment for birthweight and gestational age reduced the association (-0.11 ; -0.26 , 0.04 z-score units among singleton girls). No associations were observed among twins or for BPA.

Neonatal BPA concentrations were associated with an increased risk of rapid infant weight gain through 12 months and childhood obesity at ages 24 months or older (Table 4). For each SD increase in log BPA, the odds of being obese (defined as 95th percentile for BMI) reflected a 20% increase (aOR: 1.20; 1.04, 1.39). In sensitivity analyses, we multiply imputed the missing data and found similar results (aOR: 1.16; 1.00, 1.35). Assessing concentrations above the median relative to below revealed a 40% increase in the odds of early childhood obesity (aOR: 1.49; 1.04, 2.13); no trend was observed when assessing quartiles. There were no associations for PFOS and PFOA concentrations and rapid infant weight gain or early childhood obesity (data not shown).

Discussion

To our knowledge, this is the first study to use newborn DBS for quantifying neonatal exposure for 3 ubiquitous EDCs in a large cohort inclusive of singletons and twins and early childhood growth. We found evidence that PFOS and PFOA were associated with reduced growth. Associations for PFOS seem driven by the highest quartile while more of a dose-response was observed for PFOA than PFOS. Some sex specific differences were found in associations including stronger associations observed among boys for BPA, but weaker associations for boys than girls in terms of PFOS and PFOA. Higher BPA levels among singletons was associated with BMI and risk of rapid infant weight gain and early childhood obesity. BPA associations did not follow a clear dose-response and given the issues with its measurement as a non-persistent compound (34) and the relatively low correlation between twins' BPA measurements, our findings should be cautiously interpreted. In addition, DBS measures of BPA may represent more fully postnatal rather than prenatal exposure. We saw evidence of postnatal sources being an influence particularly among neonates with NICU stays, as previously observed elsewhere, due to exposure from medical devices (26). Findings among twins are among some of the first known published but few associations were observed.

While we recognize that the use of any blood samples to measure BPA has been cautioned against by experts in the area due to low levels found after its rapid metabolism and being highly subject to contamination even in well controlled settings (35, 36, 37), we present our findings on BPA even if they are not without limitations to foster discussion for future work. Nevertheless, our BPA findings may not be directly comparable to previous studies of prenatal exposure using maternal urine samples. Due to its short half-life, BPA is best measured in urine, and multiple samples have been recommended to have a reliable exposure during sensitive windows (38). It has been documented that due to the exposure to medical devices, BPA is higher among infants who stayed in the NICU (26). Adjustment for NICU stay did not alter our estimates of associations but residual confounding cannot be ruled out in an observational setting. Another source of BPA could be due to techniques used in assisted reproductive technologies (39), but we previously found no differences in growth by ART or other types of infertility treatment in the same cohort (30). Thus, given the concerns regarding measurement of BPA on the DBS, caution should be taken in interpreting our findings and use of urine rather than blood may prove to be a better course for future work (35). The difficulties of obtaining large samples of newborn urine samples without contamination, are non-trivial. Given the transient nature of hospital exposure,

however, potentially newborn urine measures taken after hospital stay may be a more representative assessment of early life exposure. Although a newborn's liver normally reaches adult capacity of conjugation activity days after birth, high acute exposures during hospital delivery will remain of interest, especially compounded by potential for hepatic immaturity among premature infants requiring long NICU stays (40).

Studies of PFAS also report mixed results. Our observations are congruent with two studies indicating higher exposure may result in smaller size (7, 15), while others were of larger size (10, 12, 13), null (8, 11, 14, 16), or of inverted U-shaped direction (9). The Danish National Birth Cohort first identified that PFOS and PFOA may be associated with smaller infant size, particularly in boys from 0–12 months with a subsequent analysis at 7 years showing no differences in size, albeit the direction of association remains toward lower BMI (7, 8). A study in Taiwan also suggested that PFOA was associated with lower BMI among females rather than males (15). ALSPAC identified an interaction whereby 9 year old girls of mothers in the highest education group tend to be of smaller size with increasing PFOA concentrations (11). This interaction is interesting given that our study also included higher educated women due to oversampling for infertility treatment exposure. However, it is unclear where there is a strong biological rationale for such stratification. We recognize that biologic matrices may generate unique findings rather than consistent findings across all biologic media. To this end, data focusing on BPA as quantified in various biospecimens and children's obesity are needed to more fully understand potential underlying mechanisms. With regards to measurement of PFAS, as blood is typically processed into serum or plasma, use of whole blood may explain differences in concentrations found in the blood spots (which were lower for both PFOS and PFOA compared to NHANES 2013–2014 median concentrations) (41).

Beyond the issues outlined above regarding one-time BPA measurement in DBS samples, some study limitations include its observational design and potential for residual confounding. We could not rule out confounding by dietary sources as we lacked data. If consumption of a healthy diet of fruits and vegetables and fish products are associated with higher PFOS/PFOA levels (42), it could explain the negative direction of association with BMI. On the other hand, Project Viva found no impact of adjusting for maternal diet (14). Reliance on a single neonatal measurement of EDCs does not capture postnatal exposures. Although we did not have directly measured weight and height, the prevalence of obesity (11%) was within the range estimated by NHANES 2011–2014 for 2–5 year old children (43). Relying on maternal report of pediatric visit measures and a lack of BMI data for over 40% of the cohort by age 3 years remains limitations. Families with higher socioeconomic status were more likely to respond to our surveys. However, the BPA levels did not differ by missing status and our results from multiple imputations to account for the missing BMI data under the missing at random (MAR) assumption shows that the association between BPA and obesity remained robust. Moreover, obesity at such a young age as we have examined are also unclear in terms of its predictive power for future adult outcomes. Although obesity tracks from childhood to adulthood, childhood obesity does not account for the majority of adult chronic disease development (44). As our sample was predominantly white, results may not be generalizable to diverse populations.

Conclusion

In this first prospective investigation of neonatal concentrations of PFOS and PFOA quantified in newborn blood spots known to us, we found evidence of sex-specific growth reduction. Understanding the toxicokinetic properties of these common EDCs may help delineate mechanisms observed. To this end, continued attention to mixtures, dose responses and infant sex will likely be informative for establishing any risk to children's healthy growth potential. BPA measures in DBS may be influenced by transient postnatal exposures and contamination in hospital settings, drawing caution to our findings as true effects. Other methods for large population based sampling of urine samples from newborns are needed to further study this important time window for development.

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What is already known about this subject?

- Evidence suggests that prenatal exposure to endocrine disrupting chemicals (EDCs) have “obesogenic” effects.
- Sex-specific effects have been previously observed, potentially due to the estrogen receptor pathway being involved in developmental programming.
- Multiple birth cohort studies have observed equivocal findings.

What does your study add?

- The largest prospective study to include both singletons and twins in examination of EDCs and early childhood growth, rapid infant weight gain, and obesity.
- Perfluorinated alkyl substances were associated with thinness rather than early obesity.
- BPA levels as measured in newborn DBS may be influenced by postnatal exposure and/or contamination, making associations observed with early obesity difficult to interpret.

Table 1.

Baseline characteristics of study participants, Upstate KIDS

	Mean (SD) / No. (%)
Parental characteristics	N=2480 mothers
Maternal age (years)	31.3 (5.8)
Paternal age (years)	33.7 (6.6)
Non-Hispanic White	2102 (85%)
Pre-pregnancy BMI (kg/m ²)	27.0 (6.7)
Normal weight (BMI<25)	1230 (50%)
Overweight (BMI 25–29.9)	629 (26%)
Obese (BMI ≥ 30)	621 (25%)
Paternal BMI (kg/m ²)	28.4 (5.5)
Private insurance	2014 (81%)
Married or living as married	2208 (91%)
College or higher education	1472 (59%)
Infertility treatment	830 (33%)
OI/UI	432 (17%)
ART	397 (16%)
Pre-gestational diabetes	78 (3%)
Gestational diabetes	184 (7%)
Never smoker	1626 (66%)
Infant characteristics	N=2920 infants
Male infant	1481 (51%)
Singleton	1954 (67%)
Birthweight (grams)	3,102 (697)
Gestational age (weeks)	37.8 (2.4)
NICU	468 (16%)
BPA (ng/ml) *	7.8 (3.4, 14.6)
PFOS (ng/ml) *	1.7 (1.1, 2.4)
PFOA (ng/ml) *	1.1 (0.7, 1.6)
Age at last weight (months)	23.7 (11.6)

* Median (interquartile range)

Missing data: paternal age (n=120), pre-pregnancy BMI (n=5), paternal BMI (n=217), private insurance (n=2), marital status (n=66)

Table 2. Environmental chemicals in newborn dried blood spots and growth trajectories (mean differences and 95% CI) in Upstate KIDS

	Per log SD	Singletons	Singleton Females	Singleton Males	Twins
BMI z-score	BPA	0.05 (0.01, 0.09)	0.009 (−0.04, 0.06)	0.08 (0.03, 0.13)	0.02 (−0.04, 0.07)
	PFOA	−0.08 (−0.12, −0.04)	−0.13 (−0.19, −0.07)	−0.04 (−0.09, 0.02)	0.05 (−0.03, 0.12)
	PFOS	−0.08 (−0.12, −0.04)	−0.11 (−0.17, −0.05)	−0.05 (−0.11, 0.01)	−0.03 (−0.10, 0.05)
BMI (kg/m ²)	BPA	0.07 (0.01, 0.12)	0.01 (−0.06, 0.09)	0.11 (0.04, 0.19)	0.02 (−0.05, 0.10)
	PFOA	−0.11 (−0.17, −0.05)	−0.18 (−0.27, −0.09)	−0.05 (−0.12, 0.03)	0.04 (−0.06, 0.14)
	PFOS	−0.11 (−0.17, −0.05)	−0.16 (−0.24, −0.08)	−0.06 (−0.15, 0.02)	−0.06 (−0.16, 0.04)
WFL z-score	BPA	0.05 (0.01, 0.09)	0.01 (−0.04, 0.06)	0.08 (0.03, 0.13)	0.02 (−0.04, 0.08)
	PFOA	−0.08 (−0.12, −0.04)	−0.13 (−0.19, −0.06)	−0.04 (−0.09, 0.02)	0.04 (−0.04, 0.12)
	PFOS	−0.08 (−0.12, −0.04)	−0.10 (−0.16, −0.05)	−0.05 (−0.11, 0.01)	−0.03 (−0.11, 0.05)
Weight z-score	BPA	0.05 (0.02, 0.09)	0.02 (−0.04, 0.07)	0.08 (0.04, 0.13)	−0.02 (−0.08, 0.04)
	PFOA	−0.03 (−0.07, 0.01)	−0.05 (−0.11, 0.01)	−0.01 (−0.06, 0.05)	0.09 (0.03, 0.16)
	PFOS	−0.03 (−0.08, 0.01)	−0.07 (−0.13, −0.01)	−0.001 (−0.06, 0.06)	0.04 (−0.04, 0.12)
Weight (g)	BPA	45.16 (13.09, 77.23)	13.45 (−32.28, 59.17)	77.19 (36.27, 118.11)	−11.96 (−65.06, 41.14)
	PFOA	−12.57 (−49.47, 24.33)	−30.22 (−84.05, 23.60)	6.60 (−44.69, 57.89)	94.04 (33.82, 154.26)
	PFOS	−21.99 (−59.52, 15.55)	−51.57 (−102.32, −0.82)	6.15 (−48.31, 60.61)	62.47 (−13.97, 138.92)
Length z-score	BPA	0.03 (−0.02, 0.08)	0.02 (−0.04, 0.09)	0.04 (−0.02, 0.11)	−0.08 (−0.16, −0.01)
	PFOA	0.05 (0.001, 0.11)	0.07 (−0.004, 0.15)	0.04 (−0.03, 0.11)	0.07 (−0.01, 0.15)
	PFOS	0.03 (−0.03, 0.08)	0.008 (−0.07, 0.08)	0.05 (−0.03, 0.12)	0.07 (−0.04, 0.18)
Length (cm)	BPA	0.07 (−0.04, 0.18)	0.07 (−0.09, 0.22)	0.10 (−0.05, 0.24)	−0.20 (−0.37, −0.03)
	PFOA	0.13 (0.02, 0.25)	0.19 (0.01, 0.37)	0.09 (−0.06, 0.25)	0.16 (−0.03, 0.34)
	PFOS	0.07 (−0.06, 0.19)	0.03 (−0.14, 0.20)	0.10 (−0.07, 0.27)	0.18 (−0.07, 0.42)

Mean differences (95% CI) per log SD increase in chemical concentrations

Models adjusted for: child's age at measurement (months), age-squared, age-cubed, sex*age interactions (except where stratified), maternal age (years), prepregnancy BMI categories (normal weight, overweight, obese), maternal education (less than high school, high school, some college, college, advanced), maternal race (White, Hispanic, Black, Asian, other), private insurance (yes/no)

Abbreviations: WFL, weight-for-length; BPA, bisphenol A; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid (PFOS)

Sample size: BMI z-score, BMI (kg/m²), WFL: 1850 singletons, 881 female, 969 male, 902 twins; Weight z-score and weight (g): 1954 singletons, 930 female, 1024 male, 966 twins; Length z-score and length (cm): 1863 singletons, 887 female, 976 male, 906 twins

Table 3.

Quartiles of environmental chemicals measured in newborn dried blood spot and BMI z-scores by plurality and sex, Upstate KIDS

N	Median (range)	1850 Singletons	881 Singleton Girls	969 Singleton Boys	902 Twins
BPA quartiles					
Q1	0.94 (-18.67, 3.34)	reference	reference	reference	reference
Q2	5.42 (3.35, 7.66)	0.01 (-0.10, 0.13)	-0.01 (-0.17, 0.15)	0.04 (-0.11, 0.20)	-0.06 (-0.24, 0.12)
Q3	10.42 (7.67, 14.11)	0.01 (-0.11, 0.13)	0.03 (-0.14, 0.20)	-0.007 (-0.18, 0.17)	0.03 (-0.15, 0.21)
Q4	23.01 (14.13, 2067)	0.09 (-0.03, 0.20)	0.11 (-0.05, 0.27)	0.06 (-0.10, 0.23)	0.10 (-0.07, 0.28)
PFOA quartiles					
Q1	0.47 (-0.24, 0.68)	reference	reference	reference	reference
Q2	0.87 (0.68, 1.08)	-0.189 (-0.30, -0.07)	-0.16 (-0.32, 0.01)	-0.21 (-0.37, -0.05)	0.23 (0.03, 0.42)
Q3	1.29 (1.08, 1.6)	-0.22 (-0.33, -0.10)	-0.23 (-0.39, -0.06)	-0.20 (-0.37, -0.03)	0.21 (0.01, 0.40)
Q4	2.06 (1.6, 14.06)	-0.24 (-0.35, -0.12)	-0.33 (-0.50, -0.16)	-0.16 (-0.32, 0.01)	0.19 (-0.02, 0.39)
PFOS quartiles					
Q1	0.86 (-0.22, 1.12)	reference	reference	reference	reference
Q2	1.43 (1.12, 1.7)	0.03 (-0.09, 0.15)	0.07 (-0.10, 0.24)	-0.01 (-0.16, 0.15)	0.11 (-0.09, 0.32)
Q3	2.01 (1.7, 2.42)	-0.06 (-0.18, 0.06)	0.03 (-0.16, 0.17)	-0.11 (-0.27, 0.06)	0.07 (-0.14, 0.28)
Q4	3.08 (2.42, 71.13)	-0.20 (-0.32, -0.09)	-0.26 (-0.43, -0.10)	-0.15 (-0.32, 0.02)	0.0005 (-0.20, 0.20)

Model 1: child's age at measurement (months), age-squared, age-cubed, sex*age interactions (except where stratified), maternal age (years), prepregnancy BMI categories (normal weight, overweight, obese), maternal education (less than high school, high school, some college, college, advanced), maternal race (White, Hispanic, Black, Asian, other), private insurance (yes/no);

*PFOS and PFOA models additionally adjusted for infertility treatment (none, OI/UTI, ART)

Abbreviations: BPA, bisphenol A; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid

Table 4.

Bisphenol A (BPA) and odds of rapid infant weight gain and early obesity in Upstate KIDS (n=2920)

	n total / n affected	Odds ratio (95% CI) per log SD BPA	p-value
4-months rapid weight gain	2920 / 774 (27%)	1.10 (1.01–1.19)	0.03
9-months rapid weight gain	2920 / 669 (23%)	1.13 (1.04–1.23)	0.005
12-months rapid weight gain	2920 / 669 (23%)	1.11 (1.02–1.21)	0.02
Obese (95 th percentile)	1319 / 152 (11%)	1.21 (1.03,1.41)	0.02

Adjusted for infant sex, maternal age (years), prepregnancy BMI categories (normal weight, overweight, obese), maternal education (less than high school, high school, some college, college, advanced), maternal race (White, Hispanic, Black, Asian, other), private insurance (yes/no), plurality