Associations of Mid-Childhood Bisphenol A and Bisphenol S Exposure with Adolescent Obesity

By

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Abstract

Background: Epidemiological studies suggest that Bisphenol A (BPA) exposure may increase adiposity in children. Bisphenol S (BPS), a structural analog of BPA, is increasingly used as a BPA substitute. However, few studies have examined the health effects of BPS in children.

Objectives: We estimated the association of BPA and BPS exposure at age 8 years with adiposity measures at 8 and 12 years of age and adipocytokine concentrations at 12 years.

Methods: We quantified urinary BPA and BPS concentrations in 212 8-year old children from the HOME Study, a prospective pregnancy and birth cohort study that enrolled pregnant women in Cincinnati, Ohio (2003-2006). We assessed children's adiposity at 8 years using anthropometry (n=212) and bioelectric impedance and at 12 years using dual energy X-ray absorptiometry (n=181). We measured serum adipocytokine concentrations in children at 12 years of age (n=155). Using multivariable linear regression models, we estimated covariate-adjusted associations of $\log_{10}$-transformed BPA and BPS with adiposity measures at 8 and 12 years and $\log_{10}$-transformed adiponectin and leptin concentrations at 12 years.

Results: BPA concentrations was inversely associated with body fat percentage at age 8 years (β=-1.2 95%CI: -3.4, 1.0), whereas BPS was positively associated with this measure (β=1.1 95% CI: -0.6, 2.7); the 95% CIs of these estimates included the null. Similarly, BPA was inversely associated with visceral fat area (β=-2.2 95%CI: -10.9, 6.4), whereas BPS was positively associated. (β=0.8 95% CI: -5.5, 7.2). BPA and BPS were not associated with serum adiponectin and leptin concentrations at 12 years of age. There was some evidence that sex modified the association between BPS concentrations and waist circumference at age 8 years (interaction p-value=0.13), with positive associations in girls (β=1.4 95% CI: -1.6, 4.5) and null associations in boys (β-1.2 95% CI: -4.8, 2.3).

Conclusions: We did not observe evidence of an association of BPA or BPS concentrations during childhood with measures of child adiposity at age 8 years or 12 years in this cohort.

Introduction

The prevalence of childhood obesity has increased in the United States and worldwide in the past few decades (Abarca-Gómez et al., 2017; Skinner et al., 2018). In the United States, the prevalence of obesity among adolescents in 2016 was 24.8% (Skinner et al., 2018). Childhood and adolescence obesity increases the risk of adult diabetes, heart disease, hypertension, and stroke (Reilly and Kelly, 2011). Therefore, it is essential to identify modifiable determinants of obesity. There is increasing evidence that prenatal, infancy, or early childhood exposure to some endocrine disrupting chemicals can potentially induce obesity later in life by disrupting neuroendocrine systems involved in energy metabolism and eating behavior (Janesick and Blumberg, 2016).

Bisphenol A (BPA), a suspected obesogen, is found in some polycarbonate plastics, food can linings, thermal receipts, and medical equipment (Mikołajewska et al., 2015). The primary source of BPA exposure for most individuals is diet (Mikołajewska et al., 2015). BPA may affect hormone homeostasis, adipocyte proliferation and differentiation, and DNA methylation to increase the risk of obesity (Janesick and Blumberg, 2016, Desai et al., 2018). BPA has been voluntarily phased out of many products but replaced by bisphenol S (BPS) in some plastics, food can linings, and personal care products (Rochester and Bolden, 2015). BPS is chemically similar to BPA, though it is more heat resistant and environmentally stable (Wu et al., 2018) (Supplementary Figure 1). A review of *in vivo* and *in vitro* studies found that BPS has similar estrogenic potency as BPA (Rochester and Bolden, 2015). There is also *in vitro* evidence that BPS induces adipocyte differentiation (Ahmed and Atlas, 2016). BPA may also inhibit adiponectin release from adipocytes (Hugo Eric R. et al., 2008).

Several studies suggest that higher urinary BPA concentrations during childhood are associated with obesity, although some of these studies are cross-sectional, making it difficult to establish causal relations given that the predominant source of BPA is diet. Three cross-sectional studies have found that urinary BPA concentrations were associated with obesity in boys (Trasande et al., 2012, Liu et al., 2019; Mustieles et al., 2019). Another study has found that BPA is cross-sectionally associated with waist circumference in boys (Yang et al., 2017). Other cohort studies with prospective measurements in childhood have found null or inverse associations (Hoepner et al., 2016, Braun et al., 2014, Guo et al., 2020). Two cohort studies with prospective measurements have found positive associations between childhood BPA concentrations and obesity, with no evidence of sex modification (Harley et al., 2013, Vafeiadi et al., 2016).

There have been few epidemiological studies examining the health effects of BPS. In a cross-sectional study of 6 to 17-year-old children, there was no association of urinary BPS concentrations with general obesity, and there was no evidence for sex-specific effects (Liu et al., 2019). In a recent cohort study, BPS concentrations at 6 years of age were inversely associated with body mass index (BMI) z-scores at 10 years of age (Silva et al., 2021).

Given the lack of data on the health effects of childhood BPA and BPS exposure, we investigated whether childhood BPA or BPS exposure is cross-sectionally or prospectively associated with excess adiposity in children at ages 8 and 12 years, as well as serum adiponectin and leptin at age 12 years.

Methods

Study Participants

We used data from the Health Outcomes and Measures of the Environment (HOME) Study, a prospective pregnancy and birth cohort in Cincinnati, Ohio, established to examine the potential health effects of environmental chemical exposures in children. Women were recruited between 2003 and 2006 from nine prenatal clinics affiliated with three delivery hospitals in the Cincinnati, Ohio, area. Women were eligible if they were less than 16±3 weeks pregnant, older than 18 years old, living in a home built in or before 1978, fluent in English, HIV-negative, and not taking medications for seizures and/or thyroid disorders, and had no diagnosis of diabetes, bipolar disorder, schizophrenia, or cancer resulting in radiation treatment or chemotherapy (Braun et al., 2020, 2017).

All women provided written informed consent for themselves and their children at all visits; children provided informed assent at the age 12-year visit. Study protocols were approved by the institutional review boards (IRBs) of Cincinnati Children's Hospital Medical Center (CCHMC) and the cooperating delivery hospitals. Brown University and the Centers for Disease Control and Prevention (CDC) IRBs deferred to the CCHMC IRB

The HOME study enrolled 468 women, of which 389 women delivered live singleton infants. Follow-up was completed on 237 children at 8 years of age, and on 256 children at 12 years of age. The present analyses included 212 children who have biomarker measures for BPA and BPS at 8 years of age, and anthropometric data and covariate information. Among the 256 children who completed follow-up at the 12-year study visit, 181 children had BPA and BPS measurements at 8 years of age, dual-energy X-ray absorptiometry (DXA) measurements at 12 years of age, and covariate information. Further analyses of adiponectin and leptin measurements

at 12 years of age included 155 children who had BPA and BPS measurements, adiponectin and leptin measurements, and covariate information.

Exposure assessment

Children in the HOME study provided urine samples at the 8-year follow-up visit. All samples were refrigerated until they were processed, after which they were stored at or below –20°C until shipped on dry ice to Centers for Disease Control and Prevention for analysis. BPA and BPS concentrations were measured at the CDC National Center for Environmental Health laboratories using previously described analytic chemistry methods (Ye et al., 2008). To account for urine dilution, BPA and BPS concentrations were divided by creatinine and multiplied by 100 to yield units of micrograms BPA and BPS per gram creatinine. The creatinine-normalized urinary BPA and BPS concentrations were $\log_{10}$-transformed in statistical models.

Outcome assessment.

At age 8 years, trained study staff measured children's weight, height, body fat (via bioelectric impedance with a Tanita children's body fat scale) (%), and waist circumference (cm) in triplicate following standardized protocols. We calculate child body mass index (kg/m^2) and converted it to age- and sex-specific *z*-scores using U.S references from the National Center for Health Statistics (*2000 CDC growth charts for the United States*, 2002).

At 12 years of age, we measured the same anthropometry outcomes as above, in addition to conducting dual-energy X-ray absorptiometry scans (Hologic Horizon densitometer) on children to estimate total and regional adiposity. Our adiposity measures included whole-body fat mass index (FMI) z-scores, whole body fat mass percent (%), visceral fat area (cm^2), android (%), and gynoid fat (%). We calculated age and sex-specific fat mass index (fat mass/height^2, kg/m^2) z-scores based on the reference values generated using the 1999–2004 National Health

and Nutrition Examination Survey (NHANES) (Weber et al., 2013). Visceral fat area (cm^2) is the cross-sectional area of fat inside the abdomen. We calculated android and gynoid fat percent as the regional fat mass divided by the whole-body fat mass.

We measured leptin and adiponectin from overnight-fasting serums were also quantified. We measured leptin and adiponectin concentrations in venous serum samples obtained at the 12-year visit using an ELISA sandwich assay and BioTeck microtiter ELx 808 plate reader. All assays were performed by trained technicians at the CCHMC NIH-funded Clinical Translational Research Center Core Laboratory. The LODs were 0.8 ng/mL (leptin) and < 2 μg/mL (adiponectin). We included reagent blanks and QC samples in each analytic batch, with coefficients of variation for repeated QC measurements of approximately 11% and 13% for leptin and adiponectin, respectively. We log_{10}-transformed adipocytokine concentrations for statistical models.

Covariates

We selected covariates that might be associated with BPA or BPS exposure and adiposity using a directed acyclic graph and prior knowledge (Freemark, 2018; Stacy et al., 2016) (Supplementary Figure 2). Trained research assistants collected sociodemographic data, including maternal and child race/ethnicity, age, education, marital status, employment, and insurance using standardized computer-assisted interviews in the second or third trimester. Through reviewing medical charts, we obtained the mother's pre-pregnancy weight, height, and parity.

Frequency of fresh fruit and vegetable consumption at 8 years was collected through questionnaires. Physical activity data was collected using a validated self-reported questionnaire (Kowalski et al., 2004), and we calculated 2010 Healthy Eating Index scores using data from

three 24-hour dietary recalls (NCI 2017) at age 12 years. We evaluated pubertal development by having children self-stage their pubic hair according to images illustrating the different Tanner stages of development (Liu et al., 2019).

Statistical Analysis

We described the univariate characteristics of BPA, BPS, adiposity measures, and covariates using means, standard deviations (SD), medians, interquartile range, or proportions (%). We also calculated median urinary BPA and BPS concentrations at 8 years of age and mean $\pm$ SD of whole-body FMI z-scores at 8 years of age according to categories of each covariate (Table 1). We calculated Spearman correlation coefficients between $\log_{10}$-transformed BPA and BPS concentrations. In addition, we examined potential non-linear associations of BPA and BPS concentrations with adiposity measures at ages 8- and 12-years using covariate-adjusted natural cubic splines.

We used multivariable linear regression models to estimate the association of creatinine-standardized $\log_{10}$-transformed BPA and BPS concentrations at 8 years of age with BMI z-score, body fat percentage, and waist circumference at 8 years of age. We also used multivariable linear regression models to estimate the association of creatinine-normalized $\log_{10}$-transformed BPA and BPS concentrations at 8 years of age with BMI z-scores, whole body fat mass percent, waist circumference, whole-body FMI z-scores, visceral fat area, android fat percent, gynoid fat percent, $\log_{10}$-transformed serum adiponectin, and $\log_{10}$-transformed serum leptin concentrations, and the ratio between $\log_{10}$-transformed adiponectin and leptin concentrations at 12 years of age. The adjusted models using 8-year outcome data included covariates for child age, sex, race, and fruit and vegetable consumption at the 8-year visit, as well as maternal age at delivery, pre-pregnancy BMI, education, marital status, and insurance status. Models using 12-

year data adjusted for total 2015 Healthy Eating Index scores instead of fruit and vegetable consumption, as well as physical activity and pubic hair stage.

Secondary and Sensitivity Analyses

Given that some previous studies reported sex-specific associations between BPA and adiposity (Trasande et al., 2012, Liu et al., 2019, Mustieles et al., 2019), we evaluated effect measure modification by child sex using stratified models and interaction terms between BPA or BPS and child sex. We further examined potential synergy or antagonism by modeling adiposity measures at 8 and 12 years of age as a function of BPA terciles and BPS terciles, with an interaction term of BPA× BPS tercile.

We performed all analyses using R version 3.2.3 (R Core Team, Vienna, Austria).

Results

The mean ages of the 212 children at the 8-and 12-year visits were 8.1 years (SD: 0.6, n=212), and 12.3 years (SD: 0.6, n=181). Most mothers in our analytic sample were Non-Hispanic White (61%), married (67%), and college-educated (50%) (Table 1). Mothers of the study participants at age 12 years had demographic patterns similar to mothers of study participants at age 8 years (Supplementary Table 1).

Children's median urinary BPA and BPS concentrations were 1.6 ug/L (IQR 1, 3.6) and 0.4 ug/L (IQR 0.2, 0.7), respectively (Table 1). Children whose mothers were younger at delivery, had higher pre-pregnancy BMI, and unmarried and cohabitating had higher median BPA concentrations. Mothers with lower maternal education tended to have children with higher BPS concentrations. Children who consumed fewer fresh fruits and vegetables also tended to have higher urinary BPA and BPS concentrations (Table 1). BPA and BPS were moderately correlated with each other (Spearman correlation coefficient=0.4, p-value < 0.001).

BMI z-scores at 8-years were higher in children whose mothers were overweight or obese before pregnancy, were unmarried, and had less than a high school education. Black children and girls also had higher mean BMI z-scores (Table 1). Whole-body FMI z-scores at 12 years were higher in Black children, girls, and children whose mothers were overweight or obese before pregnancy. We observed similar patterns for visceral fat area, android fat percent, and gynoid fat percent, although Black children had lower gynoid fat percent than Non-Hispanic White children and girls had lower visceral fat area than boys (Supplementary Table 2). Among 155 children with adiponectin and leptin measurements at 12 years, increased maternal education was associated with lower geometric mean concentrations of leptin and higher geometric mean concentrations of adiponectin. Leptin concentrations were higher in Black children, whereas adiponectin concentrations were lower in Black children (Supplementary Table 2).

After adjusting for covariates, each 10-fold increase in urinary BPA concentrations were inversely associated with BMI z-score, body fat percent, and waist circumference at age 8 years, although the 95% CI included the null value (Table 2). In contrast, higher urinary BPS concentrations were not associated with BMI z-score, body fat percent, and waist circumference at age 8 years.

Similar to our findings at age 8 years, each 10-fold increase in BPA was associated with decreases in whole-body FMI z-score, visceral fat area, android fat percent, and gynoid fat percent among 181 adolescents with DXA outcomes at 12 years of age, after adjustment for covariates. A 10-fold increase in BPS was not associated with whole-body FMI z-score, visceral fat area, android fat percent, and gynoid fat percent. The associations between BPA and BPS and BMI z-score, whole body fat mass percent, and waist circumference at 12 years followed the same pattern as the associations between BPA and BPS and BMI z-score, body fat percent, and

waist circumference at 8 years (Table 2). Overall, the 95% confidence intervals of all the point estimates included the null value. We also did not observe strong evidence of associations between BPA and BPS with adiponectin, leptin, and adiponectin to leptin ratio (Table 3).

In secondary analyses, we observed limited evidence that child sex modified the association between BPS and waist circumference, where there was an inverse association in boys (β=-1.2, 95% CI: -4.8, 2.3, N=96) compared to a positive association in girls (β=1.4, 95%CI: -1.6, 4.5, N=116) (BPS × Sex interaction term p-value= 0.12) (Figure 1). There was not strong evidence that child sex modified other associations between BPA and BPS and BMI z-score, body fat percent, and waist circumference at 12 years (Figure 2).

There was no evidence of a statistical interaction between BPA and BPS with adiposity outcomes at 8 years of age (continuous BPA x BPS interaction term p-values > 0.05). There was some evidence of a statistical interaction between BPA and BPS with adiposity outcomes at 12 years of age. Specifically, there was some evidence of antagonism between BPA and BPS for whole-body FMI z-score (continuous BPA x BPS interaction p-value=0.03) and gynoid fat (continuous BPA x BPS interaction p-value=0.01) (Supplementary Table 3).

We further examined these antagonistic associations for BMI z-score at 8 years of age (Supplementary Table 4), and FMI z-score as 12 years of age using BPA and BPS terciles (Supplementary Table 5). Using a two-way ANOVA test there was not strong evidence that associations at 12 years varied across the terciles (p = 0.27) (Supplementary Table 5). For instance, the adjusted difference in FMI z-score at 12 years in children with high BPA and low BPS was 0.1 (95% CI: -0.4, 0.6) compared to children with low BPA and BPS. In children with low BPA and high BPS, the adjusted difference in FMI z-score was 0.5 (95% CI: 0, 0.9). Finally,

children with high BPA and high BPS had an adjusted difference in FMI z-score of -0.4 (95% CI: -1.1, 0.3) compared to children with low BPA and BPS.

Discussion

In this cohort, urinary concentrations of BPA and BPS at age 8 years were not associated with measures of childhood adiposity at age 8 and 12 years. Moreover, it did not appear child sex modified these associations. The associations between BPA and BPS concentrations with adiponectin and leptin a age 12 years were also null.

Our results are consistent with some prior cohort studies examining BPA and adiposity in early childhood or adolescence (Hoepner et al., 2016, Braun et al., 2014). Specifically, in a prior study from this cohort, BPA concentrations in the first 2 years of life were inversely associated with BMI z-scores in 285 children aged 2 to 5 from Cincinnati, Ohio (Braun et al., 2017). Among 298 children from New York City, BPA concentrations from 3 and 5 years were inversely associated with change in BMI z-score from 5 to 7 years (Hoepner et al., 2016). In contrast, increasing BPA concentrations in 290 children at 9 years old were cross-sectionally associated with higher BMI z-score, waist circumference, and body fat percentage (Harley et al., 2013). In the RHEA cohort study in Greece, higher BPA concentrations at 4 years were associated with higher concurrent BMI z-score and waist circumference (Vafeiadi et al., 2016). Other cohort studies among 8 to 14-year-old children in Mexico City (Yang et al., 2017) and 7-year-old children in rural China (Guo et al., 2020) have found positive associations between BPA and BMI z-scores. We did not find sex-specific effects for BPA, though in a sample of 298 boys, ages 9-11, in the INMA-Granada cohort study in Spain, BPA was significantly associated with higher BMI z-scores cross-sectionally (Mustieles et al., 2019).

While we found that BPS concentrations were positively associated with adiposity at both ages 8 and 12 years, the 95% CIs of our estimates included the null value. This result is consistent with a cross-sectional study using NHANES data reporting that BPS was associated with higher odds of obesity in children age 6 to 17 years (Liu et al., 2019). Though the Generation R cohort study in the Netherlands found that BPS was inversely associated with BMI in 10-year-old children (Silva et al., 2021).

A priori, we suspected that BPS could have obesogenic effects based on mechanistic studies. BPS disrupts membrane-initiated estradiol-induced cell signaling, altering cell proliferation and death (Viñas and Watson, 2013). BPS enhances preadipocyte differentiation into adipocytes through peroxisome proliferator-activated receptor gamma (PPARg) (Ahmed and Atlas, 2016). BPS may also interfere with hormonal regulation through mRNA deregulation in adipocytes (Verbanck et al., 2017).

We found null associations between BPA, BPS and adiponectin and leptin. Adiponectin regulates glucose levels and energy homeostasis, while leptin helps control food intake and is associated with increased inflammation. Obesity is associated with decreased adiponectin expression and increased leptin expression (Rasouli and Kern, 2008). Previous studies have found that BPA inhibits adiponectin release potentially by antagonizing PPARy (Ben-Jonathan et al., 2009). Fewer studies have examined the effects of BPS on adipokine expression; however, one study suggests that human adipose tissue treated with BPS does not result in altered expression of adiponectin or leptin (Ahmed et al., 2020). Our findings suggest that BPS may not affect adiponectin or leptin expression. Future studies could examine other cardiometabolic or metabolic endpoints, including glucose-insulin homeostasis and lipid concentrations.

Our study contributes to the emerging literature on the health effects of BPA substitutes. However, there are some limitations to consider. First, we used a single urine sample to assess BPA and BPS exposure, which is subject to within-person variability of BPA and BPS concentrations; this may cause exposure misclassification and would be expected to bias our results to the null. Second, our sample size was modest, which may have reduced our statistical power and precision to completely rule out the presence of any associations. Additionally, we cannot account for residual confounding from dietary patterns (e.g., packaged versus fresh food) and exposure mismeasurement from the use of other consumer goods like toys and personal care products (Lu et al., 2018; Sharpe and Drake, 2013; Vandenberg et al., 2007). We also did not adjust for other potential chemical obesogens correlated with BPA or BPS. Finally, we did not have BPS concentrations available at during gestation or earlier in childhood. While BPA has been used in consumer goods since the 1950s, BPS was first used in thermal paper receipts approximately in 2006 (Glausiusz, 2014). Since the introduction of BPS in plastics, thermal paper, and personal care products, BPS has been increasingly detected in urine samples in multiple studies (Wu et al., 2018; Ye et al., 2015). Any exposure that women experienced during pregnancy or adolescents during early childhood would likely not affect future adiposity at the 8 year or 12 year visit due to the low or non-existent levels of exposure.

Despite these limitations, there are several strengths to our study. This included using both cross-sectional and prospective analyses to examine the associations of BPA and BPS concentrations at 8 years with adiposity at 8 and 12 years. Moreover, we used highly detailed measures to assess adiposity at 12 years, as well as metabolism biomarkers (Lindsay et al., 2001). We were also able to account for important confounders including pre-pregnancy BMI, physical activity, and diet.

Conclusion

In HOME study children we did not find evidence of an association between BPA or BPS exposure and childhood adiposity at age 8 or 12 years. Given increasing use of BPA substitutes, future studies with larger sample sizes should examine the extent and health effects of exposure.

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Table 1: Median urinary BPA and BPS concentrations in study participants at 8 years of age according to maternal and child covariates and mean body mass index z-score at 8 years of age according to maternal and child covariates

Variable	n (%)	Child median BPA ug/L (25th, 75th)	Child median BPS ug/L (25th, 75th)	BMI z-score (Mean ± SD)
Overall	212	1.6 (1, 3.6)	0.4 (0.2, 0.7)	0.5 ± 1.2
Maternal age at delivery (years)				
< 25	56 (26.4)	2.1 (1.3, 3.8)	0.4 (0.2, 1.0)	0.6 ± 1.3
25 - 35	125 (59.0)	1.6 (1.0, 3.4)	0.4 (0.2, 0.6)	0.6 ± 1.2
> 35	31 (14.6)	1.2 (0.9, 2.0)	0.4 (0.2, 0.5)	0.4 ± 1.1
Pre-pregnancy BMI				
Underweight-normal <25	111 (52.4)	1.6 (1.1, 3.2)	0.4 (0.2, 0.6)	0.2 ± 1.2
Overweight (25-<30)	55 (25.9)	1.5 (0.8, 3.4)	0.4 (0.2, 0.8)	0.6 ± 1.0
Obese (≥30)	46 (21.7)	2.2 (1.0. 4.0)	0.4 (0.2, 0.8)	1.2 ± 1.3
Maternal Marital Status				
Married	141 (66.5)	1.5 (0.9, 3.3)	0.4 (0.2, 0.6)	0.3 ± 1.1
Unmarried, cohabitating	27 (12.7)	2.3 (1.4 4.0)	0.6 (0.2, 2.3)	0.8 ± 1.1
Unmarried, living alone	44 (20.8)	1.8 (1.3, 3.4)	0.4 (0.2, 0.8)	1.0 ± 1.4
Maternal Education				
High School or Less	36 (17.0)	1.8 (1.2, 3.6)	0.6 (0.3, 1.0)	0.9 ± 1.2
Some college	70 (33.0	2.3 (1.2, 4.1)	0.4 (0.2, 1.0)	0.5 ± 1.3
Bachelors or more	106 (50.0)	1.4 (0.9, 2.2)	0.3 (0.2, 0.6)	0.5 ± 1.1
Insurance				
Private	140 (66.0)	1.5 (0.9, 3.2)	0.4 (0.2, 0.6)	0.4 ± 1.1
Public/uninsured	72 (34.0)	2.1 (1.3, 4.0)	0.4 (0.2, 1.0)	0.9 ± 1.3
Maternal Race				
Black & Other	83 (39.2)	2.1 (1.2, 4)	0.5 (0.2. 1)	0.8 ± 1.3
Non-Hispanic White	129 (60.8)	1.5 (0.9, 3)	0.3 (0.2, 0.6)	0.4 ± 1.1
Child Race				
Black & Other	89 (42.0)	2.1 (1.2, 4.0)	0.5 (0.2, 0.9)	0.8 ± 1.3
Non-Hispanic White	123 (58.0)	1.4 (0.8, 3.0)	0.3 (0.2, 0.6)	0.4 ± 1.1
Child Sex				
Female	116 (54.7)	1.6 (1.0, 3.7)	0.4 (0.2, 0.9)	0.6 ± 1.2
Male	96 (45.3)	1.6 (1.0, 3.3)	0.4 (0.2, 0.7)	0.4 ± 1.2
Child Fruit/Vegetable Consumption				
Daily	117 (55.2)	1.5 (1.0, 2.9)	0.3 (0.2, 0.6)	0.5 ± 1.3
Weekly	85 (40.1)	1.8 (1.0, 3.9)	0.4 (0.2, 0.7)	0.6 ± 1.1
Monthly	10 (4.7)	3.5 (1.5, 4.1)	0.8 (0.5, 2.5)	0.4 ± 1.3

Table 2: Unadjusted and adjusted change in body mass index z-score, body fat percentage, waist circumference at 8 and 12 years of age, whole-body fat mass index z-score, visceral fat area, android fat, and gynoid fat at 12 years of age for a 10-fold increase in child urinary BPA and BPS concentrations

Outcome	Unadjusted		Adjusted	
	BPA	BPS	BPA	BPS
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Age 8 Year (n=212)				
BMI z-score[a]	-0.1 (-0.6, 0.3)	0.1 (-0.2, 0.4)	-0.1 (-0.6, 0.3)	0.1 (-0.2, 0.4)
Body Fat %[a]	-1.2 (-3.5, 1.1)	1.0 (-0.7, 2.8)	-1.2 (-3.4, 1.0)	1.1 (-0.6, 2.7)
Waist circumference (cm)[a]	-1.2 (-4.3, 1.9)	0.3 (-2.1, 2.6)	-0.6 (-3.6, 2.4)	0.5 (-1.8, 2.8)
Age 12 Year DXA (n=181)				
BMI z-score[b]	- 0.1 (-0.5, 0.2)	0.2 (-0.2, 0.5)	-0.3 (-0.7, 0.1)	0.1 (-0.2, 0.4)
Body Fat %[b]	-1.1 (-3.6, 1.4)	0.3 (-1.5, 2.2)	- 1.6 (-4.1, 0.9)	0.1 (-1.7, 1.9)
Waist circumference (cm) [b]	-1.7 (-6.8, 3.3)	1.0 (-2.8, 4.6)	-2.6 (-7.4, 2.3)	1.2 (-2.4, 4.7)
Whole body FMI z-score[b]	-0.1 (-0.5, 0.2)	0.1 (-0.1, 0.3)	-0.2 (-0.5, 0.1)	0.1 (-0.2, 0.3)
Visceral fat Area (cm^2)[b]	-2.4 (-10.9, 6.0)	0.6 (-5.7, 6.8)	-2.2 (-10.9, 6.4)	0.8 (-5.5, 7.2)
Android fat (%)[b]	-1.7 (-4.9, 1.4)	0.6 (-1.8, 2.9)	-2.3 (-5.4, 0.9)	0.4 (-2.0, 2.7)
Gynoid fat (%)[b]	-1.2 (-3.5, 1.1)	0.3 (-1.3, 2.0)	-1.5 (-3.7, 0.8)	0.1 (-1.6, 1.7)

[a] Adjusted for child race (Black and other, Non-Hispanic White), maternal education (high school or less, some college, bachelor's or more) at 8-year visit, maternal marital status (married, unmarried and cohabitating, unmarried and living alone) at 8-year visit, insurance public/uninsured) at 8-year visit, maternal age (years) at delivery, maternal pre-pregnancy BMI (kg/m^2), fresh fruit and vegetable consumption at 8-year visit (daily, weekly, monthly). Body fat percentage and waist circumference further adjusted for child sex (boys, girls) and age (years)

[b] Adjusted for child race, child age. maternal education at 8-year visit, maternal marital status at 8-year visit, insurance at 8-year visit, maternal age at delivery, maternal pre-pregnancy BMI, total healthy eating scores (0-100), physical activity score (1-5), and self-pubertal staging at 12-year visit (Stages 1-5).Body fat %, waist circumference, visceral fat area, android fat, and gynoid fat were further adjusted for child sex and age.

Table 3: Unadjusted and adjusted percent change in adiponectin and leptin for a 10-fold increase in child urinary BPA and BPS concentrations

Outcome	n	Unadjusted		Adjusted	
		BPA	BPS	BPA	BPS
		β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Adiponectin [a]	155	16.1 (-9.7, 49.3)	11.3 (-7.6, 34.0)	21.5 (-6.9, 58.4)	15.2 (-4.9, 39.4)
Leptin [a]	155	-3.3 (-39.0, 53.4)	-4.5 (-32.1, 34.3)	-21.1 (-50.1, 25.0)	-9.7 (-35.2, 25.8)
Adiponectin: Leptin Ratio [a]	155	-1.3 (-12.0, 10.8)	-1.6 (-9.6, 7.2)	-6.3 (-16.5, 5.1)	-3.1 (-10.8, 5.3)

[a] Adjusted for child sex (boys, girls), child race (Black and other, Non-Hispanic White), child age (years), maternal education (high school or less, some college, bachelor's or more) at 8-year visit, maternal marital status (married, unmarried and cohabitating, unmarried and living alone) at 8-year visit, insurance (private, public/uninsured) at 8-year visit, maternal age (years) at delivery, maternal pre-pregnancy BMI (kg/m^2), total healthy eating scores (0-100), physical activity score (1-5), and pubertal stage at 12 year visit (Stages 1-5).

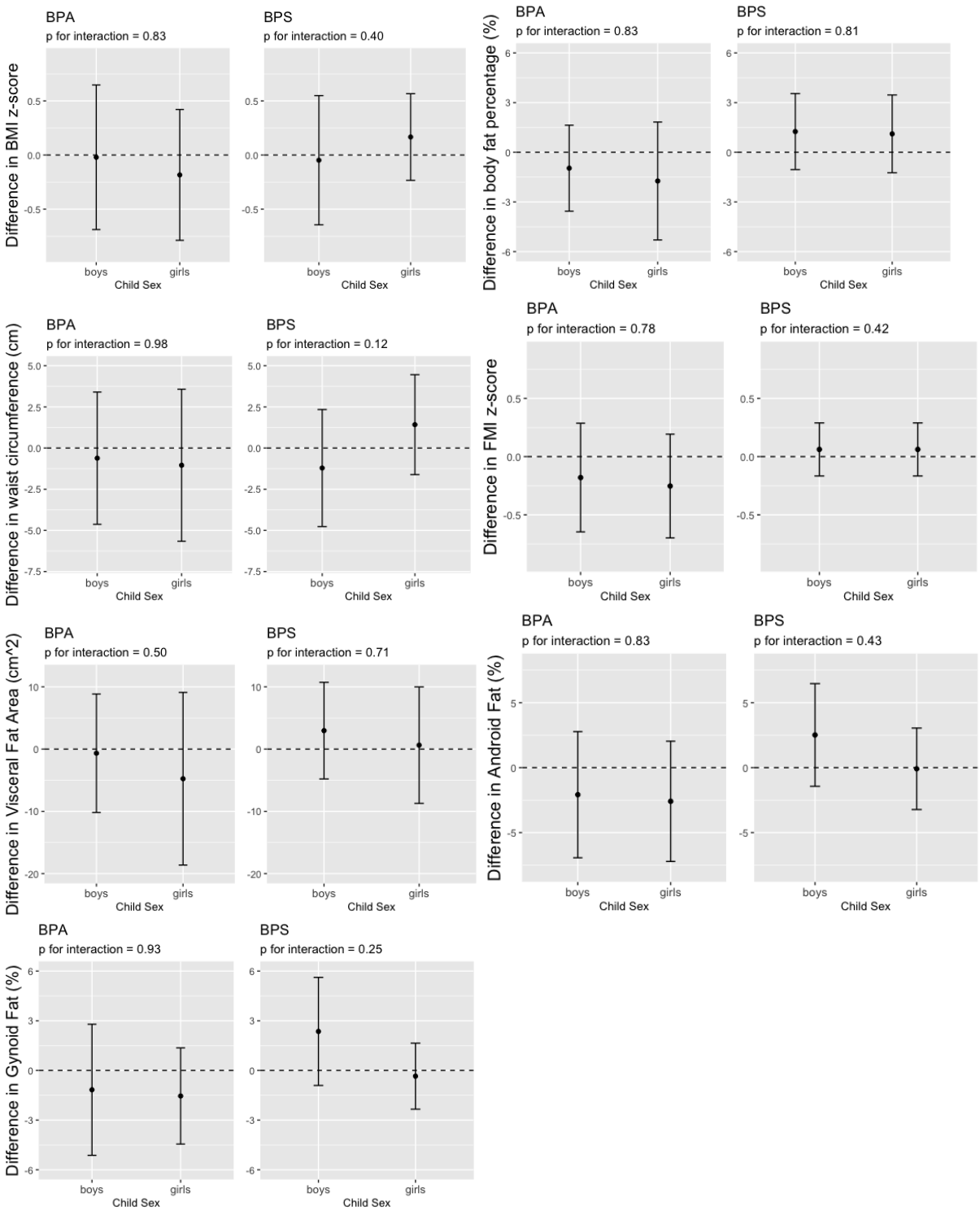

BPA
p for interaction = 0.83
BPS
p for interaction = 0.40
Difference in BMI z-score
BPA
p for interaction = 0.83
BPS
p for interaction = 0.81
Difference in body fat percentage (%)
BPA
p for interaction = 0.98
BPS
p for interaction = 0.12
Difference in waist circumference (cm)
BPA
p for interaction = 0.78
BPS
p for interaction = 0.42
Difference in FMI z-score
BPA
p for interaction = 0.50
BPS
p for interaction = 0.71
Difference in Visceral Fat Area (cm^2)
BPA
p for interaction = 0.83
BPS
p for interaction = 0.43
Difference in Android Fat (%)
BPA
p for interaction = 0.93
BPS
p for interaction = 0.25
Difference in Gynoid Fat (%)
boys
girls
Child Sex

Figure 1: Estimated differences and 95% CIs in BMI z-score, body fat percentage, waist circumference at age 8 years and whole-body FMI z-score, visceral fat area, android fat, and gynoid fat at age 12 years for a 10-fold increase in child BPA and BPS urinary concentrations by child sex. BMI z-score was adjusted for child race (Black and other, Non-Hispanic White), maternal education (high school or less, some college, bachelor's or more) at 8-year visit, maternal marital status (married, unmarried and cohabitating, unmarried and living alone) at 8-year visit, insurance public/uninsured) at 8-year visit, maternal age (years) at delivery, maternal pre-pregnancy BMI (kg/m^2), fresh fruit and vegetable consumption at 8-year visit (daily, weekly, monthly). Body fat percentage and waist circumference further adjusted for child sex (boys, girls) and age (years). Whole body FMI z-score was adjusted for child race (Black and other, Non-Hispanic White), maternal education (high school or less, some college, bachelor's or more) at 8-year visit, maternal marital status (married, unmarried and cohabitating, unmarried and living alone) at 8-year visit, insurance (private, public/uninsured) at 8-year visit, maternal age (years) at delivery, maternal pre-pregnancy BMI (kg/m^2), total healthy eating scores (0-100), physical activity score (1-5), and self-pubertal staging at 12 year visit (Stages 1-5). Visceral fat area, android fat, and gynoid fat were further adjusted for child sex and age.

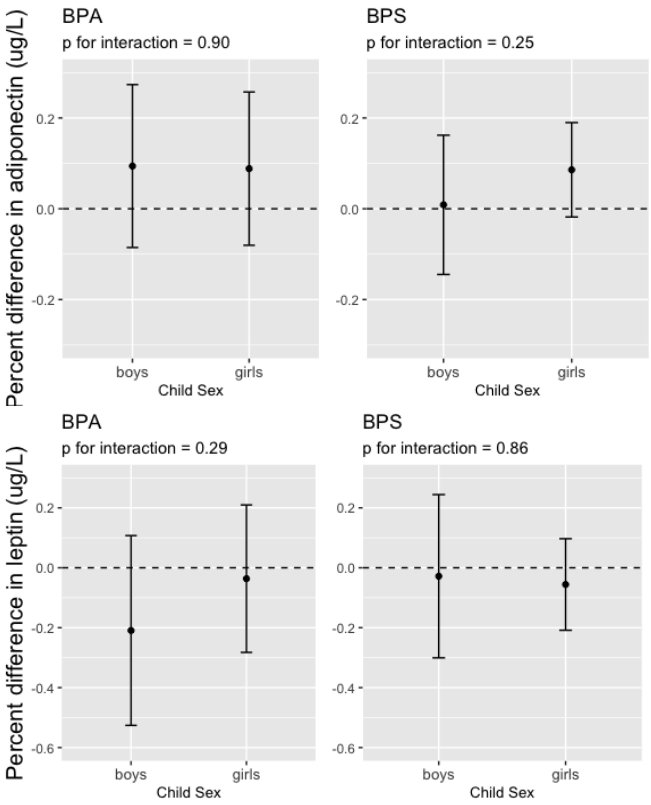


Figure 2: Percent difference and 95% CIs in adiponectin and leptin at age 12 years for a 10-fold increase in child BPA and BPS urinary concentrations by child sex. Adiponectin and leptin was adjusted for child race (Black and other, Non-Hispanic White), maternal education (high school or less, some college, bachelor's or more) at 8-year visit, maternal marital status (married, unmarried and cohabitating, unmarried and living alone) at 8-year visit, insurance (private, public/uninsured) at 8-year visit, maternal age (years) at delivery, maternal pre-pregnancy BMI (kg/m^2), total healthy eating scores (0-100), physical activity score (1-5), and self-pubertal staging at 12 year visit (Stages 1-5), and child age (years).

Supplementary Table 1: Demographic characteristics at 8 years and 12 years

Variable	8 years N (%)	12 years N (%)
Overall	212	181
Maternal age at delivery (yrs)		
< 25	56 (26.4)	47 (26.0)
25 - 35	125 (59.0)	108 (59.7)
> 35	31 (14.6)	26 (14.4)
Pre-pregnancy BMI		
Underweight-normal <25	111 (52.4)	94 (51.9)
Overweight (25-<30)	55 (25.9)	48 (26.5)
Obese (≥30)	46 (21.7)	39 (21.5)
Maternal Marital Status		
Married	141 (66.5)	116 (64.1)
Unmarried, cohabitating	27 (12.7)	25 (13.8)
Unmarried, living alone	44 (20.8)	40 (22.1)
Maternal Education		
High School or Less	36 (17.0)	27 (14.9)
Some college	70 (33.0	66 (36.5)
Bachelors or more	106 (50.0)	88 (48.6)
Insurance		
Private	140 (66.0)	117 (69.1)
Public/uninsured	72 (34.0)	64 (30.9)
Child Race		
Non-Hispanic Black & Other	83 (39.2)	78 (43.1)
Non-Hispanic White	129 (60.8)	103 (56.9)
Child Sex		
Female	89 (42.0)	102 (56.4)
Male	116 (54.7)	79 (43.6)

Supplementary Table 2: Mean whole-body fat mass index z-score, visceral fat area, android fat, gynoid fat in study participants at 12 years of age and geometric mean adiponectin and leptin at 12 years of age according to covariates

Variable	N (%)	Whole body fat mass index z-score (Mean ± SD)	Visceral fat area cm^2 (Mean ± SD)	Android fat % (Mean ± SD)	Gynoid fat % (Mean ± SD)	N (%)	Adiponectin ng/mL (Geometric Mean ± Geometric SD)	Leptin ng/mL (Geometric Mean ± Geometric SD)
Overall	181	0.2 ± 0.8	45.9 ± 21.7	29.9 ± 8.5	36.5 ± 6.4	155	13119 ± 2	8.7 ± 3.3
Maternal age at delivery (yrs)								
< 25	47 (26.0)	0.3 ± 0.9	46.9 ± 20.2	30.2 ± 9.4	36.0 ± 7.3	38 (24.5)	11837± 2	8.2 ± 3.2
25 - 35	108 (59.7)	0.2 ± 0.8	44.1 ± 19.4	29.6 ± 7.6	36.6 ± 5.9	95 (61.3)	13683± 2	8.8 ± 3.2
> 35	26 (14.4)	0.2 ± 0.9	51.3 ± 31.1	31.0 ± 10.3	37.3 ± 6.9	22 (14.2	13065± 2	8.8 ± 3.5
Pre-pregnancy BMI								
Underweight-normal <25	94 (51.9)	0.0 ± 0.7	41.6 ± 18.4	28.1 ± 7.4	35.4 ± 5.7	80 (51.6)	12883 ± 2	6.8 ± 3.0
Overweight (25-<30)	48 (26.5)	0.4 ± 0.8	48.7 ± 25.4	30.9 ± 8.6	37.4 ± 6.3	43 (27.7)	16069 ± 2	9.9 ± 3.0
Obese (≥30)	39 (21.5)	0.7 ± 0.9	52.7 ± 22.2	33.0 ± 10.1	38.1 ± 7.6	32 (20.6)	10455 ± 2	13.2 ± 3.9
Maternal Marital Status								
Married	116 (64.1)	0.1 ± 0.8	45.5 ± 22.8	29.2 ± 8.5	36.3 ± 6.4	100 (64.5)	13992 ± 2	7.4 ± 3.5
Unmarried, cohabitating	25 (13.8)	0.4 ± 0.8	44.2 ± 16.2	30.7 ± 7.5	37.1 ± 6.4	22 (14.2)	12273 ± 2	10.8 ± 2.5
Unmarried, living alone	40 (22.1)	0.5 ± 0.8	48.1 ± 21.5	31.5 ± 9.1	36.8 ± 6.6	33 (21.3)	11285 ± 2.	12.2 ± 2.9
Maternal Education								
High School or Less	27 (14.9)	0.5 ± 0.8	45.8 ± 19.1	32.0 ± 9.0	37.3 ± 6.9	23 (14.8)	10247 ± 2	13.3 ± 2.6
Some college	66 (36.5)	0.2 ± 0.9	45.6 ± 23.2	29.5 ± 9.1	36.0 ± 6.8	57 (36.8)	13604 ± 2	7.5 ± 3.3
Bachelors or more	88 (48.6)	0.2 ± 0.7	46.1 ± 21.4	29.6 ± 7.9	36.7 ± 5.9	75 (48.4)	13767 ± 2	8.4 ± 3.3
Insurance								
Private	117 (69.1)	0.1 ± 0.8	45.6 ± 22.8	29.4 ± 8.3	36.7 ± 6.0	101 (65.2)	14555 ± 2	7.4 ± 3.2
Public/uninsured	64 (30.9)	0.4 ± 0.9	43.6 ± 19.6	30.9 ± 9.0	36.2 ± 7.1	54 (34.8)	10803 ± 2	10.6 ± 3.2
Child Race								
Non-Hispanic Black & Other	78 (43.1)	0.4 ± 0.9	46.8 ± 20.1	30.5 ± 9.4	35.6 ± 7.3	69 (44.5)	11050 ± 2	9.5 ± 3.4
Non-Hispanic White	103 (56.9)	0.1 ± 0.8	45.2 ± 22.8	29.5 ± 7.8	37.3 ± 5.5	86 (55.5)	15056 ± 2	8.0 ± 3.1
Child Sex								
Female	102 (56.4)	0.3 ± 0.9	42.8 ± 25.7	32.5 ± 8.7	38.8 ± 5.3	85 (54.8)	13255 ± 2	13.6 ± 2.7

Male	79 (43.6)	0.2 ± 0.7	49.9 ± 14.2	26.5 ± 7.1	33.5 ± 6.4	70 (45.2)	12957 ± 2	5.0 ± 3.2
Healthy Eating Index Score								
Tercile 1 <41	61 (33.7)	0.4 ± 0.9	49.6 ± 23.9	30.2 ± 9.4	36.5 ± 7.2	52 (33.5)	12918 ± 2	9.8 ± 3.2
Tercile 2 (41-<50)	60 (33.1)	0.1 ± 0.8	42.0 ± 16.3	29.8 ± 7.8	36.5 ± 6.3	52 (33.5)	12997 ± 2	8.1 ± 3.4
Tercile 3 (≥50)	60 (33.1)	0.2 ± 0.8	46.0 ± 23.5	29.8 ± 8.5	36.5 ± 5.7	51 (32.9)	13455 ± 2	8.2 ± 3.2
Child Fruit/Vegetable Consumption								
Daily	97 (53.6)	0.4 ± 0.9	47.5 ± 24.9	30.5 ± 9.1	36.8 ± 6.2	81 (52.3)	13249 ± 2	8.8 ± 3.5
Weekly	75 (41.4)	0.1 ± 0.8	44.4 ± 17.3	29.1± 8.0	36.1 ± 7.0	67 (43.2)	12940 ± 2	8.4 ± 3.1
Monthly	7 (3.9)	0.2 ± 0.8	41.4 ± 17.8	30.3 ± 7.7	36.0 ± 4.1	5 (3.2)	15535 ± 1	8.1 ± 3.7
Physical Activity Score (1-5)								
Tercile 1 <2.3	61 (33.7)	0.5 ± 0.8	47.8 ± 19.9	31.2 ± 8.4	37.9 ± 6.1	52 (33.5)	13016 ± 2	13.1 ± 3.1
Tercile 2 (2.3-<2.9)	60 (33.1)	0.2 ± 0.9	46.1 ± 27.0	31.7 ± 8.8	37.7 ± 6.3	52 (33.5)	13949 ± 2	9.5 ± 3.0
Tercile 3 (≥2.9)	60 (33.1)	0.0 ± 0.8	43.7 ± 17.0	26.9 ± 7.7	34.0 ± 6.1	51 (32.9)	12424 ± 2	5.2 ± 3.1
Pubertal Staging								
Stage 1	20 (11.0	0.1 ± 0.8	41.5 ± 14.3	27.9 ± 7.9	36.1 ± 6.3	16 (10.3)	14703 ± 1	6.7 ± 3.2
Stage 2	47 (26.0)	0.1 ± 0.8	44.3 ± 20.3	29.2 ± 8.2	36.9 ± 5.9	40 (25.8)	12891 ± 2	6.0 ± 3.0
Stage 3	57 (31.5)	0.2 ± 0.9	46.6 ± 24.8	30.3 ± 8.8	36.6 ± 6.4	48 (31.0)	14174 ± 2	8.9 ± 3.2
Stage 4	34 (18.8)	0.4 ± 0.8	48.1 ± 23.6	30.1 ± 8.7	36.0 ± 7.0	30 (19.4)	12113 ± 2	10.8 ± 3.5
Stage 5	23 (12.7)	0.5 ± 0.8	47.9 ± 19.0	31.8 ± 8.9	36.9 ± 7.0	31 (13.5)	11683 ± 2	14.5 ± 3.0

Supplementary Table 3: Adjusted difference in whole body fat mass index z-score, visceral fat area, android fat percentage, gynoid fat percentage for a 10-fold increase in both child BPA and BPS with BPA*BPS interaction term)

Variable	β (95% CI)	P-value
Age 8 year (n=212)		
BMI z-score [a]		
BPA	-0.2 (-0.7, 0.2)	
BPS	0.2 (-0.2, 0.7)	
BPA*BPS	-0.3 (-1, 0.4)	0.38
Body fat (%)		
BPA	-1.9 (-4.2, 0.4)	
BPS	2.1 (-0.2, 4.4)	
BPA*BPS	-1.7 (-5.1, 1.6)	0.32
Waist circumference (cm)		
BPA	-0.6 (-3.9, 2.6)	
BPS	0.4 (-3.8, 3.6)	
BPA*BPS	0.4 (-4.3, 5.1)	0.86
Age 12 year (n=181)		
Whole body FMI z-score [b]		
BPA	-0.3 (-0.6, 0.0)	
BPS	0.3 (0.0, 0.71)	
BPA*BPS	-0.5 (-1.0, 0)	0.03
Visceral fat Area (cm^2)		
BPA	-4.2 (-13.3, 5.0)	
BPS	5.4 (-3.7, 14.5)	
BPA*BPS	-8.7 (-21.9, 4.5)	0.20
Android fat (%)		
BPA	-3.2 (-6.6, 0.1)	
BPS	2.7 (-0.6, 6.1)	
BPA*BPS	-4.1 (-8.9, 0.7)	0.10
Gynoid fat (%)		
BPA	-2.4 (-4.8, -0.1)	
BPS	2.6 (0.3, 5.0)	
BPA*BPS	-4.8 (-8.2, -1.5)	0.01

[a] Adjusted for child race (Black and other, Non-Hispanic White), maternal education (high school or less, some college, bachelor's or more) at 8-year visit, maternal marital status (married, unmarried and cohabitating, unmarried and living alone) at 8-year visit, insurance public/uninsured) at 8-year visit, maternal age (years) at delivery, maternal pre-pregnancy BMI (kg/m^2), fresh fruit and vegetable consumption at 8-year visit (daily, weekly, monthly). Body fat percentage and waist circumference further adjusted for child sex (boys, girls) and age (years)

[b] Adjusted for child race (Black and other, Non-Hispanic White), maternal education (high school or less, some college, bachelor's or more) at 8-year visit, maternal marital status (married, unmarried and cohabitating, unmarried and living alone) at 8-year visit, insurance (private, public/uninsured) at 8-year visit, maternal age (years) at delivery, maternal pre-pregnancy BMI (kg/m^2), total healthy eating scores (0-100), physical activity score (1-5), and self-pubertal staging at 12 year visit (Stages 1-5). Visceral fat area, android fat, and gynoid fat were further adjusted for child sex and age.

Supplementary Table 4: Adjusted difference in BMI z-score[a] at 8 years by terciles of creatinine adjusted BPA and BPS with interaction term (BPA tercile*BPS tercile)

	BPA Low	BPA Medium	BPA High
BPS Low	Ref	0.1 (-0.5, 0.8)	0.2 (-0.5, 0.8)
BPS Medium	-0.2 (-0.9, 0.4)	0 (-0.9, 0.9)	0.3 (-0.6, 1.3)
BPS High	0.3 (-0,3 1.0)	-0.1 (-1.0, 0.8)	-0.2 (-1.2, 0.7)

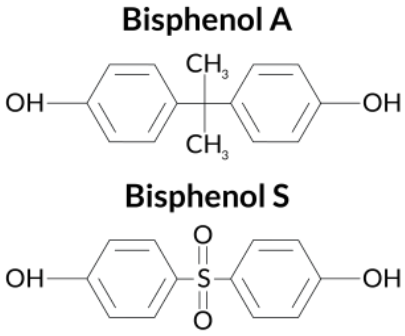
[a] Adjusted for child race (Black and other, Non-Hispanic White), maternal education (high school or less, some college, bachelor's or more) at 8-year visit, maternal marital status (married, unmarried and cohabitating, unmarried and living alone) at 8-year visit, insurance (private, public/uninsured) at 8-year visit, maternal age (years) at delivery, maternal pre-pregnancy BMI (kg/m^2), fresh fruit and vegetable consumption at 8-year visit (daily, weekly, monthly). (P-value for interaction = 0.53).

Supplementary Table 5: Adjusted difference in whole body FMI z-score[a] at 12 years by terciles of creatinine adjusted BPA and BPS with interaction term (BPA tercile*BPS tercile)

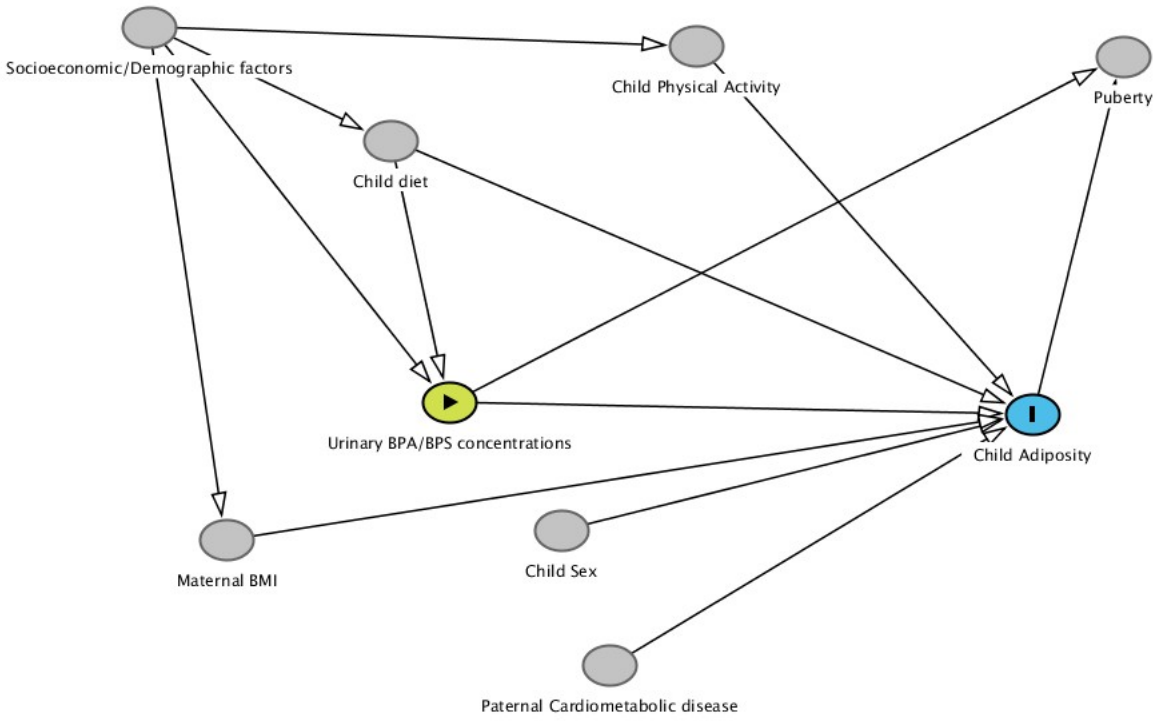
	BPA Low	BPA Medium	BPA High
BPS Low	Ref	0.3 (-0.1, 0.8)	0.1 (-0.4, 0.6)
BPS Medium	0.1 (-0.4, 0.6)	0 (-0.7, 0.7)	0.1 (-0.7, 0.8)
BPS High	0.5 (0, 0.9)	-0.3 (-1.0, 0.4)	-0.4 (-1.1, 0.3)

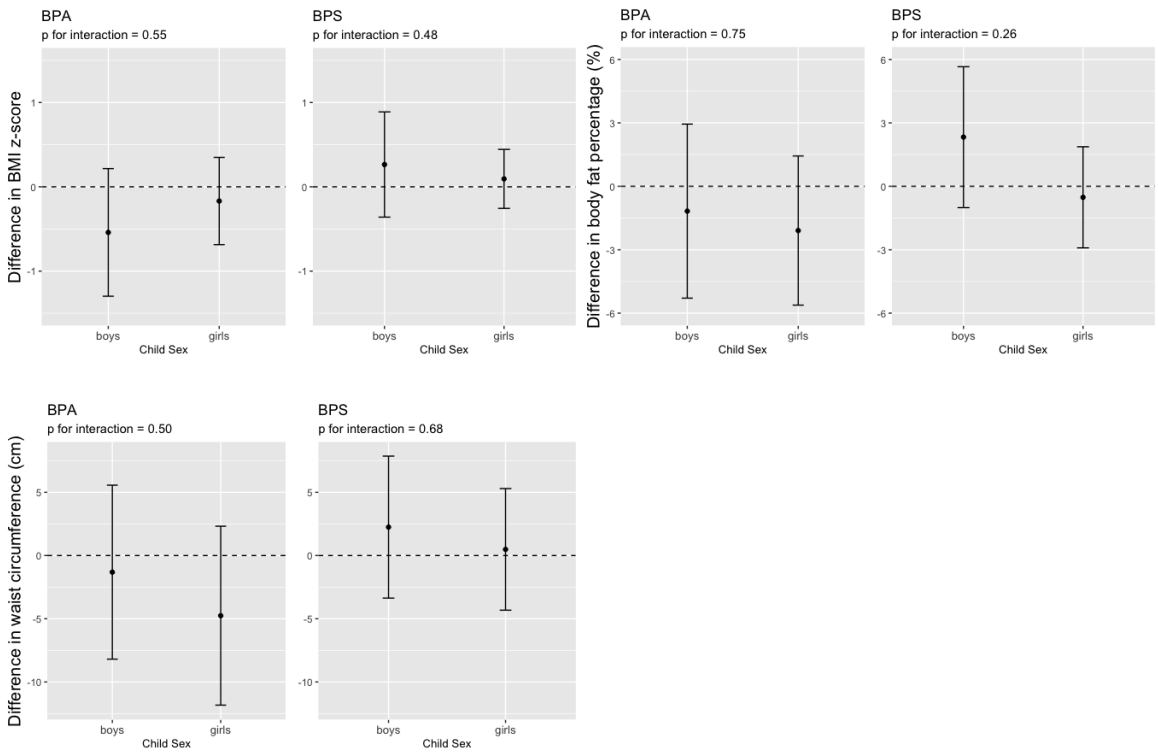
[a] Adjusted for child race (Black and other, Non-Hispanic White), maternal education (high school or less, some college, bachelor's or more) at 8-year visit, maternal marital status (married, unmarried and cohabitating, unmarried and living alone) at 8-year visit, insurance (private, public/uninsured) at 8-year visit, maternal age (years) at delivery, maternal pre-pregnancy BMI (kg/m^2), total healthy eating scores (0-100), physical activity score (1-5), and self-pubertal staging at 12 year visit (Stages 1-5). (P-value for interaction = 0.27).

Supplementary Figure 1: Chemical structure of BPA and BPS.



Supplementary Figure 2: Directed acyclic graph of potential confounders of the association between BPA/BPS and child adiposity





Supplementary Figure 3: Estimated differences and 95% CIs in BMI z-score, body fat percentage, waist circumference at age 12 years for a 10-fold increase in child BPA and BPS urinary concentrations by child sex. BMI z-score was adjusted for child race (Black and other, Non-Hispanic White), maternal education (high school or less, some college, bachelor's or more) at 8-year visit, maternal marital status (married, unmarried and cohabitating, unmarried and living alone) at 8-year visit, insurance (private, public/uninsured) at 8-year visit, maternal age (years) at delivery, maternal pre-pregnancy BMI (kg/m^2), total healthy eating scores (0-100), physical activity score (1-5), and self-pubertal staging at 12 year visit (Stages 1-5).