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Prenatal exposure to environmental phenols and childhood fat mass in the Mount Sinai Children's Environmental Health Study

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Abstract

Early life exposure to endocrine disrupting chemicals may alter adipogenesis and energy balance leading to changes in obesity risk. Several studies have evaluated the association of prenatal bisphenol A exposure with childhood body size but only one study of male infants has examined other environmental phenols. Therefore, we assessed associations between prenatal exposure to environmental phenols and fat mass in a prospective birth cohort. We quantified four phenol biomarkers in third trimester maternal spot urine samples in a cohort of women enrolled in New York City between 1998 and 2002 and evaluated fat mass in their children using a Tanita scale between ages 4 and 9 years (173 children with 351 total observations). We estimated associations of standard deviation differences in natural log creatinine-standardized phenol biomarker concentrations with percent fat mass using linear mixed effects regression models. We did not observe associations of bisphenol A or triclosan with childhood percent fat mass. In unadjusted models, maternal urinary concentrations of 2,5-dichlorophenol were associated with greater

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percent fat mass and benzophenone-3 was associated with lower percent fat mass among children. After adjustment, phenol biomarkers were not associated with percent fat mass. However, the association between benzophenone-3 and percent fat mass was modified by child's sex: benzophenone-3 concentrations were inversely associated with percent fat mass in girls ($\beta = -1.51$, 95% CI = $-3.06, 0.01$) but not boys ($\beta = -0.20$, 95% CI = $-1.69, 1.26$). Although we did not observe strong evidence that prenatal environmental phenols exposures influence the development of childhood adiposity, the potential antiadipogenic effect of benzophenone-3 in girls may warrant further investigation.

Keywords

Phenols; Pediatric Obesity; Endocrine Disruptors; Environmental Exposure

1. Introduction

Environmental phenols are high-production-volume chemicals used in a variety of common consumer products. Population-based biomonitoring surveys report ubiquitous exposure to these chemicals in the United States (Centers for Disease Control and Prevention 2015) and widespread exposures have also been observed in other industrialized countries (Engel and others 2014; Guidry and others 2015; Heffernan and others 2015; Moos and others 2014). Bisphenol A is an endocrine disrupting chemical used in the manufacture of polycarbonate plastics and resins found in the linings of cans and bottles, among other products (Rubin 2011). Other phenolic compounds, including benzophenone-3, 2,5-dichlorophenol, and triclosan, may also have endocrine disrupting properties (Kim and Choi 2014; Takahashi and others 2007; Wang and Tian 2015). Benzophenone-3 is an ultraviolet filter used in sunscreen and cosmetics; 2,5-dichlorophenol is a metabolite of 1,4-dichlorobenzene, a chemical used in mothballs, deodorizers, and fumigants; and triclosan is a microbicide used in antibacterial soaps and other personal care products.

Endocrine disrupting chemicals, including phenols, are hypothesized to be “environmental obesogens” due to their capacity to perturb biological processes regulated by the endocrine system including hormonal or nuclear receptor-signaling mechanisms related to fat accumulation (Grun and Blumberg 2009; Janesick and Blumberg 2011). The chemical structures of phenolic compounds resemble those of known thyroid agonists or antiobesogens (Wolff and others 2015), suggesting that phenols may have varied potential to interfere with processes related to obesity. The prenatal period may be an important critical window for altered developmental programming of adipogenesis and metabolic homeostasis (Newbold and others 2009). In human prospective studies, associations of gestational exposure to bisphenol A with childhood body size have been inconsistent, with studies reporting positive (Valvi and others 2013), inverse (girls only) (Harley and others 2013), and null (Agay-Shay and others 2015; Braun and others 2014; Philippat and others 2014) associations. The only prospective study of prenatal exposure to other environmental phenols assessed early postnatal growth in a cohort of male infants (Philippat and others 2014) and thus could not estimate associations among females or evaluate the potential for sex-specific effects.

Obesity is a leading cause of childhood illness that is associated with numerous comorbidities including diabetes, metabolic syndrome, depression, and asthma (Daniels and others 2005). Obese children are at increased risk of becoming obese adults (Freedman and others 2005), with the associated increased risk of chronic health conditions such as cardiovascular disease and cancer. Understanding the potential contribution of environmental chemicals to the obesity epidemic is of importance given the rapid rise in childhood obesity prevalence in the United States (Ogden and Carroll 2010) and worldwide (de Onis and others 2010). The objective of this study was to evaluate the hypothesis that prenatal exposures to environmental phenols are associated with altered body fat among children. Therefore, we estimated associations of environmental phenols with percent fat mass among children aged 4 to 9 years in a New York City prospective birth cohort.

2. Methods

2.1. Study design and sample population

The Mount Sinai Children's Environmental Health Study is a longitudinal birth cohort that enrolled 479 primiparous women with singleton pregnancies in New York City. Women were enrolled from the Mount Sinai Diagnostic and Treatment Center and two adjacent private practices between 1998 and 2002. After exclusion of 75 women for reasons described previously (Engel and others 2007), the final cohort consists of 404 healthy women and infants. At approximately ages 4-5.5 (mean=4.9), 6 (mean=6.2), and 7-9 (mean=7.8) years, children were invited to return for a follow-up visit (hereafter referred to as visit 1, 2, and 3, respectively). We obtained informed consent from women prior to participation (children aged 7 years provided assent). The Mount Sinai School of Medicine Institutional Review Board approved the study; the current analysis was approved by the University of North Carolina at Chapel Hill Institutional Review Board. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subjects research.

Phenol biomarkers data were available for 367 of the 404 infants in the birth cohort. We excluded one observation with a urinary creatinine concentration <10 mg/dL following previous work in this cohort suggesting biomarkers obtained from extremely dilute urine samples may be inaccurate (Wolff and others 2008). The current analysis therefore includes 173 children with at least one fat mass measurement between the ages of 4 and 9 years (total number of observations = 351).

2.2. Data collection

Covariate data were collected via a two hour structured interview at enrollment, a perinatal database at Mount Sinai Hospital, and questionnaires administered to caretakers at follow-up. Following the approach of Bodnar et al. (Bodnar and others 2011), we used first and last pregnancy weights to calculate adequacy of gestational weight gain based on the 2009 Institute of Medicine recommendations (Institute of Medicine and National Research Council Committee to Reexamine Institute of Medicine Pregnancy Weight Guidelines 2009). We dichotomized physical activity at each follow-up visit as active if the parent/

caretaker reported the child was “active most of the time” or as inactive if the parent/caretaker reported the child was “active some of the time” or “hardly at all”.

Trained research staff obtained body measurements at each follow-up visit from children in bare or stocking feet wearing a pediatric gown or light clothing. Bioelectrical impedance analysis was performed using a pediatric Tanita scale calibrated for use in children aged 7 years and older (model TBF-300; Tanita Corporation of America). We used the scale-estimated fat mass values to calculate percent fat mass $[(\text{fat mass} / \text{weight}) \times 100]$. We calculated BMI as $\text{weight (kg)} / \text{height (m)}^2$, used a CDC SAS macro to determine age- and sex-standardized BMI percentiles, and classified children $\geq 85^{\text{th}}$ percentile as overweight or obese (CDC 2004).

Bisphenol A, benzophenone-3, 2,5-dichlorophenol, triclosan, di-(2-ethylhexyl) phthalate (DEHP) metabolites, and creatinine were measured in third trimester (mean=31.5 weeks, range=25-40 weeks) maternal spot urine samples at CDC using previously reported laboratory and quality control methods (Kato and others 2005; Ye and others 2005). DEHP metabolites measured included mono(2-ethylhexyl) phthalate, mono(2-ethyl-5-hydroxyhexyl) phthalate, mono(2-ethyl-5-oxohexyl) phthalate, and mono(2-ethyl-5-carboxypentyl) phthalate.

2.3. Statistical analysis

We used a Bayesian modeling framework to estimate associations of prenatal phenol biomarker concentrations with percent fat mass while addressing multiple potential biases, including accounting for biomarker concentrations below the limits of detection, imputing missing covariate data, and assessing potential bias from loss to follow-up.

2.3.1. Concentrations below the limits of detection—We accounted for biomarker concentrations below the limits of detection by imputing values from a truncated normal distribution (Carmichael and others 2010; Uh and others 2008) within the Markov chain Monte Carlo (MCMC) algorithm using the WinBUGS package `djl.dnorm.trunc` (Lunn 2003). Parameters were defined as the mean and standard deviation of the observed biomarker distribution, a minimum of zero, and a maximum of the limits of detection. To compare estimated relative effect sizes on a common scale, we standardized the distribution of each biomarker to its mean and standard deviation (SD) in the study population. We specified an independent normal prior distribution for phenol beta coefficients with a mean of zero and variance of 64. This variance represents a conservative prior belief that 95% of the effects of a SD increase in natural log phenol biomarker concentration are within $\pm$ one SD of the mean percent fat mass in the study population.

2.3.2. Urinary dilution—We modeled phenol biomarker concentrations accounting for urinary dilution using a Bayesian modification of the covariate-adjusted creatinine standardization approach described by O'Brien et al. (O'Brien and others 2015). We modeled natural log creatinine as a random normal variable conditional on the following known predictors of creatinine concentrations that were associated with creatinine in our study population: maternal age, race/ethnicity, education, pre-pregnancy BMI, and height. At each iteration of the MCMC algorithm, we divided the phenol biomarker concentration

by the ratio of the participant's observed creatinine concentration to her predicted concentration and used the natural log of this value as the unit of exposure. As recommended by O'Brien et al., we also included natural log creatinine in models to adjust for residual confounding by urinary dilution.

2.3.3. Covariate adjustment—We used directed acyclic graphs to identify 1) potential confounders of associations between phenol biomarker concentrations and percent fat mass, and 2) predictors of childhood adiposity that are not on the causal pathway of interest. We adjusted for maternal sociodemographic characteristics including race/ethnicity (non-Hispanic white/non-Hispanic black/Hispanic), age (cubic), education (college degree/<college degree), and work status during pregnancy (employed/student or homemaker). We adjusted for strong correlates of childhood adiposity that may also be associated with phenol exposures, including pre-pregnancy maternal BMI (quadratic), adequacy of maternal gestational weight gain (cubic), and maternal smoking during pregnancy (yes/no) (Weng and others 2012). We adjusted for calendar date of urine collection (linear) to account for unmeasured factors that drive population time trends in both phenols exposures and childhood obesity prevalence (such as dietary patterns). Because we previously reported an inverse association of DEHP with percent fat mass in this cohort (Buckley and others 2015), and DEHP and phenols may have common sources, we adjusted for summed DEHP metabolite concentrations as a potential confounder. To improve precision of our estimates, we included predictors of childhood body size including maternal height (linear), child's sex (male/female), breastfeeding (ever/never), age at follow-up (months), and physical activity (active/inactive). We additionally included product terms between child's sex and maternal smoking during pregnancy and between child's sex and months of age at follow-up because associations of smoking and age with percent fat mass differed substantially by child's sex. To put beta coefficients for continuous and binary covariates on a common scale, we standardized continuous covariates to twice their SD in the study population (Gelman and others 2013).

Within our Bayesian framework, we multiply imputed missing values for adequacy of gestational weight gain ($n = 19$), breastfeeding ($n = 1$), and physical activity at follow-up ($n = 3$ children with 8 visits) assuming data were missing at random. We specified parametric models for each variable, conditional on covariates as described previously (Buckley and others 2015).

2.3.4. Effect estimation—We modeled adjusted associations between SD increases in natural log creatinine-standardized phenol biomarker concentrations and percent fat mass using linear mixed effects regression models with random intercepts to account for repeated outcome measurements. For the residual and random effects variances, we specified uniform prior distributions on the standard deviation with bounds of 0 and 16. We estimated posterior mean beta coefficients and 95% credible intervals (CIs), calculated as the 2.5th and 97.5th percentiles of the posterior distributions. To examine effect measure modification of associations by child's sex, we included product terms between sex and each phenol biomarker. Using a metric analogous to an alpha level of 0.2 in a frequentist analysis, we considered there to be effect measure modification if the 80% CI for the interaction term did

not cross the null value. We also assessed effect measure modification of benzophenone-3 associations with percent fat mass by maternal race/ethnicity because exposure to benzophenone-3 is predominantly through application of sunscreen, which may differ by race/ethnicity. We examined deviations from log-linear exposure-response relationships by fitting models with indicator variables for the second and third tertile of creatinine-standardized concentrations of each phenol biomarker.

2.3.5. Sensitivity analyses—To explore whether associations of phenol biomarkers with percent fat mass differed by age at follow-up, we estimated associations among children attending each of the three follow-up visits in stratified models using linear regression.

We conducted sensitivity analyses that implemented alternative approaches for creatinine normalization to facilitate comparisons with other studies and evaluate the performance of the O'Brien et al. method to account for urinary dilution. We compared the estimated associations from our primary adjusted model, which used creatinine-standardized concentrations and adjusted for natural log creatinine, to estimates using four other approaches: 1) modeling natural log phenol biomarker concentrations without accounting for urinary dilution, 2) modeling natural log phenol biomarker concentrations with adjustment for natural log creatinine as a covariate, 3) modeling natural log creatinine-corrected phenol biomarker concentrations (micrograms per gram creatinine), and 4) modeling natural log creatinine-standardized phenol biomarker concentrations, as in the primary analysis, but *without* additional adjustment for natural log creatinine.

We previously reported that the probability of a missing childhood fat mass measurement may depend on its true value (i.e., missing not at random), with evidence that children with greater fat mass were more likely to be observed at follow-up in this cohort (Buckley and others 2015). Therefore, we conducted a sensitivity analysis to assess whether loss to follow-up biased our associations between prenatal phenol biomarker concentrations and percent fat mass. Our primary models included children with at least one follow-up visit (N=173) and assumed outcomes were missing at random. We compared results from our primary models to those from a selection model approach to estimate associations among all 360 children with measured prenatal phenol biomarker concentrations (Little and Rubin 2002). We have previously described the details of this model (Buckley and others 2015). Briefly, we created a binary missing outcome indicator variable for visit attendance. We jointly fit the outcome model with a logistic mixed effects model with random intercepts for the missing outcome indicator variable, conditional on percent fat mass as well as variables associated with loss to follow-up including maternal age at delivery, race/ethnicity, pre-pregnancy BMI, adequacy of gestational weight gain, child's sex, and months of age at follow-up. For the random effects variance, we specified a uniform prior distribution on the standard deviation with bounds of 0 and 10.

2.3.6. Software—We used SAS version 9.3 (SAS Institute, Cary, North Carolina) to generate descriptive statistics and assess group differences in natural log creatinine-corrected phenol biomarker concentrations using Wilcoxon signed rank sum tests. For Bayesian analyses, we used WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK). After a 10,000 iteration burn-in, we ran our final Bayesian models for 50,000 iterations and

assessed model convergence using standard diagnostics (Gelman and others 2013). For the sensitivity analysis for loss to follow-up, we ran ten chains for inference from the MCMC procedure.

3. Results

Maternal characteristics of the study sample were similar to those of the entire birth cohort (Table 1), with a majority of mothers being Hispanic, less than 25 years old at delivery, and employed during pregnancy. Although most mothers had a normal pre-pregnancy BMI, nearly two-thirds gained more weight during gestation than recommended by the Institute of Medicine. We detected environmental phenol biomarker concentrations in 80% (triclosan) to 100% (2,5-dichlorophenol) of women (Table 2) and distributions in the follow-up sample were similar to those previously reported in the full cohort (Wolff and others 2008). Geometric mean concentrations of 2,5-dichlorophenol and triclosan were higher and bisphenol A and benzophenone-3 were lower than among female participants in the 2003-2004 U.S. National Health and Nutrition Examination Survey (Table 2). Forty percent ($n = 70$) of the children were classified as overweight or obese during at least one follow-up visit. Percent fat mass increased with age and differed by sex with boys having greater percent fat mass, particularly at younger ages (Table 3).

Unadjusted and adjusted associations of third trimester maternal urinary phenol biomarker concentrations with percent fat mass are reported in Table 4. In unadjusted analyses, associations of phenol biomarker concentrations with percent fat mass were positive for 2,5-dichlorophenol, inverse for benzophenone-3, and null for bisphenol A and triclosan. After adjustment, none of the phenol biomarkers were associated with percent fat mass in the overall sample. The benzophenone-3 association was modified by child's sex, with lower percent fat mass in girls (β per SD = -1.51 , 95% CI = -3.06 , 0.01) and no association among boys (β per SD = -0.20 , 95% CI = -1.69 , 1.26). Assessment of tertiles of phenol biomarker exposures were consistent with generally null adjusted associations and did not suggest deviations from log-linear exposure response relationships (see Supplemental Table S1).

Third trimester maternal urinary benzophenone-3 concentrations were significantly lower among children of mothers who self-identified as non-Hispanic black (median = 1.59 $\mu\text{g/g-creatinine}$) than among children of Hispanic (median = 2.16 $\mu\text{g/g-creatinine}$) or non-Hispanic white (median = 3.31 $\mu\text{g/g-creatinine}$) mothers ($p = 0.01$ and $p < 0.001$, respectively). However, associations between benzophenone-3 concentration and percent fat mass were similar among children of non-Hispanic black (β per SD = -1.10 , 95% CI = -3.63 , 1.42), Hispanic (β per SD = -0.84 , 95% CI = -2.24 , 0.55), and non-Hispanic white (β per SD = -0.52 , 95% CI = -2.94 , 1.88) mothers.

In sensitivity analyses, we observed positive associations between 2,5-dichlorophenol and bisphenol A and percent fat mass at the earliest follow-up visit (age 4-5.5 years) but associations did not persist at older ages (see Supplemental Table S2). However, our sample size at each visit was limited and estimates were imprecise.

Associations between prenatal phenol biomarkers and percent fat mass were similar using different methods to account for creatinine concentrations as a measure of urinary dilution (see Supplemental Table S3). All methods of creatinine normalization resulted in estimates that were closer to the null than estimates from models that did not account for urinary dilution, with the exception of estimates for benzophenone-3 where all methods resulted in estimates further from the null. Estimated associations using both creatinine-standardization approaches (with and without additional adjustment for natural log creatinine) were more precise than estimates using the other approaches.

Our sensitivity analysis for bias due to loss to follow-up did not alter conclusions regarding associations between third trimester maternal urinary phenol biomarker concentrations and percent fat mass (see Supplemental Table S4).

4. Discussion and conclusions

In the overall population, third trimester maternal urinary concentrations of four environmental phenol biomarkers were not associated with increased adiposity among children aged 4 to 9 years. We observed modification of the association between benzophenone-3 and percent fat mass by child's sex, with lower percent fat mass among girls and no association among boys. Consistent with this finding, we previously reported a similar sexually-dimorphic association of prenatal benzophenone-3 exposure and birth weight in this cohort, where benzophenone-3 concentrations in the highest compared to lowest concentration tertile were associated with lower birth weight in girls but higher birth weight in boys (Wolff and others 2008). Although these results suggest that benzophenone-3 may interfere with fat development, no other studies have prospectively assessed the relationship between prenatal benzophenone-3 exposure and body size in girls and the mechanisms for a sex-specific antiadipogenic effect of benzophenone-3 have not been established.

The only other study of prenatal benzophenone-3 exposure and child body size examined second trimester maternal urinary benzophenone-3 concentrations among boys in the French EDEN cohort (Philippat and others 2014). Similar to our findings for boys, benzophenone-3 was not associated with weight, length, or abdominal circumference measured at birth through 3 years of age. This study did not include female offspring and therefore could not examine differences in association by child's sex. In a multi-site prospective study of girls, Wolff and others observed an association between childhood benzophenone-3 concentrations and delayed puberty (Wolff and others 2015). The authors hypothesized that this association may be mediated by antiadipogenic activity of benzophenone-3 given that its chemical structure is similar to that of antiobesogenic chemicals such as adiporon (Okada-Iwabu and others 2013). Although sensitivity analyses did not suggest that body mass index mediated the effect of benzophenone-3 on puberty (Wolff and others 2015), benzophenone-3 concentrations were measured at age 6 to 8 years rather than prenatally as in the current study. Animal literature examining the potential mechanistic targets of benzophenone-3 is lacking, though benzophenone-3 has been reported to have antiandrogenic as well as weak estrogenic and antiestrogenic activity in vivo and in vitro (Kim and Choi 2014). To our knowledge, no experimental studies have directly assessed the influence of early life

exposure to benzophenone-3 on subsequent body fatness in animals. However, female adult ovariectomized rats exposed for three months to benzophenone-2, a structural analog of benzophenone-3, exhibited dose-dependent reductions in body weight gain, paratibial fat depot size, and serum leptin levels compared to controls (Seidlova-Wuttke and others 2005).

Bisphenol A is a suspected environmental obesogen and early life exposure has been reported to increase body weight and abdominal fat in animals (Grun and Blumberg 2009; Janesick and Blumberg 2011). However, not all studies observed increased body size associated with bisphenol A exposure, studies report differences in the direction of sex-specific effects, and controversy exists surrounding the evaluation of low-dose effects (Vom Saal and others 2012). Similar to the current analysis, most prospective epidemiologic studies of gestational bisphenol A exposure and childhood body size have reported null associations (Agay-Shay and others 2015; Braun and others 2014; Philippat and others 2014), though positive (Valvi and others 2013) and inverse (girls only) (Harley and others 2013) associations have also been reported. Several factors could explain differences between studies, including timing and number of biomarker measurements, age at outcome assessment, distributions of unmeasured confounders or effect modifiers, and underlying differences in population susceptibility. In the Spanish INMA cohort, Valvi et al. reported weak positive association of prenatal bisphenol A exposure with waist circumference and BMI z-scores at age 4 years (Valvi and others 2013). However, a subsequent study following children in this cohort until age 7 years found no association of prenatal bisphenol A with body size (Agay-Shay and others 2015). Harley et al. reported inverse associations of prenatal bisphenol A exposure with percent body fat, BMI z-scores, and risk of obesity among girls (but not boys) at age 9 years but no associations were observed at age 5 (Harley and others 2013). Because Harley et al. assessed associations among the oldest children studied to date, it is possible that effects of bisphenol A manifest later, for example due to puberty-related changes in body composition. However, Harley et al. reported stronger associations among girls who had not yet reached puberty (Harley and others 2013).

After adjustment, prenatal urinary biomarkers of 2,5-dichlorophenol and triclosan were not associated with childhood fat mass. Cross-sectional studies have reported relationships between 2,5-dichlorophenol and triclosan with body size outcomes (Buser and others 2014; Lankester and others 2013; Li and others 2015; Wei and others 2014). However, cross-sectional studies that measure concurrent exposures and outcomes cannot establish causality (Engel and Wolff 2013) and it is possible that exposures to these chemicals or their precursors may be influenced by factors associated with body size, rather than vice versa. It is also difficult to compare findings given that these studies evaluated exposure among children or adults whereas the current study evaluated prenatal exposures. In the only other study to assess prenatal exposures, second trimester 2,5-dichlorophenol and triclosan were not related to body size parameters assessed between the ages of 6 months and 3 years in a cohort of French boys (Philippat and others 2014).

Our use of a single, third trimester spot urine sample to represent environmental phenol exposures is an important limitation of this study given that these chemicals are quickly metabolized and excreted in urine, and exposures are likely episodic in nature. Studies of repeat urinary environmental phenol biomarker concentrations have reported low to

moderate reproducibility, with lowest reproducibility typically reported for bisphenol A (Braun and others 2011; Engel and others 2014; Meeker and others 2013; Philippat and others 2013; Teitelbaum and others 2008). For phenols with ubiquitous exposure sources, a single spot urine sample may be adequate to classify exposure over a period of months (Calafat and others 2015). Nevertheless, exposure misclassification may have biased results toward the null. Further, the critical window during pregnancy for an effect of phenols on mechanisms related to adipogenesis and metabolic homeostasis is unknown. We measured phenol biomarkers in urine collected during the third trimester, which may be an important developmental window given rapid fetal growth and adipogenesis during this time (Dietz 1994). Early pregnancy or postnatal exposures may also play a role and were not characterized in the current study. Although there was considerable loss to follow-up in this cohort, we conducted a state-of-the-art sensitivity analysis to examine the potential for bias from outcomes missing not at random and did not observe evidence of selection bias. However, loss to follow-up did result in a smaller sample size that reduced our ability to detect potential associations.

Availability of bioelectrical impedance analysis estimates of body composition is an important strength of our study compared to reports that rely on body mass index as a proxy for excess body fat. Body mass index does not differentiate lean and fat mass (Freedman and Sherry 2009), leading to outcome misclassification and reduced ability to detect subtle changes in fat accumulation. There is known variation in fat mass within a given body mass index and vice versa, particularly in children (Ellis 2001; Wright and others 2008). For example, a high body mass index can be achieved through greater muscle or bone mass rather than fat mass (Lohman and Going 2006). Although the Tanita equations we used to estimate fat mass are not validated for children aged <7 years, we previously compared the Tanita output to two alternative equations validated for estimating fat mass from bioelectrical impedance measures in children and concluded the Tanita-read values outperformed other equations (Buckley and others 2015). Other strengths of our study include 1) prospective evaluation of prenatal exposures, 2) repeated measures of childhood body fat, 3) adjustment for maternal sociodemographic and anthropometric characteristics, and 4) use of a Bayesian modeling framework to account for missing exposure, covariate, and outcome data.

In summary, we did not observe associations of third trimester maternal urinary environmental phenol concentrations with childhood fat mass at ages 4 to 9 years, though we cannot rule out potential bias toward the null due to exposure misclassification. In this first study of prenatal benzophenone-3 exposure and body size to include females, we observed a weak association of benzophenone-3 with lower body fat among girls but not boys. This finding requires replication in larger human cohorts as well as elucidation through animal studies designed to assess the potential of benzophenone-3 to act as an antiobesogen.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CI	Credible interval
DEHP	Di-(2-ethylhexyl) phthalate
MCMC	Markov chain Monte Carlo
SD	Standard deviation

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Highlights

- Quantified four phenol biomarkers in third trimester maternal spot urine samples.
- Assessed percent fat mass at multiple follow-up visits between ages 4 and 9 years.
- After adjustment, no association with 2,5-dichlorophenol, bisphenol A, or triclosan.
- Benzophenone-3 was weakly associated with lower percent fat mass in girls only.

Table 1

Characteristics of participants in the birth cohort and study sample, Mount Sinai Children's Environmental Health Study [*n* (%)]

Characteristic	Birth cohort	Study sample
Total (N)	404	173
Race/ethnicity		
Non-Hispanic white	86 (21.3)	32 (18.5)
Non-Hispanic black	112 (27.7)	48 (27.8)
Hispanic or other	206 (51.0)	93 (53.8)
Maternal age at delivery (years)		
< 20	142 (35.2)	52 (30.1)
20–24	132 (32.7)	59 (34.1)
25–29	44 (10.9)	26 (15.0)
30	86 (21.3)	36 (20.8)
Maternal education (college degree)	100 (24.8)	38 (22.0)
Maternal work status during pregnancy (employed)	235 (58.2)	104 (60.1)
Maternal smoking during pregnancy	67 (16.6)	29 (16.8)
Maternal pre-pregnancy BMI (kg/m ²)		
< 18.5	82 (20.3)	10 (5.8)
18.5–24.9	215 (53.2)	106 (61.3)
25–29.9	72 (17.8)	42 (24.3)
30	35 (8.7)	15 (8.7)
Maternal height (m) (mean and SD)	1.63 (0.07)	1.62 (0.10)
Adequacy of gestational weight gain		
Characteristic	Birth cohort	Study sample
Less than recommended	44 (12.3)	14 (9.1)
Recommended	75 (21.0)	39 (25.3)
More than recommended	238 (66.7)	101 (65.6)
Missing	47	19
Year of maternal urine collection		
1998	84 (21.9)	32 (18.5)
1999	127 (33.2)	54 (31.2)
2000	134 (35.0)	68 (39.3)
2001	35 (9.1)	18 (10.4)
2002	3 (0.8)	1 (0.6)
Urine not collected	21	0
Child's sex (male)	222 (55.0)	94 (54.3)
Breastfed		
Ever	206 (63.0)	108 (62.8)
Never	121 (37.0)	64 (37.2)
Missing	77	1
Physical activity at follow-up ^a		

Characteristic	Birth cohort	Study sample
Inactive		97 (57.1)
Active most of the time		73 (42.9)
Missing		3

Body mass index (BMI); standard deviation (SD)

^aProportion classified as inactive at any follow-up visit.

Distributions of phenol biomarker concentrations (µg/L) in third trimester maternal urine samples (N=173), Mount Sinai Children's Environmental Health Study 1998 – 2002

Table 2

Biomarker	LOD	Percent detected	Geometric mean ^a	Minimum	25 th percentile	75 th percentile	Maximum	NHANES ^b
2,5-dichlorophenol	0.12	100	71.1	2.80	21.7	178	8510	11.2 (8.51-14.7)
Benzophenone-3	0.34	98.3	10.4	<LOD	2.90	19.5	92700	30.7 (23.7-39.8)
Bisphenol A	0.36	86.2	1.25	<LOD	.600	2.30	35.2	2.41 (2.11-2.75)
Triclosan	2.27	79.8	14.5	<LOD	2.90	46.5	1790	10.6 (9.29-12.1)

Limits of detection (LOD) in µg/L, National Health and Nutrition Examination Survey (NHANES).

^aTo compute the geometric mean, concentrations <LOD were replaced by LOD/ 2.

^bGeometric mean (95% confidence interval) concentration among 1288 female NHANES 2003-2004 participants (Centers for Disease Control and Prevention 2015).

Table 3

Percent fat mass distributions in the Mount Sinai Children's Environmental Health Study, 2004 – 2008

Outcome/visit ^a	Overall		Girls		Boys	
	<i>n</i>	Mean ± SD	<i>n</i>	Mean ± SD	<i>n</i>	Mean ± SD
Percent fat mass ^b						
All visits	351	18.3 ± 8.26	170	17.7 ± 9.74	181	19.0 ± 6.53
Visit 1	95	15.1 ± 7.40	47	12.6 ± 8.84	48	17.5 ± 4.61
Visit 2	112	17.5 ± 7.01	55	16.7 ± 8.48	57	18.2 ± 5.19
Visit 3	144	21.2 ± 8.78	68	21.9 ± 9.54	76	20.5 ± 8.04

Standard deviation (SD)

^aMean age in years ± SD for visits 1, 2, and 3 were 4.9 ± 0.4, 6.2 ± 0.2, 7.8 ± 0.8, respectively.^bPercent fat mass estimated using bioelectrical impedance analysis (Tanita TBF-300).

Table 4

Adjusted associations between third trimester maternal urinary phenol biomarker concentrations and percent fat mass among children aged 4 to 9 years, Mount Sinai Children's Environmental Health Study (173 children with 351 follow-up visits)

Biomarker	Overall	Girls	Boys
Unadjusted ^a			
2,5-dichlorophenol	1.24 (0.08, 2.40)	2.08 (0.46, 3.69)	0.46 (−1.11, 2.04) *
Benzophenone-3	−1.13 (−2.24, 0.00)	−1.77 (−3.36, −0.20)	−0.53 (−2.05, 1.00)
Bisphenol A	0.80 (−0.26, 1.85)	1.08 (−0.36, 2.51)	0.50 (−0.94, 1.96)
Triclosan	0.66 (−0.33, 1.65)	0.42 (−0.87, 1.72)	0.93 (−0.52, 2.35)
Adjusted ^b			
2,5-dichlorophenol	0.46 (−0.80, 1.73)	0.69 (−1.02, 2.40)	0.24 (−1.40, 1.89)
Benzophenone-3	−0.83 (−1.95, 0.29)	−1.51 (−3.06, 0.01)	−0.20 (−1.69, 1.26) *
Bisphenol A	0.46 (−0.60, 1.51)	0.30 (−1.09, 1.68)	0.63 (−0.84, 2.09)
Triclosan	0.42 (−0.52, 1.36)	0.24 (−1.01, 1.48)	0.66 (−0.77, 2.08)

Beta coefficients (95% credible intervals) per standard deviation increase in natural log creatinine-standardized phenol biomarker concentration estimated in linear mixed effects regression models. Sex-specific estimates were estimated by including a product term between the phenol biomarker and child's sex.

*Met criteria for heterogeneity by child's sex (i.e., 80% credible interval for phenol by sex product term excluded the null value).

^aAdjusted only for natural log creatinine.

^bAdjusted for natural log creatinine and urine collection date; maternal race/ethnicity, age, education, work status, smoking during pregnancy, height, pre-pregnancy body mass index, and adequacy of gestational weight gain; prenatal summed di-(2-ethylhexyl) phthalate metabolite concentrations; breastfeeding; months of age and physical activity at follow-up; and, for overall models, child's sex.