View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Carolina Digital Repository

HHS Public Access

Author manuscript

*Environ Int*. Author manuscript; available in PMC 2017 May 01.

Published in final edited form as:

*Environ Int*. 2016 May ; 91: 350–356. doi:10.1016/j.envint.2016.03.019.

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

**Jessie P. Buckley**[a], **Amy H. Herring**[b], **Mary S. Wolff**[c], **Antonia M. Calafat**[d], and **Stephanie M. Engel**[e]

[a]Department of Epidemiology, University of North Carolina at Chapel Hill, McGavran-Greenberg Hall, CB #7435, Chapel Hill, NC 27599-7435, USA.

[b]Department of Biostatistics and Carolina Population Center, University of North Carolina at Chapel Hill, McGavran-Greenberg Hall, CB #7420, Chapel Hill, NC 27599-7420, USA. amy_herring@unc.edu.

[c]Department of Preventive Medicine, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place Box 1057, New York, NY 10029, USA. mary.wolff@mssm.edu.

[d]Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, 4770 Buford Hwy, MS-F17, Atlanta, GA 30341, USA. aic7@cdc.gov.

[e]Department of Epidemiology, University of North Carolina at Chapel Hill, McGavran-Greenberg Hall, CB #7435, Chapel Hill, NC 27599-7435, USA. stephanie.engel@unc.edu.

## 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

Correspondence: Jessie P. Buckley, Department of Epidemiology, University of North Carolina at Chapel Hill, CB #7435, Chapel Hill, NC 27599, (919) 260-1950, jessbuck@unc.edu.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

**Publisher's Disclaimer:** This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Financial interests:
The authors declare no competing financial interests.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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/

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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 [(fat mass / weight) × 100]. We calculated BMI as weight (kg) /height $(m)^2$, used a CDC SAS macro to determine age- and sex-standardized BMI percentiles, and classified children $\geq 85^{th}$ 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 ± 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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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 $2.5^{th}$ and $97.5^{th}$ 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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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 μg/g-creatinine) than among children of Hispanic (median=2.16 μg/g-creatinine) or non-Hispanic white (median=3.31 μg/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.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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 precurcors 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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

## Acknowledgements

We thank Xiaoyun Ye, Amber Bishop, and Jack Reidy for the measurement of the phenols metabolites. This work was supported by the National Institute of Environmental Health Sciences (NIEHS, ES021700). The Mount Sinai Children's Environmental Health Study was supported by grants from NIEHS (ES009584), EPA (R827039 and RD831711), ATSDR, and The New York Community Trust. JPB was supported by training grants from NIEHS (T32 ES007018) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (T32-HD052468-05).

## 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 |

## References

Agay-Shay K, Martinez D, Valvi D, Garcia-Esteban R, Basagana X, Robinson O, Casas M, Sunyer J, Vrijheid M. Exposure to Endocrine-Disrupting Chemicals during Pregnancy and Weight at 7 Years of Age: A Multi-pollutant Approach. Environ Health Perspect. 2015

Bodnar LM, Hutcheon JA, Platt RW, Himes KP, Simhan HN, Abrams B. Should gestational weight gain recommendations be tailored by maternal characteristics? Am J Epidemiol. 2011; 174:136–146. [PubMed: 21633118]

Braun JM, Kalkbrenner AE, Calafat AM, Bernert JT, Ye X, Silva MJ, Barr DB, Sathyanarayana S, Lanphear BP. Variability and predictors of urinary bisphenol A concentrations during pregnancy. Environ Health Perspect. 2011; 119:131–137. [PubMed: 21205581]

Braun JM, Lanphear BP, Calafat AM, Deria S, Khoury J, Howe CJ, Venners SA. Early-life bisphenol a exposure and child body mass index: a prospective cohort study. Environ Health Perspect. 2014; 122:1239–1245. [PubMed: 25073184]

Buckley JP, Engel SM, Mendez MA, Richardson DB, Daniels JL, Calafat AM, Wolff MS, Herring AH. Prenatal Phthalate Exposures and Childhood Fat Mass in a New York City Cohort. Environ Health Perspect. 2015

Buser MC, Murray HE, Scinicariello F. Association of urinary phenols with increased body weight measures and obesity in children and adolescents. J Pediatr. 2014; 165:744–749. [PubMed: 25063718]

Calafat AM, Longnecker MP, Koch HM, Swan SH, Hauser R, Goldman LR, Lanphear BP, Rudel RA, Engel SM, Teitelbaum SL, Whyatt RM, Wolff MS. Optimal Exposure Biomarkers for Nonpersistent Chemicals in Environmental Epidemiology. Environ Health Perspect. 2015; 123:A166–168. [PubMed: 26132373]

Carmichael SL, Herring AH, Sjodin A, Jones R, Needham L, Ma C, Ding K, Shaw GM. Hypospadias and halogenated organic pollutant levels in maternal mid-pregnancy serum samples. Chemosphere. 2010; 80:641–646. [PubMed: 20494400]

Centers for Disease Control and Prevention. Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables. Feb.2015 2015.

Daniels SR, Arnett DK, Eckel RH, Gidding SS, Hayman LL, Kumanyika S, Robinson TN, Scott BJ, St Jeor S, Williams CL. Overweight in children and adolescents: pathophysiology, consequences, prevention, and treatment. Circulation. 2005; 111:1999–2012. [PubMed: 15837955]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

de Onis M, Blossner M, Borghi E. Global prevalence and trends of overweight and obesity among preschool children. Am J Clin Nutr. 2010; 92:1257–1264. [PubMed: 20861173]

Dietz WH. Critical periods in childhood for the development of obesity. Am J Clin Nutr. 1994; 59:955–959. [PubMed: 8172099]

Ellis KJ. Selected body composition methods can be used in field studies. J Nutr. 2001; 131:1589S–1595S. [PubMed: 11340123]

Engel LS, Buckley JP, Yang G, Liao LM, Satagopan J, Calafat AM, Matthews CE, Cai Q, Ji BT, Cai H, Engel SM, Wolff MS, Rothman N, Zheng W, Xiang YB, Shu XO, Gao YT, Chow WH. Predictors and variability of repeat measurements of urinary phenols and parabens in a cohort of Shanghai women and men. Environ Health Perspect. 2014; 122:733–740. [PubMed: 24659570]

Engel SM, Berkowitz GS, Barr DB, Teitelbaum SL, Siskind J, Meisel SJ, Wetmur JG, Wolff MS. Prenatal organophosphate metabolite and organochlorine levels and performance on the Brazelton Neonatal Behavioral Assessment Scale in a multiethnic pregnancy cohort. Am J Epidemiol. 2007; 165:1397–1404. [PubMed: 17406008]

Engel SM, Wolff MS. Causal inference considerations for endocrine disruptor research in children's health. Annual review of public health. 2013; 34:139–158.

Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. The relation of childhood BMI to adult adiposity: the Bogalusa Heart Study. Pediatrics. 2005; 115:22–27. [PubMed: 15629977]

Gelman, A.; Carlin, JB.; Stern, HS.; Dunson, DB.; Vehtari, A.; Rubin, DB. Bayesian data analysis. CRC press; 2013.

Grun F, Blumberg B. Endocrine disrupters as obesogens. Mol Cell Endocrinol. 2009; 304:19–29. [PubMed: 19433244]

Guidry VT, Longnecker MP, Aase H, Eggesbo M, Zeiner P, Reichborn-Kjennerud T, Knudsen GP, Bertelsen RJ, Ye X, Calafat AM, Engel SM. Measurement of Total and Free Urinary Phenol and Paraben Concentrations over the Course of Pregnancy: Assessing Reliability and Contamination of Specimens in the Norwegian Mother and Child Cohort Study. Environ Health Perspect. 2015; 123:705–711. [PubMed: 25782115]

Harley KG, Aguilar Schall R, Chevrier J, Tyler K, Aguirre H, Bradman A, Holland NT, Lustig RH, Calafat AM, Eskenazi B. Prenatal and postnatal bisphenol A exposure and body mass index in childhood in the CHAMACOS cohort. Environ Health Perspect. 2013; 121:514–520. 520e511–516. [PubMed: 23416456]

Heffernan AL, Baduel C, Toms LM, Calafat AM, Ye X, Hobson P, Broomhall S, Mueller JF. Use of pooled samples to assess human exposure to parabens, benzophenone-3 and triclosan in Queensland, Australia. Environ Int. 2015; 85:77–83. [PubMed: 26368661]

Institute of Medicine and National Research Council Committee to Reexamine Institute of Medicine Pregnancy Weight Guidelines. Weight Gain During Pregnancy: Reexamining the Guidelines. Washington, DC: 2009.

Janesick A, Blumberg B. Endocrine disrupting chemicals and the developmental programming of adipogenesis and obesity. Birth Defects Res C Embryo Today. 2011; 93:34–50. [PubMed: 21425440]

Kato K, Silva MJ, Needham LL, Calafat AM. Determination of 16 phthalate metabolites in urine using automated sample preparation and on-line preconcentration/high-performance liquid chromatography/tandem mass spectrometry. Anal Chem. 2005; 77:2985–2991. [PubMed: 15859620]

Kim S, Choi K. Occurrences, toxicities, and ecological risks of benzophenone-3, a common component of organic sunscreen products: a mini-review. Environ Int. 2014; 70:143–157. [PubMed: 24934855]

Lankester J, Patel C, Cullen MR, Ley C, Parsonnet J. Urinary triclosan is associated with elevated body mass index in NHANES. PloS one. 2013; 8:e80057. [PubMed: 24278238]

Li S, Zhao J, Wang G, Zhu Y, Rabito F, Krousel-Wood M, Chen W, Whelton PK. Urinary triclosan concentrations are inversely associated with body mass index and waist circumference in the US general population: Experience in NHANES 2003-2010. Int J Hyg Environ Health. 2015

Little, RJA.; Rubin, DB. Statistical Analysis with Missing Data. John Wiley; New York: 2002.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Lohman TG, Going SB. Body composition assessment for development of an international growth standard for preadolescent and adolescent children. Food Nutr Bull. 2006; 27:S314–325. [PubMed: 17361665]

Lunn, D. WBDev shared components: truncated normal distribution. MRC Biostatistics Unit; Cambridge, UK: 2003.

Meeker JD, Cantonwine DE, Rivera-Gonzalez LO, Ferguson KK, Mukherjee B, Calafat AM, Ye X, Anzalota Del Toro LV, Crespo-Hernandez N, Jimenez-Velez B, Alshawabkeh AN, Cordero JF. Distribution, variability, and predictors of urinary concentrations of phenols and parabens among pregnant women in Puerto Rico. Environmental science & technology. 2013; 47:3439–3447. [PubMed: 23469879]

Moos RK, Angerer J, Wittsiepe J, Wilhelm M, Bruning T, Koch HM. Rapid determination of nine parabens and seven other environmental phenols in urine samples of German children and adults. Int J Hyg Environ Health. 2014; 217:845–853. [PubMed: 25008406]

Newbold RR, Padilla-Banks E, Jefferson WN. Environmental estrogens and obesity. Mol Cell Endocrinol. 2009; 304:84–89. [PubMed: 19433252]

O'Brien KM, Upson K, Cook NR, Weinberg CR. Environmental Chemicals in Urine and Blood: Improving Methods for Creatinine and Lipid Adjustment. Environ Health Perspect. 2015

Ogden, C.; Carroll, M. Health E-Stat. CDC/National Center for Health Statistics, Division of Health and Nutrition Examination Surveys; Atlanta, GA: 2010. Prevalence of Obesity Among Children and Adolescents: United States, Trends 1963–1965 Through 2007–2008. Available: http://www.cdc.gov/nchs/data/hestat/obesity_child_07_08/obesity_child_07_08.pdf [accessed 1 April 2015]

Okada-Iwabu M, Yamauchi T, Iwabu M, Honma T, Hamagami K, Matsuda K, Yamaguchi M, Tanabe H, Kimura-Someya T, Shirouzu M, Ogata H, Tokuyama K, Ueki K, Nagano T, Tanaka A, Yokoyama S, Kadowaki T. A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity. Nature. 2013; 503:493–499. [PubMed: 24172895]

Philippat C, Botton J, Calafat AM, Ye X, Charles MA, Slama R, Group ES. Prenatal exposure to phenols and growth in boys. Epidemiology. 2014; 25:625–635. [PubMed: 25061923]

Philippat C, Wolff MS, Calafat AM, Ye X, Bausell R, Meadows M, Stone J, Slama R, Engel SM. Prenatal exposure to environmental phenols: concentrations in amniotic fluid and variability in urinary concentrations during pregnancy. Environ Health Perspect. 2013; 121:1225–1231. [PubMed: 23942273]

Rubin BS. Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects. The Journal of steroid biochemistry and molecular biology. 2011; 127:27–34. [PubMed: 21605673]

Seidlova-Wuttke D, Jarry H, Christoffel J, Rimoldi G, Wuttke W. Effects of bisphenol-A (BPA), dibutylphtalate (DBP), benzophenone-2 (BP2), procymidone (Proc), and linurone (Lin) on fat tissue, a variety of hormones and metabolic parameters: a 3 months comparison with effects of estradiol (E2) in ovariectomized (ovx) rats. Toxicology. 2005; 213:13–24. [PubMed: 15951094]

Takahashi O, Oishi S, Yoneyama M, Ogata A, Kamimura H. Antiestrogenic effect of paradichlorobenzene in immature mice and rats. Archives of toxicology. 2007; 81:505–517. [PubMed: 17593412]

Teitelbaum SL, Britton JA, Calafat AM, Ye X, Silva MJ, Reidy JA, Galvez MP, Brenner BL, Wolff MS. Temporal variability in urinary concentrations of phthalate metabolites, phytoestrogens and phenols among minority children in the United States. Environ Res. 2008; 106:257–269. [PubMed: 17976571]

Uh HW, Hartgers FC, Yazdanbakhsh M, Houwing-Duistermaat JJ. Evaluation of regression methods when immunological measurements are constrained by detection limits. BMC immunology. 2008; 9:59. [PubMed: 18928527]

Valvi D, Casas M, Mendez MA, Ballesteros-Gomez A, Luque N, Rubio S, Sunyer J, Vrijheid M. Prenatal bisphenol a urine concentrations and early rapid growth and overweight risk in the offspring. Epidemiology. 2013; 24:791–799. [PubMed: 24036610]

Vom Saal FS, Nagel SC, Coe BL, Angle BM, Taylor JA. The estrogenic endocrine disrupting chemical bisphenol A (BPA) and obesity. Mol Cell Endocrinol. 2012; 354:74–84. [PubMed: 22249005]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Wang CF, Tian Y. Reproductive endocrine-disrupting effects of triclosan: Population exposure, present evidence and potential mechanisms. Environmental pollution. 2015; 206:195–201. [PubMed: 26184583]

Wei Y, Zhu J, Nguyen A. Urinary concentrations of dichlorophenol pesticides and obesity among adult participants in the U.S. National Health and Nutrition Examination Survey (NHANES) 2005-2008. Int J Hyg Environ Health. 2014; 217:294–299. [PubMed: 23899931]

Weng SF, Redsell SA, Swift JA, Yang M, Glazebrook CP. Systematic review and meta-analyses of risk factors for childhood overweight identifiable during infancy. Archives of disease in childhood. 2012; 97:1019–1026. [PubMed: 23109090]

Wolff MS, Engel SM, Berkowitz GS, Ye X, Silva MJ, Zhu C, Wetmur J, Calafat AM. Prenatal phenol and phthalate exposures and birth outcomes. Environ Health Perspect. 2008; 116:1092–1097. [PubMed: 18709157]

Wolff MS, Teitelbaum SL, McGovern K, Pinney SM, Windham GC, Galvez M, Pajak A, Rybak M, Calafat AM, Kushi LH, Biro FM. Environmental phenols and pubertal development in girls. Environ Int. 2015; 84:174–180. [PubMed: 26335517]

Wright CM, Sherriff A, Ward SC, McColl JH, Reilly JJ, Ness AR. Development of bioelectrical impedance-derived indices of fat and fat-free mass for assessment of nutritional status in childhood. Eur J Clin Nutr. 2008; 62:210–217. [PubMed: 17356557]

Ye X, Kuklenyik Z, Needham LL, Calafat AM. Quantification of urinary conjugates of bisphenol A, 2,5-dichlorophenol, and 2-hydroxy-4-methoxybenzophenone in humans by online solid phase extraction-high performance liquid chromatography-tandem mass spectrometry. Anal Bioanal Chem. 2005; 383:638–644. [PubMed: 16132150]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

## 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.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

## 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] | | |

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

| 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)

[a]Proportion classified as inactive at any follow-up visit.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript



**Table 2**

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

| Biomarker | LOD | Percent detected | Geometric mean[a] | Minimum | 25th percentile | 75th 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).

[a]To compute the geometric mean, concentrations <LOD were replaced by LOD/√2.

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

*Environ Int*. Author manuscript; available in PMC 2017 May 01.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

## Table 3

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

| Outcome/visit[a] | Overall | | Girls | | Boys | |
|---|---|---|---|---|---|---|
| | *n* | Mean ± SD | *n* | Mean ± SD | *n* | 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)

[a]Mean age in years ± SD for visits 1, 2, and 3 were 4.9 ± 0.4, 6.2 ± 0.2, 7.8 ± 0.8, respectively.

[b]Percent fat mass estimated using bioelectrical impedance analysis (Tanita TBF-300).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

## 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).

[a]Adjusted only for natural log creatinine.

[b]Adjusted 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.