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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], Stephanie M. Engel [a]

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

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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 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.

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 et al., 2014; Guidry et al., 2015; Heffernan et al., 2015; Moos et al., 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 et al., 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 et al., 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 et al., 2009). In human prospective studies, associations of gestational exposure to bisphenol A with childhood body size have been inconsistent, with studies reporting positive (Valvi et al., 2013), inverse (girls only) (Harley et al., 2013), and null (Agay-Shay

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.

* Corresponding author at: Department of Epidemiology, University of North Carolina at Chapel Hill, CB #7435, Chapel Hill, NC 27599-7435, USA.
E-mail addresses: jessbuck@unc.edu (J.P. Buckley), amy_herring@unc.edu (A.H. Herring), mary.wolff@mssm.edu (M.S. Wolff), aic7@cdc.gov (A.M. Calafat), stephanie.engel@unc.edu (S.M. Engel).

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et al., 2015; Braun et al., 2014; Philippat et al., 2014) associations. The only prospective study of prenatal exposure to other environmental phenols assessed early postnatal growth in a cohort of male infants (Philippat et al., 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 et al., 2005). Obese children are at increased risk of becoming obese adults (Freedman et al., 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 et al., 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 et al., 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 et al., 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. (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, 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 [(fat mass / weight) × 100]. We calculated body mass index (BMI) as weight (kg) / height $(m)^2$, used a CDC SAS macro to determine age- and sex-standardized BMI percentiles, and classified children ≥85th 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 et al., 2005; Ye et al., 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 et al., 2010; Uh et al., 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. (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)