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Associations of prenatal environmental phenol and phthalate biomarkers with respiratory and allergic diseases among children aged 6 and 7 years

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Abstract

Background—Prenatal environmental phenol and phthalate exposures may alter immune or inflammatory responses leading to respiratory and allergic disease.

Objectives—We estimated associations of prenatal environmental phenol and phthalate biomarkers with respiratory and allergic outcomes among children in the Mount Sinai Children's Environmental Health Study.

Methods—We quantified urinary biomarkers of benzophenone-3, bisphenol A, paradichlorobenzene (as 2,5-dichlorophenol), triclosan, and 10 phthalate metabolites in third trimester maternal samples and assessed asthma, wheeze, and atopic skin conditions via parent questionnaires at ages 6 and 7 years (n=164 children with 240 observations). We used logistic regression to estimate covariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) per

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standard deviation difference in natural log biomarker concentrations and examined effect measure modification by child's sex.

Results—Associations of prenatal 2,5-dichlorophenol (all outcomes) and bisphenol A (asthma outcomes) were modified by child's sex, with increased odds of outcomes among boys but not girls. Among boys, ORs for asthma diagnosis per standard deviation difference in biomarker concentration were 3.00 (95% CI: 1.36, 6.59) for 2,5-dichlorophenol and 3.04 (95% CI: 1.38, 6.68) for bisphenol A. Wheeze in the past 12 months was inversely associated with low molecular weight phthalate metabolites among girls only (OR: 0.27, 95% CI: 0.13, 0.59) and with benzophenone-3 among all children (OR: 0.65, 95% CI: 0.44, 0.96).

Conclusions—Prenatal bisphenol A and paradichlorobenzene exposures were associated with pediatric respiratory outcomes among boys. Future studies may shed light on biological mechanisms and potential sexually-dimorphic effects of select phenols and phthalates on respiratory disease development.

Keywords

environmental phenols; bisphenol A; phthalates; endocrine disruption; asthma; children's health

Introduction

Asthma is the leading chronic pediatric disease worldwide, causing substantial morbidity (Akinbami et al. 2016; Asher and Pearce 2014). Emerging evidence suggests that exposures to environmental contaminants during the prenatal period may increase the risk of developing respiratory and allergic disease in childhood. Environmental exposures during early life can cause irreversible changes to the immune system and have been shown to alter lung development, reduce lung function, and increase respiratory illness and allergic manifestations later in life (Harding et al. 2009; Martino and Prescott 2011; Miller and Marty 2010). In particular, the role of estrogen in immune response suggests the potential for endocrine disrupting chemicals to influence development of asthma and allergic disease (Bonds and Midoro-Horiuti 2013).

Some phenols, including bisphenol A, benzophenone-3, 2,5-dichlorophenol (a metabolite of paradichlorobenzene), and triclosan, as well as phthalates are synthetic environmental chemicals that may induce immunologic changes leading to adverse respiratory and allergic outcomes. Although these chemicals (or their precursors) are rapidly metabolized and excreted, their ubiquity in consumer products has led to widespread exposures in the general U.S. population (Centers for Disease Control and Prevention 2017b). Bisphenol A is used in the manufacture of polycarbonate plastics and epoxy resins and can be detected in products such as canned foods and beverages, toys, and dental sealants. Benzophenone-3 is used as a UV filter in sun-blocking agents and plastics. Paradichlorobenzene, also known as 1,4-dichlorobenzene, isa disinfectant used in mothballs and deodorizers. Triclosan is an antibacterial agent found in products such as detergents, textiles, and personal care products. Low molecular weight phthalates (LMWPs) are contained in cosmetics, personal care products, and medications while high molecular weight phthalates (HMWPs) are used in

plastic tubing, food packaging and processing materials, vinyl flooring, and building materials.

Prenatal bisphenol A and phthalate exposures are hypothesized to increase the risk of asthma and allergy by altering immune or inflammatory responses (Robinson and Miller 2015), potentially via endocrine disruption (Bonds and Midoro-Horiuti 2013). While the exact mechanisms by which these chemicals could impact development of respiratory and allergic disease are not well understood, early life bisphenol A and phthalate exposures in experimental animals may result in pro-inflammatory immune responses, allergic sensitization, and bronchial inflammation that may depend on exposure timing and offspring sex (Bauer et al. 2012; Chen et al. 2015; Han et al. 2014; Jahreis et al. 2017; Midoro-Horiuti et al. 2010; Nakajima et al. 2012; O'Brien et al. 2014; Petzold et al. 2014; Shin et al. 2014; Wang et al. 2017; Yanagisawa et al. 2008). In humans, several studies have reported a deleterious impact of prenatal bisphenol A exposure on respiratory outcomes in early childhood (Gascon et al. 2015; Spanier et al. 2012; Spanier et al. 2014b; Vernet et al. 2017; Zhou et al. 2017) while another study did not (Donohue et al. 2013). Similarly, most prospective birth cohort studies evaluating prenatal phthalate exposures have reported associations with respiratory and allergic outcomes, particularly for HMWPs (Gascon et al. 2015; Herberth et al. 2017; Jahreis et al. 2017; Just et al. 2012; Ku et al. 2015; Smit et al. 2015; Whyatt et al. 2014) though there are exceptions (Vernet et al. 2017; Wang et al. 2014).

Limited research suggests that early life exposures to other environmental phenols, including benzophenone-3, paradichlorobenzene, and triclosan, may also affect respiratory health. Although mechanistic studies are sparse, these environmental phenols may affect development or severity of asthma and allergic diseases via alteration of immune function or disruption of the gut or airway microbiome (Jerschow et al. 2012; Savage et al. 2012). Several cross-sectional studies have reported associations of 2,5-dichlorophenol and triclosan concentrations with increased asthma, asthma morbidity, and allergic sensitization (Bertelsen et al. 2013; Clayton et al. 2011; Jerschow et al. 2012; Jerschow et al. 2014; Savage et al. 2014; Savage et al. 2012; Spanier et al. 2014a). In the only prospective study, prenatal 2,5-dichlorophenol concentrations were associated with increased rates of wheeze, whereas benzophenone-3 was associated with decreased rates, in a French cohort of boys (Vernet et al. 2017).

In the current study, we sought to examine whether prenatal urinary concentrations of bisphenol A, benzophenone-3, 2,5-dichlorophenol, triclosan, and 10 phthalate metabolites were associated with respiratory and allergic disease among school-aged children participating in a prospective pregnancy cohort study in New York City. As a secondary aim, we assessed effect measure modification by child's sex.

Materials and Methods

Study Population

The Mount Sinai Children's Environmental Health Study is a prospective pregnancy cohort that enrolled pregnant women in New York City from 1998 to 2002. Details of this cohort have been described previously (Engel et al. 2007). Briefly, 479 primiparous women were

enrolled from the Mount Sinai prenatal clinic and two adjacent private practices. Seventy-five women were excluded because of medical complications, very premature births (<32 weeks gestation or <1500 g), delivery of an infant with birth defects, inability to obtain biological specimens before delivery, change of residence, or refusal to continue participation. Trained research assistants collected maternal baseline sociodemographic and household characteristics during an in person, two-hour structured interview conducted at third trimester prenatal care visits. Delivery characteristics and infant sex were ascertained from a computerized perinatal database at Mount Sinai Hospital.

The final cohort consists of 404 mother-infant pairs for whom birth data are available. Urine specimens were collected from 401 women and there was sufficient volume for quantification of environmental phenols in 367 specimens and phthalates in 382. Following previous analyses of this cohort, we excluded participants with a creatinine concentration <10 μg/dL (n =1) due to the potential for inaccurate biomarker measurements (Wolff et al. 2008). Outcome data were available for 164 children who attended at least one follow-up visit at 6 or 7 years of age. If the child attended both visits, we included these repeated measures in analyses of symptoms in the past 12 months. Thus, the final sample size for our current study on respiratory and allergic disease outcomes consisted of 159 children with 232 observations for the environmental phenols analyses and 164 children with 240 observations for the phthalates analyses.

Human Subjects

We obtained written informed consent from women prior to participation. At child follow-up visits, we obtained informed consent from the parent as well as assent from children aged 7 years. We received approval for the study from the Mount Sinai School of Medicine Institutional Review Board and for the present analysis from 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.

Measurement of Environmental Phenol and Phthalate Biomarkers

To assess exposure to environmental phenols and phthalates, we collected a spot urine sample from participating women during their third trimester of pregnancy (mean=31.5 weeks gestation, SD=5.1 weeks, range=25–40 weeks gestation). Samples were stored at −80°C until shipment on dry ice to the CDC for quantification of creatinine, environmental phenols and phthalates biomarkers concentrations. Environmental phenol biomarkers included bisphenol A, benzophenone-3, 2,5-dichlorophenol, and triclosan. Phthalate biomarkers included monoisobutyl phthalate (MiBP, a metabolite of diisobutyl phthalate), mono-n-butyl phthalate (MnBP, a metabolite of di-n-butyl phthalate), monoethyl phthalate (MEP, a metabolite of diethyl phthalate), monobenzyl phthalate (MBzP, a metabolite of butyl benzyl phthalate), mono(3-carboxypropyl) phthalate (MCPP, a nonspecific metabolite of di-n-octyl phthalate and other HMWPs and a minor metabolite of dibutyl phthalate), and four metabolites of di(2-ethylhexyl) phthalate (DEHP): mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethylhexyl) phthalate (MEHP). Urine samples

were analyzed for target analytes at the CDC using solid phase extraction coupled with high performance liquid chromatography–isotope dilution tandem spectrometry as described previously (Kato et al. 2005; Ye et al. 2005).

Outcome Assessment

We obtained information on asthma, wheeze, and atopic skin conditions via a health assessment questionnaire administered to parents when children were 6 and 7 years of age. The questionnaire included items from the International Study of Asthma and Allergies in Children (ISAAC) questionnaire as well as additional questions about health symptoms in the past 12 months. The ISAAC questionnaire is a validated instrument designed to ascertain asthma and wheezing symptoms in children from parental report at age 6 or 7 years (Asher et al. 1995; Jenkins et al. 1996). We focused on four ISAAC questionnaire items, including asthma diagnosis (ever), emergency department visits for asthma in the past 12 months (as a measure of severity), and wheezing or whistling in the chest (ever and in the past 12 months). Because our sample size was not sufficiently large to assess morbidity among children with asthma, we examined emergency department visits in the past 12 months as a measure of asthma severity by comparing children with a recent emergency visit due to an asthma attack to children without asthma. We also assessed atopic skin conditions using parent report of rashes, eczema, or hives in the past 12 months. There were 164 children with questionnaire responses, of whom 76 provided data at both the 6- and 7-year visits (240 total observations). For children with multiple visits, we used the child's response at age 7 to define ever occurrence of symptoms and we incorporated both responses in repeated measures analyses of symptoms in the past 12 months.

Statistical Analyses

First, we examined descriptive statistics and covariate distributions to check for outlying values. To assess whether baseline covariates were associated with loss to follow-up in our cohort, we conducted chi-square tests comparing covariate distributions in the study sample (N=164) to children without a follow-up visit at age 6 or 7 (N=240). For descriptive analyses of exposure biomarker correlations, we set exposure biomarker values below the limit of detection (LOD) to the LOD divided by the square root of two (Hornung and Reed 1990).

For inferential analyses of exposure biomarker associations with outcomes, we used multiple imputation to account for potential bias due to missing covariate data and biomarker concentrations below the LOD. Using the SAS MI procedure, we created 50 datasets to multiply impute a missing value for type of home ownership (n = 1) using fully conditional specification with the discriminant function method (van Buuren 2007). Next, we multiply imputed environmental phenol and phthalate biomarker concentrations below the LOD by drawing values from a truncated normal distribution with parameters defined by the mean and standard deviation of the observed biomarker distribution, zero as the lower bound, and the LOD as the upper bound (Buckley et al. 2016a; Uh et al. 2008). Because the DEHP metabolites MECPP, MEHHP, MEHP, and MEOHP are highly correlated, we constructed a molar sum of DEHP metabolites (ΣDEHP) in each dataset based on the imputed values of the component metabolites. Following the same procedures, we also created molar sum variables for metabolites of LMWPs (ΣLMWP, including MEP, MnBP, and MiBP) and

HMWPs (ΣHMWP, including MCPP, MBzP, and DEHP metabolites). We standardized the natural log of each environmental phenol biomarker and phthalate metabolite or molar sum to its mean and standard deviation. While this approach facilitates comparison of biomarker effect sizes relative to their distributions in the study population, we note that a standard deviation change in natural log biomarker concentration corresponds to a different magnitude of absolute change in concentration for each biomarker. For example, a standard deviation change from the mean is equivalent to the following differences in concentration (μg/L) for each biomarker: 2,5-dichlorophenol: 387; triclosan: 94; benzophenone-3: 73; bisphenol A: 4; MEP: 1081; MnBP: 122; MiBP: 19; MCPP: 9; MBzP: 62; ΣDEHP: 322; MECPP: 132; MEHHP: 80; MEHP: 21; and MEOHP: 70.

We estimated associations of environmental phenol and phthalate biomarkers with asthma, wheeze, and atopic skin conditions using logistic regression. For outcomes with repeated measures, we used generalized estimating equations with an independent working correlation matrix to account for within-person correlation. To minimize bias while maximizing precision of our estimates, we identified adjustment variables using directed acyclic graphs and included all confounders and predictors of childhood respiratory and allergic outcomes that were not on the causal pathway. These variables included sociodemographics (maternal age, race/ethnicity, pre-pregnancy body mass index (BMI), education, marital status), residential characteristics (type of residence, number of occupants, pets), predictors of asthma, wheeze, and atopic skin conditions (maternal smoking during pregnancy, persons in the household with asthma, persons in the household with allergies, child's sex, age at follow-up), and creatinine (as a measure of urinary dilution). We modeled natural log creatinine, maternal age, and maternal pre-pregnancy BMI using restricted quadratic splines (Howe et al. 2011) and age at follow-up (months) as a continuous variable. We combined maternal Hispanic and other race/ethnicities for analysis, and modeled all multi-level categorical variables using disjoint indicator coding to allow for non-monotonic associations. We estimated covariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) per standard deviation increase in natural log biomarker concentrations using the SAS GENMOD procedure and combined estimates from the 50 imputations using the MIANALYZE procedure.

As part of our analyses, we also assessed effect measure modification of associations by child's sex given that some environmental phenols and phthalates are endocrine disrupting chemicals for which we have observed sex differences in their associations with other outcomes in prior studies of our cohort (Buckley et al. 2016b; Doherty et al. 2017; Wolff et al. 2008). We accounted for potential differences in confounder-outcome associations by sex by applying a reduced augmented product term approach to limit bias while maintaining precision of our estimates (Buckley et al. 2017). For these models, we included product terms between child's sex and exposure as well as between child's sex and two variables that act as proxies for genetic predisposition (person in the household with asthma and person in the household with allergies) to adjust for potential sex-specific confounding given the male predominance of atopic disease in early childhood (Thomsen 2015).

We conducted several sensitivity analyses to assess the robustness of associations in our study. First, to examine independent associations of environmental phenol and phthalate

biomarkers with outcomes, we included all four environmental phenol biomarkers as well as ΣLMWP and ΣHMWP in the same model. Second, we examined exposure-response relationships by modeling associations between tertiles of biomarker creatinine-corrected concentrations, and respiratory and allergic outcomes. Due to the smaller sample size for sex-specific analyses, we conducted these secondary analyses for the overall population only. Third, because we had repeated measures for outcomes reported in the past 12 months for 76 participants, we conducted stratified analyses for responses at age 6 years (N= 92) and age 7 years (N = 148) to assess robustness of primary models and explore potential differences by age.

We conducted all statistical analyses using SAS software version 9.4 (SAS Institute Inc.). Our criteria for statistical significance were alpha levels of 0.05 and 0.1 for main effects and effect measure modification, respectively.

Results

Approximately 40% of the initial cohort attended at least one follow-up visit at age 6 or 7 years. Baseline characteristics of the study sample were generally similar to those of the full cohort, with most mothers being young (<25 years), Hispanic, and not married or living with the father of the child (Table 1). However, mothers of children in the current study sample were slightly older with higher pre-pregnancy BMI and lower socioeconomic status compared to those not followed-up.

Third trimester urinary environmental phenol biomarker and phthalate metabolite concentrations were widely detected in participating women (detection frequency ≥80%) (Table 2). Compared to the U.S. general population of females during a similar time period, median biomarker concentrations of women in our cohort were similar except that we observed higher 2,5-dichlorophenol and lower benzophenone-3 concentrations. Spearman correlation coefficients were low among the environmental phenol biomarkers (ρ<0.3) and moderate among phthalate metabolites (ρ range: 0.4–0.8). Correlations of environmental phenols with phthalate metabolites were moderate for 2,5-dichlorophenol and bisphenol A (ρ range: 0.3–0.4) and low for triclosan and benzophenone-3 (ρ range: 0–0.2) (Supplemental Material, Table S1).

One-quarter of the children had ever received an asthma diagnosis and nearly 40% had ever experienced wheezing or whistling in the chest (Table 3). As expected, prevalence of asthma or wheeze symptoms in the past 12 months were lower than lifetime prevalences of asthma or wheeze. Reports of rashes, eczema, or hives in the past 12 months occurred at 35% of the follow-up visits. Among the 76 participants with visits at both 6 and 7 years of age, the proportion of discordant responses for outcomes assessed in the past 12 months were 28% for wheezing or whistling in the chest, 18% for emergency room visit for asthma, and 16% for rashes, eczema or hives.

Associations of environmental phenol biomarkers with child respiratory and allergic outcomes are reported in Table 4. In overall models, we observed associations of third trimester maternal urinary 2,5-dichlorophenol concentrations with increased odds of ever

being diagnosed with asthma (OR: 1.51, 95% CI: 0.93, 2.46), emergency room visits for an asthma attack in the past 12 months (OR: 2.07, 95% CI: 1.17, 3.68), and rashes, eczema, or hives in the past 12 months (OR: 1.71, 95% CI: 1.15, 2.55). Associations between 2,5-dichlorophenol and all five outcomes were modified by child's sex, with statistically significant positive associations for boys but null associations for girls (Table 4).

Prenatal urinary bisphenol A concentrations were associated with increased odds of ever being diagnosed with asthma (OR: 1.66, 95% CI: 1.04, 2.66). This association was modified by child's sex with a positive association among boys (OR: 3.04, 95% CI: 1.38, 6.68) and no association among girls (OR: 0.94, 95% CI: 0.48, 1.84). Bisphenol A findings followed a similar pattern for other asthma and wheeze outcomes but were only statistically significant for emergency room visits for an asthma attack in the past 12 months among boys (Table 4).

Maternal urinary benzophenone-3 concentrations were associated with decreased odds of wheezing or whistling in the chest in the past 12 months in all children (OR: 0.65, 95% CI: 0.44, 0.96) and among girls (OR: 0.52, 95% CI: 0.28, 0.97). Urinary benzophenone-3 concentrations were also non-significantly associated with lower odds of an emergency room visit for asthma in the past 12 months (OR: 0.58, 95% CI: 0.27, 1.25). Maternal urinary triclosan concentrations were not associated with asthma, wheeze, or atopic skin conditions (Table 4).

Table 5 reports associations of phthalate metabolites and molar sums with child respiratory and allergic outcomes. Higher maternal urinary ΣLMWP concentrations were associated with lower odds of wheeze symptoms (ever and past 12 months) among girls but not boys. Associations with individual LMWP metabolites were uniformly inverse among girls, with statistically significant inverse associations between prenatal MEP and MnBP concentrations and wheeze outcomes in girls. HMWP metabolites (individual and summed) were not associated with asthma, wheeze, or atopic skin conditions.

Findings were similar to the primary results when including all environmental phenols in the same model to assess their independent associations (Supplemental Material, Table S2). Additionally including ΣLMWP and ΣHMWP variables in the multiple biomarker model resulted in larger, statistically significant associations of 2,5-dichlorophenol with ever being diagnosed with asthma (OR: 1.88, 95% CI: 1.09, 3.26) and wheezing or whistling in the chest in the past 12 months (OR: 1.59, 95% CI: 1.03, 2.46). Phthalate associations were unchanged upon adjustment for environmental phenols with the exception of an inverse relationship between prenatal ΣLMWP concentrations and rashes, eczema, and hives in the past 12 months (OR: 0.52, 95% CI: 0.30, 0.91) that was not observed in the single biomarker model (OR: 0.90, 95% CI: 0.60, 1.34).

Sensitivity analyses examining potential non-linear exposure-response relationships generally revealed monotonic increases or decreases in odds with increasing exposure category (Supplemental Material, Table S3). Children in the middle tertile (OR: 3.32, 95% CI: 1.09, 10.12), but not the highest tertile (OR 0.83, 95% CI: 0.23, 2.94), of prenatal triclosan concentrations had increased odds of ever being diagnosed with asthma compared to the lowest tertile but estimates were imprecise.

In stratified models estimating associations of maternal urinary biomarker concentrations with outcomes in the past 12 months separately for the age 6 and age 7 year visits, association were similar to the primary analyses though estimates were less precise (data not shown).

Discussion

In this prospective cohort study, we observed associations of higher prenatal bisphenol A and 2,5-dichlorophenol urinary concentrations with parent-reported respiratory and allergic outcomes among boys but not girls. In addition, we found associations of biomarkers of LMWPs and benzophenone-3 concentrations with reduced odds of wheeze symptoms, particularly among girls, whereas triclosan and biomarkers of HMWPs were not associated with any of the outcomes examined.

To our knowledge, the only other study to assess associations of prenatal 2,5-dichlorophenol, benzophenone-3, and triclosan with child respiratory and allergic outcomes was a French pregnancy cohort of 587 boys that measured concentrations in second trimester urine samples and examined respiratory outcomes through age 5 years (Vernet et al. 2017). While we observed positive associations of prenatal 2,5-dichlorophenol concentrations with all outcomes among boys, Vernet et al. reported associations with wheeze but not with asthma or with additional outcomes not examined in the present study, including bronchiolitis/bronchitis and forced expiratory volume in the first second of expiration (FEV_1) (Vernet et al. 2017). Like Vernet et al., we also observed inverse associations of prenatal benzophenone-3 concentrations with wheeze but not with other outcomes, and no associations with triclosan.

We observed a positive association between third trimester maternal urinary bisphenol A concentrations and odds of asthma among boys. Patterns of association were similar for parent-reported wheeze outcomes, though not statistically significant. These findings support a potential relationship between *in utero* bisphenol A exposure and adverse respiratory outcomes, which has also been suggested by the majority of prior studies (Donohue et al. 2013; Gascon et al. 2015; Spanier et al. 2012; Spanier et al. 2014b; Vernet et al. 2017; Zhou et al. 2017). While the critical window of susceptibility for effects of bisphenol A on asthma and wheeze are not known, prior studies suggests that timing of vulnerability to bisphenol A may differ by respiratory phenotype. Spanier et al. found that bisphenol A concentrations during early pregnancy were uniquely related to wheeze whereas associations with FEV_1 did not depend on timing of exposure during gestation (Spanier et al. 2012; Spanier et al. 2014b). Another study reported stronger associations of respiratory and allergic outcomes with bisphenol A concentrations measured in the third trimester compared to first trimester, with the largest difference for asthma at age 7 years (Gascon et al. 2015). Taken together, these studies suggest that bisphenol A exposures during early pregnancy may be more relevant for wheeze whereas those occurring during late pregnancy may be more important for asthma. If so, our findings of a stronger association between third trimester bisphenol A concentrations with asthma than wheeze may relate to exposure misclassification for the latter outcome.

Our study is the first to observe stronger associations of prenatal bisphenol A concentrations with respiratory outcomes among boys compared with girls. Two studies of bisphenol A that examined modification by child's sex reported no statistically significant differences in associations between boys and girls evaluated from age 6 months through 3 years (Spanier et al. 2012) or from birth through age 7 years (Gascon et al. 2015), while another reported stronger associations with wheeze or eczema among girls at 6 months of age (Zhou et al. 2017). Sexually-dimorphic associations may be due to the endocrine disrupting activity of bisphenol A or to sex differences is asthma development (Carey et al. 2007; Chang and Mitzner 2007). Alternatively, our findings may be due to chance given our limited sample size when assessing sex-specific associations. If confirmed in other populations, it would also be important to assess sex differences at older ages given the change in sex-specific prevalence of asthma from male predominance in early childhood to female predominance upon puberty (Fu et al. 2014).

We did not observe positive associations of third trimester phthalate metabolite concentrations with asthma, wheeze, or atopic skin conditions. However, biomarkers of LMWPs were associated with *reduced* odds of wheeze outcomes in girls. Animal studies examining early life exposures have focused on HMWPs with most reporting adjuvant effects on allergic and inflammatory respiratory responses (Chen et al. 2015; Han et al. 2014; Jahreis et al. 2017; Wang et al. 2017), although one found a protective effect of prenatal DEHP exposure on airway inflammation in mouse offspring (Shin et al. 2014). Although our study and one other (Vernet et al. 2017) did not observe associations of biomarkers of prenatal HMWPs with increased asthma or wheeze symptoms, several other epidemiologic studies support the animal findings (Gascon et al. 2015; Ku et al. 2015; Smit et al. 2015; Whyatt et al. 2014). Gascon et al. observed stronger associations of first trimester concentrations of metabolites of HMWPs with wheeze compared to third trimester, suggesting that our study (third trimester) and Vernet et al. (second trimester) may not have measured phthalate metabolites in the relevant critical window for wheeze which may have caused exposure misclassification biasing results toward the null (Gascon et al. 2015; Vernet et al. 2017).

In contrast to our finding of an inverse association of biomarkers of LMWPs with wheeze, two prior studies reported associations of third trimester MnBP concentrations with increased asthma diagnosis or symptoms, although neither study examined wheeze outcomes or differences by child's sex (Jahreis et al. 2017; Whyatt et al. 2014). Other studies have reported null associations of biomarkers of LMWPs with asthma and wheeze (Gascon et al. 2015; Ku et al. 2015; Vernet et al. 2017). As our findings have not been replicated in other cohorts, non-causal factors related to study design and analyses may explain these differences (e.g., small sample size among girls, multiple testing bias, unmeasured confounding). Still, given the focus of experimental studies on HMWPs, additional human and animal studies examining potential sex-specific effects of early life LMWP exposures on lung development and function could provide useful data to assess the plausibility of our findings.

With respect to atopic skin conditions, we observed an association of 2,5-dichlorophenol with increased odds of rashes, eczema, or hives in the past 12 months among boys but not

girls. While there are no other prospective studies of 2,5-dichlorophenol and atopic skin conditions, a cross-sectional study found that urinary 2,5-dichlorophenol concentrations were positively associated with levels of total serum immunoglobulin E and with asthma morbidity among atopic but not non-atopic wheezers (Jerschow et al. 2014). Similar to our findings, most previous studies of prenatal exposures to other environmental phenols and phthalates have not observed associations with atopy, immunoglobulin E, or eczema at birth or during early childhood (Ashley-Martin et al. 2016; Ashley-Martin et al. 2015; Donohue et al. 2013; Gascon et al. 2015; Stelmach et al. 2015; Wang et al. 2014), though some studies have reported isolated associations of third trimester concentrations of dibutyl or butylbenzyl phthalates with atopic outcomes (Herberth et al. 2017; Jahreis et al. 2017; Just et al. 2012).

Our study has several limitations. First, we relied on a spot urine sample collected during the third trimester of pregnancy to assess exposure to select environmental phenols and phthalates. Exposure to these non-persistent chemicals (or their precursors) is episodic, and prior studies that collected multiple biomarker samples during pregnancy report poor reproducibility (intra-class correlation coefficient, ICC<0.4) for bisphenol A and DEHP metabolites and moderate reproducibility (ICC range: 0.4 to 0.7) for other biomarkers studied in the current analysis (Adibi et al. 2008; Braun et al. 2011; Braun et al. 2012; Engel et al. 2014; Ferguson et al. 2014; Meeker et al. 2013; Philippat et al. 2013). While a single spot urine sample may be adequate to classify exposure to certain non-persistent chemicals over a period of weeks to months (Calafat et al. 2015), our study may have misclassified exposures if the third trimester is not the relevant window of susceptibility for respiratory or allergic disease development. Assuming monotonic exposure-response and independent, non-differential exposure measurement error, we expect this misclassification would likely bias associations towards the null (Perrier et al. 2016; VanderWeele and Hernan 2012). While we detected statistically significant associations of biomarkers with respiratory and allergic outcomes, measurement error may explain some differences in our study findings compared to previous reports. In addition, we lacked information on postnatal environmental phenol and phthalate exposures and thus could not explore the contribution of childhood exposures. While we conducted sensitivity analyses to account for potential confounding among these correlated chemicals, we did not have adequate sample size to examine the association of exposure mixtures with respiratory and allergic outcomes.

Additionally, we did not perform clinical confirmation of outcomes. While our children were old enough for stable asthma diagnosis, they may have self-reported a diagnosis that occurred before age 5 years when diagnoses are susceptible to misclassification (National Asthma Education and Prevention Program 2007). However, we ascertained asthma and wheeze using the ISAAC questionnaire, a validated instrument widely used in epidemiologic studies of childhood asthma (Jenkins et al. 1996). This questionnaire also allowed us to evaluate the consistency of results with ever versus recent asthma and wheeze symptoms. Although we observed some differences between the characteristics of our study sample and the original pregnancy cohort, we previously conducted state-of-the-art sensitivity analyses assessing potentially informative loss to follow-up in this cohort and did not observed evidence of selection bias (Buckley et al. 2016a; Buckley et al. 2016b). Still, substantial attrition in our cohort resulted in limited sample size for assessing sex-specific effects and

precluded us from examining the shape of exposure-response relationships by child's sex. Our sample size also limited us from evaluating additional effect measure modifiers.

Our results may not be generalizeable to other populations as our cohort is comprised of a multiethnic inner-city population with higher prevalence of ever asthma diagnosis (25%) compared to children aged 5–14 years in the United States as a whole (10%) (Centers for Disease Control and Prevention 2017a). In addition, exposures to environmental phenols and phthalates have changed over time such that exposure distributions among pregnant women in our study are not representative of present day exposures. In the U.S. population, concentrations of bisphenol A, 2,5-dichlorophenol, triclosan, and several phthalate metabolites (MEP, MnBP, MBzP, and DEHP metabolites) have decreased since our study began while benzophenone-3, MiBP, and MCPP concentrations have remained stable or increased (Centers for Disease Control and Prevention 2017b).

Despite these limitations, our study has several strengths. It is one of the first investigations of prenatal exposures to benzophenone-3, triclosan, and the precursor of 2,5-dichlorophenol in relation to childhood respiratory and allergic disease, and the only study to date to include girls. We adjusted for numerous potential confounders including multiple measures of socioeconomic status, residential characteristics, and known predictors of respiratory and allergic disease development. Finally, our findings were robust to potential confounding due to correlation among exposures.

Conclusions

In this population of New York City children, we observed sex-specific associations of prenatal urinary biomarkers of select environmental phenols and phthalates with asthma and allergic disease. Our results support prior studies linking prenatal bisphenol A exposure with worsened respiratory health in childhood. Patterns of association for other phenols were similar to the only previous study, and we further identified potential sex-dependent relationships of prenatal exposure to paradichlorobenzene (the precursor of 2,5-dichlorophenol) and benzophenone-3 with respiratory and allergic outcomes. Taken together, our study and previous investigations suggest that environmental phenol exposures during pregnancy may influence the development of respiratory and allergic disease in children. Future work would provide useful data to confirm associations observed for paradichlorobenzene and benzophenone-3 biomarkers, elucidate potential biological mechanisms, and determine whether associations persist into adulthood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Environmental phenols and phthalates may affect respiratory and allergic disease risk
- Measured urinary biomarkers in the third trimester of pregnancy
- Assessed asthma, wheeze, and atopic skin conditions by questionnaire
- 2,5 dichlorophenol and bisphenol A (boys only) positively associated with outcomes
- Benzophenone-3 and select phthalates (girls only) inversely associated with wheeze
- Prenatal chemical exposures may have sex-dependent effects on respiratory health

Table 1

Baseline characteristics of the full cohort and children attending at least one follow-up visit at age 6 or 7 years in the Mount Sinai Children's Environmental Health Study

Characteristic	Full cohort *n* (%)	Study sample *n* (%)	p-value[a]
N	404	165	
Maternal age at delivery (years)			0.09
< 18.5	142 (35)	51 (31)	
18.5–24	132 (33)	56 (34)	
25–29	44 (11)	25 (15)	
≥30	86 (21)	32 (20)	
Maternal race/ethnicity			0.4
Non-Hispanic White	86 (21)	29 (18)	
Non-Hispanic Black	112 (28)	46 (28)	
Hispanic	200 (50)	86 (52)	
Other	6 (1)	3 (2)	
Maternal pre-pregnancy BMI (kg/m^2)			0.05
< 20	82 (20)	29 (18)	
20–24.9	214 (53)	80 (49)	
25–29.9	72 (18)	39 (24)	
> 30	35 (9)	16 (10)	
Missing	1		
Maternal education			0.1
< High school	118 (29)	43 (26)	
High school	83 (21)	37 (23)	
Some college	103 (26)	50 (30)	
≥College degree	98 (24)	34 (21)	
Missing	2		
Maternal marital status			0.03
Married	117 (29)	37 (23)	
Living with father of child	98 (24)	39 (24)	
Single/divorced/widowed	189 (47)	88 (54)	
Type of residence during pregnancy			0.6
Public housing	131 (33)	56 (35)	
Rental unit/privately owned	226 (56)	91 (56)	
Owner occupied	46 (11)	16 (10)	
Missing	1	1	
Occupants in the residence (>3 total)	135 (33)	57 (35)	0.6
Pets in the residence	169 (42)	70 (43)	0.8
Maternal smoking during pregnancy	67 (17)	28 (17)	0.8
Person in household with asthma	160 (40)	67 (41)	0.7
Person in household with allergies	186 (46)	77 (47)	0.8
Child's sex (male)	222 (55)	85 (52)	0.3

BMI, body mass index

[a]Chi-square p-value for comparison of covariate distribution among those followed-up (N=164) versus those not followed (N=240)

Table 2

Third trimester urinary environmental phenols and phthalates biomarkers concentrations (μg/L), Mount Sinai Children's Environmental Health Study, 1998–2002

Biomarker	LOD	Detected (%)	Median	Minimum	25th percentile	75th percentile	Maximum	NHANES[a]
Environmental phenols (n=159)								
2,5-Dichlorophenol	0.12	100	56	2.8	23	174	8510	8.50 (6.30–12.0)
Triclosan	2.27	80	11	<LOD	2.9	62	1790	7.60 (6.10–9.10)
Benzophenone-3	0.34	98	6.8	<LOD	2.7	22	9290	26.0 (20.2–34.1)
Bisphenol A	0.36	86	1.3	<LOD	0.60	2.3	35.2	2.50 (2.20–2.80)
Phthalates (n=164)								
MEP	0.3	99	220	<LOD	83	572	29,528	110 (91.5–128)
MnBP	0.4	100	34	0.80	14	84	4043	21.7 (19.7–24.3)
MiBP	0.3	98	6.2	<LOD	2.9	15	65	2.60 (2.30–3.00)
MCPP	0.2	98	2.9	<LOD	1.6	6.4	129	3.00 (2.50–3.30)
MBzP	0.1	99	16	<LOD	5.9	36	481	11.1 (9.94–12.9)
ΣDEHP[b]	NA	NA	90	<LOD	39	163	6135	NR
MECPP	0.3	99	40	<LOD	15	69	2055	31.3 (27.5–35.8)
MEHHP	0.3	99	20	<LOD	8.8	41	2051	18.2 (14.9–22.1)
MEHP	0.9	93	5.8	<LOD	3.1	14	478	4.10 (3.50–5.00)
MEOHP	0.5	99	18	<LOD	8.2	38	1335	13.1 (11.2–15.0)

DEHP, di(2-ethylhexyl) phthalate; LOD, limit of detection; MiBP, monoisobutyl phthalate; MnBP, mono-n-butyl phthalate; MEP, monoethyl phthalate; MBzP, monobenzyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; NHANES, National Health and Nutrition Examination Survey; NR, not reported.

[a]Median (95% confidence interval) concentration among females aged ≥ 6 years in NHANES 2003–2004 (phenols and MECPP) or NHANES 2001–2002 (all other phthalates) (Centers for Disease Control and Prevention 2017b).

[b]DEHP molar sum expressed as MECPP.

Table 3

Distribution of questionnaire responses among children aged 6 and 7 years in the Mount Sinai Children's Environmental Health Study (N = 164 children with up to 240 observations)

Question	Overall		Girls		Boys	
	N	Yes *n*, (%)	N	Yes *n*, (%)	N	Yes *n*, (%)
Has a doctor or nurse ever said that your child has asthma?[a]	163	41 (25.2)	79	17 (21.5)	84	24 (28.6)
In the past 12 months, has your child visited the emergency room because of an asthma attack?[b,c]	206	25 (12.1)	102	11 (10.8)	104	14 (13.5)
Has your child ever had wheezing or whistling in the chest at any time in the past?[a]	164	62 (37.8)	79	32 (40.5)	85	30 (35.3)
Has your child ever had wheezing or whistling in the chest at any time in the past 12 months?[b]	236	62 (26.3)	114	30 (26.3)	122	32 (26.2)
In the past 12 months, has your child had rashes, eczema or hives?[b]	240	83 (34.6)	116	42 (36.2)	124	41 (33.1)

[a] Response from the child's last visit

[b] All responses

[c] Excludes children with asthma but no recent emergency room visit

Table 4

Associations of prenatal environmental phenol biomarker concentrations with asthma, wheeze, and atopic skin conditions at age 6 or 7 years in the Mount Sinai Children's Environmental Health Study

Question/Biomarker	OR (95% CI)[a]			EMM p-value[b]
	Overall	Girls	Boys	
Has a doctor or nurse ever said that your child has asthma?[c]				
2,5-dichlorophenol	1.51 (0.93, 2.46)	0.73 (0.34, 1.55)	3.00 (1.36, 6.59)	0.01
Triclosan	0.88 (0.57, 1.37)	0.70 (0.36, 1.34)	1.07 (0.57, 2.02)	0.3
Benzophenone-3	0.95 (0.60, 1.51)	0.74 (0.38, 1.44)	1.18 (0.61, 2.27)	0.3
Bisphenol A	1.66 (1.04, 2.66)	0.94 (0.48, 1.84)	3.04 (1.38, 6.68)	0.03
In the past 12 months, has your child visited the emergency room because of an asthma attack?[d]				
2,5-dichlorophenol	2.07 (1.17, 3.68)	0.98 (0.41, 2.35)	6.16 (1.42, 26.63)	0.05
Triclosan	0.64 (0.32, 1.27)	0.44 (0.16, 1.24)	0.92 (0.36, 2.33)	0.3
Benzophenone-3	0.58 (0.27, 1.25)	0.59 (0.22, 1.60)	0.53 (0.18, 1.54)	0.9
Bisphenol A	1.87 (0.79, 4.39)	0.97 (0.36, 2.59)	3.28 (1.15, 9.34)	0.1
Has your child ever had wheezing or whistling in the chest at any time in the past?[c]				
2,5-dichlorophenol	0.99 (0.65, 1.53)	0.57 (0.31, 1.06)	2.03 (1.03, 4.00)	0.01
Triclosan	0.73 (0.50, 1.07)	0.65 (0.40, 1.08)	0.81 (0.45, 1.46)	0.6
Benzophenone-3	0.88 (0.59, 1.32)	0.76 (0.44, 1.31)	1.01 (0.55, 1.87)	0.5
Bisphenol A	1.31 (0.89, 1.93)	1.04 (0.61, 1.77)	1.71 (0.93, 3.13)	0.2
Has your child ever had wheezing or whistling in the chest at any time in the past 12 months?[d]				
2,5-dichlorophenol	1.18 (0.81, 1.72)	0.73 (0.41, 1.30)	2.08 (1.18, 3.65)	0.01
Triclosan	0.76 (0.55, 1.07)	0.66 (0.42, 1.03)	0.88 (0.53, 1.46)	0.4
Benzophenone-3	0.65 (0.44, 0.96)	0.52 (0.28, 0.97)	0.82 (0.48, 1.40)	0.3
Bisphenol A	1.15 (0.81, 1.61)	1.08 (0.66, 1.77)	1.43 (0.85, 2.43)	0.5
In the past 12 months, has your child had rashes, eczema or hives?[d]				
2,5-dichlorophenol	1.71 (1.15, 2.55)	1.00 (0.59, 1.72)	2.41 (1.36, 4.26)	0.02
Triclosan	1.03 (0.75, 1.42)	0.92 (0.60, 1.4)	1.16 (0.71, 1.88)	0.5
Benzophenone-3	1.20 (0.85, 1.70)	1.17 (0.75, 1.83)	1.25 (0.76, 2.06)	0.8
Bisphenol A	1.18 (0.83, 1.67)	1.09 (0.67, 1.75)	1.23 (0.72, 2.13)	0.7

CI, confidence interval; EMM, effect measure modification; OR, odds ratio

[a] OR (95% CI) per standard deviation increase in natural log biomarker concentration estimated in separate models for each biomarker based on 50 multiply imputed datasets. Sex-specific estimates obtained using biomarker x sex product terms. Estimates are adjusted for creatinine, maternal age, race/ethnicity, pre-pregnancy body mass index, education, marital status, type of home ownership, smoking during pregnancy, person in household with asthma, person in household with allergies, number of occupants in the home, pets in the home, age at follow-up, and, for overall models, child's sex.

[b] P-value for EMM by child's sex

[c] Estimated using logistic regression models

[d] Estimated using logistic regression models with generalized estimating equations to account for within-subject correlation

Table 5

Associations of prenatal phthalate metabolite or molar sum concentrations with asthma, wheeze, and atopic skin conditions at age 6 or 7 years in the Mount Sinai Children's Environmental Health Study

Question/Biomarker	OR (95% CI)[a]			EMM p-value[b]
	Overall	Girls	Boys	
Has a doctor or nurse ever said that your child has asthma?[c]				
MEP	0.95 (0.60, 1.52)	0.47 (0.21, 1.07)	1.56 (0.84, 2.89)	0.02
MnBP	0.81 (0.47, 1.39)	0.57 (0.19, 1.72)	0.98 (0.53, 1.83)	0.4
MiBP	1.24 (0.72, 2.13)	0.83 (0.37, 1.84)	1.89 (0.85, 4.24)	0.1
MCPP	0.97 (0.56, 1.69)	1.16 (0.45, 3.00)	0.91 (0.46, 1.78)	0.7
MBzP	0.92 (0.54, 1.58)	0.60 (0.26, 1.41)	1.43 (0.67, 3.04)	0.1
ΣDEHP	0.83 (0.51, 1.36)	0.92 (0.42, 2.00)	0.86 (0.47, 1.58)	0.9
ΣLMWP	0.92 (0.58, 1.47)	0.47 (0.20, 1.12)	1.40 (0.77, 2.52)	0.04
ΣHMWP	0.84 (0.51, 1.40)	0.78 (0.34, 1.79)	0.95 (0.51, 1.76)	0.7
In the past 12 months, has your child visited the emergency room because of an asthma attack?[d]				
MEP	0.89 (0.54, 1.46)	0.41 (0.14, 1.17)	1.34 (0.67, 2.72)	0.09
MnBP	0.61 (0.32, 1.17)	0.73 (0.17, 3.06)	0.67 (0.35, 1.28)	0.9
MiBP	0.87 (0.47, 1.61)	0.45 (0.09, 2.16)	1.52 (0.56, 4.09)	0.3
MCPP	0.68 (0.34, 1.33)	0.88 (0.31, 2.46)	0.63 (0.28, 1.42)	0.6
MBzP	0.68 (0.34, 1.40)	0.30 (0.05, 1.94)	1.09 (0.40, 3.00)	0.3
ΣDEHP	0.80 (0.35, 1.83)	1.57 (0.62, 3.95)	0.62 (0.23, 1.64)	0.06
ΣLMWP	0.80 (0.48, 1.32)	0.40 (0.13, 1.19)	1.06 (0.54, 2.10)	0.2
ΣHMWP	0.77 (0.34, 1.76)	1.30 (0.55, 3.09)	0.65 (0.25, 1.70)	0.2
Has your child ever had wheezing or whistling in the chest at any time in the past?[c]				
MEP	0.80 (0.53, 1.20)	0.40 (0.19, 0.83)	1.12 (0.65, 1.94)	0.02
MnBP	0.89 (0.57, 1.39)	0.83 (0.38, 1.81)	0.88 (0.51, 1.52)	0.9
MiBP	0.96 (0.62, 1.49)	0.73 (0.40, 1.35)	1.27 (0.65, 2.50)	0.2
MCPP	1.12 (0.70, 1.80)	1.18 (0.59, 2.35)	0.97 (0.52, 1.80)	0.7
MBzP	0.89 (0.57, 1.40)	0.75 (0.40, 1.39)	1.00 (0.53, 1.88)	0.5
ΣDEHP	0.88 (0.57, 1.35)	0.69 (0.37, 1.29)	0.96 (0.54, 1.70)	0.4
ΣLMWP	0.78 (0.51, 1.18)	0.40 (0.19, 0.85)	1.04 (0.61, 1.77)	0.04
ΣHMWP	0.84 (0.54, 1.32)	0.66 (0.34, 1.28)	0.96 (0.53, 1.73)	0.4
Has your child ever had wheezing or whistling in the chest at any time in the past 12 months?[d]				
MEP	0.84 (0.59, 1.20)	0.31 (0.15, 0.66)	1.17 (0.75, 1.84)	0.003
MnBP	0.77 (0.51, 1.16)	0.40 (0.18, 0.87)	0.97 (0.6, 1.59)	0.05
MiBP	0.89 (0.61, 1.30)	0.61 (0.35, 1.08)	1.29 (0.74, 2.26)	0.06
MCPP	0.83 (0.55, 1.26)	0.57 (0.29, 1.12)	1.13 (0.66, 1.93)	0.1
MBzP	0.91 (0.61, 1.35)	0.66 (0.36, 1.22)	1.14 (0.67, 1.95)	0.2
ΣDEHP	0.81 (0.55, 1.19)	0.54 (0.28, 1.04)	0.91 (0.57, 1.46)	0.1
ΣLMWP	0.79 (0.53, 1.19)	0.27 (0.13, 0.59)	1.09 (0.68, 1.74)	0.002
ΣHMWP	0.82 (0.53, 1.27)	0.52 (0.26, 1.04)	1.01 (0.59, 1.72)	0.1

Question/Biomarker	OR (95% CI)[a]			EMM p-value[b]
	Overall	Girls	Boys	
In the past 12 months, has your child had rashes, eczema or hives?[d]				
MEP	0.93 (0.65, 1.32)	0.71 (0.37, 1.35)	1.03 (0.67, 1.57)	0.3
MnBP	0.97 (0.67, 1.41)	0.53 (0.25, 1.12)	1.21 (0.76, 1.94)	0.07
MiBP	1.18 (0.81, 1.71)	0.90 (0.53, 1.56)	1.44 (0.81, 2.56)	0.2
MCPP	1.08 (0.74, 1.59)	0.68 (0.36, 1.30)	1.36 (0.81, 2.29)	0.1
MBzP	1.05 (0.73, 1.53)	0.89 (0.51, 1.55)	1.15 (0.69, 1.91)	0.5
ΣDEHP	1.17 (0.81, 1.68)	1.24 (0.71, 2.16)	1.04 (0.66, 1.62)	0.7
ΣLMWP	0.90 (0.60, 1.34)	0.65 (0.31, 1.38)	1.00 (0.62, 1.59)	0.3
ΣHMWP	1.12 (0.75, 1.65)	1.25 (0.64, 2.46)	1.00 (0.62, 1.59)	0.6

CI, confidence interval; DEHP, di(2-ethylhexyl) phthalate; EMM, effect measure modification; HMWP, high molecular weight phthalates; LMWP, low molecular weight phthalate; MiBP, monoisobutyl phthalate; MnBP, mono-n-butyl phthalate; MEP, monoethyl phthalate; MBzP, monobenzyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; OR, odds ratio

[a] OR (95% CI) per standard deviation increase in natural log biomarker concentration estimated in separate models for each biomarker based on 50 multiply imputed datasets. Sex-specific estimates obtained using biomarker x sex product terms. Estimates are adjusted for creatinine, maternal age, race/ethnicity, pre-pregnancy body mass index, education, marital status, type of home ownership, smoking during pregnancy, person in household with asthma, person in household with allergies, number of occupants in the home, pets in the home, age at follow-up, and, for overall models, child's sex.

[b] P-value for EMM by child's sex

[c] Estimated using logistic regression models

[d] Estimated using logistic regression models with generalized estimating equations to account for within-subject correlation