Asthma in Inner-City Children at 5–11 Years of Age and Prenatal Exposure to Phthalates: The Columbia Center for Children’s Environmental Health Cohort

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Introduction

Phthalates are high-production chemicals widely used in consumer products (Sathyarayana 2008). Exposures are ubiquitous, including among inner-city populations [Centers for Disease Control and Prevention (CDC) 2009; Whyatt et al. 2012]. Diet is thought to be the main source of exposure for di(2-ethylhexyl) phthalate (DEHP), although nondietary pathways also can be substantial for other phthalates (Carlstedt et al. 2013; Koch 2013). Phthalates have short biologic half-lives, with most metabolites eliminated within 24 hr (Wittassek and Angerer 2008). Measures of phthalate metabolites in the urine are informative as internal dosimeters of exposure because urinary enzymatic activity is negligible (Kato et al. 2004). Thus, metabolite concentrations in urine reflect an individual’s internal exposure to phthalates, rather than phthalate contaminants introduced into their urine sample during collection and processing.

Prior studies have shown moderate intraclass correlation coefficients (ICCs) for most phthalate metabolites in repeat urine samples indicating reasonable reliability (Hauser et al. 2004; Teitelbaum et al. 2008; Whyatt et al. 2012). Preliminary epidemiologic findings suggest that phthalates may be associated with child asthma and other respiratory problems (Bornehag and Nanberg 2010; Kwak et al. 2009). Among Swedish children 3–8 years of age, house dust concentrations of DEHP were associated with physician-confirmed asthma, and concentrations of butylbenzyl phthalate (BBzP) were associated with child eczema and rhinitis (Bornehag et al. 2004). A follow-up study from Bulgaria reported that house dust DEHP concentrations were associated with child asthma (Kolarik et al. 2008). In cross-sectional analyses, urinary concentrations of diethyl phthalate (DEP) and di-n-butyl phthalate (DNBP) metabolites were associated with decreased forced expiratory volume in 1 sec (FEV1) in adult males but not adult females (Hoppin et al. 2004). We previously reported a statistically significant association between fractional exhaled nitric oxide (FeNO), a measure of airway inflammation, and concentrations of metabolites of DEP and BBzP, in urine collected from children at 5–9 years of age (Just et al. 2012a). In addition, two studies have shown that polyvinyl chloride (PVC) materials in the home, exposure sources for BBzP and DEHP, are associated with child asthma and other respiratory symptoms (Bornehag and Nanberg 2010; Larsson et al. 2011). However, to our knowledge no prior studies have been published on effects of prenatal phthalate exposures and child asthma. The current study was associated with increased cases of asthma.
Whyatt et al. designed to fill this gap. We hypothesized that maternal prenatal urinary metabolite concentrations of BBzP, DnBP, DEHP, and DEP would be associated with current asthma among inner-city children.

**Methods**

The study includes 300 inner-city women and their children, 5–11 years of age, participating in the Columbia Center for Children’s Environmental Health (CCCEH) longitudinal birth cohort of 727 women enrolled between 1998 and 2006 while they were pregnant with the index child. Women 18–35 years old, who self-identified as African American or Dominican and had resided in northern Manhattan or the South Bronx for at least 1 year before pregnancy, were enrolled through prenatal clinics at Harlem and New York Presbyterian Hospital (Perera et al. 2003). Women were excluded from enrollment into the cohort if they reported active smoking, used other tobacco products or illicit drugs, had diabetes, hypertension, or known HIV, or had their first prenatal visit after 20 weeks gestation. The 300 children were included in the present analysis if phthalate metabolite concentrations had been measured in a maternal spot urine sample collected during pregnancy and data were available for model covariates and to classify the child’s asthma status. Children were excluded from the present analysis if their mothers reported active smoking during pregnancy (n = 30), if prenatal maternal urine phthalate metabolite concentrations were not available (n = 281), if children were lost to follow-up (n = 89), or were missing covariate data (n = 27). The 300 children were similar to the other children in the CCCEH cohort with regard to their race/ethnicity, maternal prenatal marital status and education level, household income, household tobacco smoke exposure, maternal asthma, or maternal demoralization during pregnancy (see Supplemental Material, Table S1). All women signed an IRB-approved consent form and children signed an IRB-approved assent form beginning at age 7. The institutional review boards at the Columbia University Medical Center and the CDC approved the study.

**Urine sample collection and phthalate measurements.** A spot urine sample was collected from the women (n = 300) during the third trimester (mean ± SD, 34.0 ± 3.0 weeks gestation; median, 33.7 weeks) and from the children at ages 3 (n = 216), 5 (n = 270) and 7 years (n = 154). Samples were analyzed for the following four phthalate metabolites at the CDC using solid phase extraction coupled with high performance liquid chromatography–isotope dilution tandem mass spectrometry as described (Kato et al. 2005): mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), as described (Just et al. 2012a); monobenzyl phthalate (MBzP), a metabolite of BBzP; mono-n-butyl phthalate (MnBP), a metabolite of DnBP; and monoethyl phthalate (MEP), a metabolite of DEP. Bisphenol A (BPA) was measured in maternal and child urine samples using solid phase extraction coupled with high performance liquid chromatography–isotope dilution tandem mass spectrometry (Ye et al. 2005). Specific gravity was measured in the urine samples using a handheld refractometer and was used to control for urinary dilution (Atago PAL 10-S; Bellevue, WA) (Hauser et al. 2004).

**Diagnosis of child asthma.** At ages 5, 6, 7, 9, and 11 years, repeat questionnaires were administered to the mother or guardian to gather information on asthma-like symptoms in the child. The questionnaires were administered in English or Spanish by fully bilingual research workers. These included the well-validated International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire (Asher et al. 1995) and the Brief Respiratory Questionnaire (BRQ) (Bonner et al. 2006), as well as records of asthma rescue and/or controller medication. As described previously (Donohue et al. 2013), children were referred for physician evaluation for asthma based on the first report that the child had wheeze or whistling in the chest, a cough that lasted more than a week, other breathing problems, and/or use of asthma rescue or controller medication in the preceding 12 months on any of the follow-up study questionnaires. Examinations included a standardized history, physical examination, and prebronchiodilator and postbronchodilator pulmonary function testing. Two allergists/pulmonologists independently reviewed the results of each examination and classified their asthma status according to the following prespecified criteria: a) current asthma symptoms OR current asthma medication AND either a 12% increase in FEV1 or a 30% increase in FEF25–75 postbronchodilator; b) current asthma symptoms OR current asthma medication AND history of asthma symptoms on previous questionnaires; c) history of asthma symptoms on previous questionnaires AND wheeze on current exam.

The physician examination was conducted once during study follow-up, and the children were classified as having current asthma or as not having current asthma based on their status at the time of the examination. Children whose parents or guardians did not report wheeze or the other asthma-like symptoms or asthma medication use on any of the follow-up questionnaires were classified as nonasthmatics at the time of the last negative questionnaire.

**Statistical analyses.** Phthalate metabolite concentrations were right-skewed and transformed using the natural logarithm (ln). Concentrations that were below the limit of detection (LOD) were assigned a value of 0.5 × LOD. Variables assessed as potential confounders were selected from those known or suspected of being associated with phthalate concentrations or asthma (Just et al. 2012a; Miller et al. 2004; Whyatt et al. 2012). Variables were retained in the models if they were associated with the outcome (p ≤ 0.10) and/or addition or removal changed the coefficient for the exposure (phthalate metabolite) to outcome relationship by > 10%. Variables assessed included race/ethnicity, prenatal and postnatal household tobacco smoke exposure, maternal history of asthma, maternal education, maternal marital status, material hardship (lack of food, housing, gas, or electricity, clothing, or medicine during pregnancy), sex of the child, and child age at diagnosis (age at diagnosis as either current asthma or not current asthma for children with a history of the asthma-like symptoms seen by the physician, or age at classification as nonasthmatic at the last negative questionnaire for children without history of the asthma-like symptoms). Maternal prenatal demoralization also was assessed by validated questionnaire (Dohrenwend et al. 1978) because it previously has been associated with wheeze among children in the cohort (Reyes et al. 2011). Models were also adjusted for maternal prenatal BPA urinary concentrations (Donohue et al. 2013) but not child postnatal BPA concentrations because inclusion caused < 10% change in the phthalate exposure–outcome relationship. In addition, we assessed whether child postnatal urinary phthalate concentrations acted as a confounder using the phthalates measured at child ages 3, 5, and 7 years (2 children who had phthalates measured in urine collected at age 7 but whose asthma status was determined before age 7 were removed from the age 7 analyses). However, none of the postnatal phthalate metabolite concentrations were associated with child asthma (see Supplemental Material, Table S2), and inclusion caused < 10% change in effect size of predictor variables. The maternal phthalate urinary concentrations were included in models as ln-transformed variables, and also were categorized into tertiles and modeled using indicator variables to estimate relative risks comparing the second and third tertiles to the first tertile (referent). Metabolite concentrations were adjusted for specific gravity before categorizing using the formula described previously (Hauser et al. 2004). Consistent with our prior approach (Just et al. 2012a), relative risks were estimated using Poisson regression with robust standard error estimation using the generalized estimating equations based method of Zou (2004) (see also Lovasi et al. 2012; Spiegelman and Hertzmark 2005). Analyses were conducted using SPSS version 21 (SPSS, IBM, Chicago, IL). Results were considered significant at p < 0.05.
Results

Table 1 provides subject characteristics. Self-reported ethnicity was African American (35.7%) or Dominican (64.3%). Educational attainment was low (35.7% had not completed high school), and the majority (68%) reported never having been married. Table 2 shows the distribution of the urinary phthalate metabolite concentrations measured in maternal prenatal spot urine. All phthalate metabolites were detected in 100% of maternal prenatal urine samples except for MBzP in one sample (assigned a value of 0.11 ng/mL). Concentrations were generally comparable with those of a representative sample of the U.S. population sampled over roughly the same time period (1999–2004) (CDC 2009). Table 3 shows the correlations between the (ln)maternal prenatal phthalate metabolite concentrations adjusted for specific gravity. All metabolites were positively correlated, with correlation coefficients ranging from 0.16 (for MEP and MnBP) to 0.50 (for MnBP and MBzP) (all p-values < 0.01). A total of 1,013 repeat questionnaires on wheeze and other asthma-like symptoms were administered between ages 5 and 11 years (mean, 3.7 ± 1.1 questionnaires per child). The children were 8.1 ± 1.9 years on average at the time of the last questionnaire administration. Of the 300 children, 154 had a history of the following asthma-like symptoms at the time of the last questionnaire administration. Of the 300 children, 154 had a history of asthma-like symptoms among those in the second tertile were 1.25 (95% CI: 0.94, 1.65) and 1.39 (95% CI: 1.06, 1.82), respectively, and among those in the third tertile the RRs were 1.39 (95% CI: 1.05, 1.86) and 1.44 (95% CI: 1.09, 1.90, respectively (Table 4). There was no significant increase in risk of asthma-like symptoms in the linear models associated with either maternal MEP or MEHHP concentrations (Figure 1). However, in the categorical models (Table 4) compared with children of mothers with MEP in the first tertile, a significant increase in risk of asthma-like symptoms was seen among those in the second tertile (RR = 1.33; 95% CI: 1.03, 1.73) but not among those in the third tertile (RR = 1.08; 95% CI: 0.82, 1.42). There was no increase in risk of asthma-like symptoms across tertiles of MEHHP concentrations (Table 4).

Table 1. Characteristics of children (n = 300) from the CCCEH birth cohort.

| Characteristic                        | n (%) or mean ± SD |
|--------------------------------------|--------------------|
| Maternal age (years)                 | 25.3 ± 4.8         |
| Maternal asthma history              | 76 (25.3)          |
| Maternal demoralization\(b\)         | 1.1 ± 0.05         |
| Ethnicity                            |                    |
| African American                     | 107 (35.7)         |
| Dominican                            | 193 (64.3)         |
| Maternal education                   |                    |
| < High school                        | 107 (35.7)         |
| High school or general educational development | 114 (38.0) |
| > High school                        | 79 (26.3)          |
| Marital status                       |                    |
| Never married                        | 204 (68)           |
| Married\(b\)                         | 81 (27.0)          |
| Separated, widowed, divorced         | 15 (5.0)           |
| Household smoke exposure\(c\)        | 154 (51.3)         |
| Prenatal urinary bisphenol A (ng/mL) | 3.1 ± 4.3          |
| Child age at assessment (years)      | 8.1 ± 1.3          |
| Child sex (% female)                 | 163 (54.3)         |

\(a\)Mean of 27 items each on 5-point Likert scale (0–4) (Dohrenwend et al. 1978). \(\text{b}\)Includes women living with the same partner for > 1 years. \(\text{c}\)Whether or not others smoked in the home during the prenatal period and whether or not the mother and/or others smoked in the home during childhood gathered by repeat questionnaire.

Table 2. Distribution of phthalate metabolites in maternal prenatal urine during pregnancy (ng/mL).

| Concentration (ng/mL) | Geometric mean (95% CI) |
|-----------------------|-------------------------|
| MEP                   | (ln)MEP                 |
| MBzP\(d\)             | (ln)MBzP                |
| MnBP                  | (ln)MnBP                |
| MEHHP                 | (ln)MEHHP               |
| 0.99 (0.76, 1.23)      | 0.17*                   |
| 1.01 (0.78, 1.31)      | 0.16*                   |
| 1.01 (0.78, 1.31)      | 0.27*                   |
| 1.00 (0.77, 1.31)      | 0.27*                   |
| 1.00 (0.77, 1.31)      | 0.30*                   |
| 1.00 (0.77, 1.31)      | 0.17*                   |

\(d\)All metabolites were above the LOD except for one sample for MBzP, which was imputed (LOD × 0.05).

*Correlation between prenatal phthalate metabolite concentrations adjusted for specific gravity (n = 300).

Report of asthma-like symptoms regardless of the outcome of the asthma examination. Compared with nonasthmatic children, a significant association was seen between maternal prenatal urinary MBzP and MnBP concentrations and children with a history of asthma-like symptoms: RR = 1.12 (95% CI: 1.01, 1.24) and RR = 1.16 (95% CI: 1.02, 1.33) per ln-unit increase, respectively (Figure 1). Compared with children of mothers with MBzP and MnBP concentrations in the first tertile, the RRs for a history of asthma-like symptoms among those in the second tertile were 1.25 (95% CI: 0.94, 1.65) and 1.39 (95% CI: 1.06, 1.82), respectively, and among those in the third tertile the RRs were 1.39 (95% CI: 1.05, 1.86) and 1.44 (95% CI: 1.09, 1.90, respectively (Table 4). There was no significant increase in risk of asthma-like symptoms in the linear models associated with either prenatal MBzP or MnBP concentrations (Figure 1). However, in the categorical models (Table 4) compared with children of mothers with MBzP in the first tertile, a significant increase in risk of asthma-like symptoms was seen among those in the second tertile (RR = 1.33; 95% CI: 1.03, 1.73) but not among those in the third tertile (RR = 1.08; 95% CI: 0.82, 1.42). There was no increase in risk of asthma-like symptoms across tertiles of MEHHP concentrations (Table 4).

Diagnosis of current asthma at physician examination. Compared with nonasthmatic children, maternal prenatal MBzP and MnBP concentrations, but not the other phthalate metabolites, were associated with the diagnosis of the child with current asthma at the physician examination in the linear models: RR = 1.17 (95% CI: 1.01, 1.35) and RR = 1.25 (95% CI: 1.04, 1.51) per ln-unit increase, respectively (Figure 2). In the categorical models (Table 4), compared with children of mothers with MBzP and MnBP concentrations in the first tertile, RRs for current asthma among those in the second tertile were 1.31 (95% CI: 0.87, 1.96) and 1.87 (95% CI: 1.28, 2.67), respectively, and among those in the third tertile RRs were 1.72 (95% CI: 1.15, 2.59) and 1.78 (95% CI: 1.18, 2.70), respectively. There were no significant associations between diagnosis of current asthma and maternal prenatal MEP or MEHHP concentrations in either linear (Figure 2) or categorical (Table 4) models.

Table 3. Correlation\(a\) between prenatal phthalate metabolite concentrations adjusted for specific gravity (n = 300).

| Concentration (ng/mL) | (ln)MEP | (ln)MBzP | (ln)MnBP | (ln)MEHHP |
|-----------------------|---------|----------|----------|-----------|
| MEP                   | 5.8     | 1.01     | 0.17     | 0.16*     |
| MBzP\(d\)             | 31.9    | 1.01     | 0.17     | 0.27*     |
| MnBP                  | 80.5    | 0.17     | 0.17     | 0.30*     |
| MEHHP                 | 335.2   | 0.30*    | 0.27*    | 0.17*     |

*Correlation coefficient; \(\rho < 0.01\).
**Table 4.** RR (95% CI) for history of asthma-like symptoms (group 1, n = 154), diagnosis of current asthma (group 2, n = 94), and diagnosis of not current asthma (group 3, n = 60) compared with nonasthmatics (n = 146) by tertiles of phthalate metabolites.

| Outcome group and exposure | Müller MEP | MnBP | MEP | MEHP |
|----------------------------|-----------|------|-----|------|
| **Group 1**                | **Case/control (n)** | **RR (95% CI)** | **Case/control (n)** | **RR (95% CI)** | **Case/control (n)** | **RR (95% CI)** |
| 1st tertile                | 44/57 Referent | 46/60 Referent | 46/52 Referent | 57/47 Referent |
| 2nd tertile                | 55/47 1.25 (0.94, 1.65) | 53/41 1.39 (1.06, 1.82)* | 59/42 1.33 (1.03, 1.73)* | 46/47 0.92 (0.71, 1.20) |
| 3rd tertile                | 55/42 1.39 (1.05, 1.86)* | 55/45 1.44 (1.09, 1.90)* | 49/52 1.08 (0.82, 1.42) | 51/52 0.97 (0.74, 1.28) |
| **Group 2**                | **Case/control (n)** | **RR (95% CI)** | **Case/control (n)** | **RR (95% CI)** |
| 1st tertile                | 25/57 Referent | 27/60 Referent | 29/52 Referent | 34/47 Referent |
| 2nd tertile                | 34/47 1.31 (0.87, 1.98) | 38/41 1.87 (1.28, 2.67)** | 35/42 1.11 (0.97, 1.27) | 27/47 0.98 (0.85, 1.12) |
| 3rd tertile                | 35/42 1.72 (1.15, 2.59)** | 29/45 1.78 (1.18, 2.70)** | 30/52 1.04 (0.91, 1.19) | 33/52 1.03 (0.89, 1.20) |
| **Group 3**                | **Case/control (n)** | **RR (95% CI)** | **Case/control (n)** | **RR (95% CI)** |
| 1st tertile                | 19/57 Referent | 19/60 Referent | 17/52 Referent | 23/47 Referent |
| 2nd tertile                | 21/47 1.34 (0.90, 2.25) | 15/41 1.46 (0.81, 2.65) | 24/42 1.15 (0.99, 1.34) | 19/47 0.98 (0.84, 1.13) |
| 3rd tertile                | 20/42 1.44 (0.83, 2.49) | 26/45 1.71 (1.02, 2.88)* | 19/52 1.04 (0.91, 1.19) | 18/52 0.95 (0.82, 1.10) |

Models compare children in each outcome group with children without history of asthma-like symptoms controlling for maternal asthma, household smoke exposure, maternal prenatal BPA, maternal prenatal demoralization, maternal prenatal specific gravity, and child age (for outcome groups 2 and 3).

* p < 0.05. ** p < 0.01.

**Figure 1.** Association between maternal prenatal (ln)phthalate metabolite concentrations and presence (n = 154) compared with the absence (n = 146) of a history of asthma-like symptoms on repeat questionnaires administered between child ages 5 and 11 years. RRs were estimated using Poisson regression with robust standard error estimation using the generalized estimating equations controlling for maternal asthma, household tobacco smoke exposure, maternal prenatal BPA, maternal prenatal demoralization, and maternal prenatal specific gravity.

* p < 0.05.

**Figure 2.** Association between maternal prenatal (ln)phthalate metabolite concentrations and diagnosis of current asthma (n = 94) compared with nonasthmatics (n = 146) between child ages 5 and 11 years. RRs were estimated using Poisson regression with robust standard error estimation using the generalized estimating equations controlling for maternal asthma, household tobacco smoke exposure, maternal prenatal BPA, maternal prenatal demoralization, and maternal prenatal specific gravity.

* p < 0.05.

**Figure 3.** Association between maternal prenatal (ln)phthalate metabolite concentrations and diagnosis of not current asthma among children with a history of the asthma-like symptoms (n = 60) compared with nonasthmatics (n = 146). RRs were estimated using Poisson regression with robust standard error estimation using the generalized estimating equations controlling for maternal asthma, household tobacco smoke exposure, maternal prenatal BPA, maternal prenatal demoralization, and maternal prenatal specific gravity.

* p < 0.05.
Consistent with our prior findings (Whyatt et al. 2012), significant correlations were seen between prenatal urinary concentrations of MBzP and MnBP adjusted for specific gravity (Spearman’s rho = 0.50). This may reflect common sources of exposure and/or similar metabolic pathways. Consumer products including personal care products and home materials are sources of exposure to both of these phthalates (Buckley et al. 2012; Carlstedt et al. 2013). In addition, MnBP is a minor metabolite of BBzP, accounting for approximately 6% (Anderson et al. 2001). Nonetheless, most MnBP in urine is attributable to DnBP exposures. Several studies, including findings in the CCCEH cohort, suggest that PVC materials in the home are likely a substantial source of BBzP exposure, as indicated by measures in maternal and child urine and residential and personal air samples (Adibi et al. 2008; Carlstedt et al. 2013). Although DEHP is also a constituent of PVC, evidence suggests that exposure to this phthalate occurs primarily through the diet, likely as a result of use in food packaging (Koch 2013; Rudeil et al. 2011). Prior cross-sectional studies also have found PVC materials in the home to be associated with child asthma and other respiratory symptoms (Bornehag and Nanberg 2010), and these results provide at least some corroboration for the current findings. For example, in a prospective study of 4,779 children in Sweden without asthma or respiratory symptoms at child ages 1–3 years, PVC flooring at baseline was associated with parental report of child asthma at the 5- and 10-year follow-up (Larsson et al. 2010; Shu et al. 2014).

The significant association seen in our present study between MnBP and MBzP urinary concentrations and asthma-like symptoms, regardless of whether or not the child received a diagnosis of current asthma, was not anticipated. These findings may imply that prenatal exposure to some phthalates has effects on transient wheeze and/or nonspecific airway hyperresponsiveness. It is possible that the respiratory consequences of prenatal exposure to phthalates mimic what has been observed following prenatal exposure to cigarette smoke, where several large cohort studies have essentially established its role in recurrent wheeze in very young children (Magnusson et al. 2005). Alternatively, prenatal phthalate exposure may induce a nonspecific airway hyperresponsiveness, manifested as report of wheeze, use of asthma medication, cough, or other breathing problems, that develops into clinical asthma during childhood only in a subset of children. The development of airway hyperresponsiveness is believed to have an environmental component (Lund et al. 2007; Riley et al. 2012), and develops at a very early age (Lesouef et al. 1989). Further prospective studies are needed to resolve these important clinical questions.

Research on mechanisms whereby phthalates might induce asthma or asthma-like symptoms is extremely limited [reviewed by (Kwak et al. 2009)]. Several phthalates have shown adjuvant effects on proallergic T helper 2 differentiation and immunoglobulin (Ig) G and IgE production when administered via subcutaneous or intraperitoneal injection to BALB/c mice sensitized by ovalbumin (Bornehag and Nanberg 2010; Guo et al. 2012). Our prior research in the CCCEH cohort did not find any association between maternal prenatal urinary MBzP concentrations and child seroatopy, although we did observe an association between maternal prenatal MBzP concentrations and early-onset eczema (Just et al. 2012b). In addition, as discussed above, when we used a repeated-measures design, we saw a significant association between MBzP concentrations in child urine and FeNO, suggesting that MBzP induces airway inflammation (Just et al. 2012a). In cross-sectional analyses, urinary concentrations of MBzP also have been shown to be associated with C-reactive protein, a nonspecific marker of systemic inflammation, and both MBzP and MnBP have been associated with biomarkers of oxidative stress (Ferguson et al. 2011, 2012).

However, the relevance of these findings to the potential effect of the phthalates on respiratory health remains unclear. Mechanistic data explaining why the prenatal period of exposure may be deleterious also are limited, but our group has provided evidence of epigenetic regulation following prenatal exposure to several environmental exposures in human and mouse studies on asthma (Kundakovic 2013; Liu et al. 2008; Niedzwiecki et al. 2012; Perera et al. 2009; Tang et al. 2012).

Strengths of the current study include the standardized physician diagnosis of child asthma that is an improvement over most prior research, which used parental report of child asthma as the outcome. Additionally, this is the first study to evaluate associations between prenatal phthalate exposure and asthma during early to mid-childhood in a longitudinal birth cohort. This is a strength because most prior studies of phthalates and asthma have been cross-sectional. The rate of both maternal and child asthma in our cohort is high (31.8% and 25.2%, respectively). Asthma prevalence among New York City children ranges from 3% to 25% (Nicholas et al. 2005), with some inner-city communities having triple the asthma prevalence of their bordering neighborhoods. Although family history of asthma or atopy were not required inclusion criteria for the current cohort, pregnant mothers were informed at enrollment that the research was evaluating environmental risk factors in child asthma development, and this may have been an incentive for mothers whose children were at higher risk to participate.

Limitations also should be noted. We used as our exposure dosimeters the measurements of the phthalate metabolite concentrations in a single prenatal spot urine sample, and this could result in exposure misclassification, especially for some phthalate metabolites. Controlling for urinary dilution, we previously reported that the ICCs for phthalate metabolites in repeat prenatal spot urine samples (n = 135) collected biweekly over the last 6 weeks of pregnancy from 48 women in the CCCEH cohort were 0.77 for MBzP, 0.64 for MnBP, 0.27 for MEHHP, and 0.19 for MEP (Whyatt et al. 2012), indicating that reliability of the phthalate biomarkers differs across the phthalates. We would expect the exposure misclassification for these phthalates to be nondifferential with respect to asthma and could thus reduce our power to observe an effect for either MEP or MEHHP on asthma risk, because they had the lower ICCs. However, this is less likely to be a problem with MBzP and MnBP due to the higher ICCs in repeat prenatal urine samples, coupled with the relatively high correlations seen previously in the CCCEH cohort between BBzP concentrations in maternal 48-hr prenatal personal air samples and 2-week integrated indoor air samples (Spearman’s rho = 0.67) and between BBzP in maternal personal and indoor air samples and MBzP concentrations in maternal prenatal urine (Spearman’s rho = 0.48 and 0.71, respectively) (Adibi et al. 2008). However, the correlations between DnBP concentration in maternal prenatal personal and indoor air samples and MnBP concentrations in maternal prenatal urine were considerably lower (Spearman’s rho = 0.05 and 0.27, respectively) (Adibi et al. 2008). Missing data and loss to follow-up, as often occurs in a long-term prospective study, could also bias study results (Kurukulaaratchy et al. 2003; Matticardi et al. 2008). However, 97% of the children in the current study had questionnaire data on ISAAC wheeze and other respiratory symptoms collected at least twice, and 86% of the children had questionnaire data collected three or more times. In addition, maternal urine samples were collected during the third trimester of pregnancy, and this is another potential limitation given that the critical window of susceptibility is not known but may well be earlier in pregnancy. Additionally, the research was conducted in an inner-city...
cohort, with high rates of maternal and child asthma and was restricted to nonsmoking mothers during pregnancy. Therefore, results may well not be generalizable to other populations. Further, noncausal associations (e.g., due to confounding by some other factor associated with phthalates and asthma) cannot be ruled out. For all of these reasons, the findings should be interpreted with caution before replication in other cohorts that include evaluation of associations between child asthma and exposures during other trimesters of pregnancy.

Conclusion

These results suggest that prenatal exposure to BBP and DnBP may increase risk of childhood asthma. The findings raise new concerns that the presence of relatively ubiquitous environmental exposures may have deleterious respiratory effects. However, because, to our knowledge, this is the first study to evaluate associations between prenatal phthalate exposures and child asthma risk, results require replication.

REFERENCES

Adibi JJ, Whyatt RM, Williams PL, Calafat AM, Camadan D, Herrick R, et al. 2008. Characterization of phthalate exposure among pregnant women assessed by repeat air and urine samples. Environ Health Perspect 116:467–473; doi:10.1289/ehp.10749.

Anderson WA, Castle L, Scudder MJ, Massey RC, Springall C. 2001. Associations between prenatal phthalate exposures during other trimesters of pregnancy. Environ Health Perspect 112:1734–1740; doi:10.1289/ehp.1127121.

Hoppin JA, Rimmel R, London SJ, Bertelsen RJ, Salo PM, Sandler DP, et al. 2013. Prenatal exposure and allergy in the U.S. Population: results from NHANES 2005–2006. Environ Health Perspect 121:1128–1134; doi:10.1289/ehp.1206211.

Whyatt RM, Liu X, Rauh VA, Calafat AM, Just AC, Hoepner L, et al. 2012. At odds: concerns raised by using odds ratios for continuous or common dichotomous outcomes in research. Open Allergy J 2:45–50.

Kato K, Liu J, Ballaney M, Al-alem U, Quan C, Jin X, Perera FP, et al. 2013. Sex-specific epigenetic disruption of acne vulgaris. Skin Pharmacol Physiol 26:142–148; doi:10.1159/000333345.

Kwak ES, Just A, Whyatt R, Miller RL. 2009. Phthalates, pesticides, bisphenol A, and wheeze, and immunoglobulin E among inner-city children. Environ Health Perspect 117:58–62; doi:10.1289/ehp.0800616.

Liu J, Ballayen M, Al-alem U, Quan C, Jin X, Perera F, et al. 2008. Combined inhal ed diesel exhaust particles and allergen exposure alter methylation of T helper genes and IgE production in vivo. Toxicol Sci 102:76–81.

Lovasi GS, Undeck MS, Long MA, Marsman E, Wernick C, Rundle A, Whyatt RM, Liu X, Rauh VA, Hoepner L, et al. 2012. Temporal associations between methylation and oxidative stress and inflammatory markers in relation to urinary phthalate metabolites: NHANES 1999–2006. Environ Res 112:178–184; doi:10.1016/j.envres.2011.11.002.

Maggiunno LL, Diesen AB, Wennborg H, Olsen J. 2005. Wheezing, asthma, hayfever, and atopic eczema in childhood following exposure to tobacco smoke in fetal life. Clin Exp Allergy 35:1550–1556.

Matricardi PM, Illis S, Gruber G, Keil T, Nickel R, Wahn U, et al. 2008. Monitoring in childhood: Incidence, longitudinal patterns and factors predicting persistence. Eur Respir J 32:585–592.

Miller RL, Chew GL, Bell CA, Biedermann SA, Aggarwal M, Kinney PL, et al. 2001. Prenatal epigenetic modifications and sensitization in utero to indoor allergens in an inner-city cohort. Am J Respir Crit Care Med 164:995–1001.

Morgan DA, Delefortrie M, Platts-Mills TA, Liston DJ, Taylor WR. 2006. Identification of new mechanisms of phthalate action. Environ Health Perspect 114:527–530; doi:10.1289/ehp.837.

Morgan DA, Delefortrie M, Platts-Mills TA, Liston DJ, Taylor WR. 2006. Identification of new mechanisms of phthalate action. Environ Health Perspect 114:527–530; doi:10.1289/ehp.837.

Nicholas SW, Jean-Louis B, Ortiz B, Northridge M, Shoemaker K, Vaughan R, et al. 2005. Addressing the childhood asthma crisis in Harlem: The Harlem Children’s Zone Asthma Initiative. Am J Public Health 95:245–249.

Niedzwiecki M, Zhu H, Corson L, Grunig P, Factor PH, Chu S, et al. 2012. Prenatal exposure to allergen, DNA methylation, and allergy in grandmothers’ offspring. Allergy 67:904–910.

Perera FP, Rauh V, Tsai WY, Kinney P, Camann D, Barr D, et al. 2003. Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiracial population. Environ Health Perspect 111:718–726; doi:10.1289/ehp.5742.

Perez F, Tang WY, Herbstman J, Tang D, Levin L, Miller R, et al. 2008. Relation of DNA methylation of 5-CpG island of ACSL5 to transplacental exposure to airborne polycyclic aromatic hydrocarbons in women. Proc Natl Acad Sci U S A 105:11212–11217; doi:10.1073/pnas.0802574105.

Riley S, Wallace J, Nair P. 2012. Proximity to major roadsways is a risk factor for airway hyper-responsiveness in adults. PLoS One 7:e33048; doi:10.1371/journal.pone.0033048.

Zou G. 2004. A modified poisson regression approach to evaluate the risk of rare diseases: a case study. Stat Med 23:781–789; doi:10.1002/sim.1588.