Leti, and Merck. G. Scadding has received money for travel and meeting-related expenses from the American Academy of Allergy, Asthma & Immunology. The rest of the authors declare that they have no relevant conflicts of interest.

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Prenatal phthalate and early childhood bisphenol A exposures increase asthma risk in inner-city children

To the Editor:

We previously reported that inner-city childhood asthma was independently associated with measures of early childhood exposure to bisphenol A (BPA)[1] and prenatal, but not childhood, exposures to di-*n*-butyl phthalate and butylbenzyl phthalate (BBzP).[2] Here, we evaluate whether these 2 classes of endocrine-disrupting chemicals interact to increase the risk of asthma.

We evaluated 292 inner-city women and their children aged 5 to 11 years from the Columbia Center for Children's Environmental Health birth cohort of pregnant women who delivered between 1998 and 2006. Enrollment, exclusion criteria, and a description of the cohort have been reported previously.[3] Subjects were selected for the present study on the basis of the availability of (1) measurements of phthalates in spot urine collected from the mother during pregnancy (33.9 ± 3.1 weeks' gestation) and BPA in child urine at ages 3 (n = 237), 5 (259), and/or 7 (n = 161) years; (2) data on child asthma and wheeze-related outcomes; and (3) availability of model covariates. Demographic characteristics of Columbia Center for Children's Environmental Health subjects are provided in Table E1 in this article's Online Repository at www.jacionline.org. All participants gave written informed consent.

Samples were analyzed at the Centers for Disease Control and Prevention for concentrations of monobenzyl phthalate (MBzP, metabolite of BBzP), mono-*n*-butyl phthalate (MnBP, metabolite of di-*n*-butyl phthalate), and BPA.[4,5] Consistent with our previous approach,[1] mean urinary postnatal BPA concentrations were calculated across samples of children aged 3 to 7 years, except for a small subset (n = 10) missing respiratory questionnaire data after age 6 years for whom the mean BPA was calculated for ages 3 to 5 years. Specific gravity was measured using a hand-held refractometer (Atago PAL 10-S, Bellevue, Wash) to control for urinary dilution.

Repeat questionnaires, including the International Study of Asthma and Allergies in Childhood, were administered to the parent at child ages 5, 6 7, 9, and 11 years (n = 1202 questionnaires, average 4.1 per child). Children with report in the last 12 months of any of the following asthma-related symptoms on 1 or more questionnaire were referred to an allergist or a pulmonologist for asthma diagnosis using standardized criteria: 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.[1] Children without any of these asthma-related symptoms on the repeat questionnaires were classified as nonasthmatic. Children were evaluated for persistent wheeze (≥3 reports of wheeze in the last 12 months on ≥3 International Study of Asthma and Allergies in Childhood questionnaires), exercise-induced wheeze (≥1 report in the last 12 months of the child's chest sounding wheezy during or after exercise), and report of emergency care visits in the last 12 months to a doctor, clinic, or emergency room for asthma, wheeze, or other breathing problems on 1 or more repeat questionnaire.

Variables assessed as potential confounders have been described[1,2] and were retained in the models if they were significant ($P < .05$) and/or their inclusion resulted in more than 10% change in the predictor variables (see this article's Online Repository at www.jacionline.org). Before statistical analyses, the 1 prenatal MBzP and 15 postnatal BPA concentrations below the limit of detection (0.22 μg/L [MBzP] and 0.4 μg/L [BPA]) were assigned a value of half the limit of detection. Metabolite concentrations were right-skewed and transformed using the natural logarithm. In analyses in which metabolites were categorized, we adjusted concentrations by specific gravity before ranking as described previously.[6] Consistent with our previous approach,[2] we used a modified Poisson regression to generate relative risk (RR), and variance estimates for dichotomized outcomes (ie, child asthma) using the methods of Zou.[7] Analyses were conducted using SPSS 21 (IBM, Armonk, NY). Results were considered significant at $P < .05$.

A total of 168 of 292 (57.5%) children had a history of asthma-related symptoms on repeat questionnaires. Of these, 142 were evaluated by a study allergist or pulmonologist; 86 were diagnosed with current asthma and 56 with asthma-related symptoms but without current asthma. The remaining 124 children had no history of asthma-like symptoms and were classified as nonasthmatic. A total of 44 of 217 (20%) children had persistent wheeze, 62 of 292 (21%) had exercise-induced wheeze, and 98 of 292 (34%) had emergency care visits for asthma or other respiratory problems.

A significant association between child (ln)BPA concentrations and respiratory outcomes was observed only among those children whose mothers had prenatal MBzP concentrations above but not below the median. For children with prenatal MBzP concentrations above the median, the RR per log unit increase in child BPA concentrations was 1.46 (95% CI, 1.14-1.87) for child current asthma; 1.89 (95% CI, 1.29-2.78) for persistent wheeze; 1.67 (95% CI, 1.17-2.40) for exercise-induced wheeze; and 1.47 (95% CI, 1.13-1.89) for emergency care visits. The multiplicative interaction between child (ln)BPA and higher versus lower

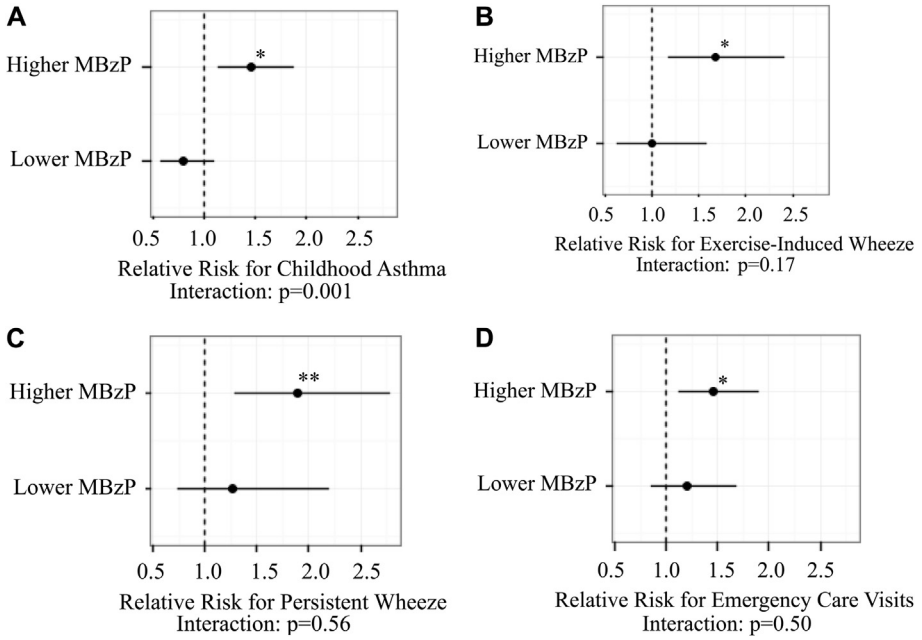

FIG 1. Association between child (ln)BPA concentrations by strata of higher versus lower prenatal MBzP (above and below median) and child asthma **(A)**, exercise-induced wheeze **(B)**, persistent wheeze **(C)**, and emergency care vists **(D)**. Models controlled for maternal asthma, household smoke exposure, maternal prenatal BPA, maternal prenatal specific gravity, maternal prenatal demoralization, child age at asthma diagnosis or classification as nonasthmatic (Fig 1, *A*), and child sex (Fig 1, *B-D*). Mutiplicative interactions between postnatal (ln)BPA concentrations and higher versus lower prenatal MBzP were also evaluated for each outcome (Fig 1, *A-D*). *$P < .01$ and **$P \leq .001$.

TABLE I. Asthma-related outcomes among children with both maternal prenatal MBzP and child BPA above the median versus one or both below the median

Relative risk (95% CI)			
Childhood asthma (n = 210)	**Persistent wheeze (n = 217)**	**Exercise-induced wheeze (n = 292)**	**Emergency care visits (n = 292)**
1.67 (1.25-2.23)*	2.02 (1.22-3.35)†	1.76 (1.13-2.72)†	1.71 (1.25-2.34)*

Models controlled for maternal asthma, household smoke exposure, prenatal BPA, maternal prenatal specific gravity, maternal prenatal demoralization, child age (at the time of asthma diagnosis included in asthma model only), and child sex (in models of other asthma-related outcomes).
*$P \leq .001$.
†$P \leq .01$.

prenatal MBzP was significant for asthma ($P = .001$) but not for other outcomes (Fig 1).

Table I presents associations between asthma and wheeze-related outcomes among children with both prenatal MBzP and child BPA concentrataions above the median compared with children with one or both measurements below the median. There was a highly significant increase in RR for all these outcomes among children with both prenatal MBzP and child BPA above the median. In contrast, there was no increase in RR if only one of the endocrine-disrupting chemicals but not both were above the median (P values ranged from 0.12 to 0.94, data not shown). There were no significant interactions between (1) prenatal BPA and either prenatal MBzP or MnBP concentrations or (2) prenatal MnBP and child BPA concentations on the risk of child asthma, frequent wheeze, exercised-induced wheeze, or emergency care visits (data not shown).

Using 2 analytic approaches, we found a novel and significant association between child BPA and risk of child asthma and other wheeze-related symptoms among inner-city children whose mothers had higher but not lower prenatal measures of exposures to BBzP. These findings suggest the possibility of a "multihit" model such that higher prenatal BBzP exposures may render the child more susceptible to adverse effects of BPA on the airways during early childhood. Although potential mechanisms for this hypothesis need to be evaluated and results require replication, findings are of concern given that exposures to these compounds are ubiquitous in the United States and other countries.

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High serum corticotropin-releasing hormone (CRH) and bone marrow mast cell CRH receptor expression in a mastocytosis patient

To the Editor:

A 36-year-old white female patient presented with flushing; contact dermatitis (Fig 1, *A*); salmon-colored macules on her legs (Fig 1, *B*); itchy, sensitive skin; rashes; nasal congestion; chronic postnasal drip; sinus infections; musculoskeletal aches; fatigue; shortness of breath; chest tightness; lightheadedness; difficulty with concentration and memory; headaches; partial blackouts; tachycardia; anxiety; insomnia; depression; lower pelvic discomfort; diarrhea; bone pain; and osteopenia. Most of these worsened perimenstrually and with exercise, pressure, heat, cold, vibration, mold, pollen, certain foods and preservatives, scents, and especially physical and emotional stress. She was also sensitive to many medications, including fluoxetine, sertraline, bupropion, meperidine, clarithromycin, amoxicillin, and corticosteroids. Results of laboratory tests, including serum immunoglobulins, were within normal limits, except for elevated cortisol. No symptoms or laboratory tests were indicative of atopic dermatitis or any autoimmune diseases.

Bone marrow (BM) biopsy revealed clusters of mast cells (MC) positive for c-kit and tryptase (Fig 2). In addition, genetic analysis showed that MC were positive for the codon D816V self-activating mutation of *KIT*, the receptor for stem cell factor; over 50% of MC expressed CD2, while 70% expressed CD117 (c-kit) and CD25; serum tryptase was elevated at 20 ng/mL); the patient had mastocytosis in the skin; and she responded to H1 and H2 receptor antagonists. These findings fulfilled the World Health Organization criteria for systemic mastocytosis (SM) as well as those for a mast cell activation disorder[1,2]; the subcategory of SM was indolent SM.

Many of the MC in the BM were degranulated, as judged by their "ruffled" surface and reduced tryptase staining (Fig 2, *A*). Given the BM findings and the sensitivity of this patient to stress, MC were counterstained with an antibody against corticotropin-releasing hormone (CRH) receptor 1 (CRHR-1), the main receptor for the first hormone secreted under stress, and showed strong expression (Fig 2, *A*).

Fluorescence-activated cell sorting analysis of human umbilical cord blood-derived cultured MC showed that most of them were positive for both c-kit and CRHR-1 (Fig 2, *B*). Serum levels of CRH were measured and were extremely elevated (42.6 times) at 3.11 $\pm$ 0.056 ng/mL, as compared to 0.073 $\pm$ 0.054 ng/mL found in an age- and sex-matched healthy control. We also measured serum neurotensin, which was elevated at 0.097 $\pm$ 0.02 ng/mL as compared to 0.03 $\pm$ 0.09 ng/mL in normal females (CRH and neurotensin were measured with ELISA kits from Phoenix Pharmaceuticals, Burlingame, Calif).

This patient did respond to a number of drugs introduced and increased over time to the dosages listed below. Although it is difficult to describe which symptoms responded to which drugs, this patient was careful in adding drugs sequentially and kept a journal to note when each drug was added. Thus, it is reasonable to state the following: ibuprofen (400 mg orally 4 times a day) helped with musculoskeletal pain and flushing; fexofenadine (180 mg orally twice a day) helped with itching and gastrointestinal cramping; ranitidine (150 to 300 mg orally 4 times a day) reduced gastroesophageal reflux; montelukast (10 mg orally twice a day) eased chest congestion and tightness; cromolyn (400 mg orally 4 times a day) helped with gastrointestinal cramping; alprazolam (1 mg extended release orally twice a day) reduced anxiety; and liposomal luteolin and quercetin dietary supplement (2 softgel capsules 3 times a day) eased gastrointestinal cramping and musculoskeletal pain as well as itching due to seasonal allergens.

SM involves BM and extramedullary proliferation and activation of MC leading to multiple symptoms, including

METHODS

Eighteen- to 35-year-old women who self-identified as African American or Dominican were enrolled through prenatal clinics at Harlem Hospital and New York Presbyterian Hospital. Women were excluded if they reported active smoking or use of other tobacco products or illicit drugs; had diabetes, hypertension, or known HIV; had their first prenatal visit after the 20th week of gestation; or had resided in the study area for less than 1 year before pregnancy. Family history of asthma was not a required inclusion criterion. Study subjects' characteristics are presented in Table E1. The 292 subjects did not differ significantly from the remaining 435 subjects in the Columbia Center for Children's Environmental Health cohort by race/ethnicity, maternal prenatal marital status and education level, household income, prenatal and postnatal tobacco smoke, or maternal history of asthma (all P values $\geq .16$). All participants provided written informed consent, children aged 7 years and older provided assent, and the institutional review boards at the Columbia University Medical Center and the Centers for Disease Control and Prevention approved the study.

Variables assessed as potential confounders were selected on the basis of our previous analyses of prenatal MBzP and postnatal BPA as described earlier[E1,E2] and were retained in the models if they were significant ($P < .05$) and/or their inclusion in the model resulted in more than 10% change in predictor variables. The variables assessed as potential confounders included maternal age, maternal education, maternal history of asthma, race/ethnicity, household smoke exposure (from others during pregnancy because the cohort was restricted to nonsmoking pregnant women at enrollment and from the mother and/or others during childhood because some mothers began smoking after delivery), number of previous live births, breast-feeding history, maternal prenatal BPA concentrations, child age at asthma diagnosis or classification as nonasthmatic, child sex, and child body mass index. Maternal prenatal demoralization (measured by using a 27-item Psychiatric Epidemiology Research Instrument-Demoralization Scale[E3]) was also assessed because it has been previously associated with wheeze among children in the cohort.[E4] Prenatal and postnatal urinary specific gravity concentrations were included in models to control for urinary dilution. We did not collect a validated history of all child viral illnesses from cohort subjects by questionnaire because we did not believe that we could do so reliably at the onset of the study. Therefore, we were not able to determine whether child viral illnesses were potential confounders. Child postnatal MBzP and MnBP concentrations were not controlled because they were not associated with any of the outcomes (all P values $\geq .4$) and inclusion did not alter results over those presented here. The cohort was predominantly full-term (97% $\geq$37 weeks' gestation) and neither gestational age nor birth weight was a confounder.

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TABLE E1. Maternal and child characteristics (n = 292)

Maternal age (y), mean ± SD	25.3 ± 4.8
Maternal asthma, n (%)	71 (24.3)
Maternal ethnicity, n (%)	
Dominican	189 (64.7)
African American	103 (35.3)
Maternal education, n (%)	
<High school	106 (36.3)
High school or general educational development	106 (36.3)
>High school	80 (27.4)
Maternal marital status, n (%)	
Never married	194 (66.4)
Married*	84 (28.8)
Separated, widowed, divorced	14 (4.8)
Child age and sex	
Child age (y), mean ± SD†	8.2 ± 1.9
Child sex (female), n (%)	157 (53.8)
Household tobacco smoke exposure	
Others in the home prenatally‡	93 (31.8)
Maternal and others early to mid-childhood	129 (44.2)
Maternal MBzP (ng/mL), geometric mean (95% CI)	13.2 (11.4-15.5)
Child BPA (ng/mL),§ geometric mean (95% CI)	3.9 (3.5-4.3)

*Includes women living with a partner for more than 7 years.
†Age at asthma diagnosis for those diagnosed with current asthma and at the last negative screen for asthmalike symptoms for those classified as nonasthmatic.
‡The study excluded active smoking women during pregnancy.
§Mean concentrations in samples of children aged 3 to 7 years, except children (n = 10) missing respiratory questionnaire data after age 6 years for whom the mean BPA was calculated for ages 3 to 5 years.