

Prenatal and postnatal bisphenol A exposure and asthma development among inner-city children

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Background: Bisphenol A (BPA) is used widely to manufacture food container linings. Mouse models suggest exposure to BPA might increase allergic inflammation.

Objectives: We hypothesized that BPA exposure, as assessed based on urinary BPA concentrations, would be associated with increased odds of wheeze and asthma and increased fraction of exhaled nitric oxide (FENO) values in children.

Methods: The Columbia Center for Children's Environmental Health recruited pregnant women for a prospective birth cohort study (n = 568). Mothers during the third trimester and children at ages 3, 5, and 7 years provided spot urine samples. Total urinary BPA concentrations were measured by using online solid-phase extraction, high-performance liquid chromatography, isotope-dilution tandem mass spectrometry. Wheeze in the last 12 months was measured by using questionnaires at ages 5, 6, and 7 years. Asthma was determined by a physician once between ages 5 and 12 years. FENO values were measured at ages 7 to 11 years.

Results: Prenatal urinary BPA concentrations were associated inversely with wheeze at age 5 years (odds ratio [OR], 0.7; 95% CI, 0.5-0.9; *P* = .02). Urinary BPA concentrations at age 3 years were associated positively with wheeze at ages 5 years (OR, 1.4; 95% CI, 1.1-1.8; *P* = .02) and 6 years (OR, 1.4; 95% CI, 1.0-1.9; *P* = .03). BPA concentrations at age 7 years were associated with wheeze at age 7 years (OR, 1.4; 95% CI, 1.0-1.9; *P* = .04) and FENO values (β = 0.1; 95% CI, 0.02-0.2; *P* = .02). BPA concentrations at ages 3, 5, and 7 years were associated with asthma (OR, 1.5 [95% CI, 1.1-2.0], *P* = .005; OR, 1.4 [95% CI, 1.0-1.9], *P* = .03; and OR, 1.5 [95% CI, 1.0-2.1], *P* = .04, respectively).

Conclusions: This is the first report of an association between postnatal urinary BPA concentrations and asthma in children. (*J Allergy Clin Immunol* 2013;131:736-42.)

Key words: Bisphenol A, asthma, wheeze, children, exhaled nitric oxide, IgE, cohort study

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Bisphenol A (BPA) is a xenoestrogen used in the manufacture of polycarbonate plastics and epoxy resins. These materials are found in toys, drinking containers, dental sealants, water pipes, and food and beverage containers, including infant formula.¹ Exposure to BPA can occur dermally or through inhalation, but the primary route is dietary.^{2,3} Two studies in preschool children found that 95% to 99% of exposure to BPA is dietary, with an exposure range in the first study of 52 to 74 ng/kg/d and a median exposure of 109 ng/kg/d in the second study.^{4,5} Exposures to BPA are ubiquitous in the United States, and BPA has been detected in more than 90% of child urine samples in several studies.^{6,7} BPA has been detected at higher concentrations in children than in adults, a finding that has been attributed to children's greater food consumption in proportion to body weight or differences in metabolism.^{7,8} BPA measurements in spot urine samples are limited by poor intraclass correlation coefficients, but they might reflect adequately average population exposure when sample sizes are large.^{6,9,10} Thus exposure to BPA is nearly ubiquitous, might begin prenatally and continue through childhood, and can be detected through the analysis of spot urine samples.

Several studies in mice suggest that exposure to BPA might augment the allergic immune response. For example, murine data suggest that exposure to BPA can reduce levels of regulatory T cells, IFN- γ , and IL-10 and increase production of IL-4 and antigen-specific IgE.¹¹⁻¹⁵ For years, human data regarding associations between BPA exposure and asthma-related outcomes were limited to case reports of occupational asthma among workers exposed to BPA in epoxy resins.^{16,17} Recently, Spanier et al¹⁸ reported that high (>2.2 $\mu\text{g/g}$ creatinine) maternal urinary BPA concentrations at 16 weeks of pregnancy were associated with increased odds of child's wheeze before age 3 years. However, Spanier et al did not assess postnatal exposures.

Abbreviations used

- BPA: Bisphenol A
- FENO: Fraction of exhaled nitric oxide
- OR: Odds ratio
- QC: Quality control

In light of these accumulating data suggesting that early exposure to BPA might be associated with allergy or asthma, we sought to determine whether prenatal exposure, postnatal exposure, or both to BPA was associated with asthma. We hypothesized that BPA exposure, as assessed based on urinary BPA concentrations prenatally and at ages 3, 5, and 7 years, would be associated with increased risk of wheeze and asthma at school age in a prospective inner-city birth cohort.¹⁷ In addition, we explored whether prenatal and early childhood exposures to BPA were associated with increased values of fraction of exhaled nitric oxide (FENO), a biomarker of airway inflammation, and sensitization to aeroallergens.

METHODS

Study population and data collection

The Columbia Center for Children’s Environmental Health recruited women during pregnancy from 1998 to 2006 from prenatal clinics affiliated with New York Presbyterian Hospital as part of an ongoing longitudinal birth cohort study.^{19,20} African American and Dominican women aged 18 to 35 years who had lived in Northern Manhattan or the South Bronx for at least 1 year were recruited for the study. By design, the study aimed to enroll a low-risk cohort. A family history of asthma or atopy was not a required inclusion criterion. Exclusion criteria included active smoking during pregnancy, drug use, diabetes, hypertension, and HIV infection. A total of 2844 mothers were screened during pregnancy, of whom 1442 met the initial inclusion criteria. The most common exclusion criteria were related to residency (18%), active smoking (13%), race/ethnicity (13%), maternal age (9.4%), and maternal illness (6.8%). Eligible women were followed until delivery; inclusion criteria for full enrollment were completion of a prenatal home visit during the third trimester, with collection of maternal prenatal urine and environmental samples and collection of a blood sample at the time of birth (cord blood, maternal blood, or both); 727 (50%) subjects met these criteria and were fully enrolled. The most common reasons for nonenrollment among mothers who met the initial inclusion criteria were refusal to participate, loss of contact during pregnancy, and lack of notification at delivery.

Informed consent was obtained from all participants in accordance with Columbia University’s and the Centers for Disease Control and Prevention’s Institutional Review Boards. For each analysis, participants were included if they had data available for urinary BPA concentration and the outcome measure.

BPA

Maternal spot urine samples were collected during the third trimester of pregnancy (n = 375). Children’s spot urine samples were collected at ages 3 (n = 408), 5 (n = 401), and 7 (n = 318) years from 2001 to 2010 (Fig 1). Samples were frozen and stored at –80°C. Total (free plus conjugated) BPA urinary concentrations (in nanograms per milliliter) were measured at the Centers for Disease Control and Prevention by using online solid-phase extraction coupled to high-performance liquid chromatography/isotope-dilution tandem mass spectrometry, as previously described.⁷ Two low-concentration and 1 high-concentration quality control (QC) materials prepared with pooled human urine were analyzed with analytic standards, reagent blanks, and study samples in each analytic run. The average concentrations of the high-QC and low-QC materials included in each run were evaluated by using standard statistical probabilities criteria.²¹ The low-concentration QC samples (approximately 2.8 µg/L) had a coefficient of variation of 5.8%, whereas the



FIG 1. Stars indicate that an assessment was made at a discrete time point. For example, BPA concentrations were assessed at 4 time points, wheeze at 3 time points, and seroatopy at 1 time point per participant. Arrows indicate that an assessment was made during a range of possible ages. For example, asthma was assessed once between ages 5 and 12 years on all participants with a maternal report of child wheeze, whistling in the chest, or use of asthma medications in the prior 12 months on questionnaires administered at ages 5, 6, 7, 9, and 11 years (n = 289). Similarly, FENO values were assessed between ages 7 through 11 years when the parent reported that the child was free of cold symptoms that day; when multiple FENO samples were available for analysis, the sample taken at the youngest age was used for analysis.

high-concentration QC samples (approximately 10 µg/L) had a coefficient of variation of 4.3% for a period spanning approximately 3 years. The limit of detection was 0.4 ng/mL. For the small proportion of results of less than the limit of detection, the value of 0.31 ng/mL was substituted.²² Specific gravity of the urine was quantified at room temperature at Columbia University with a handheld refractometer (PAL 10-S; Atago, Bellevue, Wash).

Determination of wheeze and asthma

The validated International Study of Asthma and Allergies in Childhood wheeze questionnaire was administered to participants at ages 5, 6, and 7 years (Fig 1).²³⁻²⁵ Participants were asked the following: “Has your child had wheezing or whistling in the chest in the last 12 months?”

Physician examination performed once per child between the ages of 5 and 12 years was conducted on all participants with a maternal report of child’s wheeze, whistling in the chest, or use of asthma medications in the prior 12 months on questionnaires offered at ages 5, 6, 7, 9, and 11 years (n = 289). One of 5 board-certified allergists or pediatric pulmonologists performed a standardized history and physical examination, as well as prebronchodilator and postbronchodilator pulmonary function testing. Physicians were given a report detailing a previous record of respiratory symptoms, IgE measurements, and allergy skin tests, when available. Results were reviewed independently by 2 allergists/pulmonologists who determined asthma status according to 3 prespecified criteria:

1. asthma symptoms OR asthma medications AND either a 12% increase in FEV₁ or 30% increase in forced expiratory flow at 25% to 75% of forced vital capacity after bronchodilator;
2. asthma symptoms OR asthma medications AND history of asthma symptoms on previous questionnaires; and
3. history of asthma symptoms on previous questionnaires AND wheeze on current examination.

Interobserver agreement was high (κ = 0.92). In cases of disagreement (n = 12), the cases were discussed until consensus was reached. Children who did not meet one of these 3 criteria or who were not referred for evaluation because they did not meet our screening criteria were classified as not having asthma at the time of evaluation.²⁶

FENO

Breath samples were collected from children ages 7 through 11 years when the parent reported that the child was free of cold symptoms that day (Fig 1).

TABLE I. Cohort characteristics

	Cohort overall (n = 727)	Prenatal (n = 375)*	Age 3 y (n = 408)*	Age 5 y (n = 401)*	Age 7 y (n = 318)*
Maternal asthma, no. (%)	163 (22)	93 (25)	93 (23)	93 (23)	78 (25)
Male sex, no. (%)	352 (48)	172 (46)	189 (46)	184 (46)	150 (47)
Dominican American, no. (%)	474 (65)	244 (65)	302 (69)	246 (61)	176 (55)
African American, no. (%)	255 (35)	131 (35)	162 (40)	155 (39)	142 (45)
Environmental tobacco smoke exposure,† no. (%)	362 (50)	177 (47)	222 (54)	208 (52)	176 (55)
Urinary BPA concentration (ng/mL), median (IQR)	NA	1.8 (1.0-3.5)	3.8 (1.8-7.4)	3.1 (1.7-6.4)	2.7 (1.4-6.0)
Breast-fed, no. (%)	509 (75)	285 (77)	291 (72)	281 (71)	216 (69)
Breast-feeding duration (wk), median (IQR)‡	8 (4-20)	12 (4-23)	10 (4-20)	11 (4-21)	10 (4-18)

IQR, Interquartile range.

*Characteristics of study participants with urinary samples available for BPA measures at each time point.

†Maternal report of smoking during pregnancy, maternal or cord blood cotinine level of greater than 15 ng/mL, or report of a smoker in the home postnatally.

‡Among those who breast-fed at some point.

When multiple samples were available for analysis, the sample taken at the youngest age was used for analysis. A modified Sievers offline collection device (GE Analytical Instruments, Boulder, Colo) was used to collect the samples at a flow rate of 83 mL/s, and FENO values were measured with a chemiluminescent analyzer (NOA 280i; Sievers Instruments, Boulder, Colo), as previously described.^{27,28}

IgE

Specific IgEs to cat, mouse, dog, *Dermatophagoides farinae*, cockroach, trees, mold, grass, and ragweed were measured as previously described by using the ImmunoCAP system (Phadia, Uppsala, Sweden) at age 7 years.²⁹ Children were considered seroatopic if they had measurable IgE levels (≥ 0.35 IU/mL) specific to any of the aeroallergens tested.

Covariates

Race/ethnicity and history of maternal asthma were reported on prenatal questionnaires. The child's sex was assessed by means of medical record review. Fetal exposure to environmental tobacco smoke was defined as report of a smoker in the home prenatally or active maternal smoking during pregnancy (measured based on maternal self-report after enrollment or a maternal or cord blood cotinine level >15 ng/mL). The child's exposure to environmental tobacco smoke was defined as maternal report of smoking or maternal report of a smoker in the home postnatally. Specific gravity was included as a measure of urinary dilution.

Statistics

Associations between urinary BPA concentrations and binary outcomes (wheeze, asthma, or seroatopy) were analyzed by using logistic regression models. Associations with linear outcomes, such as FENO values or specific IgE levels, were analyzed by using linear regression models. All models controlled for maternal asthma, environmental tobacco smoke exposure, sex, race/ethnicity, and urine specific gravity. Models for asthma additionally controlled for age at the time of a physician's assessment for asthma. Urinary BPA concentrations were log-transformed to approximate a normal distribution; odds ratios (ORs) represent an increase in odds per log-transformed unit of BPA concentration. Urine specific gravity measures were converted to z scores to avoid collinearity with the intercept. Analyses were performed with SAS version 9.1 software (SAS Institute, Cary, NC). Adjustment for multiple comparisons was not performed because all results were reported.³⁰

RESULTS

The characteristics of the study population determined at the time of enrollment are summarized in Table I. The cohort was 65% of Dominican ethnicity and 35% of African American race and of predominantly low socioeconomic status. Twenty-two

percent had a history of maternal asthma. Fifty percent of the cohort was exposed to prenatal or postnatal environmental tobacco smoke. The prevalence of wheeze in the past 12 months at ages 5, 6, and 7 years was 26%, 23%, and 23%, respectively. Thirty-three percent had a diagnosis of asthma, 45% had seroatopy at age 7 years, and the median exhaled nitric oxide level was 8.3 ppb (range, 2.3-74.6 ppb). There were no significant differences between children for whom BPA concentration data were available for at least 1 time point ($n = 568$) and those children without such associated data: 22% had a maternal history of asthma, 46% were male, 62% were Dominican American, and 51% were exposed to environmental tobacco smoke prenatally or postnatally. Five hundred nine participants were breast-fed at some point during the first year of life, but the duration of breast-feeding was short, with a median of 4 weeks.

Median urinary BPA concentrations were lowest in the maternal prenatal samples (1.8 ng/mL), highest at age 3 years (3.8 ng/mL), and progressively lower at ages 5 (3.1 ng/mL) and 7 (2.7 ng/mL) years (Table I). A small proportion of samples had undetectable concentrations (6.4% prenatally, 2.5% at age 3 years, 2.2% at age 5 years, and 3.8% at age 7 years). Maternal prenatal urinary BPA concentrations were not correlated with child urinary BPA concentrations measured postnatally. Child urinary BPA concentrations at ages 3 and 5 years were poorly correlated with concentrations at 7 years (Table II).

Contrary to our hypothesis, the prenatal urinary BPA concentration was associated inversely with the odds of wheeze at age 5 years (OR, 0.7; 95% CI, 0.5-0.9; $P = .02$). The prenatal BPA concentration was not associated with wheeze at age 6 or 7 years or with asthma assessed by a physician once between ages 5 and 12 years or with seroatopy at age 7 years (Table III).

Consistent with our hypothesis, urinary BPA concentrations at ages 3, 5, and 7 years were associated with increased odds of asthma (OR, 1.5 [95% CI, 1.1-2.0], $P = .005$; OR, 1.4 [95% CI, 1.0-1.9], $P = .03$; and OR, 1.5 [95% CI, 1.0-2.1], $P = .04$, respectively; Table IV). BPA concentrations at age 3 years were associated with increased odds of wheeze at ages 5 years (OR, 1.4; 95% CI, 1.1-1.8; $P = .02$) and 6 years (OR, 1.4; 95% CI, 1.0-1.9; $P = .03$). The BPA concentration at age 5 years was not associated with wheeze at age 5, 6, or 7 years. The BPA concentration at age 7 years was associated with increased odds of wheeze at age 7 years (OR, 1.4; 95% CI, 1.0-1.9; $P = .04$). Mean postnatal urinary BPA concentrations were associated with asthma and wheeze at ages 5, 6, and 7 years (Table IV). An association of borderline significance was seen between urinary

TABLE II. Pearson correlations between urinary BPA concentrations at different ages (in years)

	Age 3 y	Age 5 y	Age 7 y
Prenatal	$r = -0.02$ $P = .7$ $n = 262$	$r = 0.02$ $P = .7$ $n = 240$	$r = 0.01$ $P = .9$ $n = 169$
Age 3 y		$r = -0.01$ $P = .8$ $n = 291$	$r = 0.16$ $P = .02$ $n = 233$
Age 5 y			$r = 0.14$ $P = .01$ $n = 305$

TABLE III. Prenatal BPA concentrations and wheeze, asthma, and seroatopy

	No.*	OR (95% CI)	P value
Wheeze at age 5 y	323/84	0.7 (0.5-0.9)	.02
Wheeze at age 6 y	237/49	0.8 (0.5-1.3)	.4
Wheeze at age 7 y	210/52	0.8 (0.5-1.2)	.3
Asthma	330/106	0.8 (0.5-1.1)	.1
Seroatopy at age 7 y	151/67	1.1 (0.7-1.6)	.8

Models were controlled for maternal history of asthma, sex, race/ethnicity, prenatal and postnatal environmental tobacco smoke exposure, and urine specific gravity. Models for asthma were additionally controlled for the child's age at the time of evaluation because this assessment was performed once per child between ages 5 and 12 years. Urinary BPA concentration (ng/mL), median (IQR): 1.8 (1.0-3.5).
IQR, Interquartile range.

*Total number for analysis/number with outcome.

BPA concentrations at age 3 years and persistent wheeze ($n = 40$ participants with wheeze at age 5, 6, and 7 years) compared with never wheeze ($n = 177$ with no wheeze at ages 5, 6, and 7 years; OR, 1.6; 95% CI, 0.98-2.45; $P = .06$).

BPA concentrations measured prenatally at age 3, 5, or 7 years were not associated with seroatopy at age 7 years (Tables III and IV). BPA concentrations at age 7 years but not prenatally or at age 3 or 5 years, were associated positively with FENO values at age 7 years or greater (Table V). The associations between BPA concentrations and FENO values did not vary appreciably when stratified by seroatopy (data not shown).

Of the 289 participants with wheeze who underwent spirometry with a bronchodilator, 84 had a response to the bronchodilator, which was defined as either a 12% improvement in FEV₁ or a 30% improvement in forced expiratory flow at 25% to 75% of forced vital capacity. The postnatal urinary BPA concentration was not associated with odds of bronchodilator response, and prenatal exposure was inversely associated (see Table E1 in this article's Online Repository at www.jacionline.org).

A series of sensitivity analyses were performed to assess potential bias caused by missing data. When BPA concentrations from all 4 time points were included in the same models ($n = 116$), the results were similar for all analyses except for the association between BPA concentration at age 3 years and wheeze at age 6 years, in which the OR approached 1 (data not shown). Only 82 participants had complete data at all 4 exposure time points for all 5 outcomes tested. Median BPA levels did not differ between those with complete versus incomplete data (see Table E2 in this article's Online Repository at www.jacionline.org). We also

conducted sensitivity analyses to determine whether follow-up differed between children with reports of wheeze versus those without wheeze. Among nonwheezers at age 5 years, median 5-year urinary BPA concentrations were the same among those with and without follow-up at ages 6 or 7 years (2.9 ng/mL in both groups; $P = .7$, Kruskal-Wallis). Among those with wheeze at age 5 years, the median 5-year urinary BPA concentration was 3.7 ng/mL, and there were no participants lost to follow-up in this group.

Three additional sensitivity analyses were performed. Results were similar when stratified by atopy (see Table E3 and E6 in this article's Online Repository at www.jacionline.org). Results were unchanged after adjusting for the amount of time elapsed between collection of BPA and FENO samples (data not shown). Urinary BPA concentrations did not differ significantly by breast-feeding status, and controlling for duration of breast-feeding did not substantively change the results (see Tables E4 and E5 in this article's Online Repository at www.jacionline.org).

DISCUSSION

We found that urinary BPA concentrations at ages 3, 5, and 7 years were associated with asthma assessed at ages 5 to 12 years. Also, BPA concentrations at age 3 years were associated with wheeze at ages 5 and 6 years, and BPA concentrations at age 7 years were associated with wheeze at age 7 years. Although the strength of the associations is modest, this is the first cohort study to report an association between childhood urinary BPA concentrations and asthma in children.

Contrary to our hypothesis, prenatal urinary BPA concentrations were associated inversely with odds of wheeze at age 5 years. This finding is also contrary to the findings of Spanier et al,¹⁸ who reported maternal urinary BPA concentrations of greater than the median at 16 weeks' gestation were associated with increased odds of child's wheeze before age 3 years. Importantly, Spanier et al assessed BPA exposure during the second trimester, whereas we assessed exposure during the third trimester. The second trimester encompasses formation of the terminal bronchioli and the initiation of antigen-specific immune responses, and thus the different findings might be related to the timing of the exposure on airway and immune development.^{31,32} We found that urinary BPA concentrations were lower in maternal prenatal samples than in subsequent child samples. These results are consistent with data from the National Health and Nutrition Examination Survey and might be due to children's greater food consumption in proportion to body weight.⁷

Alternate explanations might relate to the complex metabolism of BPA in the maternal-fetal unit.³³ In pregnant mice 24 hours after exposure to BPA, only 6% of BPA was excreted in the maternal urine, whereas 90% remained in the fetoplacental unit, suggesting that measuring concentrations in maternal urine might underestimate fetal exposure.³⁴ In rats BPA-glucuronide, an inactive metabolite, is absorbed by the placenta, where it is deconjugated back to active BPA.³⁵ *In vitro*, the fetal liver does not express sufficient levels of the isozymes needed to remetabolize BPA to BPA-glucuronide,³⁶ and therefore the fetus can be exposed to higher concentrations of the active metabolite. Whether these findings in rodent models are applicable to human subjects remains an open question. Although it is possible that prenatal exposure to BPA during the third trimester might reduce the subsequent odds of wheeze in the child, we know of no

TABLE IV. Postnatal BPA concentrations and wheeze, asthma and seroatopy

	Age 3 y			Age 5 y			Age 7 y			Mean postnatal concentration		
Urinary BPA (ng/mL), mean \pm SD	7.4 \pm 11.6			5.4 \pm 7.2			5.8 \pm 9.3			6.0 \pm 6.5		
	No.*	OR (95% CI)	P value	No.*	OR (95% CI)	P value	No.*	OR (95% CI)	P value	No.*	OR (95% CI)	P value
Wheeze at age 5 y	328/86	1.4 (1.1-1.8)	.02	355/96	1.3 (0.9-1.7)	.05		NA		429/111	1.5 (1.1-2.0)	.006
Wheeze at age 6 y	272/64	1.4 (1.0-1.9)	.03	337/82	0.8 (0.6-1.1)	.2		NA		372/86	1.4 (1.0-1.9)	.04
Wheeze at age 7 y	274/65	1.2 (0.8-1.5)	.4	341/79	1.2 (0.9-1.6)	.2	305/68	1.4 (1.0-1.9)	.04	368/84	1.4 (1.0-2.0)	.04
Asthma	361/120	1.5 (1.1-2.0)	.005	390/135	1.4 (1.0-1.9)	.03	309/111	1.5 (1.0-2.1)	.04	473/154	1.6 (1.2-2.1)	.001
Seroatopy at age 7 y	225/101	1.2 (0.9-1.5)	.3	269/119	0.8 (0.6-1.0)	.08	277/124	1.0 (0.7-1.3)	.8	294/130	0.9 (0.7-1.2)	.5

Models were controlled for maternal history of asthma, sex, race/ethnicity, environmental tobacco smoke exposure, and urine specific gravity. Models for asthma were additionally controlled for child's age at the time of evaluation because this assessment was performed once per child between ages 5 and 12 years.

*Total number for analysis/number with outcome.

TABLE V. BPA concentration and mean difference in FENO values (in parts per billion)

Model	Prenatal			Age 3 y			Age 5 y			Age 7 y			Mean postnatal concentration		
	No.	β (95% CI)	P value	No.	β (95% CI)	P value	No.	β (95% CI)	P value	No.	β (95% CI)	P value	No.	β (95% CI)	P value
1	172	1.06 (0.96-1.22)	.3	231	1.02 (0.94-1.11)	.6	296	1.03 (0.95-1.11)	.5	285	1.1 (1.02-1.2)	.02	313	1.07 (0.97-1.17)	.2
2	167	1.06 (0.96-1.17)	.3	225	0.98 (0.90-1.06)	.6	289	1.01 (0.94-1.10)	.7	278	1.1 (1.02-1.2)	.02	305	1.04 (0.95-1.15)	.4

Linear regression model 1 was controlled for maternal history of asthma, sex, race/ethnicity, environmental tobacco smoke exposure, and urine specific gravity. Model 2 was additionally controlled for child's asthma.

biologically plausible mechanism through which that might occur. Instead, these studies raise the possibility that third-trimester maternal urinary BPA concentrations can underestimate the level of BPA exposure to the fetus or that the third trimester might not be the relevant window of vulnerability for asthma-related outcomes.

The mechanism by which BPA exposure during early childhood might influence asthma risk in subsequent years remains an open question. Data from the National Health and Nutrition Examination Survey 2003-2006 suggest that urinary BPA concentrations are associated positively with higher titers of anti-cytomegalovirus antibodies in adults but lower titers in children ages 6 to 17 years. This finding suggests that whether exposure to BPA augments or inhibits humoral immunity might vary with age at the time of exposure.³⁷ In a murine ovalbumin asthma model, perinatal exposure to BPA was associated with increased anti-ovalbumin IgE levels and airway hyperreactivity at age 17 days.³⁸ Exposure to BPA prenatally¹⁴ and at 5 weeks¹⁵ has been associated with higher levels of proallergic T_H2 cytokine production (increased IL-4 and reduced IFN- γ levels) in mice. Prenatal exposure to BPA in mice also has been associated with reduced percentages, although not function, of regulatory T CD4⁺CD25⁺ cells.^{14,39} Collectively, these studies suggest that BPA might influence asthma risk through upregulation of T_H2 pathways and possibly reductions in regulatory T-cell counts. FENO is thought to be a marker of eosinophilic airway inflammation, and therefore the finding that FENO levels were associated with urinary BPA concentrations at age 7 years supports the paradigm that BPA might influence asthma risk through T_H2 pathways. However, it is worth noting that we did not see an association between urinary BPA concentrations and seroatopy at age 7 years, and the association observed between BPA concentrations at age 3 years and wheeze at age 6 years occurred

primarily in participants without a maternal history of asthma, suggesting that other pathways also might play a role. Indeed, the work of Roy et al⁴⁰ in a murine model found that developmental exposure to BPA modulated innate, but not adaptive, immune responses to viral infection. Our findings were similar in those with and without seroatopy. Thus the mechanisms by which BPA can affect allergic inflammatory pathways and asthma risk remain unclear.

Several limitations should be acknowledged. This study uses spot urinary BPA concentrations as a proxy for BPA exposure. This is potentially problematic given the short half-life of BPA (approximately 6 hours) and potential for significant day-to-day variation in exposure.⁴¹ However, so long as spot urine samples are collected randomly relative to meal and void times, if the sample size is sufficiently large, they might estimate adequately the exposure of the population to BPA.⁴² The modest strength of the association between BPA concentrations and wheeze and asthma seen in this study (ORs \sim 1.4) raise the possibility that these results could be explained by unmeasured confounding, a potential limitation of all observational studies. The magnitude is comparable with what has been reported for associations between BPA and other health outcomes, although the prevalence of this outcome measure was higher.⁴³ However, one would expect measurement error to bias toward the null. Complete data were available only for a subset of participants, although BPA concentrations did not differ between those with complete versus incomplete data, and analyses with mean postnatal BPA yielded similar results. Misclassification of the wheeze outcome could have occurred because of missing data, maternal report, and gaps in follow-up that occur in long-term prospective studies,⁴⁴⁻⁴⁶ but the International Study of Asthma and Allergies in Childhood questionnaire has been validated⁴⁷ and widely published.^{48,49} An additional limitation is the absence of bronchial provocation

testing for use in determination of asthma in this study. Although many pediatric studies have included bronchial provocation challenges in their asthma determinations,⁵⁰⁻⁵⁴ others have relied on combinations of symptom history, allergen skin testing, and pulmonary function testing.^{55,56} Remes et al⁵⁷ found that provocation testing did not significantly improve the area under the receiver operating curve when added to symptom history. In addition, the gold standard used by Remes et al was diagnosis of asthma by an allergist. In light of this, despite the absence of bronchial provocation measures in this study, the blinded, independent asthma determination by 2 subspecialists ($\kappa = 0.92$) is arguably a relative strength of this study.

This is the first cohort study to report an association between postnatal urinary BPA concentrations and asthma in young children. We found that urinary BPA concentrations at ages 3, 5, and 7 years were associated with asthma assessed at ages 5 to 12 years. These findings add to the evidence that environmental exposure to BPA might be associated with adverse respiratory outcomes.

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Key message

- Postnatal urinary BPA concentrations were associated with increased odds of wheeze and asthma and increased levels of FENO in a birth cohort of school-aged children.

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TABLE E1. Urinary BPA concentration and response to bronchodilator

Urinary BPA concentration	No.*	OR (95% CI)	P value
Prenatal	375/55	0.6 (0.4-0.9)	.01
Age 3 y	408/58	0.9 (0.7-1.3)	.9
Age 5 y	401/67	1.2 (0.9-1.8)	.06
Age 7 y	317/54	1.2 (0.9-1.6)	.3

Physician's examination, including spirometry with bronchodilator, was conducted between ages 5 and 12 years on all participants with a maternal report of child wheeze, whistling in the chest, or use of asthma medications in the prior 12 months on questionnaires delivered at ages 5, 6, 7, 9, and 11 years of age (n = 289). Response to bronchodilator was defined as 12% improvement in FEV₁ or 30% improvement in forced expiratory flow at 25% to 75% of forced vital capacity. Models were adjusted for maternal history of asthma, sex, race/ethnicity, environmental tobacco smoke exposure, and urine specific gravity.

*Total number for analysis/number with outcome.

TABLE E2. Urinary BPA levels among those with complete versus incomplete data

	No.	Complete data (ng/mL), median (IQR)	No.	Incomplete data (ng/mL), median (IQR)	Kruskal-Wallis <i>P</i> value
Prenatal	82	1.9 (1.2-3.7)	293	1.8 (1.0-3.4)	.4
3 y	82	3.9 (2.1-7.6)	326	3.7 (1.7-6.3)	.3
5 y	82	3.4 (1.7-7.0)	319	3.0 (1.7-6.3)	.6
7 y	82	2.7 (1.2-5.6)	236	2.8 (1.4-6.3)	.6

IQR, Interquartile range.

TABLE E3. BPA and wheeze

	Prenatal			Age 3 y			Age 5 y			Age 7 y			Mean postnatal		
	No.	OR (95% CI)	P value	No.	OR (95% CI)	P value	No.	OR (95% CI)	P value	No.	OR (95% CI)	P value	No.	OR (95% CI)	P value
Seroatopic subjects															
Wheeze at age 5 y	64	0.5 (0.2-1.2)	.1	90	2.0 (1.1-1.8)	.02	105	0.9 (0.6-1.5)	.8		NA		114	1.6 (0.9-3.2)	.1
Wheeze at age 6 y	59	1.1 (0.5-2.3)	.9	85	2.1 (1.1-4.0)	.03	102	0.8 (0.5-1.4)	.5		NA		111	1.1 (0.6-2.2)	.7
Wheeze at age 7 y	65	0.7 (0.4-1.4)	.3	99	1.4 (0.8-2.3)	.2	114	1.3 (0.8-2.0)	.3	119	1.6 (0.9-2.7)	.08	125	1.5 (0.9-2.8)	.2
Asthma	66	0.4 (0.2-0.9)	.04	100	1.4 (0.8-2.4)	.2	118	1.1 (0.7-1.8)	.6	123	2.0 (1.0-3.8)	.04	128	1.4 (0.7-2.7)	.3
Nonseroatopic subjects															
Wheeze at age 5 y	80	0.6 (0.3-1.3)	.2	103	1.4 (0.9-2.3)	.1	128	1.3 (0.8-2.1)	.3		NA		137	1.6 (1.0-2.9)	.1
Wheeze age 6 y	70	0.8 (0.3-2.1)	.7	101	1.1 (0.7-1.9)	.6	123	0.6 (0.3-1.1)	.1		NA		133	1.3 (0.7-2.3)	.4
Wheeze at age 7 y	82	1.1 (0.5-2.3)	.8	122	1.0 (0.7-1.7)	.9	147	1.1 (0.7-1.8)	.7	150	1.4 (0.9-2.1)	.1	160	1.4 (0.8-2.4)	.2
Asthma	80	1.2 (0.5-2.7)	.6	118	1.5 (0.9-2.6)	.1	145	1.2 (0.7-2.0)	.6	148	1.4 (0.9-2.3)	.2	157	1.5 (0.8-2.7)	.2

Models were controlled for maternal history of asthma, sex, race/ethnicity, environmental tobacco smoke exposure, and urine specific gravity. Models for asthma were additionally controlled for child's age at the time of evaluation.

TABLE E4. Urinary BPA concentrations among those breast-fed versus never breast-fed

	Breast-fed (ng/mL), median (IQR)	Never breast-fed (ng/mL), median (IQR)	Kruskal-Wallis P value
Prenatal	1.8 (1.0-3.6)	2.0 (1.3-3.2)	.6
3 y	3.8 (1.7-7.6)	3.7 (1.9-6.8)	.9
5 y	2.9 (1.7-5.9)	3.5 (1.8-8.1)	.6
7 y	2.9 (1.4-6.0)	2.8 (1.5-6.4)	.8

IQR, Interquartile range.

TABLE E5. Results adjusted for duration of breast-feeding

	Prenatal			Age 3 y			Age 5 y			Age 7 y		
	No.	OR (95% CI)	P value	No.	OR (95% CI)	P value	No.	OR (95% CI)	P value	No.	OR (95% CI)	P value
Wheeze at age 5 y	323	0.7 (0.5-0.9)	.02	328	1.4 (1.0-1.8)	.02	355	1.3 (1.0-1.8)	.05	271		
Wheeze at age 6 y	237	0.8 (0.5-1.3)	.4	272	1.4 (1.0-1.9)	.03	337	0.9 (0.6-1.1)	.02	259		
Wheeze at age 7 y	210	0.8 (0.5-1.2)	.3	274	1.1 (0.8-1.5)	.5	341	1.2 (0.9-1.6)	.2	305	1.3 (1.0-1.8)	.05
Asthma	330	0.8 (0.5-1.1)	.1	361	1.5 (1.1-2.0)	.005	390	1.4 (1.0-1.9)	.03	309	1.5 (1.0-2.1)	.03
Seroatopy at age 7 y	151	1.0 (0.7-1.6)	.8	225	1.1 (0.9-1.5)	.4	269	0.8 (0.6-1.0)	.08	277	0.9 (0.7-1.3)	.7

Models were adjusted for duration of breast-feeding, maternal history of asthma, sex, race/ethnicity, environmental tobacco smoke exposure, and urine specific gravity. Models for asthma were additionally controlled for child's age at time of evaluation.

TABLE E6. Urinary BPA concentration and class II seroatopy

Urinary BPA concentration	OR (95% CI)	P value
Prenatal	1.1 (0.8-1.6)	.5
Age at 3 y	1.2 (0.9-1.6)	.1
Age at 5 y	1.0 (0.7-1.2)	.7
Age at 7 y	1.0 (0.8-1.4)	.8

Class II atopy was defined as any specific IgE level of greater than 0.70 IU/mL for cat, mouse, dog, *Dermatophagoides farinae*, cockroach, grass (*Cynodon dactylon*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis*, *Sorghum halepense*, and *Paspalum notatum*), ragweed (*Ambrosia elatior*, *Ambrosia psilostachya*, and *Ambrosia trifida*), tree (*Acer negundo*, *Betula verrucosa*, *Quercus alba*, *Ulmus americana*, and *Juglans californica*), and mold (*Penicillium chrysogenum*, *Cladosporium herbarum*, *Aspergillus fumigatus*, and *Alternaria alternata*). Models were adjusted for maternal history of asthma, sex, race/ethnicity, environmental tobacco smoke exposure, and urine specific gravity.