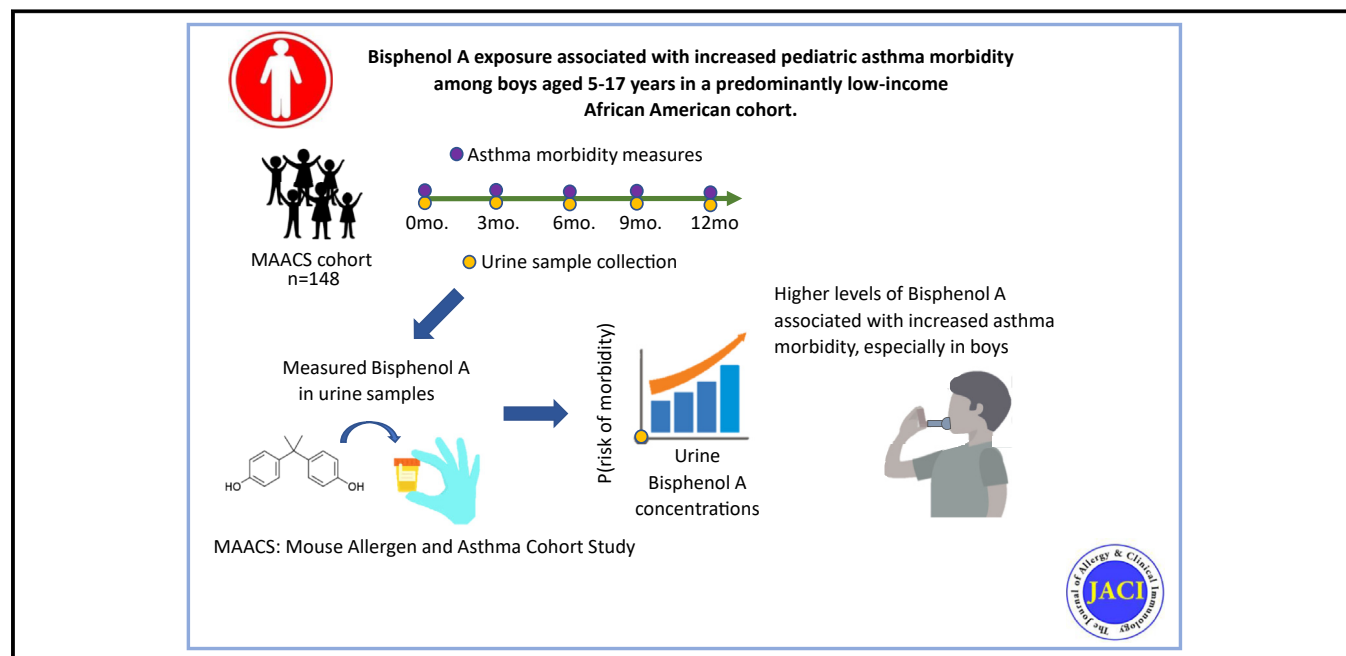


Exposure to bisphenols and asthma morbidity among low-income urban children with asthma

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GRAPHICAL ABSTRACT



Background: Bisphenol A (BPA) has been linked with pediatric asthma development and allergic airway inflammation in animal models. Whether exposure to BPA or its structural analogs bisphenol S (BPS) and bisphenol F (BPF) is associated with asthma morbidity remains unknown.

Objective: We examined associations between bisphenols and morbidity due to pediatric asthma.

Methods: We quantified concentrations of BPA, BPS, and BPF in 660 urine samples from 148 predominantly low-income, African American children (aged 5-17 years) with established

asthma. We used biobanked biospecimens and data on symptoms, health care utilization, and pulmonary function and inflammation that were collected every 3 months over the course of a year. We used generalized estimating equations to examine associations between concentrations or detection of urinary bisphenols and morbidity outcomes and assessed heterogeneity of associations by sex.

Results: We observed consistent positive associations between BPA exposure and measures of asthma morbidity. For example, we observed increased odds of general symptom days (adjusted

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odds ratio [aOR] = 1.40 [95% C = 1.02-1.92]), maximal symptom days (aOR = 1.36 [95% CI = 1.00-1.83]), and emergency department visits (aOR = 2.12 [95% CI = 1.28-3.51]) per 10-fold increase in BPA concentration. We also observed evidence of sexually dimorphic effects; BPA concentrations were associated with increased odds of symptom days and health care utilization only among boys. Findings regarding BPS and BPF did not consistently point to associations with asthma symptoms or health care utilization. **Conclusion:** We found evidence to suggest that BPA exposure in a predominantly low-income, minority pediatric cohort is associated with asthma morbidity and that associations may differ by sex. Our findings support additional studies, given the high pediatric asthma burden and widespread exposure to BPA in the United States. (J Allergy Clin Immunol 2020;■■■:■■■-■■■.)

Key words: Asthma, asthma morbidity, childhood asthma, African American, BPA, BPS, BPF, inner-city asthma

Bisphenol A (BPA), a synthetic chemical used to manufacture polycarbonate plastics and epoxy resins, can be present in canned food and beverage linings, dental sealants, and other consumer goods (eg, plastic dinnerware, toys, building materials).¹ Its pervasive use has led to widespread exposure in the US general population. Diet is the main exposure route, although other routes, including inhalation, are possible.² BPA exposure is typically higher among US children than among adults and higher among low-income and African American communities than among other socioeconomic or ethnic groups.³⁻⁵ Although disparities in BPA exposure are reported among minority and low-income populations, the reasons for these disparities are not clear. It is thought that reduced access to fresh foods, low food security, and consequential consumption of processed foods (eg, eating canned goods, heating and eating foods from plastic containers with BPA) could play a role.^{4,6,7} BPA is a xenoestrogen, and concerns exist that environmental contaminants with endocrine-disrupting properties could play a role in the development or exacerbation of allergic diseases such as asthma.⁸

In experimental studies, BPA exposure augments the allergic immune response. BPA exposure in rodents increases production of proallergic cytokine IL-4 and antigen-specific IgE, and it reduces levels of regulatory T cells, IFN- γ , and IL-10.⁹⁻¹³ Low-dose BPA exposure in juvenile rodents has been linked to allergic airway inflammation. It has been postulated that BPA may influence asthma risk through upregulation of T_H2 pathways by promoting eosinophilic airway inflammation.⁹ BPA has also been linked to oxidative stress,^{14,15} which is implicated in asthma pathogenesis¹⁶ and has been reported to contribute to poor asthma control and frequent, acute exacerbations by inducing airway inflammation and corticosteroid insensitivity.¹⁷ *In vitro* studies have also shown that BPA acts on both estrogen and androgen receptors.^{18,19} Studies indicate that activation of estrogen receptors by BPA imparts effects on gene expression, activation of nuclear estrogen receptor-dependent signaling pathways, and selective receptor modulation.²⁰ The estrogenic properties of BPA could promote dendritic cell maturation²¹ or enhance antigen presentation and induce granulation of mast cells.²² It has also been suggested that BPA-estrogen receptor interactions could explain some of the associations between asthma and estrogen activity that have been reported in epidemiologic investigations.^{22,23}

Abbreviations used

aOR:	Adjusted odds ratio
BPA:	Bisphenol A
BPF:	Bisphenol F
BPS:	Bisphenol S
BMI:	Body mass index
ED:	Emergency department
EDC:	EDC endocrine-disrupting compound
FENO:	Fraction of exhaled nitric oxide
GM:	Geometric mean
ICC:	Intraclass correlation coefficient
LOD:	Limit of detection
MAACS:	Mouse Allergen and Asthma Cohort Study
NHANES:	National Health and Nutrition Examination Survey

Although limited studies suggest that postnatal BPA exposure may increase the risk of incident asthma and wheeze in childhood,²⁴⁻²⁶ BPA's role in asthma morbidity among children with established asthma remains unknown. This is a significant data gap, particularly among pediatric subpopulations with a high asthma burden^{27,28} and disproportionate BPA exposures.³⁻⁵ Moreover, little is known about the structurally similar BPA analogs bisphenol S (BPS) and bisphenol F (BPF), which may be used as BPA replacements in consumer products, including those labeled as being BPA-free. BPS is used as a developer in thermal receipt paper and used in several industrial applications.²⁹ BPF is used to make epoxy resins and coatings for building materials and for plastics, dental sealants, and food packaging.³⁰ BPS and BPF have also been detected in personal care products (eg, hair and skin care products, toothpaste),³¹ paper products (eg, currency, mailing envelopes, airplane boarding passes),³² and food commodities (eg, dairy, meat and meat products, canned goods, cereals).³³ *In vitro* and *in vivo* studies indicate that these analogs, similar to BPA, may induce oxidative stress and have endocrine-disrupting properties.^{14,34,35}

In this study, we examined associations between urinary concentrations of BPA, BPS, and BPF and asthma morbidity among children with established asthma who reside in a low-income, urban setting. On the basis of animal and limited epidemiologic studies, we hypothesized that exposure to bisphenols would be associated with increased morbidity.

METHODS

Study participants

For the present study, we used data and biobanked biospecimens from children who had participated in the Mouse Allergen and Asthma Cohort Study (MAACS), a 12-month prospective study of 148 Baltimore City children with asthma, aged 5 to 17 years. The MAACS aimed to evaluate the impact of indoor allergens and air pollutants on clinical markers of asthma morbidity. Children were recruited between April 2007 and June 2009 from the Johns Hopkins Hospital Emergency Department (ED), health fairs, and word of mouth. Eligible children received an asthma physician diagnosis at least 1 year before study enrollment, had a controller medication prescription or met National Asthma Education and Prevention Program criteria for persistent asthma,³⁶ and experienced at least 1 asthma exacerbation in the prior year. An exacerbation was defined as asthma symptoms requiring an emergency medical visit or an oral corticosteroid burst. Enrollment was limited to nonsmokers (as confirmed with rapid urine cotinine screening) and nonpregnant females. The Johns Hopkins School of Medicine Institutional

Review Board approved the study protocols, and informed consent was obtained from the children's parents or guardians. The involvement of the US Centers for Disease Control and Prevention in laboratory sample analyses did not constitute engagement in human subjects research.

Study procedures and clinical assessments

Clinic visits were conducted at baseline and every 3 months thereafter, for a total of up to 5 visits. At baseline, trained staff administered an allergy skin prick test with the MultiTest II device (Lincoln Diagnostics, Decatur, Ill), as described previously.^{37,38} Atopy was defined as at least 1 positive skin test response, with a wheal size at least 2 mm greater than that of the negative control.^{39,40} Blood was drawn to measure total IgE by using the ImmunoCAP system (Pharmacia Diagnostics, Uppsala, Sweden).

At each visit, staff administered questionnaires to capture information on demographic characteristics (baseline only), pulmonary and allergic history, number of days with symptoms and rescue medication use in the prior 2 weeks, and asthma-related health care utilization in the prior 3 months. Asthma-related symptoms included general symptoms (chest tightness, wheeze, cough), nocturnal awakening with symptoms, exercise-related symptoms (coughing or chest tightness when running or going up stairs), coughing without a cold, and slowed activity due to asthma. The variable maximal symptom days was generated by taking the maximum number of days contributed by general symptoms, nocturnal awakening with symptoms, or slowed activity due to asthma.^{40,41} Health care utilization included acute care visits, ED visits, unscheduled physician visits, and hospitalization for asthma-related symptoms. Acute care visits included any unscheduled visit for asthma-related symptoms.

Spirometry was performed at each clinic visit with a KoKo spirometer (nSpire Health, Longmont, Colo); percent predicted values of lung function measures were determined by using Global Lung Initiative age-specific reference equations.⁴² Bronchodilator reversibility was defined as at least a 12% increase in FEV₁ value 15 minutes after administration of 2 puffs of a short-acting β -agonist. Lung inflammation was assessed by measuring the fraction of exhaled nitric oxide (FENO) levels with a NIOX Mino (Aerocrine, Solana, Sweden) following the American Thoracic Society/European Respiratory Society guidelines.⁴³

Exposure assessment

In vivo and *in vitro* studies suggest that BPF metabolism is similar to that of BPA, whereas studies on BPS are scarce.⁴⁴⁻⁴⁶ Still, BPA, BPS, and BPF are thought to be rapidly metabolized to respective glucuronides and rapidly eliminated in urine.^{47,48} Total urinary bisphenol levels, which are usually determined after deconjugation with β -glucuronidase/sulfatase, are considered to be a robust biomarker of exposure to these compounds in epidemiologic studies.⁴⁹⁻⁵² Thus, concentrations of total urinary species (free + conjugated) of bisphenols were quantified by using on-line solid phase extraction coupled with HPLC-isotope dilution tandem mass spectrometry.⁵³ At each visit, spot urine samples ($n = 660$) were collected in polypropylene urine cups, aliquoted, and stored at -80°C until shipment to the US Centers for Disease Control and Prevention (Atlanta, Ga) for analysis. The limits of detection (LODs) were 0.2 ng/mL (BPA and BPF) and 0.1 ng/mL (BPS). For concentrations less than the LOD, we used instrumental reading values when a signal was detected or randomly imputed values based on a log-normal probability distribution using maximum likelihood estimation when no signal was detected.⁵⁴ Concentrations of bisphenols were specific gravity-corrected to normalize for urine dilution.⁵⁵ Specific gravity was measured by using a digital refractometer (ATAGO 3741, Tokyo, Japan).

Data analyses

We calculated descriptive statistics to summarize baseline participant characteristics and biomarker concentrations across visits. Concentrations of BPA and BPS were log-normally distributed and log₁₀-transformed in subsequent models. BPF was not detected as frequently and modeled as a dichotomous variable ($<\text{LOD}$ vs $\geq\text{LOD}$) in subsequent analyses.

Wilcoxon-Mann-Whitney, Kruskal-Wallis, and chi-square tests were used to assess whether BPA or BPS concentrations or BPF detection frequency differed on the basis of select baseline participant characteristics. We assessed correlations between BPA and BPS concentrations across visits by using Spearman correlations and also assessed within- and between-child variability of concentrations by calculating intraclass correlation coefficients (ICCs) using mixed-effects models. ICC analyses were restricted to children who provided at least 2 urine samples. We also compared average participant biomarker concentrations with those measured among US children of similar ages (6-17 years) in the National Health and Nutrition Examination Survey (NHANES) during the same period (2007-2010) and more recently (2015-2016) by using data on 3 different subsets: (1) a representative sample of US children in the same age range as the MAACS participants, regardless of race; (2) a representative sample of African American children in the United States, given that our cohort was predominantly African American; and (3) a representative sample of US children matched on the MAACS demographic characteristics (ie, age, race, sex, and income). These comparisons were limited to uncorrected urinary biomarker concentrations, as data on specific gravity were not available in the NHANES.

To evaluate associations between concentrations of bisphenols and morbidity outcomes, we used generalized estimating equations to account for our repeated measures design. Specifically, crude and multivariable binomial regression models were fit to model relationships between repeated exposure and binary outcome measures (eg, symptoms, medication use, health care utilization) and linear regressions for continuous measures (eg, ratio of FEV₁ to forced vital capacity percent, FEV₁/FVC%). To minimize bias while maximizing effect estimate precision, we identified covariates for model inclusion using a directed acyclic graph, including confounders and predictors of morbidity due pediatric asthma that were not on the causal pathway. Covariates included age (in years), sex, race/ethnicity (black/African American vs other), caregiver's education level (less than high school, high school graduate, and some college or more), presence of smokers in the home, and season. To account for coexposures and assess the independent effects of each bisphenol, all 3 bisphenols were included in each model. Because the bisphenols assessed are known or suspected endocrine-disrupting compounds (EDCs) and prior studies have reported sexually dimorphic effects,¹⁵ we assessed effect measure modification by sex by including an interaction term in separate models.

To ensure the robustness of our results, we conducted sensitivity analyses. Because BPA and BPF exposure has been linked to obesity⁵⁶⁻⁵⁸ and obesity plays a role in asthma control and exacerbation,⁵⁹ we reran the main models including children's age- and sex-standardized body mass index (BMI) percentiles⁶⁰ modeled as a continuous covariate. We also reran models controlling for degree of atopy, which is a recognized risk factor for asthma morbidity⁶¹; we included the total number of positive skin prick test responses as a continuous model covariate to reflect each child's degree of allergic sensitization. Lastly, we ran our main models, additionally including other recognized risk factors for asthma morbidity, such as degree of atopy and exposure to particulate matter.^{40,61} Specifically, we included the total number of positive skin prick test responses as a continuous model covariate to reflect each child's degree of allergic sensitization of each child. For particulate matter, we ran our main models, additionally including log₁₀-transformed indoor concentrations of particulate matter with an aerodynamic diameter less than 2.5 μm that were measured in the participants' homes within 2 weeks before or after each clinic visit.

Analyses were performed with Stata/IC 14.2 software (StataCorp, College Station, Tex), and the statistical significance criteria were set at P less than .05 and P less than .10 for main effects and effect measure modification, respectively.

RESULTS

The mean age of the participants was 11.2 plus or minus 4.0 years, and approximately 57% were males (Table I). The children were predominantly African American (91%), were from families with an annual household income less than \$35,000 (69%), and

TABLE I. Baseline demographic characteristics for MAACS children aged 5 to 17 years (n = 148)

Demographic characteristic	n	(%)
Age*		
5-7 y	41	(27.7)
8-10 y	35	(23.7)
11-13 y	26	(17.6)
14-17 y	46	(31.1)
Sex		
Male	85	(57.4)
Female	63	(42.6)
Child's race		
Black/African American	135	(91.2)
Other†	13	(8.8)
Child BMI		
Underweight (<5th percentile)	6	(4.1)
Normal weight (5th to <85th percentile)	77	(52.7)
Overweight (85th to <95th percentile)	22	(15.1)
Obese (≥95th percentile)	41	(28.1)
Caregiver's education level		
Less than high school	42	(28.4)
High school graduate	51	(34.5)
At least some college	55	(37.2)
Annual household income		
<\$35,000	92	(68.7)
≥\$35,000	42	(31.3)
Insurance		
Private/self-pay	20	(13.7)
Government-based (public)	126	(86.3)
Smoker lives in child's home		
No	64	(43.2)
Yes	84	(56.8)

Information reported is for 148 MAACS children with BPA, BPS, and BPF biomarker data. Information was missing for select demographic characteristics at baseline (BMI, n = 2; annual household income, n = 14; and health insurance, n = 2).

*The mean age of the MAACS children was 11.2 ± 4.0 years.

†Race category other includes white (n = 6), American Indian or Alaska Native (n = 5), other Pacific Islander (n = 1), and unknown (n = 1).

were receiving government-based health insurance (86%). More than half of the caregivers (63%) reported not having any college education. Most children (91%) had at least 1 positive skin prick test response and reported having an acute health care visit for asthma in the previous year (96%), with 82% reporting an ED visit for asthma during this period (Table II). Additional clinical characteristics are presented in Table II.

Summary statistics for specific gravity-corrected concentrations of bisphenols are provided in Table III (and see Table E1 in this article's Online Repository at www.jacionline.org for uncorrected concentrations). The detection frequencies were 100% (BPA), 97% (BPS), and 66% (BPF). The GM concentrations plus or minus the geometric SD were as follows: for BPA, 3.6 plus or minus 2.2 ng/mL; for BPS, 0.4 plus or minus 3.2 ng/mL; and for BPF, 0.8 plus or minus 6.2 ng/mL. The baseline BPA concentrations differed by select demographic characteristics (see Table E2 in this article's Online Repository at www.jacionline.org), including BMI ($P = .04$), caregiver's education level ($P = .03$), and season ($P = .01$). The GM BPA concentrations were higher among children with normal body weight (versus overweight/obese), children with less-educated caregivers, and samples collected in summer months. BPS

TABLE II. Baseline clinical characteristics for MAACS children aged 5 to 17 years (n = 148)

Clinical characteristic	
Allergic sensitization characteristics	
Atopic (≥1 positive skin prick test response), no. (%)	134 (91.2)
Skin test sensitivities, no. (%)	
Cat	96 (65.3)
Cockroach	91 (61.9)
Dust mite	85 (57.8)
Mouse	78 (53.1)
Dog	26 (17.7)
Total IgE level (kU/L), median (25th percentile, 75th percentile)	190 (55.7, 458)
Lung function	
FEV ₁ (% predicted), mean ± SD	91.3 (15.6)
FVC (% predicted), mean ± SD	100.2 (13.5)
FEV ₁ /FVC (%), mean ± SD	80.6 (9.6)
Bronchodilator reversibility, no./total (%)*	37/130 (28.5)
FENO (ppb), median ± SD (25th percentile, 75th percentile)	33 (16.0, 62.0)
Asthma-related health care utilization in the prior 12 mo and medication use, no. (%)	
Acute health care visit†	142 (96.0)
ED visit	121 (81.8)
Hospitalization	29 (19.6)
Unscheduled doctor's office visit	61 (41.2)
Controller medication use‡	106 (71.6)
Days of short acting β-agonist use in the prior 2 wk, mean ± SD	4.2 (5.0)

FVC, Forced vital capacity.

Information on some participants was missing (atopic status and skin sensitivities, n = 1; IgE level, n = 3; FVC % predicted, n = 16; FEV₁ % predicted, n = 16; FEV₁/FVC % predicted, n = 16; bronchodilator reversibility, n = 18; and Feno, n = 17). ED visit refers to an ED visit for asthma.

*Bronchodilator reversibility is defined as an increase in an FEV₁ value of 12% or greater following treatment with a short-acting β-agonist.

†Acute health care visits consists of a composite measure of any unscheduled health care visit for asthma-related symptoms (eg, ED visits, hospitalization, and/or unscheduled doctor's visits for asthma).

‡Inhaled corticosteroid or leukotriene inhibitor.

concentrations were higher among children living with smokers ($P = .03$). BPF detection frequency did not differ on the basis of demographic characteristics.

At baseline, higher median BPA concentrations were observed among children who reported having acute care (median = 3.5 vs 3.0 ng/mL [$P = .04$]) and ED visits for asthma-related symptoms (median = 3.7 vs 3.1 ng/mL [$P = .02$]) in the prior year compared with among children who did not report these outcomes. This pattern was generally consistent across visits, and similar patterns were observed for other health care utilization outcomes (see Table E3 in this article's Online Repository at www.jacionline.org). For BPS, the baseline median concentrations were similar among children reporting most health care utilization outcomes; however, this pattern was not consistent across visits (see Table E3). BPA and BPS concentrations were weakly correlated at each visit (Spearman $\rho = 0.18$ - 0.30 [$P < .05$]); and concentrations varied greatly within children over the 12-month follow-up period ($ICC_{BPA} = 0.10$; $ICC_{BPS} = 0.14$). The median BPA and BPF concentrations were higher in the MAACS participants than in the NHANES children from either sampling period, regardless of

TABLE III. Summary statistics and variability measures for specific gravity–corrected BPA, BPS, and BPF concentrations in ng/mL based on the total number of urine samples collected from 148 MAACS participants ($n = 660$ samples)

Biomarker	Specific gravity–corrected concentrations, ng/mL					Measure of biomarker variability
	LOD	% >LOD	GM (GSD)*	Median (25th percentile, 75th percentile)	Max	ICC _{n≥2} (95% CI)†
BPA	0.2	100.0	3.6 (2.2)	3.4 (2.2, 5.6)	127.5	0.10 (0.05–0.20)
BPS	0.1	96.8	0.4 (3.2)	0.3 (0.2, 0.7)	135.0	0.14 (0.08–0.23)
BPF	0.2	65.9	0.8 (6.2)	0.3 (<LOD, 1.2)	629.9	—

GSD, Geometric SD; %LOD, percentage of samples with concentrations above the LOD for each specified analyte; Max, maximum.

*The GM values reported are based on detectable concentrations, including instrumental reading values, for each biomarker.

†ICC_{n≥2} (95% CI) indicates ICC values and respective 95% CIs based on data from children who provided 2 or more samples during the 12-month follow-up period.

which subset of the NHANES children was used in our comparisons (Fig 1). BPA and BPF GM concentrations were 1.2 to 2.8 times higher in the MAACS participants than in the NHANES children. The MAACS and NHANES children had similar median BPS concentrations.

Adjusted associations between concentrations of bisphenols and asthma-related outcomes are presented in Tables IV and V (and see Table E4 in this article's Online Repository at www.jacionline.org for crude associations). We observed consistent positive relationships between BPA and days of asthma symptoms in the prior 2 weeks, and between BPA and health care utilization in the prior 3 months in multivariable generalized estimating equation models. For every 10-fold increase in BPA concentrations, we observed 40% and 36% increased odds of having days with general symptoms and maximal symptoms, respectively (adjusted odds ratio [aOR] = 1.40 [95% CI = 1.02–1.92] and aOR = 1.36 [95% CI = 1.00–1.83], respectively). We also observed positive, albeit non–statistically significant, associations with other symptoms. For health care utilization, we observed 84% and 112% increased odds of reporting an acute care or an ED visit, respectively, per 10-fold increase in BPA concentration (aOR = 1.84 [95% CI = 1.11–3.03] and aOR = 2.12 [95% CI = 1.28–3.51], respectively). We also observed inverse, albeit non–statistically significant, associations between BPA and lung function parameters (Tables IV and V). Inclusion of other covariates in sensitivity analyses, including degree of atopy and exposure to particulate matter with an aerodynamic diameter less than 2.5 μ m, did not materially affect the results (see Tables E5–E7 in this article's Online Repository at www.jacionline.org).

We observed evidence suggestive of sexually dimorphic effects of BPA concentrations ($P_{\text{int}} < .10$) for days of asthma symptoms in the prior 2 weeks (Fig 2). BPA concentrations were associated with increased odds of general symptoms and maximal symptom days among boys only ($P < .05$). We observed this trend for other symptoms and health care utilization outcomes, although the effect modification P values were not significant. We did not observe sexually dimorphic effects with lung function or inflammation measures.

For BPS, we observed no consistent associations with asthma-related outcomes (Tables IV and V). The effect estimates for health care utilization outcomes were not statistically significant and not in the same direction, whereas we observed a pattern of inverse associations with symptoms. Inclusion of other covariates did not appreciably affect the inferences for BPS, and there was no evidence of sexually dimorphic effects for BPS (not shown). We observed an inverse association between BPF detection and FEV₁/FVC% ($\beta = -0.87$ [95% CI = -1.71 to -0.03]); however, we observed no other associations with BPF. Inclusion of other

covariates led to similar findings, and there was no evidence of sexually dimorphic effects. Lastly, we observed no associations between the concentrations of any bisphenols and FENO.

DISCUSSION

In this study, we assessed associations between urinary concentrations of BPA and select analogs (BPS and BPF) and (1) asthma morbidity and (2) lung function and inflammation in a cohort of predominantly low-income, urban, African American children with established asthma. Overall, we observed consistent positive associations between BPA concentrations and asthma morbidity measures, including with general and maximal symptom days, and with acute care and ED visits for asthma. We found evidence of sexually dimorphic effects, with only boys exhibiting higher odds of asthma morbidity with BPA. By contrast, we found no consistent relationships between BPS or BPF and asthma morbidity measures, and neither BPA nor its analogs were associated with lung inflammation as measured by FENO.

The BPA concentrations in our cohort were substantially higher than those observed in Mexican, Chinese, or US children from the general population,^{62,63} and they were similar to those measured in minority children in New York City.^{24,64} For example, the specific gravity–corrected GM concentration for BPA among a sample of 60 Chinese children was 0.40 ng/mL compared with 3.6 ng/mL in the MAACS children, whereas the median uncorrected BPA concentration among 159 minority children in New York City was 3.4 ng/mL compared with 3.3 ng/mL in the MAACS children. The BPS and BPF concentrations were also higher in our cohort than in 283 children from South China (eg, uncorrected median BPS concentrations of 0.30 vs 0.03, respectively, and uncorrected median BPF concentrations of 0.30 vs 0.19, respectively).⁶³ The differences in concentrations of bisphenols among populations could reflect different dietary consumption patterns (eg, differences in the amount or frequency of consumption of canned goods or beverages in polycarbonate bottles, heating foods in plastic containers with BPA) and consumer product use; with the exception of 1 study,⁶³ prior studies collected urine samples around the same time period as the present study.

Similar to in low-income New York City children,⁶⁵ the baseline BPA concentrations were highest during the summer months. Seasonal differences could relate to dietary patterns, such as greater consumption of beverages in canned or plastic containers in the summer. BPA can migrate from reusable polycarbonate water bottles into water,⁶⁶ and use of polycarbonate water bottles has been positively associated with urinary BPA concentrations,⁶⁷ particularly during the summer months.⁶⁸ Children of normal weight had higher GM BPA concentrations at baseline than

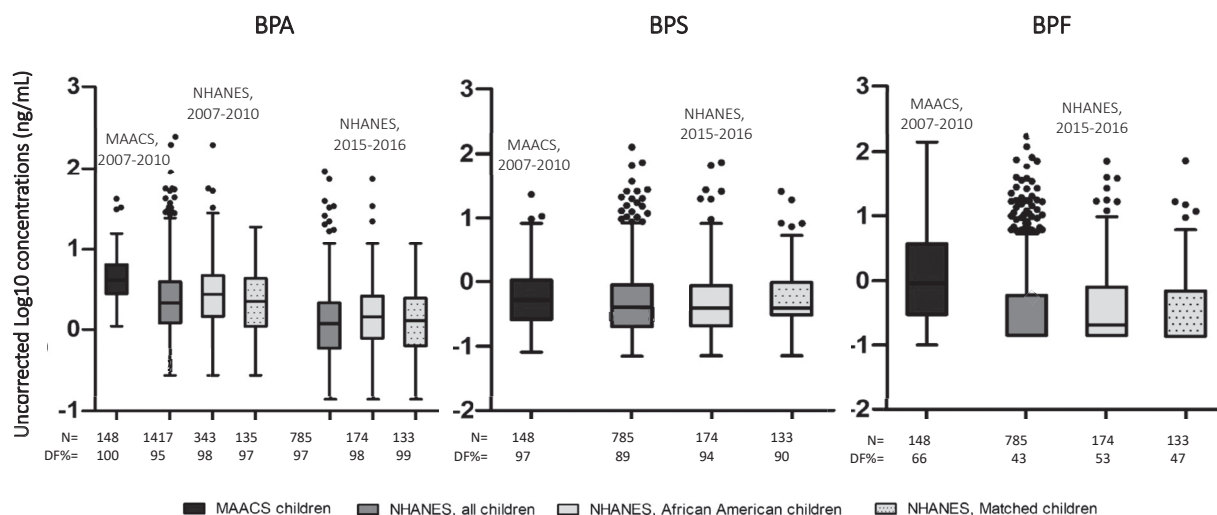


FIG 1. Distribution of uncorrected urinary concentrations (ng/mL) of BPA, BPS, and BPF among 148 MAACS participants aged 5 to 17 years and children aged 6 to 17 years from the US general population (NHANES 2007-2010, 2015-2016) using data from 3 subsets of children from the NHANES (1. all children ages 6-17 years, regardless of race; 2. African American children ages 6-17 years; and 3. subset of NHANES children matched with the MAACS participants based on age, race, sex, and income). Biomarker concentrations for each MAACS participant were first averaged before generating the distributions presented. Biomarker concentrations for MAACS participants that were less than the LOD were imputed to LOD/2 to allow for proper comparisons with the NHANES data utilizing the same imputation method. *DF*, Detection frequency.

TABLE IV. Adjusted associations between repeated urinary concentrations of BPA, BPS, and BPF and asthma morbidity measures among children aged 5 to 17 years who were participating in the MAACS

Asthma symptoms (n = 148 children)	Bisphenol A		Bisphenol S		Bisphenol F	
	aOR (95% CI)	P value	aOR (95% CI)	P value	aOR (95% CI)	P value
Coughing, wheezing, or chest tightness	1.40 (1.02-1.92)	.037	0.75 (0.57-1.00)	.046	1.14 (0.89-1.47)	.292
Nocturnal waking with symptoms	1.46 (0.93-2.29)	.096	0.69 (0.50-0.95)	.023	0.99 (0.74-1.32)	.929
Exercise-related symptoms	1.46 (0.96-2.20)	.075	0.63 (0.45-0.88)	.006	1.03 (0.77-1.38)	.823
Cough without a cold	1.19 (0.69-2.08)	.530	0.72 (0.51-1.03)	.069	0.82 (0.57-1.20)	.310
Slowed activity due to asthma	1.23 (0.82-1.83)	.320	0.74 (0.52-1.03)	.076	1.04 (0.79-1.39)	.762
Maximal symptom days	1.36 (1.00-1.83)	.048	0.78 (0.59-1.03)	.076	1.09 (0.85-1.38)	.508
Short-acting β -agonist use	1.30 (0.94-1.78)	.108	0.98 (0.76-1.27)	.880	0.97 (0.76-1.25)	.818
Health care utilization (n = 148 children)						
Acute care visit	1.84 (1.11-3.03)	.018	0.84 (0.60-1.18)	.313	1.06 (0.76-1.47)	.752
Unscheduled doctor's visit	1.23 (0.70-2.15)	.476	1.10 (0.69-1.75)	.680	1.01 (0.65-1.56)	.962
ED visit for asthma	2.12 (1.28-3.51)	.004	0.86 (0.58-1.27)	.451	0.94 (0.65-1.36)	.754
Hospitalization for asthma	2.24 (0.65-7.71)	.201	1.28 (0.61-2.71)	.514	1.80 (0.64-5.08)	.266

Information on nocturnal awakening with asthma symptoms was missing for 2 children; information on lung function parameters of 4 children was missing. Models were adjusted for age, sex, race, caregiver's education level, season, presence of smokers in the home as a proxy for environmental tobacco smoke exposure, and coexposure to other bisphenols (ie, all bisphenols were included in the same model for each outcome). For dichotomous outcomes (asthma symptoms, health care utilization), we conducted binomial regression models using generalized estimating equations and log link to obtain PRs. The analyses presented in this table represent data on up to 148 children with up to 660 urine samples collected over a 12-month period. BPA and BPS were modeled as continuous variables (log₁₀-transformed specific gravity-corrected concentrations) and BPF was modeled as a categorical variable (detected vs not detected) based on detection frequencies. Bolded effect estimates indicate statistical significance ($P < .05$).

overweight children did, contrary to findings in prior pediatric studies.^{58,69} GM BPA concentrations were also lower among participants with caregivers who were not high school graduates, a trend not reported in previous studies. Lastly, similar to the BPA concentrations in children in Ohio aged 1 to 8 years⁷⁰ and minority children in New York City aged 6 to 10 years,⁶⁴ the BPA concentrations in our study tended to vary greatly within individuals ($ICC < 0.20$). To our knowledge, no studies have assessed temporal variability of BPA analogs among children, although 1 study reported great intraindividual variability for BPA and BPF concentrations among adult men.¹⁴

Although prior studies have evaluated associations between prenatal and postnatal BPA exposures and asthma development and prevalence,^{24,71-73} no studies have assessed the role of bisphenols in asthma morbidity among children with established asthma. Yet, 1 study conducted among low-income children in New York City with comparable GM BPA urinary concentrations reported positive associations with incident asthma at age 5 to 12 years.²⁴ Postnatal BPA concentrations were also associated with increased risk of wheeze at age 7 years.²⁴ Two other pediatric studies also reported positive associations and effect sizes comparable to those observed in our study between exposure to BPA and

TABLE V. Adjusted associations between repeated urinary concentrations of BPA, BPS, and BPF and lung function measures among children aged 5 to 17 years who were participating in the MAACS

Lung function (n = 144 children)	Bisphenol A		Bisphenol S		Bisphenol F	
	β -coefficient (95% CI)	P value	β -coefficient (95% CI)	P value	β -coefficient (95% CI)	P value
FEV ₁ % predicted	-0.90 (-3.52 to 1.73)	.503	0.79 (-0.62 to 2.20)	.273	-0.24 (-1.98 to 1.50)	.785
FVC % predicted	-0.60 (-2.67 to 1.47)	.572	0.25 (-0.92 to 1.42)	.678	0.71 (-0.80 to 2.23)	.357
FEV ₁ /FVC%	-0.09 (-1.55 to 1.38)	.907	0.50 (-0.32 to 1.31)	.233	-0.87 (-1.71 to -0.03)	.042

For lung function (continuous outcomes), we ran linear regression models with generalized estimating equations to obtain β -coefficients. The analyses presented in this table represent data on up to 148 children with up to 660 urine samples collected over a 12-month period. BPA and BPS were modeled as continuous variables ($\log_{10}$ -transformed specific gravity-corrected concentrations), and BPF was modeled as a categorical variable (detected vs not detected) based on detection frequencies. Bolded effect estimates indicate statistical significance ($P < .05$).

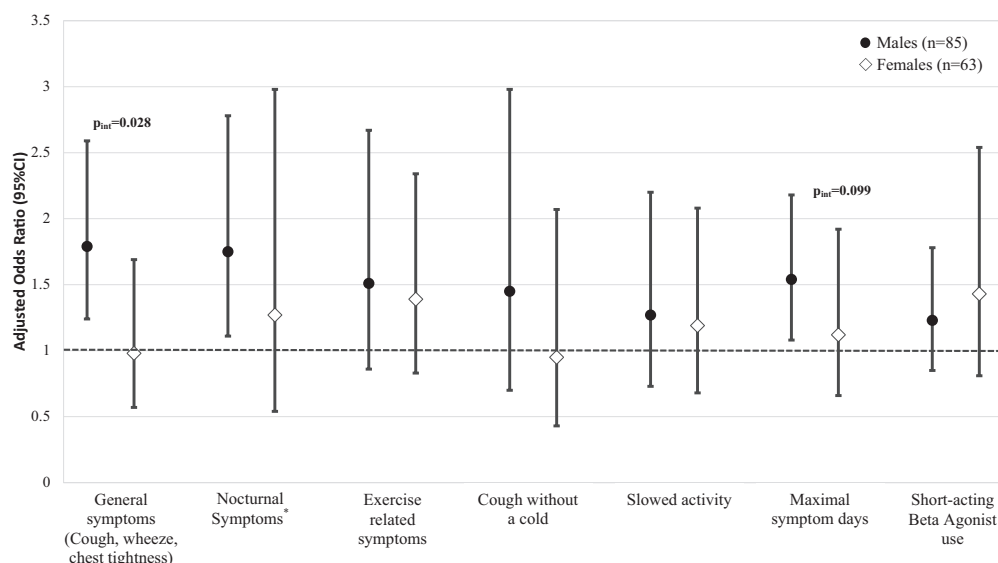


FIG 2. Adjusted associations between BPA and asthma-related symptoms by sex among the MAACS children. Models are based on generalized estimating equations using the binomial log link function to account for repeated measures of exposure and outcomes and were adjusted for age, race, caregiver's education level, season, presence of smokers in the home, $\log_{10}$ -transformed concentrations of BPS, and dichotomized (detected vs nondetected) exposure to BPF. *Information on nocturnal symptoms was missing for 1 male and 1 female. p_{int} P value for effect measure modification by sex.

incident asthma and wheeze,^{25,26} although 1 other study reported null associations between BPA and wheeze.⁷¹

Although the exact mechanisms by which BPA could elicit respiratory effects remain unknown, several have been proposed, including oxidative stress and upregulation of T_H2 pathways via promotion of eosinophilic airway inflammation.^{9,15} A recent pediatric case-control study also reported that genetic polymorphisms of oxidative stress-related genes may modulate the effect of BPA on asthma.⁷⁴ In adults, BPA has been associated with oxidative stress and inflammation markers in postmenopausal women, suggesting that BPA could bind to estrogen receptors more actively when estrogen levels are low, triggering cellular responses associated with oxidative stress and inflammation. In 1 experimental study, ovalbumin plus low-dose BPA exposure during the juvenile period of development in male mice altered serum levels of anti-inflammatory corticosterone and estrogen receptor 2 messenger RNA expression in the lungs and enhanced inflammatory cell infiltration and protein expression of T_H2 cytokines and chemokines, among other immune-activated responses, suggesting that BPA could

exacerbate allergic airway inflammation by enhancing T_H2 responses through immune system disruption. Unfortunately, no biomarkers of oxidative stress (eg, malondialdehyde and 8-hydroxydeoxyguanosine) were measured in our cohort, preventing us from examining associations between BPA and oxidative stress. We also did not observe associations with FENO, a noninvasive marker of eosinophilic airway inflammation. It is plausible that no associations were observed with FENO because most children had eosinophilic airway inflammation at baseline. Further studies are warranted to confirm our findings and identify the underlying pathways by which BPA exposure could increase asthma morbidity risk.

We observed a consistent pattern of increased odds of morbidity among boys, but not among girls, for several outcomes. Previous studies have reported similar patterns of increased risk of allergic disease and morbidity among boys in association with EDC exposure during prepubescence (at age 8-14 years).⁷⁵⁻⁷⁸ One potential explanation for these observed sex differences is that BPA exposure could enhance the allergic immune response, increasing susceptibility to adverse respiratory effects among

males. It is plausible that BPA, being a xenoestrogen, exerts different endocrine-disrupting effects in boys than in girls owing to their different hormonal milieu; current evidence suggests that sex hormones and EDCs may play a role in the development and/or function of the lungs and the immune system.⁷⁹⁻⁸³ In males with severe asthma, greater androgen levels have been associated with better lung function,⁸⁴ and it is possible that BPA exposure leads to an imbalance in circulating hormones; however, further investigations are needed to confirm findings and elucidate biologic mechanisms by which sex differences could occur.

The limitations of our study include lack of data on pubertal stage, preventing us from assessing the effects of pubertal development on our exposure-outcome relationships. Pubertal development influences asthma symptom progression differentially among males and females,⁸⁵ and it may also influence how BPA affects asthma morbidity during adolescence. Future studies should evaluate the effects of BPA exposure during different developmental stages to identify potential windows of susceptibility because disruption in the production and metabolism of sex hormones may dictate differences in susceptibility by sex and life stage. It is also plausible that the effects of BPA on asthma morbidity depend on the degree of atopy, making atopy a confounder, mediator, or effect modifier. However, we were unable to assess mediation or effect modification because 91% of participants were atopic. We also cannot rule out the possibility of unmeasured confounding and spurious findings. Additionally, our study was conducted on a predominantly low-income, urban minority pediatric cohort, limiting generalizability to other populations. Although outcomes such as health care utilization preceded exposures, collection of other outcomes obtained closer in time or concurrently with our exposures helped overcome this limitation. Although diet is the main BPA exposure route, we cannot rule out the possibility that other chemicals present in foods (eg, phthalates) may be responsible for the associations observed. Because our analyses were conducted after all data collection using biobanked biospecimens had concluded, we were also not able to prospectively collect information on potential sources of exposure to bisphenols in our study population. However, our study population is predominantly low-income and African American, and exposure in this population is thought to arise predominantly from diet.^{4,6,7} Future studies should evaluate whether dietary exposures to mixtures of immunotoxic chemicals affect asthma morbidity. Identifying specific modifiable exposure sources of BPA in low-income, urban settings will also be important.

Despite its acknowledged limitations, this study has several strengths. This is the first study to examine BPA, BPS, and BPF exposure in relation to measures of asthma morbidity in a pediatric population characterized by a high asthma burden and high exposures to select bisphenols. The prospective study design and evaluation of repeated exposure and several outcome measures are major strengths that allowed for improved exposure and outcome characterization. Prospective data collection in a diseased cohort also minimized the potential for recall bias. This is also the first study to characterize temporal variability for BPS concentrations in children. We also controlled for important confounders (eg, race, income, exposure to air pollution, BMI, degree of allergic sensitization) and bisphenol coexposures, allowing us to assess the independent effects of each bisphenol on the outcomes. Notably, although BPA is being phased out of some consumer products, recent

national biomonitoring data still demonstrate widespread exposure in the United States,⁵ underscoring the continued relevance of our findings. Furthermore, our study contributes some of the first data on BPA alternatives (BPS and BPF) in relation to human health.

In summary, we found evidence to suggest that BPA exposure among a predominantly low-income, minority cohort of children with asthma may increase asthma morbidity, at least for boys. We found no consistent associations between BPS or BPF and asthma morbidity. Our findings warrant replication given widespread BPA exposure in the US population and the potential clinical implications for asthma control guidelines. If the present findings are confirmed in future studies, then avoiding or limiting contact with BPA sources (eg, consumption of canned goods, storing or heating food in plastic containers containing BPA) may be advisable among children with asthma.

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Clinical implications: BPA exposure among predominantly low-income, African American children with asthma may be associated with asthma morbidity. The findings warrant replication, given the high asthma burden and disparate BPA exposures reported among African Americans.

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TABLE E1. Summary statistics and variability measures for uncorrected BPA, BPS, and BPF concentrations in ng/mL based on the total number of urine samples collected on 148 MAACS participants (n = 660 samples)

Biomarker	Uncorrected concentrations, ng/mL					Measure of biomarker variability*
	LOD	% >LOD	GM (GSD)†	Median (25th percentile, 75th percentile)	Max	ICC _{n≥2} (95% CI)
BPA	0.2	100.0	3.3 (2.5)	3.3 (1.9, 5.7)	166.3	0.15 (0.09-0.24)
BPS	0.1	96.8	0.4 (3.3)	0.3 (0.2, 0.6)	114.2	0.13 (0.08-0.23)
BPF	0.2	65.9	0.8(6.3)	0.3 (<LOD, 1.2)	561.7	—

GSD, Geometric SD; % >LOD, percentage of samples with concentrations above the LOD for each specified analyte; Max, maximum.

*Values under the column head ICC_{n≥2} (95% CI) are ICC values and respective 95% CIs based on data from children who provided 2 or more samples during the 12-month follow-up period.

†GM values reported are based on detectable concentrations, including instrumental reading values, for each metabolite.

TABLE E2. Demographic characteristics for the MAACS children by age with data on BPA, BPS, and BPF at baseline (n = 146)

Demographic characteristic	n	(%)	(Specific gravity–corrected concentrations)					
			BPA		BPS		BPF	
			GM (ng/mL)	P value	GM (ng/mL)	P value	DF%	P value
Age*								
5-7 y	40	(27.4)	3.6	.74	0.32	.13	72.5	.11
8-10 y	34	(23.3)	4.0		0.34		52.9	
11-13 y	26	(17.8)	3.5		0.23		69.2	
14-17 y	46	(31.5)	3.4		0.44		78.3	
Sex								
Male	85	(58.2)	3.6	.94	0.30	.13	70.6	.66
Female	61	(41.8)	3.6		0.41		67.2	
Child's race								
Black/African American	133	(91.1)	3.6	.87	0.33	.35	68.4	.39
Other	13	(8.9)	3.8		0.47		76.9	
Child BMI								
Normal weight (5th to <85th percentile)	77	(55.8)	4.2	.04	0.37	.16	68.8	.67
Overweight or obese (>85th percentile)	61	(44.2)	3.1		0.31		72.1	
Caregiver's education level								
Less than high school	42	(28.8)	2.9	.03	0.33	.76	78.6	.23
High school graduate	50	(34.3)	3.8		0.33		62.0	
Some college or more	54	(37.0)	4.3		0.35		68.5	
Annual household income								
<\$35,000	90	(68.2)	3.5	.65	0.29	.06	71.1	.61
>\$35,000	42	(31.8)	3.5		0.46		66.7	
Insurance								
Private/self-pay	20	(13.9)	3.0	.32	0.26	.22	65.0	.70
Government-based (public)	124	(86.1)	3.7		0.35		69.4	
Smoker lives in child's home								
No	64	(43.8)	3.3	.36	0.27	.03	71.9	.53
Yes	82	(56.2)	3.9		0.41		67.1	
Season during which urine sample was collected								
Spring	27	(18.5)	2.8	.01	0.24	.10	85.2	.15
Summer	27	(18.5)	5.0		0.43		59.3	
Fall	60	(41.1)	3.8		0.38		65.0	
Winter	32	(21.9)	3.0		0.31		71.9	

DF%, Detection frequency percent.

Information reported is for 146 MAACS children with BPA, BPS, and BPF biomarker data at baseline (2 of 148 children had missing data on bisphenols at baseline but did have data at other collection time points). Information was missing for select demographic characteristics at baseline (BMI, n = 2; annual household income, n = 14; and health insurance, n = 2). P values provided are for Wilcoxon-Mann-Whitney, Kruskal-Wallis, and chi-square tests (if cell sizes were small, then Fischer exact tests were conducted instead of chi-square tests) to test for differences among demographic characteristics. Bolded P values indicate statistical significance ($P < .05$).

*Spearman correlations were also conducted with age as a continuous variable, and inference of results did not differ from the results using multiple age categories.

TABLE E3. Specific gravity–corrected concentrations for BPA and BPS (ng/mL) by visit and health care utilization outcomes

Bisphenol type	Baseline visit			3-mo visit			6-mo visit			9-mo visit			12-mo visit		
	GM			GM			GM			GM			GM		
Bisphenol A	n	(median)	P value	n	(median)	P value	n	(median)	P value	n	(median)	P value	n	(median)	P value
Health care utilization outcome															
Acute care visit															
Yes	92	3.98 (3.51)	.042	37	4.27 (3.48)	.409	47	3.86 (4.16)	.338	35	4.57 (3.78)	.103	31	3.44 (3.57)	.973
No	54	3.03 (3.04)		98	3.63 (3.25)		81	3.55 (3.38)		87	3.38 (3.25)		87	3.40 (3.58)	
ED visit															
Yes	67	4.30 (3.69)	.016	22	4.19 (3.52)	.602	28	3.91 (4.45)	.423	25	5.11 (4.46)	.060	17	2.87 (3.84)	.190
No	79	3.10 (3.07)		113	3.73 (3.26)		100	3.59 (3.55)		97	3.39 (3.37)		99	3.52 (2.67)	
Unscheduled doctor's visit															
Yes	35	3.72 (3.13)	.385	17	4.11 (3.43)	.666	23	4.24 (4.16)	.276	20	4.70 (3.66)	.496	18	3.69 (3.97)	.640
No	111	3.27 (3.45)		118	3.76 (3.31)		105	3.54 (3.38)		102	3.52 (3.42)		100	3.37 (3.42)	
Hospitalization for asthma															
Yes	14	5.22 (6.35)	.093	3	4.64 (3.07)	.571	3	3.69 (1.79)	.325	0	NA	NA	1	NA	NA
No	132	3.47 (3.22)		132	3.78 (3.40)		125	2.47 (3.67)		122	3.68 (3.43)		117	3.39 (3.57)	
Bisphenol S															
Health care utilization outcome															
Acute care visit															
Yes	92	0.35 (0.27)	0.949	37	0.35 (0.26)	0.912	47	0.40 (0.33)	0.928	35	0.47 (0.37)	0.835	30	0.32 (0.27)	.126
No	54	0.32 (0.26)		96	0.32 (0.26)		77	0.41 (0.30)		87	0.56 (0.39)		87	0.44 (0.34)	
ED visit															
Yes	67	0.37 (0.26)	0.738	22	0.37 (0.28)	0.482	28	0.31 (0.26)	0.208	25	0.48 (0.38)	0.761	101	0.44 (0.34)	.045
No	79	0.31 (0.27)		113	0.33 (0.26)		100	0.44 (0.35)		97	0.55 (0.38)		17	0.27 (0.21)	
Unscheduled doctor's visit															
Yes	35	0.38 (0.27)	0.812	17	0.35 (0.28)	0.829	23	0.48 (0.33)	0.648	20	0.54 (0.47)	0.738	18	0.31 (0.27)	.243
No	111	0.32 (0.26)		116	0.34 (0.26)		105	0.39 (0.30)		102	0.53 (0.37)		100	0.43 (0.27)	
Hospitalization for asthma															
Yes	14	0.55 (0.48)	.004	3	0.31 (0.26)	.934	3	0.47 (0.57)	.526	0	NA	NA	1	NA	NA
No	132	0.32 (0.26)		132	0.34 (0.26)		125	0.40 (0.30)		122	0.53 (0.38)		117	0.40 (0.31)	

P values reported are from Wilcoxon rank sum tests; P values less than .05 are bolded, and summary statistics are reported when n is equal to or greater than 3.

TABLE E4. Crude associations between repeated urinary concentrations of BPA, BPS, and BPF and asthma morbidity measures among children aged 5 to 17 years who were participating in the MAACS

Asthma symptoms (n = 148)	Bisphenol A		Bisphenol S		Bisphenol F	
	cOR (95% CI)	P value	cOR (95% CI)	P value	cOR (95% CI)	P value
Coughing, wheezing, or chest tightness	1.30 (0.94-1.79)	.108	0.76 (0.58-0.98)	.034	1.14 (0.89-1.45)	.305
Nocturnal waking with symptoms	1.24 (0.80-1.94)	.337	0.64 (0.47-0.87)	.004	1.05 (0.79-1.38)	.750
Exercise-related symptoms	1.32 (0.89-1.94)	.162	0.68 (0.52-0.89)	.005	1.01 (0.76-1.34)	.937
Cough without a cold	1.13 (0.70-1.83)	.610	0.73 (0.52-1.02)	.066	0.82 (0.57-1.19)	.297
Slowed activity due to asthma	1.21 (0.87-1.69)	.261	0.78 (0.58-1.05)	.106	0.99 (0.77-1.29)	.961
Maximal symptom days	1.29 (0.98-1.69)	.064	0.78 (0.61-1.01)	.063	1.07 (0.85-1.34)	.565
Short-acting β -agonist use	1.25 (0.94-1.65)	.119	0.98 (0.77-1.24)	.859	0.97 (0.77-1.23)	.808
Health care utilization (n = 148)						
Acute care visit	1.60 (1.02-2.51)	.043	0.84 (0.61-1.14)	.251	1.03 (0.74-1.42)	.873
Unscheduled doctor's visit	1.21 (0.68-2.16)	.518	1.05 (0.66-1.67)	.831	0.97 (0.64-1.48)	.901
ED visit for asthma	1.85 (1.17-2.93)	.009	0.87 (0.62-1.24)	.447	0.91 (0.63-1.31)	.618
Hospitalization for asthma	2.31 (0.88-6.04)	.089	1.35 (0.82-2.22)	.236	2.16 (0.82-5.66)	.117
Lung function (n = 144)						
	β_{crude} (95% CI)	P value	β_{crude} (95% CI)	P value	β_{crude} (95% CI)	P value
FEV ₁ (% predicted)	-0.40 (-2.83 to 2.03)	.748	0.88 (-0.43 to 2.18)	.187	-0.31 (-2.05 to 1.43)	.728
FVC (% predicted)	0.02 (-1.85 to 1.89)	.982	0.40 (-0.65 to 1.46)	.455	0.69 (-0.82 to 2.21)	.368
FEV ₁ /FVC%	-0.15 (-1.61 to 1.32)	.845	0.47 (-0.34 to 1.28)	.251	-0.92 (-1.75 to -0.08)	.032

β_{crude} , Crude β -coefficient; cOR, crude odds ratio; FVC, forced vital capacity.

Information on nocturnal awakening with asthma symptoms was missing for 2 children, and information on lung function parameters was missing for 4 children. Information on main models is presented for the subset of participants with complete data. Models were adjusted for age, sex, race, caregiver education, season, presence of smokers in the home as a proxy for environmental tobacco smoke exposure, BMI percentile, and coexposure to other bisphenols (ie, all bisphenols were included in the same model for each outcome). For dichotomous outcomes (asthma symptoms and health care utilization), we conducted binomial regression models using generalized estimating equations and log link to obtain PRs, and for continuous outcomes (lung function), we ran linear regression models with generalized estimating equations to obtain β -coefficients to account for repeated measures of exposure and outcomes. BPA and BPS were modeled as continuous variables ($\log_{10}$ -transformed specific gravity-corrected concentrations), and BPF was modeled as a categorical variable (detected vs not detected) based on detection frequencies. Bolded *P* values indicate statistical significance (*P* < .05).

TABLE E5. Adjusted associations additionally including BMI percentile as a covariate in the GEE models

		BPA (additionally including child BMI as a covariate)				BPS (additionally including child BMI as a covariate)				BPF (additionally including child BMI as a covariate)			
		BPA, main model		BPA, main model		BPS, main model		BPS, main model		BPF, main model		BPF, main model	
Asthma symptoms	n	aPR (95% CI)	P value	aPR (95% CI)	P value	aPR (95% CI)	P value	aPR (95% CI)	P value	aPR (95% CI)	P value	aPR (95% CI)	P value
Coughing, wheezing, or chest tightness	148	1.40 (1.02-1.92)	.037	1.44 (1.05-1.96)	.022	0.75 (0.57-1.00)	.046	0.75 (0.57-1.00)	.048	1.14 (0.89-1.47)	.292	1.11 (0.86-1.44)	.426
Nocturnal waking with symptoms	146	1.46 (0.93-2.29)	.096	1.58 (1.02-2.44)	.042	0.69 (0.50-0.95)	.023	0.69 (0.50-0.97)	.030	0.99 (0.74-1.32)	.929	0.91 (0.68-1.22)	.539
Exercise-related symptoms	148	1.46 (0.96-2.20)	.075	1.56 (1.01-2.40)	.043	0.63 (0.45-0.88)	.006	0.62 (0.44-0.87)	.006	1.03 (0.77-1.38)	.823	1.00 (0.74-1.34)	.992
Cough without a cold	148	1.19 (0.69-2.08)	.530	1.22 (0.70-2.12)	.476	0.72 (0.51-1.03)	.069	0.71 (0.50-1.01)	.059	0.82 (0.57-1.20)	.310	0.81 (0.55-1.19)	.280
Slowed activity due to asthma	148	1.23 (0.82-1.83)	.320	1.24 (0.82-1.87)	.299	0.74 (0.52-1.03)	.076	0.73 (0.52-1.03)	.077	1.04 (0.79-1.39)	.762	1.04 (0.77-1.39)	.814
Maximal symptom days	148	1.36 (1.00-1.83)	.048	1.39 (1.02-1.89)	.035	0.78 (0.59-1.03)	.076	0.78 (0.59-1.04)	.096	1.09 (0.85-1.38)	.508	1.05 (0.81-1.36)	.703
Short-acting β -agonist use	148	1.30 (0.94-1.78)	.108	1.31 (0.95-1.81)	.095	0.98 (0.76-1.27)	.880	0.97 (0.75-1.26)	.826	0.97 (0.76-1.25)	.818	0.97 (0.76-1.25)	.839
Health care utilization													
Acute care visit	148	1.84 (1.11-3.03)	.018	1.84 (1.11-3.04)	.018	0.84 (0.60-1.18)	.313	0.84 (0.60-1.19)	.332	1.03 (0.73-1.43)	.881	1.00 (0.71-1.40)	.977
Unscheduled doctor's visit	148	1.23 (0.70-2.15)	.476	1.29 (0.72-2.31)	.386	1.10 (0.69-1.75)	.680	1.12 (0.71-1.79)	.622	0.99 (0.64-1.52)	.954	0.93 (0.60-1.45)	.746
ED visit for asthma	148	2.12 (1.28-3.51)	.004	2.10 (1.26-3.51)	.004	0.86 (0.58, 1.27)	.451	0.86 (0.58-1.27)	.441	0.92 (0.64-1.34)	.670	0.91 (0.63-1.33)	.635
Hospitalization for asthma	148	2.24 (0.65-7.71)	.201	2.17 (0.62-7.58)	.222	1.28 (0.61-2.71)	.514	1.30 (0.63-2.68)	.484	1.80 (0.64-5.08)	.266	1.92 (0.68-5.45)	.219
Lung function and lung inflammation													
	n	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
FEV ₁ (% predicted)	140	-0.23 (-2.94 to 2.47)	.865	-0.26 (-2.98 to 2.45)	.849	0.79 (-0.62 to 2.20)	.273	0.83 (-0.58 to 2.23)	.248	-0.24 (-1.98 to 1.50)	.785	-0.31 (-2.07 to 1.45)	.732
FVC (% predicted)	140	0.13 (-1.84 to 2.10)	.894	0.13 (-1.86 to 2.11)	.900	0.25 (-0.92 to 1.42)	.678	0.29 (-0.88 to 1.45)	.631	0.71 (-0.80 to 2.23)	.357	0.66 (-0.87 to 2.19)	.395
FEV ₁ /FVC%	140	-0.15 (-1.77 to 1.47)	.855	-0.17 (-1.79 to 1.45)	.839	0.50 (-0.32 to 1.31)	.233	0.50 (-0.32 to 1.31)	.230	-0.87 (-1.71 to -0.03)	.042	-0.87 (-1.72 to -0.03)	.043
FENO	140	0.04 (-0.02 to 0.11)	.182	0.04 (-0.02 to 0.11)	.196	-0.01 (-0.05 to 0.03)	.791	-0.01 (-0.05 to 0.03)	.793	-0.01 (-0.06 to 0.03)	.543	-0.01 (-0.05 to 0.03)	.642

aPR, Adjusted prevalence ratio; FVC, forced vital capacity; GEE, generalized estimating equation.

Information on nocturnal awakening with asthma symptoms was missing for 2 children, and information on lung function parameters was missing for 4 children. Information on main models is presented for the subset of participants with complete data. Models were adjusted for age, sex, race, caregiver education, season, presence of smokers in the home as a proxy for environmental tobacco smoke exposure, body mass index percentile, and coexposure to other bisphenols (ie, all bisphenols were included in the same model for each outcome). For dichotomous outcomes (asthma symptoms and health care utilization), we conducted binomial regression models using GEEs and log link to obtain PRs, and for continuous outcomes (lung function), we ran linear regression models with GEEs to obtain β -coefficients to account for repeated measures of exposure and outcomes. BPA and BPS were modeled as continuous variables ($\log_{10}$ -transformed specific gravity-corrected concentrations), and BPF was modeled as a categorical variable (detected vs not detected) based on detection frequencies. Bolded *P* values indicate statistical significance (*P* < .05).

TABLE E6. Adjusted associations additionally including total number of positive skin prick test responses as a measure of degree of allergic sensitization in the GEE models

	n	BPA, main model		BPA (additionally including child BMI as a covariate)		BPS, main model		BPS (additionally including child BMI as a covariate)		BPF, main model		BPF (additionally including child BMI as a covariate)	
		aPR (95% CI)	P value	aPR (95% CI)	P value	aPR (95% CI)	P value	aPR (95% CI)	P value	aPR (95% CI)	P value	aPR (95% CI)	P value
Asthma symptoms													
Coughing, wheezing, or chest tightness	147	1.39 (1.01-1.90)	.043	1.39 (1.01-1.91)	.043	0.75 (0.57-0.99)	.044	0.75 (0.57-0.99)	.044	1.15 (0.90-1.48)	.267	1.15 (0.90-1.48)	.268
Nocturnal awakening with symptoms	145	1.45 (0.93-2.28)	.104	1.45 (0.92-2.28)	.111	0.69 (0.50-0.95)	.022	0.69 (0.50-0.95)	.022	0.99 (0.74-1.33)	.956	1.00 (0.74-1.35)	.996
Exercise-related symptoms	147	1.44 (0.95-2.18)	.082	1.42 (0.95-2.14)	.090	0.63 (0.45-0.87)	.005	0.63 (0.45-0.87)	.005	1.04 (0.78-1.39)	.780	1.06 (0.79-1.41)	.708
Cough without a cold	147	1.18 (0.68-2.06)	.558	1.18 (0.68-2.05)	.564	0.72 (0.50-1.02)	.066	0.72 (0.50-1.02)	.065	0.83 (0.57-1.21)	.335	0.83 (0.57-1.21)	.343
Slowed activity due to asthma	147	1.21 (0.81-1.81)	.345	1.20 (0.81-1.78)	.357	0.73 (0.52-1.03)	.070	0.73 (0.52-1.02)	.066	1.05 (0.79-1.40)	.717	1.06 (0.80-1.42)	.671
Maximal symptom days	147	1.34 (0.99-1.82)	.056	1.34 (0.99-1.81)	.057	0.77 (0.58-1.02)	.071	0.77 (0.58-1.02)	.070	1.09 (0.86-1.39)	.471	1.10 (0.86-1.40)	.460
Short-acting β -agonist use	147	1.29 (0.94-1.77)	.117	1.30 (0.94-1.78)	.109	0.98 (0.75-1.27)	.863	0.98 (0.75-1.27)	.864	0.98 (0.76-1.25)	.851	0.97 (0.76-1.25)	.832
Health care utilization													
Acute care visit	147	1.81 (1.10-2.99)	.020	1.79 (1.08-2.95)	.023	0.83 (0.59-1.17)	.295	0.84 (0.59-1.18)	.305	1.04 (0.74-1.45)	.830	1.05 (0.75-1.48)	.763
Unscheduled doctor's visit	147	1.21 (0.69-2.13)	.499	1.23 (0.70-2.17)	.477	1.10 (0.69-1.74)	.696	1.10 (0.69-1.74)	.695	1.00 (0.64-1.54)	.983	0.98 (0.63-1.52)	.932
ED visit for asthma	147	2.09 (1.26-3.48)	.004	2.06 (1.24-3.43)	.005	0.86 (0.58-1.26)	.432	0.86 (0.58-1.28)	.452	0.93 (0.64-1.35)	.712	0.97 (0.66-1.42)	.876
Hospitalization for asthma	147	2.24 (0.65-7.70)	.202	2.12 (0.62-7.33)	.234	1.28 (0.61-2.71)	.516	1.28 (0.59-2.74)	.531	1.80 (0.64-5.08)	.264	1.98 (0.69-5.64)	.201
Lung function and lung inflammation													
	n	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
FEV ₁ (percent predicted)	143	-0.87 (-3.49 to 1.76)	.516	-0.83 (-3.46 to 1.80)	.536	0.80 (-0.61 to 2.21)	.267	0.79 (-0.61 to 2.19)	.270	-0.25 (-1.99 to 1.49)	.780	-0.27 (-2.01 to 1.47)	.760
FVC (percent predicted)	143	-0.54 (-2.61 to 1.53)	.612	-0.55 (-2.61 to 1.52)	.604	0.27 (-0.91 to 1.44)	.655	0.27 (-0.90 to 1.44)	.653	0.71 (-0.81 to 2.23)	.360	0.72 (-0.80 to 2.24)	.355
FEV ₁ /FVC%	143	-0.11 (-1.58 to 1.36)	.883	-0.05 (-1.52 to 1.41)	.942	0.49 (-0.33 to 1.30)	.239	0.48 (-0.33 to 1.29)	.248	-0.87 (-1.71 to -0.03)	.041	-0.90 (-1.74 to -0.07)	.035
FENO	144	0.04 (-0.02 to 0.10)	.176	0.04 (-0.02 to 0.10)	.215	-0.01 (-0.05 to 0.03)	.798	0.00 (-0.04 to 0.03)	.806	-0.01 (-0.06 to 0.03)	.535	-0.01 (-0.05 to 0.03)	.589

aPR, Adjusted prevalence ratio; FVC, forced vital capacity; GEE, generalized estimating equation.

Information on nocturnal awakening with asthma symptoms was missing for 2 children, and information on lung function parameters was missing for 4 children. Information on main models is presented for the subset of participants with complete data. Models were adjusted for age, sex, race, caregiver education, season, presence of smokers in the home as a proxy for environmental tobacco smoke exposure, total number of positive skin prick test responses (in specified models), and coexposure to other bisphenols (ie, all bisphenols were included in the same model for each outcome). For dichotomous outcomes (asthma symptoms and health care utilization), we conducted binomial regression models using generalized estimating equations and log link to obtain PRs and for continuous outcomes (lung function), we ran linear regression models with generalized estimating equations to obtain β -coefficients to account for repeated measures of exposure and outcomes. BPA and BPS were modeled as continuous variables (log₁₀-transformed specific gravity-corrected concentrations) and BPF was modeled as a categorical variable (detected vs not detected) based on detection frequencies. Bolded *P* values indicate statistical significance (*P* < .05).

TABLE E7. Adjusted associations additionally including indoor PM_{2.5} concentrations as a covariate in the GEE models

		BPA (additionally including child BMI as a covariate)				BPS (additionally including child BMI as a covariate)				BPF (additionally including child BMI as a covariate)			
		BPA, main model		BPS, main model		BPA, main model		BPS, main model		BPA, main model		BPS, main model	
	n	aPR (95% CI)	P value	aPR (95% CI)	P value	aPR (95% CI)	P value	aPR (95% CI)	P value	aPR (95% CI)	P value	aPR (95% CI)	P value
Asthma symptoms													
Coughing, wheezing, or chest tightness	143	1.50 (1.05-2.15)	.026	1.54 (1.09-2.19)	.015	0.73 (0.52-1.02)	.068	0.71 (0.51-0.99)	.041	1.23 (0.92-1.62)	.158	1.24 (0.93-1.65)	.146
Nocturnal awakening with symptoms	141	1.67 (0.95-2.92)	.075	1.67 (0.98-2.84)	.059	0.62 (0.43-0.90)	.011	0.61 (0.42-0.89)	.010	1.07 (0.75-1.52)	.716	1.08 (0.74-1.56)	.689
Exercise-related symptoms	143	1.25 (0.85-1.85)	.258	1.26 (0.85-1.88)	.255	0.74 (0.52-1.06)	.104	0.72 (0.50-1.04)	.080	1.09 (0.79-1.51)	.606	1.10 (0.79-1.54)	.569
Cough without a cold	142	1.16 (0.60-2.23)	.662	1.17 (0.63-2.17)	.623	0.69 (0.45-1.08)	.107	0.67 (0.43-1.04)	.077	1.00 (0.63-1.57)	.989	1.03 (0.64-1.65)	.916
Slowed activity due to asthma	143	1.19 (0.80-1.76)	.393	1.19 (0.77-1.83)	.431	0.76 (0.50-1.15)	.198	0.76 (0.49-1.16)	.198	1.24 (0.88-1.75)	.223	1.24 (0.87-1.76)	.242
Maximal symptom days	143	1.40 (0.99-1.98)	.057	1.45 (1.01-2.07)	.044	0.77 (0.54-1.10)	.150	0.75 (0.52-1.07)	.117	1.23 (0.92-1.65)	.154	1.24 (0.92-1.67)	.150
Short-acting β -agonist use	143	1.22 (0.86-1.72)	.261	1.25 (0.86-1.82)	.242	0.95 (0.73-1.25)	.726	0.93 (0.71-1.22)	.603	1.04 (0.79-1.36)	.805	1.03 (0.79-1.36)	.815
Health care utilization													
Acute care visit	143	1.87 (1.05-3.33)	.033	1.94 (1.07-3.52)	.030	0.69 (0.48-1.00)	.049	0.69 (0.48-0.99)	.043	1.24 (0.85-1.82)	.257	1.25 (0.85-1.84)	.249
Unscheduled doctor's visit	143	1.22 (0.63-2.37)	.556	1.24 (0.63-2.44)	.535	0.86 (0.52-1.41)	.546	0.85 (0.51-1.40)	.517	1.09 (0.68-1.75)	.714	1.10 (0.68-1.77)	.707
ED visit for asthma	143	2.39 (1.34-4.27)	.003	2.41 (1.33-4.37)	.004	0.69 (0.45-1.06)	.090	0.69 (0.45-1.06)	.089	1.17 (0.75-1.82)	.500	1.17 (0.75-1.82)	.494
Hospitalization for asthma	143	2.60 (0.73-9.24)	.139	2.53 (0.70-9.11)	.156	1.08 (0.44-2.64)	.867	1.04 (0.43-2.51)	.930	1.60 (0.59-4.39)	.359	1.47 (0.53-4.08)	.460
Lung function and lung inflammation													
	n	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
FEV ₁ (percent predicted)	139	0.02 (-2.88 to 2.93)	.988	0.02 (-2.86 to 2.89)	.991	1.46 (-0.33 to 3.25)	.111	1.50 (-0.33 to 3.32)	.108	-0.67 (-2.63 to 1.30)	.505	-0.67 (-2.63 to 1.30)	.505
FVC (percent predicted)	139	0.16 (-2.03 to 2.34)	.889	0.15 (-2.02 to 2.33)	.890	0.33 (-1.02 to 1.68)	.631	0.34 (-1.03 to 1.70)	.627	0.29 (-1.42 to 1.99)	.740	0.29 (-1.42 to 1.99)	.740
FEV ₁ /FVC%	139	0.09 (-1.57 to 1.75)	.915	0.09 (-1.57 to 1.75)	.918	1.03 (-0.05 to 2.10)	.060	1.05 (-0.04 to 2.14)	.059	-0.92 (-1.86 to 0.03)	.057	-0.92 (-1.86 to 0.02)	.056
FENO	139	0.04 (-0.03 to 0.10)	.229	0.04 (-0.02 to 0.10)	.217	0.00 (-0.04 to 0.04)	.891	0.00 (-0.04 to 0.03)	.838	-0.02 (-0.06 to 0.03)	.413	-0.02 (-0.06 to 0.02)	.407

aPR, Adjusted prevalence ratio; FVC, forced vital capacity; GEE, generalized estimating equation; PM_{2.5}, concentration of particulate matter with an aerodynamic diameter less than 2.5 μ m.

Information on nocturnal awakening with asthma symptoms was missing for 2 children, and information on lung function parameters was missing for 4 children. Information on main models is presented for the subset of participants with complete data. Models were adjusted for age, sex, race, caregiver education, season, presence of smokers in the home as a proxy for environmental tobacco smoke exposure, log-transformed PM_{2.5} values (in specified models), and coexposure to other bisphenols (ie, all bisphenols were included in the same model for each outcome). For dichotomous outcomes (asthma symptoms and health care utilization), we conducted binomial regression models using GEEs and log link to obtain PRs, and for continuous outcomes (lung function) we ran linear regression models with GEEs to obtain β -coefficients to account for repeated measures of exposure and outcomes. BPA and BPS were modeled as continuous variables (log₁₀-transformed specific gravity-corrected concentrations), and BPF was modeled as a categorical variable (detected vs not detected) based on detection frequencies. Bolded *P* values indicate statistical significance (*P* < .05).