

Paraben exposures and asthma-related outcomes among children from the US general population



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Background: Parabens are synthetic preservatives present in many consumer products. Their antimicrobial and endocrine-disrupting properties have raised concerns that they might play a role in respiratory and allergic diseases; however, studies exploring these associations are scarce.

Objective: We examined the cross-sectional association between parabens and asthma morbidity among 450 children with asthma and with asthma prevalence among 4023 children in the US general population participating in the National Health and Nutrition Examination Survey (2005-2014).

Methods: We conducted multivariable logistic regression to examine associations between urinary paraben biomarker concentrations (butyl paraben, ethyl paraben, methyl paraben [MP], and propyl paraben [PP]) and asthma attacks and emergency department visits among children with asthma and with a current asthma diagnosis among all children. We also examined heterogeneity of associations by sex.

Results: We observed an increased prevalence odds of reporting emergency department visits for every 10-fold increase in MP and PP concentrations among boys with asthma (adjusted prevalence odds ratio, 2.61 [95% CI, 1.40-4.85] and 2.18 [95% CI, 1.22-3.89, respectively]; $P_{\text{interaction-MP}} = .002$ and $P_{\text{interaction-PP}} = .003$); associations remained after adjusting for other phenolic compounds previously linked to respiratory outcomes. No other dimorphic effects of exposure by sex were observed.

Among children in the general population, no overall associations with current asthma were observed, although there was a positive trend with PP and a current asthma diagnosis.

Conclusion: We identified differential effects of exposure to select parabens by sex on asthma morbidity. Further studies are needed to replicate these findings and elucidate mechanisms by which parabens could affect respiratory health and elicit dimorphic effects by sex. (J Allergy Clin Immunol 2019;143:948-56.)

Key words: Parabens, children, asthma, respiratory, antimicrobials, endocrine disruptors

Parabens are synthetic preservatives widely used in personal care products, medications, and foods.¹⁻⁴ In the United States exposure to parabens is widespread, with select parabens detected in more than 90% of the general population.⁵ The main route of exposure to parabens is considered to be dermal absorption from personal care product use, although other routes and sources of exposure are possible.^{3,6,7} Their widespread detection in the general population has raised concerns about their potential health risks given they are antimicrobial agents and endocrine-disrupting compounds (EDCs) exhibiting weak estrogenic and antiandrogenic activity.⁸⁻¹¹ Of emerging concern is their potential effects on pediatric respiratory health given children's developing immune and respiratory systems, and their unique vulnerabilities to environmental contaminants.

Results from limited *in vivo* and *in vitro* studies support the hypothesis that parabens could play a role in modulating immune and allergic responses.¹²⁻¹⁸ EDCs can influence immune cell activation and survival and modulate cytokine production, T_H1/T_H2 balance, and IgE production.¹² In addition, it is plausible that the antimicrobial properties of parabens could promote an allergic phenotype by altering the microbiome of the gut, respiratory tract, or both.¹⁹⁻²⁴

To date, few epidemiologic studies have examined the role of paraben exposure on the risk of pediatric respiratory and allergic disease, and findings have been inconsistent. In 2 cross-sectional studies conducted on children from the US general population participating in the 2005-2006 National Health and Nutrition Examination Survey (NHANES),^{25,26} exposure to select parabens was positively associated with aeroallergen sensitization, an important risk factor for development, morbidity, and severity of asthma and allergic diseases.^{25,27-30} Dimorphic effects of paraben exposure by sex on allergic sensitization have also been reported,³¹ although no consistent associations with asthma and wheeze have been identified.^{26,31} To our knowledge, no other studies have examined these associations or whether exposure to parabens is associated with worse asthma-related outcomes among asthmatic patients.

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Abbreviations used

aPOR: Adjusted prevalence odds ratio
 BMI: Body mass index
 BP: Butyl paraben
 DF: Detection frequency
 ED: Emergency department
 EDC: Endocrine disrupting compound
 EP: Ethyl paraben
 LOD: Limit of detection
 MP: Methyl paraben
 NCHS: National Center for Health Statistics
 NHANES: National Health and Nutrition Examination Survey
 PP: Propyl paraben

In this study, we sought to address current knowledge gaps and examine whether exposure to 4 parabens (butyl paraben [BP], ethyl paraben [EB], methyl paraben [MP], and propyl paraben [PP]) commonly used in consumer products is associated with increased morbidity (ie, increased prevalence odds of asthma attacks and emergency department [ED] visits for asthma) among children with asthma from a larger subset of the US general population participating in NHANES (2005-2014). We also examined the association between exposure to parabens and the prevalence of a current asthma diagnosis among all children. Lastly, we assessed whether the effect of paraben exposure on our outcomes varied by sex given reported sex differences with paraben exposure and risk of allergic sensitization.³¹

METHODS

Data source for the study population

Our study population consisted of children between the ages of 6 and 19 years participating in NHANES, a population-based, cross-sectional survey assessing the general health and nutritional status of the US noninstitutionalized population. NHANES uses a complex, stratified, multi-stage probability sample design to be representative of the general population. All study activities were approved by the National Center for Health Statistics (NCHS) institutional review board, and proper consenting procedures were followed prior to any data collection.³² Information on participants was collected through a household interview and a standardized physical examination.³³ Paraben exposure measurements were conducted on a random one-third subsample of participants 6 years of age and older between 2005 and 2014.

Exposure assessment of parabens

Urinary biomarker concentrations for BP, EP, MP, and PP in spot urine samples provided by study participants were used to assess paraben exposure. Total concentrations (free plus conjugated species) for each of the 4 parabens were measured by using a validated laboratory method described previously.³⁴ Limits of detection (LODs) were 1.0 µg/L (MP and EP) and 0.2 µg/L (PP and BP). Urinary creatinine concentrations were also measured and used in our analyses to correct for renal function.³⁵

Respiratory outcome assessment

As part of a medical examination, participants or their caregivers completed a questionnaire that asked about several medical conditions. As part of this questionnaire, participants were asked the following: “Has a doctor or other health professional ever told you that you have asthma?” Participants who answered affirmatively to this question were then asked, “Do you still have asthma?,” which was hereafter referred to as “current asthma.” If participants reported having current asthma, they were then asked the

TABLE I. Weighted demographic characteristics for children 6 to 19 years of age from the US general population with data on current asthma (NHANES 2005-2014)

	Children with data on current asthma, regardless of paraben or covariate data available (n = 4465)		Children in the present study with data on parabens, current asthma, and covariates (n = 4023)	
	No.	Percent	No.	Percent
Sex				
Boys	2263	50.9	2068	51.6
Girls	2202	49.1	1955	48.4
Age (y)*				
6-11	2043	42.1	1832	42.7
12-19	2422	57.9	2191	57.3
Race				
Non-Hispanic white	1264	57.1	1159	58.0
Non-Hispanic black	1195	14.6	1101	14.7
Mexican American	1158	14.2	1032	13.9
Other	848	14.1	731	13.3
Poverty income ratio				
<1.0	1371	23.8	1434	23.9
≥1.0	2786	76.2	2689	76.2
Missing	308		—	

*Mean age in years among the 4465 children with data on current asthma diagnosis was 12.6 (SD, 4.0) versus 12.5 (SD, 4.0) for the 4023 children in our present study with complete data on current asthma diagnosis, parabens, and covariates used in our analyses.

following: “During the past 12 months, have you had an episode of asthma or an asthma attack?” (hereafter referred to as asthma attack[s]) and “During the past 12 months, have you had to visit an emergency room or urgent care center because of asthma?” (hereafter referred to as an ED visit for asthma). For our analyses, we focused on the following outcomes: (1) current asthma (yes/no) among all children and, among the subset of children with current asthma, whether the child experienced (2) asthma attacks (yes/no) or (3) had an ED visit or visits for asthma (yes/no). For current asthma, the comparison group was children who never received an asthma diagnosis or who reported formerly having asthma.

Of 4338 children aged 6 to 19 years with paraben biomarker data for cycle years 2005-2014, 4023 had complete data on current asthma diagnosis and main covariates, and among these 4023 children, 450 who reported having a current asthma diagnosis had complete data on asthma attacks, ED visits, and main covariates to assess morbidity (see Fig E1 in this article’s Online Repository at www.jacionline.org).

Statistical analysis

All analyses were conducted in Stata 14.0 software (StataCorp, College Station, Tex). We applied NCHS-created sampling weights, strata, and primary sampling units in our statistical analyses according to NCHS guidelines, unless otherwise noted, to yield unbiased point estimates and to account for the complex, stratified, multistage probability sample design. We calculated descriptive statistics to summarize demographic characteristics and urinary biomarker concentrations (eg, numbers, detection frequencies [DFs], geometric means, weighted percentiles, and maximum concentrations). To assess whether there were any significant differences in demographic characteristics between children who reported having the target outcomes and those who did not, we conducted χ^2 tests. We assessed differences in biomarker concentrations (for frequently detected parabens) and DFs (for less frequently detected parabens) based on outcome status and sex by conducting *t* tests and χ^2 tests, respectively.

To examine associations between urinary paraben biomarker concentrations and each outcome of interest, we used logistic regression models to

TABLE II. Prevalence of respiratory outcomes by demographic characteristics among children aged 6 to 19 years (NHANES 2005-2014)*

	All children, regardless of outcome status		Children with a current asthma diagnosis†			Children who reported ED visit(s) in the prior 12 mo‡			Children who reported asthma attacks(s) in the prior 12 mo‡		
	No.	Percent	No.	Percent	P value‡	No.	Percent	P value‡	No.	Percent	P value‡
All children	4023	—	450	10.9	—	81	16.2	—	233	53.4	—
Sex											
Boys	2068	51.6	248	51.6	.99	46	47.6	.58	135	55.4	.21
Girls	1955	48.4	202	48.4		35	52.4		98	44.6	
Age (y)											
6-11	1832	42.7	206	41.2	.57	52	52.1	.17	119	47.0	.03
12-19	2191	57.3	244	58.8		29	47.9		114	53.0	
Race											
Non-Hispanic white	1159	58.0	123	55.4	<.001	16	47.6	.27	71	57.6	.22
Non-Hispanic black	1101	14.7	181	23.5		36	25.2		89	21.2	
Mexican American	1032	13.9	75	9.8		10	9.6		31	8.3	
Other§	731	13.3	71	11.3		19	17.6		42	12.9	
Poverty income ratio											
<1.0	1434	23.9	170	28.4	.07	41	33.9	.31	90	29.6	.58
≥1.0	2689	76.2	280	71.6		40	66.1		143	70.4	

*Data presented are for children with complete data on current asthma diagnosis, parabens, and covariates (ie, age, sex, race/ethnicity, poverty income ratio, and creatinine concentrations). Values displayed are weighted to take into account the complex NHANES survey design.

†Current asthma is defined as an affirmative response to the following 2 questions: “Has a doctor or other health professional ever told you that you have asthma?” and “Do you still have asthma?” ED visits are defined as affirmative responses to the following question: “During the past 12 months, have you had to visit an emergency room or urgent care center because of asthma?” Asthma attacks are defined as affirmative responses to the following question: “During the past 12 months, have you had an episode of asthma or an asthma attack?”

‡P values reported are from χ^2 tests used to determine whether demographic characteristics differed based on outcome status.

§The “other” category includes children who self-identified as multiracial or of Asian Pacific or other Hispanic descent.

estimate crude prevalence odds ratios and adjusted prevalence odds ratios (aPORs) and corresponding 95% CIs. We constructed separate models for each paraben and each binary outcome of interest. Crude models included \log_{10} -transformed creatinine concentrations as a covariate to account for urinary dilution, whereas adjusted models included \log_{10} -transformed creatinine concentrations in addition to other covariates, as described below. Because of their low DFs (DF < 50%), both BP and EP were modeled as dichotomous independent variables (ie, < LOD vs \geq LOD). For MP and PP, we used restricted cubic splines with 3 *df* to assess the linearity of the dose-response relationship with each respiratory outcome by using \log_{10} -transformed urinary concentrations. None of the digressions from linearity tests were significant, and therefore we expressed MP and PP concentrations using \log_{10} -transformed concentrations in our models.

To increase the statistical power and precision of our effect estimates, we replaced MP and PP concentrations less than the LOD with $\text{LOD}/\sqrt{2}$.^{36,37} To assess effect modification by sex, we included a single multiplicative interaction term (sex*biomarker concentration) in separate adjusted models.

Our criteria for statistical significance were set at α levels of .05 and .10 for main effects and effect measure modification, respectively. Given that the outcome measures we assessed are not completely independent of one another and the exploratory nature of our study,³⁸ we did not perform adjustment for multiple comparisons.

Covariates

In our adjusted models we controlled *a priori* for several covariates that were identified as potential confounders by using directed acyclic graphs (not shown) or that were expected to be strong predictors of our outcome measures. These covariates included, sex, age (years), race/ethnicity (non-Hispanic white, non-Hispanic Black, Mexican American, and “other,” which included those who self-identified as multiracial, Asian Pacific, or of other Hispanic descent), poverty income ratio (modeled as a continuous variable), and survey cycle year (2005-2006, 2007-2008, 2009-2010, 2011-2012, and 2013-2014). We excluded health insurance as a covariate in our models given that it was not a significant predictor of any of our outcomes in our study population.

Sensitivity analyses

We also conducted sensitivity analyses to examine the robustness of our results in the presence of other model adjustments. First, because tobacco smoke exposure from active or passive smoking has been strongly linked to respiratory outcomes, including asthma-related symptoms,^{39,40} we ran models with and without serum cotinine as a covariate for the subset of participants with available data. We considered addition of cotinine as a covariate as part of our sensitivity analyses rather than inclusion in our main models because data on this covariate were missing for up to 30% of our study population. Although there is increasing evidence that obesity might play a role in asthma diagnosis, control, and exacerbation severity,⁴¹ we did not include body mass index (BMI) in any of our primary models because it is a potential intermediate of an association between parabens and asthma.^{24,42,43} However, as part of our sensitivity analyses, we included age- and sex-standardized BMI *z* scores as a continuous covariate in our primary models. Because other phenolic compounds (eg, triclosan, bisphenol A, and 2,5-dichlorophenol) have been previously linked to respiratory outcomes, including asthma development and morbidity,⁴⁴⁻⁴⁹ we also ran models including \log_{10} -transformed urinary biomarker concentrations for each of these phenols as covariates to assess the independent effects of parabens on each of the target respiratory outcomes assessed. Lastly, to further examine and confirm dose-response relationships, we also categorized concentrations of frequently detected parabens into tertiles of exposure and reran the main logistic regression models when significant associations were observed with our continuous exposure measures.

RESULTS

Study population characteristics

Of the 4465 children with data on current asthma diagnosis, 4023 had data available on parabens and covariates included in our analyses. Weighted demographic characteristics for the 4023 children with complete data were similar to those of the larger population of children with available data on current asthma

TABLE III. Summary statistics for urinary paraben biomarker concentrations in children aged 6 to 19 years from the US general population (NHANES 2005-2014; in nanograms per milliliter)*

	No.	Percent detected	GM	Median (p25-p75)	p95	Max	P value
BP							
All children	4,023	36.1	—	<LOD (<LOD-0.3)	9.2	1,240	
Male subjects	2,068	24	—	<LOD (<LOD-0.1)	1.7	1,240	<.001†
Female subjects	1,955	49.1	0.4	<LOD (<LOD-0.7)	17.6	353	
Children with asthma	450	33.5	—	<LOD (<LOD-0.3)	19.6	1,240	.35‡
Male subjects with asthma	248	24.4	—	<LOD (<LOD-<LOD)	1.9	1,240	.004§
Female subjects with asthma	202	43.2	0.4	<LOD (<LOD-0.5)	24.5	90	
Children with no asthma	3,573	36.5	—	<LOD (<LOD-0.3)	8.3	493	
Male subjects with no asthma	1,820	24	—	<LOD (<LOD-0.1)	1.7	493	<.001
Female subjects with no asthma	1,753	49.8	1.9	<LOD (<LOD-0.8)	14.5	353	
EP							
All children	4,023	34.6	—	<LOD (<LOD-1.9)	34.5	1,981	
Male subjects	2,068	26.3	—	<LOD (<LOD-1.0)	10.7	1,981	<.001†
Female subjects	1,955	43.4	1.1	<LOD (<LOD-3.2)	60.8	1,760	
Children with asthma	450	38.3	—	<LOD (<LOD-2.2)	60.3	1,670	.16‡
Male subjects with asthma	248	30	—	<LOD (<LOD-1.3)	34.5	1,110	.005§
Female subjects with asthma	202	47.3	2.0	<LOD (<LOD-3.4)	63.3	1,670	
Children with no asthma	3,573	34.1	—	<LOD (<LOD-1.8)	31.3	1,981	
Male subjects with no asthma	1,820	25.9	—	<LOD (<LOD-1.0)	10.4	1,981	<.001
Female subjects with no asthma	1,753	42.9	1.9	<LOD (<LOD-3.2)	60.8	1,760	
MP							
All children	4,023	98.5	38.0	31.4 (10.3-136.0)	868	149,000	
Male subjects	2,068	98.2	25.2	18.9 (7.8-66.5)	654	149,000	<.001¶
Female subjects	1,955	98.7	58.9	56.2 (17.0-209.0)	1,000	132,000	
Children with asthma	450	99.5	49.4	41.2 (12.1-174.0)	1,050	149,000	.02#
Male subjects with asthma	248	100	39.2	30.5 (9.2-107.0)	1,170	149,000	.07#
Female subjects with asthma	202	99	63.2	64.0 (16.7-261.0)	1,020	132,000	
Children with no asthma	3,573	93.3	36.8	30.1 (10.2-129.0)	847	135,000	
Male subjects with no asthma	1,820	98.1	23.9	18.3 (7.7-63.8)	621	135,000	<.001¶
Female subjects with no asthma	1,753	100	58.4	55.3 (17.0-201.0)	995	125,000	
PP							
All children	4,023	95.2	4.7	3.7 (0.9-20.5)	208	4,150	
Male subjects	2,068	93.3	2.6	1.9 (0.7-7.9)	120	3,320	<.001¶
Female subjects	1,955	97.2	8.7	8.3 (1.8-43.4)	279	4,150	
Children with asthma	450	97.2	6.7	4.9 (1.2-34.2)	283	2,650	.008#
Male subjects with asthma	248	95.9	3.9	2.5 (1.0-12.0)	210	2,020	<.001¶
Female subjects with asthma	202	98.5	11.7	11.6 (1.9-68.3)	381	2,650	
Children with no asthma	3,573	94.9	4.5	3.5 (0.9-18.6)	200	4,150	
Male subjects with no asthma	1,820	93	2.5	1.8 (0.6-7.6)	100	3,320	<.001¶
Female subjects with no asthma	1,753	97	8.4	8.0 (1.8-40.1)	276	4,150	

GM, Geometric mean; <LOD, summary statistic value of less than the detection limit for the respective paraben; Max, maximum concentration observed.

*LODs were 0.2 ng/mL (BP and PP) and 1.0 ng/mL (EP and MP). In accordance with US Centers for Disease Control and Prevention guidelines, a geometric mean is only reported when the DF is greater than 40% for the specified subgroup, and all statistics reported have been weighted to account for the complex NHANES survey design.

†P value from χ^2 test for differences in DF based on sex among all 4023 children.

‡P value from χ^2 test for differences in DF based on current asthma status among all 4023 children.

§P value from χ^2 test for differences in DF based on sex among the 450 children with current asthma.

||P value from χ^2 test for differences in DF based on sex among the 3573 children without current asthma.

¶P values reported are from *t* tests examining whether paraben biomarker concentrations differed by sex among the specified subgroups (ie, differences in concentrations between boys and girls among those with asthma and differences in concentrations between boys and girls among those without asthma).

#P values reported from *t* tests examining whether paraben biomarker concentrations among children without a current asthma diagnosis differed from those observed among children with a current asthma diagnosis.

diagnosis (n = 4465; Table I). The mean age of children included in our analyses was 13.0 (SD, 4.0) years, and approximately 52% were male. More than half of the children were non-Hispanic white, and approximately 24% reported a household income of less than the poverty level.

Prevalence of respiratory outcomes

The prevalence for each target outcome assessed is displayed in Table II. There were no significant sex or age group differences

between children who reported having a current asthma diagnosis versus those who did not, and non-Hispanic black children were more likely to report having current asthma. Among the 450 children with a current asthma diagnosis, 233 (53.4%) reported having experienced an asthma attack, and 81 (16.2%) reported having an ED visit or visits in the prior 12 months. Among children with asthma, male subjects were more likely than female subjects to report having experienced asthma attacks in the prior 12 months, although these findings were not statistically significant. The prevalence of self-reported ED visits did not significantly differ

TABLE IV. Associations of exposure to parabens with respiratory morbidity measures and current asthma prevalence among all children aged 6 to 19 years from the US general population, NHANES 2005-2014*

	cPOR	95% CI	P value	aPOR	95% CI	P value
Morbidity						
ED visits for asthma† (n = 450)						
BP (<LOD vs ≥LOD)	1.43	0.78-2.63	.24	1.44	0.73-2.84	.28
EP (<LOD vs ≥LOD)	1.07	0.56-2.05	.84	1.04	0.52-2.22	.85
MP (log ₁₀ , ng/mL)	1.22	0.70-2.14	.48	1.22	0.63-2.38	.55
PP (log ₁₀ , ng/mL)	1.10	0.72-1.66	.66	1.15	0.64-2.07	.64
Asthma attacks‡ (n = 450)						
BP (<LOD vs ≥LOD)	1.52	0.86-2.68	.15	1.78	0.94-3.39	.08
EP (<LOD vs ≥LOD)	0.69	0.41-1.16	.16	0.81	0.46-1.42	.46
MP (log ₁₀ , ng/mL)	0.76	0.55-1.05	.09	0.81	0.55-1.18	.26
PP (log ₁₀ , ng/mL)	0.77	0.56-1.06	.11	0.86	0.59-1.25	.41
Prevalence						
Current asthma† (n = 4023)						
BP (<LOD vs ≥LOD)	0.82	0.63-1.08	.15	0.83	0.62-1.10	.19
EP (<LOD vs ≥LOD)	1.14	0.89-1.47	.29	1.09	0.84-1.41	.50
MP (log ₁₀ , ng/mL)	1.21	1.01-1.45	.04	1.17	0.94-1.46	.15
PP (log ₁₀ , ng/mL)	1.21	1.04-1.41	.02‡	1.20	1.00-1.43	.05

cPOR, Crude prevalence odds ratio.

*Crude models were adjusted for log₁₀ creatinine concentrations, and adjusted models were adjusted for age in years, sex (overall crude and adjusted models only), poverty income ratio (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and "other," which includes multiracial, Asian, and other Hispanic), survey cycle year (2005-2006, 2007-2008, 2009-2010, 2011-2012, and 2013-2014), and log₁₀ creatinine concentrations.

†ED visits are defined as affirmative responses to the following question: "During the past 12 months, have you had to visit an emergency room or urgent care center because of asthma?" Asthma attacks are defined as affirmative responses to the following question: "During the past 12 months, have you had an episode of asthma or an asthma attack?" Current asthma is defined as an affirmative response to the following 2 questions: "Has a doctor or other health professional ever told you that you have asthma?" and "Do you still have asthma?"

‡P < .05.

by sex. Also, older children (12-19 years of age) with asthma were more likely to report an asthma attack in the prior 12 months compared with younger children; no age group differences were observed for ED visits.

Paraben biomarker concentrations

Summary statistics for paraben biomarker concentrations in our study population are displayed in Table III. Among the 4023 children with complete data on covariates, paraben biomarker measurements, and current asthma diagnosis, we observed that BP and EP were not widely detected (DF < 40%), whereas MP and PP were detected in more than 95% of children. Geometric mean concentrations for both MP and PP were significantly higher ($P = .02$ and $P = .008$, respectively) among children reporting a current asthma diagnosis compared with children with no current asthma diagnosis. Geometric mean concentrations for these frequently detected parabens were generally statistically significantly higher for female compared with male subjects, regardless of current asthma diagnosis status.

Associations between paraben exposure and morbidity among children with asthma

Among children with asthma, we did not observe overall associations between any of the parabens and reporting of asthma attacks or ED visits in the prior 12 months in either unadjusted or adjusted analyses (Table IV). However, we did observe effect modification by sex for ED visits for asthma in the prior 12 months for both MP and PP ($P_{\text{int}} \leq .003$), with statistically significant positive associations observed among boys with asthma (Fig 1 and Table V). For every 10-fold increase in MP and PP concentrations,

we observed a respective 2.61 (95% CI, 1.40-4.85; $P = .003$) and 2.18 (95% CI, 1.22-3.89; $P = .01$) increased prevalence odds of reporting an ED visit in the prior 12 months among boys with current asthma. We also observed a positive and statistically significant dose-response trend with ED visits among boys when using tertiles of exposure for both MP and PP (MP: aPOR_{Tertile2} of 3.02 [95% CI, 0.99-9.16] and aPOR_{Tertile3} of 4.02 [95% CI, 1.35-11.94], $P_{\text{trend}} = .01$; PP: aPOR_{Tertile2} of 2.34 [95% CI, 0.68-7.93] and aPOR_{Tertile3} of 6.56 [95% CI, 1.49-28.76], $P_{\text{trend}} = .01$). No other dimorphic effects by sex were observed.

In sensitivity analyses inclusion of BMI z scores and concentrations of other phenolic compounds in our models did not materially affect our results, although inclusion of cotinine led to a significantly increased prevalence odds of asthma attacks among children with detectable concentrations of BP (aPOR, 2.64 [95% CI, 1.32-5.31], $P = .01$; see Table E1 in this article's Online Repository at www.jacionline.org). Lastly, similar to our main models, we observed an increased prevalence odds of ED visits among boys with asthma when controlling for cotinine, BMI z scores, or other phenolic compounds but no other dimorphic effects of paraben exposure by sex among children with asthma (see Tables E1-E3 in this article's Online Repository at www.jacionline.org).

Associations between paraben exposures and prevalence of current asthma diagnosis among all children in the general population

After adjustment for confounders, among all children, we did not observe significant associations between exposure to any parabens and self-report of current asthma diagnosis, although the relationship between PP and current asthma diagnosis

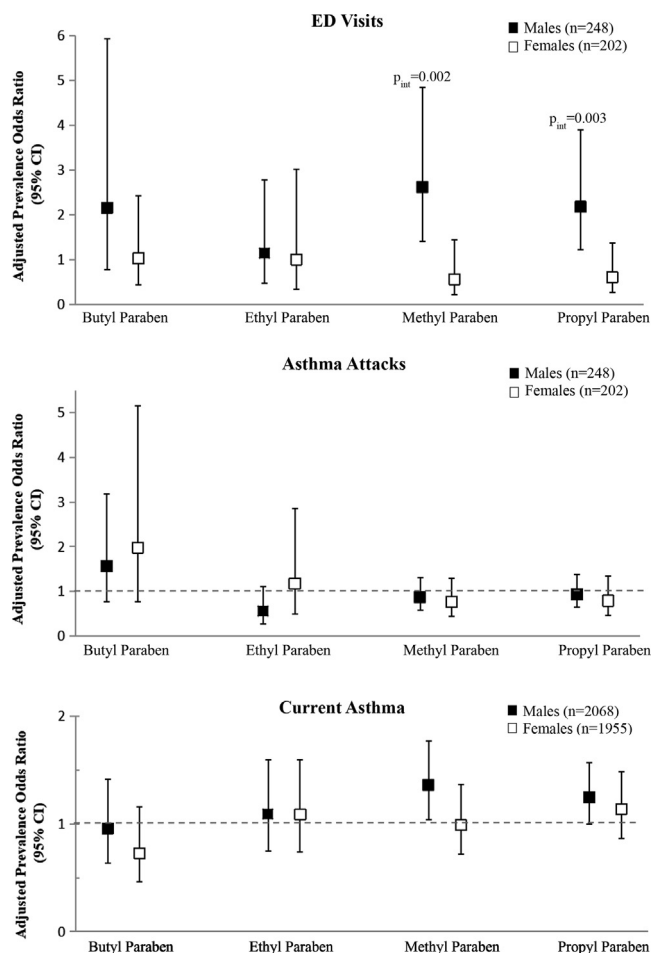


FIG 1. Adjusted associations between children’s urinary paraben biomarker concentrations and respiratory outcomes by child’s sex. We modeled BP and EP exposure as a dichotomous variable (less than LOD vs LOD or greater), whereas we used \log_{10} -transformed MP and PP concentrations in models. P_{int} , P value on interaction term (sex*biomarker concentration). Only significant interaction P values of less than .10 are reported.

approached statistical significance (aPOR, 1.20 [95% CI, 1.00-1.43]; $P = .05$). Interactions between paraben exposure and sex on current asthma diagnosis were not statistically significant (Fig 1 and Table V), and inclusion of other covariates in sensitivity analyses did not materially affect our results (see Tables E1-E3).

DISCUSSION

In this study, we examined cross-sectional associations between exposure to parabens and asthma-related outcomes in a sample of children from the US general population. We did not observe associations between any paraben and asthma prevalence or asthma morbidity in the population as a whole. However, we identified dimorphic effects of paraben exposure by sex among children with asthma. We found that exposure to both MP and PP was associated with increased prevalence odds of reporting ED visits for asthma in the prior 12 months among boys with asthma, despite boys having lower urinary paraben biomarker concentrations.

Although the association between paraben exposure and asthma morbidity has not been previously examined, sex

differences in the association between paraben exposures and allergic sensitization have been reported, with male subjects generally at a greater risk than female subjects, including in a smaller subset of our study population.^{25,31} Sexual dimorphism has also been reported for pediatric asthma and for ED visits, with boys experiencing a greater asthma prevalence and ED visits for asthma exacerbations.^{50,51} In addition, sex differences have been reported for associations between other EDCs, including some compounds with antimicrobial properties and respiratory outcomes, with more prevalent effects observed among boys.⁵²⁻⁵⁴ Given that male subjects are at a greater risk of allergic disease in general,⁵⁵ one plausible explanation for our findings with ED visits is that exposure to parabens could result in enhancement of the allergic response and increased susceptibility to adverse respiratory effects. The endocrine-disrupting actions of parabens could be more potent in boys given that their hormonal milieu is distinct from girls and existing evidence indicating that sex hormones and environmental agents with endocrine disrupting properties influence function and/or development of the lungs and the immune system.⁵⁶⁻⁶⁰ Additionally, the antimicrobial properties of parabens might have a greater influence on the risk of asthma exacerbations among boys because of their inherent phenotypic asthma features, including greater burden of atopy. It has also been suggested that potential sex differences in the risk of allergic and respiratory outcomes could be due to an interplay between the endocrine disrupting and antimicrobial properties of parabens, resulting from differences in microbiome composition, hormone function, and consequences of microbial interactions.³¹ However, more studies are needed to confirm our findings and elucidate the potential mechanisms by which parabens could result in dimorphic effects by sex.

Our results of no overall associations between exposure to parabens and current asthma diagnosis were similar to those reported in a previous study conducted by Spanier et al²⁶ in which authors examined the association between exposure to parabens and *ever* having received an asthma diagnosis based on atopic status among 837 children aged 6 to 18 years participating in the 2005-2006 NHANES cycle. The authors reported no significant associations between exposure to parabens and increased risk of *ever* having received an asthma diagnosis, regardless of atopic status. Similarly, Lee-Sarwar et al³¹ also reported null associations between prenatal and early postnatal paraben biomarker concentrations in samples collected approximately between 2011 and 2013 with asthma and wheeze among 460 three-year-old children. Similar to our study, Spanier et al²⁶ and Lee-Sarwar et al³¹ reported low detection of BP and EP in children’s urine. Geometric mean concentrations for MP and PP in our study were similar to those reported by Spanier et al²⁶ in children participating in the 2005-2006 NHANES cycle (present study: MP, 38 ng/mL; PP, 4.7 ng/mL vs Spanier et al: MP, 42 ng/mL; PP, 5.3 ng/mL). However, median concentrations for MP and PP were lower in our study population compared to those reported among 3-year-olds by Lee-Sarwar et al³¹ (present study: MP, 31.4 ng/mL; PP, 3.7 ng/mL vs Lee-Sarwar et al: MP, 62.8 ng/mL; PP, 6.8 ng/mL). Differences in concentrations between our study and those reported by Lee-Sarwar et al might be related to study population characteristics, including age and racial/ethnic composition. Nonetheless, our results on asthma prevalence are in agreement with these prior studies.

TABLE V. Associations of exposure to parabens with respiratory morbidity measures among children with asthma and with current asthma prevalence stratified by sex*

	aPOR	95% CI	P value	aPOR	95% CI	P value	<i>P</i> _{int} value
Morbidity	Boys (n = 248)			Girls (n = 202)			
ED visits for asthma†							
BP (<LOD vs ≥LOD)	2.16	0.79-5.93	.13	1.03	0.44-2.42	.95	.28
EP (<LOD vs ≥LOD)	1.14	0.47-2.78	.76	1.01	0.34-3.01	.98	.86
MP (log ₁₀ , ng/mL)	2.61	1.40-4.85	.003‡	0.57	0.23-1.44	.23	.002‡
PP (log ₁₀ , ng/mL)	2.18	1.22-3.89	.01‡	0.61	0.28-1.37	.23	.003‡
Asthma attacks†							
BP (<LOD vs ≥LOD)	1.56	0.76-3.18	.22	1.98	0.76-5.16	.16	.68
EP (<LOD vs ≥LOD)	0.55	0.27-1.11	.09	1.18	0.49-2.86	.71	.19
MP (log ₁₀ , ng/mL)	0.86	0.57-1.31	.48	0.76	0.44-1.30	.31	.67
PP (log ₁₀ , ng/mL)	0.94	0.64-1.38	.74	0.79	0.46-1.34	.37	.52
Prevalence	Boys (n = 2068)			Girls (n = 1955)			
Current asthma†							
BP (<LOD vs ≥LOD)	0.96	0.64-1.42	.83	0.73	0.46-1.16	.18	.42
EP (<LOD vs ≥LOD)	1.09	0.75-1.60	.64	1.09	0.74-1.60	.66	.98
MP (log ₁₀ , ng/mL)	1.36	1.04-1.77	.02‡	0.99	0.72-1.37	.96	.12
PP (log ₁₀ , ng/mL)	1.25	1.00-1.57	.05	1.14	0.87-1.49	.33	.58

aPOR, Crude prevalence odds ratio; *P*_{int}, *P* value for interaction term (sex*biomarker concentration term).

*Adjusted models included age in years, poverty income ratio (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and "other," which includes multiracial, Asian, and other Hispanic), survey cycle year (2005-2006, 2007-2008, 2009-2010, 2011-2012, and 2013-2014), and log₁₀ creatinine concentrations as covariates.

†ED visits are defined as affirmative responses to the following question: "During the past 12 months, have you had to visit an emergency room or urgent care center because of asthma?" Asthma attacks are defined as affirmative responses to the following question: "During the past 12 months, have you had an episode of asthma or an asthma attack?"

Current asthma is defined as an affirmative response to the following 2 questions: "Has a doctor or other health professional ever told you that you have asthma?" and "Do you still have asthma?"

‡*P* < .05.

The lack of consistency in associations between MP and PP and asthma outcomes could suggest spurious findings but could also be due to the fact that each of the 3 major outcomes we evaluated measures distinct manifestations of asthma. For example, current asthma indicates whether someone has the disease currently and does not capture the degree of symptoms or morbidity. Because exposures that can lead to an increased risk in asthma development can differ from those that lead to symptoms, exacerbations, or both among those with established asthma, as reported in prior studies,⁶¹⁻⁶³ it is possible that MP and PP contribute to symptoms among those with disease, but do not contribute to risk of developing asthma. Additionally, an "asthma attack" is defined in NHANES as an affirmative response to the question "During the past 12 months, have you had an episode of asthma or an asthma attack?" and affirmative responses to this question are much more common than affirmative responses to the question about ED visits. Thus, self-report of "asthma attacks" as queried by NHANES, could be measuring something different and milder than ED visits.

A limitation of this study is its cross-sectional design, limiting our ability to ascribe a direct cause-effect relationship between our exposures and outcomes. In addition, parabens are thought to be largely excreted within 24 hours.⁶⁴ Biomarker concentrations could thus reflect recent rather than long-term exposures. Although some studies in adults^{65,66} suggest that a single spot sample might be sufficient to characterize exposure to select parabens over a period of a few months, reliance on a single urine sample for exposure assessment might have led to nondifferential exposure misclassification, potentially attenuating our results if paraben concentrations vary widely among children. While we adjusted for several important confounders, our analyses were also limited by the variables available in this national survey.

For example, allergic sensitization is a significant risk factor for asthma development, morbidity, and severity that has been linked to paraben exposure; however, data on sensitization were not available for the cycle years assessed in our analyses. Lastly, it is possible that our findings with ED visits are not representative of the US population of children or are spurious findings based on the modest sample size for an analysis of complex survey design data.

While we examined associations between exposures to parabens and respiratory outcomes among children aged 6 to 19 years, we were not able to assess exposures among younger children or during the prenatal period because paraben biomarker data were unavailable so further studies are warranted to identify critical windows of susceptibility. Innate and adaptive immune responses are immature at birth and undergo constant development during the early postnatal period through the adolescent phase, making these stages vulnerable to environmental exposures, including EDCs.^{67,68} Although a recent study did not observe associations between prenatal or early postnatal exposure to parabens and pediatric asthma or wheeze during the preschool years,³¹ the study did not evaluate asthma among school-aged children. Thus, future studies should examine the effects of prenatal and early postnatal paraben exposures in children at different life stages.

Despite our study limitations, our study has several strengths. To our knowledge, this is the first study to examine the association between exposure to parabens and respiratory outcomes among children with asthma. We also conducted our analyses on a large sample of US children. In addition, the availability of cotinine and other phenolic compounds provided the opportunity to adjust for these exposures that have been previously associated with respiratory symptoms, and in general, associations observed remained or became stronger.

In summary, we observed differential effects of exposure to select parabens by sex on asthma morbidity, but did not observe associations between exposure to these parabens and the prevalence of current asthma. Given the cross-sectional study design, future studies are needed to replicate our findings and identify potential windows of susceptibility. Lastly, studies are needed to elucidate the mechanisms by which parabens could impact development, morbidity, or severity of respiratory outcomes, and elicit dimorphic effects by sex.

Clinical implications: Urinary concentrations of the antimicrobial agents MP and PP were associated with ED visits among asthmatic boys. These findings warrant further study given the widespread use of parabens in consumer products.

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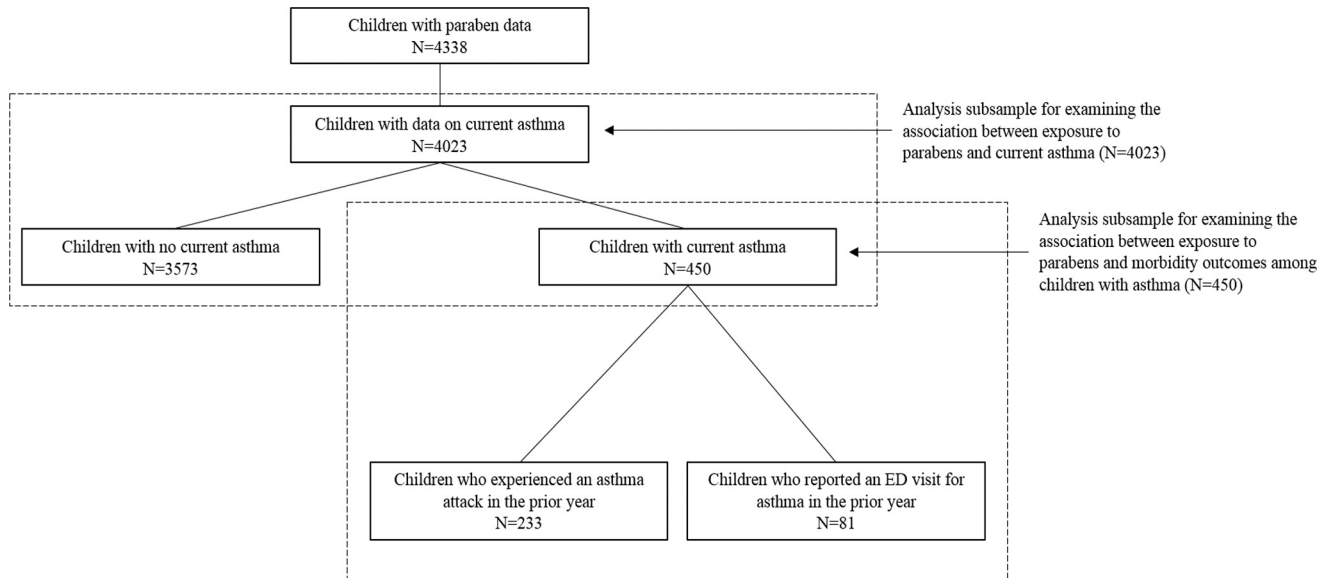


FIG E1. Analysis subsamples for examining associations between exposure to parabens and current asthma among all children and with ED visits and asthma attacks among children aged 6 to 19 years with asthma (NHANES 2005-2014).

TABLE E1. Associations of exposure to parabens with respiratory morbidity measures among children with asthma and with current asthma prevalence, adjusting for serum cotinine concentrations*

	Subsample of children with cotinine data (cotinine not in the model), cPOR			Subsample of children with cotinine data (cotinine not in the model), aPOR			Subsample of children with cotinine data and cotinine in the model, aPOR			Stratified results by sex on the subsample of children with cotinine data and cotinine in the models						
	cPOR	95% CI	P value	aPOR	95% CI	P value	aPOR	95% CI	P value	aPOR	95% CI	P value	aPOR	95% CI	P value	P _{int} value
Morbidity										Boys (n = 166)			Girls (n = 146)			
ED visits (n = 312)																
BP	1.18	0.61-2.31	.61	1.26	0.58-2.73	.56	1.25	0.58-2.72	.57	1.97	0.59-6.55	.26	0.90	0.35-2.36	.83	.32
EP	1.05	0.50-2.22	.89	1.10	0.49-2.49	.81	1.12	0.50-2.52	.78	1.08	0.40-2.96	.88	1.15	0.35-3.75	.82	.94
MP	1.01	0.54-1.89	.97	1.03	0.47-2.26	.93	1.03	0.47-2.26	.94	2.86	1.31-6.25	.01†	0.50	0.18-1.39	.18	.003†
PP	1.00	0.64-1.57	1.00	1.05	0.53-2.08	.90	1.04	0.52-2.07	.91	2.37	1.17-4.79	.02†	0.56	0.23-1.40	.21	.003†
Asthma attacks (n = 312)																
BP	1.77	0.91-3.47	.09	2.63	1.31-5.28	.01†	2.64	1.32-5.31	.01†	2.43	1.02-5.78	.04	2.81	1.03-7.70	.05	.83
EP	0.80	0.43-1.50	.49	1.13	0.58-2.20	.71	1.13	0.58-2.20	.72	0.65	0.27-1.57	.34	1.82	0.65-5.09	.25	.15
MP	0.69	0.45-1.06	.09	0.80	0.51-1.28	.35	0.81	0.51-1.28	.36	0.81	0.47-1.40	.44	0.80	0.44-1.46	.47	.99
PP	0.79	0.54-1.17	.23	1.00	0.63-1.59	1.00	1.00	0.63-1.59	.99	1.14	0.69-1.88	.61	0.91	0.50-1.65	.75	.46
Prevalence										Boys (n = 1465)			Girls (n = 1368)			
Current asthma (n = 2833)																
BP	0.83	0.59-1.18	.30	0.83	0.58-1.20	.32	0.83	0.58-1.19	.31	1.07	0.65-1.76	.80	0.69	0.40-1.17	.16	.25
EP	1.15	0.85-1.56	.37	1.10	0.81-1.50	.54	1.11	0.81-1.51	.52	1.09	0.66-1.78	.73	1.12	0.71-1.77	.61	.93
MP	1.17	0.93-1.46	.17	1.21	0.92-1.59	.17	1.21	0.92-1.60	.17	1.41	1.04-1.92	.03	1.03	0.70-1.52	.87	.16
PP	1.15	0.96-1.37	.13	1.17	0.95-1.43	.13	1.17	0.95-1.44	.13	1.24	0.96-1.59	.10	1.11	0.83-1.50	.47	.58

BP and EP values are modeled as less than LOD versus LOD or greater, and MP and PP values are modeled as log₁₀ concentrations in nanograms per milliliter.

cPOR, Crude prevalence odds ratio; P_{int}, interaction term P value (sex*biomarker concentration term).

*Crude models were adjusted for log₁₀ creatinine concentrations and multivariable models were adjusted for age in years, sex (except stratified models), poverty income ratio (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and other), survey cycle year (2005-2006, 2007-2008, 2009-2010, 2011-2012, and 2013-2014), log₁₀ creatinine concentrations, and serum cotinine concentrations.

†P < .05.

TABLE E2. Associations of exposure to parabens with respiratory morbidity measures among children with asthma and with current asthma, prevalence, adjusting for BMI z scores*

	Subsample of children with BMI data (BMI z score not in the model), cPOR			Subsample of children with BMI data (BMI z score not in the model), aPOR			Subsample of children with BMI data and BMI z score in the model, aPOR			Stratified results by sex on the subsample of children with BMI data and BMI z score in the models						<i>P</i> _{int}
	cPOR	95% CI	<i>P</i> value	aPOR	95% CI	<i>P</i> value	aPOR	95% CI	<i>P</i> value	Boys (n = 247)			Girls (n = 199)			
										aPOR	95% CI	<i>P</i> value	aPOR	95% CI	<i>P</i> value	
Morbidity																
ED visits (n = 446)																
BP	1.43	0.78-2.61	.25	1.44	0.73-2.83	.29	1.46	0.75-2.85	.26	2.19	0.78-6.12	.14	1.04	0.45-2.37	.93	.27
EP	1.07	0.56-2.05	.84	1.07	0.52-2.23	.85	1.10	0.52-2.33	.79	1.16	0.48-2.80	.74	1.06	0.36-3.13	.91	.90
MP	1.22	0.70-2.13	.48	1.22	0.63-2.38	.55	1.24	0.65-2.36	.52	2.59	1.41-4.75	.003†	0.59	0.24-1.45	.25	.001†
PP	1.09	0.72-1.66	.67	1.15	0.64-2.07	.64	1.16	0.65-2.05	.62	2.16	1.22-3.81	.008†	0.62	0.28-1.37	.23	.002†
Asthma attacks (n = 446)																
BP	1.51	0.85-2.67	.16	1.78	0.93-3.41	.08	1.74	0.92-3.27	.09	1.52	0.74-3.10	.25	1.94	0.76-4.98	.17	.67
EP	0.69	0.41-1.17	.17	0.82	0.46-1.43	.47	0.80	0.45-1.41	.43	0.54	0.27-1.09	.09	1.15	0.46-2.87	.76	.21
MP	0.76	0.55-1.06	.10	0.82	0.56-1.19	.28	0.81	0.55-1.18	.27	0.87	0.57-1.34	.53	0.75	0.43-1.30	.30	.62
PP	0.77	0.55-1.06	.11	0.86	0.59-1.25	.42	0.85	0.59-1.24	.41	0.95	0.65-1.40	.80	0.77	0.45-1.31	.33	.43
Prevalence																
Current asthma (n = 3993)																
BP	0.83	0.63-1.08	.16	0.83	0.62-1.11	.20	0.84	0.63-1.11	.22	0.95	0.64-1.41	.80	0.75	0.48-1.19	.22	.48
EP	1.15	0.90-1.48	.26	1.10	0.85-1.42	.46	1.11	0.86-1.43	.40	1.08	0.74-1.58	.69	1.14	0.78-1.67	.48	.84
MP	1.21	1.01-1.45	.04†	1.18	0.95-1.47	.14	1.20	0.96-1.48	.10	1.36	1.05-1.77	.02†	1.03	0.75-1.41	.87	.16
PP	1.21	1.04-1.41	.01†	1.20	1.01-1.44	.04†	1.22	1.02-1.45	.03†	1.25	1.00-1.56	.05	1.18	0.91-1.53	.21	.72

BP and EP values are modeled as less than LOD versus LOD or greater, and MP and PP values are modeled as log₁₀ concentrations in nanograms per milliliter.

cPOR, Crude prevalence odds ratio; *P*_{int}, interaction term *P* value (sex*biomarker concentration term).

*Crude models were adjusted for log₁₀ creatinine concentrations, and multivariable models were adjusted for age in years, sex (except stratified models), poverty income ratio (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and other), survey cycle year (2005-2006, 2007-2008, 2009-2010, 2011-2012, and 2013-2014), log₁₀ creatinine concentration, and BMI z score.

†*P* < .05.

TABLE E3. Associations of exposure to parabens with respiratory morbidity measures among children with asthma and with current asthma. prevalence, adjusting for log₁₀ triclosan, bisphenol A, and 2,5-dichlorophenol concentrations*

	All children, cPOR			All children (adjusting for log ₁₀ triclosan, bisphenol A, and 2,5-dichlorophenol concentrations), aPOR			Stratified results by sex adjusting for log ₁₀ concentrations of triclosan, bisphenol A, and 2,5-dichlorophenol						<i>P</i> _{int} value
	cPOR	95% CI	<i>P</i> value	aPOR	95% CI	<i>P</i> value	Boys (n = 248)			Girls (n = 202)			
Morbidity							Boys (n = 248)			Girls (n = 202)			
ED visits (n = 450)													
BP	1.43	0.78-2.63	.24	1.36	0.67-2.79	.39	2.22	0.78-6.28	.13	0.88	0.36-2.12	.77	.19
EP	1.07	0.56-2.05	.84	1.06	0.52-2.13	.87	1.18	0.48-2.88	.72	0.96	0.35-2.62	.94	.76
MP	1.22	0.70-2.14	.48	1.24	0.65-2.37	.51	2.70	1.42-5.14	.003†	0.57	0.25-1.30	.18	.001†
PP	1.10	0.72-1.66	.66	1.18	0.67-2.10	.56	2.24	1.25-4.02	.01†	0.60	0.30-1.24	.17	.001†
Asthma attacks (n = 450)													
BP	1.52	0.86-2.68	.15	1.81	0.93-3.55	.08	1.56	0.76-3.19	.22	2.06	0.76-5.58	.15	.63
EP	0.69	0.41-1.16	.16	0.82	0.47-1.43	.49	0.55	0.27-1.11	.09	1.22	0.50-2.98	.65	.17
MP	0.76	0.55-1.05	.09	0.81	0.56-1.18	.27	0.85	0.56-1.29	.44	0.78	0.45-1.33	.35	.77
PP	0.77	0.56-1.06	.11	0.86	0.59-1.26	.44	0.94	0.64-1.38	.74	0.80	0.47-1.36	.40	.56
Prevalence													
Current asthma (n = 4023)							Boys (n = 2068)			Girls (n = 1955)			
BP	0.82	0.63-1.08	.15	0.81	0.61-1.08	.15	0.96	0.64-1.42	.82	0.71	0.45-1.12	.14	.37
EP	1.14	0.89-1.47	.29	1.07	0.83-1.38	.61	1.08	0.74-1.58	.69	1.06	0.72-1.56	.77	.95
MP	1.21	1.01-1.45	.04†	1.16	0.93-1.44	.19	1.34	1.03-1.74	.03†	0.98	0.71-1.35	.90	.12
PP	1.21	1.04-1.41	.02†	1.18	0.99-1.41	.07	1.24	0.99-1.55	.06	1.13	0.87-1.47	.37	.58

BP and EP values are modeled as less than LOD versus LOD or greater, and MP and PP values are modeled as log₁₀ concentrations in nanograms per milliliter.

cPOR, Crude prevalence odds ratio; *P*_{int}, interaction term *P* value (sex*biomarker concentration term).

*Crude models were adjusted for log₁₀ creatinine concentrations, and multivariable models were adjusted for age in years, sex (except stratified models), poverty income ratio (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and other), survey cycle year (2005-2006, 2007-2008, 2009-2010, 2011-2012, and 2013-2014), and log₁₀-transformed creatinine, triclosan, bisphenol A, and 2,5-dichlorophenol concentrations.

†*P* < .05.