

ENVIRONMENTAL DETERMINANTS

Association of Urinary Bisphenol A Concentration with Allergic Asthma: Results from the National Health and Nutrition Examination Survey 2005–2006

SWAPNIL V. VAIDYA, M.D., PH.D.^{1,2} AND HEMANT KULKARNI, M.D.^{1,3,*}

¹Lata Medical Research Foundation, Nagpur, India.

²Allergy and Asthma Clinic of Central Texas, Killeen, TX 76542, USA.

³Texas Biomedical Research Institute, San Antonio, TX 78227, USA.

Objective. Bisphenol A (BPA) is being increasingly associated with adverse health effects. Our objective was to determine whether urinary BPA concentration is associated with allergic asthma in a representative US population. **Methods.** Data for this analysis were obtained from the National Health and Nutrition Examination Survey 2005–2006 survey and included asthma-related questions, total immunoglobulin E (IgE), 19 allergen-specific IgE levels, and urinary environmental phenol measurements. Allergic asthma was defined as a history of asthma ever, high eosinophil count, and high total IgE or atopy. Association analyses included dichotomous and polychotomous logistic regression, receiver operating characteristic curves, Akaike information criterion, and likelihood ratio χ^2 . **Results.** We found that 10-fold increase in BPA was independently associated with a higher likelihood of allergic asthma in females [odds ratio (OR) = 2.21, p = .032] but not in males (OR = 0.83, p = .474). These findings were reaffirmed when allergic asthma was defined based on atopy rather than total IgE (OR = 2.45, p = .001 in females and OR = 0.83, p = .605 in males). Urinary BPA was significantly associated with sensitization to various specific allergens in a dose–response manner. Lastly, urinary BPA independently predicted an asthma episode in the past 12 months in females but not in males. **Conclusions.** Urinary BPA is significantly associated with allergic asthma in females.

Keywords allergic asthma, allergy, asthma, bisphenol A, BPA, environmental estrogens, IgE

INTRODUCTION

The prevalence of atopic diseases, including asthma, has increased significantly in developed countries in the last few decades (1–3). Interestingly, this rise in prevalence has coincided with the introduction of various industrial chemicals (4). Bisphenol A (BPA), a commonly used industrial chemical, has been implicated in the pathogenesis of asthma and allergies (4–6). The use of BPA is ubiquitous—it is used to coat the insides of food and beverage cans and water pipes as well as many routinely used household products such as baby bottles, water bottles, dental fillings, dental sealants, and electronic items. (7).

As an endocrine-disrupting compound with estrogenic activity, BPA has been associated with various human diseases (8–12). Recent *in vitro* and animal studies suggest a possible role of BPA in the pathogenesis of allergic disease. For example, BPA has been shown to promote interleukin (IL)-4 production by T helper cell type 2 (Th2) cells and to promote T helper cell type 1 (Th1)/Th2 responses and reduce the number of CD4+CD25+ regulatory T cells (13, 14). Prenatal exposure to BPA in mice impairs development of tolerance to orally administered antigen (6) and the authors suggest that this could be related to the development of food allergy. Midoro-Horiuti et al. (5) have demonstrated that prenatal exposure to BPA enhances the development of asthma phenotype in mouse pups. More

recently, in humans, Spanier et al. (15) showed that maternal urinary BPA during pregnancy was associated with wheezing in early life in the child.

This study was based on the following three motivations. First, to our knowledge, currently there are no studies that have examined or demonstrated an association between environmental phenols and allergic disease in humans. Second, the effects of BPA in adults or after a possible late exposure are currently unclear. The emerging and existing data have preferentially focused on very early exposure (prenatal or perinatal) to BPA as a factor of concern in the developing child (4). Third, there is a lack of data on whether phenols like BPA might explain some gender differentials in asthma owing to its estrogenic activity. Considering these aspects of BPA kinetics, we hypothesized that environmental exposure to BPA is associated with an increased likelihood of allergic asthma in a gender-specific manner. We used the National Health and Nutrition Examination Survey (NHANES) 2005–2006 data to determine whether there is an association between urinary phenols and allergic asthma.

METHODS

NHANES 2005–2006 Data set

The NHANES is an annual survey conducted by the National Center of Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). It consists of a combination of interviews, physical examination,

*Corresponding author: Hemant Kulkarni, M.D., 12023 Waterway Rdg, San Antonio, TX 78249, USA; Tel: (1) 210-602-5537; Fax: (1) 210-558-3177; E-mail: hemant_kulkarnius@yahoo.com

and laboratory tests to assess the health and nutritional status of adults and children in the United States. The NHANES 2005–2006 survey contained allergy-related components, including an allergy questionnaire, asthma-related questions, and serum immunoglobulin E (IgE) measurements (total IgE and 19 allergen-specific IgEs). IgE levels were measured with the Pharmacia Diagnostics (Kalamazoo, MI, USA) ImmunoCAP 1000 System. The lower limit of detection (LLOD) for these assays was 2.00 kU/L for total IgE and 0.35 kU/L for each of the allergen-specific IgE. Urinary concentrations of eight phenols (including BPA) and parabens were quantified in 2548 survey participants. The spot urine sample was used to estimate total BPA concentration (i.e., free as well as conjugated) based on the online solid-phase extraction coupled with high-performance liquid chromatography–isotope dilution tandem mass spectrometry with peak focusing. The LLOD of this assay is 0.4 ng/mL. For the 182 samples below the LLOD, we used a value of 0.28 as suggested by Melzer et al. (16). Since the BPA concentrations were highly skewed, we used log-transformed concentrations for all analyses. The data on environmental phenols were available on subjects aged 6 years and over. The NHANES 2005–2006 survey was approved by the NCHS Ethics Review Board and all participants or parents (for minors) provided written consent. The Institutional Review Board of the Lata Medical Research Foundation does not need clearance for the use of publicly available de-identified data sets. Detailed description of the NHANES 2005–2006 survey can be found online at <http://www.cdc.gov/nchs/nhanes.htm>.

Dependent and Independent Variables

The NHANES medical conditions file contained questions related to medical history of the subjects. With regard to asthma status, there were three important questions: (i) Were you ever told you have asthma? (ii) Do you still have asthma? and (iii) Did you have an attack of asthma in the past 12 months? These three questions, conceptually, captured increasing likelihood of asthma.

Definitions of Allergic Asthma. We defined allergic asthma in two ways. Both these approaches have been used by other investigators in the past (17, 18). First, in addition to asthma ever status, we made use of two more variables available in the NHANES 2005–2006 data set—differential eosinophil count and total serum IgE levels. We dichotomized these two continuous variables based on their gender-specific sample means. Thus, we had three dichotomous variables: asthma ever, high eosinophil count, and high total serum IgE concentration. We used the eight resulting combinations to capture varying likelihood of allergic asthma. The highest likelihood of allergic asthma was conceptually considered when a subject had asthma ever, high eosinophil count, as well as high total serum IgE. Second, since it is conventional to consider the presence of one or more positive allergen-specific IgE as a marker of atopy, we reclassified allergic asthma by replacing high total IgE by the presence of atopy. Atopy was defined as the presence of one or more allergen-specific IgE in the excess of 0.35 kU/L.

Independent Variables. Our main set of independent variables were the urinary concentration of environmental phenols, gender, ethnicity, and age. We used the information for the following eight phenols and parabens available in the NHANES 2005–2006 data set—BPA, benzophenone 3, 4-*tert*-octylphenol, triclosan, methyl paraben, ethyl paraben, propyl paraben, and butyl paraben.

Statistical Analysis

Our analytical approach was aimed to demonstrate (i) the overall statistical association between urinary BPA concentration and allergic asthma; (ii) the specificity of this association in light of other urinary phenols; and (iii) gender differentials in this association. Since the “asthma ever” variable can be conceptually considered to be influenced by a potential recall bias, we also conducted the association analyses on the outcome of an asthma attack within the past 12 months as an outcome.

For demonstrating the overall association, we used the following statistical methods. Descriptive statistics included means, linearized standard errors, and proportions. The continuous variables that did not follow normal distribution were log-transformed to ensure normality. Statistical differences were tested using Student's *t*-test and χ^2 -test for categorical variables. Association with a multi-category dependent variable was tested using the multinomial (polychotomous) logistic regression analysis, while association with continuous dependent variable was tested using ordinary least squares multivariate linear regression. The goodness of fit of a model was assessed using predictive accuracy (estimated as area under a receiver characteristic curve), Akaike information criterion, and likelihood ratio χ^2 . To address the question about potential gender differentials in associations, we conducted all our analyses separately in males and females.

All the analyses were conducted using Stata 10.0 (Stata Corp., College Station, TX, USA) statistical software package. Since the NHANES data sets represent nationally representative population sampling units, we used the *svy* set of commands to adjust for the sampling weights and design variables as recommended by the CDC (<http://www.cdc.gov/nchs/tutorials/>). Statistical significance was evaluated at a type I error rate of 0.05.

RESULTS

Survey Population Characteristics

Of the 10,348 subjects in the complete NHANES 2005–2006 data set, urinary concentrations of phenols were available in 2548 (24.6%) subjects—1270 males and 1278 females. We used these subjects and data for analyses. Before commencing with the analyses, we first examined if the distribution of the key socio-demographic and asthma-related variables was comparable across the subjects included ($n = 2548$) and excluded ($n = 7800$) from this study. The results of this comparison are shown in Table 1. It can be seen from the table that the means and proportions of the key variables were similar across included and excluded subjects.

TABLE 1.—Characteristics of the subjects included in and excluded from this study.

Characteristic	Included ^a	Excluded ^a	<i>p</i> [*]
Number	2548	7800	
Age [mean (SD)], years	38.82 (0.90)	35.20 (0.75)	<.001
Race/ethnicity [n(%)]			.200
Mexican American	637 (8.7)	2210 (9.9)	
Other Hispanic	72 (3.2)	277 (4.0)	
Non-Hispanic White	1038 (70.1)	2890 (67.7)	
Non-Hispanic Black	678 (12.3)	2032 (12.4)	
Others	123 (5.8)	391 (6.1)	
Country of birth [n(%)]			0.123
The United States	2093 (86.1)	6701 (87.8)	
Mexico	279 (9.4)	682 (7.7)	
Elsewhere	176 (4.5)	417 (4.5)	
Asthma status [n(%)]			
Doctor told have asthma	341 (13.3)	1048 (15.0)	.333
Still have asthma	200 (56.1)	673 (61.3)	.829
Had asthma attack in past year	95 (54.5)	381 (61.2)	.182
Total serum IgE [mean(SD)] log ₁₀ kU/L	1.63 (0.01)	1.63 (0.02)	.781
Atopy (presence of ≥1 allergen-specific IgE) [n]	1356 (45.7)	3402 (49.7)	.010
Total white blood cell count (×1000 cells/μL)	7.45 (0.09)	7.38 (0.05)	.526
Differential white blood cell count (%)			
Neutrophils (mean) ×1000 cells/μL	4.36 (0.07)	4.18 (0.06)	.011
Lymphocytes (mean) ×1000 cells/μL	2.26 (0.05)	2.35 (0.02)	.128
Eosinophils (mean) ×100 cells/μL	2.10 (0.04)	2.23 (0.03)	.011
Monocytes (mean) ×100 cells/μL	5.74 (0.08)	5.76 (0.07)	.775
Basophils (mean) ×10 cells/μL	4.28 (0.03)	4.18 (0.01)	.719

^aNumbers in parentheses are linearized standard errors for means and sampling weight corrected proportions. These were estimated using the mean and proportion estimation subcommands, respectively, in the svy command in Stata.

^{*}Significance values were estimated using the linear (for continuous variables) and logistic (for categorical variables) estimation subcommands in the svy command in Stata.

However, the included subjects were 3.62 years older than the excluded subjects ($p < .001$), had a higher (180 cells/μL, $p = .011$) neutrophil count, a lower (13 cells/μL, $p = .011$) eosinophil count, and 4% lower ($p = .010$) prevalence of atopy. While these differences were statistically significant, we believe that their magnitude is not clinically meaningful.

The socio-demographic and clinical characteristics of the study subjects are shown in Table 2. The distribution of demographic characteristics like age, race, and country of birth was similar in males and females. The prevalence of asthma ever was 13.5% [95% confidence interval (CI) = 9.99–16.9%] in males and 13.2% (95% CI = 10.4–15.9%) in females; this difference was also not significant ($p = .853$). However, we observed that the prevalence of atopy was significantly higher in males as compared to females (55% vs. 43%). Similarly, laboratory features like blood counts, total serum IgE levels, and some urinary phenol concentrations were significantly different across gender (Table 2).

Association of Urinary BPA and Allergic Asthma

Since the distributions of most of the urinary phenol concentrations were highly skewed (data not shown), we used log-transformed urinary concentrations of these phenols in all the analyses. We found that the prevalence of allergic asthma (triple affliction in the form of asthma ever, high

TABLE 2.—Gender-specific characteristics of the subjects included in this study.

Characteristic	Males ^a	Females ^a	<i>p</i> [*]
Number	1270	1278	
Age [mean], years	38.09 (1.18)	40.06 (0.80)	.062
Race/ethnicity (n)			.166
Mexican American	313 (9.6)	324 (8.5)	
Other Hispanic	33 (2.9)	39 (3.5)	
Non-Hispanic White	520 (70.6)	518 (68.8)	
Non-Hispanic Black	349 (11.6)	329 (12.9)	
Others	55 (5.3)	68 (6.3)	
Country of birth (n)			.212
The United States	1039 (84.5)	1054 (86.8)	
Mexico	139 (9.9)	140 (9.1)	
Elsewhere	92 (5.5)	84 (4.0)	
Asthma status (n)			
Doctor told have asthma	176 (13.5)	165 (13.2)	.853
Still have asthma	102 (6.8)	98 (8.2)	.249
Had asthma attack in past year	51 (4.6)	44 (4.4)	.889
Total serum IgE [mean (SD)] log ₁₀ kU/L	1.75 (0.02)	1.51 (0.03)	<.001
Atopy (presence of ≥1 allergen-specific IgE) [n]	730 (54.9)	626 (42.9)	<.001
Total white blood cell count (mean) ×1000 cells/μL	7.27 (0.11)	7.65 (0.11)	<.001
Differential white blood cell count			
Neutrophils (mean) ×1000 cells/μL	4.17 (0.08)	4.58 (0.08)	<.001
Lymphocytes (mean) ×1000 cells/μL	2.23 (0.05)	2.28 (0.07)	.498
Eosinophils (mean) ×100 cells/μL	2.29 (0.06)	0.19 (0.03)	<.001
Monocytes (mean) ×100 cells/μL	6.04 (0.10)	5.45 (0.09)	<.001
Basophils (mean) ×10 cells/μL	4.11 (0.04)	4.55 (0.03)	.191
Urinary phenols (log ₁₀ ng/mL)			
BPA (mean)	0.32 (0.02)	0.24 (0.02)	.033
Benzophenone-3 (mean)	1.17 (0.06)	1.41 (0.03)	.003
4-tert-Octylphenol (mean)	−0.83(0.005)	−0.84 (0.004)	.125
Triclosan (mean)	1.32 (0.04)	1.21 (0.03)	.015
Methyl paraben (mean)	1.47 (0.04)	2.02 (0.05)	<.001
Ethyl paraben (mean)	0.14 (0.02)	0.47 (0.03)	<.001
Propyl paraben (mean)	0.47 (0.05)	1.31 (0.05)	<.001
Butyl paraben (mean)	−0.61 (0.03)	−0.04 (0.04)	<.001

^aNumbers in parentheses are linearized standard errors for means and sampling weight corrected proportions. These were estimated using the mean and proportion estimation subcommands, respectively, in the svy command in Stata.

^{*}Significance values were estimated using the linear (for continuous variables) and logistic (for categorical variables) estimation subcommands in the svy command in Stata.

eosinophil count, and high total serum IgE concentration) was 5.5% in males and 5.7% in females (p for difference of prevalence across genders = .831). We found that there was a trend toward an overall significant difference in the mean BPA concentration across categories as indicated by a survey design corrected ANOVA p -value of .011 in females but not in males ($p = .907$). The mean concentration of the urinary BPA in the subjects with the triple affliction group was highest in females but not in males.

The results of polychotomous logistic regression analyses indicated (Table 3) that the allergic asthma representative group was associated with a significantly higher likelihood for each 10-fold increase in urinary BPA concentration in females but not in males. It should be noted that the polychotomous logistic regression models included all other urinary phenols, ethnicity, and age as covariates.

TABLE 3.—Association of urinary BPA with allergic asthma.

Categories of allergic asthma			Males			Females		
Asthma ever	High eosinophil count	High total serum IgE	N	Mean (LSE) log ₁₀ BPA ng/mL	Adjusted OR (95% CI); <i>p</i>	N	Mean (LSE) log ₁₀ BPA ng/mL	Adjusted OR (95% CI); <i>p</i>
—	—	—	388	0.32 (0.02)	1.00	381	0.22 (0.04)	1.00
—	—	+	269	0.38 (0.04)	1.46 (0.87–2.49); .143	313	0.22 (0.04)	0.91 (0.57–1.44); .655
—	+	—	156	0.20 (0.04)	0.62 (0.40–0.98); .043	145	0.24 (0.05)	1.20 (0.78–1.86); .404
—	+	+	194	0.30 (0.06)	0.70 (0.33–1.47); .320	183	0.25 (0.04)	1.16 (0.60–2.27); .634
+	—	—	39	0.34 (0.14)	1.01 (0.19–5.46); .983	30	0.32 (0.14)	1.63 (0.40–6.66); .472
+	—	+	45	0.42 (0.14)	1.61 (0.34–7.62); .527	37	0.22 (0.13)	0.90 (0.27–2.95); .850
+	+	—	13	0.40 (0.24)	1.58 (0.16–16.0); .682	24	0.19 (0.11)	1.27 (0.43–3.76); .643
+	+	+	61	0.30 (0.06)	0.83 (0.48–1.44); .474	63	0.40 (0.07)	2.21 (1.08–4.53); .032

Notes: ORs were estimated using polychotomous logistic regression and after adjusting for other urinary phenols included in the study, ethnicity, age, and the survey design by using the svy command in Stata. OR, odds ratio; CI, confidence interval; LSE, linearized standard error.

Association of Urinary BPA with Atopy

We then examined the concentration of urinary BPA in subjects with different numbers of positive allergen-specific IgEs. Our results (Figure 1) identified a trend between a high mean log₁₀BPA concentration in male [odds ratio (OR) = 1.40, *p* = .139] and female (OR = 1.25, *p* = .285) subjects with >6 and >4 positive

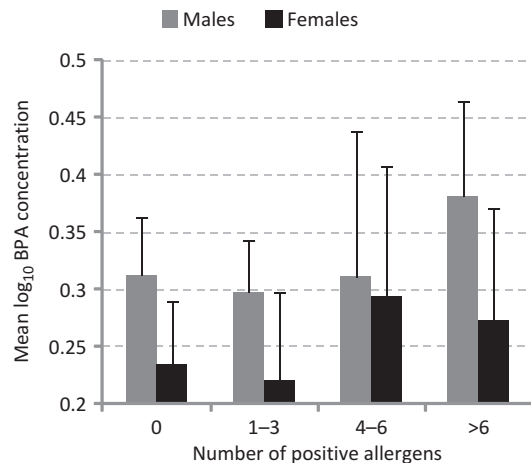


FIGURE 1.—Gender-specific distribution of urinary BPA based on atopy status. Bar graph shows the mean and 95% CIs (error bars) of log₁₀ BPA concentrations for a given number of allergens against which specific IgE was positive.

allergen-specific IgE tests, respectively. When males and females were analyzed together, a high number of positive allergen-specific IgE tests (defined as >6 for males and >4 for females) were associated with a statistically significant high mean log₁₀BPA (OR = 1.30, *p* = .05). Therefore, we ran a polychotomous multivariate logistic regression model (similar to the one specified in Table 3) for the second definition of allergic asthma that used the presence of atopy as a classifier in the place of total serum IgE levels. The results of these analyses (Table 4) fully corroborated those shown in Table 3.

Independent Association of Urinary BPA with Current Asthma

Finally, we investigated whether the urinary BPA was independently associated with current asthma. For these analyses, the dependent variable was occurrence of an asthma episode during the past 12 months. Using logistic regression analyses and receiver operating characteristic curves, we found that the most predictive variable for current asthma was high total serum IgE (Model 1 in Table 5) followed by high eosinophil count (Model 2) and then by urinary BPA concentration (Model 3) in females but not in males. Thus, the addition of urinary BPA to high eosinophil and high IgE improved the predictive performance indicating an additive and independent value of urinary BPA concentration to predict asthma episode within past 12 months in females.

TABLE 4.—Association of urinary BPA with allergic asthma (alternative definition).

Categories of allergic asthma			Males			Females		
Asthma ever	High eosinophil count	Atopy	N	Mean (LSE) log ₁₀ BPA ng/mL	Adjusted for other phenols OR (95% CI); <i>p</i>	N	Mean (LSE) log ₁₀ BPA ng/mL	Adjusted for other phenols OR (95% CI); <i>p</i>
—	—	—	362	0.34 (0.02)	1.00	417	0.22 (0.03)	1.00
—	—	+	299	0.34 (0.02)	0.95 (0.71–1.28); .736	283	0.21 (0.05)	0.85 (0.54–1.36); .477
—	+	—	132	0.25 (0.05)	0.71 (0.40–1.27); .231	178	0.24 (0.04)	1.17 (0.78–1.77); .422
—	+	+	220	0.25 (0.04)	0.47 (0.28–0.77); .006	154	0.24 (0.05)	1.12 (0.58–2.18); .718
+	—	—	30	0.32 (0.16)	0.76 (0.15–3.98); .731	28	0.37 (0.16)	2.08 (0.43–10.0); .335
+	—	+	54	0.42 (0.12)	1.34 (0.33–5.46); .661	40	0.18 (0.14)	0.77 (0.19–3.03); .685
+	+	—	13	0.22 (0.16)	0.55 (0.14–2.15); 0.365	26	0.21 (0.06)	1.31 (0.78–2.19); .285
+	+	+	61	0.34 (0.07)	0.83 (0.40–1.74); .605	61	0.43 (0.05)	2.45 (1.53–3.91); .001

Notes: ORs were estimated using polychotomous logistic regression and after adjusting for other urinary phenols included in the study, ethnicity, age, and the survey design by using the svy command in Stata. OR, odds ratio; CI, confidence interval; LSE, linearized standard error.

TABLE 5.—Additive value of clinically relevant independent variables to predict an asthma episode within past 12 months.

Parameter	Males, N = 1051	Females, N = 1062
<i>Model 0: Null model</i>		
Predictive accuracy (%)	50.00	50.00
Akaike information criterion	367.38	342.80
Likelihood chi-square	0.00	0.00
<i>Model 1: High total serum IgE only</i>		
Predictive accuracy (%)	64.51	65.73
Akaike information criterion	354.66	328.53
Likelihood chi-square	14.72	16.27
<i>Model 2: High total serum IgE and high eosinophil count</i>		
Predictive accuracy (%)	68.69	74.96
Akaike information criterion	351.09	311.25
Likelihood chi-square	20.28	35.54
<i>Model 3: High total serum IgE, high eosinophil count, and high urinary BPA</i>		
Predictive accuracy (%)	69.77	77.25
Akaike information criterion	351.09	306.86
Likelihood chi-square	21.22	41.94

DISCUSSION

Allergic Asthma, BPA, and IgE

In these analyses of the NHANES 2005–2006 data, we show that urinary BPA, which most likely indicates environmental BPA exposure (19), is associated with allergic asthma in females. This association was consistently seen when allergic asthma was defined in two different ways—(1) history of asthma ever + high eosinophil count + high total serum IgE and (2) history of asthma ever + high eosinophil count + one or more positive allergen-specific IgE. Interestingly, in both scenarios, urinary BPA was not associated with the nonallergic asthma groups. The hallmark of allergic diseases is the presence of a Th2 and allergen-specific IgE responses. Our finding that BPA is associated with allergic asthma but not nonallergic asthma suggests that it might play a role in the pathogenesis of the allergic immune response. One possible interpretation of these findings is that BPA may act as an allergic sensitizer and induce specific IgE responses. This interpretation is not supported by this cross-sectional data set, but it is compatible with previous *in vitro* and animal studies demonstrating that BPA indeed acts as an allergic sensitizer by inducing Th2 and specific IgE responses (13, 20, 21). This suggests that the association between BPA and allergic asthma is, at least in part, IgE mediated.

Gender Differentials

An interesting finding in this study was a gender difference with respect to the association between BPA and allergic asthma. When urinary BPA was considered as a continuous variable in the regression analysis, a significant association with allergic asthma was seen only in females but not in males. These findings suggest that in females there is a dose–response relationship between urinary BPA and allergic asthma—a gradual increase in the OR for allergic

asthma with increasing urinary BPA. We hypothesize that this gender difference is related to the estrogenic activity of BPA and the inherent differences in sensitivities of male and female immune systems to estrogens. Related to this concept is the human immune system sexual dimorphism that is seen with respect to autoimmune disorders, like systemic lupus erythematosus and rheumatoid arthritis that are more prevalent in females than in males. Sex hormone receptors, including estrogen receptors, are expressed on nonsexual tissues such as cells of the immune system and estrogens regulate the immune system and play a role in this sexual dimorphism (22–24).

Mechanistic Implications

The predictive modeling data show that urinary BPA is associated with asthma episode in the past 12 months independently of high total IgE and high eosinophil count. This suggests that the association between BPA and an asthma episode in the previous 12 months is at least partly non-IgE, non-eosinophilia mediated. This finding can still be explained by the hypothesis that BPA acts as an allergic or Th2 sensitizer. As a Th2 promoting agent, BPA could enhance production of all three prototypic Th2 cytokines: IL-4, IL-5, and IL-13. Of these cytokines, IL-4 plays a role in IgE class switching, while IL-5 acts as an eosinophil growth factor and chemotactic agent leading to peripheral and tissue eosinophilia. Hence, the non-IgE, non-eosinophilia effects of BPA could potentially be mediated through the actions of IL-13. While direct biological evidence for this hypothesis is lacking, we believe that the hypothesis presents an interesting direction for future research.

Study Limitations

We recognize several limitations to this study. First, since this is a secondary data analysis, any sample selection biases in the original survey will affect the interpretation and generalization of these findings. Second, we also realize that the misclassification or incorrect definition of the dependent variable (allergic asthma) will affect interpretation of the findings. To mitigate this, we have used two well-accepted definitions of allergic asthma in this study and the results in both scenarios are comparable. Third, the dichotomization of continuous variables used in the predictive modeling in this study was based on sample means, which will be specific to the survey population. As a result, findings of the predictive modeling directly apply only to the NHANES 2005–2006 survey population and cannot be extrapolated to the general population. Fourth, since the NHANES 2005–2006 was a cross-sectional survey and there is lack of data on longitudinal exposure to environmental phenols, we can only make conclusions of association between the variables and causality cannot be claimed with certainty. Fifth, urinary BPA is assumed to indicate environmental exposure to BPA (19). However, in the absence of actual exposure data and/or pharmacokinetic data for BPA, this assumption also cannot be claimed with certainty. Urinary BPA concentrations were done at a single time point and one could argue that they only

represent current exposure and not a history of exposure to BPA. This being a cross-sectional survey, assessments about temporal exposure to BPA cannot be made. However, it is felt that in a population setting averaging effects will allow for consideration of a longer exposure to BPA in the past. Furthermore, single urinary BPA measurements could be indicative of urinary BPA concentrations in the past if survey participants did not have significant lifestyle changes, and hence changes in BPA exposure, around the time of this survey. Finally, in studies of this nature it is a common practice to adjust for urinary creatinine as a surrogate for urinary dilution (25). However, for this specific data set You et al. (26) have demonstrated that there exists a correlation between the urinary BPA concentration and renal function. Therefore, if we would have attempted to correct for urinary creatinine we could have falsely negated the association between urinary BPA concentration and allergic asthma. Future studies need to address this limitation before BPA–allergic asthma association can be established.

CONCLUSIONS

In summary, although causality cannot be proved due to a cross-sectional disposition of the data set analyzed, the findings of this study are of sufficient public health concern. Our findings demonstrate a consistent, specific, and independent association of urinary BPA concentration with allergic asthma in females. Further longitudinal and mechanistic studies in humans will shed more light on the direction and strength of this association. Also it will be interesting to look at more specific subpopulations categorized on the basis of age, gender, and degree of exposure to examine the consistency and generalizability of our observations.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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