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Association of Urinary Levels of Bisphenols F and S Used as Bisphenol A Substitutes with Asthma and Hay Fever Outcomes

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Abstract

Background—Bisphenols F (BPF) and S (BPS) are bisphenol A (BPA) analogs used as substitutes in consumer products. Despite previous reports of BPA's association with asthma, no studies have examined its structural analogs in relation to asthma and allergy outcomes.

Objective—To examine the association of urinary BPF, BPS, and BPA with asthma and hay fever in a US representative sample.

Methods—We analyzed data from 3,538 participants aged 12 years or older in the 2013–2016 National Health and Nutrition Examination Survey (NHANES). Children aged 6–11 years (N=738), who did not have all covariate data available, were analyzed separately. Covariate-adjusted logistic regression was used to assess the association of the exposures with the outcomes.

Results—BPF, BPS, and BPA were detected in 57.1%, 88.4%, and 94.8% of the urine samples, respectively. Urinary BPF detection was positively associated with current asthma (odds ratio [OR]: 1.54, 95% confidence interval [CI]: 1.16–2.04) and hay fever (OR: 1.66, 95% CI: 1.12–2.46). Urinary BPS was associated with increased odds of current asthma in men (OR: 1.64, 95% CI: 1.13–2.40) and urinary BPA was associated with increased odds of asthma without hay fever in children aged 6–11 years (OR: 2.65, 95% CI: 1.05–6.68).

Conclusion—Our nationally-representative findings document that BPF and BPS exposure is common in the US and that exposure to these BPA analogs is associated with asthma and/or hay fever. Our results suggest that BPF and BPS may not be safe alternatives to BPA; however, prospective studies should be conducted to confirm these results.

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Keywords

Bisphenol; Endocrine disrupting chemicals; Bisphenol A substitutes; Asthma; Hay fever; Allergy

1. INTRODUCTION

Bisphenols are compounds with two hydroxyphenyl groups that are extensively used in the production of polycarbonate plastics and epoxy resins (Ye et al., 2015). The most common of them is bisphenol A (BPA), which was initially tested as a synthetic estrogen but later became useful in the making of plastics and is now one of the most commonly used chemicals worldwide (Eladak et al., 2015). BPA is found in thermal print paper, dental sealants, and the inside lining of some food and beverage containers (Thoene, Rytel, Nowicka, & Wojtkiewicz, 2018). The route of exposure to BPA is mainly through ingestion of contaminated food or beverages and, to a lesser extent, through skin and via inhalation of house dust (Eladak et al., 2015). BPA has been associated with cardiovascular, respiratory, metabolic, renal and reproductive disorders, leading to its restriction and ban from certain food or beverage packaging in several countries (Eladak et al., 2015; Lang et al., 2008).

The safety concerns of BPA has prompted its replacement by analogs such as bisphenol F (BPF) and bisphenol S (BPS) in products often advertised as “BPA free” (Eladak et al., 2015). BPF and BPS can be found in food packaging items and beverage containers as well as in paper products. In addition, BPF is used in pipe and tank linings because of its ability to increase the durability and thickness of materials, while BPS can be found in cleaning and corrosion inhibiting agents (Rochester & Bolden, 2015). Over the last decade, the use of these substitutes has increased significantly leading to higher environmental exposure to these compounds (Eladak et al., 2015; Rochester & Bolden, 2015).

The association of BPA with asthma and allergic diseases is well-known and has been reported in animal and human studies (Bonds & Midoro-Horiuti, 2013; Midoro-Horiuti, Tiwari, Watson, & Goldblum, 2010; Spanier, Adam J. et al., 2014; Spanier, Adam J., Fiorino, & Trasande, 2014). Animal models have shown that BPA can affect pulmonary function and cause airway inflammation (Midoro-Horiuti et al., 2010; Spanier, Adam J. et al., 2014; Spanier, Adam J. et al., 2014). Due to the presence of estrogen receptors in immunomodulatory cells, BPA can also influence immune responses by acting as a xenoestrogen to promote T-helper type 2 cell responses. This may lead to an increased production of immunoglobulin E and to enhanced mast cell and basophil degranulation (Bonds & Midoro-Horiuti, 2013). Although *in vitro* and animal studies have suggested that bisphenol analogs such as BPF and BPS might have similar health effects as BPA, only a few studies have associated them with disease in humans (Duan et al., 2018). Moreover, no published animal or human studies have investigated the relationship between BPA substitutes and asthma or allergy outcomes to date (Rochester & Bolden, 2015). In this report, we examined the association of exposure to BPF, BPS, and BPA measured by their concentration in urine with asthma outcomes and hay fever in a large, nationally representative sample of the U.S. population.

2. METHODS

2.1. Data Source

We used data from the 2013–2016 cycles of the National Health and Nutrition Examination Survey (NHANES). NHANES is a continuous, cross-sectional survey conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) designed to assess the health status of children and adults in the U.S. It uses a complex multistage sampling design to derive a sample representative of the noninstitutionalized civilian population of the U.S. and collects data through interviews, physical examinations, and laboratory tests (CDC & NCHS, 2018). NHANES measured urinary bisphenols in a subset of 4,276 participants aged 6 years or older who participated in the survey from 2013 to 2016 (25.3% of all NHANES participants). Our main analysis included participants aged 12 years or older (N=3,538) who had data on asthma and hay fever outcomes, as well as all covariates, including serum creatinine that was used to assess kidney function. Because kidney function was not estimated for children aged 6 to 11 years old, results for this age group are reported separately in the online supplement (N=738). NHANES protocols were approved by the Institutional Review Boards of the NCHS and CDC and informed consent was obtained from all participants (CDC & NCHS, 2018).

2.2. Assessment of Urinary BPF, BPS, and BPA

Spot urine samples were collected from each participant, processed, stored at −20°C and shipped for analysis to the Division of Laboratory Sciences of the National Center for Environmental Health at the CDC. Urinary BPF, BPS, and BPA were measured using on-line solid phase extraction coupled to high performance liquid chromatography and tandem mass spectrometry. The lower limit of detection (LOD) was 0.2 μg/L for BPF and BPA and 0.1 μg/L for BPS. Samples with levels below the LOD were assigned the value LOD/$\sqrt{2}$. Detailed descriptions of the laboratory procedures and methods have been described previously (CDC, 2016).

2.3. Asthma and Hay Fever Outcomes

Asthma outcomes were assessed by questionnaire administered to participants aged 15 years or older or to the household reference (HR) person for those younger than 15 years old. Current asthma was defined as affirmative responses to the questions "*Has a doctor or other health professional ever told you that you have asthma?*" and "*Do you still have asthma?*" Participants who provided a negative answer to either of the two questions were classified as not having current asthma. Asthma attacks in the past 12 months was defined using the question "*During the past 12 months, have you had an episode of asthma or an asthma attack?*" Hay fever was defined with the question *"During the past 12 months, have you had an episode of hay fever?"* and based on the use of any medication for allergic rhinitis in the past 30 days.

2.4. Covariates

Data on age, sex, race/ethnicity, annual household income, exposure to cigarette smoking, education level of HR person, and family history of asthma were collected using

questionnaires. Poverty income ratio (PIR), which was used as a proxy for socioeconomic status, was estimated using guidelines and adjustment for family size, year and state. (Beckles, Truman, & CDC, 2011). Exposure to cigarette smoking was defined as self-reported smoking or living with a household member who smoked inside the home. Family history of asthma was defined as having a close family member such as parents or siblings who had asthma. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. It was categorized into levels <25 kg/m^2 (normal), between 25 and <30 kg/m^2 (overweight), and ≥30 kg/m^2 (obese) in adults aged 18 years or older. In children and adolescent younger than 18 years old, BMI was categorized into levels <5th percentile (underweight), ≥5th percentile to <85th percentile (normal), ≥85th percentile to <95th percentile (overweight), and ≥95th percentile (obese) as suggested by the CDC (Davidson et al., 2014). Urinary creatinine was measured by quantitative enzymatic determination and served to account for urine dilution. Serum creatinine was measured with a kinetic rate Jaffe method. It was used to evaluate renal function by calculating the glomerular filtration rate (GFR) based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for adults 18 years or older and the Schwartz formula for children (Levey et al., 2009; Schwartz et al., 2009).

2.5. Statistical Analysis

Descriptive analyses were performed to examine the central tendency and variability of the creatinine-corrected levels of BPF, BPS, and BPA (calculated by dividing urinary analyte levels by creatinine concentration). The P-values for differences in bisphenol levels by characteristics were calculated using independent t-test for variables with two levels and analysis of variance for variables with three categories or more. The intercorrelation between bisphenols was explored with the Spearman correlation coefficient. Because of their log-normal skewed distributions, BPS and BPA were log_{10}-transformed to improve normality and to produce a more equal spread in the distribution of exposure. The geometric mean concentrations and the corresponding standard errors (SE) of the urinary bisphenols were calculated for the different characteristics of the study participants to identify subgroups of individuals with higher levels of exposure. Logistic regression was used to calculate the odds ratio (OR) and 95% confidence interval (CI) for the association of the urinary bisphenols with the asthma outcomes and hay fever. Current asthma was further categorized into asthma with hay fever (suggestive of atopic asthma) and asthma without hay fever (suggestive of non-atopic asthma). The ORs were modeled for the detection of BPF in urine (given the high proportion of samples with BPF levels below detection) as well as for the log_{10}-transformed BPS and BPA concentrations. The models were adjusted for socio-demographic characteristics (age, sex, race/ethnicity, PIR, and education level of HR person), known asthma risk factors (exposure to cigarette smoke, BMI, and family history of asthma), GFR, and mutually for the bisphenols. To correct for urine dilution in the regression analysis, urinary creatinine was included as a separate independent variable in the models, along with the crude bisphenol concentrations as recommended by Barr et al. (2005). This approach ensures that the associations of the exposures is independent of the effects of creatinine (Barr et al., 2005). We also adjusted for kidney function (GFR) because of reports that urinary excreted chemicals might be increased as a result of impaired kidney function, which could be caused by asthma and other respiratory outcomes (Kataria, Trasande, & Trachtman,

2015). Age (adolescents 12–17 years old, adults aged 18 to 59 years old, and adults aged 60 to 80 years old), sex, BMI (non-overweight/obese [BMI <25 kg/m^2] versus overweight/obese [BMI ≥25 kg/m^2]), and exposure to cigarette smoke (being a smoker or being exposed to secondhand smoking) were tested for effect modification on the association of the bisphenols with current asthma. Effect modification on the associations of bisphenols with asthma attacks and hay fever was not explored because of the smaller number of outcome events limiting subgroup analyses. These factors were selected based on previous reports of differential associations of BPA with asthma by age and sex (Petzold, Averbeck, Simon, Lehmann, & Polte, 2014). Obesity and smoking have also been found to modify the association of other pollutants such as polycyclic aromatic hydrocarbon or ambient air pollution with asthma (Lin, Karmaus, Chen, Hsu, & Wang, 2018; Wang, Chen, & Bornehag, 2016; Youssef et al., 2018). Stratified analyses by sex were performed on the association of bisphenols with asthma outcomes and analyses restricted to adults, after exclusion of adolescents were done and the results were reported in the supplemental materials. We additionally explored potential interactions between BPF, BPS, and BPA in their relationship with current asthma on a multiplicative scale by including interaction terms in the models. Models' performance and quality were assessed using the concordance statistic (c-statistic) and a comparison of the model Akaike information criterion (AIC) to the intercept only AIC. All the models had a c-statistic >70%, showing good performance and we found an increase in quality for each of our models compared to unadjusted models. The analyses were performed in SAS (Version 9.4; SAS Institute, Cary, NC), accounting for the NHANES sampling weights and complex survey design to provide nationally representative estimates. Two-sided p-values <0.05 were considered statistically significant.

3. RESULTS

3.1. Descriptive Results

Among the 3,538 adolescents and adults included in our study, BPF was detected in 57.1% of the urine samples, while BPS and BPA were detected in 88.4% and 94.8% of the samples, respectively. The geometric mean [SE] levels corrected for creatinine for BPF (0.46 [0.02] μg/g creatinine) and BPS (0.44 [0.02] μg/g creatinine) were comparable and both were much lower than the urinary BPA levels (1.16 [0.04] μg/g creatinine) (Table 1). Weak correlations were found between creatinine-corrected BPF and BPS (Spearman correlation coefficient [r_s]=0.04), between creatinine-corrected BPF and BPA (r_s=0.14), and between creatinine-corrected BPS and BPA (r_s=0.10). The distribution of crude bisphenol levels and the distribution of creatinine-corrected concentrations of bisphenols by NHANES cycle is described in Supplemental Tables S1 and S2.

Table 2 shows the levels of creatinine-corrected bisphenols by characteristics of study participants. Creatinine-corrected BPF was higher in non-Hispanic Whites and increased with higher PIR. Creatinine-corrected BPS increased with age and decreased with PIR as well as the education level of the HR person. It was also higher in women, in non-Hispanic Blacks and Mexican-Americans (compared to non-Hispanic Whites), and in obese individuals. Creatinine-corrected BPA also increased with age and was higher in women, in participants with a HR person who had at most a high school education and in participants

exposed to cigarette smoke. The crude levels of BPF, BPS, and BPA by characteristics of study participants are shown in Table S3

The prevalence of asthma outcomes and hay fever was 9.0% for current asthma, 4.2% for asthma attacks in the past 12 months, and 4.6% for hay fever. Creatinine-corrected levels [SE] of BPF were higher in participants with current asthma (0.59 [0.07] versus 0.45 [0.02], P=0.02) (Table 2). The prevalence of current asthma, asthma attacks in the past 12 months, and hay fever was higher in participants with detected BPF than in those with non-detected BPF (10.5% versus 7.0%, P=0.003 for current asthma; 4.8% versus 3.3% for asthma attacks, P=0.02; and 5.6% versus 3.2% for hay fever, P=0.01) (Table S4). Urinary levels of BPS or BPA did not differ by asthma or hay fever (Table 2).

3.2. Association of BPF, BPS, and BPA with Asthma and Hay Fever

In adjusted logistic regression analysis, BPF detection in urine was associated with higher odds of current asthma (OR: 1.54, 95% CI: 1.16–2.04) and hay fever (OR: 1.66, 95% CI: 1.12–2.46) (Table 3). When asthma was classified by presence or absence of hay fever, urinary BPF detection was positively associated with current asthma with hay fever (OR: 1.66, 95% CI: 1.06–2.61) and with asthma without hay fever (OR: 1.47, 95% CI: 0.99–2.19). The association between urinary BPF detection and current asthma was stronger in adults aged 18 to 59 years old (OR: 2.10, 95% CI: 1.43–3.07) ($P_{interaction}$=0.03) (Table 4).

The association of urinary BPS with current asthma was modified by sex ($P_{interaction}$=0.01). A 10-fold increase in urinary BPS was associated with increased odds of current asthma in men (OR: 1.64, 95% CI: 1.13–2.40), while in women, the association was inverse but did not reach statistical significance (OR: 0.73, 95% CI: 0.51, 1.06) (Table 4).

BPA was not associated with increased prevalence of asthma outcomes or hay fever in the main sample of participants aged 12 years or older (Table S5). However, in children aged 6 to 11 years, urinary BPA was positively associated with asthma without hay fever (OR: 2.65, 95% CI: 1.05–6.68) (Table S6).

The results of the adjusted analysis stratified by sex are shown in Supplemental Table S7 and the results of the adjusted analysis restricted to adults are shown in Supplemental Table S8. The associations of urinary BPF detection with higher prevalence of asthma outcomes were significant in women (OR: 1.54, 95% CI: 1.17–2.04 for current asthma and OR: 1.59, 95% CI: 1.04–2.43 for asthma attacks in the past 12 months), but not in men, although there was no significant interaction ($P_{interaction}$=0.85) (Table S7). After restricting the analysis to adults, we found stronger associations between BPF detection in urine and current asthma (OR: 1.71, 95% CI: 1.26–2.33) and hay fever (OR: 1.75, 95% CI: 1.11–2.75) (Table S8).

4. DISCUSSION

This nationally representative study is the first to report an association of the BPA substitutes, BPF and BPS, with asthma outcomes. Our results suggested that BPF detection in urine was associated with increased prevalence of current asthma and hay fever. The positive association of BPF with current asthma was mainly observed in adults. Higher odds

of current asthma were found in relation to urinary BPS only in men and urinary BPA was associated with increased odds of asthma without hay fever in children aged 6 to 11 years old.

In descriptive analysis, we found that urinary BPF levels increased with PIR and were higher in non-Hispanic Whites than in all the other racial/ethnic groups. It is unclear why urinary BPF was elevated in people with higher socioeconomic status; however, these participants might be more aware of potential health effects of BPA, and thus more likely to buy products labelled as “BPA free”. In contrast, levels of urinary BPS were higher in low-income participants. Because BPS is found in cleaning and corrosion inhibiting products as well as in thermal print papers, it is probable that individuals with a low socioeconomic status might be more likely to be exposed to BPS due to occupational exposures (Chen et al., 2016; Molina-Molina et al., 2019). Consistent with previously reported associations of BPS with obesity in animal models (Meng et al., 2019), urinary BPS levels were higher in obese participants. Urinary BPA levels were more elevated in participants exposed to cigarette smoking, which could be explained by reports that BPA is contained in cigarette filters (Braun et al., 2010).

BPF and BPS, which are structural analogs of BPA, are thought to have comparable estrogenicity and may exhibit effects like those of BPA that has previously been shown to be associated with asthma outcomes (Le Fol et al., 2017). Since no previous human or animal studies have examined the association of BPF and BPS with asthma and allergic diseases, we compared our results to the published data on BPA. Regarding the association of BPF with asthma and hay fever, Tajiki-Nishino et al. found that BPA exacerbates toluene diisocyanate-induced airway inflammation in BALB/c mice (Tajiki-Nishino et al., 2018). In addition, BPA has been reported to worsen lung eosinophilia and ovalbumin-induced airway inflammation in CD-1 and C3H/HeJ mice via activation of T-helper type 2 cytokines and macrophages and to increase immune system disruption (Koike, Yanagisawa, Win-Shwe, & Takano, 2018). Recent animal investigations have reported a relationship between BPA and the development of asthma (Nakajima, Goldblum, & Midoro-Horiuti, 2012; Petzold et al., 2014). In epidemiologic studies, the association of BPA with asthma has also been widely reported, especially in children who were exposed perinatally (Donohue et al., 2013; Gascon et al., 2015; Kim et al., 2014; Lin et al., 2018; Spanier, Adam J. et al., 2014; Spanier, A. J. et al., 2012; Wang et al., 2016; Youssef et al., 2018). We found that the association of BPF with asthma outcomes differed by age and that urinary BPF was mainly associated with current asthma in adults. The age-dependent effects of BPA on the risk of asthma in a murine model was studied by Pretzold et al. who exposed BALB/c mice to drinking water containing BPA at different age periods, including prenatally (Petzold et al., 2014). They found that lifelong exposure to BPA from birth to adulthood was associated with increased allergic airway inflammation, while perinatal BPA exposure was not associated with asthma. Surprisingly, BPA exposure only in adulthood decreased allergic immune response in that study (Petzold et al., 2014). On the other hand, there is evidence that the developing immune system during childhood might be particularly vulnerable to the asthma promoting effect of BPA (Petzold et al., 2014). In juvenile mice, exposure to low doses of BPA has also been observed to enhance allergic airway inflammation (Koike et al., 2018). In our study, it is unclear whether

the association of BPF with asthma outcomes observed in adults reflects a longer lifetime exposure or an increased susceptibility of adults.

Our results suggested that the relationship between BPS and current asthma was dependent on sex and was only found in men. Consistent with this finding, stronger associations of BPA with childhood asthma and wheeze have been reported in boys than in girls (Buckley et al., 2018; Wang et al., 2016; Zhou et al., 2017). Yet, in other studies, the associations between BPA and asthma have been observed mostly in females (Xie et al., 2016). In mice, prenatal exposure to BPA has been shown to increase airway and lung inflammation in female offspring but decrease inflammation in male offspring (Bauer et al., 2012). Female-specific effects have also been observed in human studies. Vaidya & Kulkarni investigated the association between urinary BPA and asthma in a large nationally representative sample of the U.S. population. They found a positive association between BPA and an allergic phenotype of asthma in women but not in men. In their study, which included both adults and children, urinary BPA levels were much higher than in the present study, and asthma outcome was defined as being ever diagnosed with asthma and was categorized into phenotypes using both serum IgE and blood eosinophils (Vaidya & Kulkarni, 2012). Two other studies, however, did not observe sex differences in the relationship between BPA and asthma outcomes (Gascon et al., 2015; Spanier, A. J. et al., 2012). The mechanisms responsible for these sex-dimorphic associations are not fully understood. It has been reported that the sex effects of xenoestrogens on the immune system might be mediated by endogenous hormones which influence T-helper type 1 or 2 immune response to xenoestrogens (Robinson & Miller, 2015). Experimentally, perinatal exposure to BPA increased the expression of estrogen receptor α in female rats but decreased it in male rats, causing sex differences in the modulation of the cytokine expression (Miao et al., 2008; Xu, Huang, & Guo, 2016). Consistent with stronger association of xenoestrogens with asthma and allergic diseases in women, xenoestrogens have been shown to increase the production of B-cell-activating factor more profoundly in females than in males. This process leads to increase B-cell survival and maturation and higher antibody production in females than in males (Edwards, Dai, & Ahmed, 2018). However, we observed an association of BPS with current asthma only in men, not in women. This could be explained by the ability of bisphenols to reduce free testosterone, mainly in males in whom xenoestrogens can interfere with androgen production and function, and increase the odds of asthma (Edwards et al., 2018).

In our study, BPA was only associated with asthma without hay fever in children aged 6 to 11 years but was not associated with asthma outcomes in adolescents and adults. This is consistent with previous findings that have found the association of BPA and asthma occurs mainly during childhood (Donohue et al., 2013; Gascon et al., 2015; Kim et al., 2014; Lin et al., 2018; Spanier, Adam J. et al., 2014; Spanier, A. J. et al., 2012; Wang et al., 2016; Youssef et al., 2018). American and European birth cohort studies have observed that exposure to BPA during pregnancy was associated with a higher risk of wheeze or asthma in the offspring by 7 years of age (Gascon et al., 2015; Spanier, Adam J. et al., 2014; Spanier, A. J. et al., 2012). Additional cross-sectional and prospective studies have also concluded that postnatal BPA exposure was positively associated with childhood wheeze or asthma (Donohue et al., 2013; Kim et al., 2014; Lin et al., 2018; Wang et al., 2016; Youssef et al.,

2018). In the literature, we found only one study reporting an association of BPA with asthma that included adult participants (Vaidya & Kulkarni, 2012). Inconsistent with most of the published literature, one report noted a protective association of prenatal BPA exposure with wheeze (Donohue et al., 2013). Although BPF and BPA are structural analogs, it is unclear why the association of BPF with asthma was predominant in adults while the association of BPA with asthma without hay fever was observed in children aged 6 to 11 years old. The underlying mechanisms for the age difference in the association of bisphenols with current asthma are unclear. Consistent with the association between BPA and asthma without hay fever in children aged 6 to 11 years old, the immature immune system in young age is known to be more vulnerable to the effect of BPA and other endocrine disrupting chemicals (Bonds & Midoro-Horiuti, 2013). BPA may affect the Th1/Th2 balance in children and lead to asthma and allergy (Bonds & Midoro-Horiuti, 2013). As an explanation of the association of BPS with current asthma in adults, it is possible that these participants are exposed to endogenous estrogens and that exposure to xenoestrogens causes hormonal surges leading to inadequate immune responses (Edwards et al., 2018).

Our study has limitations. Because of the cross-sectional design, temporality and causality between exposure to the bisphenols and asthma outcomes cannot be established. The asthma outcomes were defined by self-report and could not be verified. However, self-reported asthma has been shown to have good accuracy when compared to medical records (Bergmann, Jacobs, Hoffmann, & Boeing, 2004; Oksanen et al., 2010). The bisphenols were only measured in a single spot urine sample. The NHANES cycles in our study did not include data on serum levels of specific IgE or skin prick testing to define atopy. Our analysis on asthma attacks in the past 12 months were not adjusted for asthma controller medications, since data on medication was only available for the past 30 days. Data on early life infections to respiratory syncytial virus or human rhinovirus which have been linked to future risk of asthma was not available in NHANES and was not adjusted for (Sigurs, Bjarnason, Sigurbergsson, & Kjellman, 2000). Nevertheless, our study has major strengths. It includes a large sample representative of the U.S. population which increases the generalizability of the findings and allows for stratified analyses on a national scale. The exposures were measured with rigorous quality control and quality assurance procedures and the analysis adjusted for several relevant covariates. Importantly, our study is the first to report on the association of BPF and BPS with asthma outcomes. No previously published animal or human studies have investigated the relationship between the BPA substitutes and asthma.

5. Conclusions

Exposure to BPF was associated with current asthma and hay fever. The association of BPS with current asthma was observed only in men and BPA was associated with asthma without hay fever in children aged 6 to 11 years old. This study has important public health relevance, as BPF and BPS are being used as BPA substitutes in a variety of consumer products. Our findings suggest that BPF and BPS may not be safe alternatives to BPA; however, future prospective studies with repeated measures of exposure to these BPA analogs are needed to confirm the findings and further studies of BPF and BPS are warranted to understand the mechanism behind the current findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Urinary bisphenol F (BPF) was associated with higher odds of asthma and hay fever.
- Urinary bisphenol S (BPS) was associated with higher odds of asthma in men.
- Urinary bisphenol A (BPA) was positively associated with asthma without hay fever in children.

Table 1:

Distribution of creatinine-corrected BPF, BPS, and BPA, NHANES 2013–2016 (N=3,538)

Exposure	% detected	GM (SE)	Median (p25-p75)	5th-95th Percentile
BPF (μg/g creatinine)	57.1	0.46 (0.02)	0.38 (0.17–0.90)	0.07 – 8.24
BPS (μg/g creatinine)	88.4	0.44 (0.02)	0.41 (0.20–0.86)	0.08 – 3.47
BPA (μg/g creatinine)	94.8	1.16 (0.04)	1.10 (0.66–1.90)	0.31– 5.13

Abbreviations: BPF: bisphenol F; BPS: bisphenol S; BPA: bisphenol A; p25: 25th percentile; p75: 75th percentile; GM: Geometric Mean; SE: Standard error.

Table 2:

Geometric mean concentrations of creatinine-corrected BPF, BPS, and BPA by characteristics of study participants, NHANES 2013–2016 (N = 3,538)

Characteristics	% participants	BPF (μg/g creatinine)		BPS (μg/g creatinine)		BPA (μg/g creatinine)	
		GM (SE)	P-value	GM (SE)	P-value	GM (SE)	P-value
Age groups							
12–17 years	9.4	0.40 (0.05)	Ref	**0.29 (0.02)**	**Ref**	**1.01 (0.06)**	**Ref**
18–59 years	66.8	0.46 (0.02)	0.37	**0.45 (0.02)**	**< 0.001**	**1.16 (0.04)**	**0.02**
60–80 years	23.8	0.50 (0.04)	0.20	**0.51 (0.04)**	**< 0.001**	**1.22 (0.08)**	**< 0.001**
Sex							
Men	49.1	0.43 (0.03)	0.056	**0.40 (0.02)**	**0.001**	**1.06 (0.04)**	**< 0.001**
Women	50.9	0.49 (0.02)		**0.48 (0.02)**		**1.26 (0.04)**	
Race/ethnicity							
Non-Hispanic Whites	65.1	**0.52 (0.03)**	**Ref**	**0.41 (0.02)**	**Ref**	1.17 (0.05)	Ref
Non-Hispanic Blacks	11.3	**0.41 (0.03)**	**0.01**	**0.52 (0.03)**	**0.002**	1.18 (0.05)	0.84
Mexican-Americans	9.1	**0.31 (0.02)**	**< 0.001**	**0.58 (0.05)**	**< 0.001**	1.12 (0.05)	0.52
Other	14.5	**0.37 (0.02)**	**0.002**	0.47 (0.03)	0.09	1.11 (0.05)	0.37
Education of HR person							
< High school	15.2	0.41 (0.03)	Ref	0.49 (0.02)	Ref	1.22 (0.06)	Ref
Some college / high school diploma	53.5	0.48 (0.02)	0.06	**0.44 (0.02)**	**0.04**	1.20 (0.04)	0.81
College graduate or above	31.3	0.46 (0.03)	0.35	0.42 (0.03)	0.08	**1.06 (0.05)**	**0.02**
PIR							
≤1	16.0	**0.38 (0.02)**	**Ref**	**0.54 (0.04)**	**Ref**	1.20 (0.04)	Ref
1 to ≤3	36.0	**0.45 (0.02)**	**0.046**	**0.46 (0.02)**	**0.04**	1.19 (0.05)	0.89
>3	48.0	**0.50 (0.03)**	**0.003**	**0.40 (0.02)**	**0.001**	1.12 (0.05)	0.10
Exposure to cigarette smoke							
No	58.3	0.44 (0.02)	0.053	0.42 (0.02)	0.07	**1.09 (0.03)**	**0.004**
Yes	41.7	0.50 (0.03)		0.47 (0.03)		**1.26 (0.06)**	
BMI							
Normal	32.9	0.43 (0.03)	Ref	0.41 (0.02)	Ref	1.13 (0.04)	Ref
Underweight	1.9	0.41 (0.10)	0.88	0.49 (0.10)	0.40	1.10 (0.13)	0.80
Overweight	29.5	0.47 (0.03)	0.35	0.43 (0.03)	0.21	1.12 (0.05)	0.75
Obese	35.6	0.49 (0.03)	0.21	**0.48 (0.03)**	**0.01**	1.22 (0.05)	0.10
Family history of asthma							
No	77.4	0.46 (0.02)	0.40	0.45 (0.02)	0.46	1.14 (0.03)	0.20
Yes	22.6	0.48 (0.03)		0.42 (0.03)		1.22 (0.07)	
Current asthma							
No	91.0	**0.45 (0.02)**	**0.02**	0.44 (0.02)	0.62	1.15 (0.03)	0.66

Characteristics	% participants	BPF (μg/g creatinine)		BPS (μg/g creatinine)		BPA (μg/g creatinine)	
		GM (SE)	P-value	GM (SE)	P-value	GM (SE)	P-value
Yes	9.0	**0.59 (0.07)**		0.46 (0.04)		1.18 (0.07)	
Asthma attacks in past 12 months							
No	95.8	0.46 (0.02)	0.09	0.44 (0.02)	0.63	1.16 (0.04)	0.80
Yes	4.2	0.56 (0.07)		0.42 (0.05)		1.18 (0.11)	
Hay fever							
No	95.4	0.45 (0.02)	0.06	0.44 (0.02)	0.71	1.15 (0.04)	0.79
Yes	4.6	0.64 (0.12)		0.43 (0.05)		1.20 (0.15)	

Abbreviations: BPF: bisphenol F; BPS: bisphenol S; BPA: bisphenol A; GM: geometric mean; SE: standard error; HR: household reference; BMI: body mass index. Bolded numbers indicate statistically significant differences in bisphenol levels by characteristics of study participants. P-value for the differences were calculated using two-sample t-test for variables with two categories and analysis of variance (ANOVA) for variables with three categories or more.

Table 3:

Associations of urinary BPF, BPS, and BPA with asthma and hay fever outcomes, NHANES 2013–2016

Exposure	Current asthma (327 cases)		Asthma attacks in past 12 months (151 cases)		Hay fever (139 cases)	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Unadjusted						
Urinary BPF detection	**1.31 (1.03, 1.68)**	**0.03**	1.32 (0.97, 1.80)	0.08	1.22 (0.87, 1.73)	0.25
Log_{10}-urinary BPS	1.08 (0.85, 1.37)	0.55	1.04 (0.74, 1.46)	0.83	1.01 (0.71, 1.43)	0.97
Log_{10}-urinary BPA	1.13 (0.88, 1.44)	0.33	1.08 (0.71, 1.64)	0.73	1.11 (0.67, 1.82)	0.69
Adjusted						
Urinary BPF detection	**1.54 (1.16, 2.04)**	**0.003**	1.41 (0.97, 2.06)	0.07	**1.66 (1.12, 2.46)**	**0.01**
Log_{10}-urinary BPS	1.07 (0.79, 1.45)	0.65	0.84 (0.52, 1.36)	0.48	0.98 (0.64, 1.50)	0.92
Log_{10}-urinary BPA	0.89 (0.63, 1.25)	0.50	0.85 (0.47, 1.52)	0.58	0.97 (0.43, 2.18)	0.93

Abbreviations: BPF, bisphenol F; BPS, bisphenol S; BPA, bisphenol A.

Models are adjusted for age, sex, race/ethnicity, PIR, exposure to cigarette smoke, BMI, education level of the household reference person, family history of asthma, log_{10}-transformed urinary creatinine, and glomerular filtration rate, as well as mutually adjusted for bisphenols. Odds ratios for detected versus non-detected BPS and BPA were not reported because of the low proportion of participants with urinary concentrations of the analyte below the limit of detection. Bolded numbers indicate statistically significant associations between bisphenol exposures and asthma and hay fever outcomes. For BPS and BPA, odds ratios are reported for a 10-fold increase.

Table 4:

Subgroup analysis for associations of urinary bisphenols with current asthma, NHANES 2013–2016

Exposure	n/N	OR (95% CI)	P-value	$P_{interaction}$
Urinary BPF detection				
By age groups				
12–17 years	60/515	0.67 (0.33, 1.40)	0.29	Ref
18–59 years	177/2,087	**2.10 (1.43, 3.07)**	**< 0.001**	**0.03**
≥ 60 years	90/923	1.29 (0.64, 2.57)	0.47	0.41
By sex				
Men	114/1,699	1.51 (0.93, 2.46)	0.10	0.85
Women	213/1,826	**1.54 (1.17, 2.04)**	**0.002**	
By body mass				
No overweight or obese	114/1,369	0.94 (0.55, 1.60)	0.83	0.23
Overweight/obese	213/2,156	**1.89 (1.32, 2.70)**	**< 0.001**	
By Exposure to smoking				
Not exposed to smoking	191/2,128	1.38 (0.97, 1.98)	0.07	0.29
Exposed to smoking	136/1,397	**1.97 (1.19, 3.28)**	**0.009**	
Log_{10}-urinary BPS				
By age				
12–17 years	60/515	1.58 (0.87, 2.88)	0.13	Ref
18–59 years	177/2,087	1.22 (0.82, 1.82)	0.33	0.30
≥ 60 years	90/923	0.84 (0.42, 1.68)	0.62	0.21
By sex				
Men	114/1,699	**1.64 (1.13, 2.40)**	**0.01**	**0.01**
Women	213/1,826	0.73 (0.51, 1.06)	0.10	
By body mass				
No overweight or obese	114/1,369	0.88 (0.46, 1.66)	0.69	0.80
Overweight/Obese	213/2,156	1.22 (0.85, 1.73)	0.28	
By Exposure to smoking				
Not exposed to smoking	191/2,128	1.29 (0.85, 1.97)	0.23	0.59
Exposed to smoking	136/1,397	0.91 (0.58, 1.42)	0.67	
Log_{10}-urinary BPA				
By age				
12–17 years	60/515	0.59 (0.23, 1.48)	0.26	Ref
18–59 years	177/2,087	0.84 (0.55, 1.28)	0.41	0.86
≥ 60 years	90/923	1.29 (0.64, 2.62)	0.47	0.71
By sex				
Men	114/1,699	0.98 (0.64, 1.49)	0.92	0.53
Women	213/1,826	0.87 (0.52, 1.46)	0.60	
By body mass				
No overweight or obese	114/1,369	1.85 (0.92, 3.73)	0.08	0.09

Exposure	n/N	OR (95% CI)	P-value	$P_{interaction}$
Overweight/Obese	213/2,156	0.66 (0.43, 1.02)	0.06	
By Exposure to smoking				
Not exposed to smoking	191/2,128	0.89 (0.55, 1.42)	0.61	0.99
Exposed to smoking	136/1,397	0.85 (0.51, 1.42)	0.54	

Abbreviations: BPF, bisphenol F; BPS, bisphenol S; BPA, bisphenol A; n, number of cases; N, total number of cases and non-cases. Models are adjusted for age, sex, race/ethnicity, PIR, exposure to cigarette smoke, BMI, education level of the household reference person, family history of asthma, log_{10}-transformed urinary creatinine, glomerular filtration rate, and for BPS and BPA. Bolded numbers indicate statistically significant associations between bisphenol exposures and current asthma.