Title

Prenatal bisphenol A and S exposure and atopic disease phenotypes at age 6.

Authors

Gaylord, Abigail
Barrett, Emily
Sathyanarayana, Sheela
et al.

Publication Date

2023-06-01

DOI

10.1016/j.envres.2023.115630

Peer reviewed

HHS Public Access

Author manuscript

Environ Res. Author manuscript; available in PMC 2024 June 01.

Published in final edited form as:

Environ Res. 2023 June 01; 226: 115630. doi:10.1016/j.envres.2023.115630.

Prenatal bisphenol A and S exposure and atopic disease phenotypes at age 6

Abigail Gaylord[1], **Emily S. Barrett**[3], **Sheela Sathyanarayana**[4,5], **Shanna H. Swan**[6], **Ruby H.N. Nguyen**[7], **Nicole R. Bush**[8,9], **Kecia Carroll**[10], **Drew B. Day**[5], **Kurunthachalam Kannan**[11,12], **Leonardo Trasande**[2,11,12,13,14]

[1]Department of Environmental Health Sciences, Columbia Mailman School of Public Health, New York, NY, USA.

[2]Department of Population Health, New York University School of Medicine, New York, NY, USA.

[3]Department of Biostatistics and Epidemiology, Rutgers School of Public Health, Environmental and Occupational Health Sciences Institute, Rutgers University, Piscataway, NJ, USA.

[4]Department of Pediatrics, Department of Environmental and Occupational Health Sciences, Department of Epidemiology, University of Washington, Seattle, WA, USA.

[5]Seattle Children's Research Institute, University of Washington, Seattle, WA, USA.

[6]Department of Preventive Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

[7]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN, USA.

[8]Department of Psychiatry, University of California—San Francisco, San Francisco, CA, USA.

[9]Department of Pediatrics, University of California—San Francisco, San Francisco, CA, USA.

Corresponding author: Abigail Gaylord, PhD, MPH, Department of Environmental Health Sciences, Columbia Mailman School of Public Health; 630 West 168th Street, Room 16-421, New York, NY 10032; Phone: 518-221-6946; alg2215@cumc.columbia.edu.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author CRediT statement

Abigail Gaylord: Conceptualization, Formal analysis, Writing- Original draft
Emily S. Barrett: Writing- Review & editing, Project administration,
Sheela Sathyanarayana: Writing- Review & editing, Project administration, Funding acquisition
Shanna H. Swan: Resources, Writing- Review & editing, Project administration, Funding acquisition
Ruby H.N. Nguyen: Resources, Writing- Review & editing, Project administration, Funding acquisition
Nicole R. Bush: Writing- Review & editing, Project administration
Kecia Carroll: Writing- Review & editing, Project administration
Drew B. Day: Formal analysis, Writing- Review & editing
Kurunthachalam Kannan: Methodology, Investigation, Resources, Writing- Review & editing
Leonardo Trasande: Conceptualization, Supervision, Project administration, Funding acquisition

[10]Department of Pediatrics, Icahn School of Medicine at Mount Sinai, Kravis Children's Hospital, New York, NY, USA.

[11]Department of Pediatrics, New York University School of Medicine, New York, NY, USA.

[12]Department of Environmental Medicine, New York University School of Medicine, New York, NY, USA.

[13]New York University Wagner School of Public Service, New York, NY, USA.

[14]New York University School of Global Public Health, New York, NY, USA.

Abstract

Background: Atopic disease may be influenced by prenatal and early life exposure to endocrine disrupting chemicals, including bisphenols, but results from epidemiological studies have been mixed. This study aimed to extend the epidemiological literature, hypothesizing that children with higher prenatal bisphenol exposure are more likely to have childhood atopic disease.

Methods: Urinary bisphenol A (BPA) and S (BPS) concentrations were measured in each trimester from 501 pregnant women in a multi-center, prospective pregnancy cohort. Ever asthma, current asthma, wheeze, and food allergy) were assessed at age six via standardized ISAAC questionnaire. We constructed generalized estimating equations to examine BPA and BPS exposure jointly at each trimester for each atopy phenotype. BPA was modeled as a log-transformed continuous variable, whereas BPS was modeled as detected versus not detected. We also modelled pregnancy-averaged BPA values and a categorical indicator for number of detectable BPS values over pregnancy (0 to 3) in logistic regression models.

Results: First trimester BPA was associated with inverse odds of food allergy among the entire study sample (OR=0.78, 95% CI=0.64–0.95, p=0.01) and females only (OR=0.69, 95% CI=0.52–0.90, p=0.006). The inverse relationship persisted in pregnancy-averaged models of BPA among females (OR=0.56, 95% CI=0.35–0.90, p=0.006). Second trimester BPA was associated with greater odds of food allergy in the entire sample (OR=1.27, 95% CI=1.02–1.58, p=0.03) and among males only (OR=1.48, 95% CI=1.02–2.14, p=0.04). Odds of current asthma increased among males in the pregnancy-averaged BPS models (OR=1.65, 95% CI=1.01–2.69, p=0.045).

Conclusion: We saw opposite effects of BPA on food allergy that were trimester- and sex-specific. These divergent associations warrant further investigation. There is some evidence to suggest that prenatal BPS is associated with asthma among males, but further research is required in cohorts with a greater proportion of prenatal urine samples with detectable BPS to validate these results.

Keywords

bisphenols; prenatal exposure; asthma; wheeze; food allergy

1. Introduction

Atopic disease is characterized by an improper immunoglobulin E (IgE) antibody response to small amounts of environmental exposures (Moreno, 2016). Atopic diseases include

asthma, atopic dermatitis (eczema), allergic rhinitis, and food allergy (Thomsen, 2015). Atopy often begins early in life, and children who experience one of these diseases in early childhood are at higher risk for developing another in later childhood (Moreno, 2016). Asthma and allergy exacerbation can ultimately lead to more frequent school absences and decreased physical activity, resulting in poor academic outcomes and greater risk of obesity (Groth, Rhee, & Kitzman, 2016; Kim, Kim, Park, Kim, & Choi, 2017; Lim, Lee, Sim, Hong, & Choi, 2017; Lozier, Zahran, & Bailey, 2018; Sullivan et al., 2018), and these consequences can persist into adulthood (Fletcher, Green, & Neidell, 2010). This is of great concern given the rising prevalence of atopic disease worldwide (Dharmage, Perret, & Custovic, 2019; Stern, Pier, & Litonjua, 2020). According to the Centers for Disease Control and Prevention, the prevalence of asthma and food allergies among children was 5.8% and one in five children reported seasonal allergies nationally (Centers for Disease Control and Prevention, 2020; Zablotsky, Black, & Akinbami, 2023).

Research indicates that asthma and allergy may be linked to sex steroid hormone activity. The disease prevalence in childhood is higher among males, whereas females are more likely to be affected after puberty, suggesting a possible relationship with estrogen production (Dharmage, et al., 2019). This raises concern over the effects of endocrine disrupting chemicals (EDCs), including bisphenols, on atopic disease development. Bisphenols are synthetic chemicals used to manufacture epoxy resins and polycarbonates that make up many consumer products. They are used for coating in food packaging and water pipes as well as in thermal receipt paper. Humans may therefore be exposed to bisphenols through oral ingestion, dermal absorption, or inhalation (Mikołajewska, Stragierowicz, & Gromadzińska, 2015). While studies have identified potential lifetsyle modifications to reduce exposure, the widespread use of bisphenols makes them difficult to avoid. Bisphenols act on estrogen receptors both directly and indirectly through several proposed mechanisms, leading to many adverse health outcomes including potentiation of the allergic response (Khan & Ahmed, 2015; Narita et al., 2007; Yanagisawa, Koike, Win-Shwe, & Takano, 2019; Zaitsu et al., 2007). Mast cell exposure to estradiol potentiates the release and degranulation of allergic mediators via estrogen receptor α, and exposure to environmental estrogens may act similarly (Zaitsu, et al., 2007). β-hexosaminidase release occurring from cross-linking of immunoglobulin E on mast cells is also shown to be enhanced following exposure to environmental estrogens (Narita, et al., 2007). Studies have shown, moreover, that bisphenols and other EDCs are able to cross the placental barrier, with the potential to disrupt the developing fetal endocrine system (Balakrishnan, Henare, Thorstensen, Ponnampalam, & Mitchell, 2010). Theis is particularly concerning, given that a majority of the United States population is exposed not only to BPA, but to other bisphenol analogues such as bisphenol S (BPS) and bisphenol F (BPF) (Lehmler, Liu, Gadogbe, & Bao, 2018; Rocha et al., 2018). These analogues have recently emerged as the health effects of BPA become clearer and manufacturers develop replacement chemicals. While this allows manufacturers to label products as “BPA free”, it also exposes the population to less-studied but structurally similar chemicals that may be just as dangerous.

In mice, higher prenatal BPA exposure is associated with asthma phenotype as well as higher IgE response to ovalbumin (Midoro-Horiuti, et al., 2010; Nakajima, et al., 2012; Nygaard, et al., 2015). Epidemiologic studies that have examined the effects of BPA

on atopy in humans have shown mixed results. This variation in published findings is due, in part, to the variety of atopic phenotypes measured, the timing of outcome measurements, and timing and number of urinary bisphenol measurements. A handful of studies have shown positive associations with respiratory problems, such as asthma, wheeze, aeroallergies, and bronchitis. Among these studies, several have considered sex moderation: one reported higher odds of asthma among males at ages six and seven (Buckley et al., 2018), one reported higher odds of wheeze or eczema among females at six months of age (Zhou et al., 2017), and others reported little evidence for or did not report on sex-specific differences (Berger et al., 2019; Gascon et al., 2015; Spanier et al., 2014; Vernet et al., 2017). Most of these studies measured multiple outcomes, and while one or two outcomes showed statistically significant associations, many had null findings. Others found associations with cord blood markers of allergic disease (Ashley-Martin et al., 2015; S. L. Liao et al., 2020), but whether or not these cord blood markers truly influence disease in childhood is unclear. While many of these studies have examined the effects of other phenols in addition to prenatal BPA, none have investigated prenatal BPS exposure.

In this analysis, we aimed to contribute to the growing body of epidemiologic research of prenatal bisphenol exposure and atopic disease in childhood using data from a multi-center birth cohort. This cohort is unique in that it has urinary bisphenol measurements at each trimester of pregnancy, allowing us to identify critical windows of exposure. Additionally, both urinary BPA and BPS were measured in this cohort, enabling simultaneous consideration of the effects of prenatal BPS on childhood atopy, which has not been done before. To create a point of comparison with the existing literature, we utilized several of the outcomes that were measured in the studies discussed above—childhood wheeze and asthma—as well as food allergies. We hypothesized that children with greater prenatal exposure to these bisphenol analogues at any trimester would be more likely to develop atopic disease phenotypes by the age of six. To investigate potential sensitive periods during fetal development, we examined bisphenol exposure at each trimester. Given the existing literature and the sex-specific impacts of EDCs, we also explored differences in associations by sex.

2. Methods

2.1 Study population

The Infant Development and Environment Study (TIDES) is a multi-center pregnancy cohort that recruited pregnant women from university-based prenatal clinics in San Francisco, CA, Rochester, NY, Seattle, WA, and Minneapolis, MN beginning in 2010. Women were eligible for enrollment if they were less than 13 weeks pregnant, at least 18 years if age, English-speaking, had no serious threat to the pregnancy, and planned to deliver at the study hospital. Enrolled women provided urine samples along with completed questionnaires at each trimester. After birth, mothers who consented to follow up provided information on their child's health at an age six study visit. All participating institutions received institutional review board approval and informed consent was obtained from all participating women. A more detailed description of cohort recruitment is available elsewhere (Barrett et al., 2014).

2.2 Urinary bisphenol metabolite measurement

Maternal urine was collected in polypropylene cups at each prenatal visit and specific gravity was measured within 30 minutes of collection. Further details are provided elsewhere (C. Liao et al., 2012; Zhang et al., 2011). Eight bisphenols: A, AF, AP, B, F, P, S, and Z—were measured in maternal urine at each trimester using solid-phase extraction coupled to high performance liquid chromatography and tandem mass spectrometry (Ye, Kuklenyik, Needham, & Calafat, 2005). Bisphenols were adjusted for specific gravity using the method outlined by Boeniger and colleagues: $\text{bisphenol}_{adj} = \text{bisphenol}[(\text{SpG}_{avg} - 1)/(\text{SpG}-1)]$, where bisphenol_{adj} is the specific gravity-adjusted bisphenol, bisphenol is the raw bisphenol concentration, SpG_{avg} is the average specific gravity concentration for the cohort, and SpG is the raw specific gravity measurement (Boeniger, Lowry, & Rosenberg, 1993). Values below the LOD were imputed as LOD/√2 (Hornung & Reed, 1990). Specific gravity-adjusted bisphenols were natural log-transformed to correct for skewedness.

2.3 Atopic disease outcomes

We examined four binary (yes/no) endpoints to characterize childhood atopy—current wheeze, current asthma, ever asthma, and food allergy. All outcomes were ascertained from parental responses to the items adapted from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire at the age six visit (Asher et al., 1995). Current wheeze was determined if the mother answered “yes” to the following question: “Has [child] had wheezing or whistling in the chest in the past 12 months?” Ever asthma was determined by the replying “yes” to the following question: “Have you ever been told by a doctor or health care provider that [child] has asthma or reactive airway disease?” Current asthma was indicated if the parent answered “yes” to at least two of the following five questions:

1. “In the past 12 months, has [child] gone to the doctor’s office because of wheezing or asthma?”
2. “In the past 12 months, has [child] been to the emergency room because of wheezing or asthma?”
3. “In the past 12 months, has [child] been admitted to the hospital because of wheezing or asthma?”
4. “In the past 12 months, has a doctor prescribed steroid medicine, such as orapred, prednisone, or decadron/dexamethasone for [child] to take by mouth- not by inhaler- for wheezing or asthma?”
5. “In the past 12 months, has [child] used any type of medicines, liquids, puffers, or other medication for wheezing or asthma?”

Food allergy was determined if the parent indicated “food allergies” on a list of the child’s conditions/health problems and if the parent indicated that food allergies were diagnosed by a health care provider.

2.4 Covariates

Potential covariates were chosen based on review of the literature. From this set we identified the minimal adjustment set of covariates using Dagitty (Textor, Hardt, & Knüppel, 2011). These included history of parental atopy, maternal education, household income, pre-pregnancy body mass index (BMI), maternal age at enrollment, prenatal tobacco smoke exposure, breastfeeding, birth order, child race, child ethnicity, gestational age at birth, birth weight, and child sex. Covariates were included in the final model if they were associated with the outcome ($p<0.2$). Pregnancy-averaged urinary cotinine (continuous) was used to represent tobacco exposure during pregnancy. We also considered analytical batch, study center, and time of day of urine collection. Few urine samples from mothers of children reporting current asthma and ever asthma came from one of the batches, forcing us to exclude batch from the final models. Although there were enough children identifying as Asian American or Pacific Islander (AAPI) in the total study sample, these numbers became too small for modeling after sex stratification. We combined AAPI with the “other” race/ethnicity group in main models, and ran a model in the total study population with AAPI as its own race/ethnicity category in a sensitivity analysis. Child sex was not highly correlated with the chemical exposures, but given the extensive literature suggesting sex-specific effects of these chemicals, we hypothesized that sex may modify the effects of bisphenols on the outcomes of interest and we chose to include it in the models. Covariates included in the final models were history of parental atopy (yes or no), maternal education (less than high school/high school degree/GED or schooling beyond high school), annual household income (<$45,000, $45,001-$75,000, or >$75,001), pre-pregnancy BMI, maternal age at enrollment, urinary cotinine, child race/ethnicity (Hispanic or Latinx, non-Hispanic Black or African American, non-Hispanic White, other), child sex (male, female), study center, and time of urine collection (modelled as a spline with three degrees of freedom). The amount of missing data was small for these covariates (≤5%). Missing data on covariates were imputed by multiple imputation by predictive mean matching (k=10) using the ‘mice’ package in R (Morris, White, & Royston, 2014; van Buuren & Groothuis-Oudshoorn, 2011). Imputed values were combined by computing the mean or most likely value of the imputed data sets (Lüdecke, 2018).

2.5 Statistical analysis

Only BPA and BPS were above the LOD in at least 50% of the study sample and were included in further analyses. Due to the large number of BPS measurements below the limit of detection in this study population, we dichotomized BPS as detected versus not detected and analyzed it as binary variable. Given previous research indicating non-linear relationships between endocrine disrupting chemicals and health outcomes (Vandenberg, 2014), we examined the log odds of each outcome with log-transformed, specific-gravity adjusted BPA using generalized additive models, but found no evidence of any non-linear relationships. The associations of BPA and BPS with each atopic outcome were analyzed in generalized estimation equation (GEE), which included exposure at all three trimesters in a single model (Sánchez, Hu, Litman, & Téllez-Rojo, 2011). BPA and BPS measurements were analyzed in the same GEE model. To meet the model requirements, only participants with BPA and BPS measurements at all three time points were included.

Bisphenols are non-persistent chemicals, and single spot urinary measurements may not be indicative of typical exposure (Gys et al., 2021). As a sensitivity analysis, we analyzed the same outcomes with averaged BPA concentrations over pregnancy in logistic regression models. BPS was analyzed in complete cases using a value ranging from 0 to 3, representing the number of urine samples in which BPS was detected over pregnancy. Time of urine collection was not included in this model. Pregnancy-averaged BPA and BPS were included in the same model.

3. Results

Of the women enrolled in TIDES, 635 (65%) provided urine samples at all three time points from which bisphenols could be measured (first trimester median=12 weeks, SD=2.7 weeks; second trimester median=21 weeks, SD=4.5 weeks; third trimester median=32 weeks, SD=3.6 weeks). Of that subset, 501 mothers (79%) completed the six year follow up questionnaire and responded to items for at least one of the four atopic disease phenotypes. This resulted in a total study sample of 487 to assess wheeze, 491 to assess asthma outcomes, and 501 to assess food allergy. The prevalence of atopic disease phenotypes in this study population were 12% (n=61) for wheeze, 10% (n=48) for ever asthma, 8% (n=40) for current asthma, and 9% (n=47) for food allergies. Nearly one quarter of children (22%) had at least one atopic disease outcome. Children with any atopic disease were more likely to be Black or African American (16% versus 10%), be Hispanic or Latinx (19% versus 8%), and have a parent with a history of atopic disease (80% versus 60%) than children with no atopic disease. Mothers of atopic children were less likely to have obtained an education beyond a high school degree or GED (85% versus 89%). Annual household income of atopic children showed a U-shape, with the majority of atopic participants at the low (<$45,000, 39%) or high end (>$75,001, 44%), whereas the majority of non-atopic children were in households with annual income above $75,001 (55%) (Table 1).

Median urinary BPA was higher than BPS at each trimester (Table 2). The highest median BPA concentration occurred in the third trimester, while the highest BPS concentration was observed in the second trimester. BPA was detectable in approximately 74 and 73% of the population at the first and third trimesters, respectively, but was only detectable in 57% of the study population at the second trimester. Detection frequencies of BPS were more consistent at 52% in the first trimester, 57% in the second trimester, and 51% in the third trimester. Spearman correlation coefficients were low to moderate across time points for continuous BPA (T1 versus T2 ρ=0.31, T2 versus T3 ρ=0.30, T1 versus T3 ρ=0.33) and continuous BPS (T1 versus T2 ρ=0.26, T2 versus T3 ρ=0.31, T1 versus T3 ρ=0.28), indicating low stability across pregnancy. BPA and BPS also showed weak spearman correlation coefficients with each other at the first (0.20), second (0.21), and third (0.11) trimesters. BPA and BPS could therefore be included in the same GEE model, as colinearity was not a concern.

We observed an inverse association of first trimester BPA with food allergy among males and females combined (OR=0.78, 95% CI=0.64–0.95, p=0.01) and females only (OR=0.69, 95% CI=0.52–0.90, p=0.006). Interestingly, the association reversed direction in for second trimester BPA and food allergy in the total study sample (OR=1.27, 95% CI=1.02–1.58,

p=0.03). However, among males there was increased odds of food allergy with second trimester BPA (OR=1.48, 95% CI=1.02–2.14, p=0.04). Odds ratios of the associations of BPA with food allergy in the third trimesters were greater than one in all study samples, but were not statistically significant. We did not identify any statistically significant associations with BPS or with any of the other measured atopic outcomes in the GEE model (Table 3). Estimates did not meaningfully change when AAPI was included as its own race/ethnicity in the models for males and females combined (Table S1). There were no statistically significant results in models of pregnancy-averaged BPA and BPS among males and females combined. However, pregnancy-averaged BPA was inversely associated with food allergy among females only (OR=0.56, 95% CI=0.35–0.90, p=0.006). Among males only, detectable BPS was associated with higher odds of ever asthma (OR=1.65, 95% CI=1.01–2.69, p=0.045) in the pregnancy-averaged model (Table 4).

4. Discussion

In this study of mothers and children living across the United States, we found little evidence to support our hypothesis that prenatal exposure to BPA and BPS increases the likelihood of child atopic disease at age six. Detection of urinary BPS was associated with higher odds of ever asthma among males, but this association was observed only in the pregnancy-averaged model. We did observe inverse associations of BPA exposure in the first trimester with food allergy in childhood, and this association was stronger in females and was identified in the pregnancy-averaged BPA model as well. These conclusions show both consistencies and contradictions when compared to the existing literature. A study of a New York City-based cohort of mothers and children reported that higher third trimester urinary BPA was associated with increased odds of ever having asthma by age six or seven among males, but not among females (Buckley, et al., 2018). Cohorts based in Spain and France reported greater risk ratios of asthma at age five and hazard rates of asthma in males at age seven, respectively, but these associations bordered on statistical significance (Gascon, et al., 2015; Vernet, et al., 2017). Spanier and colleagues reported increased risk of asthma (indicated by decreased percent forced expiratory volume (%FEV1)) associated with second trimester BPA, but statistical significance was only reached by the BPA-time interaction term and not by BPA alone (Spanier, et al., 2014). Vernet and colleagues also saw no association between %FEV1 and second trimester BPA (Vernet, et al., 2017). Forced vital capacity (FVC), and therefore FEV1/FVC ratio, was not measured in either study.

Results pertaining to wheeze have been similarly mixed. Several studies have shown increased likelihood of childhood wheeze associated with prenatal BPA (Gascon, et al., 2015; Spanier, et al., 2014; Zhou, et al., 2017). However, results from a New York City-based cohort showed an inverse association between prenatal BPA and wheeze at age five, but this association became null when wheeze was evaluated at ages six and seven (Donohue, et al., 2013). The results from the present analysis align with the null associations reported by Donohue and colleagues. We are not aware of any studies that reported on either prenatal BPS exposure in relation to atopic disease phenotypes or prenatal bisphenol exposure and food allergies as the outcome in humans.

There are several differences between this analysis and the previously published studies discussed above that may account for the inconsistencies in results. First, we had a higher percentage of samples with non-detectable BPA concentrations compared with other studies, which typically detected BPA in 95% or more of the samples. Additionally, we generally observed lower median BPA concentrations than other studies (Berger, et al., 2019; Buckley, et al., 2018; Casas & Gascon, 2020; Donohue, et al., 2013; Gascon, et al., 2015; Spanier, et al., 2014; Vernet, et al., 2017; Zhou, et al., 2017). We expect that the lower BPA levels observed in this analysis stem from both chronological and geographical differences in study enrollment. Enrollment for studies which were based in the United States or Europe occurred in the late 1990s and early 2000s, while recruitment into TIDES began in 2010. Other studies were based in China and Taiwan, whose bisphenol exposure profiles differ from that of the United States and Europe. The most comparable study based on BPA concentration alone comes from Ashley-Martin and colleagues, who reported a median unadjusted urinary BPA concentration of 0.8 ng/mL in the first trimester in the Maternal-Infant Research on Environmental Chemicals (MIREC) Study. This is comparable to the third trimester BPA concentration observed in this study—0.72 ng/mL—which was the highest median concentration observed overall. However, the MIREC study measured interleukin-33 to thymic stromal lymphopoietin ratio (IL-33/TSLP) in umbilical cord plasma as a marker of fetal immune system function and found a statistically significant inverse association of BPA and elevated IL-33/TSLP in umbilical cord plasma (Ashley-Martin, et al., 2015). Despite differences in modeling, the results from the MIREC study may help to inform the inverse relationships observed here between pregnancy-averaged BPA with food allergy in females, albeit non-statistically significant. IL-33/TSLP serves as an early marker for the atopic march, which includes food allergies. There is some evidence to suggest that elevated IL-33 is correlated with food allergy (Han et al., 2018). The inverse relationship observed in this analysis and by Ashley-Martin and colleagues suggests possible divergence in the effect of BPA on allergic response based on pre- or postnatal exposure (Petzold, Averbeck, Simon, Lehmann, & Polte, 2014). Alternatively, there could be unmeasured confounding common to both of these analyses.

There are several strengths to this analysis. This is among the first studies to examine the associations of prenatal bisphenol exposure at three time points during pregnancy with child atopy phenotypes. The current analysis includes a community-based sample of participants from four cities throughout the United States, which may allow for greater inference around typical child development in the general population than clinically recruited samples. However, this type of sampling may have contributed to limited power to detect associations, despite a decent sample size. Finally, this was the first study to our knowledge of atopic disease and prenatal bisphenol exposure to include BPS and food allergy. This study may therefore serve as a starting point for future analyses of BPS, particularly in populations exposed to greater levels of BPS. Given the suggestive inverse findings of BPA and BPS with food allergy, which have not been identified before, further studies of food allergy are also recommended.

There are also several limitations to this analysis that should be considered. First, atopic disease outcomes were assessed via parental report and recall, which may have resulted in misclassification although outcomes such as wheeze have been validated (Oliveira, Penedo,

Valle, & Kuschnir, 2022). These endpoints may also be less sensitive to small changes which may still be occurring biologically during mid-childhood, even if a diagnosis has not been made. We expect that inaccurate reporting of the outcome was non-differential and therefore may have moved the effect estimate towards the null, if it had any effect. Second, because bisphenols are non-persistent, the trimester-specific estimates may be subject to misclassification, although we cannot predict the impact this may have on the direction of the effect estimates. We also did not control for other chemical exposures that may be associated with prenatal bisphenol exposure and atopic outcomes, which could lead to unmeasured confounding. Finally, non-English speaking mothers were excluded from the study, limiting the generalizability of our results.

5. Conclusion

We found some evidence to support the hypothesis that prenatal BPA and BPS are associated with atopic disease phenotypes in childhood, but the divergence in directionality of the associations between BPA and food allergy in the first and second trimesters warrants further investigation. These findings are of particular note given that other studies on prenatal BPA have not considered food allergy in childhood as a potential atopic outcome. In males, a greater number of maternal urine samples with detectable BPS throughout pregnancy was associated with higher odds of ever asthma. While the other study results were null in regards to BPS, we were only able to model the exposure as detected versus not, and suggest further investigation into the effects of BPS on atopic disease in cohorts with a greater proportion of prenatal urine samples with detectable BPS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

This work is supported by the NIH Office of the Director (NIH UG3/UH3OD023271).

References

Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. (1995). International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J, 8(3), 483–491. [PubMed: 7789502]

Ashley-Martin J, Dodds L, Levy AR, Platt RW, Marshall JS, & Arbuckle TE (2015). Prenatal exposure to phthalates, bisphenol A and perfluoroalkyl substances and cord blood levels of IgE, TSLP and IL-33. Environ Res, 140, 360–368. [PubMed: 25913155]

Bach JF (2018). The hygiene hypothesis in autoimmunity: the role of pathogens and commensals. Nat Rev Immunol, 18(2), 105–120. [PubMed: 29034905]

Balakrishnan B, Henare K, Thorstensen EB, Ponnampalam AP, & Mitchell MD (2010). Transfer of bisphenol A across the human placenta. Am J Obstet Gynecol, 202(4), 393.e391–397.

Barrett ES, Sathyanarayana S, Janssen S, Redmon JB, Nguyen RH, Kobrosly R, et al. (2014). Environmental health attitudes and behaviors: findings from a large pregnancy cohort study. Eur J Obstet Gynecol Reprod Biol, 176, 119–125. [PubMed: 24647207]

Berger K, Eskenazi B, Balmes J, Kogut K, Holland N, Calafat AM, et al. (2019). Prenatal high molecular weight phthalates and bisphenol A, and childhood respiratory and allergic outcomes. Pediatr Allergy Immunol, 30(1), 36–46. [PubMed: 30338578]

Boeniger MF, Lowry LK, & Rosenberg J (1993). Interpretation of urine results used to assess chemical exposure with emphasis on creatinine adjustments: a review. Am Ind Hyg Assoc J, 54(10), 615–627. [PubMed: 8237794]

Box GEP, & Tidwell PW (1962). Transformation of the Independent Variables. Technometrics, 4(4), 531–550.

Buckley JP, Quirós-Alcalá L, Teitelbaum SL, Calafat AM, Wolff MS, & Engel SM (2018). Associations of prenatal environmental phenol and phthalate biomarkers with respiratory and allergic diseases among children aged 6 and 7 years. Environ Int, 115, 79–88. [PubMed: 29550712]

Casas M, & Gascon M (2020). Prenatal Exposure to Endocrine-Disrupting Chemicals and Asthma and Allergic Diseases. J Investig Allergol Clin Immunol, 30(4), 215–228.

Centers for Disease Control and Prevention. (2020). Most Recent National Asthma Data.

Dharmage SC, Perret JL, & Custovic A (2019). Epidemiology of Asthma in Children and Adults. Front Pediatr, 7, 246. [PubMed: 31275909]

Donohue KM, Miller RL, Perzanowski MS, Just AC, Hoepner LA, Arunajadai S, et al. (2013). Prenatal and postnatal bisphenol A exposure and asthma development among inner-city children. J Allergy Clin Immunol, 131(3), 736–742. [PubMed: 23452902]

Fletcher JM, Green JC, & Neidell MJ (2010). Long term effects of childhood asthma on adult health. J Health Econ, 29(3), 377–387. [PubMed: 20394999]

Gascon M, Casas M, Morales E, Valvi D, Ballesteros-Gómez A, Luque N, et al. (2015). Prenatal exposure to bisphenol A and phthalates and childhood respiratory tract infections and allergy. J Allergy Clin Immunol, 135(2), 370–378. [PubMed: 25445825]

Groth SW, Rhee H, & Kitzman H (2016). Relationships among obesity, physical activity and sedentary behavior in young adolescents with and without lifetime asthma. J Asthma, 53(1), 19–24. [PubMed: 26288155]

Gys C, Bastiaensen M, Malarvannan G, Ait Bamai Y, Araki A, & Covaci A (2021). Short-term variability of bisphenols in spot, morning void and 24-hour urine samples. Environ Pollut, 268(Pt A), 115747. [PubMed: 33012567]

Han H, Roan F, Johnston LK, Smith DE, Bryce PJ, & Ziegler SF (2018). IL-33 promotes gastrointestinal allergy in a TSLP-independent manner. Mucosal Immunol, 11(2), 578. [PubMed: 29067997]

Hornung RW, & Reed LD (1990). Estimation of Average Concentration in the Presence of Nondetectable Values. Applied Occupational and Environmental Hygiene, 5(1), 46–51.

Khan D, & Ahmed SA (2015). Epigenetic Regulation of Non-Lymphoid Cells by Bisphenol A, a Model Endocrine Disrupter: Potential Implications for Immunoregulation. Front Endocrinol (Lausanne), 6, 91. [PubMed: 26097467]

Kim SY, Kim MS, Park B, Kim JH, & Choi HG (2017). Allergic rhinitis, atopic dermatitis, and asthma are associated with differences in school performance among Korean adolescents. PLoS One, 12(2), e0171394. [PubMed: 28207843]

Lehmler HJ, Liu B, Gadogbe M, & Bao W (2018). Exposure to Bisphenol A, Bisphenol F, and Bisphenol S in U.S. Adults and Children: The National Health and Nutrition Examination Survey 2013–2014. ACS Omega, 3(6), 6523–6532. [PubMed: 29978145]

Liao C, Liu F, Alomirah H, Loi VD, Mohd MA, Moon HB, et al. (2012). Bisphenol S in urine from the United States and seven Asian countries: occurrence and human exposures. Environ Sci Technol, 46(12), 6860–6866. [PubMed: 22620267]

Liao SL, Chen LC, Tsai MH, Hua MC, Yao TC, Su KW, et al. (2020). Prenatal exposure to bisphenol - A is associated with dysregulated perinatal innate cytokine response and elevated cord IgE level: A population-based birth cohort study. Environ Res, 191, 110123. [PubMed: 32905812]

Lim MS, Lee CH, Sim S, Hong SK, & Choi HG (2017). Physical Activity, Sedentary Habits, Sleep, and Obesity are Associated with Asthma, Allergic Rhinitis, and Atopic Dermatitis in Korean Adolescents. Yonsei Med J, 58(5), 1040–1046. [PubMed: 28792151]

Lozier MJ, Zahran HS, & Bailey CM (2018). Assessing health outcomes, quality of life, and healthcare use among school-age children with asthma. J Asthma, 1–8.

Lüdecke D (2018). sjmisc: Data and Variable Transformation Functions. Journal of Open Source Software, 3(26).

Midoro-Horiuti T, Tiwari R, Watson CS, & Goldblum RM (2010). Maternal bisphenol a exposure promotes the development of experimental asthma in mouse pups. Environ Health Perspect, 118(2), 273–277. [PubMed: 20123615]

Mikołajewska K, Stragierowicz J, & Gromadzińska J (2015). Bisphenol A - Application, sources of exposure and potential risks in infants, children and pregnant women. Int J Occup Med Environ Health, 28(2), 209–241. [PubMed: 26182919]

Moreno MA (2016). Atopic Diseases in Children (No. 2168–6203).

Morris TP, White IR, & Royston P (2014). Tuning multiple imputation by predictive mean matching and local residual draws. BMC Medical Research Methodology, 14(1), 75. [PubMed: 24903709]

Nakajima Y, Goldblum RM, & Midoro-Horiuti T (2012). Fetal exposure to bisphenol A as a risk factor for the development of childhood asthma: an animal model study. Environ Health, 11, 8. [PubMed: 22353195]

Narita S, Goldblum RM, Watson CS, Brooks EG, Estes DM, Curran EM, et al. (2007). Environmental estrogens induce mast cell degranulation and enhance IgE-mediated release of allergic mediators. Environ Health Perspect, 115(1), 48–52. [PubMed: 17366818]

Nygaard UC, Vinje NE, Samuelsen M, Andreassen M, Groeng EC, Bølling AK, et al. (2015). Early life exposure to bisphenol A investigated in mouse models of airway allergy, food allergy and oral tolerance. Food Chem Toxicol, 83, 17–25. [PubMed: 26048442]

Oliveira EF, Penedo C, Valle SOR, & Kuschnir FC (2022). Validation and reproducibility of the International Study of Asthma and Allergies in Childhood (ISAAC) Written Atopic Eczema Questionnaire for telephone survey in children aged 6–7 years. An Bras Dermatol, 97(2), 173–178. [PubMed: 34991900]

Petzold S, Averbeck M, Simon JC, Lehmann I, & Polte T (2014). Lifetime-dependent effects of bisphenol A on asthma development in an experimental mouse model. PLoS One, 9(6), e100468. [PubMed: 24950052]

Rocha BA, Asimakopoulos AG, Honda M, da Costa NL, Barbosa RM, Barbosa F Jr., et al. (2018). Advanced data mining approaches in the assessment of urinary concentrations of bisphenols, chlorophenols, parabens and benzophenones in Brazilian children and their association to DNA damage. Environ Int, 116, 269–277. [PubMed: 29704805]

Sánchez BN, Hu H, Litman HJ, & Téllez-Rojo MM (2011). Statistical methods to study timing of vulnerability with sparsely sampled data on environmental toxicants. Environ Health Perspect, 119(3), 409–415. [PubMed: 21362588]

Spanier AJ, Kahn RS, Kunselman AR, Schaefer EW, Hornung R, Xu Y, et al. (2014). Bisphenol a exposure and the development of wheeze and lung function in children through age 5 years. JAMA Pediatr, 168(12), 1131–1137. [PubMed: 25286153]

Stern J, Pier J, & Litonjua AA (2020). Asthma epidemiology and risk factors. Semin Immunopathol, 42(1), 5–15. [PubMed: 32020334]

Sullivan P, Ghushchyan VG, Navaratnam P, Friedman HS, Kavati A, Ortiz B, et al. (2018). School absence and productivity outcomes associated with childhood asthma in the USA. J Asthma, 55(2), 161–168. [PubMed: 28453370]

Textor J, Hardt J, & Knüppel S (2011). DAGitty: a graphical tool for analyzing causal diagrams. Epidemiology, 22(5), 745.

Thomsen SF (2015). Epidemiology and natural history of atopic diseases. Eur Clin Respir J, 2.

van Buuren S, & Groothuis-Oudshoorn K (2011). mice: Multivariate Imputation by Chained Equations in R. Journal of Statistical Software, 45(3), 1–67.

Vandenberg LN (2014). Non-monotonic dose responses in studies of endocrine disrupting chemicals: bisphenol a as a case study. Dose Response, 12(2), 259–276. [PubMed: 24910584]

Vernet C, Pin I, Giorgis-Allemand L, Philippat C, Benmerad M, Quentin J, et al. (2017). In Utero Exposure to Select Phenols and Phthalates and Respiratory Health in Five-Year-Old Boys: A Prospective Study. Environ Health Perspect, 125(9), 097006. [PubMed: 28934727]

Yanagisawa R, Koike E, Win-Shwe TT, & Takano H (2019). Oral exposure to low dose bisphenol A aggravates allergic airway inflammation in mice. Toxicol Rep, 6, 1253–1262. [PubMed: 31788436]

Ye X, Kuklenyik Z, Needham LL, & Calafat AM (2005). Quantification of urinary conjugates of bisphenol A, 2,5-dichlorophenol, and 2-hydroxy-4-methoxybenzophenone in humans by online solid phase extraction-high performance liquid chromatography-tandem mass spectrometry. Anal Bioanal Chem, 383(4), 638–644. [PubMed: 16132150]

Zablotsky B, Black LI, & Akinbami LJ (2023). Diagnosed allergic conditions in children aged 0–17 years: United States, 2021. NCHS Data Brief, no 459.

Zaitsu M, Narita S, Lambert KC, Grady JJ, Estes DM, Curran EM, et al. (2007). Estradiol activates mast cells via a non-genomic estrogen receptor-alpha and calcium influx. Mol Immunol, 44(8), 1977–1985. [PubMed: 17084457]

Zhang Z, Alomirah H, Cho H-S, Li Y-F, Liao C, Minh TB, et al. (2011). Urinary Bisphenol A Concentrations and Their Implications for Human Exposure in Several Asian Countries. Environmental Science & Technology, 45(16), 7044–7050. [PubMed: 21732633]

Zhou A, Chang H, Huo W, Zhang B, Hu J, Xia W, et al. (2017). Prenatal exposure to bisphenol A and risk of allergic diseases in early life. Pediatr Res, 81(6), 851–856. [PubMed: 28141789]

Highlights

- BPA and BPS were measured in maternal urine at each trimester of pregnancy
- First trimester BPA was associated with lower odds of food allergy
- Second trimester BPA was associated with greater odds of food allergy
- Increased detectable BPS over pregnancy was associated with current asthma in males

Table 1.

Demographic characteristics among children with and without any atopy outcome[a] at age 6 (n=501)

Variable	No atopy[b] n = 389	Any atopy[c] n = 112	p-value[d]
Infant sex, n (%)			
Male	175 (45%)	57 (51%)	0.32
Female	214 (55%)	55 (49%)	
Infant race/ethnicity, n (%)			
Hispanic or Latinx	33 (8%)	21 (19%)	0.001
Black or African American, non-Hispanic	38 (10%)	18 (16%)	
Asian American or Pacific Islander	25 (6%)	9 (8%)	
White, non-Hispanic	252 (65%)	50 (45%)	
Other[e]	41 (11%)	14 (12%)	
Maternal education, n (%)			
< high school, high school degree, or GED	35 (9%)	17 (15%)	0.10
Schooling beyond high school	348 (89%)	95 (85%)	
Annual household income, n (%)			
< $45,000	95 (24%)	44 (39%)	0.003
$45,001–$75,000	73 (19%)	^ 13 (12%)	
> $75,001	213 (55%)	49 (44%)	
Any parental atopic disease, n (%)	233 (60%)	90 (80%)	<0.001
Cigarette use during pregnancy, n (%)	12 (3%)	13 (12%)	0.001
Pre-pregnancy body mass index, mean (SD), kg/m^2	25.6 (6.0)	27.2 (6.4)	0.02
Maternal age at enrollment, mean (SD), years	31.8 (5.1)	30.4 (6.1)	0.03

[a] Atopy outcomes: wheeze: 61 (12%); ever asthma: 48 (10%); current asthma: 40 (8%); food allergy: 47 (9%)

[b] Missing data: maternal education: 6 (2%); annual household income: 8 (2%); any parental atopic disease: 9 (2%); cigarette use during pregnancy: 2 (<1%); pre-pregnancy BMI: 12 (3%); maternal age: 8 (2%)

[c] Missing data: annual household income: 6 (5%); any parental atopic disease: 1 (1%); pre-pregnancy BMI: 2 (2%); maternal age: 1 (1%)

[d] p-values calculated from chi-square tests and t-tests

[e] Includes participants who identified as American Indian, Alaska Native, or multi-racial

Table 2.

BPA and BPS concentrations in mothers at three stages of pregnancy measured in the TIDES cohort (n=501)

Bisphenol (ng/mL)	LOD	First trimester		Second trimester		Third trimester	
		% <LOD	Median (25th, 75th percentile)	% <LOD	Median (25th, 75th percentile)	% <LOD	Median (25th, 75th percentile)
BPA	0.15	26%	0.68 (0.11[a], 1.57)	42%	0.43 (0.11[a], 1.40)	27%	0.73 (0.11[a], 1.71)
BPS	0.08	48%	0.11 (0.06[a], 0.52)	43%	0.13 (0.06[a], 0.58)	49%	0.09 (0.06[a], 0.48)

[a]below LOD imputed as LOD/√2

Table 3.

Adjusted odds ratios and 95% confidence intervals of the associations of trimester-specific prenatal BPA and BPS with atopic disease outcomes at age 6 estimated from a generalized estimation equation

		Wheeze[a]	Ever Asthma[b]	Current Asthma[b]	Food Allergy[c]
First trimester					
All	BPA	0.95 (0.76, 1.19)	1.02 (0.79, 1.32)	1.06 (0.81, 1.38)	0.78 (0.64, 0.95)*
	BPS	0.98 (0.56, 1.72)	0.72 (0.38, 1.33)	1.18 (0.60, 2.31)	0.85 (0.45, 1.59)
Males	BPA	0.75 (0.54, 1.05)	0.89 (0.64, 1.22)	0.94 (0.69, 1.27)	0.82 (0.59, 1.14)
	BPS	0.85 (0.40, 1.80)	1.01 (0.44, 2.28)	1.93 (0.73, 5.09)	0.79 (0.29, 2.19)
Females	BPA	1.12 (0.80, 1.57)	1.21 (0.73, 2.03)	1.29 (0.80, 2.08)	0.69 (0.52, 0.90)*
	BPS	1.12 (0.47, 2.69)	0.41 (0.15, 1.13)	0.55 (0.19, 1.57)	0.81 (0.34, 1.96)
Second trimester					
All	BPA	0.93 (0.70, 1.24)	0.91 (0.68, 1.21)	0.89 (0.63, 1.26)	1.27 (1.02, 1.58)*
	BPS	1.12 (0.51, 2.44)	1.10 (0.49, 2.49)	1.03 (0.37, 2.85)	0.92 (0.42, 2.02)
Males	BPA	1.31 (0.87, 1.97)	1.13 (0.82, 1.55)	1.03 (0.71, 1.49)	1.48 (1.02, 2.14)*
	BPS	1.44 (0.46, 4.54)	0.84 (0.27, 2.59)	0.79 (0.19, 3.34)	1.12 (0.35, 3.60)
Females	BPA	0.72 (0.47, 1.09)	0.65 (0.35, 1.20)	0.66 (0.38, 1.16)	1.22 (0.91, 1.65)
	BPS	1.06 (0.31, 3.62)	2.13 (0.57, 7.98)	1.93 (0.39, 9.51)	1.02 (0.35, 3.02)
Third trimester					
All	BPA	1.01 (0.79, 1.29)	0.91 (0.68, 1.20)	1.07 (0.81, 1.40)	1.18 (0.93, 1.48)
	BPS	0.86 (0.45, 1.64)	1.07 (0.52, 2.21)	0.99 (0.42, 2.33)	0.69 (0.32, 1.48)
Males	BPA	1.19 (0.84, 1.68)	0.94 (0.66, 1.34)	1.18 (0.83, 1.67)	1.33 (0.95, 1.87)
	BPS	0.93 (0.39, 2.20)	0.96 (0.37, 2.51)	0.86 (0.28, 2.71)	0.46 (0.13, 1.66)
Females	BPA	0.93 (0.65, 1.32)	0.88 (0.51, 1.54)	0.86 (0.57, 1.30)	1.16 (0.84, 1.60)
	BPS	0.76 (0.28, 2.06)	11.30 (0.42, 4.03)	1.01 (0.27, 3.80)	0.99 (0.38, 2.63)

[a] all n=487; males n=227; females n=260

[b] all n=491; males n=229; females n=262

[c] all n=501; males n=232; females n=269

* Statistically significant at $p<0.05$

Table 4.

Adjusted odds ratios and 95% confidence intervals of the associations of averaged prenatal BPA and BPS with atopic disease outcomes at age 6

		Wheeze[a]	Ever Asthma[b]	Current Asthma[b]	Food Allergy[c]
Total	BPA	0.99 (0.74, 1.33)	0.86 (0.61, 1.22)	1.14 (0.80, 1.62)	0.77 (0.56, 1.07)
	BPS	1.01 (0.75, 1.35)	0.84 (0.60, 1.18)	1.20 (0.85, 1.69)	0.80 (0.57, 1.13)
Males	BPA	0.89 (0.57, 1.38)	0.71 (0.44, 1.16)	1.00 (0.59, 1.67)	1.03 (0.63, 1.70)
	BPS	1.01 (0.67, 1.53)	1.01 (0.65, 1.59)	1.65 (1.01, 2.69)*	0.83 (0.48, 1.42)
Females	BPA	1.02 (0.67, 1.56)	1.06 (0.60, 1.86)	1.18 (0.69, 2.02)	0.56 (0.35, 0.90)*
	BPS	1.02 (0.65, 1.59)	0.64 (0.36, 1.14)	0.76 (0.45, 1.30)	0.85 (0.53, 1.37)

[a] all n=487; males n=227; females n=260

[b] all n=491; males n=229; females n=262

[c] all n=501; males n=232; females n=269

* Statistically significant at $p<0.05$