Bisphenol A Exposure and the Development of Wheeze and Lung Function in Children Through Age 5 Years

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** IMPORTANCE ** Bisphenol A (BPA), a prevalent endocrine-disrupting chemical, has been associated with wheezing in children, but few studies have examined its effect on lung function or wheeze in older children.

** OBJECTIVES ** To test whether BPA exposure is associated with lung function, with wheeze, and with pattern of wheeze in children during their first 5 years.

** DESIGN, SETTING, AND PARTICIPANTS ** A birth cohort study, enrolled during early pregnancy in the greater Cincinnati, Ohio, area among 398 mother-infant dyads. We collected maternal urine samples during pregnancy (at 16 and 26 weeks) and child urine samples annually to assess gestational and child BPA exposure.

** MAIN OUTCOMES AND MEASURES ** We assessed parent-reported wheeze every 6 months for 5 years and measured child forced expiratory volume in the first second of expiration (FEV1) at age 4 and 5 years. We evaluated associations of BPA exposure with respiratory outcomes, including FEV1, child wheeze, and wheeze phenotype.

** RESULTS ** Urinary BPA concentrations and FEV1 data were available for 208 children and urinary BPA concentrations and parent-reported wheeze data were available for 360 children. The mean maternal urinary BPA concentration ranged from 0.53 to 293.55 μg/g of creatinine. In multivariable analysis, every 10-fold increase in the mean maternal urinary BPA concentration was associated with a 14.2% (95% CI, −24.5% to −3.9%) decrease in the percentage predicted FEV1 at 4 years, but no association was found at 5 years. In multivariable analysis, every 10-fold increase in the mean maternal urinary BPA concentration was marginally associated with a 54.8% increase in the odds of wheezing (adjusted odds ratio, 1.55; 95% CI, 0.91-2.63). While the mean maternal urinary BPA concentration was not associated with wheeze phenotype, a 10-fold increase in the 16-week maternal urinary BPA concentration was associated with a 4.27-fold increase in the odds of persistent wheeze (adjusted odds ratio, 4.27; 95% CI, 1.37-13.30). Child urinary BPA concentrations were not associated with FEV1 or wheeze.

** CONCLUSIONS AND RELEVANCE ** These results provide evidence suggesting that prenatal but not postnatal exposure to BPA is associated with diminished lung function and the development of persistent wheeze in children.

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Asthma rates have risen during the past 3 decades, and 1 in 10 US children has asthma.\textsuperscript{1,2} Environmental factors such as tobacco exposure and airborne pollutants have been identified as risk factors for asthma, but reasons for the increased prevalence of asthma remains poorly understood.\textsuperscript{3,4} Some investigators have suggested that exposure to endocrine-disrupting chemicals such as phthalates and bisphenol A (BPA) may contribute to the development of asthma in children.\textsuperscript{5-8}

As a chemical used in some plastics and epoxy resins, BPA is found in many consumer products, and most Americans have detectable BPA concentrations in their urine.\textsuperscript{9} Mice pups that were exposed to BPA prenatally developed an asthma phenotype.\textsuperscript{10,11} Our group previously reported an association of prenatal BPA exposure with increased odds of developing parent-reported wheeze in children through age 3 years but did not examine objective measures of lung function such as spirometry.\textsuperscript{12} Other investigators have reported that postnatal BPA exposure was associated with child asthma and wheeze, but they found no association of prenatal BPA exposure.\textsuperscript{13}

Spirometry is a valuable diagnostic tool for identification of respiratory diseases in children.\textsuperscript{14-16} Most guidelines recommend using forced expiratory volume in the first second of expiration (FEV\textsubscript{1}) for assessing respiratory status in children.\textsuperscript{16} The objectives of this study were to test whether BPA exposure is associated with lung function using FEV\textsubscript{1}, with wheeze, and with pattern of wheeze in children during their first 5 years.

**Methods**

This study included participants in the Health Outcomes and Measures of the Environment (HOME) study, a prospective birth cohort designed to investigate the effects of exposure to environmental toxicants on child health.\textsuperscript{12-17} The Cincinnati Children's Hospital Medical Center and the Centers for Disease Control and Prevention Institutional Review Boards approved the HOME study. Written informed consent was obtained from all participants. Between March 26, 2003, and January 12, 2006, we enrolled 398 English-speaking women who were 18 years or older, at 16 (+3) weeks' gestation, and lived in a home built before 1979. We tracked the women through pregnancy and followed up their children through age 5 years. Women resided within 5 counties surrounding Cincinnati, Ohio, received prenatal care from 9 participating obstetrical clinics, and delivered at 3 participating hospitals. The study included an embedded randomized trial of a lead hazard reduction intervention and injury hazard reduction.

This study included the subset of 398 live-born HOME study infants for whom both urinary BPA concentrations and respiratory outcome data were available. The BPA and wheeze data were available for 360 children (90.5%). The BPA and spirometry data were available for at least 1 time point (age 4 or 5 years) for 208 children (155 at age 4 years and 193 at age 5 years). Reasons for missing spirometry data included failure to complete the 4-year or 5-year clinic visit, completion of the visit before institutional review board approval of FEV\textsubscript{1}, child non-cooperation, and parental time constraints.

**BPA Assessment**

We measured BPA concentrations in serial spot maternal and child urine samples. We collected urine samples in glass containers at 16 weeks’ gestation and 26 weeks’ gestation home visits and annual child visits. The Centers for Disease Control and Prevention quantified total urinary BPA concentrations using online solid-phase extraction coupled with high-performance liquid chromatography isotope dilution tandem mass spectrometry.\textsuperscript{18,19} We replaced approximately 10% of BPA concentrations below the limit of detection (0.4 μg/L) with a value equal to the limit of detection divided by \(\sqrt{2}\) according to the method by Hornung and Reed.\textsuperscript{20} We standardized BPA concentrations for urinary creatinine concentrations (micrograms of BPA per gram of creatinine) at each time point and log\textsubscript{10} transformed BPA concentrations. We used the mean of creatinine standardized maternal urinary BPA concentrations as our primary measure of maternal BPA exposure.

**Covariates**

Research assistants conducted surveys at baseline and every 6 months after the children were born to collect demographic characteristics (child sex, child health insurance status, household income, and maternal education, occupation, and self-reported race/ethnicity). We measured covariates with plausible FEV\textsubscript{1}, or wheeze associations, including prenatal tobacco exposure, season, breastfeeding history, family history of asthma, family history of allergy, child eczema, child allergy, birth weight, maternal parity, pet ownership, and cockroach exposure (by self-report).\textsuperscript{21-25}

We measured prenatal tobacco exposure using maternal serum cotinine concentrations. Cotinine concentrations at 16 weeks, 26 weeks, and delivery were determined using high-performance liquid chromatography-atmospheric pressure chemical ionization tandem mass spectrometry.\textsuperscript{26,27} We imputed values for undetectable concentrations (approximately 35%) by sampling randomly from the left tail of the log-normal distribution of serum cotinine concentrations (excluding smokers), and then we calculated the mean of maternal cotinine measures as the measure of prenatal tobacco exposure.

**Outcome Measures**

During the 4-year and 5-year clinic visits, research assistants measured FEV\textsubscript{1} using a portable device (PiKo-1; nSpire Health, Inc).\textsuperscript{28,29} We attempted to collect at least 3 acceptable (meter determined) FEV\textsubscript{1} measures from each child. The FEV\textsubscript{1} was recorded in liters (resolution, 0.01 L). We used the maximum acceptable FEV\textsubscript{1}, obtained as the FEV\textsubscript{1} for each participant. We calculated the percentage predicted FEV\textsubscript{1} (%FEV\textsubscript{1}) and multiplied the calculated %FEV\textsubscript{1} value by 0.9 for children whose mothers reported their race/ethnicity as black.\textsuperscript{30}

Research assistants surveyed parents every 6 months for 5 years to collect parent-reported wheeze data. We used a question from the National Health and Nutrition Examination Survey.
Survey that asked “Has [child’s name] had wheezing or whistling in his/her chest in the last 6 months?” We used this dichotomous value as our child wheeze outcome. We also conducted a trajectory analysis to identify distinct groups of wheeze trajectories and phenotypes.  

Statistical Analysis

We calculated descriptive statistics for all demographic, exposure, and outcome data. We used the geometric mean (95% CI) to describe central tendency and dispersion for BPA concentrations. We used statistical software (SAS, version 9.3; SAS Institute, Inc) and a 2-sided 5% level to test statistical significance. We log10 transformed urinary BPA concentrations; therefore, the β estimates represent a 10-fold change in BPA concentration.

We analyzed the association of the mean maternal urinary BPA concentration and child urinary BPA concentration at 4 and 5 years with %FEV1 at 4 and 5 years after adjusting for covariates using mixed-effects linear regression. We first evaluated associations of the mean maternal urinary BPA concentration, then child urinary BPA concentration, and then both in the same analysis.

We analyzed the association of the mean maternal urinary BPA concentration with wheeze during the previous 6 months using generalized estimating equations with a logit link to account for within-individual correlation resulting from repeated outcome measurements. We made some assumptions for the analysis of associations of child BPA concentration with wheeze because wheeze was measured twice a year and BPA concentration was measured annually. First, we evaluated the intraclass correlation coefficient of child BPA concentration to determine if the mean child BPA concentration could be a proxy for child exposures. Second, we evaluated associations of the annual child BPA concentration with concurrent wheeze outcomes collapsed over each year (ie, 12-month BPA concentration aligned with child wheeze during 0-12 months). Third, we evaluated associations of the annual child BPA concentration projected on future wheeze outcomes collapsed over each year (ie, 12-month BPA concentration aligned with child wheeze during 12-24 months). Fourth, we added the mean maternal urinary BPA concentration to these concurrent and future child BPA concentration and wheeze analyses.

We also analyzed the association of the mean maternal urinary BPA concentration with wheeze phenotype using developmental trajectory analysis. This method identifies rather than assumes groups of trajectories using an objective algorithm for determining groups, and it estimates the probability that each participant belongs to each distinctive group. Individuals with missing data are estimated with less certainty using this approach. We did not adjust for other covariates, except creatinine concentration (where appropriate), because of inherent power limitations.

We tested the interactions of urinary BPA concentration with time (where applicable) in multivariable analyses. We also conducted secondary analyses to explore potential windows of vulnerability by replacing the mean maternal urinary BPA concentration variable with urinary BPA concentrations measured at each of the maternal time points (ie, 16 or 26 weeks) in separate analyses; we used nonstandardized BPA concentrations and adjusted for concurrent urinary creatinine concentrations in these analyses. Last, to determine the consistency of results, we repeated all analyses with BPA concentrations without accounting for creatinine concentrations.

Results

Participants with available FEV1 outcome data were more likely to be of white race/ethnicity, have a mother with higher than a high school education, have married parents, have a higher household income, and have a lower prenatal cotinine concentration than participants without FEV1 outcome data (Table 1). Maternal urinary BPA concentrations were similar between the children with and without FEV1 data. The mean maternal urinary BPA concentration ranged from 0.53 to 293.55 μg/g of creatinine, with a geometric mean of 2.4 (95% CI, 2.1-2.7) μg/g of creatinine. Maternal urinary BPA concentrations at 16 and 26 weeks’ gestation were weakly correlated (r = 0.18, P = 0.03).

The frequency of parent-reported wheeze during the previous 6-month period (n = 360) varied between 15.9% and 24.1% (Table 2). The correlation of %FEV1 at 4 and 5 years was 0.34 (95% CI, 0.18-0.48).

Percentage Predicted FEV1

In adjusted analysis of the association of maternal urinary BPA concentration with %FEV1, a significant interaction of BPA with time was observed (P = 0.03). The interaction demonstrated an association of increasing mean maternal BPA concentration with decreasing %FEV1 at 4 years (β = −14.2; 95% CI, −24.5 to −3.9; P = 0.007). In contrast, no statistically significant association was observed at 5 years (β = 0.04; 95% CI, −9.04 to 9.12; P = 0.99).

In an adjusted analysis evaluating the association of child urinary BPA concentration with %FEV1, no statistically significant association and no interaction with time were observed. In addition, when maternal urinary BPA concentration was added to the analysis, the results were almost identical to the analysis of maternal urinary BPA concentration alone (no association of child BPA concentration with %FEV1).

We examined the effect of the timing of maternal urinary BPA exposure by evaluating the 2 maternal BPA measures separately. Adjusting for the same factors and creatinine concentration, we found a significant interaction of 16-week maternal BPA concentration with time (P = 0.04). The interaction demonstrated a borderline association of increasing 16-week maternal urinary BPA concentration with decreasing %FEV1 at 4 years (β = −7.6; 95% CI, −16.4 to 1.3; P = 0.09) but no association at 5 years (β = 2.4; 95% CI, −5.4 to 10.2; P = 0.55). The relationships were similar for 26-week maternal urinary BPA concentration, with the interaction demonstrating a significant association (P = 0.03) of increasing 26-week maternal BPA concentration with decreasing %FEV1 at 4 years (β = −9.7; 95% CI, −18.2 to −1.3; P = 0.03) but no association at 5 years (β = −0.2;
Bisphenol A Exposure and the Development of Wheeze

Wheeze Phenotype

We identified 4 distinct developmental trajectories of wheeze, which we categorized as (1) never (31.2%), (2) early (early onset or transient) (41.4%), (3) late (late onset) (15.7%), and (4) persistent (11.7%) (Figure). The mean maternal urinary BPA concentration was not associated with wheeze phenotype, but a 10-fold increase in 16-week BPA concentration (adjusted for log-transformed urinary creatinine concentration) was associated with a 4.27-fold increase in the odds of persistent wheeze compared with no wheeze (Table 3). These findings were statistically unchanged when evaluating BPA concentration without creatinine concentration adjustment. We did not evaluate child BPA concentration in the trajectory analyses because of the low intra-class correlation coefficient of child BPA concentration.

Discussion

We found that prenatal BPA exposure, measured using maternal urinary BPA concentrations at 2 time points during gestation, was associated with a decrease in children’s lung function at age 4 years but not at age 5 years; child BPA concentrations were not associated with lung function at either age. Maternal urinary BPA concentration was marginally associated with increased odds of parent-reported wheeze, and a trend was observed for increased odds of persistent wheeze. Child BPA concentrations were not associated with wheeze. BPA exposure during early and later pregnancy was associated with %FEV₁, but BPA exposure during early pregnancy was more strongly associated with wheeze and wheeze phe-
notype. These results confirm and extend the observed increase in the odds of child wheeze associated with prenatal BPA exposure previously described in this same cohort at a younger age.12

Investigators have noted an association of exposure to plastic materials with the development of respiratory disorders in animal and epidemiologic studies.5-8 Evidence in animals suggests that BPA may affect lung development. Specifically, perinatal exposure to BPA increased airway inflammation and responsiveness in a mouse model of asthma.10 In another study,11 prenatal but not postnatal BPA exposure promoted the development of allergic asthma in mice. The mechanism for this association is unclear, but a recent study12 noted that rhesus macaques exposed to BPA had accelerated development of secretory cells in the proximal airways. However, the authors of another animal study37 reported that maternal exposure to BPA has only a subtle association with allergic inflammation, which did not lead to airway responsiveness. Human investigations have found an association of BPA exposure and asthma, but the risks of exposure and the timing of exposure are inconsistent. Our group noted an association of prenatal BPA exposure with child wheeze in young children12; however, another study37 reported a postnatal association of BPA exposure with child asthma and wheeze but did not find an association of prenatal BPA exposure. In an analysis of the 2005-2006 National Health and Nutrition Examination Survey data, Vaidya and Kulkarni39 reported a cross-sectional association of urinary BPA concentration with allergic asthma only for female sex. The design of these studies varied such that it is impossible to directly compare the timing of exposures and associated outcomes.

Spirometry is a valuable tool for the early diagnosis of respiratory diseases in preschool children.14-16 The FEV1 is the key spirometric measure in asthma management; it has been shown to predict future asthma symptoms and exacerbations.14,39 Moreover, prospective studies40,41 showed that children with wheeze have persistently lower FEV1 than children without wheeze and that poor airway function in early life is an important risk factor for poor airway function later. However, the intrindividual variability of FEV1 over time has implications for its use as a long-term vs short-term measure of lung function.42 The FEV1 can be useful in the assessment of current status, but a spot measure of FEV1 may not represent long-term trends.43 The association of maternal BPA exposure with a decrease in child lung function in the present study was inconsistent, but the association at age 4 years represents an objective and clinically relevant effect that extends our group’s earlier work showing that maternal BPA exposure was associated with the development of wheeze in young children.12 When we evaluated these patterns of wheeze, we found that gestational BPA exposure has a marginal association with increased odds of wheeze through age 5 years, especially the persistent wheeze phenotype. Although these results need to be confirmed in other cohorts, this study raises questions about the role of BPA exposure in the development of asthma and the asthma epidemic.

We also tested whether gestational urinary BPA concentrations at different time points were more strongly associated with FEV1, wheeze, and wheeze phenotype. Higher BPA concentration at 16 weeks’ gestation was associated with an increased odds of wheeze and a persistent wheeze phenotype and a borderline association with FEV1 deficits, whereas higher BPA concentration at 26 weeks’ gestation was associated with decreased FEV1, but not wheeze or wheeze phenotype. These results taken from a small birth cohort suggest that maternal BPA exposure is a risk factor for diminished lung function and wheeze in children, as well as that earlier gestation exposure may be more important than later gestation exposure.

Our study has some limitations. First, BPA concentration was weakly correlated at 16 and 26 weeks, and it is known to vary widely over time;44-47 this may result in exposure misclassification. We had serial measures of urinary BPA concentration, which diminishes but does not dismiss this limitation. Exposure misclassification would likely reduce rather than enhance the association of gestational BPA exposure

Table 2. Respiratory Outcomes at Each Child Age

<table>
<thead>
<tr>
<th>Outcome</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>42</th>
<th>48</th>
<th>54</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent-reported wheeze, %</td>
<td>19.9</td>
<td>24.1</td>
<td>22.0</td>
<td>19.3</td>
<td>15.9</td>
<td>17.1</td>
<td>16.3</td>
<td>18.7</td>
<td>16.2</td>
</tr>
<tr>
<td>FEV1, mean (SD), L</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.70 (0.25)</td>
<td>NA</td>
<td>0.89 (0.26)</td>
</tr>
<tr>
<td>%FEV1, mean (SD)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>76 (24)</td>
<td>NA</td>
<td>85 (22)</td>
</tr>
</tbody>
</table>

Abbreviations: FEV1, forced expiratory volume in the first second of expiration; %FEV1, percentage of predicted FEV1; NA, not applicable.
with wheeze or lung function. Second, FEV₁, which was available for only a subset of the children, may not predict future lung health and may not fully discriminate the effects of BPA. Third, the cohort’s mean %FEV₁ was below 100%, which suggests that these children had poorer lung function than the healthy children who were used to generate the reference sample. Fourth, wheezing was based on parental report and may have been underreported or overreported. Fifth, differential attrition occurred: minority, low-income report and may have been underreported or overreported. The cohort’s mean %FEV₁ was below 100%, which suggests that these children had poorer lung function than the healthy children who were used to generate the reference sample. Fourth, wheezing was based on parental report and may have been underreported or overreported. Fifth, differential attrition occurred: minority, low-income report and may have been underreported or overreported. Sixth, these findings may reflect concurrent exposures to other chemicals or other unknown factors that were not accounted for in this analysis.

**Conclusions**

We found that prenatal BPA exposure that occurred during early pregnancy was inconsistently associated with diminished lung function, increased odds of wheeze, and a persistent wheeze phenotype in young children. Additional research is needed to clarify the contrasting findings in recent human studies. If future studies confirm that prenatal BPA exposure may be a risk factor for impaired respiratory health, it may offer another avenue to prevent the development of asthma.

**Table 3. Association of Log10 Maternal Urinary BPA Concentration With Developmental Trajectories of Wheeze**

<table>
<thead>
<tr>
<th>Maternal Urinary BPA Concentration</th>
<th>Odds Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean†</td>
<td>Early</td>
</tr>
<tr>
<td>16 wk‡</td>
<td>1.48 (0.28-7.88)</td>
</tr>
<tr>
<td>26 wk§</td>
<td>1.31 (0.39-4.34)</td>
</tr>
</tbody>
</table>

Abbreviation: BPA, bisphenol A.

* Never wheeze is the reference group.

† Standardized for urinary creatinine concentration.

‡ Adjusted for same-time urinary creatinine concentration.

**REFERENCES**


13. Donohue KM, Miller RL, Perzanowski MS, et al. Prenatal and postnatal bisphenol A exposure and


