Bisphenol A Exposure Is Associated with Decreased Lung Function

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Objective To examine the associations of bisphenol A (BPA) exposure with lung function measures and exhaled nitric oxide (FeNO) in children.

Study design We performed a cross-sectional analysis of a subsample of US children age 6-19 years who participated in the 2007-2010 National Health and Nutrition Examination Survey. We assessed univariate and multivariable associations of urinary BPA concentration with the predicted pulmonary function measures for age, sex, race/ethnicity and height (forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], forced expiratory flow 25%-75%, and FEV1 divided by FVC) and with FeNO.

Results Exposure and outcome data were available for 661 children. Median BPA was 2.4 ng/mL (IQR: 1.3, 4.1). In multivariable analysis, a larger urinary BPA concentration was associated with significantly decreased percent predicted forced expiratory flow 25%-75% (%FEF2575) (3.7%, 95% CI 1.0, 6.5) and percent predicted FEV1 divided by FVC (%FEV1/FVC) (0.8%, 95% CI 0.1, 1.7) but not percent predicted FEV1, percent predicted FVC, or FeNO. A child in the top quartile of BPA compared with the bottom quartile had a 10% decrease in %FEF2575 (95% CI −1, −19) and 3% decrease in %FEV1/FVC (95% CI −1, −5).

Conclusions BPA exposure was associated with a modest decrease in %FEF2575 (small airway function) and % FEV1/FVC (pulmonary obstruction) but not FEV1, FVC, or FeNO. Explanations of the association cannot rule out the possibility of reverse causality. *(J Pediatr 2014;164:1403-8)*.

Asthma prevalence has risen dramatically over the past decades, and currently it affects nearly 1 in 10 children.[1,2] Although many risk factors have been identified, the reason for the rising prevalence remains poorly understood.[3,4] It is possible that novel environmental exposures may partially explain the rising prevalence.[5-8] Bisphenol A (BPA) is a chemical used in the manufacture of some plastics and epoxy resins found in many consumer products including the lining of canned foods. BPA exposure is pervasive, largely via food; over 90% Americans have detectible BPA in their urine.[9]

Animal studies suggest that BPA may adversely affect lung development. Animal models have identified an association of prenatal BPA exposure with the development of an experimental model of asthma, and one study noted that rhesus macaques exposed to BPA had accelerated development of secretory cells in the proximal airways.[10-12] However, another animal study demonstrated that maternal exposure to BPA has only subtle effects on allergic inflammation which did not lead to significant airway responsiveness.[13]

Epidemiologic studies have suggested that BPA may contribute to the development of asthma or bronchial obstruction in children.[14] The human studies note a similar association of BPA and asthma, but the timing of exposure and associated risks are conflicting. We previously reported that prenatal BPA exposure was associated with increased odds of developing parent-reported wheeze in young children.[15] However, one study reported a postnatal association of BPA exposure with child asthma and wheeze but did not find an association of prenatal BPA exposure.[14] Using 2005-2006 National Health and Nutrition Examination Survey (NHANES) data, Vaidya reported an association of urinary BPA and allergic asthma primarily in females.[16] Yet, no study has examined whether BPA exposure is associated with objective measures of lung function such as spirometry, a tool used for diagnosing and monitoring lung diseases.[17-19] This is a gap in knowledge because most asthma guidelines recommend using spirometry and the measurement of forced expiratory volume in 1 second (FEV1) for assessing respiratory status.[19] A newer measure, exhaled nitric oxide (FeNO), has been proposed as potential noninvasive method to diagnose asthma and monitor the response to anti-inflammatory therapy, yet no study has examined BPA exposure and its relationship to FeNO.[20]

%FEF2575	Percent predicted FEF2575	FeNO	Exhaled nitric oxide
%FEV1	Percent predicted FEV1	FEV1	Forced expiratory volume in 1 second
%FEV1/FVC	Percent predicted FEV1/FVC		
%FVC	Percent predicted FVC	FEV1/FVC	FEV1 divided by FVC
ATS	American Thoracic Society	FVC	Forced vital capacity
BMI	Body mass index	NHANES	National Health and Nutrition Examination Survey
BPA	Bisphenol A		
FEF2575	Forced expiratory flow 25%-75%		

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We therefore examined associations of urinary BPA with pulmonary function and FeNO in a large, representative sample of US children, the 2007-2010 NHANES.

Methods

We analyzed a concatenated set of data for children ages 6-19 years who participated in the 2007-2010 NHANES, a nationally representative survey, which includes demographic, socioeconomic, and health questions and an examination component consisting of medical, dental, and physiological measurements. The New York University School of Medicine Institutional Review Board exempted this project from review on the basis of its analysis of already collected and de-identified data.

BPA was measured in a spot urine specimen from a random, one-third subsample of participants (n = 1625) and analyzed with high-performance liquid chromatography and tandem mass spectroscopy.[21] We substituted the limit of detection divided by $\sqrt{2}$ for BPA concentrations below the limit of detection (3.3%). We log transformed BPA (natural log) to account for skew and included urinary creatinine in all analyses to adjust for urinary dilution.[9]

Measures of Respiratory Function and FeNO

Spirometry procedures in 6- to 19-year-olds followed American Thoracic Society (ATS) standards.[22-24] Participants made forced vital capacity (FVC) maneuvers to meet acceptability and reproducibility criteria. We focused our analyses on FEV1, FVC, forced expiratory flow 25%-75% (FEF2575), and FEV1 divided by FVC (FEV1/FVC) because these measures are widely used in clinical care. FEV1 is the most common measure of airway obstruction used for asthma management, FVC is a widely-used measure of lung volume, and FEF2575 is a measure of small airway function. Some investigators suggest that FEV1/FVC is a more appropriate measure of obstruction in children than FEV1.[25-28] We calculated percent predicted levels of each of these measurements (%FEV1, %FVC, %FEF2575, and %FEV1/FVC) for age, sex, race/ethnicity, and height, using standard methods and used these variables as our primary dependent variables.[29]

Health technicians measured FeNO with the NIOX MINO (Aerocrine AB, Solna, Sweden) using an electrochemical sensor to detect FeNO levels (5-300 ppb).[30] Two valid, reproducible measurements were required, following ATS guidelines.[20] ATS recommends the use of cut-points rather than reference values for interpreting FeNO levels and recommends different thresholds for children <12 years old. We used the NHANES variable average of 2 reproducible measurements, and we categorized children using the cut-point of 36 ppb (children 6-11 years) or 39 ppb (children ≥12 years).[20,31] FeNO below the cut-point indicates less eosinophilic inflammation and good corticosteroid response, whereas FeNO above the cut-point indicates inflammation and poor steroid response.[20,31]

Potential Confounders

Technicians collected data on height, weight, demographics, and medical history. Body mass index (BMI) was calculated and BMI z-scores were derived from the Centers for Disease Control and Prevention 2000 reference data.[32] We categorized overweight and obese (≥1.036 and ≥1.64) using BMI z-score. We grouped race/ethnicity into Mexican American, other Hispanic, non-Hispanic White, and non-Hispanic Black. We categorized caregiver education as: <9th grade, 9th-12th grade, high school/graduate equivalency diploma, some college, and ≥ college. We grouped the poverty-income ratio variable into quartiles. We categorized age into 6-11 and 12-19 years, to emulate NHANES prevalence reports. We included serum cotinine, a biomarker of tobacco exposure, as a covariate. We categorized cotinine into low (<0.015 ng/mL), medium (<2 and ≥0.015 ng/mL), and high (≥2 ng/mL) categories.[33] We accounted for recent respiratory illness using response to, "in the past 7 days, have you had a cough, cold, phlegm, runny nose or other respiratory illness? Do not count allergies or hay fever." We accounted for asthma diagnosis using response to, "has a doctor or other health professional ever told [you] that [study participant has] asthma?" We created "missing" categories for potential confounders (except BMI). Serum cotinine was missing in 9.2%; otherwise, <5% of values were missing for other covariates.

Statistical Analyses

We calculated descriptive statistics for all demographic, exposure, and outcome data. We accounted for the complex survey sampling design using standard techniques, using Stata 12.0 (StataCorp, College Station, Texas).[34] We employed 2-sided tests for statistical significance (defined as $P \leq .05$). We conducted linear regression analyses to examine the bivariate association of BPA and potential covariates with each pulmonary function outcome (%FEV1, %FVC, % FEF2575, and %FEV1/FVC) and logistic regression analysis to examine the associations with FeNO. To assess robustness of the bivariate associations we analyzed the association of BPA with pulmonary function using multivariable linear regression, and we used multivariable logistic regression for FeNO associations. We used the %FEV1 analysis to select covariates and applied the same covariates to each outcome. Because BPA has estrogenic effects, we tested interactions of BPA with sex. We also considered other biologically plausible covariate interactions including asthma diagnosis, race, cotinine, and obesity. Lastly, we tested strength of the findings by reprising the multivariable analysis of percent predicted lung function using z-scores rather than percent predicted pulmonary outcome, and we also examined the final multivariable percent predicted pulmonary outcome models without sample weights.

We evaluated the specificity of associations of BPA and the respiratory outcomes by examining the association of urinary concentrations of 2 other structurally similar environmental phenols with the pulmonary outcomes. We evaluated benzophenone-3, a chemical found in nonfood

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