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Maternal Bisphenol A Exposure During Pregnancy and Its Association With Adipokines in Mexican-American Children

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Bisphenol A (BPA) is a high volume production chemical that has been detected in 93% of the United States population. It is thought to have endocrine disrupting activity but human data are limited. In this study, we examined whether prenatal or concurrent urinary BPA concentrations are associated with key metabolism-related hormones, adiponectin and leptin (adipokines), in 9-year-old children. For this analysis, we used 188 mother-child pairs from the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) prospective study. BPA was measured in urinary spot samples during early (12.6 ± 3.9 weeks gestation) and late (26.3 ± 2.5 weeks gestation) pregnancy and in 9-year-old children. We found that BPA concentrations during late pregnancy were associated with increased plasma leptin in boys (β = 0.06, P = 0.01), controlling for maternal prepregnancy body mass index (BMI), pregnancy soda consumption, and smoking, years in US prior to pregnancy, maternal education, household poverty status, child BMI and child soda, fast food and sweet snack consumption at 9 years. Additionally, we found that BPA concentrations during early pregnancy are directly associated with plasma adiponectin levels in girls (β = 3.71, P = 0.03). However, we did not find any significant relationships between concurrent BPA concentrations and 9-year child adiponectin or leptin. Overall, our data suggest that prenatal BPA concentrations may influence adipokine levels in 9-year-old children. Environ. Mol. Mutagen. 54:621–628, 2013.

Key words: leptin; adiponectin; prenatal; endocrine disruptor; sex-difference

INTRODUCTION

Bisphenol A (BPA) is used to make epoxy resins and polycarbonate plastics—present in household applications such as water bottles, food containers, canned food, dental fillings and household electronics [Vandenbergh et al., 2007]. In the United States (US), BPA ranks among the highest volume production chemicals and National Health and Nutrition Examination Survey (NHANES) data show that urinary BPA is detectable in 93% of the US population [Calafat et al., 2008]. There is evidence that BPA can cross the placenta and is present in fetal circulation and amniotic fluid [Balakrishnan et al., 2010; Morck et al., 2010].

Increasing data argue that BPA may act as an “environmental obesogen”—a term used to describe chemicals that can alter energy balance, promoting adipogenesis and lipid accumulation [Grun and Blumberg, 2006]—and several reports suggest that BPA affects levels of important metabolism-related hormones, adiponectin and leptin—also known as adipokines [Miyawaki et al., 2007; Hugo et al., 2008; Ben-Jonathan et al., 2009; Somm et al., 2009]. Adiponectin, a protein hormone secreted by adipose tissue, targets muscle and liver to increase uptake and catabolism of fatty acids and carbohydrates, promoting insulin sensitivity [Kadowaki and Yamauchi, 2005]. In children, lower adiponectin levels are associated with both metabolic syndrome and type 2 diabetes [Cruz et al., 2004; Shaibi et al., 2007]. Leptin, a hormone synthesized mainly by adipose tissue...
but also by the stomach, skeletal muscle and liver, acts on the hypothalamus to convey satiety and regulate long-term energy balance [Margetic et al., 2002; Mantzoros et al., 2011]. Plasma leptin levels correlate positively with adiposity, however, obese individuals commonly develop “leptin resistance” or tolerance—a hyperleptinemic state with a lack of leptin’s regulatory effects [Considine et al., 1996; Ong and Loos, 2006].

BPA exposure may be linked to changes in metabolic health in a sex-dependent manner. Using a mouse model, Miyawaki et al. [2007] showed that perinatal exposure to BPA resulted in sex-specific increases in body and adipose tissue weight and changes in leptin levels in the offspring [Miyawaki et al., 2007]. Additionally, Somm et al. [2009] showed that although perinatal exposure to BPA resulted in greater weight of both male and female Sprague-Dawley rats on postnatal day 1, this difference persisted only in females at postnatal day 21 [Somm et al., 2009]. In in vitro cell models, BPA has been shown to promote differentiation of 3T3-L1 fibroblast cells into adipocytes [Masuno et al., 2005] and inhibit adiponectin release from human adipocytes [Hugo et al., 2008].

Few data are available on associations between prenatal BPA exposure and children’s metabolic health. Chou et al. [2011] reported that mothers in the highest quartile of BPA blood concentrations at delivery had boys with increased odds of low adiponectin and high leptin at birth [Chou et al., 2011]. However, this study assessed BPA concentrations in participants’ blood—a measure known to have severe limitations due to high risk of contamination and blood collection occurred near time of birth where medical interventions in hospitals can dramatically increase BPA exposures [Calafat et al., 2009; Vandenberg et al., 2011; Duty et al., 2013]. Data from the National Health and Nutrition Examination Survey (NHANES) and other cross-sectional studies show that increased body mass index (BMI) is associated with greater urinary BPA concentrations [Trasande et al., 2012; Wang et al., 2012]. Nevertheless, whether higher BPA concentrations actually precede the onset of obesity remains uncertain [Becker et al., 2009; Lakind and Naiman 2011; Trasande et al., 2012; Wang et al., 2012].

In the first longitudinal study of BPA and obesity, we did not observe associations of prenatal BPA urinary concentrations and increased body weight in children participating in the Center for Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort. In fact, prenatal BPA urinary concentrations were negatively associated with BMI Z-score in girls [Harley et al., 2013]. Thus, whether and how prenatal or childhood BPA exposure leads to altered metabolic health remains unclear.

In this study, we assessed whether maternal urinary BPA concentrations during the first and second halves of pregnancy are associated with plasma adiponectin and leptin levels in children when they reach 9 years of age. Additionally, we investigated whether concurrent BPA concentrations are associated with adipokine levels in children at 9 years. Given that many previous studies report different responses to BPA exposure by sex, we tested for interaction by sex in our models. Analyses were performed using data from the CHAMACOS study, a Mexican-American cohort with a high prevalence of childhood obesity.

**MATERIALS AND METHODS**

**Subjects and Study Design**

The CHAMACOS study is a longitudinal birth cohort designed to assess the health effects of environmental exposures on growth and development in children living in the Salinas Valley, CA [Eskenazi et al., 2004, 2005]. Mothers were enrolled during pregnancy between October 1999 and October 2000, with 537 mother-child pairs in the study at delivery and 327 pairs remaining at the 9-year visit. Eligible women were ≥18 years of age, <20 weeks gestation at enrollment, English or Spanish speaking, eligible for low income health insurance (Medicaid), and planning to deliver at the county hospital. Women were interviewed at ~13 and ~26 weeks gestation and anthropometric measures of the children were obtained at birth, 6 months, and 1, 2, 3, 5, 7, and 9 years of age. Adiponectin and leptin were measured on a convenience subsample of 188 children having blood samples at 9 years and complete anthropometric and demographic data. Of these children, 131 had maternal urinary BPA measures for the first half of pregnancy, 179 for the second half and 172 had 9-year urinary BPA data. No differences were observed comparing maternal and child demographic and anthropometric measures included in Table 1 between this subsample and the overall CHAMACOS cohort. All study activities were approved by the Committee for the Protection of Human Subjects at the University of California, Berkeley and the Centers for Disease Control and Prevention (CDC).

**Questionnaire Data**

Mothers were interviewed at the two prenatal visits using structured questionnaires administered in Spanish or English by bilingual, bicultural trained interviewers. We collected sociodemographic information, including maternal age at pregnancy, years of living in the US prior to pregnancy, education, household poverty category, and smoking during pregnancy. During the second prenatal interview, we used a previously validated food frequency questionnaire (FFQ) to assess dietary intake, including maternal soda consumption, during pregnancy [Block et al., 1990; Harley et al., 2005] and asked additional questions at the 9-year interview about child soda, fast food and sweet snack consumption at age 9. Maternal prepregnancy BMI was calculated using the mother’s self-reported prepregnancy weight and measured height. Infant birth weight, length, and gestational age were obtained from delivery medical records abstracted by a registered nurse. Children were categorized as “small for gestational age” if their birth weight was <10th percentile for gestational age based on their ethnicity, maternal parity, and infant sex [Overpeck et al., 1999]. Children were considered as “at term” if they were born at or after 37 weeks of gestation.

**Anthropometric Measurements**

Children’s weight and height were measured at the 9-year visit using a bioimpedance electronic scale (Tanita TBF-300A Body Composition Analyzer.) and wall-mounted stadiometer (Seca 222), respectively. Child height was measured in triplicate and the average of measurements was...
Plasma Adiponectin and Leptin Measurements

Nonfasting blood samples were collected from the children at the 9-year visit and stored at −80°C. Adiponectin and leptin were measured in plasma using enzyme-linked immunosassay (ELISA) RayBio Human Adiponectin and Human Leptin kits (Norcross, GA) as previously described [Volberg et al., 2013]. The minimum detectable concentrations for adiponectin and leptin were 10 and 6 pg mL⁻¹, respectively. All samples were run in duplicate and the values were averaged. The intra- and interplate coefficients of variance (CV) were 4 and 12%, respectively, for adiponectin and 5 and 15%, respectively, for leptin.

Maternal and Child Urinary BPA Measurement

Urinary spot samples were collected in sterile, polypropylene urine cups during the first (12.6 ± 3.9 weeks gestation) and second (26.3 ± 2.5 weeks gestation) half of pregnancy and from children at 9 years of age (9.4 ± 0.4 years). Samples were stored at −80°C and shipped to the CDC (Atlanta, GA) for analysis using online solid-phase extraction coupled with isotope-dilution high-performance liquid chromatography tandem mass spectrometry with peak focusing [Ye et al., 2005]. Total urinary concentration of BPA (free and conjugated) was measured with a limit of detection (LOD) at 0.4 μg L⁻¹. For concentrations below the LOD, we used the instrument-reported values. When no signal was detected, we imputed values at random based on a log-normal probability distribution whose parameters were determined by maximum likelihood estimation [Lubin et al., 2004]. Blanks, low (≤2.8 μg L⁻¹) and high (>10 μg L⁻¹) quality control materials were included in all runs. To account for urinary dilution, we corrected maternal BPA concentrations using specific gravity, assessed using a hand-held refractometer (National Instrument Company, Baltimore, MD). Child 9-year BPA concentrations were corrected using urinary creatinine determined by the Vitros CREA assay (Ortho Clinical Diagnostics, NJ).

Statistical Analyses

Child adiponectin levels were approximately normally distributed, but leptin levels were right-skewed. Thus, all leptin-based analyses use log₁₀-transformed values. Urinary BPA concentrations during early and late pregnancy and at 9 years were also right-skewed and were log₁₀-transformed to reduce the influence of outliers. Using multivariate linear regression, we examined separately effects of BPA exposure during first and second halves of pregnancy and at age 9 on 9-year child adiponectin and leptin. Our models included an interaction term between child sex and BPA concentrations and BPA effect coefficients for each sex were estimated using the “lincom” postregression command in Stata. Potential confounders were identified a priori using a directed acyclic graph and included maternal prepregnancy BMI, soda consumption and smoking during pregnancy, Years of residence in US, maternal education, household poverty status, and child soda, fast food and sweet snack consumption at 9 years. Many of these covariates were chosen based on previous literature showing that several risk factors for obesity, including consumption of soda, school lunches and meals prepared outside of the home, are also related to increased urinary BPA concentrations in the general US population of children [Lakind and Naiman, 2011]. Importantly, previous mechanistic evidence has shown that BPA may have direct effects on adipokines [Hugo et al., 2008; Ben-Jonathan et al., 2009]. Thus, models presented in this study control for child BMI to examine the BPA—adipokine association, independent of BMI’s effect on adipokines. All statistical analyses were conducted using STATA 12 (College Station, TX) for Windows. We set statistical significance at $P < 0.05$ for main effects and $P < 0.10$ for interaction terms.
RESULTS

Child and Maternal Characteristics

Of the 188 children in this study, 87 (46%) were boys and 101 (54%) were girls (Table 1). At time of pregnancy, mothers tended to be young (mean 26.3 ± 5.2 years), to have resided in the US for 10 years or less (75%), and to not have completed high school (80%). Almost half of mothers reported consuming one or more sodas per week (46%). During the pregnancy, the majority of families (62%) were living at or below the federal threshold for poverty (US Census Bureau, 2000). Most mothers were overweight (38%) or obese (26%) according to their prepregnancy BMI. Children were mainly delivered at term (≥37 weeks, N = 178, 95%). Approximately 5% of the children were born preterm and 4% were small for gestational age. Mothers reported that the majority of children consumed soda and fast food at least weekly (58 and 57%, respectively) and 22% consumed sweet snacks daily. At 9 years, 17% of children were overweight and 39% were obese.

Child Adiponectin and Leptin Plasma Levels

At 9 years of age, average child adiponectin plasma levels were 42.6 ± 18.6 μg/mL (Table 2). No statistically significant difference was found between levels in boys and girls. Adiponectin levels were significantly and inversely correlated with 9-year child BMI (r = −0.38, P < 0.001). Average child plasma leptin levels were 8.2 ± 1.1 ng mL−1. Boys (7.1 ± 1.0 ng mL−1) tended to have slightly lower leptin levels compared to girls (9.3 ± 1.2 ng mL−1, P = 0.08). Leptin levels were significantly and positively correlated with 9-year child BMI (r = 0.82, P < 0.001).

Maternal and Concurrent Child Urinary BPA Levels

Table 3 shows urinary BPA concentrations (both uncorrected and corrected for urinary dilution) for mothers during pregnancy and for their children at 9 years, stratified by child sex. Geometric mean (GM) concentrations presented here (0.9 and 1.1 μg L−1 for early and late pregnancy, respectively) are lower than those previously reported for pregnant women from NHANES 2003–2004 (GM = 2.53 μg L−1) [Woodruff et al., 2011]. CHAMACOS 9-year-old children tended to have lower urinary BPA concentrations (GM = 1.6 μg L−1) than those reported for NHANES children aged 6–11 (GM = 3.6 μg L−1) [Calafat et al., 2008]. Of note, a recent report indicated even higher urinary BPA levels in similar age Danish children (Average age 8.5 years, Mean = 6 μg g−1-creatinine) and their mothers (Mean = 4 μg g−1-creatinine) [Frederiksen et al., 2013]. BPA concentrations measured during the first and second halves of pregnancy were weakly but significantly correlated (r = 0.15, P = 0.01). No statistically significant difference was found in 9-year BPA concentrations between boys and girls (P = 0.74).

Prenatal and Concurrent Urinary BPA Concentration and 9-Year Child Plasma Adipokines

Table 4 shows associations between prenatal and concurrent urinary BPA measures and child adiponectin and leptin plasma levels at 9 years, controlling for maternal pre-pregnancy BMI, pregnancy soda consumption and smoking, years in US prior to pregnancy, maternal education, household poverty status, child 9-year BMI, and child soda, fast food and sweet snack consumption at 9 years. We observed significant effect modification by sex for associations between late pregnancy BPA and leptin (interaction P = 0.01) and between early pregnancy BPA and adiponectin (interaction P = 0.1).
Focused on the sex-specific associations, we found that among boys, late pregnancy urinary BPA concentrations were positively associated with 9-year leptin levels ($\beta = 0.06$, $P = 0.01$). Additionally, among girls, we found that early pregnancy BPA concentrations were positively associated with 9-year adiponectin levels ($\beta = 3.71$, $P = 0.03$). Concurrent measures of urinary BPA were not associated with adiponectin levels in 9-year-old children after controlling for BMI.

### DISCUSSION

In this cohort of Mexican-American children, we observed that the BPA–adipokine association may vary by child sex. We found that late pregnancy urinary BPA concentrations were positively associated with leptin levels in 9-year-old boys, adjusting for covariates including child BMI. Additionally, early pregnancy BPA concentrations were positively related to adiponectin levels in 9-year-old girls. While the mechanism for this sexual dimorphism remains unclear, it may be related to BPA’s ability to interfere with activity of endogenous estrogens (17β-estradiol), disrupting normal binding at either non-classical membrane or nuclear estrogen receptors [Gould et al., 1998; Kuiper et al., 1998; Alonso-Magdalena et al., 2005; Alonso-Magdalena et al., 2006; Wetherill et al., 2007]. Previous studies indicate that biosynthesis and function of 17β-estradiol, along with tissue distribution of estrogen receptors may vary by sex [Simpson et al., 1999; Nilsson et al., 2001; Gillies and McArthur, 2010]. We speculate that this may account for some of the sex-specific responses observed with respect to BPA exposure.

Our finding of a positive association between prenatal BPA and leptin in boys is consistent with several animal studies. Wei et al. [2011] showed increased leptin levels in male rats and Miyawaki et al. [2007] found increased body and adipose tissue weight in male mice as a result of perinatal BPA exposures [Miyawaki et al., 2007; Wei et al., 2011]. Although we did not observe an association of prenatal BPA with BMI in boys in this cohort [Harley et al., 2013], we now report an association with increased leptin independent of BMI. BMI may not be as sensitive an endpoint and it is plausible that BPA may directly alter fetal leptin secretion from adipocytes given that it has been shown to do so with respect to adiponectin [Hugo et al., 2008]. This, in turn, may affect leptin secretion postnatally, however, additional mechanistic data are needed to examine the BPA-leptin relationship.

Previous data on CHAMACOS children suggest that prenatal BPA concentrations are negatively associated with BMI $z$-score in girls only [Harley et al., 2013]. Here, adjusting for child BMI, we found that prenatal BPA was positively associated with adiponectin in girls. It is important to note that while many previous studies have shown perinatal BPA exposure to be positively associated with offspring obesity [Rubin et al., 2001; Miyawaki et al., 2007; Somm et al., 2009; Hiyama et al., 2011], and, in an in vitro model, with adiponectin suppression [Hugo et al., 2008], others have found no or reverse associations [Honma et al., 2002; Negishi et al., 2003; Ryan et al., 2010; Nakamura et al., 2012]. A recent study by Anderson et al. [2013] indicated that perinatally exposed male and female mice exhibited increased energy expenditure and activity and, further, females had marginally lower body weight and improved adiponectin and leptin levels throughout their lives [Anderson et al., 2013]. Overall, the reasons for differences in reported associations in animal and human studies remain unclear. Both timing and dose of BPA exposure, as well as diet, do vary for the animal studies mentioned and this may contribute to the inconsistencies in results.

Only one other study has provided data on prenatal BPA and adiponectin and leptin in children. Chou et al. [2011] examined associations between prenatal BPA and

**TABLE 4. Prenatal and Concurrent Associations Between log$_2$ BPA and Adiponectin and Leptin in 9-Year-Old Children**

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<td>Early pregnancy</td>
<td>131</td>
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<tr>
<td>Late pregnancy</td>
<td>179</td>
<td>0.06</td>
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<td>9 year child</td>
<td>172</td>
<td>−0.04</td>
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<td>Early pregnancy</td>
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<td>Late pregnancy</td>
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<td>9 year child</td>
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<td>2.69</td>
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Adjusted for: maternal pre-pregnancy BMI, Years in the US, poverty status, maternal education, smoking during pregnancy, soda consumption during pregnancy, child 9-year BMI, and child soda, fast food and sweet snack consumption at 9 years.

*Specific gravity adjusted.
*Creatinine adjusted.
$P$-value $< 0.05$. 
biological pathway in which BPA can affect leptin and adiponectin and leptin in children at birth [Chou et al., 2011]. They reported a positive association between BPA blood concentrations during pregnancy and leptin in boys at birth. They also found an inverse relationship between prenatal BPA and adiponectin in girls, which we did not. Reasons for this discrepancy remain unclear, but it is important to note that the Chou study measured BPA in maternal plasma collected at birth. There are several limitations to measurement of BPA in blood compared to urine, including higher proportion of non-detects and greater risk of cross-contamination yielding incorrect results [Calafat, 2011]. Additionally, studies have shown that exposures to medical devices in the hospital near the time of birth can dramatically increase BPA levels [Calafat et al., 2009; Vandentorren et al., 2011; Duty et al., 2013].

We did not find significant associations between concurrent BPA exposure and child adiponectins at 9 years, controlling for BMI. To our knowledge, no such data on adiponectin and leptin are available from other reports. Previously, we found positive associations between concurrent urinary BPA concentrations and child BMI [Harley et al., 2013]. Several other studies have also reported a direct association between concurrent BPA and BMI in children [Trasande et al., 2012; Wang et al., 2012]. Using NHANES 2003–2008, Trasande et al. (2012) found a positive association between urinary BPA concentrations and BMI in children aged 6–19 [Trasande et al., 2012]. Such data are limited by their cross-sectional nature and cannot address whether BPA exposure preceded development of obesity or is merely a reflection of it. Overall, our findings suggest that prenatal, and not concurrent, BPA exposure is more relevant in determining child adipokine levels. Future work should focus on further exploring potential metabolic health consequences of BPA exposure during this critical developmental period.

One of the limitations of this study is the short-term nature of the BPA exposure measurement. Urinary BPA concentrations vary widely throughout the day and the spot urine samples used in this analysis reflect only recent exposure. Ye et al. (2011) observed large within-day variance for spot collections (70%) [Ye et al., 2011]. However, we expect this misclassification to be nondifferential, biasing our results towards the null. Additionally, the cross-sectional nature of this study was conducted on a cohort of largely first generation, immigrant and relatively low socioeconomic status Mexican-American families from an agricultural community. A major strength of this study is its prospective nature, providing data on associations between prenatal BPA exposure and child adipokine levels 9 years later. Further, these results are directly relevant to the CHA-MACOS population, given its high prevalence of obesity.

Future directions include examining mechanisms of sex differences in response to BPA exposure. The exact biological pathway in which BPA can affect leptin and adiponectin levels remains unknown. BPA has been shown to interact with estrogen receptors [Gould et al., 1998; Kuiper et al., 1998; Alonso-Magdalena et al., 2005; Alonso-Magdalena et al., 2006; Wetherill et al., 2007] and may also affect key adipogenic transcriptional factors including CCAAT/enhancer binding proteins (C/EBPβ) and peroxisome proliferator-activated receptor γ (PPARγ) [Phrakonkham et al., 2008]. Downstream effects of this may result in altered adipokine levels. Further, it has been shown that estrogen and leptin both target common neuronal sites and both estrogen and leptin receptors are co-localized in several brain regions [Gao and Horvath, 2008]. Given this close relationship, it is possible that BPA-mediated alterations in estrogen signaling affect leptin levels. However, additional work is needed to clarify this pathway.

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AUTHOR CONTRIBUTIONS

VV, VD, JM and AC were involved in data collection. VV, KH, BE, NH and AC were involved in study design and manuscript writing and editing.

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