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Association of early life exposure to bisphenol A with obesity and cardiometabolic traits in childhood

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ABSTRACT

Background: Bisphenol A (BPA) is a chemical used extensively worldwide in the manufacture of plastic polymers. The environmental obesogen hypothesis suggests that early life exposure to endocrine disrupting chemicals such as BPA may increase the risk for wt gain later in childhood but few prospective epidemiological studies have investigated this relationship.
Objectives: We examined the association of early life BPA exposure with offspring obesity and cardiometabolic risk factors in 500 mother-child pairs from the RHEA pregnancy cohort in Crete, Greece.
Methods: BPA concentrations were measured in spot urine samples collected at the 1st trimester of pregnancy) and from children at 2.5 and 4 years of age. We measured birth wt, body mass index (BMI) from 6 months to 4 years of age, waist circumference, skinfold thickness, blood pressure, serum lipids, C-reactive protein, and adipokines at 4 years of age. BMI growth trajectories from birth to 4 years were estimated by mixed effects models with fractional polynomials of age. Adjusted associations were obtained via multivariable regression analyses.
Results: The prevalence of overweight/obesity was 9% at 2, 13% at 3% and 17% at 4 years of age. Geometric mean BPA concentrations were 1.2 μg/g creatinine ± 7.9 in 1st trimester, 5.1 μg/g ± 13.3 in 2.5 years and 1.9 μg/g ± 4.9 in 4 years. After confounder adjustment, each 10-fold increase in BPA at 4 years was associated with a higher BMI *z*-score (adj. β=0.2; 95% CI: 0.01, 0.4), waist circumference (adj. β=1.2; 95% CI: 0.1, 2.2) and sum of skinfold thickness (adj. β=3.7 mm; 95% CI: 0.7, 6.7) at 4 years. Prenatal BPA was negatively associated with BMI and adiposity measures in girls and positively in boys. We found no associations of early life exposure to BPA with other offspring cardiometabolic risk factors.
Conclusions: Prenatal BPA exposure was not consistently associated with offspring growth and adiposity measures but higher early childhood BPA was associated with excess child adiposity.

1. Introduction

Childhood obesity is one of the most serious public health challenges (WHO, 2004). A recent report estimated that the worldwide prevalence of childhood obesity had increased by 47.1% between 1980 and 2013 (Ng et al., 2014), while Greece has the highest prevalence worldwide with more than 40% overweight or obese children at the age of 5–17 years (IOTF, 2015). Excess food consumption and inadequate physical activity are major risk factors for obesity, but do not fully explain the current obesity epidemic (Baillie-Hamilton, 2002; Grun and Blumberg, 2006).

Emerging evidence suggests that exposure to environmental chemicals that act as obesogens-chemicals that inappropriately regulate and promote lipid accumulation and adipogenesis-might play a role in increasing obesity risk, especially when exposure occurs during pregnancy and early life (Grun and Blumberg, 2009; Romano et al., 2014; Tang-Peronard et al., 2011). However, human

Abbreviations: BMI, Body mass index; BPA, Bisphenol A; CRP, C-reactive protein; DPB, Diastolic blood pressure; GAMs, Generalized additive models; GWG, Gestational weight gain; IOM, Institute of Medicine; LOD, Limit of quantification; POPs, Persistent organic pollutants; SD, Standard deviation; SBP, Systolic blood pressure; WC, Waist circumference; 95% CI, 95% Confidence intervals

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evidence is scarce and is mainly focused on adult populations (de Cock and van de Bor, 2014). Epidemiological studies on early-life chemical exposures that may be obesogenic have mainly focused on the effects of persistent organic pollutants (POPs) (Cupul-Uicab et al., 2010, 2013; Delvaux et al., 2014; Garced et al., 2012; Mendez et al., 2011; Smink et al., 2008; Tang-Peronard et al., 2014; Vafeiadi et al., 2015; Valvi et al., 2014, 2012; Verhulst et al., 2009; Warner et al., 2013, 2014) and only few have examined other non-persistent ubiquitous chemicals, such as phthalates (Kim and Park, 2014) and bisphenol A (BPA) (Liu and Peterson, 2015; Tang-Peronard et al., 2011).

BPA is a high-production non-persistent chemical used extensively worldwide to produce polycarbonate plastics and resins which are found in many consumer products, including toys, polycarbonate water bottles and food storage containers, epoxy-lined food cans, dental sealants, water supply pipes, medical tubing, cigarette filters, and thermal receipts (Braun et al., 2011; Ehrlich et al., 2014; Vandenberg et al., 2007). BPA exposure is almost ubiquitous since it has been detected at measurable concentrations in urine samples in various populations, including pregnant women, around the world (Calafat et al., 2008; Cantonwine et al., 2015; Lee et al., 2014; Meeker et al., 2009; Myridakis et al., 2015b; Romano et al., 2015; Vandenberg et al., 2010). The main route for human exposure is considered to be dietary ingestion and to some extent inhalation of household dust, and dermal exposure (Rochester, 2013; Vandenberg et al., 2007). Detectable BPA levels have also been measured in placental and amniotic fluids (Balakrishnan et al., 2010), and human breast milk (Vandenberg et al., 2007) suggesting that exposure starts in utero and may continue postnatally via breastfeeding.

BPA is an endocrine-disrupting chemical that can act through a variety of physiological receptors, such as genomic estrogen receptors 1 and 2, membrane-bound estrogen receptors, androgen receptor, peroxisome proliferator–activated receptor γ, and thyroid hormone receptor (Peretz et al., 2014; Richter et al., 2007). Several studies in rodents have shown that perinatal exposure to BPA elicits increased body weight and adiposity (Miyawaki et al., 2007; Rubin et al., 2001; Rubin and Soto, 2009; Vom Saal et al., 2012). A small number of studies have examined the association of BPA and obesity in humans. Results from cross-sectional studies in adults and children show that higher urinary BPA concentrations are positively associated with obesity (Bhandari et al., 2013; Carwile and Michels, 2011; Eng et al., 2013; Li et al., 2013; Shankar et al., 2012; Trasande et al., 2012; Wang et al., 2012a) but overall, the literature evaluating the association between BPA levels and obesity is inconclusive (Oppeneer and Robien, 2014). Only three prospective cohort studies examined early-life BPA exposure in association with childhood obesity with contradictory findings (Braun et al., 2014; Harley et al., 2013; Valvi et al., 2013). One found higher BMI among children with higher prenatal BPA exposure (Valvi et al., 2013), and the two others reported lower BMI with higher early childhood exposure (Braun et al., 2014; Harley et al., 2013). To our knowledge, there are no other studies so far on the effect of early life BPA exposure on offspring cardiovascular traits other than adiposity.

In this study, we assessed whether urinary BPA concentrations in pregnant women and their children in early childhood were associated with birth weight, body mass index (BMI) from 6 months to 4 years of age, waist circumference (WC), skinfold thickness, blood pressure, serum lipids, C-reactive protein (CRP), and adipokines at 4 years of age in the Rhea mother-child cohort in Crete, Greece.

2. Materials and methods

2.1. Subjects and study design

The Rhea study prospectively examines a population-based sample of pregnant women and their children at the prefecture of Heraklion, Crete, Greece. Methods are described in detail elsewhere (Chatzi et al., 2009). Briefly, female residents (Greek and immigrants) who became pregnant during a period of one year starting in February 2007 were contacted and asked to participate in the study. The first contact was made at the time of the first comprehensive ultrasound examination (mean ± SD 11.96 ± 1.49 weeks) and several contacts followed (6th month of pregnancy, at birth, 9 months, 1st year, and 4 years after birth). To be eligible for inclusion in the study, women had to have a good understanding of the Greek language and be older than 16 years of age. Face-to-face structured questionnaires along with self-administered questionnaires and medical records were used to obtain information on several psychosocial, dietary, and environmental exposures during pregnancy and early childhood. The study was approved by the ethics committee of the University Hospital in Heraklion, Crete, Greece, and all participants provided written informed consent after complete description of the study.

Of 1363 singleton live births in the Rhea study, BPA concentrations were measured in spot urine samples collected during pregnancy from a random sample of 235 mothers, 235 children at 2.5 years and 500 children at 4 years of age; 500 children had at least one measure of BMI between 6 months and 4 years of age.

2.2. Maternal and child BPA exposure assessment

BPA concentrations were measured in spot urine samples collected from mothers (1st trimester of pregnancy) and their children at 2.5 and 4 years of age. All samples were collected in sterile, polypropylene urine cups, aliquoted in 4 ml cryotube vials (Thermo Fisher Scientific, USA) and stored at −80 °C. Analyses were performed at the Environmental Chemical Processes Laboratory (ECPL) in the Department of Chemistry of the University of Crete. An aliquot of each urine sample (1 mL) was analyzed for the determination of total BPA (free and conjugated forms), using a previously described analytical protocol (Myridakis et al., 2015a). Samples exceeding the upper limit of linearity (64 ng/mL) were reanalyzed, diluted with nanopure water. Two quality controls samples (spiked pooled urine) and two blank samples (synthetic urine) were analyzed with every forty six (46) urine samples. The amount of each sample was quantified by the standard curve performed in each assay. Method limit of detection (LOD) was equal to 0.01 ng/mL and samples below LOD were assigned the value of LOD/$\sqrt{2}$. To account for urine dilution, a second aliquot of 0.5 mL urine was analyzed for creatinine concentration using the OLYMPUS 2700 immunoassay system (Beckman Coulter, USA), and BPA concentrations were divided by urinary creatinine levels (i.e, creatinine-adjusted concentrations, hereafter). All samples were measured in duplicates. All creatinine-adjusted BPA concentrations were $\log_{10}$ transformed to obtain normal distributions, as the original distributions were right skewed.

2.3. Child anthropometry

Weight and length at birth were obtained from the hospital delivery logs and medical records.

At child follow-up visits, trained research assistants measured weight and length (up to 2 years old) or height (from 2 to 4 years old) using validated scales (Seca 354 baby scale, Seca Bellisima 841; Seca Corporation, Hanover, MD) and stadiometers (Seca 210 measuring mat, Seca 213; Seca Corporation) according to standard