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Urinary paraben concentrations and their associations with anthropometric measures of children aged 3 years☆

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ABSTRACT

Parabens, known as ubiquitous preservatives, have been linked to adverse health outcomes in humans. This study aimed to examine urinary paraben concentrations of children at 3 years of age and evaluate their associations with anthropometric parameters. Urinary parabens including methylparaben (MeP), ethylparaben (EtP), propylparaben (PrP), butylparaben (BuP) and benzylparaben (BeP) were measured among 436 children in a birth cohort using gas chromatography with tandem mass spectrometry. Generalized linear models were performed to evaluate associations of paraben exposures with age- and sex-specific z scores, including weight, height, weight for height and body mass index. MeP, EtP and PrP were the dominant parabens in urinary samples, with the median concentrations of 6.03 μg/L, 3.17 μg/L, 2.40 μg/L, respectively. The median values of estimated daily intake (EDI_{urine}) of five urinary paraben concentrations were 12.10, 5.68, 4.50, 0.06 and 0.17 μg/kg-body weight/day, respectively. Urinary EtP concentrations were positively associated with weight z scores [regression coefficient $\beta = 0.16$, 95% confidence interval (CI): 0.04, 0.29; $p = 0.01$] and height z scores ($\beta = 0.15$, 95% CI: 0.03, 0.27; $p = 0.01$). Positive associations were found between the sum of molar concentrations of five parabens and height z scores among all children ($\beta = 0.24$, 95% CI: 0.04, 0.45; $p = 0.02$). These significant associations were only observed in boys. Our findings suggest that exposure to parabens may be adversely associated with physical growth in 3-year-old boy children. Further prospective studies are warranted to understand the toxicological mechanisms of paraben exposures and potential risk of children.

1. Introduction

Parabens are a class of *para*-hydroxybenzoic acid with alkyl and aryl esters, which are the most extensively used preservatives in foodstuffs, pharmaceuticals, and personal care products worldwide (Błędzka et al., 2014). Commercially available parabens include methylparaben (MP), ethylparaben (EtP), propylparaben (PrP), butylparaben (BuP) and benzylparaben (BeP). Human exposure to parabens through topical contaction with or ingestion of products containing parabens (Guo et al., 2014; Liao et al., 2013). Recently, parabens have been reported to be present in water, especially at maximum concentrations of 3.14 μg/L in the Pearl River Delta and of 1.65 μg/L in urban surface water in Beijing, China, respectively (Li et al., 2016; Yu et al., 2011). The serious human exposure to parabens has led to extensive distribution in various human biological samples, including urine, serum, breast milk, placental tissue and amniotic fluid (Hines et al., 2015; Philippat et al., 2013; Valle-Sistac et al., 2016). Additionally, parabens in fatty components of human body tissues were also found, which suggested that bio-accumulation could potentially impact fat deposition (Wang et al., 2015).

Previously regarded as safe (Soni et al., 2005), parabens have recently raised concern for the evidence of potential endocrine disruptors, with a lower estrogen receptor binding affinity than 17 β-estradiol (Boberg et al., 2010). Epidemiological studies have shown associations between urinary parabens and adverse health outcomes, including reproductive toxicity (Meeker et al., 2011),

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oxidative stress (Watkins et al., 2015), immune modulation (Savage et al., 2012) and even breast cancer (Pan et al., 2015). Moreover, parabens may also interfere with thyroid hormones and activate the peroxisome proliferator-activated receptorγ(PPARγ), which was a nuclear receptor superfamily playing a key role in adipogenesis and lipid accumulation (Pereira-Fernandes et al., 2013). Furthermore, a study had reported that parabens could promote development and differentiation of multipotent cells into mature adipocyte cells (Hu et al., 2013), indicating parabens may play a role in obesity epidemic.

The long-term exposure to low-dose of parabens seemed alarming susceptibility for young children because of their immaturity of physiological functions, behaviors and potentially enhanced target organ sensitivity (SCCS, 2011). Limited epidemiological researches suggested inconsistent results that exposure to parabens was associated with adverse effects on body growth. Specifically, associations of gestational exposure to parabens with increase in birth weight (Philippat et al., 2014) and with reduction in birth weight and length (Geer et al., 2016) were found. Compared to prenatal exposure to parabens, relatively scarce data are available regarding the effects of postnatal exposure on body growth. Only one study revealed non-significant association of paraben exposure with childhood obesity, but a positive association between the paraben metabolite of 3,4-dihydroxy benzoic acid (3,4-DHB) and obesity (Xue et al., 2015). Given the widespread exposure to parabens and possible endocrine disruption, it is imperative to examine the potential risk of exposure to these pollutants in relation to childhood obesity.

Generally, parabens are rapidly absorbed, metabolized, and excreted in urine from the body (Moos et al., 2015a). Urinary paraben concentrations have been known to be valid biomarkers of exposure (Ye et al., 2006). Thus, the objectives of the present study are to assess parabens exposure of children and its potential associations with body growth at 3 years old in a birth cohort from an agricultural region in Jiangsu Province, China.

2. Materials and methods

2.1. Study participants and questionnaires

During July 2012–April 2013, 498 children were recruited in our study when they visited Sheyang Maternal and Child Health Care Centre. All children's mothers had previously participated in our longitudinal cohort study during pregnancy at hospital. Questionnaire survey was administered to each participated child's caregiver by trained interviewers. Data covering child's sociodemographics, living environment and lifestyles was collected. Information regarding pregnancy and maternal health was obtained from medical records and questionnaires previously (Qi et al., 2012). Each caregiver had signed an informed consent form and agreed to donate child's urine sample. This study was carried out with the permission of the Ethics Committees of Fudan University.

Of the 498 children, we excluded 33 children who had no or inadequate urine samples, 20 children who did not complete the questionnaires, two twins, two children who had congenital anomalies at birth, two children whose mothers suffered from serious pregnancy complication, and one child without body growth measures. Finally, 436 children at 3 years of age were enrolled in the present study. These children did not differ significantly from the initially recruited subjects on all attributes of interests, including demographic characteristics, parental and socioeconomic information (data not shown).

2.2. Urinary measurement

A spot urine sample was collected from each child in the Health Care Centre and was transferred to the high-density polypropylene centrifuge tubes (Corning Incorporated, USA). All samples were immediately stored at −20 °C, then frozen shipped to the laboratory and kept at −80 °C until analysis.

As previously described by Lu et al. (2015), urinary parabens including MeP, EtP, PrP, BuP and BeP were measured by large-volume-injection gas chromatography with tandem mass spectrometry (LVI-GC-MS/MS). Briefly, the urine samples were prepared by hydrochloric acid hydrolysis, liquid-liquid extraction, and solid-phase extraction clean up. After derivatization, the samples were analyzed by LVI-GC-MS/MS. The limits of detection (LODs) for metabolites were 0.01 μg/L, which was defined as a signal-to-noise ratio of three.

To account for variability in urinary dilution, creatinine concentrations and specific gravity (SG) of urine samples for individuals were determined. Creatinine concentration was determined by ELx800 Universal Microplate Reader (wavelength 340–750 nm; BIO-TEK, USA), and SG was measured using a handheld refractometer (Atago PAL 10-S, Tokyo, Japan).

2.3. Estimated daily intake of parabens

Estimated daily intake (EDI_{urine}) of parabens was calculated based on the measured urinary concentrations of parabens and a simple steady-state toxicokinetic model. The EDI_{urine} of parabens for children was performed using the formula (1) as described by Ma et al. (2013).

$$EDI_{urine} = \frac{50 \times C \times V}{BW} \quad (1)$$

where EDI_{urine} (μg/kg bw/day) is the estimated daily intake of individual paraben; C (μg/L) is the measured concentration of urinary paraben; V (L/day) is daily urinary excretion rate as 0.6 L/day in this study (Pei and Wen, 2004). BW (kg) is children's body weight of the child.

2.4. Child anthropometry

Anthropometry measurements of children were required without jacket and shoes by pediatric physicians who were blind to this research. Body weight was measured using a digital scale and rounded to 0.1 kg. Body height was measured to the nearest 0.1 cm using metal column height-measuring stands. The children were all stand straight against metal column. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Anthropometric outcomes were compared with sex-specific World Health Organization (WHO) child growth standards. Correspondingly, age- and sex-standardized z scores were generated using WHO child growth standards (WHO , 2006). Therefore, the final measures of body sizes were z scores for weight, height, weight for height and BMI.

2.5. Statistical analysis

Generalized linear models were used to examine associations between SG-adjusted paraben concentrations and body growth outcomes. Individual paraben concentration and the sum molar concentration of the five urinary paraben (∑paraben) adjusted for SG were examined with the models. Furthermore, analyses for quartiles of ∑parabens were conducted separately to investigate potential non-monotonic exposure-response relationships. To