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Association between prenatal bisphenol A and phthalate exposures and fetal metabolic related biomarkers: The Hokkaido study on Environment and Children's Health

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ABSTRACT

Bisphenol A and phthalates are widely detected in human urine, blood, breast milk, and amniotic fluid. Both bisphenol A and phthalates have been suggested as playing a role in obesity epidemics. Exposure to these chemicals during fetal development, and its consequences should be concerning because they can cross the placenta. Thus, this study aimed to assess the association between prenatal exposure to bisphenol A and phthalates, and cord blood metabolic-related biomarkers. Maternal serum was used during the first trimester, to determine prenatal exposure to bisphenol A and phthalates. Levels of metabolic-related biomarkers in the cord blood were also determined. Linear regression models were applied to the 365 participants with both, exposure and biomarker assessments, adjusted for maternal age, pre-pregnancy body mass index, parity, education, and sex of the child. The level of bisphenol A was negatively associated with the leptin level (β = −0.06, 95% confidence interval [CI]: −0.11, −0.01), but was positively associated with the high-molecular-weight adiponectin level, with marginal significance (β = 0.03, 95%CI: 0.00, 0.06). The mono-isobutyl phthalate (MiBP), mono-n-butyl phthalate (MnBP), mono-(2-ethylhexyl) phthalate (MEHP), and summation of MEHP and MECPP to represent DEHP exposure (ΣDEHPm) levels were inversely associated with the leptin levels (β = −0.14, 95%CI: −0.27, −0.01; β = −0.12, 95%CI: −0.24, 0.00 with marginal significance; β = 0.08, 95%CI: −0.14, −0.03; and β = −0.09, 95%CI: −0.16, −0.03, respectively). The present study provided some evidence that prenatal exposure to bisphenol A and certain phthalates may modify fetal adiponectin and leptin levels.

1. Introduction

Bisphenol A and phthalates are both known as endocrine disruptors, and there is a growing concern about exposure to these chemicals and their adverse health outcomes on humans. Bisphenol A and phthalates have been detected in the urine, blood, breast milk, and amniotic fluid (Vandenberg et al., 2009; Dobrzynska, 2016). Bisphenol A is widely used in polycarbonate products, such as epoxy resins used as coatings on the inside of many food and beverage cans (Vandenberg et al., 2007). Various phthalates are used in the manufacture of consumer products, such as food packages, polyvinyl chloride floor materials, shampoo, lotion, and fragrances. The consequences of exposure to these chemicals during fetal development should be considered because they can cross the placenta (Mose et al., 2007; Balakrishnan et al., 2010).

There is growing evidence that the *in-utero* environment programs fetal obesity risk. As molecular mechanism and epigenetic programing during fetal development may permanently affect adipogenesis and metabolism throughout the life, gestational period is highly susceptible to these environmental chemicals (Newbold et al., 2009). Bisphenol A and phthalates along with other environmental obesogenic chemicals have particularly played a role in obesity epidemic recently. Experimental studies have demonstrated that exposure to bisphenol A and phthalates modified the regulation of metabolism (Grun and Blumberg, 2009) via peroxisome proliferator (PPAR)-modulated pathways (Desvergne et al., 2009), adipogenesis (Chamorro-Garcia et al., 2012), and alternation of pancreatic β-cell function (Ropero et al., 2008; Lin et al., 2011; Soriano et al., 2012). However, whether levels of human exposure sufficiently induce such effects is unknown. Examining the disruption of metabolic regulations in newborns possibly induced by exposure to environmental chemicals during fetal development is difficult because only limited outcomes (i.e., birth size) are available and symptoms of metabolic dysfunction cannot be observed in newborns.

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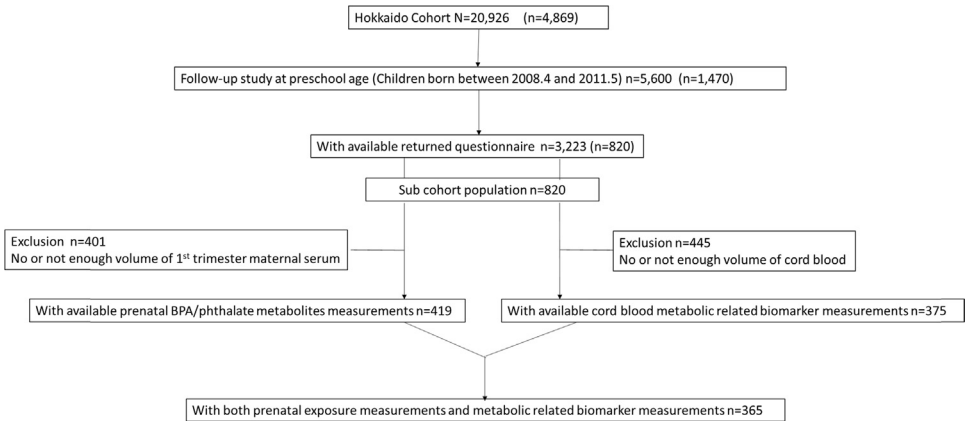

Fig. 1. Flowchart of selecting study population. Numbers in parentheses are the number of sub-cohort population. Sub-cohort population; The sub-cohort population was randomly selected from whole cohort population to represent the whole cohort population and was designated for exposure and/or biomarker assessments.

Thus, conducting epidemiological investigations on prenatal exposures to these chemicals and interpreting the findings were challenging. Despite the importance of understanding in utero exposures and their consequences on the regulation of fetal metabolism, the evidence is insufficient.

Metabolic-related biomarkers such as adiponectin, leptin, tumor necrosis factor alpha (TNF-α), and interleukin 6 (IL-6) can be used to detect and monitor metabolic dysfunctions (Srikanthan et al., 2016). Adiponectin and leptin are adipokines produced by adipocytes. Leptin is also produced by the placenta in pregnant women (Srikanthan et al., 2016). TNF-αand IL-6 are pro-inflammatory cytokines secreted by the adipose tissues. In epidemiological studies, these biomarkers have been measured in cord blood samples (Chou et al., 2011; Ashley-Martin et al., 2014; Hui et al., 2016; Huang et al., 2017). Several studies presented adverse health effects in neonates associated with increased levels of IL-6 and TNF-α (Amarilyo et al., 2011; Catarino et al., 2012; Lausten-Thomsen et al., 2014; Sorokin et al., 2014).

A fairly large number of epidemiological studies have shown a significant association between urinary levels of bisphenol A and various phthalates, and obesity and obesity-related disorders (Lind et al., 2012; Wang et al., 2012; James-Todd et al., 2016; Vafeiadi et al., 2016); however, the etiology is still largely unknown. Only limited number of studies have investigated the association between bisphenol A and phthalate exposures, and metabolic-related biomarkers. Several cross-sectional studies investigated the association between maternal bisphenol A levels, and TNF-α and IL-6; however, their findings were inconsistent (Watkins et al., 2015; Ferguson et al., 2016). Cross-sectional studies on adults and children demonstrated relationships between bisphenol A and various phthalate exposures and adipokine levels (Menale et al., 2016; Choi et al., 2017), yet studies that elicit a conclusion were insufficient. Thus, this prospective cohort study aimed to investigate the association between prenatal exposure to bisphenol A and phthalates and cord blood metabolic-related biomarkers.

2. Methods

2.1. Study design

This was one of the follow-up studies on the Hokkaido Study on Environment and Children's Health, a prospective birth cohort study. Details of the cohort profile can be found elsewhere (Kishi et al., 2011, 2013, 2017). Briefly, the whole cohort consisted of 20,926 participants enrolled from 2003 to 2012, and sub-cohort population (23.3% of the whole cohort population) designated for exposure and/or biomarker assessments was randomly selected from the whole cohort population. Defining sub-cohort population strategy was effective to avoid additional costs and time of processing the exposure assessment of all participants. Details of the sub-cohort population can be found elsewhere (Kishi et al., 2017). Participants were recruited during early pregnancy (< 13 weeks of gestational age). The baseline questionnaire including information on demographic characteristics, smoking history, alcohol consumption, and medical history was filled by pregnant women during the recruitment. Perinatal information including birth weight, infant sex, mode of delivery, and diagnosis of congenital anomalies were obtained from medical records completed by obstetricians. This follow-up study targeted cohort study participants who were born between April 2008 and May 2011 (n = 5695) and those who have reached 5 years old. Questionnaires to assess child neurobehavioral development such as strength and difficulties questionnaire and attention deficit and hyperactivity rating scale were distributed via mail to the subpopulation with child aging 5 and 6 years. A total of 3223 valid responses were received at the end of May 2016. The response rate was 56.6%. Among the 3223 sub-cohort population, 820 were included. Among the 820 sub-cohort population, those who did not have maternal serum or cord blood samples and no available medical records during delivery were excluded. A total of 419 participants presented with bisphenol A and phthalate metabolite levels in the first-trimester serum, and 375 presented with metabolic-related biomarkers in the cord blood. For the statistical analysis, those who had both exposure assessment and metabolic-related biomarker measurement were included (n = 365, Fig. 1).

This study was conducted after obtaining written informed consents from all participants. The protocol used in this study was approved by the Institutional Ethical Board for epidemiological studies at the Hokkaido University Graduate School of Medicine and Hokkaido University Center for Environmental and Health Sciences.

3. Measurements of bisphenol A and phthalates

Maternal serum in the first trimester was collected and stored at –80 °C until the analyses. Serum samples were analyzed for bisphenol A and seven variants of phthalate metabolites: mono-n-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), mono-(2-ethylhexyl) phthalate (MEHP), mono-benzyl phthalate (MBzP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), and mono-(4-methyl-7-carboxyheptyl) phthalate (cx-MiNP) using isotope-diluted liquid chromatography-tandem mass spectrometry (LC-MS/MS) for bisphenol A analysis and ultra-performance LC-MS/MS for phthalate metabolite analyses. The method detection limits (MDLs) of bisphenol A, MnBP, MiBP, MBzP, MEHP, MEHHP, MECPP, and cx-MiNP were 0.011 ng/ml, 0.57 ng/ml, 0.44 ng/ml, 0.19 ng/ml, 0.31 ng/ml, 0.23 ng/ml, 0.11 ng/ml, and 0.12 ng/ml, respectively. All analyses were conducted at Idea Consultants, Inc. (Shizuoka, Japan).

The detailed sample preparation for bisphenol A analysis can be found in our previous report (Yamamoto et al., 2016). In each serum sample, bisphenol A-d_{16} spiking solution was added and mixed by shaking, and then β-glucuronidase and 0.2 M acetate buffer solution