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分担研究報告書

Prenatal exposure to bisphenol A and child neurodevelopment: The Hokkaido Study

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研究要旨

Background: Prenatal bisphenol A (BPA) exposure may affect early child thyroid function and neurodevelopment.

Objective: To evaluate the associations between cord blood BPA levels and child mental and psychomotor development at 6 and 18 months of age. Additionally the association with thyroid stimulation hormone (TSH) and free thyroxine (FT4) of newborn were assessed. **Methods:** Cord blood samples collected from the Hokkaido study participants were analyzed for BPA levels. Child neurodevelopment was assessed using mental and psychomotor development indexes (MDI and PDI) from a Bayley Scales of Infant Development II at 6 and 18 months of age (N = 121, 86, respectively). The associations between cord blood BPA levels and child neurodevelopment were estimated using linear regression models adjusted for potential confounders. Data of TSH and FT4 were obtained from mass screening test for endocrine disorders conducted by Sapporo City Institute of Public Health. **Results:** Overall, there were no statistical significant associations between cord blood BPA levels and child neurodevelopment at 6 and 18 months of age. Among female, MDI score at 6 month of age and the TSH levels was inversely associated with cord blood BPA levels with borderline significance. **Conclusion:** This study added the evidence that relatively lower levels of prenatal BPA exposure may not affect early child neurodevelopment or levels of thyroid hormones of newborn over all. Further studies of investigating sex specific effects of BPA exposure are needed.

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A. 研究目的

Bisphnol A(BPA) is anendocrine-disrup ting chemical used in the manufacture of plastics and resins including food and drink containers, and as an additive in thermal paper, dental sealant, medical equipment and flame retardant (Biedermann et al. 2010; Geens et al. 2011). BPA exposure is nearly ubiquitous in developed countries. The predominant source of BPA exposure for general adult population is diet. According to previous study, pregnant women who regularly consume canned food have higher urinary BPA concentrations compared with women without the habit (Braun et al. 2011). BPA has a weak estrogenic properties (Akingbemi et al. 2004; Lee et al. 2003). Experimentally, BPA has shown to interact with estrogen signaling pathways through binding to the estrogen receptors (Naciff et al. 2002; Vandenberg et al. 2009; Wetherill et al. 2007) and also act as a thyroid hormone agonist (Zoeller et al. 2005). In animal studies, the association between prenatal BPA exposure and neurobehavioral effects such as anxiety (Cox et al. 2010; Xu et al. 2011), cognitive deficit (Tian et al. 2010; Viberg and Lee 2012) and social behavior (Wolstenholme et al. 2011) have indicated. Studies also have shown loss of sex differences in animal behavior (Cox et al. 2010; Patisaul et al. 2006; Rubin et al. 2006). There are limited data of BPA exposure effects on neurodevelopment in humans. Epidemiological studies have investigated the effects of prenatal BPA exposure on child neurobehavior at several different ages using different assessment scales (Braun et al. 2009, 2011, 2014; Perera et al. 2012; Miodovnik et al. 2011; Harley et al. 2013; Yolton et al. 2011). The scales used in these studies were varied such as Behavior Rating Inventory of Executive Function-Preschool (BRIEF), Child Behavior Checklist (CBCL), NICU Network Neurobehavioral Scale (NNNS), Behavioral Assessment System for Children (BASC), Conners' ADHD/DSM-IV Scales (CADS) and Social Rating Scale (SRS). Some findings from epidemiological studies may suggest maternal BPA exposure's adverse effects on child neurobehavior, on the other hand, others did not show any evidence of adverse effects of prenatal BPA exposure. Additionally several random clinical trials of dental restorations found that there was a significant reduction in scores on memory tests in children with composite fillings containing BPA at ages 6 and 10 (Bellinger et al. 2007; Bellinger et al. 2008), children with composite fillings reported significantly increased anxiety, depression, social stress, and interpersonal-relation problems at ages 11 and 16 (Maserejian et al. 2012). Among these epidemiological investigations, we did not find any published studies using Bayley Scales of

Infant Development (BSID), which is a standard series of measurements to assess the development of infants. The BSID-II mental scale assesses the age-appropriate children's level of cognitive, language, and personal/social development. The motor scale assesses fine and gross motor development. Our group have reported prenatal exposure to several isomers of dioxins may affect the motor development of 6 month-old infants (Nakajima et al. 2006).

Thyroid hormones play an essential role in pre and postnatal brain development. Several epidemiological studies including prospective cohort and cross-sectional studies have investigated the association between BPA levels and thyroid function of adults and children and showed suggestive inverse associations with TSH and T4 and positive associations with T3 (Bucker-Davis et al. 2011; Chevrier et al. 2013; Wang et al. 2012; Meeker and Ferguson, 2011; Wang et al. 2013), however, there is no human studies on BPA exposure and neonatal thyroid hormone levels along with child neurodevelopmental assessment.

Given very limited research on human thyroid function and neurobehavior in association with prenatal exposure to BPA, the aim of this study was to investigate the association between cord blood BPA levels and newborn thyroid hormone levels and child mental and psychomotor development at two distinct time points of ages 6 and 18 months.

B. 研究方法

Study population

This prospective birth cohort study was based on the Sapporo Cohort, Hokkaido Study on Environment and Child Health (Kishi et al. 2011; Kishi et al. 2013). Briefly we recruited pregnant women at 23-35 weeks of gestation between July 2002 and October 2005 from the Sapporo Toho Hospital in Hokkaido, Japan. All subjects were resident in Sapporo City or surrounding areas. The participants completed the self-administered questionnaire survey after the second trimester during their pregnancy. The questionnaire contained baseline information including their dietary habits, exposure to chemical compounds in their daily life, home environment, smoking history, alcohol consumption, caffeine intake, family income, educational levels of themselves and partners. The prenatal information of the mothers and their children was collected from their medical records. This study was conducted with the informed consent of all participants in written forms. 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 Environment and Health Sciences.

Measurement of Bisphenol A

Cord blood was obtained at delivery. All samples were stored at -80 ℃ until analysis. The concentration of BPA in cord blood was measured by using isotope dilution-liquid chromatography-tandem mass spectrometry (ID-LC/MS/MS) at IDEA Consultants, Inc. (Shizuoka, Japan). 1.0 mL whole blood was spiked with BPA-d16 as an internal standard. After addition of 0.2 M acetate buffer (pH 5.0) and β-glucuronidase, the sample was held in an incubator at 37°C for 5 hours. The diluted sample was applied to a solid-phase extraction column. BPA was extracted using acetonitrile. Then, BPA-d4 was added to the extract as an internal standard. The organic extract was concentrated and the sample was analyzed by ID-LC/MS/MS. The limit of detection (LOD) of BPA was 0.048 ng/ml.

Data from mass screening test

We obtained blood samples data of thyroid stimulating hormone (TSH), free thyroxine (FT4) from Sapporo City Institute of Public Health which conducted the mass screening test for endocrine disorders. A heel-prick blood sample of newborns was obtained as spots on a filter paper for the Guthrie card. The blood samples were obtained from infants between 4 and 7 days age of after birth. Blood samples were applied to 0.3 cm filter disks and TSH and FT4 levels were measured using Enzyme-Linked Immuno Sorbent Assay (ELISA) (TSH: Enzaplate N-TSH, Bayer Co., Tokyo, Japan; FT4: Enzaplate N-FT4, Bayer Co.). The FT4 values of all samples were detected, and for samples with TSH levels below the detection limit (0.50 μU/ml), we used a value of half the detection limit.

Developmental measurements

We used BSID-II (Bayley. 1993) to assess the infant mental and psychomotor development at age 6 and 18 months. The BSID-II is an infant developmental test tool used between 0 to 3 years of age. The BSID-II mental scale assesses the age-appropriate children's level of cognitive, language, and personal/social development. The motor scale assesses fine and gross motor development. Mental and motor raw scores were converted to a normalized scale with a mean of 100 and standard deviation of 15. Home Observation for Measurement of the Environment (HOME) was used to investigate the caregiving environmental conditions of children at 6 and 18 months of age (Anme et al. 1997).

Data analysis

We used the following eligibility for criteria for analyses of subjects; no serious illness or complications during pregnancy and delivery, singleton babies born at term (37 to 42 weeks of gestation), Apgar score of > 6 at 1 minute, babies without congenital anomalies or diseases, and BSID-II completed at ages between 166 and 195 days for 6 months

examination. Among all 514 participants of Sapporo Cohort Study, 286 cord blood samples for BPA measurements were available. For the final analyses, 121 and 86 children at 6 months and at 18 months, respectively, were included.

Since the distributions of cord blood BPA concentrations were right skewed, these variables were transformed by the natural logarithms (ln) to improve their linear relation with MDI and PDI scores. BPA concentrations below the LOD was assigned the value of one-half of the LOD, 0.024 ng/ml. To examine the relation between cord blood BPA levels and child neurodevelopment, linear regression models were used. Then models were stratified by child sex. To select covariates to include in multivariable models, risk factors known or suspected of being associated with the BPA concentrations and/or child neurodevelopment were reviewed in the literatures (Kim et al. 2011; Polanska et al. 2014). The covariates used in this study were maternal education, HOME score, annual income and child sex. Additionally, caffeine intake during pregnancy was used for the analyses of 6 month as the correlation between PDI scores at 6 month was significant. In our previous study (Nakajima et al. 2006), gestational age and maternal smoking status were used as covariates, however, these covariates were not used in this study as the correlations were not significant. Results were considered significant at $p < 0.05$. All analyses were conducted using SPSS (Version 22.0; SPSS, Chicago, IL, USA).

C．研究結果

Table 1 shows basic characteristics of participants. Compared to the Sapporo Cohort full profile data from our previous report (Kishi et al. 2011), no significant differences were observed (data not shown) in maternal age (30.7 ± 4.9 vs. 30.9 ± 4.9 years old), maternal education (55.6% vs. 61.2%, > 12 years), annual income (31.0% vs. 37.2%, ≧5M), smoking status during pregnancy (18.6% vs. 10.7%, smoker) birth weight (3065 ± 375 vs. 3158 ± 316 g) and gestational age (39.0 ± 1.4 vs. 39.7 ± 1.0 weeks). Duration of breast feeding was used as a covariates in previous reports (Kim et al. 2011; Tellez-Rojo et al. 2013), however, 34.7 % of data were missing in our study, and thus duration of breast feeding was not used as covariate for adjustment. Table 2 shows the characteristics of exposure and outcomes of participants. The median level of cord blood BPA was 0.059 ng/ml. Cord blood BPA level was detected in 73.8% of samples and the range of cord blood BPA levels was from below LOD to 0.217 ng/ml. The median TSH and FT4 levels of newborn were 1.90μU/ml and 2.00ng/ml, respectively.

Table 3 shows BPA levels and MDI, PDI scores at 6 and 18 months in relation to

participants' characteristics. Maternal caffeine intake during pregnancy was negatively correlated with both MDI and PDI scores at 6 month and statistical significance was found only with PDI score (p = 0.011). MDI score at 18 month was higher in the group of annual income was above 5 million yen compared to below 5 million yen (81.2 vs. 86.3, respectively, p = 0.043). PDI scores at 18 month was higher in the group of higher paternal education compared to lower (83.8 vs. 89.6, respectively, p = 0.043). Both MDI and PDI scores at 18 month were higher in female compared to male with statistical significance (86.4 vs. 79.4, p = 0.005 for MDI, 91.1 vs. 84.0, p = 0.006 for PDI).

Table 5 and 6 show MDI and PDI scores of BSID-II at 6 and 18 months in relation to natural log transformed cord blood BPA levels. Overall, both MDI and PDI scores at 6 months were negatively associated with cord blood BPA levels. MDI and PDI scores at 18 months were negatively associated with cord blood BPA levels without adjustment, however, after the adjustment, the associations became weakly positive. Since there have been reported that BPA may have sex-specific effects, we performed analyses for male and female separately. After stratification by child sex, MDI scores at 6 months showed opposite associations with cord blood BPA levels between male and female. The scores were positively associated in male (β = 1.38, 95% CI: -1.40, 4.16), contrary, negatively associated in female (β = -1.99, 95% CI: -4.28, 0.31) and the significance was borderline. For PDI scores, the negative association was stronger in male (β = -3.18, 95% CI: -7.70, 1.35) compared to female (β = -0.91, 95% CI: -5.52, 3.70). MDI scores at 18 months showed weak negative association with cord blood BPA levels after adjustment in both sexes. PDI scores at 18 months showed opposite association between sexes, positive association in female (β = 2.28, 95% CI: -3.10, 7.65) and negative association in male (β = -2.05, 95% CI: -9.11, 5.01). The borderline significance of negative association between female MDI scores at 6 months and cord blood BPA levels was not found at 18 months. Similarly the negative association found in PDI scores at 6 months in male with cord blood BPA levels became weaker at 18 months.

Table 4 shows the associations between cord blood BPA levels and TSH and FT4 of newborn. Overall, TSH levels were negatively associated with cord blood BPA levels. Further analysis after stratification of child sex, female showed borderline significant negative association (β = -0.232, p = 0.089), contrary male showed weak positive association (β = 0.048, p = 0.823). Cord blood BPA level showed weak positive association with FT4 levels with no

statistical significance.

D．考察

This is the first published study of examining thyroid hormone levels and child neurodevelopment at 6 and 18 months using BSID-II in relation to cord blood BPA levels. There was borderline significant inverse association between cord blood BPA levels and TSH levels in female. Meeker and Ferguson observed suggestive inverse trends for BPA quintiles and TSH (p trend = 0.14) in cross-sectional study of 1367 adults (Meeker and Ferguson. 2011). However, no association was found with FT4 in smaller study of 167 adult men (Meeker et al. 2010). Our observation on TSH and FT4 agreed with their report. Brucker-Davis et al. (2011) reported weak trend for a negative correlation between BPA and TSH in prospective cohort of 164 newborn boys and Chevrier et al. (2013) reported that maternal BPA was negatively associated with neonatal TSH in boys in CHAMACOS study. These studies found negative associations between BPA and THS levels only in male, and our findings did not agree with these previous reports as we observed stronger negative associations in female rather than in male. A study by Kaneko et al. reported that BPA suppresses TSH release from amphibian pituitary in manner independent of both the thyroid hormone feedback mechanism and the estrogenic activity of BPA (2008) which may explain our observation of negative association between BPA and TSH.

There was no significant association between cord blood BPA levels and child neurodevelopment at 6 and 18 months among all children. The different responses were observed in MDI scores at 6 months; female exhibited decreases in scores and male exhibited increases in scores. PDI scores at 6 months, negative association was stronger in male than in female. At 18 months, the different responses were observed in PDI scores; female exhibited increases in scores and male exhibited decreases in scores. Prenatal BPA exposure may have adverse influences on endocrine or neurotransmitter pathways and cause sexual differentiation of brain and alter behavior in a gender dependent manner (Manson. 2008). Limited observational evidence suggests an association between prenatal BPA exposure and adverse neurobehavioral outcomes in children. Our findings on cord blood BPA levels and child neurodevelopment were compared to the observations from previous human studies. Out of 7 available epidemiological studies regarding BPA exposure and child neurodevelopment, 5 studies suggested prenatal BPA exposure and adverse effects of child neurodevelopment. Braun et al., reported evidences of adverse effect of prenatal BPA exposure predominately in girls using the BASC at 2 years of age

and the BRIEF-P at 3 years of age (Braun et al. 2009, 2011). Perera et al. (2012) used CBCL ages between 3 and 5 years old and suggested that prenatal exposure to BPA may affect child behavior differently among boys and girls. Harley et al. (2013) reported that prenatal urinary BPA concentrations were associated with increased anxiety and depression in boys age at 7 using BASC-2. Contrary, 2 studies, Yolton et al. (2011) and Miodovnik et al. (2011) reported no evidence of an association between prenatal BPA exposure and child neurodevelopment at 5 weeks of age using NNNS and at ages between 7 and 9 years old using SRS, respectively. Those epidemiological results were conflicting and very limited. This could be due to a number of differences between the study designs, and timing and tools of outcome assessment as well as timing of exposure measurements. The assessment tool used in this study, BSID-II assesses developmental domains different from intelligence or executive function. Each unique assessment tool used in different studies had specific purpose; BASC-2 has excellent reliability and validity for assessing adaptive and maladaptive behaviors (Reynolds and Kamphaus 2004), the CBCL measures child behavior problems, the BRIEF-P assess the ability to modulate emotions, the capacity to control behavioral responses, the ability to anticipate and to plan for future events, the capacity to transition to and from events and the ability to hold information in mind for completing a task, the NNNS assesses 13 dimensions of neurobehavior (Lester and Tronick. 2004), the SRS is a scale for detecting and measuring the severity of autistic behavior, and CADS assesses attention and hyperactivity (Conners. 2001), thus these results simply were not able to be compared on the same table. Also noted that most of the studies used the same cohort. In our study, BPA in cord blood was measured as prenatal exposure whereas maternal urine samples were used in the other epidemiological studies for exposure assessment. This difference made it difficult to compare our observations with previous findings. Even studies used urinary BPA as exposure measurements, intra-individual variability of BPA concentrations were moderately correlated (Braun et al. 2009) and accurately characterizing exposure from a single measurement was difficult. On the other hand, using mean concentration of urinary BPA from several measurements would decrease the ability to identify shot time-sensitive window of development (Braun et al. 2011). To improve exposure classification during critical windows of neurodevelopment, the importance of single measurement or summary measurement of BPA concentration should be considered. The cord blood BPA levels in this study was

much lower compared to the previous reports (Aris. 2014; Zhang et al. 2013; Kosarac et al. 2012; Chou et al. 2011; Brucker-Davis et al. 2008 Lee et al. 2008) and this may imply that prenatal BPA exposure levels as low as we observed did not have significant influences on child neurodevelopment.

A recent study suggested that perinatal exposure to low-dose BPA specifically and non-monotonically impairs spatial learning and memory in male offspring rats (Kuwahara et al. 2013). Several mechanisms including epigenetic changes in gene expression in various brain regions via BPA action as weak estrogen receptor agonists and an anti-androgen were suggested from animal studies (Wolstenholme et al. 2011); synaptogenesis decrease in hippocampus and prefrontal cortex of monkeys and rats (Leranth et al. 2008; MacLusky et al, 2005), disruption in cortical development in mice (Nakamura et al. 2006, 2007), alternation in sexually dimorphic brain regions in hypothalamus (Patisaul et al. 2006; Rubin et al. 2006) and reduction of corticotropin-released hormone and DA cell number in midbrain (Funabashi et al. 2004; Tando et al. 2007; Tanida et al. 2009). In BPA exposed animals, multiple genes in tissues were differently methylated (Kundakovnic et al. 2013; Tang et al. 2012), BPA exposure may change expression and DNA methylation of nuclear estrogen receptors and/or signaling via glutamate receptor (Kundakovic et al. 2013; Xu et al. 2010), these studies suggested that BPA may also lead heritable changes in gene expression.

A couple of issues, especially dose and route of exposure, need to be consider when comparing our result to those of animal studies. Many of dose ranges used in animal studies were not relevant to human study. Route of exposure in animal studies were oral, subcutaneous and direct injection at target organs (Li et al. 2008), whereas oral exposure in human studies were predominate.

The limitations of this study need to be considered. First, there was limited statistical power with our sample size. Additionally, there have been concerns whether single drawing of cord blood sample represent the long-term prenatal BPA exposure due to short half-lives of BPA and there might be a possibility of accidental exposure near blood drawing period. Other limitation is that cord blood samples were taken at delivery, thus, the effect of fetal exposure to BPA during the earlier stages of fetal neurodevelopment have not been assessed in this study. There might be a chance of selection bias in this study as we only included participants with available cord blood samples. However, as described the comparison between original cohort profile and the present study profile did not show significant discrepancy. Another limitation is that we were not able to examine

whether postnatal exposure to BPA was associated with childhood neurodevelopment. The strength of our study was that we measured child neurodevelopment outcome at two different times along with the measurement of newborn thyroid hormone levels. Additionally, in our study we used the BPA levels of cord blood, which accurately indicated the exposure of fetus. However, more studies are necessary to confirm adverse effect BPA exposure on child neurodevelopment.

E. 結論

The findings of this study suggested that relatively lower levels of cord blood BPA levels was not notably associated with thyroid hormone levels or neurodevelopment of children. We have observed suggestive negative associations between BPA levels and TSH levels and MDI at 6 month only in female, thus, additional researches investigating sex specific effects are needed.

F. 研究発表

1. 論文発表

In preparation

2. 学会発表

Minatoya M, Sasaki S, Nakajima S, Yamamoto J, Araki A, Ito S, Miyashita C, Matsumura T, Nonomura K, Mitsui T, Cho K, Kishi R. Effects of prenatal bisphenol A exposure on birth weight, sex hormone levels and mental and motor development. International Society for Environmental Epidemiology Asia Chapter (ISEE-AC) 2014 Conference. Shanghai. Dec. 2014.

湊屋街子，佐々木成子，中島そのみ，山本潤，荒木敦子，伊藤佐智子，宮下ちひろ，松村徹，野々村克也，三井貴彦，長和俊，岸玲子．ビスフェノールＡの胎児期曝露による出生体格、臍帯血中ホルモン濃度、神経発達への影響．第17回環境ホルモン学会．東京都．2014.12.9-10

G. 知的財産権の出願・登録状況（予定を含む。）

1.特許取得

なし

2.実用新案登録

なし

3.その他

なし

参考文献

1. Akingbemi BT, Sottas CM, Koulova AI, Klinefelter GR, Hardy MP. 2004. Inhibition of testicular steroidogenesis by the xenoestrogen bisphenol a is associated with reduced pituitary luteinizing hormone secretion and decreased steroidogenic enzyme gene expression in rat leydig cells. Endocrinology 145:592-603.
2. Anme T, Shimada C, Katayama H. 1997. Evaluation of environmental

stimulation for 18 months and the related factors [in Japanese]. Jpn J Publ Health 44:346-352.
3. Aris A. 2014. Estimation of bisphenol A (BPA) concentrations in pregnant women, fetuses and nonpregnant women in Eastern Townships of Canada. Reprod Toxicol 45:8-13.
4. Bayley N. 1993. Manual for the Bayley Scales of Infant Development. 2nd ed. New York: Phsycological Corporation.
5. Bellinger DC, Trachtenberg F, Daniel D, Zhang A, Tavares MA, McKinlay S. 2007. A dose-effect analysis of children's exposure to dental amalgam and neuropsychological function: The new england children's amalgam trial. Journal of the American Dental Association (1939) 138:1210-1216.
6. Bellinger DC, Trachtenberg F, Zhang A, Tavares M, Daniel D, McKinlay S. 2008. Dental amalgam and psychosocial status: The new england children's amalgam trial. Journal of dental research 87:470-474.
7. Biedermann S, Tschudin P, Grob K. 2010. Transfer of bisphenol a from thermal printer paper to the skin. Analytical and bioanalytical chemistry 398:571-576.
8. Braun JM, Yolton K, Dietrich KN, Hornung R, Ye X, Calafat AM, et al. 2009. Prenatal bisphenol a exposure and early childhood behavior. Environmental health perspectives 117:1945-1952.
9. Braun JM, Kalkbrenner AE, Calafat AM, Bernert JT, Ye X, Silva MJ, et al. 2011. Variability and predictors of urinary bisphenol a concentrations during pregnancy. Environmental health perspectives 119:131-137.
10. Braun JM, Kalkbrenner AE, Just AC, Yolton K, Calafat AM, Sjodin A, et al. 2014. Gestational exposure to endocrine-disrupting chemicals and reciprocal social, repetitive, and stereotypic behaviors in 4- and 5-year-old children: The home study. Environmental health perspectives 122:513-520.
11. Brucker-Davis F, Ferrari P, Boda-Buccino M, Wagner-Mahler K, Pacini P, Gal J, Azuar P, Fenichel P. 2011. Cord blood thyroid tests in boys born with and without cryptorchidism: correlations with birth parameters and in utero xenobiotics exposure. Thyroid 21(10):1133-41.
12. Chevrier J, Gunier RB, Bradman A, Holland NT, Calafat AM, Eskenazi B, Harley KG. 2013. Maternal urinary bisphenol a during pregnancy and maternal and neonatal thyroid function in the CHAMACOS study. Environ Health Perspect 121(1):138-44.
13. Chou WC, Chen JL, Lin CF, Chen YC, Shih FC, Chuang CY. 2011. Biomonitoring of bisphenol A concentrations in maternal and

umbilical cord blood in regard to birth outcomes and adipokine expression: a birth cohort study in Taiwan. Environ Health 10:94.

14. Cox KH, Gatewood JD, Howeth C, Rissman EF. 2010. Gestational exposure to bisphenol a and cross-fostering affect behaviors in juvenile mice. Hormones and behavior 58:754-761.
15. Funabashi T, Kawaguchi M, Furuta M, Fukushima A, Kimura F. 2004. Exposure to bisphenol A during gestation and lactation causes loss of sex difference in corticotropin-releasing hormone-immunoreactive neurons in the bed nucleus of the stria terminalis of rats. Psychoneuroendocrinology 29(4):475-85.
16. Geens T, Goeyens L, Covaci A. 2011. Are potential sources for human exposure to bisphenol-a overlooked? International journal of hygiene and environmental health 214:339-347.
17. Harley KG, Gunier RB, Kogut K, Johnson C, Bradman A, Calafat AM, et al. 2013. Prenatal and early childhood bisphenol a concentrations and behavior in school-aged children. Environmental research 126:43-50.
18. Huang PC, Kuo PL, Chou YY, Lin SJ, Lee CC. 2009. Association between prenatal exposure to phthalates and the health of newborns. Environment international 35:14-20.
19. Hurst CH, Waxman DJ. 2003. Activation of pparalpha and ppargamma by environmental phthalate monoesters. Toxicological sciences : an official journal of the Society of Toxicology 74:297-308.
20. Ito Y, Yokota H, Wang R, Yamanoshita O, Ichihara G, Wang H, et al. 2005. Species differences in the metabolism of di(2-ethylhexyl) phthalate (dehp) in several organs of mice, rats, and marmosets. Archives of toxicology 79:147-154.
21. Jurewicz J, Hanke W. 2011. Exposure to phthalates: Reproductive outcome and children health. A review of epidemiological studies. International journal of occupational medicine and environmental health 24:115-141.
22. Kaneko M, Okada R, Yamamoto K, Nakamura M, Mosconi G, Polzonetti-Magni AM, Kikuyama S. 2008. Bisphenol A acts differently from and independently of thyroid hormone in suppressing thyrotropin release from the bullfrog pituitary. Gen Comp Endocrinol 155(3):574-80.
23. Kato K, Silva MJ, Brock JW, Reidy JA, Malek NA, Hodge CC, et al. 2003. Quantitative detection of nine phthalate metabolites in human serum using reversed-phase high-performance liquid

chromatography-electrospray ionization-tandem mass spectrometry. Journal of analytical toxicology 27:284-289.

24. Kim BN, Cho SC, Kim Y, Shin MS, Yoo HJ, Kim JW, et al. 2009. Phthalates exposure and attention-deficit/hyperactivity disorder in school-age children. Biological psychiatry 66:958-963.
25. Kishi R, Sasaki S, Yoshioka E, Yuasa M, Sata F, Saijo Y, et al. 2011. Cohort profile: The hokkaido study on environment and children's health in japan. International journal of epidemiology 40:611-618.
26. Kishi R, Kobayashi S, Ikeno T, Araki A, Miyashita C, Itoh S, et al. 2013. Ten years of progress in the hokkaido birth cohort study on environment and children's health: Cohort profile--updated 2013. Environmental health and preventive medicine 18:429-450.
27. Koch HM, Rossbach B, Drexler H, Angerer J. 2003. Internal exposure of the general population to dehp and other phthalates--determination of secondary and primary phthalate monoester metabolites in urine. Environmental research 93:177-185.
28. Koch HM, Preuss R, Angerer J. 2006. Di(2-ethylhexyl)phthalate (dehp): Human metabolism and internal exposure-- an update and latest results. International journal of andrology 29:155-165; discussion 181-155.
29. Kosarac I, Kubwabo C, Lalonde K, Foster W. 2012. A novel method for the quantitative determination of free and conjugated bisphenol A in human maternal and umbilical cord blood serum using a two-step solid phase extraction and gas chromatography/tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 898:90-4.
30. Kundakovic M, Gudsnuk K, Franks B, Madrid J, Miller RL, Perera FP, Champagne FA. 2013. Sex-specific epigenetic disruption and behavioral changes following low-dose in utero bisphenol A exposure. Proc Natl Acad Sci U S A 110(24):9956-61.
31. Kuwahara R, Kawaguchi S, Kohara Y, Cui H, Yamashita K. 2013. Perinatal exposure to low-dose bisphenol a impairs spatial learning and memory in male rats. Journal of pharmacological sciences 123:132-139.
32. Lampen A, Zimnik S, Nau H. 2003. Teratogenic phthalate esters and metabolites activate the nuclear receptors ppars and induce differentiation of f9 cells. Toxicology and applied pharmacology 188:14-23.
33. Lee HJ, Chattopadhyay S, Gong EY, Ahn RS, Lee K. 2003.

Antiandrogenic effects of bisphenol a and nonylphenol on the function of androgen receptor. Toxicological sciences : an official journal of the Society of Toxicology 75:40-46.

34. Lee YJ, Ryu HY, Kim HK, Min CS, Lee JH, Kim E, Nam BH, Park JH, Jung JY, Jang DD, Park EY, Lee KH, Ma JY, Won HS, Im MW, Leem JH, Hong YC, Yoon HS. 2008. Maternal and fetal exposure to bisphenol A in Korea. Reprod Toxicol 25(4):413-9.
35. Leranth C, Szigeti-Buck K, Maclusky NJ, Hajszan T. 2008. Bisphenol A prevents the synaptogenic response to testosterone in the brain of adult male rats. Endocrinology 149(3):988-94.
36. Lester B, Tronick E. 2004. Using the NNNS TM. NICU Network Neurobehavioral Scale (NNNS) manual. 13.
37. Li AA, Baum MJ, McIntosh LJ, Day M, Liu F, Gray LE, Jr. 2008. Building a scientific framework for studying hormonal effects on behavior and on the development of the sexually dimorphic nervous system. Neurotoxicology 29:504-519.
38. Li Y, Zhuang M, Li T, Shi N. 2009. Neurobehavioral toxicity study of dibutyl phthalate on rats following in utero and lactational exposure. Journal of applied toxicology : JAT 29:603-611.
39. MacLusky NJ, Hajszan T, Leranth C. 2005. The environmental estrogen bisphenol a inhibits estradiol-induced hippocampal synaptogenesis. Environ Health Perspect. 2005 113(6):675-9.
40. Manson JE. 2008. Prenatal exposure to sex steroid hormones and behavioral/cognitive outcomes. Metabolism 57 (suppl 2), S16-21.
41. Lin S, Ku HY, Su PH, Chen JW, Huang PC, Angerer J, et al. 2011. Phthalate exposure in pregnant women and their children in central taiwan. Chemosphere 82:947-955.
42. Maserejian NN, Trachtenberg FL, Hauser R, McKinlay S, Shrader P, Bellinger DC. 2012. Dental composite restorations and neuropsychological development in children: Treatment level analysis from a randomized clinical trial. Neurotoxicology 33:1291-1297.
43. Meeker JD, Calafat AM, Hauser R. 2010. Urinary bisphenol A concentrations in relation to serum thyroid and reproductive hormone levels in men from an infertility clinic. Environ Sci Techno 44(4):1458-63.
44. Meeker JD, Ferguson KK. 2011. Relationship between urinary phthalate and bisphenol a concentrations and serum thyroid measures in u.S. Adults and adolescents from the national health and nutrition examination survey (nhanes) 2007-2008. Environmental

health perspectives 119:1396-1402.
45. Miodovnik A, Engel SM, Zhu C, Ye X, Soorya LV, Silva MJ, et al. 2011. Endocrine disruptors and childhood social impairment. Neurotoxicology 32:261-267.
46. Naciff JM, Jump ML, Torontali SM, Carr GJ, Tiesman JP, Overmann GJ, et al. 2002. Gene expression profile induced by 17alpha-ethynyl estradiol, bisphenol a, and genistein in the developing female reproductive system of the rat. Toxicological sciences : an official journal of the Society of Toxicology 68:184-199.
47. Nakajima S, Saijo Y, Kato S, Sasaki S, Uno A, Kanagami N, Hirakawa H, Hori T, Tobiishi K, Todaka T, Nakamura Y, Yanagiya S, Sengoku Y, Iida T, Sata F, Kishi R.
48. Effects of prenatal exposure to polychlorinated biphenyls and dioxins on mental and motor development in Japanese children at 6 months of age. 2006. Environ Health Perspect 114(5):773-8.Nakamura K, Itoh K, Yaoi T, Fujiwara Y, Sugimoto T, Fushiki S. 2006. Murine neocortical histogenesis is perturbed by prenatal exposure to low doses of Bisphenol A. J Neurosci Res 84(6):1197-205.
49. Nakamura K, Itoh K, Sugimoto T, Fushiki S. 2007. Prenatal exposure to bisphenol A affects adult murine neocortical structure. Neurosci Lett. 420(2):100-5.
50. Patisaul HB, Fortino AE, Polston EK. 2006. Neonatal genistein or bisphenol-a exposure alters sexual differentiation of the avpv. Neurotoxicology and teratology 28:111-118.
51. Perera F, Vishnevetsky J, Herbstman JB, Calafat AM, Xiong W, Rauh V, et al. 2012. Prenatal bisphenol a exposure and child behavior in an inner-city cohort. Environmental health perspectives 120:1190-1194.
52. Poimenova A, Markaki E, Rahiotis C, Kitraki E. 2010. Corticosterone-regulated actions in the rat brain are affected by perinatal exposure to low dose of bisphenol a. Neuroscience 167:741-749.
53. Reynolds CR, Kamphaus RW. 2004. BASC-2: Behavior Assessment System for Children, Second edition Manual AGS Publishing, Circle Pines, NM.
54. Romero-Franco M, Hernandez-Ramirez RU, Calafat AM, Cebrian ME, Needham LL, Teitelbaum S, et al. 2011. Personal care product use and urinary levels of phthalate metabolites in mexican women. Environment international 37:867-871.
55. Rubin BS, Lenkowski JR, Schaeberle CM, Vandenberg LN, Ronsheim PM,

Soto AM. 2006. Evidence of altered brain sexual differentiation in mice exposed perinatally to low, environmentally relevant levels of bisphenol a. Endocrinology 147:3681-3691.

56. Suzuki Y, Niwa M, Yoshinaga J, Watanabe C, Mizumoto Y, Serizawa S, et al. 2009. Exposure assessment of phthalate esters in japanese pregnant women by using urinary metabolite analysis. Environmental health and preventive medicine 14:180-187.
57. Tanaka T. 2005. Reproductive and neurobehavioural effects of bis(2-ethylhexyl) phthalate (dehp) in a cross-mating toxicity study of mice. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 43:581-589.
58. Tanida T, Warita K, Ishihara K, Fukui S, Mitsuhashi T, Sugawara T, Tabuchi Y, Nanmori T, Qi WM, Inamoto T, Yokoyama T, Kitagawa H, Hoshi N. 2009. Fetal and neonatal exposure to three typical environmental chemicals with different mechanisms of action: mixed exposure to phenol, phthalate, and dioxin cancels the effects of sole exposure on mouse midbrain dopaminergic nuclei. Toxicol Lett. 189(1):40-7.
59. Tando S, Itoh K, Yaoi T, Ikeda J, Fujiwara Y, Fushiki S. 2007. Effects of pre- and neonatal exposure to bisphenol A on murine brain development. Brain Dev 29(6):352-6.
60. Tang WY, Morey LM, Cheung YY, Birch L, Prins GS, Ho SM. 2012. Neonatal exposure to estradiol/bisphenol A alters promoter methylation and expression of Nsbp1 and Hpcal1 genes and transcriptional programs of Dnmt3a/b and Mbd2/4 in the rat prostate gland throughout life. Endocrinology 153(1):42-55.
61. Tellez-Rojo MM, Cantoral A, Cantonwine DE, Schnaas L, Peterson K, Hu H, et al. 2013. Prenatal urinary phthalate metabolites levels and neurodevelopment in children at two and three years of age. The Science of the total environment 461-462:386-390.
62. Tian YH, Baek JH, Lee SY, Jang CG. 2010. Prenatal and postnatal exposure to bisphenol a induces anxiolytic behaviors and cognitive deficits in mice. Synapse (New York, NY) 64:432-439.
63. Vandenberg LN, Maffini MV, Sonnenschein C, Rubin BS, Soto AM. 2009. Bisphenol-a and the great divide: A review of controversies in the field of endocrine disruption. Endocrine

reviews 30:75-95.

64. Viberg H, Lee I. 2012. A single exposure to bisphenol a alters the levels of important neuroproteins in adult male and female mice. Neurotoxicology 33:1390-1395.
65. Wang F, Hua J, Chen M, Xia Y, Zhang Q, Zhao R, Zhou W, Zhang Z, Wang B. 2012. High urinary bisphenol A concentrations in workers and possible laboratory abnormalities. Occup Environ Med 69(9):679-84.
66. Wang T, Lu J, Xu M, Xu Y, Li M, Liu Y, Tian X, Chen Y, Dai M, Wang W, Lai S, Bi Y, Ning G. 2013. Urinary bisphenol a concentration and thyroid function in Chinese adults. Epidemiology 24(2):295-302.
67. Wetherill YB, Akingbemi BT, Kanno J, McLachlan JA, Nadal A, Sonnenschein C, et al. 2007. In vitro molecular mechanisms of bisphenol a action. Reproductive toxicology (Elmsford, NY) 24:178-198.
68. Whyatt RM, Liu X, Rauh VA, Calafat AM, Just AC, Hoepner L, et al. 2012. Maternal prenatal urinary phthalate metabolite concentrations and child mental, psychomotor, and behavioral development at 3 years of age. Environmental health perspectives 120:290-295.
69. Wittassek M, Angerer J. 2008. Phthalates: Metabolism and exposure. International journal of andrology 31:131-138.
70. Wittassek M, Angerer J, Kolossa-Gehring M, Schafer SD, Klockenbusch W, Dobler L, et al. 2009. Fetal exposure to phthalates--a pilot study. International journal of hygiene and environmental health 212:492-498.
71. Wolstenholme JT, Taylor JA, Shetty SR, Edwards M, Connelly JJ, Rissman EF. 2011. Gestational exposure to low dose bisphenol a alters social behavior in juvenile mice. PloS one 6:e25448.
72. Wormuth M, Scheringer M, Vollenweider M, Hungerbuhler K. 2006. What are the sources of exposure to eight frequently used phthalic acid esters in europeans? Risk analysis : an official publication of the Society for Risk Analysis 26:803-824.
73. Xu XH, Zhang J, Wang YM, Ye YP, Luo QQ. 2010. Perinatal exposure to bisphenol-a impairs learning-memory by concomitant down-regulation of n-methyl-d-aspartate receptors of hippocampus in male offspring mice. Hormones and behavior 58:326-333.Xu X, Tian D, Hong X, Chen L, Xie L. 2011. Sex-specific influence of exposure to bisphenol-a between adolescence and young adulthood on mouse behaviors. Neuropharmacology 61:565-573.
74. Xu X, Hong X, Xie L, Li T, Yang Y,

Zhang Q, et al. 2012. Gestational and lactational exposure to bisphenol-a affects anxiety- and depression-like behaviors in mice. Hormones and behavior 62:480-490.

75. Yolton K, Xu Y, Strauss D, Altaye M, Calafat AM, Khoury J. 2011. Prenatal exposure to bisphenol a and phthalates and infant neurobehavior. Neurotoxicology and teratology 33:558-566.
76. Zhang T, Sun H, Kannan K. 2013. Blood and urinary bisphenol A concentrations in children, adults, and pregnant women from china: partitioning between blood and urine and maternal and fetal cord blood. Environ Sci Technol 7(9):4686-94.
77. Zoeller RT, Bansal R, Parris C. 2005. Bisphenol-a, an environmental contaminant that acts as a thyroid hormone receptor antagonist in vitro, increases serum thyroxine, and alters rc3/neurogranin expression in the developing rat brain. Endocrinology 146:607-612.

Table 1. Parental and child basic characteristics (N = 121).

Parental characteristics		Mean ± S.D. or median (IQR) or number (%)
Maternal age (years)		30.9 ± 4.8
Maternal education	≦ 12 years	47 (38.8)
	> 12 years	74 (61.2)
Paternal age (years)		32.7 ± 5.9
Paternal education	≦ 12 years	37 (30.6)
	> 12 years	84 (69.4)
Family income	< 5M yen	76 (62.8)
	≧ 5M yen	45 (37.2)
Maternal working during pregnancy	Yes	12 (9.9)
	No	109 (90.1)
Maternal smoking during pregnancy	Yes	13 (10.7)
	No	108 (89.3)
Maternal prepregnancy BMI (kg/m^2)		20.9 ± 2.6
Parity	0	69 (57.0)
	1	38 (31.4)
	≧ 2	14 (11.6)
Caffeine intake during pregnancy (mg/day)		120.75 (66.75-183.50)
Alcohol consumption during pregnancy	Yes	41 (33.9)
	No	80 (66.1)
Child characteristics		
Sex	Male	53 (43.8)
	Female	68 (56.2)
Birth weight (g)		3158 ± 316
Birth length (cm)		48.5 ± 1.5
Gestational age (days)		278.5 ± 7.1
Duration of breast feeding*	< 3 months	8 (6.6)
	≧ 3 months	71 (58.7)
	Data missing	42 (34.7)

* Duration of breast feeding was obtained from questionnaire at 18 month old.
** Maximum score is 30. *** Maximum score is 38.

Table 2. Characteristics of exposure and outcomes.

Characteristics	Mean ± S.D. or median (IQR) or number (%)
Cord blood BPA level (ng/ml)	0.050 (LOD-0.076)
BSID-II MDI @ 6 month	90.7 (5.9)
BSID-II PDI @ 6 month	90.4 (11.0)
HOME score @ 6 month**	22.8 (2.6)
BSID-II MDI @ 18 month (N = 86)	83.3 (11.7)
BSID-II PDI @ 18 month (N = 86)	88.0 (12.0)
HOME score @ 18 month*** (N = 89)	28.0 (3.7)
TSH (μU/ml)	1.90 (1.10-3.20)
FT4 (ng/ml)	2.00 (1.80-2.25)

Table 3. BPA levels and MDI, PDI scores at 6 and 18 months in relation to participants' characteristics.

		BPA levels		MDI at 6 month		PDI at 6 month		MDI at 18 month		PDI at 18 month	
Parental characteristics		mean (S.D)	p-value	mean (S.D)	p-value	mean (S.D)	p-value	mean (S.D)	p-value	mean (S.D)	p-value
Maternal age (years)		ρ = -0.110	0.230	ρ = 0.098	0.284	ρ = -0.064	0.484	ρ = -0.019	0.863	ρ = -0.060	0.582
Paternal age (years)		ρ = -0.097	0.289	ρ = 0.112	0.221	ρ = -0.153	0.093	ρ = 0.001	0.993	ρ = -0.075	0.494
Maternal Education	**≦ 12 years**	0.057 (0.036)	0.578	91.2 (4.4)	0.472	90.9 (10.1)	0.722	83.2 (13.2)	0.978	86.1 (12.3)	0.252
	> 12 years	0.053 (0.036)		90.5 (6.7)		90.2 (11.6)		83.3 (10.8)		89.2 (12.7)	
Paternal Education	**≦ 12 years**	0.061 (0.043)	0.194	89.7 (5.9)	0.201	90.6 (11.4)	0.908	79.6 (11.4)	0.071	83.8 (11.6)	0.043*
	> 12 years	0.052 (0.033)		91.2 (5.9)		90.4 (10.8)		84.7 (11.6)		89.6 (11.8)	
Family income	**< 5M yen**	0.058 (0.040)	0.153	90.6 (6.1)	0.693	90.8 (11.3)	0.632	81.2 (11.3)	0.043*	87.1 (12.6)	0.388
	≧ 5M yen	0.049 (0.028)		91.0 (5.6)		89.8 (10.4)		86.3 (11.8)		89.3 (11.1)	
Maternal working during pregnancy	**Yes**	0.042 (0.033)	0.183	90.5 (5.9)	0.218	87.8 (11.5)	0.386	82.5 (10.7)	0.867	90.7 (10.4)	0.573
	No	0.056 (0.036)		92.7 (6.2)		90.7 (10.9)		83.3 (11.8)		87.8 (12.0)	
Maternal smoking during pregnancy	**Yes**	0.064 (0.031)	0.311	89.0 (7.1)	0.263	87.2 (10.6)	0.265	79.5 (8.9)	0.415	84.0 (10.4)	0.401
	No	0.054 (0.037)		91.0 (5.8)		90.8 (11.0)		83.6 (11.9)		88.3 (12.1)	
Parity	**0**	0.056 (0.035)	0.831	90.8 (5.8)	0.324	90.4 (11.8)	0.876	81.6 (12.4)	0.124	86.9 (12.1)	0.071
	1	0.056 (0.041)		89.7 (6.5)		90.3 (9.5)		86.9 (10.4)		87.2 (11.8)	
	≧ 2	0.048 (0.029)		93.0 (4.6)		90.8 (11.3)		80.2 (10.1)		96.4 (9.5)	
Caffeine intake during pregnancy (mg/day)		ρ = 0.028	0.759	ρ = -0.093	0.310	ρ = -0.230	0.011*	ρ = 0.008	0.938	ρ = -0.071	0.518
Alcohol consumption during pregnancy	**Yes**	0.053 (0.034)	0.636	90.6 (6.0)	0.885	91.4 (10.6)	0.500	83.9 (9.9)	0.704	89.6 (11.3)	0.352
	No	0.056 (0.037)		90.8 (5.9)		90.0 (11.2)		82.9 (12.7)		87.1 (12.4)	
Child characteristics											
Sex	**Male**	0.055 (0.030)	0.856	91.4 (5.5)	0.273	90.2 (9.4)	0.815	79.4 (11.3)	0.005	84.0 (10.9)	0.006*
	Female	0.054 (0.041)		90.2 (6.2)		90.6 (12.1)		86.4 (11.2)		91.1 (12.0)	
Birth weight (g)		ρ = 0.127	0.164	ρ = 0.063	0.491	ρ = 0.075	0.415	ρ = -0.037	0.737	ρ = 0.089	0.417
Birth length (cm)		ρ = 0.063	0.492	ρ = 0.009	0.918	ρ = 0.112	0.220	ρ = -0.039	0.720	ρ = -0.005	0.966
Gestational age (days)		ρ = 0.025	0.787	ρ = 0.125	0.170	ρ = 0.087	0.345	ρ = 0.209	0.053	ρ = 0.105	0.334
Duration of breast feeding*	**< 3 months**	0.042 (0.026)	0.229	90.3 (3.5)	0.879	95.4 (13.8)	0.250	80.0 (3.9)	0.123	88.7 (9.7)	0.760
	≧ 3 months	0.059 (0.039)		90.6 (6.5)		90.8 (10.3)		83.7 (11.8)		87.1 (12.4)	
HOME scale @ 6 month**		ρ = -0.009	0.822	ρ = 0.005	0.953	ρ = -0.030	0.747				
HOME scale @ 18 month***		ρ = -0.072	0.502					ρ = 0.201	0.072	ρ = 0.201	0.072

* Duration of breast feeding was determined from questionnaire at 18 month old.
** Maximum score is 30. *** Maximum score is 38.

Table 4. Association between natural log transformed TSH, FT4 levels at birth and natural log transformed cord blood BPA concentration (N=121).

	TSH		FT4	
	Adjusted[a] β (95%CI)	p-value	Adjusted[a] β (95%CI)	p-value
All	-0.15 (-0.38, 0.08)	0.206	0.03 (-0.02, 0.08)	0.289
Male	0.05 (-0.38, 0.48)	0.823	0.04 (-0.05, 0.12)	0.409
Female	-0.23 (-0.50, 0.04)	0.089	0.02 (-0.05, 0.09)	0.491

[a] Adjusted for child's age (days) at hormone measurement.

Table 5. Association between BSID-II (MDI, PDI) at 6 month and natural log transformed cord blood BPA concentration (N=121).

	Crude		Adjusted[a]	
All	β	p-value	β	p-value
MDI @ 6 month	-0.56 (-2.26, 1.15)	0.521	-0.65 (-2.39, 1.05)	0.463
PDI @ 6 month	-1.37 (-4.53, 1.78)	0.390	-1.50 (-4.71, 1.71)	0.357
Male	β	p-value	β	p-value
MDI @ 6 month	1.52 (-1.15, 4.20)	0.258	1.38 (-1.40, 4.16)	0.323
PDI @ 6 month	-2.19 (-6.72, 2.34)	0.336	-3.18 (-7.70, 1.35)	0.164
Female	β	p-value	β	p-value
MDI @ 6 month	-1.87 (-4.11, 0.36)	0.099	-1.99 (-4.28, 0.31)	0.088
PDI @ 6 month	-0.87 (-5.32, 3.58)	0.697	-0.91 (-5.52, 3.70)	0.695

[a] Adjusted for caffeine intake during pregnancy, HOME at 6 month, maternal education, annual income and child sex for all subjects.

Table 6. Association between BSID-II (MDI, PDI) at 18 month and natural log transformed cord blood BPA concentration (N=86).

	Crude		Adjusted[a]	
All	β	p-value	β	p-value
MDI @ 18 month	-0.98 (-4.91, 2.96)	0.623	0.08 (-3.71, 3.87)	0.968
PDI @ 18 month	-0.93 (-4.96, 3.11)	0.648	0.69 (-3.34, 4.72)	0.735
Male	β	p-value	β	p-value
MDI @ 18 month	-0.91 (-7.40, 5.57)	0.777	-0.09 (-6.51, 6.34)	0.978
PDI @ 18 month	-2.79 (-9.00, 3.43)	0.369	-2.05 (-9.11, 5.01)	0.557
Female	β	p-value	β	p-value
MDI @ 18 month	-0.39 (-5.21, 4.43)	0.871	-0.96 (-5.88, 3.96)	0.695
PDI @ 18 month	0.75 (-4.40, 5.91)	0.770	2.28 (-3.10, 7.65)	0.398

[a] Adjusted for HOME at 18 month, maternal education, annual income and child sex for all subjects.

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