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# Psychomotor Ability in Children Prenatally Exposed to Methylmercury: The 18-Month Follow-Up of Tohoku Study of Child Development

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Fish contain nutrients essential to the developing fetal brain, but they are contaminated with methylmercury. The Tohoku Study of Child Development, now underway in the Sanriku coastal area of Miyagi prefecture, Japan, follows mother-child pairs to examine the risks and benefits of fish consumption during pregnancy, especially the effects of prenatal exposures to methylmercury, selenium, and docosahexaenoic acid (DHA) on child neurodevelopment. Children aged 18 months were administered the Bayley Scales of Infant Development second edition (BSID-II) and Kyoto Scale of Psychological Development (KSPD) in 2004-2008. Complete data of cord-blood total mercury (THg), cord-plasma selenium, maternal-plasma DHA, the above test scores, and confounders for 566 mother-child pairs were available. The median cord-blood THg level was 15.7 (range, 2.7-96.1) ng/g. Since the BSID-II and KSPD scores were significantly lower in the 285 boys than in the 281 girls, analyses were conducted separately. The Psychomotor Development Index (PDI) of BSID-II was significantly correlated with cord-blood THg only in the boys, and significance of the association remained unchanged after adjusting for possible confounders; i.e., a 10-fold increase in cord-blood THg was associated with a 8.3-point decrease in the score of the PDI. Other significant correlations of THg were not seen in the boys or girls. Selenium and DHA showed no significant correlations with the BSID-II or KSPD scores in either sex. In conclusion, intrauterine methylmercury exposure may affect psychomotor development, and boys appear to be more vulnerable to the exposure than girls.

**Keywords:** docosahexaenoic acid; methylmercury; psychomotor development; selenium; sex difference
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## Introduction

Since methylmercury resulting from fish consumption readily crosses the placenta, fetuses are more susceptible to it than adults and children. The Faroese birth cohort study demonstrated the impacts of prenatal methylmercury exposure on neurodevelopmental disorders such as sensory deficits, motor impairment, and an overall cognitive decline (Grandjean et al. 1997; Debes et al. 2006). Regarding the adverse effects of methylmercury on other functions, a variety of results were obtained from previous research using, for instance, the Bayley Scales of Infant Development (BSID) consisting of mainly the mental and psychomotor developmental indices (MDI and PDI, respectively); some studies reported the impact of methylmercury on the MDI (Jedrychowski et al. 2006; Rothenberg et al. 2016; Marques et al. 2016a) and others described the effect on the PDI (Davidson et al. 1995, 2008; Jedrychowski et al. 2006, 2007; Lederman et al. 2008; Stokes-Riner et al. 2011; Llop et al. 2012; Hsi et al. 2014; Marques et al. 2015; Strain 2015; Prpić et al. 2017). Only one report demonstrated that prenatal methylmercury exposure affected both the MDI and PDI (Jedrychowski et al. 2006). Three possible reasons for the different results are as follows. First, the average mercury concentrations, ranging from 0.21 to 6.4 $\mu$g/g in maternal hair at parturition, differed greatly among the

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study populations. Second, the age when the BSID examination was conducted for children ranged from 6.5 to 65 months old. Finally, confounders to be considered, e.g., selenium and long-chain polyunsaturated fatty acids including docosahexaenoic acid (DHA), differed among those studies, though such substances are present in fish. Since these seem to complicate the interpretation of methylmercury neurotoxicity, it is necessary to consider them to reach a definitive conclusion.

When the methylmercury pollution in Minamata, Japan, was most severe (i.e., in 1955-1959), decreases in male births were observed in the overall city population, in fishermen, and in maternal Minamata disease patients, and an increase in the proportion of male stillborn fetuses was seen (Sakamoto et al. 2001). This finding may suggest that male fetuses are more susceptible to methylmercury than female counterparts. In fact, there was a significant association of cord-blood mercury with low birth weight in male newborns, but not in females (Tatsuta et al. 2017). Likewise, two studies found the adverse effect of methylmercury on the PDI only in male infants (Davidson et al. 1995; Marques et al. 2015); however, another study observed it only in female infants (Llop et al. 2012). Thus, sex difference must be kept in mind when assessing reproductive toxicants such as methylmercury.

We have been performing a prospective birth cohort study (Tohoku Study of Child Development, TSCD), focusing both on the potential risks and benefits of fish eating during pregnancy to clarify the effects of toxic substances on child development (Suzuki et al. 2010; Tatsuta et al. 2012, 2014). In this study, we investigated the effects of methylmercury, selenium, and DHA at birth on the developmental scores in male and female children aged 18 months of the above cohort, using the BSID second edition (BSID-II) and the Kyoto Scale of Psychological Development 2001 (KSPD). The KSPD has also been used in the Japan Environment and Children's Study.

## Methods

*Study design and subjects*

The study protocol of the TSCD has been described elsewhere (Nakai et al. 2004). The research took place in two areas, an urban area (i.e., Sendai city of Miyagi prefecture) and a coastal area (i.e., the Sanriku coastal area of the same prefecture) in the Tohoku district of Japan (Nakamura et al. 2008; Iwai-Shimada et al. 2015; Tatsuta et al. 2015). In this study, only the subjects in the coastal area were examined because they were considered to eat more fish than those in the urban area. To establish a study population, the eligibility criteria included a singleton pregnancy, Japanese as the mother tongue, and neonates born at term (36-42 weeks of gestation) with birth weight of more than 2,400 g and without obvious congenital anomalies or diseases. Information about pregnancy, delivery and newborn characteristics was obtained from medical records. The medical ethics committee of the Tohoku University Graduate School of Medicine approved this protocol.

Eight hundred seventy-nine pregnant women who gave their written informed consent were enrolled in this study, and 749 mother-child pairs were registered in the years 2003-2006 according to the eligibility criteria. Complete data on exposure biomarkers, developmental indices, and potential confounders, were available for 566 in the present study.

*Exposure biomakers*

Maternal blood was collected one day postpartum by venipuncture into a tube containing heparin. Cord blood samples were collected into a tube containing heparin at delivery, and centrifuged within 4 hours for 20 minutes at 3,000 rpm; plasma and whole blood were stored at −80°C until the analysis. Hair samples 3 cm long was collected from the occipital area of each mother four days after delivery. Total mercury (THg) concentrations in hair and whole blood were measured using cold vapor atomic absorption spectrometry (CVAAS, HG-201, Sanso Seisakusho Co. Ltd., Tokyo, Japan). The analytical method of CVAAS has been fully described elsewhere (Iwai-Shimada et al. 2015). Accuracy was ensured using a certified reference material (Seronorm Trace Elements Whole Blood L-2, Lot 0503109, Sero, Norway) for quality control. The mean ± standard deviation (SD) of THg determinations was 7.51 ± 0.50 ng/g (coefficient of variation in 17 subjects, 6.6%), and the certified value and acceptable range were 8.7 ng/mL and between 6.1 and 11.3 ng/mL. Cord-blood THg was used for the data analysis and maternal-hair THg was for a comparable index of prenatal methylmercury exposure. Cord plasma selenium concentrations were determined fluorometrically after ashing the plasma samples with a mixture of nitrate and perchloric acid (Watkinson 1966). Accuracy was ensured using a certified reference material (Seronorm Trace Elements Serum L-1, Lot 0903106, Sero, Norway) for quality control. The mean ± SD of selenium determinations was 107.8 ± 6.2 ng/g (coefficient of variation in 24 subjects, 5.7%), and the certified value (acceptable range) was 106 (94 ~ 118) ng/mL. Maternal plasma DHA was analyzed by SRL, Inc. (Tokyo, Japan) using gas chromatography.

Maternal fish/seafood intake during pregnancy was assessed using a food frequency questionnaire (FFQ) that was administered by trained interviewers after delivery. We selected several kinds of seafood that were often found at fish markets in the study area and classified them into 18 items with consideration to methylmercury levels and type of seafood (large predatory fish (e.g., tuna, swordfish and marlin), bonito, whale, salmon, eel, yellowtail, silvery blue fish, white-meat fish, other fish, squid, oyster, shellfish, scallop/short-necked clam, sea squirt, salmon roe, canned tuna, fish sausage, sea alga and crab). It was thought that these items covered almost all fish and shellfish consumed in this area. Methylmercury intake was estimated from fish/seafood consumption determined using the FFQ and methylmercury concentrations in each type of seafood. The calculation method has been described elsewhere (Yaginuma-Sakurai et al. 2009).

*Outcome variables*

The BSID-II and KSPD were used for 18-month-old (range, 17-20 months old) children of our study. The BSID-II is categorized into two main domains, the mental and psychomotor scales (Bayley 1993). The resulting raw scores for each scale are converted into the MDI and PDI, based on their age-appropriate norms. Since there was no standardized Japanese version of the BSID-II, we prepared a Japanese version by ourselves. The reliability of administration has been described elsewhere (Tatsuta et al. 2013). The KSPD, a standardized developmental assessment tool for Japanese children, con-

sists of 328 items covering the cognitive-adaptive (C-A), language-social (L-S), and postural-motor (P-M) areas (Ikuzawa et al. 2002). Scores from these three areas are combined to form the developmental quotient (DQ). The DQ was calculated by dividing the developmental age by the chronological age and multiplying the quotient by 100. For the reliability of administration, the testers were trained and certified by the Kyoto International Social Welfare Exchange Center, Kyoto, Japan.

*Possible confounders*

Major potential confounders included child sex, birth weight, birth order (first-born or not), family income, drinking and smoking habits during pregnancy. Information about family income and drinking (yes/no) and smoking habits (yes/no) was obtained from a questionnaire, and these habits were scored as "absence" = 0 and "presence" = 1. The maternal IQ was evaluated using the Raven standard progressive matrices (Raven 1958). Home environment was assessed using the Evaluation of Environmental Stimulation (EES) questionnaire (Anme et al. 1986), which has been established in Japan modified after home observation for measurement of the environment score (Caldwell and Bradley 1984). The mother was asked to fill in the EES when her child was 18 months old. The reliability and validity of the Japanese version of the EES have already been confirmed (Anme and Takayama 2009).

*Statistical analysis*

The THg concentration in cord blood was logarithmically transformed ($\log_{10}$) because of the skewed distributions. Sex differences in basal characteristics and exposure levels were analyzed by Student *t* test, Mann-Whitney *U* test or Fisher exact test. Pearson product-moment correlation coefficients (*r*) were calculated to determine the relationships between exposure biomarkers and both the BSID-II and KSPD scores. Multiple regression analysis was employed to adjust for possible confounders. Independent variables in the analysis were child gender, birth weight, birth order, drinking and smoking habits, the Raven score, EES score, testers of the BSID-II and KSPD (for which dummy variables were used), cord-blood THg, cord-plasma selenium, and maternal-plasma DHA. All analyses, with two-sided *P* values, were performed using SPSS Ver. 23.0 (SPSS Japan, Tokyo) and the statistical significance was set at $P < 0.05$.

## Results

Table 1 shows a summary of basal characteristics and exposure biomarkers in 566 mother-child pairs living in the coastal area. There were no significant differences between the boys and girls for any variables except for birth weight. The median THg concentration in maternal hair was 2.5 $\mu$g/g (range, 0.3-11.0 $\mu$g/g) in the study participants, and the correlation between the maternal hair THg and cord-blood THg was statistically significant (Spearman rank correlation coefficient = 0.858). The tolerable weekly intake (TWI) for methylmercury of 2.0 $\mu$g/kg body weight/week for pregnant and potentially pregnant women was proposed by the Japan Food Safety Commission (2005), and 18.2% of the participants of this study exceeded the TWI, whereas only 12.5% of the urban participants did in the TSCD (Yaginuma-Sakurai et al. 2009). A summary of the BSID-II and KSPD is provided in Table 2. All the scores except for the P-M area of KSPD were significantly lower in the 285 boys than in the 281 girls.

Table 3 shows Pearson moment-product correlation coefficients between the BSID-II and KSPD scores and exposure biomarkers in the boys, girls, and the total. Cord-blood THg was negatively correlated with the PDI score in

Table 1. Basal characteristics and exposure levels in 566 mother-child pairs living in the coastal area in Miyagi prefecture.

| | 285 Boys | 281 Girls | *P* value[a] |
|---|---|---|---|
| | Mean ± SD (or median and 5-95th percentiles or number and %) | Mean ± SD (or median and 5-95th percentiles or number and %) | |
| Basal characteristics | | | |
| Birth weight (g) | 3180 ± 376 | 3108 ± 333 | 0.017 |
| Birth order (first children, %) | 112 (39.3) | 121 (43.1) | 0.393 |
| Drinking habit during pregnancy (drinkers, %) | 36 (12.6) | 52 (18.5) | 0.063 |
| Smoking habit during pregnancy (smokers, %) | 33 (11.6) | 35 (12.5) | 0.797 |
| Raven standard progressive matrices | 50.1 ± 6.0 | 50.4 ± 5.9 | 0.911 |
| Family income (Numbers, %) | | | 0.989 |
| Less than 3,000,000 Japanese Yen/year | 110 (38.6) | 108 (38.4) | |
| Less than 6,000,000 Japanese Yen/year | 112 (39.3) | 112 (39.9) | |
| 6,000,000 Japanese Yen/year and over | 63 (22.1) | 61 (21.7) | |
| Evaluation of environmental stimulation | 26.4 ± 3.9 | 26.9 ± 5.0 | 0.075 |
| Estimated methylmercury intake (μg/kg body weight/week) | 0.9, 0.1-3.8 | 0.9, 0.2-3.0 | 0.604 |
| Exposure biomarkers | | | |
| Cord-blood total mercury (ng/g) | 16.5, 5.7-36.9 | 15.0, 4.8-39.3 | 0.139 |
| Maternal-plasma docosahexaenoic acid (μg/mL) | 169.0 ± 47.9 | 174.8 ± 50.9 | 0.165 |
| Cord-plasma selenium (ng/g) | 66.3 ± 10.2 | 67.0 ± 9.6 | 0.400 |

[a]Student *t* test, Mann-Whitney *U* test or Fisher exact test were used.

Table 2. Scores of the Bayley scales of infant development second edition (BSID-II) and Kyoto scale of psychological development 2001 (KSPD) at 18 months of age.

| | 285 Boys | 281 Girls | *P* value[a] |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| Scores of the BSID-II | | | |
| Mental developmental index (MDI) | 84.5 ± 10.1 | 89.6 ± 10.0 | < 0.001 |
| Psychomotor developmental index (PDI) | 82.8 ± 10.2 | 86.4 ± 10.1 | < 0.001 |
| Scores of the KSPD | | | |
| Developmental quotient (DQ) | 92.3 ± 8.0 | 95.1 ± 8.8 | < 0.001 |
| Cognitive-adaptive (C-A) | 94.0 ± 9.4 | 97.0 ± 10.7 | 0.001 |
| Language-social (L-S) | 94.8 ± 11.2 | 98.9 ± 11.1 | < 0.001 |
| Posture-motor (P-M) | 85.1 ± 12.5 | 85.0 ± 12.8 | 0.985 |

[a]Student *t* test.

Table 3. Pearson product-moment correlation coefficients (*r*) between exposure biomarkers (total mercury (THg), docosahexaenoic acid (DHA), and selenium) and the BSID-II and KSPD scores[a].

| | Cord-blood THg[b] | | Maternal-plasma DHA | | Cord-plasma selenium | |
|---|---|---|---|---|---|---|
| | *r* | *P* value | *r* | *P* value | *r* | *P* value |
| 285 Boys | | | | | | |
| BSID-II | | | | | | |
| MDI | −0.054 | 0.365 | 0.016 | 0.792 | 0.082 | 0.168 |
| PDI | −0.138 | 0.020 | 0.018 | 0.759 | 0.029 | 0.630 |
| KSPD | | | | | | |
| DQ | 0.049 | 0.411 | 0.052 | 0.380 | −0.004 | 0.951 |
| C-A | 0.045 | 0.448 | −0.002 | 0.972 | 0.018 | 0.757 |
| L-S | 0.009 | 0.884 | 0.096 | 0.108 | 0.065 | 0.271 |
| P-M | 0.055 | 0.357 | 0.075 | 0.210 | 0.025 | 0.672 |
| 281 Girls | | | | | | |
| BSID-II | | | | | | |
| MDI | −0.024 | 0.687 | 0.003 | 0.960 | 0.014 | 0.819 |
| PDI | −0.044 | 0.459 | −0.016 | 0.786 | −0.030 | 0.614 |
| KSPD | | | | | | |
| DQ | 0.017 | 0.779 | −0.003 | 0.957 | 0.002 | 0.975 |
| C-A | 0.044 | 0.465 | −0.052 | 0.387 | 0.004 | 0.951 |
| L-S | 0.004 | 0.944 | −0.054 | 0.363 | −0.029 | 0.631 |
| P-M | 0.026 | 0.670 | −0.030 | 0.615 | −0.007 | 0.907 |
| Total children | | | | | | |
| BSID-II | | | | | | |
| MDI | −0.053 | 0.210 | 0.023 | 0.579 | 0.056 | 0.181 |
| PDI | −0.099 | 0.019 | 0.011 | 0.797 | 0.007 | 0.876 |
| KSPD | | | | | | |
| DQ | 0.028 | 0.505 | 0.028 | 0.507 | 0.015 | 0.729 |
| C-A | 0.022 | 0.607 | 0.030 | 0.473 | 0.004 | 0.918 |
| L-S | 0.032 | 0.449 | −0.016 | 0.704 | 0.018 | 0.675 |
| P-M | 0.006 | 0.880 | 0.018 | 0.670 | 0.020 | 0.643 |

[a]BSID-II, KSPD, MDI, PDI, DQ, C-A, L-S and P-M, see Table 2.
[b]Cord-blood THg was logarithmically transformed.

Table 4. Relations of total mercury (THg), docosahexaenoic acid (DHA), selenium, and possible confounders to the psychomotor development index of BSID-II: Standardized regression coefficients ($\beta$) of multiple regression analysis[a].

| | 285 Boys | | 281 Girls | | Total children | |
|---|---|---|---|---|---|---|
| | $\beta$ | $P$ value | $B$ | $P$ value | $\beta$ | $P$ value |
| Cord-blood THg[a] | −0.196 | 0.003 | −0.039 | 0.538 | −0.119 | 0.009 |
| Maternal-plasma DHA | 0.120 | 0.071 | −0.037 | 0.571 | 0.034 | 0.448 |
| Cord-plasma selenium | 0.015 | 0.803 | 0.018 | 0.765 | 0.013 | 0.747 |
| Child gender | | | | | −0.154 | < 0.001 |
| Birth order | 0.101 | 0.108 | −0.012 | 0.845 | 0.049 | 0.252 |
| Drinking habit during pregnancy | −0.069 | 0.261 | −0.011 | 0.854 | −0.025 | 0.549 |
| Smoking habit during pregnancy | 0.029 | 0.634 | 0.121 | 0.048 | 0.074 | 0.076 |
| Raven standard progressive matrices | 0.084 | 0.165 | 0.019 | 0.759 | 0.066 | 0.113 |
| Evaluation of environmental stimulation | 0.094 | 0.121 | 0.147 | 0.020 | 0.105 | 0.014 |
| Birth weight | 0.108 | 0.084 | −0.005 | 0.940 | 0.059 | 0.164 |
| Contribution rate, $R^2$ | 0.037 | 0.049 | 0.053 | 0.014 | 0.063 | < 0.001 |

[a]One more confounder was testers of the BSID-II (Bayley scales of infant development, second edition).
[b]Cord-blood THg was logarithmically transformed.
[c]$R$ indicates a multiple correlation coefficient.

the boys and the total. On the other hand, neither cord-plasma selenium nor maternal-plasma DHA was significantly correlated with any scores of the BSID-II or KSPD. For this reason, we focused on the PDI score of the BSID-II and performed the multiple regression analysis with adjustment for possible confounders as shown in Table 4, though family income (Table 1) was excluded from the confounders because a collinearity between family income and scores of the Raven standard progressive matrices was observed (Spearman rank correlation $r_S = 0.177$, $P < 0.001$). The association of cord-blood THg with the PDI in the boys and the total remained statistically significant even after adjusting for cord-plasma selenium and maternal-plasma DHA, indicating that a 10-fold increase in cord-blood THg was associated with a 8.3-point decreased score of the PDI in the boys. The maternal-plasma DHA concentration had a marginally positive relation to PDI score of the BSID-II (Table 4).

## Discussion

The principal finding of this study is that prenatal exposure to methylmercury was negatively associated with the PDI, but not MDI, of the BSID-II, even after adjustment for DHA and selenium. Of 20 previous studies using the BSID (Davidson et al. 1995, 2008; Jedrychowski et al. 2006, 2007; Lederman et al. 2008; Plusquellec et al. 2010; Stokes-Riner et al. 2011; Llop et al. 2012; Watson et al. 2012; Valent et al. 2013; Boucher et al. 2014; Hsi et al. 2014; Strain et al. 2015; Marques et al. 2015, 2016a,b,c; Rothenberg et al. 2016; Julvez et al. 2016; Prpić et al. 2017), 11 reported adverse effects of methylmercury on the PDI, and three observed such effects on the MDI; that is, these rates of 11/20 and 3/20 differed significantly (Fisher exact test, $P = 0.019$). Thus, psychomotor development appeared to be more susceptible to methylmercury than mental development.

In the present study, a significant association of cord-blood THg with the PDI was seen in the boys rather than all the subjects. This is consistent with results from two studies (Davidson et al. 1995; Marques et al. 2015). In contrast, Llop et al. (2012) showed that the coefficient between prenatal mercury exposure and psychomotor scale in girls was negative and almost reached statistical significance, when this analysis was conducted for all subjects including boys and girls. According to previous research on methylmercury, the proportion of stillborn fetus due to prenatal exposure and the strength of associations with intrauterine growth seemed to be higher for males than for females (Foldspang and Hansen 1999; Sakamoto et al. 2001; Tatsuta et al. 2017). Taken together, these results suggest that psychomotor development of males is more likely to be affected by prenatal exposure to methylmercury than that of females. Since there are few sex-specific analyses with regard to the effects of methylmercury on the BSID-II except for four reports (Davidson et al. 1995; Llop et al. 2012; Valent et al. 2013; Marques et al. 2015), future research on the developmental effect of reproductive toxicants should be carried out for boys and girls separately.

The maternal-hair THg levels at parturition in the participants living in the coastal area of this study ranged from 0.3 $\mu$g/g to 11.0 $\mu$g/g and were significantly higher than those in the urban participants of the TSCD (median 1.96 $\mu$g/g, range 0.29-9.35 $\mu$g/g) (Suzuki et al. 2010). The previous research found significant associations between total polychlorinated biphenyls (PCBs) in cord blood and internalizing behavior of the child behavior checklist at 30 months of age (Tatsuta et al. 2012) and between highly chlorinated PCB homologs (i.e., 9CB) in cord blood and

intellectual ability of the Kaufman assessment battery for children at 42 months of age (Tatsuta et al. 2014), in addition to between THg in maternal hair and motor cluster of neonatal behavioral assessment scale at 3 days (Suzuki et al. 2010). In the three results, the exposure biomarker affecting developmental indicators changed with aging, possibly because of the relatively low levels and narrow range of methylmercury exposure. By contrast, since the participants of the current study had been exposed to a somewhat higher level of methylmercury than the urban participants, we could observe a significant association of methylmercury with the psychomotor development at 18 months of age. Therefore, exposure level of the study population (e.g., median THg in maternal hair of 2 $\mu$g/g and over) may be important for detecting such a significant result. Additional follow-up study with other toxic substances such as lead and PCBs is needed to validate this hypothesis.

None of the KSPD scores in our study showed significant correlations with cord-blood THg, cord-plasma selenium or maternal-plasma DHA, though the KSPD and BSID-II have been reported to be comparable when examining the relationship between their psychometric indices (Tatsuta et al. 2013). One possible explanation for this paradox is as follows: The PDI of BSID-II is a composite of gross motor and fine motor skills and the P-M area of the KSPD consists of items related only to gross motor skills (Tatsuta et al. 2013). Psychomotor development of the BSID third edition (BSID-III), published in 2006, can evaluate fine motor and gross motor skills separately (Bayley 2006). For this reason, Prpić et al. (2017) found a negative association of cord-blood THg with fine motor skills in 18-month-old children prenatally exposed to methylmercury. In this way, the KSPD appears to be less sensitive to methylmercury-related dysfunctions than the PDI of the BSID-II or BSID-III.

There are several limitations in the current study. First, we could not investigate levels of lead, arsenic, and PCBs, which might have adverse effects on neurodevelopment (Wasserman et al. 2004; Lanphear et al. 2005; Stewart et al. 2006; Kippler et al. 2012), because of our limited research fund, whereas exposure to a mixture of chemicals is ubiquitous in real life and all children are exposed to multiple toxic chemicals (Bellinger 2009). We did control for the effects of selenium and DHA, which are thought to be strong antagonists and/or confounders related to methylmercury neurotoxicity. Second, the BSID-II and KSPD scores can be changed not only by individual developmental abilities but also the testers, which induces a measurement bias. We employed well-trained testers and also dummy variables for each tester in the data analysis. Thus, our data should not be heavily influenced by confounders or measurement bias.

In conclusion, psychomotor development, specifically fine motor skills, in boys may be affected by intrauterine methylmercury exposure at relatively low levels. Boys are suggested to be more vulnerable to this exposure than girls. Further study with multiple toxic chemical substances including lead, PCBs, and arsenic is required to reconfirm these conclusions, inasmuch as such chemicals can affect child neurodevelopment. Finally, the BSID-II appears to be more useful for assessing methylmercury neurotoxicity than the KSPD.

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## Conflict of Interest

The authors declare no conflict of interest.

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