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Altered Fine Motor Function at School Age in Inuit Children Exposed to PCBs, Methylmercury, and Lead

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1. Introduction

The developmental neurotoxicity of methylmercury (MeHg) was first discovered in 1956 following the poisoning episode in Minamata, Japan, when hundreds of people suffered from neurological impairment after ingesting contaminated seafood (Tsubaki and Irukayama 1977). Neuromotor deficits (e.g., ataxia, tremors) and visual impairments were frequently seen in adults with MeHg poisoning, whereas more extensive and more severe effects have been observed in children (Eto 2000). Another MeHg poisoning episode occurred in early 1972 in Iraq, due to consumption of home-made bread made of wheat treated with a MeHg fungicide (Amin-Zaki et al. 1974). Again, motor symptoms such as weakness and exaggerated reflexes were observed among the intoxicated mothers, and dose-related psychomotor deficits ranging from mild retardation to cerebral palsy were observed among children exposed *in utero* (Marsh et al. 1980). Two large prospective birth-cohort studies were initiated in the 1980's to assess the effects of exposure to environmental sources of MeHg on neurodevelopment. In the Faroe Islands, where exposure arises mainly from seafood, particularly pilot whale consumption, prenatal MeHg exposure was associated with impairments on a wide range of neuropsychological endpoints at school age, including attention, language, visuospatial skills, memory, and fine motor functions (Grandjean et al. 1997; Debes et al. 2006). By contrast, postnatal exposure had a minimal influence on most

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outcomes (Grandjean et al. 2014). In the Seychelles Islands, where fish is the main source of exposure, virtually no adverse effects were reported (Davidson et al 2011; Myers et al. 1995, 2003). It has been hypothesized that nutrients contained in seafood, such as long-chain polyunsaturated fatty acids (LC-PUFAs) and selenium (Se), are responsible for the absence of adverse MeHg effects in this cohort (Stokes-Riner et al. 2011).

Polychlorinated biphenyls (PCBs) are persistent organochlorine compounds used historically for a wide variety of industrial purposes that were banned in the 1970s and 1980s. PCBs in the environment are mixtures of specific congeners, each with its own molecular structure and potential neurotoxic effects. Several birth-cohort studies have been conducted to determine the effects of PCB exposure on child development (Boucher et al. 2009). Effects of PCBs were detected in infancy on visual recognition memory in several studies (Jacobson et al., 1985; Darvill et al., 2000; Boucher et al., 2014). In most studies, prenatal exposure was associated with adverse effects on cognition in childhood, including poorer IQ scores and response inhibition (Jacobson and Jacobson 1996, 2003; Stewart et al. 2005). Altered motor development has also been reported, especially gross motor function during infancy as assessed using the Psychomotor Development Index of the Bayley Scales of Infant Development (Koopman-Esseboom et al. 1996; Rogan and Gladen 1991; Walkowiak et al. 2001). Exposure during childhood was not measured in most cohorts, and only one study reported detrimental effects of postnatal exposure from breastfeeding in a sample of 42-month-old children assessed on the Kaufman Assessment Battery for Children (Walkowiak et al. 2001), which were no longer evident when these children were re-assessed at 6 years of age (Winneke et al. 2005).

Lead (Pb) toxicity has been recognized for centuries, and the neurodevelopmental consequences of childhood Pb exposure have been extensively studied over the last 20 years. There is now consistent evidence supporting the existence of adverse effects of postnatal Pb exposure on several aspects of child development, including intelligence and specific cognitive functions, academic achievement, behavior (e.g., attention deficit/hyperactivity symptoms), and motor functions (Banks et al. 1997; Braun et al., 2006; Chiodo et al. 2004; Lanphear et al. 2000, 2005; Surkan et al. 2007; Zhang et al. 2013). Many of these effects have been reported in children with very low levels of exposure ($< 5 \mu\text{g/dL}$), and no threshold for 'safe' Pb exposure in children has yet been identified (e.g., Lanphear et al., 2005). Although less well characterized, adverse effects on child cognition have also been reported in relation to prenatal low-level Pb exposure in several studies (Schnaas et al. 2006; Wasserman et al. 2000; Yorifuji et al. 2011).

Despite the growing evidence linking exposure to neurotoxic contaminants from environmental sources to neurodevelopmental impairments, recent birth-cohort studies that have followed children until school age have tended to focus primarily on intellectual function. Little attention has been paid to fine motor functions even though neuromotor deficits are a salient element of MeHg neurotoxicity and psychomotor impairments during infancy have been found in relation to several contaminants. Moreover, exposure levels in many of the studies to date have been relatively modest, and few have examined the degree to which effects associated with some of these contaminants may be attributable to confounding by the others.

The Inuit from Nunavik (Arctic Québec, Canada) are heavily exposed to MeHg and PCBs from sea mammal and fish consumption (Muckle et al. 2001), and Pb exposure is also a concern in this population because of the use of Pb pellets for hunting game (Lévesque et al. 2003). Mean cord blood Hg concentrations in the Environmental Contaminant and Child Development Study in Nunavik (1996–2000) (18.5 µg/L) approached the levels reported in the Faroe Islands, and were nearly 20 times higher than those measured in children from Southern Québec during the same period (Muckle et al. 2001). A comparative study of PCB levels across birth cohorts estimated the median cord PCB congener 153 serum level to 100 ng/g lipid, which was comparable to the estimations for the Michigan and Dutch cohorts, where adverse effects of prenatal exposure were found (Longnecker et al. 2003). In our prospective longitudinal study of Inuit children assessed at 11 years of age, higher cord mercury (Hg; used as an index of MeHg exposure because seafood diet is the predominant exposure source in this population) and cord Pb concentrations were associated with reduced IQ scores (Jacobson et al. 2015), and cord Hg and child Pb levels with higher prevalence of behaviors consistent with attention deficit hyperactivity disorder (Boucher et al. 2012a). The present study examined the relation of pre- and postnatal exposure to MeHg, PCB, and Pb to fine motor functions, which were also assessed at 11 years in the children from this cohort.

2. Methods

2.1 Participants

The study participants were 265 school-age Inuit children from Nunavik, for whom umbilical cord blood samples had been obtained under the auspices of the Arctic Cord Blood Monitoring Program (Muckle et al., 1998). The Nunavik region of Québec, where these children live, is located north of the 55th parallel. Mothers were contacted by phone, provided with information about the study protocol, and invited to participate with their children to the Nunavik Child Development Study. Exclusion criteria were birth weight < 2.5 kg, gestation duration < 35 weeks, presence of a major birth defect and/or major neurological or health problems or pervasive development disorders. Assessments were conducted in the three largest Nunavik villages between October 2005 and February 2010. Participants who resided in other communities were transported by plane to one of the larger villages for testing. Written informed consent was obtained from a parent of each participant; oral assent, from each child. A maternal interview was conducted to provide information on demographic background, smoking, alcohol and drug use during pregnancy as well as other maternal characteristics. One participant with a history of epilepsy, one with a history of meningitis associated with coma, and one with multiple sclerosis were excluded from the analyses reported here. The research was approved by the Université Laval and Wayne State University ethics committees and was performed in accordance with ethical standards of the Helsinki Declaration.

2.2 Assessment of fine motor functions

Santa Ana Form Board (Lezak 1995)—The child is presented with a form board with 4 rows of 12 square holes into which square pegs with a cylindrical head will fit. Half of the top of each peg is white and the other half black. The child is asked to lift each peg from its hole, rotate it 180° clockwise as rapidly as possible, and place it back in its hole—first with

dominant hand, then with the non-dominant hand, and then with both hands in alternation. The total number of pegs turned within 60 sec is tabulated for each condition, and a total score was computed by summing the scores for the three conditions. This task measures manual dexterity and assesses the ability to make skillful arm and hand movements (Fleishman and Hempel 1954).

NES-3 Finger Tapping Test (Letz and Baker 1988)—The child is asked to tap a key as fast as possible with the index finger for 15 s. After a practice trial using the dominant hand, two trials are performed with the dominant hand, and two with the non-dominant hand. For each hand, the total number of taps recorded during both trials is tabulated. Scores obtained from both hands were summed together to compute a total score. This task measures fine motor speed.

Stanford-Binet Copying Subtest (Thorndike et al. 1986)—The child duplicates designs made from blocks (first 12 items) and drawings (16 following items). Items are in increasing degree of difficulty. The number of correct designs is tabulated using a standard scoring system. This task assesses visuo-motor integration.

Children assessed between October 2005 and April 2007 ($n = 215$) performed all three tasks of motor function, but those assessed after this period ($n = 50$) were only assessed with the Stanford-Binet Copying subtest due to time restrictions.

2.3 Biological samples

Umbilical cord and child blood samples were analysed for concentrations of mercury (Hg), PCBs, Pb, as well as Se and LC-PUFAs. A blood sample (30 mL) obtained from the umbilical cord was used to indicate prenatal exposure, and a venous blood sample (20 mL) obtained from each child was used to document body burden at time of testing. In cord blood samples, total Hg concentrations were determined using cold vapour atomic absorption spectrometry. Pb levels were determined by graphite furnace atomic absorption spectroscopy, with Zeeman background correction. Se concentrations were measured by using inductively coupled plasma mass spectrometry (ICP-MS). Total Hg, Pb, and Se concentrations in child blood samples were determined by ICP-MS. The most prevalent PCB congeners were measured in purified cord plasma extracts using gas chromatography/mass spectrometry (cord: International Union of Pure and Applied Chemistry numbers 28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183 and 187; child: numbers 99, 101, 105, 118, 128, 138, 153, 156, 163, 170, 180, 183 and 187). Because PCB congeners in cord and in the child's plasma samples were found to be strongly inter-correlated, the most abundant PCB congener, PCB153, expressed on a lipid basis, was used as the main indicator of PCB exposure (Ayotte et al. 2003). LC-PUFA composition of plasma phospholipids was analysed using capillary gas-liquid chromatography with flame ionisation detection. Concentrations of docosahexaenoic acid (DHA) in cord and at time of testing were expressed as percentages of the total area of all fatty acid peaks from C14:0 to C24:1 (percent weight), as described in Jacobson et al. (2008). The limits of detection (LODs) in cord samples were 0.2 µg/L for Hg and Pb, 7.1 µg/L for selenium, and 0.02 µg/L for all PCB congeners. LODs in child blood sample were 0.1 µg/L for Hg, 0.002 µg/dL for Pb, 7.1 µg/L for Se, and less than 0.05 µg/L

for most PCB congeners. A value equal to half the LOD was entered whenever a substance was not detected. More details on the analytical procedures can be found elsewhere (Dallaire et al. 2014; Muckle et al. 2001).

2.4 Control variables

The following control variables were documented: child age at testing; sex; child adopted (yes/no); a social environment composite score (Jacobson et al. 2015) constructed by averaging four measures after transformation to z – scores socioeconomic status (Hollingshead 2011), primary caregiver's years of education, Peabody Picture Vocabulary Test (Dunn and Dunn 1997), and Raven Progressive Matrices (Raven et al. 1992); parity (0–1 vs. 2); marital status (single vs. not single); mother sufficiently fluent to be interviewed in English or French (yes/no), an indicator of assimilation to Western culture (yes/no); age of biological mother at child's birth; and tobacco (yes/no), binge alcohol drinking (at least one episode of 5 standard alcohol drinks; yes/no), and illicit drug use (yes/no) during pregnancy.

2.5 Statistical analyses

Log transformations were performed on each contaminant variable and on cord Se, since these variables followed log-normal distributions. Child Se was transformed in tertiles and coded in two dummy variables since its distribution was neither normal nor log-normal. The following variables with extreme values (>3 standard deviations from the mean) were recoded to one point greater than the highest observed non-outlying value as recommended by Winer (1971) (number of outliers are indicated in parentheses): maternal age at delivery ($n = 1$), social environment composite ($n = 2$), cord DHA ($n = 2$), and child DHA ($n = 1$), and Stanford-Binet Copy raw score ($n = 3$).

The associations of each of the contaminant variables with each of the motor performance variables were examined using a series of linear regression analyses. Child age, sex, and social environment were used as mandatory covariables. Other covariates were selected using a backward selection procedure with a $p < 0.20$ cut-off level (Budtz-Jørgensen et al. 2007), in which all control variables (except alcohol and illicit drug use during pregnancy, since they were missing for a significant part of the study sample – 19.1% and 18.6%, respectively) were included in a single regression model predicting a given outcome. Then, the covariate showing the weakest association with the outcome in question was removed from the model. This procedure was repeated until each covariate in the model was associated with the outcome at $p < 0.20$. A second model additionally controlled for other contaminants, and a third model, for other contaminants and nutrient biomarkers (cord and current DHA and Se). Selection of the contaminants and nutrients in these models followed the same criteria as for the other covariates. For all significant associations, analyses were rerun to include maternal binge drinking and illicit drug use during pregnancy at the end of the model to assess their impact on the beta coefficient for the association between the exposure variable and outcome.

Interactions between contaminants were explored by adding the following interaction terms to the regression analyses: cord Hg x cord PCB, cord Hg x cord Pb, cord Pb x cord PCB,

child Hg x child PCB, child Hg x child Pb, and child PCB x child Pb. Given the low power of interaction terms in observational studies, the critical p -value was relaxed to $p < 0.20$ for testing statistical interactions (Selvin et al. 2004). Each significant interaction was explored further using stratified analyses, in which linear regression analyses, for the association between one of the exposure variable involved and the outcome, were conducted separately for children with low and high levels to the other exposure variable, using median split. Analyses were conducted using IBM SPSS Statistics Version 22.0.

3. Results

3.1 Descriptive statistics

Descriptive statistics of the study sample are summarized in Table 1. Mean Hg concentrations were high in cord blood (21.4 µg/L) and were reduced by a factor of ≈ 4.5 in child blood samples. Comparatively, PCB153 concentrations remained relatively high until school age. Regarding Pb exposure, 75 (29.3%) participants had cord levels higher than 5 µg/dL and 23 (9.0 %) higher than 10 µg/dL, whereas 27 participants (10.3 %) had blood Pb levels higher 5 µg/dL at time of testing, and 6 (2.3 %) higher than 10 µg/dL. Hg, PCB153, Pb, and biomarkers of seafood nutrients in cord and child blood samples are moderately associated with each other (Supplementary material, Table S1), presumably because these substances are found in high concentrations in traditional Inuit food and families vary in the degree to which they consume traditional food.

Performance on motor assessments for the retained participants is summarized in Table 2. Santa Ana Form Board data were excluded for five participants, four who did not follow the instructions appropriately and one who could not attend to the task. Finger Tapping data were excluded for three children who did not follow the task instructions appropriately (one of whom had also been excluded for the Santa Ana Form Board). Because of the strong correlations between the task conditions for the Santa Ana Form Board ($r^2 = 0.60$, $p < 0.001$) and for the Finger Tapping Test ($r = 0.63$, $p < 0.001$), total scores obtained from the sum of each condition were used in the analyses for both tasks. Child age and social environment showed positive correlations with motor performance, especially for speeded tasks (Supplementary material, Table S2).

3.2 Associations between contaminants and motor performance

Results from the regression analyses examining the associations between contaminants in cord and child blood samples and motor performance are summarized in Table 3. Cord blood Hg, current blood Hg, and current plasma PCB153 concentrations were associated with poorer performance on the Santa Ana Form Board after statistical control for covariates. However, after adjustment for other contaminants, only the effect of current PCB153 remained statistically significant, nor were the results altered by the inclusion of seafood nutrients in the model. Adding cord PCB153 (which did not fulfil the criteria for inclusion in the regression) to the latter model did not alter the relation of current PCB153 to Santa Ana Form Board performance (std $\beta = -0.21$, $p = 0.015$), suggesting that the effect is solely attributable to postnatal exposure.

On the Finger Tapping Test, all contaminant variables except cord plasma PCB153 were significantly associated with poorer performance after control for covariates. No single contaminant remained independently associated with performance after mutual adjustment for other contaminant variables, but inclusion of seafood nutrients in the models revealed significant associations with current Hg and PCB153 concentrations. Again, these associations were not altered when adding cord Hg and PCB153 concentrations to the regression models for current Hg (std $\beta = -0.23$, $p = 0.011$) and current PCB153 (std $\beta = -0.20$, $p = 0.023$), respectively, reflecting ‘purely’ postnatal exposure effects on Finger Tapping performance. However, after exclusion of a multivariate outlier from analyses (standardized residual < -3.0), only the effect of current Hg remained significant, and the association with current PCB153 fell short of statistical significance ($\beta = -0.13$, $p = 0.10$).

There were no significant associations between any of the contaminants and Stanford-Binet Copying performance. Adding maternal binge drinking or illicit drug consumption during pregnancy at the end of the regression models had a negligible impact on the regression coefficients for the associations between exposure variables and outcomes ($< 10\%$ change in beta value for all significant exposure-outcome associations).

To examine associations between contaminants and specific task conditions, analyses were re-conducted using the different subscores of the Santa Ana Form Board (dominant hand, non-dominant hand, two hands in alternation) and the Finger Tapping Tasks (dominant hand, non-dominant hand) as outcomes. On the Santa Ana Form Board, current PCB153 concentrations were associated with poorer performance in the condition involving both hands in alternation ($p < 0.01$; Supplementary material, Table S3). On the Finger Tapping Test, current Hg ($p < 0.01$) and Pb ($p < 0.05$) concentrations were associated with poorer performance with the dominant hand, and current PCB153 concentrations were associated with poorer performance with the non-dominant hand ($p < 0.01$; Supplementary material, Table S4). Again, additional control for maternal binge drinking or illicit drug consumption during pregnancy at the end of the regression models had no major impact on the regression coefficients for the associations between exposure variables and outcomes ($< 10\%$ change in beta value for all significant exposure-outcome associations).

3.3 Interaction effects

Testing for interaction effects did not reveal any pattern of synergistic effects of contaminants. Conversely, there were two significant interactions suggesting an association between one exposure variable and the outcome that was stronger with lower levels of the other exposure variable: current Hg x PCB153 vs Santa Ana Form Board ($p = 0.111$) and current Pb x PCB153 vs Stanford-Binet Copying ($p = 0.144$). Stratified analyses showed that the association between current PCB153 and Santa Ana Form Board was statistically significant after control for selected covariates among children from the lower half of current Hg exposure ($\beta = -0.29$, $p = 0.004$), but not among those from the higher half of current Hg exposure ($\beta = -0.06$, $p = 0.552$). For Stanford-Binet Copying, there was a beneficial association between current Pb concentrations and performance after control for selected covariates among children within the lower half of current PCB153 exposure ($\beta = 0.22$, $p = 0.020$), but not among those within the higher half of PCB exposure ($\beta = -0.08$, $p = 0.413$).

3.4 Associations with specific PCB congeners

PCB153 concentrations in cord and current plasma samples are strongly correlated with those of the other three most prevalent PCB congeners (118, 138, and 180) that were also measured, with Pearson correlation coefficients ranging between 0.70 and 0.98. Each of the regression analyses involving PCB153 as a predictor was rerun by replacing the exposure measure by each of the other PCB congeners and also by the sum of the 13 PCB analyzed congeners. Associations between these compounds in current child plasma samples and performance on the two fine motor tasks that were found to be most sensitive to PCB153 effects (Santa Ana Form Board and Finger Tapping Test) are presented in Table 4. As can be seen, all results are very similar to what was observed for PCB153 whichever exposure marker is used, suggesting that the observed effects cannot be attributed to any single congener.

4. Discussion

This study examined the relation of developmental exposure to MeHg, PCBs, and Pb to fine motor function in 11-year-old children. Current PCB plasma concentrations were associated with poorer manual dexterity and slower fine motor speed. Results were virtually the same regardless of which PCB congener was used as the exposure marker. Postnatal MeHg exposure was also independently associated with slower fine motor speed. Testing for interactions did not reveal any synergistic effect between the contaminants on the outcomes assessed. Conversely, effects of postnatal PCB exposure were more easily detected among children with lower concurrent MeHg exposure. Visuo-motor integration measured using Stanford-Binet copying was not related to the contaminants under study.

This study is the first to document adverse effects of postnatal PCB exposure on fine motor function in school-age children. We have previously reported adverse effects attributed to postnatal PCB exposure on neurophysiological and cognitive measures in the same cohort of children (Boucher et al. 2011, 2012b; Saint-Amour et al. 2006). Interestingly, in a recent birth-cohort study conducted in Eastern Slovakia, postnatal PCB exposure, but not prenatal exposure, was associated with impaired cochlear function in 45-month old children as revealed by distortion product otoacoustic emissions (Jusko et al., 2014). These findings contrast with a large majority of PCB studies, which have concluded that neurodevelopmental effects in children are uniquely observed with prenatal rather than postnatal exposure (e.g., Jacobson and Jacobson 1996; 2003; Forns et al. 2012a). The typically long periods of breast-feeding in this Inuit sample (exceeding one year on average and sometimes extending to preschool age in this cohort; Boucher et al. 2010; Verner et al. 2015) and the substantially higher quantities of PCB-contaminated traditional Inuit food eaten by these children compared with children from other populations, leading to postnatal transmission of much larger quantities of these contaminants than in the other PCB cohorts studied to date, likely contributed to the finding of adverse effects of postnatal exposure in our study. By contrast, we found no association between prenatal PCB exposure and motor performance. Although prenatal PCB exposure has been associated with altered psychomotor development during infancy in some reports (Forns et al. 2012b; Koopman-Elseboom et al. 1996; Rogan and Gladen 1991; Walkowiak et al. 2001), most studies that

assessed motor function beyond infancy have failed to find significant associations, even in the presence of cognitive effects (Després et al. 2005; Forns et al. 2012a; Grandjean et al. 2012; Jacobson et al. 1990).

Our findings of poorer performance on speeded tasks of fine motor function as a function of postnatal PCB exposure suggest a specific impairment in motor speed. Deleterious effects on motor function might indicate cerebellar damage (Roegge and Schantz 2006), but other mechanisms might also be involved. Experimental studies conducted with animals have shown that PCBs perturb dopamine function (Seegal 1995; Lyng and Seegal 2008), which plays a crucial role in motor control and regulation (Volkow et al. 1998; Yang et al. 2003). Slower motor speed might also reflect altered myelination of white matter. The corpus callosum, the largest white matter structure in the brain, has been shown to be a preferential site for PCB153 accumulation in the brain of prepubertal rats (Saghir et al. 2000). Degree of myelination in the corpus callosum in children has been shown to be related to Finger Tapping performance, particularly for the left-hand and alternating hands conditions (Muetzel et al. 2008); the alternating (Santa Ana Form Board) and non-dominant hand (Finger Tapping Test) conditions were most sensitive to PCB exposure in our study. We recently reported an association between 11-year PCB concentrations and delayed reaction times on a visual go/no-go event-related potential protocol (Boucher et al. 2012b), an effect which may also be attributable to slower motor speed. These results were accompanied by decreased amplitude in response-related potentials at fronto-central scalp sites, suggesting that the effects of postnatal PCBs on motor function are mediated, at least in part, by structural and/or functional alterations within the anterior portion of the brain.

Our finding that postnatal MeHg exposure impairs fine motor function in school-age children is consistent with our previous report in a subsample of this cohort tested at 5 years of age, indicating that child blood Hg concentrations were associated with increased tremor amplitude during pointing movements (Després et al. 2005). These findings are also consistent with reports from cross-sectional studies conducted among riverine populations in Brazil and French Guiana, where gold mining activities and deforestation have resulted in MeHg contamination of freshwater fish, indicating that higher hair Hg levels were associated poorer performance on motor and visuospatial tasks in children (Cordier et al. 2002; Grandjean et al. 1999) and also in adults (Dolbec 2000; Yokoo et al. 2003). Tremors and motor coordination deficits are also core features of adult MeHg poisoning, which has been related to cerebellar damage (Eto 2000). The cerebellum is known to play an important role in several aspects of motor function, and cerebellar size has been specifically correlated with Finger Tapping performance in healthy adults (Paradiso et al. 1997). The absence of a MeHg effect on the Stanford-Binet Copying subtest, which assesses visuo-motor integration and visuospatial skills, may be related to the influence of cultural factors upon completion of such tasks (Henry 2001), which can limit its sensitivity to the effects of biological and socio-environmental factors known to influence neurodevelopment. This interpretation is supported by the absence of effects of the other contaminants on this test and by its weak correlations with potential confounders compared to the other motor tasks employed.

Although cord Hg concentrations was associated with poorer fine motor performance after statistical control for general confounders, the associations were largely reduced and were

no longer significant after adjustment for other contaminants. This contrasts with the findings from the larger Faroese cohort, where prenatal exposure to similar levels was associated with impairments in motor function (Debes et al. 2006; Grandjean et al. 1997). Part of this inconsistency might be explained by lower statistical power in our sample, which was considerably smaller than the Faroese sample. These results also underscore the difficulty of disentangling effects of multiple contaminants arising from similar sources.

We recently reported that prenatal MeHg and Pb exposure are associated with poorer performance on a test of general intellectual function at school age in the same cohort of Inuit children (Jacobson et al. 2015). Postnatal exposures were not associated with intellectual performance after adjustment for confounders. By contrast, the present study reports associations between postnatal exposure to seafood contaminants and fine motor function, whereas associations with prenatal exposures are weaker and disappear after adjusting for postnatal exposures. That postnatal MeHg and PCB exposure, assessed from blood concentrations at 11 years, specifically affected fine motor function in our cohort suggests an enhanced vulnerability in this specific domain to the effects of these contaminants when exposure occurs after birth, whereas prenatal exposure apparently results in more diffuse effects that manifest on tasks of general cognitive function. Failure to assess the domains that are specifically affected may lead investigators to incorrectly conclude that an exposure has no effect on neurodevelopment.

Conclusion

This study adds to the growing body of evidence that chronic exposure to seafood contaminants early in life can impair fine motor function. In contrast with previous studies and with what was found with measures of general intellectual functioning in the same cohort of children, effects were found specifically in association with postnatal exposures, suggesting that children remain vulnerable to neurotoxic contaminants years after birth. PCB and Hg levels at school age were independently associated with poorer fine motor function. These findings underscore the importance of documenting postnatal exposure and of incorporating measures of specific neuropsychological domains in addition to tests of general intellectual abilities in epidemiological studies on neurodevelopment; otherwise, important neurotoxic effects may be left undetected.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

DHA	docosahexaenoic acid
Hg	mercury
LC-PUFA	long-chain polyunsaturated fatty acid
MeHg	methylmercury
Pb	lead
PCB	polychlorinated biphenyl
Se	selenium

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Highlights

- Fine motor function was assessed in school-aged children from Nunavik;
- Postnatal PCBs were related to poorer manual dexterity and slower fine motor speed;
- Postnatal Hg exposure was independently associated with slower fine motor speed;
- There was no synergistic effect between the contaminants on motor outcomes;

Table 1

Descriptive statistics for the study sample.

Variables	N	Mean	Median	S.D.	Range	%
Child characteristics						
Age (years)	265	11.3	11.3	0.8	8.5 – 13.3	
Sex (% girls)	265					51.7
Adoption status (% adopted)	265					17.4
Primary Caregiver						
Marital status (% single)	264					25.8
Fluent in English or French (% yes)	265					89.8
Education (years of schooling)	264	8.4	9.0	2.5	0 – 16	
Hollingshead score	265	28.4	28.0	12.0	8 – 66	
Raven Progressive Matrices score	259	34.9	37.0	10.0	4 – 56	
Peabody Picture Vocabulary Test score	236	87.8	86.0	32.7	23 – 168	
Social environment composite ^a	265	−0.0	0.0	0.8	−2.5 – 2.3	
Pregnancy history						
Maternal age at delivery (years)	265	23.9	23.0	5.7	15 – 42	
Parity (% > 1)	265					52.8
Tobacco smoke (% yes)	257					85.2
Binge drinking of alcohol (% yes) ^b	223					35.0
Illicit drug use (% yes)	225					31.6
Cord blood analyses at birth						
Mercury (µg/L)	256	21.4	17.2	17.3	1.0 – 99.3	
Lead (µg/dL)	256	4.7	3.7	3.4	0.8 – 20.9	
PCB congener 118 (µg/kg fat)	255	22.4	18.0	17.8	3.4 – 121.0	
PCB congener 138 (µg/kg fat)	255	81.6	63.4	63.1	6.8 – 435.1	
PCB congener 153 (µg/kg fat)	255	124.3	93.8	101.9	9.7 – 653.6	
PCB congener 180 (µg/kg fat)	255	50.2	35.1	44.1	3.4 – 285.6	
DHA acid (% phospholipids)	251	3.7	3.5	1.3	1.1 – 7.7	
Se (µg/L)	239	339.4	278.7	178.8	110.5 – 1579.2	
Child blood analyses at 11 years						

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Variables	N	Mean	Median	S.D.	Range	%
Mercury (µg/L)	261	4.8	3.0	4.8	0.1 – 34.1	
Lead (µg/dL)	261	2.7	2.0	2.1	0.4 – 12.8	
PCB congener 118 (µg/kg fat)	259	11.2	8.8	8.3	0.7 – 56.5	
PCB congener 138 (µg/kg fat)	259	35.7	25.5	33.5	2.3 – 261.9	
PCB congener 153 (µg/kg fat)	259	73.6	45.9	82.1	3.5 – 809.5	
PCB congener 180 (µg/kg fat)	259	32.5	18.6	42.2	1.0 – 404.8	
DHA (% phospholipids)	260	2.5	2.3	1.0	0.1 – 5.5	
Se (µg/L)	261	200.9	181.6	93.8	67.9 – 947.5	

^aBased on caregiver years of education, Hollingshead score, Peabody Picture Vocabulary Test raw score, and Raven Progressive Matrices raw score, which were converted to z-scores and averaged;

^bBinge drinking defined as consumption of 5 standard drinks or more per occasion, one standard drink corresponding to 0.5 oz of absolute alcohol, which is equivalent to 350 ml of beer (12 oz), 175 ml of wine (6 oz), or 44 ml of liquor (1.5 oz).

Table 2

Fine motor performance for the study sample.

Variables	N	Mean	Median	S.D.	Range
Santa Ana Form Board (# correct)					
Dominant hand	210	31.5	31.0	5.9	13 – 48
Non-dominant hand	210	27.6	27.0	5.5	13 – 44
Two hands in alternation	210	27.6	27.0	7.3	10 – 47
Total	210	84.5	86.0	16.2	37 – 136
Finger Tapping (# taps)					
Dominant hand	211	136.7	137.0	14.1	86 – 174
Non-dominant hand	211	120.2	119.0	14.1	76 – 163
Total	211	256.9	257.0	25.5	162 – 319
Stanford-Binet Copying (# correct)					
Copy	262	15.0	15.0	2.8	5 – 27

Table 3

Associations between contaminant concentrations and fine motor performance.

Contaminant	Santa Ana Form Board – Total score					Finger Tapping Test – Total score					Stanford-Binet Copying				
	N	β_0	β_1	β_2	β_3	N	β_0	β_1	β_2	β_3	N	β_0	β_1	β_2	β_3
Cord blood															
Mercury	190	-0.19**	-0.15*	-0.05	-0.05	203	-0.21**	-0.15*	0.02	0.04	248	-0.01	0.03	0.03	0.02
PCB153	191	-0.04	-0.02	0.10	0.08	200	-0.16*	-0.12 [†]	0.02	0.01	248	0.01	0.01	0.01	0.00
Lead	190	-0.11	-0.08	-0.04	-0.04	203	-0.21**	-0.19**	-0.11 [†]	-0.09	248	-0.02	-0.01	-0.02	-0.03
Current blood															
Mercury	191	-0.21**	-0.11	0.04	0.04	203	-0.32**	-0.26**	-0.13	-0.22*	257	-0.05	-0.02	-0.04	-0.11
PCB153	190	-0.29**	-0.25**	-0.20*	-0.18*	203	-0.32**	-0.28**	-0.15 [†]	-0.17*	255	0.04	0.06	0.04	0.02
Lead	191	-0.20**	-0.17*	-0.09	-0.10	203	-0.20**	-0.21**	-0.10	-0.11	257	0.03	0.10	0.10	0.08

Note. Values are standardized regression coefficients for the log-transformed contaminant variable. Variables included in the models are: β_0 = the contaminant of interest; β_1 = β_0 + selected covariates (Form Board: child age and sex, social environment, maternal age, parity, marital status, smoking during pregnancy; Finger Tapping: child age and sex, social environment; Stanford-Binet: child age and sex, social environment, marital status); β_2 = β_1 + other contaminants (Form Board: cord Hg and child Pb for child PCB153 analyses, child PCB153 for other contaminants; Finger Tapping: cord Pb, child Pb, child Hg, child PCB153; Stanford-Binet: child Pb); β_3 = β_2 + nutrient biomarkers (Form Board: cord DHA, child DHA, child Se; Finger Tapping: child DHA for child Hg analyses, child DHA and child Se for other contaminants; Stanford-Binet: child Se).

** $p < 0.01$;

* $p < 0.05$;

[†] $p < 0.10$.

Table 4

Associations between concentrations of specific PCB congeners at 11 years and fine motor performance.

PCB congener	Santa Ana Form Board – Total score				Finger Tapping Test – Total score			
	β_0	β_1	β_2	β_3	β_0	β_1	β_2	β_3
PCB congener 118	-0.24**	-0.19**	-0.14 [†]	-0.14 [†]	-0.31**	-0.27**	-0.15 [†]	-0.23**
PCB congener 138	-0.28**	-0.24**	-0.18*	-0.16 [†]	-0.31**	-0.27**	-0.14 [†]	-0.16*
PCB congener 180	-0.28**	-0.26**	-0.22**	-0.20*	-0.30**	-0.28**	-0.16*	-0.16*
Sum of 13 congeners	-0.28**	-0.24**	-0.19*	-0.17*	-0.31**	-0.28**	-0.15 [†]	-0.17*

Note. Values are standardized regression coefficients for the log-transformed contaminant variable. β_0 = the contaminant of interest; $\beta_1 = \beta_0$ + selected covariates (Form Board: child age and sex, social environment, maternal age, parity, marital status, smoking during pregnancy; Finger Tapping: child age and sex, social environment); $\beta_2 = \beta_1$ + other contaminants (Form Board: cord Hg and child Pb; Finger Tapping: cord Pb, child Pb, child Hg); $\beta_3 = \beta_2$ + nutrient biomarkers (Form Board: cord DHA, child DHA, child Se; Finger Tapping: child DHA, child Se).

** $p < 0.01$;

* $p < 0.05$;

[†] $p < 0.10$.