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Association between Prenatal Exposure to Methylmercury and Visuospatial Ability at 10.7 years in the Seychelles Child Development Study¹

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Abstract

The Seychelles Child Development Study was designed to test the hypothesis that prenatal exposure to MeHg from maternal consumption of a diet high in fish is detrimental to child neurodevelopment. To date, no consistent pattern of adverse associations between prenatal exposure and children's development has appeared. In a comprehensive review of developmental studies involving MeHg, a panel of experts recommended a more consistent use of the same endpoints across studies to facilitate comparisons. Both the SCDS and the Faeroe Islands studies administered the Bender Visual Motor Gestalt Test. However, the method of test administration and scoring used was different. We repeated the test on the SCDS Main Study children (mean age 10.7 years) using the same testing and scoring procedure reported by the Faeroe studies to obtain Copying Task and Reproduction Task scores. We found no association between prenatal MeHg exposure and Copying Task scores which was reported from the Faeroese study. However, our analysis did show a significant adverse association between MeHg and Reproduction Task scores with all the data ($p = 0.04$), but not when the single outlier was removed ($p = 0.07$). In a population whose exposure to MeHg is from fish consumption, we continue to find no consistent adverse association between MeHg and visual motor coordination.

Keywords

Methylmercury; Prenatal Exposure; Visual Motor Development

Harada (1962, first described prenatal methylmercury (MeHg) exposure (Fetal Minamata disease) as a severe developmental brain disorder following exposure to very high dosages

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from maternal consumption of fish polluted by industrial contamination. Since the first report, and one subsequent prenatal case following a similar industrial contamination at Niigata, no cases of prenatal or fetal Minamata disease from fish consumption have been reported (Myers & Davidson, 2007). However, epidemiological studies have low level prenatal exposure from fish consumption have reported finding associations with some developmental outcomes (Grandjean, et al., 1997; Kjellstrom, et al., 1986; 1989). These reports have resulted in questions about the safety of fish consumption by pregnant women. Exposure to MeHg from consuming a diet high in ocean fish (e.g., multiple meals per week) that has not been overtly contaminated with MeHg can lead to prenatal exposures from trace levels to about 30 ppm as measured in maternal hair samples. These levels are many times lower than was experienced in the Japanese poisonings. Because millions of pregnant women around the world depend upon fish as a primary and readily available source of essential nutrients, the question of whether fish consumption is safe has high public health significance (FAO, 2000).

Two studies have been following large cohorts of children whose mothers experienced dietary exposure to MeHg during pregnancy, one in the Faeroe Islands (Grandjean, et al., 1997) and the other, the Seychelles Child Development Study (SCDS) in the Republic of Seychelles (Davidson, et al., 1998; Myers, et al., 2003; Davidson et al., 2006). The two studies were organized in the late 1980s, differ in a number of ways, and have reached different conclusions. In 1998, the National Institute of Environmental Health Sciences and the White House Office of Science and Technology Policy held a jointly sponsored workshop to review, discuss and evaluate these two studies as well as several other smaller studies (Lucier & Goyer, 1998). The Workshop Report identified several endpoints that were common to both the Faeroese and the Seychelles studies but for which apparently different results were obtained. One such endpoint was the Bender Visual Motor Gestalt Test (Bender).

The Bender tests the child's ability to copy geometric figures (the *Copying Task*). In clinical settings, a non-standardized *Reproduction Task* may be added to test the child's spatial memory (Sattler, 2002). At the 66 month evaluation of the SCDS main cohort (Davidson, et al., 1998), we administered the Copying Task to determine the child's developmental level of visual motor integration, and scored it following the Koppitz (1964) method. The Reproduction Task was not administered. No association between the Koppitz Copying Task error scores and prenatal MeHg level was found. However, there was an association between the Koppitz Copying Task error scores for boys only and recent postnatal exposure (measured by determining the MeHg content of the 1-cm segment hair closest to the child's scalp from hair samples cut at the time of the 66 month examination). Boys with higher postnatal exposures made fewer Koppitz Copying Task errors (Davidson, et al., 1998).

At age 7 years, the Faeroese study (Grandjean, et al., 1997) gave the Bender, using a system referred to as *Der Göttinger Form reproduktions-test (G-F-T)* for administration and scoring of the Copying Task (Schlange, et al., 1972a). They also administered the Reproduction Task. They reported declining G-F-T Copying Task scores with increasing prenatal MeHg exposure (Grandjean, et al., 1997). They also found that the Reproduction Task proficiency declined with increasing prenatal MeHg exposure, but only when subjects with prenatal MeHg levels above >10 ppm in maternal hair were excluded from the analysis (Grandjean, et al., 1997, p. 423).

The Workshop report recommended that the SCDS and the Faeroes researchers "adopt some common assessments allowing direct comparisons" (Lucier & Goyer, 2000, p. 21). To accommodate this recommendation, we re-examined the SCDS Main Cohort subjects using the G-F-T system for administration and scoring of the Bender. We also gave the Reproduction Task. To assure that these new outcome results from this alternative method of test

administration and scoring would be compared to our original results, we followed the analysis plan described by Myers and colleagues.

Method

The Bender Visual Motor Gestalt Test

The Bender is used widely as an objective measure of the developmental level of visual-motor integration in children between 5-0 and 11-11 years of age, but it probably also measures other visual perceptual functions. It has also been used in clinical settings as a means to subjectively identify emotional difficulties and brain damage, but there are limited data on the validity of either usage. Sattler (2002) warned that inadequate visual motor ability may or may not reflect underlying brain injury. The Bender yields scores for a Copying Task and a Reproduction Task depending upon how it is administered.

The Copying Task—The standard protocol for administration and scoring the Bender Copying Task for a developmental level was described by Koppitz (1964; 1975). The Koppitz method is widely used around the world both clinically and for research. The Koppitz Copying Task is normed for children 5-0 to 11-11 years. The median test-retest reliability is 0.77 and inter-examiner reliability ranges from 0.79 to 0.99 (Koppitz, 1975). The Koppitz Copying Task error scores have good validity as a general measure of visual-motor integration (Snow & Desch, 1989). Because of specific differences in administration rules, the drawings obtained by the Koppitz method are not suitable for scoring using the G-F-T system.

The G-F-T system includes an alternative administration and scoring method for the Copying Task only. It is designed to estimate brain damage (Schlange, et al., 1972b). It is designed and normed for use with children 6-0 to 15-11 years and has been used in some research settings, mainly in Europe (cf. Trillingsgaard, Hansen & Beese, 1985; Winneke, Hrdina & Brockhaus, 1982). Schlange and colleagues (1972b) report a test-retest reliability coefficient of 0.96, but do not report inter-examiner reliability. Jungmann and Göbel (1983) reported poor diagnostic relevance of the G-F-T for differentiating between children with and without brain-damage. The G-F-T is not included in Sattler's (2002) comprehensive review of psychological tests.

The rules for administering the Copying Task for the Koppitz and the G-F-T systems are similar but not identical. Both systems present each card individually and it is available for the child to see for as long as required until the child indicates he or she is finished copying. With the Koppitz method the child can do all the figures on one page and can rotate the paper if they choose. With the G-F-T system each drawing is copied using a #2 pencil with no eraser on a separate piece of A4 paper with a vertical line drawn along the left margin 1" from the page edge. The child is free to copy the stimulus anywhere on the paper, but is prevented from changing the orientation of the paper. Testing continues in this manner until all nine designs are presented and copied. With both systems, the figures are presented sequentially as each figure is completed.

The scoring systems for the Koppitz and G-F-T systems also differ. The G-F-T system requires careful analysis of the angles and rotations. The Koppitz scoring is less rigorous. Scoring rules for the G-F-T Copying Task have been outlined by Schlange and colleagues (1977). The Koppitz scoring method employs the use of global criteria applied to each design, but the G-F-T scoring method uses four to five specific criteria applicable for each design. The criteria used in the Koppitz system include the presence or absence of certain elements in the design and the special relationship between the elements. The criteria used by the G-F-T system require the geometric measuring of elements of the design as well as the spatial relationship of those elements. Each protocol required between 45 minutes and 1 hour to complete the scoring using the G-F-T system.

Reproduction Task—An optional *Reproduction Task* may also be added to the Bender. After all of the design cards have been shown and the copying is completed, the cards are removed and a clean piece of A4 paper is presented to the child. He or she is then asked to draw on the paper as many of the Bender design stimuli as can be recalled without seeing the stimulus cards again. The task ends when the child indicates he or she is finished. The Reproduction Task is typically used in clinical settings. The Reproduction Task for each figure is scored as correct if the child's reproduced figure approximates the stimulus card depiction. Detailed scoring rules for the Reproduction Task are not described by Sattler (2002).

Administration and Scoring in the SCDS—We followed the practice described in the literature for administering the G-F-T version of the Bender and scored it using the specific criteria reported for this method. This was the same method reported for the Faeroes study (Grandjean, et al., 1997). We followed the G-F-T scoring system for the Copying Task. For the Reproduction Task we scored the drawing correct if the drawing of the figure resembled the original. The number of recognizable figures was summed to yield a total recall score. The best possible score was a total of nine.

Study Design

The SCDS Main Cohort of mother-child pairs was enrolled in 1989–1990 during the child's sixth month of life. Hair was taken from the mothers at or near the time of delivery and again at enrollment (six months post-delivery). We analyzed the hair sample that recapitulated the longest pregnancy time period. The children were then followed serially with neurodevelopmental evaluations beginning at enrollment, and repeated at 19, 29, 66, and 107 months of age. The first Bender was administered at the 66 month visit using the Koppitz rules of administration and without the Reproduction Task. The second Bender was administered at age 10.7 years so that the Reproduction Task could be given and the test could be scored using the protocols of the G-F-T system. A total of 613 children participated.

Testing took place at the Child Development Centre at the Victoria Hospital, Victoria, Mahé, Republic of the Seychelles (the same testing venue used for previous cohort evaluations). We followed the G-F-T system of administration and scoring outlined by Shlange and colleagues (1972a). Subjects were tested, starting with the oldest child. Each child was given first the Copying Task. The Reproduction Task was given immediately after the child completed the copying task. We followed the specific protocol described by Sattler (2002). Following completion of the test, the child's protocol was retained in the Child Development Centre until transported to Rochester for scoring.

Training the Scorer—The second author (JR) completed a three-week long training course dealing with administration and scoring of the Bender using the G-F-T system. The course consisted of a series of tutorial sessions followed by scoring of actual protocols with feedback from the tutor. The training took place in Aarhus, Denmark and was conducted by the third author (ONH), who also scored some of the protocols from the Faeroese study (see Grandjean, et al., 1997).

Scoring—All test protocols were scored in the order of testing by hand by the second author (JR). The scorer was blinded regarding the subject's identity, MeHg exposure, and earlier score on the Bender. Scoring reliability was determined on the Copying Task protocols. The tutor (ONH) scored twelve percent of randomly selected tests. The selected protocols were assigned blinded IDs and sent to Denmark for scoring. Once scored, the protocols were returned to Rochester and the results entered into the SCDS database.

Dosimetry—Prenatal MeHg exposure was measured by determining the average maternal hair Hg in hair growing during pregnancy. For each hair sample, total and inorganic Hg was measured using the Magos reagents (Cernichiari, et al., 1995). This biomarker is known to correlate with infant brain Hg levels (Cernichiari, et al., 1995) and is believed to reflect the species of Hg that is transported across the blood-brain barrier (Clarkson & Magos, 2006). It is not known if this relationship exists for other biomarkers like cord blood.

Our primary analyses of data collected at 66 months (Davidson et al., 1998) and at 9 years of age (Myers et al., 2003) also included a measure of recent postnatal exposure. Postnatal exposure was measured as the MeHg level in the one-centimeter of hair immediately adjacent to the scalp. In the present study, we included the postnatal exposure value from the 107 month assessment as a covariate² since prenatal and postnatal exposures are not correlated (Davidson, et al., 1998).

Mercury values from the SCDS have always been reported on a linear scale. Transformation has not been considered necessary. This decision differed from the approach followed by the Faeroese group, which used log-transformed values based on cord blood.

Statistical Analysis—The endpoints in this study were (1) total G-F-T Copying Task errors; and (2) total correctly reproduced figures on the Reproduction Task. For each endpoint, we performed a maximum of three linear-regression analyses for prenatal MeHg exposure using SAS version 8.2. For all analyses, the principal predictor variable was prenatal MeHg exposure, expressed as a continuous variable.

Primary Analysis—The primary analysis plan used by Myers and colleagues (2003) was repeated in the present study with these new endpoints. That plan called for adjustment of the association between each endpoint and prenatal MeHg exposure for potential confounding variables. Covariates that were believed to affect development were considered in the analyses. These included sex, maternal age (in years), the child's medical history (positive if the child was born with intrauterine growth retardation or had a head circumference greater than 2 standard deviations from the mean), the child's age at testing, the tester who administered the Bender, the preschool version of the Home Observation for Measurement of the Environment (HOME), caregiver intelligence (Matrices subtest of the Kaufman Brief Intelligence Test or K-Bit), and the Hollingshead measure of socioeconomic status (SES), the Family Resource Scale (FRS) and the Henderson Environmental Learning Profile Scale (HELPS) to measure the quality of stimulation in the current home environment. We also adjusted for recent postnatal MeHg exposure.

The child's hearing status measured by audiometry at age 9 years was also included as a covariate. Behavioral audiologic pure-tone threshold testing was completed on each ear at octave intervals from 500–8000 Hz (500, 1000, 2000, 4000 and 8000 Hz). In addition, all subjects received tympanometric testing to assess the pathologic status of the middle ear system. The audiometry scores were categorized into two groups (≤ 25 dB and > 25 dB).

All covariates were treated as continuous variables except for the HOME, and SES scores which were categorized as in previous analyses (Davidson, et al., 1998). All primary analysis models used the same list of covariates. The SCDS statistical analysis strategy has always been to specify covariates *a priori* based upon the expectation that each may influence developmental outcomes. This approach allows us to examine the effects of all covariates on

²Postnatal hair was collected when the cohort was examined at 107 months of age (see Myers, et al., 2003) and analyzed at that time. Funds were not available to repeat this procedure when the present study commenced one year and 8 months later. So the postnatal exposure measure at 107 months was used in the present study.

each endpoint and evaluate whether or not the expected effects occurred. This approach provides at least some help in limiting Type I statistical errors.

Since differential effects of prenatal exposure to MeHg on males and females have been reported, every model was run first with and then without a MeHg by sex interaction term for both prenatal and recent postnatal exposure. We assessed the model with interactions first. If neither interaction was significant, we report the model without interactions. If only the prenatal or postnatal interaction were significant, we reran the model, dropping only the non-significant interaction.

All statistically significant regression models were assessed for statistical outliers (scores with standardized residual values >3 or <-3). As described later, there was one outlier in the linear model for the Reproduction Task and no outliers for the Copying Task. The model with the outlier was rerun without the outlying value and the results with and without were compared and both are reported. There were no influential data points identified in any analysis.

In addition to linear regression, we also fitted semiparametric models to explore the possibility that a nonlinear association existed between MeHg exposure and the endpoints. A Generalized Additive Modeling (GAM) approach (Hastie and Tibshirani, 1990) was employed for both the G-F-T Copying Task and the Reproduction Task scores by allowing non-linear trends for all continuous independent variables including prenatal MeHg exposure. In addition, we used a proportional odds model (McCullagh and Nelder 1989) for the Reproduction Task because it yielded categorical scores³.

Secondary Analysis—Some of the covariates used in the primary analysis would not be expected to have a large independent influence on the Bender Copying or Reproduction tasks. Thus, there was a risk that the primary analysis could have been over adjusted. For this reason, we repeated the primary analysis adjusting only for covariates that might be expected to influence the Copying and the Reproduction Tasks. The covariates in this secondary analysis included: Prenatal MeHg, Postnatal MeHg, Maternal Age, Age at Testing, Tester, HOME score, SES and Sex. Both linear and proportional odds analyses were repeated following the same analysis plan described earlier.

We also re-ran both the linear and proportional odds models for the Reproduction Task and the linear model for the Copying Task without correcting for postnatal exposure to more closely approximate the models reported by Grandjean and colleagues (1997).

Results

The mean prenatal MeHg exposure for the cohort participating in this study ($n = 613$) was 6.83 ppm (SD = 4.4 ppm). The mean recent postnatal exposure for this cohort was 6.07 ppm (SD = 3.5 ppm). Although the G-F-T Copying Task was administered to all cohort subjects, scored data were available on only a subset of 346 subjects⁴. The mean prenatal MeHg exposure for these 346 subjects was 7.00 ppm (SD = 4.6 ppm) and their mean postnatal exposure was 6.15 ppm (SD = 3.6 ppm).

Table 1 shows the summary statistics for the two endpoints of interest, the G-F-T Copying Task score and the Reproduction Task score, classified by arbitrarily determined MeHg

³Only 1 subject achieved a score of 1 and only three subjects received a score of 9 on the Reproduction Task. These subjects were grouped with those who scored 2 and 8 respectively. The PO model is a linear model for the log of the odds for the cumulative response probabilities $P(\text{score} \leq j)$, $j=2, \dots, 7$, [the cumulative probability $P(\text{score} \leq 8)$ is 1]. The parameters in the PO model describing the effects of prenatal MeHg exposure and other covariates are independent of j .

⁴The substantial time commitment to scoring G-F-T protocols limited the total number of protocols that could be scored.

exposure groupings. These data suggest little difference occurred in G-F-T Copying Task scores as prenatal exposure increased. There was a small decrement in Reproduction Task scores present with increasing MeHg groupings.

There were only six subjects in the abnormal hearing group for the Reproduction Task score analysis and none for the Copying Task score analysis. Therefore the models were analyzed with the abnormal hearing category combined with the borderline hearing category.

Reliability of G-F-T Copying Task Scoring

Percent agreement for G-F-T Copying Task scores between the second and fourth authors were computed for 42 subjects (12% of the subjects who had G-F-T Copying Task scores). The mean agreement was 79.6% (range = 47.6 to 100%). Primary Regression Analysis for the Copying Task:

Because we had only 346 valid observations for the G-F-T Copying Task scores, we used two-sample Student *t*-tests and χ^2 tests to compare the group that had copying error scores with the group that did not. These results indicated that the two groups did not differ in their mean pre- or postnatal MeHg exposure levels. They did differ in that those who completed the G-F-T Copying Task had a significantly lower mean value for the Family Resources Scale, maternal IQ, and Hollingshead SES and a significantly higher maternal age.

Regression Analyses: G-F-T Copying Task Scores

Table 2 shows the results of the multiple linear regression analysis involving the G-F-T Copying Task scores. The models with both interaction terms included indicated no significant prenatal interaction effects. The overall model with postnatal interaction effects included was significant [$F(20, 258) = 2.88, p = 0.0001, R^2 = 0.18$] and indicated no significant effect of prenatal exposure [$F(1, 277) = 1.07, p = 0.30$]. There was a significant sex by postnatal MeHg exposure effect [$F(1, 277) = 6.64, p = 0.01$] with increasing G-F-T Copying Errors as MeHg increased, but only for female subjects ($p = 0.01$). Finally, G-F-T Copying Task error scores were inversely related to maternal IQ ($p = 0.0002$) but not to either SES or HOME scores.

G-F-T Copying Task Non-linear Analysis Results—The GAM modeling indicated that neither pre- nor postnatal non-linear components were significant, implying that the linear models were adequate.

Regression Analyses for the Reproduction Task Scores

The analyses for Reproduction Task scores are summarized in Table 3. The Reproduction Task score represented the number of drawings judged to be correctly reproduced out of a total of 9.

Columns 2 and 3 of Table 3 show the results of the linear regression analysis of the Reproduction Task scores. Neither the prenatal MeHg by sex nor the postnatal MeHg by sex interaction was significant in any model. Therefore, the final analysis involved a model containing only main effects (column 2). This differs from the analyses presented in Table 2, which included a significant postnatal MeHg by sex interaction. The overall model was significant [$F(19, 519) = 2.30, p = 0.002, R^2 = 0.08$]. There was a significant adverse effect of prenatal exposure [$F(1, 537) = 3.90, p = 0.04$]. Several covariates typically associated with child cognition were also significant, including the home environment (HOME) and SES. These indicated associations between better Reproduction Task scores and higher social status and between lower Reproduction Task scores and lower home stimulation as measured by the HOME. Unlike the results of the analysis for the G-F-T Copying Task, maternal IQ did not affect Reproduction Task scores. There was only one statistical outlier and when the model

was re-run with that value removed, the prenatal MeHg effect was no longer significant. The outlier has a studentized residual of 3.02. The child had the highest possible memory score of 9 while the estimate from the linear model was 4.8. This child had a very low prenatal mercury value of 1.6 ppm. Given that this child was in the low exposure range, we did not think further statistical analysis was needed. Figure 1 depicts a partial residual plot of the prenatal MeHg effect that was found for the Reproduction score, derived from the analysis that included this outlier.

Reproduction Task Non-Linear Analysis Results—The proportional odds modeling indicated that neither prenatal nor postnatal non-linear components were significant, implying that the linear models were adequate. The test of proportionality was not significant ($p = 0.54$) indicating the assumption of proportionality was reasonable. The results were consistent with the linear model analysis with a coefficient of 0.04 ($p = 0.03$) for prenatal MeHg⁵.

Secondary Analyses

The use of a reduced list of covariates in the linear and proportional odds models for the Reproduction Task resulted in associations with Prenatal and Postnatal MeHg of >0.05 . The reduced model for the linear analysis of the Copying Task with Prenatal MeHg and Postnatal MeHg exposure also had an association of >0.05 . Re-running our models without including postnatal MeHg exposure also did not alter the results of the primary analyses.

Discussion

In this sample from a population exposed to MeHg prenatally primarily from fish consumption, we found no association with the Bender Copying Task using the G-F-T administration and scoring procedures. We did find an adverse association between the Reproduction Task and prenatal MeHg exposure. However, when the single outlier was removed the association lost significance. The Faroese group (Grandjean et al., 1997) also reported an adverse association between The Reproduction Task and children's prenatal MeHg exposure at exposure levels that were lower than those in the Seychelles. This is the second endpoint from among over 70 where the SCDS has found an adverse association with prenatal MeHg exposure and the first endpoint where the Faroese study and the SCDS have found the same result. Both studies seem to have found different outcomes for the G-F-T Copying Task and the Reproduction Task. There were different patterns of covariate effects on each of these endpoints in our study, suggesting that the two tasks themselves may tap different skill sets and cognitive domains.

We also found an adverse association between recent postnatal MeHg exposure and the Copying Task scores using the G-F-T method. However, this was only present among female students. This association varies from our earlier results that showed a decrease in the Copying Task errors with increasing postnatal exposure using the Koppitz method. This result was attributed to an unmeasured covariate, which we hypothesized might be nutrients in fish (Davidson, et al., 1998). Recent results have suggested that fish consumption (used as a surrogate for dietary nutrients in fish) may have a beneficial effect on child development even in the presence of MeHg (Budtz-Jørgensen, Grandjean & Weihe, 2007) or may not (Daniels, 2004). Our recent studies have suggested that -3 and -6 long-chain polyunsaturated acids present in fish and fruits may modulate or suppress the adverse effects of MeHg (Davidson, et al., in review; Strain, et al., in review). Neither our study nor the Faeroese study (Grandjean, et al., 1997) corrected for fish intake or for the effects of nutrients in earlier studies. Indeed, Davidson and colleagues (in review) found no correlation between key nutrients in fish and

⁵In the Proportional Odds model formulation in SAS, positive values of the parameters lead to a decrease of probability in the higher-numbered categories.

fish meals per week. They concluded that fish consumption cannot be considered as a surrogate for maternal dietary and nutrient status. Moreover, we know of no reason that a change in scoring strategy would produce such a different result, but very little data are available on postnatal MeHg exposure effects. We are not able to interpret this finding and it awaits further clarification. There is no biological basis for one to expect a gender by postnatal MeHg interaction. We also cannot attribute the gender effects seen in this study to multiplicity because only two endpoints were tested. Nevertheless, this result may merit further examination

Other investigators (Grandjean et al., 1997) have reported that prenatal MeHg exposure among Faeroese children was associated with increasing Copying Task errors on the Bender. However, using the same administration and scoring system as the Faeroese group we found different results.

Despite using a different administration methodology and scoring technique, the present data continue to support the conclusion that prenatal MeHg does not appear to affect visual spatial and visual motor skills required for copying geometric line drawings in this population. The results of this study are similar to those we reported earlier, namely no association present between prenatal MeHg exposure from fish consumption and Bender Copying Task scores using the Koppitz scoring method in this population (Davidson, et al., 1998). Moreover, a similar copying test assessing developmental levels of visual motor integration of the same children using the Beery-Butkenica Visual Motor Integration Test when they were 107 m old (Myers, et al., 2003) also showed no influence of prenatal MeHg exposure. These results suggest an absence of evidence for any latent neurotoxicity.

The present study also showed that prenatal MeHg exposure was negatively associated with the child's ability to reproduce from memory at least the general characteristics of drawings copied earlier. This same outcome was reported by the Faeroese group (Grandjean, et al., 1997). It is also the first time we have found an association for an endpoint measuring a memory function. In particular, Palumbo (2000) and colleagues found (1) no association between prenatal exposure and memory functions as measured by the McCarthy Scales of Children's Abilities (MSCA) and (2) increasing MSCA memory scores with increasing postnatal exposure. Table 1 suggests that Reproduction Task scores for exposure levels above 10 ppm dropped slightly below those for prenatal exposure levels below 10 ppm, where most of our exposures occurred. This may suggest that spatial memory (presumed necessary for reproduction of the drawings) may be affected by higher prenatal MeHg exposures rather than those in the range generally found in non-fish consuming populations. Moreover, Table 3 shows that this association was no longer significant when one outlier was removed from the analysis, suggesting that it was an influential point. A similar finding of a single value making a major difference was reported from New Zealand where the reanalysis of that data by Crump and colleagues found a significant adverse association between prenatal MeHg exposure and outcomes only when the child with the highest mercury value was dropped from the analysis (Crump et al., 1998). However, dropping subjects with higher mercury values and presumably at higher risk seems counterintuitive. In any case, this finding does replicate the Faeroese study's report using the same endpoint (Grandjean, et al., 1997) and merits further study.

Conclusions

This study found no association between prenatal MeHg exposure from fish consumption and the Bender Copying Task using the G-T-F method of administration and scoring using either linear or proportional odds analysis. However, we did find a significant adverse association present between prenatal exposure and the Reproduction Task when the single outlier was included in the analysis. Our results were affected in some cases by inclusion or exclusion of a single influential point, and the study may have been slightly underpowered. We therefore

view the outcomes and conclusions with some caution. This study is consistent with our earlier findings in the SCDS and does not support an adverse association between prenatal MeHg exposure at the levels studied and test outcomes on the Bender.

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Figure 1.

Plot of Partial Residuals for the Bender Reproduction Task Scores. Each score is adjusted for all covariates except prenatal MeHg exposure. The point marked as “A” is the outlier. The solid line indicates the linear relationship with all scores included and the dashed line with the outlier excluded.

Table 1
Mean (SD) G-F-T Copying Task and Reproduction Task Scores by MeHg Grouping
Mean (SD)[n] Score by Prenatal MeHg Exposure Grouping (ppm)

Bender Task	≤ 3	>3-6	>6-9	>9-12	>12
G-F-T Copying Task (Σ Errors)	21.3 (4.6) [72]	22.0 (5.5) [97]	21.4 (4.9) [81]	21.7 (4.4) [43]	21.5 (5.0) [53]
Reproduction Task (Σ Correct out of 9)	5.3 (1.5) [132]	5.2 (1.4) [179]	5.4 (1.4) [136]	4.9 (1.5) [84]	5.1 (1.5) [82]

Table 2**G-F-T Copying Task Score Analysis Results**

Parameter Estimate	Linear Model [*]		
	Regression Coefficient	SE	p-value
Prenatal MeHg	0.07	0.06	0.30
Sex, female	−0.03	1.13	0.98
Sex × Postnatal MeHg			
Female × Postnatal MeHg	0.30	0.12	0.01
Male × Postnatal MeHg	−0.13	0.12	0.28
Child's medical history [‡]	0.31	0.79	0.69
Child's age at testing	−2.79	1.51	0.06
Maternal age	−0.05	0.05	0.29
Family Resource Scale	−0.003	0.01	0.84
HELPS	−0.04	0.03	0.21
Maternal IQ (K-Bit)	−0.08	0.02	0.0002
Hearing level (<=25 dB)	−0.11	1.50	0.94
HOME [P for overall test]			0.63
Low (<31)	0.74	0.78	0.34
Medium (31–35)	0.28	0.73	0.70
SES [P for overall test]			0.69
Unskilled	−0.33	1.03	0.75
Semiskilled	−1.003	1.03	0.33
Skilled	−0.29	1.01	0.78
Family Status [P for overall test]			0.96
0 Bio parents	−0.32	1.55	0.84
1 Bio parent	−0.18	1.55	0.91
Tester [P for overall test]			0.72
1	−0.31	0.67	0.65
2	−0.54	0.68	0.43
3	0.28	0.38	0.45

* n=279. At least one covariate was missing for a total of 67 subjects.

[‡] Reference group is negative

Table 3

Reproduction Task Score Regression Analyses Results

Parameter Estimate	Linear Model with Outlier (n=501)		Linear Model Outlier Removed (n=500)	
	R ² = 0.08	SE	R ² = 0.09	SE
	Regression Coefficient	p-value	Regression Coefficient	p-value
Prenatal MeHg	-0.03	0.01	-0.03	0.01
Postnatal MeHg	0.01	0.02	0.009	0.02
Sex (Female)	0.08	0.07	0.09	0.06
Sex (Male)	-0.08	0.07	-0.09	0.06
Child's medical history				
Negative	-0.11	0.09	-0.08	0.09
Positive	0.11	0.09	0.08	0.09
Child's age at testing	1.04	0.37	1.13	0.37
Maternal age	-0.01	0.01	-0.01	0.01
Family Resource Scale	0.0002	0.003	0.0007	0.003
HELPS	-0.0002	0.008	0.0005	0.008
Maternal IQ (K-Bit)	0.003	0.005	0.003	0.005
Hearing level				
Normal (≤25)	0.33	0.15	0.33	0.15
Borderline or Abnormal (>25)	-0.33	0.15	-0.33	0.15
HOME [P for overall test]				
Low	-0.03	0.10	-0.04	0.10
Medium	0.20	0.09	0.21	0.09
High	-0.17	0.10	-0.17	0.10
SES [P for overall test]				
Unskilled	-0.28	0.12	-0.29	0.12
Semiskilled	0.10	0.11	0.11	0.11
Skilled	-0.11	0.13	-0.10	0.12
Professional	0.29	0.16	0.28	0.15
Family Status [P for overall test]				
No Biological parents	-0.26	0.14	-0.25	0.14
One Biological parent	-0.19	0.14	-0.19	0.14
Two Biological parents	0.45	0.24	0.44	0.23
Tester [P for overall test]				
Tester 1	0.26	0.09	0.27	0.09
Tester 2	-0.13	0.10	-0.13	0.10
Tester 3	-0.13	0.09	-0.15	0.09