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Fish Consumption and Prenatal Methylmercury Exposure: Cognitive and Behavioral Outcomes in the Main Cohort at 17 Years from the Seychelles Child Development Study

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Abstract

Introduction—People worldwide depend upon daily fish consumption as a major source of protein and other nutrients. Fish are high in nutrients essential for normal brain development, but they also contain methylmercury (MeHg), a neurotoxicant. Our studies in a population consuming fish daily have indicated no consistent pattern of adverse associations between prenatal MeHg and children's development. For some endpoints we found performance improved with increasing prenatal exposure to MeHg. Follow up studies indicate this association is related to the beneficial nutrients present in fish.

Objectives—To determine if the absence of adverse outcomes and the presence of beneficial associations between prenatal MeHg and developmental outcomes previously reported persists into adolescence.

Methods—This study was conducted on the Main Cohort of the Seychelles Child Development Study (SCDS). We examined the association between prenatal MeHg exposure and subjects' performance at 17 years of age on 27 endpoints. The test battery included the Wisconsin Card Sorting Test (WCST), the California Verbal Learning Test (CVLT), the Woodcock-Johnson (W-J-II) Achievement Test, subtests of the Cambridge Neuropsychological Test Automated Battery (CANTAB), and measures of problematic behaviors. Analyses for all endpoints were adjusted for postnatal MeHg, sex, socioeconomic status, maternal IQ, and child's age at testing and the child's IQ was added for problematic behavioral endpoints.

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Results—Mean prenatal MeHg exposure was 6.9 ppm. There was no association between prenatal MeHg and 21 endpoints. Increasing prenatal MeHg was associated with better scores on four endpoints (higher W-J-II math calculation scores, reduced numbers of trials on the Intra-Extradimensional Shift Set of the CANTAB, fewer reports of substance use and incidents of and referrals for problematic behaviors in school. Increasing prenatal MeHg was adversely associated with one level of referrals to a school counselor.

Conclusions—At age 17 years there was no consistent pattern of adverse associations present between prenatal MeHg exposure and detailed domain specific neurocognitive and behavioral testing. There continues to be evidence of improved performance on some endpoints as prenatal MeHg exposure increases in the range studied, a finding that appears to reflect the role of beneficial nutrients present in fish as demonstrated previously in younger subjects. These findings suggest that ocean fish consumption during pregnancy is important for the health and development of children and that the benefits are long lasting.

The United Nations Food and Agriculture Organization estimates that "…globally, fish provides more than 1.5 billion people with almost 20 percent of their average *per capita* intake of animal protein, and nearly 3.0 billion people with 15 percent of such" (Food and Agriculture Organization of the United Nations 2008). All fish contain small amounts of methylmercury (MeHg). High exposures to MeHg are known to be related to adverse neurodevelopmental consequences and the fetus is known to be especially vulnerable. However, the exposure level at which such effects can first be detected is not presently known and epidemiologic studies of MeHg exposure from fish consumption have not provided clear answers. Some studies report adverse associations at low levels of exposure albeit in populations exposed to a diet high in pilot whale meat and blubber (Grandjean et al., 1997) or shark (Kjellstrom et al., 1986a, Kjellstrom et al., 1986b) while others with just ocean fish consumption do not (Davidson et al., 1998, Myers et al., 2003). Fish are also high in nutrients such as n-3 and n-6 long chain polyunsaturated fatty acids (LCPUFA), which are essential for normal brain development (Food and Agriculture Organization of the United Nations 2008). Higher fish consumption during pregnancy with presumably higher LCPUFA intake has been associated with beneficial neurodevelopmental outcomes in offspring (Hibbeln et al., 2007, Jacobson et al., 2008, Oken et al., 2008).

The Seychelles Child Development Study (SCDS) is a longitudinal cohort study designed to test the hypothesis that prenatal MeHg exposure from a diet high in fish is associated with adverse neurodevelopmental outcomes. The Seychellois consume ocean fish daily and do not consume sea mammals or fresh water fish. In addition, ocean fish in Seychelles has a MeHg content similar to commercially available fish in most parts of the world. Comprehensive neurodevelopmental assessments at seven ages between 6 months and 10 years have found no evidence to support the hypothesis that prenatal MeHg exposure from fish consumption is associated with delays in neurodevelopment. We have found no association between prenatal MeHg exposure and the majority of the 44 primary endpoints examined prior to the present study. Adverse associations have rarely been found. In contrast, we have found improving performance associated with increasing prenatal MeHg in the range achieved by fish consumption observed in some endpoints as early as 29 months (Davidson et al., 1995) and still present at 10 years of age (Myers et al., 2003). These findings have been attributed to the influence of the nutritional benefits of fish, but nutritional status during pregnancy was not measured in the Main Study cohort. However, maternal nutritional status was measured in a subsequent SCDS birth cohort (Davidson et al., 2008, Stokes-Riner et al., 2010, Strain et al., 2008). This study revealed a beneficial association between maternal n-3 LCPUFA status during pregnancy and the Bayley Scales of Infant Development (BSID-II) Psychomotor Index (PDI) and an adverse association between prenatal MeHg exposure and this same test only when nutrients were included in

the models (Stokes-Riner et al., 2010, Strain et al., 2008). These associations did not change significantly from 9 to 30 months (Stokes-Riner et al., 2010).

It is currently unclear if the lack of adverse associations or presence of beneficial associations with increasing prenatal MeHg exposure will persist into adolescence. It is also unknown whether these results might extend to non-cognitive outcomes such as problematic behaviors. Many of the neurocognitive tasks used in our earlier studies concurrently tap multiple skills which are difficult to separately evaluate until children reach full maturity. The current study of young adults from the SCDS Main Cohort examined the association of prenatal MeHg exposure and specific domains of learning, reversal learning, perseveration, working memory, and attention along with measures of scholastic achievement and problematic behaviors.

Method

Participants and MeHg Exposure

Of the 779 Seychellois infant-mother pairs originally enrolled in 1989–1990 (Marsh et al., 1995), 705 subjects were still eligible for this evaluation. Seventy-four subjects were excluded for specific reasons including lack of prenatal exposure data, medical conditions that might affect development (Davidson et al., 1995), or withdrawal from the study. Prenatal MeHg exposure was measured in maternal hair samples as previously described (Cernichiari et al., 1995). Recent postnatal exposure was measured in a 1-cm length of each child's hair closest to the scalp taken at the time of testing. A total of 600 subjects ranging in age from 15.7 to 18.4 years participated in the test battery. However, full data sets were available for 371 to 462 depending upon the specific outcome measure.

Neurocognitive and Behavioral Testing Procedures

Neurocognitive and behavioral testing was carried out on individual participants in a quiet dedicated test room. Subjects first completed a confidential behavior questionnaire (adapted specifically for the Seychellois culture with items from the WHO global school-based student health survey and the US Centers for Disease Control and Prevention *Youth Risk Behavior Survey* (Centers for Disease Control and Prevention 2003, Prevention). The questionnaire assessed aspects of substance use, anti-social behavior, injuries and mental health. Subsequently, paper-based versions of the California Verbal Learning Test (CVLT) and five subtests of the Woodcock-Johnson Test of Scholastic Achievement-II (W-J-II) (passage comprehension, calculation, letter-word, applied problems and math fluency) were administered.

Paper and pencil testing was followed by computer-based administration of selected subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the Wisconsin Card Sorting Test (WCST) with minimal instructions in Creole or English, dependent upon the participant. The CANTAB battery included multiple tests of three different domains including learning and reversal learning, memory, and attention. The battery was comprised of eight tests each of which has several endpoints: Intra-Extra Dimensional Shift Set (IED), Paired Associates Learning (PAL), Delayed Match to Sample (DMS), Pattern Recognition Memory (PRM), Spatial Recognition Memory (SRM), Spatial Working Memory (SWM), Reaction Time (RT) and Rapid Visual Information Processing (RVP). The CANTAB tests are sensitive and specific for detecting outcomes typically associated with neurotoxicant exposure (Davidson et al., 2006). School records were reviewed for information about a student's referrals to a school counselor for a problematic behavior and any further actions resulting from referrals.

Covariates

All models were adjusted for sex, socioeconomic status (9 year old Hollingshead Four-Factor Socioeconomic Status modified for use in the Seychelles), maternal intelligence (Kaufman Brief Intelligence Test Matrices; K-BIT) and recent postnatal MeHg exposure. All neurocognitive endpoints were also adjusted for the child's age at testing. The YRBS and problematic behavior endpoints were also adjusted for the child's WISC-III Full Scale IQ measured at 107 months (Myers et al., 2003). Prenatal nutritional status and maternal dietary intake were not measured in this cohort.

Statistical Analysis

Primary endpoints for each W-J-II achievement and CANTAB test and for the CVLT and the WCST outcomes were first formulated, and associations of each with prenatal MeHg exposure examined using covariate-adjusted linear regression (log transformed if the assumption of normally distributed errors with constant variance was violated). All models first included sex by prenatal MeHg and sex by postnatal MeHg interaction terms and if not significant rerun without the interaction terms. Interactions are reported where significant. Models were run with and without influential points (defined as observations with a Cook's distance greater than 0.5), and with and without any outliers which were extreme compared to the other observations. Four subjects who tested as color blind were excluded from the CANTAB analyses.

Substance use, antisocial behavior, injuries and mental health responses obtained from the YRBS, incidents per year reported to a school counselor and subsequent referrals per year to a school counselor for action were categorized by the number of positive responses or frequency of occurrence where higher numbers reflect riskier behavior. These distributions were classified into four to six categories and fit using multinomial logistic regression. Category 0 (no problematic behaviors) served as the baseline, and negative coefficients indicated improved behavior. Multinomial logistic regression analyses for prenatal MeHg exposure using all the covariates were fit for each endpoint. Each model was first run with prenatal MeHg by sex and postnatal by sex interaction term and if not significant, rerun without interactions. Models were examined for statistical outliers (scores with standardized residual values >3 or <–3). All models with outliers were rerun without the outliers and the results with and without outliers were compared.

Results

The means and SDs for all covariates and the neurodevelopmental endpoints are shown in Table 1a. The first five columns show data for the cohort members with a full set of covariates. The five columns to the right show data for remaining subjects who were excluded from analyses because they lacked a full set of covariates. The two groups appear comparable. By and large, scores are similar to a US reference sample (Davidson et al., 2006). The frequency distributions for the behavioral endpoints are shown in Table 1b. There are no norms for the behavioral questionnaire but distributions show declining numbers of subjects engage in risky behaviors, an expected result.

Among subjects with at least one neurocognitive endpoint and a full set of covariates, the mean prenatal exposure measured as total Hg was 6.9 ppm (n = 462, SD = 4.4 ppm; range 0.54 – 23 ppm). There were no influential points in any models, and model results from which outliers were removed were similar to results with all observations.

Regression analysis results are summarized in Tables 2a (neurodevelopmental endpoints) and 2b (behavioral endpoints). Increasing prenatal MeHg exposure was associated with a reduction in total trials to complete the CANTAB IED test (Figure 1 Panel A) with all

observations and after removal of four outliers ($p = 0.03$). Improved W-J-II Calculation scores were also associated with increasing prenatal MeHg exposure (Figure 1 Panel B).

Table 2b shows that the prenatal MeHg by sex interaction was significant for substance use and mental health, so associations were considered separately by sex. Prenatal MeHg was associated with reduced reports of substance use for males at two intermediate categories and females at the highest count of substance use behaviors. Prenatal MeHg exposure was also associated with significant reductions in the highest number of behavioral incidents reported to a school counselor with the significant association reflecting reductions at the highest level. There were no associations between prenatal MeHg and >3 referrals per year, but increasing exposure was associated with a significant increase in the likelihood of having 1–3 referrals to a school counselor compared to no referrals.

Covariates such as maternal IQ and SES were directly associated with test outcomes as expected. Sex associations were task specific and varied. Males generally responded more poorly than females. Recent postnatal MeHg exposure was not associated with any health behavior outcomes, but was associated with weaker performance on the W-J-II Passage Comprehension. We found negative coefficients for age-at testing for W-J-II Passage Comprehension, Applied Problems and Math Fluency subtests, indicating that scores decreased with increasing age within the age ranged of the subjects. Similar age-at-testing results were found for CANTAB PAL scores, DMS % Correct, 0 second delay and PRM endpoints (Table 2A). We are uncertain why this shift occurred within a relatively narrow age range. It most likely reflects the fact that at the later ages, the subjects are now out of school and may be less motivated to or interested in performing the tests to the maximal level of effort.

Discussion

We found improved performance or no association between prenatal MeHg exposure and 26 out of 27 primary endpoints measured in this study. We found only one adverse association with prenatal MeHg and this appeared in the lowest category of a multi-category endpoint (referrals to a school counselor), but there was no association for higher categories that represented more frequent referrals. These results do not support the hypothesis that prenatal MeHg exposure at levels achieved by fish consumption adversely affect adolescent development and are consistent with our earlier reports. On repeated and increasingly more detailed and extensive evaluations, we have found no consistent pattern of adverse associations between prenatal MeHg exposure and developmental outcomes. We have now studied over 70 primary and secondary endpoints including tests of global and specific neurocognitive domains, achievement and problematic behaviors. This finding is reassuring because the MeHg exposure in the SCDS Main Cohort is one of the highest in the world, over ten times that of samples in the United States (Schober et al., 2003; McDowell, et al., 2004) and Sweden (Björnberg, et al., 2003; 2005). Our cohort's mean prenatal hair MeHg level of 6.9 ppm was also higher than the median of 4.5 ppm reported in the Faeroe Islands Study (Grandjean, et al., 1997).

As in our earlier studies (Davidson et al., 1998, Myers et al., 2003), we found improved performance with increasing prenatal MeHg exposure for some endpoints. There is no reason to believe that MeHg exposure at any concentration should improve performance, so it is most likely that prenatal MeHg measurements are a surrogate marker for fish consumption. For humans, fish is the primary source for some LCPUFA that are essential for neural development. The human body has a very limited ability to synthesize the n-3 LCPUFA docosahexaenoic acid (DHA) and eicosapentanoic acid (EPA), and fish is the primary human dietary source. These n-3 LCPUFA have been shown to improve cognitive

and behavioral function in young children (Decsi and Koletzko 2005, Dunstan et al., 2008, Helland et al., 2003, Judge et al., 2007). Although maternal nutrient levels were not measured in this cohort, we did measure them in another SCDS cohort. In that study we found beneficial associations between total maternal n-3 LCPUFA and the BSID-II PDI score at 9 months and the association was further strengthened when the prenatal MeHg exposure level was included in the regression model (Davidson et al., 1998). That study also found an adverse association with prenatal MeHg when nutrients were included in the model. Other studies have reported associations between total fish consumption and developmental outcomes, but they did not specifically measure LCPUFA (Davidson et al., 2006, Decsi and Koletzko 2005, Dunstan et al., 2008, Schober et al., 2003).

If improved performance with increasing prenatal MeHg exposure indeed reflects the influence of n-3 LCPUFA or other benefits associated with fish consumption on development, then these findings would suggest a modest but prolonged duration of such benefits. Improved scores on the W-J-II Calculation subtest and CANTAB IED total trials indicate enhanced problem solving ability. Our findings indicate benefits that are behavioral domain specific and extend to behaviors likely to positively influence a successful life trajectory.

Recent postnatal MeHg has been included in our analyses since fish consumption in Seychelles starts early and by age 5 years is fairly consistent. We have reported both adverse and beneficial associations with postnatal MeHg exposure when the Main Cohort was evaluated at earlier ages (Myers et al., 2009). There was an adverse association with one of 27 endpoints in this study and likely represents a chance finding. We are cautious in interpreting associations with postnatal exposure since the SCDS was designed to determine associations with prenatal exposure. In addition, our postnatal measure is a convenience sample representing only one month exposure and there is no accepted metric of postnatal exposure.

Strengths of the current study include its high prenatal MeHg exposure, large cohort, high retention rate, longitudinal design, repeated testing at multiple ages and extensive characterization of the Seychellois study population. In addition, the tests we used have both clinical and environmental validity and include ones that are behavioral domain specific (Davidson et al., 2006). One limitation of this cohort study is the absence of maternal nutritional information which would permit a direct assessment of prenatal nutrition influence on subjects' development. We did not assay any biomarkers for maternal nutritional status during pregnancy, such as LCPUFA, nor did we collect any information on dietary behaviors. Fish are also high in selenium and when prepared in palm oil, as is the practice in the Seychelles, that may increase levels of vitamin E. Both selenium and vitamin E may act as antioxidants and reduce oxidative stress resulting from MeHg. These issues are being addressed in other Seychellois cohorts (Davidson et al., 2008, Strain et al., 2008).

The current findings are reassuring regarding the rewards and risks of fish consumption and indicate that exposure to MeHg during pregnancy from consumption of ocean fish is not adversely associated with neurocognitive and behavioral outcomes measured in late adolescence. Our findings should be of interest to policymakers and regulators as they formulate public health guidance concerning ocean fish consumption during pregnancy. Current guidelines appear to be limiting fish consumption by pregnant women (Bloomingdale et al., 2010, Oken et al., 2003) and thereby depriving the fetus of nutrients important to the developing brain.

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Highlights

- People worldwide depend upon daily fish consumption as a major source of protein and other nutrients.
- Fish are high in nutrients essential for normal brain development, but they also contain methylmercury (MeHg), a neurotoxicant.
- The objective of this study was to determine if the absence of adverse outcomes and the presence of beneficial associations between prenatal MeHg and developmental outcomes previously reported persists into adolescence.
- This study was conducted on the Main Cohort of the Seychelles Child Development Study (SCDS). We examined the association between prenatal MeHg exposure and subjects' performance at 17 years of age on 27 endpoints.
- There was no association between prenatal MeHg and 21 endpoints. Increasing prenatal MeHg was associated with better scores on four endpoints.
- These findings suggest that ocean fish consumption during pregnancy is important for the health and development of children and that the benefits are long lasting.

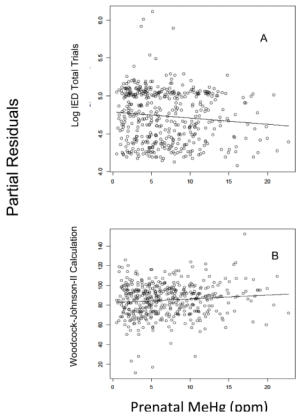

Figure 1.

Relationship between prenatal MeHg values and total trials from the IED test (panel A) and the Woodcock Johnson calculation subtest (panel B).

Points show the observed values. Lines show predicted values from the covariate-adjusted linear regression model for hypothetical individuals with the mean value of all other covariates. Both plots show improved performance as MeHg exposure increases in the range studied.

Table 1a

Summary Statistics for Covariates and Neurodevelopmental Endpoints

	Subjects with Full Covariates					Subjects with Missing Covariates				
	n	**mean**	**SD**	**min**	**max**	**n**	**mean**	**SD**	**min**	**max**
sex (male=1)	462	0.45	0.50	0.00	1.00	243	0.56	0.50	0.00	1.00
prenatal MeHg	462	6.89	4.40	0.54	22.74	243	6.50	4.64	0.63	26.73
postnatal MeHg	462	7.98	4.64	0.33	28.33	93	8.56	4.90	0.53	22.60
SES	462	25.63	10.87	3.00	58.00	158	22.82	10.99	3.00	58.00
Mother's IQ	462	81.29	14.88	47.00	125.00	135	76.97	15.84	45.00	118.00
child's age	462	17.14	0.47	15.74	18.36	138	17.26	0.52	15.74	18.37
CVLT short delay (scaled)	456	−0.65	1.25	−4.50	1.50	136	−0.84	1.25	−4.50	1.50
CVLT long delay (scaled)	456	−0.74	1.26	−4.50	1.50	136	−0.98	1.29	−4.50	1.50
WJ passage comprehension	400	76.59	20.35	1.00	143.00	123	72.71	21.31	1.00	117.00
WJ calculation	454	85.14	16.60	11.00	152.00	138	81.12	17.96	11.00	121.00
WJ letter-word	417	100.03	26.81	1.00	134.00	126	98.47	27.04	1.00	133.00
WJ applied problems	451	86.28	14.31	29.00	134.00	136	82.46	14.20	46.00	134.00
WJ math fluency	457	73.88	12.02	37.00	109.00	137	71.62	11.98	40.00	107.00
IED total trials	455	120.74	45.48	59.00	450.00	134	133.70	52.41	64.00	412.00
IED stages completed	455	8.19	1.11	0.00	9.00	134	7.96	1.37	1.00	9.00
IED pre-ED errors	455	9.94	6.45	3.00	55.00	134	10.90	6.68	4.00	45.00
IED completed stage errors	455	16.52	9.96	0.00	76.00	134	18.17	11.83	1.00	50.00
PAL total errors	455	9.48	9.16	0.00	99.00	134	12.54	19.18	0.00	174.00
PAL total trials	455	11.26	2.54	8.00	27.00	134	12.12	4.55	8.00	48.00
PAL stages completed	455	6.03	0.90	3.00	8.00	134	5.91	0.96	2.00	8.00
WCST total error (%)	420	29.25	26.83	0.00	96.00	127	29.46	26.74	0.00	94.00
WCST categories completed (%)	420	2.14	0.92	0.00	3.00	127	2.13	0.98	0.00	3.00
RTI simple reaction time	454	314.87	61.21	209.33	766.88	134	321.87	86.52	198.11	807.29
RTI 5-choice reaction time	454	339.50	54.65	204.71	538.62	134	339.69	58.08	250.88	589.88
RVP total misses	455	13.89	5.15	1.00	27.00	134	14.74	5.26	3.00	27.00
RVP total false alarms	455	2.80	5.44	0.00	81.00	134	3.51	5.07	0.00	30.00
RVP mean latency	453	451.34	115.27	234.83	1190.00	130	464.81	126.22	276.05	1107.00
DMS % correct simultaneous	455	97.16	5.52	70.00	100.00	134	96.57	6.73	60.00	100.00

	Subjects with Full Covariates					Subjects with Missing Covariates				
	n	**mean**	**SD**	**min**	**max**	**n**	**mean**	**SD**	**min**	**max**
DMS % correct 0 sec	455	86.37	12.86	40.00	100.00	134	86.64	11.76	40.00	100.00
DMS % correct 4 sec	455	86.40	13.25	40.00	100.00	134	84.33	13.62	30.00	100.00
DMS % correct 12 sec	455	77.32	16.29	30.00	100.00	134	76.64	16.50	20.00	100.00
PRM % correct	455	86.01	10.74	54.17	100.00	134	85.91	10.52	54.17	100.00
SRM % correct	455	81.09	9.78	45.00	100.00	134	79.55	11.98	40.00	100.00
SWM between errors	455	26.89	17.11	0.00	106.00	134	30.04	17.56	1.00	91.00
SWM within errors	455	2.17	3.83	0.00	31.00	134	2.07	3.71	0.00	18.00
SWM total errors	455	27.66	17.65	0.00	112.00	134	30.66	17.88	1.00	92.00
SWM strategy	455	33.87	3.92	20.00	44.00	134	34.16	3.73	21.00	43.00

IED = Intra-Extra Dimensional Shift Set, PAL = Paired Associates Learning, RT = Reaction Time, RVP = Rapid Visual Information Processing, DMS = Delayed Match to Sample, PRM = Pattern Recognition Memory, SRM = Spatial Recognition Memory, SWM = Spatial Working Memory.

Table 1b

Categorical Behavioral Endpoint Distributions

Behavior Outcome	N	Observations in regression model
Substance Use*		
0	191	156
1	146	109
2	92	74
3	62	44
4	36	26
5 and 6	44	33
Mental Health**		
0	371	298
1	151	108
2	49	36
Antisocial***		
0	375	284
1	127	103
2	43	35
3 and 4	26	20
Injury****		
0	443	346
1	71	50
2	31	27
3 through 7	26	19
Total Reports/Year†		
0	257	207
1 to 3	47	32
4 to 12	42	34
≥ 13	25	22
Total Referrals/Year††		
0	237	192
1 to 3	55	43
4 to 12	48	34
≥ 13	31	26

* Sum of positive responses to frequency of alcohol, drug, or cigarette consumption

** Sum of positive responses to feeling sad or contemplating suicide

*** Sum of positive responses to school suspension, arrest, fighting, or carrying a weapon

**** Positive response to serious injury during preceding 12 months

† Defined as a school-related behavior resulting in a report to a school counsellor

†† Defined as a referral to a school counselor following a report

Table 2a

Regression Analysis Results for Neurodevelopmental Endpoints*

Endpoint	Prenatal MeHg	*p*	Sex (Male)	*p*	Recent Postnatal MeHg	*p*	SES	*p*	Maternal IQ	*p*	Child's Age at Test	*p*
CVLT												
Short Delay (scaled)	0.02	0.14	**−0.35**	**<0.01**	−0.01	0.31	**0.02**	**0.00**	0.01	0.27	0.10	0.43
Long delay (scaled)	0.02	0.12	**−0.37**	**<0.01**	−0.02	0.22	**0.02**	**0.00**	0.00	0.69	0.09	0.49
W-J-II												
Passage Comprehension	0.25	0.25	**−4.93**	**0.01**	**−0.42**	**0.05**	**0.37**	**0.00**	**0.23**	**<0.01**	**−4.27**	**0.03**
Letter-Word	0.15	0.61	**−10.07**	**0.00**	−0.40	0.15	**0.25**	**0.05**	**0.34**	**<0.01**	−3.08	0.24
Calculation	**0.39**	**0.02**	**−3.68**	**0.02**	−0.04	0.82	**0.27**	**0.00**	**0.16**	**<0.01**	−2.91	0.07
Applied problems	0.19	0.20	−0.97	0.46	−0.08	0.57	**0.25**	**0.00**	**0.15**	**<0.01**	**−3.24**	**0.02**
Math Fluency	0.05	0.68	**−6.17**	**<0.01**	−0.00	1.00	0.10	0.07	**0.10**	**0.01**	**−3.82**	**<0.01**
Wisconsin Card Sorting Test % Total Errors	−0.03	0.92	0.96	0.72	0.47	0.10	**0.43**	**0.00**	0.02	0.82	−1.24	0.65
CANTAB												
IED												
Log Total Trials	**−0.01**	**0.02**	**−0.07**	**0.04**	0.00	0.66	−0.00	0.28	−0.00	0.18	−0.01	0.70
Log pre-ED Errors)	−0.01	0.16	0.02	0.62	0.01	0.33	**−0.01**	**0.00**	−0.00	0.73	−0.06	0.24
PAL												
Log Total Errors + 1	0.01	0.37	0.03	0.68	0.00	0.95	**−0.01**	**0.04**	−0.00	0.32	**0.19**	**0.01**
Log Total Trials	0.00	0.71	0.01	0.42	−0.00	0.63	**−0.00**	**0.04**	−0.00	0.39	**0.04**	**0.03**
Stages Completed	−0.01	0.57	−0.02	0.79	−0.00	0.83	**0.01**	**0.04**	0.00	0.21	**−0.23**	**0.01**
RVP Total Misses	−0.01	0.82	−0.05	0.92	0.00	0.96	**−0.07**	**0.00**	−0.01	0.59	−0.14	0.79
DMS												
% Correct 0 Sec	−0.11	0.42	−0.35	0.78	−0.17	0.22	0.11	0.08	0.02	0.70	**−2.62**	**0.04**
% Correct 12 Sec	−0.04	0.80	0.22	0.89	−0.31	0.07	0.07	0.41	0.15	0.01	−0.36	0.82
PRM % Correct	−0.02	0.85	**2.08**	**0.04**	−0.02	0.85	0.06	0.26	0.04	0.32	**−2.29**	**0.03**
SRM												
% Correct	0.08	0.44	0.36	0.70	−0.03	0.76	0.08	0.11	0.06	0.06	−1.30	0.18
Square Root Between Errors	−0.02	0.19	−0.16	0.33	0.01	0.75	**−0.02**	**<0.01**	−0.01	0.08	−0.33	0.06

Endpoint	Prenatal MeHg	*p*	Sex (Male)	*p*	Recent Postnatal MeHg	*p*	SES	*p*	Maternal IQ	*p*	Child's Age at Test	*p*
Square Root Total Errors	−0.02	0.27	−0.18	0.29	0.01	0.72	**−0.02**	**0.01**	−0.01	0.09	−0.33	0.06
Strategy	−0.05	0.25	−0.38	0.30	−0.00	0.94	−0.04	0.06	**−0.03**	**0.02**	−0.39	0.31

*Coefficients and *p* values are shown only for models where the overall model was statistically significant. Estimates with significance $p \leq 0.05$ are bolded.

Table 2b

Regression Analysis Results for Behavioral Endpoints

Endpoint	Prenatal MeHg	*P*	Sex (Male)	*p*	Postnatal MeHg	*p*	SES	*p*	Mother's IQ	*p*	Child's IQ	*p*
Substance Use		**0.02****										
1	F 0.029	0.41	1.121	0.28	0.037	0.21	−0.010	0.45	0.005	0.63	0.017	0.16
	M −0.021	0.65										
2	F 0.023	0.58	**3.400**	**<0.01**	0.012	0.72	**−0.053**	**<0.01**	−0.006	0.57	0.017	0.25
	M −0.141	**0.01**										
3	F 0.016	0.79	**4.234**	**<0.01**	0.017	0.67	−0.023	0.23	0.008	0.55	−0.022	0.22
	M −0.129	**0.03**										
4	F −0.170	0.16	2.169	0.21	0.001	0.98	−0.033	0.15	0.026	0.12	−0.009	0.67
	M −0.058	0.37										
5 and 6	**F −0.584**	**0.03**	0.009	0.99	0.004	0.93	0.007	0.74	−0.027	0.10	−0.013	0.52
	M −0.031	0.56										
Mental Health		**0.02****										
1	F 0.0014	0.97	0.359	0.67	0.006	0.82	−0.004	0.72	0.002	0.78	−0.023	0.05
	M −0.076	0.08										
2	F −0.111	0.09	**−5.845**	**<0.01**	0.067	0.16	−0.002	0.93	**−0.040**	**0.02**	**−0.070**	**<0.01**
	M 0.116	0.12										
Antisocial												
1	−0.024	0.38	**2.193**	**<0.01**	−0.009	0.74	−0.014	0.25	0.014	0.14	−0.016	0.18
2	−0.092	0.07	**3.688**	**<0.01**	−0.026	0.55	−0.035	0.11	0.010	0.51	**−0.058**	**0.01**
3 and 4	0.082	0.23	**7.908**	**<0.01**	−0.104	0.14	0.033	0.41	**−0.173**	**<0.01**	**−0.078**	**0.03**
Injury												
1	0.028	0.39	0.832	0.18	0.019	0.56	0.002	0.88	−0.010	0.41	−0.008	0.59
2	−0.028	0.58	**3.326**	**<0.01**	−0.056	0.27	0.003	0.89	−0.016	0.35	0.011	0.59
3 through 7	−0.109	0.23	**6.398**	**<0.01**	−0.115	0.18	0.020	0.69	**−0.187**	**<0.01**	**−0.178**	**<0.01**
Total Incidents/Year												
1–3	0.079	0.06	−0.408	0.61	0.051	0.19	0.012	0.57	−0.012	0.41	−0.035	0.07

Endpoint	Prenatal MeHg	*P*	Sex (Male)	*p*	Postnatal MeHg	*p*	SES	*p*	Mother's IQ	*p*	Child's IQ	*p*
4–12	−0.006	0.90	**1.594**	**0.04**	0.015	0.71	0.033	0.10	−0.022	0.14	−0.036	0.06
≥ 13	**−0.186**	**0.03**	**3.023**	**0.01**	0.085	0.09	0.052	0.09	**−0.048**	**0.02**	**−0.066**	**0.01**
Total Referrals/Year												
1–3	**0.077**	**0.04**	0.458	0.51	0.050	0.15	0.014	0.44	−0.012	0.37	−0.015	0.39
4–12	0.018	0.69	**2.113**	**0.01**	0.040	0.32	0.027	0.18	**−0.042**	**0.01**	−0.016	0.41
≥ 13	−0.090	0.15	**2.075**	**0.03**	0.045	0.33	0.009	0.72	−0.023	0.17	**−0.050**	**0.02**

*Category 0 served as baseline for each endpoint. Negative estimates indicate improved behavior. Estimates with significance p ≤ 0.05 are bolded.

**p value for MeHg × Sex interaction.