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Postnatal methylmercury exposure and neurodevelopmental outcomes at 7 years of age in the Seychelles Child Development Study Nutrition Cohort 2

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Abstract

Background: Consumption of fish yields many nutritional benefits, but also results in exposure to methylmercury (MeHg). The developing brain is known to be particularly susceptible to MeHg toxicity in high doses. However, the potential impact of low-level environmental exposure from fish consumption on children's neurodevelopment remains unclear.

Methods: We investigated postnatal MeHg exposure at 7 years and its association with a battery of 17 neurodevelopmental outcomes in a subset of children (n=376) from 1535 enrolled mother-child pairs in Nutrition Cohort 2 of the Seychelles Child Development Study (SCDS NC2). Each outcome was modeled in relation to postnatal MeHg exposure using linear regression, adjusting for prenatal MeHg exposure, levels of maternal polyunsaturated fatty acids (PUFA), and several other covariates known to be associated with neurodevelopmental outcomes.

Results: Median postnatal MeHg exposure at 7 years was 2.5 ppm, while the median prenatal MeHg exposure was 3.5 ppm. We found no statistically significant associations between postnatal MeHg exposure and any of the 17 neurodevelopmental outcomes after adjusting for prenatal MeHg exposure and other covariates.

Conclusions: These findings are consistent with previous cross-sectional analyses of the SCDS Main Cohort. Continued follow-up of the entire NC2 cohort at later ages with repeated exposure measures is needed to further confirm these findings.

Keywords

Mercury; neurodevelopment; Seychelles; postnatal exposure

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1. Introduction

Methylmercury (MeHg) is produced naturally by environmental bacteria and is present in all fish. At high levels of exposure MeHg is known to have detrimental effects on children's neurodevelopment (Bakir et al., 1973; Harada, 1995). However, the potential impact of low-level environmental exposure from fish consumption on children's neurodevelopment remains unclear (Strain et al., 2015; Vejrup et al., 2016; van Wijngaarden et al., 2017). Previous studies have focused primarily on prenatal MeHg exposure because the developing brain is known to be the most vulnerable during gestation (Spyker et al., 1972; Choi, 1989). Current fish consumption guidelines primarily rely on studies examining prenatal exposure (FAO/WHO, 2011; FDA/EPA, 2022). However, neurodevelopment is an ongoing process that extends throughout childhood, adolescence, and early adulthood (Shonkoff et al., 2000; Tau & Peterson, 2010), and ongoing MeHg exposure during postnatal development may impact neurodevelopmental and neurobehavioral outcomes.

MeHg is known to readily cross the blood-brain barrier and accumulate in the brain, and experimental studies have shown that MeHg can disrupt key neurodevelopmental processes such as neuronal migration, synaptogenesis, and myelination (Clarkson & Magos, 2006). These processes are essential for the establishment of normal neural circuitry, and they continue well into adolescence (Shonkoff et al., 2000; Tau & Peterson, 2010). Thus, the brain is susceptible to environmental exposures during postnatal development. However, the epidemiologic literature on postnatal MeHg exposure and neurodevelopment appears inconclusive (Murata et al., 1999; Murata et al., 2004; Despres et al., 2005; Debes et al., 2006; Saint-Amour et al., 2006; Ha et al., 2009; Boucher et al., 2010; Cao et al., 2010; Freire et al., 2010; Plusquellec et al., 2010; Dorea et al., 2012; Deroma et al., 2013; Grandjean et al., 2014; Wang et al., 2014; Jacobson et al., 2015; Marques et al., 2015; Boucher et al., 2016; Llop et al., 2020; Lee et al., 2021; Lozano et al., 2021).

In the Seychelles Child Development Study, we have not reported consistent adverse associations between prenatal MeHg exposure and neurodevelopmental outcomes across analyses of our cohorts (Strain et al., 2012; Strain et al., 2015; van Wijngaarden et al., 2017; Strain et al., 2021). In our Main Cohort, where children were followed until 24 years of age, we observed some adverse associations with postnatal exposure (Myers et al., 2009; van Wijngaarden et al., 2017; Thurston, Myers, et al., 2022). In the present study we sought to further clarify postnatal MeHg associations in early childhood data from the more recent Nutrition Cohort 2.

2. Methods

2.1 Study Population

The Seychelles Child Development Study (SCDS) Nutrition Cohort 2 (NC2) was originally designed to assess the association between prenatal MeHg exposure from fish consumption and child neurodevelopmental outcomes, while considering the potential influence of nutrition (Strain et al., 2015). Between 2008 and 2011, a total of 1535 mother-child pairs were recruited at their first prenatal visit on Mahé, the main island of the Seychelles. Inclusion criteria were native Seychellois, age ≥ 16 years, and no known health concerns.

For this analysis, we selected a subset of the NC2 cohort that included the first 389 participants evaluated at age 7 years with measured postnatal MeHg data available. Of these, 11 were missing data on maternal polyunsaturated fatty acid (PUFA) status using the omega-6:omega-3 (n-6:n-3) ratio, 1 was missing both prenatal MeHg exposure and maternal PUFA levels, and 1 was missing a maternal Kaufman Brief Intelligence Test (KBIT-2) score, resulting in 376 mother-child pairs with complete covariate data.

2.2 Neurodevelopmental and Neurobehavioral Outcomes

This study focused on the 17 primary endpoints derived from a battery of 14 neurodevelopmental tests administered to the children in the cohort, and three questionnaires completed by their parents. The neurodevelopmental tests included the Clinical Evaluation of Language Fundamentals (CELF-5), consisting of six endpoints: Total, Follow Directions, Linguistic Concepts, Recalling Sentences, Sentence Comprehension, and Understand Spoken Paragraphs. Additionally, the KBIT-2 contributed two endpoints: Word Knowledge and Matrices. Other tests included the Boston Naming Test (BNT; total score), Trailmaking A (TM-A), Finger Tapping (FT) for dominant and non-dominant hands; and the Woodcock-Johnson Test for Achievement (WJ-III), with endpoints for letter word identification and applied math. The remaining three instruments used as primary endpoints were the parent-reported Child Behavior Checklist (CBCL Total), Social Responsiveness Scale 2 (SRS-2), and Social Communication Questionnaire (SCQ). Altogether, these 14 neurodevelopmental tests and three parent-reported instruments constituted the 17 primary endpoints evaluated for all children in the NC2 cohort. For more detailed information about these tests and the specific neurodevelopmental domains they assess, we refer the reader to Strain, et al. (2021).

2.3 Methylmercury Assessment

Determinations of prenatal MeHg exposure were performed by analyzing total Hg in maternal hair samples collected at delivery (Strain et al., 2015). Mercury in hair that best recapitulated growth during pregnancy was analyzed using the longest hair segment available emanating from the scalp. Hair was assumed to grow at a rate of 1.1 cm per month. Mercury deposited in hair is more than 80% MeHg and is known to correlate with mercury deposited in the infant brain (Cernichiari et al., 1995). Determination of MeHg in prenatal hair samples were performed using cold vapor atomic absorption spectroscopy with previously-described quality control procedures (Cernichiari et al., 1995).

We measured total Hg concentrations in child's hair collected at 7 years using inductively coupled plasma mass spectrometry (ICP-MS) (NexION2000, Perkin-Elmer, Waltham, MA). Consistent with previous assessments (Thurston, Myers, et al., 2022), concurrent postnatal MeHg exposure in the children was measured as total Hg in the 1 cm of hair closest to the scalp at the time of testing. Hair samples were prepared with a standard microwave-concentrated acid digestion (3:1 HNO_3:HCl, ultra trace grade) followed by dilution prior to ICP-MS determinations in a 1400W power standard mode, measuring the Hg^{202} isotope using Bi^{209} as an internal standard. The limit of detection (LOD) for was 0.1 ng/mL (0.1 ppb), and the limit of quantification is 10 times the LOD, 1 ng/mL (1 ppb). The ICP-MS was calibrated using National Institute of Standards and Technology (NIST) certified reference

material containing Hg. Duplicate analyses were performed on all sample batches unless sample material was limited.

2.4 Covariates

The statistical analysis in this study followed a similar approach to prior analyses of children in the NC2 cohort at 20 months (Strain et al., 2015) and 7 years (Strain et al., 2021). The primary analysis was determined *a priori* and consisted of linear regression with adjustment for covariates known to be associated with child neurodevelopment. Maternal-related covariates included mother's age at delivery, her IQ as measured by the Kaufmann Brief Intelligence Test (KBIT-2 Matrices), prenatal MeHg from maternal hair collected at delivery, and the n-6:n-3 ratio using maternal serum PUFA from a blood sample collected at 28 weeks of gestation. Child-related covariates included the age at the time of testing, sex, socioeconomic status (Hollingshead SES), and family status (i.e. whether both parents were living with the child, represented by a binary variable). Additionally, for models of all six CELF-5 endpoints, the interviewer's identity (a categorical variable with four levels) was included as a covariate since interviewer was a significant predictor of outcomes for this assessment in prior analyses (Strain et al., 2021).

2.5 Statistical Analysis

The goal of this analysis was to assess the main effect of postnatal MeHg exposure at 7 years, while accounting for prenatal MeHg exposure and the previously outlined maternal biomarkers and covariates. Several endpoints were transformed to align with our previous report (Strain et al., 2021), including the BNT, CBCL, CELF-5 understanding spoken paragraphs, SCQ and SRS (square root), CELF-5 linguistic concepts and WJ-III applied problems (squared), and TM-A (log10). A separate linear regression model was fit for each transformed endpoint. Participants who had missing values for any of the specified covariates were excluded from this analysis. If a participant had missing data for an endpoint but had records available for other endpoints, they were included in the models for which data were available.

All statistical analyses were performed using R version 4.2.1 on RStudio Server (R Core Team, 2022). The assumptions of the linear regression model were assessed visually using residual versus fitted value plots to examine linearity and constant variance. Normality was checked using QQ plots, and Cook's distance was utilized to identify potentially influential observations. No significant deviations from linearity or constant variance were observed. Although a few models exhibited minor deviations from the normality of residuals, results from the linear model are typically robust to this assumption (Seber & Lee, 2003). The transformations applied to the outcomes were re-evaluated using Box-Cox criteria on the subset of the NC2 cohort included in this study, and the recommended transformations were consistent with those used in our previous report (Strain et al., 2021).

For each of the 17 transformed primary endpoints, we report the regression coefficients (slopes), standard errors, and p-values regarding the main effect of postnatal MeHg exposure at 7 years. The statistical significance of this main effect was assessed using a nominal type I error rate (α) of 0.05 in each model.

3. Results

Summary statistics for covariates, primary endpoints, and postnatal MeHg are presented in Table 1. Of the 389 participants for whom postnatal MeHg was measured, all had measurements for at least one of the 17 primary endpoints. Most participants had measurements for all or nearly all the endpoints. Forty-nine participants did not have a measurement for Trailmaking A. The median postnatal MeHg concentration was 2.5 ppm, while the median prenatal MeHg concentration (in maternal hair) was 3.5 ppm. Measures of postnatal and prenatal MeHg concentration in hair were weakly correlated, with a Pearson correlation of 0.05. The summary statistics for this subset of the NC2 cohort were similar to those reported in a previous analysis of prenatal MeHg exposure in the overall NC2 cohort (Strain et al., 2021).

The primary results of regressing the transformed endpoints on postnatal MeHg and covariates are reported in Table 2. At a significance level of 0.05, postnatal MeHg at 7 years did not demonstrate a significant association with any of the 17 primary endpoints. The estimated slopes for MeHg exposure were generally small and negative for square root CBCL, FT dominant hand, FT non-dominant hand, and square root SCQ total. Positive slopes were estimated for all CELF-5, KBIT-2, and WJ-III outcomes, as well as log10 TM-A and square root SRS total. A slope of zero was estimated for square root BNT total.

To address the issue of transformed endpoints, which can result in models with less interpretable coefficients, we refit the models for the 17 primary endpoints using either untransformed or log10 transformed values of the endpoints. This approach altered the coefficients and their standard errors but did not change our conclusions. The details of the results of these secondary analyses can be found in the supplementary materials (Appendix 1).

The covariate slopes with 95% confidence intervals most commonly excluding zero (indicating an association) across the models for all 17 endpoints were Hollingshead SES, mother's KBIT-2 matrices score, and child sex. The direction of associations between these three covariates and endpoints were generally consistent within groups of tests (e.g., all CELF-5 endpoints). Prenatal MeHg exposure was not significantly associated with any of the endpoints. A summary of the covariate slopes across all 17 endpoints is available in supplementary materials (Appendix 2).

4. Discussion

This cross-sectional study of postnatal exposure found no evidence to support the hypothesis that concurrent postnatal MeHg exposure influences neurodevelopmental and neurobehavioral outcomes in childhood. The slopes of postnatal MeHg exposure were small in magnitude, and not statistically significant for any of the 17 neurodevelopmental outcomes. Previous cross-sectional analyses of the NC2 cohort found no significant associations between neurodevelopmental outcomes and prenatal MeHg exposure at either 20 months or 7 years of age (Strain et al., 2015; Strain et al., 2021). This study demonstrates

a similar result for postnatal MeHg exposure while controlling for prenatal MeHg exposure and other covariates (Appendix 3).

More generally, the literature on postnatal MeHg exposure is mainly cross-sectional and associations with neurodevelopment are inconsistent. Some longitudinal birth cohort studies have reported associations between postnatal MeHg exposure and neurodevelopmental outcomes at differing ages throughout childhood, including the Faroese birth cohort (Murata et al., 2004; Debes et al., 2006; Grandjean et al., 2014), the Canadian Nunavik study of school-age Inuit children (Despres et al., 2005; Saint-Amour et al., 2006; Boucher et al., 2016), and the Spanish INMA birth cohort (Freire et al., 2010; Lozano et al., 2021). However, other studies have been unable to confirm such associations, sometimes in the same cohorts listed above that reported some adverse associations (Murata et al., 1999; Ha et al., 2009; Boucher et al., 2010; Cao et al., 2010; Plusquellec et al., 2010; Dorea et al., 2012; Deroma et al., 2013; Wang et al., 2014; Jacobson et al., 2015; Marques et al., 2015; Llop et al., 2020; Lee et al., 2021). Differences in study findings may be explained by methodological variability in exposure and outcome assessment across the different studies. Furthermore, some of the cohorts studied (e.g. Faroese and Nunavik cohorts) consumed sea mammals, resulting in co-exposure to multiple toxicants. While the brain is susceptible to postnatal MeHg exposure, these studies do not provide strong support for an association between postnatal MeHg exposure and neurodevelopment during childhood and adolescence.

Prior analysis of the SCDS Main Cohort using different postnatal exposure metrics that accounted for repeated measures of exposure over time did find some adverse associations with neurodevelopment outcomes. However, there was considerable uncertainty about the nature and implications of these findings (Davidson et al., 1998; Myers et al., 2009). A recent analysis of the Main Cohort using more refined time-weighted metrics of postnatal MeHg exposure (Thurston, Harrington, et al., 2022) also found some adverse associations (Thurston, Myers, et al., 2022). The time-weighted metrics accounted for the additional years of exposure data from following this cohort up to 24 years of age. Among the 85 neurodevelopmental outcomes measured in children from ages 9-24 years, there were 13 adverse associations and one beneficial association with a time-weighted postnatal MeHg exposure metric (Thurston, Myers, et al., 2022). None of the remaining associations with postnatal MeHg were statistically significant. Strengths of this prior analysis includes the use of a time-weighted metric that is potentially representative of a long-term postnatal exposure, and follow up of a relatively large cohort with ~80% success at 24 years. We noted, however, that the potential clinical significance of these findings was unclear and required follow-up in future cohorts. The present NC2 cohort also had lower average postnatal exposure levels of 2.5 ppm, as compared to 5.0-8.0 ppm in the Main Cohort (Thurston, Myers, et al., 2022). This lower exposure along with the lack of a longitudinal component may explain some of the differences in findings between these analyses. In addition, other than the Boston Naming Test, we did not measure the same neurodevelopmental outcomes in executive function, attention, and achievement domains that were associated with postnatal exposure in our previous paper.

Strengths of this study include excellent participant retention, the comprehensive nature of the neurodevelopmental examination administered at 7 years, and the fact that the environmental exposure to MeHg among the Seychellois population is from fish and thus not potentially confounded by co-exposures to other toxicants typically found at elevated levels in ocean mammals.

Limitations of the study include the relatively small number of participants, and the possibility that we did not collect or include some important covariates. We also view the cross-sectional nature of the current analysis as limitation, since an observation at a single point in time provides less information about exposure and how it relates to neurodevelopmental outcomes than repeated measures of exposure and outcomes throughout childhood and adolescence.

In conclusion, this analysis did not identify any associations between concurrent postnatal MeHg exposure at 7 years and a battery of 17 neurodevelopmental outcomes. Continued follow-up of the NC2 cohort into adolescence and adulthood, measuring postnatal exposure repeatedly in the entire cohort, and focusing on outcomes previously reported to be associated with MeHg exposure may help clarify any potential associations.

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Appendix

Appendix 1:

Regression model results for the main effect of MeHg exposure when endpoints were either log10 transformed or untransformed.

Outcome	n	Slope	SE	Lower	Upper	p-value
log10, BNT total	375	0.000	0.002	−0.004	0.005	0.95
CBCL total	369	−0.608	0.560	−1.710	0.494	0.28
CELF-5 total	369	0.651	0.381	−0.099	1.401	0.09
CELF-5 FD	376	0.186	0.100	−0.010	0.382	0.06
CELF-5 LC	376	0.124	0.065	−0.004	0.253	0.06
CELF-5 RS	374	0.170	0.179	−0.183	0.522	0.35
CELF-5 SC	372	0.117	0.098	−0.075	0.309	0.23
CELF-5 USP	374	0.027	0.080	−0.130	0.185	0.73
FT dominant hand	376	−0.084	0.117	−0.315	0.146	0.47
FT non-dominant hand	376	−0.005	0.108	−0.217	0.207	0.96
KBIT-2 word knowledge	376	0.204	0.191	−0.172	0.580	0.29
KBIT-2 matrices	376	0.178	0.121	−0.061	0.416	0.14

Outcome	n	Slope	SE	Lower	Upper	p-value
SCQ total	369	−0.042	0.101	−0.241	0.157	0.68
SRS total	375	0.068	0.407	−0.733	0.868	0.87
log10, trailmaking time A	337	0.003	0.005	−0.006	0.012	0.46
log10, WJ-III applied problems	375	0.002	0.002	−0.001	0.006	0.20
WJ-III letter word	374	0.942	0.545	−0.129	2.014	0.08

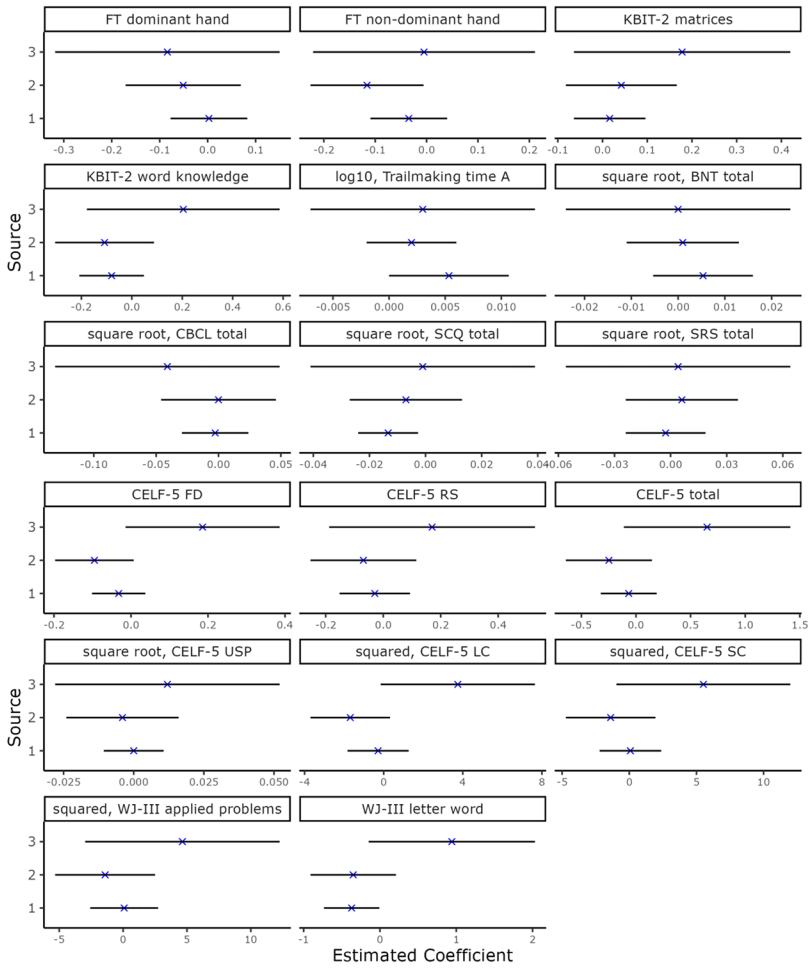
Note: n = sample size, slope = regression coefficient for MeHg, SE = standard error of slope, Lower = 2.5% lower confidence bound for slope, Upper = 97.5% upper confidence bound for slope. All outcomes were regressed on child's 7 year hair MeHg (ppm) and the following covariates: mother's age at delivery, maternal KBIT-2 matrices, prenatal MeHg from maternal hair at delivery (ppm), n-6:n-3 ratio, child's age at 7 year testing, child sex (female = 1), family status at 7 years (both parents with child = 1), Hollingshead SES at 7 years.

Appendix 2:

Coefficient values and 95% confidence intervals for covariates from models for all 17 transformed endpoints.

	Mom Age	Mom KBIT	Prenatal Hg	n-6:n-3	Child Age (yrs)	Child Sex (F)	Family Status	SES
square root, BNT total	0 (−0.01, 0.01)	0.01 (0, 0.02)	0 (−0.01, 0.01)	0.02 (−0.01, 0.05)	−0.11 (−0.7, 0.49)	0 (−0.1, 0.1)	0.15 (0.04, 0.25)	0.01 (0.01, 0.02)
square root, CBCL total	−0.05 (−0.08, −0.01)	−0.03 (−0.06, 0)	0 (−0.04, 0.05)	0.05 (−0.06, 0.17)	2.11 (−0.08, 4.29)	−0.87 (−1.23, −0.51)	0.06 (−0.32, 0.44)	−0.05 (−0.07, −0.03)
CELF-5 total	0.04 (−0.24, 0.32)	0.3 (0.04, 0.55)	−0.25 (−0.63, 0.14)	0.84 (−0.12, 1.81)	−4.15 (−24.6, 16.3)	4.67 (1.53, 7.81)	−1.56 (−4.83, 1.71)	0.28 (0.12, 0.44)
CELF-5 FD	0.05 (−0.02, 0.13)	0.05 (−0.02, 0.11)	−0.09 (−0.2, 0.01)	0.2 (−0.06, 0.45)	−1.27 (−6.58, 4.03)	0.71 (−0.1, 1.52)	−0.17 (−1.02, 0.68)	0.04 (0, 0.09)
squared, CELF-5 LC	1.08 (−0.36, 2.53)	1.03 (−0.25, 2.32)	−1.69 (−3.67, 0.29)	6.18 (1.23, 11.12)	−22.08 (−126.05, 81.89)	16.12 (0.16, 32.09)	−8.96 (−25.63, 7.7)	1 (0.18, 1.81)
CELF-5 RS	−0.03 (−0.16, 0.1)	0.05 (−0.07, 0.17)	−0.07 (−0.25, 0.11)	0.3 (−0.16, 0.75)	−1.67 (−11.24, 7.91)	1.33 (−0.14, 2.8)	−0.41 (−1.94, 1.13)	0.08 (0, 0.16)
squared, CELF-5 SC	−1.1 (−3.49, 1.29)	3.21 (1.07, 5.36)	−1.38 (−4.66, 1.9)	1.84 (−6.38, 10.06)	11.57 (−161.47, 184.61)	31.32 (4.72, 57.93)	−6.22 (−33.97, 21.53)	3.04 (1.69, 4.39)
square root, CELF-5 USP	0.01 (−0.01, 0.02)	0.01 (0, 0.03)	0 (−0.02, 0.02)	0.03 (−0.02, 0.08)	−0.22 (−1.29, 0.85)	0.3 (0.14, 0.47)	−0.06 (−0.23, 0.12)	0.01 (0, 0.02)
FT dominant hand	0.01 (−0.07, 0.1)	−0.02 (−0.09, 0.06)	−0.05 (−0.17, 0.07)	−0.08 (−0.38, 0.22)	3.7 (−2.04, 9.44)	−0.79 (−1.75, 0.17)	0.22 (−0.79, 1.22)	0.1 (0.05, 0.15)
FT non-dominant hand	0.1 (0.02, 0.18)	0.01 (−0.07, 0.08)	−0.12 (−0.23, −0.01)	−0.1 (−0.38, 0.17)	5.59 (0.31, 10.86)	−1.64 (−2.52, −0.75)	−0.21 (−1.13, 0.72)	0.07 (0.03, 0.12)
KBIT-2 word knowledge	−0.04 (−0.18, 0.1)	0.06 (−0.07, 0.18)	−0.11 (−0.3, 0.08)	0.39 (−0.09, 0.88)	−5.42 (−14.77, 3.94)	0.45 (−1.12, 2.02)	0.58 (−1.06, 2.21)	0.03 (−0.05, 0.11)
KBIT-2 matrices	0.02 (−0.07, 0.11)	0.1 (0.02, 0.18)	0.04 (−0.08, 0.16)	0.14 (−0.17, 0.44)	−1.25 (−7.19, 4.69)	0.46 (−0.54, 1.45)	−0.43 (−1.47, 0.61)	0.08 (0.03, 0.13)

	Mom Age	Mom KBIT	Prenatal Hg	n-6:n-3	Child Age (yrs)	Child Sex (F)	Family Status	SES
square root, SCQ total	−0.01 (−0.02, 0.01)	−0.02 (−0.03, −0.01)	−0.01 (−0.03, 0.01)	0 (−0.05, 0.05)	0.16 (−0.81, 1.12)	−0.28 (−0.44, −0.12)	−0.11 (−0.28, 0.06)	−0.01 (−0.02, 0)
square root, SRS total	−0.02 (−0.04, 0)	−0.03 (−0.05, −0.01)	0.01 (−0.02, 0.04)	−0.01 (−0.09, 0.06)	−0.31 (−1.76, 1.14)	−0.35 (−0.6, −0.11)	−0.19 (−0.44, 0.07)	−0.04 (−0.05, −0.03)
log10, trailmaking time A	0 (0, 0)	0 (0, 0)	0 (0, 0.01)	−0.01 (−0.02, 0)	0.01 (−0.22, 0.24)	−0.04 (−0.08, −0.01)	−0.01 (−0.05, 0.03)	0 (0, 0)
squared, WJ-III applied	2.97 (0.15, 5.8)	2.41 (−0.11, 4.93)	−1.41 (−5.25, 2.44)	−0.67 (−10.31, 8.98)	66.44 (−119.78, 252.66)	37.73 (6.5, 68.96)	−14.35 (−46.97, 18.27)	3.02 (1.42, 4.62)
WJ-III letter word	0.26 (−0.15, 0.66)	0.36 (0, 0.72)	−0.35 (−0.9, 0.2)	0.44 (−0.94, 1.83)	−12.6 (−39.32, 14.12)	3.53 (−0.95, 8)	−0.9 (−5.57, 3.78)	0.39 (0.16, 0.62)



Appendix 3:

Comparison of regression coefficients of (1) prenatal MeHg from Strain, et al. (2021)*, (2) prenatal MeHg from the present analysis, (3) postnatal MeHg at 7 years from the present analysis. Each plot denotes the point estimate and 95% confidence interval (Coef. ± 2*SE)

for the regression coefficient. Strain, et al. accounted for prenatal exposure only (n=1237), while the present analysis included prenatal and postnatal MeHg exposure in the same model (n=376).

*Strain, et al. (2021) reported prenatal MeHg exposure regression coefficients in terms of an IQR difference (3.75 ppm). The coefficients and corresponding standard errors from Strain in the figure above were rescaled so that they are comparable to those from the present analysis, i.e. they correspond to a 1 ppm difference in MeHg exposure.

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Highlights

1. Fish consumption guidelines rely primarily on studies of prenatal exposure.
2. The literature on exposure to MeHg from fish and neurodevelopment is inconclusive.
3. We examined 17 neurodevelopmental outcomes in relation to postnatal MeHg exposure.
4. We found no association between postnatal MeHg and neurodevelopment at 7 years.
5. Strengths are the prospective design and comprehensive neurodevelopmental testing.

Table 1:

Descriptive statistics for outcomes, exposures, and covariates.

Variable	n	Mean	SD	Min	Median	Max
Outcomes						
BNT total	388	22.14	4.97	10.00	22.00	39.00
CBCL total	381	42.89	23.96	0.00	40.00	148.00
CELF-5 total	382	79.55	16.48	6.00	80.00	132.00
CELF-5 FD	389	11.31	4.06	0.00	11.00	23.00
CELF-5 LC	389	17.62	2.68	1.00	18.00	24.00
CELF-5 RS	387	25.78	7.42	4.00	25.00	49.00
CELF-5 SC	385	19.31	4.24	1.00	20.00	26.00
CELF-5 USP	387	5.54	3.43	0.00	5.00	16.00
FT dominant hand	389	30.51	4.83	16.20	30.40	47.40
FT non-dominant hand	389	26.69	4.53	14.60	26.60	40.60
KBIT-2 word knowledge	389	19.79	7.61	5.00	21.00	41.00
KBIT-2 matrices	389	16.89	4.98	0.00	16.00	32.00
SCQ total	381	8.52	4.14	0.00	8.00	21.00
SRS total	388	47.81	17.82	6.00	47.00	121.00
Trailmaking time A	350	100.73	46.44	37.00	89.50	300.00
WJ-III applied problems	388	23.16	3.59	7.00	23.50	32.00
WJ-III letter word	387	50.16	22.54	3.00	58.00	76.00
Exposure						
Child’s 7 year hair MeHg, ppm	389	3.10	2.12	0.16	2.50	18.25
Prenatal biomarkers						
Mother’s age at delivery	389	26.57	5.93	16.27	25.65	44.84
Maternal KBIT-2 matrices	388	29.18	6.85	13.00	30.00	43.00
Mother’s hair MeHg, ppm	388	4.72	4.23	0.12	3.54	31.66
n-6:n-3 ratio	377	4.10	1.63	1.56	3.78	15.81
Other Covariates						
Child’s age at 7 year testing	389	7.18	0.08	7.02	7.16	7.50
Child sex, female	389	0.45	-	-	-	-
Family status at 7 years, both parents with child	389	0.52	-	-	-	-
SES at 7 years	389	32.89	10.78	14.00	32.00	63.00

Table 2:

Regression model results for the main effect of postnatal MeHg exposure for all 17 transformed endpoints

Outcome	n	Slope	SE	Lower	Upper	p-value
square root, BNT total	375	0.000	0.012	−0.024	0.024	1.00
square root, CBCL total	369	−0.041	0.045	−0.129	0.046	0.35
CELF-5 total	369	0.651	0.381	−0.099	1.401	0.09
CELF-5 FD	376	0.186	0.100	−0.010	0.382	0.06
squared, CELF-5 LC	376	3.747	1.951	−0.090	7.584	0.06
CELF-5 RS	374	0.170	0.179	−0.183	0.522	0.35
squared, CELF-5 SC	372	5.517	3.235	−0.845	11.879	0.09
square root, CELF-5 USP	374	0.012	0.020	−0.027	0.051	0.55
FT dominant hand	376	−0.084	0.117	−0.315	0.146	0.47
FT non-dominant hand	376	−0.005	0.108	−0.217	0.207	0.96
KBIT-2 word knowledge	376	0.204	0.191	−0.172	0.580	0.29
KBIT-2 matrices	376	0.178	0.121	−0.061	0.416	0.14
square root, SCQ total	369	−0.001	0.020	−0.040	0.039	0.98
square root, SRS total	375	0.004	0.030	−0.055	0.062	0.90
log10, trailmaking time A	337	0.003	0.005	−0.006	0.012	0.46
squared, WJ-III applied problems	375	4.642	3.805	−2.840	12.124	0.22
WJ-III letter word	374	0.942	0.545	−0.129	2.014	0.08

Note: n = sample size, slope = regression coefficient for MeHg, SE = standard error of slope, Lower = 2.5% lower confidence bound for slope, Upper = 97.5% upper confidence bound for slope. All outcomes were regressed on child's 7 year hair MeHg (ppm) and the following covariates: mother's age at delivery, maternal KBIT-2 matrices, prenatal MeHg from maternal hair at delivery (ppm), n-6:n-3 ratio, child's age at 7 year testing, child sex (female = 1), family status at 7 years (both parents with child = 1), Hollingshead SES at 7 years.