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Methyl mercury exposure and neurodevelopmental outcomes in the Seychelles Child Development Study Main Cohort at age 22 and 24 years

Edwin van Wijngaarden[1], **Sally W. Thurston**[1], **Gary J. Myers**[1], **Donald Harrington**[1], **Deborah A. Cory-Slechta**[1], **JJ Strain**[2], **Gene E. Watson**[1], **Grazyna Zareba**[1], **Tanzy Love**[1], **Juliette Henderson**[3], **Conrad F. Shamlaye**[3], and **Philip W. Davidson**[1]

[1]University of Rochester School of Medicine and Dentistry, Rochester, NY, United States

[2]Ulster University, Coleraine, Northern Ireland, United Kingdom

[3]Ministry of Health, Republic of Seychelles, Seychelles

Abstract

Background—All fish contain methyl mercury (MeHg), a known neurotoxicant at adequate dosage. There is still substantial scientific uncertainty about the consequences, if any, of mothers consuming fish with naturally-acquired levels of MeHg contamination. In 1989-1990, we recruited the Main Cohort of the Seychelles Child Development Study to assess the potential developmental effects of prenatal MeHg exposure. We report here on associations with neurodevelopmental outcomes obtained at 22 and 24 years of age.

Methods—Neurodevelopmental tests at 22 years included the Boston Naming Test, Cambridge Neuropsychological Test Automated Battery (CANTAB), and the Profile of Mood States. At 24 years, we administered the Stroop Word-Color Test, the Barkley Adult ADHD Rating Scale, the Test of Variables of Attention, and the Finger Tapping test. We also administered a healthy behaviors survey at both ages. Primary analyses examined covariate-adjusted associations in multiple linear regression models with prenatal MeHg exposure. In secondary analyses we also examined associations with recent postnatal MeHg exposure.

Results—We did not observe adverse associations between prenatal MeHg exposure and any of the measured endpoints. Some measures of attention, executive function, and delayed recall showed improved performance with increasing exposure. Secondary analysis did not show consistent patterns of association with postnatal exposure.

Conclusions—Our cohort has been examined at ten different ages over 24 years of follow-up. Findings suggest that prenatal and recent postnatal MeHg exposure from ocean fish consumption

Please address correspondence to: Edwin van Wijngaarden, PhD, Department of Public Health Sciences, University of Rochester School of Medicine and Dentistry, 265 Crittenden Blvd, CU 420644, Rochester, NY 14642, Phone: 585-275-1985, Fax: 585-461-4532, edwin_van_wijngaarden@urmc.rochester.edu.

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is not adversely associated with neurobehavioral development at levels that are about ten times higher than typical U.S. exposures.

1. Introduction

All fish contain a small amount of methyl mercury (MeHg) that is naturally present in the environment. MeHg is a known neurotoxicant in adequate dosage and has been associated with severe neurological deficits in children exposed prenatally when their mothers consumed heavily contaminated seafood or seed grain (WHO, 1990). Fish also contain nutrients that are essential for maternal and fetal health and are the primary source of preformed docosahexanonic acid (DHA), a major lipid in the brain. DHA is essential for normal brain development and function and the human body has a limited capacity to synthesize it from precursor lipids (Kuratko et al., 2013).

There is still substantial scientific uncertainty about the consequences, if any, of mothers or children consuming fish with naturally-acquired MeHg contamination. In 2004 the EPA and the FDA jointly issued fish consumption guidelines for women on the possibility of adverse health consequences for the developing fetus (EPA/FDA, 2004). These guidelines were based on studies in the Faroe Islands and New Zealand that reported some adverse associations between prenatal MeHg exposure and developmental outcomes (Crump et al., 1998; Grandjean et al., 1997). However, evidence from studies of populations consuming only fish with naturally-occurring MeHg contamination and not sea mammals does not support those conclusions. Our studies in the Republic of Seychelles (Davidson et al., 1998; van Wijngaarden et al., 2013b) and those of others in the UK and Spain (Daniels et al., 2004; Llop et al., 2012) have found no consistent evidence of adverse consequences on children's development associated with prenatal MeHg exposure. Recent advisories from U.S. and international agencies have encouraged fish consumption by women of childbearing age based on the beneficial nutrients present in fish and their known association with improved child development (EPA/FDA, 2014; FAO/WHO, 2011).

While regulatory fish consumption guidelines in the U.S. have also addressed fish intake in children, they are based on the same assumptions as guidelines for women of childbearing age. There are no studies that have been designed specifically to evaluate postnatal MeHg exposure in children, but a number of studies have included a biomarker of postnatal exposure in their analyses. Associations of increasing exposure with developmental outcomes have been inconsistent with some studies reporting worse performance (Freire et al., 2010; Hsi et al., 2014; Myers et al., 2009; van Wijngaarden et al., 2013b), some reporting better performance (Davidson et al., 1998), and others reporting no associations (Cao et al., 2010; Deroma et al., 2013).

Brain maturation develops throughout childhood and well into adolescence and young adulthood. Associations may not become apparent until the children mature or reported associations at early ages may not be present at older ages. Therefore, longitudinal studies are essential to determine if there are long-term consequences of prenatal or postnatal exposure. The Seychelles Child Development Study (SCDS) was designed specifically to address the question of whether MeHg exposure from fish consumption during pregnancy is

related to children's development. It is a prospective, longitudinal observational study in the Republic of Seychelles where fish consumption is daily, maternal MeHg exposure is about 10 times that in the US, and MeHg contamination in fish is from natural background levels. Levels of MeHg in fish consumed in Seychelles are similar to those found in ocean fish in the U.S. (unpublished data). Marine mammals, which can contain polychlorinated biphenyls (PCBs), other toxicants, and much higher MeHg concentrations than fish, are not consumed in the Seychelles. Environmental assessments have indicated relatively low exposure levels to other pollutants and contaminants in Seychelles, such as lead, PCBs, and pesticides (Shamlaye et al., 2004).

We recruited participants in the Main Cohort of the Seychelles Child Development Study in 1989-1990 to study the potential developmental effects of prenatal MeHg exposure, and have evaluated them 10 times during 24 years of follow up. Throughout 19 years of follow up, we have found no consistent evidence for adverse associations with prenatal exposure. However, in secondary analyses we have found some adverse associations with a measure of concurrent postnatal exposure (Davidson et al., 2011; Myers et al., 2003; Myers et al., 2009; van Wijngaarden et al., 2013b). We report here on associations of prenatal and recent postnatal MeHg exposure with developmental outcomes at 22 and 24 years of age.

2. Methods

2.1 Study Population

In 1989-1990, the Main cohort of 779 mother and their children were enrolled at 6 months (+/- 2 weeks) postpartum from among the women who had, during or after their pregnancy, agreed to give a hair sample. Participants were excluded if there was inadequate maternal hair to recapitulate prenatal MeHg exposure, were twins, or had illnesses or injuries known to adversely affect neurodevelopment (e.g. prematurity, severe perinatal illness, closed head trauma with loss of consciousness, encephalitis, and meningitis). There were 740 children eligible for further study. Cohort children were previously evaluated at 19, 29, 66, and 107 months of age, and at 10.5, 17, and 19 years of age (van Wijngaarden et al., 2013b). All study procedures were approved by the Institutional Review Board at the University of Rochester and the Research Review Board of the Republic of Seychelles.

2.2 Neurodevelopmental and Behavioral Assessment

Our neurodevelopmental and behavioral battery at 22 years assessed specific and subtle developmental and learning behaviors that are part of more global developmental functions, such as intelligence, cognition, memory, language ability, fine motor coordination, and emotional and social adjustment. Neurodevelopmental tests at 22 years included the Boston Naming Test (BNT) which measures language and executive functioning (Kaplan et al., 2001); the Profile of Mood States: Bipolar Version (POMS-Bi) which assesses mood and feeling including both positive and negative affect (Lorr et al., 1982); and a confidential healthy behaviors (HB) 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. (Davidson et al., 2011). We also administered the Cambridge Neuropsychological Test Automated Battery (CANTAB)

which is sensitive and specific for detection of subtle deficits in all components of complex cognitive function (Ismatulina et al., 2014). The administered battery included Reaction Time (RT), a measure of attention; Intra-/Extra Dimensional shift set (IED), a measure of executive function; Paired Associates Learning (PAL), a measure of executive function; Delayed Match to Sample (DMS), a short-term memory task; Rapid Visual Information Processing (RVP), a measure of memory function during performance of executive task; Spatial Working Memory (SWM), a short-term memory task; and Stockings of Cambridge (SOC), a measure of executive function. Participants who were colorblind did not complete the CANTAB assessment.

At 24 years of age, we focused on measures of attention to follow up on reports that prenatal Hg exposure may be associated with attention deficit disorder-related behavior (Sagiv et al., 2012; Yoshimasu et al., 2014). Accordingly, the 24-year battery included the Stroop Word-Color Test (for participants who were not colorblind), a measure of directed attention (Homack and Riccio, 2004); and the Barkley Adult ADHD Rating Scale IV (BAARS-IV) which assesses current and childhood ADHD symptoms and was administered in either English or Creole based on participant preference (Barkley, 2011). If BAARS-IV data were missing on one item of the full scale, a value of 1 (never or rarely) was imputed; if data on more than 1 item were missing the BAARS-IV test was considered invalid. We also administered both the auditory and visual components of the Test of Variables of Attention (TOVA) which is a non-language-based computerized and standardized continuous performance test (measuring attention and impulsivity). Outcome measures included are D Prime (d'), mean response time (milliseconds), response time variability (milliseconds), omission errors (%), and commission errors (%). (Greenberg and Waldman, 1993). Finally, we administered the Finger Tapping test (FT) for dominant and non-dominant hand as a measure of subtle motor and cognitive impairment (Schatz, 2011), and repeated the HB survey with the exception of questions on injury risk to reduce the length of the questionnaire and overall test battery.

Tables 1 (22-year battery) and 2 (24-year battery) indicate whether higher or lower test scores are indicative of better performance. Training procedures and reliability checks followed standard SCDS protocols. Participants and evaluators were blinded to pre- and postnatal MeHg concentrations and evaluators were specifically trained on the administered tests (Davidson et al., 1995).

2.3 Exposure Measures

Prenatal exposure to MeHg was determined by measuring total maternal hair Hg in the sample that best recapitulated growth during pregnancy using cold vapor atomic absorption spectroscopy with previously-described quality control procedures (Cernichiari et al., 1995). Over 80% of Hg in hair is known to be organic. We assumed a hair growth rate of 1.1 cm per month and a delay of 20 days between current blood concentrations and appearance of Hg in the first centimeter of scalp hair (Cernichiari et al., 1995). Recent postnatal MeHg exposure at 22 and 24 years of age was measured using the same approach in a 1 cm length of each participant's hair closest to the scalp taken at the time of testing.

2.4 Covariates

In addition to pre- and postnatal Hg, covariates were chosen to be consistent with analyses of the same or similar outcomes in this cohort at previous ages (Davidson et al., 2011; Davidson et al., 1998; van Wijngaarden et al., 2013b) and included child sex, socioeconomic status, maternal and child IQ, and life course stress. As in previous recent analyses of this cohort (Davidson et al., 2011; van Wijngaarden et al., 2013b), child sex was a covariate for all outcomes and socioeconomic status (SES) at 9 years of age was included as a covariate for all outcomes except POMS because the association between SES and measures of positive and negative affect, especially as measured by POMS, is currently not clear (Chiang et al., 2015). We operationalized SES through the use of the Hollingshead Social Status Index modified for use in the Seychelles (Davidson et al., 1998; Hollingshead, 1975). The Hollingshead Index is a measure of social status based on educational attainment (seven codes; no education to postgraduate) and occupational prestige (nine codes; menial service to higher executive). Higher codes indicate higher educational attainment or higher occupational status. We combined occupational and educational codes through a weighted formula into a continuous score (Hollingshead, 1975). Maternal IQ, determined by the Matrices subtest of the K-BIT given to mothers at the child's 10-year evaluation, was included in CANTAB and Finger Tapping analyses as a continuous variable (Davidson et al., 2011; van Wijngaarden et al., 2013b). Child full scale IQ as measured by the Wechsler Intelligence Scale-III at 9 years of age was a covariate for HB outcomes and for attention outcomes at 24 years (Davidson et al., 2011; Weyandt et al., 2002). Life course stress up to 22 years of age was included as a covariate for POMS outcomes and was defined here as the sum of significant life events (separations or divorces, death of someone close to the subject, severe illness in the immediate family, and household disasters) throughout the duration of follow up reported by the mother up to 17 years of age, which was subsequently updated with information provided by the participant (19 years and older) at the time of developmental testing at 19 and 22 years of age (van Wijngaarden et al., 2013b). At each follow up period, we inquired about new events since the last time the participant was tested in order to not double-count events.

2.5 Statistical Analysis

Descriptive analyses of endpoints, primary predictors and covariates were conducted on non-excluded subjects with data on at least one outcome separate for the 22- (n=571) and 24-year (n=577) assessments. The mean, median and standard deviation for continuous measures, and proportions for nominal and ordinal variables were computed.

A priori multivariable regression models tested the associations between endpoints and prenatal MeHg exposure. As mentioned above, CANTAB models adjusted for child sex, maternal IQ and SES; POMS models adjusted for child sex and lifecourse stress; BNT models adjusted for child sex and SES; and all remaining models adjusted for child sex, child IQ, and SES. We did not evaluate sex-MeHg interactions because analyses of previous developmental evaluations in this cohort have shown no consistent evidence for the presence of such interactions (Davidson et al., 2011; Myers et al., 2003; van Wijngaarden et al., 2013b).

Prenatal and postnatal exposures were modeled separately. Consistent with recent analyses, our primary prenatal exposure models did not include recent postnatal exposure as a covariate (van Wijngaarden et al., 2013a). Secondary postnatal models did include prenatal exposure as a covariate, and we present prenatal results from both models. A two-tailed alpha level of 0.05 was used to determine the significance of independent variable effects.

Regression assumptions were checked for each model. Continuous outcomes were modeled with linear regression. For models in which the assumption of normally distributed errors with constant variance was violated, the dependent variable was transformed to stabilize the variance and produce more normally distributed errors. These transformations consisted of either the natural logarithm or the inverse of the outcome variable. Statistical outliers (defined as observations with standardized residuals greater than 3 in absolute value) and influential points (defined as observations with a Cook's distance larger than 0.50) were identified for each model, and models which contained influential points or extreme outliers relative to other observations (such as standardized residuals greater than 4 in absolute value) were then run with and without these values. Regression results for two 24-year outcomes are presented without one extreme value on the TOVA D-prime visual measure and without a different extreme value for the TOVA D-prime auditory measure. After outcome transformations (when necessary), there were no other extreme outliers or influential points for continuous outcomes. Models for categorical outcomes were proportional odds (PO) models; the PO assumption was assessed by visual diagnostics as recommended by Harrell (Harrell, 2015). For some outcomes, extreme categories with small numbers of participants were collapsed, resulting in fewer categories; results were unaffected by this collapsing. After collapsing, when warranted, none of the models showed violation of the PO assumption. The beta coefficient in a PO model represents the increase in log odds of having a more adverse developmental outcome per unit increase of a predictor variable.

3. Results

3.1 Descriptive Analyses

Characteristics of study participants at 22 years (n=571) are presented in Table 1. Slightly more than half of the participants were female. The average prenatal MeHg exposure was 6.8 ppm in maternal hair. Recent postnatal MeHg exposure in the participant's hair was lower with an average of about 5 ppm; exposure was significantly greater for men (6.57 ppm) than for women (4.05 ppm). Pre- and postnatal exposure was not associated with any of the other covariates of interest. The correlation between prenatal exposure and recent postnatal exposure was low (r=0.11). Men performed somewhat better on several CANTAB measures (e.g. intra-extra dimensional shift, delayed matched to sample, spatial working memory) as compared to women. Women less frequently reported substance abuse, antisocial behavior and injury problems on the healthy behavior questionnaire but reported more mental health problems on this questionnaire as well as on the POMS.

Descriptive statistics of study participants at 24 years (n=577) are presented in Table 2. Demographic and exposure characteristics were similar to those at age 22. Recent postnatal exposure was again greater for men (6.28 ppm) than for women (3.87 ppm). As at 22 years,

other covariates were not associated with exposure and the correlation between prenatal and recent postnatal exposure was low (r=0.07). Men had worse scores than women on the BAARS (total, inattention, and hyperactivity) but scored better on the Finger Tapping test and most of the visual and auditory TOVA measures (data not shown). Similar to 22 years, women less frequently reported substance abuse and antisocial behavior but reported more mental health problems. Data suggest that risky behaviors, in particular substance abuse and antisocial behavior, declined between 22 and 24 years of age.

3.2 Regression Analyses

Associations between prenatal and recent postnatal MeHg exposure and cognitive and behavioral outcomes at 22 years of age are presented in Tables 3 and 4. Primary regression analyses were based on 439 to 560 participants at 22 years and 478 to 521 participants at 24 years who had complete information on cognitive endpoints and covariates, with the sample size varying depending upon the specific outcome measure and relevant covariates. Prenatal MeHg exposure was associated with several of the developmental outcomes assessed (5-choice reaction time, DMS % correct 12 ms delay, and SOC 5-move problem), but all regression coefficients indicated improved performance with increasing prenatal exposure. Postnatal MeHg exposure was associated with one of 26 outcomes at age 22 years; higher hair MeHg levels were associated with worse performance on the IED total errors adjusted measure.

24-year associations for outcomes are presented in Table 5. There were no clear patterns of association with either prenatal or recent postnatal MeHg. Only the TOVA auditory mean response time showed improved performance with increasing prenatal MeHg exposure.

4. Discussion

Prenatal MeHg exposure at ages 22 and 24 years in the SCDS Main Cohort was not adversely associated with neuropsychological endpoints in this study. Maternal consumption of fish (about 12 fish meals per week) and prenatal MeHg exposure in our cohort is higher than in many other epidemiological studies addressing low-level MeHg exposure (Karagas et al., 2012). Because our population does not consume sea mammals, co-exposure to PCBs and other toxicants is of little concern. Developmental examinations have been extensive and have successively increased in sophistication and complexity, and the test battery reported here is one of the more detailed and sophisticated evaluations of our cohort to date. After 24 years of follow up of the SCDS Main cohort, our findings show that prenatal MeHg exposure from fish consumption during pregnancy is not adversely associated with neurobehavioral outcomes in offspring. These results are consistent with those we reported after each of the previous eight evaluations, and the probability that we have missed adverse associations in this cohort appear to be increasingly small.

Other studies of large fish consuming mother-child cohorts in the United Kingdom, (Daniels et al., 2004) and Spain (Llop et al., 2012) have also reported finding no adverse associations between prenatal MeHg exposures and subsequent developmental testing. In contrast, studies in the Faroe Islands, New Zealand, and elsewhere have reported finding adverse associations at lower levels of exposure than those found in Seychelles (Crump et al., 1998;

Grandjean et al., 1997; Oken et al., 2005). In the Faroe Islands study, adverse associations were reported at 22 years of age but were smaller than associations reported at younger ages (Debes et al., 2016).

The reason for differences in findings is not entirely clear. However, the association between MeHg exposure from fish consumption and child developmental outcomes is complex, and different findings across studies may be partially explained by variability in the developmental test battery and measures of MeHg exposure used. Findings may also be inconsistent due to variation in concomitant exposure to other contaminants (e.g. polychlorinated biphenyls) and nutrients (e.g. polyunsaturated fatty acids or selenium) in fish and other seafood that may influence MeHg associations with developmental outcomes. (Strain et al., 2015) Finally, evidence is accumulating that genetics influencing the metabolism of MeHg (Julvez et al., 2013) and nutrients (Yeates et al., 2015) in fish may result in geographic variability in MeHg associations due to differences in the distribution of relevant genes in the different study populations.

Rather than adverse effects of prenatal MeHg exposure, throughout follow up we have observed improved performance on some developmental tests with increasing exposure (van Wijngaarden et al., 2013b). Our current study continues this pattern with improved performance on some CANTAB and TOVA measures, although these beneficial associations are relatively few given the large number of outcomes assessed and they span various cognitive domains. We have surmised that these associations reflect the presence of possible beneficial nutrients also present in fish that confound any MeHg associations. We did not measure maternal nutritional status during pregnancy in the current cohort, but we did ask the mothers at enrollment 6 months postpartum how many fish meals they consumed per day at that time. The response to this question was not correlated with hair MeHg levels covering the prenatal period (r=0.05). However, we have investigated this hypothesis with maternal biomarkers in two subsequent nutrition cohorts enrolled in 2001 and 2008-2011 (Davidson et al., 2008; Strain et al., 2015). Findings from these younger cohorts suggest that nutrients, in particular long-chain polyunsaturated fatty acids (PUFAs), are capable of modifying the association between prenatal MeHg and developmental outcomes with possible adverse MeHg associations at high n-6/n-3 PUFA status, a marker for a pro-inflammatory milieu. As in the Main cohort, however, we have not found consistent overall associations with MeHg exposure in these nutrition cohorts and associations have not meaningfully changed after adjusting for biomarkers of maternal nutrient status such as PUFAs, selenium and vitamin E in multivariable models (Strain et al., 2015). This suggests that these nutrients are not strong confounders and cannot entirely explain the improved performance on some developmental tests with increasing exposure found in the current cohort. Alternatively, while biomarkers provide a direct indication of nutritional status as opposed to measures of self-reported fish intake which are less reliable, our nutritional assessments may not have fully captured the nutritional benefits of fish consumption resulting in residual confounding. Further study of factors that may influence the toxicokinetics and -dynamics of mercury and nutrients, such as the role of genetics, may shed additional light on the associations reported here. Nevertheless, SCDS findings to date do not provide a clear explanation for the observed associations suggesting better test performance with increasing MeHg at the exposure levels being studied.

Throughout the study in secondary analyses we have also measured recent postnatal exposure at eight of ten developmental assessments and examined its association with developmental outcomes. Postnatal exposure has repeatedly been adversely associated with developmental outcomes, including measures of attention (Connors Teacher Rating Scale ADHD Index) and motor coordination (Grooved Pegboard) at 9 years (Myers et al., 2003; Myers et al., 2009), reading comprehension at 17 years (Woodcock-Johnson (W-J) Test of Scholastic Achievement-II Passage Comprehension) (Davidson et al., 2011), and motor speed (Finger Tapping) and problem solving (Kaufman Brief Intelligence Test (K-BIT) Matrices) at 19 years of age (van Wijngaarden et al., 2013b). We also found an adverse association with IED total errors adjusted, a sensitive measure of executive function, at 22 years of age. We did not observe associations with any of the measures in the 24-year battery. Although we did not obtain nutritional biomarkers at 22 or 24 years of age, analyses at age 19 years showed that concurrent PUFA status did not confound postnatal MeHg associations (van Wijngaarden et al., 2013b). While one adverse association amongst numerous outcomes assessed at the two time points may indicate a spurious finding, it continues the pattern of sporadic postnatal associations seen in previous examinations of this cohort. Future studies should add to the currently inconclusive literature on postnatal MeHg exposure by using more comprehensive exposure metrics to better capture longitudinal variability in exposure and associations with developmental outcomes.

Postnatal MeHg studies have been limited by the lack of a comprehensive postnatal MeHg exposure profile (Grandjean et al., 2014). The one-time assessment of postnatal exposure used in nearly all studies, including ours, is not likely to be an adequate reflection of lifetime exposure or temporal variability in exposure (Myers et al., 2009). In the current cohort, recent postnatal exposure increased from an average of about 6 ppm in childhood to 8 ppm at 17 years of age and 10 ppm at 19 years of age (van Wijngaarden et al., 2013b) before declining to about 5 ppm in this study. The reasons for this fluctuation are not known. Although men at 22 years of age consumed on average two more fish meals than women which may partially explain why men have higher postnatal exposure, the higher MeHg levels in late adolescence cannot be explained by increased fish consumption (data not shown). There is a need to better account for temporal variability in exposure. Furthermore, most studies were done in children of elementary school age and did not evaluate whether adverse associations persist or appear later in adolescence when more detailed neurodevelopmental testing can be performed. Finally, despite growing evidence that genetics influence MeHg metabolism and therefore body burden (Julvez et al., 2013), none of the earlier studies have evaluated whether genetic susceptibility may explain population differences. Future targeted studies of postnatal MeHg exposure need to include a more extensive longitudinal characterization of exposure and determine its association with developmental outcomes throughout childhood and adolescence, and evaluate the impact of genetics on MeHg body burden and developmental outcomes.

Clarkson and colleagues have proposed that the Seychelles population can be considered a sentinel one for the study of MeHg toxicity from consumption of fish with only natural background levels of contamination. The Seychelles population consumes ocean fish daily, the fish MeHg content is similar to that consumed in the U.S., sea mammals are not consumed, and MeHg exposures are about ten times higher than in the U.S. (Clarkson et al.,

1998). Additional strengths of our study include minimal exposure to other pollutants and contaminants that can adversely influence children's neurodevelopment and confound MeHg associations (Davidson et al., 1998), repeated examinations using developmental tests that increase in specificity as the children have aged and that have both clinical and environmental validity (Davidson et al., 2006), and successful follow up with over 80 percent of eligible participants examined at 24 years of age. Very few, if any, cohorts have been characterized this extensively with respect to environmental and social factors that may influence child development. Further, the study has been double blind from its inception and all primary analyses have been pre-specified. Study limitations are those inherent to all observational studies, and include the potential for measurement error and residual confounding due to omission of important covariates.

In conclusion, results from the SCDS Main cohort followed for 24 years suggest that prenatal exposure to MeHg from ocean fish consumption at the levels studied here is not adversely associated with neurobehavioral development. Further studies of postnatal MeHg exposure with improved exposure metrics are needed to better guide evidence-based public health advice on fish consumption in childhood and adolescence. The SCDS continues to provide policy makers with comprehensive evidence to guide public health advisories concerning fish consumption based on balanced scientific findings.

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Highlights

- Studies of prenatal and postnatal exposure to MeHg and child development are inconclusive
- We found no adverse association between prenatal and postnatal MeHg exposure and development in young adults
- Study strengths include the prospective design, high follow-up rate, and high hair MeHg levels

Table 1

22-year summary statistics for covariates and neurodevelopmental endpoints among participants with at least one outcome: Seychelles Child Development Study Main cohort.

Outcomes and Relevant Covariates[†]	N	Mean (SD) or %	Median
MeHg Exposure (ppm)			
Prenatal	571	6.83 (4.51)	6.03
Recent postnatal (22 yr)	537	5.17 (4.02)	4.40
Covariates			
Child Sex (female = 1, %)			
Female	301	52.7%	
Male	270	47.3%	
Child Life course stress	571	3.16 (1.83)	3.00
Child full scale IQ at 9 years	532	80.48 (11.34)	81.00
Family Hollingshead SES at 9 years	522	24.75 (10.57)	23.25
Maternal IQ	510	79.91 (15.17)	77.00
Profile of Mood States (POMS)			
Negative affect ↓	560	37.68 (19.30)	36.50
Positive affect ↑	560	69.56 (16.97)	72.00
Boston Naming Test (BNT) total score ↑	567	40.66 (7.20)	41.00
CANTAB			
Reaction Time (RT)			
5-choice accuracy ↑	564	14.87 (0.44)	15.00
5-choice reaction time[a]	564	370.77 (70.24)	360.33
Intra/Extra dimensional shift (IED)			
Total errors adjusted ↓	564	42.31 (26.76)	49.00
Stages completed ↑	564	7.92 (1.21)	8.00
Pre-ED errors ↓	564	7.79 (5.76)	6.00
Completed stages errors ↓	564	14.37 (10.45)	11.00
Paired Associate Learning (PAL)			
Stages completed ↑	564	4.89 (0.37)	5.00
Total errors adjusted ↓	564	20.04 (21.08)	14.00
Stages completed on first trial ↑	564	3.01 (0.72)	3.00
Delayed Match to Sample (DMS)			
% correct 0 ms delay ↑	564	85.50 (15.64)	80.00
% correct 4 ms delay ↑	564	85.28 (17.51)	80.00
% correct 12 ms delay ↑	564	83.09 (18.65)	80.00
% correct simultaneous ↑	564	97.87 (6.72)	100.00
Rapid Visual Information Processing (RVP)			
Total misses ↓	564	12.37 (5.28)	13.00
Total false alarms ↓	564	8.10 (20.62)	2.00
Mean latency ↓	562	462.83 (149.39)	423.04
Spatial Working Memory (SWM)			

Outcomes and Relevant Covariates[†]	N	Mean (SD) or %	Median
Strategy ↓	564	35.33 (3.92)	35.00
Between errors ↓	564	32.24 (21.07)	27.00
Within errors ↓	564	1.67 (3.18)	1.00
Total errors ↓	564	32.86 (21.29)	28.00
Stockings of Cambridge (SOC)			
Mean moves for 3 move problem ↓	564	3.39 (0.58)	3.00
Mean moves for 4 move problem ↓	564	5.62 (1.04)	5.50
Mean moves for 5 move problem ↓	563	7.16 (1.47)	7.00
Healthy Behaviors (HB) (%) ↓			
Substance Abuse	555	100.0%	
0	84	15.1%	
1	142	25.6%	
2	133	24.0%	
3	96	17.3%	
4+	100	18.0%	
Mental Health[b]	555	100.0%	
0	279	50.3%	
1	106	19.1%	
2	73	13.2%	
3+	97	17.5%	
Antisocial	555	100.0%	
0	369	66.5%	
1	116	20.9%	
2+	70	12.6%	
Injury	555	100.0%	
0	475	85.6%	
1	52	9.4%	
2+	28	5.0%	

[†]RT: simple; IED: total trials adjusted; PAL: total trials adjusted not included because of their high correlation with other measures included in the table; arrows indicate direction of better performance (↓ = lower scores are better; ↑ = higher scores are better)

[a]RT scores indicate response speed and not necessarily better or worse.

[b]Rounding results in the sum of the percentages to be 100.1%

Table 2

24-year summary statistics for covariates and neurodevelopmental outcomes among participants with at least one outcome: Seychelles Child Development Study Main cohort

Outcomes and Relevant Covariates†	N	Mean (SD) or %	Median
MeHg Exposure (ppm)			
Prenatal	577	6.80 (4.49)	5.91
Recent postnatal (24 yr)	542	4.95 (3.66)	4.08
Covariates			
Child Sex (female = 1)			
Female	301	52.2%	
Male	276	47.8%	
Child full scale IQ at 9 years	533	80.63 (11.36)	81.00
Family Hollingshead SES at 9 years	523	24.71 (10.51)	23.50
Stroop Interference ↑	559	-26.87 (11.45)	-26.00
Barkley Adult ADHD Rating Scale			
Inattention ↓	562	12.67 (3.09)	12.00
Hyperactivity ↓	562	7.33 (2.26)	7.00
Impulsivity ↓	562	5.40 (1.68)	5.00
Sluggish cognitive ↓	562	13.25 (3.62)	13.00
Total ↓	562	25.41 (5.57)	24.00
Test of Variables of Attention - Visual			
D-Prime ↑	575	5.01 (1.29)	4.76
Response Time Mean ↓	575	356.92 (61.22)	348.16
Response Time Variance ↓	575	90.24 (30.92)	82.80
Omission Errors ↓	575	1.72 (5.73)	0.31
Commission Errors ↓	575	3.09 (4.65)	2.16
Test of Variables of Attention - Auditory			
D-Prime ↑	575	5.09 (1.54)	4.71
Response Time Mean ↓	575	430.33 (99.72)	419.27
Response Time Variance ↓	575	140.43 (54.38)	131.45
Omission Errors ↓	575	2.45 (5.86)	0.93
Commission Errors ↓	575	1.88 (4.35)	1.23
Finger Tapping			
Dominant ↑	574	52.79 (7.21)	53.00
Non-dominant ↑	573	47.29 (6.65)	47.20
Healthy Behaviors (HB) (%) ↓			
Substance Abuse	563	100%	
0	100	17.8%	
1	152	27.0%	
2	141	25.0%	
3	125	22.2%	
4+	45	8.0%	

Outcomes and Relevant Covariates†	N	Mean (SD) or %	Median
Mental Health	563	100%	
0	285	50.6%	
1	122	21.7%	
2	76	13.5%	
3+	80	14.2%	
Antisocial	563	100%	
0	473	84.0%	
1	70	12.4%	
2+	20	3.6%	

† arrows indicate direction of better performance (↓ = lower scores are better; ↑ = higher scores are better)

Table 3

22-year associations (β coefficient and 95% CI) between pre- and postnatal MeHg exposure and CANTAB cognitive outcomes[*^]

Outcome [†]	Prenatal model		Pre- and Postnatal model		
	N	Prenatal MeHg[‡]	N	Prenatal MeHg[‡]	Postnatal MeHg[‡]
RT					
5-choice accuracy ↑	470	-0.04 (-0.10, 0.03)	441	-0.04 (-0.11, 0.03)	-0.01 (-0.09, 0.07)
5-choice reaction time (inverse)[a]	**470**	**0.01 (0.00, 0.02)**	441	0.01 (-0.00, 0.02)	-0.01 (-0.02, 0.00)
IED					
Total errors adjusted (log) ↓	470	4.22 (-9.87, 18.30)	441	-0.02 (-14.79, 14.74)	**25.63 (8.58, 42.68)**
Stages completed ↑	470	-0.03 (-0.07, 0.01)	441	-0.01 (-0.06, 0.03)	-0.05 (-0.10, -0.00)
Pre-ED errors (inverse) ↓	470	-0.35 (-1.83, 1.12)	441	-0.35 (-1.89, 1.18)	-1.25 (-3.02, 0.52)
Completed stages errors+1 (log) ↓	468	-10.23 (-23.68, 3.22)	439	-5.00 (-19.05, 9.05)	-9.49 (-25.70, 6.72)
PAL					
Stages completed ↑	470	0.04 (-0.03, 0.12)	441	0.08 (-0.01, 0.18)	-0.05 (-0.12, 0.04)
Total errors adjusted+1 (log) ↓	470	-1.05 (-17.56, 15.47)	441	-4.24 (-21.25, 12.77)	13.82 (-5.82, 33.45)
Stages completed on first trial ↑	470	0.01 (-0.03, 0.05)	441	0.01 (-0.04, 0.05)	-0.01 (-0.06, 0.04)
DMS					
% correct 0 ms delay ↑	470	-0.00 (-0.04, 0.04)	441	-0.00 (-0.04, 0.04)	0.03 (-0.02, 0.08)
% correct 4 ms delay ↑	470	0.02 (-0.02, 0.06)	441	0.02 (-0.02, 0.06)	0.01 (-0.04, 0.06)
% correct 12 ms delay ↑	470	**0.04 (0.00, 0.08)**	441	**0.05 (0.01, 0.09)**	-0.03 (-0.07, 0.01)
% correct simultaneous ↑	470	0.00 (-0.06, 0.07)	441	0.02 (-0.05, 0.10)	0.05 (-0.04, 0.15)
RVP					
Total misses ↓	470	0.01 (-0.10, 0.11)	441	-0.00 (-0.11, 0.11)	0.00 (-0.13, 0.13)
Total false alarms+1 (log) ↓	470	2.16 (-19.35, 23.67)	441	5.01 (-17.36, 27.37)	20.32 (-5.50, 46.13)
Mean latency (inverse) ↓	469	-0.00 (-0.01, 0.01)	440	-0.01 (-0.02, 0.01)	-0.00 (-0.02, 0.01)
SWM					
Strategy ↓	470	-0.05 (-0.13, 0.03)	441	-0.06 (-0.15, 0.02)	0.02 (-0.07, 0.12)
Between errors (square root) ↓	470	-0.00 (-0.04, 0.04)	441	-0.01 (-0.06, 0.04)	0.01 (-0.04, 0.06)
Within errors+1 (inverse) ↓	470	-5.02 (-12.08,2.05)	441	-5.86 (-13.20,1.47)	0.40 (-8.06,8.87)
Total errors (square root) ↓	470	-0.00 (-0.04, 0.04)	441	-0.01 (-0.05, 0.04)	0.01 (-0.04, 0.06)
SOC					

Outcome †	Prenatal model		Pre- and Postnatal model		
	N	Prenatal MeHg‡	N	Prenatal MeHg‡	Postnatal MeHg‡
3 move problem ↓	470	-0.01 (-0.05, 0.03)	441	-0.01 (-0.05, 0.03)	-0.01 (-0.06, 0.04)
4 move problem (log) ↓	470	-0.27 (-4.14, 3.59)	441	-0.49 (-4.59, 3.61)	-1.82 (-6.55, 2.92)
5 move problem (log) ↓	470	**-5.11 (-9.25, -0.97)**	441	**-5.59 (-9.92, -1.25)**	0.86 (-4.14, 5.87)

*Regression coefficients and 95% confidence intervals. Regression coefficients scaled by 1,000 for log and inverse transformed outcomes. All models are adjusted for child sex, maternal KBIT, and SES.

^Logistic regression models: RT 5-choice accuracy, DMS simultaneous; proportional odds models: IED stages completed, PAL stages completed, PAL stages completed on first trial, DMS 0, 4 and 12 ms delay, SOC 3 move problem; All other models are linear regression models.

†arrows indicate direction of better performance (↓ = lower scores are better; ↑ = higher scores are better). Applied transformation, where necessary, in parentheses.

‡Regression coefficients that are statistically significant (p<0.05) are bolded.

[a]RT scores indicate response speed and not necessarily better or worse.

Table 4

22-year associations (β coefficient and 95% CI) between pre- and postnatal MeHg exposure and other cognitive and behavioral outcomes *

Outcome†	Prenatal model		Pre- and Postnatal model		
	N	Prenatal MeHg	N	Prenatal MeHg	Postnatal MeHg
BNT total score ↓	518	0.09 (-0.04, 0.23)	486	0.10 (-0.04, 0.24)	-0.10 (-0.27, 0.06)
POMS					
Negative affect ↓	560	0.03 (-0.31, 0.38)	527	-0.02 (-0.39, 0.34)	0.03 (-0.40, 0.46)
Positive affect ↑	560	0.03 (-0.28, 0.35)	527	0.01 (-0.32, 0.33)	0.14 (-0.24, 0.52)
Healthy Behavior ↓					
Substance Abuse	509	-0.02 (-0.06, 0.01)	478	-0.02 (-0.06, 0.01)	0.03 (-0.01, 0.07)
Mental Health	509	-0.01 (-0.05, 0.03)	478	-0.02 (-0.06, 0.02)	0.03 (-0.01, 0.07)
Antisocial	509	-0.01 (-0.05, 0.03)	478	-0.03 (-0.07, 0.02)	0.02 (-0.03, 0.07)
Injury	509	-0.01 (-0.07, 0.05)	478	-0.02 (-0.08, 0.04)	0.03 (-0.04, 0.10)

*Regression coefficients and 95% confidence intervals. BNT models are linear regression adjusted for child sex and SES; POMS models are linear regression adjusted for child sex and life course stress; Healthy Behavior models are proportional odds adjusted for child sex, SES, and child full scale IQ.

†arrows indicate direction of better performance (↓ = lower scores are better; ↑ = higher scores are better)

Table 5

24-year associations (β coefficient and 95% CI) between pre- and postnatal MeHg exposure and cognitive and behavioral outcomes*

Outcome †	Prenatal model		Pre- and Postnatal model		
	N	Prenatal MeHg‡	N	Prenatal MeHg‡	Postnatal MeHg‡
Stroop Interference+97 ↑	509	-0.12 (-0.34, 0.11)	478	-0.15(-0.38,0.08)	0.22(-0.08,0.52)
Barkley Adult ADHD Rating Scale					
Inattention (log) ↓	511	-1.71(-5.91,2.50)	480	-1.35(-5.69,2.99)	0.62(-5.01,6.24)
Hyperactivity (log) ↓	511	1.23(-4.11,6.56)	480	1.09(-4.43,6.61)	0.32(-6.83,7.48)
Impulsivity (log) ↓	511	-1.79(-6.99,3.40)	480	-1.50(-6.89,3.90)	-0.49(-7.49,6.50)
Sluggish cognitive (log) ↓	511	-0.70(-5.55,4.14)	480	0.10(-4.90,5.11)	-2.96(-9.45,3.53)
Total (log) ↓	511	-0.88(-4.78,3.02)	480	-0.68(-4.71,3.36)	0.26(-4.97,5.50)
Test of Variables of Attention - Visual					
D-Prime+5 (log)# ↑	520	-1.46(-3.81,0.88)	486	-1.47(-3.88,0.93)	-0.56(-3.69,2.58)
Response Time Mean (log) ↓	521	-0.89(-4.01,2.23)	487	-0.95(-4.14,2.23)	-0.40, (-4.54,3.73)
Response Time Variance (log) ↓	521	-0.25(-6.13,5.63)	487	-0.25(-6.33,5.84)	0.52(-7.39,8.43)
Ommission Errors+1 (inverse) ↓	521	-3.21(-8.80,2.38)	487	-3.64(-9.39,2.11)	-0.31(-7.79,7.16)
Commission Errors+2 (inverse) ↓	521	0.06(-1.89,2.02)	487	0.22(-1.79,2.23)	-1.65(-4.27,0.96)
Test of Variables of Attention - Auditory					
D-Prime+6 (log)# ↑	520	0.71(-1.77,3.19)	486	0.53(-2.02,3.09)	0.21(-3.52,3.11)
Response Time Mean (log) ↓	521	**-4.70(-8.97,-0.42)**	487	**-5.06(-9.44,-0.68)**	3.32(-2.37,9.02)
Response Time Variance (log) ↓	521	-7.04(-14.27,0.19)	487	-7.19(-14.71,0.32)	6.75(-3.02,16.52)
Omission Errors+1 (inverse) ↓	521	1.56(-4.42,7.55)	487	0.81(-5.37,6.99)	-0.04(-8.07,8.00)
Commission Errors+1 (inverse) ↓	521	2.36(-2.55,7.27)	487	2.25(-2.79,7.29)	0.56(-5.99,7.11)
Finger Tapping					
Dominant ↑	521	-0.03(-0.15,0.10)	487	-0.06(-0.18,0.07)	-0.06(-0.21,0.10)
Non-dominant ↑	521	0.07(-0.04,0.18)	487	0.05(-0.07,0.16)	-0.00(-0.15,0.14)
Healthy Behavior ↓					
Substance Abuse	513	-0.00(-0.04,0.03)	481	-0.00(-0.04,0.03)	0.02(-0.03,0.07)
Mental Health	513	-0.01(-0.05,0.03)	481	-0.01(-0.04,0.03)	-0.05(-0.10,0.00)
Antisocial	513	-0.00 (-0.06,0.05)	481	0.01(-0.05,0.06)	0.02(-0.05,0.08)

[*] Regression coefficients and 95% confidence intervals. Regression coefficients scaled by 1,000 for log and inverse transformed outcomes. Models for Stroop, Barkley, TOVA and Finger Tapping outcomes are linear regression models adjusted for child sex, child full scale IQ, and SES; Healthy Behavior models are proportional odds models that are adjusted for child sex, child full scale IQ, and SES.

[†] arrows indicate direction of better performance (↓ = lower scores are better; ↑ = higher scores are better). Applied transformation, where necessary, in parentheses.

[‡] Regression coefficients that are statistically significant ($p<0.05$) are bolded.

[#] One influential observation removed from regression.