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

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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 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 docosahexaenoic 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

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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.