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Is susceptibility to prenatal methylmercury exposure from fish consumption non-homogeneous? Tree-structured analysis for the Seychelles Child Development Study

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Abstract

Studies of the association between prenatal methylmercury exposure from maternal fish consumption during pregnancy and neurodevelopmental test scores in the Seychelles Child Development Study have found no consistent pattern of associations through age 9 years. The analyses for the most recent 9-year data examined the population effects of prenatal exposure, but did not address the possibility of non-homogeneous susceptibility. This paper presents a regression tree approach: covariate effects are treated non-linearly and non-additively and non-homogeneous effects of prenatal methylmercury exposure are permitted among the covariate clusters identified by the regression tree. The approach allows us to address whether children in the lower or higher ends of the developmental spectrum differ in susceptibility to subtle exposure effects. Of 21 endpoints available at age 9 years, we chose the Weschler Full Scale IQ and its associated covariates to construct the regression tree. The prenatal mercury effect in each of the nine resulting clusters was assessed linearly and non-homogeneously. In addition we reanalyzed five other 9-year endpoints that in the linear analysis had a two-tailed p-value <0.2 for the effect of prenatal exposure. In this analysis, motor proficiency and activity level improved significantly with increasing MeHg for 53% of the children who had an average home environment. Motor proficiency significantly decreased with increasing prenatal MeHg exposure in 7% of the children whose home environment was below average. The regression tree results support previous analyses of outcomes in this cohort. However, this analysis raises the intriguing possibility that an effect may be non-homogeneous among children with different backgrounds and IQ levels.

Keywords: Child development; Methylmercury; Prenatal exposure; Regression tree

1. Introduction

Mercury is naturally present in the environment and human activities bring it in close contact with people. In aquatic environments, some bacteria can methylate inorganic mercury to form methylmercury (MeHg) and it enters the food chain. It is known that MeHg can damage the developing fetal central nervous system at high doses. Pregnant women who consume fish expose their fetus to low dosages of MeHg. It has been proposed that prenatal exposures to MeHg, measured as total mercury (THg) concentrations above 10 ppm in maternal hair, may be associated with declines in neurodevelopment (Cox et al., 1989). Frequent fish consumers are known to reach such

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levels of exposure (Airey, 1983). Epidemiologic studies have examined this possibility of an association between prenatal MeHg exposure from fish consumption and child development and reported both its presence (Grandjean et al., 1997, 1999, 2003; Myers et al., 1995a,b) and absence (Davidson et al., 1995, 1998; Marsh et al., 1995a; Myers et al., 1995c, 2003). Recent scientific reviews have reexamined the data from human studies of the prenatal MeHg health risks from fish consumption (National Institute of Environmental Health Sciences, 1998; National Research Council, 2000), but many questions remain unresolved. Given that fish consumption is reported to have significant nutritional benefits, it continues to be controversial whether public health authorities should encourage fish consumption for health benefits or discourage it for possible risk from MeHg. Huang et al. (2005) suggested that the effect of MeHg exposure through fish consumption might be non-linear. They found that dosages between background and about 10–12 ppm were not associated with any changes in neurodevelopmental outcomes while higher exposures were associated with a decline in endpoint scores.

The Seychelles Child Development Study (SCDS) has examined the association between prenatal exposure to MeHg from maternal fish consumption and child development. The study population is a cohort of 779 children in the Republic of Seychelles. Prenatal exposure to mercury was assessed in a segment of maternal hair corresponding to growth during pregnancy. The children's neurological and developmental status was evaluated at age 6.5, 19, 29, 66, and 107 months (approximately 9 years) (Davidson et al., 1995, 1998; Myers et al., 1995b, 2003) using standard multiple linear regression analysis. Through age 9 years, no consistent association between prenatal MeHg exposure and child development has been identified in this cohort. The most recent data at 9 years of age using conventional linear regression analysis (Myers et al., 2003) found only one association where a developmental score decreased with increasing prenatal exposure and one association where the endpoint score improved with increasing exposure out of 21 endpoints. Myers et al. (2003) concluded that the data provided little evidence for a declining association between prenatal MeHg exposure at the levels studied (mean prenatal MeHg 6.9 ppm) and child development. A more flexible analysis using semiparametric additive models (Huang et al., 2005) confirmed these findings, but raised the possibility that there may be associations where outcomes declined in the prenatal exposure range above 12 ppm, supporting the Iraq study (Cox et al., 1989).

The analyses of the Seychelles 9-year data assume that the relationship between MeHg and child development is homogeneous across all children in the population, i.e., a population model. A population model is useful for examining the overall exposure/outcome relationship. However, if the relationship is non-homogeneous, i.e., different between subgroups of the population, a population model may fail to detect subgroups that are possibly at risk. For example, although there was no evidence for an association between IQ and prenatal MeHg exposure in the 9-year analysis (Myers et al., 2003), there could be subgroups of children that are more susceptible. It may be hypothesized that children with less home environmental stimulation might be more likely to show subtle effects of prenatal MeHg exposure on specific developmental domains than children from more stimulating home environments. This does occur with some toxins such as lead (Bellinger et al., 1988). If this were the case for MeHg, such a non-homogeneous relationship would not have been detected by either conventional linear regression analysis or semiparametric additive models unless the model contained interactions between MeHg and subgroup indicators. However the subgroups are not likely to be known in advance and hence conventional models rarely include such interactions. To test the hypothesis of non-homogeneity, we reanalyzed the 9-year data using regression tree methods (Breiman et al., 1984).

2. Materials and methods

2.1. Subjects

The SCDS main cohort consists of 779 mother-child pairs who were enrolled in 1989–1990, representing about 50% of the live births during that time period. There were 717 children from the cohort still eligible for the study at age 9 years, and 643 returned for testing at an average age of 107 months. Detailed descriptions of the cohort and exclusion criteria have been published elsewhere (Davidson et al., 1998; Marsh et al., 1995b; Myers et al., 1995c, 1997, 2003; Shamlaye et al., 1995). The study was approved by the research subjects boards of the University of Rochester and the Ministry of Health in the Republic of Seychelles. Informed consent was obtained from each child's parent or guardian before the child participated in the study.

2.2. Exposure assessment

Prenatal exposure was measured using the mean of the total mercury (THg) concentration in the longest available segment of maternal hair representing growth during pregnancy, as discussed previously (Cernichiari et al., 1995). This is the prenatal exposure index used in the SCDS analyses and in nearly all earlier studies. Total mercury was used as the measure of exposure because 80% of THg in hair samples collected from fish eating populations is MeHg (Cernichiari et al., 1995; Phelps et al., 1980). Total mercury was measured by cold vapor atomic absorption and correlates well with MeHg levels in maternal blood and infant brain (Cernichiari et al., 1995; WHO, 1990).

2.3. Developmental assessment

At 9 years of age, each child was given a battery of developmental tests that resulted in 21 endpoints assessing cognition, language, memory, motor, perceptual-motor and behavioral functions (Myers et al., 2003). We selected for this analysis the WISC III Full Scale IQ (FSIQ, Wechsler, 1991), an well-known measure of global cognition, and those endpoints from the linear regression analysis for which the coefficient describing an effect of prenatal exposure was different from 0 with a p-value of less than 0.2 (Myers et al., 2003). The other