

# Semiparametric Modeling of Age at Achieving Developmental Milestones After Prenatal Exposure to Methylmercury in the Seychelles Child Development Study

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Controversy exists concerning the fetal risk associated with exposure to low-dose methylmercury from maternal fish consumption. Previous studies of the effects of acute prenatal mercury exposure identified delays in achieving developmental milestones among exposed children. This led to public health concern that prenatal low-dose exposure from fish consumption could adversely affect the fetus. We evaluated the effects of prenatal methylmercury exposure (through maternal fish consumption) on the age that children walked and first said words in the main study cohort of the Seychelles Child Development Study. We used semiparametric generalized additive models to identify nonlinearities in the relationships between prenatal exposure and developmental outcomes, after adjusting for covariates, and to evaluate their importance. Very slight delays (<1 day) in walking were seen as mercury levels increased from 0 to 7 ppm, but this effect did not persist at the higher exposure levels represented by the cohort, making it difficult to conclude that a cause and effect relationship existed at the exposure levels seen in this cohort. There was no evidence for any association between prenatal exposure and age at talking. *Key words:* child development, developmental milestones, generalized additive models, methylmercury, semiparametric modeling. *Environ Health Perspect* 106:559–564 (1998). [Online 10 August 1998] <http://ehpnet1.niehs.nih.gov/docs/1998/106p559-564axtell/abstract.html>

The Seychelles Child Development Study (SCDS) is an ongoing longitudinal study of the effects of prenatal mercury exposure through maternal fish consumption on neurodevelopmental outcomes in children. Previous studies of the effects of acute mercury exposure in pregnant Iraqi women who consumed bread made from seed grain treated with a fumigant containing methylmercury identified delays in achieving developmental milestones among exposed children. The dose–response relationship between methylmercury exposure and clinical outcomes determined following the Iraqi poisoning was based upon two end points, developmental milestones and neurological findings (1,2) The Iraq study led to public health concern that prenatal low-dose exposure from fish consumption could adversely affect the fetus and was used by the World Health Organization (WHO) (3) as a basis for its recommendations concerning low-level fetal exposure. Other studies from Canada (4) and New Zealand (5,6) supported this concern, but developmental milestones were not evaluated. Studies of fish-eating populations in the Republic of Seychelles and the Faroe Islands have not confirmed an association between exposure and delayed developmental milestones (7,8). Presently there is significant controversy about the fetal risk associated with exposure to low-dose methylmercury and how aggressively levels in commercially available fish should be regulated.

The relationships between two developmental milestones, age at walking without holding on (walking) and age at first saying words other than “mama” or “dada” (talking), as determined by maternal recall when the child was 19 months of age, and maternal hair mercury levels and covariates were evaluated previously in the SCDS cohort using multiple regression analysis (8). While no definite relationship between methylmercury exposure and milestone achievement was found, a significant mercury effect ( $p = 0.04$ ) was identified among males in a regression model that included an interaction term between mercury and sex. A 10-ppm increase in maternal hair mercury during pregnancy was associated with a 2-week delay in walking in males. Although the test for the model was significant, the interaction term was not ( $p = 0.13$ ), and the mercury association in males was not significant ( $p = 0.16$ ) when five statistical outliers (four males and one female) were removed. Overall, Seychellois males walked early, at a mean age of 10.6 months.

We conducted more extensive analyses of these developmental data to examine this relationship in greater detail. Standard multiple regression analysis, which was used previously, assumes a linear relationship between continuous predictor variables and outcomes. Although it is possible to model nonlinear relationships using ordinary regression methods and while these methods offer some advantages, a

nonparametric approach based on smoothing is available, which has the advantage that a specific functional form for the relationship does not have to be assumed (9). A convenient family of models, referred to as generalized additive models (GAMs), has been developed, which yields estimates of general, functional relationships using smoothing techniques (9). These models have been applied in a number of observational studies (10–12) This analysis was designed to identify nonlinear relationships between methylmercury exposure and milestone achievement and to evaluate the importance of these relationships.

## Methods

**Subjects.** The study population consisted of 779 Seychellois children from the main study cohort of the SCDS. Informed consent was obtained from parents for all children in the cohort. The cohort and criteria for exclusion have been described in detail elsewhere (8,13–15). At the 19-month evaluation, 738 children were available for testing (16). An interview with the child’s parent or caregiver was conducted prior to the examination, and the ages at which the child walked without support and said words other than “mama” or “dada” were recorded.

**Measurement of exposure.** The measure of exposure was the mean of the total mercury concentration in segments of maternal hair, representing growth during pregnancy. Total mercury in each hair segment was measured by cold vapor atomic absorption as described previously (17). Maternal hair mercury has been shown to correlate well

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with infant brain mercury levels as measured by cold vapor atomic absorption (18).

**Statistical analyses.** The relationships between the two developmental milestones (age at walking and talking) and maternal hair mercury levels and covariates were evaluated using GAMs. Each developmental outcome was modeled as the sum of terms that were linear functions of categorical independent variables and terms that were smoothed functions of the continuous independent variables. The model makes no assumptions about the functional form of the relationship between the dependent variable and mercury or other continuous independent variables. It does assume, however, that the effects of the various independent variables are additive. This makes it possible to look at the relationship between the outcome and each independent variable one at a time, while controlling for the other independent variables. Smoothed functions are essentially produced using local averaging. At each value of the independent variable ( $X$ ), the smoothed value of the dependent variable ( $Y$ ) is a weighted average of  $Y$  values corresponding to observations with "nearby"  $X$  values. Different methods for choosing the weights result in different smoothers.

The dependent variables walking and talking were transformed by taking logs because the distributions of the raw data were skewed, and the error terms for the parametric portion of the model were assumed to be normally distributed. This transformation was also used in the original multiple regression analysis. Full and reduced models with and without mercury by sex interaction terms, specified *a priori*, were fit for each developmental milestone. Because of the local nature of the fitting process, the overall form of the estimated trend in the outcome variable for each model was not expected to be sensitive to outliers, at least in areas where the data were not sparse. Consequently, all observations without missing values were included in each analysis.

The covariates in the full model included maternal hair mercury level, sex, gestational age, birth weight, birth order, child's medical history (positive medical history defined as a medical diagnosis of intrauterine growth retardation made at birth or a head circumference greater than two standard deviations above or below the Seychellois mean at any age), regular maternal use of alcohol during pregnancy (yes/no), maternal use of tobacco during pregnancy (yes/no), maternal medical history, and history of breast feeding. Covariates associated with the child's environment included a measure of the child's home environment [the Caldwell-Bradley

preschool version of the Home Observation for Measurement of the Environment (HOME) (19)], family income and language spoken in the home (97% of Seychellois speak Creole at home). Finally, covariates measuring characteristics of the parents included maternal age, maternal and paternal education level, and care-giver intelligence.

The reduced model included the subset of these covariates thought to be most important in the Seychelles (8). The covariates in the reduced model were the child's sex, birth weight, and medical history; the mother's age and educational level; the home environment score; and the language spoken in the home. Each model was estimated with and without an interaction between mercury and sex because previous studies have suggested that the effect of exposure is greater in males than in females (1,4,8).

The reduced models for walking and talking were also estimated using a log transformation of the mercury variable. The log of the exposure variable is often used in toxicological studies. In particular, studies of human health risks of lead exposure have taken this approach (20–22).

Two types of approximate F tests were used to evaluate the significance of the smoothed terms in the model (9). An approximate F test for nonlinearity was used to determine whether the nonlinear component of each smooth term was significantly better than the fit assuming a linear relationship. This test compared the fit of the model with mercury (a continuous covariate) included as a smoothed term to that of a model with mercury (the continuous covariate) included as a linear term. A second type of approximate F test was used to test the overall significance of the continuous predictor variables in each model by comparing the fit of the model with and without the smooth term. The  $p$ -values for the approximate F tests should be used only for guidance in determining which variables or nonlinear components of a smooth are important in a given model. The test statistics calculated from these models do not have exact or even asymptotic F distributions (9). However, Hastie and Tibshirani report that simulations show them to be useful approximations (9).

The S-Plus software package (MathSoft, Seattle, WA) was used to fit the GAM models for age at walking and talking (23). Smoothing splines with 4 degrees of freedom ( $df$ ) were used to compute the smooth term for each continuous predictor variable. The number of degrees of freedom of a smoother is an adjustable parameter that determines the degree of smoothing. As the degrees of freedom are decreased, the fitted curve becomes smoother; increasing

the number of degrees of freedom allows the smooth to follow the data points more closely and thus to fluctuate more. More parsimonious models with 2  $df$  for each smoothed term were also estimated, and these results were compared with those for the 4- $df$  models. Smooths with varying degrees of freedom were also computed for predictors whose smooth had a significant nonlinear component in one of the models estimated.

To fit a model with separate mercury slopes for males and females, two new variables were created, representing mercury levels in males and females. The new variable representing mercury level in a given sex was set equal to the maternal hair mercury level for that sex and was set to zero for children of the other sex, as is done when modeling interactions in linear models. These two new mercury variables were included in the models in place of a single mercury variable for the entire cohort. This approach for estimating the separate mercury smooths by sex is not entirely adequate because the left-most section of the mercury smooth for one sex incorporates points for the other sex, for which the mercury values are zero. However, methods that allow for interactions with smooth terms are still under development and have not been made available in statistical software packages. Because there was some evidence for a mercury effect in males but not in females in the original analysis (8), it was important to include approximate smooths for mercury separately, by sex.

An alternative method was also used for generating separate mercury smooths by sex, where the new variable representing mercury level in one sex was set equal to maternal hair mercury level for that sex and was set to missing for children of the other sex. Missing values were not used to calculate the respective smooths for each sex, and their fitted values were assigned a value of zero (24).

For each model, the estimated association between each continuous predictor and the response variable was examined graphically. Each plot describes the contribution of the particular independent variable to the additive predictor for the log of age at walking or talking. The points are partial residuals for mercury [scaled values of the dependent variable adjusted for all of the independent variables, continuous and categorical, except the one of interest for the plot (23,24)]. Similar partial residual plots were used in the original paper (8) to illustrate the results of the multiple regression analysis. Nonsimultaneous, approximate confidence bands were included in the smoothed plots for the continuous independent variables. These bands provide an indication of the precision with which the smooth curve

**Table 1.** Mean and standard deviation (SD) of age at walking without holding on and age at saying words other than “mama” or “dada,” overall and by maternal hair mercury level

Milestone <sup>b</sup>	Sex		Overall	Maternal hair mercury level (ppm) <sup>a</sup>				
				≤3	>3–≤6	>6–≤9	>9–≤12	>12–27
Walking	Female	<i>n</i>	356	72	113	81	39	51
		Mean ± SD	10.72 ± 1.91	10.58 ± 1.75	10.76 ± 2.08	10.88 ± 2.16	10.72 ± 1.49	10.61 ± 1.58
Talking	Male	<i>n</i>	364	92	99	73	55	45
		Mean ± SD	10.61 ± 2.03	10.22 ± 1.96	10.78 ± 2.00	10.84 ± 2.14	10.55 ± 1.91	10.78 ± 2.15
Walking	Female	<i>n</i>	333	68	104	76	36	49
		Mean ± SD	10.50 ± 2.60	10.56 ± 2.91	10.70 ± 2.46	10.64 ± 2.20	10.08 ± 2.83	10.04 ± 2.85
Talking	Male	<i>n</i>	347	85	93	72	52	45
		Mean ± SD	11.05 ± 2.88	11.09 ± 2.80	10.96 ± 3.05	11.24 ± 2.89	11.15 ± 2.82	10.73 ± 2.84

<sup>a</sup>The mean (median) maternal hair mercury levels were as follows: ≤3 ppm, 1.9 (2.0); >3–≤6 ppm, 4.5 (4.4); >6–≤9 ppm, 7.4 (7.4); >9–≤12 ppm, 10.3 (10.3); >12–27 ppm, 15.2 (14.2).

<sup>b</sup>Data on developmental milestones as determined by primary care-giver recall were collected when the child was 19 months ± 2 weeks of age. There were 738 children in the cohort at 19 months of age, including 365 females and 373 males.

has been estimated across the range of values of the independent variable, with the precision at a given point depending on the amount of data in the immediate neighborhood. The rug plot (vertical marks) along the bottom of each graph illustrates the distribution of the values of the independent variable in the data set.

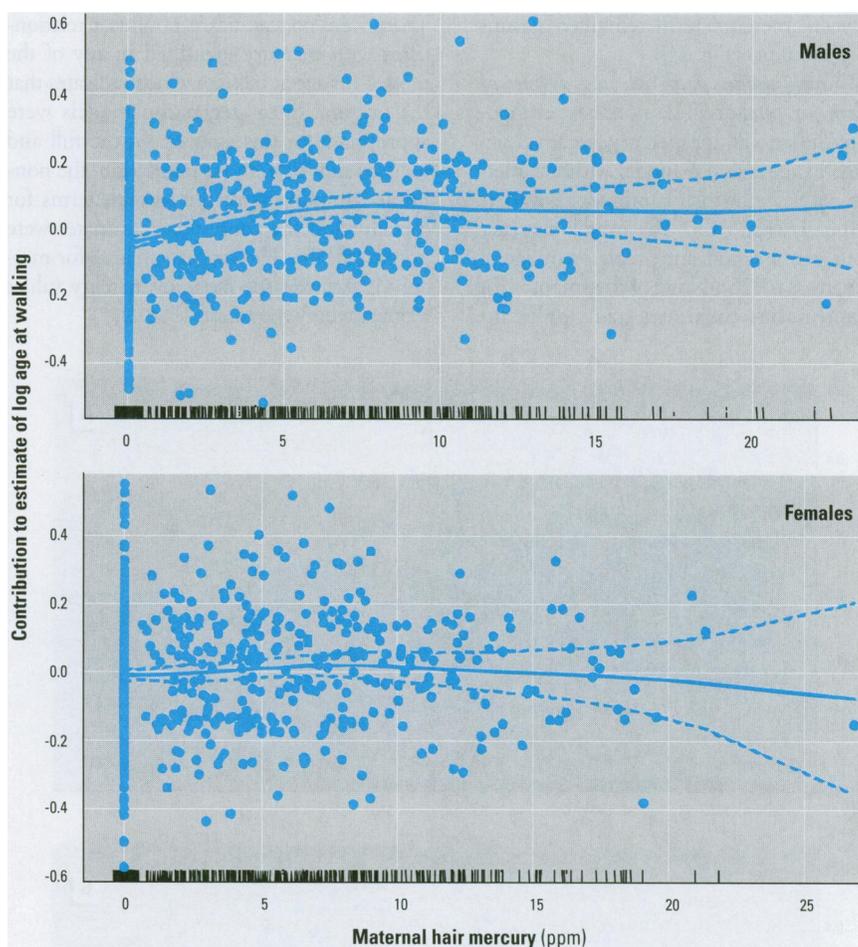
## Results

Descriptive statistics for age at walking and talking, overall and by mercury category, are shown in Table 1. The unadjusted mean age at walking without holding on was relatively constant across mercury category, although there was an increase in males, i.e., the milestone appeared slightly later in development, for each higher category as compared to the lowest category (≤3 ppm). The mean age at talking was essentially constant across exposure categories for males. Among females, age at talking declined slightly, i.e., the milestone appeared later in development for the three lowest categories as compared to the two highest exposure categories.

The results for the full and reduced models for both developmental milestones were very similar. For the sake of brevity, only the reduced model results are reported below.

### Age at Walking

**Reduced model with interaction.** The nonlinear components of the mercury values in the reduced model with separate mercury variables for males and females were not significant ( $p = 0.10$  and  $0.59$  for males and females, respectively). Thus, there was no evidence for a specifically nonlinear relationship between the log of age at walking and maternal hair mercury for either males or females. The nonlinear components of the covariates were also not significant, indicating that the original linear model was acceptable. The overall smooth term for mercury was significant for males ( $p = 0.028$ ) but not for females ( $p = 0.74$ ). Figure 1 illustrates the contribution of the smoothed mercury term



**Figure 1.** Results from the reduced model with mercury by sex interaction term for age at walking. The estimated relationship (fitted smooths; solid lines) between maternal hair mercury level and the log of age at walking for males and females was adjusted for covariates. The dashed lines are twice the pointwise standard error curves, and the points are partial residuals for the mercury variables, calculated by adding the estimated smoothed mercury term back to the scaled residuals.

for males and females to the predicted value of log age at walking from the reduced model with interaction.

**Reduced model without interaction.** The nonlinear component of the mercury term was significant ( $p = 0.045$ ), suggesting that a linear model may not be adequate for evaluating this relationship. None of the other continuous variables had significant nonlinear components. The smoothed mercury

term was a significant predictor of age at walking ( $p = 0.036$ ). The estimated smooth for mercury showed an increase in the log of age at walking as mercury increased from 0 to approximately 7 ppm, and a very slight decrease as mercury increased from 7 to 25 ppm (Fig. 2A). The confidence bands are wide above 15 ppm, reflecting the sparsity of the data beyond this exposure level. The estimated change in age at walking resulting

from an increase in exposure from 1 to 5 ppm was +0.04 months, and from 5 to 15 ppm was -0.03 months (Table 2). Walking at a slightly earlier age was associated with a higher home environment score. Children walked later when they had a positive medical history and when their mothers were more well-educated. These associations were similar to those in the original multiple regression analysis (8).

When the reduced model without interaction model was estimated using a log transformation of maternal hair mercury, the nonlinear component of the smooth was no longer significant ( $p = 0.18$ ), but the overall mercury term remained significant ( $p = 0.034$ ) (Fig. 2B).

**Walking models with varying degrees of freedom for smooths.** The nonlinear component of the smooth for mercury remained significant in the reduced model without interaction with 2df for each continuous covariate ( $p = 0.022$ ) (Fig. 3C). The overall mercury smooth was a significant predictor of age at walking ( $p = 0.026$ ). None of the smooths for the continuous covariates had significant

nonlinear components. The estimated curves showed that children walked earlier as the home environment score increased and maternal education level decreased.

Allocating more than 4 df for the mercury smooth did not provide any meaningful new patterns in the estimated relationship between mercury and log of age at walking. Figure 3 presents the curves for mercury in the reduced model using 1, 2, 4, and 6 df. Two degrees of freedom were allocated for the continuous covariates in all of these models.

### Age at Talking

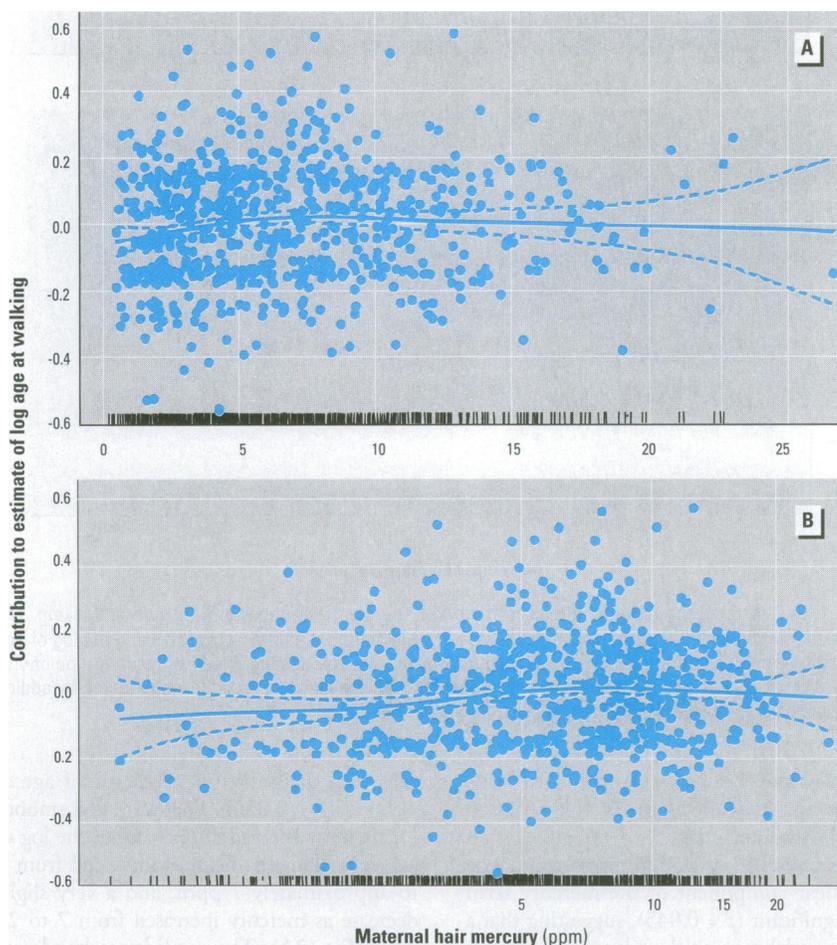
There were no significant nonlinear relationships with mercury identified in any of the models for age at talking, which indicates that the original linear regression models were appropriate for this analysis. In the full and reduced models without interaction, the nonlinear components of the smooth terms for mercury and the continuous covariates were not significant. The estimated curve for mercury is flat over the range of mercury values represented by the cohort (Fig. 4).

## Discussion

The GAM analysis indicated that the relationship between maternal hair mercury level and age at walking may not be entirely linear. Walking appeared at a later age as exposure increased in the range from 0 to 7 ppm. Walking appeared slightly earlier with increasing mercury levels above 7 ppm. There was no evidence in any of the models that higher levels of mercury exposure resulted in further delays in walking. Overall, this does not appear to be the kind of monotonic increasing relationship hypothesized as the result of prenatal exposure to methylmercury. It is unclear why there was an apparent increase in age at walking at the lowest levels of mercury exposure and not at higher levels. There is no biological or developmental hypothesis that would explain such an outcome at these exposure levels. The effect may be spurious. The size of the effects predicted by the model over the range of exposures represented by this cohort were small, on the order of  $\pm 1$  day.

The increase in the log of age at walking as maternal hair mercury levels increased from 0 to 7 ppm or so appears to have been largely responsible for the positive slope for mercury in the original multiple regression analysis, as illustrated by the graphs with 1 and 2 df in Figure 3. Similarly, the positive slope for mercury in males in the original analysis with a mercury by sex interaction term is likely to be due to the upward trend at low mercury levels in the smooth for mercury among males found in this analysis. The two methods for estimating separate mercury smooths by sex produced curves that were very similar. The separate smooths estimated for males and females in the models with interaction were similar to the estimated smooth for mercury in the walking model without interaction. The rise in the curve from 0 to 7 ppm is steeper for males than females; the overall curve for both sexes combined lies somewhere in between.

Figure 2 illustrates the effect that taking the log of the mercury values had on the



**Figure 2.** Results from the reduced model without interaction for age at walking. The figure shows the fitted smooths (solid lines), twice the pointwise standard error curves (dashed lines), and the partial residuals (points). The partial residuals for mercury (A) and the log of mercury (B) [degrees of freedom (df) = 4] were estimated using separate models.

**Table 2.** Change in age at walking and talking associated with an increase in maternal hair mercury level as estimated from the reduced models without mercury by sex interaction

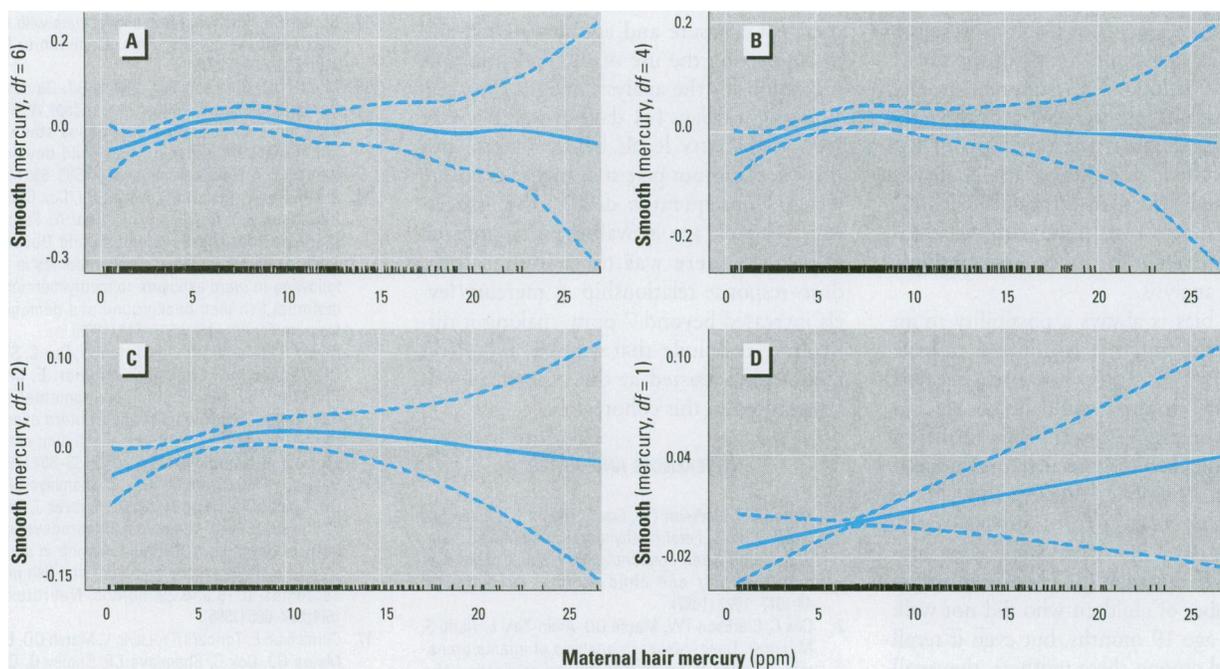
Increase in maternal hair mercury (ppm)		Change in age at walking (months) <sup>a</sup>	Change in age at talking (months) <sup>a</sup>
From	To		
1	3	+ 0.02	+ 0.01
3	5	+ 0.02	+ 0.00
5	10	- 0.00	+ 0.00
10	15	- 0.03	+ 0.00
15	20	- 0.02	+ 0.02

<sup>a</sup>Entries of  $\pm 0.00$  correspond to a change with absolute value  $< 0.005$ .

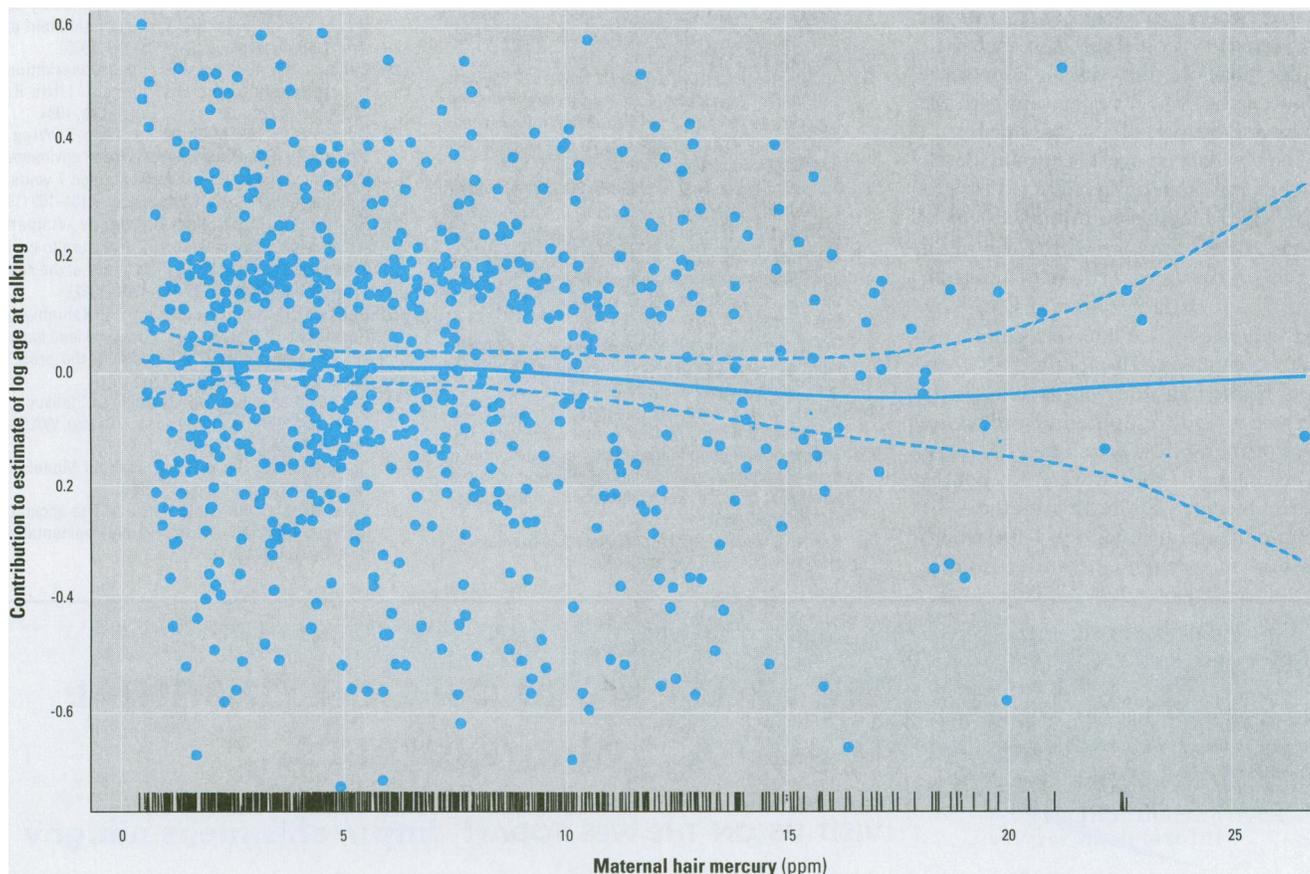
estimation of the curve for mercury. The lower mercury values, from 0 to 5 ppm or so, dominate the estimate of the association

when the log of mercury is used. In the region from 10 to 20 ppm on the other hand, where harmful effects may be more likely, the

exposure values are compressed by the log transformation, and consequently they influence a smaller portion of the estimated curve.



**Figure 3.** Results from the reduced model without interaction showing fitted smooths (solid lines) for mercury with 6 (A), 4 (B), 2 (C), and 1 (D) degree of freedom ( $df$  for other continuous predictors = 2). Note that the scale of the y-axis varies from plot to plot in this figure. Dashed lines indicate twice the pointwise standard error curves.



**Figure 4.** Results from the reduced model without interaction for age at talking showing the fitted smooth (solid line), twice the pointwise standard error curves (dashed lines), and partial residuals for mercury (points) ( $df = 4$ ).

There was no evidence for a nonlinear effect or, in fact, any effect of mercury exposure on age at talking. This is consistent with the fact that no effect of mercury was identified in the original analysis. The nonlinear components of mercury were not identified as significant in any of the GAM analyses for talking. This supports the use of standard multiple regression for the talking analysis. In fact, the direction of the estimated effects for the covariates in the full and reduced GAM models without interaction were consistent with the signs of the coefficients in the original multiple regression analysis.

Recall bias is always a possibility in an observational study. It is unlikely to have occurred in this study, however, because none of the children could be considered cases. On average, Seychellois children walked and talked early relative to American children, for example. Consequently, there would be no reason for a subset of the mothers to recall age at first walking or talking in a differential way. There was a very small number of children who did not walk or talk by age 19 months, but even if recall bias existed among these mothers, the small numbers make it very unlikely that the overall results would be affected. It is also true that the cohort members and their mothers do not know the concentration of methylmercury as measured in their hair samples; therefore, they do not know their exposure status, which depends on both the amount and the type of fish consumed.

The raw data on age at achieving developmental milestones were collected by asking the child's mother or primary caregiver the age, in months, at which the child walked or first said words other than "mama" or "dada." This question was asked in a face-to-face interview conducted when the child was 19 months  $\pm$  2 weeks of age. In the Iraq study of methylmercury exposure and developmental milestone achievement, mothers were asked this question when their children were 30 months old, on average. While this method for determining age at milestone achievement does rely on mothers' memories, studies

suggest that mothers are fairly good at recalling this information (25).

The generalized additive models analysis used here was helpful in identifying a possible nonlinear relationship between mercury exposure and age at walking, and in supporting the use of standard multiple regression for the analysis of age at talking. Very slight delays (<1 day) in walking were seen at mercury levels below 7 ppm, but this effect did not persist at higher exposure levels. Consequently, despite the association between age at walking and prenatal exposure, there was no evidence for a dose-response relationship as mercury levels increased beyond 7 ppm, making it difficult to conclude that a cause and effect relationship existed at the exposure levels represented in this cohort.

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