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Exploring nonlinear association between prenatal methylmercury exposure from fish consumption and child development: evaluation of the Seychelles Child Development Study nine-year data using semiparametric additive models

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Abstract

Studies of the association between prenatal methylmercury exposure from maternal fish consumption and neurodevelopmental test scores in the Seychelles Child Development Study have not found adverse effects through age 9 years. The analysis for the most recent 9-year data (Lancet 361 (2003) 1686) employed conventional linear regression models. In this study we reanalyzed the same Seychelles 9-year data using semiparametric additive models with different degrees of smoothing to explore whether nonlinear effects of prenatal exposure were present. Of 21 endpoints in the linear analysis, we chose only those with a two-tailed P value less than 0.2 for the effect of prenatal exposure. Six endpoints met the criterion. A nonlinear effect was identified with the more smooth model for only one endpoint. The test for an overall effect of prenatal exposure was also significant, with a P value of 0.04, while the corresponding P value in the linear regression analysis was 0.08. The nonlinear curve appeared to be nearly flat when the level was below approximately 12 ppm in maternal hair, with a linear trend above that level, suggesting a possible adverse effect in the uppermost range of prenatal exposure included in this cohort. Because of the descriptive nature of semiparametric additive models, the P values are not precise, and certainly there are fewer data above 12 ppm. We conclude that this reanalysis supports the primary linear analysis, showing little evidence for a prenatal adverse effect.

Keywords: Child development; Fish consumption; Generalized additive models; Methylmercury; Semiparametric models

1. Introduction

Methylmercury (MeHg) is a known neurotoxin that can have severe effects on the developing fetal central nervous system. The study on the outbreak of MeHg poisoning in Iraq (Cox et al., 1989) indicated that adverse effects of prenatal exposure might occur at MeHg levels of 10–20 ppm in maternal hair, the upper range of mercury levels known to occur in high fish consumers. Subsequently, epidemiologic studies have reported both association (Myers et al., 1995a, b; Grandjean et al., 1997, 1999) and lack of association (Marsh et al., 1995b; Myers et al., 1995c, 2003;

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Davidson et al., 1995, 1998) between child development and prenatal MeHg exposure at the levels achieved by regular fish consumption. Recent scientific reviews have reexamined the data from human studies of the MeHg health risks from fish consumption (National Institute of Environmental Health Sciences, 1998; National Research Council, 2000), but controversy persists. The question is especially important since fish consumption is reported to have health benefits and its consumption is recommended by many health agencies. Additionally it is an important part of nutrition for many populations.

The Seychelles Child Development Study (SCDS) is an ongoing longitudinal study of the effects of prenatal MeHg exposure on child development from a maternal diet high in fish. It was originally designed to determine if risk predictions from the Iraq study (Cox et al., 1989) were correct. 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 6.5, 19, 29, 66, and 107 months (9 years) of age (Myers et al., 1995b; Davidson et al., 1995, 1998; Myers et al., 2003) using standard methods of assessment. Based on multiple linear regression analysis, the primary analysis plan at each evaluation determined the relationship between prenatal exposure and child development. Through 9 years of age, no consistent adverse association between prenatal MeHg exposure and child development has been identified in this cohort. Specifically, for the most recent data at 9 years of age, the primary linear analysis (Myers et al., 2003) found a significant association between prenatal exposure in 2 out of 21 endpoints, one adverse and the other beneficial. Because of the large number of endpoints in this study, either of these associations could be a type-I error or a false positive. Another possible explanation for the beneficial association is that mercury exposure is confounded with fish consumption, and the mercury level may in fact be a surrogate measure of nutrition. The conclusion of Myers et al. (2003) was that the 9-year data reflected little evidence for an adverse association between child development and prenatal MeHg exposure.

The primary analysis at 9 years employed multiple linear regression since it is the standard method in such observational studies. One advantage of this approach is that exact statistical tests are available for evaluating the strength of the evidence that the slope of the line describing the exposure/outcome relationship differs from zero (no effect). If the true exposure/outcome relationship is nonlinear, however, forcing a straight line fit to the data may lead to biased inference about the nature of the association. This concern led Axtell et al. (1998, 2000) to consider semiparametric additive modeling (Hastie and Tibshirani, 1990) as a secondary analysis of the ages at which subjects walked and said their first words, and of the 66-month SCDS data. They identified a very slight delay (<1 day) for age at first walking as the maternal mercury levels increased from 0 to 7 ppm. For the 66-month data, small nonlinearities were found between prenatal exposure and two out of six developmental endpoints, the Preschool Total Language Score (PLS) (Zimmerman et al., 1979) and the Child Behavior Checklist (CBCL) Total *T* score (Achenbach, 1991). The PLS curve showed a small downward trend below 10 ppm and then an upward trend, representing improvement, above 10 ppm. The CBCL had a small downward (improvement) trend below 15 ppm and then an upward trend above this level. Since any nonlinear trends might have persisted through age 9 years, and would not have been detected by conventional linear regression analysis, we reanalyzed the 9-year data using semiparametric additive models.

2. Materials and methods

2.1. Subjects

A cohort of 779 mother–child pairs was enrolled in 1989–1990, representing about 50 percent of live births during that period. There were 717 children from the cohort still eligible for the study, from which 643 children returned for testing at an average age of 107 months. Detailed descriptions of the cohort and exclusion criteria have been published elsewhere (Myers et al., 1995c, 1997, 2003; Marsh et al., 1995a; Shamlaye et al., 1995; Davidson et al., 1998). 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 nearly all earlier studies and in all of the SCDS analyses. THg was used as the measure of exposure because 80 percent of THg in hair samples collected from fish-eating populations is MeHg (Cernichiari et al., 1995; Phelps et al., 1980). THg was measured by cold vapor atomic absorption and correlates well with MeHg levels in maternal hair and blood (WHO, 1990; Cernichiari et al., 1995).

2.3. Developmental assessment

Each child was given a battery of developmental tests, yielding 21 endpoints that assessed cognition, language, memory, motor, perceptual-motor, and behavioral functions. All tests were translated into Creole (the language spoken at home by nearly all Seychelles families) and administered by a team of three Seychelles child development professionals. All testing took place in a dedicated child development center and all children received the tests in the same order. We chose to reanalyze only those endpoints for which the coefficient for prenatal exposure had a two-tailed P value less than 0.2 in the linear regression analysis (Myers et al., 2003). The endpoints analyzed were the WISC-III Full-Scale IQ (Wechsler, 1991) and the California Verbal Learning Test (CVLT)—Short Delay (Delis et al., 1994) which both measure global intelligence; the Grooved Pegboard (Knights and Moule, 1968) (both the dominant and nondominant hands) and the Bruininks–Oseretsky (B–O) Test of Motor Proficiency (Bruininks, 1978) for motor function; and the Connors Teacher Rating Scale (CTRS) (Connors, 1985) for the child's activity level. With the exception of the Grooved Pegboard and the CTRS, an increase in the score is associated with improved performance on the test.

2.4. Covariates

In addition to maternal hair THg levels as an independent variable, the primary linear analysis included the following covariates, which were chosen a priori: sex, maternal age, test examiner, caregiver's intelligence (Kaufman Brief Intelligence Test (K-Bit), Kaufman and Kaufman, 1990), child's medical history, the Family Resource Scale (FRS) (Dunst et al., 1994), a family status code (2, 1, or none biological parents at home), the Hollingshead measure of socioeconomic status (SES), Henderson Environmental Learning Profile Scale (HELPS) (Henderson et al., 1972), child's age at testing, child's home environment during toddlerhood (the Caldwell–Bradley Home Observation for Measurement of the Environment (HOME) (Caldwell and Bradley, 1984)), child's hearing score, and a measure of recent postnatal MeHg exposure. Recent postnatal MeHg exposure was determined in a sample of child hair taken at the 9-year evaluation. A 1-cm segment of hair closest to the scalp was analyzed, representing approximately 1 month of recent exposure. The HOME, SES, and hearing score were categorized as in the primary linear analyses. The remaining continuous predictors are prenatal and recent postnatal exposure, maternal age, FRS, HELPS, K-Bit, and child's age at testing.

2.5. Statistical analysis

Using semiparametric additive models (Hastie and Tibshirani, 1990), the relationships between prenatal THg exposure and the six developmental measures at 9-years of age were evaluated, first without adjustment for covariates and then with adjustment as in the linear analysis (Myers et al., 2003). For the unadjusted case, each developmental outcome was modeled only as a smooth function of prenatal exposure. For the model with covariate adjustment, the outcome was modeled as the sum of terms that were linear for categorical independent variables and terms that were smoothed functions of the continuous independent variables denoted by s(variable name) (see, e.g., Table 1). The model makes no assumptions about the functional form of the relationships between the dependent variable and THg or other continuous independent variables. It does assume, however, that the effects of the various independent variables are additive. All observations without missing values were included in each analysis.

The Grooved Pegboard and CTRS were transformed (negative reciprocal and log transformation, respectively) to stabilize the variance and to produce more normally distributed errors in the primary linear analysis. For fitting semiparametric additive models, we tried two approaches, using the transformed response as in the linear analysis or using the original nontransformed dependent variables and modeling the mean by a reciprocal or log link function, i.e., "generalized linear models" with nonparametric terms (Green and Silverman, 1994). The results differed very little and hence we chose to present the model using the transformed response, for ease of comparison.

In the primary linear analysis (Myers et al., 2003) interaction effects between gender and mercury exposure were considered, and if significant, a model with interactions was reported. The interaction terms are equivalent to variables created to represent pre- or postnatal mercury levels in males and females. The new variable for mercury level in a given gender was set equal to the level for that gender and zero for the opposite. These new variables were included in our covariate-adjusted semiparametric additive models if they were in the final linear analysis. The new variables are not continuous, and, as suggested by Chambers and Hastie (1993), the zero values were not used to calculate the respective smooth term for each gender and remained zero in the fitted values.

The S-PLUS (Mathsoft, 2000) software package, Version 6.0, was used to fit the semiparametric additive models. We ran S-PLUS with the default settings first and then with stricter convergence criteria recommended by Dominici et al. (2002), and the results differed only in the third decimal place. We reported the results using the stricter criteria to assure correct estimates. Smoothing splines (Green and Silverman, 1994) with 3 and 5 degrees of freedom (df) were used to compute the smooth term for each continuous independent variable, while linear regression uses only 1df. The

Table 1
Approximate *P* values for nonlinear effects and overall significance of the smooth term for maternal hair THg levels, denoted by s(merc) in covariate-adjusted semiparametric additive models with 3 and 5 degrees of freedom (df), and the *P* value for overall significance from general linear model (GLM) in Myers et al. (2003)

Endpoint	Smoothing term	Approximate *P* value				*P* value
		df = 3		df = 5		GLM
		Nonlinearity	Overall	Nonlinearity	Overall	Overall
WISC III Full Scale IQ	s(mercs)	0.284	0.181	0.324	0.280	0.196
CVLT Short Delay Recall	s(mercs)	0.811	0.643	0.720	0.673	0.194
B-O Test of Motor Proficiency	s(mercs)	0.364	0.271	0.402	0.335	0.096
Grooved Pegboard Dominant Hand	s(mercs)	0.050	0.044	0.073	0.081	0.084
Grooved Pegboard	s(female mercs)	0.073	0.120	0.170	0.242	0.340
Nondominant Hand	s(male mercs)	0.243	0.030	0.262	0.062	0.010
CTRS	s(mercs)	0.246	0.021	0.321	0.049	0.004

3-df models are more parsimonious and therefore smoother than the 5-df models, but the latter have more flexibility to follow local trends in the data and therefore typically show some form of local oscillation. An *F* test was used to assess model significance as compared to the null model with intercept only. For each independent variable, an approximate *F* test (Hastie and Tibshirani, 1990) was used to evaluate the significance of an overall effect, by comparing models with and without the independent variable. For the continuous smooth terms, a second approximate *F* test was used to evaluate the significance of the nonlinearity, to determine whether including the nonlinear component of each smooth term in the model resulted in a significantly better fit than a linear relationship. Although the test statistics do not have exact or even asymptotic *F* distributions, Hastie and Tibshirani (1990) report that simulations show them to be useful approximations.

For each model, if the estimated nonlinear association between a continuous independent variable and the response variable was significant, then the nonlinear trend was examined graphically. A plot shows the curve of the fitted smooth function, which describes the contribution of the particular independent variable to the additive predictor for the developmental outcome, and has been centered to have a mean of zero. The points on the plot are partial deviance residuals for the independent variable. In the case of adjusted analysis, the deviance residuals are the values of the dependent variable adjusted for all of the continuous and categorical independent variables except the one of interest for the plot (Hastie and Tibshirani, 1990). Nonsimultaneous, approximate confidence bands ($\pm 2\times$ standard error) were included in the plots for the continuous independent variables. The rug plot (vertical marks) along the bottom of each graph illustrates the distribution of the values of the independent variable in the dataset.

3. Results

3.1. Prenatal exposure

The unadjusted, no-covariate model was not significant for any of the six outcomes, indicating that prenatal exposure alone did not contribute to the prediction of the dependent variables. The models with covariate adjustment were all significant, and we therefore focused the discussion below on the adjusted results.

Among the 3-df semiparametric additive models, there was some evidence for a nonlinear relationship between prenatal THg levels and the Grooved Pegboard dominant hand score (*P* value for nonlinearity 0.05) (Table 1). The overall effect for prenatal THg was also significant (*P* value 0.04), while the effect in the linear analysis (from Myers et al., 2003) was not (*P* value 0.08). The nonlinear portion of this relationship became less significant when df = 5 was allocated for the smoothed terms (*P* value for nonlinearity, 0.07; for overall effect, 0.08). The curves from the 3- and 5-df models are illustrated in Fig. 1. As expected, the 5-df curve showed more oscillation than the 3-df curve. Both curves were flat (no association) at lower THg levels by visual examination, approximately below 12 ppm, and showed a slight upward trend above 12 ppm, indicating a possible adverse effect above this exposure level. Since the response was transformed by the negative reciprocal function for analysis, the interpretation of the magnitude of a possible adverse effect is complicated. We chose to summarize the curve values at exposure levels of 1, 5, 10, 15, and 20 ppm in Table 2. Note that it is the change of values that is important in Table 2, not the individual values, as each smoothing term has an expected value of zero, an explicit assumption in a semiparametric additive model. For ease of comparison, the table also includes the slope estimate for prenatal exposure and its associated standard error from the multiple linear regression analysis in Myers et al. (2003).

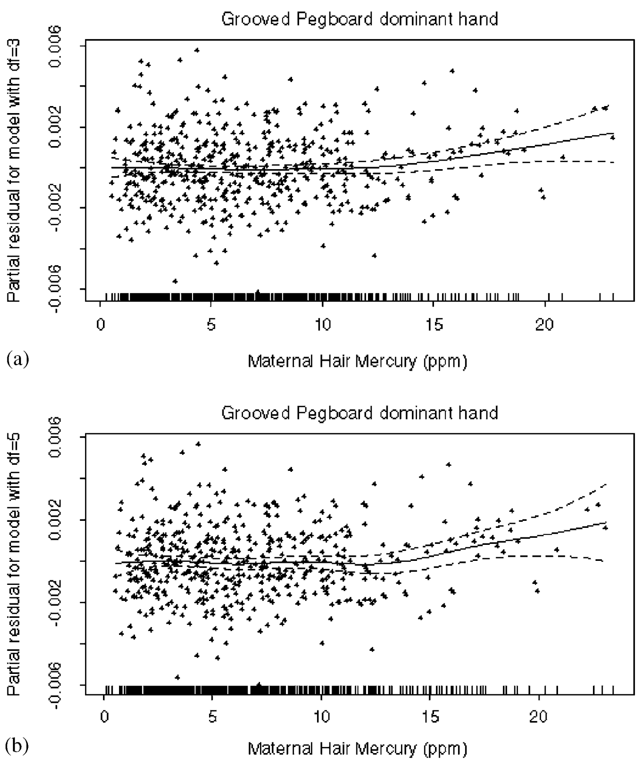

Fig. 1. Partial residuals plots from the semiparametric additive models with 3 (panel a) and 5 (panel b) degrees of freedom for smoothed term of prenatal THg hair level for the Grooved Pegboard on the dominant hand, adjusted for covariates. The dashed lines in the plots are twice the pointwise standard error bounds. The vertical marks along the bottom illustrate the distribution of maternal hair THg levels.

An interaction with gender was included in the model for the Grooved Pegboard nondominant hand because there was a gender interaction in the linear analysis. For females, the nonlinear association between prenatal THg and the Grooved Pegboard nondominant hand was marginally significant with df = 3 (*P* value for nonlinearity 0.07). The 3-df curve (Table 2) decreases slightly at approximately <10 ppm (beneficial effect) and then increases slowly (adverse effect). Its overall effect has a smaller *P* value, 0.12, as compared to that of the linear analysis (*P* value 0.34). For males the nonlinear relationship was not significant in a 3-df curve, but the overall effect (*P* value 0.03) remained adverse and significant as in the linear analysis (*P* value 0.01).

The nonlinear relationships between the remaining four outcomes and prenatal THg levels were nonsignificant (Table 1). The CTRS had a significant beneficial effect of prenatal exposure in the linear analysis (*P* value 0.004). In the nonlinear analysis its overall effect remained significant for both 3- and 5-df models (*P* values 0.021 and 0.049, respectively), with the 3-df curve showing a decreasing (beneficial) trend approximately below 15 ppm and an increasing trend above, as seen in Table 2. Note also in Table 2 the WISC-III Full Scale IQ and the B-O Test of Motor Proficiency showed small improving scores at lower levels and decreasing values at higher levels.

3.2. Covariates

The expected covariate effects were found in nearly all models. These are presented in Table 3. For brevity, we

Table 2
The smoothed curve values associated with an increase in maternal hair THg level as estimated with 3 and 5 degrees of freedom in covariate-adjusted semiparametric additive models, and the slope estimate and standard error (SE) from general linear models (GLM) in Myers et al. (2003)

Endpoint	Smoothing term	Degrees of freedom	Prenatal exposure					GLM slope (SE)
			1 ppm	5 ppm	10 ppm	15 ppm	20 ppm	
WISC III	s(mercs)	3	0.058	0.665	−0.441	−1.276	−3.726	−0.13
Full scale IQ		5	−0.619	1.025	−0.605	−0.349	−4.390	(0.10)
CVLT short	s(mercs)	3	−0.075	−0.016	0.036	0.102	0.139	0.013
Delay recall		5	−0.056	−0.008	0.017	0.127	0.125	(0.010)
B-O test of	s(mercs)	3	−0.768	−0.069	0.388	0.782	0.110	0.093
Motor proficiency		5	−0.906	0.053	0.208	1.058	−0.221	(0.056)
Grooved pegboard	1000*s(mercs)	3	−0.011	−0.008	−0.071	0.301	1.133	0.000033
Dominant hand		5	−0.063	−0.090	−0.058	0.231	1.231	(0.000019)
Grooved pegboard	1000*s(female mercs)	3	0.570	−0.068	−0.281	−0.031	0.568	−0.000025
Nondominant hand		5	0.647	−0.154	−0.284	−0.052	0.863	(0.000026)
	1000*s(male mercs)	3	−0.347	−0.091	0.085	0.527	1.402	0.000065
		5	−0.492	−0.062	0.121	0.418	1.453	(0.000025)
CTRS	s(mercs)	3	0.028	0.020	−0.033	−0.064	−0.046	−0.0067
		5	0.008	0.028	−0.037	−0.077	−0.026	(0.0023)

Table 3
Covariates effects: for continuous covariates, approximate *P* values for the nonlinear effects and overall significance for the smooth term; for discrete covariates, approximate *P* values for overall significance, in semiparametric additive models with 3 and 5 degrees of freedom; and the *P* value for overall significance from general linear model (GLM) in Myers et al. (2003)

Endpoint	Covariate	Approximate *P* value				*P*-value
		df = 3		df = 5		GLM
		Nonlinearity	Overall	Nonlinearity	Overall	Overall
WISC III Full scale IQ	s(FRS)	0.011	0.026	0.013	0.040	0.367
	s(HELPS)	0.031	0.051	0.049	0.080	0.208
	s(maternal age)	0.430	0.079	0.411	0.155	0.015
	s(K-Bit)	0.229	0.000	0.264	0.001	<0.0001
	s(female postnatal Hg)	0.343	0.023	0.322	0.036	0.012
	s(male postnatal Hg)	0.421	0.444	0.615	0.612	0.453
CVLT short delay recall	s(child's age)	0.200	<0.001	0.062	<0.001	<0.001
B-O test of motor proficiency	s(K-Bit)	0.084	0.084	0.197	0.169	0.090
	s(child's age)	0.170	0.028	0.251	0.079	0.006
	s(postnatal Hg)	0.062	0.138	0.090	0.180	0.748
	Hearing	NA	0.262	NA	0.311	0.049
Grooved pegboard Dominant hand	s(FRS)	0.008	0.015	0.009	0.016	0.588
	s(K-Bit)	0.250	0.010	0.207	0.014	0.003
	s(child's age)	0.292	0.018	0.297	0.029	0.003
	HOME	NA	0.072	NA	0.125	0.028
	Examiner	NA	0.177	NA	0.252	0.035
	Sex	NA	0.028	NA	0.022	0.929
Grooved pegboard Nondominant hand	s(K-Bit)	0.348	0.064	0.330	0.057	0.023
	s(child's age)	0.197	0.003	0.169	0.004	0.001
	s(female postnatal Hg)	0.208	0.024	0.227	0.067	0.013
	s(male postnatal Hg)	0.295	0.189	0.400	0.317	0.097
	Sex	NA	<0.001	NA	<0.001	0.357
CTRS	s(postnatal Hg)	0.524	0.001	0.382	0.003	<0.001
	Hearing	NA	0.045	NA	0.067	0.029

Note. NA, not applicable; FRS, Family Resource Scale; HELPS, Henderson Early Learning Process Scale; K-Bit, Kaufman Brief Intelligence Test to determine caregiver intelligence; Postnatal Hg, child's hair mercury concentration; Hearing hearing status classified as normal (⩽25 dB) borderline (>25–35 dB) or abnormal (>35 dB) HOME, Home Observation for Measurement of the Environment score classified as ⩽31, >31 to 35, or >35; Examiner, test examiner 1,2 or 3.

present the *P* values for nonlinearity and overall effects of the smoothed functions of continuous covariates when one or more of the associated *P* values was at least marginally significant (*P* value<0.10), and the *P* values for discrete covariates when they differed from the results of the linear analysis in either 3- or 5-df models. Table 3 (GLM column) also gives the corresponding *P* values for the linear regression analysis (Myers et al., 2003). The covariate effects are important since they confirm the sensitivity of the endpoints to known influences on child development. Since they are of less interest than prenatal exposure effects, we discuss here only those terms with both nonlinear and overall effects significant (*P* value<0.05). These were the Family Resource Scale for the WISC-III Full Scale IQ, and for the Grooved Pegboard dominant hand, in either the 3-df or 5-df models (Fig. 2). The curves show a beneficial effect when the FRS is approximately 110 or greater. Overall the associations between the covariates and the six outcomes in this reanalysis were consistent with the linear analysis and with developmental theory. For example, the HOME, SES, maternal age, and caregiver intelligence were all positively associated with improvements in the WISC-III Full IQ.

4. Discussion

Using semiparametric additive models, we explored nonlinear relationships between prenatal MeHg exposure from maternal fish consumption and child development in order to check the results of the original

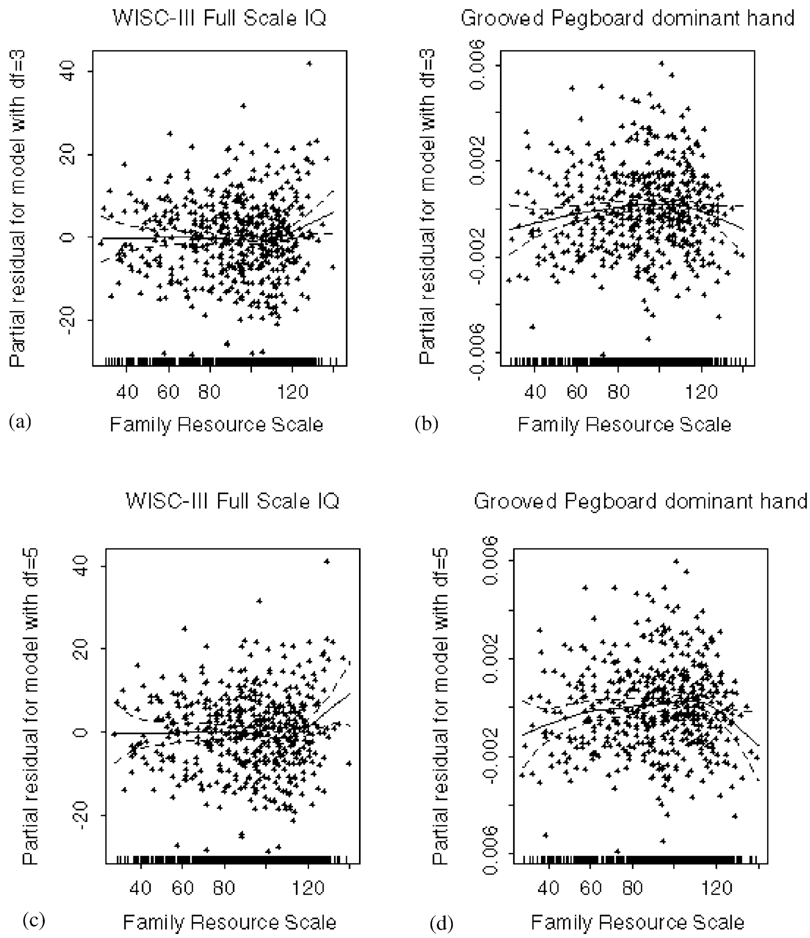

Fig. 2. Partial residuals plots from the covariate-adjusted semiparametric additive models for the WISC-III Full Scale IQ with (a) df = 3, (b) df = 5, for Family Resource Scale; the Grooved Pegboard dominant hand with (c) df = 3, (d) df = 5, for Family Resource Scale. The dashed lines in the plots are twice the pointwise standard error curves. The vertical marks along the bottom illustrate the distribution of the independent variable.

linear analysis. We found evidence for a nonlinear relationship for one of 6 endpoints, which were selected from the 21 endpoints used in the primary linear regression analysis. The nonlinear association was present only for the df = 3 fitted function on the Grooved Pegboard dominant hand. It suggested no-effect with increasing prenatal exposure levels in the 0–12 ppm exposure range, and an indication of a slight adverse effect above 12 ppm exposure. However, in the region above 12 ppm, both 3- and 5-df curves are estimated with less precision (as seen in the increasing width of the confidence bands in Fig. 1) because there were fewer data points. The curves for 3 other endpoints, the Grooved Pegboard nondominant hand in females, the WISC-III Full Scale IQ, and the B-O Test of Motor Proficiency, appeared to behave similarly, but the nonlinear components were not statistically significant as compared to their linear counterparts. These results support the linear relationship assumed in the primary multiple regression analysis plan, developed a priori and used consistently throughout the study.

The significant associations found in the primary linear analysis (an adverse effect on the Grooved Pegboard nondominant hand in males, and a beneficial effect on the Connors Teacher Rating Scale) remain significant in this analysis. As discussed in Myers et al. (2003), both of these outcomes are probably due to chance given that there were 21 endpoints in the linear analysis.

In summary, these results confirm the findings of the primary linear regression analysis (Myers et al., 2003). We continue to find no consistent evidence for adverse effects from prenatal MeHg secondary to fish consumption at the exposure levels found in the Seychelles cohort. However, the current data raise an interesting point that goes beyond previous analyses. The association for 1 of 6 endpoints suggests a possible adverse effect in the uppermost range (above 12 ppm) of prenatal exposure included in this cohort. This trend is similar to that found by Axtell et al. (2000) for the CBCL Total T score outcome with a possible adverse effect above 15 ppm. At this point, it is tempting to explore further nonlinear modeling to determine if there is a ‘‘hockey stick’’ relationship, but that is beyond the present analysis. Such nonlinear relationships are known in toxicology (see Davis and Svendsgaard, 1990, for a review).

A WHO expert committee (WHO, 1990) concluded that the Iraq data (Cox et al., 1989) suggested a threshold in the range of 10–20 ppm maternal hair. This analysis provides a suggestion that this may be the case. Perhaps there is a competition between the beneficial effects of fish consumption and the adverse effects of mercury. Nutritional effects may occur at the low mercury levels whereas mercury effects may occur only at the higher levels. We are currently studying nutritional relationships in Seychelles on a new cohort.

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