ARTICLE

Prenatal Exposure to Mercury and Fish Consumption During Pregnancy and Attention-Deficit/Hyperactivity Disorder–Related Behavior in Children

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Objective: To investigate the association of prenatal mercury exposure and fish intake with attention-deficit/hyperactivity disorder (ADHD)–related behavior.

Methods: For a population-based prospective birth cohort recruited in New Bedford, Massachusetts (1993-1998), we analyzed data for children examined at age 8 years with peripartum maternal hair mercury measures (n=421) or maternal report of fish consumption during pregnancy (n=515). Inattentive and impulsive/hyperactive behaviors were assessed using a teacher rating scale and neuropsychological testing.

Results: The median maternal hair mercury level was 0.45 μg/g (range, 0.03-5.14 μg/g), and 52% of mothers consumed more than 2 fish servings weekly. In multivariable regression models, mercury exposure was associated with inattention and impulsivity/hyperactivity; some outcomes had an apparent threshold with associations at 1 μg/g or greater of mercury. For example, at 1 μg/g or greater, the adjusted risk ratios for mild/markedly atypical inattentive and impulsive/hyperactive behaviors were 1.4 (95% CI, 1.0-1.8) and 1.7 (95% CI, 1.2-2.4), respectively, for an interquartile range (0.5 μg/g) mercury increase; there was no confounding by fish consumption. For neuropsychological assessments, mercury and behavior associations were detected primarily for boys. There was a protective association for fish consumption (>2 servings per week) with ADHD-related behaviors, particularly impulsive/hyperactive behaviors (relative risk=0.4; 95% CI, 0.2-0.6).

Conclusions: Low-level prenatal mercury exposure is associated with a greater risk of ADHD-related behaviors, and fish consumption during pregnancy is protective of these behaviors. These findings underscore the difficulties of balancing the benefits of fish intake with the detriments of low-level mercury exposure in developing dietary recommendations in pregnancy.

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Childhood behavioral disorders are increasingly prevalent and result in substantial costs to families and society, with effects on the educational system, quality of life, and, often, productivity into adulthood.[1] Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders of childhood, affecting 8% to 12% of children worldwide,[2] yet the etiology is not well understood.[3,4] Increasing evidence supports associations between metals and ADHD-related behaviors, including prenatal and postnatal lead exposures.[5-7]

The developmental neurotoxicity of mercury is well-established, as demonstrated by mass poisoning episodes in Japan[8,9] and Iraq.[10] Central nervous system effects of mercury have been shown in animal models,[11] including changes in rodent dopaminergic function,[12] providing a biological basis for effects on ADHD.[13] Findings from epidemiological studies of lower-dose mercury exposure are inconsistent,[14] with some studies[15,16] showing associations between mercury exposure and ADHD-related behaviors and others[17-20] reporting null associations.

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Nonoccupational methylmercury exposure results primarily from fish consumption, which has led the US Environmental Protection Agency and the US Food and Drug Administration to issue a joint federal advisory recommending that pregnant women limit their total fish intake to no more than two 6-ounce servings per week.[21] Fish is also a source of nutrients, such as ω-3 fatty acids, which have been shown to benefit brain development,[22-25] potentially confounding mercury-related risk estimates.[26]

We investigated the association of peripartum maternal hair mercury levels and prenatal fish intake with ADHD-related behaviors at age 8 years in a prospective birth cohort.

METHODS

STUDY POPULATION

The New Bedford cohort consists of 788 infants recruited at birth between 1993 and 1998 at St Luke's Hospital of Southcoast Hospitals Group, the main hospital serving the greater New Bedford, Massachusetts, area. This study was designed to investigate the association between exposure to polychlorinated biphenyls (PCBs), which were discharged into the New Bedford harbor for decades before their ban in the United States in the 1970s, and neurodevelopment. Associations between PCB exposure and ADHD-related behaviors in infancy and at school age have been documented in New Bedford[27,28] despite low cord serum PCB levels compared with other PCB-exposed populations.[29,30]

Eligible mothers were 18 years and older, resided in 1 of the 4 towns adjacent to the contaminated harbor (New Bedford, Acushnet, Fairhaven, or Dartmouth) for at least the duration of pregnancy, and spoke English or Portuguese. Study infants were generally healthy at birth; eligibility requirements included the ability to undergo neonatal examination and vaginal birth. We conducted neuropsychological assessments at approximately age 8 years on 607 children (78% of those eligible for follow-up); 421 children had measures of maternal hair mercury and 515 had fish consumption data. We excluded multiple births (n=3 children) from the present analysis.

EXPOSURE ASSESSMENT

We collected and archived maternal hair samples approximately 10 days postpartum. Total hair mercury concentration (which approximates methylmercury) was analyzed at the Harvard School of Public Health Trace Metals Analysis Laboratory. The hair samples were cleaned using sonication, rinsed with distilled deionized water, and dried at 60°C for 24 hours. We analyzed the 3 cm proximal to the scalp to represent mercury levels closer to the end of pregnancy.[31] When the cut end was indeterminable, a random 3 cm was analyzed. We performed the analysis using a direct mercury analyzer (DMA-80; Milestone Inc). Samples were weighed in a nickel boat, thermally decomposed, and amalgamated; via rapid heating of the amalgamator, released mercury was measured by atomic absorption spectroscopy with a limit of detection of 50 ng/g. Quality control measures included daily calibration verification with high- and low-concentration standards using GBW 07601 (human hair; Shanghai Institute of Nuclear Research, Academia Sinica), a procedural blank, and certified reference material CRM-397 (human hair; Community Bureau of Reference).

We collected data on prenatal fish consumption using a food frequency questionnaire administered shortly after the birth. The food frequency questionnaire quantified the consumption of dark fish (eg, salmon, mackerel, bluefish, and swordfish), tuna (including canned tuna), shellfish (eg, lobster and clams), eel, and other fish. We summed these frequencies to estimate total fish servings per week.

OUTCOME ASSESSMENT

We assessed inattentive and impulsive behaviors using a rating scale and 2 neuropsychological tests. The Conners Rating Scale–Teachers (CRS-T)[32] is a 59-item questionnaire used to evaluate problem behaviors. We analyzed 3 *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*) CRS-T Subscales: inattentive, hyperactive-impulsive, and total (subtypes combined). The CRS-T scores were standardized to age- and sex-adjusted *t* scores (mean [SD], 50 [10]); a higher score indicates more adverse behavior. For the Neurobehavioral Evaluation System 2 Continuous Performance Test (CPT),[33] a computer-assisted examination, random animal silhouettes are displayed and the child is instructed to press a button only on the appearance of a cat, to respond as quickly as possible, and to refrain from pressing the button for another animal. We analyzed 4 components of the CPT: (1) mean reaction time (longer reflects inattention), (2) reaction time variability (standard deviation of reaction time, a measure of performance inconsistency that may represent fluctuations/lapses in attention), (3) errors of omission (nonresponses), and (4) errors of commission (incorrect responses). We focused on 2 age-standardized Subscales of the Wechsler Intelligence Scale for Children–Third Edition (WISC-III),[34] a test that evaluates intellectual abilities, for which children with ADHD are found to score lowest: processing speed (includes coding and symbol search) and freedom from distractibility (includes digit span and arithmetic).

STATISTICAL ANALYSIS

We estimated associations of prenatal mercury exposure and fish consumption with behavioral outcomes using multivariable regression. We log-transformed continuous CRS-T *t* scores to better satisfy model assumptions (ie, homoscedasticity) and fit multivariable linear regression models. To identify children with more extreme behavioral patterns suggestive of a possible ADHD diagnosis, we dichotomized outcomes at the 86th percentile ($t \geq 61$), which identifies children with mild to markedly atypical scores,[32] and used log risk models to estimate risk ratios (RRs). The CPT mean reaction time and reaction time variability and WISC-III outcomes were approximately normally distributed, met regression model assumptions, and were modeled using linear regression. The CPT errors of omission and commission are Poisson-distributed count data and were modeled with negative binomial regression models to correct for overdispersion (variance > mean). We expressed mercury-related effect estimates per interquartile range in exposure and dichotomized fish consumption at 2 servings per week. We explored the nonlinearity of mercury-outcome associations using nonparametric models.

We assessed sex differences in associations of prenatal mercury exposure and fish consumption with behavioral outcomes by including an interaction term between sex and mercury exposure/fish consumption in the model. For RRs, we computed the relative excess risk for interaction and associated 95% CIs,[35] which quantifies additive interaction on the RR scale, a better indication of biological interaction.[36]

Data about covariates came from maternal and pediatric medical records and study questionnaires administered 2 weeks after the birth and at the 8-year examination. The 8-year examination also included assessment of maternal intelligence and depression symptoms using the Kaufman Brief Intelligence Test (KBIT) and the Beck Depression Inventory (BDI), respectively, and family and home characteristics using the Home Observation for Measurement of the Environment (HOME).[37] We used directed acyclic graphs,[38] causal diagrams based on a priori

Table 1. Statistics for Mercury Exposure, Total Fish Consumption, and ADHD-Related Outcomes for 8-Year-Old Children Born in New Bedford, 1993-1998

Exposure or Outcome Measure	Children, No.	Mean (SD)	Median (range)
Hair mercury, μg/g	421	0.62 (0.57)	0.45 (0.03-5.14)
Total fish consumption, servings/wk	515	3.7 (3.9)	2.3 (0.0-22.6)
Conners Rating Scale–Teachers score			
DSM-IV inattentive	505	53.2 (10.5)	50.0 (40.0-89.0)
DSM-IV impulsive/hyperactive	505	51.7 (10.1)	47.0 (42.0-90.0)
DSM-IV total	505	52.9 (10.0)	50.0 (41.0-89.0)
NES2 Continuous Performance Test			
Mean reaction time, ms	511	648.7 (64.8)	646.9 (492.4-861.7)
Reaction time variability, ms	511	128.3 (30.8)	127.4 (57.5-393.9)
Errors of omission, No.	511	2.3 (2.2)	2.0 (0.0-14.0)
Errors of commission, No.	511	2.3 (2.6)	1.0 (0.0-14.0)
Wechsler Intelligence Scale for Children–Third Edition score			
Processing speed	515	104.6 (14.6)	104.0 (58.0-146.0)
Freedom from distractibility	515	98.6 (12.7)	98.0 (50.0-134.0)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); NES2, Neurobehavioral Evaluation System 2.

knowledge of relationships between variables of interest, to identify confounders[39]; all multivariable models included characteristics of the mother (age at child's birth, prenatal smoking status and alcohol consumption, illicit drug use in the year before the child's birth, and, at the 8-year examination, educational level, marital status, IQ, and depression) and the child (age at examination, sex, and race) and household income, paternal educational level, and HOME[37] score assessed at the time of the 8-year examination.

We investigated confounding by prenatal diet, including total fish consumption and intake of ω-3 polyunsaturated fatty acids, estimated using data from the food frequency questionnaire. We also assessed the sensitivity of the results to ADHD medication use, 2-year blood lead levels (from pediatric medical records), and cord serum PCB levels. We measured cord serum PCB levels using gas chromatography, as described previously,[29] and represented PCB levels as the sum of 4 prevalent congeners (118, 138, 153, and 180).

The study protocol was reviewed and approved by the human subjects committees of Harvard School of Public Health and Brigham and Women's Hospital and Southcoast Hospitals Group. Written informed consent was obtained from all the participating families before study evaluation.

RESULTS

For the 604 singleton births who had an 8-year examination, 421 (69.7%) had prenatal mercury data and 515 (85.3%) had fish consumption data. Summary statistics for mercury exposure, fish consumption, and outcome measures are presented in **Table 1**. Participants with maternal mercury levels (n=421) were similar to all the participants with 8-year follow-up data (n=604) and were diverse regarding sociodemographic indicators, including educational level (39% of mothers and 67% of fathers had no college education), household income (18% earned <$20 000 per year), marital status (39% of mothers were unmarried), and race (26% of children were nonwhite) (**Table 2**). The child's age at the 8-year examination ranged from 7 to 10 years. Table 2 also shows higher mercury levels in mothers who were older, were married, had a higher household income, did not smoke during pregnancy or use illicit drugs the year before birth, consumed more fish during pregnancy, and had children of white race. Mercury-education associations were U-shaped, with higher levels in parents with the lowest and highest educational statuses. Mercury levels were also positively correlated with HOME score, prenatal ω-3 and fish servings per week, and cord serum PCB levels and inversely correlated with maternal depression symptoms (**Table 3**).

MERCURY EXPOSURE AND ADHD

Several ADHD-related end points had nonlinear associations with hair mercury levels. The **Figure**, which shows the covariate-adjusted association between hair mercury levels and log-transformed CRS-T *DSM-IV* total *t* scores from a penalized spline,[40] demonstrates an apparent threshold for exposure-response at approximately 1 μg/g. For outcomes with this threshold exposure-response pattern, we used piecewise linear regression, which produces separate mercury-behavior associations at mercury levels less than 1 μg/g (n = 355) and 1 μg/g or greater (n = 66).

Unadjusted and adjusted associations between hair mercury levels and ADHD-related behaviors are reported in **Table 4**. Mercury level and CRS-T score associations were consistent for continuous and dichotomized CRS-T scores; we present RRs for the dichotomized CRS-T scores in Table 4 for ease of interpretation. We detected an apparent threshold at mercury levels of 1 μg/g for the CRS-T, and piecewise regression suggested a slightly protective association between mercury levels and inattentive, impulsive/hyperactive, and combined behaviors with increasing mercury levels less than 1 μg/g and an increase in the risk of these behaviors with increasing mercury levels of 1 μg/g or greater, particularly for impulsivity/hyperactivity (adjusted RR for an interquartile range increase in mercury = 1.7; 95% CI, 1.2 to 2.4). Higher hair mercury levels were also associated with higher risk of errors of commission (RR = 1.1; 95% CI,

Table 2. Study Characteristics (Catagorical Variables) of 604 Children With 8-Year Data vs 421 Children With Maternal Hair Mercury Data and Unadjusted Associations With Maternal Hair Mercury Levels in New Bedford, 1993-1998

Demographic	8-y Data (n = 604) Children, No. (%)	8-y Data and Maternal Mercury Data (n = 421) Children, No. (%)	Hair Mercury, μg/g Mean	Hair Mercury, μg/g Median (Range)	*P* Value[a]
Maternal age at child's birth, y					
<20	79 (13.1)	56 (13.3)	0.37	0.31 (0.04-1.12)	<.01
20-29	317 (52.5)	209 (49.6)	0.56	0.40 (0.03-3.27)	
30-34	131 (21.7)	100 (23.8)	0.76	0.57 (0.09-5.14)	
≥35	77 (12.7)	56 (13.3)	0.79	0.62 (0.07-3.14)	
Maternal educational level at child's 8-y examination					
<12th grade	65 (10.9)	34 (8.2)	0.83	0.64 (0.13-3.27)	.03
HS graduate	193 (32.3)	127 (30.5)	0.54	0.42 (0.04-5.14)	
Some college	340 (56.9)	255 (61.3)	0.63	0.46 (0.03-3.09)	
Missing	6	5	NA	NA	
Paternal educational level at child's 8-y examination					
<12th grade	140 (24.4)	95 (23.5)	0.65	0.47 (0.09-5.14)	<.01
HS graduate	247 (43.0)	176 (43.5)	0.53	0.41 (0.03-3.14)	
Some college	188 (32.7)	134 (33.1)	0.73	0.52 (0.07-3.09)	
Missing	29	16	NA	NA	
Annual household income at child's 8-y examination, $					
<20 000	124 (20.8)	74 (17.8)	0.54	0.30 (0.03-5.14)	.09
20 000-39 999	165 (27.7)	112 (27.0)	0.56	0.41 (0.03-3.27)	
≥40 000	307 (51.5)	229 (55.2)	0.67	0.52 (0.05-3.04)	
Missing	8	6	NA	NA	
Maternal marital status at child's 8-y examination					
Married	353 (58.4)	257 (61.0)	0.68	0.49 (0.04-5.14)	<.01
Unmarried	251 (41.6)	164 (39.0)	0.51	0.38 (0.03-3.09)	
Maternal smoking during pregnancy					
Nonsmoker	394 (70.4)	277 (66.6)	0.68	0.51 (0.04-5.14)	<.01
1-10 cigarettes/d	122 (21.8)	102 (24.5)	0.49	0.38 (0.03-3.04)	
>10 cigarettes/d	44 (7.9)	37 (8.9)	0.50	0.37 (0.03-1.52)	
Missing	44	5	NA	NA	
Maternal illicit drug use in year before birth					
No	439 (85.6)	352 (85.6)	0.64	0.48 (0.03-5.14)	.05
Yes	74 (14.4)	59 (14.4)	0.49	0.37 (0.03-2.59)	
Missing	91	10	NA	NA	
Maternal local fish consumption during pregnancy					
No	459 (89.1)	367 (88.9)	0.62	0.44 (0.03-5.14)	.73
Yes	56 (10.9)	46 (11.1)	0.59	0.54 (0.17-1.49)	
Missing	89	8	NA	NA	
Maternal total fish consumption during pregnancy					
≤2 servings/wk	248 (48.2)	196 (47.5)	0.55	0.36 (0.04-3.27)	.03
>2 servings/wk	267 (51.8)	217 (52.5)	0.68	0.53 (0.03-5.14)	
Missing	89	8	NA	NA	
Child's sex					
Female	296 (49.0)	209 (49.6)	0.62	0.45 (0.03-5.14)	.82
Male	308 (51.0)	212 (50.4)	0.61	0.44 (0.03-3.14)	
Child's race					
White	411 (69.3)	308 (74.2)	0.67	0.51 (0.05-5.14)	<.01
Nonwhite	182 (30.7)	107 (25.8)	0.47	0.36 (0.03-3.09)	
Missing	11	6	NA	NA	

Abbreviations: HS, high school; NA, not applicable.
[a] Unadjusted covariate-mercury *P* value from analysis of variance.

1.0 to 1.2) and lower scores on the WISC-III Subscales, particularly processing speed (β = −1.5; 95% CI, −2.9 to −0.1).

Adjusting for total fish consumption (Table 4) and ω-3 intake (data not shown) did not consistently change associations between mercury levels and ADHD-related end

Table 3. Study Characteristics (Continuous Variables) of Children With 8-Year Data vs Children With Maternal Hair Mercury Data and Spearman Rank Correlation Coefficients With Maternal Hair Mercury Levels for Children Born in New Bedford, 1993-1998

	8-y Data (n = 604)		8-y and Maternal Mercury Data (n = 421)			
					Spearman Rank Correlation Coefficients With Mercury	
Demographic	Children, No.	Mean (SD)	Children, No.	Mean (SD)	*r*	*P* Value
Child's age at examination	603	8.2 (0.6)	421	8.2 (0.6)	−0.04	.42
Maternal IQ	600	97.9 (10.4)	419	98.7 (10.2)	0.05	.26
Maternal depression	601	8.3 (8.8)	419	8.0 (8.5)	−0.17	<.01
HOME score	589	45.6 (5.4)	410	45.8 (5.4)	0.19	<.01
ω-3 Intake, g/mo	509	28.5 (15.0)	413	28.4 (14.9)	0.20	<.01
Fish intake, servings/wk	515	3.7 (3.9)	413	3.7 (3.8)	0.32	<.01
Cord serum PCBs, ng/g	587	0.3 (0.3)	406	0.3 (0.3)	0.42	<.01

Abbreviations: HOME, Home Observation for Measurement of the Environment; PCBs, polychlorinated biphenyls.

points. The PCB levels, although moderately correlated with mercury (ρ = 0.42), neither confounded nor modified mercury-ADHD associations (data not shown). Finally, adjusting for 2-year lead levels and excluding children who were treated with ADHD medications (n = 26) did not change associations between mercury levels and end points (data not shown).

SEX DIFFERENCES

Table 5 reports sex-specific effect estimates generated using a single model with a mercury × sex interaction term. Mercury level and CRS-T score associations were similar across sex, and relative excess risk for interaction estimates were close to 0, indicating no interaction on the additive scale (the same pattern was found using raw CRS-T scores that were not sex and age standardized). Estimates were most notably different across sex for CPT errors of omission and WISC-III outcomes, especially processing speed, where associations were considerably stronger in boys (β = −4.0; 95% CI, −6.0 to −1.9) than in girls (β = 0.2; 95% CI, −1.6 to 2.0). The interpretation of the relative excess risk for interaction for CPT errors of omission is that there is a 0.4 (95% CI, −0.1 to 0.8) increase in the RR of an error over what the RR would be if there was no interaction between mercury level and sex. Protective associations between mercury at levels less than 1 μg/g and CPT reaction time (faster mean reaction time and lower reaction time variability) were found in girls.

MATERNAL FISH CONSUMPTION AND ADHD

We found strong protective associations for prenatal fish consumption with CRS-T outcomes (**Table 6**), particularly for *DSM-IV* impulsivity/hyperactivity (adjusted RR for a score greater than the 86th percentile = 0.4; 95% CI, 0.2 to 0.6 for >2 vs ≤2 fish servings per week). After adjusting for mercury level and other covariates, fish consumption was associated with higher scores for the WISC-III outcomes, particularly processing speed (β = 2.0; 95% CI, −0.8 to 4.8). We did not see protective associations for the CPT outcomes but rather slightly higher risk of errors of commission (RR = 1.1; 95% CI, 0.9 to 1.3) with greater than 2 vs 2 servings per week or fewer. No consistent differences were noted in the association between fish consumption and ADHD-related behaviors by sex.

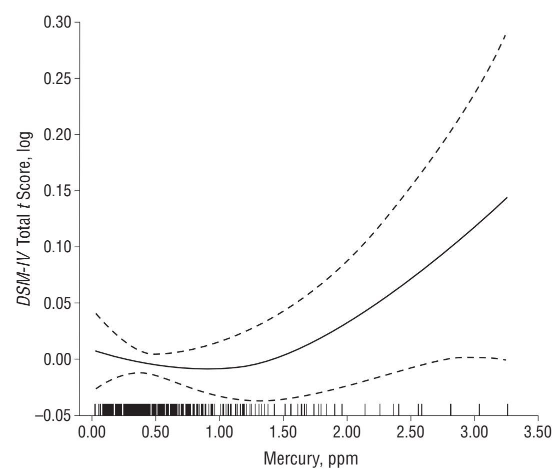

Figure. Penalized spline of the adjusted association of perinatal maternal hair mercury levels with log-transformed *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*) total *t* scores (centered on 0) from the Conners Rating Scale–Teachers for 8-year-old children born in New Bedford, 1993-1998.

COMMENT

In this population-based prospective cohort study, hair mercury levels were consistently associated with ADHD-related behaviors, including inattention and hyperactivity/impulsivity. We also found that higher prenatal fish consumption was protective for these behaviors. Results are supported by data from a well-characterized birth cohort with prospectively measured exposure and covariate data, including important confounders.

Hair is a well-established biomarker of methylmercury, and maternal hair mercury levels correlate well with fetal brain and blood mercury levels.[41] Median hair mercury levels for this cohort were higher (0.45 μg/g) than were those reported in women of childbearing age during 1999-2000 in the National Health and Nutrition

Table 4. Unadjusted and Adjusted Associations Between Peripartum Maternal Hair Mercury Levels and ADHD-Like Behaviors for 8-Year-Old Children Born in New Bedford, 1993-1998

Outcome Measure	Mercury Categories	Unadjusted: Children, No.	Unadjusted: β or RR (95% CI)	Adjusted[a]: Children, No.	Adjusted[a]: β or RR (95% CI)	Adjusted[a] + Fish Consumption[b]: Children, No.	Adjusted[a] + Fish Consumption[b]: β or RR (95% CI)
Conners Rating Scale–Teachers dichotomized at the 86th percentile							
DSM-IV inattentive (RR)	<1 μg/g[c]	412	0.7 (0.5 to 0.9)	362	0.8 (0.5 to 1.1)	362	0.8 (0.6 to 1.2)
	≥1 μg/g[c]		1.3 (1.0 to 1.6)		1.4 (1.0 to 1.8)		1.3 (1.0 to 1.7)
DSM-IV impulsive/hyperactive (RR)	<1 μg/g[c]	412	0.6 (0.4 to 0.8)	362	0.8 (0.5 to 1.2)	362	0.8 (0.5 to 1.3)
	≥1 μg/g[c]		1.6 (1.3 to 2.0)		1.7 (1.2 to 2.4)		1.6 (1.1 to 2.4)
DSM-IV total (RR)	<1 μg/g[c]	412	0.6 (0.4 to 0.8)	362	0.7 (0.5 to 1.0)	362	0.7 (0.5 to 1.1)
	≥1 μg/g[c]		1.5 (1.2 to 1.8)		1.6 (1.2 to 2.1)		1.5 (1.1 to 2.0)
NES2 Continuous Performance Test							
Mean reaction time (β)	<1 μg/g[c]	417	−8.6 (−20.4 to 3.2)	359	−9.6 (−22.9 to −3.8)	359	−11.9 (−25.7 to 1.8)
	≥1 μg/g[c]		6.5 (−2.8 to 15.7)		2.5 (−9.5 to 14.5)		3.6 (−8.5 to 15.7)
Reaction time variability (β)	<1 μg/g[c]	417	−3.9 (−9.3 to 1.5)	359	−3.1 (−8.7 to 2.4)	359	−3.0 (−8.8 to 2.7)
	≥1 μg/g[c]		3.5 (−0.7 to 7.8)		4.7 (−0.3 to 9.7)		4.6 (−0.4 to 9.7)
Errors of omission (RR)	Continuous	417	1.0 (0.9 to 1.1)	359	1.0 (0.9 to 1.2)	359	1.0 (0.9 to 1.2)
Errors of commission (RR)	Continuous	417	1.0 (1.0 to 1.1)	359	1.1 (1.0 to 1.2)	359	1.1 (1.0 to 1.2)
Wechsler Intelligence Scale for Children–Third Edition							
Processing speed (β)	Continuous	421	−0.5 (−1.7 to 0.7)	362	−1.5 (−2.9 to −0.1)	362	−1.6 (−3.0 to −0.2)
Freedom from distractibility (β)	Continuous	421	−0.5 (−1.5 to 0.5)	362	−0.9 (−2.2 to 0.3)	362	−1.0 (−2.2 to 0.3)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; β, change in outcome score for an interquartile range increase (75%-25% = 0.48 μg/g) in mercury; *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)*; NES2, Neurobehavioral Evaluation System 2; RR, risk/rate ratio for an interquartile range increase in mercury.

[a] Adjusted for child's age (continuous), sex, and race (white vs nonwhite); maternal age (continuous), educational level (<12 vs ≥12 years), marital status (married vs unmarried), IQ (continuous), depression symptoms (continuous), prenatal smoking (yes vs no and average number of cigarettes per day), prenatal alcohol consumption (yes vs no and average grams per day), and illicit drug use (ever vs never during year before birth); paternal educational level (<12 vs ≥12 years); household income (<$20 000 vs ≥$20 000 per year); and Home Observation for Measurement of the Environment score (continuous).

[b] Total fish consumption: greater than 2 vs 2 servings per week or fewer.

[c] Modeled using piecewise linear regression producing separate slopes at less than 1 μg/g and 1 μg/g or greater of hair mercury.

Table 5. Sex-Specific Associations of Hair Mercury Levels With ADHD-Like Behaviors for 8-Year-Old Children Born in New Bedford, 1993-1998

Outcome Measure	Mercury Categories	Children, Total No.	Adjusted β or RR (95% CI)[a]: All	Adjusted β or RR (95% CI)[a]: Girls	Adjusted β or RR (95% CI)[a]: Boys	Sex Interaction, *P* Value	RERI
Conners Rating Scale–Teachers dichotomized at the 86th percentile							
DSM-IV inattentive (RR)	<1 μg/g[b]	362	0.8 (0.5 to 1.1)	0.8 (0.5 to 1.3)	0.7 (0.4 to 1.3)	.90	0.0 (−1.2 to 3.3)
	≥1 μg/g[b]		1.4 (1.0 to 1.8)	1.4 (1.0 to 1.9)	1.3 (0.8 to 2.1)		−0.45 (−3.8 to 3.4)
DSM-IV impulsive/hyperactive (RR)	<1 μg/g[b]	362	0.8 (0.5 to 1.2)	0.9 (0.5 to 1.6)	0.6 (0.3 to 1.3)	.72	−0.1 (−3.8 to 5.8)
	≥1 μg/g[b]		1.7 (1.2 to 2.4)	1.5 (0.9 to 2.4)	2.1 (1.2 to 3.6)		0.3 (−4.1 to 7.0)
DSM-IV total (RR)	<1 μg/g[b]	362	0.7 (0.5 to 1.0)	0.7 (0.4 to 1.2)	0.6 (0.3 to 1.3)	.97	0.1 (−1.2 to 3.5)
	≥1 μg/g[b]		1.6 (1.2 to 2.1)	1.5 (1.1 to 2.2)	1.6 (0.9 to 2.8)		−0.4 (−4.6 to 5.5)
NES2 Continuous Performance Test							
Mean reaction time (β)	<1 μg/g[b]	359	−9.6 (−22.9 to 3.8)	−20.7 (−38.2 to −3.2)	2.1 (−17.1 to 21.3)	.01	
	≥1 μg/g[b]		2.5 (−9.5 to 14.5)	−2.6 (−17.7 to 12.6)	13.0 (−6.6 to 32.6)		
Reaction time variability (β)	<1 μg/g[b]	359	−3.1 (−8.7 to 2.4)	−7.5 (−14.9 to −0.2)	1.7 (−6.3 to 9.8)	.09	
	≥1 μg/g[b]		4.7 (−0.3 to 9.7)	4.1 (−2.2 to 10.5)	6.2 (−2.0 to 14.4)		
Errors of omission (RR)	Continuous	359	1.0 (0.9 to 1.2)	0.9 (0.8 to 1.1)	1.2 (1.0 to 1.4)	.06	0.4 (−0.1 to 0.8)
Errors of commission (RR)	Continuous	359	1.1 (1.0 to 1.2)	1.1 (1.0 to 1.2)	1.1 (1.0 to 1.3)	.68	0.1 (−0.2 to 1.0)
Wechsler Intelligence Scale for Children–Third Edition							
Processing speed (β)	Continuous	362	−1.5 (−2.9 to −0.1)	0.2 (−1.6 to 2.0)	−4.0 (−6.0 to −1.9)	<.01	
Freedom from distractibility (β)	Continuous	362	−0.9 (−2.2 to 0.3)	0.3 (−1.3 to 1.9)	−2.6 (−4.5 to −0.7)	.02	

Abbreviation: ADHD, attention-deficit/hyperactivity disorder; β, change in outcome score for an interquartile range increase (75%–25% = 0.48 μg/g) in mercury; *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); NES2, Neurobehavioral Evaluation System 2; RERI, relative excess risk for interaction; RR, risk/rate ratio.

[a] Adjusted for child's age (continuous), sex, and race (white vs nonwhite); maternal age (continuous), educational level (<12 vs ≥12 years), marital status (married vs unmarried), IQ (continuous), depression symptoms (continuous), prenatal smoking (yes vs no and average number of cigarettes per day), prenatal alcohol consumption (yes vs no and average grams per day), and illicit drug use (ever vs never during the year before birth); paternal educational level (<12 vs ≥12 years); household income (<$20 000 vs ≥$20 000 per year); and Home Observation for Measurement of the Environment score (continuous).

[b] Modeled using piecewise linear regression producing separate slopes at less than 1 μg/g and 1 μg/g or greater of hair mercury.

Table 6. Unadjusted and Adjusted Associations of Fish Consumption With ADHD-Like Behaviors for 8-Year-Old Children Born in New Bedford, 1993-1998

Outcome Measure	Fish Consumption, Servings/wk	Unadjusted Children, No.	Unadjusted β or RR (95% CI)	Adjusted[a] Children, No.	Adjusted[a] β or RR (95% CI)	Adjusted + Mercury[b] Children, No.	Adjusted + Mercury[b] β or RR (95% CI)
Conners Rating Scale–Teachers dichotomized at the 86th percentile							
DSM-IV inattentive (RR)	≤2	245	1 [Reference]	222	1 [Reference]	173	1 [Reference]
	>2	260	0.8 (0.6 to 1.0)	235	0.6 (0.4 to 0.8)	189	0.6 (0.4 to 0.9)
DSM-IV impulsive/hyperactive (RR)	≤2	245	1 [Reference]	222	1 [Reference]	173	1 [Reference]
	>2	266	0.5 (0.3 to 0.8)	235	0.4 (0.2 to 0.6)	189	0.4 (0.2 to 0.6)
DSM-IV total (RR)	≤2	245	1 [Reference]	222	1 [Reference]	173	1 [Reference]
	>2	260	0.7 (0.5 to 1.0)	235	0.5 (0.4 to 0.7)	189	0.6 (0.4 to 0.9)
NES2 Continuous Performance Test							
Mean reaction time (β)	≤2	245	0 [Reference]	219	0 [Reference]	170	0 [Reference]
	>2	266	5.9 (−5.3 to 17.1)	235	7.7 (−3.8 to 19.3)	189	10.1 (−3.9 to 24.1)
Reaction time variability (β)	≤2	245	0 [Reference]	219	0 [Reference]	170	0 [Reference]
	>2	266	3.6 (−1.8 to 8.9)	235	1.5 (−3.6 to 6.7)	189	−0.5 (−6.3 to 5.4)
Errors of omission (RR)	≤2	245	1 [Reference]	219	1 [Reference]	170	1 [Reference]
	>2	266	1.1 (0.9 to 1.3)	235	1.0 (0.8 to 1.3)	189	0.9 (0.7 to 1.2)
Errors of commission (RR)	≤2	245	1 [Reference]	219	1 [Reference]	170	1 [Reference]
	>2	266	1.2 (1.0 to 1.3)	235	1.1 (1.0 to 1.3)	189	1.1 (0.9 to 1.3)
Wechsler Intelligence Scale for Children–Third Edition							
Processing speed (β)	≤2	248	0 [Reference]	222	0 [Reference]	173	0 [Reference]
	>2	267	−0.4 (−2.9 to 2.2)	235	1.3 (−1.2 to 3.8)	189	2.0 (−0.8 to 4.8)
Freedom from distractibility (β)	≤2	248	0 [Reference]	222	0 [Reference]	173	0 [Reference]
	>2	267	−0.8 (−3.0 to 1.4)	235	0.3 (−1.9 to 2.6)	189	1.5 (−1.1 to 4.0)

Abbreviations: β, change in outcome score for an interquartile range (75%–25% = 0.48 μg/g) increase in mercury; *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)*; NES2, Neurobehavioral Evaluation System 2; RR, risk/rate ratio.

[a] Adjusted for child's age (continuous), sex, and race (white vs nonwhite); maternal age (continuous), educational level (<12 vs ≥12 years), marital status (married vs unmarried), IQ (continuous), depression symptoms (continuous), prenatal smoking status (yes vs no and average number of cigarettes per day), prenatal alcohol consumption (yes vs no and average grams per day), and illicit drug use (ever vs never during year before birth); paternal educational level (<12 vs ≥12 years); household income (<$20 000 vs ≥$20 000 per year); and Home Observation for Measurement of the Environment score (continuous).

[b] Hair mercury was modeled using piecewise linear regression (cutoff point at 1 μg/g) for Conners Rating Scale–Teachers outcomes and Continuous Performance Test mean reaction time and reaction time variability and as a continuous variable for Continuous Performance Test errors and Wechsler Intelligence Scale for Children–Third Edition outcomes.

Examination Survey (geometric mean = 0.12 μg/g) but were comparable with levels in National Health and Nutrition Examination Survey participants who were frequent fish consumers (geometric mean = 0.38 μg/g).[42]

There is uncertainty concerning the effect of low-level mercury exposure on neurodevelopment.[14] Two seminal studies of prenatal mercury exposure report inconsistent results regarding behavioral outcomes. For 1022 children born in the Faroe Islands during 1986-1987 with high mercury levels (geometric mean = 22.9 μg/L in cord blood and 4.27 μg/g in maternal hair), higher cord blood mercury levels were associated with more errors of omission and longer mean reaction times on the Neurobehavioral Evaluation System 2 CPT at 7 and 14 years.[15,43] In contrast, a study of 779 children born in the Seychelles Islands during 1989-1990 with high mercury levels (mean = 6.8 μg/g in maternal hair) reported null associations with neurodevelopmental outcomes, including measures from the Child Behavior Checklist, and the Conners CPT, and improved scores on the impulsivity/hyperactivity index of the CRS-T.[17,19,20] Mixed results have also been reported in other studies of mercury exposure and behavior.[16,18,44]

One explanation for the inconsistency is that nutrients in fish that promote neurodevelopment, such as ω-3 fatty acids, may offset the neurotoxicant effects of mercury exposure[26]; this is supported by previous studies[25,45] that report enhanced deleterious associations between mercury exposure and neuropsychological end points after adjusting for fish consumption (benefits of fish consumption were also stronger after adjusting for mercury exposure) and by a second study[46,47] in the Seychelles Islands that reported deleterious mercury effects on neurodevelopment only after adjusting for ω-3 and ω-6 fatty acids measured in prenatal maternal blood. Adjusting for fish consumption (or ω-3 intake) did not change mercury-behavior associations in the present study. Measurement error in collecting self-reported dietary intake of fish and related nutrients may have resulted in residual confounding by these factors. In addition, the degree of confounding by fish consumption is likely a function of the fish species (and their respective nutrient contents) consumed by the study population. Fish consumption was associated with better behavioral scores for most of the study outcomes, however, and for the CRS-T outcomes in particular. These associations were protective for fish consumption during pregnancy of greater than 2 servings per week, which is higher than the Food and Drug Administration–Environmental Protection Agency federal advisory limit.[21] Adjusting for mercury exposure enhanced the protective association of fish consumption with WISC-III outcomes. Previous studies[48] report associations between greater childhood ω-3 fatty acid intake and reduced risk of ADHD, although mostly in the context of alleviating clinical ADHD symptoms. To our knowledge, this is the first study to report a protective association of prenatal fish consumption with offspring ADHD-related behavior.

We previously reported associations of PCB exposure with ADHD-related behaviors in this cohort.[27,28] Although PCB exposure was moderately correlated with mercury level, adjusting for PCB levels did not change mercury-ADHD associations. We did not find an interaction between PCB and mercury levels on ADHD-related behavior, in contrast to 2 previous studies of cognitive and behavioral outcomes.[49,50]

For CRS-T outcomes and CPT reaction time, threshold associations between mercury exposure and ADHD-related behavior were detected at approximately 1 μg/g. This is consistent with a study of hair mercury levels and neurodevelopment that also found a threshold for adverse effects between 0.5 and 1 μg/g.[51] In addition, the US Environmental Protection Agency reference dose for mercury (0.1 μg/kg/d)[31] is equivalent to 1.2 μg/g in hair,[52] which is approximately the level for the threshold we report in this study. We detected slightly protective associations of mercury exposure with ADHD-related behavior at mercury levels less than 1 μg/g. Because fish is the main source of mercury, this may reflect the beneficial effect of fish consumption, for which adjustment may have been inadequate due to measurement error. At higher mercury levels ($\geq$1 μg/g), these nutritional benefits may have been outweighed by neurotoxicity from mercury exposure.

We detected sex differences for mercury exposure and some ADHD-related behaviors, with associations found primarily in boys. Previous studies[15,19,53] have reported stronger mercury-related associations in boys vs girls. Although the mechanism underlying sex differences in exposure-related neurotoxicity is unknown, a growing literature shows differences in the impact of endocrine-disrupting chemicals (including mercury, bisphenol A,[54] and phthalates[55]) on neurodevelopment in males and females.[56]

We did not assess clinical ADHD diagnosis in this study. Although common, clinically diagnosed ADHD is too rare to study in moderate-sized prospective population-based samples. Measuring behavior on a continuum in this study has several advantages, including (1) minimization of bias due to outcome misclassification, where categorization is often made at an arbitrary cutoff point that may change over time; (2) detection of early or milder manifestations of a disorder that a clinical diagnosis could miss; and (3) enhancement of power to detect an effect of exposure.[57] A limitation of using the CPT and WISC-III outcomes as markers for inattentive and hyperactive/impulsive behaviors is that these outcomes may also reflect other skills that could compromise or enhance resulting scores for these neuropsychological tests.

In summary, these results suggest that prenatal mercury exposure is associated with a higher risk of ADHD-related behaviors, and fish consumption during pregnancy is associated with a lower risk of these behaviors. Although a single estimate combining these beneficial vs detrimental effects vis-á-vis fish intake is not possible with these data, these findings are consistent with a growing literature showing risk of mercury exposure and benefits of maternal consumption of fish on fetal brain development and are important for informing dietary recommendations for pregnant women.

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REFERENCES

1. Brauner CB, Stephens CB. Estimating the prevalence of early childhood serious emotional/behavioral disorders: challenges and recommendations. *Public Health Rep.* 2006;121(3):303-310.
2. Faraone SV, Sergeant J, Gillberg C, Biederman J. The worldwide prevalence of ADHD: is it an American condition? *World Psychiatry.* 2003;2(2):104-113.
3. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. *Lancet.* 2005;366(9481):237-248.
4. Rowland AS, Lesesne CA, Abramowitz AJ. The epidemiology of attention-deficit/hyperactivity disorder (ADHD): a public health view. *Ment Retard Dev Disabil Res Rev.* 2002;8(3):162-170.
5. Bellinger D, Leviton A, Allred E, Rabinowitz M. Pre- and postnatal lead exposure and behavior problems in school-aged children. *Environ Res.* 1994;66(1):12-30.
6. Braun JM, Kahn RS, Froehlich T, Auinger P, Lanphear BP. Exposures to environmental toxicants and attention deficit hyperactivity disorder in U.S. children. *Environ Health Perspect.* 2006;114(12):1904-1909.
7. Needleman HL, Gunnoe C, Leviton A, et al. Deficits in psychologic and classroom performance of children with elevated dentine lead levels. *N Engl J Med.* 1979;300(13):689-695.
8. Harada M. Congenital Minamata disease: intrauterine methylmercury poisoning. *Teratology.* 1978;18(2):285-288.
9. Harada M. Minamata disease: methylmercury poisoning in Japan caused by environmental pollution. *Crit Rev Toxicol.* 1995;25(1):1-24.
10. Bakir F, Damluji SF, Amin-Zaki L, et al. Methylmercury poisoning in Iraq. *Science.* 1973;181(4096):230-241.
11. Castoldi AF, Onishchenko N, Johansson C, et al. Neurodevelopmental toxicity of methylmercury: laboratory animal data and their contribution to human risk assessment. *Regul Toxicol Pharmacol.* 2008;51(2):215-229.

12. Dreiem A, Shan M, Okoniewski RJ, Sanchez-Morrissey S, Seegal RF. Methylmercury inhibits dopaminergic function in rat pup synaptosomes in an age-dependent manner. *Neurotoxicol Teratol*. 2009;31(5):312-317.
13. Faraone SV, Biederman J. Neurobiology of attention-deficit hyperactivity disorder. *Biol Psychiatry*. 1998;44(10):951-958.
14. Karagas MR, Choi AL, Oken E, et al. Evidence on the human health effects of low-level methylmercury exposure. *Environ Health Perspect*. 2012;120(6):799-806.
15. Grandjean P, Weihe P, White RF, et al. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicol Teratol*. 1997;19(6):417-428.
16. Stewart P, Reihman J, Gump B, Lonky E, Darvill T, Pagano J. Response inhibition at 8 and 9 1/2 years of age in children prenatally exposed to PCBs. *Neurotoxicol Teratol*. 2005;27(6):771-780.
17. Davidson PW, Myers GJ, Cox C, et al. Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment: outcomes at 66 months of age in the Seychelles Child Development Study. *JAMA*. 1998;280(8):701-707.
18. Grandjean P, White RF, Nielsen A, Cleary D, de Oliveira Santos EC. Methylmercury neurotoxicity in Amazonian children downstream from gold mining. *Environ Health Perspect*. 1999;107(7):587-591.
19. Myers GJ, Davidson PW, Cox C, et al. Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study. *Lancet*. 2003;361(9370):1686-1692.
20. Myers GJ, Davidson PW, Palumbo D, et al. Secondary analysis from the Seychelles Child Development Study: the child behavior checklist. *Environ Res*. 2000;84(1):12-19.
21. Environmental Protection Agency and Food and Drug Administration. What you need to know about mercury in fish and shellfish: 2004 EPA and FDA advice for women who might become pregnant, women who are pregnant, nursing mothers and young children. http://www.fda.gov/Food/FoodSafety/Product-SpecificInformation/Seafood/FoodbornePathogensContaminants/Methylmercury/ucm115662.htm. Accessed January 12, 2012.
22. Cohen JT, Bellinger DC, Connor WE, Shaywitz BA. A quantitative analysis of prenatal intake of n-3 polyunsaturated fatty acids and cognitive development. *Am J Prev Med*. 2005;29(4):366-374.
23. Helland IB, Smith L, Saarem K, Saugstad OD, Drevon CA. Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. *Pediatrics*. 2003;111(1):e39-e44.
24. Hibbeln JR, Davis JM, Steer C, et al. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. *Lancet*. 2007;369(9561):578-585.
25. Oken E, Wright RO, Kleinman KP, et al. Maternal fish consumption, hair mercury, and infant cognition in a U.S. cohort. *Environ Health Perspect*. 2005;113(10):1376-1380.
26. Choi AL, Cordier S, Weihe P, Grandjean P. Negative confounding in the evaluation of toxicity: the case of methylmercury in fish and seafood. *Crit Rev Toxicol*. 2008;38(10):877-893.
27. Sagiv SK, Nugent JK, Brazelton TB, et al. Prenatal organochlorine exposure and measures of behavior in infancy using the Neonatal Behavioral Assessment Scale (NBAS). *Environ Health Perspect*. 2008;116(5):666-673.
28. Sagiv SK, Thurston SW, Bellinger DC, Tolbert PE, Altshul LM, Korrick SA. Prenatal organochlorine exposure and behaviors associated with attention deficit hyperactivity disorder in school-aged children. *Am J Epidemiol*. 2010;171(5):593-601.
29. Korrick SA, Altshul LM, Tolbert PE, Burse VW, Needham LL, Monson RR. Measurement of PCBs, DDE, and hexachlorobenzene in cord blood from infants born in towns adjacent to a PCB-contaminated waste site. *J Expo Anal Environ Epidemiol*. 2000;10(6, pt 2):743-754.
30. Longnecker MP, Wolff MS, Gladen BC, et al. Comparison of polychlorinated biphenyl levels across studies of human neurodevelopment. *Environ Health Perspect*. 2003;111(1):65-70.
31. National Research Council. *Toxicological Effects of Methylmercury*. Washington, DC: National Academy Press; 2000.
32. Conners CK. *Conners' Rating Scales-Revised Technical Manual*. North Tonawanda, NY: Multi-Health Systems; 1997.
33. Letz R. *NES2 User's Manual, Version 4.7*. Atlanta, GA: Neurobehavioral Systems Inc; 1998.
34. Wechsler D. *Wechsler Scale for Infant Intelligence*. 3rd ed. San Antonio, TX: Psychological Corp; 1991.
35. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. *Epidemiology*. 1992;3(5):452-456.
36. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
37. Caldwell B, Bradley R. *Home Observation for Measurement of the Environment*. Rev ed. Little Rock: University of Arkansas; 1984.
38. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999;10(1):37-48.
39. Weng HY, Hsueh YH, Messam LL, Hertz-Picciotto I. Methods of covariate selection: directed acyclic graphs and the change-in-estimate procedure. *Am J Epidemiol*. 2009;169(10):1182-1190.
40. Peng RD, Dominici F. *Statistical Methods for Environmental Epidemiology With R: A Case Study in Air Pollution and Health*. New York, NY: Springer Science; 2008.
41. Cernichiari E, Brewer R, Myers GJ, et al. Monitoring methylmercury during pregnancy: maternal hair predicts fetal brain exposure. *Neurotoxicology*. 1995;16(4):705-710.
42. McDowell MA, Dillon CF, Osterloh J, et al. Hair mercury levels in U.S. children and women of childbearing age: reference range data from NHANES 1999-2000. *Environ Health Perspect*. 2004;112(11):1165-1171.
43. Debes F, Budtz-Jørgensen E, Weihe P, White RF, Grandjean P. Impact of prenatal methylmercury exposure on neurobehavioral function at age 14 years. *Neurotoxicol Teratol*. 2006;28(5):536-547.
44. Ha M, Kwon HJ, Lim MH, et al. Low blood levels of lead and mercury and symptoms of attention deficit hyperactivity in children: a report of the children's health and environment research (CHEER). *Neurotoxicology*. 2009;30(1):31-36.
45. Budtz-Jørgensen E, Grandjean P, Weihe P. Separation of risks and benefits of seafood intake. *Environ Health Perspect*. 2007;115(3):323-327.
46. Davidson PW, Strain JJ, Myers GJ, et al. Neurodevelopmental effects of maternal nutritional status and exposure to methylmercury from eating fish during pregnancy. *Neurotoxicology*. 2008;29(5):767-775.
47. Strain JJ, Davidson PW, Bonham MP, et al. Associations of maternal long-chain polyunsaturated fatty acids, methyl mercury, and infant development in the Seychelles Child Development Nutrition Study. *Neurotoxicology*. 2008;29(5):776-782.
48. Richardson AJ. Omega-3 fatty acids in ADHD and related neurodevelopmental disorders. *Int Rev Psychiatry*. 2006;18(2):155-172.
49. Grandjean P, Weihe P, Burse VW, et al. Neurobehavioral deficits associated with PCB in 7-year-old children prenatally exposed to seafood neurotoxicants. *Neurotoxicol Teratol*. 2001;23(4):305-317.
50. Stewart PW, Reihman J, Lonky EI, Darvill TJ, Pagano J. Cognitive development in preschool children prenatally exposed to PCBs and MeHg. *Neurotoxicol Teratol*. 2003;25(1):11-22.
51. Surkan PJ, Wypij D, Trachtenberg F, et al. Neuropsychological function in school-age children with low mercury exposures. *Environ Res*. 2009;109(6):728-733.
52. Rice DC, Schoeny R, Mahaffey K. Methods and rationale for derivation of a reference dose for methylmercury by the U.S. EPA. *Risk Anal*. 2003;23(1):107-115.
53. Cordier S, Garel M, Mandereau L, et al. Neurodevelopmental investigations among methylmercury-exposed children in French Guiana. *Environ Res*. 2002;89(1):1-11.
54. Braun JM, Yolton K, Dietrich KN, et al. Prenatal bisphenol A exposure and early childhood behavior. *Environ Health Perspect*. 2009;117(12):1945-1952.
55. Engel SM, Miodovnik A, Canfield RL, et al. Prenatal phthalate exposure is associated with childhood behavior and executive functioning. *Environ Health Perspect*. 2010;118(4):565-571.
56. Weiss B. Same sex, no sex, and unaware sex in neurotoxicology. *Neurotoxicology*. 2011;32(5):509-517.
57. Bellinger DC. What is an adverse effect? a possible resolution of clinical and epidemiological perspectives on neurobehavioral toxicity. *Environ Res*. 2004;95(3):394-405.