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Blood Mercury Levels and Neurobehavioral Function

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MERCURY IS UBIQUITOUS IN the environment and enters the air during fossil-fuel combustion, mining, smelting, solid-waste incineration, and natural degassing of the earth.¹ It is converted to methylmercury by microorganisms, enters the food chain, and bioaccumulates in predatory fish. Consumption of certain fish and crustaceans (hereafter referred to as fish) is the primary source of methylmercury exposure in the general population.^{1,2}

Methylmercury distributes rapidly throughout the body and easily crosses the blood-brain barrier into the brain, where it may become trapped after demethylation.¹ Generally, changes in nervous system function are considered the most sensitive health end point^{1,3}; however, recent evidence indicates that adverse cardiovascular effects may occur at even lower levels,³ possibly leading to further cognitive effects.⁴⁻⁹ Total blood mercury is considered the most valid biomarker of recent methylmercury exposure.¹⁰

Recent regulations for mercury emissions, the increasing trend in fish-consumption advisories, clinical studies, and heightened media attention have led to the emergence of mercury as a leading public health concern.¹¹⁻¹⁶ The US Environmental Protection Agency, the US Food and Drug Administration, and the National Research

Context Due to its cardiovascular benefits, fish consumption is widely encouraged among older Americans. However, this fast-growing population is at increased risk of cognitive impairment and may be particularly sensitive to methylmercury, a neurotoxicant found in fish.

Objective To describe associations of blood mercury levels with neurobehavioral test scores in an urban adult population.

Design, Setting, and Participants Cross-sectional analysis to determine the effect of mercury levels on neurobehavior in 474 randomly selected participants in the Baltimore Memory Study, a longitudinal study of cognitive decline involving 1140 Baltimore residents aged 50 to 70 years. We measured total mercury in whole blood samples and used multiple linear regression to examine its associations with neurobehavioral test scores. First-visit data were obtained in 2001-2002.

Main Outcome Measures Twenty scores from 12 neurobehavioral tests.

Results The median blood mercury level was 2.1 µg/L (range, 0-16 µg/L). After adjustment for covariates, increasing blood mercury was associated with worse performance on Rey complex figure delayed recall, a test of visual memory (β , -0.224; 95% confidence interval, -0.402 to -0.047). However, increasing blood mercury levels were associated with better performance on finger tapping, a test of manual dexterity (β for dominant hand, 0.351; 95% confidence interval, 0.017-0.686).

Conclusion Overall, the data do not provide strong evidence that blood mercury levels are associated with worse neurobehavioral performance in this population of older urban adults.

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Council all recently addressed the risks associated with eating mercury-contaminated fish, focusing on children and women of child-bearing age.^{3,17-20} Fish consumption, however, is frequently recommended for older adults due to its high omega-3 fatty acid content, well-documented cardiovascular benefits, and, more recently, its possible protective association with Alzheimer disease.²¹⁻²⁴ Since the aging nervous system is more sensitive to neurotoxins, there is reason for concern about mercury contamination in fish, especially now that baby boomers are approaching that point when age-related cognitive decline becomes apparent.²⁵⁻²⁷ Given the longer life expectancy of that generation, a dramatic increase in the prevalence of cognitive

dysfunction is anticipated.²⁸ For this reason, investigating mercury exposure in the older population is considered a public health priority.

We analyzed blood mercury levels and neurobehavioral test scores in 474 participants from the Baltimore Memory Study, which involved 1140 randomly selected, 50- to 70-year-old

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Baltimore, Md, residents. To our knowledge, this is the first study to examine associations between mercury exposure and neurobehavioral outcomes in a representative sample of older adults in the United States.

METHODS

Study Population and Design

The population, design, sampling, and recruitment methods for the Baltimore Memory Study have been described.²⁹ In brief, residents were sampled by neighborhood to ensure variability by socioeconomic status, race, and ethnicity. A total of 18 826 households with telephone numbers were randomly selected and recruited. Eligibility requirements included living in a targeted neighborhood for at least 5 years and being between 50 and 70 years old. Among the 2351 eligible residents, 1430 (60.8%) were scheduled for a clinic visit and 1140 were enrolled. The first of 3 study visits occurred between May 30, 2001, and September 20, 2002. The Committee for Human Research at the Johns Hopkins Bloomberg School of Public Health approved the study. All participants provided written informed consent before testing and were paid \$50 for their time. The current study involved cross-sectional analysis of first-visit data from 474 randomly selected participants of the Baltimore Memory Study with complete first-visit data and adequate blood specimens for mercury measurement. Sample size was based on power calculations³⁰ (2-tailed $\alpha = .05$; power = 0.89; effect size = 0.03) and budget available for mercury measurement.

Data Collection

Data collection methods have been described.²⁹ In brief, trained technicians administered 20 neurobehavioral tests in the following 7 domains: nonverbal reasoning and intelligence, Ravens coloured progressive matrices^{31,32}; language, Boston naming test,^{33,34} letter fluency,³⁵ category fluency³⁵; verbal memory, Rey auditory verbal learning test³⁶; visual memory, Rey complex fig-

ure–delayed recall,³⁷ symbol-digit paired associate learning³⁸; visuconstruction and visuoperception, Rey complex figure–copy³⁷; motor and manual dexterity, Purdue pegboard,³⁹ finger tapping,⁴⁰ simple reaction time⁴¹; and executive function, Purdue pegboard–assembly,³⁹ Stroop test,⁴² trail-making tests.⁴⁰ A structured interview obtained self-reported information on race or ethnicity, sex, age, medications, medical history, alcohol and tobacco use, educational achievement, and household income and household assets. Race and ethnicity was ascertained to ensure representativeness of the population and because it is associated with both mercury level and cognitive function. All testing was performed without knowledge of blood mercury level or dietary history. Technicians weighed and measured the height of the participants, and a phlebotomist obtained a blood specimen. Specimens were stored at -20°C (mean 7.3 days) and later transferred to -70°C (mean 252 days) until analysis.

Blood Mercury Measurements

Total mercury was measured in whole blood using a flow-injection mercury system with on-line microwave digestion and cold-vapor, atomic-absorption spectrometry in the Trace Elements Laboratory of the New York State Department of Health's Wadsworth Center. The methods were based on the comparison method described in Barbosa et al⁴³ and required a 0.2-mL sample. Collection tubes and storage containers were screened for mercury contamination. Samples were analyzed in duplicate, and all quality-control specifications were met. The intraday and interday coefficient of variation (CV) for the 1.1- $\mu\text{g}/\text{L}$ mercury control was 17.6% and 13.9%, respectively. The intraday and interday CV for the 5.4- $\mu\text{g}/\text{L}$ mercury control was 8.7% and 8.8%, respectively. The detection limit was 0.1 $\mu\text{g}/\text{L}$. For the statistical analysis, results below the detection limit ($n=7$) were assigned a value equal to the detection limit divided by the square root of 2.

Other Laboratory Measurements

A commercial laboratory measured serum homocysteine levels using fluorescence polarization immunoassay (Abbott AxSYM, Abbott Park, Ill); the CV ranged from 2.2% to 3.6%. The metals laboratory of the Kennedy Krieger Institute, Baltimore, Md, measured blood lead using anodic stripping voltammetry.⁴⁴ The intraday CV was 11% and the interday CV was 7% (for 5.9 $\mu\text{g}/\text{dL}$ of lead). Another commercial laboratory measured serum cholesterol levels using an Olympus AU5200 or AU600 (Olympus America, Melville, NJ), with the CV ranging from 2.15% to 2.28%. Serum triglycerides were measured on an AU5200 (CV from 2.88% to 3.32%). Apolipoprotein E (APOE) genotyping was performed by the Malaria Institute laboratory at the Johns Hopkins Bloomberg School of Public Health using previously published methods.⁴⁵

Fish Consumption

Participants completed the Block 98.2 Food Frequency Questionnaire (Berkeley Nutrition Services, Berkeley, Calif) before their second study visit. Completed forms were optically scanned, and data were returned electronically. The questionnaire assessed the participant's "usual eating habits in the past year or so" for the following foods: oysters, shellfish, tuna, fried fish, and other fish. Participants estimated average serving sizes by choosing 1 of 4 pictures that looked like the portion size they normally eat, ranging from a quarter cup to 2 cups. Frequency information was divided into 9 categories ranging from "never consumed" to "one serving per day." Berkeley Nutrition Services also provided an estimate of average daily intake of omega-3-fatty acids (grams) using US Department of Agriculture data⁴⁶ and the following formula: (portion size \times nutrient content \times daily food frequency \times seasonality factor)/100.^{47,48}

Statistical Analyses

The main objectives were to (1) explore associations between blood mer-

cury concentration and neurobehavioral test scores, adjusting for age, race and ethnicity, sex, educational achievement, neurobehavioral testing technician, fish consumption, and other potential confounding variables and (2) evaluate whether these associations were influenced by potential effect modifiers, such as *APOE* genotype; race and ethnicity; sex; age; homocysteine, cholesterol, and triglyceride levels; blood lead; body mass index, calculated as weight in kilograms divided by the square of height in meters; antihypertensive medication use; diabetes; and tobacco use. Intercooled Stata 7.0 (Stata Corp, College Station, Tex) software was used.

Treatment methods for the outcome variables have been reported.²⁹ In brief, some of the measures were natural-log transformed because of departures from normality, were negated to standardize the signs of the β coefficients so that a negative coefficient always indicates that test performance worsens with increasing blood mercury levels, or both.

Multiple linear regression was used to evaluate associations of blood mercury levels with neurobehavioral test scores, adjusting for confounders; only associations that achieved statistical significance ($P < .05$) are discussed. In the base model, mercury was regressed on neurobehavioral score, adjusting for age, race and ethnicity, sex, educational achievement, and testing technician. Race and ethnicity was categorized as white (reference group), black, black-mixed, or other.²⁹ Educational achievement was divided into 9 categories, based on years of education and possession of degrees or trade certificates, or both. The reference group possessed a high school diploma and a trade certificate. Finally, the testing-technician variable was modeled as 3 dummy variables, using the technician who tested the largest number of participants as the reference.

To arrive at a final model, other covariates were added to the base model using a biologically driven, forward, stepwise technique. These variables were

chosen a priori and added to the model individually: time of day of the interview (morning, afternoon, or evening), household income and assets (both natural-log transformed to minimize the influence of very large values), blood lead level, *APOE* genotype (presence of the $\epsilon 4$ allele vs none), body mass index, smoking status (current, previous, or never), alcohol consumption in the past month (yes vs no), history of diabetes (yes vs no), history of myocardial infarction (yes vs no), use of antihypertensive medications in the past 2 weeks (yes vs no), history of stroke (yes vs no), use of antidepressant medications in past 2 weeks (yes vs no), use of anti-anxiety medications in past 2 weeks (yes vs no), homocysteine level, total cholesterol level, and triglycerides. Variables were retained if they fulfilled at least 1 of the following: (1) they were significant predictors of neurobehavioral test scores or (2) their inclusion changed the mercury coefficient by 25% or more. In addition to the covariates in-

cluded in the base model, the final model included assets, body mass index, alcohol consumption, and diabetes.

Because 58 participants did not complete the food questionnaire, a third model (base-for-food model) served as a base with which to compare 2 models containing food variables: a model that controlled for fish consumption and a model that controlled for omega-3 fatty acid intake. All 3 models were based on the final model. For each fish type, consumption frequency and portion size were multiplied to estimate annual consumption. These estimates were then added to yield an estimate of total annual fish consumption. This was divided into quartiles and entered into models as 3 dummy variables.

The final model was used for evaluation of effect modification by the variables listed previously. For these analyses, we evaluated the significance of the cross-product term that resulted from multiplying mercury by each variable, one at a time. For continuous variables,

Table 1. Description of Study Participants Selected for Mercury Analysis Compared With Those Not Selected

Variable	In Mercury Study (n = 474)	Not in Mercury Study (n = 666)	P Value*
Age, mean (SD), y	59.32 (5.88)	59.29 (6.04)	.93
Women, No. (%)	325 (68.57)	424 (63.66)	.09
Black, No. (%)	185 (39.03)	289 (43.39)	.14
Educational category, No. (%)			.01
<10th grade	15 (3.16)	33 (4.96)	
≥10th grade, no diploma	25 (5.27)	76 (7.67)	
High school diploma, no trade school	84 (17.72)	110 (16.52)	
Trade school, no diploma	5 (1.05)	25 (3.75)	
High school diploma and trade school†	93 (19.62)	151 (22.71)	
Some college education or associate's degree	35 (7.38)	31 (4.66)	
Baccalaureate degree	57 (12.03)	79 (11.88)	
Some postbaccalaureate education	47 (9.92)	63 (9.47)	
Postbaccalaureate degree	113 (23.84)	122 (18.35)	
Household assets, geometric mean, US \$	38 707.94	15 721.74	.005
BMI, mean (SD)	29.97 (7.03)	29.60 (6.79)	.36
Diabetes, No. (%)	83 (17.51)	113 (16.97)	.81
Alcohol use in previous month, No. (%)	281 (59.28)	392 (58.86)	.89
Total fish consumption, mean (SD), cups/y	74.73 (72.69)	64.56 (71.42)	.03
Omega-3 fatty acid intake, mean (SD), g/d	1.83 (1.13)	1.78 (1.10)	.48
Blood mercury concentration, mean (SD), $\mu\text{g/L}$	2.76 (2.35)		

Abbreviation: BMI, body mass index, which is calculated as weight in kilograms divided by the square of height in meters.
 *P values for means are derived from 2 sample t tests with unequal variances; P values for percentages are derived from χ^2 tests.
 †High school diploma and trade school was the reference group for education in the models.

we used quartiles and tested the significance of all 3 cross-product terms at once.

Adequacy of the final models was evaluated by (1) examining added variable plots showing adjusted regression lines,⁴⁹ (2) comparing these lines with lowess regression lines,⁵⁰ and (3) plotting residuals against predicted values. To evaluate the magnitude of the associations, test scores were Z transformed and then multiplied by mercury's interquartile range (2.4 µg/L).

RESULTS

Description of Study Subjects

The 474 study participants consisted of 325 women (68.57%), 185 blacks

(39.03%), and 263 whites (55.49%). These individuals did not differ by age, race and ethnicity, or sex from the 666 participants who were not selected. They were, however, more likely to have a postbaccalaureate education, greater assets, and higher fish consumption than those not selected for the study (TABLE 1). Blood mercury levels were consistent with those found in populations that do not have high fish consumption.^{1-3,51}

Associations of Blood Mercury With Neurobehavioral Test Scores

In the base model, higher blood mercury was associated with worse perfor-

mance on Rey complex figure delayed recall and better performance on finger tapping and Purdue pegboard (TABLE 2). Comparing the base model with the final model, we observed an increase in the magnitude of the association between mercury and the Rey complex figure delayed recall, a decrease in the magnitude of the associations between mercury and finger tapping), and a loss of significance on Purdue pegboard (FIGURE).

In the base-for-food model (TABLE 3), the association of blood mercury with the Rey complex figure delayed recall was of larger magnitude compared with the original base model

Table 2. Results From Multiple Linear Regressions of Neurobehavioral Test Score on Mercury

Cognitive Domain	Base Model (n = 474)*		Final Model (n = 474)†	
	β Coefficients for Blood Mercury (95% CI)‡	P Value	β Coefficients for Blood Mercury (95% CI)‡	P Value
Nonverbal reasoning to measure intelligence Colored progressive matrices	0.038 (-0.124 to 0.201)	.64	0.000 (-0.164 to 0.164)	.99
Language				
Boston naming	-0.013 (-0.119 to 0.093)	.82	-0.032 (-0.139 to 0.075)	.55
Category fluency	0.368 (-0.125 to 0.861)	.14	0.258 (-0.241 to 0.756)	.31
Letter fluency	-0.077 (-0.532 to 0.378)	.74	-0.078 (-0.540 to 0.386)	.74
Verbal memory				
Rey auditory verbal learning Trials 1-5	-0.017 (-0.328 to 0.294)	.91	-0.044 (-0.360 to 0.273)	.79
Recognition	-0.069 (-0.155 to 0.016)	.11	-0.066 (-0.153 to 0.021)	.14
Delayed recall	-0.083 (-0.182 to 0.016)	.10	-0.086 (-0.187 to 0.015)	.09
Visual memory				
Rey complex figure delayed recall	-0.205 (-0.380 to -0.030)	.02	-0.224 (-0.402 to -0.047)	.01
Symbol digit	0.136 (-0.039 to 0.310)	.13	0.113 (-0.063 to 0.289)	.21
Visuoconstruction and visuoperception Rey complex figure copy	0.047 (-0.146 to 0.241)	.63	0.018 (-0.178 to 0.214)	.86
Motor and manual dexterity				
Finger tapping				
Dominant hand	0.404 (0.076 to 0.733)	.02	0.351 (0.017 to 0.686)	.04
Nondominant hand	0.353 (0.081 to 0.626)	.01	0.323 (0.046 to 0.600)	.02
Purdue pegboard				
Dominant hand	0.098 (0.019 to 0.177)	.02	0.059 (-0.018 to 0.137)	.13
Nondominant hand	0.096 (0.019 to 0.174)	.02	0.069 (-0.008 to 0.145)	.08
Both hands	0.058 (-0.015 to 0.132)	.12	0.026 (-0.046 to 0.099)	.47
Simple reaction time, %	0.004 (-0.004 to 0.012)	.38	0.002 (-0.006 to 0.010)	.69
Executive function				
Purdue pegboard (assembly)	0.340 (0.058 to 0.622)	.02	0.211 (-0.065 to 0.488)	.13
Stroop test (negated)	0.485 (-0.584 to 1.554)	.38	0.273 (-0.808 to 1.354)	.62
Trail making, %§				
Test A	0.004 (-0.009 to 0.017)	.51	0.002 (-0.012 to 0.015)	.82
Test B	-0.002 (-0.017 to 0.013)	.81	-0.005 (-0.020 to 0.011)	.57

*The base model was adjusted for age (continuous), race and ethnicity (categorical), sex (binary), technician (categorical), and education (categorical).
 †Final model included household assets (natural-log transformed continuous); body mass index, which is calculated as weight in kilograms divided by the square of height in meters (continuous); drinking (binary); and diabetes (binary) in addition to the variables included in the base model.
 ‡All coefficients were standardized for direction so that a negative coefficient means that test performance worsens with increasing blood mercury.
 §Trails A and B and simple reaction time were natural-log transformed.

(Table 2). The coefficients for Purdue pegboard and finger tapping declined in both significance (except for non-dominant finger tapping) and magnitude. There were only small differences in the magnitude and significance of associations comparing the base-for-food models, the fish model, and the omega-3 model (Table 3). Exploratory analysis did not reveal any consistent evidence of effect modification by the variables examined.

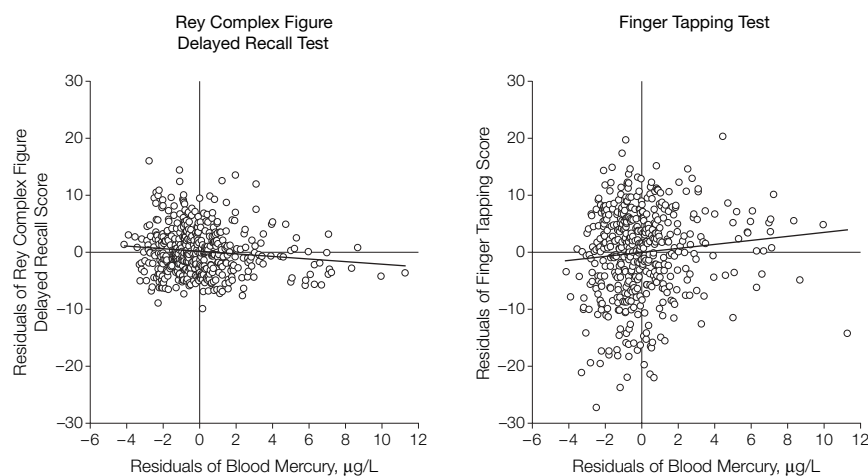
Because results across models were similar, we only present magnitude analysis for the final model. For Rey complex figure delayed recall, on average, an increase of blood mercury from the 25th to the 75th percentile was associated with a 0.12 SD decline in performance. Four SD units encompass approximately 95% of a normal distribution; therefore, a decline of 0.12 SD units is approximately equivalent to a 3% decline in performance. For finger tapping, an increase of blood mercury from the 25th to the 75th percentile was associated with approximately a 2% improvement.

COMMENT

To our knowledge, this is the first study to investigate whether mercury is associated with adverse neurobehavioral outcomes in older adults from the general US population. This study was important given the levels of mercury found in fish,⁵² the growing population of older adults at risk of cognitive impairment, the well-known benefits of fish consumption, and evidence that such benefits may counteract the negative effects of consuming mercury-contaminated fish.²³

In summary, the study provided no compelling evidence that blood mercury levels were adversely associated with neurobehavioral test scores. There were some consistent associations across models but because of the large number of comparisons and the observation that statistically significant associations were in different directions (ie, worse performance on a test of visual memory and better performance on tests of manual dexterity), we cannot exclude the possibility that associations were due to chance.

Figure. Added Variable Plot From the Final Model of the Rey Complex Figure Delayed Recall Test and the Finger Tapping Test of the Dominant Hand



The x-axis represents the residuals of mercury regressed on age, race and ethnicity, sex, technician, educational achievement, assets, body mass index, alcohol use, and diabetes. The y-axis represents the residuals of Rey complex figure delayed recall and finger tapping scores regressed on the same variables.

This study had many design strengths including the random selection of participants with diversity by race and ethnicity, extensive neurobehavioral battery in a broad set of cognitive domains, assessment of and control for a large number of potential confounders and effect modifiers, and a relatively large sample size. Previous epidemiological studies have documented overt neurological outcomes following mercury-poisoning incidents including dysarthria, ataxia, constriction of visual fields, distal paresthesias, hearing loss, muscle weakness, and tremor.⁵³⁻⁵⁵ However, effects of long-term exposure to lower levels of methylmercury are likely to be sub-clinical, similar to effects associated with lead and other neurotoxins.^{3,27,56} Several recent studies have investigated the neurobehavioral effects of such exposures in adults; the majority concluded that higher mercury levels were associated with poorer performance on neurobehavioral tests. Of these studies, not one looked at the general US population⁵⁷⁻⁶⁴ and most focused on frequent fish consumers,^{57,59,61-64} populations with mercury levels higher than that found in the general US population, or both.^{10,57,59,60,63} Furthermore, many of the studies focused on populations living in

highly contaminated areas (eg, the Amazon)^{57-60,62,63} and with little racial or ethnic diversity (such as that typically seen in the United States).^{57-59,61-64} Many had a small sample size with insufficient power,^{57,59,60} lack of appropriate statistical techniques (such as only looking at correlation and not using regression modeling),^{58,60,64} possibly biased sampling of study participants,^{57,60,64} and inadequate neurobehavioral assessment.⁶⁴ It is difficult to draw strong conclusions from these studies or to determine whether the findings have relevance to the general adult US population.

In evaluating whether toxicants have adverse effects on central nervous system function, it is important to consider whether exposure was recent or cumulative, whether effects are acute or chronic, and whether the biomarker is adequate to assess differing dose patterns. Clearance half-time of mercury in blood is approximately 50 days, so blood mercury likely represents integrated dose over the past 5 to 6 months. In frequent regular fish consumers, blood mercury levels reach a steady state and may provide a better picture of cumulative dose.³ If patterns of fish consumption vary dramati-

cally over a lifetime, then a single blood-mercury level may not be adequate to assess longer latency effects or effects related to cumulative dose, particularly if individuals were exposed in utero. Hair mercury is thought to provide a longer-term estimate of dose, but average concentration of mercury in hair is highly correlated with the concentration of mercury in blood.^{1,3,53,65,66} Two additional factors favor use of blood mercury. First, the concentration of methylmercury in blood is considered to be the best indicator of not only total body burden but also dose to the brain.⁶⁵ Second, blood mercury is the most relevant clinical measure and

the one with which patients are most likely to be familiar.

Our study has some relative limitations. First, cross-sectional assessment precluded evaluation of the temporality or causality of any associations. Second, although self-reported fish consumption was associated with blood mercury (evidence of the validity of the food questionnaire), the questionnaire may not accurately measure omega-3 fatty acid dose. Third, fish consumption was assessed at the second study visit while blood mercury was determined during the first; however, the questionnaire did use an intake period of 1 year. A final limitation is that

our subsample had individuals with more graduate degrees, higher assets, and higher fish intake than the Baltimore Memory Study participants not selected, possibly reducing the external validity of the sample. Otherwise, the results may be expected to be generalizable to other urban-dwelling, 50- to 70-year-old US residents.

Current fish consumption recommendations are based on risk assessments for children and women of child-bearing age; according to the Environmental Protection Agency and the National Research Council an “acceptable” blood mercury level for this group is 5.8 µg/L or less.^{3,19} Since the aging

Table 3. Results From Multiple Linear Regressions of Neurobehavioral Test Score on Mercury in Food Models

Cognitive Domain	Base for Food Models (n = 416)*		Fish Model (n = 416)†		Omega-3 Model (n = 416)‡	
	β Coefficients for Blood Mercury (95% CI)§	P Value	β Coefficients for Blood Mercury (95% CI)§	P Value	β Coefficients for Blood Mercury (95% CI)§	P Value
Nonverbal reasoning for intelligence Colored progressive matrices	-0.016 (-0.180 to 0.148)	.85	-0.004 (-0.172 to 0.164)	.96	-0.016 (-0.180 to 0.149)	.85
Language						
Boston naming	-0.036 (-0.145 to 0.073)	.52	-0.036 (-0.147 to 0.075)	.53	-0.032 (-0.141 to 0.077)	.56
Category fluency	0.253 (-0.266 to 0.772)	.34	0.269 (-0.263 to 0.802)	.32	0.275 (-0.242 to 0.792)	.30
Letter fluency	0.079 (-0.385 to 0.544)	.74	0.056 (-0.421 to 0.533)	.82	0.098 (-0.366 to 0.562)	.68
Verbal memory						
Rey auditory verbal learning Trials 1-5	-0.061 (-0.390 to 0.267)	.71	-0.064 (-0.400 to 0.271)	.71	-0.056 (-0.386 to 0.273)	.74
Recognition	-0.050 (-0.140 to 0.040)	.27	-0.034 (-0.126 to 0.058)	.46	-0.051 (-0.141 to 0.039)	.27
Delayed recall	-0.089 (-0.194 to -0.016)	.10	-0.081 (-0.188 to 0.026)	.14	-0.088 (-0.193 to 0.017)	.10
Visual memory						
Rey complex figure delayed recall	-0.256 (-0.443 to -0.069)	.007	-0.262 (-0.454 to -0.070)	.008	-0.255 (-0.443 to -0.068)	.008
Symbol digit	0.090 (-0.086 to 0.266)	.32	0.095 (-0.085 to 0.276)	.30	0.093 (-0.083 to 0.270)	.30
Visuoconstruction and visuoperception Rey complex figure copy	-0.058 (-0.257 to 0.141)	.57	-0.092 (-0.295 to 0.112)	.38	-0.053 (-0.251 to 0.146)	.60
Motor and manual dexterity						
Finger tapping						
Dominant hand	0.317 (-0.026 to 0.661)	.07	0.334 (-0.019 to 0.687)	.06	0.322 (-0.022 to 0.666)	.07
Nondominant hand	0.294 (0.014 to 0.574)*	.04	0.313 (0.027 to 0.599)	.03	0.300 (0.020 to 0.580)	.04
Purdue pegboard						
Dominant hand	0.065 (-0.017 to 0.147)	.12	0.074 (-0.010 to 0.157)	.08	0.062 (-0.019 to 0.143)	.13
Nondominant hand	0.072 (-0.008 to 0.153)	.08	0.083 (0.001 to 0.164)	.05	0.069 (-0.011 to 0.148)	.09
Both hands	0.036 (-0.040 to 0.111)	.36	0.038 (-0.039 to 0.116)	.33	0.033 (-0.043 to 0.108)	.39
Simple reaction time, %	0.001 (-0.007 to 0.009)	.84	0.001 (-0.008 to 0.009)	.87	0.001 (-0.007 to 0.009)	.81
Executive function						
Purdue pegboard assembly	0.208 (-0.079 to 0.495)	.16	0.238 (-0.055 to 0.532)	.11	0.207 (-0.081 to 0.495)	.16
Stroop test (negated)	0.218 (-0.892 to 1.328)	.70	0.279 (-0.858 to 1.416)	.63	0.225 (-0.888 to 1.339)	.69
Trail making, %						
Test A	-0.000 (-0.014 to 0.013)	.99	-0.001 (-0.015 to 0.013)	.92	-0.000 (-0.014 to 0.013)	.96
Test B	-0.003 (-0.019 to 0.013)	.70	-0.004 (-0.020 to 0.012)	.63	-0.003 (-0.019 to 0.013)	.69

*Base-for-food models include the variables from the final model but only for the 416 people who had food data.

†Fish model is the base-for-food model plus fish (categorical).

‡Omega-3 model is the base-for-food model plus omega-3 fatty acids (continuous).

§All coefficients were standardized for direction so that a negative coefficient means test performance worsens with increasing blood mercury.

||Trails A and B and simple reaction time were natural-log transformed.

population may be particularly vulnerable to neurotoxicants, this study was an attempt to examine whether this rapidly growing group is sensitive to even lower levels of exposure. Since the blood mercury levels in our study did not appear to be associated with adverse neurobehavioral effects, our results suggest that these levels of exposure may not present a concern for older adults. Studies with more detailed dose assessment are necessary to confirm this conclusion since a single blood-mercury level may not be an optimal estimate of cumulative dose.

Author Contributions: Ms Weil had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Weil, Schwartz.

Acquisition of data: Weil, Bressler, Parsons, Bolla, Glass, Schwartz.

Analysis and interpretation of data: Weil, Bolla, Glass, Schwartz.

Drafting of the manuscript: Weil, Bolla, Schwartz.

Critical revision of the manuscript for important intellectual content: Bressler, Parsons, Glass, Schwartz.

Statistical analysis: Weil, Glass, Schwartz.

Obtained funding: Weil, Glass, Schwartz.

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Study supervision: Bressler, Bolla, Glass, Schwartz.

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REFERENCES

- Agency for Toxic Substances and Disease Registry. *Toxicological Profile for Mercury (Update)*. Atlanta, Ga: US Dept of Health and Human Services, Public Health Service; 1999.
- World Health Organization. *Methylmercury*. Geneva, Switzerland: International Programme on Chemical Safety; 1990.
- National Academies of Science. *Toxicological Effects of Methylmercury*. Washington, DC: National Research Council; 2000.
- Sadowski M, Pankiewicz J, Scholtzova H, et al. Links between the pathology of Alzheimer's disease and vascular dementia. *Neurochem Res*. 2004;29:1257-1266.
- Lopez OL, Jagust WJ, Dulberg C, et al. Risk factors for mild cognitive impairment in the Cardiovascular Health Study Cognition Study, II. *Arch Neurol*. 2003;60:1394-1399.
- Skoog I. The relationship between blood pressure and dementia: a review. *Biomed Pharmacother*. 1997;51:367-375.
- Breteler MM, Bots ML, Ott A, Hofman A. Risk factors for vascular disease and dementia. *Haemostasis*. 1998;28:167-173.
- Starr JM. Blood pressure and cognitive decline in the elderly. *Curr Opin Nephrol Hypertens*. 1999;8:347-351.
- Haan MN, Shemanski L, Jagust WJ, Manolio TA, Kuller L. The role of APOE ε4 in modulating effects of other risk factors for cognitive decline in elderly persons. *JAMA*. 1999;282:40-46.
- Schober SE, Sinks TH, Jones RL, et al. Blood mercury levels in US children and women of childbearing age, 1999-2000. *JAMA*. 2003;289:1667-1674.
- Kales SN, Goldman RH. Mercury exposure: current concepts, controversies, and a clinic's experience. *J Occup Environ Med*. 2002;44:143-154.
- Hightower JM, Moore D. Mercury levels in high-end consumers of fish. *Environ Health Perspect*. 2003;111:604-608.
- Weaver V. Clinical evaluation of elevated mercury levels. Presented at: Johns Hopkins Bloomberg School of Public Health; October 11, 2003; Baltimore, Md.
- Fish mercury risk underestimated. Atlanta, Ga: Cable News Network; April 12, 2001. Available at: <http://www.cnn.com/2001/HEALTH/parenting/04/12/fish.pregnant/index.html>. Accessed November 10, 2003. Accessibility verified March 21, 2005.
- Raines B. Your deadly diet. *Health*. 2003;120:188.
- Gorman J. Does mercury matter? experts debate the big fish question. *New York Times*. July 29, 2003;sect F:5. Available at: <http://query.nytimes.com/gst/abstract.html?res=F0B815FF345B0C7A8EDDAE0894DB404482>. Accessed November 10, 2003. Accessibility verified March 21, 2005.
- US Environmental Protection Agency. Mercury: frequently asked questions Web page. Available at: <http://www.epa.gov/mercury/information1.htm>. Accessed September 3, 2003. Updated August 20, 2003.
- US Food and Drug Administration. *Rationale for Issuance of Revised Advisory on Methylmercury and Fish Consumption*. Rockville, Md: Center for Food Safety and Applied Nutrition; 2001.
- 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;23:107-115.
- Plaisier MK. Letter to the Honorable Trent Lott. January 31, 2001. Available at: <http://www.cfsan.fda.gov/~acrobat/hgcong76.pdf>. Accessed May 10, 2002. Accessibility verified March 21, 2005.
- Specific types of fat. American Diabetes Association Web site. Available at: <http://www.diabetes.org/nutrition-and-recipes/nutrition/foodlabel/specific-fats.jsp>. Accessed July 25, 2004. Accessibility verified March 21, 2005.
- Morris MC, Evans DA, Bienias JL, et al. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. *Arch Neurol*. 2003;60:940-946.
- Guallar E, Sanz-Gallardo ML, van't Veer P, et al. Mercury, fish oils, and the risk of myocardial infarction. *N Engl J Med*. 2002;347:1747-1754.
- Simon JA, Hodgkins ML, Browner WS, Neuhaus JM, Bernert JT Jr, Hulley SB. Serum fatty acids and the risk of coronary heart disease. *Am J Epidemiol*. 1995;142:469-476.
- Calne DB, Eisen A, McGeer E, Spencer P. Alzheimer's disease, Parkinson's disease, and motoneuron disease: abiotrophic interaction between ageing and environment? *Lancet*. 1986;2:1067-1070.
- Rice DC. Evidence for delayed neurotoxicity produced by methylmercury. *Neurotoxicology*. 1996;17:583-596.
- Weiss B, Clarkson TW, Simon W. Silent latency periods in methylmercury poisoning and in neurodegenerative disease. *Environ Health Perspect*. 2002;110(suppl):851-854.
- Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Arch Neurol*. 2003;60:1119-1122.
- Schwartz BS, Glass TA, Bolla KI, et al. Disparities in cognitive functioning by race/ethnicity in the Baltimore Memory Study. *Environ Health Perspect*. 2004;112:314-320.
- Power Analysis SOLO. Los Angeles, Calif: BMDP Statistical Software Inc; 1991.
- Raven J. *The Coloured Progressive Matrices Test*. London, England: Lewis Publishers; 1965.
- Raven JC, Court JH, Raven J. *Manual for Raven's Coloured Progressive Matrices and Vocabulary Scales (1995 Edition)*. Oxford, England: Oxford Psychologists Press; 1965.
- Kaplan E, Goodglass H, Weintraub S. *Boston Naming Test*. 2nd ed. Baltimore, Md: Lippincott Williams & Wilkins; 2001.
- Mackay AI, Connor LT, Albert ML, Obler LK. Noun and verb retrieval in healthy aging. *J Int Neuropsychol Soc*. 2002;8:764-770.
- Gladys JA, Schuman CC, Evans JD, Peavy GM, Miller SW, Heaton RK. Norms for letter and category fluency: demographic corrections for age, education, and ethnicity. *Assessment*. 1999;6:147-178.
- Schmidt M. *Rey Auditory Verbal Learning Test—A Handbook*. Los Angeles, Calif: Western Psychological Services; 1996.
- Ferraro FR, Grossman J, Bren A, Hoverson A. Effects of orientation on Rey complex figure performance. *Brain Cogn*. 2002;50:139-144.
- Kapur N, Butters N. Visuo-perceptive deficits in long-term alcoholics and alcoholics with Korsakoff's psychosis. *J Stud Alcohol*. 1977;38:2025-2035.
- Quick Reference Guide for the Purdue Pegboard #32020 - Test Administrator's Manual*. Lafayette, Ind: Lafayette Instrument Co; 1999.
- Reitan RM, Wolfson E. *The Halstead-Reitan Neuropsychological Test Battery*. Tucson, Ariz: Neuropsychology Press; 1985.
- Wilkinson RT, Houghton D. Field test of arousal: a portable reaction timer with data storage. *Hum Factors*. 1982;24:487-493.
- Uttl B, Graf P. Color-Word Stroop test performance across the adult life span. *J Clin Exp Neuropsychol*. 1997;19:405-420.
- Barbosa F, Palmer CD, Krug FJ, Parsons PJ. Determination of total mercury in whole blood by flow injection cold vapor atomic absorption spectrometry with room temperature digestion using tetramethylammonium hydroxide. *J Anal At Spectrom*. 2004;19:1000-1005.
- Bannon DI, Chisolm JJ Jr. Anodic stripping voltammetry compared with graphite furnace atomic absorption spectrophotometry for blood lead analysis. *Clin Chem*. 2001;47:1703-1704.
- Schafer JH, Glass TA, Bolla KI, Mintz M, Jedlicka AE, Schwartz BS. Homocysteine and cognitive function in a population-based study of older adults. *J Am Geriatr Soc*. 2005;53:381-388.
- Jones DP, Coates RJ, Flagg EW, et al. Glutathione in foods listed in the National Cancer Institute's Health Habits and History Food Frequency Questionnaire. *Nutr Cancer*. 1992;17:57-75.
- Block G, Wakimoto P, Block T. A revision of the Block Dietary Questionnaire and database, based on NHANES III data. 1998. Available at: http://www.nutritionquest.com/B98_Dev.pdf. Accessed March 21, 2005.
- Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. *Am J Epidemiol*. 1986;124:453-469.
- Kleinbaum DG, Kupper LL, Muller KE, Nizam A. *Applied Regression Analysis and Other Multivari-*

able Methods. 3rd ed. Pacific Grove, Calif: Brooks/Cole Publishing Co; 1998.

50. Cleveland WS. Robust locally weighted regression and smoothing scatterplots. *J Am Stat Assoc.* 1979;74:829-836.
51. Centers for Disease Control and Prevention. *Second National Report on Human Exposure to Environmental Chemicals.* Atlanta, Ga: National Center for Environmental Health; March 2003. Available at: <http://www.cdc.gov/exposurereport/2nd/pdf/secondner.pdf>. Accessibility verified March 21, 2005.
52. US Environmental Protection Agency. National listing of fish advisories [fact sheet]. Washington, DC: US Environmental Protection Agency. Available at: <http://www.epa.gov/waterscience/fish/advisories/factsheet.pdf>. Accessed October 2004. Accessibility verified March 21, 2005.
53. Bakir F, Damluji SF, Amin-Zaki L, et al. Methylmercury poisoning in Iraq. *Science.* 1973;181:230-241.
54. Uchino M, Tanaka Y, Ando Y, et al. Neurologic features of chronic minamata disease (organic mercury poisoning) and incidence of complications with aging. *J Environ Sci Health B.* 1995;30:699-715.
55. Eto K. Minamata disease. *Neuropathology.* 2000;20(suppl):S14-S19.
56. Weiss B. Long ago and far away: a retrospective on the implications of Minamata. *Neurotoxicology.* 1996;17:257-263.
57. Dolbec J, Mergler D, Sousa Passos CJ, Sousa de Morais S, Lebel J. Methylmercury exposure affects motor performance of a riverine population of the Tapajós river, Brazilian Amazon. *Int Arch Occup Environ Health.* 2000;73:195-203.
58. Valciukas JA, Lilis R. Psychometric techniques in environmental research. *Environ Res.* 1980;21:275-297.
59. Lebel J, Mergler D, Lucotte M, et al. Evidence of early nervous system dysfunction in Amazonian populations exposed to low-levels of methylmercury. *Neurotoxicology.* 1996;17:157-167.
60. Beuter A, Edwards R. Tremor in Cree subjects exposed to methylmercury: a preliminary study. *Neurotoxicol Teratol.* 1998;20:581-589.
61. Ahlqvist M, Bengtsson C, Lapidus L, Gergdahl IA, Schutz A. Serum mercury concentration in relation to survival, symptoms, and diseases: results from the prospective population study of women in Gothenburg, Sweden. *Acta Odontol Scand.* 1999;57:168-174.
62. Yokoo EM, Valente JG, Grattan L, Schmidt SL, Platt I, Silbergeld EK. Low level methylmercury exposure affects neuropsychological function in adults. *Environ Health.* 2003;2:8.
63. Lebel J, Mergler D, Branches F, et al. Neurotoxic effects of low-level methylmercury contamination in the Amazonian Basin. *Environ Res.* 1998;79:20-32.
64. Johansson N, Basun H, Winblad B, Nordberg M. Relationship between mercury concentration in blood, cognitive performance, and blood pressure, in an elderly urban population. *Biometals.* 2002;15:189-195.
65. Kershaw TG, Clarkson TW, Dahir PH. The relationship between blood levels and dose of methylmercury in man. *Arch Environ Health.* 1980;35:28-36.
66. Phelps RW, Clarkson TW, Kershaw TG, Wheatley B. Interrelationships of blood and hair mercury concentrations in a North American population exposed to methylmercury. *Arch Environ Health.* 1980;35:161-168.

The greatest obstacle to discovering the shape of the earth, the continents, and the oceans was not ignorance but the illusion of knowledge.
—Daniel Boorstin (1914-2004)