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. 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.

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

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. The US Environmental Protection Agency, the US Food and Drug Administration, and the National Research Council all recently addressed the risks associated with eating mercury-contaminated fish, focusing on children and women of child-bearing age. 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. 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. Given the longer life expectancy of that generation, 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. The US Environmental Protection Agency, the US Food and Drug Administration, and the National Research Council all recently addressed the risks associated with eating mercury-contaminated fish, focusing on children and women of child-bearing age. 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. 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. Given the longer life expectancy of that generation, a dramatic increase in the prevalence of cognitive dysfunction is anticipated. 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 older adults 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.

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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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. 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 23,511 eligible residents, 14,301 (60.8%) were scheduled for a clinic visit and 11,401 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 calculations (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. In brief, trained technicians administered 20 neurobehavioral tests in the following 7 domains: nonverbal reasoning and intelligence, Ravens colored progressive matrices, language, Boston naming test, letter fluency, category fluency, verbal memory, Rey auditory verbal learning test, visual memory, Rey complex figure–delayed recall, symbol-digit paired associate learning, visuoconstruction and visuo perception, Rey complex figure–copy, motor and manual dexterity, Purdue pegboard, finger tapping, simple reaction time, and executive function, Purdue pegboard–assembly, Stroop test, trail-making tests. 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 al 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 coefficients of variation (CV) for the 1.1-µg/L mercury control was 17.6% and 13.9%, respectively. The intraday and interday CV for the 5.4-µg/L mercury control was 8.7% and 8.8%, respectively. The detection limit was 0.1 µg/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. The intraday CV was 11% and the interday CV was 7% (for 5.9 µg/dL of lead). Another commercial laboratory measured serum cholesterol levels using an Olympus AU5200 or AU600 (Olympus America, Melville, NY), 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.

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 data and the following formula: (portion size × nutrient content × daily food frequency × seasonality factor)/100.

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. 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. 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 ε4 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 anti-hypertensive 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 antianxiety 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 included 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,
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, (2) comparing these lines with lowess regression lines, 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.

Associations of Blood Mercury With Neurobehavioral Test Scores

In the base model, higher blood mercury was associated with worse performance 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.
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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.

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. However, effects of long-term exposure to lower levels of methylmercury are likely to be subclinical, similar to effects associated with lead and other neurotoxicants. 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 population and most focused on frequent fish consumers, populations with mercury levels higher than that found in the general US population, or both. Furthermore, many of the studies focused on populations living in highly contaminated areas (eg, the Amazon and with little racial or ethnic diversity (such as typical seen in the United States). Many had a small sample size with insufficient power, lack of appropriate statistical techniques (such as only looking at correlation and not using regression modeling), possibly biased sampling of study participants, and inadequate neurobehavioral assessment. 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. If patterns of fish consumption vary dramati-

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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.1,3,5,6,7 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.8 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.3,9 Since the aging

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<th>Table 3. Results From Multiple Linear Regressions of Neurobehavioral Test Score on Mercury in Food Models</th>
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*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.
|||
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.

Administrative, technical, or material support: Weil, Bressler, Parsons, Schwartz.

Study supervision: Weil, Bolla, Glass, Schwartz.

None reported.

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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)