ORIGINAL RESEARCH

Effect of Mercury Levels and Seafood Intake on Cognitive Function in Middle-aged Adults

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Abstract

Context: Little agreement exists as to whether low-level mercury (Hg) exposure causes damage to the central nervous system in adults. Although eating fish is associated with intake of methylmercury, researchers in this field have generally thought that the beneficial effects of a diet rich in long-chain, n-3 fatty acids (N3FA) can outweigh the cognitive neurotoxicity of mercury.

Objective: This study intended to clarify the impact of Hg and intake of seafood on cognition.

Design: The study was a retrospective, cross-sectional analysis.

Setting: The research team performed the study at the Carillon Outpatient Center in St Petersburg, Florida.

Participants: Participants were 384 men and women, primarily corporate executives, who were attending an all-day comprehensive physical evaluation.

Outcome Measures: At participants' initial evaluations, the research team made measurements of body composition, evaluated cardiovascular status, assessed fitness, documented dietary habits (including specific types of seafood intake), and performed laboratory measures, including tests for whole-blood Hg (BHg). The team tested each subject using CNS Vital Sign, which is a computerized, neurocognitive test battery comprised of seven familiar neuropsychological tests that generate 10 independent scores.

Results: Participants' average BHg level was 7.2 µg/L. The relationship between Hg and cognitive performance was quadratic. Compared to participants with Hg levels in the 5 µg/L–to–14 µg/L range, participants with high Hg levels tested 4% to 5% lower for complex-information processing (CIP), and participants with normal Hg levels tested 2% lower. An increase in N3FA was associated with a linear improvement in CIP up to three servings of fish per week. A direct linear relationship existed between N3FA intake and BHg levels, and the interaction of Hg and N3FA intake accounted for the relationship between mercury levels and cognition.

Conclusions: Excessive seafood intake, particularly large-mouth fish, elevates Hg levels and causes cognitive dysfunction, especially for mercury levels ≥15 µg/L. Higher N3FA intake initially is associated with improved cognitive function, but rising Hg levels ultimately overwhelm the moderating effect of N3FA intake.

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The toxic potential of low-level mercury (Hg) exposure is a controversial subject.[1] The notorious incidents of Hg poisoning that occurred in Japan and Iraq and that were associated with profound damage to the nervous system were the result of extraordinary exposures.[2,3] Little agreement exists as to whether low-level Hg exposure causes damage to the central nervous system in adults. Because the developing nervous system is more vulnerable to the neurotoxicity of methylmercury (MeHg),[4] the relevant advisories concerned with fish consumption largely address women who may become pregnant.[5]

Indeed, for most people, fish consumption is the primary source of organic Hg exposure. People with a high fish intake—island and coastal populations, people of East Asian background, individuals following healthful diets—can have MeHg exposures substantially higher than the general population.[6] Since fish contains a number of beneficial nutrients, researchers[7] have thought that the beneficial effects of a diet rich in long chain N-3 fatty acids (N3FA) can outweigh the potential toxicity of small doses of Hg. Researchers have advanced this argument around the issues of the cardiovascular toxicity[1,8,9] and neurotoxicity of Hg.[10,11]

In the current study of healthy, well-educated American adults without overt cardiovascular disease and with no history of workplace Hg exposure, the objective was to assess the relationship between whole-blood Hg (BHg) levels and cognitive measures, controlling for long chain N3FA.

METHODS

This study was a cross-sectional analysis of 384 patients. The research team performed the study at the Carillon Outpatient Center in St Petersburg, Florida, and the institutional review board at St Anthony's Hospital, St Petersburg, approved the study.

Participants

Participants were 384 adult patients, ages 23 to 65 (mean = 48.2), who enrolled for a comprehensive physical at a private

clinic. This population is unique because companies paid for the evaluations of 65% of the participants as part of an executive physical for corporate executives. Of the remaining individuals, >50% were corporate executives (usually the chief executive officer, the president, the chief financial officer, or a vice president), and the remaining patients came from the general community.

The research team collected data during the individuals' first comprehensive, all-day examination and analyzed it retrospectively. All participants signed a consent form to allow the research team to analyze their anonymous data for research purposes. The physical evaluations included a comprehensive medical assessment that included detailed laboratory studies, fitness testing, stress electrocardiographic (ECG) testing, nutritional intake analysis, anthropometric measures, and a computerized neurocognitive test battery. The team enrolled participants consecutively from 2006 until 2010 without exclusion.

Biometric Indicators

Anthropometric Measures. These measures included body composition, body fat, and weight that the research team obtained using a Tanita 310 Analyzer (Tanita Corporation of America, Arlington Heights, Illinois). The team calculated each participant's body mass index on the basis of the weight obtained using the analyzer and the participant's measured height. The team also measured waist circumference in the horizontal plane as the smallest circumference above the iliac crest and below the 12th rib with a relaxed abdomen after two large expirations. The team obtained blood pressures in individuals' right and left arms after participants were seated for at least 5 minutes, with the lower of the two blood-pressure numbers entered.

Fitness Testing. The research team evaluated fitness with a Woodway Cortex Metalyzer and a Reynolds Cardio Collect system during stress ECG testing on a Woodway treadmill using a standard Bruce protocol.[12] Measures included the maximum volume of oxygen burned during peak exercise (VO2max as mL/kg/min), and the test aimed to push subjects to a respiratory exchange ratio (RER) between 1.05 and 1.1. RER is the ratio of carbon dioxide output to oxygen uptake (VCO2/VO2), measured at the mouth. The team also measured blood pressure at baseline and after 1 minute and 30 seconds during each 3-minute stage of fitness testing, determining the diastolic blood-pressure change from baseline to peak exercise. In addition, the team measured the total duration achieved on the Bruce protocol treadmill test in minutes and collected data on the peak heart rate at maximum exertion as well as the heart rate 1 minute after stopping the stress ECG test.

Laboratory Studies. The research team performed these studies—total cholesterol, low-density lipoprotein, high-density lipoprotein, glucose, homocysteine and C-reactive protein (CRP)—using blood drawn after a minimum 9-hour fast. The team assessed Hg levels from whole blood at Special Laboratories, Valencia, California. The team evaluated total Hg through nebulization of whole blood into an aerosol container desolvating, vaporizing, exciting, ionizing, and finally transporting the blood for inductively coupled, plasma mass spectrometry. The testing expressed whole blood Hg levels in µg/L. (Note: When expressing Hg levels, 1 nmol/L = 0.20 µg/L = 0.20 parts per billion.)

Nutritional Intake Analysis. The research team collected nutritional data from a dietary record, in which participants wrote down their food intake over 3 days, including both food and supplements ingested. A registered dietician reviewed the food record, and the team analyzed it using the Nutribase 7 software (CyberSoft Incorporated, Phoenix, Arizona) that uses data directly from the US Department of Agriculture nutritional database. The team used computerized dietary analyses to measure macronutrient and micronutrient intake, including N3FAs. The team assessed N3FA dietary intake by combining reported weekly fish intake with fish-oil intake in supplemental form. A separate questionnaire inquired about participants' weekly consumption of seafood in general and of large-mouth fish in particular. Large-mouth species are those that the US Food and Drug Administration has documented to have more than 0.2 parts per million (ppm) of Hg in tissue. The questionnaire listed the fish using their common names: tuna, grouper, snapper, bass, shark, and swordfish.

Cognitive Indicators

The CNS Vital Sign (VS7) is a computerized, neurocognitive test battery comprised of seven familiar neuropsychological tests that generate 10 independent scores. The test scores comprise four factors or cognitive domains: (1) complex information processing (CIP), (2) effortful attention, (3) memory, with components for verbal and visual memory, and (4) motor speed.

Complex Information Processing. Commonly referred to as executive function, CIP comprises three tests: (1) symbol digit coding, which is based on the symbol digit modalities test[13]; (2) the Stroop test,[14] which has three parts that generate simple and complex reaction times; averaging the two scores for complex reaction time generates the response-time score; and (3) the shifting attention test, which measures an individual's ability to shift from one instruction set to another quickly and accurately.[15,16]

Effortful Attention. The second factor comprises two tests: (1) the number of errors committed during the Stroop test and (2) a conventional, continuous performance test (CPT), which is a measure of vigilance or sustained attention.[17]

Memory With Verbal Memory and Visual Memory Components.[18] For verbal memory, 15 words are displayed for the viewer. After 1 minute, those 15 words are mixed with 15 additional words, and the viewer must select the initial 15 words. This same test is repeated at the end of the test, approximately 30 minutes later. For visual memory, first 15 shapes are displayed for the viewer. After 1 minute, those 15 shapes are mixed with 15 additional shapes, and the viewer must select the initial 15 shapes. This same test is repeated at the end of the test, approximately 30 minutes later.

Motor Speed. The fourth factor comprises three tests: (1) the finger-tapping test, (2) the simple reaction-time score from the Stroop test, and (3) the choice reaction-time score from the CPT.

The VS7 standardizes scores by adjusting for age—on the basis of data from 4400 normal subjects, ages 6 to 96—to a mean of 100 with a standard deviation of 15. Test-retest reliability and concurrent validity of the VS7 battery are comparable to similar conventional neuropsychological tests.[19] Studies have established

the discriminant validity of VS7 for individuals with mild cognitive impairment and early dementia,[20] postconcussion syndrome and severe traumatic brain injury,[21] attention deficit/hyperactivity disorder,[22,23] depression,[24,25] schizophrenia and bipolar disorder,[26] and malingering.[19]

ANALYSES

The research team log-transformed or standardized scores that did not have a normal distribution, eliminating outliers who scored more than six standard deviations from the mean. The team used multiple analyses of variance (MANOVA) for group comparisons—controlling for age, race, gender, education, alcohol intake, and self-reported computer familiarity and finger-tapping speed—and one-way analysis of variance (ANOVA) with Bonferroni-adjusted post hoc testing. The team performed regression analysis using the generalized linear model (SPSS, PASW Statistics GradPack 18, SPSS, Inc, Chicago, Illinois).

RESULTS

Table 1 shows the demographic information for the entire group, organized by gender and by the five relevant levels of Hg exposure: (1) all subjects; (2) normal, <5 µg/L; (3) elevated, 5 µg/L to 14 µg/L; (4) high, 15 µg/L to 24 µg/L; or (5) very high, ≥25 µg/L. The participants were predominantly white (94.5%), well educated (>16 years), and mostly in good health. They ranged in age from 23 to 65 (mean age 48.2), and the majority were males (71.4%). Self-reported computer familiarity was high (1 = none, 2 = some, 3 = frequent; mean = 2.84).

The most remarkable observation in Table 1 is the comparatively high level of BHg levels in the group as a whole (7.2 ± 6.5 µg/L); 43% of the individuals had Hg levels above the EPA reference standard of 5.8 µg/L. Hg levels were positively correlated with weekly seafood consumption ($P < .0001$) and with monthly consumption of large-mouth fish ($P < .0001$). The only significant difference between the genders was age. None of the other demographic or biometric variables differed significantly.

Neurocognition improved linearly as N3FA intake increased up to three servings per week. The research team compared subjects with the lowest quartile of fish intake to those with the highest quartile and noted a 4% change in CIP ($P < .001$) (Table 2).

The best regression line to describe the relationship between N3FA intake and CIP was linear, but the best regression line for BHg and CIP was quadratic (r2 = 0.006) (Figure 1). Figure 2 plots the CIP score and the scores from the three tests that comprise the CIP factor against BHg, dividing the results into three levels. Because of the similarity of the results for the original high and very-high groups, the research team found it appropriate to reduce the sample to three groups for subsequent analysis: normal, elevated, and high, containing the original high and very-high groups. For the remainder of this article, the term high with respect to BHg refers to the combined group. Participants with BHg levels from 5 µg/L to 14 µg/L (elevated BHg) generated normal scores for CIP; those with levels <5 µg/L (normal BHg) were about 2% lower; individuals with levels ≥15 µg/L (high and very-high BHg) were about 4% lower. The differences are small but highly significant (Tables 3a, 3b, and 3c).

Examining the various biometric parameters, the research team found that some of the variables were positively correlated with Hg. The strongest correlation with Hg level was N3FA intake, which was significantly correlated with Hg ($P < .001$) and increased with Hg level in a linear relationship ($P < .0001$).

To illustrate the cognitive effects of different levels of Hg burden, the research team made a series of pairwise comparisons among the normal-Hg, elevated-Hg, and high Hg groups, employing MANOVA and using the covariates of age, race, gender, education, and computer familiarity. Alcohol intake, race, gender, education, and computer familiarity did not modify the results. Participants with normal whole BHg levels and low N3FA intake scored significantly lower in tests for the CIP domain, compared to subjects in the elevated Hg group with higher N3FA intake (Table 3a). The high Hg group scored significantly lower, compared to participants in the elevated Hg group, in tests for the CIP domain and also in composite memory and choice reaction time (Table 3b). When the research team compared the group with the high Hg level to the normal Hg group, significant differences existed in measures of CIP (Table 3c).

Table 4 compares the biometric variables across the three BHg groups by ANOVA. Of interest, individuals in the group with a high Hg level were leaner and fitter, consumed more foods containing N3FA, and drank more alcohol. Controlling for alcohol intake did not alter these findings.

The research team's best model, developed by generalized regression, indicated a main effect for the interaction of Hg level and N3FA ($P = .003$) when education, homocysteine, highly sensitive C-reactive protein, and mean arterial pressure were covariates. Gender and biometric variables did not have an impact on the model. The research team examined the specific relationship between fish consumption, Hg, and N3FA by generalized regression. The team measured seafood consumption in terms of weekly servings and consumption of large-mouth fish in terms of monthly servings. When the team regressed consumption against Hg level, the relationship was strongly positive, and the results were highly significant, especially for >3 servings of seafood weekly or >3 servings of large-mouth fish monthly (Figure 3).

DISCUSSION

In this study, modestly elevated Hg level, coupled with increased seafood intake, is associated with the highest cognitive function. As seafood intake increases, especially with more large-mouth fish consumption, an association exists with increased Hg levels, and the increased Hg levels appear to be associated with cognitive dysfunction when above 15 µg/L.

Hg exposure is widespread in the United States. MeHg is the predominant chemical, and fish is the predominant source; the likely source of Hg in this group of health-conscious executives was eating fish. The research team confirmed the high fish consumption by a questionnaire administered to participants regarding that consumption. None of the subjects in this study worked in facilities where Hg exposure might occur. The research team did not evaluate dental amalgam as a possible contributor, but the Hg burden from amalgam is not likely to exceed 5 µg/L.[27]

Table 1. Demographic Variables Related to Gender and Whole-blood Mercury-level Burden

		Whole-blood Mercury-level, µg/L									
		All		<5		5-15		15-25		≥25	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
All	n	384		191		151		32		10	
	Mercury level, µg/L	7.2	6.5	2.8	1.0	8.7	2.9	18.8	2.4	31.9	5.7
	Age, y	48.2	7.4	48.2	7.3	48.0	7.3	47.6	8.5	53.3	7.6
	Male, %	71.4		75.9		66.9		65.6		70.0	
	White, %	94.5		94.2		94.7		93.8		100.0	
	Education, y	16.8	2.1	16.8	2.2	16.8	2.0	16.8	1.9	16.4	0.9
	Computer experience score	2.8	0.4	2.9	0.4	2.8	0.4	2.9	0.2	2.6	0.7
Male	n	274		145		101		21		7	
	Mercury level, µg/L	7.0	6.4	2.9	1.0	8.8	2.8	18.7	2.5	31.8	6.1
	Age, y	48.7	6.8	48.4	6.6	48.8	6.8	48.4	7.4	52.1	8.3
	White, %	94.5		93.1		97.0		90.5		100.0	
	Education, y	16.9	2.1	16.7	2.4	17.0	1.8	17.1	1.6	16.6	1.0
	Computer experience score	2.8	0.4	2.9	0.4	2.8	0.4	3.0	0.2	2.9	0.4
Female	n	110		46		50		11		3	
	Mercury level, µg/L	7.8	6.7	2.7	1.0	8.6	3.0	18.9	2.3	31.9	6.1
	Age, y	46.9	8.7	47.3	9.0	46.3	7.8	46.0	10.6	56.0	6.1
	White, %	94.5		97.8		90.0		100.0		100.0	
	Education, y	16.5	2.1	16.8	1.8	16.3	2.2	16.1	2.4	16.0	0.0
	Computer experience score	2.8	0.5	2.9	0.3	2.8	0.5	2.9	0.3	2.0	1.0

Abbreviation: SD, standard deviation.

Table 2. Cognitive Test Results Relative to Long-chain Omega-3 Intake and Mercury Intake[a]

	Long-chain N3FA Intake		Whole-blood Mercury-level, µg/L	
Cognitive Domain Scores	F	Sig	F	Sig
Memory	1.952	.001	.737	.971
Complex information processing	4.915	<.001	1.911	<.001
Effortful attention	1.025	.432	1.256	.075
Complex reaction time				
Verbal memory	2.108	<.001	.715	.981
Visual memory	.924	.609	.707	.984
Shifting attention test	2.310	<.001	1.413	.015
Symbol digit coding	3.615	<.001	1.453	.009
Response time	4.206	<.001	1.675	.001
Stroop test	.802	.807	.861	.824
Choice performance test	.992	.489	.980	.547

[a] Using multiple analyses of variance controlling for covariates age, race, gender, education, computer familiarity, and motor speed.
Abbreviations: N3FA, n-3 fatty acids; sig, significance.

Figure 1. Comparison of Complex Information Processing Speed to Mercury Levels Resulting in a Quadratic Regression Line, r2 = 0.006

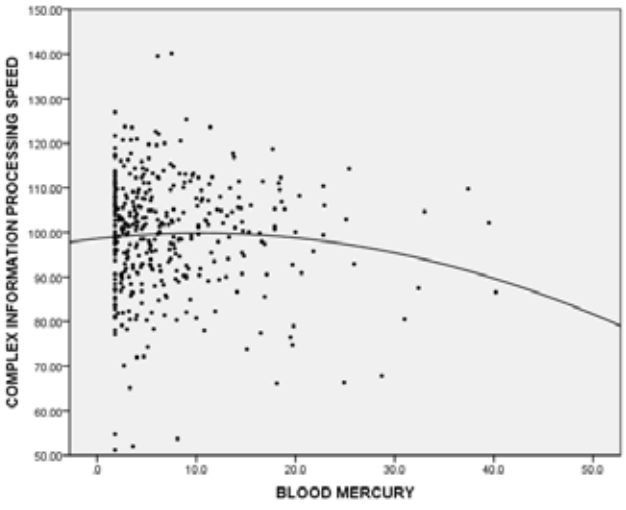


Figure 2. Normal, elevated, and high whole blood mercury levels (µg/L) compared with complex information processing (CIP), Shifting attention test (SAT), simple digit coding (SDC), and response time (RT) scores. Standard deviations for this figure are included in Tables 3a, 3b, and 3c.

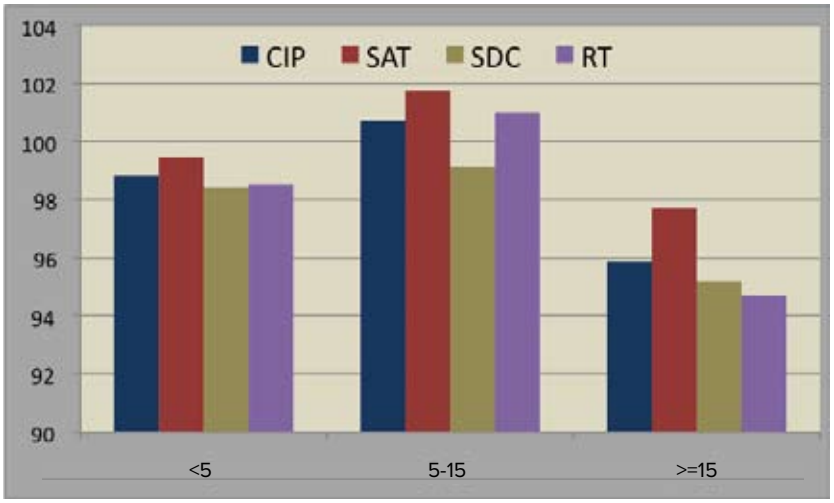
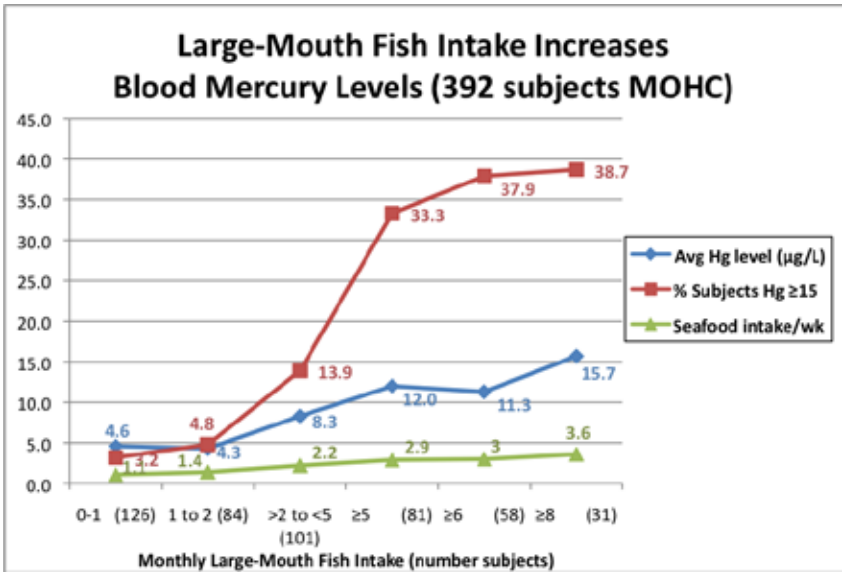


Figure 3. Comparison of Whole Blood Mercury Levels With Servings of Large-mouth Fisha Intake in Servings per Month



[a] Grouper, tuna, snapper, bass, swordfish.

At least 43% of the group of 384 executives had Hg levels higher than the US Environmental Protection Agency's reference level (5.8 µg/L), below which exposures are considered to be free of adverse effects.[28] In contrast, about 8% of women in the United States have concentrations higher than the reference level. The mean background Hg level in people who do not eat fish is approximately 2 µg/L. BHg levels in people who eat fish range from 2 µg/L to 20 µg/L and individuals who consume large quantities of seafood may have values as high as 75 µg/L.[29] Researchers have found BHg levels to be positively correlated with age[30] and education.[9] A correlation also exists between Hg levels in the blood and brain.[31]

Neurotoxicity is the hallmark of Hg exposure, and neurodevelopmental deficits are the most sensitive and well-documented effects.[32] Researchers have associated prenatal exposure to Hg through maternal fish consumption with reduced performance on tests of neurologic function in children, including tests of general cognitive development, attention, motor speed, and reaction time.[32,33] Studies of developmental disability related to low-level exposure to MeHg, however, have had mixed results.[34,35] Researchers have suggested, therefore, that nutrients from fish may counteract the adverse effects of MeHg on the developing nervous system.[36] The results of studies of industrial exposure to Hg vapor have been more consistent, probably because of higher levels of exposure. In exposed industrial workers, researchers have reported cognitive deficits in information-processing speed, attention, motor speed, verbal memory, abstract thinking, and verbal comprehension.[37,38-43]

The current study's participants are different from the populations in other studies of Hg toxicity. They are a community-based sample, albeit a comparatively elite group of well-educated participants who either had corporate benefits that covered or the financial ability to pay for an all-day, comprehensive physical evaluation. The research team's results indicate that the negative cognitive effects of Hg are not apparent until an individual exceeds a threshold of 15 µg/L. Beyond that level, BHg level significantly affects tests of CIP speed (symbol digit coding, Stroop test, shifting attention test). The effect sizes on cognition were small, up to 4.8%; however, these effects are a decrement that no one, let alone a health-conscious and achievement-oriented person, is likely to welcome.

In a number of preliminary analyses, the research team was able to demonstrate statistically significant differences; for example, between the normal and the high Hg–level groups on different measures. The most consistent effect of Hg level upon cognitive function, however, occurred in the three tests that comprise the CIP domain, also referred to as executive function. Not only did the CIP domain show the most consistent effects in this study from increasing Hg levels, but in other studies, the research team

Table 3a. Cognitive Tests Scores in Normal and Elevated Whole Blood Mercury Groups

	Whole Blood Mercury, µg/L						
Cognitive Domain Scores			<5		5-15		
	F	Sig (*P*)	Mean	SD	Mean	SD	d
Memory	1.737	.100	98.7	23.9	101.1	21.4	–0.10
Complex information processing	15.328	<.0001	98.8	13.1	100.7	12.1	–0.15
Effortful attention	1.520	.160	97.3	17.9	97.3	18.6	0.00
Complex reaction time	1.452	.184	98.9	20.7	100.9	20.8	–0.10
Verbal memory	1.273	.263	97.2	22.6	98.5	19.2	–0.06
Visual memory	1.669	.116	99.1	21.1	102.9	16.3	–0.20
Shifting attention test	6.162	<.0001	99.5	15.2	101.8	11.6	–0.16
Symbol Digit Coding	11.979	<.0001	98.4	17.8	99.1	14.3	–0.04
Response time	10.047	<1.000	98.5	17.5	101.0	18.1	–0.14
Stroop test	1.407	.202	99.9	10.7	98.7	12.1	0.11
Choice performance test	1.128	.345	97.8	20.0	98.9	20.1	–0.06

Abbreviations: d, difference; SD, standard deviation; sig, significance.

Table 3b. Cognitive Test Scores in Elevated and High Whole Blood Mercury Level Groups

	Whole Blood Mercury, µg/L						
Cognitive Domain Scores			5-15		≥15		
	F	Sig (*P*)	Mean	SD	Mean	SD	d
Memory	2.191	.038	101.1	21.4	95.2	22.8	0.26
Complex information processing	12.092	<.0001	100.7	12.1	95.9	14.1	0.38
Effortful attention	.585	.767	97.3	18.6	101.2	7.5	–0.22
Complex reaction time	2.542	.017	100.9	20.8	95.0	13.2	0.29
Verbal memory	1.748	.102	98.5	19.2	94.6	22.3	0.18
Visual memory	1.680	.117	102.9	16.3	100.5	14.7	0.13
Shifting attention test	3.997	<.0001	101.8	11.6	97.7	18.6	0.28
Symbol digit coding	8.680	<.0001	99.1	14.3	95.2	16.7	0.24
Response time	10.326	<.0001	101.0	18.1	94.7	16.8	0.36
Stroop test	.941	.477	98.7	12.1	101.0	8.5	–0.21
Choice performance test	.696	.675	98.9	20.1	101.3	10.9	–0.12

Abbreviations: d, difference; SD, standard deviation; sig, significance.

Table 3c. Cognitive Test Scores in the Normal and High Whole Blood Mercury Level Groups

	Whole Blood Mercury, µg/L						
Cognitive Domain Scores			<5		>15		
	F	Sig (*P*)	Mean	SD	Mean	SD	d
Memory	1.266	.269	98.7	23.9	95.2	22.8	0.16
Complex information processing	10.268	<.0001	98.8	13.1	95.9	14.1	0.23
Effortful attention	2.001	.057	97.3	17.9	101.2	7.5	–0.22
Complex reaction time	.213	.982	98.9	20.7	95.0	13.2	0.19
Verbal memory	1.002	.431	97.2	22.6	94.6	22.3	0.12
Visual memory	.677	.691	99.1	21.1	100.5	14.7	–0.07
Shifting attention test	4.502	<.0001	99.5	15.2	97.7	18.6	0.12
Symbol digit coding	8.196	<.0001	98.4	17.8	95.2	16.7	0.20
Response time	6.638	<.0001	98.5	17.5	94.7	16.8	0.22
Stroop test	1.288	.258	99.9	10.7	101.0	8.5	–0.11
Choice performance test	1.468	.181	97.8	20.0	101.3	10.9	–0.18

Abbreviations: d, difference; SD, standard deviation; sig, significance.

Table 4. Biometric Variables in the Three Whole-blood Mercury-level Groups

Whole Blood Mercury Level, µg/L	<5 (1)		5-15 (2)		≥15 (3)		ANOVA		Bonferroni		
	Mean 1	SD	Mean 2	SD	Mean 3	SD			1v2	1v3	2v3
n	191		151		42		F	Sig (*P*)	Sig (*P*)	Sig (*P*)	Sig (*P*)
BMI	28.3	5.3	27.3	4.3	27.5	3.6	1.80	.167	.194	1.000	1.000
Systolic BP, mmHg	118.8	16.3	117.5	15.0	118.7	15.3	0.29	.752	1.000	1.000	1.000
Diastolic BP, mmHg	76.2	11.0	76.1	10.3	74.6	9.8	0.42	.656	1.000	1.000	1.000
Waist circ, cm	95.8	16.1	93.6	13.6	94.0	9.4	0.95	.388	.544	1.000	1.000
Bodyfat, %	30.0	8.1	27.8	6.8	26.2	5.2	6.66	.001	.017	.007	.652
Carotid IMT, mm	0.7	0.1	0.7	0.1	0.7	0.1	0.03	.967	1.000	1.000	1.000
ETT VO_{2max}, mL/kg/min	30.9	7.3	31.8	8.2	36.3	4.6	8.12	<.0001	.832	<.0001	.004
1-min heart rate recovery	22.8	9.4	24.8	10.7	26.7	8.7	3.41	.034	.187	.072	.836
Bruce ETT duration, min	11.7	2.5	12.6	2.7	13.9	2.1	13.61	<.0001	.004	<.0001	.021
Fiber, g/d	17.3	9.2	18.7	7.6	18.0	7.3	1.20	.303	.368	1.000	1.000
Saturated fat intake g/d	22.5	11.0	21.3	10.0	22.8	8.9	0.65	.524	.891	1.000	1.000
N3FA g/d	0.6	0.6	0.9	0.6	1.3	0.7	26.01	<.0001	<.0001	<.0001	.001
Folate mg/d	472.0	297.5	497.5	355.2	503.7	354.4	0.32	.730	1.000	1.000	1.000
Vitamin B_{12}, µg/d	30.1	95.2	32.8	89.2	56.9	121.8	1.27	.281	1.000	.342	.488
Vitamin D, IU/d	233.3	233.3	265.2	261.3	209.3	199.7	1.15	.319	.701	1.000	.600
Caffeine, mg/d	184.4	275.0	153.9	155.7	214.2	489.3	0.99	.374	.913	1.000	.638
Alcohol, g/d	10.4	13.4	18.1	17.7	27.4	46.5	12.97	<.0001	<.0001	<.0001	.042
TC, mg/dL	200.9	35.8	210.6	37.0	218.8	46.6	4.37	.013	.109	.030	.753
LDL, mg/dL	127.4	30.8	131.8	32.1	141.4	40.0	2.86	.059	.802	.058	.360
TC/HDL ratio	8.6	42.0	4.1	1.3	4.1	1.4	0.86	.423	.670	1.000	1.000
Glucose, mg/dL	99.8	15.1	99.6	20.4	98.9	9.9	0.05	.953	1.000	1.000	1.000
Homocysteine, µmol/L	10.7	3.4	10.9	4.0	12.5	3.6	3.81	.023	1.000	.019	.054
HsCRP, mg/L	2.3	2.5	2.1	2.5	1.7	1.9	0.76	.468	1.000	.716	1.000

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; BP, blood pressure; ETT, exercise tolerance test; HDL, high-density lipoprotein; HsCRP, high-sensitivity C-reactive protein; IMT, intima-media thickness; LDL, low-density lipopotein; N3FA, n-3 fatty acids; TC, total cholesterol; VO_{2max}, maximum oxygen consumption; SD, standard deviation; sig, significance.

also has found that CIP is the domain most sensitive to medication effects and to many different psychiatric and neurological conditions.[20,23,24,44]

It is worth identifying the irony in this situation; that is, the fact that corporate executives who chose to overconsume seafood for health reasons sustained a drop in their executive functions. Yet, if a 4.8% drop in executive function due to excessive seafood intake occurs in highly functioning, healthy adults with ample cognitive reserve, the major concern for further study is whether similar Hg-level elevations in individuals already suffering from cognitive decline might result in substantially greater declines. As cognitive decline and dementia are increasing in prevalence as our population ages and seafood consumption is rising, this relationship could have a large impact on quality of life, morbidity, and health-care costs into the distant future.

The beneficial effects of long chain N3FA intake and other nutrients supposedly outweigh the potentially toxic effects of Hg in fish on the cardiovascular system. This concept is consistent with the hypothesis that N3FA and other nutrients in fish reduce the risk of cardiotoxicity related to ingesting Hg.[45-47] By the same token, our study results show that the relationship between N3FA and Hg levels is the strongest driver of performance in tests of CIP. At BHg levels <5 µg/L, cognitive function is reduced; the individuals are also less fit and have lower N3FA intake. At Hg levels >15 µg/L, cognition function is lower still, despite superior aerobic capacity and high levels of N3FA intake. This finding suggests that high levels of Hg can overwhelm the protective effects of N3FA.

Although the high Hg–level group had superior fitness, they evidenced subtle cognitive toxicity. Incidentally, a trend also existed for the high Hg group to consume more alcohol; not only

do they eat well, they enjoy a tipple as well. Joannes Antonius Scopoli first appreciated that alcohol enhances mercurialism in 1754.[48] Preclinical studies have confirmed this association.[49,50] Alcohol intake alone, however, cannot explain the negative cognitive effects of Hg; controlling for alcohol intake does not change the effect of a high BHg level on CIP.

A number of cross-sectional studies have explored associations between Hg levels in hair or blood and subclinical neurologic function in adults. Studies from the 1980s found no evidence of neurologic impairment in groups with BHg of 10µg/L to 20 µg/L but did find a correlation of neurologic dysfunction with rising BHg concentrations in the 60 µg/L–to–120 µg/L range.[51-54] In studies of villagers in the Amazon where riverine Hg contamination is a problem due to Hg release from gold-mining activities and of an aboriginal population in Quebec, dose-dependent nervous-system alterations occurred at hair Hg levels below 50 µg/g.[55-57]

In contrast, a cross-sectional study of 474 residents of Baltimore from diverse backgrounds, ages 50 to 70, found that BHg levels were not associated with cognitive impairment.[58] In this group, the median Hg level was only 2.1 µg/L and ranged from 0 µg/L to 16 µg/L. In an elderly Swedish urban population, researchers found no relation between whole BHg levels and cognitive scores on the Mini-Mental State Exam.[59] Yet the conflicting results are not so disparate from the current study's findings, as our findings support that these researchers would not be likely to discover neurocognitive effects at Hg levels below 15 µg/L.

The current study has several strengths, including a rich and comprehensive clinical database enabling control for a large number of potential confounders; a relatively large sample of healthy, high-functioning adults; and a comprehensive neurocognitive test battery that can measure reaction times with accuracy in milliseconds.[19] Limitations include the selection of a single BHg level to assess the association between Hg and neurocognition. Furthermore, the homogeneity of the participants compromises the degree to which the research team might generalize the findings to a wider population. On the other hand, if cognitive neurotoxicity occurs in healthy, highly productive individuals with ample cognitive reserves, the effect is likely to be amplified in more vulnerable populations. Despite these limitations, it is reasonable to suggest that the nutrients associated with fish intake, especially N3FA, can exercise a protective effect only to a point, and beyond a certain threshold, the neurotoxicity of MeHg can overwhelm some aspects of cognition, such as executive functioning.

CONCLUSION

The research team's data support the prevailing view that the benefits of moderate fish consumption (1-3 servings/wk) outweigh the risks among adults and excepting a few selected fish species, among women of childbearing age.[1] The research team, however, raises a note of caution for individuals with high fish intake, in particular people who eat more than three servings of fish weekly or more than three to four servings per month of large-mouth fish (tuna, grouper, snapper, bass, swordfish, and shark). People with high fish consumption should consider lowering their intake or measuring their whole BHg level to determine if they are at risk. Further studies are warranted to confirm these findings.

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