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Methyl mercury exposure in populations at risk: Analysis of NHANES 2011–2012

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ABSTRACT

Background: Ingestion of fish contaminated with methyl mercury can lead to adverse health outcomes, particularly when exposure occurs in utero. NHANES 2011–2012 includes total blood mercury (TBHg) and methyl mercury (MeHg) measurements as well as a unique race/ethnicity category for Asians, allowing for improved analysis of determinants of risk.

Objective: Our objective was to characterize the current burden of MeHg exposure in the US among subgroups who are at risk of health effects due to their physiologic vulnerability to MeHg's effects and/or due to frequent fish consumption, specifically women of childbearing age (WCBA) and adults $\geq$ 50 years of age.

Methods: We calculated 90th and 95th percentile estimates as well as geometric means of MeHg for predictive variables. We used multivariable linear regression analyses to estimate the proportional change in mean MeHg associated with each category of all predictive variables. We calculated the validity of screening procedures using fish consumption questions and TBHg testing to predict elevated MeHg.

Results: The geometric mean MeHg levels were highest among Asian WCBA (1.17 μg/L) and Asians $\geq$ 50 years old (2.49 μg/L). Over 23% of Asian WCBA had levels $\geq$ 3.5 μg/L and 25% of Asians $\geq$ 50 years old had levels $\geq$ 5.8 μg/L. Frequency of fish consumption explained 21–23% of the variation in MeHg. Twenty-five percent of women eating fish $\geq$ twice per week had MeHg $\geq$ 3.5 μg/L. TBHg showed high validity for MeHg $\geq$ 5.8 μg/L, and two-step screening using $\geq$ 2 fish meals/month followed by TBHg also showed high validity.

Conclusion: Asian WCBA continue to have increased MeHg exposure from fish consumption, putting their offspring at risk. Screening for MeHg among high-risk groups should be considered.

1. Background

Environmental pollution in global waterways has resulted in the contamination of fish with methyl mercury (MeHg). Exposure to MeHg via fish consumption during pregnancy results in blood levels that cross the placenta and concentrate in the fetal brain, leading to risk of behavioral and cognitive abnormalities in offspring (Grandjean et al., 1997; Seafood Choices, 2007; Oken et al., 2005; Stokes-Riner et al., 2011). In adults, possible health effects of MeHg include cardiovascular atherosclerosis, myocardial infarction, heart rate variability, and hypertension via pro-oxidant effects and other mechanisms (Guallar et al., 2002; Stern, 2005; Virtanen et al., 2005). The consumption of fish during pregnancy also confers health benefits such as improved vision and cognitive development in offspring (Koletzko et al., 2008; Oken et al., 2005), and in adults, lower risk of sudden cardiac death (Kris-Etherton et al., 2002; Whelton et al., 2004) at least in part due to the omega-3 fatty acids in fish (Adkins and Kelley, 2010). Therefore, optimal health requires a balance of the risks and benefits of fish consumption.

One approach to reducing exposure to MeHg is to issue fish consumption guidelines that target specific population groups at risk. However, such advice can result in decreased healthy fish consumption; this was seen in a cohort of pregnant women after the US Food and Drug Administration (USFDA) disseminated advice to limit fish consumption and avoid fish high in mercury (Oken et al., 2003). An alternate approach is to identify individuals with excessive MeHg exposure and intervene with individually targeted advice—a process suited to the clinical setting. However, no guidelines currently exist regarding screening for methyl mercury in routine health care. With recent data showing the high prevalence of elevated MeHg levels among at-risk groups, routine

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screening, either with fish consumption screening questions or screening questions plus blood testing, have been proposed (Chen et al., 2014; Mortensen et al., 2014).

The National Health and Nutrition Examination Survey (NHANES) 2011–2012 for the first time speciated total blood mercury to include a direct measurement of MeHg. It also included a separate race/ethnicity category for Asians, a known high risk group for MeHg exposure due to frequent fish consumption (Hightower et al., 2006; McKelvey et al., 2007; Tsuchiya et al., 2008). The addition of these two variables allows for a more precise evaluation of the MeHg exposure in the US population. Mortensen et al. (2014) recently reported MeHg exposures in this data set and found higher mean MeHg levels for Asians compared to the other race/ethnic groups. In this paper we extend the analyses of MeHg in the NHANES 2011–2012 database to characterize the current burden of MeHg focusing on subgroups that are at risk of health effects from mercury exposure due to frequent fish consumption (Asians) or due to their physiologic vulnerability to methyl mercury's effects (the developing fetus in women of childbearing age (WCBA), and the aging cardiovascular system in older adults). Children are also vulnerable to the neurocognitive effects of low level MeHg exposure (Freire et al., 2010; Karagas et al., 2012), but we chose not to include children in our analysis since Mortensen et al. (2014) reported low prevalence of elevated MeHg levels in this group.

Clinical screening with MeHg blood levels may be not be feasible since speciating TBHg into its components (MeHg, ethyl mercury and inorganic mercury) may be cost prohibitive to perform on a routine basis. Therefore, we assessed the validity of using total blood mercury (TBHg) to screen for elevated MeHg. We also assessed fish consumption screening questions used alone or in a sequential screening procedure (asking a fish consumption question followed by the TBHg test those responding "yes" to the fish consumption question) to identify participants with elevated MeHg. Determining the performance of TBHg and fish consumption questions to detect elevated MeHg is a first step toward establishing recommendations for clinical screening for mercury exposure.

2. Methods

Analyses were based on data obtained from participants in 2011–2012 NHANES conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention. The NHANES program produces vital and health statistics for the United States by performing interviews and physical examinations of a nationally representative sample of approximately 5000 persons across the country each year. It is a complex, multistage, probability cluster sample designed to represent the US population based on age, gender, and race/ethnicity (US NHANESa, 2014). In this database the race/ethnicity designation "Asian" includes those who reported having origins in China, Japan, Southeast Asia and the Indian subcontinent.

TBHg and MeHg were measured in eligible participants aged 1 year and older (US NHANESb, 2014; US NHANESc 2014). For this paper we analyzed participants ≥ 18 years of age only. We restricted the analyses to participants in whom both blood MeHg and TBHg were reported. This resulted in the exclusion of 1919 participants, including 83 with TBHg and 4 with MeHg measurements, for a total of 7837 adults. With further exclusion of persons outside of the age/gender categories selected for subgroup analysis and with missing predictor variables (see below), the final subgroups we analyzed consisted of 1070 women 18–44 years of age and 2061 adults ≥ 50 years of age. The limit of detection (LOD) for MeHg concentration was 0.12 μg/L. Measurements below the LOD were imputed as the LOD/$\sqrt{2}$. Overall, MeHg measurements were below the LOD in 14.4% of WCBA and 10% of adults ≥ 50 years of age.

The predictor variables chosen for the analyses were gender, race (Non-Hispanic White, Non-Hispanic Black, Mexican American, other Hispanic, Non-Hispanic Asian, and Other Race including Multi-Racial); age group categorized into groups (50–64 and ≥ 65 years for the older adult analysis); born in the US or not born in the US (missing for 3 persons); annual family income ($<$ \$20,000 and $>$ \$20,000; missing for 169 persons); body mass index (BMI, kg/m^2), which was missing for 63 persons and was coded as underweight and normal weight (<25 kg/m^2), overweight (25 to <30 kg/m^2) and obese (≥ 30 kg/m^2); and fish and shellfish consumption, which was missing for 343 persons. We calculated the total number of fish meals, shellfish meals, and seafood (sum of fish and shellfish) meals consumed in the past month (see Table 1 for types of seafood). For some analyses, we converted fish consumption within last 30 days to weekly consumption.

We applied sampling weights for Mobile Examination Center (MEC) exam to adjust for differential selection probabilities in NHANES for our descriptive statistics and estimates from regression analyses. We conducted statistical analyses with SAS (version 9.3; SAS Institute Inc., Cary, NC) and included survey design variables to account for the complex sampling design. For all categories of predictive variables we calculated 90th and 95th percentile estimates for MeHg concentrations. Geometric means and 95% confidence intervals were calculated by taking the antilog of the mean of the natural log-transformed values. We used multivariable linear regression to compare categorical mean estimates and considered a difference to be statistically significant at $p<0.05$. We fitted multiple linear regressions of the natural log-transformed MeHg concentrations on the predictor variables and present the exponentiated model coefficients, which can be interpreted as the proportional change in the geometric mean associated with each category of the predictor, relative to a referent category, with adjustment for other predictors in the model.

For this analysis we examined the data relative to two blood mercury levels of concern. One level is 5.8 μg/L, (NRC, 2000) which is based on EPA's Reference Dose (RfD) for MeHg of 0.1 μg/kg/day that is "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population that is likely to be without an appreciable risk of deleterious effects during a lifetime" (IRIS, 2001). In addition, we analyzed our results for women of childbearing age using a MeHg level at 3.5 μg/L. This lower level has been proposed to account for the concentration of mercury in the fetus compared to levels in maternal circulation, a fetal/maternal ratio estimated to be 1.7 (Mahaffey et al., 2004; Stern and Smith, 2003), and is therefore more protective of this sensitive sub-population. We calculated the percentage of individuals with MeHg ≥ 5.8 μg/L and MeHg ≥ 3.5 μg/L, testing differences between predictor variables using Rao-Scott Modified Chi-square tests for dichotomous variables and Wald Chi-square tests for BMI and race/ethnicity.

Lastly we calculated the sensitivity and specificity of TBHg as a measure of MeHg exposure using the measured blood MeHg as the "gold standard", and considered a value of ≥ 5.8 μg/L as a positive test result (Gordis, 2009). We also examined fish consumption as a screening test for elevated MeHg. We created a series of dichotomous variables that indicated ingestion of more than a certain number of fish meals in the past 30 days, with cut points for these variables set at 1–16, and calculated the sensitivity and specificity for each dichotomous variable using measured blood MeHg ≥ 5.8 μg/L as the "gold standard". Receiver operator characteristic (ROC) curves were created by plotting the calculated sensitivity against 1-specificity at each fish meal cut point. Finally sensitivity and specificity was examined for various sequential screening sequences. The first test evaluated ≥ 1, ≥ 2, ≥ 4, or ≥ 8 meals of

Table 1
Mercury content and frequency of fish and shellfish consumption in past 30 days by women 18–44 years of age and adults ≥50 years of age.

Seafood (Fish and Shellfish) Type	Hg μg/g wet weight in Seafood[a]	Women 18–44 years of age				Adults ≥50 years of age			
		% Consuming in past 30 d	Servings in past 30 d			% Consuming in past 30 d	Servings in past 30 d		
			Median	95th % tile	Maximum		Median	95th % tile	Maximum
Breaded fish	0.013	8	0	1	5	10	0	2	8
Bass	0.263	1	0	0	5	1	0	0	10
Catfish	0.107	9	0	1	6	11	0	2	15
Cod	0.089	6	0	1	4	11	0	1	10
Flatfish	0.054	3	0	0	6	6	0	1	7
Haddock	0.069	1	0	0	2	6	0	1	8
Mackerel	0.639	1	0	0	8	1	0	0	30
Perch	0.143	0.5	0	0	2	3	0	0	20
Pike	0.301	<0.1	0	0	1	0.5	0	0	2
Pollock	0.013	3	0	0	5	2	0	0	30
Porgy	0.315	0.5	0	0	5	0.5	0	0	15
Salmon	0.041	24	0	3	25	32	0	4	20
Sardines	0.023	2	0	0	6	3	0	0	20
Sea bass	0.188	1	0	0	4	2	0	0	8
Shark	0.628	0.5	0	0	1	0.1	0	0	5
Swordfish	1.265	1	0	0	14	3	0	0	10
Trout	0.045	3	0	0	3	4	0	0	6
Tuna	0.242	34	0	4	25	39	0	4	25
Walleye	0.265	1	0	0	3	2	0	0	2
Other fish type known	0.097	15	0	2	25	17	0	3	31
Other fish type unknown	0.139	6	0	1	8	8	0	1	10
Fish Total		**66**	**1**	**10**	**42**	**81**	**3**	**12**	**67**
Clams	0.026	6	0	1	12	7	0	1	6
Crabs	0.057	15	0	2	30	11	0	2	10
Crayfish	0.028	1	0	0	14	1	0	0	15
Lobster	0.190	5	0	0	10	5	0	0	5
Mussels	0.026	3	0	0	12	4	0	0	8
Oyster	0.027	4	0	0	14	8	0	1	12
Scallops	0.017	6	0	1	15	9	0	1	8
Shrimp	0.014	47	0	4	30	45	0	4	20
Other shellfish type known	0.032	5	0	0	24	2	0	0	10
Other shellfish type unknown	0.026	0.5	0	0	1	<0.1	0	0	3
Shellfish Total		**54**	**1**	**7**	**65**	**52**	**1**	**7**	**48**
Seafood (Fish and Shellfish) Total		**76**	**2**	**15**	**77**	**86**	**4**	**17**	**103**

[a] Estimates from US EPA, 2013.

fish in the past 30 days as a positive result. The second test, which was conducted only in persons testing positive to the first test, was measured TBHg. Measured blood MeHg ≥5.8 μg/L was used as the "gold standard" for both sequential tests. Positive predictive values and negative predictive values were calculated for the various screening tests using observed prevalence of elevated MeHg in the entire population and in different population subgroups.

3. Results

We analyzed data from adult participants and report results for women of childbearing age (WCBA: 18–44 yrs of age) and participants ≥50 years old. Table 2 shows the population weighted means for MeHg among WCBA by demographic and fish consumption categories. The geometric mean MeHg levels were highest among Asian and non-Mexican Hispanic women, followed by Blacks. The geometric mean MeHg for Asians (1.17 μg/L) was almost 3 times the geometric mean for whites (0.42 μg/L). Geometric means were also significantly higher among participants with annual household incomes >$20,000, those who were non-US born, and those with a BMI <25.

Table 2 also shows the percent of participants with MeHg levels ≥5.8 μg/L, the blood equivalent of the EPA Reference Dose, and ≥3.5 μg/L, the proposed level that accounts for fetal concentration of MeHg (Chen et al., 2014; Mahaffey et al., 2004). Overall, over 5% of WCBA had MeHg levels ≥3.5 μg/L. Among Asians, over 23% had levels ≥3.5 μg/L; 9.5% had levels ≥5.8 μg/L. Among other ethnicities, 4.7% of whites, 4.5% of non-Mexican Hispanics, and 3.6% of Blacks had levels ≥3.5 μg/L.

Regarding fish consumption, WCBA who reported eating fish or shellfish ≥twice per week had significantly higher MeHg levels than those who reported eating no fish (Table 2). Twenty-five percent of women eating fish ≥twice per week had MeHg ≥3.5 μg/L; 14.6% had MeHg ≥5.8 μg/L.

Table 3 shows results for adults ≥50 years old. Overall, the levels of MeHg were higher for this group than for WCBA. The geometric mean MeHg of 0.71 μg/L was greater than the mean for WCBA (0.47 μg/L). By race/ethnicity among adults ≥50, highest geometric means were found among Asians followed by non-Mexican Hispanics, then Blacks, similar to the distribution of geometric means among WCBA. Among this age group, 25.3% of Asians had MeHg levels ≥5.8 μg/L compared to 4.6% of Whites. Table 3 also shows that 23.6% of participants who reported eating fish ≥two times per week had elevated MeHg (≥5.8 μg/L).

Data on levels of Hg in fish and shellfish (USEPA, 2013) and frequency of consumption from NHANES 2011–2012 are shown in Table 1. Seventy-six percent of WCBA and 86% of participants ≥50

Table 2
Women of childbearing age (18–44 years of age): population weighted methyl mercury (μg/L) 90th and 95th percentiles, geometric means, adjusted proportional change in means, and prevalence with ≥3.5 μg/L and ≥ 5.8 μg/L by population subgroups and fish consumption.

Variable		*n*	90th percentile	95th percentile	Geometric mean MeHg (95% CI)	Adjusted proportional change in mean MeHg (95% CI)	N MeHg ≥5.8 μg/L	Percentage with MeHg ≥5.8 μg/L (95% CI)	N MeHg ≥3.5 μg/L	Percentage with MeHg ≥3.5 μg/L (95% CI)
Total		1070	2.48	3.60	0.47 (0.39, 0.56)	–	23	1.7 (0.5, 2.9)	74	5.3 (2.9, 7.7)
Race/Ethnicity	White[a]	361	2.48	3.43	0.42 (0.33, 0.54)	1.00	5	1.8 (0, 3.5)	16	4.7 (1.5, 7.9)
	Black	288	2.03	2.84	0.52 (0.35, 0.76)	1.12 (0.80, 1.57)	1	0.4 (0, 1.2)	12	3.6 (0.1, 7.1)
	Mexican	132	1.11	1.32	0.39 (0.32, 0.47)	0.90 (0.74, 1.10)	0	–	1	0.8 (0, 2.6)*
	Hispanic	101	2.52	3.24	0.65 (0.55, 0.76)**	1.51 (1.23, 1.86)**	1	1.1 (0, 3.3)*	5	4.5 (1.2, 7.9)
	Asian	152	5.76	7.59	1.17 (0.84, 1.63)**	1.77 (1.19, 2.62)**	15	9.5 (5.5,13.6)**	38	23.4 (14.5, 32.3)**
	Other	36	3.60	3.60	0.42 (0.23, 0.75)	0.99 (0.64, 1.54)	1	1.4 (0, 4.5)**	2	11.7 (0, 31.6)
Family income	<$20,000[a]	326	1.57	2.29	0.38 (0.33, 0.44)	1.00	1	0.1 (0, 0.3)	9	2.2 (0.3, 4.0)
	>$20,000	744	2.76	3.91	0.50 (0.40, 0.63)*	1.14 (0.94, 1.38)	22	2.3 (0.6, 3.9)*	65	6.4 (3.3, 9.4)*
US Born	Yes[a]	767	2.34	3.43	0.43 (0.35, 0.53)	1.00	10	1.5 (0.05, 3.0)	35	4.7 (1.9, 7.5)
	No	303	2.89	4.79	0.67 (0.58, 0.78)**	1.13 (0.94, 1.37)	13	2.5 (1.1, 4.0)	39	7.8 (3.9, 11.7)
BMI	<25	428	3.00	4.35	0.54 (0.41, 0.69)*	1.24 (1.03, 1.49)*	16	2.4 (0.5, 4.3)**	44	7.6 (4.9, 10.3)**
	25-29	268	2.36	4.41	0.47 (0.38, 0.58)	1.17 (0.96, 1.43)	7	2.8 (0, 6.1)**	20	6.4 (2.0, 10.8)
	≥30[a]	374	1.54	2.32	0.40 (0.34, 0.47)	1.00	0	–	10	1.6 (0.1, 3.1)
Shellfish meals/week	None[a]	451	1.52	2.34	0.30 (0.25, 0.36)	1.00	4	0.4 (0, 0.9)	12	1.6 (0.1, 3.1)
	>0 to <2	553	2.91	4.05	0.65 (0.52, 0.79)**	1.41 (1.19, 1.67)**	12	2.4 (0.4, 4.3)	45	7.2 (3.9, 10.6)
	≥2	66	5.59	7.45	1.39 (0.96, 2.02)**	1.92 (1.34, 2.75)**	7	7.9 (0.1, 15.7)**	17	22.7 (11.2, 34.1)**
Fish meals/week	None[a]	360	0.66	0.99	0.21 (0.18, 0.24)	1.00	0	–	3	0.4 (0, 0.9)
	>0 to <2	606	2.48	3.58	0.61 (0.51, 0.75)**	2.60 (2.01, 3.35)**	6	0.7 (0, 1.6)**	38	5.1 (2.6, 7.6)
	≥2	104	6.74	8.31	1.88 (1.43, 2.48)**	6.40 (4.48, 9.15)**	17	14.6 (6.8, 22.3)**	33	25.1 (16.2, 34.0)**

* $0.01 < p < 0.05$.
** $p < 0.01$ compared with reference group.
[a] Reference group.

years of age consumed at least one meal of fish or shellfish in the prior 30 days. In general, Hg concentrations are higher in fish than shellfish, suggesting that fish are a more important source of MeHg than shellfish. Table 4 evaluates this observation quantitatively. We modeled the effects of demographic covariates, consumption of fish, shellfish, and total seafood (fish + shellfish) on the proportional change in geometric mean MeHg. Frequency of consumption of fish meals explained 21–23% of the variation in MeHg, controlling for demographic factors. Furthermore, accounting for shellfish meals did not substantially increase explained variance (0.6–2.2%). Based on this data we selected the number of fish meals (excluding shellfish) in the past 30 days as a potential screening question for MeHg. Receiver operator characteristic (ROC) curves were created for number of fish meals in past 30 days for both of the population subgroups of interest, and demonstrated better performance in WCBA (than adults ≥50 years old Supplemental Fig. 1).

Table 5 shows the validity of the use of fish consumption screening questions and TBHg testing to identify participants with MeHg ≥5.8 μg/L. Using the TBHg test alone results in sensitivity and specificity of ≥94% for elevated MeHg. It also has excellent positive and negative predictive value. Asking fish consumption questions alone (without blood testing) results in high negative predictive value, low positive predictive value, and variable sensitivity and specificity depending on the fish consumption cut point. Asking about fish consumption ≥1 or 2 times per month results in high sensitivity and negative predictive value for identifying elevated MeHg, desirable characteristics for the first step in a sequential screening process (Gordis, 2009), but the low specificity and low positive predictive values would yield many false positives.

Table 5 also shows results of the use of a sequential screening procedure: asking a fish consumption question followed by the TBHg test in those responding "yes" to the fish consumption question. The net sensitivity and specificity of sequential screening are comparable to that of TBHg alone when using the fish consumption question of ≥1 meal/mo. for adults ≥50 years old and ≥2 meals/mo. for WCBA. At higher fish consumption levels, sensitivity declines and specificity increases slightly. Adding a fish consumption question to the screening process results in the avoidance of 50% of blood tests in WCBA and 21% of TBHg tests for adults ≥50 years that would be drawn in a universal blood testing procedure.

Table 6 presents the effect of population prevalence of elevated MeHg on the positive and negative predictive values of the screening tests among the sub-groups shown to have the highest (Asians), intermediate (Caucasians) and lowest (Mexicans) prevalence of elevated MeHg in our NHANES analysis. As expected, when prevalence of elevated MeHg in the sub-population increases, the positive predictive value of all tests increases. In the sequential screening procedure, adding the fish consumption screening question of ≥2 meals/m does not improve the testing validity among Mexicans, since the population prevalence of elevated MeHg is so low. Among Asians, the testing validity is high in both the blood testing alone and sequential testing procedures.

4. Discussion

Methyl mercury levels in subgroups of the US population reach levels of concern for adverse neurodevelopment and cardiovascular disease. In women of childbearing age and adults ≥50 years old, MeHg levels are highest in persons of Asian ethnicity. Other potentially important determinants of MeHg exposure include being born outside of the US and higher family income.

Table 3
Adults ≥50 years of age: population weighted methyl mercury (μg/L) 90th and 95th percentiles, geometric means, adjusted proportional change in means, prevalence with ≥5.8 μg/L by population subgroups and fish consumption

Variable		N	90th percentile	95th percentile	Geometric mean MeHg (95% CI)	Adjusted proportional change in mean MeHg (95% CI)	N MeHg ≥5.8 μg/L	Percentage with MeHg ≥5.8 μg/L
Total		2061	3.69	5.83	0.71 (0.57, 0.90)	–	115	5.0 (2.1, 7.9)
Race/Ethnicity	White [a]	873	3.46	5.19	0.69 (0.52, 0.91)	1.00	29	4.6 (0.9, 8.3)
	Black	575	3.05	5.61	0.77 (0.59, 1.00)	1.16 (0.90, 1.48)	24	4.8 (1.9, 7.6)
	Mexican	157	1.34	1.86	0.37 (0.27, 0.50)**	0.58 (0.43, 0.77)**	1	0.5 (0, 1.3)**
	Hispanic	229	3.84	5.72	1.10 (0.92, 1.33)**	1.47 (1.12, 1.94)**	12	4.9 (2.6, 7.2)
	Asian	183	9.15	13.33	2.49 (1.91, 3.23)**	2.04 (1.52, 2.73)**	48	25.3 (17.0, 33.6)**
	Other	44	2.45	2.90	0.43 (0.29, 0.64)*	0.71 (0.53, 0.96)*	1	0.8 (0, 2.7)
Sex	Male	1016	4.16	6.51	0.74 (0.59, 0.93)	1.09 (0.95, 1.24)	69	6.0 (2.4, 9.7)*
	Female [a]	1045	3.46	4.83	0.69 (0.54, 0.89)	1.00	46	4.1 (1.7, 6.5)
Age group	50–64 y	1151	3.69	5.39	0.75 (0.61, 0.94)*	1.18 (1.10, 1.26)**	72	4.4 (2.1, 6.8)
	≥65 y [a]	910	3.81	6.90	0.65 (0.50, 0.85)	1.00	43	6.0 (1.4, 10.6)
Family income	<$20,000 [a]	600	2.54	3.43	0.51 (0.41, 0.65)	1.00	24	2.2 (0.6, 3.8)
	>$20,000	1461	4.01	6.42	0.77 (0.60, 0.99)**	1.22 (1.00, 1.48)	91	5.6 (2.1, 9.1)
US Born	Yes [a]	1518	3.30	5.09	0.67 (0.52, 0.87)	1.00	52	4.5 (1.2, 7.8)
	No	543	5.57	7.90	1.13 (0.91, 1.41)**	1.38 (1.06, 1.79)*	63	9.0 (6.0, 12.1)*
BMI	<25	546	4.73	7.65	0.83 (0.58, 1.20)*	1.25 (0.94, 1.66)	51	8.2 (2.7, 13.7)**
	25–29	704	3.78	6.38	0.79 (0.62, 1.02)**	1.21 (1.04, 1.41)*	41	5.3 (1.7, 8.9)
	≥30 [a]	811	2.86	4.31	0.58 (0.47, 0.71)	1.00	23	2.6 (0.5, 4.7)
Shellfish meals/week	None [a]	1043	2.45	3.43	0.44 (0.35, 0.55)	1.00	24	1.6 (0.5, 2.7)
	>0 to <2	919	4.51	7.61	1.03 (0.80, 1.33)**	1.69 (1.38, 2.07)**	67	7.0 (2.7, 11.2)
	≥2	99	11.86	13.88	2.43 (1.57, 3.75)**	2.54 (1.90, 3.41)**	24	20.4 (8.5, 32.2)**
Fish Meals/week	None [a]	431	0.85	1.25	0.24 (0.20, 0.28)	1.00	2	0.5 (0.0, 1.3)
	>0 to <2	1360	3.04	4.31	0.77 (0.62, 0.96)**	2.71 (2.37, 3.09)**	60	2.8 (0.5, 5.0)
	≥2	270	9.06	11.86	2.35 (1.76, 3.16)**	6.70 (5.31, 8.45)**	53	23.6 (13.2, 34.0)**

[a] Reference group.
* $0.01 < p < 0.05$,
** $p < 0.01$ compared with reference group.

Table 4
Variation in MeHg by number of fish and shellfish meals consumed in past 30 days.

Base model	Additional seafood variable	Women 18–44 Years of Age			Adults ≥50 Years of Age		
		Proportional change in geometric mean MeHg (95% CI) per unit increase in frequency of seafood consumed	Model R^2	Partial R^2 seafood	Proportional change in geometric mean MeHg (95% CI) per unit increase in frequency of seafood consumed	Model R^2	Partial R^2 seafood
Covariates [a]	None	na	0.075	na	na	0.081	na
Covariates [a]	Shellfish	1.07 (1.02, 1.12)	0.125	0.050	1.14 (1.10, 1.18)	0.182	0.101
Covariates [a]	Fish	1.16 (1.14, 1.19)	0.311	0.236	1.13 (1.11, 1.15)	0.295	0.214
Covariates [a] and fish meals/m	Shellfish	1.02 (0.99, 1.05)	0.317	0.006	1.07 (1.04, 1.10)	0.317	0.022
Covariates [a] and shellfish meals/m	Fish	1.15 (1.13, 1.18)	0.317	0.192	1.11 (1.09, 1.13)	0.317	0.103
Covariates [a]	Sum fish and shellfish	1.08 (1.05, 1.12)	0.261	0.186	1.10 (1.08, 1.11)	0.313	0.232

[a] Covariates include BMI, race/ethnicity, US born, family income; and for older adults-gender and age group.

In 2013 the US EPA reported an 18% decrease in mean TBHg and 34% decrease in mean MeHg among women of childbearing age (WCBA) between NHANES 1999–2000 and NHANES 2001–2010. Means in 1999–2000 were 1.01 μg/L TBHg and 0.94 μg/L MeHg; in 2009–2010 they were 0.69 μg/L TBHg and 0.86 μg/L MeHg (MeHg calculated indirectly from total and inorganic blood mercury) (USEPA 2013). However, Caldwell et al. (2009) analyzed mean levels from NHANES 1999–2006 among women ages 16–49 and found TBHg levels to be stable across that period. Jain (2013) examined Hg levels among women ages 17–39 in NHANES 2003–2010, noting that "no marked decline over survey cycles was found for Hg." (Jain, 2013) In our analysis of NHANES 2011–2012 for WCBA, we calculated a geometric mean of 0.47 μg/L for MeHg overall, which is lower than means from analyses of prior NHANES, and 1.17 μg/L for MeHg in Asians. However, our analysis of the percent of women with elevated MeHg indicates that many women continue to be at risk of adverse birth outcomes due to MeHg exposure. The effects on neurodevelopment from *in utero*

Table 5
Fish consumption question and TBHg as screening tests for elevated MeHg: sensitivity and specificity, positive and negative predictive value.

Age/gender	Population prevalence of MeHg ≥ 5.8 μg/L	Screening test	Sensitivity[a]	Specificity[a]	Positive predictive value	Negative predictive value	% THg Tests avoided by sequential screening[b]
		Blood test alone:					
Adults ≥ 50 y	5.0%	TBHg ≥ 5.8 μg/L	0.94	0.995	0.91	0.997	–
		Fish consumption question alone:					
	5.0%	≥ 1 fish meals/m	0.98	0.22	0.06	0.996	
	5.0%	≥ 2 fish meals/m	0.95	0.37	0.07	0.993	–
	5.0%	≥ 4 fish meals/m	0.76	0.65	0.10	0.98	–
	5.0%	≥ 8 fish meals/m	0.46	0.89	0.18	0.97	–
		Fish consumption question plus blood test:					
	5.0%	≥ 1 fish meals/m and TBHg ≥ 5.8 μg/L[c]	0.92	0.996	0.93	0.996	21%
	5.0%	≥ 2 fish meals/m and TBHg ≥ 5.8 μg/L[c]	0.89	0.997	0.83	0.998	36%
	5.0%	≥ 4 fish meals/m and TBHg ≥ 5.8 μg/L[c]	0.71	0.998	0.88	0.995	64%
	5.0%	≥ 8 fish meals/m and TBHg ≥ 5.8 μg/L[c]	0.43	0.999	0.93	0.990	88%
		Blood test alone:					
WCBA	1.7%	TBHg ≥ 5.8 μg/L	0.96	0.994	0.74	0.999	–
		Fish consumption question alone:					
	1.7%	≥ 2 fish meals/m	1	0.51	0.03	1	–
	1.7%	≥ 4 fish meals/m	0.91	0.74	0.06	0.998	–
	1.7%	≥ 8 fish meals/m	0.74	0.92	0.13	0.995	–
		Fish consumption question plus blood test:					
	1.7%	≥ 2 fish meals/m & TBHg ≥ 5.8 μg/L[c]	0.96	0.997	0.85	0.999	50%
	1.7%	≥ 4 fish meals/m & TBHg ≥ 5.8 μg/L[c]	0.87	0.998	0.91	0.998	73%
	1.7%	≥ 8 fish meals/m & TBHg ≥ 5.8 μg/L[c]	0.71	0.999	0.96	0.995	91%

[a] Sensitivity and specificity calculated for screening test using blood methyl Hg ≥ 5.8 μg/L as "gold standard".
[b] Defined as the number who responded "no" to the fish consumption question/total number screened × 100.
[c] Fish consumption question asked first, if answer is "no": no further testing; if answer is yes: perform TBHg test.

Table 6
Fish consumption question and TBHg as screening tests for elevated MeHg among population subgroups: sensitivity and specificity, positive and negative predictive value.

Age/gender	Screening test	Sensitivity[a]	Specificity[a]	Population prevalence of MeHg ≥ 5.8 μg/L	Positive predictive value	Negative predictive value
Adults ≥ 50 years of age	TBHg ≥ 5.8 μg/L	0.94	0.99	Mexican = 0.5%	0.48	0.999
				Caucasian = 4.6%	0.90	0.997
				Asian = 25.3%	0.98	0.980
	≥ 2 fish meals/m and TBHg ≥ 5.8 μg/L[b]	0.89	0.997	Mexican = 0.5%	0.59	0.999
				Caucasian = 4.6%	0.93	0.995
				Asian = 25.3%	0.99	0.965
WCBA	TBHg ≥ 5.8 μg/L	0.96	0.994	Mexican = 0.2%	0.25	0.999
				Caucasian = 1.8%	0.75	0.999
				Asians = 9.5%	0.95	0.995
	≥ 2 fish meals/m and TBHg ≥ 5.8 μg/L[b]	0.96	0.997	Mexican = 0.2%	0.39	0.999
				Caucasian = 1.8%	0.86	0.999
				Asians = 9.5%	0.97	0.995

[a] From Table 5.
[b] Fish consumption question asked first, if answer is "no": no further testing; if answer is yes: perform TBHg test.

MeHg exposure are well known. Several research cohorts have shown decreased performance on Bayley Scales of Infant Development (Stokes-Riner et al., 2011), neuropsychiatric measures of language, attention, and memory (Grandjean et al., 1997), and visual recognition memory (Oken et al., 2005) among offspring of women with elevated mercury levels from fish consumption during pregnancy. Using Mahaffey's translation of percentage of WCBA with elevated Hg to number of newborns at risk (Mahaffey et al., 2004: (%WCBA with elevated MeHg ≥ 5.8 μg/L) × (#births in US each year) (US Census, 2012)), our analyses show that over 75,000 infants born in the US annually may be at risk of adverse neurodevelopmental outcomes from maternal fish consumption. Using the lower level of concern of 3.5 μg/L results in an even higher number of infants at risk at 225,311. This estimate should be interpreted with the recognition that the EPA reference dose equivalent of 5.8 μg/L was calculated with an Uncertainly Factor of 10. (IRIS, 2001) On the other hand, recent investigations now document adverse health effects at low mercury levels, well within the window of uncertainty (Karagas et al., 2012). Clearly, more research is needed to determine the risk/benefit threshold for different types of fish that account for both MeHg content and omega-3 fatty acids in fish.

Southeast and Pacific Rim Asians in the US have been shown in multiple studies to be at risk for elevated mercury due to increased fish consumption compared to other Americans (Hightower et al. 2006; McDowell et al., 2004; McKelvey et al., 2007; Tsuchiya et al., 2008). Specifically, two recent studies (McKelvey et al., 2007; Tsuchiya et al., 2008) evaluated fish consumption among Asian subpopulations in urban centers and found high prevalence of elevated Hg levels (46% in New York City; 33% in Seattle) attributed to frequency of fish consumption. Our pilot study of Chinese, Korean, and Filipino participants at two Asian health fairs in Chicago (Buchanan et al., 2015, under review) found that 28% of participants had elevated hair Hg levels (> 1 μg/gm). Analyses of NHANES 1999–2000 (Mahaffey et al. 2004) and 1999–2002 (Hightower et al., 2006) reported results among women from the "other" race ethnicity category which included Asians, Native Americans, Pacific Islanders: 27% and 31.5% had blood mercury levels > 3.5 μg/L, respectively. The 2011–2012 NHANES dataset used in the current study was the first to include Asians as a separate race/ethnicity category, and recent analysis of the dataset has found that 15.9% of Asians overall had MeHg levels > 5.8 μg/L (Mortensen et al., 2014). Our evaluation of the data for WCBA and adults over 50 years of age, subgroups particularly vulnerable to the health effects of MeHg exposure, found that Asians from both subgroups carry the highest burden of MeHg exposure compared to other ethnicities. Among WCBA, our analysis found that 23% of Asians had levels ≥ 3.5 μg/L, the level of concern that accounts for fetal concentration of maternal MeHg.

In adults, higher mercury levels have been associated with higher risk of myocardial infarction and cardiovascular disease (CVD) (Guallar et al., 2002; Virtanen et al., 2005.) Using 2013 US population estimates (US Census, 2013), over 5.6 million adults > 50 years old in the US may be at risk of adverse cardiovascular outcomes due to elevated blood mercury. In general, Southeast Asians have comparatively lower risk for CVD than other race/ethnicities in the US (Palaniappan et al., 2010). Nevertheless, we found that the geometric mean MeHg levels among Asians were over 2.5 times the geometric mean among whites, and 25% had elevated levels ≥ 5.8 μg/L. Moreover, between 2000 and 2010 Asians were the fastest growing race/ethnicity in the US, and this trend has continued through 2012 (Hoeffel et al., 2010). With the increased numbers of older Asians it will be important to consider the potential contribution of dietary mercury to CVD in this population. Future research on CVD risk in Asian American ethnic subgroups should include dietary and acculturation assessments.

In addition to Asian ethnicity, we found higher income to be a predictor of elevated mercury. This has been shown in previous work (Hightower and Moore, 2003; Karimi et al., 2014; Razzaghi et al., 2014; USEPA, 2013), and may be due to the financial ability to purchase larger fish (swordfish, tuna steaks) which in general carry higher concentrations of MeHg. Other predictors of elevated MeHg in our analyses included having a lower BMI. Jain (2013) found similar results for lower BMI in an analysis of NHANES 2003–2010. Rothenberg et al. (2015) recently published an analysis of NHANES data on obesity and mercury levels and suggest that changes in metabolism, distribution, or excretion of mercury in obese adults may account for their lower blood levels. Or perhaps lower BMI indicates a more healthful diet that includes regular consumption of fish. Analyses of other cohorts have similarly found higher blood Hg with increasing age (Karimi et al., 2014; Knobeloch et al., 2007; McKelvey et al., 2007; Morrissette et al., 2004). Our finding of lower blood Hg among Mexican American WCBA has also been found in previous NHANES datasets (Razzaghi et al., 2014; Caldwell et al., 2009; USEPA, 2013).

Regarding fish consumption, our results are consistent with a large body of data demonstrating that increasing frequency of fish consumption increases mercury levels. Current EPA/FDA guidelines recommend that WCBA consume fish twice weekly. Our results show that up to 14% of WCBA and 24% of adults over age 50 eating fish ≥ 2 times per week have elevated MeHg. We found tuna to be the most commonly consumed fish. The NHANES dataset does not specify types of tuna such as chunk light, steak, or skipjack, albacore, blue fin, yellow fin, etc, yet the levels of MeHg among these fish species vary considerably (Groth, 2010). Because of this variation and the high prevalence of tuna consumption, published fish consumption guidelines should include specific recommendations regarding consumption frequency for different types of tuna. Analysis at this level of detail is not possible with the NHANES dataset, so other studies should be used to inform such guidelines.

Our analysis of screening tests for MeHg showed that using TBHg as a biomarker for MeHg among WCBA and adults ≥ 50 years old is valid. This is important because measuring TBHg is less expensive than speciating MeHg and therefore more likely to be used for screening purposes. However, even though using TBHg screening alone performed well on tests for validity, universal blood screening would likely be cost-prohibitive and unnecessarily invasive. Moreover, we found that blood screening among populations with low prevalence of elevated MeHg results in low positive predictive value (high false positives), limiting its use among these populations. Also, the validity of TBHg as a biomarker for MeHg among low fish consumption populations is affected by the ratio of MeHg to TBHg, which is usually reported as $> 80\%$ (Karimi et al., 2014, Mahaffey et al., 2004). But Mortensen et al. found a ratio of 0.67 in Mexican Americans compared to 0.85 among Asians. Perhaps this variable ratio should be taken into consideration when drawing conclusions about MeHg using TBHg as the biomarker.

We also examined the use of fish consumption screening questions alone and in a sequential process with TBHg testing (blood test performed if response to fish consumption screening question is "yes"). When used alone, the sensitivity of the fish consumption screening questions was highest using the fish consumption cut-offs of ≥ 1 or 2 times per month, but would result in many false positives. Informing patients falsely that they may have elevated MeHg might raise alarm and decrease fish consumption unnecessarily. The high sensitivity and negative predictive value for the questions identifying fish consumption of ≥ 1 or 2 times per month are desirable characteristics for the first step in a sequential screening process (Gordis, 2009). When analyzing sequential testing, we found that using fish consumption ≥ 2/m in

WCBA and ≥1/m in adults ≥50 years of age as screening questions resulted in the avoidance of up to 50% of the blood tests that would be conducted in universal blood testing. It is interesting to note that while tuna was the type of fish most commonly consumed, using tuna consumption frequency as a screening question did not perform as well as the overall fish consumption questions in our analyses (results not shown).

We also examined sequential screening among specific sub-populations. We found that among Asians adding the fish consumption screening question did not increase the validity compared to universal blood testing. Among Mexicans, whose population prevalence of elevated MeHg was extremely low, both universal blood testing and sequential screening would result in more false positives compared to Asians, a group for whom blood testing alone may be a valid screening procedure. Unfortunately, the dataset does not provide sufficient numbers to analyze these trends in more detail. Analyzing multiple cycles of NHANES might be warranted to better evaluate the validity of screening sub-populations.

Currently no guidelines exist for mercury screening in clinical care. The results presented in this paper show that TBHg is a valid screening test for elevated MeHg among high risk groups, and that adding a fish consumption question to a sequential screening procedure among WCBA and adults ≥50 years of age has similar validity to the TBHg used alone but requires drawing blood from only 50–80% of those who would receive blood testing in universal blood screening. These preliminary findings should be used to pursue additional research evaluating ways to incorporate screening and prevention education into routine clinical care. Studies already show that warning patients about contaminants in fish can result in decreased fish consumption to below recommended frequencies (two servings per week) (Oken et al., 2003). The fish consumption message to eat fish low in mercury twice a week (USEPA, 2014) needs to be delivered to patients in a manner that empowers them to make healthy choices for themselves and their families. Clinical screening can be used in conjunction with patient education to identify those most at risk from the health effects of contaminants in fish, but more research is needed to evaluate its efficacy.

Conclusion: Our analysis of NHANES 2011–2012 found that a concerning percentage of Asian women of childbearing age and Asian adults ≥50 years of age are at risk of health effects due to methyl mercury exposure. Screening these high risk groups using sequential testing with fish consumption questions followed by blood testing has high validity, but the validity varies by ethnic group due to varying prevalence of elevated MeHg from fish consumption. More work is needed using larger datasets before screening guidelines can be tailored for specific ethnic groups or according to fish consumption frequency. It will be important to identify and resolve unintended negative outcomes of screening such as a decrease in the consumption of healthy fish and a resulting loss of the health benefits of omega-3 fatty acids in fish.

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None of the authors has any competing financial interests to declare.

Appendix A. Supplementary information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2015.03.005.

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