Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Mercury Exposure and Risk of Cardiovascular Disease in Two US Cohorts

Supplementary Appendix

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Assessment of Mercury and Selenium Exposures

Total mercury and selenium concentrations were assessed in the stored toenails of cases and controls using neutron-activation analysis (University of Missouri Research Reactor). Validity, reproducibility, and reliability have been described.[1-5] Samples of nail clippings from all toes were combined which, due to the elimination half-life of methylmercury, the growth rate of toenails, and the differential length of time (distance) from cuticle synthesis to time of clipping across the smallest to largest toes, provides a time-integrated measure of exposure over approximately the prior year. Sample mass was adequate for neutron activation analysis in all participants. Matched case-control sets were handled identically and in the same analytical run, but in random order with case-control status unknown to the laboratory personnel. Selenium determinations were performed in 41 analytical batches between 2007 and 2008, and mercury determinations in 72 analytical batches between 2009 and 2010. Potential laboratory drift was controlled by both standard comparison procedures for neutron activation analysis and repeated analysis of representative sample subsets, as well as during analysis by use of matched-pair conditional logistic regression. Intra-assay coefficients of variation were 5.5% for mercury and 2.4% for selenium.

In prior analyses,[1-5] we have shown that toenail mercury and selenium concentrations are excellent biomarkers of usual methylmercury and selenium exposure. Consumption of tuna and other saltwater fish are primary dietary factors positively associated with toenail mercury.[1-3] Toenail selenium concentrations respond to long-term changes in dietary consumption and correlate with serum or whole blood selenium levels.[4,5] Toenail mercury concentrations at one time also predict future exposure, with Spearman correlation(r)=0.56 ($p<0.001$) for levels assessed in clippings obtained 6 years apart,[2] similar to correlations of 0.6 to 0.7 typically observed, over similar time intervals, for widely used epidemiologic measures such as blood pressure.[6] Variability of toenail selenium over time is slightly higher but still reasonable (r=0.48 for levels in clippings obtained 6 years apart).[2] In one study comparing several exposure biomarkers, mercury concentrations in toenails had stronger cross-sectional associations with some intermediate cardiovascular disease risk factors compared with blood or hair concentrations.[7]

For assessing population health effects, the primary mercury species of interest is methylmercury, derived principally from fish intake.[8] Absent unusual occupational/environmental exposures to mercury vapor, methylmercury is the principal determinant of variation in hair and toenail mercury concentrations. When hair mercury levels are speciated, total mercury and methylmercury levels correlate nearly perfectly: r=0.99.[9] Similarly, when we speciated toenail mercury levels[10] from a subset of nondentist controls (Quicksilver Scientific, LLC, Lafayette, CO), total mercury and methylmercury concentrations correlated nearly perfectly: r=0.97, p<0.001.

Stroke Subtypes

Stroke subtypes were also classified as previously described.[11,12] Ischemic stroke was defined as cerebral infarction caused by thrombi (thrombotic stroke) or extracranial emboli (embolic stroke). Subarachnoid hemorrhage was defined as hemorrhage in the subarachnoid space, usually caused by saccular cerebral artery aneurysm rupture, less commonly by arteriovenous malformations or other causes. Intraparenchymal hemorrhage was defined as hemorrhage in intraparenchymal regions not due to aneurysm or arteriovenous malformation. Mercury exposure was not associated with risk of any of the major stroke subtypes, including ischemic stroke (643 cases; extreme-quintile relative risk=0.79, 95%CI=0.53-1.18; P for trend=0.33), hemorrhagic stroke (139 cases; extreme-quintile relative risk=0.89, 95%CI=0.35-2.26; P for trend=0.50), or unknown stroke types (282 cases; extreme-quintile relative risk=0.96, 95%CI=0.49-1.89; P for trend=0.85).

Power Calculations

Power calculations demonstrated over 80% power to detect extreme-quintile relative risks (i.e., for the comparison of the top to the bottom quintile) greater than 1.25 and over 90% power to detect extreme-quintile relative risks greater than 1.30. For the test for trend across quintiles, power calculations demonstrated over 80% power to detect extreme-quintile relative risks greater than 1.20 and over 90% power to detect extreme-quintile relative risks greater than 1.25.

Additional Sensitivity Analyses

In sensitivity analyses to minimize potential misclassification due to exposure changes over time, mercury concentrations were not associated with higher cardiovascular disease risk when restricting the analysis to events occurring within 10 years of toenail sampling (extreme-quintile relative risk=0.86, 95%CI=0.66-1.13; P for trend=0.32) or stratified by duration of follow-up since toenail sampling (Supplementary Appendix Table 4). By end of follow-up, 76, 15, and 9 percent of individuals had increased or decreased their fish consumption by less than 1 quintile, 2 quintiles, or more than 2 quintiles compared to baseline. In analyses restricted to individuals without substantial changes ($\leq$2 quintiles) in fish consumption during follow-up, mercury concentrations were not associated with higher cardiovascular disease risk (extreme-quintile relative risk=0.83, 95%CI=0.66-0.99; P for trend=0.06). There was also little evidence for statistical interaction between fish intake and mercury levels (P for interaction=0.76 for coronary heart disease, 0.16 for stroke, and 0.55 for total cardiovascular disease). Findings were similar for risk of coronary heart disease and stroke evaluated separately (not shown).

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Supplementary Table 1. Baseline Characteristics According to Mercury Levels Among 3,427 Controls in Two Prospective US Cohorts of Men and Women.

	Sex-Specific Quintiles of Toenail Mercury					
Quintiles	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	
Mercury concentration (μg/g)						
Mean	0.09	0.17	0.25	0.38	0.95	P for
Median	0.09	0.17	0.25	0.36	0.68	Trend
Age, years	56.4	56.3	56.4	56.6	56.2	0.84
Sex, % female	64.7	64.7	64.7	64.7	64.7	1.00
Smoking status,						
Never	42.8	40.7	36.2	34.6	35.3	0.21
Past	25.6	31.0	35.5	35.0	37.1	
Current	31.4	28.2	27.4	30.0	27.2	
Family history of MI, %	23.8	23.5	24.6	28.9	26.0	0.16
Hypertension, %	11.2	13.1	11.8	13.9	14.0	0.15
Hypercholesterolemia, %	3.4	6.7	7.1	7.0	10.7	<0.001
Diabetes mellitus, %	1.3	2.0	1.6	1.3	1.5	0.75
Body mass index, kg/m^2	25.2	25.1	25.0	24.7	24.6	0.001
Physical activity, METS/week	7.7	8.8	8.3	8.8	10.4	0.01
Alcohol, drink/week	0.4	0.5	0.7	0.8	0.9	<0.001
Toenail selenium, μg/g	0.81	0.84	0.83	0.81	0.84	0.44
Fish, servings/week	1.1	1.5	1.9	2.1	2.8	<0.001
EPA and DHA, mg/week	131	172	220	239	297	<0.001
Total energy, kcal/day	1940	1900	1852	1803	1738	<0.001
Total fat, %E	35.1	34.9	33.5	33.5	32.5	<0.001
Saturated fat, %E	12.7	12.7	12.0	11.8	11.3	<0.001
Monounsaturated fat, %E	13.3	13.1	12.6	12.5	12.0	<0.001
Polyunsaturated fat, %E	6.1	6.2	6.1	6.3	6.3	0.01
Trans fat, %E	1.9	1.8	1.7	1.6	1.6	<0.001
Protein, %E	17.1	17.8	18.3	18.3	18.7	<0.001
Dietary cholesterol, mg/day	323	326	312	310	292	<0.001
Whole grains, g/day	17.7	16.7	18.0	19.0	16.9	0.73

Values are mean (continuous characteristics) or percent (categorical characteristics).

Supplementary Table 2. Relative Risk of Cardiovascular Diseases According to Deciles of Toenail Mercury in Two Prospective US Cohorts of Men and Women.

	Sex-Specific Deciles of Toenail Mercury – Men and Women Combined										
Deciles	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**P for Trend**
Mercury level, µg/g											
Mean	0.07	0.11	0.15	0.19	0.23	0.27	0.35	0.42	0.59	1.62	
Median	0.07	0.12	0.15	0.18	0.22	0.25	0.31	0.39	0.54	1.00	
CHD					Total cases = 2,363						
No. of cases	272	270	269	237	224	222	228	222	210	209	
Multivariable RR*	1.00	0.99	1.04	0.94	0.84	0.91	0.84	0.89	0.80	0.90	0.32
(95%CI)	(reference)	(0.76, 1.29)	(0.79, 1.36)	(0.71, 1.23)	(0.64, 1.11)	(0.69, 1.21)	(0.64, 1.10)	(0.67, 1.17)	(0.60, 1.06)	(0.68, 1.21)	
Stroke					Total cases = 1,064						
No. of cases	123	110	117	109	121	88	96	113	96	91	
Multivariable RR*	1.00	0.80	0.83	0.87	1.09	0.65	0.80	0.96	0.75	0.71	0.23
(95%CI)	(reference)	(0.54, 1.19)	(0.55, 1.23)	(0.59, 1.30)	(0.73, 1.64)	(0.43, 0.99)	(0.52, 1.22)	(0.65, 1.44)	(0.49, 1.14)	(0.46, 1.09)	
Total CVD					Total cases = 3,427						
No. of cases	395	380	386	346	345	310	324	335	306	300	
Multivariable RR*	1.00	0.93	0.97	0.92	0.93	0.82	0.83	0.92	0.80	0.85	0.16
(95%CI)	(reference)	(0.75, 1.16)	(0.78, 1.21)	(0.74, 1.15)	(0.74, 1.16)	(0.65, 1.03)	(0.66, 1.05)	(0.74, 1.16	(0.63 1.01	(0.67 1.08)	

*Based on conditional logistic regression with risk-set sampling, in which the odds ratio directly estimates the hazard ratio or relative risk (RR), with matching factors of age, sex, race, month of toenail return, and smoking status (never, former, current) and further adjusted for body mass index (kg/m^2, quintiles), physical activity (METS/wk, quintiles), alcohol (drinks/wk, quintiles), diabetes (yes, no), hypertension (yes, no), elevated cholesterol (yes, no), and estimated dietary intake of EPA and DHA (mg/wk, quintiles).

Supplementary Table 3. Relative Risk of Cardiovascular Diseases According to Quintiles of Toenail Mercury Among 3,427 Cases and 3,427 Matched Controls in Two Prospective US Cohorts of Men and Women.

	Women						Men					
Quintiles	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**P for Trend**	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**P for Trend**
Range of mercury levels in controls, μg/g	0.013 - 0.127	0.128 - 0.187	0.188-0.268	0.269 - 0.410	0.411 -14.78		0.005 - 0.139	0.140 - 0.241	0.242 - 0.375	0.376 - 0.609	0.610 - 5.00	
CHD	Total cases = 1,455						Total cases = 908					
No. of cases	357	314	278	271	235		185	192	168	179	184	
Multivariable RR*	1.00	0.90	0.75	0.72	0.68	0.001	1.00	1.10	0.96	0.98	0.98	0.64
(95% CI)	(reference)	(0.72, 1.12)	(0.59, 0.95)	(0.57, 0.91)	(0.53, 0.86)		(reference)	(0.82, 1.48)	(0.71, 1.28)	(0.74, 1.30)	(0.73, 1.31)	
Multivariable RR†	1.00	0.94	0.81	0.76	0.72	0.01	1.00	1.12	1.02	1.06	1.08	0.87
(95% CI)	(reference)	(0.74, 1.19)	(0.63, 1.05)	(0.59, 0.98)	(0.55, 0.94)		(reference)	(0.81, 1.54)	(0.74, 1.42)	(0.77, 1.47)	(0.77, 1.51)	
Stroke	Total cases = 761						Total cases = 303					
No. of cases	177	152	154	146	132		56	74	55	63	55	
Multivariable RR*	1.00	0.85	0.92	0.92	0.69	0.03	1.00	1.11	0.82	1.03	1.13	0.73
(95% CI)	(reference)	(0.63, 1.16)	(0.67, 1.28)	(0.66, 1.27)	(0.50, 0.95)		(reference)	(0.66, 1.87)	(0.48, 1.39)	(0.63, 1.69)	(0.64, 1.99)	
Multivariable RR†	1.00	0.91	1.01	1.00	0.74	0.09	1.00	1.14	0.86	1.03	1.28	0.55
(95% CI)	(reference)	(0.65, 1.27)	(0.71, 1.44)	(0.70, 1.43)	(0.52, 1.06)		(reference)	(0.63, 2.05)	(0.48, 1.56)	(0.59, 1.80)	(0.65, 2.54)	
Total CVD	Total cases = 2,216						Total cases = 1,211					
No. of cases	534	466	432	417	367		241	266	223	242	239	
Multivariable RR*	1.00	0.88	0.80	0.78	0.68	<0.001	1.00	1.11	0.92	1.00	1.01	0.84
(95% CI)	(reference)	(0.74, 1.06)	(0.67, 0.97)	(0.65, 0.94)	(0.56, 0.82)		(reference)	(0.86, 1.43)	(0.71, 1.19)	(0.79, 1.28)	(0.78, 1.31)	
Multivariable RR†	1.00	0.93	0.88	0.84	0.74	0.005	1.00	1.12	0.94	1.04	1.10	0.65
(95% CI)	(reference)	(0.77, 1.12)	(0.72, 1.08)	(0.69, 1.03)	(0.60, 0.91)		(reference)	(0.85, 1.47)	(0.71, 1.25)	(0.79, 1.37)	(0.82, 1.48)	

*Based on conditional logistic regression with risk-set sampling, in which the odds ratio directly estimates the hazard ratio or relative risk (RR), with matching factors of age, sex, race, month of toenail return, and smoking status (never, former, current).

†Further adjusted for body mass index (kg/m^2, quintiles), physical activity (METS/wk, quintiles), alcohol (drinks/wk, quintiles), diabetes (yes, no), hypertension (yes, no), elevated cholesterol (yes, no), and estimated dietary intake of EPA and DHA (mg/wk, quintiles).

Supplementary Table 4. Relative Risk of Cardiovascular Diseases According to Quintiles of Toenail Mercury, Restricted to Events within 0-5, 5-10, 10-15, and ≥ 15 Years of Toenail Sampling**.**

	Sex-Specific Quintiles of Toenail Mercury – Men and Women Combined					
Quintiles	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**P for Trend**
During 0 – 5 years of follow-up						
No. of cases (n = 637)	140	136	117	128	116	
Multivariable RR* (95% CI)	1.00 (reference)	1.15 (0.79, 1.69)	0.94 (0.64, 1.37)	1.16 (0.78, 1.73)	1.00 (0.67, 1.51)	0.90
During 5 – 10 years of follow-up						
No. of cases (n = 798)	187	163	153	157	138	
Multivariable RR* (95% CI)	1.00 (reference)	0.77 (0.54, 1.08)	0.93 (0.64, 1.34)	0.87 (0.61, 1.24)	0.72 (0.49, 1.05)	0.17
During 10 – 15 years of follow-up						
No. of cases (n = 1056)	246	231	199	189	191	
Multivariable RR* (95% CI)	1.00 (reference)	0.98 (0.74, 1.30)	0.87 (0.64, 1.18)	0.81 (0.60, 1.08)	0.84 (0.61, 1.16)	0.25
During 15+ years of follow-up						
No. of cases (n = 936)	202	202	186	185	161	
Multivariable RR* (95% CI)	1.00 (reference)	1.08 (0.80, 1.45)	0.92 (0.67, 1.26)	0.92 (0.67, 1.27)	0.91 (0.65, 1.26)	0.43

*Based on conditional logistic regression with risk-set sampling, in which the odds ratio directly estimates the hazard ratio or relative risk (RR), with matching factors of age, sex, race, month of toenail return, and smoking status (never, former, current), and further adjusted for body mass index (kg/m^2, quintiles), physical activity (METS/wk, quintiles), alcohol (drinks/wk, quintiles), diabetes (yes, no), hypertension (yes, no), elevated cholesterol (yes, no), and estimated dietary intake of EPA and DHA (mg/wk, quintiles).

Supplementary Table 5. Relative Risk of Coronary Heart Disease According to Quintiles of Toenail Mercury Among Individuals in Different Strata of Fish Consumption in Two Prospective US Cohorts of Men and Women.

	Sex-Specific Quintiles of Toenail Mercury – Men and Women Combined*					
Quintiles	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**P for Trend**
Stratified by Total Fish Consumption †						
<1 servings/week (1023 cases)	1.00 (reference)	0.94 (0.74, 1.19)	0.90 (0.69, 1.17)	0.80 (0.60, 1.06)	0.90 (0.65, 1.25)	0.33
1 to <2 servings/week (705 cases)	1.00 (reference)	1.02 (0.71, 1.45)	0.95 (0.66, 1.37)	0.80 (0.56, 1.15)	0.79 (0.54, 1.16)	0.10
2+ servings/week (635 cases)	1.00 (reference)	0.90 (0.53, 1.51)	0.61 (0.37, 1.00)	0.87 (0.54, 1.39)	0.78 (0.49, 1.25)	0.80
Stratified by Tuna or Dark-Meat Fish Consumption †						
<1 servings/week (1720 cases)	1.00 (reference)	1.00 (0.83, 1.23)	0.90 (0.73, 1.12)	0.86 (0.69, 1.07)	0.94 (0.74, 1.19)	0.42
1 to <2 servings/week (326 cases)	1.00 (reference)	0.68 (0.35, 1.33)	0.67 (0.35, 1.28)	0.89 (0.47, 1.69)	0.66 (0.35, 1.22)	0.50
2+ servings/week (317 cases)	1.00 (reference)	0.73 (0.34, 1.56)	0.53 (0.26, 1.08)	0.54 (0.27, 1.08)	0.52 (0.26, 1.01)	0.18
Stratified by Other Fish Consumption †						
<0.5 servings/week (1447 cases)	1.00 (reference)	0.98 (0.79, 1.21)	0.86 (0.68, 1.09)	0.80 (0.63, 1.02)	0.88 (0.68, 1.15)	0.23
0.5 to <1 servings/week (657 cases)	1.00 (reference)	1.01 (0.68, 1.50)	0.91 (0.62, 1.35)	0.89 (0.60, 1.32)	0.76 (0.51, 1.13)	0.08
1+ servings/week (259 cases)	1.00 (reference)	0.82 (0.35, 1.90)	0.79 (0.36, 1.73)	1.01 (0.48, 2.13)	1.13 (0.54, 2.38)	0.25

*Quintile cutpoints are based on the overall control population (see Supplementary Table 1). Thus, in every stratum of fish consumption, higher quintiles reflect individuals who have similarly high mercury exposure. In the setting of low fish consumption (e.g., <1/week), this would be consistent with more exclusive consumption of relatively mercury-contaminated fish (i.e., similar methylmercury exposure coming from fewer fish meals, indicating a greater proportion of more highly contaminated fish in the diet).

†Total fish consumption reflects the sum of tuna or dark-meat fish consumption and other fish consumption. Strata were set at logical cutpoints that provided reasonable numbers of cases per stratum.

Based on unconditional logistic regression as appropriate for stratified subgroup analyses. Values are odds ratios (95% CI), adjusted for age, sex, race, month of toenail return, smoking status (never, former, current), body mass index (kg/m^2, quintiles), physical activity (METS/wk, quintiles), alcohol (drinks/wk, quintiles), diabetes (yes, no), hypertension (yes, no), elevated cholesterol (yes, no), and estimated dietary intake of EPA and DHA (mg/wk, quintiles).

Supplementary Table 6. Relative Risk of Stroke According to Quintiles of Toenail Mercury Among Individuals in Different Strata of Fish Consumption in Two Prospective US Cohorts of Men and Women.

	Sex-Specific Quintiles of Toenail Mercury – Men and Women Combined*					
Quintiles	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**P for Trend**
Stratified by Total Fish Consumption †						
<1 servings/week (477 cases)	1.00 (reference)	1.12 (0.77, 1.62)	0.95 (0.63, 1.42)	0.79 (0.51, 1.21)	0.91 (0.57, 1.44)	0.38
≥1 servings/week (587 cases)	1.00 (reference)	0.80 (0.53, 1.22)	0.99 (0.66, 1.50)	1.20 (0.80, 1.80)	0.82 (0.55, 1.23)	0.48
Stratified by Tuna or Dark-Meat Fish Consumption †						
<0.5 servings/week (492 cases)	1.00 (reference)	0.95 (0.65, 1.37)	0.95 (0.64, 1.42)	0.81 (0.53, 1.23)	0.83 (0.53, 1.28)	0.32
≥0.5 servings/week (572 cases)	1.00 (reference)	0.97 (0.64, 1.46)	0.96 (0.63, 1.44)	1.16 (0.77, 1.75)	0.81 (0.53, 1.23)	0.27
Stratified by Other Fish Consumption †						
<0.5 servings/week (674 cases)	1.00 (reference)	1.03 (0.74, 1.43)	1.05 (0.75, 1.48)	1.04 (0.73, 1.49)	0.82 (0.55, 1.20)	0.27
≥0.5 servings/week (390 cases)	1.00 (reference)	0.87 (0.52, 1.46)	0.90 (0.54, 1.51)	1.05 (0.63, 1.76)	0.87 (0.53, 1.43)	0.76

*Quintile cutpoints are based on the overall control population (see Supplementary Table 1). Thus, in every stratum of fish consumption, higher quintiles reflect individuals who have similarly high mercury exposure. In the setting of low fish consumption (e.g., <1/week), this would be consistent with more exclusive consumption of relatively mercury-contaminated fish (i.e., similar methylmercury exposure coming from fewer fish meals, indicating a greater proportion of more highly contaminated fish in the diet).

†Total fish consumption reflects the sum of tuna or dark-meat fish consumption and other fish consumption. Strata were set at logical cutpoints that provided reasonable numbers of cases per stratum.

Based on unconditional logistic regression as appropriate for stratified subgroup analyses. Values are odds ratios (95% CI), adjusted for age, sex, race, month of toenail return, smoking status (never, former, current), body mass index (kg/m^2, quintiles), physical activity (METS/wk, quintiles), alcohol (drinks/wk, quintiles), diabetes (yes, no), hypertension (yes, no), elevated cholesterol (yes, no), and estimated dietary intake of EPA and DHA (mg/wk, quintiles).