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Mercury Exposure and Risk of Hypertension in US Men and Women in Two Prospective Cohorts

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Abstract

Cross-sectional studies and animal-experiments suggest that methylmercury exposure could increase risk of hypertension. This relationship has not been evaluated in large prospective studies. Using data from prior nested case-control studies in two separate prospective cohorts, we measured toenail mercury, a valid biomarker of long-term methylmercury exposure, among 6,045 US men and women free of hypertension at baseline. Median toenail mercury concentrations were 0.09 μg/g in the lowest quintile and 0.64 μg/g in the highest quintile, the latter corresponding to exposures about 1.7-fold higher than the EPA reference dose (RfD). Participants were followed prospectively (mean±SD=14.9±7.9 years) for a new self-report of physician-diagnosed hypertension (3,540 cases), shown to be >95% sensitive and specific for diagnosing hypertension in these cohorts as compared with review of medical records and direct blood pressure measurement, respectively. After adjustment for demographic, clinical, and lifestyle risk factors, the hazard ratio (95% CI) for incident hypertension in the highest vs. lowest quintile of mercury exposure was 0.96 (0.84–1.09) in women, 0.82 (0.62–1.08) in men, and 0.94 (0.84–1.06) in both cohorts combined. Findings were similar when more extreme categories of mercury were compared (across deciles, with median levels in highest decile about 2.5-fold higher than the RfD); and in analyses stratified by fish or omega-3 consumption, selenium levels, body mass index, and age. These findings from two separate large prospective cohort studies do not support any clinically apparent adverse effects of methylmercury exposure on risk of hypertension in men or women, including at levels up to 2.5-fold higher than the RfD.

Keywords

Mercury; Hypertension; Prospective Studies; Selenium; Diet; Population Science; Environmental Medicine

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INTRODUCTION

Although seafood consumption is considered part of a healthy diet and is recommended by numerous organizations worldwide,[1–3] seafood are also the major source of exposure to methylmercury.[4] In adults, the main health concern has been potential cardiovascular toxicity, suggested by animal experiments and limited human studies.[5–7] We recently investigated the relationships between mercury exposure and incident coronary heart disease and stroke in two large US cohorts, finding no evidence for increased risk of these clinical events.[8]

However, methylmercury could influence other cardiovascular outcomes. In particular, experimental studies in animals[9–11] and findings from some cross-sectional observational studies[12–15] suggest a potential link between exposure to methylmercury and higher blood pressure (BP) or hypertension. However, other cross-sectional studies failed to observe a significant association.[16, 17] Additionally, these cross-sectional studies were mostly of small size and were limited by the potential for reverse causation – i.e., unable to distinguish whether methylmercury exposure is related to development of hypertension, or whether persons with pre-existing hypertension are more likely to consume fish and have higher methylmercury levels. The only reported prospective study evaluated children from the Faroe Islands: an initially observed relationship between prenatal methylmercury exposure and BP at age 7 was equivocal and not statistically significant with additional follow-up to age 14.[18, 19]

Because hypertension is a leading cause of preventable deaths in the US and worldwide,[20, 21] an effect of methylmercury exposure on hypertension would have tremendous implications both for scientific understanding of methylmercury's health effects and for creating guidelines for the general adult population to balance benefits and risks of seafood consumption versus methylmercury exposure. To elucidate the potential effects of chronic methylmercury exposure on development of hypertension, we prospectively investigated the relationship between mercury exposure and incidence of hypertension in two separate US cohorts of 6,045 men and women free of hypertension at baseline.

METHODS

Population and Design

The Health Professionals Follow-up Study (HPFS) enrolled 51,529 male US health professionals aged 40–75 years in 1986; and the Nurses' Health Study (NHS), 121,700 female US registered nurses aged 30–55 years in 1976.[8] In both cohorts, participants were followed with biennial questionnaires on medical history, risk factors, lifestyle, and disease incidence. For this analysis, we utilized prospectively collected data on toenail mercury concentrations from nested case-control studies of incident cardiovascular disease in both cohorts[8] -see Online Supplement for details. The study was approved by the human subjects committees of all author institutions. All participants provided implied consent by return of completed questionnaires and toenail samples. After excluding 3,263 participants with prevalent hypertension at baseline, a total of 6,045 individuals with measured toenail mercury concentrations were included in the present analysis of incident hypertension.

Assessment of Toenail Mercury Concentrations

Toenail concentrations of mercury and of selenium, which in some animal models mitigate toxicity of mercury,[6] were measured using neutron activation analysis by personnel unaware of the participants' clinical information.[8] See Online Supplement for details on analytic methods and validity of these measures.

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Ascertainment of Hypertension

In both cohorts, biennial questionnaires asked participants to report physician-diagnosed hypertension, including calendar year of diagnosis, and medication use. The validity of this endpoint was confirmed in validation studies in these cohorts based on review of medical records and direct BP measurements. The positive predictive value was 100%, and the negative predictive value >95% (see Online Supplement).[22, 23] Several lifestyle factors have been significantly related to incident hypertension in these cohorts, including dietary fiber, potassium, and magnesium; alcohol use; and baseline weight, weight loss, and weight gain.[23–25] Incident hypertension has also been highly predictive of subsequent clinical cardiovascular events in these cohorts.[23, 26] For this prospective analysis, we excluded participants if they reported a physician diagnosis of hypertension on any questionnaire or were taking anti-hypertensive medication before the return of toenail samples. Among the remaining participants in each cohort, incident hypertension was diagnosed as the first self-report of hypertension on any of the subsequent biennial questionnaires for which the date of diagnosis was after the return of toenail samples.

In addition to the above validated methods for diagnosing incident hypertension, participants were also asked to report their usual systolic and diastolic BP in 1986 and 1990 within one of multiple categories: e.g., systolic <105, 105–114, 115–124, 125–134, 135–144, 145–154, 155–164, 165–174, or ≥ 175 mm Hg; and diastolic <65, 65–74, 75–84, 85–89, 90–94, 95–104, or ≥105 mm Hg. Details of types and number of readings of BP measurements were not collected from the participants. To evaluate this as a continuous variable, we used the median value in each category or, in the lowest or highest categories, 5 mm Hg less or 10 mm Hg more than the cutpoint, respectively. Because these data were not separately validated, we evaluated this information in secondary analyses to assess associations between mercury exposure and BP in 1986 (approximating a cross-sectional analysis), BP in 1990, and change in BP between 1986–1990.

Covariates

Data on demographics, risk factors, and lifestyle habits were collected via validated self-administered questionnaires, using the questionnaire from each participant closest in time to their toenail sample collection. See Online Supplement for details.

Analysis

Associations of toenail mercury concentrations with incident hypertension were evaluated using Cox proportional hazards, with time at-risk from the time of toenail sampling until the diagnosis of hypertension, death, or the date of return of the last questionnaire in 2008, whichever came first. Potential confounding was assessed using multivariable models adjusted for demographics, major cardiovascular risk factors, and lifestyle and dietary habits, including fish and omega-3 fatty acid consumption. See Online Supplement for detailed statistical methods. All analyses were performed using SAS version 9.1 (SAS Institute), two-tailed alpha=0.05.

RESULTS

At baseline, mean±SD age was 60.2±9.2 years among men and 53.1±6.4 years among women (Table 1). Median concentrations of toenail mercury were 0.21 μg/g in women and 0.30 μg/g in men. The exposure distribution was more right-skewed in men than in women (95th percentile: 1.31 vs. 0.76 μg/g, respectively), consistent with greater fish consumption in men and also suggesting greater selection of larger, long-lived species including sportsfish that might be higher in mercury among the men with highest exposures. Across both cohorts combined, median toenail mercury concentrations were 0.64 μg/g in the

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highest quintile, and 0.92 μg/g in the highest decile. These levels would be equivalent to about 1.7 and 2.5 μg/g in hair,[8] respectively, or about 1.7-fold and 2.5-fold higher than the US EPA reference dose corresponding to about 1 μg/g in hair.[27]

In unadjusted (bivariate) analyses, higher mercury levels were associated with less never smoking and greater former smoking, more frequent hypercholesterolemia, and slightly lower body mass index (Table 2). As expected, higher mercury levels were also associated with greater consumption of fish and omega-3 fatty acids and with factors that would be associated with fish consumption, including greater physical activity and intakes of alcohol, fruits, and vegetables; and lower consumption of meats. Toenail mercury concentrations were not associated with other risk factors for hypertension including family history, prevalence of diabetes, or consumption of whole grains.

During 14.9±7.9 years (89,790 person-years) of follow-up, a total of 3,540 new cases of hypertension were diagnosed. The median duration of follow-up from time of toenail sampling to diagnosis of hypertension was 11.4 years (interquartile range: 5.6–16.5 years). After adjustment for age and sex, toenail mercury concentrations were not associated with a higher incidence of hypertension in men, women, or both cohorts combined (Table 3). Further adjustment for other risk factors, including clinical characteristics, lifestyle behaviors, and dietary habits, had little effect on these results. In the fully adjusted model, the hazard ratio (95% CI) for incident hypertension in the highest compared with the lowest quintile was 0.96 (0.84, 1.09) in women, 0.82 (0.62–1.08) in men, and 0.94 (0.84–1.06) in both cohorts combined. Results were not appreciably altered with further adjustment for toenail selenium concentrations or use of aspirin or lipid-lowering medications; if we adjusted for estimated long-chain omega-3 consumption rather than fish consumption; or if findings in women were additionally adjusted for hormone replacement use, age at first birth, and parity (not shown).

Findings were generally similar in analyses stratified by fish consumption, long-chain omega-3 consumption, toenail selenium levels, body mass index, or age (Table 4). Among younger participants (age<50 y), higher mercury exposure was associated with lower risk of incident hypertension (across quintiles, HR=0.77, 95% CI=0.61–0.98), although interaction by age was not statistically significant (P-interaction=0.10). Findings were also similar across a broader dose-response of deciles of toenail mercury (Table 5). In the highest decile of exposure, there was actually a lower incidence of hypertension (HR=0.82, 95% CI=0.69–0.96; P-trend=0.03). Mercury exposure was also not associated with higher risk of hypertension in sensitivity analyses correcting for measurement error in mercury measures, or excluding cases of hypertension within the first two years of follow-up or restricting to hypertension cases occurring within the first ten years of follow-up (**Supplementary Tables S1–S2**).

We evaluated self-reported BP levels in secondary analyses. In unadjusted analyses, higher mercury exposures were associated with slightly lower systolic BP assessed in 1986, the year of BP assessment closest to the toenail sampling in both cohorts (Table 2). In crude cross-sectional analyses (i.e., not using sex-specific quintiles), higher mercury exposures were not associated with systolic BP and were associated with higher diastolic BP in 1986 (not shown). After multivariable-adjustment, no significant associations were seen between mercury exposure and either diastolic or systolic BP in 1986, diastolic or systolic BP in 1990, or change in diastolic or systolic BP between 1986 and 1990 (**Supplementary Table S3**).

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DISCUSSION

Our findings in these two separate large prospective cohorts do not support clinically apparent adverse effects of chronic methylmercury exposure on development of hypertension at usual exposure levels seen in these men and women. In the top quintile, median mercury exposures were about 1.7-fold – and in the top decile, about 2.5-fold – higher than the US EPA reference dose.[27] Findings were similar in men, women, and various stratified subgroups.

These ranges of mercury exposure are comparable to those in national US surveys[28] and prior European studies.[29, 30] In the NHS, median exposure was 0.23 μg/g, or about 0.62 μg/g in hair, similar to the 75th percentile exposure among US women age 40–49 (hair mercury 0.55 μg/g; 95% CI: 0.40, 0.69).[28] In the top decile of NHS, median exposure was 0.76 μg/g, or about 2.05 μg/g in hair, similar to the top decile among white US females age 16–49 (hair mercury 1.84 μg/g; 95% CI: 0.82, 2.86).[28] Exposure was even higher in the top decile of the HPFS cohort, consistent with their higher fish consumption compared to the average population, and also suggesting a greater selection of higher mercury fish (e.g., bluefin sushi, swordfish, shark, etc.) in these individuals. Overall, the similar or higher methylmercury exposure levels in our cohorts makes the absence of evidence for higher risk of hypertension more robust.

For assessing population health effects, the primary mercury species of interest is methylmercury, derived principally from fish intake.[31] In the absence of unusual occupational exposures, toenail mercury concentration is a useful biomarker of usual methylmercury exposure.[32–34] We excluded dentists from measurements, so it is unlikely that any meaningful number of these health professionals were exposed to appreciable sources of occupational mercury. Consumption of tuna and other saltwater fish are the main dietary factors positively associated with toenail mercury.[32–34] In addition, when we speciated toenail mercury concentrations in a subset of 29 participants, total mercury and methylmercury concentrations correlated nearly perfectly: Spearman correlation (r)=0.97.[8] Toenail mercury concentrations at one time point also predict future exposure, with a correlation of 0.56 for levels assessed in clippings obtained 6 years apart,[32] similar to correlations over time for widely used epidemiologic measures such as BP or blood cholesterol.[35, 36] Toenail selenium concentrations are also valid biomarkers of selenium exposure, responding to long-term changes in diet and correlating with whole blood and serum selenium.[37, 38] Reliability of toenail selenium levels over time is also reasonable, with a correlation of 0.48 for levels in clippings obtained 6 years apart.[32]

Among prior cross-sectional studies, 4 studies,[12–15] but not 2 others,[16, 17] suggested a link between higher methylmercury exposure and higher BP or prevalent hypertension. Most of these studies were relatively small, including only a few hundred participants; and several focused on specific ethnicities such as Nunavik Inuits, Cree Indians, French Polynesians, or Brazil Amazonians, potentially limiting generalizability. Perhaps due to their small size, most of these studies also adjusted for a limited set of potential confounders. Additionally, all these studies could be limited by reverse causation, as a cross-sectional design cannot distinguish whether methylmercury exposure is related to higher BP, or whether persons with higher BP may have reasons to consume more fish and thus have higher methylmercury levels. In an initial prospective follow-up of a Faroese birth cohort at 7 years, prenatal methylmercury exposure was associated with higher childhood BP after adjustment for body weight.[18] However, this relationship was equivocal and not statistically significant after additional follow-up to age 14 years.[19]

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Overall, prior literature suggested a potential link between methylmercury exposure and hypertension, but with mixed findings across studies and multiple relevant limitations including cross-sectional design, low statistical power, and potential for residual confounding due to limited covariate adjustment. Interestingly, in unadjusted cross-sectional analyses at baseline in our cohorts, mercury levels were positively associated with diastolic BP, as well as with hypercholesterolemia, suggesting that persons with more cardiovascular risk factors may choose to consume more fish (i.e., reverse causation). However, mercury exposure was not related with higher risk of hypertension longitudinally. Adjustment for self-reported fish consumption at baseline did not materially alter these results, although such adjustment may incompletely account for residual confounding due to potential benefits of fish intake. Our findings provide the most robust evidence to-date that chronic methylmercury exposure, at least at doses commonly seen in the US and many other countries, does not increase risk of hypertension.

For some environmental toxins, such as lead or bisphenol A, harms can be assessed independent of any potential health benefits derived from the source of exposure. In comparison, the major source of methylmercury exposure is fish consumption, which provides several cardiovascular and potentially other benefits.[39] Thus, population recommendations for methylmercury exposure should simultaneously consider both potential harms and benefits of fish consumption, including of fish that contain methylmercury.[3] Guidelines regarding fish intake exist for women who may become pregnant, infants, and young children to optimize brain development during gestation and infancy, aiming to balance benefits of fish consumption versus the effects of methylmercury exposure.[3] However, no corresponding guidelines exist for the general adult population, largely due to insufficient evidence for any significant long-term effects of chronic methylmercury exposure in adults. Although we found no adverse association between toenail mercury and hypertension risk, we cannot exclude residual confounding due to benefits of fish or omega-3 consumption on BP,[40, 41] even though we adjusted for and stratified by fish consumption and estimated dietary omega-3 consumption. Such benefits, for example, could account for trends toward lower incidence of hypertension with higher mercury exposure in both cohorts. This trend was especially evident in younger adults (<50 years), in whom fewer competing risks from other causes of hypertension might make it easier to detect a clinically relevant BP-lowering effect of fish intake. Overall, our findings do not provide support that chronic methylmercury exposure from seafood consumption increases risk of hypertension.

Our analysis has potential limitations. Our findings were based on toenail measurements at baseline, and changes in methylmercury exposure over time could attenuate true relationships toward the null. Conversely, a single toenail mercury concentration provides an excellent biomarker of integrated usual methylmercury exposure over the past year, and a reasonable correlation between concentrations in nails collected six years apart indicates that a single measure also represents exposure over longer periods. Our findings were also similar in sensitivity analyses limited to shorter durations of follow-up. Our secondary analysis of participant-reported BP could be limited by imperfect measurements and reporting that would attenuate findings toward the null. On the other hand, given that these cohorts comprised educated health professionals, the reported measures are likely reasonably valid, at least within the broad categories that were assessed. Although we adjusted for a range of demographic, clinical, and lifestyle risk factors, residual confounding cannot be excluded, particularly from other benefits of fish consumption. Whereas findings were similar in two separate cohorts and there is little reason to believe that biological effects of methylmercury in these populations would be different than among women and men in general, these cohorts comprised largely white, educated US adults, potentially limiting generalizability.

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References

1. U.S. Department of Agriculture, U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2010. 7. Washington, DC: U.S. Government Printing Office; 2010.
2. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation. 2010; 121:586–613. [PubMed: 20089546]
3. Food and Agriculture Organization of the United Nations, World Health Organization. Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption. Rome, Italy; Geneva, Switzerland: Food and Agriculture Organization of the United Nations, World Health Organization; 2011.
4. Groth E 3rd. Ranking the contributions of commercial fish and shellfish varieties to mercury exposure in the United States: implications for risk communication. Environ Res. 2010; 110:226–236. [PubMed: 20116785]
5. Rice DC. The US EPA reference dose for methylmercury: sources of uncertainty. Environ Res. 2004; 95:406–413. [PubMed: 15220074]
6. Mozaffarian D. Fish, mercury, selenium and cardiovascular risk: current evidence and unanswered questions. Int J Environ Res Public Health. 2009; 6:1894–1916. [PubMed: 19578467]
7. Yaginuma-Sakurai K, Murata K, Shimada M, Nakai K, Kurokawa N, Kameo S, Satoh H. Intervention study on cardiac autonomic nervous effects of methylmercury from seafood. Neurotoxicol Teratol. 2010; 32:240–245. [PubMed: 19732823]
8. Mozaffarian D, Shi P, Morris JS, Spiegelman D, Grandjean P, Siscovick DS, Willett WC, Rimm EB. Mercury exposure and risk of cardiovascular disease in two U.S. cohorts. N Engl J Med. 2011; 364:1116–1125. [PubMed: 21428767]
9. Wakita Y. Hypertension induced by methyl mercury in rats. Toxicol Appl Pharmacol. 1987; 89:144–147. [PubMed: 3590186]
10. da Cunha V, Souza HP, Rossoni LV, Franca AS, Vassallo DV. Effects of mercury on the isolated perfused rat tail vascular bed are endothelium-dependent. Arch Environ Contam Toxicol. 2000; 39:124–130. [PubMed: 10790511]
11. Grotto D, de Castro MM, Barcelos GR, Garcia SC, Barbosa F Jr. Low level and sub-chronic exposure to methylmercury induces hypertension in rats: nitric oxide depletion and oxidative damage as possible mechanisms. Arch Toxicol. 2009; 83:653–662. [PubMed: 19468715]
12. Vupputuri S, Longnecker MP, Daniels JL, Guo X, Sandler DP. Blood mercury level and blood pressure among US women: results from the National Health and Nutrition Examination Survey 1999–2000. Environ Res. 2005; 97:195–200. [PubMed: 15533335]
13. Fillion M, Mergler D, Sousa Passos CJ, Larribe F, Lemire M, Guimaraes JR. A preliminary study of mercury exposure and blood pressure in the Brazilian Amazon. Environmental health: a global access science source. 2006; 5:29. [PubMed: 17032453]
14. Valera B, Dewailly E, Poirier P. Cardiac autonomic activity and blood pressure among Nunavik Inuit adults exposed to environmental mercury: a cross-sectional study. Environmental health: a global access science source. 2008; 7:29. [PubMed: 18538022]
15. Valera B, Dewailly E, Poirier P. Environmental mercury exposure and blood pressure among Nunavik Inuit adults. Hypertension. 2009; 54:981–986. [PubMed: 19805642]
16. Valera B, Dewailly E, Poirier P. Impact of mercury exposure on blood pressure and cardiac autonomic activity among Cree adults (James Bay, Quebec, Canada). Environ Res. 2011; 111:1265–1270. [PubMed: 21962568]

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17. Valera B, Dewailly E, Poirier P, Counil E, Suhas E. Influence of mercury exposure on blood pressure, resting heart rate and heart rate variability in French Polynesians: a cross-sectional study. Environmental Health. 2011; 10:99. [PubMed: 22078280]

18. Sorensen N, Murata K, Budtz-Jorgensen E, Weihe P, Grandjean P. Prenatal methylmercury exposure as a cardiovascular risk factor at seven years of age. Epidemiology. 1999; 10:370–375. [PubMed: 10401870]

19. Grandjean P, Murata K, Budtz-Jorgensen E, Weihe P. Cardiac autonomic activity in methylmercury neurotoxicity: 14-year follow-up of a Faroese birth cohort. The Journal of Pediatrics. 2004; 144:169–176. [PubMed: 14760255]

20. Danaei G, Ding EL, Mozaffarian D, Taylor B, Rehm J, Murray CJ, Ezzati M. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. PLoS Med. 2009; 6:e1000058. [PubMed: 19399161]

21. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ. Selected major risk factors and global and regional burden of disease. Lancet. 2002; 360:1347–1360. [PubMed: 12423980]

22. Colditz GA, Martin P, Stampfer MJ, Willett WC, Sampson L, Rosner B, Hennekens CH, Speizer FE. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. Am J Epidemiol. 1986; 123:894–900. [PubMed: 3962971]

23. Ascherio A, Rimm EB, Giovannucci EL, Colditz GA, Rosner B, Willett WC, Sacks F, Stampfer MJ. A prospective study of nutritional factors and hypertension among US men. Circulation. 1992; 86:1475–1484. [PubMed: 1330360]

24. Witteman JC, Willett WC, Stampfer MJ, Colditz GA, Sacks FM, Speizer FE, Rosner B, Hennekens CH. A prospective study of nutritional factors and hypertension among US women. Circulation. 1989; 80:1320–1327. [PubMed: 2805268]

25. Huang Z, Willett WC, Manson JE, Rosner B, Stampfer MJ, Speizer FE, Colditz GA. Body weight, weight change, and risk for hypertension in women. Ann Intern Med. 1998; 128:81–88. [PubMed: 9441586]

26. Fiebach NH, Hebert PR, Stampfer MJ, Colditz GA, Willett WC, Rosner B, Speizer FE, Hennekens CH. A prospective study of high blood pressure and cardiovascular disease in women. Am J Epidemiol. 1989; 130:646–654. [PubMed: 2773913]

27. U.S. Environmental Protection Agency. [Accessed December 14, 2011.] Integrated Risk Information System. Methylmercury (MeHg) (CASRN 22967-92-6): Reference Dose for Chronic Oral Exposure (RfD). 2001. http://www.epa.gov/iris/subst/0073.htm

28. McDowell MA, Dillon CF, Osterloh J, Bolger PM, Pellizzari E, Fernando R, Montes de Oca R, Schober SE, Sinks T, Jones RL, Mahaffey KR. Hair mercury levels in U.S. children and women of childbearing age: reference range data from NHANES 1999–2000. Environ Health Perspect. 2004; 112:1165–1171. [PubMed: 15289161]

29. Guallar E, Sanz-Gallardo MI, van't Veer P, Bode P, Aro A, Gomez-Aracena J, Kark JD, Riemersma RA, Martin-Moreno JM, Kok FJ. Mercury, fish oils, and the risk of myocardial infarction. N Engl J Med. 2002; 347:1747–1754. [PubMed: 12456850]

30. Virtanen JK, Voutilainen S, Rissanen TH, Mursu J, Tuomainen TP, Korhonen MJ, Valkonen VP, Seppanen K, Laukkanen JA, Salonen JT. Mercury, fish oils, and risk of acute coronary events and cardiovascular disease, coronary heart disease, and all-cause mortality in men in eastern Finland. Arterioscler Thromb Vasc Biol. 2005; 25:228–233. [PubMed: 15539625]

31. U.S. Environmental Protection Agency. Mercury Study Report to Congress 1997. 2006.

32. Garland M, Morris JS, Rosner BA, Stampfer MJ, Spate VL, Baskett CJ, Willett WC, Hunter DJ. Toenail trace element levels as biomarkers: reproducibility over a 6-year period. Cancer Epidemiol Biomarkers Prev. 1993; 2:493–497. [PubMed: 8220096]

33. MacIntosh DL, Williams PL, Hunter DJ, Sampson LA, Morris SC, Willett WC, Rimm EB. Evaluation of a food frequency questionnaire-food composition approach for estimating dietary intake of inorganic arsenic and methylmercury. Cancer Epidemiol Biomarkers Prev. 1997; 6:1043–1050. [PubMed: 9419401]

34. Joshi A, Douglass CW, Kim HD, Joshipura KJ, Park MC, Rimm EB, Carino MJ, Garcia RI, Morris JS, Willett WC. The relationship between amalgam restorations and mercury levels in male

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dentists and nondental health professionals. J Public Health Dent. 2003; 63:52–60. [PubMed: 12597586]

35. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002; 360:1903–1913. [PubMed: 12493255]
36. Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet. 2007; 370:1829–1839. [PubMed: 18061058]
37. Longnecker MP, Stampfer MJ, Morris JS, Spate V, Baskett C, Mason M, Willett WC. A 1-y trial of the effect of high-selenium bread on selenium concentrations in blood and toenails. Am J Clin Nutr. 1993; 57:408–413. [PubMed: 8438776]
38. Longnecker MP, Stram DO, Taylor PR, Levander OA, Howe M, Veillon C, McAdam PA, Patterson KY, Holden JM, Morris JS, Swanson CA, Willett WC. Use of selenium concentration in whole blood, serum, toenails, or urine as a surrogate measure of selenium intake. Epidemiology. 1996; 7:384–390. [PubMed: 8793364]
39. Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol. 2011; 58:2047–2067. [PubMed: 22051327]
40. Geleijnse JM, Giltay EJ, Grobbee DE, Donders AR, Kok FJ. Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. J Hypertens. 2002; 20:1493–1499. [PubMed: 12172309]
41. Xun P, Hou N, Daviglus M, Liu K, Morris JS, Shikany JM, Sidney S, Jacobs DR, He K. Fish oil, selenium and mercury in relation to incidence of hypertension: a 20-year follow-up study. J Intern Med. 2011; 270:175–186. [PubMed: 21205024]

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PERSPECTIVES

In summary, in two large prospective US cohorts of men and women, we found no evidence for a relationship between mercury exposure and increased risk of hypertension. Our findings do not substantiate prior concerns, which were largely based on some cross-sectional studies, that chronic methylmercury exposure from seafood consumption commonly occurring in the US increases risk of hypertension in adults. These results do not support a need to broaden existing focused guidelines, which recommend that women of childbearing age and young children avoid specific higher-mercury fish species, to the general population based on concern for effects on hypertension.

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Novelty and Significance: 1) What Is New, 2) What Is Relevant?

What Is New?

- Although some animal experiments suggest that mercury exposure could increase risk of hypertension, few well designed studies have tested this in humans.
- We evaluated this question in two separate large studies, including more than 6,000 US men and women without hypertension at baseline.
- We measured mercury exposure using specialized testing of toenail clippings, which provides an excellent measure of long-term exposure; and followed participants for long-term development of hypertension.

What Is Relevant?

- This is by far the largest study to look at how mercury, which comes from eating certain fish, relates to long-term development of hypertension. This has major public health implications, for example related to guidelines for eating fish or avoiding mercury in the general populations.
- We included both men and women having a wide range of mercury exposure, increasing relevance and applicability of the findings.

Summary

- During an average follow-up of 15 years, 3,540 participants developed hypertension.
- Adjusting for other risk factors, higher mercury exposure had no association with risk of developing hypertension.
- These findings from two separate large studies do not support any clinically noticeable harmful effects of mercury exposure on risk of hypertension in men or women.

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Table 1

Baseline Characteristics of 6,045 US Men and Women in Two Separate Prospective Cohorts.

Characteristic	Men (n=1,624)	Women (n=4,421)
Age, years	60.2±9.2	53.1±6.4
Smoking, %		
Never	44	37
Past	44	25
Current	12	38
Family history of myocardial infarction, %	35	21
Family history of hypertension, %	22	39
CVD case-control status, % future case	43	44
Diabetes mellitus, %	3	1
Hypercholesterolemia, %	10	4
Lipid-lowering medication use, %	1	3
Aspirin use*, %	31	26
Body mass index, kg/m^2	25.5±2.9	24.1±4.4
Physical activity, METS/week	19.0±26.0	13.7±19.2
Alcohol, drinks/day	0.8±1.1	0.5±0.9
Toenail selenium, μg/g	0.92±0.63	0.79±0.20
Toenail mercury, median (5th, 95th percentile), μg/g	0.30 (0.07, 1.31)	0.21 (0.07, 0.76)
Fish, servings/week	2.0±1.8	1.8±1.6
Processed meat, servings/day	0.4±0.6	0.3±0.4
Unprocessed red meat, servings/day	0.7±0.5	0.7±0.5
Vegetable, servings/day	3.2±2.4	3.2±1.8
Fruit, servings/day	1.6±1.3	2.1±1.4
Whole grains, g/day	20.8±19.5	15.9±14.7
EPA and DHA, mg/day	257±222	180±158
Total energy, kcal/day	2057±638	1738±543
Saturated fat, % energy	11.5±2.8	12.7±3.0
Monounsaturated fat, % energy	12.6±2.7	12.9±2.9
Polyunsaturated fat, % energy	5.8±1.5	6.4±1.8
Trans fat, % energy	1.3±0.5	1.9±0.6
Protein, % energy	18.3±3.3	17.8±3.4

Values are mean±SD (continuous characteristics) or percent (categorical characteristics) except for toenail mercury which is reported as median (5th, 95th percentile).

*Due to questionnaire differences, defined as 2+ times/week in men and 4+ times/week in women.

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Table 2

Baseline Characteristics According to Quintiles of Mercury Exposure Among 6,045 US Men and Women in Two Separate Prospective Cohorts.

Characteristic	Quintiles of Toenail Mercury Concentration*					
	Q1	Q2	Q3	Q4	Q5	P for Trend
Mercury, median, μg/g	0.09	0.16	0.23	0.33	0.64	
Mercury, geometric mean, μg/g	0.08	0.16	0.23	0.34	0.72	
Age, years	55.4±7.9	54.7±8.0	55.0±8.1	55.0±7.9	54.9±7.5	0.62
Smoking,%						
Never	43	40	38	36	34	<0.001
Past	26	28	31	33	35	<0.001
Current	31	32	31	31	31	0.95
Family history of myocardial infarction, %	23	24	26	25	26	0.25
Family history of hypertension, %	36	34	34	33	36	0.73
Diabetes mellitus, %	1	1	1	2	1	0.35
Hypercholesterolemia, %	4	4	5	6	8	<0.001
Lipid-lowering medication use, %	1	2	3	3	2	0.03
Aspirin use, %	27	28	28	28	26	0.32
Body mass index, kg/m^2	24.7±4.2	24.6±4.2	24.2±4.0	24.4±4.1	24.2±3.8	0.001
Physical activity, METS/week	13.5±19.4	13.5±19.0	14.9±20.0	15.5±23.1	19.0±25.1	<0.001
Alcohol, drinks/day	0.4±0.8	0.5±0.8	0.6±1.0	0.7±1.0	0.8±1.1	<0.001
Toenail selenium, μg/g	0.83±0.43	0.81±0.24	0.82±0.38	0.83±0.44	0.82±0.33	0.82
Fish consumption, servings/week	1.1±1.0	1.5±1.2	1.8±1.5	2.1±1.7	2.6±2.2	<0.001
EPA & DHA, mg/day	126±115	163±126	204±176	232±197	280±224	<0.001
Processed meat, servings/day	0.4±0.6	0.4±0.4	0.4±0.5	0.3±0.3	0.3±0.3	<0.001
Unprocessed red meat, servings/day	0.8±0.5	0.7±0.5	0.7±0.6	0.6±0.4	0.5±0.4	<0.001
Vegetable, servings/day	3.0±1.7	3.1±2.0	3.1±1.8	3.3±2.5	3.5±2.1	<0.001
Fruit, servings/day	1.9±1.4	1.9±1.4	2.0±1.4	2.0±1.4	2.1±1.5	0.001
Whole grains, g/day	17.7±15.6	17.5±16.8	17.0±17.1	17.6±15.4	16.9±16.9	0.30
Diastolic BP in 1986, mm Hg†	78.5±7	78.2±7	78.5±7	78.5±7	78.6±7	0.50
Systolic BP in 1986, mm Hg†	127.2±11	126.5±11	126.8±11	126.7±11	125.8±11	0.01
Diastolic BP in 1990, mm Hg	78.3±8	77.7±8	77.9±9	77.9±9	77.9±8	0.58

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Characteristic	Quintiles of Toenail Mercury Concentration*					
	Q1	Q2	Q3	Q4	Q5	P for Trend
Systolic BP in 1990, mm Hg	128.1±14	126.7±13	126.7±14	126.6±13	126.4±13	0.05

Values are mean±SD (continuous characteristics) or percent (categorical characteristics), except for toenail mercury which is median and geometric mean.

*Based on sex-specific quintile cutpoints.

†The year of BP assessment closest to the baseline toenail sampling in both cohorts (1982–83 in women; 1987 in men). In crude (i.e., not using sex-specific quintiles), higher mercury exposures were not associated with systolic BP in 1986 and were associated with higher diastolic BP in 1986 (not shown).

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Table 3

Multivariable-Adjusted Relative Risk of Incident Hypertension According to Mercury Exposure Among 6,045 US Men and Women in Two Separate Prospective Cohorts.

Cohort	Quintiles of Toenail Mercury Concentration*					
	Q1	Q2	Q3	Q4	Q5	P for Trend
Men (HPFS)						
Mercury Median, μg/g	0.10	0.18	0.30	0.46	0.92	
Geometric Mean, μg/g	0.08	0.18	0.30	0.46	1.00	
No. Events	144	152	155	149	138	
Hazard Ratio (95% CI)						
Age and Sex-Adjusted	1.00 (reference)	1.07 (0.85–1.34)	1.05 (0.84–1.32)	1.04 (0.82–1.30)	0.88 (0.70–1.11)	0.12
Multivariable†	1.00 (reference)	1.06 (0.84–1.34)	1.07 (0.84–1.36)	1.01 (0.79–1.30)	0.86 (0.66–1.12)	0.10
Multivariable+Diet‡	1.00 (reference)	1.02 (0.81–1.30)	1.03 (0.81–1.32)	0.97 (0.75–1.25)	0.82 (0.62–1.08)	0.06
Women (NHS)						
Mercury Median, μg/g	0.09	0.15	0.21	0.31	0.55	
Geometric Mean, μg/g	0.08	0.15	0.21	0.31	0.64	
No. Events	578	558	561	553	552	
Hazard Ratio (95% CI)						
Age and Sex-Adjusted	1.00 (reference)	0.95 (0.84–1.07)	0.96 (0.85–1.08)	0.93 (0.83–1.05)	0.89 (0.79–1.00)	0.06
Multivariable†	1.00 (reference)	0.99 (0.88–1.12)	1.02 (0.90–1.15)	1.00 (0.88–1.13)	0.94 (0.83–1.07)	0.29
Multivariable+Diet‡	1.00 (reference)	0.99 (0.88–1.12)	1.01 (0.90–1.14)	1.00 (0.89–1.14)	0.96 (0.84–1.09)	0.46
Men and Women Combined						
Mercury Median, μg/g	0.09	0.16	0.23	0.34	0.64	
Geometric Mean, μg/g	0.08	0.16	0.23	0.34	0.74	
No. Events	726	737	718	702	657	
Hazard Ratio (95% CI)						
Age and Sex-Adjusted	1.00 (reference)	1.02 (0.92–1.13)	0.97 (0.88–1.08)	0.96 (0.87–1.07)	0.91 (0.82–1.01)	0.03
Multivariable†	1.00 (reference)	1.04 (0.94–1.16)	0.99 (0.89–1.11)	0.99 (0.89–1.11)	0.94 (0.84–1.05)	0.12
Multivariable+Diet‡	1.00 (reference)	1.04 (0.93–1.15)	0.99 (0.89–1.11)	1.00 (0.90–1.12)	0.94 (0.84–1.06)	0.18

*Cohort-specific analyses are based on sex-specific quintile cutpoints. Combined analyses are based on pooling of individual-level data and using overall quintile cutpoints among men and women combined, with adjustment for sex. Use of sex-specific cutpoints in pooled analyses produced very similar results.

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[†]Adjusted for age (years), sex, race (white, nonwhite), month of toenail return, family history of hypertension (yes, no), smoking status (never, former, current), body mass index (quintiles), diabetes (yes, no), hypercholesterolemia (yes, no), future cardiovascular disease status (case, control), physical activity (quintiles), alcohol use (quintiles), and fish consumption (quintiles).

[≠]Further adjusted for consumption of whole grains, unprocessed meats, processed meats, fruits, and vegetables (each in quintiles).

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Table 4

Multivariable-Adjusted Relative Risk of Incident Hypertension According to Mercury Exposure in Subgroups of 6,045 US Men and Women in Two Separate Prospective Cohorts.*

Subgroups	N	Cases of Incident Hypertension	Quintiles of Toenail Mercury Concentration					
			Q1	Q2	Q3	Q4	Q5	P for Interaction†
Stratified by Fish Consumption‡								
<1 servings/week	2,739	1,608	1.00 (reference)	1.01 (0.88–1.16)	0.97 (0.84–1.12)	0.91 (0.78–1.07)	0.89 (0.74–1.06)	0.34
1 to <2 servings/week	1,770	1,034	1.00 (reference)	1.06 (0.86–1.32)	1.14 (0.93–1.41)	1.04 (0.84–1.29)	1.03 (0.82–1.30)	
2+ servings/week	1,536	898	1.00 (reference)	1.24 (0.92–1.66)	1.00 (0.75–1.34)	1.19 (0.90–1.57)	1.03 (0.78–1.37)	
Stratified by Omega-3 Consumption								
Tertile-1 (<105 mg/day)	2,088	1,237	1.00 (reference)	1.06 (0.90–1.23)	1.00 (0.85–1.18)	0.98 (0.82–1.17)	0.93 (0.75–1.15)	0.09
Tertile-3 (105–239 mg/day)	1,924	1,160	1.00 (reference)	0.97 (0.80–1.17)	0.96 (0.80–1.16)	0.89 (0.73–1.09)	0.87 (0.70–1.07)	
Tertile-3 (240+ mg/day)	2,033	1,143	1.00 (reference)	1.16 (0.91–1.49)	1.07 (0.84–1.37)	1.26 (0.99–1.59)	1.09 (0.86–1.38)	
Stratified by Toenail Selenium Levels								
Tertile-1 (<0.72 μg/g)	2,015	1,245	1.00 (reference)	0.87 (0.73–1.04)	0.93 (0.78–1.12)	0.97 (0.80–1.17)	0.87 (0.71–1.06)	0.69
Tertile-3 (0.73–0.82 μg/g)	2,015	1,191	1.00 (reference)	1.14 (0.94–1.37)	1.07 (0.89–1.29)	0.94 (0.77–1.14)	1.02 (0.83–1.25)	
Tertile-3 (0.83+ μg/g)	2,015	1,104	1.00 (reference)	1.14 (0.94–1.37)	0.97 (0.79–1.18)	1.12 (0.92–1.36)	0.94 (0.77–1.16)	
Stratified by Body Mass Index								
<25 kg/m^2	3,653	2,054	1.00 (reference)	1.02 (0.88–1.17)	0.91 (0.79–1.04)	0.96 (0.83–1.11)	0.92 (0.79–1.08)	0.37
≥25 kg/m^2	2,392	1,486	1.00 (reference)	1.06 (0.90–1.24)	1.14 (0.96–1.34)	1.02 (0.86–1.21)	0.95 (0.80–1.14)	
Stratified by Age								
<50 years	1,575	949	1.00 (reference)	1.03 (0.84–1.25)	0.85 (0.69–1.05)	0.92 (0.74–1.15)	0.77 (0.61–0.98)	0.10
50 to 59 years	2,989	1,809	1.00 (reference)	1.03 (0.89–1.19)	1.05 (0.90–1.22)	1.05 (0.90–1.22)	1.00 (0.85–1.18)	
60+ years	1,481	782	1.00 (reference)	0.99 (0.77–1.26)	0.98 (0.77–1.24)	0.91 (0.72–1.16)	0.98 (0.76–1.25)	

*Values are hazard ratios (95% CI), adjusted for age (years), sex, race (white, nonwhite), month of toenail return, family history of hypertension (yes, no), smoking status (never, former, current), body mass index (quintiles), diabetes (yes, no), hypercholesterolemia (yes, no), future cardiovascular disease status (case, control), physical activity (quintiles), and consumption of alcohol, fish, whole grains, unprocessed meats, processed meats, fruits, and vegetables (each in quintiles).

†Based on the likelihood ratio test comparing nested models with or without a multiplicative interaction term for the subgroup categories multiplied by the quintile medians of toenail mercury. Evaluation of continuous interaction terms gave similar results.

‡For all analyses, quintile cut points for mercury are based on the overall population. Thus, in every stratum of fish intake, higher quintiles reflect individuals who have similarly high mercury exposure. In the setting of low fish intake (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).

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Table 5

Multivariable-Adjusted Risk of Incident Hypertension According to Deciles of Mercury Exposure Among 6,045 US Men and Women in Two Separate Prospective Cohorts.

	Deciles of Toenail Mercury Concentration										
	D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**P for Trend**
Median, μg/g	0.07	0.11	0.14	0.17	0.21	0.25	0.31	0.38	0.52	0.92	
Geometric Mean, μg/g	0.06	0.11	0.14	0.17	0.21	0.25	0.31	0.38	0.52	1.06	
No. Events	372	354	382	355	354	364	343	359	349	308	
Age and Sex-Adjusted HR (95% CI)	1.00 (reference)	0.87 (0.75–1.01)	1.03 (0.90–1.19)	0.87 (0.76–1.01)	0.89 (0.77–1.03)	0.92 (0.79–1.06)	0.86 (0.74–1.00)	0.94 (0.81–1.08)	0.91 (0.78–1.05)	0.79 (0.67–0.92)	0.01
Multivariable-Adjusted HR (95% CI) *	1.00 (reference)	0.89 (0.77–1.03)	1.08 (0.93–1.25)	0.90 (0.78–1.04)	0.94 (0.81–1.09)	0.94 (0.81–1.09)	0.91 (0.78–1.06)	0.96 (0.82–1.12)	0.95 (0.82–1.11)	0.81 (0.69–0.96)	0.02
Multivariable+Diet-Adjusted HR (95% CI) †	1.00 (reference)	0.89 (0.77–1.03)	1.08 (0.93–1.25)	0.89 (0.77–1.03)	0.93 (0.80–1.08)	0.94 (0.81–1.09)	0.92 (0.79–1.07)	0.96 (0.83–1.12)	0.96 (0.82–1.12)	0.82 (0.69–0.96)	0.03

* Adjusted for age (years), sex, race (white, nonwhite), month of toenail return, family history of hypertension (yes, no), smoking status (never, former, current), body mass index (quintiles), diabetes (yes, no), hypercholesterolemia (yes, no), future cardiovascular disease status (case, control), physical activity (quintiles), alcohol use (quintiles), and fish consumption (quintiles).

† Further adjusted for consumption of whole grains, unprocessed meats, processed meats, fruits, and vegetables (each in quintiles).

Hypertension. Author manuscript; available in PMC 2013 September 01.