

FISH CONSUMPTION, METHYLMERCURY, AND HUMAN HEART DISEASE

F.W. Lipfert¹ and T. M. Sullivan²

1. consultant, Northport, NY

2. Brookhaven National Laboratory, Upton, NY

ABSTRACT

Environmental mercury continues to be of concern to public health advocates, both in the U.S. and abroad, and new research continues to be published. A recent analysis of potential health benefits of reduced mercury emissions has opened a new area of public health concern: adverse effects on the cardiovascular system, which could account for the bulk of the potential economic benefits¹. The authors were careful to include caveats about the uncertainties of such impacts, but they cited only a fraction of the applicable health effects literature. That literature includes studies of the potentially harmful ingredient (methylmercury, MeHg) in fish, as well as of a beneficial ingredient, omega-3 fatty acids or “fish oils.” The U.S. Food and Drug Administration (FDA) recently certified that some of these fat compounds that are primarily found in fish “may be beneficial in reducing coronary heart disease.”

This paper briefly summarizes and categorizes the extensive literature on both adverse and beneficial links between fish consumption and cardiovascular health, which are typically based on studies of selected groups of individuals (cohorts). Such studies tend to comprise the “gold standard” of epidemiology, but cohorts tend to exhibit a great deal of variability, in part because of the limited numbers of individuals involved and in part because of interactions with other dietary and lifestyle considerations. Note that eating fish will involve exposure to both the beneficial effects of fatty acids and the potentially harmful effects of contaminants like Hg or PCBs, all of which depend on the type of fish but tend to be correlated within a population. As a group, the cohort studies show that eating fish tends to reduce mortality, especially due to heart disease, for consumption rates up to about twice weekly, above which the benefits tend to level off. A Finnish cohort study² showed increased mortality risks in the highest fish-consuming group (~3 times/wk), which had mercury exposures (mean hair content of 3.9 ppm) much higher than those seen in the United States.

As an adjunct to this cursory review, we also present some new “ecological” analyses based on international statistics on hair Hg, fish consumption, other dietary and lifestyle factors, and selected cardiovascular health endpoints. We searched for consistent differences between primarily fish-consuming nations, like Japan or the Seychelles, and others who traditionally eat much less fish, such as in central Europe, for example. We use data on cigarette sales, smoking prevalence surveys, and national lung cancer mortality rates to control for the effects of smoking on heart disease. These ecological analyses do not find significant adverse associations of either fish consumption or hair Hg with cardiovascular health; instead, there is a consistent trend towards beneficial effects, some of which are

statistically significant. However, such ecological studies cannot distinguish differences due to variations in individual rates of fish consumption.

We conclude that the extant epidemiological evidence does not support the existence of significant heart disease risks associated with mercury in fish, for the United States. The most prudent advice would continue to be that of maintaining a well-balanced diet, including fish or shellfish at least once per week. There may be additional benefits from fatty fish.

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The extant literature is rife with contradiction about effects on the human cardiovascular system due to eating fish or to its methylmercury (MeHg) and fatty acid content. Beneficial effects have been claimed for eating fish, especially in terms of certain fatty acids (“fish oils”), but adverse effects have been claimed for MeHg exposure. Since virtually all fish species contain MeHg at some level, this conflict is difficult to resolve. However, almost all of this evidence is based on limited samples, i.e., cohorts, which inherently differ in ways that may be difficult to fully capture in mathematical models. Persons who eat a lot of fish must necessarily eat less of some other foods that may or may not be beneficial to cardiovascular health; thus a complete dietary assessment may be required for an adequate understanding of the risks and benefits of eating fish.

This paper briefly summarizes and synthesizes some of the relevant literature on this topic and then presents a “macro” or “ecological” analysis, based on international statistics gleaned from existing sources. By using entire countries as the units of observation, a large range is obtained for the dietary variables of interest, and the inherent variability seen in the selected cohorts is avoided, albeit at the expense of data on individuals.

LITERATURE REVIEW

The literature on the health effects of fish consumption is voluminous and may have begun with observations of rates in populations that subsist on fish and marine mammals of cardiac mortality that were lower than expected³. We searched MEDLINE for articles that mentioned “methylmercury” or “fish” or “cardiovascular” in various combinations, which produced about 500 hits, even when limited to human effects and to mentions in titles or abstracts. These were winnowed down to about 160, including 92 summary or review papers; there were many fewer papers providing useful epidemiological data. This seems to be a very high ratio of reviews to original contributions.

The specific purpose of this literature search was to find studies of cardiovascular (CV) health in relation to diet, fish consumption, and fish-oil dietary supplements that might help elucidate the role of MeHg on CV health. A corollary to this objective is the realization that *all* studies involving long-term consumption of fish in the general population implicitly include the effects of MeHg, if any. This follows from the facts that all fish and shellfish contain MeHg, and in the long-term, the per-meal MeHg intake of people who eat a variety

of fish will converge on some average value^{4,5}. Thus, in the long term, eating more fish implies increased intake of MeHg, as well of certain fatty acids, especially eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids, which are part of the group of compounds referred to as omega-3 (ω -3) fatty acids. Extracts of EPA and DHA are often known as “fish oil” and are commercially available as dietary supplements.

Synopses of Selected Review Papers

Six review papers specifically involve considerations of MeHg. A statement by the American Heart Association (AHA)⁶ discussed mechanisms for the benefits of fatty acids and possible adverse effects of MeHg and PCBs. Whereas the 2000 statement of the AHA recommended eating two fish meals per week, the 2002 statement⁶ quoted the U.S. Food and Drug Administration (FDA) as qualifying that recommendation in terms of the MeHg contents involved: 1 meal/wk with $<\sim 1$ ppm MeHg and 2 meals with $<\sim 0.5$ ppm MeHg (for persons other than pregnant women). It also noted conflicting results among several studies of MeHg effects on CHD risks. AHA recommends an intake of 1 g/d of EPA+DHA for persons with CHD; depending on the type of fish, this may require more than 2 meals/wk.

Stern⁷ considers both adult and childhood studies^{8,9} and notes that the childhood effects do not appear to persist into later years. He notes the difficulty of relating Hg exposures based on the content of toenail clippings^{10,11} to the more conventional Hg measures in hair or blood. Stern concludes that the studies of a small cohort of Finnish men^{2,12} are the most suitable for risk assessment, but he does not discuss the threshold effect seen in those studies. These studies are discussed in more detail below.

Mahaffey¹³ notes the interplay between fatty acids and MeHg and provides data on typical contents by species of fish or shellfish. She also notes the need to consider other contaminants in fish, such as PCBs. Figure 1 is a cross-plot of her data, indicating which species might be considered “good” (salmon, herring, mackerel) and “bad” (shark, swordfish), thus conforming to the conventional wisdom. However, the vast majority of seafood species fall into the bottom left corner of the plot, for which these simple characterizations do not apply. Note that data for most freshwater sport fish are not included, but these species are believed to be relatively low in fatty acids.

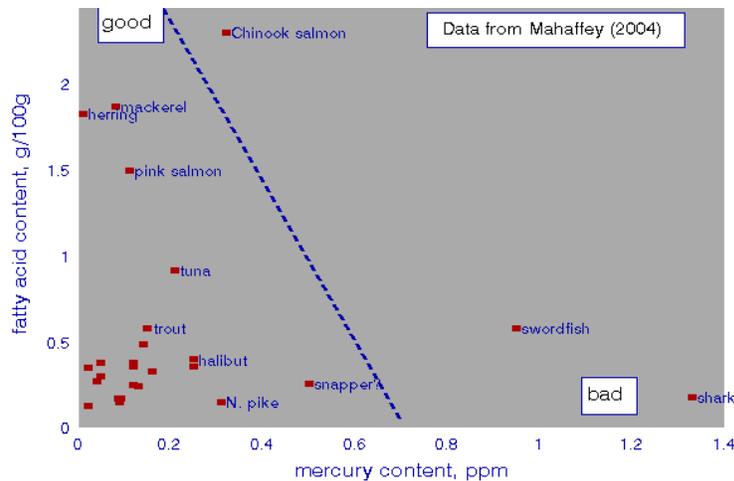


Figure 1. Cross-plot of fatty acid and mercury content of selected marine species. Data from Mahaffey (2004)¹³.

Wilson¹⁴ noted that the current EPA reference dose (RfD) for MeHg implies “a large margin of safety for adults” and also that fish (including farmed salmon) are a major source of dietary PCBs, which have been identified as probably carcinogenic. She mentioned possible PCB effects on heart disease, but mercury was not discussed in this context.

Chan and Egeland¹⁵ discuss the status of knowledge of cardiac effects of Hg and conclude that “further evaluation” is needed. They cite some of the conflicting evidence and noted that “it would be premature to issue additional fish consumption advisories” on this basis.

Gochfield and Burger¹⁶ also review the epidemiological literature and present a “compound dose-response curve”, intended to reveal levels of fish consumption above the benefit threshold and below the harm threshold. They conclude that 15 g/d (~ 3 meals/mo) seems to be a common threshold for benefits and about twice that level may be a “worst-case” threshold for harm. They note uncertainties as to the types of fish consumed and possible roles of PCBs, but they do not discuss the role of “factors of safety” on this potentially useful concept. For example, it is widely recognized that EPA used a safety factor of 10 in developing the current RfD, ostensibly because of uncertainties about Hg effects on the developing fetus. Obviously, imposition of a safety factor as low as 2 on either benefit or harm to CV health could substantially affect the optimal rate of fish consumption; probabilistic considerations of uncertainties should be included in this concept.

Syntheses of Selected Cohort Studies

Based on the premise that increased consumption of fish implies increased exposure to MeHg, cohort studies that showed at least some benefits from fish consumption were selected for detailed comparison. In addition, meta-analyses^{17,18} were considered. Studies that fail to show such benefits are also discussed briefly.

Kromhout et al.¹⁹ enrolled 852 middle-aged Dutchmen who were initially free of CHD and followed them for 20 years (1960-80). The cohort was divided into quintiles according to rates of daily fish consumption. Relative risks of CHD mortality were adjusted for age, blood pressure, cholesterol, smoking, body mass, exercise, diet, and occupation. The authors concluded that eating as few as one or two fish meals per week may help prevent CHD.

Ascherio et al.²⁰ considered about 45,000 U.S. male health professionals who were enrolled in 1986 and followed for 6 years. Relative risks were computed for quintiles of omega-3 fatty acid intake and for groups by rate of fish consumption. The analyses adjusted for age, body mass, smoking, alcohol, hypertension, diabetes, cholesterol, and family history. The results for various CHD outcomes were mixed: significant benefits for heart attacks but not for all CHD outcomes.

Salonen et al.¹² and Virtanen et al.² present the results of the Kuopio Ischemic Heart Disease Risk Factor Study, in which 1871 randomly men from eastern Finland were followed for an average of about 14 years. Mercury exposures were based on hair samples from 1992-3,

with a mean of 1.9 and a maximum of 16 ppm. Fish consumption was based on self-recorded data over 4 days, with a mean of 47 g/d and a maximum of 619 g/d. The cohort was divided into tertiles by hair Hg; the mean of the highest group was estimated to be 3.9 ppm. The analysis of coronary endpoints was based on comparisons of these three subgroups. For both coronary heart disease (CHD) and cardiovascular (CVD=CHD+stroke) deaths, the middle exposure group had lower risks and the higher exposure group had higher risks, with respect to the low exposure group. The low risks were nearly statistically significant, but the elevated risks were not. The authors then combined the low and middle exposure groups, and showed that the risks of the high exposure group were statistically significantly higher than this new combined baseline. Virtanen et al. also showed significant interactions between Hg in hair and fatty acids in blood. Risk estimates were adjusted for age, cholesterol, body mass, family history of heart disease, blood pressure, smoking, and alcohol. This study is limited by its consideration of only three levels of hair Hg; given the skewed distribution, it is possible that a higher Hg threshold might have resulted from using more than three sub-groups.

Daviglus et al.²¹ used data from the Chicago Western Electric Study of 1822 middle-age men, over 30 years, from 1957. Mortality risks were computed for 4 levels of fish consumption, adjusted for age, education, religion, blood pressure, cholesterol, smoking, body mass, diabetes, EKG abnormalities, and daily intake of energy, vitamins, fatty acids, alcohol, and other dietary items. The authors concluded that there was an inverse association between fish consumption and death from CHD.

Albert et al.²² followed about 20,000 U.S. male physicians who were initially free of heart attack, stroke and cancer for 11 years. Daily rates of fish consumption were determined by questionnaire at 12 and 18 months. Relative risks were determined for 5 groups of fish intake and of fatty acids. They were adjusted for age, aspirin use, evidence of cardiovascular disease, body mass, smoking, diabetes, hypertension, alcohol, exercise, and use of vitamins. A statistically significant benefit of fish consumption was seen for sudden deaths (n=133), but the benefit was not significant for all cardiovascular deaths (n=548).

Morris et al.²³ had also analyzed this cohort, after only four years of follow-up, and found generally increasing risks with additional fish consumption, based on 121 CVD deaths. She cited two other publications that reported such contrary results, but both of them were letters instead of peer-reviewed papers. It appears that the additional follow-up analyzed by Albert et al.²² changed the direction of the fish consumption effect.

Hu et al.²⁴ used data from the Nurses Health Study (~85,000 females), after 16 years of follow-up, beginning in 1976. Dietary information was collected in 1980 and 1984 by questionnaire. The analysis adjusted for age, time periods, smoking, body mass, alcohol, hormone use, exercise, aspirin or vitamin use, hypertension, cholesterol, and diabetes, and considered quintiles of either fish consumption or fatty acid intake. These two sets of risk estimates are very similar (Figure 2) and indicated significant CHD mortality reductions associated with eating fish more often than about twice weekly.

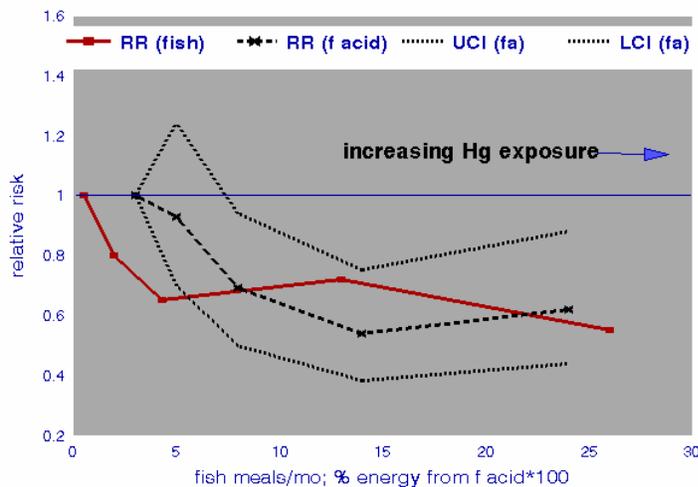


Figure 2. Relative risks of dying from coronary heart disease in a cohort of American nurses²⁴. Data are plotted against the number of monthly fish meals (solid line) and against the percentage of dietary energy from fatty acids (x100, dashed lines).

Guallar et al.¹⁰ collected data from eight European countries and Israel from 684 first-heart-attack patients and 724 matched controls and analyzed heart attack risks as a function of the Hg content of toenail clippings and the fatty acid content of tissue. They concluded that “high mercury exposure may diminish the cardioprotective effect of fish intake.” However, these risks were highly dependent on adjustment for covariates, and there was an apparent threshold at about the 93rd percentile of Hg exposures in American females.

Yoshizawa et al.¹¹ used data from about 34,000 American male health professionals (dentists, veterinarians, optometrists, etc.), among whom there were 470 cases of coronary heart disease (heart surgery, heart attacks, CHD fatalities). Each patient was matched with a randomly selected control. Data were also available on fish consumption, for which the median for the highest quintile was about 10 meals/month. Mercury exposures were based on toenail clippings; the median equivalent hair Hg level in the highest quintile was about 3.5

ppm. Note that dentists are often exposed to inorganic Hg, and their mean Hg levels were about twice those of nondentists. There was no association between Hg exposure and risk of CHD, either before or after adjustment for age and other risk factors, including intake of fatty acids.

Folsom and Demissie²⁵ studied a cohort of about 42,000 Iowa women aged 55-69 at recruitment in 1986. Deaths were tabulated through 2000, and diet was assessed by means of a questionnaire at entry. Relative risks of mortality from various causes were assessed according to quintiles of either fish consumption or intake of fatty acids. Adjustments were made for age, energy intake, education, physical activity, alcohol, smoking, age at first livebirth, vitamin use, body mass index, diabetes, hypertension, and other dietary items (red meat, whole grains, fruits, vegetables, cholesterol, saturated fats). The authors concluded that this study does not support an independent health benefit from fish, but that they could not “argue against recommending fish as part of a healthy diet.”

Figure 3 compares the dose-response relationships found in six of these studies, in terms of monthly fish meals. Note that the range of fish consumption for the three studies of U.S. health professionals far exceeds the others; some of these papers also indicate that higher rates of fish consumption are accompanied by other indications of healthier diets, such as

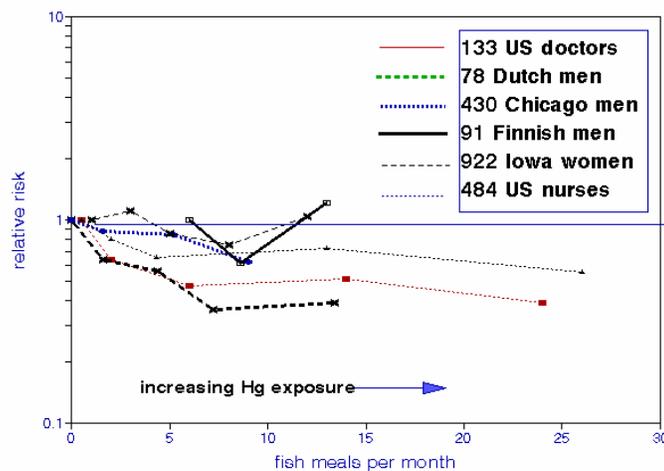


Figure 3. Relative risks of death from cardiac causes, as found in selected cohort studies. Each fish meal is assumed to comprise 150 g.

more fruits and vegetables and less red meat. The six studies are similar in showing consistent benefits for moderate fish rates of fish consumption, indicating eating fish 2-3 times per week may be optimal. The greatest fish benefits are seen in the Dutch study¹⁹ and the least in the Finnish study² and for Iowa women²⁵. It is noteworthy that no study indicates adverse effects from moderate rates of fish consumption and by extension, for the moderate rates of concomitant mercury exposure that are implied.

Meta-Analyses of Selected Cohort Studies

He et al.^{17,18} performed meta-analyses of 13 cohort studies; their results for CHD and stroke mortality are shown in Figure 4. They show clear benefits to increased rates of fish consumption, with no “optimal” levels. However, He et al. did not include the Finnish or Iowa studies, which may partly account for the relatively uniform (and thus highly significant) results shown.

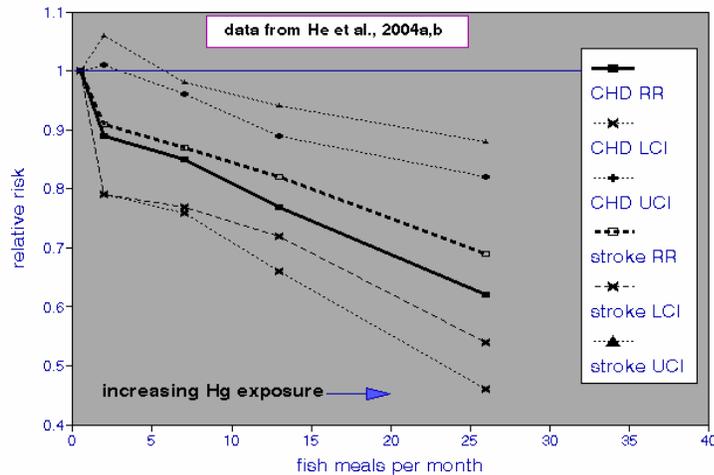


Figure 4. Relative risks of death from coronary heart disease (CHD) and stroke, as estimated from the meta-analyses of He et al.^{17,18} Each fish meal is assumed to comprise 150 g.

ECOLOGICAL ANALYSIS

Data and Methods

One of the key data sources is the paper of Zhang et al.²⁶, who found that fish consumption is protective against lung cancer, especially for men and when other risk factors are high, such as smoking and consumption of animal fats. Their paper was based on international statistics for 36 countries, in all continents except Africa. The dietary data were for the period 1961-1994 and included fish, fruits, vegetables, and animal fats less fish fats, and were expressed as percentages of total energy intake. National smoking data were for 1970-1992 and were expressed as annual cigarette consumption. Lung cancer mortality was based on combined rates for ages 45-54, 55-64, and 65-74, for three years around 1993.

The present analysis builds on this foundation by adding corresponding national data on heart disease and cardiovascular risks, obtained from two sources:

- The WHO MONICA Project²⁷: daily rates of coronary events for cohorts in 14 matching countries.

- WHO World Data Tables: annual heart disease mortality rates and disability days for 35 countries, from www.who.int/cardiovascular_diseases/resources/atlas/en/index.html.

None of these heart disease indicators is ideal for this purpose; the MONICA data are based on individual members of selected cohorts, not on entire national populations. The WHO data may not be age-standardized (this information was not available). For this reason, we considered all three heart disease indicators. In addition, we considered international data on the mercury content of human hair samples²⁸ from 35 countries, ca. 1980, insofar as they could be matched with the WHO heart disease data. The roughly 20-y lag between exposure and outcome is not inconsistent with the latency period for the development of heart disease. We performed both bivariate and multivariate analyses; a previous analysis of WHO data²⁹ considered only bivariate relationships and concluded that fish consumption was associated with reduced mortality risks for stroke, ischemic heart disease, and all causes. We considered other dietary components and smoking as possible confounders of the association between fish consumption and health. We also considered lung cancer mortality rates as perhaps the best indicator of the prior effects of smoking. We varied the inclusion of confounding variables in the analysis according to their statistical significance and their effect on the overall precision of the model (i.e., the standard error of estimate).

Results for Coronary Events

The MONICA project (MONitoring of trends and determinants in CARdiovascular disease) established 24 cohorts living in widely different climates and socioeconomic conditions. Barnett et al.²⁷ used age- and sex-standardized data on fatal and non-fatal coronary “events”, which include heart attacks and deaths. These values ranged from 0.3 (Beijing) to 2.7 (Finland, Moscow) daily events per 100,000 population. The bivariate relationship with the dietary data of Zhang et al.²⁶ is shown in Figure 5; Figure 5(a) shows no relationship with fish consumption, but Figure 5(b) shows a clear beneficial relationship with fruit intake, which was the best predictor of daily CHD events in these 14 countries. However, in all multivariate regression models, the effect of fish was negative (beneficial), although it was never statistically significant. In this set of 14 countries, cigarette consumption was a highly significant predictor of lung cancer, but not of CHD events. Also, CHD events were not correlated with lung cancer, suggesting different causal factors.

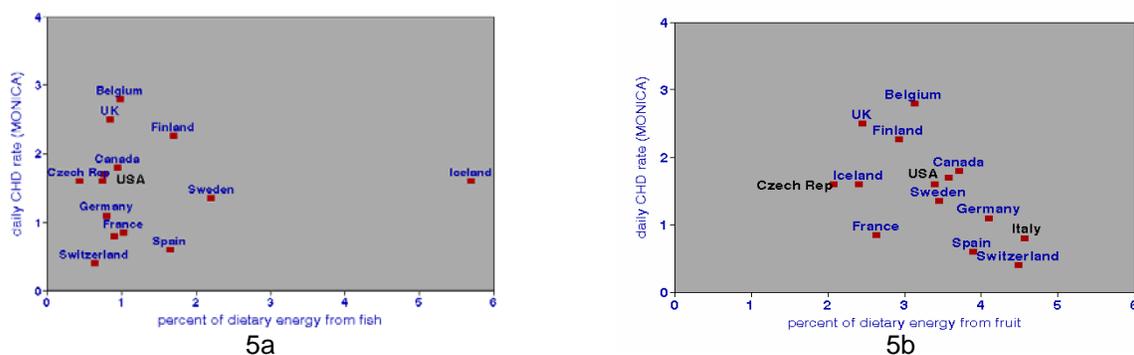


Figure 5. (a) Relationship between coronary heart disease mortality²⁷ and fish consumption²⁶, by country cohorts in the MONICA study. (b) for fruit consumption²⁶.

Results for Heart Disease Mortality

Including the WHO cardiovascular outcome data expanded the number of countries from 14 to 35 (Hong Kong is no longer a separate country and is not included in the current WHO tables). This dataset also includes smoking prevalence among males and females. Figure 6(a) shows the bivariate relationship with dietary fish intake; the slope is negative but not significant. Although we have no national average data for the Seychelles on fish consumption, it is known to be extraordinarily high there, with many people eating fish twice daily³⁰. However, we have a WHO value for heart disease mortality, which is low, as indicated by the arrow. The Seychellois tend to eat predatory ocean fish, resulting in MeHg levels perhaps an order of magnitude higher than those found in larger, more developed countries. The relative position of the Seychelles on Figure 6(a) thus indicates no evidence that might link MeHg with increased heart disease. Figure 6(b) shows the relationship with dietary vegetable intake, which is the best predictor for this set of heart disease mortality rates. In multiple regression models, fish consumption had a consistent negative but nonsignificant effect, while vegetable intake had a significant beneficial effect. The association of lung cancer mortality with CHD mortality was positive and nearly significant. The effects of smoking on both cancer and heart disease tend to lag by a decade or more; this may be the reason that lung cancer acts as a better predictor of heart disease than do current rates of smoking, even though tobacco smoking is an underlying cause for both.

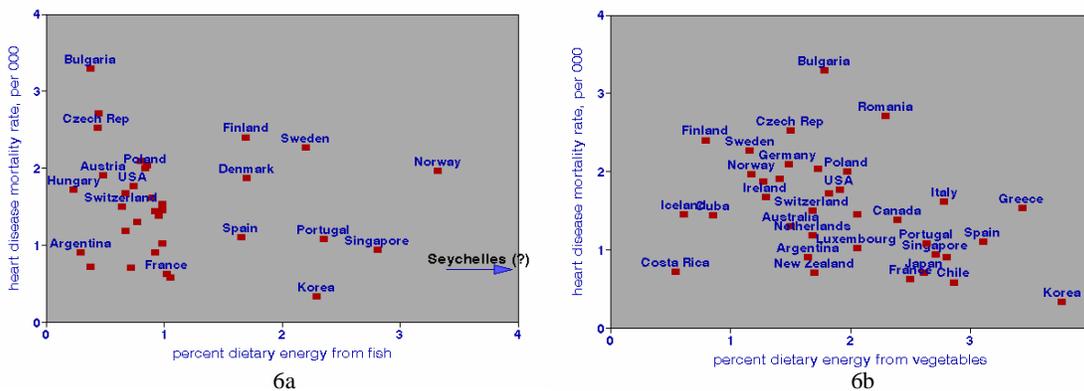


Figure 6. (a) Relationship between heart disease mortality from WHO statistics and fish consumption²⁶, by country. (b) for vegetable consumption²⁶.

Results for Heart Disease Disability

The WHO tables include data on disability days lost per 100 population, due to heart disease. This is an index of morbidity, since nonfatal events are included. Figure 7 shows the relationship with fish consumption, which is statistically significant (negative). The Seychelles has a somewhat less advantageous position on this plot, but still within the total envelope of a negative relationship. The best predictive model was obtained by using the logarithms of all variables, in which fish and vegetable consumption rates were significantly beneficial and lung cancer mortality was a significant positive predictor.

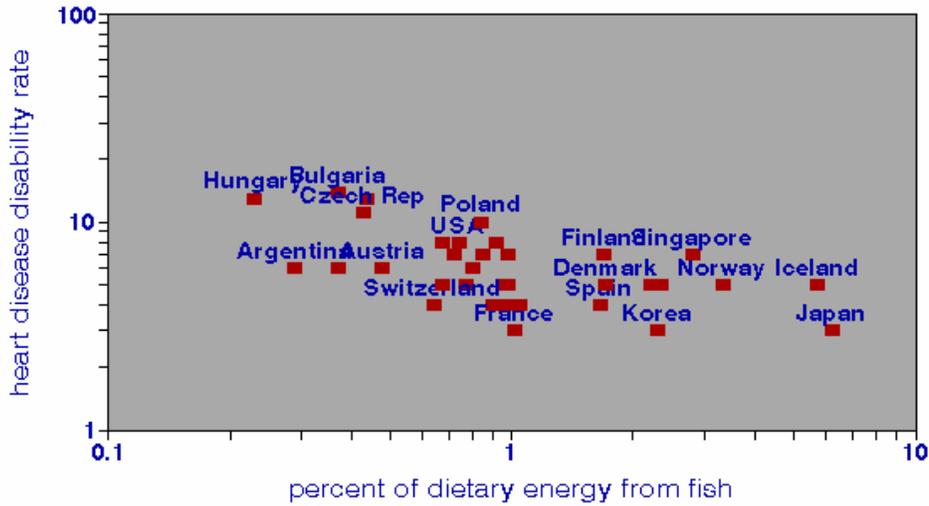


Figure 7. Relationship between heart disease disability from WHO statistics and fish consumption²⁶, by country.

Correlations with Data on Mercury in Hair

We matched hair Hg data²⁸ with the current WHO data on heart disease mortality and disability, as shown in Figure 8(a) and (b), respectively. Both cardiovascular endpoints are negatively correlated with hair Hg, but not significantly so. Note that the range of hair Hg concentrations, which are thought to be total Hg, not MeHg, is higher than current values, in many cases. The current average hair concentration of total Hg for U.S. females is 0.2 ppm, for example (Figure 9, based on NHANES data³¹). The hair Hg value for the Seychelles was taken from the Seychelles Child Development Study³⁰.

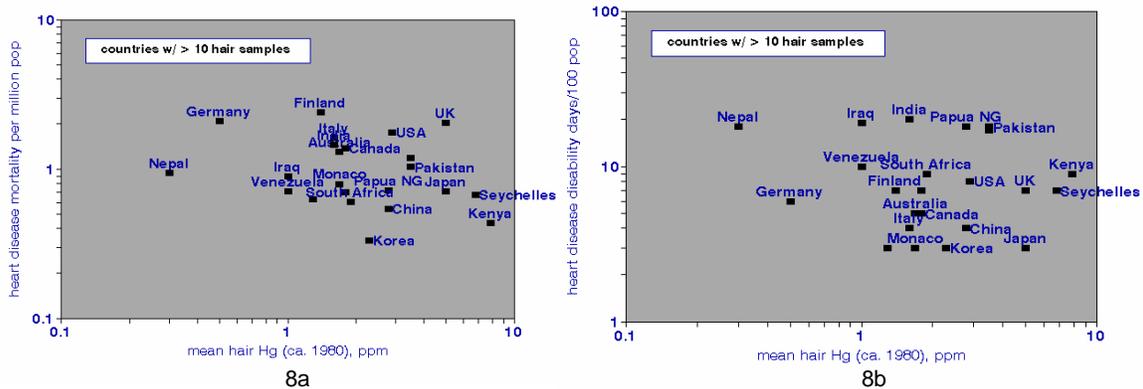


Figure 8. (a) Relationship between heart disease mortality from WHO statistics and average mercury concentrations in hair²⁸, by country. (b) for heart disease disability from WHO data

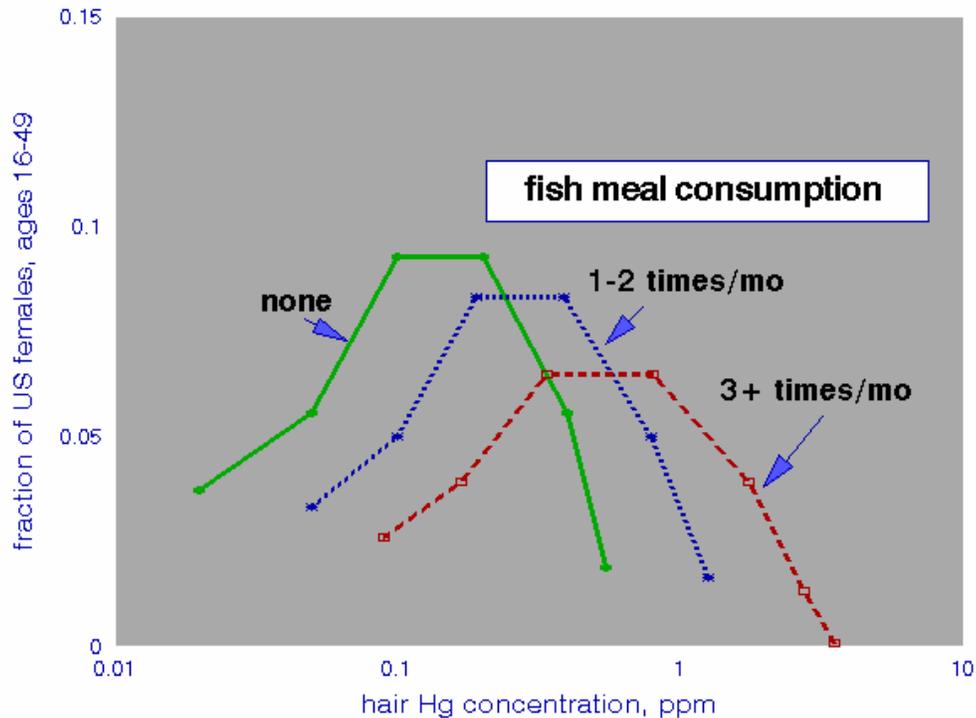


Figure 9. Distribution of mercury levels in the hair of American females of childbearing age, by fish consumption rate³¹.

CONCLUSIONS

As a group, the cohort studies show that the beneficial effects of fatty acids in fish are far stronger than any potentially harmful effects of MeHg, especially at fish consumption rates typical of the United States. Moreover, the diversity among ostensibly equally valid cohort studies illustrates the uncertainty involved in relying on any one of them for policy purposes. None of three ecological indicators of cardiovascular health show adverse effects of fish consumption; all three showed beneficial effects, although only the indicator for heart disease disability days was statistically significant. In all cases, the results with multivariate regression models differed from those based on bivariate relationships, such as scatter plots, which illustrates the importance of a comprehensive multivariate analysis. We thus conclude that neither the synthesis of existing cohort studies nor our new comparisons of international statistics support the hypothesis that eating fish containing normal levels of mercury might lead to increased cardiovascular risks in the United States. It thus follows that prudent dietary advice would continue to be that of maintaining a well-balanced diet, including fish or shellfish at least once per week. There may be additional benefits from fatty fish.

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