Risks and Benefits of Fish Intake

To the Editor: In their Clinical Review, Drs Mozaffarian and Rimm[1] provide analyses that balance the risks and benefits of consuming fish and n-3 polyunsaturated fatty acids (n-3 PUFAs). We are concerned, however, with the analysis in their Figure 2, which suggests that the benefits for death from coronary heart disease (CHD) plateau at a 250-mg/d intake of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). This conclusion was based on a comparison of CHD mortality rates and intake of n-3 PUFAs, but it included 4 Japanese cohorts with EPA and DHA intakes greater than 2000 mg/d. Because of these 4 data points, the benefits appeared not to extend beyond 250 mg/d.

The rate of CHD death among Japanese individuals is very low, and their intake of EPA and DHA is very high compared with Western populations, but it seems inappropriate to include those cohorts in this analysis because of the marked differences between overall Western and Japanese diets. If these 4 studies are eliminated from Figure 2, it appears that risk for CHD death continues to decrease, reaching a plateau at approximately 1000 mg/d. Recent dietary recommendations from both Great Britain[2] and Australia[3] encourage daily intake of 400 to 600 mg of long-chain n-3 PUFAs for reduction of CHD risk. It would be of interest to know what intake the analysis would suggest when it was confined to populations consuming less than 2000 mg/d of EPA and DHA.

Future studies examining the relations between CHD end points and intake of n-3 PUFAs would benefit from using biomarkers of intake such as the Omega-3 Index,[4] rather than relying on food frequency questionnaires to assess exposure.

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To the Editor: In the Clinical Review of the health effects of fish intake and contaminants by Drs Mozaffarian and Rimm,[1] mercury contamination was evaluated as a potential risk factor for cardiovascular disease, in their Figure 5 and the accompanying text. However, both the figure and the conclusions seem to be misleading because the meta-analysis includes studies that are not relevant to the issue examined. Dentists and participants mainly exposed to inorganic mercury from amalgam should have been excluded.

Also, while the authors note that the 2 studies from Sweden tend to point toward lower CHD risk at higher levels of mercury intake, they do not mention that the overall mercury levels in the Swedish participants are far less than those in the Finns. In addition, one of the Swedish studies[2] primarily examined the long-term health effects of inorganic mercury from amalgam fillings, as reflected in the serum concentration, not the methylmercury exposure from fish.

The increased risk in the European multicenter study[3] occurred at a relatively high exposure, as did the increased risk in the Finnish studies.[4] Hence, it is likely that the adverse cardiovascular effects of methylmercury only begin to overcome the beneficial effects of fish at higher exposure levels. The meta-analysis erroneously combined populations with low and high exposures. A more appropriate meta-analysis could have been achieved by using the Finnish data,[4] data from the study by Guallar et al,[3] and the nondentist participants of the study by Yoshizawa et al.[5] A more precise definition of "higher levels of mercury exposure" should have been presented when examining the individual results or the pooled result. The given relative risks are derived from different exposure quantiles in different studies. For example, in the study by Virtanen et al,[4] the relative risk is for the highest third, and in the study by Guallar et al,[3] the relative risk is for the highest fifth.

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In Reply: Mr Lucas and Dr Harris highlight the important evidence for a nonlinear benefit of EPA and DHA intake for preventing CHD death. Pooling evidence from 20 prospective observational studies and randomized clinical trials, we found that the majority of benefit occurs with modest intake—some consumption is much better than none at all. At EPA and DHA intakes between 0 and 250 mg/d, CHD mortality risk was lower by 14.6% (95% confidence interval [CI], 8% to 21%; $P<.001$) per each 100 mg/d, while at intakes greater than 250 mg/d, risk was not further lowered (0.0% lower risk per each 100 mg/d; 95% CI, –0.9% to 0.8%; $P=.94$).

Exclusion of studies in Japanese populations did not greatly alter these findings. At EPA and DHA intakes between 0 and 250 mg/d, CHD mortality risk was lower by 14.3% (95% CI, 8% to 21%; $P<.001$) per each 100 mg/d, while at intakes greater than 250 mg/d, risk was slightly lowered, but not significantly so (1.5% lower risk per each 100 mg/d; 95% CI, –1.2% to 4.2%; $P=.26$). Thus, after excluding the Japanese studies, the CIs at higher intakes are wider and include the possibility of some additional modest benefit. Nevertheless, the big picture is unchanged: the majority of benefit for CHD death is obtained with relatively low consumption.

Lucas and Harris suggest using biomarkers rather than dietary questionnaires to assess intake of n-3 PUFAs. Biomarkers and dietary questionnaires both provide valid estimates of dietary consumption, but the strengths and limitations of each are different, eg, relating to periods assessed; effect of memory vs metabolism; and issues of cost, availability, and practicality.[1] Thus, these tools provide complementary methods to investigate the health effects of dietary habits.

We agree with Dr Tuomainen and colleagues that the published studies of mercury and cardiovascular risk have several limitations, including varying study designs, sample sizes, exposure assessment methods, population exposure ranges, and statistical cutpoints and adjustments. These limitations will best be overcome by new and larger investigations of the potential effects of methylmercury exposure on cardiovascular risk, rather than by attempts to reanalyze existing data by focusing only on studies showing higher risk (which could also exacerbate potential publication bias, given that positive studies would more likely be published).

Importantly, even the positive studies do not suggest that potential adverse effects of methylmercury exposure ever exceed the benefits of fish consumption. For example, in the Finnish study, men who frequently consumed fish (as assessed by serum fatty acid levels) had lower risk of cardiovascular events than those who did not consume fish, whether mercury exposure was high or low.[2] These findings did not suggest that fish intake was harmful, only that mercury may partially attenuate the protective effects of fish consumption. This important public health message of overall benefits vs risks should not be overlooked by focusing only on contaminants. Although it may turn out that consumption of fish with lower mercury levels provides greater cardiovascular benefits than consumption of fish with higher mercury levels, the current evidence indicates that consumption of either is better than no fish consumption at all. We look forward to additional studies addressing these questions.

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Cyclooxygenase Inhibitors and Cardiovascular Risk

To the Editor: The systematic review by Drs McGettigan and Henry[1] provides a timely summary of the observational studies investigating the cardiovascular risk associated with nonsteroidal anti-inflammatory drugs. Nonethe-