Risk/Benefit Analysis of Great Lakes Fish for Cardiovascular Outcomes

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Background and Methods

Fish have been promoted as a benefit in preventing cardiovascular disease (CVD) potentially due to the content of beneficial fish oils (e.g., omega-3 fatty acids or O-3 FAs). However, fish also contain methyl mercury (Hg), which in a number of epidemiology studies has been associated with an increase in acute myocardial events (Stern 2005; Wennberg et al. 2012; Guallar et al. 2002; Rissanen et al. 2000; Salonen et al. 1995; Virtanen et al. 2005). This risk/benefit potential of fish on CVD can thus be seen within the context of the comparison between the O-3 FAs and the Hg content of individual species, although other constituents may also play a role. To predict the net effect of O-3 FAs and Hg on CVD outcomes it is helpful to have separate risk (Hg) and benefit (O-3 FA) slopes for this outcome. Such risk/benefit models have in the past (e.g., Rice et al. 2010, Ginsberg et al. 2009) been based upon studies showing benefits of fish oils mainly through intervention trials (summarized in Mozzafarian and Rimm 2006) and have quantitated Hg-related CVD risks from epidemiological associations seen in European populations (e.g., Guallar et al. 2002; Salonen et al. 1995; Virtanen et al. 2005). In a previous publication we utilized Guallar et al. 2002 to develop a risk slope of 23% increase in CV events per ppm hair Hg and a O-3 FA benefit slope from Mozzafarian and Rimm 2006 (14.6% improved CVD risk per 100 mg/d O-3FA ingestion) to predict the CVD risks and benefits associated with individual fish species (Ginsberg and Toal 2009).

The current analysis updates the previous publication by using a calibration against epidemiology approach to reset the slopes for the fish oil benefit and Hg risk on CVD. Epidemiology results uncorrected for the opposite effects of fish oils and Hg show the net effect of a fish meal on CVD outcomes. However, exposure assessment in such epidemiology studies often lacks sufficient detail on the fish oil and Hg content of the diet to create a dose response slope for the CVD outcome. As described in Ginsberg et al. (2015), the current analysis uses a composite marketshare fish meal based upon data on the overall consumption of fish in the US so that when an epidemiological association is found between fish consumption or a fish-related biomarker (e.g., hair or toenail Hg) and CVD, the amount of O-3 FAs ingested by such subjects can also be estimated.

Figure 1 shows a series of attempts to match the apparent dose response between mercury exposure and CVD benefit seen in Mozaffarian et al. 2011. Their association between increasing toenail mercury levels and decreased cardiovascular risk (uncorrected for O-3 FA ingestion) forms the basic calibration dataset in Figure 1. This association was a statistically significant dose response that was opposite to that which is expected based upon other literature (Guallar et al. 2002; Salonen et al. 1995; Virtanen et al. 2005) and likely stems from the fact that mercury in this case is a biomarker for overall fish ingestion and this ingestion yields a net benefit in spite of the presence of methyl Hg. When statistical corrections were applied for dietary O-3 intake, the association between mercury biomarker and cardiovascular benefit was lost (Mozaffarian et al. 2011). However, the uncorrected epidemiology data (actually it is adjusted for other host factors that could influence cardiovascular risk) indicate the net effect of Hg and O-3 FA ingestion and shows a trend (Figure 1) similar to that seen in other studies (Hallgren et al. 2001; Wennberg et al. 2012). Since the risk/benefit model can predict both the level of mercury biomarker

and the net risk or benefit associated with fish intake, its simulations were compared to results reported in Mozaffarian et al. (2011). That study involved the pooling of two large cohorts with the results indicative of the effects of an average fish diet (and its mercury content) on cardiovascular risk in the United States (Mozaffarian et al. 2011).

Use of the marketshare fish meal (Ginsberg et al. 2015) to represent the source of O-3 FA and Hg in the Mozzafarian et al. 2011 study group enabled the calibration of risk and benefit slopes as shown in Figure 1. To use the Mozzafarian et al. mercury biomarker data it was necessary to convert the toenail mercury results to hair mercury which was done according to the equation reported by Ohno et al. 2007 as described in Ginsberg and Toal (2009). Figure 1A shows that the baseline model and slopes used in Ginsberg and Toal (2009) yield a reasonable fit to the low end of the Mozzafarian et al. 2011 dataset (low mercury exposure corresponding to low fish intake) but there was divergence at the high end. The overshoot of benefit at high rates of fish ingestion is presumably due to the saturation of fish oil benefit on CVD as described in Mozzafarian and Rimm 2006. That summary analysis showed an apparent plateau in benefit at approximately 500 mg/day of O-3 FAs for a maximal benefit of approximately 30% lowered CVD risk (Figure 2). When this saturation of benefit was simulated (Figure 3) and incorporated into the model, the result was not only a plateau in fish-related CVD benefit but a net risk at higher levels of mercury biomarker (Figure 1B). Since this does not match the Mozzafarian et al. 2011 data, a modified meHg risk slope was tried, the one coming from the Eastern Finland dataset of Wennberg et al. 2012 and Salonen et al. 1995 as derived by Rice et al. 2010. That slope (CVD risk of 6.6% per ppm hair Hg) is less steep than that from the Guallar et al. 2002 but it also does not involve a threshold Hg dose below which there is no apparent effect. Use of the Eastern Finland slope yields the calibration data shown in Figure 1.C which indicates a reasonable fit to the underlying Mozzafarian et al. 2011 epidemiological association. Figure 1D simply shows the necessity of having a Hg risk slope in the model as without it, the model does not come close to the underlying data, predicting instead a consistent overestimate of benefit even when saturation of benefit is modeled. Based upon this calibration exercise, the fish oil benefit slope (with saturation) shown in Figure 3 and the mercury risk slope from Eastern Finland (6.6% per ppm hair Hg) were used in estimating the CVD risk or benefit associated with Great Lakes fish.

The Great Lakes case study species and constituent data are the same as in the companion report on neurodevelopmental outcomes previously submitted (Ginsberg 2016).

Results

As shown in Table 1, four of the 8 case study species, both Lake Superior species and lake trout from both NYS and MN, showed a substantial CVD benefit of over 10% reduction in CVD risk. The other 4 species showed a slight to substantial increase in risk. This shows that while fish are generally considered to have a CVD benefit, it is possible that locally caught species with moderate amounts of mercury and insufficient fish oil content can present a net risk for CVD outcomes. Table 1 results are for one meal/week. As the frequency of fish consumption increases, the potential for saturation of CVD benefit increases which can create a loss of benefit and even a net risk. Table 2 shows the CVD implications of consuming 2 or 3 fish meals/week for the case study species which showed a net benefit at 1 meal per week. The results for 2 meals/week were not that dissimilar to 1 meal/week but at 3 meals/week two of the beneficial species became a net risk. Interestingly, Lake Superior herring cisco

did not experience any decline in benefit in spite of some saturation of benefit. That is because of the low Hg content of this species which did not amount to much risk, even at three meals/day.

A simplified variability analysis with respect to constituent concentrations in fish is shown in Tables 3 and 4. The best case scenario (75th % O-3FA, 25th % Hg) indicates whether variability in constituent concentrations can combine to create a net benefit where the average concentrations predict otherwise at 1 meal/week. Comparing Tables 1 and 3 we see that the 4 species which in the average case represented a net risk now are estimated to provide a net benefit. However, these net effects are relatively small, less than 5% improvement in risk, under the best case, low probability scenario. Regarding walleye, the best actual ratio of omega-3 FA to mercury is for a lake in MN (Lake Winnibigoshish). This ratio was slightly better than the 25th/75th ratio for walleye shown in Table 3, and the net CVD benefit (+6.53) is also slightly better. Therefore, for the 4 lake/species combinations where the average case predicts a net risk, Table 3 suggests that it's unlikely that this conclusion would be reversed in most of the fish caught in those categories but that in select lakes (e.g., Winnibigoshish) such a reversal may be possible. This would require waterbody-specific sampling data. The worst case analysis (Table 4) indicates that for the 4 lake/species combinations which were a net benefit in the average case (Table 1), this is still a net benefit for 3 of the species under worst case constituent concentrations. Only lake trout from NYS reversed to a net CVD risk in this case. This suggests a high level of confidence in the net CVD benefit of the 2 Lake Superior species and MN lake trout but not for the benefit associated with NYS lake trout.

An analysis was also run for the once per month ingestion advice for walleye, which is based upon prevention of neurodevelopmental risk with implications for CV risk that have yet to be evaluated. Table 5 shows the evaluation for MN, WI and NY walleye for both once per week and once per month meal frequency. Using NY walleye as an example because it has the highest mercury content for the same O-3 FA content as the other walleye (O-3 FA data not available for walleye from the different states), the results show a substantial net CVD risk at once per week (-11.14) that declines to -2.9 at once per month. This is a very small deflection given the various uncertainties and can be characterized as unlikely to provide any CV benefit and possibly a slight but uncertain CV risk that would not merit a warning. The CV risks associated with monthly consumption of the other walleye are even smaller (Table 5).

A cutpoint analysis was constructed based upon the ranges of Hg fish concentration associated with meal frequency advice for neurodevelopmental outcomes in the Great Lakes states (Table 6). The goal was to determine whether the O-3 FA content of these case study species would provide a CVD benefit when fish are consumed according to the recommended meal frequency advice used to avoid neurodevelopmental risks. The O-3 FA concentration requirements to yield a net CVD benefit shown in Table 5 can then be compared back to what is present in the fish. At the first Hg cutpoint, < 0.05 ppm for unlimited consumption, only 300 ppm O-3FA is needed to support this advice in terms of CVD risk/benefit. This concentration is attained by all 8 case study species as shown in Table 1. As the Hg content goes up and the meal frequency advice goes down, more O-3 FA is needed to maintain the CVD benefit, but the requirement is still low relative to the O-3FA contents of the 8 case study species for cutpoints of up to 0.22 ppm Hg (compare Tables 6 and 1). The one exception is WI black crappie which has low O-3 FA such that the 0.22 ppm cutpoint (1 meal/wk) would be a net risk for CVD in this species/lake combination. For the 1/month cutpoint (>0.22 ppm Hg) the highest Hg fish, NYS walleye is used as an example. A moderate amount of O-3FA is needed in this case (4626 ppm). This

concentration is not attained in this species indicating a net CVD risk and it is only attained in 3 of the 8 species analyzed. This suggests that fish in the lower consumption category due to mercury > 0.22 ppm may constitute a net CVD risk at the recommended consumption advice for pregnancy and it would be important to know the O-3 FA content of such species as part of a comprehensive fish advisory approach.

Summary and Conclusions

The 8 Great Lakes case studies provides a range of Hg and O-3 FA combinations that represent a net CVD benefit in some cases and a net risk in others at one meal/wk (Table 1) with this benefit decreasing substantially in most species when going up to 3 meals/week frequency. Therefore, one may consider a general rule for Great Lakes species that 2 meals/week is the maximum frequency one might recommend in order to maintain the O-3 FA CVD benefit. However, as shown in Table 1, for some species even 1 meal/week is a net CVD risk and best case constituent concentrations don't provide much confidence that these species would be a net CVD benefit under any circumstances (Table 3). In contrast, the beneficial fish shown in Table 1 maintain their benefit in most cases even under worst case constituent concentrations. CVD benefits can be expected for these 8 case studies for the lower Hg cutpoints (< 0.22 ppm Hg) but this is not necessarily the case for the higher cutpoint (> 0.22 ppm). Overall, this analysis demonstrates the utility of collecting Great Lakes O-3 FA content data and modeling this information to develop an understanding of the net effect of fish consumption on CVD risk. An uncertainty with respect to these conclusions is that while the risk/benefit model adopts published O-3 FA and Hg slopes and calibrates against a well cited epidemiology study (Mozzafarian et al. 2011), the epidemiology relating Hg ingestion to CVD risk is mixed and has been debated. Hg effects on upstream endpoints indicative of increased CVD risk (lowered PON1, Ginsberg et al. 2014; increased intima media thickness, Salonen et al. 2000) suggest that the associations with CVD risk are valid and important from a public health perspective (Roman et al. 2011).

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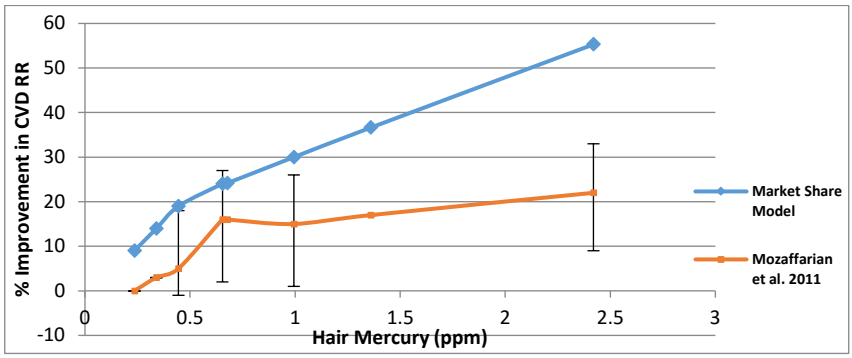
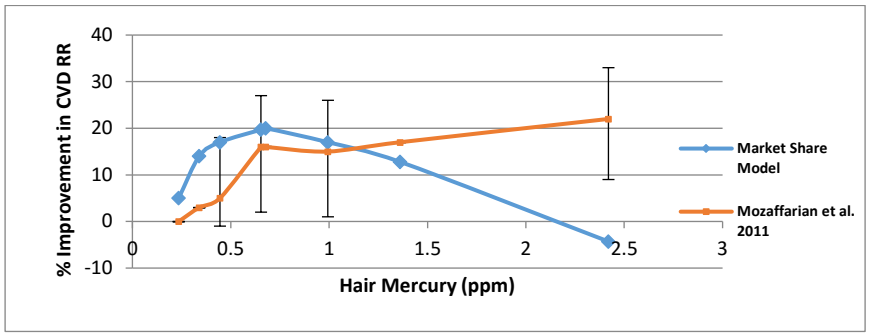
Figure 1. Comparison of Marketshare Model Results to CVD Benefit Seen in Mozaffarian et al. 2011 Using Alternative O-3 fatty acid and Mercury Slopes

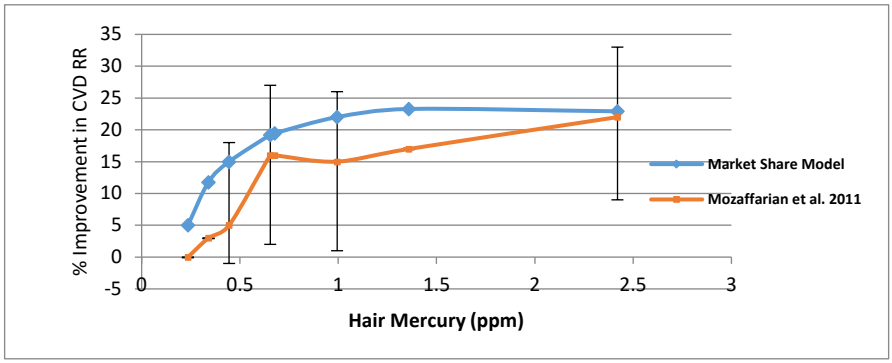
A. Baseline Risk/Benefit Model



B. Saturable O-3 Fatty Acids, Guallar Slope



C. Saturable O-3, Alternative Mercury Slope



D. Saturable O-3 Fatty Acids, No Mercury Slope

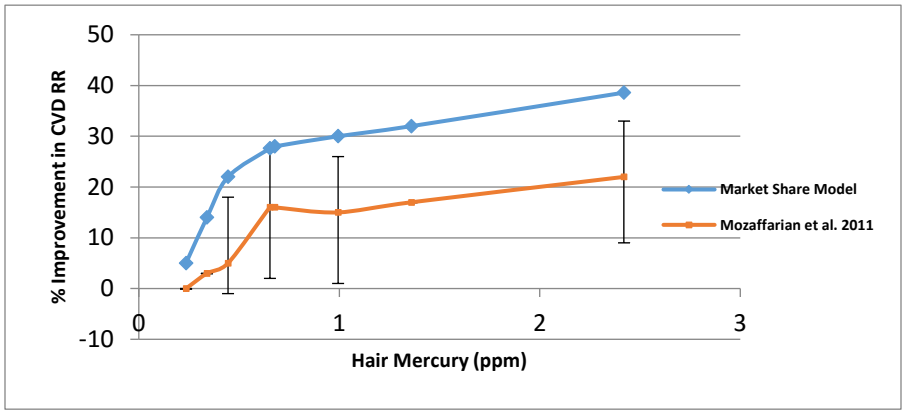


Figure 2. O-3 Fatty Acid CVD Benefit Slope with Saturation (Mozaffarian and Rimm (2006) Compilation Across 20 Studies)

Figure 2. Relationship Between Intake of Fish or Fish Oil and Relative Risks of CHD Death in Prospective Cohort Studies and Randomized Clinical Trials

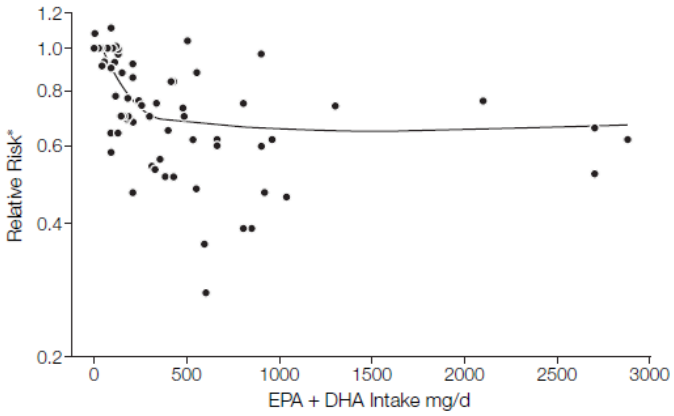
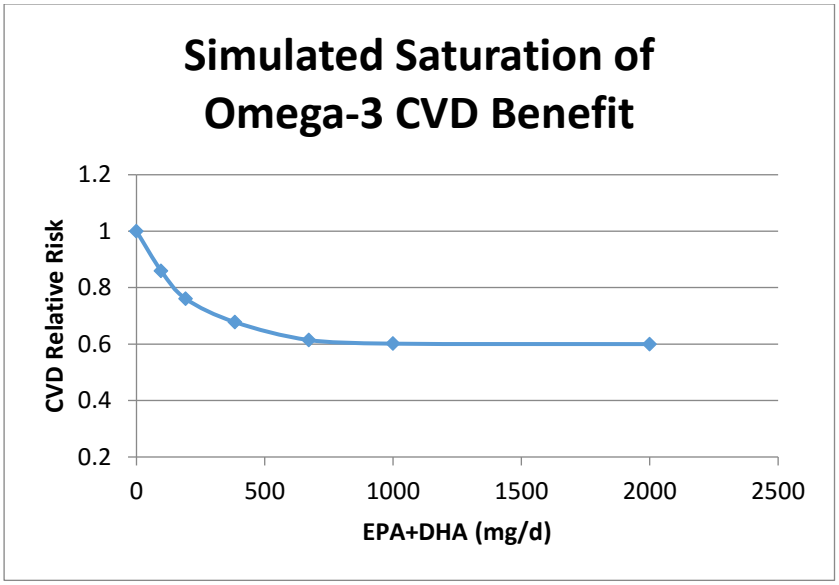


Figure 3. Model Simulation of O-3 Saturation of Benefit



$$\text{Benefit} = (\text{O-3 FA}_{1\text{-}125\text{mg/d}} * 0.14) + (\text{O-3 FA}_{250\text{-}125\text{mg/d}} * 0.085) + (\text{O-3 FA}_{500\text{-}250\text{mg/d}} * 0.025) + (\text{O-3 FA}_{800\text{-}500\text{mg/d}} * 0.02)$$

Table 1. Risk/Benefit Results for Great Lakes Case Studies Species: One Meal/Week

Waterbody	Species	Hg Mean[1]	O-3 Mean[1]	Net Effect on CVD[2]
Superior	Lean LT	0.4	9079	15.90385
Superior	Herring Cisco	0.078	4255	16.60542
MN	Lake Trout	0.298	6411	14.80297
MN	Walleye	0.311	1855	-2.1665
WI	Bl Crappie	0.245	1108	-3.37925
WI	Walleye	0.403	1855	-5.4049
NY	Lake Trout	0.375	6411	12.09257
NY	Walleye	0.566	1855	-11.1425

[1]Hg and O-3 content in fish are the average concentrations, in ppm;
[2]Net effect on CVD in terms of % decrease – positive numbers, or increase – negative numbers in CVD risk

Table 2. CVD risk/benefit implications of 2 or 3 meals per week of case study GL fish

A. Two Meals/Week

Waterbody	Species	Hg Mean	O-3 Mean	Net CVD Risk/Ben
Superior	Lean LT	0.4	9079	8.739166
Superior	Herring Cisco	0.078	4255	24.03146
MN	Lake Trout	0.298	6411	12.03849
NY	Lake Trout	0.375	6411	6.617689

B. Three Meals/Week

Waterbody	Species	Hg Mean	O-3 Mean	Net CVD Risk/Ben
Superior	Lean LT	0.4	9079	-1.115
Superior	Herring Cisco	0.078	4255	24.73469
MN	Lake Trout	0.298	6411	6.127427
NY	Lake Trout	0.375	6411	-2.00377

Table 3. CVD Analysis of Great Lakes Case Study Species: Best Case Concentrations[1]

Waterbody	Species	Hg 25th	O-3 75th	Net CVD Risk/Ben
Superior	Lean LT	0.14	12887	28.1
Superior	Herring Cisco	0.044	4990	19.8
MN	Lake Trout	0.136	8896	25.0
MN	Walleye	0.142	1980	4.4
WI	Bl Crappie	0.14	1304	1.2
WI	Walleye	0.204	1980	2.2
NY	Lake Trout	0.215	8896	22.3
NY	Walleye	0.133	1980	4.7

[1]Net benefit (positive values) or risk (negative values) calculated based upon 25th percentile O-3FA and 75th percentile Hg concentrations in each case.

Table 4. CVD Analysis of Great Lakes Case Study Species: Worst Case Concentrations[1]

Waterbody	Species	Hg 75th	O-3 25th	Net CVD Risk
Superior	Lean LT	0.44	5273	6.668446
Superior	Herring Cisco	0.099	3414	12.67547
MN	Lake Trout	0.368	3157	1.99015
MN	Walleye	0.394	1163	-8.36371
WI	Bl Crappie	0.291	878	-6.08716
WI	Walleye	0.529	1163	-13.1157
NY	Lake Trout	0.475	3157	-1.77625
NY	Walleye	0.727	1163	-20.0853

[1]Net benefit (positive values) or risk (negative values) calculated based upon 25th percentile O-3FA and 75th percentile Hg concentrations in each case.

Table 5. Analysis of Hg Cutpoints for Neurodevelopmental Risk: O-3 FA Concentration Needed for CVD Benefit[1]

Hg Cutpoint	ND-Based Meal Freq	Needed O-3 Conc
<0.05	unlimited	300
0.05 -0.10	2/week	833
0.11 to 0.22	1/week	1665
0.566[2]	1/month	4626

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[1]All concentrations are in ppm. Needed O-3FA concentration refers to concentration in fish needed for net CVD benefit at the mercury concentration and meal frequency shown for the cutpoints.

[2]Since the 1/month cutpoint covers a broad range, only one concentration in this range, the highest mercury concentration of any species in the case study analysis, was us