Myocardial infarction in relation to mercury and fatty acids from fish: a risk-benefit analysis based on pooled Finnish and Swedish data in men[1–4]

Maria Wennberg, Ulf Strömberg, Ingvar A Bergdahl, Jan-Håkan Jansson, Jussi Kauhanen, Margareta Norberg, Jukka T Salonen, Staffan Skerfving, Tomi-Pekka Tuomainen, Bengt Vessby, and Jyrki K Virtanen

ABSTRACT

Background: Exposure to methylmercury from fish has been associated with increased risk of myocardial infarction (MI) in some studies. At the same time, marine n−3 (omega-3) PUFAs are an inherent constituent of fish and are regarded as beneficial. To our knowledge, no risk-benefit model on the basis of data on methylmercury, PUFA, and MI risk has yet been presented.

Objective: The objective of this study was to describe how exposure to both marine n−3 PUFAs and methylmercury relates to MI risk by using data from Finland and Sweden.

Design: We used matched case-control sets from Sweden and Finland that were nested in population-based, prospective cohort studies. We included 361 men with MI from Sweden and 211 men with MI from Finland. MI risk was estimated in a logistic regression model with the amount of mercury in hair (hair-Hg) and concentrations of n−3 PUFAs (EPA and DHA) in serum (S-PUFA) as independent variables.

Results: The median hair-Hg was 0.57 μg/g in Swedish and 1.32 μg/g in Finnish control subjects, whereas the percentage of S-PUFA was 4.21% and 3.83%, respectively. In combined analysis, hair-Hg was associated with higher ($P = 0.005$) and S-PUFA with lower ($P = 0.011$) MI risk. Our model indicated that even a small change in fish consumption (ie, by increasing S-PUFA by 1%) would prevent 7% of MIs, despite a small increase in mercury exposure. However, at a high hair-Hg, the modeled beneficial effect of PUFA on MI risk was counteracted by methylmercury.

Conclusions: Exposure to methylmercury was associated with increased risk of MI, and higher S-PUFA concentrations were associated with decreased risk of MI. Thus, MI risk may be reduced by the consumption of fish high in PUFAs and low in methylmercury. *Am J Clin Nutr* 2012;96:706–13.

INTRODUCTION

Fish consumption has been associated with protection against myocardial infarction (MI)[5] (1). Mainly, the marine n−3 (omega-3) PUFAs EPA and DHA (defined as PUFAs throughout this article) are the nutrients identified as protective, although selenium and vitamin D have also been discussed (2, 3). Several mechanisms have been proposed to explain the beneficial effect of these fatty acids (1).

However, fish is the major source of methylmercury exposure. Methylmercury has oxidative properties and can counteract the protective effect of n−3 PUFAs (4). An association between the amount of mercury in hair (hair-Hg) (an index of methylmercury exposure) and risk of MI was observed in Finnish men from the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study (5–7). Associations have also been seen for MI and the amount of mercury in toenails in a European multicenter study (8).

In contrast, no evidence was shown of any adverse cardiovascular effects of hair-Hg in subjects from 2 US cohorts (9), and within the Northern Sweden Health and Disease Study (NSHDS), a higher mercury concentration in erythrocytes (Ery-Hg) (which is also an index of methylmercury) was associated with lower MI

[1] From the Departments of Public Health and Clinical Medicine, Occupational and Environmental Medicine (MW and IAB), Medicine (J-HJ), and Epidemiology and Global Health (MN), Umeå University, Umeå, Sweden; the Division of Occupational and Environmental Medicine, Lund University, Lund, Sweden (US and SS); the Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland (JK, T-PT, and JKV); Metabolic Analytical Services Oy, Helsinki, Finland (JTS); and the Department of Public Health and Caring Science, Uppsala University, Uppsala, Sweden (BV).

[2] This article reflects the views of the authors only; the European Union is not liable for any use that may be made of the information. Funding sources had no role in the study design; the collection, analysis, or interpretation of data; the writing of the report; or the decision to submit the manuscript for publication.

[3] Supported by the European Union [Sixth Framework Programme: PHIME (Public Health Impact of long-term, low-level Mixed Element Exposure in susceptible population strata); grant FOOD-CT-2006-016253] and the Swedish Research Council Formas. Additional support was provided by the Academy of Finland (grant 121206; to JKV), the Foundation of Medical Research in Skellefteå, and the Research Unit, Department of Medicine, Skellefteå Hospital.

[4] Address reprint requests and correspondence to M Wennberg, Occupational and Environmental Medicine, Umeå University, 901 87 Umeå, Sweden. E-mail: maria.wennberg@envmed.umu.se.

[5] Abbreviations used: apo A-I, apolipoprotein A-I; apo B, apolipoprotein B; DBP, diastolic blood pressure; Ery-Hg, mercury concentration in erythrocytes; hair-Hg, amount of mercury in hair; KIHD, Kuopio Ischaemic Heart Disease Risk Factor; MI, myocardial infarction; MONICA, Multinational Monitoring of Trends and Determinants in Cardiovascular Disease; NSHDS, Northern Sweden Health and Disease Study; NSHDS1, Northern Sweden Health and Disease Study 1; NSHDS2, Northern Sweden Health and Disease Study 2; SBP, systolic blood pressure; S-PUFA, PUFAs in serum; VIP, Västerbotten Intervention Programme.

Received December 29, 2011. Accepted for publication May 9, 2012.

First published online August 15, 2012; doi: 10.3945/ajcn.111.033795.

risk (10, 11). The suggested explanation for the NSHDS finding was that Ery-Hg was a biomarker of fish consumption, and the higher methylmercury exposure in Finland compared with in Sweden explained the conflicting findings. In both populations, marine n−3 PUFAs were associated with lower risk of MI (7, 10). The results of epidemiologic studies have created a need for a risk assessment of fish consumption that takes both risks and benefits into account (12). An approach for how to deal with this need was recently suggested (13).

To our knowledge, no modeling has previously been published on how the combination of mercury and PUFA relates to MI risk. The combination of data from studies in Sweden (10, 11) and Finland (5–7) allows for a data set with a wide enough range of methylmercury exposure and, thus, facilitates modeling of associations of methylmercury and marine n−3 PUFAs EPA and DHA [PUFAs in serum (S-PUFA)] with MI risk. Thus, the aim of this work was to describe how the exposure to both PUFA and methylmercury relates to MI risk in these combined materials.

SUBJECTS AND METHODS

Populations and design

We used a prospective design with 3 nested case-control data sets from the NSHDS and the KIHD Study. The study protocols were approved by the respective research ethics committees. All subjects gave written informed consent.

The NSHDS data sets have been previously described (10, 11). In brief, the NSHDS consists of subcohorts within the population of the 2 northernmost counties in Sweden (14). In the current study, the following 2 cohorts were used: the Västerbotten Intervention Programme (VIP) (15), which began in 1985 and continuously invites inhabitants of Västerbotten county who are aged 40, 50, and 60 y and, until 1995, also included 30-y-olds; and the WHO Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Study in northern Sweden (16), which invites a population-based sample from the 2 northernmost Swedish counties approximately every fifth year since 1986 (ages 25–74 y; ages 25–64 y in the first 2 surveys). Both studies are programs for risk factors of cardiovascular disease and diabetes, in which participants fill out an extensive questionnaire, undergo a medical examination, and are asked to donate blood samples. By the end of 1999, ~74,000 individuals had participated. The participation rate was 71–82% in the MONICA Study and 59% in the VIP. Approximately 90% of NSHDS participants were from the VIP. For individuals who participated in both the VIP and MONICA studies, only data from the first participation were included in this study.

Linkages were made between NSHDS and incidence registries (16), with the identification of MI cases without previous MI, stroke, or cancer. Control subjects were matched with cases for sex, age, date of health examination, and municipality.

From the first study (10), 55 male MI cases up to 1994 were included with 1:2 control subjects [Northern Sweden Health and Disease Study 1 (NSHDS1)]. From the other study (11), 306 cases up to 1999 were included with 1:1 control subjects [Northern Sweden Health and Disease Study 2 (NSHDS2)]. The average follow-up was 18 mo in NSHDS1 (10) and 3 y and 11 mo in NSHDS2 (11).

The KIHD Study is an ongoing population-based study that was designed to investigate risk factors of cardiovascular disease and other chronic diseases in middle-aged men from eastern Finland (5–7, 17). Baseline examinations were carried out in 1984–1989 in 2682 men aged 42–60 y (82.9% of eligible subjects). Subjects donated hair and fasting venous blood. MI events in 1984–1992 were registered as part of the MONICA project (18) and in 1993–2005 by using computer linkage with the national hospitalization registry. In total, 1957 men without a history of ischemic heart disease and with data on hair-Hg were included. In these subjects, 211 men with a first definite MI until 31 December 2005 and information on both hair-Hg and S-PUFA were included in this study. In a nested case-control (1:3) dataset, 623 control subjects were matched with these cases for age and examination year by using incidence sampling of control subjects. The average follow-up was 16 y and 6 mo.

Baseline variables

BMI (in kg/m^2) was calculated as weight divided by the square of height. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were used as continuous variables. Diabetes was defined as self-reported disease from the questionnaire or a fasting glucose concentration ≥7 mmol/L. A 2-h glucose test was performed in the Swedish study but not in the Finnish study and was, therefore, not considered in the definition of diabetes. Total cholesterol was measured in serum that was sampled after >4 h of fasting. Apolipoprotein A-I (apo A-I) and B (apo B) were analyzed in plasma by using immunoturbidimetry. Smoking habits were classified as never smoker (including occasional smokers), former smoker, or current smoker. Educational level was categorized as low (elementary school), medium (upper secondary school), or high (university degree). The total intake of alcohol (strong beer, wine, and spirits) was categorized as <1, 1 to <2, or ≥2 times/wk. Data on the frequency of alcohol consumption was available but not on quantities. The level of physical activity was categorized as no (including never or hardly ever) or any physical activity.

Blood sampling

NSHDS

Venous blood was drawn without stasis into evacuated tubes after >4 h of fasting. Erythrocytes and plasma were separated by centrifugation for 15 min at 1500 × *g* and then stored at −80°C until analysis (19).

KIHD Study

Venous blood was drawn without stasis into evacuated tubes after the subject had abstained from the ingestion of alcohol for 3 d, smoking for 12 h, and eating for 12 h. A hair sample was taken at the same occasion.

Mercury analysis

NSHDS

Mercury was determined in duplicate in acid-digested erythrocytes by using the atomic fluorescence technique (20). The detection limit was 0.2 ng Hg/g erythrocytes in the NSHDS1 (10)

and 0.14 μg Hg/L in the NSHDS2 (11). The imprecision (CV = CV at duplicate determinations) varied between 3% and 5%.

KIHD Study

Hair-Hg was determined by using cold vapor atomic absorption spectrometry. Briefly, the quality-control materials with certified mercury content for hair-Hg measurement were hair pool, flour that contained mercury, and pig kidney (6). The imprecision (CV) was 7.3%, 3.9%, and 6.1%, respectively.

Transformation

We transformed Ery-Hg into hair-Hg. The ratio of hair-Hg to the amount of mercury in blood was set to 250:1 (21–24). The ratio was similar in 9 blood samples from Finland in which hair-Hg had been analyzed at baseline; the mean ratio of hair-Hg to the amount of mercury in blood was 272:1 (*see* Table 6S under "Supplemental data" in the online issue). The packed cell volume was set to 0.44 (25), and the ratio of Ery-Hg to plasma mercury was set to 4.3 (21, 23, 26, 27).

Fatty acid analysis

NSHDS

Fatty acids in plasma were separated by using thin-layer chromatography and transmethylation and determined by using gas-liquid chromatography (28). The relative amounts of fatty acids were expressed as the percentage of all fatty acids in plasma phospholipids. The method of imprecision (CV) was <1% to 5.5% (29).

KIHD Study

Serum concentrations of esterified and nonesterified fatty acids were determined in one gas-liquid chromatography run (30). The imprecision (CV) was ~5% for esterified and ~15% for nonesterified fatty acids.

Transformation

To make values for PUFA comparable between the NSHDS and the KIHD Study, 33 samples were analyzed with both methods and had strong associations [EPA (R^2 = 0.96) and DHA (R^2 = 0.78)]. Thus, plasma PUFA was transformed to S-PUFA on the basis of the straight-line equation (*see* Figure 2S under "Supplemental data" in the online issue).

Statistical analysis

Our statistical approach to estimating and evaluating the effects of the fish intake–related biomarker variables (hair-Hg and S-PUFA) on MI risk included *1*) detailed descriptions of biomarker distributions in the study populations, *2*) work on finding a parametric model that fairly reflected the multiplicative effects of S-PUFA and hair-Hg on MI risk within wide biomarker ranges (including the vast majority of data), *3*) work on estimating and illustrating model-based RRs, and *4*) work on calculating a relevant epidemiologic measure (ie, the expected preventable fraction of cases) that reflected the potential public health impact of achieving a systematic change in the biomarker distribution for a population.

A crucial task was to find a logistic regression model that well described the effects of S-PUFA and hair-Hg on MI risk. First, we categorized biomarker variables by using 4 categories for S-PUFA and 3 categories for hair-Hg (ie, 4 × 3 = 12 combined S-PUFA and hair-Hg categories) (*see* Table 5S under "Supplemental data" in the online issue). Adjacent categories were collapsed to 2 × 2 = 4 combined S-PUFA and hair-Hg categories (**Table 1**). We proceeded with model building without categorizing biomarker variables, which was a more efficient way of analyzing data. *See* "Supplemental data" in the online issue for a more detailed description of statistical methods. We considered first-degree fractional polynomial transformations of biomarker variables (31). Altogether, we considered 36 different functional formas of the model-based RR within our chosen inference domain (ie, hair-Hg ≤8 μg/g and S-PUFA ≥2% to S-PUFA ≤8%). Several aspects were taken into consideration when deciding a suitable model, including the generalizability of the model across pooled studies, model fit, and confounding adjustments. We carried out sensitivity analyses by addressing *1*) the influence of covariate adjustments and *2*) model diagnostics. Sensitivity analyses focused on the robustness of the model-based RRs within the inference domain. *See* "Supplemental data" in the online issue for a presentation of results on the model fit and sensitivity analyses. Smoking, BMI, DBP, SBP, diabetes, apo B and apo A-I, education, alcohol intake, and physical activity were considered as covariates. DBP and SBP

TABLE 1
Unconditional ORs for combined categories of low or high hair-Hg and S-PUFA[1]

			No. of cases and control subjects (in crude analyses)					
			KIHD Study		NSHDS1		NSHDS2	
S-PUFA and hair-Hg	Crude OR (95% CI)	Adjusted OR (95% CI)	Cases	Control subjects	Cases	Control subjects	Cases	Control subjects
<5.5% and <2.0 μg/g	1.0	1.0	109	367	48	89	262	245
≥5.5% and <2.0 μg/g	0.72 (0.49, 1.04)	0.75 (0.49, 1.15)	8	40	6	15	39	51
<5.5% and ≥2.0 μg/g	1.34 (0.96, 1.86)	1.24 (0.87, 1.77)	74	162	1	4	3	7
≥5.5% and ≥2.0 μg/g	1.00 (0.59, 1.69)	0.98 (0.55, 1.71)	20	54	0	2	2	5

[1] There was no significant interaction between hair-Hg and serum PUFA. Crude ORs (95% CIs) were adjusted for age and study. Adjusted ORs (95% CIs) were adjusted as for crude ORs (95% CIs) with additional adjustment for variables with significant difference in concentrations between cases and control subjects in any of the cohorts (ie, apolipoprotein B and A-I ratio, diastolic blood pressure, smoking, BMI, diabetes, and educational level). hair-Hg, amount of mercury in hair; KIHD, Kuopio Ischaemic Heart Disease Risk Factor; NSHDS1, Northern Sweden Health and Disease Study 1; NSHDS2, Northern Sweden Health and Disease Study 2; S-PUFA, PUFAs in serum.

TABLE 2
Baseline characteristics of subjects with different combinations of amounts of S-PUFA and hair-Hg[1]

	n	Low S-PUFA and low hair-Hg	High S-PUFA and low hair-Hg	Low S-PUFA and high hair-Hg	High S-PUFA and high hair-Hg
Hair-Hg (μg/g)	1613	0.570 (0.590)[2]	0.930 (0.620)	2.96 (1.88)	3.22 (2.68)
S-PUFA (%)	1613	3.78 (1.14)	6.22 (1.18)	3.93 (1.37)	6.89 (2.28)
Age (y)	1613	53.1 ± 6.54[3]	54.1 ± 6.11	54.2 ± 4.41	54.3 ± 3.90
Smoking habits (%)	1581				
Never		36.6	41.8	28.2	23.5
Former		31.6	35.3	36.7	44.7
Current		31.8	22.9	35.1	31.8
BMI (kg/m^2)	1585	26.2 (4.30)	25.8 (4.10)	26.9 (4.10)	27.4 (5.90)
Systolic blood pressure (mm Hg)	1578	136 ± 16.6	136 ± 17.0	137 ± 17.2	138 ± 16.5
Diastolic blood pressure (mm Hg)	1578	87.6 ± 9.78	86.7 ± 8.98	90.0 ± 10.3	90.1 ± 9.80
Diabetes (%)	1581	4.57	10.5	6.43	4.71
Serum cholesterol (mmol/L)	1582	6.08 ± 1.17	6.11 ± 1.16	6.17 ± 1.21	6.17 ± 0.861
apo B and apo A-I ratio	1598	1.00 ± 0.252	0.989 ± 0.248	1.10 ± 2.33	1.08 ± 0.181
Educational level (%)	1562				
Low		58.8	41.4	83.1	68.2
Medium		32.4	33.6	12.1	20.0
High		8.82	25.0	4.84	11.8
Alcohol consumption (%)	1274				
<1 time/wk		74.6	67.4	55.0	46.5
1 to <2 times/wk		17.7	21.0	27.8	35.2
≥2 times/wk		7.70	11.6	17.2	18.3
Physical inactivity (%)	1486	26.5	29.9	17.9	10.7

[1] Low S-PUFA: <5.5%; high S-PUFA: ≥5.5%; low hair-Hg: <2.0 μg/g; and high hair-Hg: ≥2.0 μg/g. apo A-I, apolipoprotein A-I; apo B, apolipoprotein B; hair-Hg, amount of mercury in hair; S-PUFA, PUFAs in serum.
[2] Median; IQR in parentheses (all such values).
[3] Mean ± SD (all such values).

were highly correlated; when added simultaneously, only DBP contributed significantly. Alcohol intake and physical activity did not contribute significantly to the crude model. Therefore alcohol intake, physical activity, and SBP were excluded from the most extensive model. The different models yielded somewhat various variable estimates β^*_1 and β^*_2 (*see* Table 2S under "Supplemental data" in the online issue), but this variation was only marginal and did not notably affect the model-based RR estimates. Therefore, we advocated the crude, unconditional model for describing the effects of S-PUFA and hair-Hg. Data were analyzed with the software programs SPSS (15.0 and 18.0 for Windows; SPSS Inc). $P \leq 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics for biomarkers in categories are shown in **Table 2**. Traditional risk factors differed between control subjects in Finland (higher BMI, DBP, and apo B and apo A-I) and in Sweden (higher serum total cholesterol; s*ee* Table 3S under "Supplemental data" in the online issue). The established risk factors smoking, BMI, blood pressure, diabetes, serum total cholesterol, apo B and apo A-I, and low education were all significant predictors of risk in the total material as well as in the 3 individual studies (although not always significant), whereas alcohol intake and physical inactivity were not significant predictors of risk (s*ee* Table 4S under "Supplemental data" in the online issue).

Hair-Hg was higher in Finland (medians in control subjects: NSHDS, 0.57 μg/g; KIHD Study, 1.32 μg/g; $P < 0.001$), whereas S-PUFA was higher in Sweden (NSHDS: 4.21%; KIHD: 3.83%, $P < 0.001$) (*see* Table 3S under "Supplemental data" in the online issue). The median hair-Hg in combined control subjects was 0.88 μg/g and median S-PUFA was 4.00%.

Individual hair-Hg and S-PUFA correlated positively, both in the pooled material (Spearman's rank-correlation coefficient $r_s = 0.29$; $P < 0.001$) and in the 3 individual studies ($r_s = 0.36$ in the KIHD Study, $r_s = 0.52$ in NSHDS1, and $r_s = 0.54$ in NSHDS2) (**Figure 1**). Data were sparse for hair-Hg >8 μg/g and S-PUFA >8% or <2%.

With the use of categorized biomarker variables, with S-PUFA <5.5% and hair-Hg <2.0 μg/g as the reference category, a tendency toward an elevated risk was seen by solely increasing hair-Hg (≥2.0 μg/g; $P = 0.07$), whereas a tendency for reduced risk was indicated by solely increasing S-PUFA (≥5.5%; $P = 0.08$) (Table 1). Adjustment for significant covariates weakened point estimates somewhat, although not pronouncedly (Table 1). In logistic regression, with continuous biomarker variables, hair-Hg was associated with higher MI risk ($P = 0.005$), and S-PUFA was associated with lower MI risk ($P = 0.011$) (*see* Table 2S under "Supplemental data" in the online issue). We checked whether there was evidence for an additional interaction effect between biomarkers by adding the term $\beta_3 f_1$ (S-PUFA) $\times f_2$ (hair-Hg) to the model by using Wald's test for the null hypothesis $\beta_3 = 0$. Although there was no significant interaction between hair-Hg and S-PUFA ($P = 0.8$) (*see* Table 1S under "Supplemental data" in the online issue), the harmful effect that was related to hair-Hg appeared to be attenuated by increasing concentrations of S-PUFA at all mercury concentrations. Likewise, the beneficial effect of PUFA on MI was counteracted by

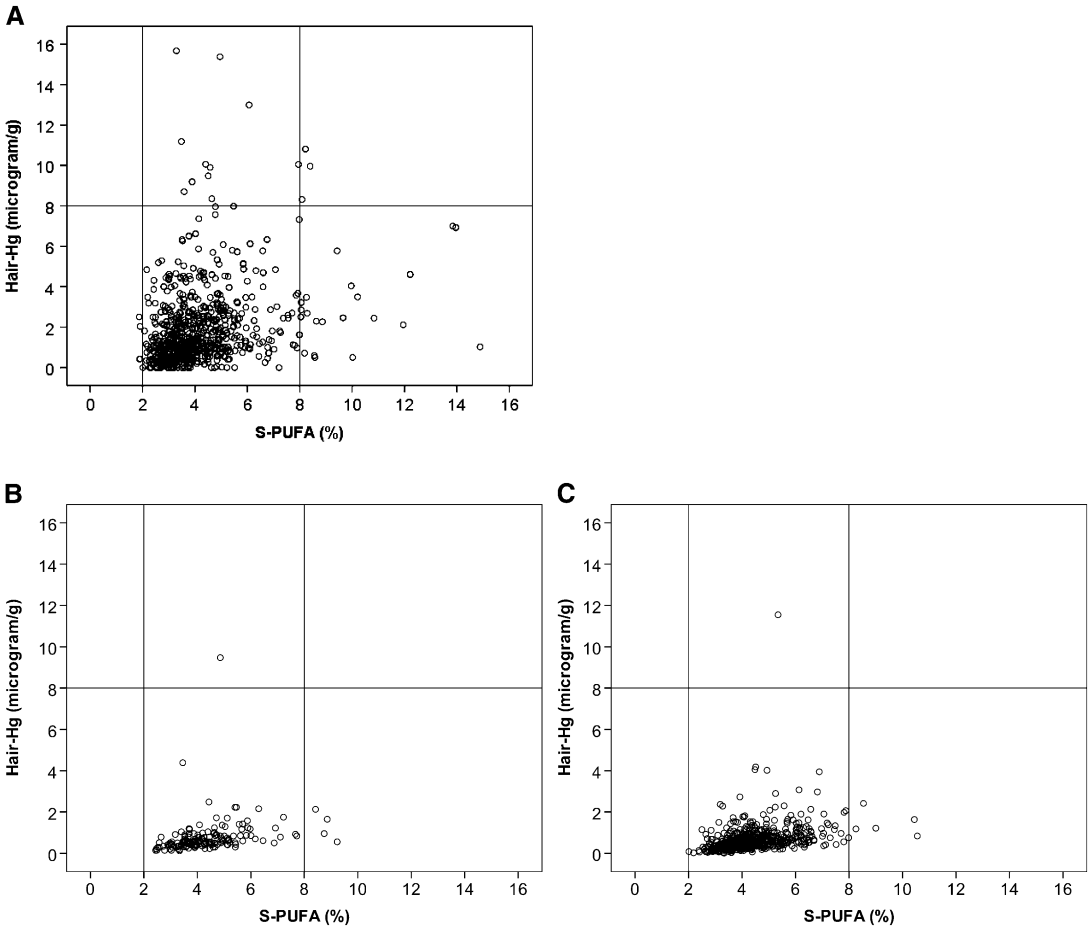

FIGURE 1. Correlations between Hair-Hg and long-chain n−3 S-PUFA in one Finnish study [ie, the Kuopio Ischaemic Heart Disease Risk Factor Study (A)] and 2 Swedish studies [Northern Sweden Health and Disease Study 1 (B) and Northern Sweden Health and Disease Study 2 (C)]. Hair-Hg, amount of mercury in hair; S-PUFA, PUFAs in serum.

methylmercury but only at a high hair-Hg (**Figure 2**). Furthermore, we checked whether each candidate crude model seemed to hold across pooled studies (KIHD Study, NSHDS1, and NSHDS2). We tested the hypothesis of no modification of fish intake–related biomarker effects by study by using Wald's test for interaction effects of f_1 (S-PUFA) $\times$ study and f_2 (hair-Hg) $\times$ study, respectively. There was no evidence for a modification by study (*see* Table 1S under "Supplemental data" in the online issue).

To estimate RRs, we set the reference point (RR = 1.0) at the median amounts for control subjects (reference S-PUFA of 4% and hair-Hg of 1 μg/g). The model-based adjusted RRs varied between 0.56 and 1.97 (Figure 2). If the point with the lowest RR (high S-PUFA and low hair-Hg; RR = 0.56) was used as the reference, risk in the low–S-PUFA and high–hair-Hg corner approached RR = 1.97 $\div$ 0.56 = 3.5.

By calculating the (approximate) 95% CIs around model-based RRs, we were able to assess what values for hair-Hg and S-PUFA implied significant harmful (lower CI above RR = 1.0) and protective (upper CI below RR = 1.0) effects (**Figure 3**). The fully adjusted model (Figure 2) provided similar results; covariate adjustments did not notably affect model-based RRs for biomarker values that yielded nonsignificant effects (Figure 3, yellow area). Moreover, results for categorized biomarker variables (Table 1; *see* Table 5S under "Supplemental data" in the online issue) were in reasonable accord with these model-based results.

To assess the potential public health impact of a systematic change in the biomarker distribution for a population, we calculated the expected preventable fraction of MI cases (*see* Calculation of the expected preventable fraction of cases under "Supplemental data" in the online issue). If the Finnish cohort changed to the S-PUFA and hair-Hg of Swedish control subjects, 8% of MI cases would be expected to be prevented. If the Swedish control subjects increased their S-PUFA by 1% and concomitantly hair-Hg by 0.2 μg/g, an additional 7% of MIs would be expected to be prevented.

DISCUSSION

The results from this study suggested that the balance between methylmercury and PUFA intakes is important for MI risk. However, a significant net harm of hair-Hg was not seen before amounts reached >2 μg/g and with simultaneously low S-PUFA (Figures 2 and 3). Because both S-PUFA and hair-Hg are associated with fish consumption, this is an unusual combination, at least in Western countries (8–10, 32). The optimal situation is to have high concentrations of PUFAs and low amounts of mercury. With the assumption of a causal relation, the impact on public health would be significant if populations moved toward the optimal situation.

We have previously observed increased MI risk with increasing mercury in the Finnish population (7) but a decreased MI

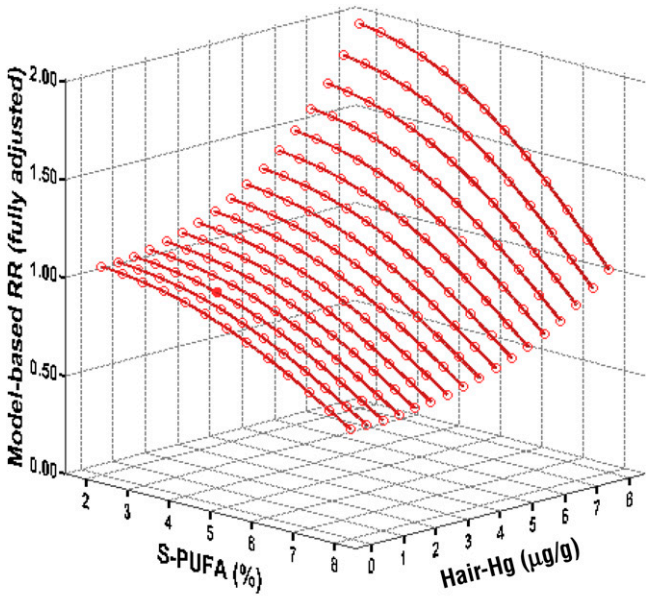

FIGURE 2. Adjusted risk of myocardial infarction as a function of Hair-Hg and long-chain n−3 S-PUFA. Model-based RRs are shown. The reference point (RR = 1.0) was set to S-PUFA = 4.0% and Hair-Hg = 1.0 μg/g (indicated by a filled red circle). The model can be expressed as $\ln(RR) = -0.127 \times [(\text{S-PUFA}^3 \div 100) - (4^3 \div 100)] + 0.096 \times [(\text{Hair-Hg}^2 \div 10) - (1 \div 10)]$. Hair-Hg, amount of mercury in hair; S-PUFA, PUFAs in serum.

risk in the Swedish population (10, 11). These observations first appeared contradictory, but when data on both PUFA and mercury were pooled, risk relations could be modeled coherently. Because of the difference in ratios between mercury and PUFA, increased fish consumption makes the Swedish and Finnish populations move in different directions in the plane shown in Figure 2, which gives rise to either an increase or a decrease in MI risk. The estimated risk-benefit model (Figure 2) showed the best fit in a flexible set of candidate models (fractional polynomials). We stress that there was notable statistical uncertainty related to the fitted model reflected in Figure 3 (as well as the effect estimates with relatively wide 95% CIs on the basis of the 4 × 3 categorization of the 2 biomarkers) (*see* Table 5S under "Supplemental data" in the online issue). With statistical uncertainty taken into account, the inference concerning the correct risk-benefit model should be made with caution.

There were some other limitations of this study. The Finnish and Swedish populations overlapped only to a limited extent concerning amounts of mercury. In practice, the majority of subjects (59 of 98 individuals) in the interval that implied protective effects (Figure 3, green circles) were from Sweden, and a vast majority of subjects (77 of 81 individuals) in the interval that implied harmful effects (red circle) were from Finland. Established risk factors were associated with MI risk in both countries, but there were some differences in prevalence of these risk factors between countries (*see* Table 3S under "Supplemental data" in the online issue). However, control subjects were selected from the same population as the corresponding cases, which minimized any bias from differences in MI risk factors between countries. There may be dietary or lifestyle factors that were not controlled for in this study that differ between Swedish and Finnish populations. We could not rule out the possibility that genetic differences between populations affect the metabolism of mercury (33) or the association between Hg and MI risk (34).

We have used biomarker data, which are more suitable for modeling than fish-consumption data. The dietary-assessment methods used in the 2 cohorts are different, and neither method is optimal for the assessment of fish consumption. Therefore, we did not include fish consumption in the model. It is outside the scope of this study to elucidate why mercury amounts are higher and S-PUFA concentrations are lower in the Finnish compared with Swedish populations. However, the significantly lower S-PUFA and concurrently higher hair-Hg in the KIHD Study than in the NSHDS indicated a higher consumption of lean, predatory fish in Finland. Predatory fish species (such as pike and perch) have generally higher concentrations of methylmercury because of the accumulation through the food chain than do nonpredatory fish species, and predatory fish species consumed in both of these regions are low in fat.

To be able to pool the studies, we transformed plasma PUFA into S-PUFA and Ery-Hg into hair-Hg. For PUFA, a strong correlation between plasma and serum was demonstrated. For mercury, there are data available in the literature although mainly from studies on relatively high concentrations (21–23). However, we do not think that this is an important bias, because a similar ratio was shown in the KIHD Study. Our data were sparse for hair-Hg >8 μg/g and S-PUFA outside the range of 2–8%. Thus, there was no rationale for extrapolations outside these limits.

The hair-Hg in control subjects in our study (median: 0.9 μg/g) was higher than in the United States [geometric mean: 0.2 μg/g in adult women (32)]. The S-PUFA data were in accord with findings in other materials from Western countries (35).

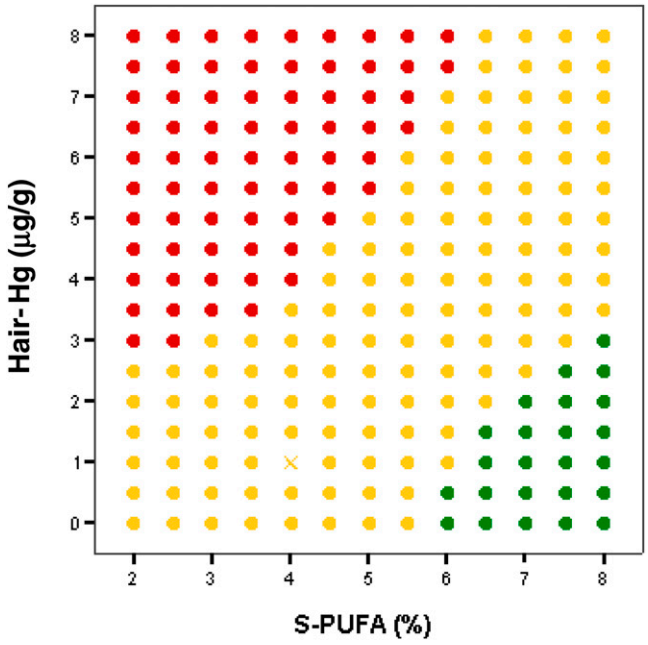

FIGURE 3. Associations of concentrations of long-chain n−3 S-PUFA and Hair-Hg with risk reduction (green circles; upper 95% CI limit for model-based RR <1.0) or increased risk of myocardial infarction (red circles; lower 95% CI limit RR >1.0), with the reference point (RR = 1.0; yellow X) set to S-PUFA = 4.0% and Hair-Hg = 1.0 μg/g; yellow circles denote no statistical evidence of an effect. Hair-Hg, amount of mercury in hair; S-PUFA, PUFAs in serum.

Given the strong association between MI risk and fish-related biomarkers, it appears that a change in methylmercury contamination in the fish consumed and a change in the fish consumption pattern could notably affect MI incidence in a general population. The calculation of the expected preventable fraction of MI cases showed that a change in the Finnish cohort to Swedish S-PUFA and methylmercury concentrations (ie, by a change from consumption of lean, predatory fish to more of fat nonpredatory fish) would prevent 8% of MI cases. This rough calculation indicates mainly the beneficial effect of a reduction of methylmercury contamination in fish. In the Swedish population, a moderate increase in S-PUFA (ie, by an increase in fish consumption) would prevent 7% of MIs, despite a concomitant small increase in mercury exposure. It would have been of interest to express these biomarker changes in terms of increased fish intakes, but unfortunately, the correlations between biomarkers and self-reported fish intakes were too weak to allow reliable predictions. However, these rough calculations show that small changes in fish consumption can be expected to notably affect the MI incidence, at least in a population of middle-aged men.

In estimates of RRs at a varying hair-Hg and S-PUFA, we used (approximate) medians in the combined material as references (Figures 2 and 3); the combined estimate of the study-specific reference log odds in the logistic regression model then became relatively stable. Instead, if we used the high–S-PUFA and low–hair-Hg corner point as a reference, RRs ranged up to 3.6, which indicated what may potentially be achieved by the optimization of the intake of PUFA and methylmercury in the fraction of the population that carries the greatest risk.

Studies on fish intake and health have usually focused on risk of methylmercury or benefits of PUFA. Our results showed that these should be considered together when methylmercury concentrations are high. The results suggested that a higher fish consumption is beneficial when concentrations of methylmercury are low (Figure 2). This finding means that the health-based tolerable limits of methylmercury in fish may differ between populations and that recommendations by authorities to the general public regarding fish consumption may differ between populations. Instead of targeting the individual, if we focus on policy and food production, our model predicted that a decrease of methylmercury in polluted fish would decrease the incidence of MI.

The current study is an example of the risk-benefit concept (ie, the balance between beneficial and harmful components in the diet). It is a simple concept, which deals with only one outcome. There may be a similar situation for the methylmercury-induced risk and PUFA-associated benefit for other outcomes, such as the development and disorders of the central nervous system of the fetus or infant (36, 37).

In conclusion, high exposure to methylmercury was associated with increased risk of MI, and high exposure to S-PUFA was associated with decreased risk of MI. Therefore, the balance between intakes of PUFA and methylmercury from fish is important, and risk of MI may be reduced by the consumption of fish high in PUFA and low in methylmercury, at least in middle-aged men.

The authors' responsibilities were as follows—SS and US: designed the research; J-HJ, MN, JK, JTS, T-PT, JKV, and BV: provided essential materials; MW and US: performed statistical analyses; MW, IAB, JTS, SS, US, and JKV: interpreted data; MW: wrote the manuscript; IAB, J-HJ, JK, MN, JTS, SS, US, T-PT, BV, and JKV: critically revised the manuscript for important intellectual content; MW and JKV: had primary responsibility for the final content of the manuscript; and all authors: read and approved the final manuscript. None of the authors had a conflict of interest.

REFERENCES

1. He K. Fish, long-chain omega-3 polyunsaturated fatty acids and prevention of cardiovascular disease–eat fish or take fish oil supplement? Prog Cardiovasc Dis 2009;52:95–114.
2. Giovannucci E. Vitamin D and cardiovascular disease. Curr Atheroscler Rep 2009;11:456–61.
3. Navas-Acien A, Bleys J, Guallar E. Selenium intake and cardiovascular risk: what is new? Curr Opin Lipidol 2008;19:43–9.
4. Virtanen JK, Rissanen TH, Voutilainen S, Tuomainen TP. Mercury as a risk factor for cardiovascular disease. J Nutr Biochem 2007;18: 75–85.
5. Rissanen T, Voutilainen S, Nyyssonen K, Lakka TA, Salonen JT. Fish oil-derived fatty acids, docosahexaenoic acid and docosapentaenoic acid, and the risk of acute coronary events: the Kuopio ischaemic heart disease risk factor study. Circulation 2000;102:2677–9.
6. Salonen JT, Seppanen K, Nyyssonen K, Korpela H, Kauhanen J, Kantola M, Tuomilehto J, Esterbauer H, Tatzber F, Salonen R. Intake of mercury from fish, lipid peroxidation, and the risk of myocardial infarction and coronary, cardiovascular, and any death in eastern Finnish men. Circulation 1995;91:645–55.
7. Virtanen JK, Voutilainen S, Rissanen TH, Mursu J, Tuomainen TP, Korhonen MJ, Valkonen VP, Seppanen K, Laukkanen JA, Salonen JT. Mercury, fish oils, and the risk of myocardial infarction. Arterioscler Thromb Vasc Biol 2005;25:228–33.
8. 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;347:1747–54.
9. Mozaffarian D, Shi P, Morris JS, Spiegelman D, Grandjean P, Siscovick DS, Willet WC, Rimm EB. Mercury exposure and risk of cardiovascular disease in two U.S. cohorts. N Engl J Med 2011;364: 1116–25.
10. Hallgren CG, Hallmans G, Jansson JH, Marklund SL, Huhtasaari F, Schutz A, Stromberg U, Vessby B, Skerfving S. Markers of high fish intake are associated with decreased risk of a first myocardial infarction. Br J Nutr 2001;86:397–404.
11. Wennberg M, Bergdahl IA, Hallmans G, Norberg M, Lundh T, Skerfving S, Stromberg U, Vessby B, Jansson JH. Fish consumption and myocardial infarction: a second prospective biomarker study from northern Sweden. Am J Clin Nutr 2011;93:27–36.
12. Roman HA, Walsh TL, Coull BA, Dewailly E, Guallar E, Hattis D, Marien K, Schwartz J, Stern AH, Virtanen JK, et al. Evaluation of the cardiovascular effects of methylmercury exposures: current evidence supports development of a dose-response function for regulatory benefits analysis. Environ Health Perspect 2011;119:607–14.
13. Stern AH, Korn LR. An approach for quantitatively balancing methylmercury risk and omega-3 benefits in fish consumption advisories. Environ Health Perspect 2011;119:1043–6.
14. Hallmans G, Agren A, Johansson G, Johansson A, Stegmayr B, Jansson JH, Lindahl B, Rolandsson O, Soderberg S, Nilsson M, et al. Cardiovascular disease and diabetes in the Northern Sweden Health and Disease Study Cohort – evaluation of risk factors and their interactions. Scand J Public Health Suppl 2003;61:18–24.
15. Norberg M, Wall S, Boman K, Weinehall L. The Vasterbotten Intervention Programme: background, design and implications. Glob Health Action 2010;Mar 22:3 (DOI:10.3402/gha.v3i0.4643).
16. Stegmayr B, Lundberg V, Asplund K. The events registration and survey procedures in the Northern Sweden MONICA Project. Scand J Public Health Suppl 2003;61:9–17.
17. Salonen JT. Is there a continuing need for longitudinal epidemiological research? The Kuopio Ischaemic Heart Disease Risk Factor Study. Ann Clin Res 1988;20:46–50.
18. Tuomilehto J, Arstila M, Kaarsalo E, Kankaanpaa J, Ketonen M, Kuulasmaa K, Lehto S, Miettinen H, Mustaniemi H, Palomaki P, et al. Acute myocardial infarction (AMI) in Finland-baseline data from the FINMONICA AMI register in 1983-1985. Eur Heart J 1992;13: 577–87.

19. Van Guelpen B, Hultdin J, Johansson I, Hallmans G, Stenling R, Riboli E, Winkvist A, Palmqvist R. Low folate levels may protect against colorectal cancer. Gut 2006;55:1461–6.
20. Sandborgh-Englund G, Elinder CG, Langworth S, Schutz A, Ekstrand J. Mercury in biological fluids after amalgam removal. J Dent Res 1998;77:615–24.
21. Birke G, Johnels AG, Plantin LO, Sjostrand B, Skerfving S, Westermark T. Studies on humans exposed to methyl mercury through fish consumption. Arch Environ Health 1972;25:77–91.
22. Choi AL, Weihe P, Budtz-Jorgensen E, Jorgensen PJ, Salonen JT, Tuomainen TP, Murata K, Nielsen HP, Petersen MS, Askham J, et al. Methylmercury exposure and adverse cardiovascular effects in Faroese whaling men. Environ Health Perspect 2009;117:367–72.
23. Skerfving S. Methylmercury exposure, mercury levels in blood and hair, and health status in Swedes consuming contaminated fish. Toxicology 1974;2:3–23.
24. Methylmercury WHO. Environmental health criteria 101. International Programme on Chemical safety. Geneva: World Health organization, 1990.
25. Fernlund PFG, Hanson A, Stenflo J, Lundh B. Laurells clinical chemistry in practical medicine. Lund, Sweden: Studentlitteratur; 1991.
26. Molin M, Schutz A, Skerfving S, Sallsten G. Mobilized mercury in subjects with varying exposure to elemental mercury vapour. Int Arch Occup Environ Health 1991;63:187–92.
27. Svensson BG, Schutz A, Nilsson A, Akesson I, Akesson B, Skerfving S. Fish as a source of exposure to mercury and selenium. Sci Total Environ 1992;126:61–74.
28. Boberg M, Croon LB, Gustafsson IB, Vessby B. Platelet fatty acid composition in relation to fatty acid composition in plasma and to serum lipoprotein lipids in healthy subjects with special reference to the linoleic pathway. Clin Sci (Lond) 1985;68:581–7.
29. Smedman AE, Gustafsson IB, Berglund LG, Vessby BO. Pentadecanoic acid in serum as a marker for intake of milk fat: relations between intake of milk fat and metabolic risk factors. Am J Clin Nutr 1999;69:22–9.
30. Laaksonen DE, Lakka TA, Lakka HM, Nyyssonen K, Rissanen T, Niskanen LK, Salonen JT. Serum fatty acid composition predicts development of impaired fasting glycaemia and diabetes in middle-aged men. Diabet Med 2002;19:456–64.
31. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. Int J Epidemiol 1999;28:964–74.
32. McDowell MA, Dillon CF, Osterloh J, Bolger PM, Pellizzari E, Fernando R, Montes de Oca R, Schober SE, Sinks T, Jones RL, et al. Hair mercury levels in U.S. children and women of childbearing age: reference range data from NHANES 1999-2000. Environ Health Perspect 2004;112:1165–71.
33. Custodio HM, Broberg K, Wennberg M, Jansson JH, Vessby B, Hallmans G, Stegmayr B, Skerfving S. Polymorphisms in glutathione-related genes affect methylmercury retention. Arch Environ Health 2004;59:588–95.
34. Engström KS, Wennberg M, Stromberg U, Bergdahl IA, Hallmans G, Jansson JH, Lundh T, Norberg M, Rentschler G, Vessby B, et al. Evaluation of the impact of genetic polymorphisms in glutathione-related genes on the association between methylmercury or n−3 polyunsaturated long chain fatty acids and risk of myocardial infarction: a case-control study. Environ Health 2011;10:33.
35. Andersen LF, Solvoll K, Johansson LR, Salminen I, Aro A, Drevon CA. Evaluation of a food frequency questionnaire with weighed records, fatty acids, and alpha-tocopherol in adipose tissue and serum. Am J Epidemiol 1999;150:75–87.
36. Choi AL, Cordier S, Weihe P, Grandjean P. Negative confounding in the evaluation of toxicity: the case of methylmercury in fish and seafood. Crit Rev Toxicol 2008;38:877–93.
37. Strain JJ, Davidson PW, Bonham MP, Duffy EM, Stokes-Riner A, Thurston SW, Wallace JM, Robson PJ, Shamlaye CF, Georger LA, et al. Associations of maternal long-chain polyunsaturated fatty acids, methyl mercury, and infant development in the Seychelles Child Development Nutrition Study. Neurotoxicology 2008;29:776–82.