# Evaluation of Chowdhury Meta-Analysis on the Association of Fatty Acids with Coronary Risk, Part 2

"There are three kinds of lies: lies, damned lies and statistics."1

Fred Pollack April 29, 2014

This is part 2 of my review of the <u>Chowdhury meta-</u> analysis study [1] that was published online at the Annals of Internal Medicine on March 18, 2014. The study effectively said that the current guidelines on saturated fatty acid (SFA) intake (<10% of calories from SFA) were not justified by the evidence and should be reconsidered. That led Mark Bittman, the NY Times Magazine's lead food columnist to write, <u>Butter is Back</u>, and said, *"Julia Child, goddess of fat, is beaming somewhere. Butter is back, and when you're looking for a few chunks of pork for a stew, you can resume searching for the best pieces — the ones with the most fat."* 

#### About Fred

I live with my wife, Iris, in Miami Beach. We are both 65. I worked at Intel for 23 years, and retired in early 2001. For most of my last 8 years at Intel, I directed the planning for Intel's future microprocessors. In January 1993, I was named an Intel Fellow.

My wife and I have been eating a low-fat whole-food plant-based diet since February 2009.

From my own extensive reading of the medical/nutritional research, I doubted Chowdhury's conclusion, and thus

was compelled to do an in-depth review. And, the only way to do this is to read and analyze all 20 of the SFA intake studies that were used in the Chowdhury meta-analysis. Part 1 of my review, published in last month's McDougall Newsletter, looked at just 2 of the 20 studies - one that showed the most benefit to higher intakes of SFA (MALMO) and one that showed the most harm (Oxford Vegetarian). My analysis of MALMO study described the major flaws, which were pointed out by the authors themselves in the paper that Chowdhury referenced. And, the conclusions in the paper are quite different than what Chowdhury's analysis indicated.

Last month, my expectation was that I could complete and document my analyses of all 20 studies, provide a summary for the newsletter, which would have a link to download my detailed (and, as my wife says, esoteric and boring) analyses of all 20 papers. But there just wasn't enough time. So for that, you will have to wait for part 3, next month.

So what is this part about? Two related topics. One is how one country, Finland, which had the highest coronary heart disease mortality in the world in the early 1970's, reduced their rate by 80% over a 35 year period. The other is about a study in east Finland (part of the Chowdhury et al meta-analysis), the Kuopio Ischaemic Heart Risk Factor (KIHD) study. With the data that I uncovered, the KIHD paper (2005) [3] should not have passed the peer-review process and been published.

<sup>&</sup>lt;sup>1</sup> Attributed by Mark Twain in his autobiography to Disraeli. But the origin is more complex than that. See <u>http://</u><u>www.york.ac.uk/depts/maths/histstat/lies.htm</u>

When does the sin of omission become a *lie*? I will show that there were very relevant blatant omissions in the KIHD paper. Does that make it a *damned lie*? When *statistics* are applied to give the illusion of truth, we end up with *"Lies, Damned Lies, and Statistics"*.

A day's of research on the internet by Chowdhury et al should have uncovered the flaws in the KIHD study, and thus, excluded it from their meta-analysis. But of the 20 studies in the Chowdhury meta-analysis, the KIHD study was the only one marked by Chowdhury as "Estimates were available through correspondence with the study authors." The other 19 studies had sufficient data in their published papers for Chowdhury et al to construct a Relative Risk (RR) for increased SFA intake with a 95% confidence interval (CI), but not the KIHD study. They had to communicate with KIHD researchers to get the extra data. And, nothing was said about the flaws? Nothing? Really?

The next section, i.e. the good news, describes what happened in Finland over a 35-year period, which I found fascinating. And, it provides a story of SFA intake and societal change. That will then give me the context to discuss the KIHD study.

Since this is a long article for a newsletter, at the beginning of each section, I have the key messages. So just read those, if you want a quick read.

## Finland (1972 to 2007)

Key Messages:

- In 1973, Finland had a highest country death rate for men from CHD.
- By 2007, the CHD death rate for men dropped by 80% 3/4 due to a reduction in risk factors.
- The decrease in serum cholesterol was 2/3 of that reduction.
- Saturated fat (SFA) intake went from 22% of dietary energy intake to 13%.
- From 1965 to 2005, butter consumption fell from 40lbs to 7lbs per person per year.



## CHD Mortality per 100,000 men in 1973

In Finland, sample data was collected every 5 years, beginning in 1972. Beginning with the 1982 measurement, about 2-3 years after each measurement year, a summary article was often published in a medical journal [6, 7, 8, 9, 10]. The most recent one was published in 2009 [5], "Thirty-five-year trends in cardiovascular risk factors in Finland," and covers the period from 1972 to 2007. My summary draws from that paper, as well as a 2009 presentation [11] from Pekka Puska, Director General of Finland's National Institute for Health and Welfare (THL) and President of the World Health Federation. Below, all quotes are from the paper, and all graphs/charts are from the presentation (unless otherwise noted).

From the above chart of CHD mortality, clearly Finland had a problem in the early 1970's. The first risk factor surveys were carried out in East Finland (North Karelia and Kuopio provinces). "In 1972, a comprehensive community-based intervention programme, as a national pilot, was launched in North Karelia to reduce the burden of exceptionally high CHD morbidity and mortality. . . .After the initial 5-year period of the North Karelia Project (1972–1977), national preventive activities were gradually implemented."

"A remarkable decline in serum cholesterol levels was observed between 1972 and 2007. Blood pressure declined among both men and women until 2002 but leveled off during the last 5 years. Prevalence of smoking decreased among men. . . .Body mass index (BMI) has continuously increased among men. . . .*Risk factor changes explained a 60% reduction in coronary mortality in middle-aged men while the observed reduction was* **80%**."

Figure 1 is from the paper. Note that the most significant component of the risk factors is the drop in total serum cholesterol, i.e. two-thirds of the 60% decline in risk factors.<sup>2</sup> "Since the mid-1980s, many new treatments and invasive procedures for coronary patients have become more common and can probably explain most of the remaining decline in observed CHD



Figure 1 Observed and predicted decline in CHD mortality in men

mortality. In Finland, the change of risk factors seems to be more important than in many other countries. Based on different models, the impact of risk factors on mortality varied from 60% in New Zealand to 44% in the USA, and the impact of treatment varied from 23% in Finland to 47% in the USA."

What was responsible for the drop in serum cholesterol? From the paper, "Saturated fatty acids play the key role in the regulation of serum cholesterol." And, *"The total intake of* 

<sup>&</sup>lt;sup>2</sup> As noted in the paper, "There was a levelling-off period in serum cholesterol level between 1997 and 2002. This was parallel with the changes in saturated and polyunsaturated fat intake."

## saturated fat has declined in Finland from 22% of energy intake to 13% between 1972 and 2007."



## Milk Consumption in Finland in 1970 and 2006 (kg per capita)



## Fat Intake as Percentage of Energy in Finland



"During the past 30 years, the greatest change in health behavior in Finland has indisputably been the changes in diet, especially in the type and amount of fat and intake of fresh vegetables and fruit. In the early 1970s, Finland was a country with much dairy farming. Butter



## Use of Vegetable Oil for Cooking (men age 30–59)



## Estimates of S-Chol changes in 1982–2002\*



and milk production was subsidized and all vegetable oil was imported. The domestic vegetable oil industry was developed in the late 1970s and the popularity of vegetable oil grew remarkably in the 1980s. People were 'educated' in the effects of the types of fat and so could avoid fatty milk products and spreads with high saturated fat content as well as food products high in cholesterol."



To summarize, the CHD death rate in Finland over a 35 year period dropped 80%. Threefourths of this (60%) was explainable by a reduction in risk factors. About two-thirds of that was due to the major drop in serum cholesterol, and that was due principally to the drop in SFA intake from 22% of energy intake (i.e. calories) to 13%.

#### Mortality Changes in Finland from 1969–71 to 2006 (Men 35–64 Years, Age Adjusted)

	Rate (per 1	00.000)	Change from		
	1969–71	2006	1969–71 to 2006		
All causes	1328	583	- 56%		
All cardiovascular	680	172	- 75%		
Coronary heart disease	489	103	- 79%		
All cancers	262	124	- 53%		

#### **Finland Has Shown**

- Prevention of cardiovascular diseases is possible and pays off
- Population based prevention is the most cost effective and sustainable public health approach to CVD control
- Prevention calls for simple changes in some lifestyles (individual, family, community, national and global level action)
- Influencing diet and especially quality of fat is a key issue
- Many results of prevention occur surprisingly quickly (CVD, diabetes) and also at relatively late age
- Comprehensive action, broad collaboration with dedicated leadership and strong government policy support

### Kuopio Ischaemic Heart Risk Factor (KIHD) Study

#### **Key Messages**

- 1551 middle-aged men from East Finland recruited from 1984-1989. Ended in Dec-2001.
- · Studied PUFA intake effect on CVD death.
- Data (Food, lifestyle, blood-work, etc) collected only at beginning of study.
- Failed to disclose dramatic changes in Finnish diet during the study period in the paper.
- Failed to disclose major confounders (Trans-fats, mercury, excess body iron).
- When I say, "Failed", I mean that they knew, and blatantly omitted relevant data in the paper.
- Insufficient data in the paper to assess SFA intake why Chowdhury et al had to contact researchers.
- One-day's internet research on the KIHD study would have been sufficient for any one to reject this study from a meta-analysis. Why didn't Chowdhury et al?

This 2005 paper [5], cited by Chowdhury, is titled, "Prediction of Cardiovascular Mortality in Middle-aged Men by Dietary and Serum Linoleic and Polyunsaturated Fatty Acids." Thus, as

the title implies, the paper did not present any data on the risk of CHD with increased SFA intake. Rather, it presented data on the reduced risk of CHD with increasing PUFA (and Linoleic) intake. To get the SFA-intake/CHD-death relationship, Chowdhury et al had to request that data from the authors of the paper.

Before getting into my criticism of the authors, w.r.t. their sin of omissions, I'll present a quick summary of the study. Any quotes are taken directly from the paper.

"The study population comprised a random age-stratified sample of 2682 men living in eastern Finland who were 42, 48, 54, or 60 years old at baseline between 1984 and 1989. . . . all men with a history of CVD, diabetes, or cancer at baseline (n = 1123) were excluded. Men with missing data for both dietary and serum fatty acids were also excluded, leaving 1551 men for the analyses."

Dietary intake was based on 4-day food records (3 workdays and 1 weekend day). The consumption of foods was assessed at the time of blood sampling at baseline. Other measurements (e.g. blood pressure, weight, height), lifestyle (e.g. leisure time physical activity), and history (e.g. medical history, medications) were also determined.

"All deaths that occurred between study entry (March 1984–December 1989) and December 2001 were included." The median follow-up was 14.6 years. 78 men died of CVD (which included CHD and stroke). 225 men died from other causes.

Some info on fat intake, as % of Energy intake, for the entire cohort, as Mean (SD): Total fat, 39.7 (5.8); SFA, 19.4% (4.0); MUFA, 12.4 (2.2); PUFA, 4.5 (1.7). Note that the SFA intake is very high.

The paper presented 4 forms of multivariate analysis. Models 3 and 4 were over-adjustments, in my view. The analysis was done in thirds (tertiles). With Model 2,<sup>3</sup> men with a PUFA intake in the upper third were up to 54% less likely to die of CVD than those with an intake in the lower third (RR, 0.46 [95% CI, 0.24-0.86]).

Although the paper does not provide a similar analysis for SFA intake, it does provide results for dietary PUFA/SFA ratio, i.e. the higher the ratio, the lower risk of CVD. For model 2, men with a ratio in the upper third were up to 40% less likely to die of CVD than those with an intake in the lower third (RR, 0.60 [95% CI, 0.48-0.92]). But as PUFA intake goes up, does SFA intake go down?

<sup>&</sup>lt;sup>3</sup> "model 2, adjusted for age, year of examination, smoking, alcohol consumption, adult socioeconomic status and moderate to vigorous leisure-time physical activity. model 3, adjusted for model 2 and plasma lipid-standardized alpha-tocopherol levels, plasma ascorbic acid, and dietary total energy and energy-adjusted saturated fat and fiber intake; and model 4, adjusted for model 3 and low-density lipoprotein cholesterol concentrations, systolic blood pressure, blood pressure medication, family history of ischemic heart disease, C-reactive protein concentrations, fasting concentrations of insulin and nonesterified fatty acids, and body mass index."

Can we learn anything about SFA intake from this study, as represented by the paper. Quantitatively, no. But we can qualitatively based on some statements in the paper:

"Dietary PUFA and SAFA intake were inversely correlated (r = -0.34)."

"The inverse correlations of dietary PUFA and SAFA intake indicate that the apparent benefit of PUFA intake probably comes about in part through substitution of PUFA for SAFA intake (in these men, by substitution of margarine for butter). This, coupled with the inverse association of the dietary PUFA/SAFA ratio with CVD mortality, **provides support for increasing PUFA intake at the expense of SAFA intake in the primary prevention of CVD** and underscores the importance of dietary fat quality over quantity. These findings agree with those from the Western Electric Study, in which coronary death was the outcome, and the Nurses Health Study, in which myocardial infarction was the outcome."

In other words, nothing surprising in this study, but they could have done a better job in showing data that directly supports the above statement in *Bold*.

### The Problems with the KIHD Study [published in 2005]

Key Messages

- Based on the major changes in the Finnish diet during the 14.6yr study period, using measurements taken at the beginning to predict CVD deaths is absurd, and the paper failed to disclose this.
- There were 3 well-documented confounders (trans-fats, mercury, and iron) that had to be known to the authors, but were never mentioned in the KIHD paper.

The dietary intake and blood work were done only at the beginning of this 14.6 year study, approximately from 1986 through 2001. What did the authors of the paper say about this (emphasis is mine):

"The correlation of serum linoleic acid proportions measured 4 years later with dietary linoleic acid intake at baseline in 895 men participating in the KIHD Study 4-year followup was 0.36 (data not shown). Serum esterified fatty acid proportions are thus a good measure of habitual dietary fat composition. Saturated fat intake in Finland has decreased since the mid-1980s [**ref to a 1996 paper**] when the KIHD Study began, but our data indicate that the relative ranking of these men with respect to dietary fat quality *may be stabile, at least during the first 4 years of follow-up.*"

The 1996 paper that they referenced is the 20yr Finland follow-up study (1972-1992) [8]. Yet from the Thirty-Five year follow-up study discussed in the previous section, data was gathered every 5 years, and the authors would have access to the data through 2002 well before they published their 2005 paper. Also, a 25yr follow-up (1972-1997) was published in 2000 [10], never mentioned or referenced in the KIHD paper (published in 2005).

Thus, given what was going on Finland, the authors' various associations (e.g. U. of Kuopio and Finland's Research Institute of Public Health), the authors must have known that diet and

serum cholesterol levels had major changes between 1987 to 1997 not just in Finland as a whole, but specifically in East Finland. While it is possible that their study population did not change their diet, it seems highly unlikely. At the very least, they should have communicated this in the paper, and specifically made reference to the data that indicated the major changes in East Finland.

For example, from the 25yr paper [10], in Kuopio province, mean serum cholesterol dropped by almost 10% between 1987 and 1997 (240 to 218 mg/dl). Perhaps, more importantly, the percent of men with cholesterol above 250 mg/dl dropped from 38% to 18%.

If the authors had cited this data, would the peer reviewers have approved the article for publication? Perhaps, but they might have insisted that a summary statement like the following be included: Given the major changes that took place in the Finnish diet between 1987 to 2002, the results reported in this study have no credibility.

Why did Chowdhury et al include this study in their meta-analysis? When they contacted the authors of the 2005 paper were the problems with the study communicated?

### 2. Other Confounders, undoubtedly known, but Not Mentioned.

In looking at some related research from Finland, I came across three major confounders that were not even mentioned in the KIHD 2005 paper: trans-fats, mercury, and iron.

Key Messages:

- **Trans-fats.** In a large SW Finland study, men in the highest quintile of Trans-Fat intake had a **38% higher risk of CHD death** than men in the lowest quintile.
- Mercury. From the same population of men in the KIHD study, men in the upper third of mercury hair content, had a 68% greater risk of CVD death than men who had a lower content.
- Iron. From the same population of men in the KIHD study, men in the highest third of body iron stores had a 2.9-fold risk of Acute Myocardial Infarction (AMI) compared with men in the lowest third of body iron stores.
- No mention in the KIHD 2005 paper of Trans-Fats, Mercury, and Iron. Why? The Mercury, Iron, and KIHD papers shared an author. The Trans-Fat paper was a huge study (21,930 men), started at the same time as the KIHD study.

### Trans-Fats

A different Finish study looked at the "Intake of Fatty Acids and Risk of Coronary Heart Disease in a Cohort of Finnish Men" [12]. This was just a 6 year study, but involved 21,930 men from Southwestern Finland - vs. Eastern Finland, the area of KIHD study. This study consisted of all smokers (at least 5 cigarettes per day), aged 50-69, free from heart disease and diabetes. The original intent of this double-blind/placebo controlled study was to determine whether supplements of Alpha-Tocopherol or Beta-Carotene (**ATBC**) would provide a reduction in lung-cancer incidence. It didn't. But there was so much data collected in this study that it could also be used to analyze other things. Food intake was determined at the beginning of the study, and data was presented for both coronary events and coronary death. Since the KIHD just looked at death, just that data will be presented. In this excerpt from table 2 of the study, the data is for guintiles of trans-fat intake (each guintile is defined by the mean of the intake). Thus, men in the 5th quintile of Trans-Fat intake had a ~38% higher risk of CHD death than ones in the 1st quintile.<sup>4</sup>

trans-Fatty acids							
Intake (g)	Cases/ person- years	Age-adjusted RR	Multivariate RR				
1.3	109/25,070	1.00	1.00				
1.7	122/25,756	1.05 (0.81–1.36)	1.05 (0.81-1.36)				
2.0	136/26,112	1.14 (0.88–1.47)	1.12 (0.87-1.45)				
2.7	111/26,265	0.92 (0.71-1.20)	0.90 (0.69-1.18)				
5.6	157/26,186	1.38 (1.08–1.76)	1.39 (1.09–1.78)				

Could the intakes of trans-fats also been a factor in the KIHD study? Table 4 on the ATBC study provides an additional clue. This table gives us the intake and measurements by quintile of Trans-fat intake. A few things to note:

- Q5 had less than 15% of the butter intake as any of the other 4 quintiles.
- Q5 had 3-9 times the margarine intake as the other guintiles (i.e. 9X Q1)
- Q5 had the least saturated fat intake (i.e. 40% less than the average intake of Q1-Q4) and the highest PUFA intake (i.e. 2.2x the average of Q1-Q4). This should have been a protective effect, but was evidently trumped by the Trans-fat intake.

TABLE 4. Relation of energy-adjusted transfatty acid intake to selected coronary heart disease risk factors, as well as intake of nutrients and foods at baseline.\* Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, 1985-1988

Quintile	Median	Medians of								
of trans-fatty acid intake	daily intake of <i>trans-</i> fatty acids (g)	Age (years)	Smok (year	No. ing of s) cigaret day	les/ (l	Body mass index kg/m²)	Serum cholesterol (mmol/liter)	HDL cholesterol† (mmoViter)	Systolic BP† (mmHg)	Diastolic BP (mmHg)
1	1.3	56.4	36.	3 19.6	5	26.2	6.1	1.1	140	88
2	1.7	56.6	36.	5 19.6	6	25.8	6.2	1.1	140	88
3	2.0	57.0	37.	1 19.8	3	25.6	6.3	1.1	139	87
4	2.7	56.9	36.9	9 19.6	6	25.6	6.2	1.1	139	87
5	5.6	56.2	36.9	€ 20.0	)	26.0	6.0	1.1	140	88
		group		Median daily intake of						
	Education (>11 years)	Physical activity (>2 times per week)	Energy (kcal)	Triglycerides (g)	Saturated fatty acids (g)	<i>cis</i> -Mono- unsaturated fatty acids (g)	Poly- d unsaturated fatty acids (g)	Linoleic acid (g)	Linolenic acid (g)	Omega-3 fish fatty acids (g)
1	11.1	20.5	2,657	88.1	43.9	29.1	8.9	6.4	1.5	0.4
2	9.7	17.6	2,794	101.2	53.4	31.7	8.6	6.1	1.4	0.4
3	8.8	17.3	2,844	110.2	60.1	33.4	8.6	6.0	1.3	0.4
4	10.9	17.9	2,770	101.0	57.8	33.5	10.1	7.4	1.5	0.4
5	13.6	19.6	2,673	100.2	38.1	30.3	19.7	16.6	2.2	0.4
	Median daily intake of									
	Cholesterol (mg)	Dietary fiber (g)	Alcohol (g)	Beta- carotene (mg)	Vitamin C (mg)	Vitamin E (mg)	Butter (g)	Margarine (g)	Red meat (g)	Fish (g)
1	517	24.5	16.9	1.75	102	9.7	35.7	5.4	60.4	34.2
2	574	25.0	12.6	1.75	101	9.5	44.2	8.9	63.4	32.8
3	599	24.4	10.0	1. <b>71</b>	96	9.4	51.2	10.2	62.9	31.3
4	584	23.3	9.6	1.70	93	10.6	43.9	17.3	60.7	30.6
5	465	24.6	10.9	1.67	96	17.8	5.1	49.4	56.3	32.2

\* Directly age standardized to distribution of whole cohort. † HDL cholesterol, high density lipoprotein cholesterol; BP, blood pressure.

<sup>&</sup>lt;sup>4</sup> Age-adjusted column adjusted for age (5-year category) and treatment group. The Multivariate column was adjusted for smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7-11, >11 years), and physical activity (<1,1-2, >2 times per week). Inclusion of fiber may be an over-adjustment, e.g. see MALMO study. But in this case, there is not a significant difference.

Recall the following quote from the KIHD study, "*The inverse correlations of dietary PUFA and SAFA intake indicate that the apparent benefit of PUFA intake probably comes about in part through substitution of PUFA for SAFA intake (in these men, by substitution of margarine for butter)*." I think it is reasonable to assume that the margarine in SW Finland is the same as the margarine in East Finland. Thus, if the KIHD paper is right about the substitution of margarine for butter, then it is likely that Trans-fats were a factor in the KIHD study. And, the Food surveys for both studies (KIHD and ATBC) occurred in the same time-frame (late 1980's).

We further know from the overall Finland data, that butter consumption plummeted between 1985 and 2005. This further suggests that trans-fat intake was likely a factor in the KIHD study, and KIHD paper makes no mention of this. WHY?

What did Chowdhury et al know about this? The ATBC paper is one of the 20 in their metaanalysis. (And, I'll get to that one in Part 3, next month.) But you can see why from the above data on SFA intake being the lowest in the highest Trans-fat quintile that the ATBC paper is not a good study for Chowdhury to include. And, did Chowdhury et al ask the KIHD researchers about the possible problem in their study w.r.t. trans-fat intake, when they were contacted for the SFA data?

## Mercury

The ATBC paper provides a clue that mercury could be another confounder in the KIHD study. Here is the quote from the ATBC paper, "Among Finnish men living in the eastern lake area, a high intake of nonfatty freshwater fish and the consequent accumulation of mercury in the body were associated with an excess risk of myocardial infarction as well as death from coronary heart disease, cardiovascular disease, and all causes combined [13, JT Salonen et al 1995 paper]."

Rather than use the 1995 paper, I found a 2005 paper [14]. JT Salonen was one of the authors on both of these Mercury papers. JT Salonen was also one of the authors on the KIHD 2005 paper. So all is connected.

First lets compare the study groups in the KIHD 2005 paper to the Mercury 2005 one. Both start with exactly the same study population from East Finland. Both start with exactly the same number of men, 2,682.

- The Mercury study excluded men with a history of CHD or stroke, and of those remaining, DHA+DPA concentrations were available for 1842 men for the CVD death analysis. "Risk of all-cause mortality was estimated excluding only men without data on serum DHA+DPA concentrations; thus, the analyses for all-cause mortality included 2480 men."
- The KIHD study, "all men with a history of CVD, *diabetes, or cancer* at baseline (n = 1123) were excluded. Men with missing data for both dietary and serum fatty acids were also excluded, leaving 1551 men for the analyses." Thus, it seems that the men in the KIHD study are a subset of the 1842 men in the Mercury study.

One other minor difference. The KIHD study ended 1-year earlier (December 2001 vs December 2002). 78 CVD deaths in the KIHD study and 91 in the Mercury one (explainable by the difference in study sizes).

# Men in the upper third of mercury hair content (>=2.03ug/g) had about a 68% greater risk of CVD death than men who had a lower content (i.e. the bottom 2 tertiles combined).<sup>5</sup>

Thus, Mercury hair content was a more significant factor in CVD death in the Kuopio Ischaemic Heart Study that any factor reported in the KIHD 2005 paper. Yet, the KIHD 2005 paper never even mentioned mercury as a factor. Why?

What is going on in East Finland with mercury, you might ask. The lakes in East Finland are contaminated with very high levels of mercury. There are a lot of large fish (e.g. pike) taken from these lakes and eaten. I suspect that the source of the lake mercury is from the air pollution of various coal-fired power plants, but I was unable to confirm this. But I was able to confirm that the mercury content of Finnish men is significantly higher than those in Sweden.

It is also interesting that the large fresh water fish, e.g. pike, are very low in all types of fat (i.e. saturated as well as DHA, DPA, and EPA). For example, looking at USDA database, 100g of raw northern pike contains just 0.60g of total fat (88mg of DHA+DPA). In comparison, 100g of raw Atlantic farmed salmon contains 13.4g of total fat (1,400mg of DHA+DPA).

Now an interesting thought experiment, combining all that I have written so far, in Part 2. Imagine a East Finnish man, in the early1990's, eating a lot of fresh-water fish from his local lakes, and pan-frying his fish in margarine. He has a low intake of SFA due to low-fat content of the lake fish, and his choice of margarine (vs butter) increases his heart-healthy PUFA, while reducing his SFA intake. His cardiologist is so happy with him. However, the combination of the trans-fat in the margarine and mercury in the lake fish might just kill him. And, if not, suppose, he is using an cast-*iron* pan to cook his fish. Read on, it gets even worse.

#### Iron

The previous subsection discussed a 2005 Mercury paper. That mercury paper never mentioned iron, but it did contain a reference to a 1992 paper by JT Salonen et al, titled "High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men." [15] That was a controversial paper. So, using a different measuring technique, JT Salonen et al published a 1998 paper, with the same conclusion [16]. Title of the 1998 paper, "Association Between Body Iron Stores and the Risk of Acute Myocardial Infarction in Men."

<sup>&</sup>lt;sup>5</sup> Model 4 which adjusted for age, examination year, serum HDL and LDL cholesterol, family history of ischemic heart disease, systolic blood pressure, BMI, maximal oxygen uptake, urinary excretion of nicotine metabolites, serum selenium, serum DHA+DPA, and intake of alcohol, saturated fatty acids, fiber, and vitamins C and E. More precisely, an RR of 1.68 (95%CI, 1.15 to 2.44). With less adjustment, i.e. just age and examination years, the RR was 1.53 (95% CI, 1.08 - 2.18).

First, the 1992 study, which I'll refer to as K-Iron 1992. Similar to the other KIHD studies, i.e. it starts with 2,682 men, and then eliminates some for various reasons. This study eliminated those with some signs of ischemic heart disease, leaving 2005 men. Of these, 1931 had available blood work. In this study, in addition to data on serum cholesterol levels (including LDL and HDL), serum ferritin and blood hemoglobin concentrations were important. Ferritin level is a measure of stored iron.

The mean follow-up in this study was short - just 3 years. The mean serum ferritin concentration in the subjects was 166 ug/L, higher than adult men in most previous studies, eg one study in the state of Washington, the average was 94 ug/L. The median value in adult men is 69-149 ug/L. 25% of men in the K-Iron 1992 study had levels above 200 ug/L, and 6% above 400 ug/L.

From the paper, after "adjusting for age, examination year, cigarette pack-years, ischemic ECG in exercise test, maximal oxygen uptake,systolic blood pressure, blood glucose, serum copper, blood leukocyte count,and serum high density lipoprotein cholesterol,apolipoprotein B,and triglyceride concentrations, *men with serum ferritin* >=200g/l had a 2.2-fold (95%Cl,1.2-4.0; p<0.01) risk factor-adjusted risk of acute myocardial infarction compared with men with a lower serum ferritin. An elevated serum ferritin was a strong risk factor for acute myocardial infarction in all multivariate models. This association was stronger in men with serum low density lipoprotein cholesterol concentration of 5.0 mmol/l (193 mg/dl) or more than in others."

As the authors note, "The present data provide the first empirical evidence in humans of the role of high stored iron measured as elevated serum ferritin concentration as a risk factor for ischemic heart disease. . . . A major proportion of our subjects had serum ferritin levels that put them at increased risk of AMI."

And most interesting is their hypothesis at the end of the article, "Our findings do not undermine the role of LDL cholesterol in the etiology of CHD but rather help to explain why high serum LDL cholesterol concentration is more predictive of CHD in some individuals and populations than in others. The observed synergistic association of serum ferritin and serum LDL cholesterol concentration with the risk of AMI fits into the theory that iron overload would elevate the risk of AMI by promoting the oxidation of LDL."

Now for the 1998 study, which I'll refer to a K-Iron 1998, "Association Between Body Iron Stores and the Risk of Acute Myocardial Infarction in Men". The cases and controls for this study were nested from the KIHD cohort of 1931 men (as described in K-Iron 1992). The measure for iron body iron stores in this study was the concentration ratio of serum transferrin receptor to serum ferritin (TfR/ferritin), a state-of-the-art measurement of body iron stores. The measurements were carried out in 99 men who had an AMI during the 6.4 years of follow-up and 98 control men (matched for age, examination year, and residence). With this measurement a low ratio of TfR/ferritin indicates a high iron store.

Adjusting for the other strongest risk factors for AMI and indicators of inflammation and alcohol intake, *men in the lowest third of the TfR/ferritin ratio (i.e. a high-level of body iron store)* 

*had a 2.9-fold (95% CI, 1.3 to 6.6, P=.011) risk of AMI compared with men in the highest third.* "These data show an association between increased body iron stores and excess risk of AMI, confirming previous epidemiological findings," i.e., confirming the findings of K-Iron 1992.

To consider the synergism of iron stores and LDL cholesterol, the TfR/ferritin ratio was analyzed for men in 2 groups, below and above the LDL median level, which was 4.2 mmol/L (162mg/dl). After adjustment, in the high LDL cholesterol group, men in the lowest third of TfR/ ferritin (i.e. those with a high iron store) had a 4.20-fold risk of AMI (P=0.0226) vs. men in the highest third (those with a low iron store). In men with low cholesterol, and the ratio was 2.43 (P=.148).

The paper also states: "We recently conducted another study in the KIHD cohort, in which we analyzed the association of voluntary blood donation (loss of iron >200 mg per donation) and AMI risk. In a multivariate model adjusted for the main coronary risk factors, blood donors had a relative AMI risk of 0.14 (95% CI, 0.02 to 0.97; P=.047) compared with nondonors. These results provide support for the iron-CHD hypothesis from an additional perspective."

So why the high iron content? The human body has no significant way of ridding itself of excess iron (other than bleeding). Instead, our intestines have a mechanism for controlling the absorption of iron - more absorbed when we need it, and less when we don't. There are 2 forms of dietary iron, heme and non-heme. Animals have both. Plants have just non-heme. Our intestines do a good job of controlling the amount of non-heme iron that is absorbed. But that does not work well for heme iron.<sup>6</sup> Sources of heme iron (highest to lowest) include clams, oysters, organ meats, beef, poultry, and fish. The presence of heme iron in our intestines increases the absorption of non-heme iron. A diet high in beef (about 60% heme, 40% non-heme) increases absorption of the non-heme portion even if the body already has plenty of iron stores. Alcohol also increases iron absorption. And, cooking in an iron skillet/pot adds iron to the food. Coincidentally, a very popular brand of iron cookware comes from Finland. To quote from that website: "The Sarpaneva pot is a classic piece of Finnish cookware design, so famous that it once graced one of Finland's postage stamps. Inspired by his blacksmith grandfather, Timo Sarpaneva designed the *cast-iron* Sarpaneva pot in 1960."

## Summary

Enough criticizing the authors of the KIHD study. OK, so they stubbed a toe on the way to winning the marathon. Big deal. Everyone screws up from time to time.

The big important story is the amazing accomplishment of Finnish people (led by the medical community with the support of government) to transform their diet, e.g. dropping saturated fat intake from 22% of calories to 13%, and thereby reducing CHD death by 80% over a 35 year period.

<sup>&</sup>lt;sup>6</sup> For a good overview of this, see Dr. Greger's video, <u>http://nutritionfacts.org/video/risk-associated-with-iron-supplements/</u>

And, that's not all that Finland has done. You may have read how <u>Finland transformed its</u> <u>educational system</u> over this same period of time. In the 1970's, Finland's student achievement was low, but they steadily upgraded their education system, and reached the top about 5 years ago. And they took a wide achievement gap between rich and poor, and reduced it until it's smaller than nearly all other wealthy nations.

Will our government, industry, and media leaders learn from the Finnish experience? Will we hold them accountable? Or, will we just pass the butter...

## **Related Information**

Travis, who Dr. McDougall has featured in previous newsletters, wrote an <u>excellent critique</u> of both the Chowdhury et al article and Siri-Tarino one (<u>Clearing up the Confustion Surrounding Saturated Fat</u>). If you have any doubts about the medical/nutrition research that supports a low-fat whole-food plant-based (LF-WFPB) diet, simply read all posts on his <u>blog site</u>, and follow the links to the research he references.

Jeff Novick is always bombarded with emails whenever a new article comes out like the Chowdhury one, or the Siri-Tarino one. Check out his many comments on this thread in the forum:

http://www.drmcdougall.com/forums/viewtopic.php?f=22&t=15506

The go-to website for debunking all the low-carb, Paleo, etc folk is Plant Positive's website: <u>http://www.plantpositive.com</u>

His newest series is Drivers of the Herd.

This recent Dr. Greger short video describes well what a low-carb diet does: <u>http://nutritionfacts.org/video/low-carb-diets-and-coronary-blood-flow/</u> Below the video, you will see "Sources Cited". Click on it to expose the links to all the medical/ nutritional research referenced in the video.

Fun short video on Wheat Belly & Grain Brain, by Vegsource: <a href="https://www.youtube.com/watch?v=DemGcWQAnpw">https://www.youtube.com/watch?v=DemGcWQAnpw</a>

And, Dr. McDougall's Feb 2014 video on Wheat-Belly/Grain-Brain/low-carb: <u>http://www.drmcdougall.com/health/education/videos/free-electures/dr-mcdougall-criticizes-low-carb-diets/</u>

For someone who is just looking for a relatively short intro, I put together a youtube playlist about 15 months ago. It consists of 6 2012 Tedx talks, each is about 17 minutes, from 6 different doctors: Esselstyn, Campbell, Barnard, McDougall, Lisle, and Ornish. http://www.youtube.com/playlist?list=PL\_fyN-QMR\_RfvtJ3Hd45P1gnPwXdLfcJh

## References

- 1. Chowdhury R, Warnakula S, Kunutsor S, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk. Ann Intern Med 2014; 160(6):398-406.
- Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular dis- ease. Am J Clin Nutr. 2010;91:535-46. [PMID: 20071648]
- Laaksonen DE, Nyyssonen K, Niskanen L, Rissanen TH, Salonen JT. Prediction of cardiovascular mortality in middleaged men by dietary and serum linoleic and polyunsaturated fatty acids. Arch.Intern.Med. 2005;165:193-199.
- 4. 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;102:2677-2679.
- 5. Vartiainen E, Laatikainen T, Peltonen M, Juolevi A, Männistö S, Sundvall J, Jousilahti P, Salomaa V, Valsta L, and Puska P. Thirty-five-year trends in cardiovascular risk factors in Finland. Int. J. Epidemiol. (2010) 39 (2): 504-518 first published online December 3, 2009.
- 6. Puska P, Salonen JT, Nissinen A, Tuomilehto J, Vartiainen E, Korhonen H et al. Change in risk factors for coronary heart disease during 10 years of a community intervention programme (North Karelia project). Br Med J (Clin Res Ed) 1983;287:1840–44.
- 7. Vartiainen E, Korhonen HJ, Pietinen P et al. Fifteen-year trends in coronary risk factors in Finland, with special reference to North Karelia. Int J Epidemiol 1991;20: 651–62.
- 8. Pietinen P, Vartiainen E, Seppanen R, Aro A, Puska P. Changes in diet in Finland from 1972 to 1992: impact on coronary heart disease risk. Prev Med. 1996; 25:243-250.
- 9. Vartiainen E, Puska P, Jousilahti P, Korhonen HJ, Tuomilehto J, Nissinen A. Twenty-year trends in coronary risk factors in North Karelia and in other areas of Finland. Int J Epidemiol 1994;23:495–504.
- 10. Vartiainen E, Jousilahti P, Alfthan G, Sundvall J, Pietinen P, Puska P. Cardiovascular risk factor changes in Finland, 1972-1997. Int J Epidemiol 2000;29:49–56.
- 11. Puska P. The Finnish Experience. 25-Sep-2009. Slides from the Nutrition and Lifestyle Seminar. Downloaded from <u>http://www.thl.fi/thl-client/pdfs/7a10f4ba-b000-4bd4-8de2-1f18281b222b</u> on 23-Apr-2014.
- 12. Pietinen P, Ascherio A, Korhonen P, Hartman AM, Willett WC, Albanes D, Virtamo J et al. Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Am J Epidemiol. 1997;145:876-887.
- 13. Salonen JT, Seppanen K, Nyyssonen K, et al. 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.
- 14. Virtanen JK, Voutilainen S, Rissanen TH, Mursu J, Tuomainen TP, Korhonen MJ, Valkonen VP, Seppanen K, Laukkanen JA, Salonen JT. Mercury, fish oils, and risk of acute coronary events and cardiovascular disease, coronary heart disease, and all-cause mortality in men in eastern Finland. Arterioscler Thromb Vasc Biol. 2005;25:228–233.
- Salonen JT, Nyyssönen K, Korpela H, Tuomilehto J, Seppänen R, Salonen R. High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men. Circulation. 1992; 86: 803–811.
- 16. Tuomainen T, Punnonen K, Nyyssönen K, and Salonen JT. Association Between Body Iron Stores and the Risk of Acute Myocardial Infarction in Men. Circulation. 1998;97:1461-1466.