

Evaluation of the Chowdhury Meta-Analysis on the Association of Saturated Fatty Acids with Coronary Risk, Part 3

They “*can’t see the forrest for the trees*”¹

Fred Pollack
May 31, 2014

This is the concluding chapter (i.e. part 3) of my review of the [Chowdhury meta-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, [Butter is Back](#), 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.*”

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. I have now completed that analysis, writing up each and every one. The result is a 100+ page document that you can download the PDF, by clicking [supplement](#).

The purpose of this newsletter article is to provide an overall summary of my analysis. Section 1 will provide the big picture (i.e. the forest), including a very brief overview of just 3 of the studies that are illustrative of the big picture view. Section 2 will highlight the common flaws present in almost all of the 20 studies. Section 3 will provide a brief synopsis and grading of each of the 20 studies. And, of course, the last section is the conclusion.

Big Picture

In part 2 ([McDougall April Newsletter](#)), I began with a chart from Finland that showed Coronary Heart Disease (CHD) mortality for men in 1973 from various countries. Here is that same chart again (top of the next page). Note that Finland has the highest CHD mortality and Japan has the lowest. But what about the most recent data. Below is the most recent data from [OECD 2013 Health at a Glance Report](#), measuring Ischemic Heart Disease Mortality (IHD)² for

About Fred

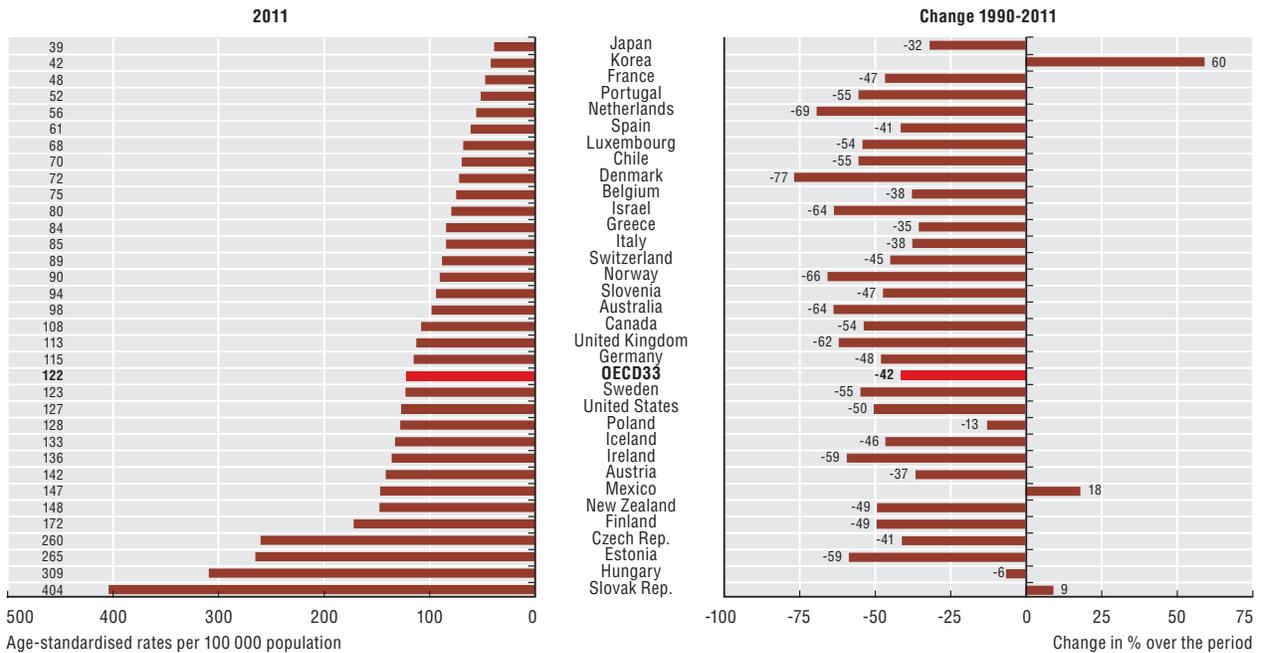
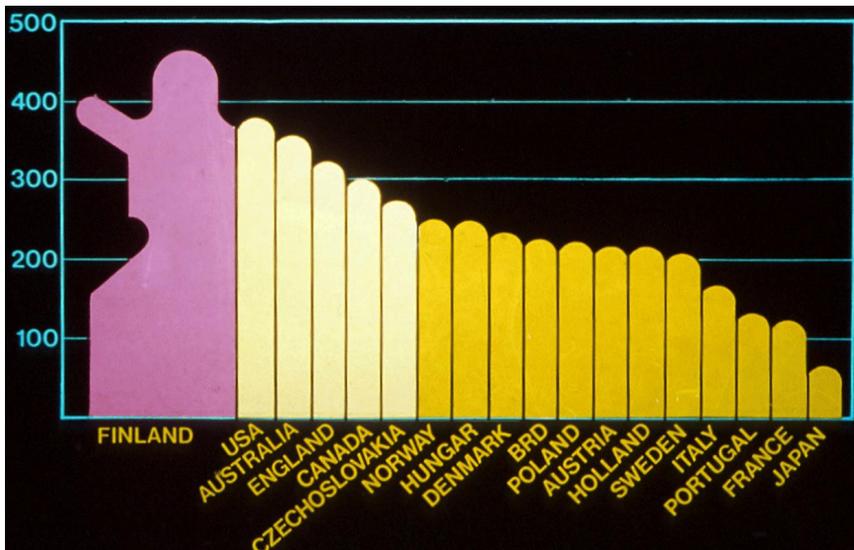
I live with my wife, Iris, in Miami Beach. We are both 66. I worked at Intel for 23 years, and retired in early 2001. For most of my last 8 years at Intel, I directed the planning for Intel’s future microprocessors. In January 1993, I was named an Intel Fellow.

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

¹ Meaning: http://www.englishclub.com/ref/esl/Idioms/American/can_t_see_the_forest_for_the_trees_149.htm.

² IHD and CHD are used interchangeably.

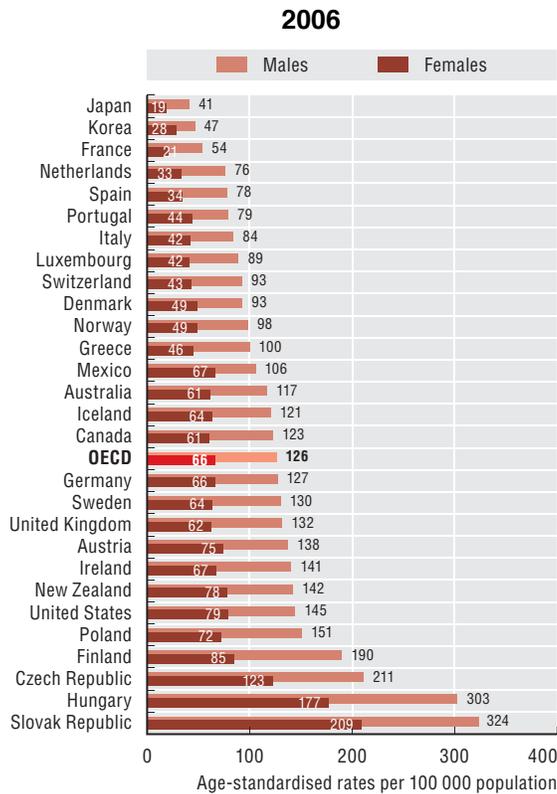
CHD Mortality per 100,000 men in 1973



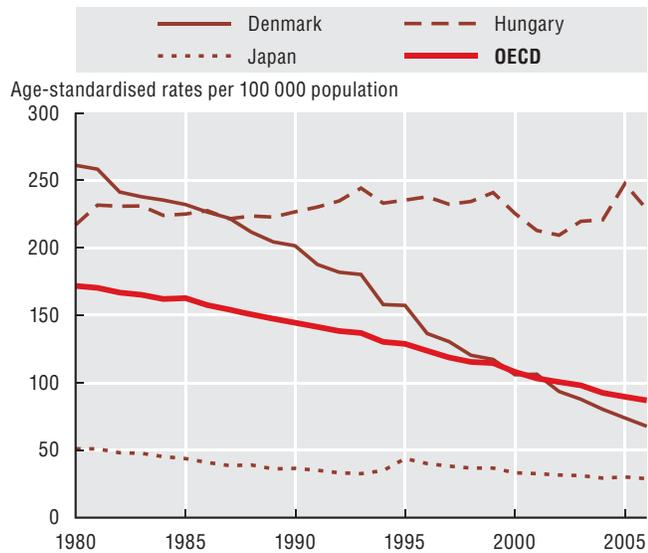
2011, including both men and women. The chart next to it, also shows the changes by country since 1990. Going back to the [2009 OECD Health at a Glance Report](#), you can see the IHD mortality data for 2006, as well as a graph for rates going back to 1980 for the OECD average plus a few select countries.³ For the countries in which the 20 studies took place, I wanted to go back to 1970. So, I've included a table from [OECD Health at a Glance from 2003](#) for just these countries.⁴

³ Note that the graph on the right is not quite comparable to the table on the left. The graph is "age-standardised to the 1980 OECD population."

⁴ From table 1.15 (page 98 of the PDF).



1.4.3 Trends in ischemic heart disease mortality rates, selected OECD countries, 1980-2006



IHD Mortality per 100,000
 standardized to the OECD standard population (1980)
 Finland and Japan 1999 data is actually 2000 data.

	Men	1970	1980	1990	1999	Women	1970	1980	1990	1999
Canada		412	322	214	164		218	159	108	81
Denmark		371	366	282	172		200	180	141	83
Finland		451	411	344	244		188	169	155	115
Greece		92	115	129	115		45	44	60	51
Japan		78	68	49	51		46	40	28	26
Sweden		364	388	261	182		209	188	116	83
United Kingdom		373	367	295	207		171	162	142	99
United States		481	330	228	194		266	169	122	110

The two key points in all this data is: (1) The vast difference in IHD mortality rates in countries; and, (2) the significant decrease in IHD mortality since 1970. Right now, I want to focus on the first point.

In the OECD countries there are 3 dietary patterns that are often described: (1) Northern European (e.g. Finland, Sweden, UK, USA) - high in animal products, and low in fruits,

vegetables, and legumes; (2) Mediterranean (e.g. Greece, Italy, France, Spain) - lower in animal products and higher fruits, vegetables, and legumes; and, (3) Asian (e.g. Japan, Korea, China) - much lower in animals, higher in legumes, and higher in grains (i.e. rice). W.r.t. saturated fat intake, it is highest in the Northern-European style and lowest in the Asian.

18 of the 20 studies in the Chowdhury meta-analysis on SFA-intake involved just a single country. The other 2 involved 2 countries, but with comparable diet patterns. 19 of the 20 involved a homogenous study population, i.e. eating effectively the same diet. In other words, there is a relatively small variation in SFA intake in each of these 19 studies. In addition in 18 of the 19 studies, dietary input is only assessed at the beginning of the study, and the assumption is made that the subjects do not change their diets over the study period, which is, in most cases, over 10 years. And, the assessment of an individual's diet at the beginning of these studies is subject to significant human error in judgement.

Thus, given the homogenous population in 19 studies, it is not surprising to find relatively little effect on diet in each of these studies. Two types of a meta-analysis could be envisioned:

1. **Combining study populations.** If all the studies were constructed in the same manner (e.g. same food frequency questionnaire, same lifestyle parameter input, and same output - e.g. CHD mortality), then all the subjects could be combined into one super-study. This would assure a very large range of SFA-intake (from about 5% to 30% of SFA-intake as percent of total energy consumed).
2. **Combining Statistics.** If the studies are totally different, as is the case with these 20 studies, it is not possible to do (1). Instead you just combine the statistical outcomes.

I'll illustrate the difference in these 2 approaches by an *extreme* example. Suppose we have 2 studies to measure the effect of increasing altitude w.r.t. mortality. Both studies divide their study populations into quintiles (fifths). Study 1 uses altitudes from 2,000 to 10,000 feet in 2,000 ft increments. Study 2 uses altitudes 30,000 to 42,000 ft also in 3,000 ft increments. Each study, by itself, shows no effect from increased altitude (i.e. in study 1, all lived⁵, and in study 2, all died). Thus, each study reported that there was no statistically significant difference in outcomes between quintiles 5 and 1 (study 1: 10,000 vs 2,000; study 2: 42,000 vs 30,000). If we simply *combine statistics* from these 2 studies, we conclude that there is no effect of increasing altitude on mortality.

At this point, you should be thinking, "Surely, Fred, the 19 studies and the Chowdhury analysis could not be this bad or even close. I'll show you the data, and let you be the judge. In the Japan study (JACC), the mean intake of SFA was 14.4 g with a standard deviation (SD) of ~3 g. Whereas in the Finnish KIHD study, it was 55 g with an SD of 12 g. Even after adjustment for SFA-intake as % of Energy intake, quintile 1 of the KIHD study (i.e. mean of lowest fifth of SFA-intake) would still be higher than that of the JACC study's quintile 5 (i.e. mean of highest fifth of SFA-intake).

⁵ Actually, 5% of quintile 5 (10,000 ft) died, but after adjustment for age, lung function, BMI, and sense-of-humor, this was no longer statistically significant.

Both the Japanese study and the Finnish KIHD study reported no harm of increased SFA intake. Here are the specific numbers reported by Chowdhury in his meta-analysis for both of these studies, plus the mortality rate for men from IHD in 1990 and 1999 (from the table of OECD data)⁶:

	RR	95% CI	1990	1999
JACC (Japan)	0.99	(0.77,1.28)	49	51
KIHD (Finland)	0.92	(0.74,1.14)	344	244

An RR (Relative Risk) of >1.00 indicates increased risk of IHD mortality with increased SFA intake. <1.00 indicates benefit. But to reach statistical significance, the confidence interval needs to be above 1.00 for harm, or below 1.00 for benefit. Thus, both Japanese and Finnish studies indicated a very slight benefit to increased SFA-intake, but this did not reach statistical significance.

But now look at the difference in IHD mortality rates (per 100,000 for men) for 1990 and 1999 (the most applicable dates for these 2 studies - on average about a 6X difference). And, as I noted above, the Finnish/KIHD SFA-intake per day for men (in grams) was about ~4X that of Japanese/JACC men. After adjustment for total energy intake, this difference was about 2.5X.

Thus, from looking at the homogenous studies (i.e. 19 of the 20 in the Chowdhury meta-analysis), it is very difficult to conclude anything about diet that might explain the huge IHD mortality rate differences, whether it be SFA-intake, or some other nutrient or lifestyle variable.

And, there are a lot more problems with the 20 studies than just the homogenous aspect, and I'll get to those soon. But first, what about that 1 study that was not homogenous?

The non-homogenous one was the Oxford-Vegetarian study that I described in part 1 (in [McDougall March 2014 newsletter](#)). I'll briefly describe it here just to complete this picture.⁷

Using the above extreme analogy, this one study used altitudes in increments of 7,000 ft, beginning at 7,000 ft, and thus, had a range of 7,000 to 35,000 ft.

Although participants of the Oxford-Vegetarian study were drawn from an overall homogeneous population, namely England and Wales, the way they recruited assured a heterogenous composition. As the authors note, "The study differs from previous prospective studies of diet and IHD in that the volunteers were individuals whose self selected diet resembled, in nutrient content, current dietary recommendations rather than the relatively high saturated fat diet typical of most affluent societies."

⁶ The KIHD study only used men.

⁷ Details also available in my full report of each of the 20 studies.

Participant Selection: “Vegetarian participants were recruited through the Vegetarian Society of the United Kingdom and news media. The non-vegetarian controls were their friends and relatives.” Meat-eaters made up over 50% of the study group.

The mean SFA-intake for men was ~27.4 g, with a standard deviation of ~13 g.⁸ Thus, this study has a much larger range than either the Japanese/JACC study (14.4, SD:3) and the Finland/KIHD study (55g, SD:13g). Note the difference of SD as percent of mean: almost 50% for the Oxford-Vegetarian study, but just about 20-25% for the JACC and KIHD studies.

Thus, the Oxford-Vegetarian study has a range of SFA-intake that overlaps the JACC study higher-half and the KIHD study lower-third.⁹

The Oxford-Vegetarian study (and the Chowdhury meta-analysis) reported an RR of 2.77, with 95% CI (1.25 - 6.13). This implies that a man in the highest third of animal SFA-intake has 2.77 times the risk as a man in the lowest third animal SFA-intake. And, since the confidence interval is >1.00, this was statistically significant.

The authors of the Oxford-Vegetarian study had the best summary on my point about homogeneity of studies: “In the present study there was a wide range of dietary fat intakes, resulting from the inclusion of vegans, vegetarians, semi-vegetarians, and meat eaters. *Most other cohort studies have involved more homogeneous populations with a relatively narrow range of fat intakes. It is impossible to identify even strong disease associations if there is little variation in a dietary variable in the study population.*”

The other approach to seeing the big picture with SFA-intake is to look what happened in Finland over time. This was presented in part 2 (April McDougall newsletter). The CHD death rate in Finland over a 35 year period dropped 80%. Three-fourths 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%.

Key messages:

1. There is huge difference in IHD mortality rates between countries, e.g.in 2011, the rate in Finland was 4.4X the rate of Japan. But a study involving a homogenous population does not provide sufficient differences to determine relationships between dietary intake and outcome. 19 of the 20 studies in the Chowdhury meta-analysis had this problem.
2. Of the 20 studies, the KIHD Finland study had one of the highest SFA-intakes - a mean of ~2.5X (as percent of calories/day) that in the Japanese/JACC study, which had the lowest. But due to the homogeneity problem, neither showed a relationship to SFA intake.

⁸ One of the flaws in this study is that it only reported on SFA-intake from animal sources. Total SFA-intake is likely to be a little higher. Another flaw is that the study does not report on total energy intake. So, no estimates of % of SFA-intake of energy. The UK NHS estimates the average calorie intake of men at 2500 kcal/day. I suspect it is somewhat lower in this study's population.

⁹ The amount of overlap is just an approximation on my part, using a back-of-the-envelope calculation.

3. The one study of the 20 (the Oxford-Vegetarian one) that did not have the homogeneity problem did show a statistically significant harmful effect of increased SFA-intake, RR: 2.77, with a 95% CI of (1.25, 6.13).
4. Finland's 35-year experience of reducing IHD mortality by 80%, and the associated drop in SFA-intake from 23% to 13% is telling.

The Other Problems

In Part 1, I described the criteria that I would be using to grade the different studies. These were based, at that time, on the 9 studies that I had read by then. I am going to repeat their description here, with very minor changes:

- 1) *Over-adjustment with Lipids.* As the Chowdhury paper notes including an adjustment for serum lipids (i.e. serum cholesterol) may act as a potential mediator between fatty acids and coronary heart disease. Thus, the meta-analysis tried to include the most adjusted results that did not include an adjustment for serum lipids. However, as Chowdhury notes, 6 of the 20 studies included in the meta-analysis did include adjustment for serum lipids, because adjustments without it were not available. In other words, in my opinion, these 6 studies should have been excluded, but were not. But not quite true. In my reading and analyses of the 20 studies, there were actually 8, whose multivariate adjustments included serum lipids; i.e. really 8 of the 20 should have been excluded.
- 2) *Sufficient Test of SFA Guidelines.* Most studies divide the study population into fifths (quintiles), fourths (quartiles), or thirds (tertiles). Other studies just provide a mean and a standard deviation. To test the validity of the $\leq 10\%$ of energy from SFA intake, it would be appropriate to have 20-33% meeting the SFA intake guidance, and have the SD (standard deviation) at least 33% of the mean. Here is what the MALMO authors said about this issue w.r.t their study, "Further, one should note that *only 1.2 percent of the present study population actually followed national Swedish recommendations (less than 10 energy percent) on saturated fat intake. **Strictly speaking, the SFA- CVD hypothesis is thus not fully testable in this population.***"
- 3) *Homogeneity.* I covered this problem in the previous section. But I should also note that there is a spectrum in this.
- 4) *Food/Lifestyle Questionnaire.* This involves a Food Frequency Questionnaire (FFQ), as well as a Lifestyle one about health status, medications, exercise, smoking habits, etc. In 19 of the 20 studies,¹⁰ FFQ/Lifestyle data is only obtained at the beginning of the study, and there is no knowledge of any changes from then on. Some studies are very diligent in their process to get the FFQ/Lifestyle right, e.g. using a diet-history method, and a diet interview. many also have an exam (e.g. an ECG to exclude participants that may have a pre-existing heart condition and not know it, a blood glucose test to exclude those with diabetes, a blood pressure measurement, since BP is known risk factor for IHD, and should be an adjustment factor in analysis). Some studies are very diligent in gathering the initial data. Some are quite poor. Nevertheless, over the period of time that these studies last (5 to 20 years), the socioeconomic changes (e.g. growth of eating out, more fast food restaurants, more

¹⁰ The exception is the Nurses Health Study.

emphasis on not smoking, people retiring, new medication prescriptions e.g. for cholesterol and blood pressure, etc), how valid is a study that lasts 10+ years with no new information on diet and lifestyle of the population?

- 5) *Missing Data in the Study*. Many of the studies did not include TFA (trans-fatty acid intake), and this is mentioned in some of the papers as a shortcoming of the respective studies. Many of the studies do not do a blood test to look at cholesterol and blood glucose or measure blood pressure at the beginning of the study.
- 6) *Missing Data in the Paper*, but in the study itself. There are almost an infinite number of ways to slice and dice the info of a study's population, but only a small amount can reasonably be published in an article. Thus, the data necessary to try to figure out what is going on with a particular variable, e.g. SFA, is often not in the article.
- 7) *Confounders*, potentially leading to Over-adjustment or under-adjustment. For example, consider a study that adjusts for dietary cholesterol - that is likely to be an over-adjustment due to its correlation with SFA-intake. Similarly, when the adjustments include all fatty acids, that may also result in over-adjustment. Under-adjustment can be due to missing data, e.g. TFA. For example, substituting margarine (with TFA) for butter reduces SFA intake, but may have worse CHD outcomes; and, many studies realized this problem too late to do anything about it. In the Japanese/JACC study, hypertension was determined by a yes/no question (versus a measurement). This underestimated the percent of hypertension by ~3X. So, this likely resulted in under adjustment. And, there are many factors that I found that were unique to specific studies that may or may not be factors in others (e.g. mercury, iron, arsenic, salt). But even in specific studies where there should have been adjustments for these, there wasn't.
- 8) *Food vs. Nutrients*. The problem is best summarized by a comment in the 2012 MALMO paper, "*This illustrates one of the major problems with studies of nutrient intake: the nutrient variables are also, perhaps even primarily, markers of the foods they derive from. **Foods contain many nutrients and other bioactive substances that interact in complex ways and may therefore differ in their health effects in ways not captured by differences in the content of single nutrients.***" Anyone following Dr. Michael Greger, who reviews the latest in nutrition research on his free [website](#) knows this to be the case. Consider one somewhat humorous/bizarre example of interaction. In researching the Glostrup/Denmark study, I came across this study of men in Copenhagen, Denmark, [1996 BMJ article](#). Consider a group of men, all with LDL ≥ 203 mg/dl. "those who did not drink alcohol had **five times the risk** of ischaemic heart disease compared with those who consumed three alcoholic beverages or more a day." So, if you have sky high cholesterol, and don't want to change your diet, a rather high intake of alcohol would seem to be a better choice than a statin. But note that alcohol intake was not significant factor in subjects with lower LDL cholesterol.¹¹

Having now looked at all 20 studies, I've noticed a 2 other problems with some of them that need to be described.

¹¹ This is just meant as a humorous story about interactions, in this case a high animal SFA diet and alcohol. It is really meant as an illustration of how studies that just look at nutrients (vs food) can lead one to rather strange results.

Age

Almost all studies exclude subjects with a pre-existing heart condition and diabetes. The former may just be a survived heart attack (determined by asking the patient or hospital records). It can also involve asking if the patient if he/she experiences angina. In a few studies, it also involved an ECG to detect a possible silent heart attack that the patient was unaware of. Diabetes is determined by asking the patient and also taking blood and measuring blood glucose levels. A level of 120 or above would exclude the patient from the study.

Some studies only include middle-age subjects (e.g. 45-59) at study entry. Many others include older subjects (e.g. up to 79). In a few of these, middle-aged and elder subjects were evaluated separately. In such studies, increased SFA-intake was often statistically associated with increased IHD in the middle-aged, but not the elderly.

Why?

The exclusion is at the beginning of the study. Arteriosclerosis is a life-long pursuit. The individuals eating the worst diet (e.g. high in SFA-intake, cholesterol intake, low fruits and vegetables) and worse lifestyle (e.g. smoking, lack-of-exercise) are the ones most likely to be excluded from the study, due to signs of CHD and/or diabetes. Genetics may also be a factor. Thus, a person in the elder group (e.g. aged 60 to 75, with a mean age of 66) that doesn't have any signs of heart disease or diabetes at the start of the study is more likely to die from other causes than would otherwise be.

How does this age/exclusion problem affect the Chowdhury's meta-analysis? Two ways.

First consider the studies that broke up the study population into 2 age groups (middle and elder), and that increased SFA-intake was a significant risk factor for IHD in the middle-aged population, but not the elder one. In this case, Chowdhury's meta-analysis will only use the combined population, which usually doesn't show a significant statistical effect for increased SFA-intake.

Now consider a study that doesn't divide the age groups, and has a study population of both middle and elderly. In my view, if the mean age of the study population is around 55 and the age cut-off is 70 or higher, this has the same problem as the 1st example - we just don't get to see if there is an association with the middle-aged. One example of this is the Malmö/Sweden study which had an age range of 44 to 79 with a mean of 58 y. Another is the Japan/JACC study, with an age range of 40 to 79 with a mean of 57 y.

End Points

In some studies, the only end point was *death*. In others, it was *incidence* of IHD, e.g. AMI (acute myocardial infarction), or a procedure (e.g. a bypass or a stent put in) or another ECG done at the end of the study or the patient reporting angina pectoris. And some reported both, i.e. death and incidence. Chowdhury had the preference in the meta-analysis for incident rates, but in the studies that only reported on death, the meta-analysis would use that.

But is this fair in a meta-analysis? Consider a study that reports both, and with CHD death reports a statistically significant relationship with increased SFA-intake, but there isn't one with incidence. Chowdhury only uses the latter. Is that reasonable? Clearly, it takes more work for the researchers to look at incidence. Death is much easier to monitor. In other words, if the researchers were lazier, the results used in the meta-analysis would have been different.

And 10 of the 20 studies report incidence, and the other 10 just death.

Even More Problems

Just the general problems are more than enough to really disqualify all of the 20 studies, even the Oxford-Vegetarian one (e.g. see my grading of it in Part 1 or the supplement).

There are a few studies that I spent way too much time on, e.g. the KIHD/Finland study (see part 2), the JACC/Japan study (1st one in my analysis supplement), and the Strong Heart Study/American-Indians, digging up a lot of additional-related information to these. I don't see how these 3 papers passed a peer review process. In each of these, there was information that should have been in the paper and other related studies referenced. The omissions appear blatant.

Key Learnings

This section will try and summarize key points of each of the 20 studies. The Siri-Tarino et al paper [2] was another meta-analysis that looked at SFA intake relationship to IHD, and came to essentially the same conclusion as the Chowdhury paper. All of Siri-Tarino's 16 referenced studies are a proper subset of the 20 that Chowdhury referenced. They used a slightly different methodology in adapting the reported results in these 16 studies, so their RR's and CI for the same study are sometimes different. Along with my terse analysis of each of the 20 studies, I'll give you the scoring used in the Chowdhury/Siri-Tarino meta-analyses.

First though is a table summarizing all 20 studies: the scoring (RR, 95% CI) of each of the studies by both the Chowdhury and Siri-Tarino meta-analyses. The RR's in **bold** are the ones that reached statistical significance. The rest of the columns (labeled 1 to 8, A, E) are my grading of each of the studies. Below the table is the key for it.

Study	Country	Chowdhury		Siri-Tarino		1	2	3	4	5	6	7	8	A	E
		RR	CI	RR	CI										
JACC	Japan	0.92	(0.74, 1.14)			N	F	F	F	F	D	F	C	T	D
KIHD	Finland	0.99	(0.77, 1.28)			N	F	F	D	D	D	F	F	M	D
SHS	USA	1.09	(0.84,1.42)	1.91	(0.31, 11.84)	Y	C	F	F	F	F	D	F	T	I
Oxford-Veg	UK	2.77	(1.25, 6.13)	2.77	(1.25, 6.13)	N	B	B	D	C	C	C	B	M	D
EPIC-Greece	Greece	3.10	(0.99, 9.63)			N	C	F	C	D	D	D	B	T	D
MALMO	Sweden	0.83	(0.70, 0.99)	0.95	(0.74, 1.21)	N	F	F	C	C	B	D	D	T	I
BLSA	USA	1.22	(0.31, 4.77)	1.22	(0.31, 4.77)	N	C	C	B	D	D	C	C	T	I
Glostrup	Denmark	1.26	(0.87, 1.82)	1.03	(0.66, 1.60)	N	F	F	D	D	F	D	F	S	I
WES	USA	1.07	(0.98,1.17)	1.11	(0.91, 1.36)	Y	F	F	F	C	D	D	F	M	D
Euroaspire	Finland	1.00	(0.68, 1.46)			Y	D	F	C	C	D	F	F	T	I
HPFS	USA	1.07	(0.88, 1.29)	1.11	(0.87, 1.42)	N	B	C	C	C	C	B	C	T	I
HLS	UK	1.04	(0.97, 1.11)	1.37	(1.17, 1.60)	N	F	F	F	F	D	D	F	S	D
LRC	US/Can	1.14	(1.01, 1.27)	0.97	(0.80, 1.18)	Y	C	D	D	D	D	D	F	S	D
IIHD	Israel	0.90	(0.65, 1.24)	0.86	(0.56, 1.35)	Y	F	B	D	D	F	D	F	T	D
NHS	USA	0.98	(0.79, 1.21)	0.97	(0.74, 1.27)	N	D	D	B	C	D	C	F	M	I
HHS	USA	1.00	(0.68, 1.47)	0.86	(0.67, 1.12)	Y	B	D	F	C	D	D	D	T	I
FRAM	USA	1.04	(0.97, 1.11)	0.92	(0.68, 1.24)	Y	D	F	F	C	D	D	F	S	D
ATBC	Finland	0.90	(0.78, 1.03)	0.93	(0.60, 1.44)	N	F	F	D	B	D	D	F	T	I
IBDH	US/Ireland	1.07	(1.00, 1.14)	1.33	(0.95, 1.87)	Y	F	D	D	C	D	D	D	T	D
Caerphilly	UK	0.92	(0.78, 1.09)	1.57	(0.56, 4.42)	N	F	F	D	D	D	F	D	M	I

Key for Grading

Columns 2 through 8, are graded **A** (Excellent) to **F** (Bad). Analysis of each study with the rationale for the grading of each is in the supplement.

- 1) *Overadjustment with Lipids. Yes or No.*
 - 2) *Sufficient Test of SFA Guidelines.*
 - 3) *Homogeneity.*
 - 4) *Food/Lifestyle Questionnaire.*
 - 5) *Missing Data in the Study.*
 - 6) *Missing Data in the Paper.*
 - 7) *Confounders.*
 - 8) *Food vs. Nutrients.*
- A) *Age.* **M** - study population is middle-aged; **S** - study population is both middle-aged and elderly, and analysis is done of each cohort; **T** - study population is both middle-aged and elderly, but analysis is only done as a combined cohort.
- E) *End-Point.* **D** - IHD death; **I** - IHD incident.

Below, I've provided some of the interesting information about each study. My long analysis of each study is in the supplement.

Japan Collaborative Cohort Study (JACC)

- In 2011, Japan's rate of IHD mortality was 31% of the USA's rate and 23% of Finland's.
- The JACC SFA-intake was 1/3 to 1/2 of that seen in almost all the other studies.
- For men, only the highest quintile of SFA-intake exceeded the $\leq 10\%$ of energy recommendation.
- Homogenous study population, e.g. 2.5g of SFA separated adjoining quintiles.
- Serious flaws in baseline data, e.g. underestimation of hypertension by $\sim 3X$.
- Japanese low-IHD rate is not due to fruit, vegetable, and bean intake. In a different paper using same study group, upper quartile of each < 1 serving/day.
- 3 likely confounders (sodium, mercury, and arsenic) not mentioned or included in the study.

Kuopio Ischaemic Heart Risk Factor (KIHD) Study

- Data (Food, lifestyle, blood-work, etc) collected only at beginning of study.
- Failed to disclose dramatic changes in Finnish diet during the 14.6 y study period in the paper.
- Failed to disclose significant confounders (Trans-fats, mercury, excess body iron).
- When I say, "Failed", I mean that they knew, and blatantly omitted relevant data in the paper.
- 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?

Strong Heart Study (SHS) of American Indians

- Over-adjustment. In the multivariate analysis, adjustments (w.r.t. SFA-intake) included serum cholesterol, dietary cholesterol, and PUFA (i.e. polyunsaturated fat) intakes. Thus, not surprising that SFA-intake did not reach statistical significance w.r.t. *CHD incidence*.
- But surprisingly (given the over-adjustments), SFA-intake for 47-59 y cohort did reach statistical significance for CHD mortality, RR: **5.17** (CI: 1.64, 16.36) - highest quartile of SFA-intake vs lowest quartile. This was higher than any of the other 20 studies.

The Oxford Vegetarian Study

- This was the only study that involved a study population with a non-homogenous diet. As the authors note, "Most other cohort studies have involved more homogeneous populations with a relatively narrow range of fat intakes. It is impossible to identify even strong disease associations if there is little variation in a dietary variable in the study population"

- As reported by both Chowdhury and Siri-Tarino, highest tertile of SFA-intake had **2.77** times the risk of CHD mortality compared to the lowest third (CI: 1.25, 6.13).
- The highest tertile of **egg-intake had 2.68** times the risk of CHD mortality compared to the lowest tertile (CI: 1.19, 6.02).

Diabetics from the Greek Arm of the European Prospective Investigation into Cancer and Nutrition (EPIC-Greece)

- Chowdhury's scoring did not report statistical significance; however, but the EPIC-Greece paper reports that a 10 g increase in SFA-intake resulted in a RR of **1.93** (CI:1.08, 3.42) for CHD deaths.
- Also from the EPIC-Greece paper, "**one egg (40 g) [per day] increases the risk of death overall threefold and the risk of coronary death more than fivefold.**"

MALMO (Sweden) Study

- Homogenous population, with high SFA-intake. From the Malmo paper, ". . . one should note that only 1.2 percent of the present study population actually followed national Swedish recommendations (less than 10 energy percent) on saturated fat intake. Strictly speaking, the SFA- CVD hypothesis is thus not fully testable in this population.
- The Chowdhury scoring notes a benefit for higher SFA-intake that was statistically significant. And, one can see this by just looking at the numbers in tables. But here is what the paper says, "there was no protective effect of SFA on iCVD risk neither in men, nor in women, when inadequate energy reporters were excluded and fiber was not included in the multivariate model (p for trend = 0.80 in both genders)." In other words, including fiber in the multivariate analysis resulted in an over-adjustment.

Baltimore Longitudinal Study of Aging (BLSA)

- The Chowdhury/Siri-Tarino scoring indicate no statistically significant benefit with lower SFA-intake, but . . . from the BLSA paper:
- Men consuming either a low-SFA diet or a high FV [fruit and vegetable] diet, but not both, had a 64-67% lower risk of CHD mortality (P<0.05) relative to those doing neither.
- **Men consuming both a low-SFA diet and a high FV diet had a 76% lower risk of CHD mortality (P<0.001), relative to those doing neither.**
- Authors conclude (last sentence of abstract): "These results confirm the protective effects of low SF and high FV intake against CHD mortality. In addition, they extend these findings by demonstrating that the combination of both behaviors is more protective than either alone, suggesting that their beneficial effects are mediated by different mechanisms."

Glostrup Multi-centre Study (Glostrup)

- This study used a different mode of analysis than any of the other studies.
- "In the models used, total energy and protein intake were fixed. Differences in intake of energy from fat thus reflected complementary differences in intake of energy from carbohydrates." The evaluation was the risk of CHD according to intake of 5% higher level of energy from dietary fat, and thus 5% lower energy from carbohydrates. Results could be looked at 4 ways: sex (men, women) and age (young: <60 y, old: ≥60 y)
- The mean SFA intake of all participants was ~20% of energy. The mean of the lowest 10% (decile) in SFA intake was ~14%, and the median of the highest decile in SFA intake was ~25%.
- Of the 4 groups, one did reach statistical significance w.r.t. increased **SFA intake with younger (<60 y) women, RR: 2.68, 95% CI: (1.40, 5.12)**, as noted in the abstract of the paper. For these younger women, total fat and MUFA intake also reached statistical significance (both harmful), but this was likely due to the strong correlation with SFA intake.

- Why didn't younger men also see this effect? The paper suggests the possibility that, “. . .intakes of complementary carbohydrates were qualitatively different between the genders. In the present study, only types of fat, but not types of carbohydrates, were considered.”

Western Electric Study (WES)

- “When the risk of death from CHD was analyzed in terms of the component dietary variables, it was inversely related to intake of polyunsaturated fatty acids and positively related to intake of dietary cholesterol. The amount of saturated fatty acids in the diet was not significantly associated with the risk of death from CHD, although there was a slight but consistent tendency for risk to increase from the low third to the high third of the distribution. Other base-line variables significantly related ($P < 0.001$) to risk of death from CHD in this multivariate analysis were age, systolic blood pressure, cigarette smoking, and *serum cholesterol* concentration.”
- The failure of SFA intake to show statistical significance is likely do to over-adjustment (e.g. serum cholesterol being included).

Finnish Cohort of EUROASPIRE (European Action on Secondary Prevention through Intervention to Reduce Events) Study

- This study is about secondary prevention of CAD with a focus on n-3 Fatty Acids, using a Finnish cohort.
- Various dietary nutrient variables w.r.t. various end-points. The only one that reached statistical significance was SFA-intake w.r.t. **all-cause mortality: 1.57** (1.13, 2.17).
- Virtually all patients were on cardiovascular drugs, and serum cholesterol was included in the adjustments.

Health Professionals Follow Up (HPFS) Study

- A large study of male health professionals of ages 40 to 75 followed for 6.1 years.
- For CHD incidence (i.e. combined fatal CHD and myocardial infarction incidence), SFA-intake did not reach statistical significance. And, this is what Chowdhury and Siri-Tarino put in their analysis.
- But for CHD **mortality**, the HPFS paper reports an RR of **2.21** (CI:1.38, 3.54) comparing highest quintile of **SFA-intake** to lowest one.
- When fiber is added to this adjustment, the RR drops from 2.21 to **1.72** (CI: 1.01, 2.90) - so still statistically significant. In general, people who eat less saturated fat, eat more whole plant-based foods that have fiber. In fact, in the HPFS study the mean fiber intake in quintile 1 of SFA-intake was ~50% higher than that in quintile 5 (26.2 g/d vs. 16.2).

Health and Lifestyle Survey (HLS) in Great Britain

- Siri-Tarino scoring indicated a statistical significant harmful effect for SFA-intake, whereas Chowdhury did not.
- From the HLS paper, using their multivariate analysis for relative risk of CHD death, a 100g/wk increase in SFA-intake results in an RR for women of 1.40 (CI: 1.09, 1.79). But the results for men are 1.00 (0.86, 1.18). Why?¹²
- This study only looks at grams of fat intakes, it doesn't adjust for fat (any type) as percent of energy consumed as do the other studies. As the HLS paper says, “A potential source of non-random error arises from the lack of an adjustment for total energy intake of the participants (Willett, 1990). Any apparent effect on CHD risk of dietary fat could, in principle, be due to the effect of total energy intake. . . . Therefore, not adjusting dietary fats for total energy intake could be expected to reduce their apparent effects on CHD, leading to the relative risks for fat reported in this paper being

¹² “Men are from Mars, women are from Venus?”

underestimates.” Thus, I don’t understand why this was included in both the Siri-Tarino and Chowdhury meta-analysis.

Lipid Research Clinics (LRC) Prevalence Follow-up Study

- Chowdhury indicated a statistical harm to increased SFA intake 1.14 (1.01, 1.27), whereas Siri-Tarino did not.
- The study population was separated into 2 age groups: 30-59 and 60-79 y. There were no statistically significant relationships w.r.t. nutrient intake (other than alcohol) in the 60-79 y cohort. The multivariate analysis included adjustments for *serum cholesterol*.
- W.r.t. the 30-59 age group, the paper included this observation, “Our estimates indicate coronary risk reductions of 4%, **10%**, and 9% for a **1% reduction** in total fat, **saturated fat**, and monounsaturated fat, respectively, among 30 to 59 year olds. For example, a decrease in total fat intake from 39.8% (the mean of the sample of 30 to 59 year olds) to 30% (currently recommended levels) would translate into an estimated risk reduction of 34% (relative risk 0.66, 95% confidence interval 0.47-0.91), which is comparable to the estimates obtained from the Framingham Heart Study.”

Israeli Ischemic Heart Disease (IIHD) Study

- As the IIHD paper notes, “*Weak associations of long-term coronary mortality with the dietary intake patterns of fatty acids, as reported at baseline, were probably fully mediated by the effect of the diet on serum cholesterol.*”
- Thus, the only interesting data point in the IIHD paper is the association of total serum cholesterol and CHD mortality: an increase of 40mg/dl is associated with an increased risk of CHD death of 1.29 (1.20, 1.39).

Nurses’ Health Study (NHS)

- Only 1 of the 20 studies that had follow-up questionnaires on diet/lifestyle - every ~4 years. NHS paper used was from 2005 - reporting on 20 years (1980 to 2000)
- Excluded from study at start: ~2% for history of cardiovascular disease, and 5% for **hypercholesterolemia**. This was the only study of the 20 that excluded people with high cholesterol. And, these were the more likely ones to develop CHD.
- From 1980 to 1998, as percent of energy, decreases in total fat (39% to 29%), SFA (15.6% to 9.4%), MUFA (16.0% to 11.5%), and TFA (2.2% to 1.6%); and, PUFA increased (5.3% to 5.6%).
- In the analysis, to represent long-term dietary patterns, they used cumulative average method. Thus, in the analysis, the median energy intake percent for SFA, ranged from 10.1% for quintile 1 to 17.6% for quintile 5. Thus, this is a homogenous study population w.r.t. SFA-intake.
- NHS paper shows 2 kinds of analysis: Age-adjusted and multivariate in comparing various fat intakes (quintile 5 to quintile 1). The multivariate includes a boat-load of adjustments (besides what you would expect): the other fats (not being measured), cereal fiber, fruits and vegetable, dietary cholesterol, aspirin use, multivitamin, vitamin E supplement use, protein, etc.
- In the Age-adjusted analysis, all RR’s for various fat-types reach statistical significance. But after this multivariate analysis, it disappears for total fat, SFA, and MUFA; but it remains for TFA and PUFA. In fact, PUFA looks better under the multivariate: from 0.80 (0.69, 0.94) to 0.75 (0.60, 0.92). Whereas, SFA goes from 1.52 (1.30, 1.79) to 0.97 (0.73, 1.27). The last number corresponds to the numbers used by Chowdhury and Siri-Tarino meta-analysis.
- The implication is adding ~0.75 TBS of Safflower oil (~75% Linoleic acid) to a diet, without reducing anything else would have a net benefit in reducing CHD risk. For example, this would move someone in quintile 1 of PUFA into quintile 5. Sounds crazy (and I think it is), and no one would suggest this right? Wrong: <http://researchnews.osu.edu/archive/saffoil.htm>.

- In multivariate analysis by age (<65 and older), benefit of increased PUFA was not statistically significant in older women, RR:0.96 (0.66, 1.39).
- In multivariate analysis by BMI (<25 and higher), benefit of increased PUFA was not statistically significant in the <25 BMI cohort, RR: 0.91 (0.67, 1.26).
- Going back to a 1997 NHS paper, covering 14 years of the study: “**Replacing 5 percent of energy from saturated fat with energy from unsaturated fats was associated with a 42 percent lower risk (95 percent confidence interval, 23 to 56 percent; P=0.001).**” The 2005 paper did not have this kind of analysis.
- The 1997 paper also provided an additional multivariate analysis, one that did not include the other fats. PUFA only reached statistical significance in the multivariate+other-fats model.

The Honolulu Heart Study

- Study of ~7,000 men of Japanese ancestry living in Oahu. Age 45 to 68 y. Examined in 1965-1968 and followed for 10 years. Prevalent cases of CHD, stroke, or cancer excluded. Negative outcomes fell into 2 categories: (1) severe: CHD death or myocardial infarction; (2) moderate: angina pectoris or coronary insufficiency. Total CHD was a combination of both.
- Chowdhury and Siri-Tarino used Total CHD (i.e. severe + moderate). Multivariate analysis included *serum cholesterol*. So no statistically significant scores for SFA-intake.
- All baseline numbers in the paper are reported as mean ± SD (std. deviation).
- SFA-intake as percent of calories: 12.3% ± 4.0. Implies a good test for SFA-intake recommendation.
- When just the severe category is considered, **higher increased intakes of SFA, total fat, and protein were significantly and directly related to the 10-year incidence of myocardial infarction or CHD death (P<0.01) with the multivariate analysis (which included serum cholesterol).**
- With just the Age adjustment increased total fat and SFA intakes were even more strongly related to the severe category (P<0.001).

The Framingham (FRAM) Study

- A sub-study of the much larger Framingham study. About 800 men divided into 2 approximately equal cohorts, (45-55 y and 56-65 y). Negative outcome was evidence of CHD disease (CHD death, myocardial infarction, agina pectoris, or coronary insufficiency). Multivariate analysis *included adjustments for serum cholesterol*. Started in 1966-1969, and followed for 16y.
- All baseline numbers in the paper are reported as mean ± SD (std. deviation).
- In the 45-55 yr cohort, in the multivariate model, “total fat intake and monounsaturated fatty acid intake had a significant, independent association with the 16-year incidence of CHD [P<0.01]. Saturated fatty acid intake was *marginally significant* [P = 0.052].” “In men aged 56 years and older, none of the dietary lipid variables was associated significantly with the 16-year incidence of CHD morbidity and mortality.” Thus, combining both cohorts, it is not surprising that Chowdhury and Siri-Tarino reported no statistical significance w.r.t. SFA-intake.
- But there is a Part 2 to the FRAM paper. This compared men at the mean-level of total fat, MUFA, and SFA to those at upper-end of NCEP guidelines, i.e. 39.7%/30%, 16.2%/10%, and 15.2%/10%. In the 45-55y cohort, the relative risk (RR), with 95% CI, for each was: total fat, 0.71 (0.56, 0.90); MUFA, 0.64 (0.48, 0.87); and **SFA, 0.78 (0.61, 1.00). Thus, SFA was marginally significant.** But this is with the multivariate analysis that *includes adjustments for serum cholesterol*.

ATBC Study

- The original purpose of this study was to determine if giving Alpha-Tocopherol and/or Beta-Carotene supplements to *Finnish men smokers aged 50-69* would reduce their cancer risk. With the data collected they realized that they could use the collected data to assess the risk of CHD based on intakes of specific fatty acids. There were 6.1 years of follow-up from 1985-1988.

- Men in the top quintile of TFA (trans-fatty acid) had a multivariate risk of Coronary death of 1.39 (1.09, 1.78) as compared to men in the lowest quintile.
- The intake of omega-3 fatty acids from fish was also directly related to the risk of coronary death in the multivariate model, 1.30 (1.01, 1.67) for men in the highest quintile of intake compared with the lowest.
- There was **no association between intakes of saturated** or c/s-monounsaturated fatty acids, linoleic or linolenic acid, or dietary cholesterol and the risk of coronary deaths.
- The dietary questionnaire exaggerated the range of intakes of all nutrients. From the validation study, the range of SFA-intake was actually 57% narrower.
- Last sentence of paper: “The selective nature of this cohort (***middle-aged, smoking men eating a diet high in fat***) warrants relatively cautious extrapolation to other populations.”

The Ireland-Boston Diet Heart (IBDH) Study

- Study consisted of ~1,000 men (30-69 y) followed for 18 years starting in the early 1960's. 3 cohorts, but since the CHD death rates were similar, they were combined.
- The multivariate analysis included *serum cholesterol*. But even with this, increased SFA-intake (harmful) and fiber-intake (helpful) were marginally statistically significant (P=0.05).
- Missing from the study: physical activity and diabetes indication.
- Based on dietary information, this was a homogenous population that also had a high smoking rate (mean of ~1.7 packs/day).
- Most interesting observation in the IBDH paper (general, not applicable to the study itself):
*“The principal nutritional change that has occurred since the early 1900s has been a **decrease** in the consumption of **dietary carbohydrates**, not including sugar, of about **45 per cent** during the period **1909 to 1976**. In contrast, changes in the consumption of dietary lipids have been much smaller. **Assuming that the rise in death rates from coronary heart disease was real, the changes in dietary levels of complex carbohydrates match the rise more closely than the changes in dietary lipid levels.**”*

Caerphilly Study

- The study population consisted of 2,423 men, ages 45-59, from small towns in of South Wales, England (Caerphilly and 5 adjacent towns - total population, 41,000) in the early 1980's. Data determined at the beginning of the 5-yr study: a one-time self-administered food-frequency questionnaire and an examination including an ECG.
- No measurement of blood pressure, or indication of hypertension. No measurement of glucose, or indication of diabetes. No information of physical activity.
- The homogenous study population had little dietary differences.
- No statistically significant relationship of CHD incidence with any nutrient - not surprising given length of the study and homogenous study population.

Conclusion

A meta-analysis study seems to have instant credibility. Why? Because the lead-in sentence sounds so compelling, e.g. something like, “we combined the results of 15 studies involving over 200,000 people, and found that” Sounds extremely credible, doesn't it?

But my background is computer science, and one of the common acronyms is GIGO - Garbage In, Garbage Out. So, I thought a bit about this in the context of the Chowdhury and

Siri-Tarino meta-analyses. What if the studies used in a meta-analysis aren't very good? What if, the choice of studies, or the data selected from the studies involves some flaws?

GIGO is the fundamental problem in this case as well. None of the 20 studies is good. Only 1 of the 20 had the possibility of being a good study (the Oxford-Vegetarian one), and even that one had flaws.

What are Chowdhury and co-authors, and Siri-Tarino and co-authors trying to do? If they are truly interested in trying to explain the relationship between diet/lifestyle and IHD, what is their hypothesis for explaining the current 4X difference in IHD death rates between Japan and Finland?

I really don't understand their motives. Unfortunately this kind of thing occurs in other endeavors as well. First read this recent excerpt from a Nobel Laureate's blog of a few week's ago (I'll tell you by who and fill in the blank below):

“So why are people busy trying to come up with stories in which the opposite happens? Yes, if you work hard enough at it you can produce a model for perverse outcomes (that's pretty close to a theorem). But what empirical motivation is there for doing all of this?”

What I think happened here was actually that some _____ said something silly, not out of deep conviction, but because they weren't really thinking about what their equations meant; and that rather than back off, they have now spent the past few years trying to justify their initial claims. But there's no reason to take this stuff seriously.”

The missing noun is “economists”. And, the author is Paul Krugman, and here is a link to that particular post, from May 17, 2014, “[Interest Rates and Inflation and Evidence.](#)”

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