**A Preliminary Evaluation of Chowdhury Meta-Analysis
on the Association of Fatty Acids with Coronary Risk**

Fred Pollack
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I'm an active reader/researcher on nutrition, finance, climate change, and politics. The NY Times piece on the Chowdhury paper made me at first angry, and then very concerned. From previous research into these areas plus my work experience as an Intel engineer, I know how data can be cherry-picked and distorted. Thus, I felt compelled to do an objective evaluation of the saturated-fat claim in the Chowdhury paper, because it is this aspect that the mainstream media has latched on to. Could the net effect become as bad as Atkins in the 1990's, Gary Taubes in the previous decade, and the Paleo-diet proponents are doing in this decade? Too soon to tell.

Am I biased? Sure. I'm biased by all the research that I have read, and by my own experiences. But as a trained scientist and engineer, I know how to do an objective evaluation, and that is all that I can promise. In finance, they say "follow the money." In this case, I will follow the data to see where it takes me.

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.

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Preamble

The Chowdhury et al article [1] was published online at the Annals of Internal Medicine http://annals.org/article.aspx?articleID=1846638]. on March 18, 2014. It is behind a paywall, and can be purchased for $20, as I did. If you decide to do this, be sure to also download the two supplements. Also, click on the "Comments" tab to see some of the negative comments by Chowdhury's peers, e.g. by Dr. Walter Willet, Chairman of Nutrition of the Harvard school of Public Health. Dr. Willet, in an online Science Magazine article, http://news.sciencemag.org/health/2014/03/scientists-fix-errors-controversial-paper-about-saturated-fats, was quoted to say, "They have done a huge amount of damage . . . I think a retraction with similar press promotion should be considered."

My analysis is written for the reader who wants to understand the details behind this study, and related research. This is Part 1 - Part 2 will be in the next newsletter.

Introduction

The meta-analysis of dietary fatty acids and risk of coronary heart disease by Chowdhury et al. [1] concludes that *"Current evidence does not clearly support cardiovascular guidelines that encourage high consumption of polyunsatuated fatty acids and <u>low consumption of total saturated fats.</u>"* This paper will examine this claim w.r.t. the intake of Saturated Fat Acids (SFAs) and its relationship to coronary disease. To make the claim, the Chowdhury

analysis cites 20 observational studies. The next version of this paper will include a detailed review of each of these. To date, I've read and analyzed about 9 of these studies. Thus, my general observations/conclusions are preliminary.

In this paper, I'll present my detailed analysis of 2 of the 20 studies - one that shows the most benefit to higher intakes of SFA (MALMO) and one that shows the most harm (Oxford Vegetarian). And, I'll also present some data from a 3rd study - the Nurses Health Study (NHS), but time does not permit a full analysis in this version.

What is the dietary guideline for SFA intake? The USDA guideline is ≤10% of daily calories. This is the same as several other countries' guideline. The American Heart Association recommends <7% of calories. And, the DASH (Dietary Approaches to Stop Hypertension) has the nutrient goal of 6% of calories from SFA.

As noted in the FAO/Who Report [3], "The relationship between dietary fats and CVD, especially coronary heart disease, has been extensively investigated, with strong and consistent associations emerging from a wide body of evidence accrued from animal experiments, as well as observational studies, clinical trials and metabolic studies conducted in diverse human populations." And, from the Scientific Conference on Dietary Fatty Acids and Cordiovascular Health Summary [4]: "Based on a large body of evidence, it is apparent that the optimal diet for reducing risk of chronic diseases is one in which saturated fatty acids are reduced and trans fatty acids from manufactured fats are virtually eliminated. Because of the growing health benefits recognized for unsaturated fatty acids, it is likely that a mixture of these fatty acids in the diet will confer the greatest health benefits within the context of a total fat intake that is considered moderate." And, this study notes, "Current dietary guidance in general recommends a diet that contains ≤30% of energy as fat, ≤10% of energy as saturated fatty acids, up to 10% of energy as PUFAs[1], and <300 mg of cholesterol per day."

Thus, for Chowdhury et al to challenge the SFA guidelines based on the vast body of existing research is an *extraordinary* claim.

"Extraordinary claims require extraordinary evidence"[2]

Meta-analyses are viewed as the "gold-standard", because they combine the results of a collection of different studies performed by different researchers. Thus, if a few turn out to be bad (e.g. poorly constructed, researcher bias, incorrect analysis), the expectation is that they will be overwhelmed in the meta-analysis by all the good or valid studies. But what if: the reverse occurs, i.e. the majority of studies are not good; and/or, the chosen studies do not test the proposed hypothesis. In these cases, the meta-analysis is not made of "gold" - it's just "paper".

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[1] PUFA - Polyunsaturated Fatty Acids. MUFA - Monounsaturated Fatty Acids.

[2] Made popular by Carl Sagan on *Cosmos*.

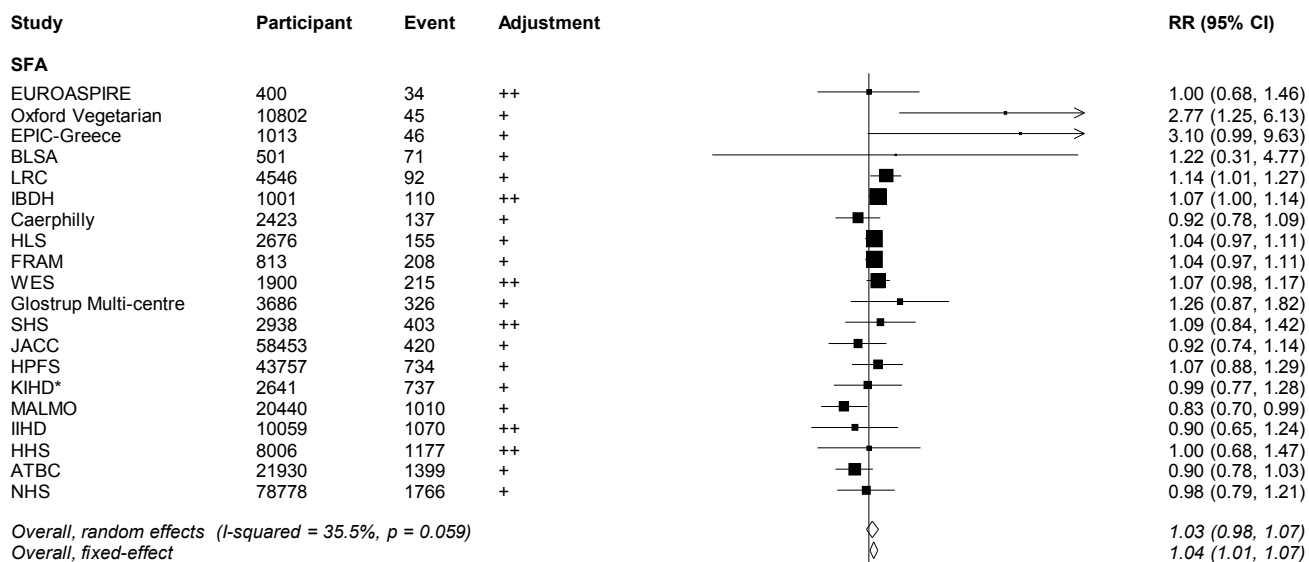*"Things are seldom what they seem, Skim milk masquerades as cream"[3]*

The only way to tell if we are dealing with Skim milk or Cream is to dig into Chowdhury et al's referenced studies. As scientists, we need to be both "open to challenging the common wisdom," but skeptical.

Based on my initial analysis, Chowdhury has not chosen "good" studies to back up his claim, and few are applicable to Chowdhury's claim w.r.t. dietary guidelines for Saturated Fat intake. The next section of this paper will discuss several shortcomings in the referenced studies. After that, I'll present my analysis of the MALMO and Oxford Vegetarian studies.

But first, I want to point you to a comparable meta-analysis, and its analysis. In 2010, Siri-Tarino et al published the paper "Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease," in the American Journal of Clinical Nutrition[2]. As the Chowdhury paper says about the Siri-Tarino paper, ". . .prospective observational studies have questioned whether there really are associations between saturated fat consumption and cardiovascular disease." Most of the 20 studies of the Chowdhury meta-analysis are also used in the Siri-Tarino meta-analysis. Plant Positive has reviewed some of the studies referenced in the Siri-Tarino paper, and his analysis is online at http://www.plantpositive.com/siri-tarinos-meta-analysis-par/.

Preliminary Analysis

First, look at Supplement Figure 2 from the Chowdhury paper summarizing the SFA impact on Coronary outcomes:

Study	Participant	Event	Adjustment		RR (95% CI)
SFA					
EUROASPIRE	400	34	++		1.00 (0.68, 1.46)
Oxford Vegetarian	10802	45	+		2.77 (1.25, 6.13)
EPIC-Greece	1013	46	+		3.10 (0.99, 9.63)
BLSA	501	71	+		1.22 (0.31, 4.77)
LRC	4546	92	+		1.14 (1.01, 1.27)
IBDH	1001	110	++		1.07 (1.00, 1.14)
Caerphilly	2423	137	+		0.92 (0.78, 1.09)
HLS	2676	155	+		1.04 (0.97, 1.11)
FRAM	813	208	+		1.04 (0.97, 1.11)
WES	1900	215	++		1.07 (0.98, 1.17)
Glostrup Multi-centre	3686	326	+		1.26 (0.87, 1.82)
SHS	2938	403	++		1.09 (0.84, 1.42)
JACC	58453	420	+		0.92 (0.74, 1.14)
HPFS	43757	734	+		1.07 (0.88, 1.29)
KIHD*	2641	737	+		0.99 (0.77, 1.28)
MALMO	20440	1010	+		0.83 (0.70, 0.99)
IIHD	10059	1070	++		0.90 (0.65, 1.24)
HHS	8006	1177	++		1.00 (0.68, 1.47)
ATBC	21930	1399	+		0.90 (0.78, 1.03)
NHS	78778	1766	+		0.98 (0.79, 1.21)
Overall, random effects (I-squared = 35.5%, p = 0.059)					*1.03 (0.98, 1.07)*
Overall, fixed-effect					*1.04 (1.01, 1.07)*

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[3] From *HMS Pinafore.* Gilbert & Sullivan. Obviously, not vegans.

Note that only 2 studies reached statistical significance, i.e. the full range of the confidence interval (CI) was either fully below or above 1.0: MALMO (higher SFA intake is helpful) and Oxford Vegetarian (higher SFA intake is harmful), thus, completely opposite conclusions. We will cover both in detail after the next section.

Grading of Studies

With each of the 20 studies, I am going to apply a subjective qualitative grading based on 8 parameters. These are not meant to replace the ones that the Chowdhury paper employed, but rather to supplement them. In this section, I will explain each parameter, and also provide a summary assessment based on the 9 studies that I have read/analyzed so far.

1) *Over-adjustment with Lipids.* In the above figure, 6 studies are marked (++) to indicate that in addition to adjusting for conventional risk factors, lipids (i.e. cholesterol levels) were also included in the adjustment. From the main Chowdhury paper, "Studies that reported RRs with differing degrees of adjustment for other risk factors used the most adjusted estimate that did not include adjustment for blood lipids or circulating fatty acids (because *circulating lipids may act as potential mediators for the associations between fatty acids and coronary disease*)." But apparently 6 of the studies only published adjustments that included "blood lipids". This results in an over-adjustment, since SFA intake causes an increase in LDL and Total Cholesterol. This alone suggests that these 6 studies (i.e. 30% of the studies) should not have been included in the meta-analysis.

2) *Sufficient Test of SFA Guidelines.* Most of the studies that I've reviewed to date, divide the study population into either fifths (quintiles), fourths (quartiles), or thirds (tertiles). Now suppose a study divides the population into quintiles (of equal sizes). Ideally to test the validity of the ≤10% of energy from SFA intake, it would be appropriate for 2 of the quintiles to have mean SFA intakes ≤10%. Or, if divided into quartiles or tertiles, then 1. Until I review all 20 studies, I won't know how many this screen would eliminate. My current estimate is that it will probably eliminate about 15 or more of them. But Chowdhury et al make it more interesting. Whenever a study uses quartiles or quintiles, they readjust the data using statistical means, to transform the analysis into tertiles. So how many of the studies would this filter out of the 20, because not even 1 tertile would have a mean of ≤10% from SFA? Probably about 17. And, 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, <u>the SFA- CVD hypothesis is thus not fully testable in this population.</u>**"

3) *Homogeneity.* The question to examine is whether a study population is from a single area and eats approximately the same diet. For example, consider the population for the Caerphilly study - ~2,400 men, ages 45-59, from small a town in of South Wales, England

(Caerphilly and 5 adjacent towns - total population, 41,000) in the early 1980's. In the next section, the MALMO study is discussed. Malmo is the 3rd largest city in Sweden, probably also homogenous (e.g. relatively few citizens from countries with a different diet pattern; in fact, any candidates that were not sufficiently fluent in Swedish were excluded; and, any candidates that indicated that they had changed their diet in the past, were also excluded). As one measure consider the mean SFA intake (% of energy) for each quintile of the Malmo study population: men (13.0, 15.2, 16.8, 18.9, 22.7), women (12.9, 15.1, 16.7, 18.6, 22.1). An increase of 2 pats of butter (5.2g of SFA, ~1.8% of energy for men and ~2.2% for women) is enough to move a person 1 quintile. Also, note the ratio in SFA intake from the 5th quintile to the 1st one is ~1.7, but with the tertile transformation, this probably drops to ~1.5.

4) *Food/Lifestyle Questionnaire.* This involves a Food Frequency Questionaire (FFQ), as well as a Lifestyle one about health status, medications, exercise, smoking habits, etc. In almost all the studies, FFQ/Lifeststyle 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. MALMO seemed to be quite good at this, from what they describe. Nevertheless, over the period of time that many of these studies last (5 to 20+ years), the socioeconomic changes (e.g. growth of eating out, more fast food restaurants, more 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 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 at the beginning of the study. Such tests might be a check on the FFQ/Lifestyle information.

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 Overadjustment. This is an area that is way outside of my expertise. When I do see the raw data the way that I would like to see it presented, in many of the studies there are correlations, for example, in the highest quintile of SFA intake it usually contains people that also have a higher intake of dietary cholesterol, a lower intake of fiber, lower physical activity, and a higher smoking level when compared to the people in lowest quintile of SFA intake. The 2012 Malmo paper summarizes this problem best, "Like many other studies, our study suffers from relatively high correlations between some nutrients." When you combine this with the homogeneity and the 1-time FFQ/Lifestyle problems, it is challenging to have confidence in the fully adjusted numbers. And, sometimes when you just look at the adjusted numbers (vs less adjusted ones), it looks more like "noise."

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." T. Colin Campbell (author of the China Study) wrote a whole book about this, "Whole: Rethinking the Science of Nutrition." To quote from there, "Every apple contains thousands of antioxidants whose names, beyond a few like vitamin C, are unfamiliar to us, and each of these powerful chemicals has the potential to play an important role in supporting our health. They impact thousands upon thousands of metabolic reactions inside the human body. But calculating the specific influence of each of these chemicals isn't nearly sufficient to explain the effect of the apple as a whole. Because almost every chemical can affect every other chemical, there is an almost infinite number of possible biological consequences."

Studies

In this section, I'm going to describe only 2 of the 20 studies of the Chowdhury meta-analysis w.r.t. the effect of SFA intake on Coronary Events. The studies that I am going to cover are the only 2 that reached statistical significance according to the statistics presented in the supplementary section of the Chowdhury paper. The Figure presented in the Preliminary Analysis section shows this. Another good reason for choosing these 2 studies is that they reach completely opposite conclusions - according to Chowdhury paper, the MALMO study shows that a *high SFA intake results in less coronary events*, and the Oxford Vegetarian study shows the opposite. Note that despite its name, the Oxford Vegetarian study includes *both meat eaters and Vegetarians*. It is also worth noting that both of these studies were also included in the Siri-Tarino meta-analysis.

MALMO Study

The Chowdhury paper references two MALMO studies [5, 6] - one from 2012 and the other from 2007. The 2012 paper is the better one, but the 2007 paper has some data that is not in the 2012 paper, and thus is also useful. The Siri-Tarino paper (published in 2010) also uses MALMO in its meta-analysis, but only references the 2007 paper.

Note that Chowdhury and Siri-Tario score the MALMO study differently:

	RR	(95% CI)
Chowdhury	0.83	(0.70 - 0.99)
Siri-Tarino	0.95	(0.74 - 1.21)

The Study Population. As noted in the 2012 abstract: "data from 8,139 male and 12,535 female participants (aged 44–73 y) of the Swedish population-based Malmö Diet and Cancer cohort. The participants were without history of CVD and diabetes mellitus, and had reported stable dietary habits in the study questionnaire. Diet was assessed by a validated modified diet history method, combining a 7-d registration of cooked meals and cold beverages, a 168-item food questionnaire (covering other foods and meal patterns), and a 1-hour diet interview. Sociodemographic and lifestyle data were collected by questionnaire. iCVD cases, which included coronary events (myocardial infarctions or deaths from chronic ischemic heart disease) and ischemic strokes, were ascertained via national and local registries."

Recruitment was between 1991-1996, and mean follow-up was 13.5 years in the 2012 paper and 8.4 years in the 2007 one.

And from the 2012 conclusion: "In this well-defined population, a high fiber intake was associated with lower risk of iCVD, but **there were no robust associations between other macronutrients and iCVD risk."** This included associations for total Fat and SFA. Thus, I can't explain why the Chowdhury statistical analysis finds that there is an association of a high-SFA diet with lower iCVD risk.

From the 2007 conclusion: "In relation to risks of cardiovascular events, our results do not suggest any benefit from a limited total or saturated fat intake, nor from relatively high intake of unsaturated fat."

The 2007 article focused on Fat (including SFA) and used quartiles. The 2012 article focused on these as well plus many others (e.g. Fiber, Carbs, Protein, etc). Both articles look at the Fat issue in slightly different ways. So it is worth covering both - first, the 2007 paper.

The 2007 results section (from abstract) state: "No trend towards higher cardiovascular event risk for women or men with higher total or saturated fat intakes, was observed. Total fat: HR (95% CI) for fourth quartile was 0.98 (0.77–1.25) for women, 1.02 (0.84–1.23) for men; saturated fat: 0.98 (0.71–1.33) for women and 1.05 (0.83–1.34) for men. Inverse associations between unsaturated fat intake and cardiovascular event risk were not observed." Note that these numbers are different from both Siri-Tarino and Chowdhury numbers.

In Malmo, iCVD is both coronary events (CE) and ischemic strokes. Haemorrhagic strokes were excluded because the causes for them are believed to be different than ischemic strokes (which are believed to have similar causes as CEs).

Table 1 of the 2007 article (produced below) provides one way to view the Study population:

Table 1 Baseline characteristics and diet composition within quartiles of total fat intake for women (left) and men (right)

	1st	2nd	3rd	4th	1st	2nd	3rd	4th
N (n)	4193 (153)	4222 (140)	4224 (139)	4228 (151)	2565 (225)	2611 (239)	2674 (247)	2677 (262)
Age (years)	57.8	57.7	57.2	56.9	59.1	59.3	59.0	58.9
% current smoker	20.8	24.4	29.4	37.4	21.5	24.9	28.1	40.4
BMI (kg/m^2)	25.7	25.6	25.4	24.9	26.3	26.3	26.2	26.1
SBP (mmHg)	140	139	139	139	144	144	144	144
Alcohol intake (g/day)	5.9	7.3	8.2	9.3	12.8	14.2	16.7	18.7
Physical activity score	8425	8083	7674	7539	9035	8509	8163	7809
Energy intake (kcal/day)	1834	1965	2041	2164	2425	2556	2668	2808
% energy from fat	30.8	36.5	40.3	46.1	31.8	37.8	41.7	47.7
% from saturated fats	12.7	15.5	17.5	20.9	12.8	15.7	17.7	21.3
% from monounsaturated fats	10.8	12.7	14.0	15.7	11.2	13.4	14.8	16.6
% from polyunsaturated fats	5.1	5.8	6.3	6.8	5.5	6.2	6.7	7.1
% energy from carbohydrates	52.2	47.0	43.8	38.7	51.7	46.2	42.9	37.6
% energy from protein	16.6	16.3	15.8	15.2	16.1	15.8	15.3	14.8
Fibre intake[a] (g/day)	22.6	19.9	18.0	15.4	26.3	22.7	20.4	17.3
Fruit and vegetable intake[a] (g/day)	488	420	369	304	429	364	323	272

Numbers are presented as percentages. [a]Age and energy-adjusted means. BMI, body mass index; (*n*), number of events; *N*, number of individuals within each quartile; SBP, systolic blood pressure.

Please note the following correlations with %Energy intake from Fat, which defines each quartile:
1) For both men and women, positive correlations with: %current-smoker, alcohol-intake, energy-intake, and % Energy from all total fat components (i.e. SFA, MUFA, PUFA)
2) For both men and women, inverse correlations with: physical-activity, % energy from carbs, % energy from protein, Fibre intake, and Fruit-and-vegetable intake.
3) For both men and women the values that remain about the same across all 4 quartiles: Age, BMI, and SBP.

In case you are wondering about trans-fats, the paper says, "*The fact that trans-fatty acids were not recorded as a separate variable could have confounded the results considerably.* Also, the range of unsaturated fat intake was relatively modest, diminishing the possibilities of revealing statistically significant differences between the quartiles. Further more, diet was only assessed at one point in time, decreasing the reliability of the dietary assessment."

Observations:
1) None of the quartiles indicate a healthy population with a healthy diet and lifestyle.
2) As I mentioned in the previous section, a homogenous population like this one leads to small differences. The unsaturated fat difference is modest. And, even with SFA, an increase of ~1tbsp butter (7g SFA, 100kcal) or about 2 to 3 inch cubes of cheese is enough to move an individual 1 quartile.
3) Based solely on the above "raw" (i.e. unadjusted numbers), the identified trends (Fat, SFA, Smoking, Fibre-intake, Fruit-Vegetable intake, physical activity) imply that we should see a correlation with number of events, in particular, far more events in the 4th quartile than the 1st one. Yet for women, quartiles 1 and 4 are effectively the same, 2 and 3 are about the same, and both 1 and 4 are more than 2 and 3. For men, we do see the expected trend, but it is not substantial and could conceivably be due to "smoking".

Turning to the adjusted results, table 2 from the 2007 paper, below. Note w.r.t. quartiles, this is different from Table 1. In Table 2, each category of fat defines the quartile. When you look at the mean fat intake for each quartile in table 2, it is different from table 1, except for total fat. Thus, one cannot look at the characteristics in table 1 and apply them to SFA quartiles in table 2. However, since there is a close correlation with this population of %SFA of energy intake with that of %Total fat, it should be close.

The only quartile that reached statistical significance (P<0.05) w.r.t. %SFA intake was women in quartile 3 with the "Crude" adjustment, RR 0.74 (0.56-0.97). "Crude" is never defined in the article, but based on context, I think it is principally Age. "Adjusted" though is defined as "Adjusted for age, smoking habits, alcohol consumption, socio-economic status, marital status, physical activity, body mass index, fibre intake, and blood pressure."

As the 2007 paper says: "Even though 1556 endpoints were registered, *the difference in HR between the first and the fourth quartiles would have needed to be 30–40% to be significantly detectable. Such differences were not observed for any of the types of fat analysed in our study.* It should be noted that traditional cardiovascular risk factors such as current smoking [HR 2.49 (2.03–3.05) for women; 2.16 (1.81–2.57) for men] and systolic blood pressure [10

mmHg increase – HR 1.24 (1.18–1.29) for women; 1.20 (1.16–1.23) for men] were highly significant (P<0.0001) in our multivariate analysis. This emphasizes that even though a weak relationship exists in our study between fat intake and CVE, the association between dietary fats and CVE risk would thus, not be in the order of the association with smoking and blood pressure."

So, the above implies that we cannot deduce an HR for SFA w.r.t. coronary events or cardiovascular events (i.e. coronary events + ischemic stroke).

Now on to the 2012 article, which is the far better one.

Unlike the 2007 article, the 2012 one gives us quintiles AND we can look at 13 different nutrient quintiles (Carbs, Monosaccharides, Disaccharides, Starch, Fiber, Fat, SFA, MUFA, PUFA, n-3 FA, Long-chain n-3 FA, n-6 FA, Protein). Each distribution is in terms of non-alcohol energy percentages.

Table 2. Distribution of non-alcohol energy percentages from selected nutrients in participants of the Malmö Diet and Cancer cohort with stable dietary habits (medians).

	Sex									
	Men (n = 8,139)					Women (n = 12,535)				
	Quintiles					Quintiles				
	1	2	3	4	5	1	2	3	4	5
Carbohydrate	36.6	41.2	44.2	47.2	51.7	37.8	42.1	45.0	47.9	52.2
Monosaccharides	3.6	4.9	6.0	7.3	9.5	4.5	6.2	7.4	8.9	11.2
Disaccharides	7.4	10.0	11.9	14.1	17.5	8.8	11.2	12.9	14.9	18.2
Starch	20.0	23.1	25.3	27.7	31.3	19.1	21.9	23.8	25.9	29.1
Fiber[a]	5.8	7.1	8.2	9.3	11.4	6.5	8.1	9.3	10.6	12.9
Fat, total	33.0	37.4	40.3	43.5	48.1	32.0	36.2	39.1	42.1	46.5
Saturated fat	13.0	15.2	16.8	18.9	22.7	12.9	15.1	16.7	18.6	22.1
Monounsaturated fat	11.4	13.1	14.2	15.3	17.0	11.0	12.5	13.6	14.6	16.1
Polyunsaturated fat	4.5	5.5	6.2	7.1	8.5	4.3	5.1	5.8	6.6	8.0
n-3 fatty acids	0.70	0.86	0.99	1.14	1.40	0.67	0.82	0.94	1.08	1.34
Long-chain n-3 fatty acids	0.08	0.13	0.19	0.30	0.53	0.07	0.12	0.18	0.27	0.49
n-6 fatty acids	3.5	4.3	5.0	5.8	7.1	3.3	4.0	4.7	5.4	6.7
Protein	12.5	14.0	15.2	16.4	18.4	12.9	14.5	15.7	16.9	18.9

[a]Expressed as grams per 1000 kcal reported energy intake.
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Next are the tables for Risk of iCVD looking at each macronutrient. Tables 3 and 4 below are for women and reproduced from the paper. Following that is Table S5 for men and reproduced from the supplementary info available online.

First lets look at SFA, for men and women? With both Basic and Full adjustment, quintile 5 vs quintile 1 did not reach statistical significance. Nevertheless, it is interesting to look at quintile 5 numbers for both men and women. With the Basic adjustment, increased SFA is harmful. With the Full adjustment it is helpful. Given the correlations with SFA (in particular, fiber,

smoking, physical activity), perhaps there is over-adjustment. Again, with Basic or Full adjustments, statistical significance was not reached for men or women.

Now consider other macronutrients intake. The story is almost the same for both men and women. With just the Basic adjustment, statistical significance was reached for monosaccharides, starch, fiber, and MUFA. More was helpful for the first 3 of these and more was harmful for MUFA. But after Full adjustment, the only one that retained statistical significance was fiber, but just for women (although it was close for men). But note that fiber was in the full adjustment. Since whole fruits contain monosaccharides (glucose and fructose) and fiber, the Full adjustment for monosaccharides could be an over-adjustment. Similarly, since root vegetables, whole grains, and legumes contain both starch and fiber, the Full adjustment for starch could be an over-adjustment, as well.

Tables 3 and 4 combined from the 2012 article: Risk of total ischemic cardiovascular disease in 12,535 *women* (687 cases)[a] by intake of macronutrient intake (multivariate hazard ratios with 95% confidence intervals per quintile of energy-adjusted intake).

Women (n = 12,535)		1 (n = 2,507)	2 (n = 2,507)	3 (n = 2,507)	4 (n = 2,507)	5 (n = 2,507)	P for trend
Carbohydrates	c/py[b]	138/29,599	135/29,633	137/30,078	124/30,021	153/30,241	
	Basic[c]	1.00	0.91 (0.72–1.16)	0.88 (0.69–1.11)	0.75 (0.58–0.95)	0.90 (0.71–1.13)	0.14
	Full[d]	**1.00**	**1.02 (0.80–1.31)**	**1.08 (0.84–1.38)**	**0.89 (0.69–1.16)**	**1.18 (0.91–1.54)**	**0.48**
Monosaccharides	c/py	142/29,225	131/29,791	140/30,044	124/30,090	150/30,421	
	Basic	1.00	0.78 (0.61–0.99)	0.75 (0.59–0.95)	0.64 (0.50–0.81)	0.72 (0.58–0.91)	0.003
	Full	**1.00**	**0.96 (0.75–1.22)**	**1.00 (0.78–1.28)**	**0.89 (0.68–1.16)**	**1.10 (0.84–1.43)**	**0.67**
Disaccharides	c/py	129/29,908	124/29,982	126/30,195	136/29,940	172/29,546	
	Basic	1.00	0.85 (0.66–1.09)	0.76 (0.59–0.97)	0.81 (0.64–1.04)	1.06 (0.84–1.34)	0.55
	Full	**1.00**	**0.87 (0.68–1.12)**	**0.79 (0.62–1.02)**	**0.80 (0.62–1.03)**	**0.94 (0.74–1.19)**	**0.57**
Starch	c/py	181/29,551	146/29,818	116/29,931	128/29,782	116/30,491	
	Basic	1.00	0.79 (0.64–0.99)	0.65 (0.52–0.82)	0.74 (0.59–0.94)	0.68 (0.54–0.87)	0.001
	Full	**1.00**	**0.89 (0.71–1.11)**	**0.77 (0.61–0.99)**	**0.89 (0.69–1.13)**	**0.88 (0.68–1.15)**	**0.34**
Fiber	c/py	173/28,876	131/29,510	133/29,990	125/30,265	125/30,930	
	Basic	1.00	0.67 (0.53–0.84)	0.63 (0.50–0.79)	0.56 (0.44–0.71)	0.54 (0.42–0.68)	<0.001
	Full	**1.00**	**0.77 (0.61–0.97)**	**0.80 (0.64–1.02)**	**0.71 (0.56–0.91)**	**0.76 (0.59–0.97)**	**0.022**
Protein	c/py	168/29,838	127/30,261	124/30,002	128/29,766	140/29,705	
	Basic	1.00	0.76 (0.60–0.95)	0.79 (0.62–0.99)	0.83 (0.66–1.05)	0.92 (0.72–1.17)	0.66
	Full	**1.00**	**0.81 (0.64–1.03)**	**0.85 (0.67–1.08)**	**0.88 (0.69–1.12)**	**0.97 (0.76–1.24)**	**0.96**
Fat, total	c/py[b]	144/30,265	128/29,925	139/29,851	134/29,985	142/29,546	
	Basic[c]	1.00	0.91 (0.72–1.16)	1.06 (0.84–1.35)	1.07 (0.84–1.35)	1.15 (0.91–1.46)	0.12
	Full[d]	**1.00**	**0.86 (0.67–1.09)**	**0.95 (0.75–1.22)**	**0.89 (0.69–1.15)**	**0.86 (0.66–1.13)**	**0.44**
Saturated fat	c/py	145/30,428	135/29,989	133/29,976	131/29,697	143/29,483	
	Basic	1.00	0.96 (0.76–1.22)	0.98 (0.77–1.24)	1.00 (0.79–1.27)	1.11 (0.88–1.41)	0.38
	Full	**1.00**	**0.94 (0.74–1.19)**	**0.89 (0.69–1.14)**	**0.84 (0.64–1.08)**	**0.87 (0.66–1.14)**	**0.22**
Monouns. fat	c/py	138/30,141	130/30,084	126/29,822	135/29,797	158/29,727	
	Basic	1.00	0.97 (0.76–1.24)	0.95 (0.75–1.22)	1.09 (0.86–1.39)	1.28 (1.02–1.62)	0.019
	Full	**1.00**	**0.90 (0.71–1.15)**	**0.86 (0.67–1.11)**	**0.94 (0.73–1.22)**	**0.98 (0.76–1.27)**	**0.94**
Polyuns. fat	c/py	145/29,559	135/29,696	134/29,933	142/30,259	131/30,125	
	Basic	1.00	0.93 (0.73–1.17)	0.98 (0.78–1.24)	1.08 (0.85–1.36)	1.06 (0.84–1.34)	0.34
	Full	**1.00**	**0.90 (0.71–1.14)**	**0.94 (0.74–1.20)**	**1.04 (0.82–1.32)**	**0.94 (0.74–1.20)**	**0.91**
n-3 fatty acids	c/py	121/29,935	121/30,024	130/30,030	150/29,833	165/29,749	
	Basic	1.00	0.92 (0.71–1.18)	0.96 (0.75–1.23)	1.07 (0.84–1.36)	1.09 (0.86–1.38)	0.22
	Full	**1.00**	**0.91 (0.71–1.18)**	**0.92 (0.71–1.18)**	**1.02 (0.80–1.30)**	**1.03 (0.81–1.38)**	**0.50**
Long-chain n-3	c/py	109/29,809	117/29,815	133/30,046	154/29,937	174/29,965	
	Basic	1.00	0.86 (0.66–1.11)	0.87 (0.68–1.13)	0.98 (0.77–1.26)	0.99 (0.78–1.27)	0.51
	Full	**1.00**	**0.88 (0.68–1.15)**	**0.94 (0.72–1.21)**	**1.02 (0.80–1.32)**	**1.07 (0.83–1.37)**	**0.25**
n-6 fatty acids	c/py	145/29,437	154/29,642	130/29,982	131/30,206	127/30,306	
	Basic	1.00	1.14 (0.91–1.43)	0.98 (0.77–1.24)	1.08 (0.85–1.37)	1.11 (0.87–1.42)	0.59
	Full	**1.00**	**1.07 (0.85–1.35)**	**0.96 (0.76–1.22)**	**1.04 (0.81–1.32)**	**0.98 (0.76–1.25)**	**0.75**

[a]12,402 women and 676 cases in the full model due to missing values.
[b]Cases/person years.
[c]Basic model: Adjusted for age, method version, total energy intake (continuous), and season.
[d]Full model: Adjusted for age, method version, total energy intake (continuous), season, BMI class, smoking category, education, alcohol category, systolic blood pressure, antihypertensive treatment, antihyperlipidemic treatment, leisure time physical activity (quartiles) and quintiles of energy-adjusted dietary fiber.
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Table S5: Risk of total ischemic cardiovascular disease in 8,139 *men* (1089 cases) by macronutrient intake (multivariate hazard ratios with 95% confidence intervals per quintile of energy-adjusted intake).

		1 (n=1,627)	2 (n=1,628)	3 (n=1,628)	4 (n=1,628)	5 (n=1,628)	*P for trend*
Carbohydrates	c / py[13]	214 / 18,706	225 / 18,688	222 / 18,945	212 / 18,940	216 / 18,922	
	Basic[14]	1.00	0.98 (0.82-1.19)	0.96 (0.80-1.16)	0.86 (0.71-1.04)	0.90 (0.74-1.09)	0.12
	Full[15]	**1.00**	**1.09 (0.90-1.32)**	**1.12 (0.92-1.36)**	**1.04 (0.85-1.28)**	**1.09 (0.88-1.35)**	**0.63**
Monosaccharides	c / py	229 / 18,408	233 / 18,830	211 / 19,053	217 / 18,963	199 / 18,947	
	Basic	1.00	0.91 (0.76-1.10)	0.74 (0.62-0.90)	0.74 (0.62-0.90)	0.69 (0.57-0.84)	<0.001
	Full	**1.00**	**1.03 (0.85-1.24)**	**0.91 (0.74-1.11)**	**0.95 (0.77-1.16)**	**0.91 (0.73-1.14)**	**0.31**
Disaccharides	c / py	195 / 19,205	208 / 19,043	211 / 19,037	236 / 18,646	239 / 18,270	
	Basic	1.00	1.02 (0.84-1.24)	1.00 (0.82-1.22)	1.10 (0.91-1.34)	1.13 (0.93-1.37)	0.13
	Full	**1.00**	**1.07 (0.88-1.31)**	**1.04 (0.85-1.27)**	**1.11 (0.91-1.35)**	**1.04 (0.85-1.27)**	**0.66**
Starch	c / py	245 / 18,312	216 / 18,657	225 / 18,900	193 / 19,086	210 / 19,246	
	Basic	1.00	0.86 (0.72-1.03)	0.90 (0.75-1.08)	0.77 (0.64-0.93)	0.88 (0.73-1.06)	0.083
	Full	**1.00**	**0.94 (0.78-1.14)**	**0.99 (0.82-1.21)**	**0.94 (0.76-1.16)**	**1.10 (0.88-1.37)**	**0.50**
Fiber	c / py	246 / 18,095	219 / 18,714	213 / 18,916	220 / 18,972	191 / 19,504	
	Basic	1.00	0.84 (0.70-1.01)	0.78 (0.65-0.94)	0.79 (0.66-0.95)	0.65 (0.54-0.79)	<0.001
	Full	**1.00**	**0.93 (0.78-1.12)**	**0.93 (0.77-1.12)**	**1.00 (0.82-1.20)**	**0.85 (0.70-1.04)**	**0.30**
Fat, total	c / py	211 / 19,060	218 / 18,736	203 / 19,002	226 / 18,813	231 / 18,589	
	Basic	1.00	1.04 (0.86-1.25)	0.97 (0.80-1.18)	1.10 (0.91-1.34)	1.18 (0.98-1.43)	0.071
	Full	**1.00**	**0.99 (0.82-1.20)**	**0.92 (0.75-1.13)**	**1.01 (0.82-1.24)**	**0.95 (0.77-1.18)**	**0.77**
Saturated fat	c / py	217 / 19,010	221 / 19,027	209 / 19,065	212 / 18,743	230 / 18,355	
	Basic	1.00	0.99 (0.82-1.20)	0.97 (0.80-1.17)	1.01 0.83-1.22)	1.08 (0.89-1.30)	0.4
	Full	**1.00**	**0.94 (0.78-1.14)**	**0.94 (0.77-1.15)**	**0.91 (0.74-1.12)**	**0.89 (0.72-1.11)**	**0.32**
Monouns. fat	c / py	201 / 18,996	216 / 18,759	218 / 18,947	234 / 18,818	220 / 18,681	
	Basic	1.00	1.04 (0.86-1.26)	1.07 (0.88-1.30)	1.15 (0.96-1.40)	1.16 (0.96-1.40)	0.064
	Full	**1.00**	**0.97 (0.80-1.18)**	**1.00 (0.82-1.23)**	**1.02 (0.84-1.25)**	**0.92 (0.74-1.14)**	**0.64**
Polyuns. fat	c / py	226 / 18,331	218 / 18,752	220 / 18,959	194 / 19,165	231 / 18,993	
	Basic	1.00	0.97 (0.80-1.16)	1.00 (0.83-1.21)	0.87 (0.72-1.06)	1.08 (0.90-1.29)	0.81
	Full	**1.00**	**0.95 (0.79-1.14)**	**0.97 (0.80-1.17)**	**0.85 (0.70-1.03)**	**1.05 (0.87-1.27)**	**0.98**
n-3 fatty acids	c / py	200 / 19,053	199 / 18,914	232 / 18,809	221 / 18,869	237 / 18,556	
	Basic	1.00	1.01 (0.83-1.22)	1.11 (0.92-1.35)	1.05 (0.86-1.27)	1.05 (0.87-1.27)	0.52
	Full	**1.00**	**1.00 (0.82-1.21)**	**1.10 (0.91-1.33)**	**0.97 (0.80-1.18)**	**1.02 (0.84-1.24)**	**0.92**
Long-chain n-3	c / py	175 / 19,250	230 / 18,647	240 / 18,730	222 / 18,856	222 / 18,717	
	Basic	1.00	1.22 (1.00-1.49)	1.24 (1.02-1.50)	1.10 (0.90-1.34)	1.03 (0.84-1.26)	0.66
	Full	**1.00**	**1.24 (1.02-1.51)**	**1.22 (1.00-1.48)**	**1.09 (0.89-1.33)**	**1.03 (0.84-1.26)**	**0.59**
n-6 fatty acids	c / py	228 / 18,274	223 / 18,514	208 / 19,031	201 / 19,230	229 / 19,151	
	Basic	1.00	1.02 (0.85-1.23)	0.95 (0.79-1.15)	0.93 (0.77-1.13)	1.10 (0.91-1.32)	0.65
	Full	**1.00**	**1.02 (0.85-1.23)**	**0.95 (0.78-1.15)**	**0.94 (0.78-1.14)**	**1.10 (0.91-1.32)**	**0.62**
Protein	c / py	243 / 18,516	222 / 18,823	234 / 18,773	195 / 19,072	195 / 19,017	
	Basic	1.00	0.91 (0.76-1.09)	1.00 (0.83-1.20)	0.84 (0.70-1.02)	0.90 (0.74-1.09)	0.19
	Full	**1.00**	**0.92 (0.77-1.11)**	**1.07 (0.89-1.28)**	**0.88 (0.72-1.07)**	**0.90 (0.73-1.10)**	**0.28**

The MALMO paper also separated out the components of iCVD into Coronary Events (CE) and ischemic stroke. It is not clear to me whether or not the Chowdhury paper includes or excludes ischemic stroke in their analysis. So with that in mind, here are the most relevant

Excerpts from the MALMÖ 2012 supplement for both Men (S1) and Women (S2) looking at just coronary events (i.e. iCVD - ischemic strokes).

Table S1. Risk of coronary event in 8,139 men (508 cases) by macronutrient intake (multivariate hazard ratios with 95% confidence intervals per quintile of energy-adjusted intake).

Excerpts:

		1 (n=1,627)	2 (n=1,628)	3 (n=1,628)	4 (n=1,628)	5 (n=1,628)	P for trend
Carbohydrates	c / py	127 / 18,406	147 / 18,688	139 / 18,945	130 / 18,940	145 / 18,922	
	Basic[2]	1.00	1.10 (0.87-1.40)	1.03 (0.81-1.31)	0.92 (0.72-1.17)	1.05 (0.82-1.33)	0.74
	Full[3]	1.00	1.21 (0.95-1.54)	1.18 (0.92-1.51)	1.08 (0.83-1.41)	1.21 (0.92-1.59)	0.41
Monosaccharides	c / py	123 / 18,408	141 / 18,830	135 / 19,053	146 / 18,963	143 / 18,947	
	Basic	1.00	1.04 (0.82-1.32)	0.95 (0.74-1.22)	1.00 (0.77-1.30)	0.92 (0.70-1.22)	0.55
Disaccharides	c / py	118 / 19,205	136 / 19,043	138 / 19,037	141 / 18,646	155 / 18,270	
	Basic	1.00	1.11 (0.87-1.42)	1.10 (0.87-1.42)	1.11 (0.87-1.42)	1.24 (0.97-1.58)	0.12
	Full	1.00	1.15 (0.90-1.48)	1.13 (0.88-1.45)	1.10 (0.85-1.41)	1.12 (0.87-1.44)	0.58
Starch	c / py	138 / 18,312	129 / 18,657	147 / 18,900	120 / 19,086	154 / 19,246	
	Basic	1.00	0.77 (0.60-0.97)	0.94 (0.75-1.18)	0.83 (0.65-1.05)	0.92 (0.73-1.16)	0.68
Fiber	c / py	150 / 18,095	129 / 18,714	130 / 18,830	141 / 19,067	120 / 19,504	
	Basic	1.00	0.87 (0.69-1.10)	0.82 (0.64-1.03)	0.85 (0.68-1.08)	0.72 (0.57-0.91)	0.018
	Full	1.00	0.93 (0.74-1.17)	0.88 (0.68-1.13)	0.93 (0.73-1.18)	0.80 (0.61-1.06)	0.12
Fat, total	c / py	150 / 19,060	147 / 18,861	108 / 19,065	130 / 18,870	152 / 18,874	
	Basic	1.00	1.04 (0.82-1.31)	0.80 (0.62-1.03)	0.90 (0.70-1.16)	0.97 (0.76-1.24)	0.56

[2] Basic model: Adjusted for method version, total energy intake, and season.
[3] Full model: Adjusted for method version, total energy intake, season, BMI categories, alcohol categories, smoking, education, antihypertensive treatment, antihyperlipidemic treatment, leisure time physical activity (quintiles), and quintiles of energy-adjusted dietary fiber. There are only 8,038 men (506 cases) in the full model due to missing values.

Table S2. Risk of coronary event in 12,535 women by macronutrient intake (multivariate hazard ratios with 95% confidence intervals per quintile of energy-adjusted intake).

Excerpts:

		1 (n=2,507)	2 (n=2,507)	3 (n=2,507)	4 (n=2,507)	5 (n=2,507)	P for trend
Saturated fat	Basic	1.00	0.85 (0.58-1.23)	0.82 (0.57-1.19)	1.00 (0.70-1.42)	1.00 (0.71-1.42)	0.55
	Full	1.00	0.90 (0.62-1.31)	0.89 (0.62-1.29)	1.07 (0.75-1.52)	1.10 (0.77-1.57)	0.31
n-6 fatty acids	c / py	65 / 29,437	75 / 29,642	66 / 29,982	59 / 30,206	68 / 30,306	
	Basic	1.00	1.22 (0.88-1.71)	1.10 (0.78-1.54)	1.06 (0.74-1.52)	1.30 (0.92-1.83)	0.34
	Full	1.00	1.18 (0.84-1.65)	1.09 (0.77-1.54)	1.06 (0.74-1.51)	1.19 (0.84-1.68)	0.55
Protein	c / py	78 / 29,838	63 / 30,261	65 / 30,002	59 / 29,766	68 / 29,705	

After Full adjustment, only a high SFA intake was protective, but in just women. But now look at that entire line. Quintiles 2 through 5 all show about the same benefit (all versus quintile 1), and all are statistically significant. What does this imply? If a woman in quintile 1 is eating the mean SFA intake of 12.9% of her calories from SFA, she can significantly reduce her chances of a coronary event (e.g., a heart attack) by adding 2 pats of butter to her diet.

With Basic adjustments of the CE data, statistical significance is reached only for fiber for both men and women. And, it does not reach significance with the Full adjustment. But look in

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quintile 4 for women, Full adjustment, fiber did reach statistical significance. This would seem to imply that a woman in quintile 5 for fiber, may want to lower her fiber intake.

The authors go on to note, "Among women, there was a protective association between fiber and CE after exclusion of low and high energy reporters. *There was also a protective association between saturated fat intake and CE among women;* t***his association, however, was dependent on fiber being present in the statistical model****. Indeed, we discovered statistical interactions between intake of fiber and saturated fat, which also were different between men and women.*"

Now lets turn to more of the comments by the authors in the discussion. Some of their comments refer to analysis/adjustments that were not shown in tables or graphs in the article or supplement. Emphasis is mine, below.

1) "…the lower risk of iCVD associated with a high fiber intake among women was clearly the most consistent and robust in multivariate analyses."

2) "*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.[4]* **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.**"

3) "Like many other studies, our study suffers from relatively high correlations between some nutrients."

4) "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.** On the other hand, fiber intake in Sweden is generally low, compared to other European countries. It is therefore noteworthy that the apparent effects of higher fiber intake are rather strong in the present study."

5) "The fiber-SFA interactions are not easily explained. *We do not know of any experimental evidence giving any clues to potential biological mechanisms that would be involved to produce a protective effect of SFA, . . .* **Further, 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).**"

6) "In addition, the Spearman correlation coefficient between the saturated fat and fiber quintiles was -0.49 in both men and women. Further, ***the fiber-SFA interaction made SFA appear protective against CE in women.***"

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[4] Here is the article they reference (note the title): Jacobs DR, Jr., Tapsell LC (2007) Food, not nutrients, is the fundamental unit in nutrition. Nutr Rev 65: 439–450.

7) "The strengths of this study include the high-quality dietary data, the size of the population-based cohort, the 99.3% complete follow-up, the high-quality case ascertainment and the inclusion of persons with stable dietary habits only, the latter being an advantage few comparable studies have. The importance of good quality confounder data may be appreciated by considering the differences between the results of the basic and the more fully adjusted models. *It may be noted that BMI, smoking, education, alcohol habits, blood pressure and hyperlipidemia were all significantly associated with iCVD risk (data not shown).* **Weaknesses (in addition to those already mentioned) include the facts that we only had one dietary measurement and no available biomarkers of intake.**"

MALMO Grading

1) *Overadjustment with Lipids*. **Not applicable**.
2) *Sufficient Test of SFA Guidelines*. **F**. The lowest quintile of SFA was 13%. And, the authors note that only 1.2% of the population met the Swedish guideline for SFA intake, 10% or less.
3) *Homogeneity*. **F**.
4) *Food/Lifestyle Questionnaire*. **C**. An **A/B** for diligence for the initial process and data gathering. But no follow-up over the mean 13.5 year follow-up. Looking at some online data for Sweden, overall butter consumption fell in the 1990's. I suspect smoking also declined. And, based on the profile of the population at the beginning of the study, it seems likely that many more were put on statins and blood pressure meds during the study period.
5) *Missing Data in the Study*. **C**. As one example, the authors note that trans-fat data was not collected. Another is that they did not do any blood work, e.g. cholesterol and glucose.
6) *Missing Data in the Paper*. **B**. The paper did not present the characteristics by SFA quintile. On the positive side, the 2007 paper did have some of this by Total Fat, and it seems likely that an SFA breakdown would be close.
7) *Confounders*. **D**. This problem was mentioned in the 2012 paper, and noted predominantly in the interaction with fiber and SFA.
8) *Food vs. Nutrients*. **D**. I suspect that this is going to be a problem in almost all the studies. The only reason that I grade this a D and not an F, is that the authors point this out as a problem with their study, and all such comparable macronutrient studies.

The grades for both (2) and (3) alone make the study an inappropriate one for testing the validity of the existing SFA guidelines.

The Oxford Vegetarian Study

Both the Chowdhury and Siri-Tarino reference the same paper [8]. They graded them identically:

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RR    (95% CI)
2.77 (1.25 - 6.13)
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Thus, this study found a major coronary risk to a high SFA diet.

Although participants 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."

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. A semiquantitative food frequency questionnaire was completed and information gathered concerning smoking and exercise habits, social class, weight, and height at the time of recruitment to the study (September 1980 to January 1984, median year of recruitment 1981)." "Subjects under 16 years and those with diagnosed cancer (excluding non-melanoma skin cancer) at entry were excluded from the analyses as were those who failed to provide full information concerning smoking habits, height, weight, and employment category." Some of the characteristics of the group are in table 1, below:

Table 1   Number (percentage) of men and women with various lifestyle related characteristics and with pre-existing disease at the time of entry to the study

	Men	Women
Number of subjects	4102	6700
Median age at entry (years)	34	33
Diet group		
Meat eater	2147 (52.3)	2751 (41.1)
Semi-vegetarian	387 (9.4)	962 (14.4)
Vegetarian/vegan	1568 (38.2)	2987 (44.6)
Smoking habits		
Never smoked	1787 (43.6)	4021 (60.0)
Ex-smoker	1302 (31.7)	1588 (23.7)
Current smoker		
< 10 cigarettes/day	531 (12.9)	487 (7.3)
≥ 10 cigarettes/day	482 (11.8)	604 (9.0)
Body mass index (kg/m²)		
< 20	592 (14.4)	1777 (26.5)
20–	1560 (38.0)	2804 (41.9)
22.5–	1259 (30.7)	1425 (21.3)
≥ 25	691 (16.8)	694 (10.4)
Social class		
I–II	2190 (53.4)	3040 (45.4)
III–V	1088 (26.5)	2017 (30.1)
Others	824 (20.1)	1643 (24.5)
*Pre-existing disease**∗*		
No	3832 (93.4)	6148 (91.8)
Yes	270 (6.6)	552 (8.2)

∗ Angina, heart disease, hypertension, diabetes or stroke.

"Vegetarianism was defined as never eating fish or meat or foods derived from animal products other than dairy foods and eggs. Individuals who ate meat occasionally but less than once a week or who ate fish but not meat were described as semi-vegetarians."

The distribution of intakes was in tertiles (thirds). The lowest intake was regarded as the reference group. Table 2 below looks at the tertiles for the intake of fiber, animal fat, animal saturated fat, and cholesterol:

Table 2   Tertiles of the distribution of intake of total fat, saturated fat, and dietary cholesterol from animal foods

	Men		Women	
	Tertiles	*Median intake for each tertile*	*Tertiles*	*Median intake for each tertile*
Total animal fat	43.6 and 61.9 g/day	25.5 52.4 74.8	37.0 and 55.1 g/day	23.6 45.2 67.0
Saturated animal fat	23.9 and 34.0 g/day	14.6 27.4 41.0	20.6 and 31.0 g/day	13.7 26.3 38.1
Dietary cholesterol	214.0 and 345.1 mg/day	155.6 277.1 431.4	195.8 and 291.1 mg/day	137.7 244.6 378.1
Dietary fibre	22.4 and 32.5 g/day	17.9 27.3 39.6	20.9 and 29.1 g/day	16.5 24.7 35.0

Animal foods include meat, eggs, milk, and cheese. Plant foods, especially oils, nuts and seeds, contain significant amounts of fats, including some saturated fat (but a very low percentage compared to animal foods). And, this paper does not provide this data.

To describe the mortality of the study group as a whole, they calculated standardized mortality ratios (SMRs) for men and women for all major causes of death using national mortality data for England and Wales. "A total of 525 deaths were observed in more than 143,000 person-years at risk; overall mean duration of follow up 13.3 years. SMRs for all cause mortality in the entire cohort were 0.48 (95% CI 0.42 to 0.54) for men, and 0.57 (0.50 to 0.64) for women. SMRs for IHD were 0.44 (0.35 to 0.56) for men, and 0.46 (0.35 to 0.61) for women, and for all malignant neoplasms 0.56 (0.44 to 0.69) and 0.75 (0.63 to 0.89) for men and women, respectively." Thus, as the title of the paper implies, the recruited population were made up of health-conscious individuals. From the paper, "These findings relate to people who are mainly non-smokers, of high social class, and relatively lean. It is not surprising that all cause mortality is about half that expected for the population of England and Wales."

Table 4 presents the adjusted Death Rate ratio for subjects with *no pre-existing disease* for selected dietary factors. Just 5 factors reached statistical significance for Ischemic Heart Disease: total animal fat, saturated animal fat, dietary cholesterol, eggs, and cheese. The figures for saturated animal fat were exactly the ones reported in both Chowdhury and Siri-

Tarino meta-analyses. Interestingly, dietary fiber did not reach statistical significance (but it did come close.)

Table 4   Death rate ratio (95% confidence interval) for selected dietary factors, each adjusted for age, sex, smoking and social class for subjects with no evidence of pre-existing disease at the time of recruitment

	Ischaemic heart disease			All causes of death		
	No of deaths (64)	*Death rate ratio*	*Trend*	*No of deaths (392)*	*Death rate ratio*	*Trend*
Diet group						
Meat eater	32	100		170	100	
Semi-vegetarian	7	108 (47–248)	NS	45	102 (73–143)	NS
Vegetarian/vegan	25	83 (48–143)		177	102 (82–127)	
Meat						
None eaten	29	100		209	100	
Less than daily	18	153 (84–279)	NS	83	102 (79–133)	NS
Daily	17	118 (64–218)		94	101 (79–130)	
Eggs (per week)						
< 1	8	100		89	100	
1–5	33	128 (59–279)	p < 0.01	203	74 (58–96)★	NS
6+	23	268 (119–602)★		89	92 (68–123)	
Milk (pints per day)						
Less than half	18	100		138	100	
Half	21	76 (40–143)	NS	139	70 (55–88)★★	NS
More than half	24	150 (81–278)		106	87 (68–113)	
Cheese (excluding cottage)						
< once per week	5	100		55	100	
1–4 times per week	16	123 (45–335)	p < 0.01	120	86 (62–118)	NS
≥ 5 times per week	43	247 (97–626)		208	102 (76–137)	
Total animal fat						
1st tertile	9	100		116	100	
2nd tertile	15	179 (78–409)	p < 0.01	95	85 (65–112)	NS
3rd tertile	21	329 (150–721)★★		99	105 (80–138)	
Saturated animal fat						
1st tertile	9	100		111	100	
2nd tertile	17	211 (94–474)	p < 0.01	100	95 (73–125)	NS
3rd tertile	19	277 (125–613)★		99	106 (80–139)	
Dietary cholesterol						
1st tertile	8	100		116	100	
2nd tertile	15	181 (77–429)	p < 0.001	90	74 (56–97)★	NS
3rd tertile	22	353 (157–796)★★		104	102 (78–134)	
Fish						
Never eaten	26	100		184	100	
< once per week	13	121 (62–238)	NS	82	97 (74–126)	NS
≥ once per week	25	123 (70–217)		123	96 (76–121)	
Green vegetables						
< once per week	4	100		39	100	
1–4 times per week	29	119 (42–340)	NS	171	74 (52–105)	NS
≥ 5 times per week	30	134 (47–384)		176	89 (63–126)	
Carrots						
< once per week	14	100		60	100	
1–4 times per week	29	57 (30–108)	NS	226	107 (80–142)	NS
≥ 5 times per week	18	76 (37–157)		96	99 (72–138)	
Fresh or dried fruit						
< 5 times per week	17	100		106	100	
5–9 times per week	29	107 (58–196)	NS	151	89 (69–114)	NS
≥ 10 times per week	17	89 (44–180)		128	97 (74–127)	
Nuts						
< once per week	30	100		188	100	
1–4 times per week	21	119 (68–210)	NS	123	99 (79–125)	NS
≥ 5 times per week	13	87 (45–168)		72	77 (58–101)	
Dietary fibre						
1st tertile	7	100		82	100	
2nd tertile	14	192 (77–479)	NS	88	101 (75–137)	NS
3rd tertile	17	225 (92–553)		93	98 (73–133)	
Alcohol						
0 or < 1 unit per week	24	100		158	100	
1–7 units per week	25	131 (74–234)	NS	122	88 (69–113)	NS
> 7 units per week	15	102 (51–203)		108	104 (79–135)	

*2p < 0.05; **2p < 0.01.
Numbers of deaths may not total 64 or 392 because values of the dietary factors were unknown for some subjects.

Death ratios were also computed for all subjects (i.e. including ones with pre-existing disease), but not included in the paper. "The trends for all subjects were similar to those presented for the group with no prior disease except that IHD mortality was significantly lower in the vegetarian/vegan group than in the meat eaters (death rate ratio 63; 95% CI 42–93)."
Some interesting extracts from the paper in the discussion section w.r.t. IHD:

1) "These results may therefore indicate which dietary factors are determinants of IHD mortality when populations comply with current dietary guidelines that emphasise the need to reduce the intake of saturated fatty acids and increase the intake of foods rich in dietary fibre."
2) "The findings support the hypothesis that the nature and quantity of dietary fat and cholesterol are key determinants of IHD mortality. A gradient of risk is apparent with increasing intake of total animal fat, saturated fat, and dietary cholesterol as well as some of the major food sources of these nutrients."
3) "Other recent studies have suggested that the deleterious effect of saturated fat and cholesterol is less important than the protective effects of dietary fibre and linolenic acid. However, 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.*** Conversely, the absence of an effect of dietary fibre in our data could be due to the fact that our cohort had average intakes above that observed in other studies and that a gradient of risk is no longer apparent with intakes in this higher range."
4) "The semiquantitative food frequency questionnaire was a relatively crude instrument, having been designed before the development of the more sophisticated food frequency questionnaires currently employed in large scale epidemiological studies. However, we are confident of its ability to provide reasonable estimates of dietary fat, cholesterol, and fibre. Special attention was given to the food sources of these nutrients as they were of particular interest when the study was planned."
5) "We were unable to detect a protective effect of either fish intake or alcohol, which have been reported in several other studies. The most likely explanation is a relatively narrow spread of intakes."
6) "We were not able to examine the potentially protective effects of antioxidant nutrients or of long chain unsaturated fatty acids. When the study started there were no clear hypotheses concerning effects of these nutrients so the questionnaire did not include details of relevant foods."

Oxford Vegetarian Grading

1) *Overadjustment with Lipids*. **Not applicable**.
2) *Sufficient Test of SFA Guidelines*. **B**. The total kcal intake per day was not calculated. But we can assume typical averages to estimate percentages. Also, SFA intake was only provided for animal sources. But the guidelines advise cutting SFA, by reducing animal sources - not from plant sources, which are small in comparison. The 1st tertile of animal saturated fat intake for men and women respectively are: 14.6g and 13.6g. Assuming a

     daily energy intake of 2500 for men and 2000 for women[5], the resulting percentages are: 5.3% and 6.1%. And the range of saturated fat over the 3 tertiles is significant - 2.8 for tertile-3/tertile-1 means.

3) *Homogeneity.* **B.** I didn't give it an **A** because the meat-eaters were a healthier group than average from the UK.

4) *Food/Lifestyle Questionnaire.* **D**. No follow-up over the mean 13.3 year follow-up. And, as noted in the paper, the semi-quantitative FFQ was a relatively crude instrument.

5) *Missing Data in the Study.* **C.** As one example, No trans-fat data. Another is that they did not do any blood work, e.g. cholesterol and glucose.

6) *Missing Data in the Paper.* **C.** The paper did not present the characteristics by SFA tertile. Also, the paper only presented animal sources for fat. And, no data on MUFA and PUFA was presented.

7) *Confounders.* **C.** Since the characteristics per SFA tertile were not presented, it is difficult to say if there may have been confounders or not. However, this was a healthy study group (e.g. w.r.t. BMI, smoking, alcohol). So, confounders are less likely.

8) *Food vs. Nutrients.* **B.** They did identify and present data for the foods highest in saturated fat (e.g. Meat, eggs, milk, cheese). But it would have been useful to see many other foods or categories, e.g. poultry, legumes, whole grains, processed foods. To calculate fat and cholesterol, they must have this data. So, it is likely they didn't present it, because it wasn't significant.

Based on the above grading, I think this is a worthwhile study to include in the meta-analysis.

Nurses Health Study (NHS)

This study is referenced by both Chowdhury and Siri-Tarino. They both reference the same 2005 paper [8]. But there is also a 1997 paper on this study that has other useful additional information [9]. Here are the SFA scores from Chowdhury and Siri-Tarino:

	RR (95% CI)
Chowdhury	0.98 (0.79, 1.21)
Siri-Tarino	0.97 (0.74, 1.27)

I don't have time to present the details of the NHS papers to provide a detailed analysis. That will be in the revision.

One aspect of the dietary guidelines is the recommendation on how to reduce SFA, i.e. to replace it with plant sources of polyunsaturated fat (PUFA). And, here is an excerpt from the 1997 NHS article:

"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)."

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[5] From UK's NHS, http://www.nhs.uk/chq/pages/1126.aspx?categoryid=51

Shortly, after the Chowdhury article was available on the internet, some of the same authors of the NHS papers (e.g. Drs. Willet and Stamfer from the Harvard School of Public Health) posted a comment. Here is a related excerpt:

"Further, the authors did not mention a pooled analysis [10] of the primary data from prospective studies, in which a significant inverse association between intake of polyunsaturated fat (the large majority being the N-6 linoleic acid) and risk of CHD was found. Also, in this analysis, substitution of polyunsaturated fat for saturated fat was associated with lower risk of CHD. Chowdhury et al. also failed to point out that most of the monounsaturated fat consumed in their studies was from red meat and dairy sources, and the findings do not necessarily apply to consumption in the form of nuts, olive oil, and other plant sources. Thus, the conclusions of Chowdhury et al. regarding the type of fat being unimportant are seriously misleading and should be disregarded."

Summary

Based on my initial analysis, Chowdhury has not chosen "good" studies to back up his claim, and few are applicable to Chowdhury's claim w.r.t. the dietary guideline for Saturated Fat intake. I will be improving and expanding my analysis to cover all 20 of the studies that Chowdhury cites. I expect that this will take a few weeks due to other Obligations.

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