Evaluation of the 20 SFA-Intake Studies Used in the Chowdhury Meta-Analysis on the Association of Saturated Fatty Acids with Coronary Risk

by

Fred Pollack
fjpollack@gmail.com

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Preface

This is a Supplement to Part 3 of my article in the May 2014 McDougall Newsletter. I would like thank Dr. McDougall for his encouragement in doing this analysis. It has been a great learning experience.

The table of contents, after this preface, provides the page numbers for my analyses of each of the 20 studies within this document - just click on the page number to take you to the one that interests you. For convenience, I've reproduced my scoring table and the Key for the grading below. More detail about the grading methodology can be found in my main article, via the link above. The rationale for my scoring is within my analysis of each study.

Based on time constraints and this new experience for me, I may have made some mistakes in my analyses. I greatly welcome corrections and discussions.

		Chowdhury		Siri-Tarino										
Study	**Country**	**RR**	**CI**	**RR**	**CI**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**A**	**E**
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*. **Y**es or **N**o.
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.

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Japan Collaborative Cohort Study (JACC)

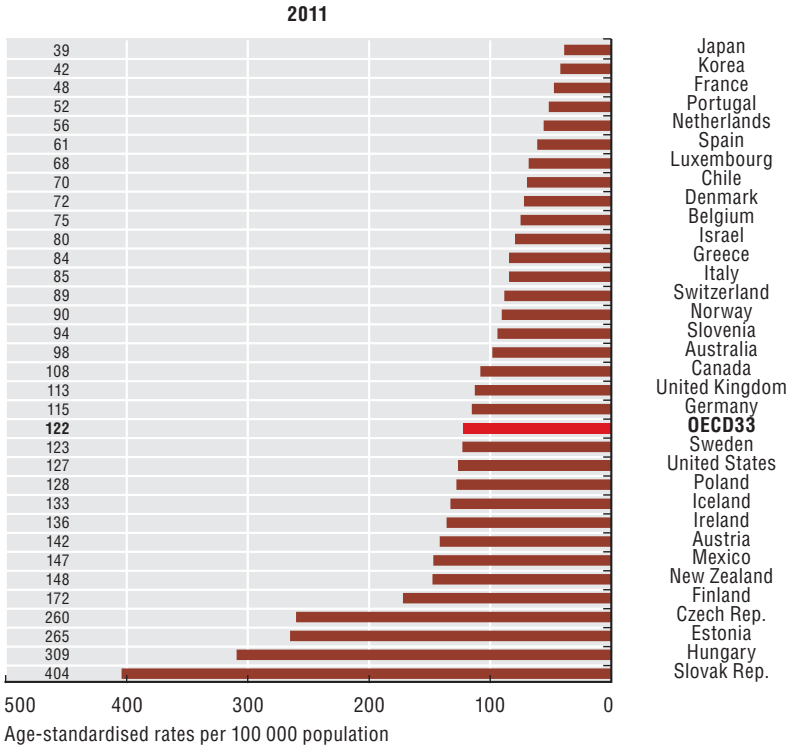
Yamagishi K, Iso H, Yatsuya H, Tanabe N, Date C, Kikuchi S, Yamamoto A, Inaba Y, Tamakoshi A. Dietary intake of saturated fatty acids and mortality from cardiovascular disease in Japanese: the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC) Study. Am J Clin.Nutr. 2010;92:759-765.

	RR (95% CI)
Chowdhury	0.92 (0.74, 1.14)

This paper (which I'll refer to as the JACC/SFA paper) was only covered in the Chowdhury meta-analysis, probably because it was published after the Siri-Tarino paper was accepted for publication. Chowdhury et al indicated a benefit of increased SFA-intake, but this did not reach statistical significance (i.e. upper-end of the confidence interval needed to be <1.0 vs 1.14).

The corresponding result reported in the paper was RR=0.89, CI: (0.68, 1.15); i.e. about the same - the difference due to the methodology used in the meta-analysis so that results of studies could be combined.

Before getting to the key messages and analysis of the study, it is important to put this study of Japanese into the proper context. The Japanese have about the longest-lived people of the large industrialized counties,[1] and the lowest incidence of coronary heart disease (CHD). Here is a chart from the OECD 2013 Health at a Glance Report, measuring Ischemic Heart Disease Mortality for 2011.



[1] 2011 data from OECD 2013 report. For life expectancy at birth, Japan is #2 at 82.7 vs. Switzerland at 82.8 (and 78.7 for USA #26). For life expectancy at age 65, Japan is #2 at 18.7/23.8 for men/women vs. #1 France at 19.3/23.8 (and 17.8/20.4 for USA #25).

Key Messages:

- W.r.t. SFA intake, a very homogenous study population, with a very low intake of SFA:
  - ✦ Men. Of the 5 quintiles of SFA-intake, 4 had a mean SFA-intake <10% and each of these 4 had a cholesterol intake <300mg/day. Men in the 5th quintile of SFA-intake, had a mean SFA-intake of 20.3 g and a cholesterol intake of 302mg/day.
  - ✦ Women. Of the 5 quintiles of SFA-intake, 3 had a mean SFA-intake <10%, and all quintiles had a mean cholesterol intake of <300mg/day. Women in the 4th and 5th quintile of SFA-intake, had a mean SFA-intake of 16.5 g and 19.8 g, respectively. Note that the energy intakes (in kcal) for men and women were very low compared to other studies, i.e. ~1,650 and ~1325, respectively.
  - ✦ Small range of SFA-intake across the 5 quintiles for men and women - just ~2.5 g of SFA intake from the mean of one quintile to the next higher one. The paper notes, ". . .the low distribution of SFA intake among Japanese."
- All input (diet, lifestyle, medical history) was done via self-administered questionnaire only at the beginning of the study. No examinations or interviews. Follow-up period for the 58,453 participants, aged 40-79 at baseline (1988-1990) was 14 years. Measured end-point was death.

Quick summary: (1) the homogeneous study population and method of input (above) make this a questionable study; (2) SFA-intake of this study population (which represents the Japanese as a whole) is about 1/3 to 1/2 the SFA intake of almost all the other studies in the Chowdhury meta-analysis; (3) as noted in the paper, "for example, the median intake of SFAs for the highest quartile of a Japanese rural population (1970–1980s) was 17 g/d lower than that for the lowest quartile of intake in the Nurses' Health Study in 1980 (20 g/d)"; and (4) Japan, as indicated in the above chart, has 23% (Finland) to 55% (Denmark) of the IHD mortality of the other countries in these studies.

SPOILER ALERT: At this point, you may be thinking that perhaps the low-incidence of IHD mortality in the Japanese population is due more to their *fruit, vegetable, and bean* intake vs. their low-SFA intake. *WRONG!* According to another paper using the same study population, *the highest quartile of intake for each of these is <1 serving per day*.

After I get through with my review of this JACC/SFA study, I'll cover the JACC/FVB (Fruit-Vegetable-Bean) paper, and relate it back the JACC/SFA paper (which is up first). But one brief point before that.

Hypertension. The only indication of hypertension in the study population was a yes/no response by participants in the study - no actual measurements (as was done in almost all the other studies). The "yes" response was about 19% for men and 22% for women. However, at the same time, a large study to actually measure the blood pressure of the Japanese was undertaken (1990). That study indicated a much higher prevalence of hypertension (defined as either an SBP>140 or DBP>90 or on BP medication): for men, aged 45-64, 56%; aged 65+, 72%; for women, aged 45-64, 50%; aged 65+, 76%. Thus, given the mean age of JACC participants of ~56 y, ***hypertension was underestimated by a factor of 3X.*** Since BP is a major

risk factor for both stroke and CHD and is thus part of the multivariate analysis in JACC/SFA study, this alone is a sufficient flaw to cast doubt on the results.

About JACC/SFA Paper

The JACC study is a community-based sample of 110,792 persons aged 40-79 during a baseline period of (1988-1990), from 45 communities in Japan. "Briefly, we excluded persons who reported a history of heart disease, stroke, or cancer at baseline and those with incomplete answers for the foods making a major contribution to SFA intake in the dietary questionnaire. Participants from 11 communities were also excluded because the complete version of the food-frequency questionnaire (FFQ) was not distributed in these communities. As a result, we included 23,024 men and 35,429 women from 34 communities."

TABLE 1
Baseline cardiovascular disease risk factors and select dietary variables in a cohort of 23,024 men and 35,429 women according to quintile of saturated fatty acid (SFA) intake[1]

	Quintile of SFA intake (g/d)[2]					
	2.5 to <11.0	11.0 to <13.4	13.4 to <15.4	15.4 to <17.9	17.9–40.0	*P* value[3]
Men						
Median SFA intake (g/d)[2]	9.2	12.2	14.4	16.5	20.3	
Number at risk	5076	4573	4194	4157	5024	
Age at baseline (y)[4]	55.2 ± 9.7	55.7 ± 9.8	55.7 ± 9.6	56.5 ± 10.1	56.5 ± 10.3	<0.001
Mean BMI (kg/m^2)	22.7	22.8	22.8	22.6	22.5	<0.001
History of hypertension (%)	22.1	21.3	18.6	17.4	15.3	<0.001
History of diabetes (%)	5.6	5.6	6.3	5.7	7.4	<0.001
Current smoker (%)	60.0	53.8	52.4	51.2	51.6	<0.001
Current drinker (%)	83.1	80.5	76.5	72.8	62.6	<0.001
Sports ≥1 h/wk (%)	26.3	28.7	29.6	34.6	36.9	<0.001
Walking ≥1 h/d (%)	51.1	51.6	50.8	48.2	47.1	<0.001
College or higher education (%)	14.0	16.1	16.9	20.2	24.9	<0.001
High perceived mental stress (%)	22.5	21.9	24.3	25.3	28.2	<0.001
Mean energy intake (kcal/d)	1607	1698	1699	1657	1592	<0.001
Dietary cholesterol (mg/d)	164	226	250	271	302	<0.001
MUFAs (g/d)	6.2	8.5	9.7	10.7	12.4	<0.001
PUFAs (g/d)	6.4	7.9	8.4	8.8	9.2	<0.001
ω-3 PUFAs (g/d)	1.2	1.6	1.7	1.8	1.9	<0.001
ω-6 PUFAs (g/d)	5.1	6.3	6.7	7.0	7.2	<0.001
Animal protein intake (g/d)	17	23	26	29	34	<0.001
Plant protein intake (g/d)	27	30	30	29	28	<0.001
Vegetable intake (g/d)	70	87	95	102	108	<0.001
Fruit intake (g/d)	90	108	125	131	143	<0.001
Women						
Median SFA intake (g/d)[2]	9.4	12.3	14.4	16.5	19.8	
Number at risk	6614	7118	7497	7534	6666	
Age at baseline (y)[4]	58.0 ± 9.9	56.8 ± 9.9	56.2 ± 9.7	55.8 ± 9.6	54.5 ± 9.8	<0.001
Mean BMI (kg/m^2)	23.2	23.1	23.0	22.9	22.6	<0.001
History of hypertension (%)	22.2	20.5	22.0	19.5	18.2	<0.001
History of diabetes (%)	2.9	3.0	3.5	3.6	4.1	<0.001
Current smoker (%)	6.7	4.6	3.7	3.7	5.6	<0.001
Current drinker (%)	23.2	23.7	23.2	23.0	24.4	0.28
Sports ≥1 h/wk (%)	17.5	20.6	23.8	25.2	28.4	<0.001
Walking ≥1 h/d (%)	54.5	53.8	51.3	50.1	48.2	<0.001
College or higher education (%)	7.2	8.6	10.1	11.8	15.7	<0.001
High perceived mental stress (%)	20.1	19.9	20.6	21.8	22.0	0.005
Mean energy intake (kcal/d)	1309	1352	1347	1348	1283	<0.001
Dietary cholesterol (mg/d)	165	223	248	273	287	<0.001
MUFAs (g/d)	6.5	8.7	9.7	10.8	11.9	<0.001
PUFAs (g/d)	6.5	7.8	8.1	8.4	8.2	<0.001
ω-3 PUFAs (g/d)	1.3	1.6	1.7	1.8	1.8	<0.001
ω-6 PUFAs (g/d)	5.2	6.2	6.3	6.6	6.4	<0.001
Animal protein intake (g/d)	17	24	27	30	33	<0.001
Plant protein intake (g/d)	27	27	27	26	24	<0.001
Vegetable intake (g/d)	87	101	109	113	114	<0.001
Fruit intake (g/d)	124	144	152	155	157	<0.001

[1] All values are age-adjusted means or percentages unless otherwise indicated. MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids.
[2] Energy-adjusted values were derived by using a nutrient residual model. Ranges and median values for SFA were divided by an underestimation rate of 63.3%.
[3] *P* values for overall differences between quintiles based on ANCOVA.
[4] Values are unadjusted means ± SDs.

The FFQ (Food Frequency Questionnaire) included *just* 33 food items and 5 choices for frequency of intake offered for each item. To validate the SFA-intakes, a validation study examined the dietary records of 85 people (mostly female), which found that SFA-intake was underestimated by 36.7%. Thus, the SFA-intake values were adjusted by dividing them by 63.3%. Were other nutrients adjusted based on the subsample (e.g. total energy intake)? The paper doesn't say. Table 1 includes the baseline characteristics of the study population.

TABLE 2
Multivariate hazard ratios (HRs) (and 95% CIs) for mortality from stroke, ischemic heart disease, cardiac arrest, heart failure, and total cardiovascular disease according to quintiles of saturated fatty acid (SFA) intake in 23,024 men and 35,429 women combined[1]

	Quintile of SFA intake (g/d)[2]					
Mortality endpoint	2.5 to <11.0	11.0 to <13.4	13.4 to <15.4	15.4 to <17.9	17.9–40.0	*P* for trend
Person-years	147,057	148,710	149,314	148,995	145,920	
Total stroke (*n*)	245	213	193	177	148	
Absolute rate	1.67	1.43	1.29	1.19	1.01	
HR (95% CI)						
Model 1	1.0	0.90 (0.75, 1.08)	0.86 (0.71, 1.03)	0.76 (0.63, 0.93)	0.66 (0.53, 0.80)	<0.001
Model 2	1.0	0.90 (0.74, 1.09)	0.89 (0.72, 1.10)	0.80 (0.64, 1.00)	0.69 (0.53, 0.89)	0.004
Intraparenchymal hemorrhage (*n*)	63	48	45	45	23	
Absolute rate	0.43	0.32	0.30	0.30	0.16	
HR (95% CI)						
Model 1	1.0	0.78 (0.54, 1.14)	0.77 (0.52, 1.12)	0.75 (0.51, 1.10)	0.39 (0.24, 0.63)	<0.001
Model 2	1.0	0.87 (0.58, 1.29)	0.89 (0.58, 1.36)	0.90 (0.57, 1.42)	0.48 (0.27, 0.85)	0.03
Subarachnoid hemorrhage (*n*)	29	46	28	30	20	
Absolute rate	0.20	0.31	0.19	0.20	0.14	
HR (95% CI)						
Model 1	1.0	1.59 (1.00, 2.53)	0.98 (0.58, 1.64)	1.05 (0.63, 1.75)	0.77 (0.44, 1.36)	0.14
Model 2	1.0	1.77 (1.08, 2.89)	1.12 (0.64, 1.98)	1.22 (0.68, 2.20)	0.91 (0.46, 1.80)	0.47
Ischemic stroke (*n*)	86	66	64	54	51	
Absolute rate	0.58	0.44	0.43	0.36	0.35	
HR (95% CI)						
Model 1	1.0	0.79 (0.58, 1.09)	0.81 (0.59, 1.13)	0.65 (0.47, 0.92)	0.62 (0.44, 0.88)	0.004
Model 2	1.0	0.74 (0.53, 1.04)	0.79 (0.55, 1.14)	0.63 (0.42, 0.93)	0.58 (0.37, 0.90)	0.01
Ischemic heart disease (*n*)	108	80	79	76	77	
Absolute rate	0.73	0.54	0.53	0.51	0.53	
HR (95% CI)						
Model 1	1.0	0.76 (0.57, 1.02)	0.79 (0.59, 1.06)	0.73 (0.55, 0.99)	0.76 (0.56, 1.01)	0.08
Model 2	1.0	0.83 (0.61, 1.13)	0.93 (0.68, 1.28)	0.89 (0.63, 1.24)	0.93 (0.65, 1.35)	0.86
Myocardial infarction (*n*)	88	65	64	53	60	
Absolute rate	0.60	0.44	0.43	0.36	0.41	
HR (95% CI)						
Model 1	1.0	0.76 (0.55, 1.05)	0.79 (0.57, 1.08)	0.63 (0.45, 0.88)	0.72 (0.52, 1.00)	0.03
Model 2	1.0	0.82 (0.58, 1.14)	0.92 (0.65, 1.31)	0.74 (0.50, 1.10)	0.85 (0.56, 1.29)	0.40
Cardiac arrest (*n*)	29	22	19	21	16	
Absolute rate	0.20	0.15	0.13	0.14	0.11	
HR (95% CI)						
Model 1	1.0	0.77 (0.44, 1.34)	0.71 (0.40, 1.26)	0.74 (0.42, 1.31)	0.59 (0.32, 1.09)	0.12
Model 2	1.0	0.73 (0.41, 1.31)	0.64 (0.34, 1.21)	0.69 (0.36, 1.34)	0.50 (0.23, 1.10)	0.11
Heart failure (*n*)	77	61	46	65	60	
Absolute rate	0.52	0.41	0.31	0.44	0.41	
HR (95% CI)						
Model 1	1.0	0.83 (0.59, 1.16)	0.66 (0.46, 0.95)	0.91 (0.65, 1.26)	0.87 (0.62, 1.22)	0.62
Model 2	1.0	0.88 (0.62, 1.25)	0.75 (0.50, 1.11)	1.01 (0.69, 1.48)	0.99 (0.64, 1.52)	0.83
Total cardiovascular disease (*n*)	507	424	383	392	346	
Absolute rate	3.45	2.85	2.57	2.63	2.37	
HR (95% CI)						
Model 1	1.0	0.86 (0.76, 0.98)	0.82 (0.72, 0.94)	0.82 (0.72, 0.93)	0.74 (0.65, 0.85)	<0.001
Model 2	1.0	0.89 (0.78, 1.02)	0.89 (0.77, 1.03)	0.89 (0.77, 1.04)	0.82 (0.69, 0.97)	0.05

[1] Absolute rate is presented per 1000 person-years. HRs for each outcome were calculated by using a Cox proportional hazards model. Model 1 was adjusted for age and sex. Model 2 was adjusted as for model 1 and for a history of hypertension and diabetes, smoking status, alcohol consumption, BMI, mental stress, walking, sports, educational level, and dietary intakes of total energy, cholesterol, ω-3 and ω-6 polyunsaturated fatty acids, vegetables, and fruit.
[2] Energy-adjusted values were derived by using a nutrient residual model. Ranges and median values for SFA were divided by an underestimation rate of 63.3%.

Table 2 presents the various results by types of stroke and heart disease. As the OECD report notes, "Ischemic heart disease (IHD) is caused by the accumulation of fatty deposits lining the

inner wall of a coronary artery, restricting blood flow to the heart." Thus, this relates to serum cholesterol, and from that, SFA intake. Smoking and high-blood pressure relate to both IHD and stroke, and both smoking and high-blood pressure are very high in the Japanese population. Whereas, SFA-intake and serum cholesterol are far less important in stroke. Therefore, Japan's ratio of stroke to IHD death approaches 2 to 1, whereas in USA and northern Europe, the ratio is reversed.

Remember: *My analysis of the Chowdhury/Siri-Tarino papers is focused on heart disease and* ***not stroke****. But the next 2 paragraphs will briefly discuss the stroke results in table 2 of this paper.*

Table 2 of the JACC paper indicates that higher SFA-intake (by Japanese standards, i.e. around 10-14% of Energy intake) may protect against stroke (when compared to those with a <6% of SFA intake). As the paper notes SFA intake increases LDL-cholesterol concentrations, and previous studies have shown inverse association of LDL and intraparenchymal hemorrhage. Thus, the inverse association of SFA-intake with this kind of stroke in this study is not surprising. Perhaps the some build-up of plaque in blood vessels due to higher SFA-intake has a somewhat protective effect from blood vessel hemorrhage, especially when diet/lifestyle (e.g. high blood pressure and smoking) has damaged the endothelial (i.e. the smooth muscle) cells that line the blood vessels.[2]

W.r.t. Ischemic stroke, the paper notes, "Ischemic stroke is considered to be an atherosclerotic disease because a large proportion of cases are large-artery occlusive infarctions in Western countries; however, in Asia, most ischemic strokes are lacular infarctions in perforator areas. We speculated that SFA may play different roles in intracranial large arteries as opposed to intracranial small vessels, and hemorrhage and ischemia in perforator areas may have a common pathophysiologic etiology, that is, very low blood cholesterol concentrations lead to angionecrosis in intracerebral arterioles through disappearance of medial smooth muscle cells and increased fragility of the vascular wall."

Now back to the coronary heart disease discussion.

The multivariate analysis (model 2) for heart disease deaths was HR=0.89 (0.68, 1.15); i.e. an increasing benefit of higher SFA-intake (5th quintile vs. 1st quintile), but this was not statistically significant. The pooled causes for these were IHD[3], cardiac arrest, and heart failure. The authors also ran a substitution model for SFA intake. From the paper, "We found no protective effects on IHD when SFA was replaced with MUFA, PUFA, or carbohydrates; the respective HRs were 0.95 (0.74, 1.23), 1.02 (0.89, 1.16), and 1.00 (0.91, 1.11) (data not shown in the tables)."

The authors note the following limitations of this study:

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[2] In my analysis of the Denmark study, I noted a Copenhagen study that showed a high intake of alcohol (≥3 drinks/day) was protective against IHD for those men with a very high LDL level (above 203mg/dl). In other words, perhaps one toxic substance counters the effects of another, in some cases.

[3] Myocardial Infarction is a subclass of Ischemic Heart Disease.

1. "We used an FFQ with only 33 food items[4] to identify SFA intake and death certificates to define events. Diet misclassification will attenuate findings toward the null in this prospective study; outcome misclassification would also attenuate findings toward the null, because this misclassification was unlikely to be related to baseline SFA intake."
2. "The exclusion of missing dietary information may affect generalizability, although it may not greatly affect the present results as discussed previously."
3. "The possibility of residual confounding by unmeasured or incompletely adjusted stroke risk factors also applies to this study."
4. "We did not include MUFA intake in the multivariate models because it was highly correlated with both SFA and animal protein intakes (Spearman's r = 0.82 and 0.85, respectively)."

My view of some additional limitations (besides the ones that I'll discuss in my grading at the end):

1. This multivariate analysis may involve some under-adjustments and some over-adjustments. The latter involves the adjustment for dietary cholesterol, fruit, and vegetable intake. The under-adjustments involve hypertension and diabetes. Hypertension was only determined by the questionnaire, asking subjects whether they suffer from hypertension or not, i.e. a yes or no answer. Similarly, the same issue occurs with diabetes status (e.g. no test was done to measure glucose levels of participants at study entry).
2. Hypertension underestimated by 3X. At the beginning of my analysis, I referenced a study done at the same time as the JACC, which showed that the incidence of hypertension in the Japanese population was 3X higher than that in the JACC paper. That paper also indicated that the majority that had hypertensive measurements were unaware of their condition. Note that in table 1, quintile 1 of SFA intake had the highest incidence of "yes" responses to hypertension, and quintile 5, the lowest. ***If*** the measurements had been done on the JACC study population, and the distribution followed the same pattern, the results w.r.t. SFA-intake in this study would have likely been significantly different.
3. Key Missing Data. Note that in Table 1 there are no entries for fiber and carbohydrates. Other studies have found fiber to be a significant confounder. Thus, its omission is important. Carbohydrates per SFA quintile could be approximated by the data provided, i.e. the using the mean of the fats and proteins in table 1. So, why not provide it?
4. Other studies partitioned their analysis into middle-aged (e.g. 50-59 y) and older (60-79) cohorts. As I have noted in other studies, by omitting at the beginning of the study subjects without CHD that are old, you are only including people who have not built up significant amounts of plaque in their arteries due to diet, lifestyle, or genetics. In the JACC study, the mean age of subjects was ~56 y and included those up to 79 y.
5. Note that the authors used an "escape" clause in their #3 limitation above. From a little bit of research, I think that they probably have a few confounders: sodium (definitely), mercury (likely), and arsenic (possibly), which I will get into, after discussing the JACC/FVB study.

About the JACC/FVB Study

Nagura J, Iso H, Watanabe Y, Maruyama K, Date C, Toyoshima H, Yamamoto A, Kikuchi S, Koizumi A, Kondo T, Wada Y, Inaba Y, Tamakoshi A. Fruit, vegetable and bean intake and mortality from cardiovascular disease among Japanese men and women: the JACC Study. British Journal of Nutrition. 2009;102:285–292.

[4] In the Nurses Health Study, the 1984 FFQ included 116 items.

The JACC/FVB paper (above) was published in January 2009 - 20 months prior to the JACC/SFA paper. There are 4 common authors on both papers. Both papers use the same study population and used the same questionnaire (w.r.t. food intake, lifestyle, medications). The JACC/FVB paper is referenced by neither JACC/SFA paper nor the Chowdhury paper; and, you will see why this is significant.

The JACC/FVB paper has 3 large tables, quartiles for fruit, vegetable, and bean intake with the study population characteristics within each quartile. Thus, each table is similar to table 1 in the SFA/Intake paper, but one each for fruits, vegetables, and beans, but divided into quartiles vs quintiles (as was done for SFA-Intake). But there is no need to present all that information. Here is the important data from these 3 tables:

Servings per week	Q1	Q4
Fruits	0.9	5.9
Vegetables	1.2	5.2
Beans	0.8	4.5

Note that the table shows mean servings per ***week.*** This implies in the highest quartile of each, there is less than 1 serving per day. So, would you expect to see a significant difference in reduced risk when comparing Q4 to Q1 w.r.t. total stroke, CHD, and total CVD mortality?[5] Here are the results:

RR Q4/Q1 (95% CI)	Stroke - MV	Stroke - MV +Other	CHD - MV	CHD - MV +Other	CVD - MV	CVD - MV +Other
Fruits	**0.67** (0.55,0.81)	**0.65** (0.53,0.80)	**0.74** (0.55, 0.99)	0.79 (0.58,1.08)	**0.75** (0.66,0.85)	**0.77** (0.67,0.88)
Vegetables	0.97 (0.81,1.16)	1.09 (0.90,1.33)	0.77 (0.58,1.00)	0.85 (0.64,1.14)	**0.88** (0.78,0.99)	0.96 (0.84,1.10)
Beans	0.90 (0.75,1.08)	0.95 (0.79,1.16)	0.80 (0.61,1.05)	0.88 (0.66,1.18)	**0.84** (0.74,0.95)	0.89 (0.78,1.01)
HR Q5/Q1 (95% CI)						
SFA		**0.69** (0.53,0.89)		0.89 (0.68,1.15)		**0.82** (0.69,0.97)

The multivariate analysis (**MV**) includes adjustments for age, sex, BMI (sex- specific quintiles), smoking category (never, ex- and current smokers of ≤19 or ≥20 cigarettes per d), alcohol in-

[5] total CVD includes stroke, CHD, and other CVD

take category (never, ex- and current ethanol intake of 1 – 22, 23 – 45, 46 – 68 and ≥69 g/d), hours of walking (rarely, 30, 30 – 60 and ≥60 min per d), sports (<1 and ≥1 h per week), education (<10, 10 – 12, 13 – 15 and ≥16 years), perceived mental stress (low, medium and high), history of hypertension or diabetes and sex-specific quartiles of dietary cholesterol, SFA, n-3 PUFA and sodium intake (sex-specific quartiles).

For the table of results see the next page. For Fruits, **MV+Other**, includes MV plus adjustments for Vegetable and Bean intake, and similarly, for the other MV+Other columns. The bottom row is excerpted from the JACC/SFA paper, model 2 results, which includes adjustments for fruits and vegetables. All the Risk Reduction (RR) rates in Bold are ones that met statistical significance.

Note that from table 1 of the JACC/SFA-intake paper, the highest quintile of SFA was also the quintile that had the highest fruit and highest vegetable intake. Similarly, the lowest quintile of SFA was also the quintile with the lowest fruit and lowest vegetable intake.

What does the above table imply? Consider an individual in the lowest quartile of fruit intake and the lowest quintile of SFA intake. To significantly reduce his risk of stroke (or total CVD), he would do best by upping his fruit intake to just 1 fruit a day. This would have a greater effect than increasing his SFA intake to quintile 5 (i.e. to ~20 g/day, which is about 11% of energy intake).

In other words, the benefit of increasing fruit intake to just 1/day seems rather unbelievable, and likely points to flaws in the study, e.g. over-adjustment in the MV analysis, and/or problems in the questionnaire.

Similarly, in the JACC/SFA paper, the results of increased SFA-intake also seem to be over-adjusted, e.g. with dietary cholesterol, PUFA, fruits, and vegetables. At the very least, it would have been informative to see the results for SFA-intake without adjustment for these factors.

Big Picture

Japan has achieved the lowest rates of CHD mortality with the lowest SFA-intake of the OECD countries, but also with 3 major risk factors: (1) very, very low fruit and vegetable intake; (2) high smoking rates; and, (3) high-incidence of hypertension.

Now, if you go back and look at the Table 1 of the JACC/SFA paper (1st table in this analysis), you will see that the Japanese are not getting a lot of calories from their animal protein nor their fat intake. So, from where? Neither of the 2 JACC papers answer the question. But I would guess that its from white rice, noodles made from white flour, and perhaps a few other starch based foods (e.g. sweet potatoes). In other words, from a calorie perspective, it would be more appropriate to classify them as *Starchivores - and not fish eaters*.

With much higher intakes of fruits and vegetables, their CHD, stroke, and total CVD mortality would be even lower. And, reducing Japan's high-smoking rate and sodium intake (next up) would yield even further progress.

Omitted Confounders

By doing a little research, sodium, mercury, and arsenic were *possibly* significant confounders in the JACC study. I'll briefly describe some of the research that suggests this.

Mercury

As I noted in my analysis of the Finnish KIHD study, mercury was a significant confounder that was not reported in the KIHD paper cited by Chowdhury and Siri-Tarino. Specifically, I found a paper that proved this. Thus, I wondered whether mercury could also be a factor in the Japanese study/population. I could not find any Japanese studies that looked at this. Thus, I can't provide a definitive answer. However, I did find some data about mercury levels in the Japanese. This can then be related to the results of the Finnish mercury results to form a plausible hypothesis.

So, what are the levels of mercury in the Japanese population. A 2003 article provided the results from a large sample study done across Japan. The older population had higher mercury levels than the younger population. From figure 3 of the article, the geometric mean level of MeHG (methylmecury) hair samples for ages 50-65 y: **men ~3.5 ug/g; women 2.0ug/g**.

The US EPA and FAO/WHO both say that mercury intakes should be kept low enough so that a hair sample indicates MeHG level below 2.2 ug/g, and recommends significantly lower levels for children and women of child-bearing age.

Now about the Finnish KIHD Mercury study, "The population-based prospective Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) cohort of 1871 Finnish men aged 42 to 60 years and free of previous coronary heart disease (CHD) or stroke at baseline" was followed for an average of 13.9 years. To relate to the JACC study, some different terms are used. I believe that "cardiovascular disease (CVD)" relates to primarily to stroke in the JACC study, and CHD relates to heart disease.

The men were equally divided into tertiles of MeHG in hair samples (ug/g): <0.84; 0.84 - 2.02; and >2.02. Table 2 (next page) provides the key results. The key hazard ratios are in the last column - the highest tertile vs the 2 lower-ones combined. W.r.t. CVD death (i.e. stroke) all adjustment models indicate a statistical harmful effect for a high MeHG level. W.r.t. CHD death, model 3 reaches statistical significance, but model 4 just misses it.

To summarize, men in the highest third of hair mercury content (>2.03 ug/g) had an adjusted 1.68-fold (95% CI, 1.15 to 2.44) risk of CVD death, and a 1.56-fold (95% CI, 0.99 to 2.46) risk of CHD death compared with men in the lower two thirds.

It is difficult to relate the Finnish mercury results to the Japanese ones, due to the vast differences in diets, and the unpredictable interactions of various nutrients.

At best, it suggests that the high mercury levels in the Japanese diets may be responsible for a portion of their strokes and possibly heart disease deaths - especially in men.

TABLE 2. Relative Risk (RR) and 95% CI of Acute Coronary Events and CVD and CHD Death, and Any Death in Men in Thirds of Hair Mercury Content

	Lowest Third RR	Middle Third RR (95% CI)	Highest Third RR (95% CI)	*P* for Trend	Highest vs lower Two Thirds Combine RR (95% CI)
Incidence of acute coronary event					
Model 1*	1	1.02 (0.74–1.41)	1.61 (1.20–2.17)	0.001	1.59 (1.25–2.03)
Model 2†	1	1.04 (0.75–1.44)	1.55 (1.14–2.11)	0.003	1.52 (1.19–1.94)
Model 3‡	1	1.08 (0.77–1.50)	1.67 (1.22–2.30)	0.001	1.60 (1.24–2.06)
Model 4§	1	1.07 (0.77–1.49)	1.66 (1.20–2.29)	0.001	1.60 (1.24–2.06)
Incidence of CVD death					
Model 1*	1	0.65 (0.40–1.04)	1.24 (0.83–1.87)	0.213	1.53 (1.08–2.18)
Model 2†	1	0.61 (0.38–0.99)	1.17 (0.77–1.79)	0.364	1.49 (1.04–2.15)
Model 3‡	1	0.67 (0.41–1.08)	1.36 (0.88–2.11)	0.126	1.67 (1.15–2.43)
Model 4§	1	0.66 (0.41–1.07)	1.35 (0.87–2.11)	0.141	1.68 (1.15–2.44)
Incidence of CHD death					
Model 1*	1	0.59 (0.33–1.05)	1.17 (0.72–1.89)	0.416	1.50 (0.99–2.29)
Model 2†	1	0.57 (0.32–1.03)	1.07 (0.65–1.77)	0.650	1.41 (0.91–2.18)
Model 3‡	1	0.63 (0.35–1.13)	1.27 (0.75–2.16)	0.296	1.61 (1.03–2.53)
Model 4§	1	0.61 (0.34–1.10)	1.21 (0.71–2.06)	0.398	1.56 (0.99–2.46)
Incidence of any death					
Model 1*	1	0.93 (0.72–1.20)	1.36 (1.09–1.70)	0.001	1.41 (1.19–1.69)
Model 2†	1	0.88 (0.68–1.14)	1.23 (0.98–1.54)	0.025	1.31 (1.10–1.57)
Model 3‡	1	0.92 (0.71–1.19)	1.30 (1.03–1.65)	0.007	1.37 (1.14–1.64)
Model 4§	1	0.92 (0.71–1.19)	1.31 (1.03–1.66)	0.007	1.38 (1.15–1.66)

*Adjusted for age and examination years; †adjusted for model 1 and HDL and LDL cholesterol, BMI, family history of ischemic hea disease, systolic blood pressure, maximal oxygen uptake, urinary excretion of nicotine metabolites, serum selenium, and alcoh intake; ‡adjusted for model 2 and serum DHA+DPA as proportion of all fatty acids in serum; §adjusted for model 3 and intake saturated fatty acids, fiber, and vitamins C and E.

Sodium (i.e. Salt)

The Japanese have a high incidence of Hypertension (i.e. high blood pressure), and this is primarily blamed on their high intake of salt (i.e. think soy sauce). High blood pressure is a major risk factor in stroke and to a somewhat lesser extent CHD. In almost all the multivariate analysis that look at other factors (e.g. SFA-intake), blood pressure is part of the adjustment. I've already mentioned that one flaw in the JACC analysis is lack of an adjustment for measured blood pressure based on a graduated scale (as done in other studies); instead, the JACC study adjustment is just based on the subjects answering the question as to whether or not they had hypertension.

But does the effect of a high sodium (i.e. salt) intake result in higher stroke and possibly CHD beyond that indicated by blood pressure? As it turns out, a study using the same subjects as the JACC SFA-intake paper was done and published 2 years earlier, Relations between dietary sodium and potassium intakes and mortality from cardiovascular disease: the Japan Collaborative Cohort Study for Evaluation of Cancer Risks.

With their multivariate analysis (including an adjustment for potassium), *the increased risk of* ***stroke mortality*** *for highest quintile of sodium intake vs the lowest quintile was* ***1.55*** *(95% CI: 1.21, 2.00; P for trend < 0.001).* But the increased risk for CHD mortality did not reach statisti-

cal significance, 1.19 (CI: 0.82, 1.73). The multivariate analysis did include an adjustment for hypertension, but only based on the yes/no response on the questionnaire.

Thus sodium intake is a major factor in stroke mortality. ***Why didn't the authors of the JACC/SFA paper include sodium as a confounder in their analysis?*** Nowhere in the JACC/SFA paper is sodium even mentioned. The stroke hazard rate for sodium was greater than that for a low SFA-intake.[6]

Before saying more about JACC/Sodium-Potassium paper, I want to mention a Finnish paper on this subject, "Urinary sodium excretion and cardiovascular mortality in Finland: a prospective study". This was a relative small study - 1173 men and 1263 women followed from 8-13 years. Most importantly instead of measuring dietary intake of sodium by a diet questionnaire, urine levels were collected over a 24 hour period and measured for sodium - a far more accurate assessment method. Women consumed about 25% less sodium than men, and no statistically significant relationships were found (for CHD death/incidence, stroke death/incidence). For men, there was no statistically significant relationships for death from stroke or stroke incidence. However, for **CHD death**, a 100 mmol/day increase is urinary sodium output in a 24 hr period had a hazard rate (HR) of **1.55** (95% CI: 1.12-2.13). A 100 mmol/day increase is enough to shift a man 2 quartiles in this study (e.g. from 1st to 3rd quartile or 2nd to 4th, the highest. The multivariate analysis for these results were age, study year, smoking, serum total and HDL cholesterol, systolic blood pressure, and body mass index.

Thus, the JACC/Sodium study indicates harm w.r.t. stroke, but not CHD; whereas Finish study indicates harm w.r.t. CHD for men, but not for stroke. To avoid going further down this rabbit hole, most of the studies suggest increased sodium intake leads to increased stroke risk, but not CHD risk. However, there are other studies that indicate no statistically risk to either. All this assumes an adjustment for blood pressure and other factors. There is plenty of research that indicates higher systolic blood pressure is a risk for both CHD and stroke.

I'm now going to return to the JACC/Sodium-Potassium paper. Next page is table 5 from this paper which looks at high/low combinations of sodium/potassium. What can we learn from this table? **MOST IMPORTANT:** ***When we see interesting/plausible results from a very badly constructed study, we really, really, want to believe the results.*** In that spirit,[7] what does table 5 tell us, only looking at the statistically significant results and just considering total stroke death and CHD death?

(1) Stroke death: A high sodium diet increases risk, and the amount of potassium intake does not matter;
(2) CHD death: On a high sodium diet, a high (vs. low) potassium-intake reduces risk.

(2) implies it is more important to increase potassium-intake than reduce salt intake; whereas,
(1) implies it is more important to reduce salt intake than increase potassium intake.

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[6] I searched the PDF of the JACC/SFA-intake paper for sodium, salt, and potassium, individually. Not one occurrence.

[7] In other words, this may be an example of my "confirmation bias". But it is also true that many other studies have shown a significant benefit of increased fruit and vegetable intake.

TABLE 5
Hazard ratios (HRs) and 95% CIs of mortality from stroke, coronary heart disease, and total cardiovascular disease according to the combination of sodium and potassium intakes

	Low sodium intake		High sodium intake	
	Low potassium intake	High potassium intake	Low potassium intake	High potassium intake
No. of subjects	20 760	8605	8605	20 760
Person-years	256 676	106 909	110 817	270 759
Reference = low sodium and high potassium intake				
Total stroke				
n	293	93	198	402
Multivariable HR[1]	1.15 (0.89, 1.48)	1.00	1.46 (1.13, 1.89)	1.44 (1.15, 1.82)
Ischemic stroke				
n	133	44	110	223
Multivariable HR[1]	1.13 (0.78, 1.63)	1.00	1.61 (1.12, 2.33)	1.61 (1.16-2.24)
Coronary heart disease				
n	152	47	88	137
Multivariable HR[1]	1.28 (0.89, 1.84)	1.00	1.36 (0.94, 1.98)	0.93 (0.66, 1.30)
Total cardiovascular disease				
n	641	224	408	814
Multivariable HR[1]	1.08 (0.92, 1.28)	1.00	1.28 (1.08, 1.53)	1.19 (1.03, 1.39)
Reference = high sodium and low potassium intake				
Total stroke				
n	293	93	198	402
Multivariable HR[1]	0.79 (0.66, 0.95)	0.69 (0.53, 0.89)	1.00	0.99 (0.81, 1.21)
Ischemic stroke				
n	133	44	110	223
Multivariable HR[1]	0.70 (0.54, 0.91)	0.62 (0.43, 0.90)	1.00	1.00 (0.76, 1.31)
Coronary heart disease				
n	152	47	88	137
Multivariable HR[1]	0.94 (0.72, 1.24)	0.74 (0.51, 1.07)	1.00	0.68 (0.50, 0.93)
Total cardiovascular disease				
n	641	224	408	814
Multivariable HR[1]	0.85 (0.74, 0.96)	0.78 (0.66, 0.93)	1.00	0.93 (0.81, 1.07)

[1] Cox proportional hazard models adjusted for age (y), sex, BMI (sex-specific quintiles), smoking status (4 categories), ethanol intake (6 categories), history of hypertension (yes or no), history of diabetes (yes or no), menopause (yes or no), hormone replacement therapy (yes or no), time spent on sports activity (4 categories), walking time (4 categories), educational status (4 categories), perceived mental stress (4 categories), and calcium intake (high or low).

Vegetables and fruits are some of the best sources of potassium and very low in sodium. High sodium foods include many processed foods, and the following are usually very high in sodium: bacon, ham and smoked meats; cheese; pickles; salami; salted and dry roasted nuts; salt fish and smoked fish; soy sauce; gravy granules, stock cubes and yeast extract.

What does all the above mean for the JACC/SFA-intake study? The researchers should have brought salt (i.e. sodium) intake into the study parameters. And, if they did, it might have significantly affected their stroke results. At the very least, they should have mentioned sodium-intake as a possible confounder and cited the earlier JACC/Sodium-Potassium paper. Why didn't they?

Arsenic

The intake of inorganic arsenic is primarily associated with increased forms of cancer, but as the WHO arsenic overview notes[8], it can also be associated with cardiovascular disease. One of the 20 studies cited in the Chowdhury SFA-intake meta-analysis was the Strong Heart Study (SHS), which involved 4 populations of American Indians. The same researchers recently pub-

[8] "Soluble inorganic arsenic is acutely toxic. Intake of inorganic arsenic over a long period can lead to chronic arsenic poisoning (arsenicosis). Effects, which can take years to develop depending on the level of exposure, include skin lesions, peripheral neuropathy, gastrointestinal symptoms, diabetes, renal system effects, ***cardiovascular disease*** and cancer. "

lished (November 2013) on the same study population: "Association Between Exposure to Low to Moderate Arsenic Levels and Incident Cardiovascular Disease: A Prospective Cohort Study."

From the abstract: "When the highest and lowest quartiles of arsenic concentrations (>15.7 vs. <5.8 μg/g creatinine) were compared, the hazard ratios for cardiovascular disease, **coronary heart disease**, and **stroke** mortality after adjustment for sociodemographic factors, smoking, body mass index, and lipid levels were 1.65 (95% CI, 1.20 to 2.27; P for trend < 0.001), **1.71** (CI, 1.19 to 2.44; P for trend < 0.001), and **3.03** (CI, 1.08 to 8.50; P for trend = 0.061), respectively." Note that these results were statistically significant, and adjustment included that for lipids (i.e. serum cholesterol) levels.

I cannot relate this study directly to the Japanese, i.e. I did not find any Japanese study that examined an association of arsenic levels with CVD. However, it is known that the typical Japanese diet is relatively high in inorganic arsenic, as noted in this study: "Inorganic arsenic in the Japanese diet: daily intake and source." From the abstract: "Daily intake of InAs from cereals was greatest (13 μg/person/day) followed by algae (5.7 μg/person/day), and the intake from the two categories constituted 90 % of the total daily InAs intake of adults (21 μg/person/day on a bioaccessible-fraction basis and **24 μg/person/day** on a content basis). Analysis of individual food items showed that **rice** and **hijiki** contributed virtually 100 % of InAs from cereals and algae, respectively. The present survey indicated that InAs from rice and hijiki consumption contributed to total daily InAs intake and consequently to significant cancer risk of the general Japanese population." Looking at various websites from different countries[9], there is more concern about hijiki, because the content per serving is high and some people will eat a lot more of it than others.

I cannot relate the Japanese intake of inorganic arsenic to the SHS study. There may or may not be an issue. Also, the SHS study was based on just one urine measurement at baseline of the study.[10] The affects of inorganic arsenic intake does seem to be an area of ongoing research, as indicated in this slide set from Johns Hopkins Bloomberg School of Public Health.

Summary of Possible Confounders
Mercury, Sodium, and Arsenic

All 3 of these are possible confounders in the JACC/SFA-intake study. The most significant evidence is with sodium, since this was studied and documented with the same population, but just in a different paper. The least evidence is with arsenic. Mercury is in between the two.

Summary

The JACC study is representative of Japan. Of all the 20 studies in the Chowdhury meta-analysis, this homogenous study population had the lowest intake of SFA, e.g. 4 of the 5 quintiles of men had an SFA-intake of <10% - most other studies had no quintile, quartile, or tertile <10%, a few had 1, and only one other study had 2 quintiles <10%. And, of all the countries represented in the 20 studies, Japan had the lowest in CHD mortality rate.

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[9] For example, http://www.cfs.gov.hk/english/programme/programme_rafs/programme_rafs_fc_02_08.html

[10] And my analysis SHS/SFA-Intake paper analysis documented a number of shortcomings, which also apply to the SHS/Arsenic study.

But Japan does have its problems with stroke (which is not a subject of my analysis). As many sources note this is a consequence of their high sodium intake, their high blood pressure, their smoking rate, and perhaps other factors (e.g. mercury).

JACC/SFA-Intake Study Grading

1) *Over-adjustment with Lipids*. **No**. No adjustment for lipids; but, the multivariate analysis was adjusted for ω-3, ω-6, and dietary cholesterol intakes, which likely results in an over-adjustment. This would be especially true of dietary cholesterol intake which is likely highly correlated with SFA-intake (see table 1). To a lesser extent, it may also be true for PUFA (ω-3 + ω-6). Note that the highest quintile of SFA-intake had the highest intake of PUFA, and dietary cholesterol.
2) *Sufficient Test of SFA Guidelines*. **F**. For example, 4 of the 5 quintiles of SFA-intake for men were all <10%. And, just ~2.5 g of increased SFA-intake was enough to boost someone from one quintile to the next.
3) *Homogeneity.* **F.** Almost all eating the typical Japanese diet.
4) *Food/Lifestyle Questionnaire*. **F**. All input (diet, lifestyle, medical history) was done via self-administered questionnaire only at the beginning of the study. The FFQ included *just* 33 food items and 5 choices for frequency of intake offered for each item. No examinations or interviews. Insufficient verification of FFQ. One example of how bad the FFQ was: in the JACC/FVB paper, the authors noted that it was not possible to determine with amount of soyabean intake, because the FFQ just asked about beans.
5) *Missing Data in the Study.* **F**. No measurements and examination at the beginning of the study. For example, hypertension was only assessed as yes or no, versus an actual measurement. And, as I have indicated, this study underestimated the prevalence of hypertension in the Japanese population (and thus this study) by 3X. Given the importance/frequency of hypertension in Japan, and its relation to both stroke and CHD, this is significant. Mercury is a likely confounder in the study - no mention. Arsenic (via rice and hijiki) may also be - no mention.
6) *Missing Data in the Paper*. **D**. Since the JACC researchers had previously published a paper using the same study population w.r.t. sodium/potassium intake and its significant relationship to both stroke and CHD mortality, no accounting of this in the paper (nor even a mention of it) is a MAJOR short-coming of this paper. In fact, I don't understand why reviewers of this paper did not catch this. Also, table 1 is missing alcohol intake, amount of smoking, fiber intake and carbohydrate intake. On the positive side, table 1 presented the food intake and lifestyle characteristics by SFA-intake quintile, which is absent in most of the other studies.
7) *Confounders*. **F**. I've previously mentioned the possible confounders of sodium (definitely), mercury (likely), and arsenic (possibly) that were not covered or mentioned in the paper. In addition, the age of the population ranged from 40-79 y, with a mean of ~56 y. Based on other studies (and comments in still others), there is a problem of entering older people into a study with the qualification of no indication of heart disease. Other studies get around this problem by dividing the population into 2 age cohorts. This study should have done the same. Other studies have seen fiber as a confounder. Yet, the paper does not provide any information on fiber.
8) *Food vs. Nutrients*. **C**. On the positive side, the paper shows fruit, vegetable, animal protein, and vegetable protein intakes by SFA-intake quintile. Note that quintile 5 of SFA-intake has the highest intakes of animal protein, fruit intake, vegetable intake, PUFA-intake, and MUFA-intake, and quintile 1 of SFA-intake has the lowest of all these. Yet, calorie intake of

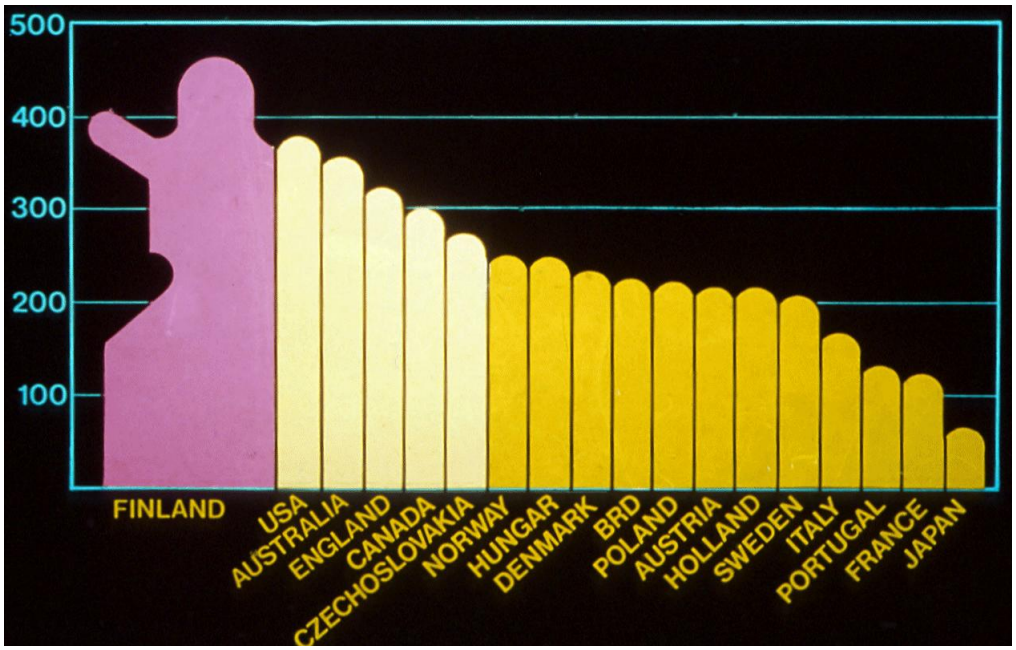
quintiles 1 and 5 are about the same, as is plant protein intake. So, where is quintile 1 getting its additional calories? Is it from rice (a key source of inorganic arsenic)?

Finland (1972 to 2007) - Not One of the Studies

Before describing the Finnish KIHD study, it is important to describe Finland's story. This and the KIHD study were previously presented in part 2 (McDougall April 2014 Newsletter). All paper references are at the end of the KIHD study section.

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

CHD Mortality per 100,000 men in 1973



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

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

tality. . . .After the initial 5-year period of the North Karelia Project (1972–1977), national preventive activities were gradually implemented."

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

Figure 1 is from the paper. Note that the most significant component of the risk factors is the drop in total serum cholesterol, i.e. two-thirds of the 60% decline in risk factors.[11] "Since the mid-1980s, many new treatments and invasive procedures for coronary patients have become more common and can probably explain most of the remaining decline in observed CHD mortality. In Finland, the change of risk factors seems to be more important than in many other countries. Based on different models, the impact of risk factors on mortality varied from 60% in New Zealand to 44% in the USA, and the impact of treatment varied from 23% in Finland to 47% in the USA."

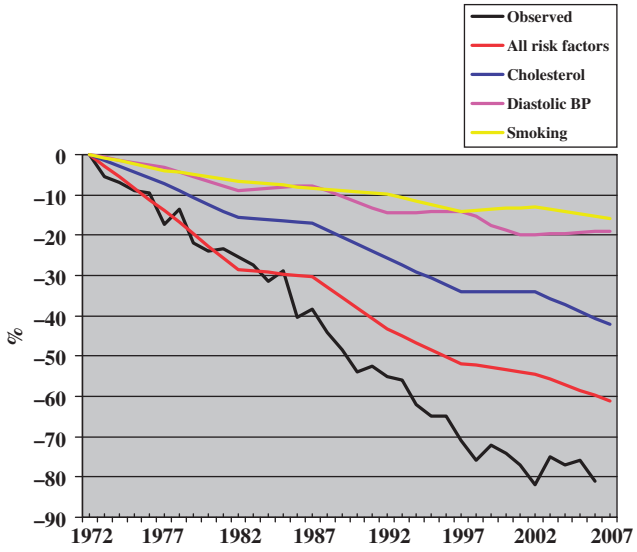


Figure 1 Observed and predicted decline in CHD mortality in men

What was responsible for the drop in serum cholesterol? From the paper, "Saturated fatty acids play the key role in the regulation of serum cholesterol." And, ***"The total intake of saturated fat has declined in Finland from 22% of energy intake to 13% between 1972 and 2007." See charts on the following 2 pages.***

"During the past 30 years, the greatest change in health behavior in Finland has indisputably been the changes in diet, especially in the type and amount of fat and intake of fresh vegetables and fruit. In the early 1970s, Finland was a country with much dairy farming. Butter and milk production was subsidized and all vegetable oil was imported. The domestic vegetable oil industry was developed in the late 1970s and the popularity of vegetable oil grew remarkably in the 1980s. People were 'educated' in the effects of the types of fat and so could avoid fatty milk products and spreads with high saturated fat content as well as food products high in cholesterol."

To summarize, the CHD death rate in Finland over a 35 year period dropped 80%. 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%.

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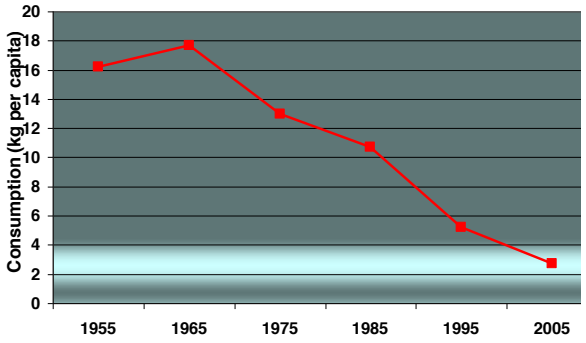
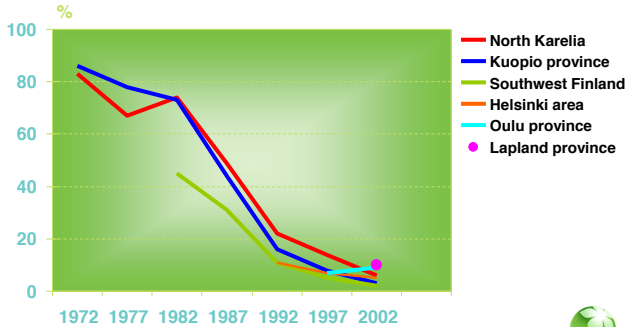
[11] As noted in the paper, "There was a levelling-off period in serum cholesterol level between 1997 and 2002. This was parallel with the changes in saturated and polyunsaturated fat intake."

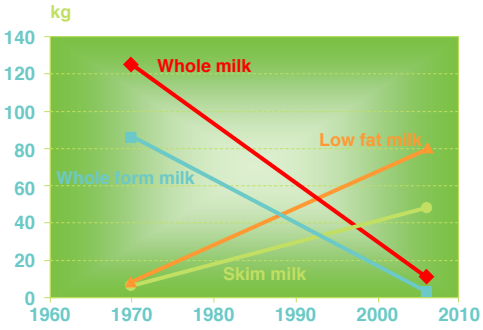
Butter consumption per capita in Finland



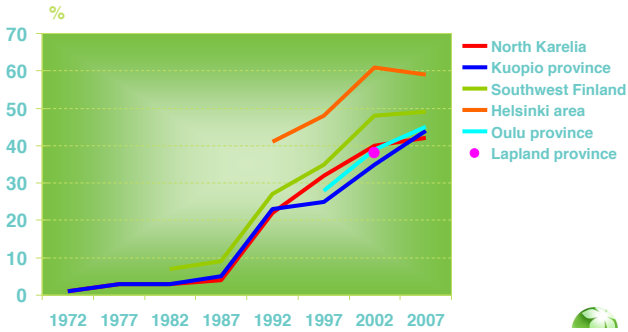
Use of Butter on Bread (men age 30–59)



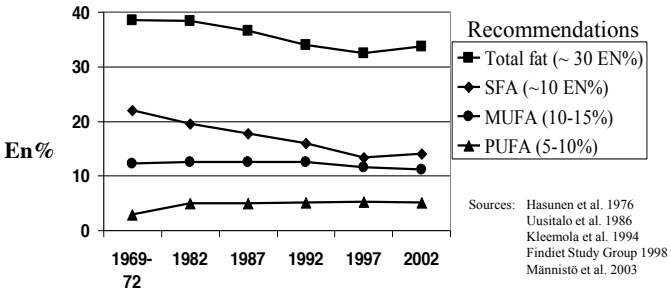
Milk Consumption in Finland in 1970 and 2006 (kg per capita)



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

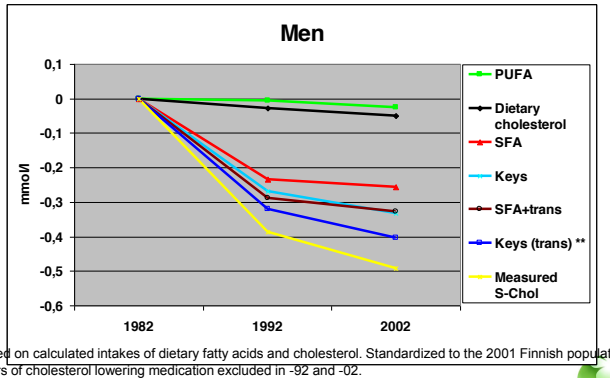


Fat Intake as Percentage of Energy in Finland



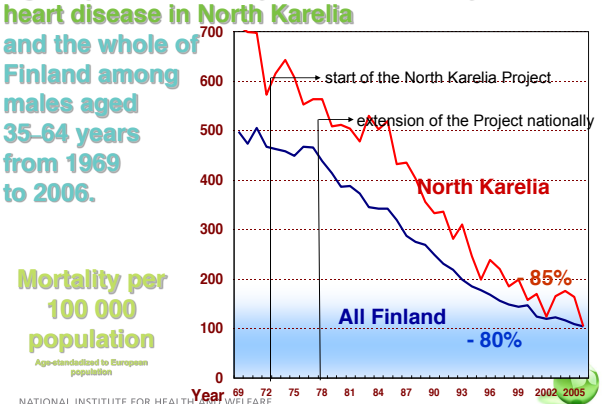
Sources: Hasunen et al. 1976
Uusitalo et al. 1986
Kleemola et al. 1994
Findiet Study Group 1998
Männistö et al. 2003

Estimates of S-Chol changes in 1982–2002*



* Based on calculated intakes of dietary fatty acids and cholesterol. Standardized to the 2001 Finnish population. Users of cholesterol lowering medication excluded in -92 and -02.

Age-adjusted mortality rates of coronary heart disease in North Karelia and the whole of Finland among males aged 35–64 years from 1969 to 2006.



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

	Rate (per 100.000) 1969–71	2006	Change from 1969–71 to 2006
All causes	1328	583	- 56%
All cardiovascular	680	172	- 75%
Coronary heart disease	489	103	- 79%
All cancers	262	124	- 53%

Finland Has Shown

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

Kuopio Ischaemic Heart Risk Factor (KIHD) Study

Laaksonen DE, Nyyssonen K, Niskanen L, Rissanen TH, Salonen JT. Prediction of cardiovascular mortality in middleaged men by dietary and serum linoleic and polyunsaturated fatty acids. Arch.Intern.Med. 2005;165:193-199.

Only Chowdhury's meta-analysis uses this study.

	RR (95% CI)
Chowdhury	0.99 (0.77, 1.28)

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

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

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

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

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

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

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

The paper presented 4 forms of multivariate analysis. Models 3 and 4 were over-adjustments, in my view. The analysis was done in thirds (tertiles). With Model 2,[12] men with a PUFA intake in the upper third were up to 54% less likely to die of CVD than those with an intake in the lower third (RR, 0.46 [95% CI, 0.24-0.86]).

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

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

> "Dietary PUFA and SAFA intake were inversely correlated (r = –0.34)."
>
> "*The inverse correlations of dietary PUFA and SAFA intake indicate that the apparent benefit of PUFA intake probably comes about in part through substitution of PUFA for SAFA intake (in these men, by substitution of margarine for butter).* This, coupled with the inverse association of the dietary PUFA/SAFA ratio with CVD mortality, ***provides support for increasing PUFA intake at the expense of SAFA intake in the primary prevention of CVD*** and underscores the importance of dietary fat quality over quantity. These findings agree with those from the Western Electric Study, in which coronary death was the outcome, and the Nurses Health Study, in which myocardial infarction was the outcome."

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

The Problems with the KIHD Study

Key Messages

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

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

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

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

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

Thus, given what was going on Finland, the authors' various associations (e.g. U. of Kuopio and Finland's Research Institute of Public Health), the authors must have known that diet and serum cholesterol levels had major changes between 1987 to 1997 not just in Finland as a whole, but specifically in East Finland. While it is possible that their study population did not change their diet, it seems highly unlikely. At the very least, they should have communicated this in the paper, and specifically made reference to the data that indicated the major changes in East Finland.

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

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

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

Other Confounders, undoubtedly known, but Not Mentioned.

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

Key Messages:

- **Trans-fats.** In a large SW Finland study, men in the highest quintile of Trans-Fat intake had a **38% higher risk of CHD death** than men in the lowest quintile.
- **Mercury.** From the same population of men in the KIHD study, men in the upper third of mercury hair content, had a **68% greater risk of CVD death** than men who had a lower content.
- **Iron.** From the same population of men in the KIHD study, men in the highest third of body iron stores had a **2.9-fold risk of Acute Myocardial Infarction (AMI)** compared with men in the lowest third of body iron stores.

- **No mention in the KIHD 2005 paper of Trans-Fats, Mercury, and Iron.** Why? The Mercury, Iron, and KIHD papers shared an author. The Trans-Fat paper was a huge study (21,930 men), started at the same time as the KIHD study.

Trans-Fats

A different Finish study looked at the "Intake of Fatty Acids and Risk of Coronary Heart Disease in a Cohort of Finnish Men" [12]. This was just a 6 year study, but involved 21,930 men from Southwestern Finland - vs. Eastern Finland, the area of KIHD study. This study consisted of all smokers (at least 5 cigarettes per day), aged 50-69, free from heart disease and diabetes. The original intent of this double-blind/placebo controlled study was to determine whether supplements of Alpha-Tocopherol or Beta-Carotene (**ATBC**) would provide a reduction in lung-cancer incidence. It didn't. But there was so much data collected in this study that it could also be used to analyze other things.

Food intake was determined at the beginning of the study, and data was presented for both coronary events and coronary death. Since the KIHD just looked at death, just that data will be presented. In this excerpt from table 2 of the study, the data is for quintiles of trans-fat intake (each quintile is defined by the mean of the intake). Thus, **men in the 5th quintile of Trans-Fat intake had a ~38% higher risk of CHD death than ones in the 1st quintile.**[13]

trans-Fatty acids

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

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

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

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

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

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

Quintile of *trans*-fatty acid intake	Median daily intake of *trans*-fatty acids (g)	Medians of							
		Age (years)	Smoking (years)	No. of cigarettes/ day	Body mass index (kg/m²)	Serum cholesterol (mmol/liter)	HDL cholesterol† (mmol/liter)	Systolic BP† (mmHg)	Diastolic BP (mmHg)
1	1.3	56.4	36.8	19.6	26.2	6.1	1.1	140	88
2	1.7	56.6	36.5	19.6	25.8	6.2	1.1	140	88
3	2.0	57.0	37.1	19.8	25.6	6.3	1.1	139	87
4	2.7	56.9	36.9	19.6	25.6	6.2	1.1	139	87
5	5.6	56.2	36.9	20.0	26.0	6.0	1.1	140	88

	% of group		Median daily intake of							
	Education (>11 years)	Physical activity (>2 times per week)	Energy (kcal)	Triglycerides (g)	Saturated fatty acids (g)	*cis*-Mono-unsaturated fatty acids (g)	Poly-unsaturated fatty acids (g)	Linoleic acid (g)	Linolenic acid (g)	Omega-3 fish fatty acids (g)
1	11.1	20.5	2,657	88.1	43.9	29.1	8.9	6.4	1.5	0.4
2	9.7	17.6	2,794	101.2	53.4	31.7	8.6	6.1	1.4	0.4
3	8.8	17.3	2,844	110.2	60.1	33.4	8.6	6.0	1.3	0.4
4	10.9	17.9	2,770	101.0	57.8	33.5	10.1	7.4	1.5	0.4
5	13.6	19.6	2,673	100.2	38.1	30.3	19.7	16.6	2.2	0.4

	Median daily intake of									
	Cholesterol (mg)	Dietary fiber (g)	Alcohol (g)	Beta-carotene (mg)	Vitamin C (mg)	Vitamin E (mg)	Butter (g)	Margarine (g)	Red meat (g)	Fish (g)
1	517	24.5	16.9	1.75	102	9.7	35.7	5.4	60.4	34.2
2	574	25.0	12.6	1.75	101	9.5	44.2	8.9	63.4	32.8
3	599	24.4	10.0	1.71	96	9.4	51.2	10.2	62.9	31.3
4	584	23.3	9.6	1.70	93	10.6	43.9	17.3	60.7	30.6
5	465	24.6	10.9	1.67	96	17.8	5.1	49.4	56.3	32.2

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

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

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

Mercury

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

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

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

- The Mercury study excluded men with a history of CHD or stroke, and of those remaining, DHA+DPA concentrations were available for 1842 men for the CVD death analysis. “Risk

of all-cause mortality was estimated excluding only men without data on serum DHA+DPA concentrations; thus, the analyses for all-cause mortality included 2480 men."

- The KIHD study, "all men with a history of CVD, ***diabetes, or cancer*** at baseline (n = 1123) were excluded. Men with missing data for both dietary and serum fatty acids were also excluded, leaving 1551 men for the analyses." Thus, it seems that the men in the KIHD study are a subset of the 1842 men in the Mercury study.

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

Men in the upper third of mercury hair content (>=2.03ug/g) had about a 68% greater risk of CVD death than men who had a lower content (i.e. the bottom 2 tertiles combined).[14]

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

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

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

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

Iron

The previous subsection discussed a 2005 Mercury paper. That mercury paper never mentioned iron, but it did contain a reference to a 1992 paper by JT Salonen et al, titled "High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men." [15] That was a controversial paper. So, using a different measuring technique, JT Sa-

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

lonen et al published a 1998 paper, with the same conclusion [16]. Title of the 1998 paper, "Association Between Body Iron Stores and the Risk of Acute Myocardial Infarction in Men."

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

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

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

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

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

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

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

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

To consider the synergism of iron stores and LDL cholesterol, the TfR/ferritin ratio was analyzed for men in 2 groups, below and above the LDL median level, which was 4.2 mmol/L (162mg/dl). After adjustment, in the high LDL cholesterol group, men in the lowest third of TfR/ferritin (i.e. those with a high iron store) had a 4.20-fold risk of AMI (P=0.0226) vs. men in the highest third (those with a low iron store). In men with low cholesterol, the ratio was 2.43 (P=.148) - thus, not statistically significant.

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

So why the high iron content? The human body has no significant way of ridding itself of excess iron (other than bleeding). Instead, our intestines have a mechanism for controlling the absorption of iron - more absorbed when we need it, and less when we don't. There are 2 forms of dietary iron, heme and non-heme. Animals have both. Plants have just non-heme. Our intestines do a good job of controlling the amount of non-heme iron that is absorbed. But that does not work well for heme iron.[15] Sources of heme iron (highest to lowest) include clams, oysters, organ meats, beef, poultry, and fish. The presence of heme iron in our intestines increases the absorption of non-heme iron. A diet high in beef (about 60% heme, 40% non-heme) increases absorption of the non-heme portion even if the body already has plenty of iron stores. Alcohol also increases iron absorption. And, cooking in an iron skillet/pot adds iron to the food. Coincidentally, a very popular brand of iron cookware comes from Finland. To quote from that website: "The Sarpaneva pot is a classic piece of Finnish cookware design, so famous that it once graced one of Finland's postage stamps. Inspired by his blacksmith grandfather, Timo Sarpaneva designed the ***cast-iron*** Sarpaneva pot in 1960."

KIHD Study Grading

1) *Over-adjustment with Lipids*. **N**.
2) *Sufficient Test of SFA Guidelines*. **F**. The mean intake of SFA was 19.4% of total calories with a standard deviation of 4.0%. This suggests few if any men getting <10% of their calories from SFA.
3) *Homogeneity.* **F.** All the men were from East Finland, eating a similar diet - very high in SFA and low in PUFA.
4) *Food/Lifestyle Questionnaire*. **D**. Dietary intake based on recall of 4-days (3 work-days and 1 weekend day. There was a follow-up with 895 men 4 years into the study. The authors note, "Saturated fat intake in Finland has decreased since the mid-1980s[27] when the KIHD Study began, but our data indicate that the relative rank- ing of these men with respect to dietary fat quality may be stabile, at least during the first 4 years of follow-up." The paper that they reference was the 20yr follow-up (1972 - 1992). But the 25yr follow-up was pub-

[15] For a good overview of this, see Dr. Greger's video, http://nutritionfacts.org/video/risk-associated-with-iron-supplements/

lished in 2000 - 4 years before this paper was accepted. That paper would have provided more than sufficient information to know about the significant diet changes underway, and would have effectively invalidated the KIHD study. And, why didn't Chowdhury dig a little to realize this? Why didn't the authors of the KIHD study share this information with Chowdhury? But most importantly, we know from other Finnish papers that diet (in particular SFA intake) decreased significantly during the study period.

5) *Missing Data in the Study.* **D**. There were no updates in dietary intake and blood work during the study period, and we know that the Finnish diet was changing significantly during this period.
6) *Missing Data in the Paper*. **D**. The paper did not present the characteristics (dietary/lifestyle measurements) by SFA tertile.
7) *Confounders*. **F**. Without knowing the characteristics by SFA tertile, it is not possible to make this judgment.
8) *Food vs. Nutrients*. **F**. No information about the Food consumed.

Summary

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

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

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

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

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Strong Heart Study (SHS) of American Indians

Xu J, Eilat-Adar S, Loria C, Goldbourt U, Howard BV, Fabsitz RR et al. Dietary fat intake and risk of coronary heart disease: the Strong Heart Study. Am J Clin.Nutr. 2006;84:894-902.

	RR (95% CI)
Siri-Tarino	1.91 (0.31, 11.84)
Chowdhury	1.09 (0.84, 1.42)

Both meta-analysis papers referenced exactly the same paper, but reported somewhat different results. Both indicated harm of SFA intake, but neither reached statistically significance.

The primary endpoints were CHD, nonfatal CHD, and fatal CHD events. Both men and women were involved and ranged in age from 47 to 79 y. *47-59 y were evaluated separately from 60-79 y.*

Key Messages:

- Since the multivariate analysis included adjustment for serum cholesterol, in particular, LDL, HDL, and triacylglycerol (log-transformed), this is an over adjustment w.r.t SFA intake, as well as that for cholesterol and PUFA intakes.
- Nevertheless (and quite surprisingly), fatal CHD events for 47-59 y did reach statistical significance. As noted in the abstract, *"Participants aged 47–59 y in the highest quartile of intake of total fat, **saturated fatty acids**, or monounsaturated fatty acids had higher CHD mortality than did those in the lowest quartile [hazard ratio (95% CI): 3.57 (1.21, 10.49), **5.17 (**1.64, 16.36), and 3.43 (1.17, 10.04), respectively] after confounders were controlled for."*
- Two ways to look at the **5.17X** for increased risk of CHD death for middle-aged people, w.r.t. SFA intake: (1) Since some studies only look at CHD death as an outcome, and focus on just on middle-age, this is a significant finding; or, (2) Given the major shortcomings of this study, which I'll get into, it is best to discard this number, as well as all the other results of this study.

About SHS

"The SHS is a population-based study of American Indians who reside in central Arizona, Oklahoma, and North and South Dakota." Adults with CHD or who were under dialysis treatment, or had a kidney transplant or liver cirrhosis were excluded. The resultant population consisted of 2938 men and women participants aged 47–79 y. Participants were examined and interviewed between 1993 and 1995 to determine demographic data, personal medical history, health habits, family history of cardiovascular disease and diabetes, blood pressure, body mass index (BMI), to collect fasting blood samples for measurements of lipids and lipoproteins, and to determine dietary intake via a **single 24-h dietary recall**.

The primary endpoints for this study were CHD, nonfatal CHD, and fatal CHD events. CHD events comprised the first non-fatal CHD or fatal CHD event occurring after the examination but before 31 December 2002. Nonfatal CHD events included definite MI, definite CHD, and

[16] Non-fatal CHD events were determined at an exams in 1998-1999, of which 525 did not participate, or by reviewing the records of those who did not participate in the 1998-1999 exam.

TABLE 1
Coronary heart disease (CHD) risk factors at baseline of 2938 American Indian men and women included in the Strong Heart Study[1]

	47–59 y		60–79 y	
	CHD (n = 185)	No CHD (n = 1474)	CHD (n = 218)	No CHD (n = 1061)
CHD risk factors				
Age (y)	54.5 ± 3.5[2,3]	53.8 ± 3.3[4]	67.8 ± 5.1	67.2 ± 5.1
Male sex [n (%)]	88 (48)[2]	558 (38)[4]	90 (41)[5]	315 (30)
Diabetes [n (%)]	128 (70)[2]	644 (44)	141 (65)[5]	472 (45)
BMI (kg/m^2)	31.8 ± 5.6[3]	32.0 ± 6.9[4]	30.5 ± 5.9	30.6 ± 5.9
HDL (mg/dL)	38.7 ± 12.3[2,3]	41.1 ± 13.2	39.1 ± 12.5[5]	42.4 ± 13.5
LDL (mg/dL)	123.8 ± 33.7	119.2 ± 33.8	121.7 ± 36.0[5]	116.6 ± 32.9
Total triacylglycerol (mg/dL)	192 ± 124[2,3]	159 ± 117	171 ± 113[5]	146 ± 92
Current smokers [n (%)]	81 (45)[2,3]	494 (34)[4]	58 (27)	241 (23)
Current alcohol consumers [n (%)]	75 (41)[3]	614 (42)[4]	49 (23)	246 (23)
Hypertension [n (%)]	87 (47)[2,3]	561 (38)[4]	136 (62)[5]	524 (49)
Dietary intake				
Energy (kcal)	1940 ± 830[3]	1916 ± 821[4]	1672 ± 724	1709 ± 670
Total fat				
(g)	80.6 ± 43.2[3]	77.2 ± 41.2[4]	64.4 ± 37.3	65.6 ± 33.6
(% of energy)	36.9 ± 9.9[3]	35.8 ± 9.7[4]	33.9 ± 9.7	34.1 ± 9.4
Saturated fatty acids				
(g)	27.7 ± 16.0[3]	26.1 ± 15.1[4]	21.9 ± 13.1	22.4 ± 12.2
(% of energy)	12.6 ± 4.2[3]	12.1 ± 4.0[4]	11.5 ± 3.9	11.6 ± 3.8
Monounsaturated fatty acids				
(g)	30.8 ± 17.8[3]	29.6 ± 16.6[4]	25.2 ± 15.6	25.0 ± 13.7
(% of energy)	14.0 ± 4.3[3]	13.7 ± 4.3	13.2 ± 4.3	13.0 ± 4.2
Polyunsaturated fatty acids				
(g)	14.6 ± 8.9[3]	14.6 ± 10.0[4]	11.2 ± 7.7	12.1 ± 7.8
(% of energy)	6.8 ± 3.0[3]	6.7 ± 3.3[4]	5.9 ± 2.5	6.3 ± 3.0
trans Fatty acids				
(g)	5.3 ± 4.3[3]	5.1 ± 3.8	4.6 ± 3.7	4.6 ± 3.4
(% of energy)	2.3 ± 1.3	2.4 ± 1.4	2.5 ± 1.4	2.4 ± 1.3
Cholesterol (mg)	381 ± 295[3]	343 ± 276	336 ± 268	309 ± 234

[1] All data are $\bar{x}$ ± SD for continuous variables and n (%) for categorical variables.
[2] Significantly different from those without CHD among ages 47–59 y, $P < 0.05$.
[3] Significantly different from those aged 60–79 y among those with CHD, $P < 0.05$.
[4] Significantly different from those aged 60–79 y among those without CHD, $P < 0.05$.
[5] Significantly different from those without CHD among ages 60–79 y, $P < 0.05$.

electrocardiogram-evident definite MI events.[16] Participants were followed for an average of 7.2 y ± 2.3 y.

The basic data is in table 1. Note: (1) based on BMI, more than 50% are obese; (2) about 50% have diabetes at the start of the study; (3) ~36% of 47-59 y are current smokers; (4) ~40% of 47-59 y have hypertension, and ~50% of 60-79 y. This is not a healthy population.

In the multivariate analysis there were: 2 categories of smoking (current vs past or never) and 2 for alcohol consumption (current versus past or never). These seem inadequate. For example, in other studies, there were typically 4 categories for each of these.

The only mention of medications in the paper was w.r.t. to that of diabetes as part of data collection at the beginning of the study. Given the high-prevalence of diabetes, high blood pressure, smoking, and obesity, it seems likely that many participants were on medications, including statins.

TABLE 3
Hazard ratio (HR) and 95% CI of each quartile of dietary fat intake associated with coronary heart disease (CHD) and nonfatal CHD events for all participants in the Strong Heart Study[1]

	Dietary fat intake quartiles				
	1	2	3	4	*P* for trend[2]
Total fat					
Median intake (% of energy)	24.0	32.3	38.4	45.9	
CHD event (*n*)	104	103	92	104	
HR (95% CI)	1	1.04 (0.78, 1.40)	0.91 (0.67, 1.23)	1.03 (0.77, 1.40)	0.97
Nonfatal CHD (*n*)	74	77	66	81	
HR (95% CI)	1	1.09 (0.77, 1.54)	0.92 (0.64, 1.31)	1.12 (0.79, 1.59)	0.71
Saturated fatty acids					
Median intake (% of energy)	7.5	10.6	12.9	16.5	
CHD event (*n*)	99	95	105	104	
HR (95% CI)	1	1.05 (0.78, 1.43)	1.12 (0.83, 1.51)	1.11 (0.82, 1.51)	0.45
Nonfatal CHD (*n*)	73	62	84	79	
HR (95% CI)	1	0.90 (0.62, 1.30)	1.21 (0.85, 1.71)	1.15 (0.81, 1.63)	0.24
Monounsaturated fatty acids					
Median intake (% of energy)	8.5	12.0	14.7	18.2	
CHD event (*n*)	97	101	103	102	
HR (95% CI)	1	1.12 (0.82, 1.51)	1.01 (0.81, 1.49)	1.09 (0.80, 1.48)	0.64
Nonfatal CHD (*n*)	68	76	74	80	
HR (95% CI)	1	1.18 (0.83, 1.69)	1.11 (0.77, 1.59)	1.23 (0.86, 1.76)	0.32
Polyunsaturated fatty acids					
Median intake (% of energy)	3.5	5.1	6.9	9.9	
CHD event (*n*)	92	118	105	88	
HR (95% CI)	1	1.31 (0.98, 1.76)	1.30 (0.96, 1.76)	1.12 (0.82, 1.54)	0.69
Nonfatal CHD (*n*)	68	86	79	65	
HR (95% CI)	1	1.34 (0.94, 1.89)	1.40 (0.98, 1.99)	1.18 (0.81, 1.71)	0.55
trans Fatty acids					
Median intake (% of energy)	0.9	1.8	2.6	3.9	
CHD event (*n*)	90	113	100	100	
HR (95% CI)	1	1.17 (0.87, 1.57)	1.13 (0.84, 1.54)	1.06 (0.78, 1.44)	0.88
Nonfatal CHD (*n*)	62	85	74	77	
HR (95% CI)	1	1.25 (0.87, 1.78)	1.22 (0.85, 1.75)	1.21 (0.85, 1.74)	0.41
Cholesterol					
Median intake (mg)	83	188	378	607	
CHD event (*n*)	91	90	117	105	
HR (95% CI)	1	0.97 (0.70, 1.34)	1.13 (0.82, 1.55)	1.09 (0.77, 1.54)	0.43
Nonfatal CHD (*n*)	67	63	87	81	
HR (95% CI)	1	0.88 (0.60, 1.30)	1.16 (0.80, 1.67)	1.14 (0.76, 1.70)	0.23

[1] Multivariate model was adjusted for the variable of interest as a percentage of energy (quartiles), sex, age, study center (South Dakota was the reference center), diabetes status, BMI, HDL, LDL, triacylglycerol (log-transformed), smoking (current vs ever and never), alcohol consumption (current vs ever and never), hypertension, percentage of energy from protein, and total energy intake.

[2] Tests for trend were conducted by modeling the median of each quartile-defined category as a continuous variable in Cox proportional hazards models.

Table 3 presents the multivariate analysis for CHD incidence. Intake of total fat and its components were not associated with CHD incidence. Table 4 (next page) is the multivariate analysis, but just CHD mortality as the outcome. "A higher intake of total fat, SFAs, and MUFAs was associated with higher CHD mortality among participants aged 47–59 y but not among those aged 60–79 y. Participants aged 47–59 y in the highest quartile of total fat, **SFAs**, and MUFAs had adjusted hazard ratios (HRs) of 3.57 (95% CI: 1.21, 10.49), **5.17** (95% CI: 1.64, 16.36), and 3.43 (95% CI: 1.17, 10.04), respectively.

Surprisingly, buried in the middle of a paragraph of page 4 of the article (i.e. pg 897), the authors disclose that they did an analysis without adjusting for HDL and LDL cholesterol for 47 n-59 y w.r.t. just CHD mortality. Here is the exact excerpt (emphasis is mine):

> "Omitting HDL cholesterol and LDL cholesterol from the model did not change the results. When evaluating the association between SFAs and MUFAs and CHD death separately, both SFAs and MUFAs remained significant predictors of CHD death among persons aged 47–59 y [HR for increasing quartiles of **SFAs**: 1.00, 3.31 (95% CI: 1.04, 10.55), 1.69 (95% CI: 0.43, 6.60), and **5.65** *(95% CI: 1.71, 18.68)*, P for trend < 0.01; for MUFAs: 1.00, 1.32 (95% CI: 0.38, 4.58), 3.56 (95% CI: 1.07, 11.81), and 5.16 (95% CI: 1.45, 18.32), P for

trend < 0.01] after adjustment for the above risk factors as well as PUFAs and TFAs as a percent of energy."[17]

TABLE 4
Hazard ratio (HR) and 95% CI of each quartile of dietary fat intake associated with coronary heart disease (CHD) death by age group in the Strong Heart Study[1]

	Dietary fat intake quartiles				
	1	2	3	4	*P* for trend[2]
Total fat					
Median intake (% of energy)[3]	24.8	33.0	39.1	46.6	
Median intake (% of energy)[4]	23.0	31.2	37.3	44.7	
CHD death (*n*)[3]	7	8	13	18	
CHD death (*n*)[4]	27	22	21	22	
HR (95% CI)[3]	1	1.44 (0.45, 4.58)	2.42 (0.83, 7.06)	3.57 (1.21, 10.49)	0.01
HR (95% CI)[4]	1	1.20 (0.67, 2.17)	0.73 (0.38, 1.40)	0.77 (0.41, 1.45)	0.24
P for interaction[5]		0.37	0.11	<0.01	
Saturated fatty acids					
Median intake (% of energy)[3]	7.8	10.8	13.1	16.7	
Median intake (% of energy)[4]	7.2	10.2	12.7	16.1	
CHD death (*n*)[3]	6	14	6	20	
CHD death (*n*)[4]	23	32	18	19	
HR (95% CI)[3]	1	3.23 (1.03, 10.14)	1.58 (0.42, 6.04)	5.17 (1.64, 16.36)	0.01
HR (95% CI)[4]	1	1.59 (0.89, 2.83)	0.81 (0.41, 1.63)	0.80 (0.41, 1.54)	0.22
P for interaction		0.30	0.40	0.02	
Monounsaturated fatty acids					
Median intake (% of energy)[3]	8.7	12.3	15.1	18.6	
Median intake (% of energy)[4]	8.2	11.7	14.3	17.7	
CHD death (*n*)[3]	7	8	14	17	
CHD death (*n*)[4]	27	25	22	18	
HR (95% CI)[3]	1	1.13 (0.34, 3.74)	2.55 (0.88, 7.43)	3.43 (1.17, 10.04)	0.01
HR (95% CI)[4]	1	1.05 (0.58, 1.91)	0.89 (0.49, 1.65)	0.54 (0.27, 1.06)	0.07
P for interaction		0.90	0.16	<0.01	
Polyunsaturated fatty acids					
Median intake (% of energy)[3]	3.5	5.3	7.2	10.4	
Median intake (% of energy)[4]	3.4	4.8	6.6	9.5	
CHD death (*n*)[3]	8	16	10	12	
CHD death (*n*)[4]	24	25	27	16	
HR (95% CI)[3]	1	1.78 (0.71, 4.47)	1.02 (0.36, 2.84)	1.47 (0.55, 3.96)	0.78
HR (95% CI)[4]	1	1.03 (0.57, 1.86)	1.11 (0.61, 2.01)	0.69 (0.35, 1.36)	0.30
P for interaction		0.31	0.24	0.07	
trans Fatty acids					
Median intake (% of energy)[3]	0.9	1.8	2.6	4.0	
Median intake (% of energy)[4]	1.0	1.8	2.6	3.9	
CHD death (*n*)[3]	14	8	9	15	
CHD death (*n*)[4]	20	27	25	20	
HR (95% CI)[3]	1	0.84 (0.32, 2.18)	0.84 (0.33, 2.18)	1.15 (0.49, 2.68)	0.66
HR (95% CI)[4]	1	1.33 (0.72, 2.46)	1.43 (0.76, 2.67)	0.83 (0.42, 1.66)	0.54
P for interaction		0.60	0.55	0.38	
Cholesterol					
Median intake (mg)[3]	85	197	396	641	
Median intake (mg)[4]	79	170	357	587	
CHD death (*n*)[3]	5	10	20	11	
CHD death (*n*)[4]	27	22	21	22	
HR (95% CI)[3]	1	1.90 (0.60, 6.04)	2.64 (0.88, 7.88)	1.53 (0.46, 5.13)	0.77
HR (95% CI)[4]	1	0.93 (0.49, 1.77)	0.81 (0.42, 1.56)	0.76 (0.38, 1.54)	0.41
P for interaction		0.38	0.05	0.19	

[1] Multivariate model was adjusted for the variable of interest as a percentage of energy (quartiles), sex, age, study center (South Dakota was the reference center), diabetes status, BMI, HDL, LDL, triacylglycerol (log-transformed), smoking (current vs ever and never), alcohol consumption (current vs ever and never), hypertension, percentage of energy from protein, and total energy intake.
[2] Tests for trend were conducted by modeling the median of each quartile-defined category as a continuous variable in Cox proportional hazards models.
[3] For participants aged 47–59 y.
[4] For participants aged 60–79 y.
[5] *P* for interaction between dietary fat and age group (47–59 or 60–79 y).

The paper does not say what happens if HDL and LDL adjustments are excluded from the analysis in table 3 (all CHD incidents).

Note that there was no association between PUFAs, TFAs, and cholesterol intake.

[17] Adjustment for PUFA and TFA may be an over adjustment - not clear to me, but worth noting.

Why do MUFAs increase risk of CHD mortality? “In our study population, the main sources of MUFAs were meat, poultry, and fish (46%) and these same food groups provided almost the same contributions of SFAs (45%). These mutual food sources for both fatty acids may explain the high correlation between SFAs and MUFAs and the lack of independent associations of them with CHD death. For most previous studies that found MUFAs to be associated with lower CHD death, the main MUFA source was olive oil (1), whereas in our study, olive oil and olives contributed only 0.3% of MUFA intake.”

The authors do not have an explanation of for the lack of an association for TFA intake, i.e. “merits further investigation.”

Why no association with fat intake in the 60-79 y cohort? The authors note that 4 prospective studies examined differences by age, like theirs. “Our findings are consistent with their findings that CHD death increases with higher intakes of total fat, SFAs, and MUFAs among participants aged 47–59 y but not among participants aged 60–79 y. This may arise from differences in baseline risk, because the magnitude of baseline risk determines the magnitude of the relative effect. Another possibility is that participants aged 60 –79 y comprise a selected group given that many older cohort members were excluded because of existing CHD. In addition, older cohort members who did not have preexisting CHD may have been more likely than younger cohort members to have one or more CHD risk factors, such as diabetes, and may have changed their diets as a consequence.”

I think one other conjecture of mine is appropriate. It takes a lifetime to build up the plaque of arteriosclerosis. Those eating the worst diets over their life die before reaching 60, or have developed CHD by then. In either case, they are not in the 60+ cohort.

Why no association with any kind of fat with all CHD incidents? The study population makes no mention of medications. Given the prevalence of diabetes, hypertension, and obesity at the beginning of the study, it seems likely that many were likely on medications at the beginning of study and that more medications were added/increased during the study period. Yet the paper makes no mention of medications in the paper.

Immediately after the examination at the beginning of the study of this unhealthy study group, wouldn’t doctors discuss the results (i.e. hypertension, obesity, indication of type 2 diabetes, high cholesterol) with subjects? And, might this lead to some lifestyle/diet changes (e.g. reduced smoking, drinking, exercise, improved diet), as well as medications being prescribed? It would be unethical not to do so. Yet, no mention of this in the paper.

SHS Study Grading

1) *Over-adjustment with Lipids*. **Y**. All the results in tables were presented with adjustments for lipids. But the paper does report results without LDL/HDL adjustment for cardiac mortality in the 47-59 y group.
2) *Sufficient Test of SFA Guidelines*. **C**. The positive aspect is that one quartile did have a mean intake of SFA of <10%. But we don’t know the characteristics of this low SFA-intake quartile, e.g. did they substitute trans-fat margarine for butter, did they get an excess of calories from alcohol, did this quartile simply eat a lot of simple carbs? Or, did they eat a more traditional healthy diet, e.g. more plant sources, corn and beans, and less meat?
3) *Homogeneity.* **F.** All American indians, with a high-prevalence of unhealthy characteristics.

4) *Food/Lifestyle Questionnaire*. **F**. Dietary intake based a single 24-hr diet recall at the start of the study. Comparison done with NHANES III data on energy intake suggested that energy input data was likely underestimated.
5) *Missing Data in the Study.* **F**. Just 2 categories of smoking and alcohol consumption. No information of socio-economic status, exercise, or medications (other than that for diabetes at the start of the study).
6) *Missing Data in the Paper*. **F**. Amazingly, no data on non-CHD deaths in the study, e.g. no data stating number of 60-79 y olds at start of study survived to the end of the study, excluding those that died from CHD. No info on fiber, protein, carbohydrates. No info on amount of smoking and alcohol consumption. No info on characteristics by quartile of SFA intake. In general, only raw data and full-multivariate analysis presented. Other papers/studies have shown different models of multivariate analysis. This paper does not even present a simple age-adjusted model analysis. A follow-up exam was conducted in 1998-1999 (except for the 525 that did not participate in this). But the only data reported from this exam is CHD incidence, e.g. determined by ECG. Why? Had more developed diabetes? Were more on statins, high-blood pressure meds, etc. than at the beginning of the study (which we don't know either).
7) *Confounders*. **D**. Categories in some confounders too few, e.g. smoking, alcohol. Adjustment also made for protein % of energy intake - most other studies do not seem to include this. Why did this study? As I mentioned in the JACC analysis, arsenic is a likely confounder.[18]
8) *Food vs. Nutrients*. **F**. No significant mention of food.

There is much I don't understand about this study. The data is in sharp contrasts. On the one hand, it reports the highest risk factor of SFA intake for CHD mortality for a middle-aged group of all the 20 studies in Chowdhury's meta-analysis: ***5.17 with LDL/HDL adjustment, and 5.65 without it (in comparing 4th quartile of SFA intake vs 1st quartile).*** Yet, there is no association of any type of fat intake for CHD incidence. As one example, besides SFA intake, given the amounts of TFA (trans-fat) intake, I would expect to see some association with both CHD incidence and CHD mortality. But there was none. Why?

I also feel compelled to ask some difficult, perhaps politically incorrect questions. As the paper notes, "The Indian Health Service, participating institutional review boards, and the participating tribes approved the SHS." Is the information on medications at the beginning of the study, and from the 1998-1999 exam missing, because, given the unhealthy population, it would shed a bad light on the Indian Health Service, i.e. not providing the care that this population deserves? Is this also why non-CHD related deaths were not reported in the paper? Is the lack of more detail on alcohol consumption, degree of smoking, socio-economic status, exercise frequency, etc. missing because it might serve as an embarrassment to the tribes?

[18] The same researchers recently published (November 2013) on the same study population: "Association Between Exposure to Low to Moderate Arsenic Levels and Incident Cardiovascular Disease: A Prospective Cohort Study." But the arsenic issue was probably not known at the time of SHS 2005 paper in this analysis.

The Oxford Vegetarian Study

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

RR (95% CI)
2.77 (1.25 - 6.13)

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.

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 4 factors reached statistical significance for Ischemic Heart Dis-

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.

ease: ***total animal fat, saturated animal fat, dietary cholesterol, and eggs***. The figures for saturated animal fat were exactly the ones reported in both Chowdhury and Siri-Tarino meta-analyses. Interestingly, cheese and dietary fiber did not reach statistical significance (but both came close.)

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*. **No**.
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 dai-

ly energy intake of 2500 for men and 2000 for women[19], 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.

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

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

Trichopoulou A, Psaltopoulou T, Orfanos P, Trichopoulos D. Diet and physical activity in relation to overall mortality amongst adult diabetics in a general population cohort. J Intern.Med. 2006;259:583-591.

	RR (95% CI)
Chowdhury	3.10 (0.99, 9.63)

Only Chowdhury et al included this study. The Chowdhury paper reported very high harm from SFA-intake, i.e. 3.10; however, it was not statistically significant, i.e. the lower bound of the 95%confidence interval (CI) was 0.99 vs. >1.00. *But the EPIC-Greece paper reports that* ***a 10 g increase in SFA-intake[20] resulted in relative risk (RR) of 1.93 with a 95% CI of 1.08 to 3.42 for CHD deaths.***

The study population consisted of 1,013 men and women in Greece who were taking drugs for diabetes mellitus, and were without cancer and CHD at baseline. The main outcome measures were mortality ratios overall and from cardiovascular causes.

Key Messages:

- From the abstract: "Two nutritional variables were significantly associated with *diabetic mortality*, with hazard ratios for increases of daily intake by one standard deviation being 1.31 for eggs [95% confidence interval (95% CI) 1.07 to 1.60] and 1.82 for *saturated lipids (95% CI, 1.14 to 2.90)*. These two associations were considerably stronger for cardiovascular mortality." (I noted SFA-intake/CHD-death association above in bold.)
- W.r.t. CHD deaths, a 10 g increase in egg consumption[21] resulted in relative risk (RR) of 1.54 with a 95% CI of 1.20 to 1.97.
- "For diet, two findings are consistent across genders and models: a striking positive association between egg intake and diabetic mortality, implying that increased daily intake by ***one egg (40 g) increases*** *the risk of death overall threefold and the* ***risk of coronary death more than fivefold***; monounsaturated lipids appear, in comparison with other lipids, preferable for the management of diabetes, as they are the only ones which are unrelated to mortality in all models."

About Greece-EPIC Diabetic Study

"Between 1993 and 1999, 28,572 adult volunteers were recruited throughout Greece to participate in the European Prospective Investigation into Cancer and Nutrition (EPIC). . . .1013 participants had reported that they had diabetes at enrollment without coexistent prevalent cancer or cardiovascular disease and they have presented information about their anti-diabetic drugs." The participants were followed until mid-2004.

"The study participants with diabetes were followed up for a mean period of 4.5 years (range 2– 114 months) generating 4579 person-years. During this period, 80 deaths have occurred,

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[20] 10 g is ~1 std deviation (SD) in intake. More specifically, the mean intake for men was 28 g with an 11 g SD, and for women, it was 23 g with a 9.6 g SD.

[21] An egg is about 40 g. 10 g is ~1 SD in intake. The mean intake for men was 14 g with a 10g SD, and for women, it was 12 g with a 9.3 g SD.

46 from cardiovascular causes, 19 from cancer and 15 from other causes." The death rate from this population was almost twice that from the non-diabetic population of the EPIC-Greece study (after appropriate adjustments for age and gender).

"Dietary intake during the year preceding enrollment was assessed through a validated, interviewer-administered food frequency questionnaire including approximately 150 items."

Both occupational and leisure-time physical activities were recorded for each participant. Total daily physical activity was measured in MET-hours (MET = metabolic equivalent task).

Table 1 (the key parts from the study) provides the distributions of 1013 participants by selected variables and deaths during follow-up.

Table 1

Variables	*N*	Person years	Deaths	% of deaths
Gender				
Men (m)	424	1906.3	45	10.6
Women (w)	589	2673.2	35	5.9
Age (years)				
<55	155	768.5	3	1.9
55–64	326	1537.9	10	3.1
65–74	475	2014.6	56	11.8
≥75	57	258.5	11	19.3
Educational level (years)				
<6	389	1659.3	34	8.7
6–11	493	2158.2	40	8.1
≥12	131	762.0	6	4.6
Smoking				
Never	624	2821.2	39	6.3
Ever	389	1758.3	41	10.5
Physical activity (MET h day^{-1})				
1st quintile (<30)	203	826.0	29	14.3
2nd quintile (30 to <32)	203	901.2	20	9.9
3rd quintile (32 to <34)	202	914.1	12	5.9
4th quintile (34 to <37)	203	957.2	11	5.4
5th quintile (≥37)	202	981.0	8	4.0
Body mass index (kg m^{-2})				
<25	128	599.1	13	10.2
25 to <30	402	1831.7	34	8.5
≥30	483	2148.7	33	6.8

Table 2 (next page) characterizes the daily intakes of the participants. Unlike the northern European and US studies, MUFA intake greatly exceeded SFA intake. This was obviously due to the intake of olive oil. Whereas, in the other studies, MUFA was principally coming from animal sources and was highly correlated with SFA intake.

Of the 20 studies cited by Chowdhury, this was the only one of the 20 that reported on legume intake.[22] As I have read elsewhere, the one food group that all long-lived societies have in common is legumes.

[22] The only other mention of legumes was in the 2012 MALMO study paper. It was mentioned in the context of where women were getting their fiber content: ". . .on average, women of the MDC cohort obtained 23.5 percent of their fiber intake from fruit and berries, 23.7 percent from vegetables (including potatoes and other tubers, carrots and **legumes**), . . ."

Table 2

	Men			Women		
Dietary intakes (g day^{-1})	Mean	SD	% of mean of healthy individuals[a]	Mean	SD	% of mean of healthy individuals[a]
Vegetables	548	215	93	497	206	92
Legumes and potatoes	66	46	60	55	39	68
Fruits and nuts	254	171	65	238	152	62
Dairy products	239	149	107	221	151	102
Cereals[b]	150	67	79	129	51	88
Meat and products	107	54	83	86	37	90
Fish and seafood	27	21	100	23	15	106
Olive oil	43	23	81	38	19	85
Eggs	14	10	75	12	9.3	78
Sugar and confectionery	5.6	8.4	21	5.8	8.6	25
Soft drinks and juices	60	86	43	54	82	52
Tea and coffee	218	166	88	163	129	85
Monounsaturated lipids	47	18	80	41	15	83
Saturated lipids	28	11	81	23	9.6	80
Polyunsaturated lipids	15	9.8	88	13	7.9	85
Ethanol intake	9.3	15	49	1.4	3.5	41
Energy intake (kcal day^{-1})	1842	601	76	1528	482	79

[a]Individuals without diagnoses of coronary heart disease, cancer or diabetes mellitus at enrolment.
[b]Including flour, flakes, starches, pasta, rice, other grain, bread, crisp bread, rusks, breakfast cereals, biscuits, dough and pastry, etc.

Tables 4 and 5 are the hazard ratios of death (all causes) based on the nutrients reported in table 2, with the adjustments indicated in the footnotes. As the authors note w.r.t. overall mortality, "Of the nutritional variables shown in Tables 4 and 5, only two are significantly, consistently and substantially associated with diabetic mortality; eggs with hazard ratio of 1.31 for increase of daily intake by 10 g (no gender-interaction; P = 0.49) and saturated lipids with hazard ratio of 1.82 for increase of daily intake by 10 g (no gender-interaction; P = 0.35). . . .We have run model II for eggs and model III for saturated lipids, *restricting outcome to the 46* ***cardiovascular deaths.*** *Hazard ratio for increase of daily* ***egg consumption by 10 g*** *is now higher (****1.54****; 95% CI, 1.20 to 1.97) with no evidence for gender interaction (P = 0.60). Hazard ratio for increase of daily intake of* ***saturated lipids by 10 g*** *is also higher (****1.93****; 95% CI, 1.08 to 3.42) with essentially no difference between men and women*, whereas hazard ratio for increase of daily intake of polyunsaturated lipids by 9 g is now lower (1.20; 95% CI, 0.78 to 1.84)."

"We found no evidence that increased consumption of food groups rich in complex or simple carbohydrates is associated with increased mortality of diabetic persons, but these food groups were consumed at relatively low quantities."

Limitations of this study from the paper. "A limitation of our study is the enrollment of prevalent cases of diabetes. Nevertheless, mortality of diabetic persons is not so high as to create distortions because of exclusion of diabetic persons with very bad prognosis. Another limitation is that the database used *did not contain information on trans fatty-acids, some quantities of*

which are likely to have been introduced amongst the polyunsaturated lipids, although such lipids are less prevalent in the European than in the US diet."

Tables 4 and 5

Variables	Chosen increment[a]	Model type[b]	Hazard ratio	*P*	95% confidence interval
Vegetables	210	I	1.10	0.58	0.80–1.51
		II	1.10	0.56	0.80–1.52
Legumes and potatoes	40	I	0.85	0.26	0.63–1.13
		II	0.90	0.45	0.68–1.19
Fruits and nuts	163	I	0.93	0.65	0.69–1.26
		II	0.98	0.90	0.72–1.33
Dairy products	150	I	1.02	0.85	0.80–1.32
		II	0.92	0.53	0.71–1.19
Cereals[c]	60	I	0.71	0.04	0.51–0.99
		II	0.76	0.08	0.57–1.03
Meat and products	45	I	1.22	0.21	0.89–1.66
		II	1.16	0.29	0.88–1.54
Fish and seafood	18	I	1.02	0.85	0.80–1.30
		II	1.06	0.64	0.82–1.37
Eggs	10	I	1.34	0.01	1.09–1.64
		II	1.31	0.01	1.07–1.60
Sugar and confectionery	9	I	0.85	0.37	0.59–1.21
		II	0.91	0.61	0.62–1.32
Soft drinks and juices	85	I	0.82	0.27	0.57–1.17
		II	0.83	0.32	0.58–1.20
Tea and coffee	150	I	0.75	0.12	0.52–1.08
		II	0.75	0.13	0.52–1.09
Ethanol intake	5	I	0.96	0.51	0.84–1.09
		II	0.95	0.43	0.84–1.08
Olive oil	21	I	0.85	0.31	0.62–1.16
		II	0.82	0.22	0.59–1.13

[a]The chosen increment for the calculation of the mortality ratio by each dietary variable are arbitrary round values, close to the corresponding standard deviation around the mean daily intake of the corresponding variable. [b]Model I is adjusted for gender (males, females), age (<55, 55–64, 65–74, ≥75, ordered), educational level (<6, 6–11, ≥12, ordered), smoking (never, former and 1–10, 11–20, 21–30, 31–40, ≥41 cigarettes per day, ordered), waist-to-height (continuously per standard deviation), hip circumference (continuously per standard deviation), MET score (quintiles, ordered), total energy intake (continuously per standard deviation), treatment with insulin (no, yes), treatment for hypertension at enrolment (no, yes), and treatment for hypercholesterolaemia at enrolment (no, yes). Model II is adjusted for all the above variables except for energy intake, plus all other indicated food groups. [c]Including flour, flakes, starches, pasta, rice, other grain, bread, crisp bread, rusks, breakfast cereals, biscuits, dough and pastry, etc.

Variables	Chosen increment[a]	Model type[b]	Hazard ratio	*P*	95% confidence interval
Monounsaturated lipids	16	I	1.04	0.86	0.66–1.65
		III	1.28	0.35	0.76–2.16
Saturated lipids	10	I	1.76	0.01	1.12–2.78
		III	1.82	0.01	1.14–2.90
Polyunsaturated lipids	9	I	1.30	0.05	0.99–1.68
		III	1.44	0.02	1.06–1.96

[a]The chosen increment for the calculation of the mortality ratio by each dietary variable are arbitrary round values, close to the corresponding standard deviation around the mean daily intake of the corresponding variable. [b]Model I is adjusted for the variables indicated in the corresponding footnote in Table 4. In model III the three types of lipids are also mutually adjusted for.

EPIC-Greece Study Grading

1) *Over-adjustment with Lipids*. **No**.
2) *Sufficient Test of SFA Guidelines*. **C**. From table 2, there is insufficient information to tell what percent of the study population were consuming a diet of <10% SFA. But the information in table 2 for SFA-intake and Energy intake suggest that if the population was divided into quintiles (perhaps even quartiles), then one segment would be below 10% in SFA intake. On the other hand, the study population differs significantly from the general Greek population, as well as most other developed countries. Besides the diabetes, the study population has a high percentage of overweight and obese individuals (per table 1). Thus, it is unclear as to whether the results of this study should be applied to other populations.
3) *Homogeneity.* **F.** All are diabetic and from Greece, and almost all are overweight or obese. W.r.t. diet, the mean and SD for olive oil (as well as other foods and lipids) suggest a similar diet among most of the study group.
4) *Food/Lifestyle Questionnaire*. **C**. This was somewhat ambiguous from the paper. On the one hand, it says that dietary intake during the year preceding enrollment was assessed. But this was done via interviewer-administered food frequency questionnaire. But was this just one interview, or several over the period of a year? The lifestyle and medical info gathered was as good or better than most studies. For example, the level of detail w.r.t. to both work and leisure time physical activities was better than other studies. Due to the shortness of this study and that all participants were diabetics and had been for some time, it is more likely (than other studies) that diet/lifestyle did not change much over the study period.
5) *Missing Data in the Study.* **D**. No information on TFA-intake. No values for blood pressure and cholesterol;[23] and, no data on CHD incidence (just death).
6) *Missing Data in the Paper*. **D**. On the positive side, this paper provided more data on various food groups sorely missing from other studies. But there are a lot of negatives: (1) no division of foods/nutrients into segments (i.e. quintiles, quartiles, or tertiles); (2) SFA-intake, it would have instructive to see the characteristics of each segment of SFA-intake; (3) Rather than on grams of intake, it would be better to see as % of energy intake; (4) no data on fiber intake, protein intake, and carbohydrate intake; (5) all the data in tables 4 and 5 were for overall mortality vs. just CHD mortality; and, (6) given the relatively high age of the study population, and that 284 were excluded due to pre-existing CHD or cancer, the analysis should have been split up into those under 60 and those over 60.
7) *Confounders*. **D**. Given the plethora of adjustments in all 3 models (I, II, and III), plus the lack of missing data in the paper and study, it seems likely that there is over-adjustment (and/or under-adjustment).
8) *Food vs. Nutrients*. **B**. More data on food consumption than any of the other 20 studies in the Chowdhury analysis.

[23] The paper did note that 46% of participants at enrollment were under treatment of high-blood pressure, and 14% for high cholesterol.

MALMO Study

Leosdottir M, Nilsson PM, Nilsson JA, Berglund G. Cardiovascular event risk in relation to dietary fat intake in middle-aged individuals: data from The Malmo Diet and Cancer Study. Eur.J Cardiovasc.Prev.Rehabil. 2007;14:701-706.

Wallstrom P, Sonestedt E, Hlebowicz J, Ericson U, Drake I, Persson M et al. Dietary fiber and saturated fat intake associations with cardiovascular disease differ by sex in the Malmo Diet and Cancer Cohort: a prospective study. PLoS One. 2012;7:e31637.

The Chowdhury paper references two MALMO studies [above] - 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 Malmo¨ 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.
doi:10.1371/journal.pone.0031637.t002

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 MALMO 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 (688 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*
Fiber	c / py	150 / 18,095	137 / 18,714	133 / 18,916	142 / 18,972	126 / 19,504	
	Basic	1.00	0.87 (0.69-1.10)	0.82 (0.64-1.03)	0.86 (0.68-1.08)	0.72 (0.57-0.92)	0.018
	Full	**1.00**	**0.97 (0.77-1.23)**	**0.98 (0.77-1.24)**	**1.09 (0.86-1.38)**	**0.97 (0.75-1.25)**	**0.85**
Fat, total	c / py	139 / 19,060	147 / 18,736	119 / 19,002	131 / 18,813	152 / 18,589	
	Basic	1.00	1.06 (0.84-1.33)	0.86 (0.67-1.09)	0.96 (0.75-1.22)	1.15 (0.91-1.45)	0.51
	Full	**1.00**	**1.02 (0.80-1.29)**	**0.83 (0.65-1.08)**	**0.91 (0.70-1.18)**	**0.97 (0.74-1.27)**	**0.58**
Saturated fat	c / py	139 / 19,010	155 / 19,027	128 / 19,065	126 / 18,743	140 / 18,355	
	Basic	1.00	1.09 (0.86-1.37)	0.92 (0.72-1.17)	0.92 (0.72-1.17)	1.00 (0.79-1.28)	0.56
	Full	**1.00**	**1.04 (0.82-1.31)**	**0.92 (0.71-1.18)**	**0.86 (0.66-1.11)**	**0.86 (0.66-1.13)**	**0.12**

[1] Cases / person years.
[2] Basic model: Adjusted for age, method version, total energy intake (continuous), and season.
[3] 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. There are only 8,038 men and 680 cases in the full model due to missing values.

Table S2 Risk of coronary event in 12,535 women (333 cases) 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*
Fiber	c / py	87 / 28,876	71 / 29,510	59 / 29,990	55 / 30,265	61 / 30,930	
	Basic	1.00	0.73 (0.53-1.00)	0.56 (0.40-0.79)	0.50 (0.36-0.71)	0.54 (0.38-0.75)	<0.001
	Full	**1.00**	**0.84 (0.62-1.17)**	**0.73 (0.52-1.03)**	**0.65 (0.46-0.93)**	**0.78 (0.55-1.11)**	**0.067**
Fat, total	c / py	71 / 30,265	62 / 29,925	65 / 29,851	60 / 29,985	75 / 29,546	
	Basic	1.00	0.89 (0.63-1.25)	0.99 (0.70-1.39)	0.94 (0.66-1.33)	1.19 (0.85-1.66)	0.29
	Full	**1.00**	**0.81 (0.57-1.14)**	**0.88 (0.62-1.24)**	**0.77 (0.53-1.12)**	**0.87 (0.60-1.28)**	**0.52**
Saturated fat	c / py	82 / 30,428	58 / 29,989	63 / 29,976	59 / 29,697	71 / 29,483	
	Basic	1.00	0.72 (0.52-1.02)	0.80 (0.57-1.12)	0.77 (0.55-1.09)	0.93 (0.67-1.30)	0.77
	Full	**1.00**	**0.68 (0.48-0.95)**	**0.68 (0.48-0.96)**	**0.60 (0.41-0.86)**	**0.67 (0.46-0.97)**	**0.037**

After Full adjustment (Table S2), 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 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 associa-*

*tion 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." But look at the Full adjustment in table 3 for fiber. Women in quintile 2 the same benefit as quintile 5, even though mean fiber intake for quintile 5 is 50% higher.

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.[24] 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.***"

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*

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[24] 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.

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*. **No**.
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.
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**. This is 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.

Baltimore Longitudinal Study of Aging (BLSA)

Tucker KL, Hallfrisch J, Qiao N, Muller D, Andres R, Fleg JL. The combination of high fruit and vegetable and low saturated fat intakes is more protective against mortality in aging men than is either alone: the Baltimore Longitudinal Study of Aging. J Nutr. 2005;135:556-561.

	RR (95% CI)
Siri-Tarino	1.22 (0.31, 4.77)
Chowdhury	1.22 (0.31, 4.77)

The above numbers indicate the saturated fat (SFA) "may" be harmful (the 1.22 number), but we can only say "may" because the 95% confidence interval (CI) range was not above 1.0, i.e. it extended both above and below 1.0.

This is a **gross misrepresentation** of the BLSA study.

Key Messages (w.r.t. CHD death) from the BLSA study:

* Low SFA diet defined as ≤12% energy from SFA intake.
* High Fruit and Vegetable (FV) diet defined as ≥5 servings/day.
* Men consuming either a low-SFA diet or a high FV 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[25] 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."

About the Study

"The BLSA, begun in 1958, was designed to study normal human aging and precursors to disease and death. The current analysis includes 501 BLSA men who met the following criteria: 1) at least 4 completed days of 7-d diet record for ≥1 biennial visit; 2) born before 1929 and age ≤80 y at first dietary record; and 3) no history of angina pectoris or myocardial infarction (MI) at baseline. These men completed dietary records for 4 – 49 d (mean = 19 d) at 1–7 visits over a mean follow-up of 18 y. Because diet may be affected by major illness, we excluded dietary records obtained ≤2 y before death or subsequent to the development of clinical CHD. . . .Dietary data were collected by 7-d diet record during 4 time periods: 1961–1965; 1968 –1975; 1984 –1991; and 1993 to the present time. BLSA participants were trained to record their food intake by dietitians during their examination visit. Ambiguous or incomplete records were clarified by telephone inter- view." "Participants in the BLSA are not a random population sample, but are predominantly white men of relatively high socioeconomic status."

The reference group consisted of men consuming < 5 servings of FV/day and >12% of energy from SF. As the authors note, fewer than 12% of men achieved a diet of <10% SF.

[25] In the BLSA article, Saturated Fatty Acid intake is abbreviated as SF.

Over a mean follow-up of 18 years, there were195 survivors, 71 deaths from CHD, and 235 from other causes. "The age range at baseline, 34 - 80 y, was similar for all 3 groups." Table 1 is a summary of characteristics.

Table 2 is adjusted for covariates. In model 1, vegetable intake was inversely associated with CHD mortality (P<0.01), with a risk reduction of 40% per serving, and ***each gram* of SF intake was associated with 7% increased risk of CHD death**.

Model 2 (in table 2) adjusted SF for the FV intakes, and vice versa. SF remained almost significantly associated with CHD mortality after adjustment for FV intake, 1.05 (1.00, 1.09).

"After adjusting for secular trend (Model 3, Table 2), the tendencies observed remained, but were significant only for vegetable intake for CHD mortality (P<0.05)."

TABLE 1

Characteristics of male BLSA participants, by survival status and cause of death[1]

	Survivors $n = 195$	CHD deaths $n = 71$	Other deaths $n = 235$
Age at first visit,[2] *y*	57.9 ± 0.8	63.4 ± 1.3*	65.6 ± 0.6*
BMI, *kg/m*[2]	25.5 ± 0.2	25.3 ± 0.3	25.3 ± 0.2
Smoking,[3] %	20.5	28.2*	20.9
Former smoking,[4] %	18.5	15.5	16.6
Physical activity score	13.8 ± 0.2	13.5 ± 0.3	13.3 ± 0.2*
Supplement use,[5] %	36.4	30.1	43.4
Dietary intake[6]			
Energy intake, *kJ/d*	2213 ± 34	2178 ± 54	2167 ± 30
Alcohol intake, *g/d*	14.4 ± 1.5	14.8 ± 2.4	15.5 ± 1.4
Saturated fat, *% energy*	12.3 ± 0.2	13.8 ± 0.3*	14.0 ± 0.2*
Fruit, *servings/d*	2.6 ± 0.1	2.1 ± 0.1*	2.0 ± 0.1*
Vegetables, *servings/d*	2.8 ± 0.1	2.0 ± 0.1*	2.1 ± 0.1*
Dietary fiber, *g*	21.8 ± 0.5	16.4 ± 0.9*	17.0 ± 0.5*
Magnesium, *mg*	341 ± 7.2	262 ± 11.6*	275 ± 6.5*
β-Carotene, *μg*	4495 ± 190	3902 ± 303	4455 ± 171
Folate, *μg*	408 ± 14.1	353 ± 22.6*	371 ± 12.7
Vitamin C, *mg*	208 ± 15	149 ± 24*	163 ± 13*

[1] Born before 1929 and aged ≤80 y at baseline.
[2] Mean ± SE of all observations (n = 1–7/person) adjusted for age at first visit.
[3] Those who reported smoking at any point during the follow-up period were defined as smokers.
[4] At baseline (first visit).
[5] Reported use of any vitamin or mineral supplement.
[6] Mean from diet records.
* Significantly different from survivor group by t test, $P < 0.05$.

TABLE 2

Mortality in male BLSA participants by fruit and vegetable intake and saturated fat intake

	Multivariate hazard risk ratio/unit increment (95% CI)		
	Model 1[1]	Model 2[2]	Model 3[3]
Total mortality			
Fruit and vegetables, *servings/d*	0.94 (0.89–1.00)*	0.95 (0.90–1.01)	0.95 (0.89–1.01)
Fruit	0.91 (0.83–1.00)*	0.93 (0.85–1.03)	0.93 (0.84–1.03)
Vegetables	0.93 (0.85–1.02)	0.94 (0.86–1.04)	0.94 (0.85–1.04)
Saturated fat, *g*	1.01 (1.00–1.03)*	1.01 (0.99–1.03)	1.01 (0.99–1.03)
CHD mortality			
Fruit and vegetables, *servings/d*	0.79 (0.69–0.92)**	0.84 (0.72–0.99)*	0.90 (0.76–1.05)
Fruit	0.86 (0.70–1.05)	0.97 (0.78–1.20)	0.97 (0.79–1.20)
Vegetables	0.60 (0.46–0.78)***	0.65 (0.50–0.85)**	0.73 (0.54–0.97)*
Saturated fat, *g*	1.07 (1.03–1.11)***	1.05 (1.00–1.09)*	1.04 (0.99–1.08)

[1] Adjusted for age at first visit, total energy intake, BMI, smoking, alcohol use, physical activity score and supplement use.
[2] Adjusted for all of the above and for saturated fat, in fruit and/or vegetable models; fruit and vegetables, in saturated fat model; or both, for supplement use model.
[3] Adjusted for all of the above plus secular trend (year of first visit before vs. after 1980).
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Table 3 (not shown) looked at magnesium, beta-Carotene, and fiber intake. Even after model 3 adjustment (which included SF intake), each gram of fiber resulted in a 6% reduction in CHD mortality.

As the authors note, "Intake of FV and SF are often inversely correlated in the diet, making it difficult to assess their independent contributions to health risk. In these data, they were correlated at -0.18 (P<0.0001). Table 4, thus shows a combination. "Those men consuming high-FV

+ low-SF intake were 76% less likely to die from CHD (P<0.001) then those consuming the high- SF and low-FV intake. After the secular trend adjustment, this was reduced somewhat to 63% (P<0.05)." Comparing the 2 groups of men with low-FV intake, a low-SF intake resulted in a CHD mortality risk-reduction of 64% (P<0.05), and 59% after the secular trend adjustment (P<0.05).

TABLE 4

Total and CHD mortality in male BLSA participants by intake combinations[1]

	Multivariate hazard risk ratio (95% CI)			
	Low FV + High SF	High FV + High SF	Low FV + Low SF	High FV + Low SF
Total mortality				
n[2]	274	88	57	82
Deaths	188	51	33	34
Model 1[3]	1	0.81 (0.59–1.11)	0.85 (0.58–1.22)	0.69 (0.49–0.97)*
Model 2[4]	1	0.81 (0.59–1.11)	0.85 (0.58–1.23)	0.69 (0.49–0.97)*
CHD mortality[5]				
n[2]	130	48	31	57
Deaths	44	11	7	9
Model 1[3]	1	0.33 (0.15–0.71)**	0.36 (0.15–0.84)*	0.24 (0.11–0.52)***
Model 2[4]	1	0.46 (0.21–0.99)*	0.41 (0.17–0.98)*	0.37 (0.16–0.81)*

[1] Low SF ≤ 12% energy; High SF > 12%. High FV ≥ 5 servings/d; Low FV < 5.
[2] Number of subjects per group; groups were defined by means of FV and SF intakes over multiple observations.
[3] Adjusted for age at first visit, total energy intake, BMI, smoking, alcohol use, physical activity score, and dietary supplement use.
[4] Adjusted for all of the above and for secular trend (year of first visit before vs. after 1980).
[5] Parallel results for Model 2 with CHD incident diagnosis as the outcome and low FV + high SF as the reference category were: 0.64 (0.33–1.24) high FV + high SF; 0.50 (0.24–1.03) low FV + low SF; 0.46 (0.23–0.94) high FV + low SF.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

There is one aspect of BLSA analysis that comes closer to the Chowdhury and Siri-Tarino scoring. "Results for CHD incident events (defined by first event: CHD mortality, non-fatal MI, or diagnosis by Q-wave), relative to survivors, were similar but slightly weaker than for CHD mortality. *Consumption of either high FV or low SF alone was not significantly protective against CHD incidence (P>0.05), whereas the combination of both high FV and low SF reduced the likelihood of developing CHD by 54% (P<0.05) relative to the combination of low FV and high SF intakes.*"

"In conclusion, *the results of this study support earlier observations that dietary intakes l**ow in SF or high in FV** each offer protection against CHD mortality.* In addition, however, our data suggest that the combination of ***both high FV with relatively low SF intake offers greater protection** against both total and CHD mortality than either practice alone.*"

BLSA Study Grading

1) *Over-adjustment with Lipids*. **No**.
2) *Sufficient Test of SFA Guidelines*. **C**. The mean intake of SFA was 13% of energy intake. Less than 12% had an intake of 10%. But no real indication of standard deviation, or division of intakes in into tertiles, quartiles, etc.
3) *Homogeneity.* **C.** All the men lived in Baltimore area, and of a higher socioeconomic level. On the positive side, there was sufficient variation to achieve statistical significant in a number of important parameters, e.g. SFA intake, fiber intake, fruit intake, vegetable intake.
4) *Food/Lifestyle Questionnaire*. **B**. Periodic re-interviews (over 4 time periods). 7-day diet record at each interviews. On average about 20 days of diet records per person.

5) *Missing Data in the Study.* **D**. No blood work. No Blood pressure. No indication of diabetes.
6) *Missing Data in the Paper*. **D**. Only presented data in halves, e.g. SFA intake < or > 12%, FV < or ≥5 servings/day PUFA, trans-fat, cereals, legumes, etc. The authors note, "Further adjustment for intake of (n-3), polyunsaturated, total nonsaturated or trans-fat, or for intake of whole grains, did not meaningfully change any of the results (not shown)." No information on carbohydrates (and their sources), protein (and its sources), and cholesterol intake. It seems that a daily diet of 8 ounce of glass OJ, 1 banana, 1/2 cup white potato (possibly french fies), 1 ear of corn, and a medium salad of 1/2 cup of iceberg lettuce with a large carrot, and a 6 ounce glass of tomato juice would be considered in the category of high FV diet (i.e. count as 6 or 7 FV servings).
7) *Confounders*. **C**. Mostly unknown. The correlation between low-SF intake with high FV was known. From table 1, the average age is ~62 y. Subjects were excluded who had any sign of heart disease (including just angina). Thus, this is an elderly population, and has the problems that I have previously written about.
8) *Food vs. Nutrients*. **C**. Fruit and Vegetables a key part of the study.

Glostrup Multi-centre Study (Glostrup)

Jakobsen MU, Overvad K, Dyerberg J, Schroll M, Heitmann BL. Dietary fat and risk of coronary heart disease: possible effect modification by gender and age. Am J Epidemiol. 2004;160:141-149.

	RR (95% CI)
Siri-Tarino	1.03 (0.66, 1.60)
Chowdhury	1.26 (0.87, 1.82)

Both meta-analysis papers referenced exactly the same paper, but reported somewhat different results. Chowdhury et al indicated more harm of SFA intake, but neither meta-analysis paper reported a statistically significant result (i.e. the range of the 95% confidence interval was not above 1.0).

The paper combines 4 population studies conducted by the same group of Danish researchers begun at different times (the first started in 1964, and the latest in the early 1990's) and all involved subjects "from the same background population of approximately 300,000 inhabitants from the western suburbs of Copenhagen, Denmark." "In a 16-year follow-up study (ending in 1998) of 3,686 Danish men and women aged 30–71 years at recruitment, the association between energy intake from dietary fat and the risk of coronary heart disease was evaluated while assessing the possible modifying role of gender and age."

Key Messages:

- "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)
- Of the 4 groups, one did reach statistical significance w.r.t. ***SFA intake****, 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.
- The median SFA intake of all participants was ~20% of energy. The median of the lowest 10% in SFA intake was ~14%, and the median of the highest 10% in SFA intake was ~25%.

About Glostrup

"The four cohorts met the following two criteria: 1) usual dietary intake was determined using a 7-day weighed food record or a dietary history interview, and 2) information on intake of total fat and on intakes of saturated, monounsaturated, and polyunsaturated fat (major types of fat) was available. The participants were recruited and examined between 1964 and 1991, with a participation of from 70 percent to 88 percent. The examinations included self-administered questionnaires containing detailed questions regarding sociodemographic factors, life- style, and health, as well as a general health examination. . . .In total, information on diet was obtained from 3,959 participants. . . . Persons with a previous diagnosis of coronary heart disease (80 persons) and persons reporting diabetes mellitus (77 persons) were also excluded."

"*The final population consisted of* ***3,797 persons*** *examined* ***between 1974 and 1993***. . . A total of 3,553 participants were given comprehensive verbal and written instructions on how to

complete a 7-day weighed food record and requested to complete it within 3 weeks. The remaining 244 participants underwent a dietary history interview by the same trained dietician." Thus, compared to other studies which only involved a 24-h diet recall, this one was far more robust. Smoking habits were classified into 5 categories, leisure time physical activity into 4, education into 3, alcohol into 4.[26]

CHD events included both fatal and non-fatal ones."The observation time for each participant was the period from the date of examination (participants from the 1936 cohort who underwent the examination in 1976 were followed from 1977) until the incidence of or mortality from coronary heart disease, death of another cause, date of emigration, or December 31, 1998, whichever came first. The analyses included the 3,686 persons (1,849 women and 1,837 men) who provided information on all potential confounding variables."

Table 1 has the baseline characteristics and risk factors for CHD. To convert MJ (megajoules) to kcal multiply by 239. For example, median energy intake for women is 1,744 kcal, and 2,390 for men. For cholesterol, to convert mmol/liter to mg/dl multiply by 38.67. For example, median serum total cholesterol for women is 236 mg/dl and 240 for men. Note the high SFA % intake, e.g. the median for the lowest 10% is 14.1% of energy intake (well above the <10% recommended). And, if we could see the the study population divided into quartiles, the differences would be quite small. Similar observations are true for the other nutrients. In other words, this is a very homogenous population - not surprising since they all come from the western suburbs of Copenhagen, Denmark.

TABLE 1. Baseline characteristics and risk factors for coronary heart disease among 3,686 Danish women and men aged 30–71 years who participated in a 16-year prospective study ending in 1998

	Women by percentiles			Men by percentiles		
	10	50	90	10	50	90
Age (years)	31	50	61	31	51	61
Body mass index (kg/m^2)	19.7	23.1	28.8	21.4	25.0	29.6
Systolic blood pressure (mmHg)	104	120	148	108	126	152
Serum total cholesterol (mmol/liter)	4.7	6.1	7.8	4.8	6.2	7.9
Serum triglyceride (mmol/liter)	0.6	1.0	1.8	0.7	1.2	2.4
Alcohol (g/day)	0	6.8	24.9	2.4	19.0	56.0
Daily nutrient intake						
Cholesterol (mg/MJ*)	30.5	46.4	71.3	29.5	44.6	66.1
Fiber (g/MJ)	1.5	2.1	3.1	1.4	2.0	2.8
Total energy (MJ)	5.0	7.3	10.2	6.6	10.0	13.6
% of energy from						
Total protein	11.2	14.6	19.2	11.2	14.1	17.9
Total carbohydrate	31.1	38.9	47.4	31.1	38.9	48.0
Total fat	36.6	46.0	54.4	37.4	46.9	55.1
Saturated fatty acids	14.1	19.5	24.8	14.5	19.7	24.8
Monounsaturated fatty acids	11.3	15.2	18.6	12.1	15.8	19.4
Polyunsaturated fatty acids	4.5	6.5	9.5	4.4	6.5	9.3

* MJ, megajoule.

[26] But in the multivariate analysis less granularity was used, i.e. 2 for leisure time physical activity, 4 for smoking, 2 for education.

3 models were used for investigation of the associations of fat and CHD (Table 3):

- **Model 1**: fat intake as a % of total energy intake, and cohort identification as a covariate.
- **Model 2a**: model 1 plus % of energy derived from protein and the percentages of energy derived from the other major types of fatty acids (in analyses where the major types of fatty acids were the variables of interest).
- **Model 2b**: model 2a plus non-dietary and dietary CHD risk factors: familial history of myocardial infarction (yes, no, do not know); smoking (never, former, and current of 1– <15 g per day and ≥15 g per day); leisure-time physical activity (sedentary, active); educational attainment (0–7 years, 8 years or more); alcohol (grams per day) (nondrinkers, drinkers by tertiles); dietary fiber (grams per MJ per day) (as a continuous variable); and, and dietary cholesterol (mg per MJ per day) (as a continuous variable). Adjustments for systolic blood pressure and BMI were also included (but too esoteric to describe here).

TABLE 3. Age-related risk of coronary heart disease according to intake of 5% higher level of energy from dietary fat in a 16-year prospective study (ending in 1998) of 3,686 Danish women and men aged 30–71 years

	Women				Men			
	<60 years		≥60 years		<60 years		≥60 years	
	HR*	95% CI*	HR	95% CI	HR	95% CI	HR	95% CI
Total fat								
Model 1†	1.66	1.12, 2.47	1.03	0.88, 1.21	1.17	0.96, 1.42	0.96	0.86, 1.07
Total fat for carbohydrates								
Model 2a‡	1.77	1.15, 2.55	1.05	0.89, 1.23	1.16	0.95, 1.41	0.95	0.85, 1.06
Model 2b§	1.74	1.15, 2.64	1.05	0.86, 1.28	1.15	0.93, 1.41	0.93	0.81, 1.06
Saturated fatty acids								
Model 1	2.48	1.33, 4.65	1.12	0.87, 1.44	1.29	0.92, 1.80	0.96	0.79, 1.17
Saturated fat for carbohydrates								
Model 2a	2.49	1.30, 4.77	1.11	0.80, 1.54	1.16	0.79, 1.61	0.86	0.65, 1.14
Model 2b	2.68	1.40, 5.12	1.22	0.86, 1.71	1.29	0.87, 1.91	0.94	0.70, 1.28
Monounsaturated fatty acids								
Model 1	2.98	1.38, 6.44	1.03	0.68, 1.57	1.47	0.91, 2.37	0.95	0.73, 1.24
Monounsaturated fat for carbohydrates								
Model 2a	2.85	1.22, 6.69	0.89	0.49, 1.61	1.61	0.93, 2.78	1.04	0.71, 1.53
Model 2b	2.56	1.15, 5.73	0.75	0.40, 1.41	1.37	0.78, 2.40	0.85	0.57, 1.28
Polyunsaturated fatty acids								
Model 1	0.68	0.20, 2.34	0.86	0.51, 1.44	1.12	0.60, 2.09	0.79	0.53, 1.16
Polyunsaturated fat for carbohydrates								
Model 2a	0.67	0.19, 2.44	0.86	0.48, 1.56	1.09	0.58, 2.05	0.76	0.51, 1.14
Model 2b	0.66	0.19, 2.35	0.94	0.51, 1.74	1.06	0.56, 1.99	0.72	0.47, 1.10
Polyunsaturated fat for saturated fat								
Model 2a	0.60	0.17, 2.12	0.75	0.44, 1.28	1.09	0.58, 2.05	0.76	0.51, 1.14
Model 2b	0.54	0.15, 1.95	0.75	0.43, 1.30	1.06	0.56, 1.99	0.72	0.47, 1.10

* HR, hazard ratio; CI, confidence interval.

† Model 1 included the variable of interest as the percentage of total energy intake (5% unit), total energy intake (megajoule), and cohort identification.

‡ Model 2a included the variables of model 1 plus the percentage of energy derived from protein and the percentages of energy derived from the other major types of fatty acids (in analyses where the major types of fatty acids were the variables of interest). When we studied the difference in risk associated with a higher level of polyunsaturated fat, where the lower intake of energy is due to a lower intake of energy from saturated fat, the percentage of energy from carbohydrates was added to model 2a, and the percentage of energy from saturated fatty acids was removed from the model.

§ Model 2b included the variables of model 2a and the other nondietary and dietary coronary heart disease risk factors.

"During the 7–22 years (median, 16 years) of follow-up from 1974 to 1998, 326 participants (98 women and 228 men) with fatal or nonfatal events of coronary heart disease were identified."

From table 3, in all 3 models (1, 2a, 2b), a 5% increase in total fat, SFA intake, or MUFA was associated with a statistically significant increase in CHD incidence in younger (<60 y) women, e.g. for **SFA intake, model 2b, HR=2.68** (CI: 1.40, 5.12). However, there was no statistically significant relationship with older women, or men. Also, w.r.t. PUFA, there was no statistically significant relationship in any of the 4 groups, regardless of whether PUFA was substituted for carbohydrates or SFA.

The paper notes limitations to the study:

- Small number of cases caused wide confidence intervals.
- Only baseline information regarding diet and lifestyle was available.
- Random error in dietary intake. 7 Days may be too short to give information on habitual food intake.
- "In observational studies, diets differing in fat content—both quantitatively and qualitatively—inevitably differ in other dietary constituents that may influence coronary heart disease risk."
- The multivariate analysis included an adjustment for total energy. This models a substitution of one macronutrient for another. "Consequently, adjusting for total energy excludes the possibility of addressing hypotheses on the effects of increased intake of selected nutrients. . . .The present study showed that we may be able to provide evidence that saturated fat increases risk more than carbohydrates do, but we cannot, as also emphasized by Freedman et al., predict whether fat promotes disease or whether carbohydrates prevent disease."
- Intake of trans-fatty acids (TFA) was not measured, and other studies have shown that an intake increases CHD.
- "The usual mix of carbohydrates in the Western diet contains many high-glycemic foods, such as potatoes and baked goods. The possibility remains that the positive association between saturated fat intake and risk of coronary heart disease would have been even stronger if compared with a mix of carbohydrates from low-glycemic foods, such as whole grain cereals and vegetables."

The paper notes a few possible reasons for the gender differences:

- "Because the magnitude of the relative effect depends on the magnitude of the baseline risk, the same absolute effect in two populations can correspond to greatly differing relative associations."
- "Another possibility is 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."

W.r.t. age-related differences, the paper notes that "differences in baseline risk may be an explanation. ***It is also possible that older participants may be a selected group (a large number of the study base has already died or has been excluded because of coronary heart disease)*** and may be less vulnerable to environmental factors." As the authors note, and as been evident in some of the other studies that I have analyzed, the lack of an association with any kind of fat for people entering a study over the age of 60 is common.

Some additional info about this study. Unlike the Finnish study (KIHD) of my analysis, I was unable to find additional Danish study that would explain the key anomaly, i.e. why the difference between men and women in the younger cohort. However, I was able to find some data that suggest the Glostrup study results are less credible than they appear to be, involving 3 data histories that indicate that the diet/lifestyle data determined at baseline changed significantly over the the median study period (i.e. 16 years). The historical data in question involves TFA (i.e. trans-fat) in the food supply, smoking, and the overall decline in first AMI (acute myocardial infarction). I also found a study on alcohol intake w.r.t. LDL levels that might partially explain the difference between younger men and women.

Trans-Fat (TFA)

The Glostrup paper notes that TFA intake was not determined and that this may have been a factor. As noted in a 2006 paper, "The content of trans fatty acids (TFA) in Danish food has been monitored for the last 30 years. In margarines and shortenings the content of TFA has steadily declined from about 10 g/100 g margarine in the seventies to practically no TFA in margarines in 1999." Besides margarine TFA is also present in various fried foods (like french fries), microwave popcorn, and various bakery products.

Thus, even if a subject in the Glostrup study didn't change his or her diet, the intake of TFA likely changed over the course of the study.

Smoking

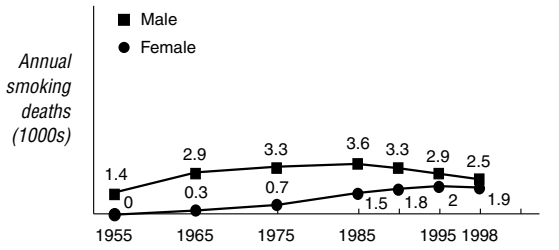
I found a short 2-pager on smoking in Denmark from the World Health Organization. Here is an excerpt:

Numbers of Deaths Attributed to Smoking/Total Deaths (thousands), 1998

	Males (by age)			*Females (by age)*		
Cause	*0-34*	*35-69*	*70+*	*0-34*	*35-69*	*70+*
Lung cancer	–/0.0	0.8/0.8	1.0/1.1	–/0.0	0.6/0.7	0.6/0.7
All cancer	–/0.1	1.2/3.0	1.6/4.6	–/0.1	0.8/2.9	0.8/4.5
Vascular	–/0.0	0.6/2.5	1.0/7.9	–/0.0	0.3/1.1	1.1/9.8
Respiratory	–/0.0	0.3/0.5	1.1/2.0	–/0.0	0.4/0.6	1.1/2.1
All other	–/0.7	0.4/3.2	0.4/4.2	–/0.3	0.3/1.7	0.6/6.2
All causes	–/0.9	2.5/9.2	4.0/19	–/0.4	1.9/6.2	3.6/23

Source: Peto, Lopez, et al., 1992, 1994 (update 2003)

Smoking-Attributed Numbers of Deaths per Year, Ages 35-69 Only



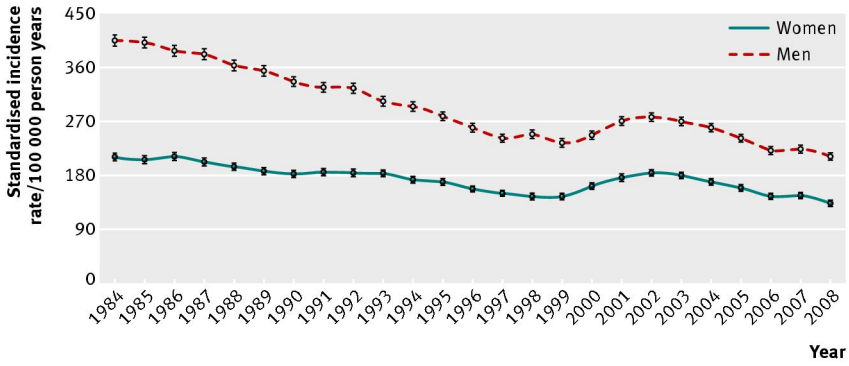
Focus on just the 35-69 age category (most applicable to the "young" cohort of the Glostrup study). From the table on the left, about 1/4 of the vascular deaths in 1998 were attributed to smoking. Now look at the table on the right, and the difference between men and women due to smoking deaths over time. ***From 1975 to 1995, smoking deaths for women almost tripled. Yet over this same period, smoking deaths for men declined by more than 10%.***

Caveat: We don't know the percentage of deaths in each time period in the vascular category. We don't know the percentage of CHD deaths of vascular deaths. And, we don't know CHD incidents, which is what is measured in Glostrup.

Yet, this difference may be part of the explanation of the difference between young men and women in the Glostrup study.

Decline in MI Incidence over the Study Period

A 2012 paper in the BMJ provides an interesting graph, "Standardised incidence rates for first time hospitalisation for myocardial infarction in Denmark between 1984 and 2008 among men and women":



Transient increase in incidence starting around 2000 was presumably due to new diagnostic criteria for myocardial infarction[41 46]

The Glostrup study ended in 1998. Why the major decline for both men and women from 1984 to 1998? Diet and Lifestyle were likely factors, but I have no data that shows this. Also, the above data is for all of Denmark, whereas the Glostrup study involves only the suburbs of west Copenhagen.

Also note that the decline for men is greater from a percentage aspect than that for women. Thus, this *might* be a possible contribution to the difference in CHD incidence between young men and women in the Glostrup study.

Alcohol

Results reported in a 1996 BMJ article, "Alcohol consumption, serum low density lipoprotein cholesterol concentration, and risk of ischaemic heart disease: six year followup in the Copenhagen male study." This study involved 2826 men aged 53-74 years without overt ischaemic heart disease (IHD). Outcome measure was incidence of IHD over a 6 year period.

"The risk of ischaemic heart disease in men with a high concentration of serum low density lipoprotein cholesterol was strongly modified by use of alcohol: ***those who did not drink al-***

Table 4—*Relative risks (95% confidence intervals) of ischaemic heart disease during six years according to concentration of low density lipoprotein cholesterol and alcohol consumption. In analyses alcohol abstention group is regarded as reference category*

Low density lipoprotein concentration (mmol/l)	Alcoholic beverages/week			P value†
	0 (n=298)	1-21 (n=1681)	⩾22 (n=847)	
−3·62	1 (n=58)	0·5 (0·1 to 2·2) (n=301)	1·1 (0·3 to 4·3) (n=199)	0·32
3·63-5·24	1 (n=185)	0·8 (0·5 to 1·5) (n=1031)	0·7 (0·3 to 1·3) (n=488)	0·28
⩾5·25	1 (n=55)	0·4 (0·2 to 1·0)* (n=349)	0·2 (0·1 to 0·8)** (n=160)	0·01

†P value represents probability outcome of test for trend in logistic model after adjustment for factors significantly associated with risk of ischaemic heart disease in table 3 (except low density lipoprotein cholesterol and interaction terms).
.*P<0·05; **P<0·01.

cohol had five times the risk of ischaemic heart disease compared with those who consumed three alcoholic beverages or more a day." High LDL level was defined as ≥5.25 mmol/l (i.e. ≥203 mg/dl). "One drink corresponded to 10-12 g ethanol." Table 4 contains the applicable data. Note that the moderate drinkers (1-21 drinks per week) in the high LDL group had 60% less chance of IHD than the non-drinkers (i.e. HR=0.4, 95% CI: 0.2 to 1.0).

So, how does this relate to the Glostrup study? Looking back at table 1, the men were much heavier drinkers than the women. For example, the median daily intake of the top 10% of alcohol intake for men was 56 g / day (about 35 drinks / wk). The overall median for men was 19 g/day (12 drinks/ wk). This would seem to suggest that about 25% of the men in the Glostrup study were in the ≥22 drinks/wk category. Table 1 provides serum total cholesterol, but not LDL. But with some reasonable assumptions, 20+% of the Glostrup men could be in the high LDL category.

From many other studies, we know that high SFA-intake is highly correlated with high-LDL levels. Thus, the Copenhagen LDL/Alcohol study of men suggest that the Glostrup men with the highest SFA-intake who were also consuming moderate to high levels of alcohol may have been protected from IHD.

Model 2b in the Glostrup study did include an adjustment for alcohol intake (in fact, 3 tertiles for just the drinkers). But was the adjustment made in relation to serum LDL cholesterol, since the effect seems to be confined to men with high LDL cholesterol?

Glostrup Study Grading

1) *Over-adjustment with Lipids*. **No**.
2) *Sufficient Test of SFA Guidelines*. **F**. The median of lowest 10% in SFA-intake was about 14%.
3) *Homogeneity.* **F.** All from the western suburbs of Copenhagen Denmark. And, based on the limited data in table 1, the variation in nutrient intake is relatively small.
4) *Food/Lifestyle Questionnaire*. **D**. Dietary intake primarily based using a 7-day weighed food record. This is better than most studies. However, given the 16yr average follow-up, with no further food intake information, that's a problem. Lifestyle interview has the same problem, i.e. good baseline, but no follow-up.
5) *Missing Data in the Study.* **D**. No information on TFA-intake, and carbohydrate intake. Given the length of the study, the authors had knowledge from other sources in changes of the diet and lifestyle of the Danish people over the time period. Providing such data might have provided some additional insight into interpreting the results of this study.
6) *Missing Data in the Paper*. **F**. Paper looked at just CHD events. No mention of number of CHD deaths, and thus no separate analysis HR for CHD deaths. Although paper states the number of CHD events for men and for women, the paper does not provide the number for each age group. In fact, the paper does not provide the number of subjects in each age group either. There is no breakdown of data by tertiles, quartiles, or quintiles. For example, it would be useful to see a breakdown of SFA-intake by quartiles, and the characteristics of subjects in each quartile.
7) *Confounders*. **D**. Although there are many relatively fine-grained adjustments in the multivariate analysis, there doesn't appear to be any within the big age groups. Other studies would have broken down the 30-59 age group into 5 yr intervals as part of the multivariate analysis. As the authors note, this study provides an adjustment for total energy intake, which only allows for a "substitute" nutrient model. This makes it difficult to compare this

study to others. With all the confounders that the authors try to adjust for (especially in model 2b), it seems likely (in my view) that there is over-adjustment. Some bivariate analysis may have provided some insight into this issue.

8) *Food vs. Nutrients*. **F**. No significant mention of food.

Western Electric Study (WES)

Shekelle RB, Shryock AM, Paul O, Lepper M, Stamler J, Liu S et al. Diet, serum cholesterol, and death from coronary heart disease. The Western Electric study. N.Engl.J Med. 1981;304:65-70.

	RR (95% CI)
Siri-Tarino	1.11 (0.91, 1.36)
Chowdhury	1.07 (0.98, 1.17)

Chowdhury indicates that this study did include an adjustment for lipids (i.e. *serum cholesterol*). As indicated in the above scoring, the harmful effects of SFA did not reach statistical significance. The last sentence of the abstract: "The results support the conclusion that lipid composition of the diet affects serum cholesterol concentration and risk of coronary death in middle-aged American men."

About WES

"The participants in the Western Electric Study were selected in 1957 through random sampling of 5397 men who were 40 to 55 years of age. Dietary data were obtained at the initial examination and at the second examination one year later (reexamination) by two nutritionists using standardized interviews and questionnaires. . . . A detailed review of 195 specific foods was then conducted to determine the number of times in the past 28 days each food had been eaten and the usual size of the portions." Blood was also drawn at both examinations to measure serum cholesterol." 2,107 men participated in the 1st examination. After exclusion for various reasons (e.g. evidence of CHD at 1st exam), 1900 men were left for the study.

Table 1 shows the characteristics of the men at Initial examination.

A diet score for each participant was calculated based on the Keys and Hegsted formulas:

Table 1. Distributions of the Dietary Variables, Serum Cholesterol, and Body-Mass Index at the Initial Examination of 1900 Middle-Aged Men.

Variable	Mean ±S.D.	Skewness	Kurtosis	Percentile Values			Reliability Coefficient *
				1st	50th	99th	
Energy intake/day (kcal) †	3183.2±974.5	2.4	23.8	1521.7	3055.1	6162.0	0.656
Saturated fatty acids (per cent cal)	16.7±2.6	0.1	0.7	10.8	16.6	23.5	0.567
Polyunsaturated fatty acids (per cent cal)	3.9±0.9	0.8	2.3	2.0	3.8	6.8	0.444
Dietary cholesterol (mg/1000 kcal)	240.5±68.0	1.0	1.8	125.4	229.7	442.4	0.653
Diet score ‡							
Keys	60.2±8.3	0.1	0.6	40.6	60.1	80.8	0.589
Hegsted	45.9±8.4	0.2	0.5	27.0	45.6	68.2	0.601
Serum cholesterol (mg/dl) §	247.7±54.4	0.9	2.2	143.0	242.0	394.0	0.651
Body-mass index (kg/m²)	25.4±3.2	0.5	0.8	18.8	25.3	33.8	0.964

*Correlations between measurements made at initial examination and at reexamination one year later in the 1556 men who reported no systemic change in diet between the two periods.

†Total energy from foods and beverages, including alcohol.

‡See Methods for formulas from which values are derived.

§To convert serum cholesterol from milligrams per deciliter to millimoles per liter, multiply by 0.02586.

Keys: 1.26 * (2*S - P) + 1.5 * SQRT (1000*C/E)
Hegsted: 2.16*S - 1.65*P + 0.0677*DC
where
S = % of dietary calories from SFA
P = % of dietary calories from PUMA
C = dietary cholesterol in milligrams per day,
DC = dietary cholesterol in mg/ 1000kcal
E = the daily energy intake in kilocalories.

Both scores were highly correlated to serum cholesterol. And, "*Further analysis demonstrated that serum cholesterol concentration varied positively with dietary saturated fatty acids and cholesterol; it tended to vary inversely with polyunsaturated fatty acids*."

Table 4. Risk of Death from Coronary Heart Disease over 19 Years in 1900 Men, According to Base-Line Level of Dietary Variables.

Dietary Variables *	Coronary Deaths (per Cent) †			Logistic Regression ‡	
	Low 3d	Middle 3d	High 3d	Coefficient	P
Hegsted et al. diet score §	9.8	10.6	13.6	0.029	0.004
Keys et al. diet score §	9.3	11.2	13.4	0.027	0.010
Saturated fatty acids (per cent cal)	10.9	11.2	11.8	0.031	0.144
Polyunsaturated fatty acids (per cent cal)	13.5	10.4	10.1	−0.258	0.010
Dietary cholesterol (mg/1000 kcal)	10.9	9.5	13.6	0.003	0.008

*The base-line level of each variable in each participant was the mean of the values obtained at the initial examination and at reexamination. The numbers of participants in the low, middle, and high thirds were 631, 636, and 633, respectively, for polyunsaturated fats; they were 633, 634, and 633, respectively, for the other four variables.

†Low, middle, and high thirds refer to the distribution of each dietary variable.

‡Coefficients and P values were based on three competing-risk, multivariate logistic-regression analyses. One included Hegsted's score, a second included Keys' score, and a third included the three lipids. The other regressors in each analysis were age, systolic blood pressure, number of cigarettes smoked per day, serum cholesterol concentration, number of alcoholic drinks per month, and body-mass index (weight/height^2). Also included were three variables that indicated whether a participant or his parents had been born in Western or Northern Europe, in Middle Europe, or in other areas outside the United States. These latter variables were included because ethnicity might have affected diet and risk of coronary heart disease.

§See Methods for formulas and definitions of these variables.

Table 4 shows the risk of death from CHD over 19 years. "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).

WES Study Grading

1) *Over-adjustment with Lipids*. **Y**. SFA intake was divided into thirds (tertiles). Only fully adjusted results were presented, and one of the adjustments was serum cholesterol.
2) *Sufficient Test of SFA Guidelines*. **F**. The mean intake of SFA was 16.7% of total calories with a standard deviation of 2.6. Also, as indicated in Table 1, the average SFA intake for the lowest 1% was 10.8%.
3) *Homogeneity.* **F.** All the men lived in Chicago and worked for Western Electric, eating a similar diet - high in SFA, low in PUFA, and high in dietary cholesterol; and, SD for each was relatively small.
4) *Food/Lifestyle Questionnaire*. **C**. Dietary intake based on a 1 hr interview asking about general pattern of eating on a work day and weekend. Process repeated 1 year later. Also, blood collected to measure serum cholesterol at both interviews were well correlated with food consumption. But there was no subsequent follow-up over the following 18 years. So no way to assess any changes in diet. Other than smoking, no lifestyle data (e.g. physical activity level, education, socio-economic status) were collected.
5) *Missing Data in the Study.* **D**. There were no updates in dietary intake and blood work during the study period.
6) *Missing Data in the Paper*. **D**. The paper did not present the characteristics (dietary/lifestyle measurements) by SFA tertile. No information presented on fiber, monounsaturated fat, carbohydrate breakdown, etc. No multivariate results without serum cholesterol.
7) *Confounders*. **D**. Without knowing the characteristics by SFA tertile, it is not possible to make this judgment.
8) *Food vs. Nutrients*. **F**. No information about the Food consumed.

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

Erkkila AT, Lehto S, Pyorala K, Uusitupa MI. n-3 Fatty acids and 5-y risks of death and cardiovascular disease events in patients with coronary artery disease. Am J Clin.Nutr. 2003;78:65-71.

	RR (95% CI)
Chowdhury	1.00 (0.68, 1.46)

Chowdhury indicates that this study did include an adjustment for lipids (i.e. *serum cholesterol*). The Chowdhury scoring does agree with the paper (Table 3, column 3, row 2 [SFA intake], below) w.r.t. the outcomes of CAD death or AMI (acute myocardial infarction).

But the paper also makes this point: ***"an increase in dietary saturated fat intake was associated with an increase in the risk of death."*** This was also indicated in Table 3 (row 2, column 1): RR 1.57 (1.13, 2.17)." "Death" in this case referred to all causes.

About EUROASPIRE

This study is about secondary prevention of CAD with a focus on n-3 Fatty Acids, using a Finnish cohort. This involved the same University (Kuopio) as the KIHD study. Patients were selected who had been admitted to the Kuopio University Hospital in 1991-1994, were <71 at time of admission, and fit into one of "4 diagnostic categories: 1) patients having their first elective or emergency coronary artery bypass grafting (CABG), 2) patients having their first elective or emergency percutaneous trans- luminal coronary angioplasty (PTCA) but with no previous CABG, 3) patients having their first or a recurrent AMI but with no previous CABG or PTCA, 4) patients admitted with symptoms compatible with acute myocardial ischemia (AMIS)

TABLE 1
Baseline characteristics

	Patients who died (n = 28 M, 8 F)	Patients who survived (n = 257 M, 122 F)
Age (y)	63.8 ± 8.3[1]	60.7 ± 8.0[2]
Serum cholesterol (mmol/L)		
Total	6.61 ± 1.26	6.07 ± 1.17[3]
LDL	4.69 ± 1.04	4.22 ± 1.04[4]
HDL	1.20 ± 0.34	1.23 ± 0.29
Serum total triacylglycerol (mmol/L)	2.23 ± 1.09	1.92 ± 1.54[5]
Plasma glucose (mmol/L)	6.09 ± 1.44	5.97 ± 1.78
Systolic blood pressure (mm Hg)	145 ± 27	140 ± 22
Diastolic blood pressure (mm Hg)	85 ± 16	82 ± 12
BMI (kg/m^2)	28.2 ± 4.2	28.1 ± 4.0
Waist-to-hip ratio	0.95 ± 0.08	0.93 ± 0.08
Diabetes (diagnosis or plasma glucose ≥7 mmol/L) [n (%)]	8 (22)	62 (16)
Lipid-lowering drugs [n (%)]	10 (28)	152 (40)
Education <12 y [n (%)]	35 (97)	327 (86)
Smoking [n (%)]	5 (14)	48 (13)

[1] $\bar{x}$ ± SD.
[2,5] Significantly different from patients who died (Mann-Whitney U test): [2] P = 0.009, [5] P = 0.024.
[3,4] Significantly different from patients who died (ANOVA with adjustment for sex and age): [3] P = 0.002, [4] P = 0.010.

TABLE 2
Nutrient intakes[1]

	Patients who died (n = 34)	Patients who survived (n = 367)
Energy (kJ/d)	6945 ± 1937	7272 ± 2159
Fat (% of energy)	34.8 ± 7.1	32.5 ± 6.5[2]
Saturated fat (% of energy)	14.9 ± 5.5	12.7 ± 3.6[3]
Monounsaturated fat (% of energy)	11.6 ± 2.3	11.2 ± 2.7
Polyunsaturated fat (% of energy)	5.5 ± 1.7	5.8 ± 1.8
Cholesterol (mg/d)	228 ± 108	217 ± 90
Protein (% of energy)	16.7 ± 2.9	17.4 ± 3.0
Carbohydrates (% of energy)	44.9 ± 7.0	46.5 ± 6.8
Fiber (g/d)	19.1 ± 7.8	21.6 ± 8.4[4]
Alcohol (% of energy)	2.2 ± 5.1	2.2 ± 4.5

[1] $\bar{x}$ ± SD.
[2–4] Nearly significantly different from patients who died (ANOVA with adjustment for sex and age): [2] P = 0.107, [3] P = 0.074, [4] P = 0.064.

but in whom the diagnosis of AMI could not be confirmed (patients with unstable angina pectoris) and who had no previous CABG, PTCA, or AMI." The examinations occurred in 1995.

Patients from each category: CABG, 109; PTCA, 106; AMI, 101; and AMIS, 99. "The median time interval between hospital admission and examination was 20 mo (range: 10–48 mo). The Finnish center was the only one of the EUROASPIRE centers to carry out detailed dietary studies and measurements of the fatty acid composition of serum lipid fractions."

"The censoring date was the date of the earliest event or the end of the follow-up period (30 April 2001 for deaths and 31 December 2000 for hospitalizations). The endpoints included deaths from all causes, CVD, and CAD; nonfatal AMI; nonfatal stroke; CABG; and PTCA."

Tables 1 and 2 are baseline characteristics divided into Patients who survived the 5 years of the study, and those who did not (all causes).[27] As the paper states, virtually all patients were taking cardiovascular drugs. Surprisingly (to me), only 28% of patients who died and 40% who survived were taking lipid-lowering drugs at the time of examination. Given the cholesterol numbers and previous cardiac episodes, I would have expected almost all patients to be on lipid-lowering drugs (in particular, a statin).

TABLE 3
Relative risks (RRs) and 95% CIs of death and cardiovascular disease (CVD) events per 1-SD increment in nutrient intake[1]

	Death (n = 34/400)[2]		CAD death (n = 16/400)		CAD death or AMI (n = 34/400)		CVD death, AMI, or stroke (n = 44/400)		Revascularization (n = 38/400)	
	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
Fat	1.38 (0.98, 1.95)	0.065	1.03 (0.63, 1.70)	0.902	1.05 (0.73, 1.52)	0.799	1.22 (0.89, 1.67)	0.216	1.31 (0.94, 1.82)	0.113
Saturated fat	1.57 (1.13, 2.17)	0.007	1.01 (0.61, 1.69)	0.966	1.00 (0.68, 1.46)	0.993	1.23 (0.89, 1.68)	0.211	1.19 (0.85, 1.66)	0.304
Polyunsaturated fat	0.92 (0.64, 1.31)	0.631	0.92 (0.55, 1.54)	0.758	1.08 (0.78, 1.51)	0.642	1.08 (0.82, 1.42)	0.571	1.10 (0.83, 1.44)	0.516
Cholesterol	1.07 (0.76, 1.50)	0.698	0.76 (0.45, 1.28)	0.302	0.97 (0.68, 1.40)	0.887	1.10 (0.81, 1.50)	0.583	1.23 (0.91, 1.66)	0.184
Fiber	0.81 (0.55, 1.19)	0.287	1.11 (0.68, 1.81)	0.684	1.10 (0.75, 1.61)	0.618	1.02 (0.73, 1.43)	0.899	0.85 (0.59, 1.23)	0.389
Alcohol	1.07 (0.74, 1.55)	0.710	0.96 (0.56, 1.66)	0.885	1.08 (0.73, 1.61)	0.692	0.99 (0.69, 1.41)	0.939	1.01 (0.69, 1.49)	0.942
Keys score[3]	1.51 (1.12, 2.04)	0.006	1.00 (0.61, 1.62)	0.990	1.00 (0.71, 1.41)	0.982	1.19 (0.89, 1.60)	0.250	1.21 (0.88, 1.66)	0.247

[1] Models were adjusted for age, sex, diagnostic category [coronary artery bypass grafting or percutaneous transluminal coronary angioplasty compared with acute myocardial infarction (AMI) or acute myocardial ischemia], energy intake, serum cholesterol, serum triacylglycerol, diabetes (diagnosis or plasma glucose concentration ≥7 mmol/L), BMI, and education (<12 compared with ≥12 y). The intakes of fat, saturated fat, polyunsaturated fat, cholesterol, fiber, and alcohol were adjusted for energy intake by using the residual method (37). CAD, coronary artery disease.

[2] Number of cases/total *n*.

[3] Calculated from the intakes of saturated fat, polyunsaturated fat, and cholesterol (38).

Table 3 presents the Relative Risks with a lot of adjustments, including serum cholesterol. Chowdhury used column 3 in his analysis (which was the correct choice). I would have liked to see the results without adjustment for serum cholesterol. **Note that just 1 entry in this matrix of results reached statistical significance: Saturated Fat associated with all-cause death: 1.57 (1.13, 2.17).**

The paper went on to look at the fatty acids in serum cholesterol esters. This analysis was divided into tertiles (i.e. thirds). In looking at tertile 3 vs. 1, statistical significance was reached *only* for all-cause death. For this, there were benefits for increased, ALA, EPA, and DHA. Last sentence from the paper, "In conclusion, ALA, EPA, and DHA are nutritional factors that could potentially reduce the risk of death in patients with CAD."

[27] To convert the cholesterol numbers from mmol/L (in table) to the more common use in the US of mg/dL, multiply by 38.61. To convert kJ to kcal, multiply by 0.239 - to approximate mentally, divide by 4. W.r.t. glucose, i.e. Diabetes, 7 mmol/L = 126 mg/dl.

EUROASPIRE Study Grading

1) *Over-adjustment with Lipids*. **Y**. Two results were reported. One minimally adjusted (sex and age), and the other fully adjusted, which included serum cholesterol.
2) *Sufficient Test of SFA Guidelines*. **D**. Mean intake between patients who died and those who survived was significant (14.9 vs. 12.7, with the associated SDs of 5.5 and 3.6). But study population was small, and likely too many confounders.
3) *Homogeneity.* **F.** All were from Kuopio area of Finland, and seemed to be eating a comparable diet.
4) *Food/Lifestyle Questionnaire*. **C**. "The patients completed a 4-d food record (3 weekdays and 1 weekend day) at home and estimated the amounts of foods consumed by comparing them with portion sizes listed in a booklet. The patients returned the food records at the interview, and all the records were checked by a clinical nutritionist." Blood samples collected after subjects had fasted for 12+ hours. Medications were noted at the beginning of the study.
5) *Missing Data in the Study.* **C**. There were no updates in dietary intake, blood work, and medications during the study period, but given the short time of the study, this was not as big a deal as in other long-term studies. No information on Trans-fats.
6) *Missing Data in the Paper*. **D**. The paper did not present the characteristics (dietary/lifestyle measurements, medications) by SFA intake tertile. No multivariate analysis without serum cholesterol.
7) *Confounders*. **F**. Without knowing the characteristics by SFA tertile, it is not possible to make this judgment. A more significant factor was that about 1/3 of patients were on lipid-lowering medications. Without knowing the distribution by SFA tertile, this may have affected the results. No adjustment was made for this.
8) *Food vs. Nutrients*. **F**. No information about the Food consumed.

Health Professionals Follow Up (HPFS) Study

Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer M, Willett WC. Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States. BMJ. 1996;313:84-90.

	RR (95% CI)
Siri-Tarino	1.11 (0.87, 1.42)
Chowdhury	1.07 (0.88, 1.29)

Key Messages:

- A large study 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).

About HPFS

"The health professionals follow up study began in 1986 when 51 529 [USA men] health professionals aged 40 to 75 years completed a 131 item food frequency questionnaire and provided information about medical history, risk factors for heart disease, and dietary changes during the past 10 years. Follow up questionnaires were sent in 1988, 1990, and 1992. We excluded from analysis 1595 men who did not satisfy the a priori criteria of daily energy intake between 3.34 and 17.56 MJ and fewer than 70 blanks out of 131 total listed food items. In addition, we excluded 6177 men with previous diagnosis of myocardial infarction, angina, coronary artery surgery, stroke, transient ischaemic attack, peripheral arterial disease, or diabetes. We followed the 43,757 eligible men for incidence of coronary disease during the subsequent **six** years." There was also a detailed validation study done on a random sample of 127 men, and results were corrected for measurement errors from this study.

End points were fatal coronary disease (including sudden death) and non-fatal myocardial infarction occurring between the return of the baseline questionnaire of January 31, 1992. Thus, although this was a large study (43,757 men), it was shorter (6 years) than others.

Table 1 provides the baseline values for the population, divided into quintiles, by SFA intake. Note that the mean SFA intake for the quintiles 1 and 2 both met the SFA guidelines (i.e. <10% of energy from SFA). SFA intake was associated both directly and inversely with several risk factors.

Table 1—*Relation of intake of saturated fatty acid to selected variables at baseline among men*

	Fifth of saturated fat intake adjusted for energy				
Detail	**1**	**2**	**3**	**4**	**5**
Mean saturated fat intake (g/day)	15.9	21.5	24.8	27.7	32.4
Mean saturated fat intake (% of energy)	7.2	9.5	10.9	12.3	14.8
Currently smoking (%)	5.7	7.5	9.1	10.9	14.4
Mean alcohol consumption (g/day)	15.4	14.2	12.0	10.4	8.0
Mean body mass index (kg/m^2)	24.0	24.7	25.0	25.2	25.5
Family history of myocardial infarction (%)	13.5	12.2	11.3	11.4	11.0
History at baseline of:					
Hypertension (%)	20.7	20.1	20.0	18.8	18.2
High cholesterol (%)	16.2	11.3	9.8	7.9	6.6
Mean serum cholesterol (mmol/l)*	5.2	5.3	5.3	5.3	5.3
Mean physical activity (MET/week)	30.1	25.4	24.5	21.3	19.9
Mean daily intake of:					
Total fat (% of energy)	23.9	29.4	32.3	34.9	39.1
Trans fatty acids (% of energy)	0.8	1.1	1.3	1.4	1.6
Linoleic acid (% of energy)	4.6	5.1	5.2	5.3	5.2
Linolenic acid (% of energy)	0.4	0.5	0.5	0.5	0.6
Cholesterol (mg/1000 kcal;4 MJ)	118	141	152	165	185
Polyunsaturated:saturated fat ratio	0.8	0.6	0.6	0.5	0.4
Dietary fibre (g/day)	26.2	22.1	20.6	18.8	16.2
Carotene (IU/day)	13 968	10 736	9646	8486	7203
Vitamin E (IU/day)	127	94	86	77	72
Servings/day (mean):					
Fish	0.5	0.4	0.4	0.3	0.3
Red meat	0.4	0.8	1.0	1.2	1.4
Chicken	0.4	0.4	0.4	0.3	0.3
Cereals	3.7	3.4	3.3	3.2	2.9
Vegetables	4.6	3.8	3.5	3.2	2.8
Fruit	3.5	2.6	2.3	2.0	1.6
Sweets	1.0	1.4	1.5	1.6	1.5
Low fat dairy	1.0	1.1	1.0	1.0	0.8
High fat dairy	0.5	0.8	1.1	1.4	2.4

*Based on 17 339 men without history of hypercholesterolaemia who reported their blood cholesterol concentration at baseline.

Table 2—*Relative risk of myocardial infarction according to intake of total fat, saturated fat, and cholesterol adjusted for energy. Figures are relative risks (95% confidence intervals) unless stated otherwise*

	Fifth						
Variable	**1**	**2**	**3**	**4**	**5**	**χ^2 For trend**	**P value**
Saturated fat							
Median intake (g/day)	17	21	24	27	33		
Person years	43 963	47 098	48 148	49 049	48 525		
Total myocardial infarction*:							
No of cases	125	148	131	150	180		
Age adjusted	1.0	1.16 (0.91 to 1.47)	1.05 (0.82 to 1.34)	1.21 (0.95 to 1.53)	1.44 (1.14 to 1.81)	3.04	0.002
Multivariate†	1.0	1.11 (0.87 to 1.42)	0.97 (0.75 to 1.24)	1.08 (0.84 to 1.38)	1.22 (0.96 to 1.56)	1.48	0.14
Adjusted for fibre intake‡	1.0	1.01 (0.79 to 1.30)	0.84 (0.65 to 1.10)	0.90 (0.69 to 1.18)	0.96 (0.73 to 1.27)	−0.40	0.69
Fatal coronary heart disease:							
No of cases	27	45	45	46	66		
Age adjusted	1.0	1.63 (1.02 to 2.62)	1.73 (1.08 to 2.78)	1.79 (1.12 to 2.87)	2.55 (1.65 to 3.95)	3.98	<0.0001
Multivariate†	1.0	1.57 (0.97 to 2.54)	1.60 (0.98 to 2.59)	1.60 (0.98 to 2.61)	2.21 (1.38 to 3.54)	3.15	0.0016
Adjusted for fibre intake‡	1.0	1.41 (0.87 to 2.31)	1.38 (0.83 to 2.28)	1.32 (0.79 to 2.22)	1.72 (1.01 to 2.90)	1.68	0.09

*Includes non-fatal myocardial infarction and fatal coronary heart disease.
†Model includes age (seven categories); body mass index (five categories); smoking habits (current smoker (number of cigarettes smoked), former smoker, never smoked); alcohol consumption (four categories); physical activity (fifths); history of hypertension or high blood cholesterol; family history of myocardial infarction before age 60; and profession.
‡Additionally adjusted for fibre intake adjusted for energy (continuous variable).

Table 2 shows the results for SFA intake.[28] As indicated above, the multivariate analysis for

[28] This is just the results from table 2 for SFA. The rest of table 2 (not shown) has results for cholesterol, Total fat, and Keys score. Table 3 (not shown) shows the results for linoleic and linolenic acids.

quintile 5 vs. quintile 1 of SFA-intake shows an increased relative risk (RR) for ***fatal*** CHD of 2.21 (1.38, 3.54). When an additional adjustment for fiber is included this drops to an RR of 1.72 (1.01, 2.90). Chowdhury and Siri-Tarino meta-analyses use incidence (vs fatality), when available. For incidence, both the multivariate and the multivariate+fiber did not reach statistical significance. 10 of the 20 studies only report death. If the HPFS researchers chosen to do so, the score reported in the Chowdhury and Siri-Tarino meta-analysis would have been quite different.

The last paragraph of the HPFS paper: "Meanwhile, a prudent approach for prevention of coronary disease consistent with the results of this study and other evidence is to recommend a reduced intake of saturated fat, cholesterol, and trans unsaturated fatty acids accompanied by an increased consumption of foods rich in fibre, including cereals, vegetables, and fruit."

Nutrients vs. Food. The HPFS paper emphasized how fiber attenuated so many of the results. One of their key messages was "Diets high in saturated fat and cholesterol are associated with an increased risk of coronary heart disease, but these adverse effects are at least in part explained explained by their low fibre content and associations with other risk factors." Or, to put it more simply, reduce animal foods and increase whole plant-based foods.

HPFS Study Grading

1) *Over-adjustment with Lipids*. **N**.
2) *Sufficient Test of SFA Guidelines*. **B**. Quintiles 1 and 2 had mean SFA-intake as % of Energy consumed of 7.2% and 9.5% - from table 1. This was the only study of the 20, in which exactly 2 quintiles met the SFA intake guidelines
3) *Homogeneity.* **C.** The study consisted of USA male health professionals, and were thus more likely to be eating a healthy diet, e.g. the mean SFA-intake as % of Energy in quintile 5 was just 14.8%.
4) *Food/Lifestyle Questionnaire*. **C**. The 1986 questionnaire asked about average frequency of intake over the previous year of specified portions of 131 foods. Serum cholesterol was self-reported by about 1/4 of participants. History at baseline of hypertension and high cholesterol was also self-reported.
5) *Missing Data in the Study.* **C**. Actual measured blood pressure, glucose levels, and serum cholesterol levels for all participants. Medication information to manage cholesterol. But given the timeframe and length of this study, it might not be important.
6) *Missing Data in the Paper*. **C**. Mean age of participants, and mean age per SFA-intake quintile. Since the age of participants extended to 75 y, results should have also been presented in 2 cohorts, e.g. 40-59 y, 60-75 y. Given the size of this study, a bivariate analysis with fiber and SFA intakes might have provided more insight into the relative importance of each.
7) *Confounders*. **B**. Without actual blood pressure measurement, history of hypertension might have resulted in an under adjustment. Without a measurement of glucose, some participants with glucose levels above 120 could have been admitted to the study. On the other hand, since the participants are health professionals, the glucose measurement is probably not a problem.
8) *Food vs. Nutrients*. **C**. Various information about food categories was presented in table 1, but no analysis of this was presented. I would have liked to see eggs as a separate category (especially given the results of Oxford Vegetarian study on egg intake).

Health and Lifestyle Survey (HLS) in Great Britain

Boniface DR, Tefft ME. Dietary fats and 16-year coronary heart disease mortality in a cohort of men and women in Great Britain. Eur.J Clin.Nutr. 2002;56:786-792

	RR (95% CI)
Siri-Tarino	1.37 (1.17, 1.60)
Chowdhury	1.04 (0.97, 1.11)

Both meta-analysis papers referenced exactly the same paper, but reported significantly different results. Chowdhury indicated a tiny, insignificant harm to SFA intake (1.04), and this did not reach statistical significance, whereas Siri-Tarino indicated significant harm (1.37), and this did reach statistical significance (i.e. 95% confidence interval above 1.0, specifically, 1.17 to 1.60).[29]

The HLS paper reported on the results for men and women separately. Here are the direct results from the paper using their multivariate analysis for relative risk of CHD death from **100g/week increase in SFA intake**:

Men	1.00 (0.86-1.18)	- OK for bacon/eggs for breakfast, prime rib for dinner.
Women	1.40 (1.09 - 1.79)	- Reduce significantly: butter, eggs, meat, chicken, etc.

I realize “Men are from Mars, and Women are from Venus”, but seriously . . .

Key Messages:

- Food intake and lifestyle only considered at the start of the 16 year study. One of the poorest in data gathering of all the studies.
- No accounting for Trans-fats or types of PUFA (e.g. omega-3’s). No info on total energy intake, fiber, protein, carbohydrates, or food categories (e.g. fruits, vegetables, fish, meat, etc.)
- Just 2 categories for smoking in multivariate adjustment: Moderate/Heavy smokers (≥10 cigarettes/day); Everyone else (i.e. never smoked, former smokers, <10 cigarettes/day).
- All other studies looked at fat intake as % of energy intake, but HLS only considered intake of grams of fat intake. Why might this matter? 68% of men (age 40-59) in the 5th quintile of SFA intake were in the “manual social class”, vs. 42% in the 1st quintile. Thus, men in the 5th quintile likely expended more energy in their work. In other words, if men were categorized by SFA intake as % of energy intake, like every other study, many men would have ended up in different quintiles. Even the authors note, “***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 underestimates.***”
- For women, the SFA intake per week was ~260g higher in the 5th quintile than the 1st quintile; thus, the RR of 5th to 1st quintile is likely significantly higher than 1.40.

About HLS

Started out by sending out Health and Lifestyle Survery in 1984-85 to a random sample of 9003 people in Great Britain. 73.5% response rate.

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[29] Perhaps, we should invite Gary Taubes to clarify the science for us.

"To demonstrate a possible effect of diet on subsequent CHD death it was necessary to exclude individuals whose diet was likely to have been influenced by awareness of a specific illness or condition itself carrying a raised CHD risk." This would seem to imply that anyone who knew about what foods might increase CHD risk were excluded. ***Really?!***

In particular, anyone *reporting* heart disease, diabetes, anti-hypertensive treatment, or being on a special diet were excluded. Most other studies determined this by examination.

"Information was obtained about general dietary habits through questions about the quantities and frequency of consumption of bread, butter, margarine, milk, coffee, tea, sugar in coffee, sugar in tea, and the frequency of consumption of 30 different food groups according to six categories ranging from never to more than once a day. The 30 food groups were selected in order to cover all commonly eaten foods and, in particular, all foods that make a significant contribution to dietary fat." The emphasis in this study is just to collect information about intake of fat.

After exclusions, the study ended up with 1,225 men and 1,451 women, ages 40-75. In each case, about 2/3 were from 40-59 years.

Table 3 CHD 16 y death rates (95% confidence intervals) according to fifths of intake of total fat, saturated fat, polyunsaturated fat and Keys' fat difference in men and women aged 40–75

		Fifth of dietary intake					
Type of dietary fat	*mean (s.d.) g/week*	*1 (lowest)*	*2*	*3*	*4*	*5 (highest)*	*P-value (trend)*
Men (n = 1225)							
Total fat	734.5 (240.8)	6.6% (3.8–10.5)	6.2% (3.5–10.0)	8.8% (5.6–13.0)	10.2% (6.7–14.8)	8.2% (5.1–12.3)	0.1928
Saturated fat	328.5 (130.0)	7.4% (4.4–11.4)	7.8% (4.8–11.9)	6.5% (3.8–10.4)	10.1% (6.6–14.5)	8.2% (5.1–12.4)	0.4706
Polyunsaturated fat	93.7 (45.7)	7.4% (4.5–11.5)	11.0% (7.4–15.6)	7.0% (4.1–11.0)	5.6% (3.1–9.2)	9.0% (5.7–13.3)	0.6611
Keys' fat difference: 2(saturated fat) − polyunsaturated fat	563.4 (255.7)	8.2% (5.1–12.4)	8.2% (5.1–12.4)	3.7% (1.7–6.8)	10.9% (7.3–15.5)	9.0% (5.7–13.3)	0.4364
Women (n = 1451)							
Total fat	523.2 (173.7)	1.4% (0.4–3.5)	2.7% (1.2–5.3)	4.1% (2.2–7.1)	6.2% (3.7–9.6)	5.2% (2.9–8.4)	0.0025
Saturated fat	240.2 (96.9)	2.4% (1.0–4.9)	1.7% (0.6–4.0)	3.4% (1.7–6.2)	6.2% (3.7–9.6)	5.8% (3.4–9.2)	0.0018
Polyunsaturated fat	63.1 (28.4)	2.4% (1.0–4.9)	5.2% (2.9–8.4)	3.8% (1.9–6.6)	3.8% (1.9–6.8)	4.4% (2.4–7.4)	0.4613
Keys' fat difference: 2(saturated fat) − polyunsaturated fat	417.3 (191.1)	3.1% (1.4–5.8)	1.0% (0.2–3.0)	4.1% (2.1–7.1)	5.2% (2.9–8.4)	6.2% (3.7–9.6)	0.0043

Table 2 Description of measures of potentially confounding variables

Measure	*Levels*	*Level 1*	*Level 2*	*Level 3*	*Level 4*
Alcohol RCP recommended weekly limits for men and women of 21 and 14 units, respectively[a]	4	Non-drinker	Up to half the RCP limit	More than half but not beyond the RCP limit	Greater than the RCP limit
Smoking light is ≤9, moderate/heavy is ≥10 cigs/day	2	Light, non- or ex-smokers	Moderate or heavy cigarette smokers		
Exercise number of episodes of 20 + min of moderate or vigorous activity in past 2 weeks[b]	2	None	One or more		
Body shape low BMI[g] is ≤25.0 in men and ≤23.8 in women[c]; low WHR[h] is ≤0.90 in men and ≤0.80 in women[d]	2	Lean (low BMI and low WHR)	Not lean		
Blood pressure (mm Hg)[e]	3	Normotensive (≤140/90)	Borderline (141/91 to 159/94)	Hypertensive (≥160/95)	
Social class based on UK Registrar General's Social Class classifications	2	Non-manual (I, II and IIIN)	Manual (IIIM, IV and V)		
Deprivation index[f] larger value implies greater deprivation	Continuous				

[a]Royal College of Physicians (1995). [b]White *et al* (1993). [c]Oshaug *et al* (1995). [d]Egger (1992). [e]WHO (1978). [f]Duncan *et al* (1999). [g]BMI (body mass index) = weight (kg)/height^2 (m^2). [h]WHR (waist-to-hip ratio) = waist(cm)/hips(cm).

In table 3, Men and Women were divided into quintiles by SFA intake per week in grams. Shown is the % of CHD deaths in each quintile for various fats over the 16 yr study period.- Does table 3 provide any useful info? The mean and SD intakes are interesting. For example, if mean energy intake of men was 2500 kcal/day, then the mean SFA intake would be about 16% per day. But the death % by quintile/fat-type really tells us nothing, for a couple of reasons: (1) no adjustments, and age range is significant (40-75); and, (2) It is based on absolute fat intake vs % fat of energy intake.

Besides age, what are confounders that the researchers adjust for. This is presented in table 2. Note the following:

- Smoking. Just 2 categories, and non-smokers, ex-smokers, and ≤10 cigarettes/day are in the same category.
- Exercise. 2 categories: none; and, one or more episodes of 20+ minutes of moderate or vigorous activity in past 2 weeks.
- Social Class. 2 categories: Manual and Non-Manual. I suspect the former category would include for men a waiter, a construction worker, and a coal miner. Yet the energy expenditure of each is different. And energy intake is not being accounted for in this study.

Table 4 Relation of behavioural, physical and demographic factors to saturated fat intake and survival by sex and age

	Fifth of saturated fat intake			*Survival status*		
Factor	*1 (lowest)*	*5 (highest)*	*P-value (trend)*	*Alive*	*dead — CHD (P-value)*	*Dead — other causes (P-value)*
Men aged 40–59 (n = 824)				*(n = 704)*	*(n = 39)*	*(n = 81)*
Mean saturated fat (g/week)	177	544	0.0000	325	360 (0.1095)	351 (0.1006)
Mean age (y)	48	50	0.0003	48	53 (0.0000)	53 (0.0000)
Proportion non-drinkers (%)	15	22	0.1634	18	33 (0.0161)	18 (0.8904)
Mean alcohol consumption amongst drinkers (units/week)	20.2	14.2	0.0118	17.1	13.3 (0.3233)	23.3 (0.0187)
Proportion moderate/heavy smokers (%)	23	42	0.0002	29	46 (0.0193)	45 (0.0025)
Proportion not participating in exercise activity (%)	70	88	0.0000	75	95 (0.0053)	83 (0.1447)
Proportion not of lean body shape (%)[a]	68	67	0.8741	70	86 (0.0752)	73 (0.7016)
Proportion hypertensive (%)	9.8	11.0	0.8690	9.1	23.1 (0.0043)	11.1 (0.5533)
Proportion manual social class (%)	42	68	0.0000	58	77 (0.0167)	56 (0.7339)
Mean deprivation index	− 0.3455	0.0576	0.4164	− 0.1929	0.6030 (0.1693)	0.3576 (0.1890)
Men aged 60–75 (n = 401)				*(n = 164)*	*(n = 59)*	*(n = 178)*
Mean saturated fat (g/week)	184	510	0.0000	331	326 (0.7937)	330 (0.9399)
Mean age (y)	66	68	0.0405	66	68 (0.0005)	69 (0.0000)
Proportion non-drinkers (%)	20	28	0.0362	26	34 (0.2230)	23 (0.5788)
Mean alcohol consumption amongst drinkers (units/week)	15.2	13.6	0.7770	14.6	12.3 (0.5156)	12.2 (0.2561)
Proportion moderate/heavy smokers (%)	20	34	0.0401	23	36 (0.0636)	32 (0.0630)
Proportion not participating in exercise activity (%)	82	87	0.3336	84	95 (0.0280)	89 (0.1170)
Proportion not of lean body shape (%)[b]	74	69	0.4522	70	94 (0.0048)	74 (0.5096)
Proportion hypertensive (%)	20.5	22.0	0.5689	14.0	27.1 (0.0232)	22.5 (0.0441)
Proportion manual social class (%)	58	66	0.6968	58	64 (0.3664)	67 (0.0629)
Mean deprivation index	− 0.0771	0.1064	0.7000	− 0.3358	− 0.1435 (0.7017)	0.0948 (0.2340)
Women aged 40–59 (n = 965)				*(n = 874)*	*(n = 14)*	*(n = 77)*
Mean saturated fat (g/week)	119	376	0.0000	228	264 (0.1574)	260 (0.0041)
Mean age (y)	48	49	0.0083	48	55 (0.0000)	53 (0.0000)
Proportion non-drinkers (%)	31	38	0.3317	33	36 (0.8058)	31 (0.7959)
Mean alcohol consumption amongst drinkers (units/week)	6.7	5.8	0.3106	6.1	6.3 (0.8993)	5.4 (0.4680)
Proportion moderate/heavy smokers (%)	24	40	0.0002	28	43 (0.2106)	43 (0.0038)
Proportion not participating in exercise activity (%)	69	80	0.0040	72	93 (0.0806)	87 (0.0038)
Proportion not of lean body shape (%)[c]	68	62	0.4124	63	91 (0.0571)	77 (0.0627)
Proportion hypertensive (%)	6.7	7.3	0.8529	5.5	28.6 (0.0003)	13.0 (0.0084)
Proportion manual social class (%)	47	56	0.1240	52	57 (0.6875)	61 (0.1169)
Mean deprivation index	− 0.9001	0.0056	0.0044	− 0.4796	1.2789 (0.0604)	− 0.0021 (0.2491)
Women aged 60–75 (n = 486)				*(n = 307)*	*(n = 43)*	*(n = 136)*
Mean saturated fat (g/week)	140	409	0.0000	245	293 (0.0023)	278 (0.0010)
Mean age (y)	66	67	0.0406	66	69 (0.0000)	68 (0.0000)
Proportion non-drinkers (%)	45	54	0.1582	49	56 (0.4156)	53 (0.4659)
Mean alcohol consumption amongst drinkers (units/week)	4.2	4.4	0.7035	5.2	3.7 (0.3304)	4.0 (0.1985)
Proportion moderate/heavy smokers (%)	13	17	0.0506	14	26 (0.0503)	29 (0.0001)
Proportion not participating in exercise activity (%)	86	96	0.0097	89	98 (0.0733)	92 (0.3372)
Proportion not of lean body shape (%)[d]	83	82	0.5571	79	71 (0.3859)	78 (0.9460)
Proportion hypertensive (%)	20.0	17.3	0.4522	18.2	25.6 (0.2519)	17.6 (0.8808)
Proportion manual social class (%)	53	64	0.1105	54	83 (0.0004)	66 (0.0276)
Mean deprivation index	− 0.4591	0.2857	0.0544	− 0.2537	1.2823 (0.0046)	0.7146 (0.0069)

[a] $n = 498$ (426 alive; 28 dead — CHD; 44 dead — other causes), [b] $n = 257$ (113 alive; 33 dead — CHD; 111 dead — other causes), [c] $n = 618$ (560 alive; 11 dead — CHD; 47 dead — other causes), [d] $n = 322$ (211 alive; 28 dead — CHD; 83 dead — other causes).

With table 2, it is possible to examine table 4 and see some of the challenges in being able to discern any info from this study. For example, in men 40-59, the difference in "manual social class" suggests that quintile 5 probably has a higher expenditure of energy. This implies if this study had classified men by SFA as % of Energy, like all other studies, many men would have been in different quintiles. Alcohol intake may also create a problem. Men in quintile 1 of SFA intake probably have lower % of energy intake, and thus alcohol intake (which is quite high) may be even higher when viewed in the context of % of energy, and have a serious adverse health effect.

The net results of this study are presented in table 5, which I discussed at the beginning of this analysis; i.e., with the multivariate analysis for relative risk of CHD death from **100g/week increase in SFA intake**: Men 1.00 (0.86-1.18); Women 1.40 (1.09 - 1.79).

The authors note: "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 underestimates.***"

HLS Study Grading

1) *Over-adjustment with Lipids*. **No**.
2) *Sufficient Test of SFA Guidelines*. **F**. Used absolute SFA intake vs. % of energy intake like all the other studies. Plus, mean SFA intake and SD indicate unlikely that any significant % of study subjects had an SFA intake < 10%.
3) *Homogeneity.* **F.** But can't be sure, based on data provided.
4) *Food/Lifestyle Questionnaire*. **F**. Focused just on fat, with no checks and follow-up.
5) *Missing Data in the Study.* **F**. No blood work. Apparently, no examination at the start of the study. No accounting for Trans-fats or types of PUFA. No info on total energy intake, fiber, protein, carbohydrates, or food categories (e.g. fruits, vegetables, fish, meat, etc.). Given the age range, analysis should have been split into 2 age cohorts, 40-59 y, and 60-75 y.
6) *Missing Data in the Paper*. **D**. Table 5 should have been presented by quintile.
7) *Confounders*. **D**. Categories in some confounders too few, e.g. smoking, exercise.
8) *Food vs. Nutrients*. **F**. Focus was only on fat, and, actually only some kinds.

There is much I don't understand about this study: (1) Why the researchers structured it this way; (2) Why it was approved and funded? (3) Why it was continued? (4) Why it was written up? (5) Why the peer reviewers thought it worthwhile to publish? and, (6) ***Why would any one think this was a reasonable study to include in a meta-analysis?***

Lipid Research Clinics (LRC) Prevalence Follow-up Study

Esrey KL, Joseph L, Grover SA. Relationship between dietary intake and coronary heart disease mortality: lipid research clinics prevalence follow-up study. J Clin.Epidemiol. 1996;49:211-216.

	RR (95% CI)
Siri-Tarino	0.97 (0.80, 1.18)
Chowdhury	1.14 (1.01, 1.27)

Quite a discrepancy between Chowdhury and Siri-Tarino, although both cited the exact same study. Chowdhury indicates that increased SFA intake was harmful, and this did reach statistical significance. ***Although Chowdhury indicates that adjustment did not include serum cholesterol, it does (both models 2 and 3)***.

There is somewhat of an explanation for the discrepancy between Siri-Tarino and Chowdhury. The LRC study divided the studied population into 2 groups by age, one 30-59, and the other 60-79, at the beginning of the study. From the abstract, the corresponding RR (95% CI) for saturated fat was 1.11 (1.04 - 1.08) for the 30-59 age group. But for the 60-79 age group, there was no association with any of the dietary components, including SFA intake.

From the paper, “Briefly, from 1972 to 1976, a sample of individuals who had been screened (Visit 1) as part of a cross-sectional survey of various North American populations was asked to take part in a second clinic visit (Visit 2). All those aged 30 years and older were subsequently followed for an average of 12.4 years, until June 1987, to determine their vital status. This report is restricted to 4904 individuals participating in the follow-up study who were initially selected for Visit 2 as part of a random subsample of those screened at Visit 1. A total of 355 individuals were excluded from our analyses for one or more of the following reasons: taking lipid-lowering medications (n = 40), having a history of cardiovascular disease (n = 213), older than 79 years (n = 25), or having missing values for any of the risk factors tested in the multivariate analysis (n = 92). Among the final sample of 4546 individuals, 92 (2,0%) died of coronary heart disease during the follow-up period. . . . Among those aged 30 to 59 years (n = 3925) there were 186 total deaths, including 52 coronary deaths. Among those aged 60 to 79 years (n = 621), there were 192 total deaths, including 40 coronary deaths.”

Note a few factors. The 60 to 79 group was about 15% the size of 30 to 59 one; (2) 253 people were excluded from the study due to having a history of CVD or on lipid-lowering medications - these conditions more likely in the 60 to 79 group, but the paper doesn’t provide the data. We also don’t know how many of either group were put on lipid-lowering medications during the 12.5 year of follow-up. The 25% of the 60 to 79 group that died from non-CHD causes might have had CHD, but other causes resulted in their deaths. And, individuals who had the worst diets and lifestyles through their lives are also the ones most likely to die from CHD before reaching 60. Thus, the results for the 60 to 79 group are not surprising.

“Visit 2 consisted of an extensive examination to record the medical and family history of each subject, including use of medications, blood pressure measurement, lipid and lipoprotein measurements, resting and exercise electrocardiograms, and anthropometric variables. . .Nutrient intake was assessed using a 24-hour dietary recall, administered by a trained nutritionist.”

The endpoint was CHD death within the 12yr follow-up. Note that there were no exams/interviews after the initial data collection.

Table 1 covers the non-nutritional risk factors, and outcomes. To convert the cholesterol numbers from mmol/L (in table) to the more common use in the US of mg/dL, multiply by 38.61.[30] For example, the LDL figure in the 1st column of 4.12 ± 0.94 mmol/L converts to 159 ± 36 mg/dL.

TABLE 1. Coronary heart disease risk factors of 4546 men and women included in the North American Lipid Research Clinics Prevalence Follow-Up Study: 1972 to 1976

	30 to 59 years of age		60 to 79 years of age	
Risk factor	**CHD death (*n* = 52)**	**No CHD death (*n* = 3873)**	**CHD death (*n* = 40)**	**No CHD death (*n* = 581)**
Age (years)	50.6 ± 6.6[a]	43.1 ± 8.4***	68.4 ± 5.5	66.3 ± 4.6*
Male sex (%)	38 (73.1)	2033 (52.5)**	27 (67.5)	255 (43.9)**
Current smokers (%)	31 (59.6)	1374 (35.5)***	10 (25.0)	124 (21.3)
Body mass index (kg/m^2)	27.7 ± 6.3	25.4 ± 4.1**	26.3 ± 4.7	25.5 ± 4.0
Total serum cholesterol (mmol/liter)	6.01 ± 0.96	5.25 ± 0.98***	5.91 ± 0.87	5.75 ± 1.05
High-density lipoproteins (mmol/liter)	1.06 ± 0.28	1.34 ± 0.40***	1.39 ± 0.70	1.50 ± 0.44
Low-density lipoproteins (mmol/liter)	4.12 ± 0.94	3.41 ± 0.89***	4.09 ± 0.92	3.82 ± 0.98
Systolic blood pressure (mmHg)	135 ± 24	120 ± 16***	149 ± 24	140 ± 21*

[a]Mean ± standard deviation.
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.
Abbreviation: CHD, Coronary heart disease.

Table 2 covers the dietary intakes and results without any adjustment. On average, the study group was eating a high-fat (high SFA, low PUMA), high-cholesterol[31] diet. Higher intakes of Fat, SFA, and MUFA were associated increased risk of CHD death, whereas higher intakes of carbohydrates was associated with lower risk of CHD death.

Tables 3 and 4 provide the multivariate results. "Three models were used as a base for our multivariate analyses. Model 1 included age, sex, and energy intake as independent variables. The second model included the variables of the first model, plus ***serum lipids (total cholesterol and HDL)***. Model 3 included all the independent variables of the second model, plus the established non-dietary coronary heart disease risk factors: systolic blood pressure, smoking, glucose intolerance, and body mass index." This is somewhat disappointing. It would have been interesting to see a modified model 3, i.e. one that excluded serum lipids. In other words, in my opinion, model 1 is under-adjusted and models 2 and 3 are over adjusted. Nevertheless, the model 2 and 3 adjustments do not appear to affect the results that much.

The same associations in the unadjusted numbers for 30-59 group continue to hold in the multivariate analysis. The association with MUFA is likely due to higher meat intake. Unlike some other studies, the benefits of higher PUFA (usually viewed in the context of substitution of SFA) and harm of higher cholesterol intake did not show up in this study.

[30] For a quick mental approximation, just multiply by 40. If you want a little more accuracy, then subtract 3%.

[31] 5000 kJ = 1195 kcal. Thus, 253 mg of cholesterol per 5000 kJ converts to 212mg/1000kcal

TABLE 2. Dietary intake, as measured by the 24-hour recall, of 4546 men and women included in the North American Lipid Research Clinics Prevalence Follow-Up Study: 1972 to 1976

Dietary intake	30 to 59 years of age		60 to 79 years of age	
	CHD death (n = 52)	No CHD death (n = 3873)	CHD death (n = 40)	No CHD death (n = 581)
Total energy intake				
(kJ)	9047 ± 3643[a]	9201 ± 4043	8580 ± 3030	7742 ± 2661
(kcal)	2162 ± 870	2199 ± 966	2051 ± 724	1850 ± 636
Total fat				
(g)	102.6 ± 45.9	98.9 ± 52.7	88.5 ± 39.9	79.1 ± 33.4
% of energy	42.5 ± 8.7	39.8 ± 9.0*	38.0 ± 8.4	38.0 ± 8.3
Saturated fat				
(g)	40.8 ± 19.9	37.7 ± 21.6	32.7 ± 17.1	29.9 ± 14.1
% of energy	16.8 ± 4.7	15.1 ± 4.3**	13.8 ± 3.9	14.3 ± 4.2
Monounsaturated fat				
(g)	40.9 ± 19.9	38.6 ± 22.1	35.1 ± 16.9	30.6 ± 14.3
% of energy	16.9 ± 4.4	15.5 ± 4.2*	15.1 ± 4.0	14.7 ± 4.0
Polyunsaturated fat				
(g)	14.3 ± 9.0	15.8 ± 10.6	14.5 ± 9.1	12.9 ± 7.4
% of energy	6.0 ± 3.1	6.5 ± 3.3	6.4 ± 3.2	6.2 ± 2.9
Dietary cholesterol				
(mg)	427 ± 253	416 ± 305	423 ± 314	355 ± 236
per 5000 kJ	253 ± 198	233 ± 163	250 ± 175	234 ± 145
Carbohydrate				
(g)	201.8 ± 98.6	221.2 ± 104.5	218.5 ± 92.7	195.2 ± 78.7
% of energy	37.1 ± 9.8	40.7 ± 10.1**	42.9 ± 10.1	42.4 ± 9.6
Protein				
(g)	86.1 ± 36.6	83.6 ± 37.8	77.4 ± 40.3	70.2 ± 25.9
% of energy	16.5 ± 5.1	15.8 ± 5.0	15.5 ± 6.5	15.7 ± 4.6
Alcohol				
(g)	12.5 ± 25.4	12.8 ± 28.6	10.2 ± 21.2	11.0 ± 19.4
% of energy	3.9 ± 7.7	3.7 ± 7.1	3.7 ± 8.4	3.8 ± 6.3

[a]Mean ± standard deviation.
*$p < 0.05$.
**$p < 0.01$.
Abbreviation: CHD, Coronary heart disease.

TABLE 3. Cox regression estimates of the effect of dietary intake measured at baseline on coronary heart disease death among 3925 men and women 30 to 59 years of age after 12.4 years follow-up in the North American Lipid Research Clinics Prevalence Follow-Up Study

Variable	Model 1 (adjusted for age, sex, energy intake)			Model 2 (adjusted for age, sex, energy intake, serum lipids[a])			Model 3 (adjusted for age, sex, energy intake, serum lipids, and other risk factors[b])		
	Estimate	RR	(95% CI)	Estimate	RR	(95% CI)	Estimate	RR	(95% CI)
% Fat									
Total	0.044**	1.04	(1.01–1.08)	0.043**	1.04	(1.01–1.08)	0.043*	1.04	(1.01–1.08)
Saturated	0.104**	1.11	(1.04–1.18)	0.095**	1.10	(1.03–1.17)	0.103**	1.11	(1.04–1.18)
Monounsaturated	0.095**	1.10	(1.03–1.17)	0.094**	1.10	(1.03–1.18)	0.080*	1.08	(1.01–1.16)
Polyunsaturated	−0.040	0.96	(0.88–1.05)	−0.027	0.97	(0.89–1.07)	−0.014	0.99	(0.90–1.08)
% Carbohydrate	−0.034**	0.97	(0.94–0.99)	−0.040**	0.96	(0.93–0.99)	−0.036*	0.96	(0.94–0.99)
% Protein	0.020	1.02	(0.97–1.08)	0.013	1.01	(0.96–1.07)	0.011	1.01	(0.95–1.07)
% Alcohol + alcohol^2	−0.019	0.98	(0.92–1.05)	0.001	1.00	(0.94–1.06)	0.0001	1.00	(0.95–1.07)
Cholesterol (10 mg) per 5000 kJ	0.004	1.00	(0.99–1.02)	0.006	1.01	(0.99–1.02)	0.004	1.00	(0.99–1.02)

[a]Serum lipids (mmol/liter) included total serum cholesterol and high-density lipoproteins.
[b]Other risk factors were systolic blood pressure (mmHg), cigarette smoking status (current smoker/nonsmoker), body mass index (kg/m^2), and glucose intolerance (present/absent).
*$p < 0.05$.
**$p < 0.01$.
RR = Relative risk for coronary heart disease mortality, defined as $\exp(\beta)$, associated with a 1-unit increase in the dietary variable; 95% CI = 95% confidence interval, defined as $\exp(\beta \pm 1.96\ \mathrm{SE})(z_1 - z_2)$, where SE is the standard error of β, and z_1 and z_2 represent the two levels of the dietary variable being compared; % = percentage of total energy provided by the dietary variable.

That there were no associations with diet (other than alcohol) in the 60-79 group is not surprising, as previously discussed.

TABLE 4. Cox regression estimates of the effect of dietary intake measured at baseline on coronary heart disease death among 621 men and women 60 to 79 years of age after 12.4 years follow-up in the North American Lipid Research Clinics Prevalence Follow-Up Study

	Model 1 (adjusted for age, sex, energy intake)			Model 2 (adjusted for age, sex, energy intake, serum lipids[a])			Model 3 (adjusted for age, sex, energy intake, serum lipids, and other risk factors[b])		
Variable	**Estimate**	**RR**	**(95% CI)**	**Estimate**	**RR**	**(95% CI)**	**Estimate**	**RR**	**(95% CI)**
% Fat									
Total	−0.0004	1.00	(0.96–1.04)	−0.002	1.00	(0.96–1.04)	−0.011	0.99	(0.95–1.03)
Saturated	−0.031	0.97	(0.89–1.05)	−0.026	0.97	(0.90–1.06)	−0.038	0.96	(0.88–1.05)
Monounsaturated	0.025	1.03	(0.95–1.11)	0.019	1.02	(0.94–1.11)	−0.005	1.00	(0.91–1.08)
Polyunsaturated	0.006	1.01	(0.91–1.11)	−0.004	1.00	(0.90–1.10)	−0.004	1.00	(0.90–1.10)
% Carbohydrate	0.004	1.00	(0.97–1.04)	0.003	1.00	(0.97–1.04)	0.016	1.02	(0.98–1.05)
% Protein	0.017	1.02	(0.94–1.10)	0.015	1.02	(0.94–1.10)	0.0002	1.00	(0.93–1.08)
% Alcohol + alcohol[2]	−0.114**	0.89	(0.84–0.94)	−0.116**	0.89	(0.83–0.95)	−0.124**	0.88	(0.83–0.95)
Cholesterol (10 mg) per 5000 kJ	0.011	1.01	(0.99–1.03)	0.011	1.01	(0.99–1.03)	0.006	1.01	(0.98–1.03)

[a]Serum lipids (mmol/liter) included total serum cholesterol and high-density lipoproteins.
[b]Other risk factors were systolic blood pressure (mmHg), cigarette smoking status (current smoker/nonsmoker), body mass index (kg/m^2), and glucose intolerance (present/absent).
**$p < 0.01$.
RR = Relative risk for coronary heart disease mortality, defined as $\exp(\beta)$, associated with a 1-unit increase in the dietary variable; 95% CI = 95% confidence interval, defined as $\exp(\beta \pm 1.96\ \mathrm{SE})(z_1 - z_2)$, where SE is the standard error of β, and z_1 and z_2 represent the two levels of the dietary variable being compared; % = percent of total energy provided by the dietary variable.

Looking at tables 3 and 4, I don't see how either Siri-Tarino or the Chowdhury scores for this study were reasonably derived, although the Chowdhury one is the closest one, and does show a statistically significant positive association with SFA intake and CHD death.

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.*"

LRC Study Grading

1) *Over-adjustment with Lipids*. **YES**. Model 1 adjusted for just age, sex and energy intake, whereas models 2 and 3 included adjustment for serum cholesterol (a likely over-adjustment). It would have been useful to see the model 3 adjustments, but without serum cholesterol. Nevertheless, the SFA results for all 3 models for the 30-59 age group were about the same.
2) *Sufficient Test of SFA Guidelines*. **C**. The mean intake of SFA was ~15.5% with an SD of ~4.4% for the 30-59 age group. This compares to 16.7% (SD: 2.6) in the Western Electric Study. The mean and SD suggest that there were some reasonable percentage of the study group eating a diet <= 10% SFA. But we really can't tell for sure.
3) *Homogeneity.* **D.** Men and women were included in the study. The participants were drawn from the United States and Canada. The study consisted of people eating the standard diet.
4) *Food/Lifestyle Questionnaire*. **D**. "Nutrient intake was assessed using a 24-hour dietary recall, administered by a trained nutritionist." This was done just once, at the beginning of the study. Blood was collected at the beginning to measure cholesterol, and an extensive exam was done. But there was no subsequent follow-up over the following 12 years. So no way

to assess any changes in diet. Other than smoking, no lifestyle data (e.g. physical activity level, education, socio-economic status) were collected.

5) *Missing Data in the Study.* **D**. There were no updates in dietary intake and blood work during the study period. No information on Trans-fats. No lifestyle data (other than smoking) collected.
6) *Missing Data in the Paper*. **D**. The paper did not present the characteristics (dietary/lifestyle measurements) by SFA intake level (e.g. by tertile). No information presented on fiber, PUMA/SFA ratio, carbohydrate breakdown, etc.
7) *Confounders*. **D**. Without knowing the characteristics by SFA intake level, it is not possible to make this judgment.
8) *Food vs. Nutrients*. **F**. No information about the Food consumed.

Israeli Ischemic Heart Disease (IIHD) Study

Goldbourt U, Yaari S, Medalie JH. Factors predictive of long-term coronary heart disease mortality among 10,059 male Israeli civil servants and municipal employees. A 23-year mortality follow-up in the Israeli Ischemic Heart Disease Study. Cardiology. 1993;82:100-121.

	RR (95% CI)
Siri-Tarino	0.86 (0.56, 1.35)
Chowdhury	0.90 (0.65, 1.24)

Chowdhury indicates that this study did include an adjustment for lipids (i.e. *serum cholesterol*). As indicated in the above scoring, the "beneficial" (indicated by an RR < 1.0) effects of SFA did not reach statistical significance.

Directly from the abstract: "Over 10,000 male civil servants and municipal employees in Israel, aged 40 years and above, underwent an extensive clinical, biochemical, anthropometric, sociodemographic and psychosocial evaluation in 1963. 1965 and 1968. Follow-up for mortality was continued through 1986. Over 23 years, a number of previously established risk factors for coronary heart disease (CHD) incidence were found to predict mortality. The long-term follow-up assisted in illustrating temporal patterns. A single casual assessment of blood pressure retained high prediction for long-term mortality. Blood lipids, while significantly associated with both coronary and all-cause mortality, exhibited a small contribution to the latter, when compared to hypertension, cigarette smoking habits and diabetes. ***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, since the results were adjusted for serum cholesterol, we can't draw any conclusions about SFA intake effects on CHD death.

All data was collected in 1963. There were follow-ups in 1965 and 1968, but these did not include updates on food intake. The cholesterol levels assessed in 1963 are what is used in the paper.

Table 2. CHD and total mortality, 1963–1986 in six ethnic-geographic strata defined by area of birth

Area of birth	Subjects	Person-years of follow-up	CHD mortality			Total mortality		
			n	rates		n	rates	
				crude	age-adjusted		crude	age-adjusted
Israel[a]	1,431	28,427	172	60.5	60.6	529	186.1	186.0
Eastern Europe	1,928	38,127	258	67.7	57.9	750	196.7	166.9
Balkan countries	1,735	34,777	214	61.5	57.8	653	187.8	174.6
Central Europe	1,374	27,952	156	55.8	55.5	446	159.6	158.6
North Africa	1,219	25,439	107	42.2	51.8	395	155.8	202.5
Mideast	2,372	49,349	191	38.7	42.2	700	141.8	153.6
Total	10,059	203,982	1,098	53.8	53.8	3,473	170.3	170.3

[a] Pre-1948 borders of League of Nations British Mandate on Palestine.
Rates are directly age-adjusted to the overall study age distribution, per 10,000 person-years of follow-up.

Most interestingly, "The sampling aimed at obtaining approximately equal numbers of study subjects born in five different geographic-cultural Jewish immigrant groups, as well as Jews born in the pre-1948 British Mandate of Palestine. Those invited to participate included 5/7 of all Jewish men, aged 40 and over, born in central Europe (FRG, Czechoslovakia. Hungary. Austria and Switzerland), 1/4 of eastern European born (USSR and Poland, including those born during the short independence period of the Baltic republics). 5/6 of those born in the Balkan countries (southeastern Europe) all of those born in the pre-1948 borders of British-dominated Palestine, mostly within the post-1948 borders of independent Israel, and the middle-eastern Asian countries as well as all such Jewish male employees born in northern Africa (Morocco. Algeria. Tunisia. Libya and Egypt)."

The mortality rates for the different ethnic groups is shown in table 2. It would be nice to know the differences in diet composition in these groups. But this is not available in the paper, nor could I find it in other papers that I looked at. However, we do from other studies that SFA intake is lower in the middle-eastern Asian countries and North African countries compared to the others in the groups. Also, the build-up of cardiovascular disease is a life-long process, and that immigrants to country adjust slowly to the common diet patterns of their new country. Thus, the data in table 2 is not surprising.

Table 3. CHD and total mortality, 1963–1986 by percentiles of risk factors

Deciles	Mortality							
	SBP		DBP[a]		total cholesterol		% cholesterol in HDL	
	CHD	total	CHD	total	CHD	total	CHD	total
1	25	100			36	149	105	228
2	33	129	33	129	35	150	85	199
3	35	136			32	149	64	177
4	36	116	33	128	44	166	58	168
5	44	153			44	142	59	166
6	46	145	44	149	49	156	43	145
7	50	161			57	173	47	155
8	61	190	59	173	68	178	36	156
9	82	217			79	204	25	141
10	128	357	96	266	98	233	27	142

Rates are age adjusted per 10,000 person-years of follow-up.
[a] Approximate quintiles (see methods).

Table 3 has mortality data by percentiles of risk factors. Note that the rates are age adjusted per 10,000 person-years of follow-up. For total cholesterol (mg/dl), the deciles are defined as: < 161, 161-176, 177-187,188-197,198-206, 207-216, 217-227, 228- 241, 242-260, and >260. For percent cholesterol in HDL fraction: <11.7, 11.7-13.5, 13.5-14.9, 14.9-16.1, 16.1-17.3, 17.3-18.7, 18.7-20.2, 20.2-22.3, 22.3-25.5, and >25.5%. For SBP: <114, 114-118, 119-123, 124-127, 128-130, 131-137, 138-140, 141-148, 149-162, and >162.

Figure 1 looks at the combination of SBP and TC. From this chart, one should keep TC<198 and SBP<140. Figure 2 looks at the combination of TC and %HDL. Unfortunately, the study does not include LDL data (which is a better predictor of CHD). Some favor non-HDL choles-

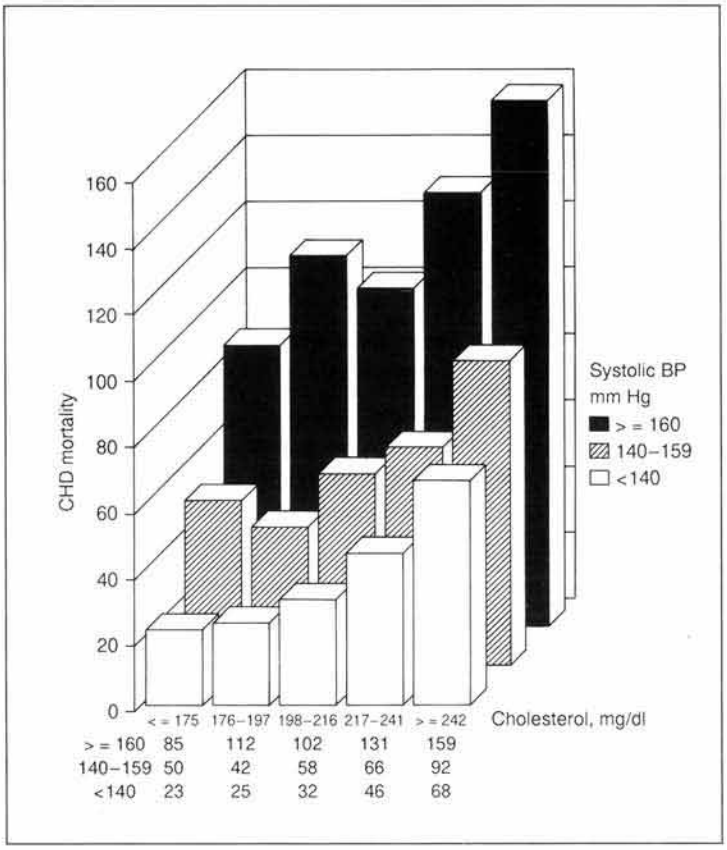

Fig. 1. Age-adjusted 23-year CHD mortality in quintiles of cholesterol, divided according to 'normal' (<140), 'borderline' (140–159) and elevated (≥160 mm Hg) levels of SBP. Rates per 10,000 person-years.

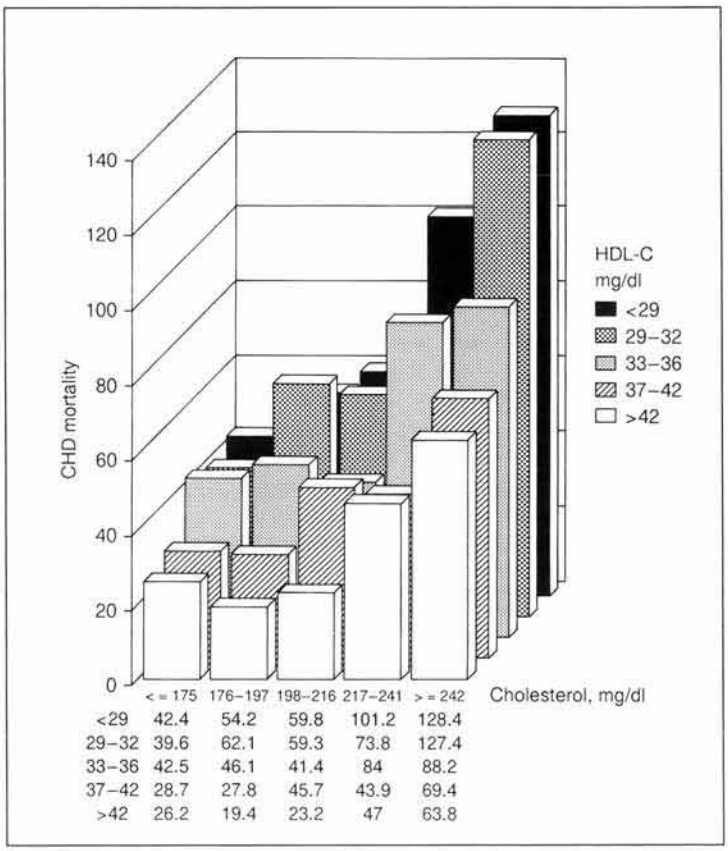

Fig. 2. Age-adjusted 23-year CHD mortality in quintiles of HDL cholesterol by quintiles of total cholesterol. Rates per 10,000 person-years.

terol (i.e. TC-HDL). Looking at figure 2 in this context, one should keep non-HDL cholesterol < 110.

Table 5. CHD and total mortality by estimated intake of dietary nutrients 1963–1986

Quintiles	Saturated fat intake				Linoleic acid		P/S ratio		M/S ratio	
	absolute		as percent of fat							
	CHD	total	CHD	total	CHD	total	CHD	total	CHD	total
1	61	192	48	170	63	199	57	188	58	183
2	56	173	55	163	55	169	58	174	57	166
3	54	172	53	165	54	166	53	166	53	168
4	50	155	57	173	51	166	52	157	53	162
5	49	161	58	182	47	155	49	169	50	175

P/S = Ratio of linoleic (polyunsaturated) to saturated fatty acid intake, M/S = ratio of oleic (monounsaturated) to saturated fatty acid intake.

Rates are age-adjusted by 10,000 person-years of follow-up.

Table 5 looks at mortality w.r.t. the components of fat. But it looks at SFA different than all the other studies that I have looked at. "Absolute" is grams of SFA per week, and SFA percent refers to percent of total fat (and not % total energy, as other studies do). Intake quintiles: for SFA (g/week), < 131, 131- 173, 173-213, 214-267, and >=267; SFA intake as % of total fat: <27.6, 27.6-30.6, 30.6-33.3, 33.3-36.4, and >=36.4%; linoleic acid intake (g/week): <82, 82-114, 115-146,147-192, and >= 192: linoleic acid intake as a fraction of the saturated fat intake (P/S ratio): <0.47, 0.47-0.62, 0.62-0.76, 0.76- 0.96, and >=0.96; and oleic acid intake as a fraction of the saturated fat intake (M/S ratio): <0.93, 0.93-1.02, 1.02-1.12, 1.12-1.26, and >=1.26.

Table 5 is very frustrating. The paper does not give data on total energy intake per day, let alone energy intake intake per SFA quintile. Thus, it is difficult to relate this study to others. Hypothetically, consider two men each consuming the identical number of calories and exactly the same SFA intake, eg 12% of total calories. But suppose one man's intake of total fat is

Table 6. Multivariate analysis of CHD and all-cause mortality, 1963–1986

Risk factor	CHD mortality (723 deaths)		All-cause mortality (2,233 deaths)[a]		Difference associated with RR
	RR	95% CI	RR	95% CI	
Age	2.02	1.80–2.26	2.31	2.07–2.35	10 years
SBP	1.50	1.42–1.59	1.40	1.35–1.45	20 mm Hg
Smoking	1.35	1.22–1.50	1.42	1.34–1.51	11–20 cigs/day vs. never
Cholesterol					
Total	1.29	1.20–1.39	1.07	1.03–1.12	40 mg/dl
HDL	1.36	1.25–1.49	1.09	1.04–1.14	10 mg/dl (reduced)
Diabetes	2.73	2.16–3.44	2.16	1.86–2.50	previously known or newly diagnosed
History of MI	5.26	3.94–7.01	2.61	2.08–3.27	verified vs. none or refuted
Angina pectoris	1.48	1.11–1.98	1.44	1.19–1.73	definite vs. none

RR = Relative risk; CI = confidence interval.

[a] RRs for total mortality adjusted also for presence of initial malignant disease.

33% and the other's is 44% of total calories. This would put one man in quintile 1 of this study and the other in quintile 5. Whereas, if both men were in the MALMO study, both would be in quintile 1 of SFA intake.

Table 6 is the multivariate analysis, but doesn't include dietary intake.

What do the authors have to say about dietary intake and CHD mortality:

"Upon examination of the above-mentioned dietary fat intake-CHD mortality associations in multivariate analysis, the adjustment of each of these associations for serum cholesterol eliminated the statistical significance, and the age- and cholesterol-adjusted RRs have approached 1 (data not tabulated)."

IIHD Study Grading

1) *Over-adjustment with Lipids*. **Y**. SFA intake was divided into quintiles (w.r.t. absolute g/week and % of total fat). Age adjusted and fully adjusted results (which included serum cholesterol) were presented.
2) *Sufficient Test of SFA Guidelines*. **F**. The SFA quintiles were based on % of total fat, and not % of Total Energy.
3) *Homogeneity.* **B.** Although all the men lived in Israel, they chose men who had immigrated from different regions outside of Israel. However, no dietary data was presented on this basis.
4) *Food/Lifestyle Questionnaire*. **D**. Dietary intake taken in an interview in 1963. Subjects also underwent electrocardiographic, biochemical, blood and genetic (blood group) testing. Repeat examination were done in 1965 and 1968. But dietary intake and cholesterol levels were all based on the data collected in 1963.
5) *Missing Data in the Study.* **D**. There were no updates in dietary intake and blood work from 1968 through 1986 (the end of the study).
6) *Missing Data in the Paper*. **F**. The paper did not present the characteristics (dietary/lifestyle measurements) by SFA quintile. And, the SFA quintiles were based on % of Fat (versus % of total energy intake). No information presented on fiber, carbohydrate breakdown, etc. The paper did not present an adjustment without serum cholesterol.
7) *Confounders*. **D.** Without knowing the characteristics by SFA quintile, it is not possible to make this judgment.
8) *Food vs. Nutrients*. **F**. No information about the Food consumed.

Nurses' Health Study (NHS) Study

Oh K, Hu FB, Manson JE, Stampfer MJ, Willett WC. Dietary fat intake and risk of coronary heart disease in women: 20 years of follow-up of the nurses' health study. Am J Epidemiol. 2005;161:672-679.

Hu FB, Stampfer MJ, Manson JE, et al. Dietary fat intake and the risk of coronary heart disease in women. N Engl J Med 1997;337:1491–9.

Both Chowdury and Siri-Tarino used the 2005 paper in their meta-analysis of SFA/CHD. The 2005 paper referenced the earlier 1997 NHS paper, which neither used. The 1997 paper has some data that was not made available in the 2005 paper. The 1997 paper covers the 1st 14 years of the study. So, I think it too is useful.

Chowdhury and Siri-Tarino.

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

Key Messages

- 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.
- 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: Check out this link: A DOSE OF SAFFLOWER OIL EACH DAY MIGHT HELP KEEP HEART DISEASE AT BAY.

- 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.

About NHS

"The Nurses' Health Study was initiated in 1976 when 121,700 female registered nurses aged 30–55 years completed a mailed questionnaire about their lifestyle factors and medical history, including previous cardiovascular disease, cancer, diabetes, hypertension, and high cholesterol levels. Follow-up questionnaires have been sent to these women every 2 years to update information and identify newly diagnosed major illnesses. A food frequency questionnaire was first administered in 1980. In this analysis, we included participants who returned the 1980 questionnaire and excluded those who left 10 or more food items blank or whose total energy intake was implausible (n = 5,579), and those who had a history of cardiovascular disease (angina, myocardial infarction, stroke, other cardiovascular disease; n = 1,645), cancer (n = 3,610), diabetes (n = 1,410), or **hypercholesterolemia (n = 4,269)** before June 1, 1980; women may have changed their diet because of the presence of these conditions. After these exclusions, data on 78,778 women remained in the analysis." Subsequent food frequency questionnaires were sent out in 1986, 1990, 1994, and 1998.

From the 2005 abstract:
Polyunsaturated fat intake was inversely associated with CHD risk (multivariate RR for the highest vs. the lowest quintile 0.75, whereas trans-fat intake was associated with an elevated risk of CHD 1.33. No mention of Sat-Fat in the abstract, but there is in the article.

One fascinating aspect of this study is that dietary fat intake did change over time (figure 1). "From 1980 to 1998, the average intake of total fat decreased from 39.0 percent to 29.0 percent, saturated fat intake decreased from 15.6 percent to 9.4 percent, monounsaturated fat intake decreased from 16.0 percent to 11.5 percent, and trans-fat intake decreased from 2.2 percent to 1.6 percent. Polyunsaturated fat intake increased from 5.3 percent to 5.6 percent (figure 1)."

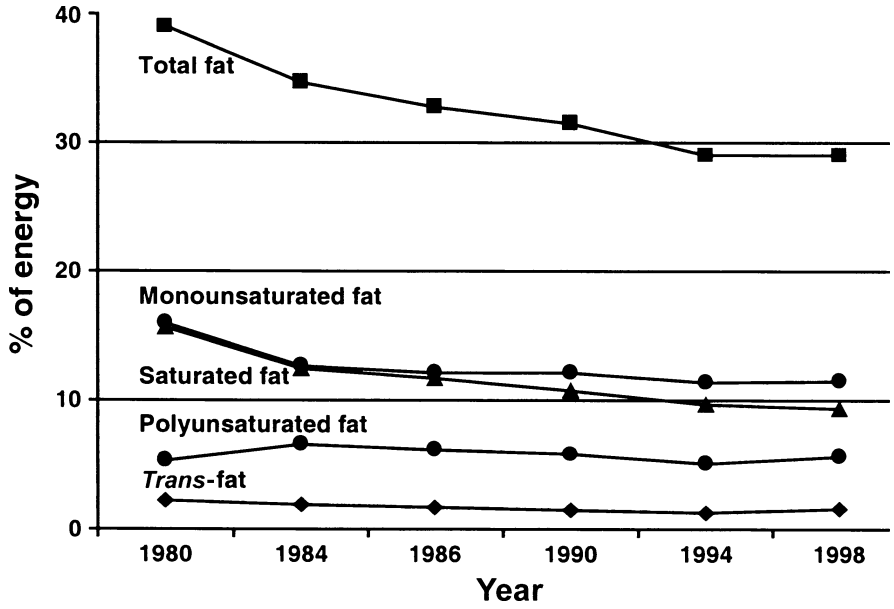

FIGURE 1. Trends in intakes of total fat and specific types of fat over time in the Nurses' Health Study, United States, 1980–2000.

To represent long-term dietary patterns, they used cumulative average method.

Table 1 was interesting for context:

TABLE 1. Characteristics and risk factors for coronary heart disease according to intake of specific types of fat* in 1990, Nurses' Health Study, United States

	Saturated fat		Monounsaturated fat		Polyunsaturated fat		*Trans*-fat	
	1	5	1	5	1	5	1	5
Age (years)	57	55	57	55	57	55	57	55
Body mass index (kg/m^2)	24	24	24	24	24	25	24	24
Current smoking (%)	14	23	15	22	20	18	16	19
Physical activity (hours/week)†	3.6	2.9	3.7	2.9	3.3	3.0	3.8	2.7
History of hypertension (%)	15	16	15	16	16	15	15	16
Parental history of MI‡ (%)	20	19	20	19	20	20	20	19
Current hormone use (%)	31	25	29	26	26	30	30	25
Aspirin use (%)	51	45	51	46	46	54	50	49
Multivitamin use (%)	34	23	35	23	29	28	36	23
Total energy (kcal/day)	1,698	1,721	1,684	1,715	1,672	1,764	1,676	1,758
Cholesterol (mg/day)	200	244	203	240	219	223	216	222
Protein (g/day)	75	76	76	76	76	74	78	73
Dietary fiber (g/day)	21	18	21	18	20	19	21	18
Alcohol (g/day)	6.5	4.3	6.4	4.1	6.8	4.3	7.1	3.5

* 1, lowest quintile; 5, highest quintile.
† Hours spent engaging in moderate to vigorous exercise/week.
‡ MI, myocardial infarction.

Table 2 below contains the information on SFA that needs to be discussed:

TABLE 2. Relative risks of coronary heart disease according to intake of specific types of dietary fat, Nurses' Health Study, United States, 1980–2000

	Quintile					p_{trend}
	1 (lowest)	2	3	4	5 (highest)	
Total fat						
Median (% of energy)	28.3	32.6	35.6	38.7	44.0	
Age-adjusted RR*	1	0.97	1.02	1.17	1.26	0.001
95% CI*		0.84, 1.12	0.88, 1.18	1.01, 1.35	1.07, 1.47	
Multivariate† RR	1	0.94	0.91	0.98	0.92	0.49
95% CI		0.81, 1.08	0.79, 1.06	0.84, 1.15	0.77, 1.09	
Saturated fat						
Median (% of energy)	10.1	11.9	13.3	14.8	17.6	
Age-adjusted RR	1	1.05	1.16	1.35	1.52	<0.0001
95% CI		0.91, 1.21	1.00, 1.34	1.16, 1.56	1.30, 1.79	
Multivariate‡ RR	1	0.94	0.96	1.01	0.97	0.93
95% CI		0.80, 1.11	0.79, 1.16	0.81, 1.26	0.73, 1.27	
Monounsaturated fat						
Median (% of energy)	10.6	12.5	13.8	15.3	18.0	
Age-adjusted RR	1	1.01	1.11	1.18	1.30	0.0003
95% CI		0.87, 1.16	0.96, 1.28	1.02, 1.37	1.11, 1.53	
Multivariate‡ RR	1	0.94	0.95	0.91	0.82	0.19
95% CI		0.79, 1.11	0.78, 1.17	0.72, 1.16	0.62, 1.10	
Polyunsaturated fat						
Median (% of energy)	4.1	5.0	5.6	6.3	7.4	
Age-adjusted RR	1	0.93	0.81	0.83	0.80	0.002
95% CI		0.81, 1.07	0.70, 0.94	0.72, 0.97	0.69, 0.94	
Multivariate‡ RR	1	0.98	0.83	0.84	0.75	0.004
95% CI		0.84, 1.14	0.70, 0.99	0.70, 1.02	0.60, 0.92	
Trans-fat						
Median (% of energy)	1.3	1.6	1.9	2.2	2.8	
Age-adjusted RR	1	1.11	1.31	1.24	1.39	<0.0001
95% CI		0.96, 1.28	1.14, 1.52	1.07, 1.44	1.19, 1.63	
Multivariate‡ RR	1	1.08	1.29	1.19	1.33	0.01
95% CI		0.92, 1.26	1.09, 1.53	0.99, 1.44	1.07, 1.66	

* RR, relative risk; CI, confidence interval.

† Adjusted for age (continuous), body mass index (five categories), smoking (never, past, current 1–14, 15–24, ≥25 cigarettes/day), alcohol intake (four categories), parental history of myocardial infarction, history of hypertension, menopausal status and hormone use, aspirin use (five categories), multivitamin use, vitamin E supplement use, physical activity (hours/week, five categories), and energy, protein, and cholesterol intake (quintiles).

‡ Adjusted for the variables cited above and intakes of saturated, monounsaturated, polyunsaturated, and *trans*-fat; α-linolenic acid; marine n-3 fatty acids; cereal fiber; and fruits and vegetables (quintiles).

Note the footnotes. For SFA looking at table 1's data there are some confounders: Current smoking, Physical activity, cholesterol, fiber intake. And, the multivariate analysis goes well beyond that, e.g. various fats, cereal fiber, and fruits-and-vegetables. So looking at just the "age-adjusted RR, both Total Fat and SFA reach statistical significance. For 5th versus 1st quintile, 1.26 for total fat and 1.52 for SFA. And, note that SFA has the highest RR than any of the fats.

Looking at all the multivariate RR for PUFA, 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.[32] 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: Check out

[32] In table 1, energy intake in quintile 5 of PUFA is ~90 calories higher than quintile 1. Thus, this addition does not need to replace something else.

this article, from Ohio State University: A DOSE OF SAFFLOWER OIL EACH DAY MIGHT HELP KEEP HEART DISEASE AT BAY.

The paper also has results for PUFA and TFA by 2 age cohorts (<65 and older), and by BMI (<25, and higher). These results are in table 3:

TABLE 3. Relative risks* of coronary heart disease according to intakes of specific types of fat, stratified by age and body mass index, Nurses' Health Study, United States, 1980–2000

	Quintile					p_{trend}
	1 (lowest)	2	3	4	5 (highest)	
Age (years)						
<65 (n = 1,111)						
Polyunsaturated fat						
RR†	1	0.87	0.68	0.74	0.66	0.002
95% CI†		0.72, 1.05	0.55, 0.85	0.59, 0.93	0.50, 0.85	
Trans-fat						
RR	1	1.20	1.35	1.37	1.50	0.01
95% CI		0.97, 1.48	1.08, 1.70	1.07, 1.75	1.13, 2.00	
≥65 (n = 655)						
Polyunsaturated fat						
RR	1	1.22	1.18	1.08	0.96	0.60
95% CI		0.94, 1.59	0.89, 1.57	0.78, 1.49	0.66, 1.39	
Trans-fat						
RR	1	0.94	1.22	0.96	1.15	0.49
95% CI		0.74, 1.19	0.94, 1.58	0.71, 1.31	0.80, 1.66	
Body mass index (kg/m^2)						
<25 (n = 752)						
Polyunsaturated fat						
RR	1	1.08	0.84	0.92	0.91	0.43
95% CI		0.86, 1.36	0.65, 1.10	0.69, 1.23	0.67, 1.26	
Trans-fat						
RR	1	1.28	1.42	1.48	1.53	0.02
95% CI		1.00, 1.62	1.09, 1.86	1.11, 1.99	1.09, 2.15	
≥25 (n = 1,014)						
Polyunsaturated fat						
RR	1	0.90	0.81	0.78	0.63	0.002
95% CI		0.73, 1.11	0.65, 1.02	0.60, 1.00	0.47, 0.84	
Trans-fat						
RR	1	0.94	1.21	1.02	1.19	0.26
95% CI		0.76, 1.16	0.97, 1.51	0.79, 1.31	0.88, 1.60	

* Adjusted for the variables listed as multivariate in table 2.
† RR, relative risk; CI, confidence interval.

From table 3, the benefit of increased PUFA was not statistically significant in older women, RR:0.96 (0.66, 1.39), nor in normal weight women, RR: 0.91 (0.67, 1.26). The older women result is understandable, as I've commented on this effect (seen in other studies as well). But the result for normal weight women is not apparent to me.

The authors note, "Improvements in diet during follow-up may have contributed to the weaker relations between dietary fat and the risk of CHD. Hu et al. (30) also reported a substantial decline in CHD incidence in this cohort due to changes in dietary intake and other risk factors." And, "A limitation of our study is that we did not measure blood lipid levels, which could be useful in determining whether the effects of dietary fats on CHD risk are mediated by blood lipid levels."

And, now I'll turn to the 1997 paper. Instead of 20 years, it covers 14 years, which is still more time than most studies.

First, some excerpts from the abstract w.r.t. SFA, "Each increase of 5 percent of energy intake from saturated fat, as compared with equivalent energy intake from carbohydrates, was associated with a 17 percent increase in the risk of coronary disease (relative risk, 1.17; 95 percent confidence interval, 0.97 to 1.41; P=0.10)." And, this was with multivariate analysis, and was not statistically significant. And, the conclusion: "Our findings suggest that replacing saturated and trans unsaturated fats with unhydrogenated monounsaturated and polyunsaturated fats is more effective in preventing coronary heart disease in women than reducing overall fat intake."

Here are the baseline characteristics (compare to Table 1 from 2005 article, above):

TABLE 2. BASE-LINE CHARACTERISTICS AND RISK FACTORS FOR CORONARY HEART DISEASE ACCORDING TO THE INTAKE OF SPECIFIC TYPES OF FAT AT BASE LINE IN 1980.*

VARIABLE	SATURATED FAT			MONOUNSATURATED FAT			POLYUNSATURATED FAT			TRANS UNSATURATED FAT		
	LOWEST	INTER-MEDIATE	HIGHEST	LOWEST	INTER-MEDIATE	HIGHEST	LOWEST	INTER-MEDIATE	HIGHEST	LOWEST	INTER-MEDIATE	HIGHEST
						mean value						
Age — yr	47	46	46	47	46	46	47	46	45	47	46	45
Body-mass index	24	24	24	24	24	24	24	24	24	24	24	24
Alcohol — g/day	9	6	5	9	7	4	10	6	5	10	6	4
Cholesterol — mg/1000 kcal/day	183	210	245	187	211	243	214	216	203	218	213	206
Folate — μg/day†	434	358	306	442	363	298	398	359	340	450	352	303
Vitamin B_6 — mg/day†	3	3	3	4	3	3	3	3	3	4	3	2
Fiber — g/day	17	13	10	17	13	11	14	13	13	16	13	12
						percent of women						
Parental history of myocardial infarction before 65 yr	20	20	20	21	20	20	20	20	20	20	20	20
Current smoking	27	27	33	27	27	32	32	27	28	28	28	30
History of hypertension	15	14	13	15	14	14	16	14	13	14	14	14
Multivitamin use	37	34	31	38	34	30	36	34	32	41	33	27
Vitamin E supplement use	16	12	11	16	12	11	13	12	13	19	11	9
Vigorous exercise‡	50	45	40	51	45	40	49	45	41	53	45	37
Regular aspirin use§	45	47	46	45	47	46	45	47	47	44	48	47
Current estrogen-replacement therapy (postmenopausal women only)	15	15	15	15	15	16	16	15	15	16	15	14

*Values have been adjusted for age. The women were divided into five groups for each type of fat according to quintiles for dietary intake. "Lowest" denotes the first quintile, "intermediate" the third quintile, and "highest" the fifth quintile.

†The values for folate and vitamin B_6 include multivitamin supplements.

‡Vigorous exercise was defined as vigorous exercise one or more times per week.

§Regular aspirin use was defined as aspirin use one or more times per week.

One correction to the above. I read in one of the subsequent comments by the authors that Fiber was g/1000kcal/day.

And, now the results - Table 3 next page. There is more stuff (e.g. Cholesterol, Animal Fat, Vegetable Fat). The "Age-Adjusted" is the same. But the Multivariate is broken into 2 kinds: one including adjustment for other fats, and one not. *The Ptrend for SFA is significant for Age-Adjusted **and Multivariate***, but not when the other fats are added in (i.e. .001, 0.04, 0.37 respectively, with the corresponding RRs for quintile 5, at 1.38, 1.16, 1.07); but the RR was only statistically significant for age-adjusted. For PUFAs, the corresponding numbers: Ptrend - .28, .07, .003; RRs for quintile 5 - 0.89, 0.83, 0.68, but only reached statistical significance for the last one (i.e. multivariate + other fats).

W.r.t., total fat, from the paper, "In age-adjusted analyses, a higher total fat intake was significantly associated with increased risk (Table 3). However, the association virtually disappeared

TABLE 3. RELATIVE RISK OF CORONARY HEART DISEASE ACCORDING TO QUINTILES OF SPECIFIC TYPES OF DIETARY FAT, DIETARY CHOLESTEROL, AND KEYS SCORE.*

VARIABLE†	QUINTILE					P FOR TREND
	1	2	3	4	5	
Total fat						
Intake (% of energy)	29.1	33.9	37.1	40.6	46.1	
RR (95% CI)						
Age-adjusted	1.0	1.02 (0.83–1.26)	1.08 (0.88–1.32)	0.99 (0.80–1.23)	1.30 (1.07–1.58)	0.02
Multivariate	1.0	0.91 (0.74–1.13)	1.01 (0.82–1.25)	1.03 (0.83–1.27)	1.04 (0.83–1.28)	0.50
Animal fat						
Intake (% of energy)	17.4	21.6	25.1	29.2	36.4	
RR (95% CI)						
Age-adjusted	1.0	0.97 (0.78–1.19)	0.96 (0.78–1.19)	1.05 (0.86–1.30)	1.30 (1.06–1.58)	0.001
Multivariate	1.0	1.01 (0.81–1.26)	0.89 (0.70–1.12)	1.13 (0.90–1.41)	1.17 (0.92–1.48)	0.05
After additional adjustment for vegetable and trans unsaturated fats	1.0	0.97 (0.78–1.21)	0.82 (0.64–1.04)	1.01 (0.79–1.27)	0.97 (0.74–1.26)	0.55
Vegetable fat						
Intake (% of energy)	5.4	8.8	11.2	13.5	17.2	
RR (95% CI)						
Age-adjusted	1.0	0.87 (0.72–1.06)	0.88 (0.73–1.07)	0.93 (0.76–1.13)	0.82 (0.67–1.01)	0.12
Multivariate	1.0	0.85 (0.70–1.04)	1.03 (0.84–1.25)	0.90 (0.73–1.12)	0.79 (0.63–1.00)	0.09
After additional adjustment for animal and trans unsaturated fats	1.0	0.82 (0.67–1.01)	0.96 (0.78–1.20)	0.82 (0.64–1.04)	0.67 (0.51–0.88)	0.009
Saturated fat						
Intake (% of energy)	10.7	12.8	14.3	16.0	18.8	
RR (95% CI)						
Age-adjusted	1.0	0.97 (0.79–1.20)	1.00 (0.81–1.24)	1.11 (0.91–1.37)	1.38 (1.13–1.68)	<0.001
Multivariate	1.0	0.91 (0.73–1.14)	0.90 (0.72–1.12)	1.12 (0.90–1.38)	1.16 (0.93–1.44)	0.04
After additional adjustment for monounsaturated, polyunsaturated, and trans unsaturated fats	1.0	0.87 (0.68–1.11)	0.85 (0.65–1.11)	1.05 (0.79–1.40)	1.07 (0.77–1.48)	0.37
Monounsaturated fat						
Intake (% of energy)	11.0	13.1	14.6	16.3	19.3	
RR (95% CI)						
Age-adjusted	1.0	1.03 (0.83–1.27)	1.18 (0.96–1.44)	1.15 (0.93–1.41)	1.30 (1.07–1.59)	0.004
Multivariate	1.0	1.08 (0.87–1.34)	1.05 (0.84–1.30)	1.12 (0.90–1.39)	1.18 (0.95–1.46)	0.14
After additional adjustment for saturated, polyunsaturated, and trans unsaturated fats	1.0	1.11 (0.86–1.43)	1.05 (0.79–1.41)	1.03 (0.74–1.43)	0.95 (0.64–1.39)	0.57
Polyunsaturated fat						
Intake (% of energy)	2.9	3.9	4.6	5.3	6.4	
RR (95% CI)						
Age-adjusted	1.0	0.92 (0.76–1.11)	0.92 (0.76–1.12)	0.91 (0.74–1.10)	0.89 (0.73–1.09)	0.28
Multivariate	1.0	0.99 (0.82–1.20)	0.97 (0.79–1.18)	0.93 (0.76–1.15)	0.83 (0.67–1.02)	0.07
After additional adjustment for saturated, monounsaturated, and trans unsaturated fats	1.0	0.94 (0.77–1.14)	0.88 (0.71–1.14)	0.81 (0.65–1.03)	0.68 (0.53–0.88)	0.003
Trans unsaturated fat						
Intake (% of energy)	1.3	1.7	2.0	2.4	2.9	
RR (95% CI)						
Age-adjusted	1.0	1.07 (0.86–1.32)	1.21 (0.98–1.49)	1.21 (0.99–1.49)	1.34 (1.09–1.64)	0.002
Multivariate	1.0	1.07 (0.86–1.33)	1.10 (0.89–1.37)	1.13 (0.91–1.39)	1.27 (1.03–1.56)	0.02
After additional adjustment for saturated, monounsaturated, and polyunsaturated fats	1.0	1.09 (0.87–1.37)	1.16 (0.91–1.47)	1.24 (0.96–1.60)	1.53 (1.16–2.02)	0.002
Cholesterol						
Intake (% of energy)	132	163	188	217	273	
RR (95% CI)						
Age-adjusted	1.0	1.16 (0.95–1.43)	1.09 (0.88–1.33)	1.08 (0.88–1.33)	1.12 (0.91–1.38)	0.49
Multivariate	1.0	1.19 (0.96–1.47)	1.14 (0.91–1.42)	1.32 (1.06–1.65)	1.25 (0.99–1.58)	0.07
After additional adjustment for saturated, monounsaturated, polyunsaturated, and trans unsaturated fats	1.0	1.15 (0.93–1.43)	1.08 (0.87–1.36)	1.24 (0.99–1.56)	1.17 (0.92–1.50)	0.24
Keys score‡	35.7	41.8	46.6	52.1	61.1	
RR (95% CI)						
Age-adjusted	1.0	1.09 (0.88–1.36)	1.06 (0.85–1.32)	1.31 (1.07–1.61)	1.32 (1.08–1.63)	0.002
Multivariate	1.0	1.09 (0.87–1.37)	1.16 (0.93–1.44)	1.35 (1.09–1.68)	1.27 (1.02–1.60)	0.01

*Values for intake are medians for each quintile, computed as the cumulative updated average (see the Methods section). RR denotes relative risk, and CI confidence interval.

†The multivariate models included the following: age (5-year categories); time period (7 periods); body-mass index (5 categories); cigarette smoking (never, past, and current smoking of 1 to 14, 15 to 24, and ≥25 cigarettes per day); menopausal status (premenopausal, postmenopausal without hormone-replacement therapy, postmenopausal with past hormone-replacement therapy, and postmenopausal with current hormone-replacement therapy); parental history of myocardial infarction before 65 years of age; multivitamin use; vitamin E supplement use; alcohol consumption (4 categories); history of hypertension; aspirin use (none, 1 to 6 times per week, ≥7 times per week, and dose unknown); vigorous exercise ≥1 time per week; percentage of energy from protein; and total energy intake. Dietary cholesterol was also included in models for total and specific fats.

‡Keys score = $1.26(2S - P) + 1.5(\sqrt{C})$, where S and P are the percentages of total energy from saturated and polyunsaturated fats, respectively, and C is the daily cholesterol intake in milligrams per 1000 kcal. Higher scores indicate higher projected changes in serum cholesterol (milligrams per deciliter).

in the multivariate analysis, primarily because of confounding by smoking, but also in part because of adjustment for alcohol use, vigorous exercise, and vitamin E supplementation."

"Next, we treated the percentages of total energy obtained from specific types of fat as continuous variables, with adjustment for the intake of other types (Table 4). We observed positive associations be- tween the incidence of coronary heart disease and the intake of saturated fat (P = 0.10) and trans un- saturated fat (P=0.001) and inverse associations with monounsaturated fat (P = 0.05) and polyunsaturated fat (P = 0.003). These associations did not differ significantly between current smokers and nonsmokers." Table 4:

TABLE 4. MULTIVARIATE RELATIVE RISK OF CORONARY HEART DISEASE ASSOCIATED WITH INCREASES IN THE PERCENTAGE OF ENERGY FROM SPECIFIC TYPES OF FAT AND INCREASES IN DIETARY CHOLESTEROL.*

VARIABLE	UPDATED DIETARY INFORMATION		BASE-LINE DIETARY INFORMATION ONLY	
	RR (95% CI)	P VALUE	RR (95% CI)	P VALUE
Saturated fat (each increase of 5% of energy)	1.17 (0.97–1.41)	0.10	1.14 (0.97–1.34)	0.12
Monounsaturated fat (each increase of 5% of energy)	0.81 (0.65–1.00)	0.05	0.84 (0.70–1.01)	0.06
Polyunsaturated fat (each increase of 5% of energy)	0.62 (0.46–0.85)	0.003	0.74 (0.55–1.00)	0.05
Trans unsaturated fat (each increase of 2% of energy)	1.93 (1.43–2.61)	<0.001	1.62 (1.23–2.13)	<0.001
Cholesterol (each increase of 200 mg/1000 kcal)	1.12 (0.91–1.40)	0.29	1.07 (0.88–1.30)	0.50

*The multivariate models included the variables listed in Table 3. Intakes of specific types of fat and cholesterol were entered into the model simultaneously, so that the effects of fats were compared with those of an equivalent amount of energy from carbohydrates. RR denotes relative risk, and CI confidence interval.

And most important quote from the 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).**"

Given this last statement, both the Chowdhury and Siri-Tarino RRs for SFA of 0.98 and 0.97 are totally absurd.

NHS Grading

1) *Over-adjustment with Lipids*. **N**.
2) *Sufficient Test of SFA Guidelines*. **D**. Quintile 1 was 10.1%, which implies about 50% of this quintile met the <10% SFA recommendation. Also, the range of SFA-intake over the 5 quintiles was small.
3) *Homogeneity.* **D.** All participants were female registered nurses, aged 34-59 y at the start of the study. Women who reported high serum cholesterol were excluded (5% of the study population) - this is the only study of the 20 that has done this. These are the ones that are most likely to develop CHD, and the most likely to have a high SFA diet.
4) *Food/Lifestyle Questionnaire*. **B**. Only 1 of the 20 studies that had follow-up questionnaires on diet/lifestyle - every ~4 years, and use them. But data only gathered via mail-in questionnaires. Participants reported on whether they had hypertension or diabetes. No measurements done, e.g. actual blood pressure and fasting glucose. But since these were nurses they were more likely to have these measures done than the general population.
5) *Missing Data in the Study.* **C**. No measurements done or reported, e.g. blood pressure, cholesterol levels, glucose levels.

6) *Missing Data in the Paper*. **D**. No information about medications. Fruits and Vegetables are adjusted for, but no information on fruit and vegetable consumption. In the 2005 paper, only 1 kind of multivariate analysis was performed. Given the large number of adjustments, seeing 3 or 4 kinds would have been useful; e.g. I would like to see a multivariate adjustment without other fats, cholesterol, fruits/vegetables, and cereal fiber.
7) *Confounders*. **C**. Only adjusting for "history of hypertension" may result in an under adjustment. The interaction of all the nutrients and lifestyle factors is complex, and may lead to over-adjustments. But without seeing more data, these kind of judgements are impossible. No information about medications (missing from study, or just omitted from analysis). For example, suppose the nurses in the highest SFA-intake had a high-percentage taking statins.
8) *Food vs. Nutrients*. **F**. No information about the Food consumed.

The Honolulu Heart Study

McGee DL, Reed DM, Yano K, Kagan A, Tillotson J. Ten-year incidence of coronary heart disease in the Honolulu Heart Program. Relationship to nutrient intake. Am J Epidemiol. 1984;119:667-676.

Both Chowdhury and Siri-Tarino reference the same study.

	RR (95% CI)
Chowdhury	1.00 (0.68, 1.47)
Siri-Tarino	0.86 (0.67, 1.12)

Key Messages:

- 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). Adjusted results 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).

TABLE 2

Mean level (± standard deviation) of specified variables, by age (The Honolulu Heart Program)

Variable	Age (years) at first examination					
	45–49 (*n* = 1638)	50–54 (*n* = 2498)	55–59 (*n* = 1424)	60–64 (*n* = 1156)	65–68 (*n* = 372)	Total (*n* = 7088)
Calories	2485 ± 741	2379 ± 710	2285 ± 673	2051 ± 617	1850 ± 562	2303 ± 711
Protein (g)	102.1 ± 36.2	98.1 ± 35.0	95.0 ± 32.6	84.9 ± 29.9	76.9 ± 27.7	95.1 ± 34.4
Fat (g)	96.8 ± 40.0	90.7 ± 38.6	84.1 ± 36.2	72.6 ± 32.3	62.0 ± 29.4	86.3 ± 38.3
Saturated fatty acids (g)	35.8 ± 16.1	33.5 ± 15.5	31.1 ± 14.7	26.4 ± 12.9	22.9 ± 11.7	31.8 ± 15.4
Monounsaturated fatty acids (g)	36.9 ± 16.0	34.6 ± 15.4	32.2 ± 14.8	27.7 ± 12.9	23.6 ± 11.6	32.9 ± 15.3
Polyunsaturated fatty acids (g)	17.3 ± 10.4	16.2 ± 9.8	14.8 ± 9.0	13.3 ± 8.0	11.1 ± 7.0	15.4 ± 9.5
Carbohydrates (g)	278.2 ± 99.8	267.5 ± 94.3	266.9 ± 93.7	246.9 ± 87.7	227.7 ± 83.6	264.4 ± 94.8
Sugar (g)	52.3 ± 38.1	47.6 ± 37.8	45.9 ± 37.2	37.7 ± 32.0	32.8 ± 31.8	46.0 ± 37.0
Starch (g)	171.7 ± 75.0	165.6 ± 69.8	168.9 ± 71.8	162.2 ± 67.9	151.4 ± 66.7	166.4 ± 71.4
Other carbohydrates (g)	54.0 ± 37.1	54.2 ± 36.1	51.6 ± 36.0	46.8 ± 32.3	43.4 ± 29.8	51.8 ± 35.7
Cholesterol (mg)	583.3 ± 319.5	573.4 ± 322.0	540.9 ± 299.5	510.2 ± 306.0	453.8 ± 291.6	552.6 ± 315.9
Alcohol (g)	13.3 ± 29.1	14.6 ± 32.8	11.8 ± 26.5	10.2 ± 24.2	10.5 ± 22.2	12.8 ± 29.2
Percentage of calories from						
Protein	16.6 ± 3.8	16.6 ± 3.1	16.8 ± 3.9	16.7 ± 3.9	16.8 ± 3.8	16.7 ± 3.8
Fat	34.9 ± 8.9	34.0 ± 9.1	32.8 ± 9.1	31.5 ± 9.5	29.8 ± 9.7	33.4 ± 9.3
Carbohydrates	45.1 ± 10.1	45.5 ± 10.7	47.0 ± 10.5	48.5 ± 10.8	49.8 ± 11.8	46.4 ± 10.7
Saturated fatty acids	12.9 ± 3.9	12.6 ± 3.9	12.1 ± 4.0	11.4 ± 4.0	11.0 ± 4.1	12.3 ± 4.0
Cholesterol/1000 calories	238.2 ± 123.9	242.8 ± 126.0	240.0 ± 128.3	249.2 ± 140.3	247.9 ± 147.5	242.5 ± 130.1

The study consisted of about 8,000 men of Japanese ancestry who resided in Oahu in 1965. First examination took place between 1965 and 1968. The examination included a complete cardiovascular exam and numerous laboratory, physical, and personal characteristics. Evaluation of nutrient intake was based on a 24-hour recall, based on an interview with a dietician. 918 were excluded: (1) could not recall their dietary intake, and said that ate atypically in the last 24 hours (n = 502); or, (2) prevalent cases coronary heart disease (n = 301), stroke (n = 111), or cancer (n=49). Table 2 has a profile of the men.

Like some of the other studies, the population was not broken down into quintiles, quartiles, or tertiles. The paper just presents a statistical analysis. Table 3 contains results adjusted just for age. To be consistent with other studies, I'm only going to consider columns 1 and 3.[33] Men who died from CHD or had an myocardial infarction (vs. Non-CHD) had higher intakes (as per-

TABLE 3

Age-adjusted mean levels of specified nutrients by coronary heart disease (CHD) status after 10 years (The Honolulu Heart Program)†

Variable	Non-CHD (n = 6632)	Total CHD (n = 456)	MI‡ or CHD death (n = 309)	AP or CI‡ (n = 147)
Calories	2309	2229*	2205**	2280
Protein (g)	95.1	94.7	94.6	94.9
Fat (g)	86.3	86.4	86.9	85.2
Saturated fatty acids (g)	31.9	31.7	32.4	30.4
Monounsaturated fatty acids (g)	32.9	33.0	33.4	32.0
Polyunsaturated fatty acids (g)	15.4	15.7	15.2	16.7
Carbohydrates (g)	265.4	249.8***	246.4***	256.9
Sugar (g)	46.0	45.1	45.3	44.8
Starch (g)	167.2	155.1***	154.9**	155.3*
Other carbohydrates (g)	52.0	49.3	46.0**	56.1
Cholesterol (mg)	552.2	558.1	561.8	550.3
Alcohol (g)	13.0	10.4	8.3**	15.0
Animal protein (g)	71.2	72.0	72.3	71.3
Vegetable protein (g)	23.9	22.7*	22.3**	23.6
Percentage of calories from				
Protein	16.6	17.2**	17.3**	16.9
Fat	33.3	34.7**	35.2***	33.7
Carbohydrates	46.5	45.0**	44.8**	45.5
Saturated fatty acids	12.3	12.7*	13.0***	12.0
Polyunsaturated fatty acids	6.0	6.3*	6.2	6.6*
Cholesterol/1000 calories	241.5	256.6*	259.6*	250.3

* $p < 0.05$, mean differs significantly from non-CHD mean.
** $p < 0.01$, mean differs significantly from non-CHD mean.
*** $p < 0.001$, mean differs significantly from non-CHD mean.
† Age adjustment and tests for differences in means were accomplished by analysis of covariance.
‡ MI, myocardial infarction; AP, angina pectoris; CI, coronary insufficiency.

[33] Why ignore soft endpoints? To quote from the paper, "The diagnostic certainty of the soft endpoints (angina pectoris or coronary insufficiency) is much less than that of the hard endpoints (myocardial infarction or coronary heart disease death). This could result in attenuation of a true relationship. A similar problem involves classification. In our analysis, we classified according to the worst manifestation. Any man who had both a myocardial infarction and documented angina is classified as a case of myocardial infarction for our analysis. Thus, our category of angina pectoris or coronary insufficiency does not include all men who had ever had angina pectoris or coronary insufficiency, but rather only those cases that did not develop the more severe manifestation." And, other studies in the meta-analysis of Chowdhury did not include soft endpoints.

cent of calories) of protein, total fat, and saturated fat, and a lower intake of carbohydrates. Also, these men had lower intakes (in absolute amounts, i.e. grams) of vegetable protein, carbohydrates, starch, and "other carbohydrates"[34].

The multivariate analysis included age, systolic blood pressure, physical activity index, body weight, serum cholesterol, and cigarettes smoked per day. Table 5 presents the results - positive number indicates higher intake implies higher incidence of event. Again, only the middle

TABLE 5

Standardized multivariate† logistic coefficients for relating specified nutrients to noted coronary heart disease (CHD) manifestation (The Honolulu Heart Program)

Variable	Total CHD	MI‡ or CHD death	AP or CI‡
Calories	−0.1057*	−0.1464*	−0.0135
Carbohydrates (g)	−0.1022	−0.1329*	−0.0318
Starch (g)	−0.1136*	−0.1063	−0.1158
Other carbohydrates (g)	−0.0506	−0.1624*	0.1376
Alcohol (g)	−0.1978**	−0.3878***	0.0602
Vegetable protein (g)	0.0196	0.0356	−0.0127
Percentage of calories from			
Protein	0.1273**	0.1699**	0.0219
Fat	0.1308**	0.1908**	−0.0064
Saturated fatty acids	0.0871	0.1812**	−0.1169
Polyunsaturated fatty acids	0.0926	0.0438	0.1704*
Carbohydrates	−0.0511	−0.0576	−0.0328
Cholesterol/1000 calories	0.0962*	0.1177*	0.040

* $p < 0.05$, coefficient differs significantly from zero.
** $p < 0.01$, coefficient differs significantly from zero.
*** $p < 0.001$, coefficient differs significantly from zero.
† Additional variables in the model were age, systolic blood pressure, serum cholesterol, cigarettes smoked per day, body weight (in pounds), and physical activity index.
‡ MI, myocardial infarction; AP, angina pectoris; CI, coronary insufficiency.

column (CHD death and MI) is of interest. Note that higher intakes of both total fat and saturated fat indicated higher incidence of CHD death and MI, even though the multivariate analysis included adjustment for serum cholesterol ($p < 0.01$). From the paper, *"Several other variables were significantly and directly related to the 10-year incidence of myocardial infarction or coronary heart disease death: percentage of calories from protein, fat, and saturated fat acids, and cholesterol per 1000 calories."* In absolute amounts (i.e. grams) vegetable protein and starch lost significance in the multivariate analysis, but "other carbohydrates" did not - this might be due to the inclusion of serum cholesterol in the multivariate analysis.

HHS Grading

1) *Overadjustment with Lipids*. **Y**. W.r.t. dietary intake (e.g. SFA), study provided age-adjusted and multivariate. The multivariate included serum cholesterol.
2) *Sufficient Test of SFA Guidelines*. **B**. The mean intake of SFA was 12.3% of total calories with a standard deviation of 4.0. This suggests a reasonable amount of men getting <10% of their calories from SFA.

[34] Paper doesn't define "other carbohydrates". I suspect that fiber may be part of this.

3) *Homogeneity.* **D.** All the men were of Japanese ancestry and lived in Oahu. But the population size was large, and with the variation in SFA, it was possible to find some statistically significant correlations.
4) *Food/Lifestyle Questionnaire*. **F**. Dietary intake based on recall of the last 24 hours. No follow-up on dietary intake over the10 years of the study.
5) *Missing Data in the Study.* **C**. No trans-fat data. But given the years of this study, this probably was not a factor. Neither HDL nor LDL was measured. The authors conjectured that the increasing alcohol intake, which was a benefit, could be due to alcohol increasing HDL. But this could not be tested in this study.
6) *Missing Data in the Paper*. **D**. The paper did not present the characteristics (dietary/lifestyle measurements) by SFA tertile, quartile, or quintile. Without this, it is difficult to judge whether there might have been over adjustment. Also, no information about fiber. And, most importantly, a multivariate analysis without serum cholesterol is missing.
7) *Confounders*. **D**. Since the characteristics per SFA tertile, quartile, or quintile were not presented, it is difficult to say if there may have been confounders or not. The authors are aware of this challenge, and note: ***"The selection of which covariables to include in the multivariate analyses presents problems in large studies. Arbitrary rules which include all variables related both to the characteristic and to the event being considered, while attractive, are both impractical and (in our opinion) improper. They are impractical because of the large number of variables included in studies such as the Honolulu Study. Because of the size of the cohort being studied, many "significant" correlations of rather small magnitude are noted. They are improper <u>because they lead to the inclusion of highly correlated variables in the model, which may lead to results that are either paradoxical or uninterpretable.</u>"***
8) *Food vs. Nutrients*. **D**. No information about the Food consumed. However some food categories were reported: animal protein, vegetable protein, Starch, Sugar, "other carbohydrates".

The Framingham Study

Posner BM, Cobb JL, Belanger AJ, Cupples LA, D'Agostino RB, Stokes J, III. Dietary lipid predictors of coronary heart disease in men. The Framingham Study. Arch.Intern.Med. 1991;151:1181-1187.

Both Chowdhury and Siri-Tarino reference the same study.

	RR (95% CI)
Chowdhury	1.04 (0.97, 1.11)
Siri-Tarino	0.92 (0.68, 1.24)

From the abstract, "The relationship between dietary lipids and the 16-year incidence of coronary heart disease (CHD) morbidity and mortality was examined in two male cohorts, aged 45 to 55 years (n = 420) and 56 to 65 years (n = 393) from the Framingham Study. Dietary lipids were assessed through a single 24-hour recall at the initiation of follow-up in 1966 to 1969." The Framingham study started in 1948 with 5029 men and women, who were followed biennially to assess cardiovascular disease risk, track heart disease morbidity/mortality, and all-cause death. Apparently, until this sub-study, diet was not part of the study. All male subjects in the study between 45 and 65 (n=859) were invited to participate. Men with pre-existing evidence of CVD (n=46) were excluded from the study.

From above, 2 obvious problems are: (1) A single 24-hour recall at the start of the study; and, (2) A relatively small population, i.e. only about 400 men in each group.

Unfortunately, all the data in the paper was presented in terms of Mean and standard deviation (SD). Thus, we don't get to see any data in terms of tertiles, quartiles, or quintiles. Table 1 shows the characteristics of the population.

Table 1.—Male Cohort Characteristics: Framingham 16-Year Analysis

Variable	Mean (±SD) Age 45-55 y (n=420)	Mean (±SD) Age 56-65 y (n=393)
Age, y	52.0±2.0	59.8±2.6
Metropolitan relative weight, %*	123.6±16.6	120.9±15.9†
Serum total cholesterol, mmol/L (mg/dL)	5.79±1.04 (224.0±40.1)	5.71±0.98 (220.8±37.7)
Cigarettes, No./d	11.2±14.9	9.1±14.1†
Nonsmokers, %	55.7	61.3
Systolic blood pressure, mm Hg	133.3±20.2	139.5±20.3‡
Physical activity score§	34.7±7.2	34.2±7.1
Glucose intolerance, % yes	10	14
Left ventricular hypertrophy, % yes	1	4.5‖

*Relative to Metropolitan Life Insurance Co data.
†$P<.05$.
‡$P<.001$.
§Twenty-four–hour weighted activity score (range, 24 to 120; complete bed rest equals 24).
‖$P<.01$.

Table 2.—Male Cohort Mean Daily Dietary Intake: Framingham 16-Year Analysis

Variable	Mean (±SD) Age 45-55 y (n=420)	Mean (±SD) Age 56-65 y (n=393)
Energy intake, kJ	11 195±3155	10 671±2833*
Total fat, g	118.4±41.9	109.3±39.2*
% of energy intake	39.7±8.4	38.3±8.9†
Saturated fatty acid, g	45.3±18.2	42.3±17.6†
% of energy intake	15.2±4.4	14.8±4.5
Polyunsaturated fatty acid, g	16.5±8.7	15.0±7.5*
% of energy intake	5.5±2.5	5.4±2.4
Monounsaturated fatty acid, g	48.5±18.3	44.3±17.2‡
% of energy intake	16.2±4.0	15.5±4.0*
Polyunsaturated-saturated ratio	0.4±0.2	0.4±0.2
Dietary cholesterol, mg	529.6±269.1	531.8±291.3
Total carbohydrate, g	254.8±89.7	248.1±89.3
Protein, g	102.8±31.9	98.1±36.2†
Alcohol, g	24.0±37.1	24.6±32.3
% of energy intake	5.8±7.9	6.7±8.6

*$P<.01$.
†$P<.05$.
‡$P<.001$.

Table 2 has the daily dietary intake. Both groups consumed high percentages of both total fat, saturated fat (15%), and monounsaturated fat, and a relatively low percentage of polyunsaturated fat. Total fat was highly correlated with saturated fat and monounsaturated fat.

Part 1 of Analysis

This part analyzes the 2 cohorts as a continuum. Part 2 instead compares those in each cohort adhering to the NCEP guidelines to the mean dietary intake of the 2 cohorts. Part 2 is really the more applicable one to Chowdhury's challenge.

Tables 4 (45-55 Years) and 5 (56 Years or more) contain the regression results for the dietary variables and CHD morbidity and mortality. "In the first step (unadjusted model), the independent variable was the dietary component of interest. In the next step (the energy-adjusted or bivariate model),we controlled for energy intake.The standard list of risk factors was then added in the multivariate model." This included, "**serum total cholesterol level**, systolic blood pressure, glucose intolerance, left ventricular hypertrophy, cigarette smoking, Metropolitan relative weight[35], and physical activity."

Table 4.—Cox Regression Coefficients for Men Aged 45 to 55 Years: Framingham 16-Year Analysis*

	Unadjusted		Energy Adjusted‡		Multivariate§	
Dietary Variable	β	P†	β	P†	β	P†
Energy intake	−.0003	.076	...	...	−.0002	.148
Total fat	.001	.984	.010	.021	.011	.013
% of energy intake	.030	.016	.031	.011	.035	.005
Saturated fatty acid	.002	.973	.014	.085	.013	.108
% of energy intake	.043	.060	.045	.050	.047	.052
Monounsaturated fatty acid	.001	.854	.021	.019	.024	.006
% of energy intake	.059	.021	.060	.017	.071	.004
Polyunsaturated fatty acid	.003	.796	.021	.128	.022	.120
% of energy intake	.057	.157	.059	.133	.065	.100
Dietary cholesterol	−.0001	.777	.0002	.689	.0000	.920

*The sample includes only those who had complete data on all variables; 20 persons were excluded due to missing values. N = 400, with 94 cases of coronary heart disease.
†Two-tailed tests of significance.
‡Energy-adjusted models include energy intake and the dietary variable of interest.
§Multivariate models include the dietary variable of interest, energy intake, serum cholesterol level, physical activity level, systolic blood pressure, left ventricular hypertrophy, cigarette smoking, glucose intolerance, and Metropolitan relative weight.

Table 5.—Cox Regression Coefficients for Men Aged 56 Years or More: Framingham 16-Year Analysis*

	Unadjusted		Energy Adjusted‡		Multivariate§	
Dietary Variable	β	P†	β	P†	β	P†
Energy intake	−.0002	.175	...	...	−.0003	.067
Total fat	−.002	.378	.001	.877	.0004	.916
% of energy intake	.001	.906	.002	.862	.004	.973
Saturated fatty acid	−.006	.319	−.001	.896	−.003	.692
% of energy intake	−.007	.744	−.004	.840	.011	.611
Monounsaturated fatty acid	−.005	.387	.001	.870	.001	.912
% of energy intake	−.003	.888	.001	.972	−.004	.867
Polyunsaturated fatty acid	.001	.940	.009	.507	.015	.293
% of energy intake	.043	.252	.039	.295	.051	.187
Dietary cholesterol	.002	.465	.0004	.206	.0003	.364

*The sample includes only those who had complete data on all variables; 20 persons were excluded due to missing values. N = 393, with 114 cases of coronary heart disease.
†Two-tailed tests of significance.
‡Energy-adjusted models include energy intake and the dietary variable of interest.
§Multivariate models include the dietary variable of interest, energy intake, serum cholesterol level, physical activity level, systolic blood pressure, left ventricular hypertrophy, cigarette smoking, glucose intolerance, and Metropolitan relative weight.

First in men aged 45 to 55, "the energy-adjusted regressions suggested that total fat and monosaturated fat, each considered individually, are significant direct predictors of CHD incidence. Saturated fatty acid intake had a marginally significant positive association with CHD incidence (P = 0.085 and 0.050 for gram intake and percentage of energy intake, respectively.) In multivariate models, which included the nutrient of interest, energy intake, and the cardiovascular disease risk factors, the regression coefficients for a given nutrient and significance

[35] "Metropolitan relative weight was computed as the ratio of weight measured at the present examination to the midpoint of the desirable weight range for a medium-framed man at a given height as determined by the Metropolitan Life Insurance Co in 1959." Back-of-the-envelop calculations imply a mean BMI of around 26.

levels were altered only slightly. This suggested that total fat intake and monounsaturated fatty acid intake had a significant, independent association with the 16-year incidence of CHD. *Saturated fatty acid intake was marginally significant.*" But note that the multivariate analysis included adjusting for serum cholesterol plus possibly other confounders.

"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."

Part 2: Comparison of Mean to NCEP Guidelines

At the time of this report, NCEP guidelines were: <30% energy from total fat; <10% from saturated fat; <10% from monounsaturated fat; and >10% from polyunsaturated fat.

With the multivariate analysis for 45 to 55, "those persons who consumed 30% of energy intake from fat (vs the sample's mean intake of 39.7%) had a 29% lower risk for CHD (relative risk, 0.71; 95% confidence interval, 0.56 to 0.90). The relative risk associated with a monounsaturated acid intake of 10% of total energy intake was 0.64 (95% confidence interval, 0.48 to 0.87),compared with the mean level of 16.2%. ***Those who consumed 10% of energy intake from saturated fatty acid, compared with the mean level of 15.2%, had a CHD relative risk of 0.78 (95% confidence interval, 0.61 to 1.00).***"

But in the older cohort (56 and older), there were no statistically significant differences in relative risk.

Comment from Authors

As to why this study in the younger cohort showed that higher levels of monounsaturated fat are associated with higher CHD, whereas other studies have shown a beneficial effect: *"monounsaturated fatty acids were derived from animal food products concentrated in both monounsaturated and saturated fats, as demonstrated by the high degree of correlation between these variables."* In other studies, monounsaturated fats were largely obtained from vegetable sources (such as olive oil).

Why were there were no observed significant relationships between dietary variable and CHD incidence in data from the o*lder Framingham male cohort. "The reasons for this result are not clear. However, 30-year follow-up studies in the Framingham cohort suggest a weakened influence of certain risk factors, including serum total cholesterol levels, on the incidence of CHD in older persons. This may be due in part to early excess CHD mortality in persons who have elevated serum total cholesterol levels. It may also be influenced by the increased mortality from other diseases in older persons,* or a more complicated clinical presentation of heart disease in older individuals. An alternative explanation may be that our results were confounded by errors in dietary assessment associated with a single 24-hour recall, or changes that may have occurred in dietary intake during the 16 years of follow- up."

Last paragraph from the paper:

"In conclusion, we report an independent association between the dietary levels of total fat and monounsaturated fatty acids and the 16-year incidence of CHD among Framingham men aged 45 to 55 years. *We observed a marginally significant association between saturated fatty acid intake and CHD in these men as well.* These data suggest that levels of total fat and saturated and monounsaturated fatty acids that are consistent with the new NCEP dietary recommendations are associated with a reduced risk of developing CHD in younger men. The demonstration of these relationships in the younger male cohort supports population-based recommendations for early preventive dietary intervention in CHD."

Framingham Grading

1) *Overadjustment with Lipids*. **Y**. W.r.t. dietary intake (e.g. SFA), study provided unadjusted, energy adjusted, and multivariate. The multivariate included total cholesterol.
2) *Sufficient Test of SFA Guidelines*. **D**. Part 1 of study was really an **F**. We have no idea how many men in each of the 2 age cohorts of ~400 men were eating a diet of <10% of calories from SFA. And, the mean SFA intake was somewhat high, at 15%. Part 2 compared the mean to the men who met the NCEP guideline (e.g. <10% SFA intake), but the paper gives no clue exactly how this was done, how many men met the guideline, and whether there were potentially additional confounders.
3) *Homogeneity.* **F.** All the men were from Framingham, MA area, and from the data presented appeared to be eating similar diets. And, the sample size was relatively small.
4) *Food/Lifestyle Questionnaire*. **F**. Dietary intake based on recall of the last 24 hours. No follow-up on dietary intake over the16 years of the study.
5) *Missing Data in the Study.* **C**. No trans-fat data. As noted in the paper, LDL was not measured - "It is also possible that the influence of diet may be on risk factors for cardiovascular disease that we were unable to study in this cohort (in particular, serum low-density lipoprotein [LDL] cholesterol level)."
6) *Missing Data in the Paper*. **D**. The paper did not present the characteristics (dietary/lifestyle measurements) by SFA tertile, quartile, or quintile. Without this, it is difficult to judge whether there might have been over adjustment. Every 2 years, various measurements were collected in the subjects (cholesterol, blood pressure, weight, glucose tolerance). But none of this was included in the paper. Also, no information about fiber. And, most importantly, a multivariate analysis without serum cholesterol is missing.
7) *Confounders*. **D**. Since the characteristics per SFA tertile were not presented, it is difficult to say if there may have been confounders or not.
8) *Food vs. Nutrients*. **F**. No information about the Food consumed. Other contemporary studies (e.g. Honolulu Heart Study, HHS) provided some useful food categories (e.g. animal vs vegetable protein, Starch, Sugar).

The Alpha-Tocopherol, Beta-Carotene (ATBC) Study

Pietinen P, Ascherio A, Korhonen P, Hartman AM, Willett WC, Albanes D, Virtamo J et al. Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Am J Epidemiol. 1997;145:876-887.

Chowdhury and Siri-Tarino papers reference this paper in their meta-analysis.

	RR (95% CI)
Chowdhury	0.90 (0.78, 1.03)
Siri-Tarino	0.93 (0.60, 1.44)

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.

Key Messages:

1) 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.
2) The intake of omega-3 fatty acids from fish was also directly related to the risk of coronary death in the multivariate model - RR = 1.30 (1.01, 1.67) for men in the highest quintile of intake compared with the lowest.
3) 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.
4) The dietary questionnaire exaggerated the range of intakes of all nutrients. From the validation study, the range of SFA-intake was actually 57% narrower.
5) 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."*

Diet was assessed at baseline using a self-administered, modified diet history method. They excluded men who reported at baseline any prior diagnosis of myocardial infarction, angina, stroke, or diabetes. Men who experienced exercise-related chest pain were also excluded.

As they note, "One could argue that maybe the range of saturated fat intake was not large enough to detect an association with coronary risk. The median intake was 11 percent of energy in the lowest quintile and 21.9 percent of energy in the highest quintile. The median intake of polyunsaturated fatty acids in these quintiles of saturated fat intake was 5.3 percent of energy and 2.3 percent of energy in the highest, and that of cholesterol was 168 mg/1,000 kcal versus 214 mg/1,000 kcal."

But, "the dietary questionnaire probably exaggerates the true range of intakes of all nutrients. Based on our validation study where we used 24 days of food records as the reference method, the range was, in fact, 57 percent narrower for saturated fatty acids, 82 percent narrower for polyunsaturated fatty acids, and 79 percent narrower for dietary cholesterol intake." But the authors state that using the Keys equation, the estimated de-

crease in coronary death would be 31%, which they should have been able to detect if such an association existed.

The problem with this study is about the same as the other studies. And, to gain a better insight into what could be going on, they don't present the data in a way to facilitate this. Although they present in Tables 1 and 2 quintiles and results for each type of fatty-acid (FA) and cholesterol, they only present the detailed characteristics for the quintiles of TFA - Table 4. For example, Table 4 shows SFA intake (as well as ~25 other measures) for each quintile of TFA.

It would be useful to see data with SFA quintiles. Why? 1) to see the amount of TFA in each quintile of SFA - does lowest quintile of SFA have highest TFA? I think the answer is Yes, because the highest quintile of TFA, had the lowest SFA intake.
2) Does Serum cholesterol increase with each quintile of SFA? It does in other studies. 3) ***Is fiber inversely correlated with SFA intake?*** *It does in some other studies.* In MALMO study, in the multivariate analysis, higher SFA-intake had a beneficial effect, but this included an adjustment for fiber. When they took out the fiber, the beneficial effect disappeared. In this study, how would taking out fiber from the multivariate analysis affect the SFA-intake, and other results?

1) *Overadjustment with Lipids*. **N**.
2) *Sufficient Test of SFA Guidelines*. **F**. Mean of lowest quintile of SFA-intake was 11%. And, from the validation study of food questionnaire, the SFA-intake range was actually 57% narrower.
3) *Homogeneity.* **F.** All the men were from southwestern Finland, all were smokers, and ate a similar diet.
4) *Food/Lifestyle Questionnaire*. **D**. On the one hand, they had one of the most robust methods that I have read about. But the validation study indicated that the actual range of various fatty acids and dietary cholesterol were much narrower, e.g. 79% narrower for dietary cholesterol.[36]
5) *Missing Data in the Study.* **B.** <discussed below>
6) *Missing Data in the Paper*. **D**. The paper did not present the characteristics (dietary/lifestyle measurements) by SFA quintile (as it did for TFA intake). Without this, it is difficult to judge whether there might have been over-adjustment or under-adjustment. Given the KIHD results, I would have liked to see a multivariate analysis without a fiber adjustment. A bivariate analysis of fiber/SFA-intake would have provided some clarity.
7) *Confounders*. **D**. Given my analysis of the KIHD study, could mercury (from lake fish) or iron stores been confounders.
8) *Food vs. Nutrients*. **F**. No information about the Food consumed.

[36] Makes me wonder about all the other studies that didn't have as rigorous validation study.

The Ireland-Boston Diet-Heart Study (IBDH)

Kushi LH, Lew RA, Stare FJ, Ellison CR, el Lozy M, Bourke G et al. Diet and 20-year mortality from coronary heart disease. The Ireland-Boston Diet-Heart Study. N.Engl.J Med. 1985;312:811-818.

Both Chowdury and Siri-Tarino use this 1985 paper in their meta-analysis of SFA/CHD. .

Chowdhury and Siri-Tarino.

	RR (95% CI)
Chowdhury	1.07 (1.00, 1.14)
Siri-Tarino	1.33 (0.95, 1.87)

Although both say that the IBDH study says that SFA is harmful, they disagree on the scoring significantly, and Chowdhury's scoring marginally reached statistical significance, but Siri-Tarino's did not.

First, Chowdhury correctly notes that this study adjusts for lipids, and says, "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*)." Thus, when a referenced study did not provide an adjustment that excluded lipids, they so noted it in their Supplement (Figure 2).

In addition to lipids (i.e. total serum cholesterol) being including in the IBDH adjustment, other components were age, systolic blood pressure (SBP), cigarette smoking, and alcohol intake.

The Study Population. It consisted of about 1000 men (30-69 y) using dietary information collected in the early 1960's and subsequent mortality from coronary heart disease within the subsequent 18 year period. The men were initially enrolled in 3 cohorts: one of men born in Ireland, but emigrated to Boston at least 10 years before the study; the 2nd of the brothers of the previous group who remained in Ireland, and the 3rd of those born in the Boston area of Irish immigrants. There were no statistically significant differences in mortality from coronary heart disease among the 3 cohorts. Thus, they combined the 3 cohorts into one population. For each nutritional component to analyze, the population was divided into tertiles (but this was not presented in paper).

Unfortunately, the article did not report on the RR's for SFA w.r.t. SFA tertiles. But there are statistical results (with the multivariate adjustments) reported in table 5, below. Note that higher SFA intake (harmful) marginally reached statistical significance (P=0.05). This is consistent with the Chowdhury scoring. Also, fiber intake was inversely associated (also, P=0.05). But note that these results were after adjustment for *serum cholesterol*.

Table 5. Regression Coefficients of Death from Coronary Heart Disease for Dietary Variables.*

Dietary Variable	Logistic Regression †		Proportional-Hazards Regression ‡	
	Coefficient	P value	Coefficient	P value
Keys score §	0.025	0.03	0.022	0.03
Modified Hegsted score §	0.010	0.04	0.0083	0.04
Saturated fatty acids (% of calories)	0.068	0.05	0.061	0.05
Polyunsaturated fatty acids (% of calories)	−0.069	0.52	−0.070	0.45
Cholesterol (mg/1000 kcal)	0.0021	0.11	0.0017	0.10
Vegetable-foods score §	−0.066	0.25	−0.054	0.27
Vegetable protein (% of calories)	−0.097	0.45	−0.043	0.70
Starch (% of calories)	−0.012	0.50	−0.004	0.80
Fiber (g/1000 kcal)	−0.704	0.13	−0.768	0.05

*Estimates adjusted for age, systolic blood pressure, total serum cholesterol level, cigarette smoking, alcohol intake, and cohort. Separate regression models were fit for each dietary variable.

†Outcome was defined as coronary-heart-disease mortality status on the 19th anniversary of the base-line examination. A total of 102 men died from coronary heart disease, leaving 899 men in the "other" category.

‡Outcome was defined as the length of time to coronary-heart-disease death. Coronary-heart-disease mortality status was determined as of December 31, 1982. At that time, 110 men had died of coronary heart disease, leaving 891 men in the "other" category.

§See Methods section for definitions of these variables.

Lots of interesting comments in the discussion section.

"*It is difficult to separate the effects of increased consumption of saturated fatty acids and dietary cholesterol from those of decreased consumption of vegetable protein and fiber, since the two usually go hand in hand in individual diets.* In this study, the correlation between the vegetable-foods score and the Keys dietary-lipid was -0.33 (P<0.0001). *This pattern is obvious in geographic studies [1], in which the intake of saturated fatty acids and that of carbohydrates are both highly correlated with coronary heart disease, but in opposite directions.*"

"Support for the hypothesis that consumption of complex carbohydrates may decrease the risk of coronary heart disease independently of an effect of dietary lipids comes from historical trends of food consumption patterns and mortality rates from coronary heart disease in the United States. It is generally recognized that such mortality rates were quite low until about 1920, despite difficulties in the interpretation of data resulting from changing trends in the reporting of cause of death. After 1920 there was steady increase in the mortality rate until 1968, when a decline began. *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.*"

"Further support for a role of vegetable foods in the pathogenesis of coronary heart disease comes from feeding studies. Fraser et al, studied the effect on the serum cholesterol of the isocaloric substitution of vegetable foods for sucrose. They observed a decrease in the serum cholesterol level during the vegetable feeding period. Wright et al. reported that feeding a diet

high in fiber decreased both systolic and diastolic blood pressure. *These findings suggest that vegetable foods could modify risk by lowering blood pressure or serum cholesterol levels.*"

"This study also suggest that vegetable foods may operate at least in part through those risk factors. The significant association of the vegetable-foods score with the death rate from coronary heart disease adjusted only for age and cohort ($\beta = -0.102$, $P = 0.03$) was weakened when further adjustments were made for systolic blood pressure, electrocardiogram readings, and serum cholesterol level ($\beta = -0.054$, $P = 0.27$). Thus, the former estimate may be more appropriate for examining the impact of the vegetable-foods score on the risk of death from coronary heart disease."

IBDH Study Grading

1) *Overadjustment with Lipids*. **Y**.
2) *Sufficient Test of SFA Guidelines*. **F**. The mean SFA-intake was ~17% of energy with an SD of 3.5%. Thus, very few, if any, had an SFA-intake <10%; and, the range of SFA-intake was relatively narrow.
3) *Homogeneity.* **D** Although the initial thought of the researchers that the diet of the 3 cohorts would be different, as they discovered, they weren't, and thus combined them
4) *Food/Lifestyle Questionnaire*. **D**. Dietary history method collected by interview with a dietician. But only done at the beginning of the 18 y study period. No information on physical activity and diabetes (e.g. no glucose measurement at baseline).
5) *Missing Data in the Study.* **C.** See above. Also, no info on TFA.
6) *Missing Data in the Paper*. **D**. The paper did not present the characteristics (dietary/lifestyle measurements) by SFA tertile. Also, a multivariate analysis without serum cholesterol was not presented. I would have liked to see the study population divided into 2 age groups, 30-55, and 56-69 - especially since the study lasted 18 years.
7) *Confounders*. **D**. No physical activity information. The means of Energy intake of the Irish cohort was 1,000 calories higher than the 2 Boston one (~4000 vs ~3000). Diabetes may have been a confounder.
8) *Food vs. Nutrients*. **D**. A little information on vegetable intake.

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Caerphilly Study

Fehily AM, Yarnell JW, Sweetnam PM, Elwood PC. Diet and incident ischaemic heart disease: the Caerphilly Study. Br.J Nutr. 1993;69:303-314.

	RR (95% CI)
Chowdhury	0.92 (0.78, 1.09)
Siri-Tarino	1.57 (0.56, 4.42)

So both papers (Chowdhury and Siri-Tarino) cited the same Caerphilly study, and came up with significantly different assessments: Chowdhury - SFA slightly helpful in Caerphilly; Siri-Tarino - SFA harmful in Caerphilly. But neither reached statistical significance.

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. 25% of the men either reported existing IHD, or the ECG indicated that they had. Outcomes were IHD incidence (e.g. hospitalization, death) or ECG determination at the end of the study.

The multivariate analysis had adjustments just for age, BMI and smoking. Analysis was done using quintiles for applicable nutrient. Separate analysis was done for men free of IHD at baseline and those that were not. W.r.t. fats only total fat and animal fat were known. Animal fat was a stand-in for SFA.

Table 2. *Mean daily nutrient intakes estimated at baseline in men who had no evidence of ischaemic heart disease (IHD) at baseline, subdivided into those who went on to experience an IHD event during the next 5 years and those who did not**

(Mean values and standard deviations)

	n ...	Men who had no IHD event 1686–1743		Men who experienced an IHD event 70–74		
Nutrient		Mean	SD	Mean	SD	*t*
Energy:						
MJ		9·7	2·4	9·5	2·3	−0·80
kcal		2328	580	2271	577	
Protein (g)		74·5	17·3	73·0	18·7	−0·71
Fat (g)		102·8	30·6	100·7	29·1	−0·57
Animal fat (g)		76·3	29·0	75·3	24·3	−0·30
Carbohydrate (g)		250·5	73·2	240·2	66·3	−1·17
Starch (g)		155·1	57·2	148·8	56·0	−0·93
Sugars (g)		95·3	37·6	92·9	30·3	−0·54
Fibre (g):						
Total		16·4	5·7	15·1	5·7	−1·88
Cereal		7·9	4·6	7·3	4·6	−1·25
Fruit/vegetable		8·4	2·7	7·8	2·3	−1·81
Vitamin C (mg)		51·5	20·3	49·1	20·3	−1·01
Alcohol (g)		23·2	28·5	24·1	28·2	+0·05†

* For details of subjects and procedures, see pp. 303–305.
† Calculated after log transformation.

The dietary differences within this homogenous study population was relatively small. This combined with the small size of the study (~1,700 men free of IHD at the beginning), and the short duration of the study (~5 years) resulted in practically no statistically significant results.

Table 2 above provides the mean daily nutrient intakes estimated for the free-IHD men. None of the dietary nutrients reached significance. Table 7 below shows the results for animal fat. Note the high-percentage, and the relatively narrow range.

Table 7. *Animal fat intake at baseline and ischaemic heart disease (IHD) incidence in the total cohort, in men who had evidence of IHD at baseline and in men who had no such evidence**

		All men in the cohort			Men with no evidence of IHD at baseline			Men with IHD at baseline		
			Incident IHD			Incident IHD			Incident IHD	
'Fifth' of men	% Energy from animal fat	No. of men	No.	Relative odds†	No. of men	No.	Relative odds†	No. of men	No.	Relative odds†
1	⩽ 22·3	467	33	1·0	341	14	1·0	126	19	1·0
2	22·4–27·2	466	17	0·5	351	11	0·8	115	6	0·3
3	27·3–31·3	467	25	0·8	371	12	0·9	96	13	0·8
4	31·4–36·2	467	31	1·0	350	18	1·3	117	13	0·7
5	> 36·2	467	31	0·9	343	15	0·9	124	16	0·8

* For details of subjects and procedures, see pp. 303–305.
† Adjusted for the effects of age, body mass index, smoking and, in the figures for the total cohort, for evidence of IHD at baseline.

Caerphilly Study Grading

1) *Overadjustment with Lipids*. **N**.
2) *Sufficient Test of SFA Guidelines*. **F**. The mean of Animal fat intake was 29.5% with an SD 7.2%. And then with Chowdhury collapsing into tertiles, the differences get even smaller compared to the quintiles in table 7.
3) *Homogeneity.* **F.** All the men were from neighboring small towns in South Wales, and eating a similar diet.
4) *Food/Lifestyle Questionnaire*. **D**. From the FFQ, fat components (SFA, PUFA, MUFA, TFA) could not be determined. The only lifestyle parameter was smoking.
5) *Missing Data in the Study.* **D.** No measurement or information on blood pressure, an important risk factor for CHD. No glucose measurement or indication of diabetes - another important risk factor. No indication of physical activity.
6) *Missing Data in the Paper*. **D**. The paper did not present the characteristics (dietary/lifestyle measurements) by SFA quintile.
7) *Confounders*. **F**. Most importantly, blood pressure and diabetes.
8) *Food vs. Nutrients*. **D**. A little information on fruit/vegetable and cereal intakes, but not used in any analysis.