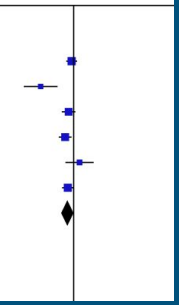
Seed oils and CHD

Matthew Nagra, BSc ND

Hooper, 2020

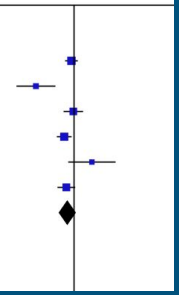
Analysis 1.45. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 45: CVD events, subgroup by main substitution

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.45.1 replaced by PUFA						
DART 1989	136	1018	147	1015	21.8%	0.92 [0.74 , 1.15]
Houtsmuller 1979	8	51	30	51	7.7%	0.27 [0.14 , 0.52]
MRC 1968	62	199	74	194	19.4%	0.82 [0.62 , 1.07]
Oslo Diet-Heart 1966	64	206	90	206	20.1%	0.71 [0.55 , 0.92]
Rose corn oil 1965	15	28	11	26	9.8%	1.27 [0.72 , 2.23]
Veterans Admin 1969	97	424	122	422	21.2%	0.79 [0.63 , 1.00]
Subtotal (95% CI)		**1926**		**1914**	**100.0%**	**0.78 [0.62 , 0.97]**
Total events:	382		474			
Heterogeneity: Tau² = 0.05; Chi² = 15.17, df = 5 (P = 0.010); I² = 67%						
Test for overall effect: Z = 2.25 (P = 0.02)						



Analysis 2.78. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 78: CHD events, subgroup by main substitution

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.78.1 replaced by PUFA						
DART 1989	132	1018	144	1015	22.4%	0.91 [0.73 , 1.14]
Houtsmuller 1979	8	51	30	51	10.1%	0.27 [0.14 , 0.52]
MRC 1968	50	199	50	194	18.7%	0.97 [0.69 , 1.37]
Oslo Diet-Heart 1966	64	206	90	206	21.3%	0.71 [0.55 , 0.92]
Rose corn oil 1965	12	28	6	26	7.8%	1.86 [0.82 , 4.22]
Veterans Admin 1969	60	424	78	422	19.7%	0.77 [0.56 , 1.04]
Subtotal (95% CI)		**1926**		**1914**	**100.0%**	**0.79 [0.60 , 1.04]**
Total events:	326		398			
Heterogeneity: Tau² = 0.07; Chi² = 17.71, df = 5 (P = 0.003); I² = 72%						
Test for overall effect: Z = 1.68 (P = 0.09)						



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Reduction in saturated fat intake for cardiovascular disease (Review)

Hooper L, Martin N, Jimoh OF, Kirk C, Foster E, Abdelhamid AS

Sacks, 2017

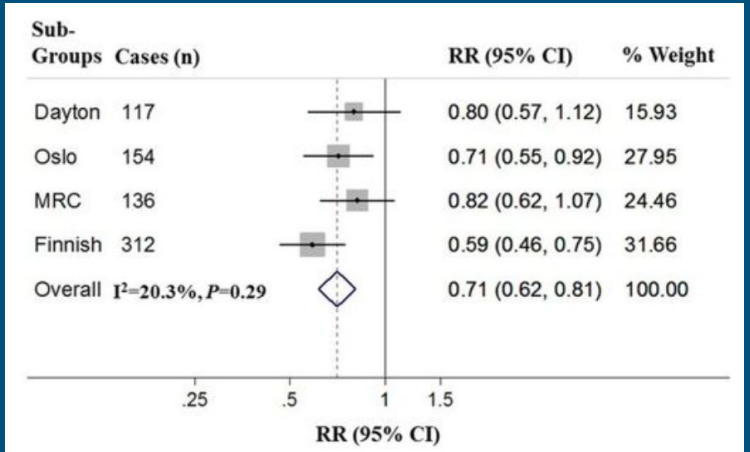

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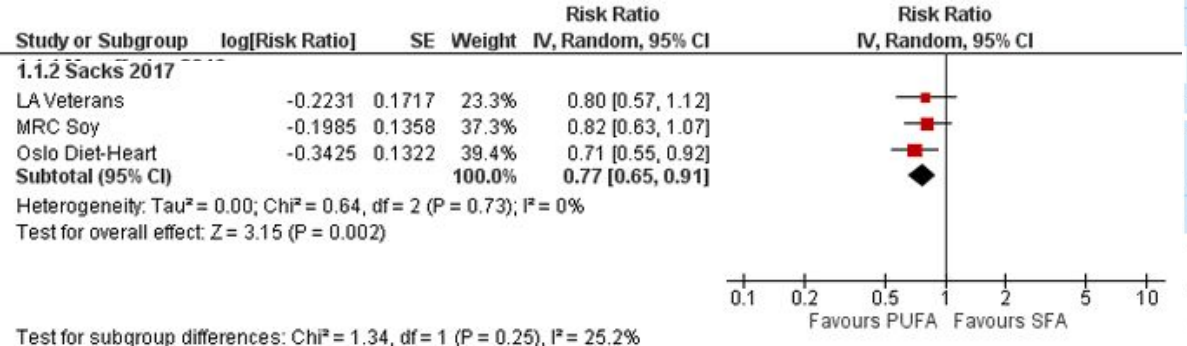
Figure 2. Meta-analysis of core trials on replacing saturated with polyunsaturated fat.



Dietary Fats and Cardiovascular Disease: A Presidential Advisory From the American Heart Association

Frank M. Sacks, Alice H. Lichtenstein, Jason H.Y. Wu, Lawrence J. Appel, Mark A. Creager, Penny M. Kris-Etherton, Michael Miller, Eric B. Rimm, Lawrence L. Rudel, Jennifer G. Robinson, ... See all authors
and On behalf of the American Heart Association

Originally published 15 Jun 2017 | https://doi.org/10.1161/CIR.0000000000000510 | Circulation. 2017;136:e1–e23

prevented CVD. We examined several recent systematic reviews and meta-analyses[9,10,16] from which we identified and here discuss 4 trials[20–22,30] that make up the core evidence on this important question on the basis of quality of study design, execution, and adherence. These trials compared high saturated with high polyunsaturated fat intake; did not include *trans* unsaturated fat as a major component; controlled the dietary intake of the intervention and control groups; had at least 2 years of sustained intake of the assigned diets; proved adherence by objective biomarkers such as serum cholesterol or blood or tissue levels of polyunsaturated fatty acids; and collected and validated information on cardiovascular or coronary disease events. The reason for the 2-year minimum duration is that changes in polyunsaturated fatty acids very slowly equilibrate with tissue fatty acid levels; it takes ≈2 years to achieve 60% to 70% of the full effect.[20,30]

Hooper, 2018

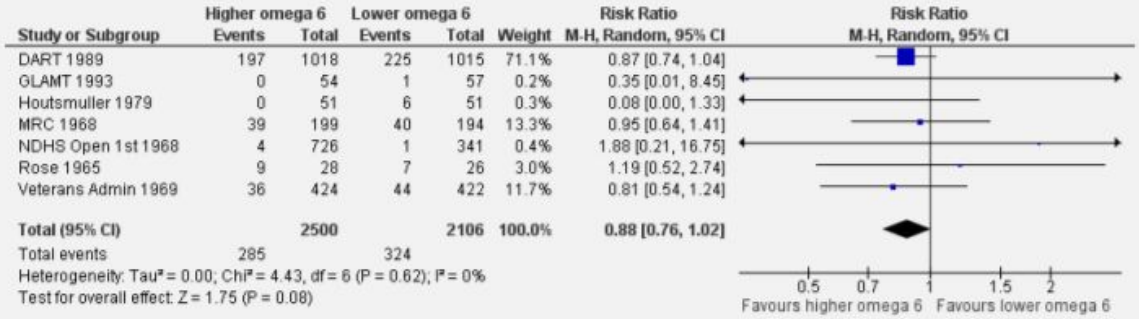
Cochrane Database of Systematic Reviews | Review - Intervention

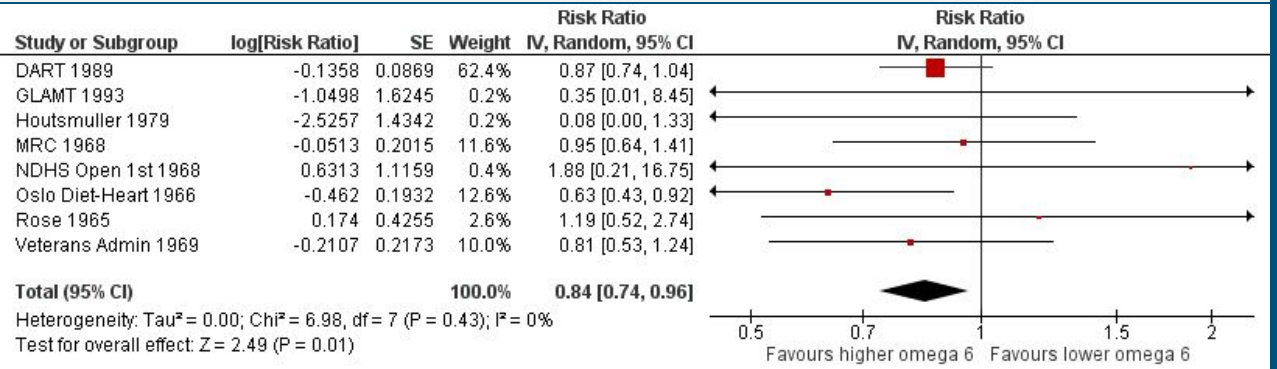
Omega-6 fats for the primary and secondary prevention of cardiovascular disease

Lee Hooper, Lena Al-Khudairy, Asmaa S Abdelhamid, Karen Rees, Julii S Brainard, Tracey J Brown, Sarah M Ajabnoor, Alex T O'Brien, Lauren E Winstanley, Daisy H Donaldson, Fujian Song, Katherine HO Deane
Authors' declarations of interest

Version published: 18 July 2018 Version history
https://doi.org/10.1002/14651858.CD011094.pub3

Figure 5. Forest plot of comparison: 2 Secondary outcomes - higher omega-6 vs lower omega-6, outcome: 2.1 Myocardial infarction (MI), overall.





Dayton, 1969

A Controlled Clinical Trial of a Diet High in Unsaturated Fat in Preventing Complications of Atherosclerosis

By Seymour Dayton, M.D., Morton Lee Pearce, M.D., Sam Hashimoto, M.S., Wilfrid J. Dixon, Ph.D., and Uwamie Tomiyasu, M.D.

Choice of Diet and Mode of Food Service

The circumstances of this trial—in particular the fact that most of the subjects were not highly motivated toward self-deprivation—rendered it mandatory that both diets be highly palatable by conventional criteria. It appeared on culinary grounds that a staff skilled in dietetics, with some industrial help on certain food products, could achieve a diet closely simulating the conventional institutional diet if, and only if, the total amount of dietary fat remained nearly unchanged. This restriction led to a decision to test a replacement of the saturated animal fats and hydrogenated shortenings of the conventional diet by equal quantities of unsaturated fat in the form of vegetable oils in the experimental diet. Because of uncertainty at the start of the trial about the importance of dietary cholesterol content, this was decreased as a secondary modification. A pilot study demonstrated that a varied and palatable diet could be developed in line with these specifications and that it was acceptable to most potential subjects, whereas low-fat diets were rejected forthwith. The diet chosen for study offered the incidental advantage that if it were ultimately found to be of value, it might be adopted by the general public more readily than would a diet requiring gastronomic sacrifice.

Most persons in the Domicile and all subjects in this study ate in a single large facility with one kitchen and two dining rooms. The food was served *ad libitum*, cafeteria style, with the two groups of subjects separated physically from each other and from men not on the study. To minimize errors in food preparation and service, cooking and serving containers were color-coded.

Since the participants had access to the community as well as to a canteen, total adherence to the study diet was the exception. Because rigid adherence could not be enforced, the level of adherence was monitored. Each man in the Home, including those not on the study, was issued a meal ticket of distinctive color which was punched at each meal. The punched ticket served as a record of meal attendance. This system also assured that each man remained on his assigned diet. All participants in the study were personally known to the dietitians and food service workers, who were thus further able to minimize deviations from prescribed diet within the dining room.

Diets

The control diet was a conventional food pattern containing 40% fat calories, mostly of animal origin. It was similar to the regular diet but not identical to it. The design of the experimental diet involved substitution of vegetable oils for about two-thirds of the animal fat, total fat content being kept around 40%. An attempt was made to stabilize the iodine value of the mixed fat in the control diet at 55 and that in the experimental diet at 100. Multiple vegetables oils were used, including corn, soybean, safflower, and cottonseed, the choice in an individual instance being largely pragmatic.

Because the potential importance of restricting dietary cholesterol intake was unclear at the time the study was begun, and because rigorous restriction of cholesterol-containing foods seemed likely to violate the goal of palatability, a compromise was arrived at by restriction of egg yolks to seven per week in the experimental diet. Largely because of this restriction and the absence of butterfat from the experimental diet, it was substantially lower in cholesterol than was the control ration.

Vegetable oils were incorporated into the experimental diet in the form of filled milk,* imitation ice cream, "unsaturated" margarine, special sausage products, and filled cheeses. Vegetable oils were used liberally in cooking and baking. Meat fat was minimized by the use of specially trimmed lean cuts. Further dietetic details are given in a separate publication.[7]

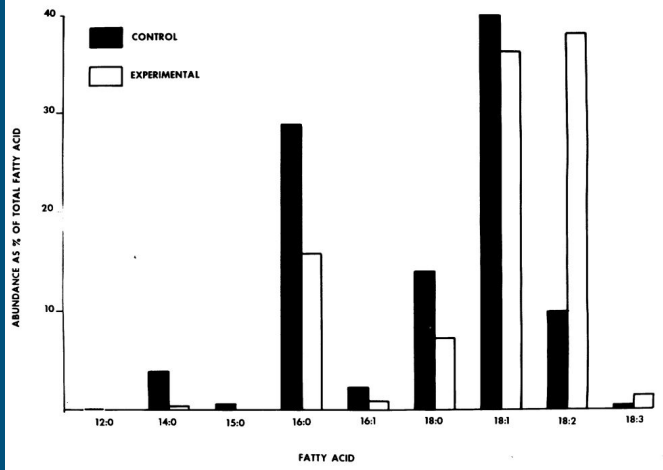


Figure 2

Fatty acids in dietary fat. The data are means of 19 eight-week collections analyzed at intervals during the study. Fatty acids are identified by chain length and number of double bonds.

Table 16

Composition of Diets

	Control	Experimental	*P*
Total daily calories†	2,496 ± 159	2,496 ± 122	
Protein (g/day)†	96.3 ± 8.8	97.4 ± 8.5	> 0.05*
Fat (g/day)†	111.2 ± 9.1	107.9 ± 7.3	< 0.001*
Fat calories (% of total)†	40.1 ± 2.2	38.9 ± 1.9	< 0.001*
Iodine value of fat†	53.5 ± 3.5	102.4 ± 4.6	< 0.001*
Cholesterol (mg/1,000 cal)‡	262	146	< 0.01**
Cholesterol (mg/day)‡	653	365	< 0.01**
β-sitosterol (mg/day)‡	< 50	215	< 0.01**

* By *t*-test.

** By sign test, using paired values.

† Mean ± SD of 412 to 427 one-week pooled collections.

‡ Mean of 19 analyses, each representing a four- to ten-week pool, weighted as to collection period.

Table 27

Summary Tabulation of Deaths by Category

Category	Number of cases	
	Control	Experimental
Due to acute atherosclerotic event (sole cause)	60	39
Mixed causes, including acute atherosclerotic event	10	9
Due to atherosclerotic complication without acute event	1	2
Mixed causes, including atherosclerotic complication without acute event	10	7
Other cause	71	85
Uncertain cause	25	32
Total	177	174

Table 30

Incidence Rates for Major Categories of Events After Stratification of the Study Population by Baseline Serum Cholesterol Level

	Cumulative incidence rates					
	Four-year		Eight-year		*P* for curve*	*P* for eight-year incidence†
	Con.	Exp.	Con.	Exp.		
Sudden death						
Low cholesterol‡	0.07	0.06	0.12	0.11	0.76	>0.8
High cholesterol§	0.05	0.05	0.22	0.06	0.08	<0.02
Definite myocardial infarct (overt or silent)						
Low cholesterol	0.10	0.05	0.17	0.16	0.41	>0.8
High cholesterol	0.12	0.10	0.30	0.21	0.67	>0.2
Definite cerebral infarct						
Low cholesterol	0.06	0.04	0.07	0.06	0.34	>0.6
High cholesterol	0.07	0.03	0.17	0.06	0.20	$0.1 > P > 0.05$
Sudden death or Definite myocardial infarct or Definite cerebral infarct						
Low cholesterol	0.20	0.12	0.31	0.28	0.08	>0.6
High cholesterol	0.23	0.16	0.54	0.28	0.01	<0.001
All "hard" end points						
Low cholesterol	0.20	0.13	0.34	0.30	0.06	>0.5
High cholesterol	0.26	0.17	0.56	0.32	0.04	<0.005
Fatal atherosclerotic events						
Low cholesterol	0.11	0.07	0.21	0.17	0.31	>0.4
High cholesterol	0.14	0.09	0.29	0.18	0.15	<0.05

* Computed by the method of Forsythe and Frey,[28] comparing the control (Con.) group incidence curve with the experimental (Exp.) group incidence curve.

† Computed by *t*-test. At four years none of the incidence rates showed significant differences between control and experimental groups.

‡ Baseline serum cholesterol ≤233 mg/dl.

§ Baseline serum cholesterol > 233 mg/dl.

Table 31

Rates for Combined Incidence of Sudden Death, Definite Myocardial Infarction (Silent or Overt), and Definite Cerebral Infarction by Quartiles of Initial Serum Cholesterol Level

Quartile	Four-year incidence		Eight-year incidence		*P* for eight-year incidence*
	Con.	Exp.	Con.	Exp.	
Lowest	0.14	0.11	0.24	0.25	N.S.
Second	0.26	0.13	0.37	0.30	N.S.
Third	0.20	0.15	0.54	0.27	< 0.025
Highest	0.27	0.18	0.53	0.27	< 0.05

*By *t*-test. None of the four-year incidence figures revealed significant differences between the control (Con.) and experimental (Exp.) groups. N.S. = not significant.

Farvid, 2014

Circulation
Volume 130, Issue 18, 28 October 2014; Pages 1568-1578
https://doi.org/10.1161/CIRCULATIONAHA.114.010236

ORIGINAL ARTICLE

Dietary Linoleic Acid and Risk of Coronary Heart Disease: A Systematic Review and Meta-Analysis of Prospective Cohort Studies

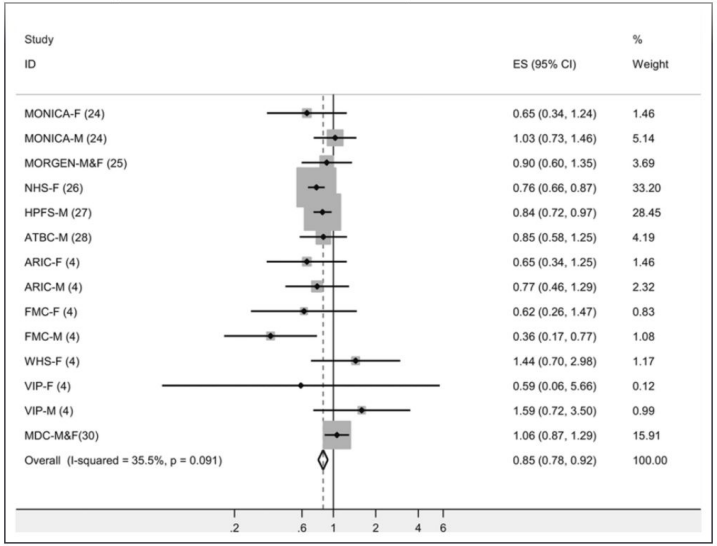


Figure 2. Dietary intake of linoleic acid and relative risk of total coronary heart disease events (highest category versus lowest category). The relative risk was pooled by using fixed-effects meta-analysis. ARIC indicates Atherosclerosis Risk in Communities; ATBC, Alpha-Tocopherol and Beta-Carotene Cancer Prevention; CI, confidence interval; ES, effect size; F, female; FMC, Finnish Mobile Clinic Health; HPFS, Health Professional Follow-Up Study; M, male; MDC, Malmo Diet and Cancer Cohort; MONICA, Multinational Monitoring of Trends and Determinations in Cardiovascular Disease; MORGEN, Monitoring Project on Risk Factors for Chronic Diseases; NHS, Nurses' Health Study; VIP, Västerbotten Intervention Program; and WHS, Women's Health Study.

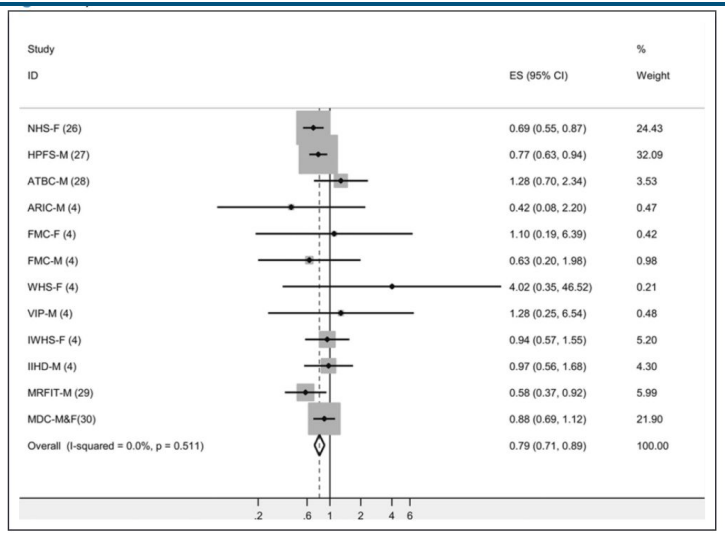


Figure 3. Dietary intake of linoleic acid and relative risk of coronary heart disease deaths (highest category versus lowest category). The relative risk was pooled by using fixed-effects meta-analysis. ARIC indicates Atherosclerosis Risk in Communities; ATBC, Alpha-Tocopherol and Beta-Carotene Cancer Prevention; CI, confidence interval; ES, effect size; F, female; FMC, Finnish Mobile Clinic Health; HPFS, Health Professional Follow-Up Study; IIHD, Israeli Ischemic Heart Disease; IWHS, Iowa Women's Health Study; M, male; MDC, Malmo Diet and Cancer Cohort; MRFIT, Multiple Risk Factor Intervention Trial; NHS, Nurses' Health Study; VIP, Västerbotten Intervention Program; and WHS, Women's Health Study.

Zhang, 2021

Research article | Open Access | Published: 15 April 2021

Cooking oil/fat consumption and deaths from cardiometabolic diseases and other causes: prospective analysis of 521,120 individuals

Yu Zhang ✉, Pan Zhuang, Fei Wu, Wei He, Lei Mao, Wei Jia, Yiju Zhang, Xiaoqian Chen & Jingjing Jiao ✉

BMC Medicine **19**, Article number: 92 (2021) | Cite this article

Margarine contains *trans*-fat, a well-documented risk factor for arterial calcification and coronary heart disease [26], and has a negative impact on plasma lipid profiles in both healthy individuals and patients with hypercholesterolemia [27]. Our findings were consistent with a recent meta-analysis, showing a positive association of *trans*-fat with all-cause and CVD mortality [28]. The observed association of margarine intake with modestly higher diabetes mortality was in line with a European multi-center study [29]. In addition, higher incidence of asthma onset was contributed by the intake of margarine [30], supporting our finding of elevated RD mortality. Compared with tub/soft margarine, our secondary analysis showed that stick margarine consumption turned to be much stronger for its positive association with AD mortality, which could be explained by higher *trans*-fat content (15–21%) [31] and supported by previous evidence suggesting a negative effect of *trans*-fat on dementia [32]. Taken together, our results suggest the importance of restricting intake of *trans*-fat containing margarines to decrease the incidence of cardiometabolic diseases.

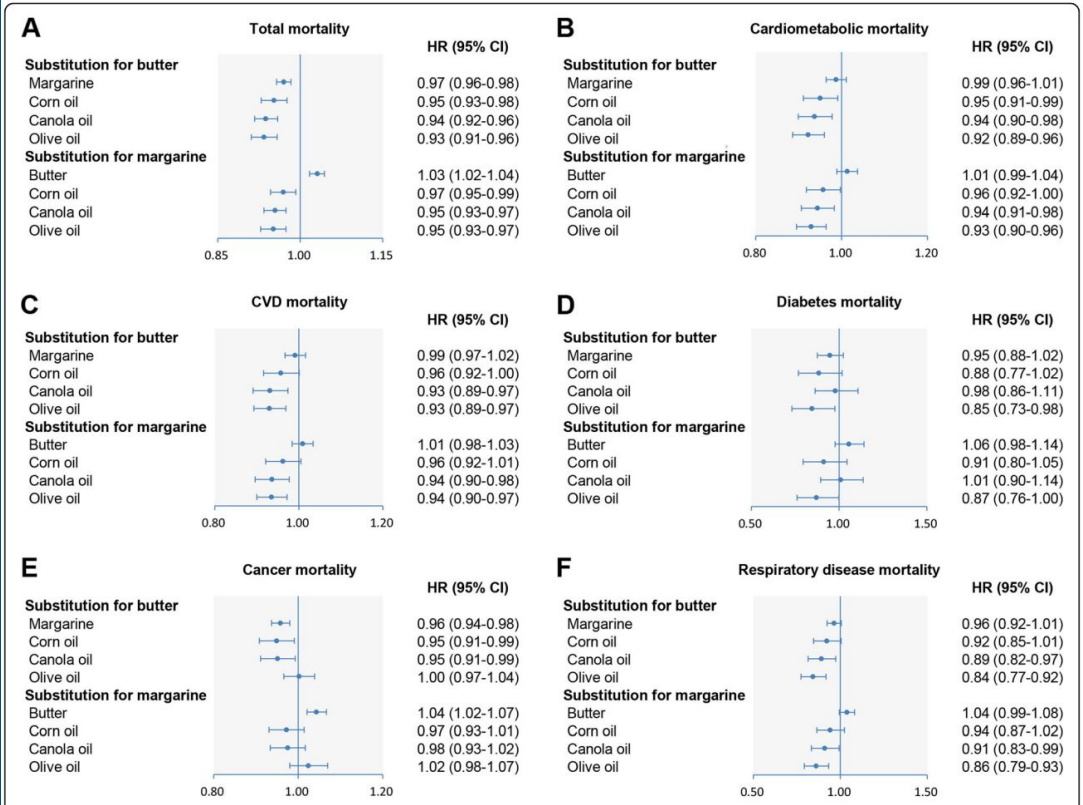


Fig. 3 Multivariable-adjusted hazard ratios of total and cause-specific mortality by substitution of 1 tablespoon/day individual cooking oils/fats for butter and margarine. Forest plots show the multivariable HRs of total and cause-specific mortality associated with substitution of 1 tablespoon/day individual cooking oils/fats for equivalent amounts of butter and margarine. HRs were adjusted for age, sex, BMI, race, education, marital status, household income, smoking, alcohol, vigorous physical activity, usual activity at work, perceived health condition, history of heart disease, stroke, diabetes, and cancer at baseline, Healthy Eating Index-2015, and total energy intake. Horizontal lines represent 95% CIs

Marklund, 2019

Table 2. Risk of Incident CVD According to Objective Biomarker Levels of Linoleic Acid (18:2n6) and Arachidonic Acid (20:4n6) in 30 Pooled Prospective Cohort Studies

Outcome	Biomarker	Studies, n	Cases, n	Multivariable-Adjusted Hazard Ratio (95% CI) per Interquintile Range*	
				Linoleic Acid	Arachidonic Acid
Total CVD	Phospholipid	14	6853	1.00 (0.92–1.09)	0.95 (0.87–1.03)
	Total plasma	6	2742	0.90 (0.78–1.03)	0.81 (0.70–0.94)
	Cholesterol esters	4	1300	0.74 (0.63–0.88)	1.03 (0.88–1.20)
	Adipose tissue	2	1412	0.87 (0.75–1.01)	0.98 (0.87–1.10)
	Overall†	21	10477	0.93 (0.88–0.99)	0.95 (0.90–1.01)
CVD mortality	Phospholipid	9	3057	0.89 (0.79–1.00)	0.93 (0.83–1.05)
	Total plasma	4	679	0.66 (0.50–0.86)	0.85 (0.66–1.09)
	Cholesterol esters	3	473	0.56 (0.43–0.73)	0.99 (0.76–1.29)
	Adipose tissue	2	418	0.60 (0.44–0.82)	1.02 (0.84–1.23)
	Overall†	17	4508	0.78 (0.70–0.85)	0.94 (0.86–1.02)
Total CHD	Phospholipid	14	6075	1.01 (0.93–1.10)	0.96 (0.90–1.03)
	Total plasma	7	2430	0.86 (0.74–1.00)	0.86 (0.74–1.01)
	Cholesterol esters	5	1178	0.78 (0.65–0.94)	1.02 (0.85–1.23)
	Adipose tissue	3‡	3255	0.88 (0.74–1.03)	1.10 (0.98–1.23)
	Overall†	26‡	11857	0.94 (0.88–1.00)	0.99 (0.94–1.04)
Ischemic stroke	Phospholipid	12	2327	0.95 (0.82–1.10)	0.98 (0.85–1.13)
	Total plasma	6	1105	0.84 (0.66–1.06)	0.93 (0.73–1.18)
	Cholesterol esters	4	598	0.67 (0.51–0.88)	1.13 (0.89–1.43)
	Adipose tissue	2	405	0.87 (0.65–1.15)	0.91 (0.74–1.11)
	Overall†	21	3705	0.88 (0.79–0.98)	0.99 (0.90–1.10)

Biomarkers of Dietary Omega-6 Fatty Acids and Incident Cardiovascular Disease and Mortality

An Individual-Level Pooled Analysis of 30 Cohort Studies

Matti Marklund, Jason H.Y. Wu, Fumiaki Imamura, Liana C. Del Gobbo, Amanda Fretts, Janette de Goede, Peilin Shi, Nathan Tintle, Maria Wennberg, Stella Aslibekyan, Tzu-An Chen, … See all authors

Originally published 11 Apr 2019 | https://doi.org/10.1161/CIRCULATIONAHA.118.038908 | Circulation. 2019;139:2422–2436

Park, 2021

Open Access Article

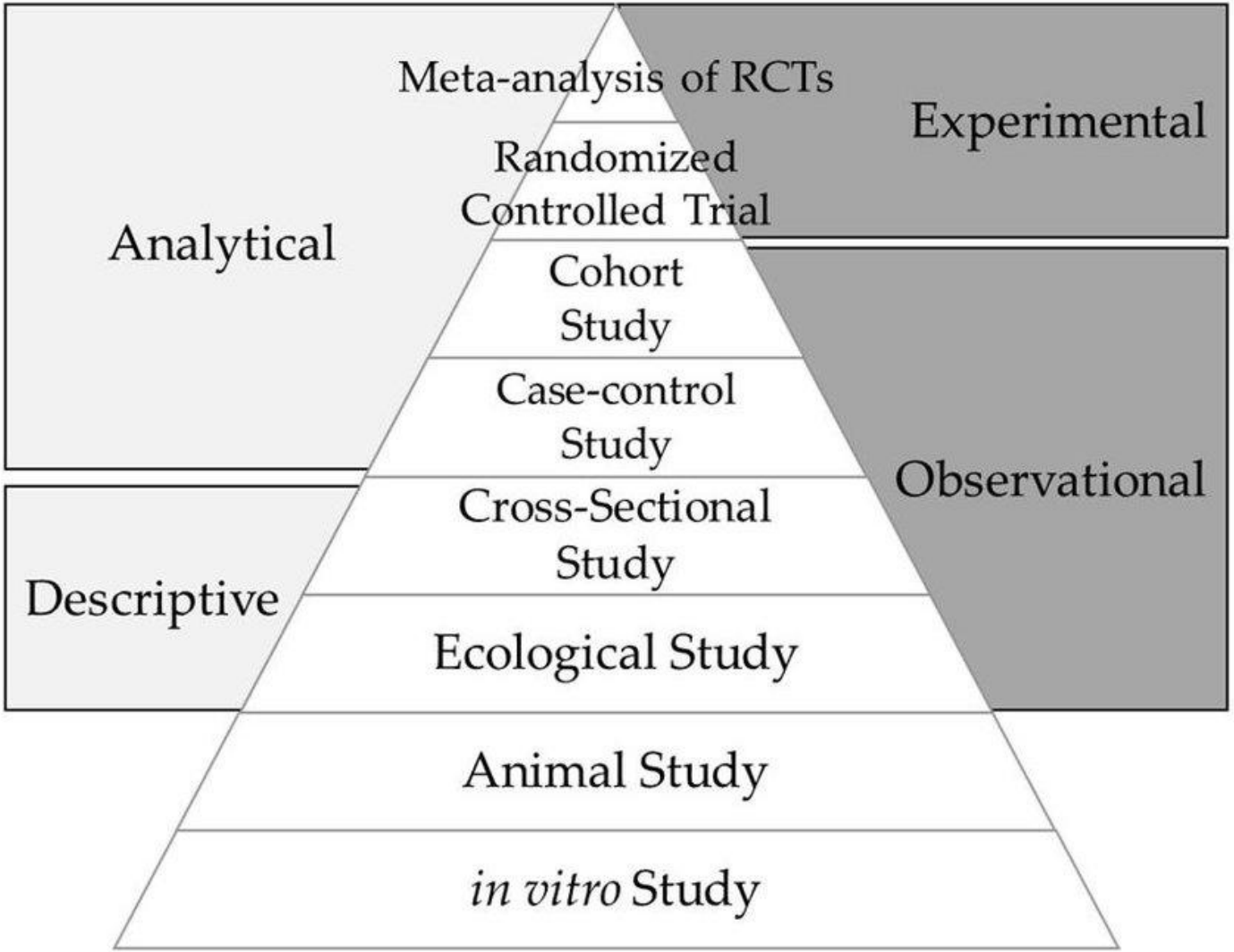
Causal Effects of Serum Levels of n-3 or n-6 Polyunsaturated Fatty Acids on Coronary Artery Disease: Mendelian Randomization Study

by Sehoon Park [1,2], Soojin Lee [3], Yaerim Kim [4], Yeonhee Lee [3], Min Woo Kang [5], Kwangsoo Kim [6], Yong Chul Kim [5], Seung Seok Han [5,7], Hajeong Lee [5,7], Jung Pyo Lee [7,8,9], Kwon Wook Joo [5,7,8], Chun Soo Lim [7,8,9], Yon Su Kim [1,5,7,8] and Dong Ki Kim [5,7,8,*]

Table 3. Allele-score based Mendelian randomization results in the UK Biobank data for MI outcome.

Genetically Predicted PUFA Level by Allele–Scores (1 Standard Deviation Increase)	Main Analysis [a]		Sensitivity Analysis Adjusted for Phenotypical Covariates [b]	
	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
n-3 PUFAs				
Eicosapentaenoic acid	0.973 (0.956–0.991)	0.003	0.969 (0.949–0.989)	0.002
Docosapentaenoic acid	1.027 (1.009–1.046)	0.004	1.029 (1.008–1.050)	0.006
Docosahexaenoic acid	1.000 (0.982–1.018)	0.986	1.003 (0.982–1.023)	0.804
n-6 PUFAs				
Linoleic acid	0.975 (0.957–0.992)	0.005	0.967 (0.947–0.987)	0.001
Gamma-linolenic acid	1.022 (1.003–1.040)	0.020	1.028 (1.007–1.049)	0.009
Dihomo-gamma-linolenic acid	0.972 (0.955–0.990)	0.002	0.969 (0.950–0.989)	0.003
Arachidonic acid	1.027 (1.009–1.046)	0.004	1.034 (1.013–1.056)	0.001
Adrenic acid	1.004 (0.986–1.022)	0.672	1.008 (0.987–1.029)	0.458

PUFA = polyunsaturated fatty acids; OR = odds ratio; CI = confidence interval; MI = myocardial infarction. All allele scores were scaled to a one standard deivation increase. [a] The logistic regression model was adjusted for age, sex, and the first 10 principal components of the genetic information. [b] The phenotypical hypertension, diabetes mellitus, obesity, dyslipidemia medication history, smoking, laboratory values for low-density lipoprotein, high-density lipoprotein, and triglycerides were added to the main model.


Meta-analysis of RCTs
Randomized Controlled Trial
Cohort Study
Case-control Study
Cross-Sectional Study
Ecological Study
Animal Study
in vitro Study
Analytical
Descriptive
Experimental
Observational

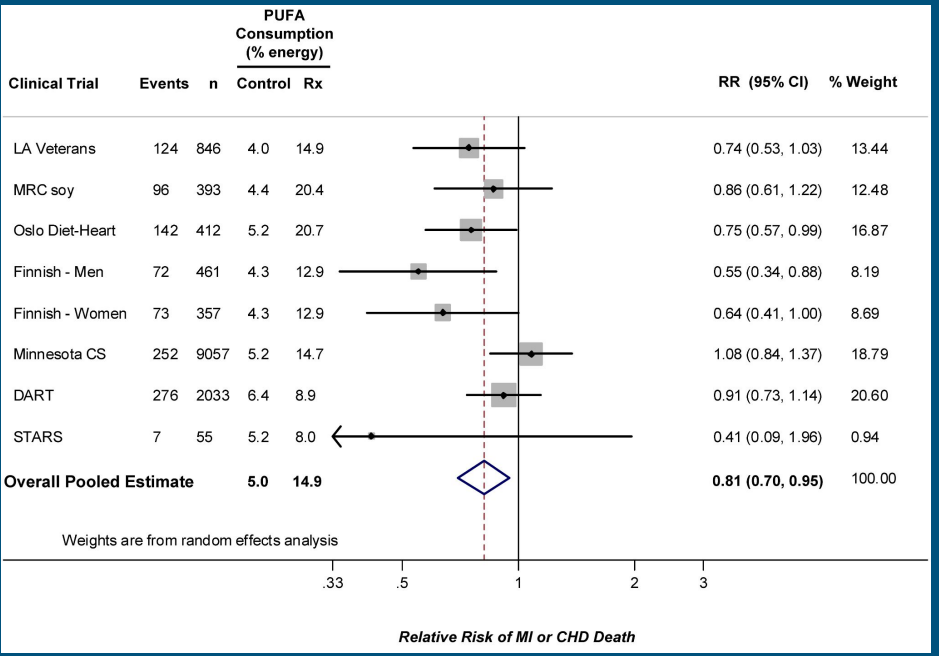
All References

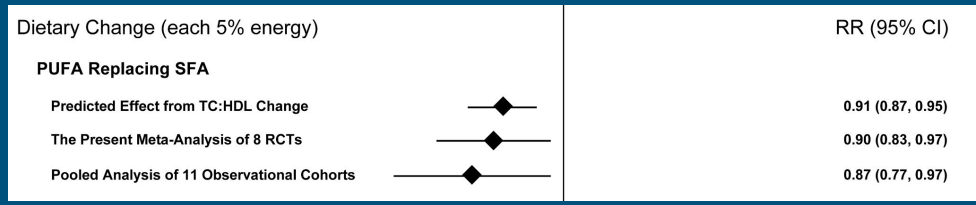
Mozaffarian, 2010

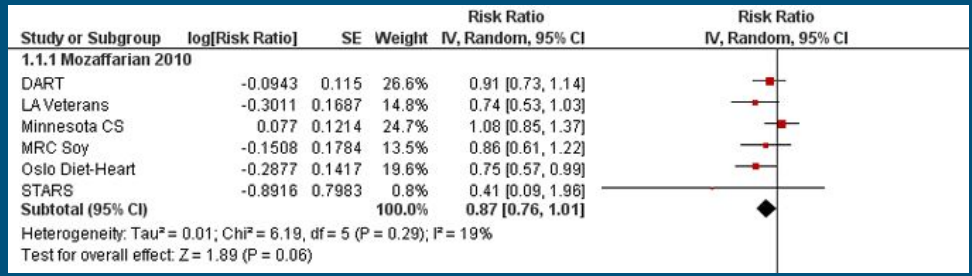
Effects on Coronary Heart Disease of Increasing Polyunsaturated Fat in Place of Saturated Fat: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Dariush Mozaffarian, Renata Micha, Sarah Wallace

Published: March 23, 2010 • https://doi.org/10.1371/journal.pmed.1000252



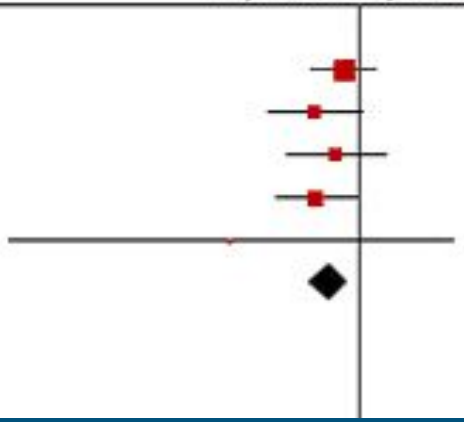




Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
1.2.1 Mozaffarian 2010				
DART	-0.0943	0.115	39.1%	0.91 [0.73, 1.14]
LA Veterans	-0.3011	0.1687	18.2%	0.74 [0.53, 1.03]
MRC Soy	-0.1508	0.1784	16.2%	0.86 [0.61, 1.22]
Oslo Diet-Heart	-0.2877	0.1417	25.7%	0.75 [0.57, 0.99]
STARS	-0.8916	0.7983	0.8%	0.41 [0.09, 1.96]
Subtotal (95% CI)			**100.0%**	**0.82 [0.71, 0.95]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.41$, $df = 4$ ($P = 0.66$); $I^2 = 0\%$

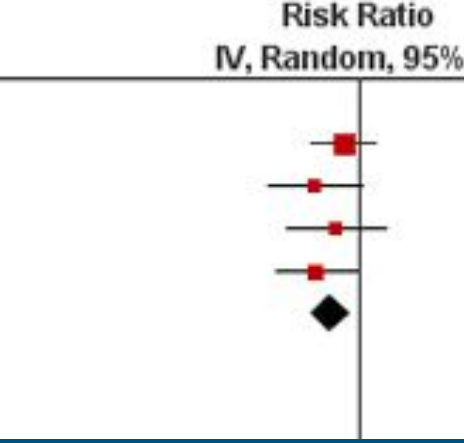
Test for overall effect: $Z = 2.74$ ($P = 0.006$)



Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
1.3.1 Mozaffarian 2010				
DART	-0.0943	0.115	39.4%	0.91 [0.73, 1.14]
LA Veterans	-0.3011	0.1687	18.3%	0.74 [0.53, 1.03]
MRC Soy	-0.1508	0.1784	16.4%	0.86 [0.61, 1.22]
Oslo Diet-Heart	-0.2877	0.1417	25.9%	0.75 [0.57, 0.99]
Subtotal (95% CI)			**100.0%**	**0.83 [0.72, 0.95]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.65$, $df = 3$ ($P = 0.65$); $I^2 = 0\%$

Test for overall effect: $Z = 2.65$ ($P = 0.008$)



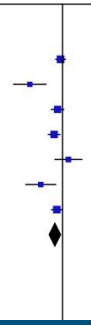
Hooper, 2020

Analysis 1.44. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 44: CVD events, subgroup by any substitution

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.44.1 replaced by PUFA						
DART 1989	136	1018	147	1015	19.5%	0.92 [0.74 , 1.15]
Houtsmuller 1979	8	51	30	51	7.7%	0.27 [0.14 , 0.52]
MRC 1968	62	199	74	194	17.6%	0.82 [0.62 , 1.07]
Oslo Diet-Heart 1966	64	206	90	206	18.2%	0.71 [0.55 , 0.92]
Rose corn oil 1965	15	28	11	26	9.6%	1.27 [0.72 , 2.23]
STARS 1992	8	27	20	28	8.5%	0.41 [0.22 , 0.78]
Veterans Admin 1969	97	424	122	422	19.0%	0.79 [0.63 , 1.00]
Subtotal (95% CI)		**1953**		**1942**	**100.0%**	**0.73 [0.58 , 0.92]**
Total events:	390		494			

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 19.30$, $df = 6$ ($P = 0.004$); $I^2 = 69\%$

Test for overall effect: $Z = 2.68$ ($P = 0.007$)

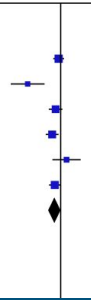


Analysis 1.45. Comparison 1: SFA reduction vs usual diet - primary outcomes, Outcome 45: CVD events, subgroup by main substitution

Study or Subgroup	lower SFA Events	lower SFA Total	higher SFA Events	higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
1.45.1 replaced by PUFA						
DART 1989	136	1018	147	1015	21.8%	0.92 [0.74 , 1.15]
Houtsmuller 1979	8	51	30	51	7.7%	0.27 [0.14 , 0.52]
MRC 1968	62	199	74	194	19.4%	0.82 [0.62 , 1.07]
Oslo Diet-Heart 1966	64	206	90	206	20.1%	0.71 [0.55 , 0.92]
Rose corn oil 1965	15	28	11	26	9.8%	1.27 [0.72 , 2.23]
Veterans Admin 1969	97	424	122	422	21.2%	0.79 [0.63 , 1.00]
Subtotal (95% CI)		**1926**		**1914**	**100.0%**	**0.78 [0.62 , 0.97]**
Total events:	382		474			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 15.17$, $df = 5$ ($P = 0.010$); $I^2 = 67\%$

Test for overall effect: $Z = 2.25$ ($P = 0.02$)



Cochrane Library

Cochrane Database of Systematic Reviews

Reduction in saturated fat intake for cardiovascular disease (Review)

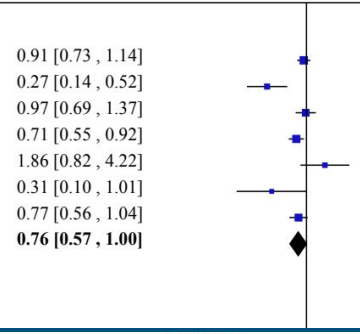
Hooper L, Martin N, Jimoh OF, Kirk C, Foster E, Abdelhamid AS

Analysis 2.77. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 77: CHD events, subgroup by any substitution

Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.77.1 replaced by PUFA						
DART 1989	132	1018	144	1015	21.1%	0.91 [0.73 , 1.14]
Houtsmuller 1979	8	51	30	51	9.9%	0.27 [0.14 , 0.52]
MRC 1968	50	199	50	194	17.9%	0.97 [0.69 , 1.37]
Oslo Diet-Heart 1966	64	206	90	206	20.2%	0.71 [0.55 , 0.92]
Rose corn oil 1965	12	28	6	26	7.7%	1.86 [0.82 , 4.22]
STARS 1992	3	27	10	28	4.5%	0.31 [0.10 , 1.01]
Veterans Admin 1969	60	424	78	422	18.7%	0.77 [0.56 , 1.04]
Subtotal (95% CI)		**1953**		**1942**	**100.0%**	**0.76 [0.57 , 1.00]**
Total events:	329		408			

Heterogeneity: Tau² = 0.08; Chi² = 20.25, df = 6 (P = 0.002); I² = 70%

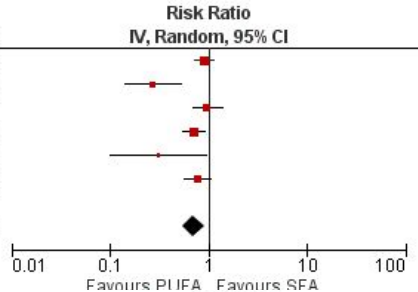
Test for overall effect: Z = 1.97 (P = 0.05)



Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
DART 1989	-0.0943	0.115	23.1%	0.91 [0.73, 1.14]
Houtsmuller 1979	-1.3093	0.3344	10.5%	0.27 [0.14, 0.52]
MRC 1968	-0.0305	0.1762	19.0%	0.97 [0.69, 1.37]
Oslo Diet-Heart 1966	-0.3425	0.1322	22.0%	0.71 [0.55, 0.92]
STARS 1992	-1.1712	0.5773	4.7%	0.31 [0.10, 0.96]
Veterans Admin 1969	-0.2614	0.1534	20.6%	0.77 [0.57, 1.04]
Total (95% CI)			**100.0%**	**0.70 [0.54, 0.92]**

Heterogeneity: Tau² = 0.07; Chi² = 16.46, df = 5 (P = 0.006); I² = 70%

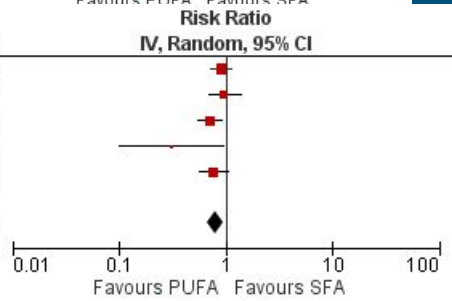
Test for overall effect: Z = 2.53 (P = 0.01)



Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
DART 1989	-0.0943	0.115	30.9%	0.91 [0.73, 1.14]
MRC 1968	-0.0305	0.1762	18.2%	0.97 [0.69, 1.37]
Oslo Diet-Heart 1966	-0.3425	0.1322	26.5%	0.71 [0.55, 0.92]
STARS 1992	-1.1712	0.5767	2.3%	0.31 [0.10, 0.96]
Veterans Admin 1969	-0.2614	0.1534	22.1%	0.77 [0.57, 1.04]
Total (95% CI)			**100.0%**	**0.81 [0.68, 0.97]**

Heterogeneity: Tau² = 0.01; Chi² = 5.93, df = 4 (P = 0.20); I² = 33%

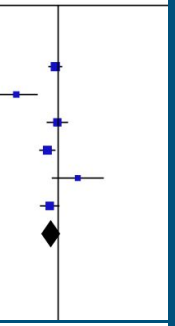
Test for overall effect: Z = 2.36 (P = 0.02)



Analysis 2.78. Comparison 2: SFA reduction vs usual diet - secondary health events, Outcome 78: CHD events, subgroup by main substitution

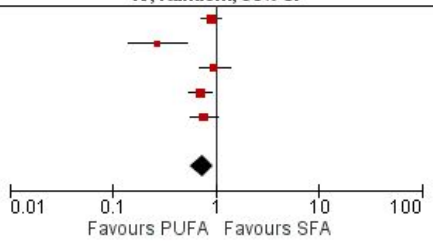
Study or Subgroup	Lower SFA Events	Lower SFA Total	Higher SFA Events	Higher SFA Total	Weight	Risk Ratio M-H, Random, 95% CI
2.78.1 replaced by PUFA						
DART 1989	132	1018	144	1015	22.4%	0.91 [0.73 , 1.14]
Houtsmuller 1979	8	51	30	51	10.1%	0.27 [0.14 , 0.52]
MRC 1968	50	199	50	194	18.7%	0.97 [0.69 , 1.37]
Oslo Diet-Heart 1966	64	206	90	206	21.3%	0.71 [0.55 , 0.92]
Rose corn oil 1965	12	28	6	26	7.8%	1.86 [0.82 , 4.22]
Veterans Admin 1969	60	424	78	422	19.7%	0.77 [0.56 , 1.04]
Subtotal (95% CI)		**1926**		**1914**	**100.0%**	**0.79 [0.60 , 1.04]**
Total events:	326		398			

Heterogeneity: Tau² = 0.07; Chi² = 17.71, df = 5 (P = 0.003); I² = 72%
Test for overall effect: Z = 1.68 (P = 0.09)



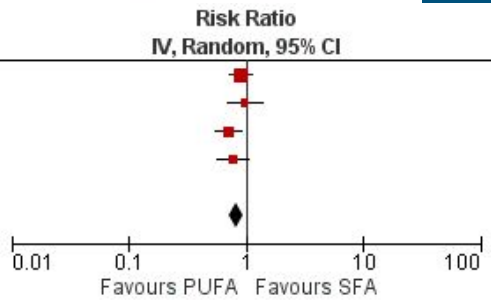
Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
DART 1989	-0.0943	0.115	24.6%	0.91 [0.73, 1.14]
Houtsmuller 1979	-1.3093	0.3344	10.6%	0.27 [0.14, 0.52]
MRC 1968	-0.0305	0.1762	19.9%	0.97 [0.69, 1.37]
Oslo Diet-Heart 1966	-0.3425	0.1322	23.3%	0.71 [0.55, 0.92]
Veterans Admin 1969	-0.2614	0.1534	21.6%	0.77 [0.57, 1.04]
Total (95% CI)			**100.0%**	**0.74 [0.57, 0.96]**

Heterogeneity: Tau² = 0.06; Chi² = 13.86, df = 4 (P = 0.008); I² = 71%
Test for overall effect: Z = 2.25 (P = 0.02)



Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
DART 1989	-0.0943	0.115	36.2%	0.91 [0.73, 1.14]
MRC 1968	-0.0305	0.1762	15.7%	0.97 [0.69, 1.37]
Oslo Diet-Heart 1966	-0.3425	0.1322	27.6%	0.71 [0.55, 0.92]
Veterans Admin 1969	-0.2614	0.1534	20.6%	0.77 [0.57, 1.04]
Total (95% CI)			**100.0%**	**0.83 [0.72, 0.95]**

Heterogeneity: Tau² = 0.00; Chi² = 3.06, df = 3 (P = 0.38); I² = 2%
Test for overall effect: Z = 2.67 (P = 0.008)



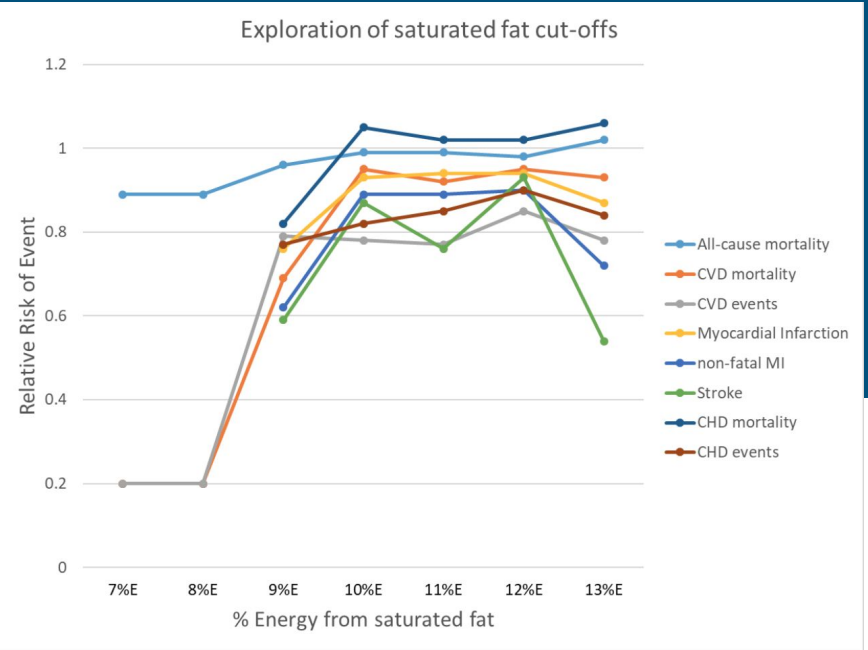


Table 4. Meta-regression of effects of SFA reduction on cardiovascular events

Regression factor	No. of studies	Constant	Coefficient (95% CI)	P value	Proportion of between study variation explained
Change in SFA as %E	8	0.01	0.05 (-0.03 to 0.13)	0.16	89%
Change in SFA as % of control	8	0.26	0.01 (-0.01 to 0.03)	0.14	89%
Baseline SFA as %E	8	0.68	-0.06 (-0.15 to 0.04)	0.19	81%
Change in TC, mmol/L	12	0.03	0.69 (0.05 to 1.33)	0.04	99%
Change in PUFA as %E	5	-0.01	-0.02 (-0.08 to 0.03)	0.25	100%
Change in MUFA as %E	5	-0.26	-0.03 (-0.14 to 0.09)	0.50	-87%
Change in CHO as %E	7	-0.11	-0.00 (-0.05 to 0.05)	0.92	-273%
Change in total fat intake as %E	9	-0.17	-0.01 (-0.03 to 0.01)	0.28	100%
Gender*	13	-0.17	-0.14 (-0.63 to 0.35)	0.55	-13%
Study duration	13	-0.47	0.00 (-0.01 to 0.02)	0.76	-24.8%
CVD risk at baseline**	13	-0.44	0.03 (-0.48 to 0.55)	0.89	-39%

Sacks, 2017

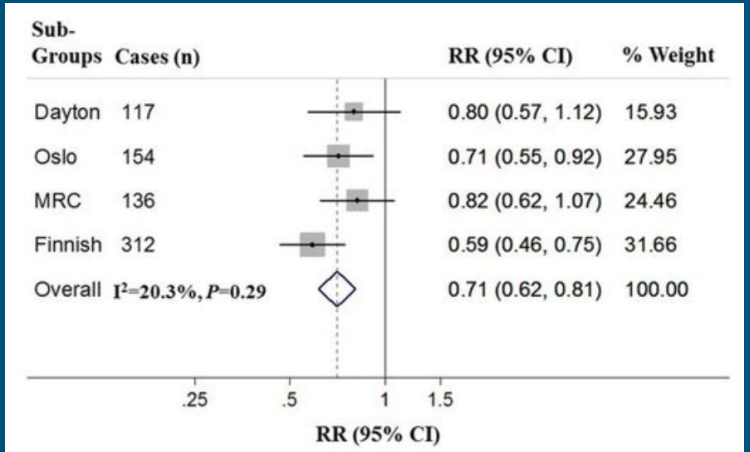


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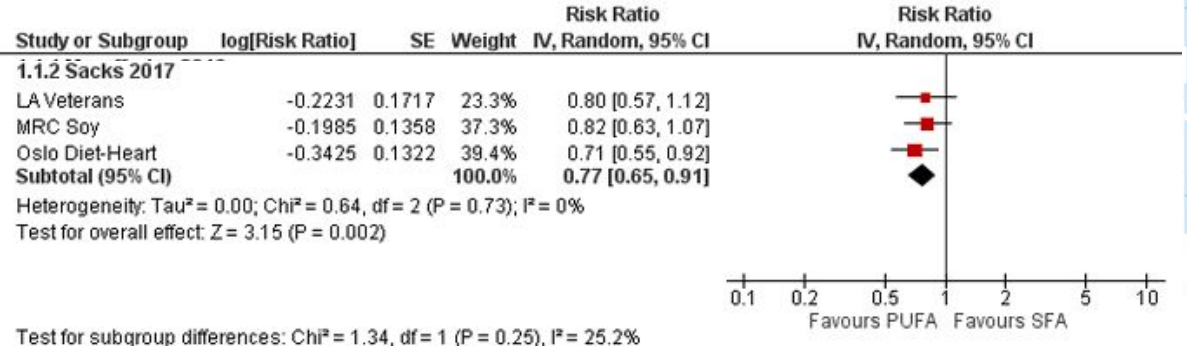
Figure 2. Meta-analysis of core trials on replacing saturated with polyunsaturated fat.



Dietary Fats and Cardiovascular Disease: A Presidential Advisory From the American Heart Association

Frank M. Sacks, Alice H. Lichtenstein, Jason H.Y. Wu, Lawrence J. Appel, Mark A. Creager, Penny M. Kris-Etherton, Michael Miller, Eric B. Rimm, Lawrence L. Rudel, Jennifer G. Robinson, ... See all authors
and On behalf of the American Heart Association

Originally published 15 Jun 2017 | https://doi.org/10.1161/CIR.0000000000000510 | Circulation. 2017;136:e1–e23

prevented CVD. We examined several recent systematic reviews and meta-analyses[9,10,16] from which we identified and here discuss 4 trials[20–22,30] that make up the core evidence on this important question on the basis of quality of study design, execution, and adherence. These trials compared high saturated with high polyunsaturated fat intake; did not include *trans* unsaturated fat as a major component; controlled the dietary intake of the intervention and control groups; had at least 2 years of sustained intake of the assigned diets; proved adherence by objective biomarkers such as serum cholesterol or blood or tissue levels of polyunsaturated fatty acids; and collected and validated information on cardiovascular or coronary disease events. The reason for the 2-year minimum duration is that changes in polyunsaturated fatty acids very slowly equilibrate with tissue fatty acid levels; it takes ≈2 years to achieve 60% to 70% of the full effect.[20,30]

Leren, 1970

Table 1

Daily Food Intake of Experimental Group as Measured During Initial 5-Year Study

	Grams	% of calories
Carbohydrates (total)	269	45.5
Sugar	51	
Protein	92	15.0
Fat (total)	104	39.0
Saturated fat	22	8.5
Monounsaturated fat	27	10.1
Polyunsaturated fat	55	20.7
Dietary cholesterol	0.264	
P/S ratio	2.4	

Abbreviation: P/S = ratio of polyunsaturated fat to saturated fat.

The Oslo Diet-Heart Study

Eleven-Year Report

PAUL LEREN

Originally published 1 Nov 1970 | https://doi.org/10.1161/01.CIR.42.5.935 | Circulation. 1970;42:935–942

The Experimental Diet for the 5-Year Trial

This cholesterol lowering diet was low in animal fats and dietary cholesterol and rich in vegetable oil. Much emphasis was laid on continuous instruction and supervision of the dieters during the first 5 years of the trial. To obtain more precise information about the diet, 17 dieters were selected, and their diet was weighed or measured under the supervision of the dietitian for a period of 7 to 14 days. The results are presented in table 1. The average reduction in serum cholesterol of these selected dieters was 29% over the period of 5 years. The serum cholesterol values in the two groups are presented in figure 1.

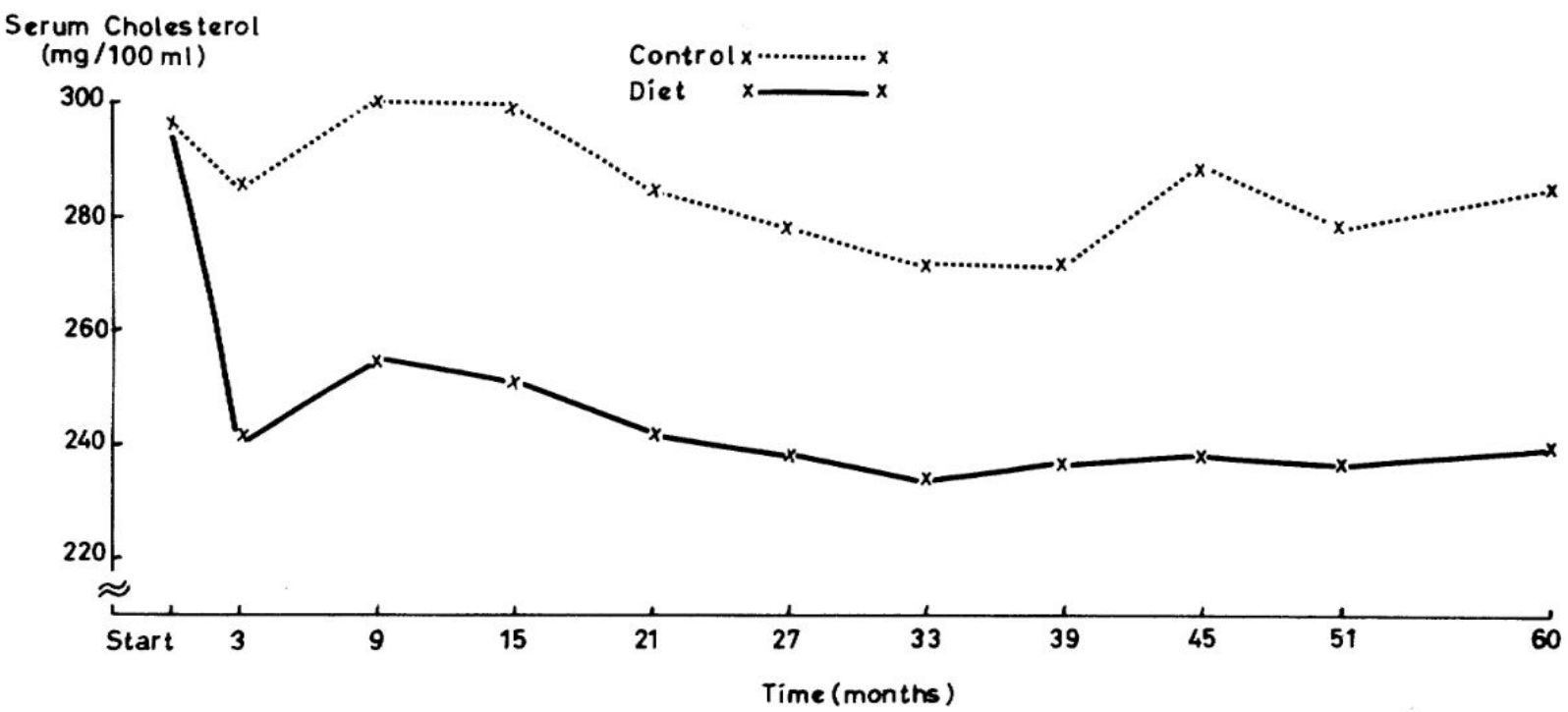


Figure 1

Mean serum cholesterol levels during the first 5 years of observation time.

	N (at entry)	*Value at entry (mg/100 ml)*	*Mean reduction (mg)*	*(%)*
Control	*206*	*296*	*11*	*3.7*
Diet	*206*	*296*	*52*	*17.6*

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Five-Year Results

There was a statistically significant lower incidence of myocardial reinfarction and of new angina pectoris in the diet group. The incidence of sudden death, however, was the same in the two groups. Table 2 recapitulates the major "harder" events after 5 years (omitting acquired angina). A statistically significant reduced incidence of major CHD relapses was demonstrated. The difference in total cardiovascular deaths and total deaths is large but is not significant on the 5% level of probability.

Further details about selection of the patients, randomization, the experimental diet, CHD relapse incidence in various subgroups are presented in the 5-year report.[1]

Table 2

Five-Year Results

	Diet	Control
No. of men at risk	206	206
Fatal myocardial reinfarction	10	23
Sudden death	27	27
Nonfatal myocardial reinfarction	24	31
Major CHD relapses*	61	81
Total cardiovascular mortality†	38	52
Total mortality‡	41	55

*$P = 0.05$ †$P = 0.09$ ‡$P = 0.13$

Table 5

Cardiovascular Mortality

	Diet	Control
Fatal myocardial reinfarction	25	34
Fatal heart failure	2	7
Death preceded by chest pains	5	16
Fatal myocardial infarction*	32	57
Instantaneous deaths	33	30
Unwitnessed deaths	14	7
Total CHD mortality †	79	94
Cerebral vascular deaths	7	5
Other vascular deaths	2	3
Total cardiovascular mortality‡	88	102

*$P = 0.004$ †$P = 0.097$ ‡$P = 0.13$

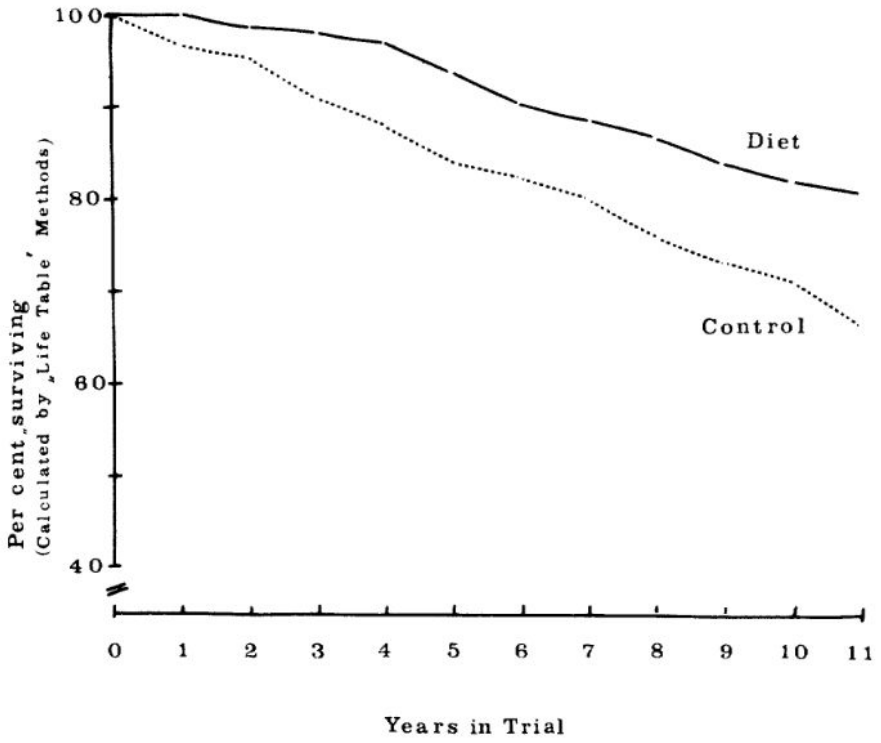


Figure 2

Fatal myocardial infarction: 11-year survival curves.

	Estimated % survival		*Standard error*
Diet	*80.5*		*3.2*
Control	*66.1*	$P = 0.004$	*3.8*

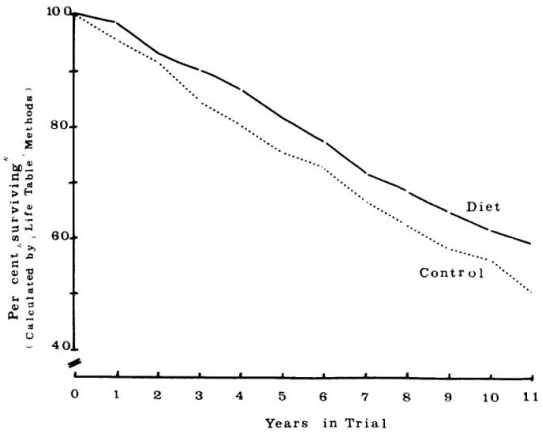


Figure 3

Overall CHD mortality: 11-year survival curves.

	Estimated % survival		*Standard error*
Diet	*59.4*		*3.6*
Control	*50.8*	$P = 0.097$	*3.8*

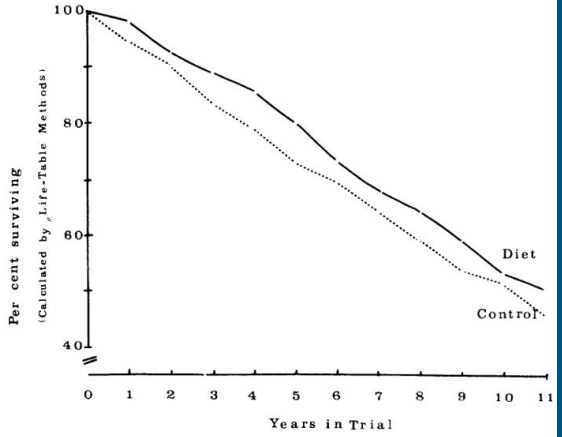


Figure 4

Overall mortality: 11-year survival curves.

	Estimated % survival		*Standard error*
Diet	*50.3*		*3.5*
Control	*45.6*	$P = 0.35$	*3.6*

Table 6

Eleven-Year Incidence of CHD Mortality in Relation to Age.

	Age < 60		Age > 60	
	Diet	Control	Diet	Control
At risk	134	123	72	83
Fatal infarction	23	29	9	28
Sudden deaths	26	21	21	16
Total CHD deaths	49	50	30	44
%	36.5	40.7	41.7	53.0

Medical Research Council, 1968

CONTROLLED TRIAL OF SOYA-BEAN OIL IN MYOCARDIAL INFARCTION

REPORT OF A RESEARCH COMMITTEE TO THE MEDICAL RESEARCH COUNCIL*

TABLE I—COMPARISON BETWEEN PATIENTS ON TEST DIET AND CONTROLS AT ENTRY TO TRIAL

Factor	Test diet %*	Control %*
Angina present before first infarct†	32	26
First infarct graded "severe"†	14	18
Absent peripheral pulses†	11	17
Intermittent claudication†	8	4
Phlebitis or venous thrombosis†	3	5
Arcus senilis, complete ring†	10	7
Aged 50 and over	65	59
Parent died aged 40–64	44	49
Height under 5 ft. 6 in.	23	33
Weight 180 lb. and over	20	19
Serum-cholesterol 325 mg. per 100 ml. and over	15	18
Systolic blood-pressure 160 mg. Hg and over	8	12
Diastolic blood-pressure 100 mg. Hg and over	13	11
Cigarette smokers	81	84
Smokers of 30 or more cigarettes per day	20	20
Social classes I and II‡	24	29
Sedentary occupation§	64	62
All patients	199	194

* % of those for whom factor was recorded.
† Diagnosis before randomisation to the two regimens.
‡ Classification of the Registrar General (1960).
§ Classification developed for the Social Medicine Research Unit (Morris and Crawford 1958).

Dietary Regimen

As far as possible, saturated fats were removed from the diet. Patients on the test diet were instructed to take 3 oz. (85 g.) of soya-bean oil daily. This oil was chosen because it is highly unsaturated and, when used previously in a similar diet, had been shown to cause a satisfactory fall in serum-cholesterol (Pilkington et al. 1960). The soya-bean oil from various sources used by the patients was analysed and found to be a fully standardised product.

At least 43 g. of soya-bean oil daily had to be taken unheated, and it was often drunk with fruit juice. The remainder could be used in cooking. In 10 patients who developed intolerance to the oil, such as nausea and diarrhœa, corn oil was substituted. Up to 35 g. of other fat per day was also allowed. 14 g. of this was taken as a moderately unsaturated margarine (' Blue Band '). Foods allowed daily included lean meat (up to 85 g.), any fish, skimmed milk, and clear soups. Foods forbidden included butter, other margarines, cooking-fat, other oils, fat meat, whole milk, cheese, egg yolk, and most biscuits and cakes.

Control Diet

Patients in the control group ate the diet they would ordinarily have taken.

Reducing Diets

174 of the men were placed on reducing diets for a time during the trial because of persistent weight gain or for slight obesity at the start of the trial. Of this number, 163 were put on a reduced carbohydrate diet (73 in the test group and 90 controls). Only 11 were on a strict 1000 C. reducing diet (5 on the test diet and 6 controls). In the 5 on the test diet the oil was reduced from 85 to 57 g. per day.

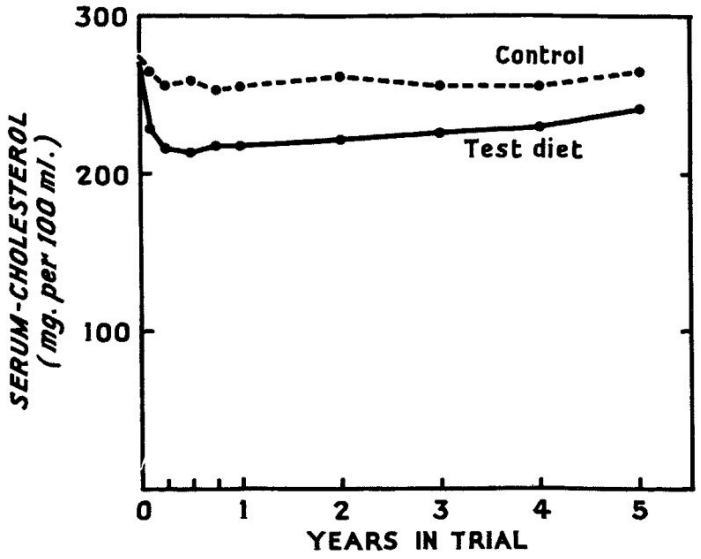


Fig. 2—Serum-cholesterol.

TABLE V—RELAPSES AND DEATHS DURING TRIAL

Category	Test diet		Control	
No. of men	199		194	
First relapses:	62		74	
Major	40		39	
(*a*) Fatal		15		14
(*b*) Non-fatal definite reinfarctions		25		25
Other non-fatal relapses	22		35	
Men who had a major relapse at any time during trial:	45		51	
Fatal		25		25
Non-fatal definite reinfarctions		20		26
All deaths from cardiovascular disease	27*		25	

* 1 death was from subarachnoid hæmorrhage and 1 from cerebral embolism.

In addition there were 7 deaths from carcinoma (6 controls and 1 in the test group). The patients concerned were excluded from the trial from the time malignant disease was diagnosed. There were no other deaths during the trial.

recorded oil consumption and mortality. The first relapse rate, however, showed a consistent trend from a low rate in those who recorded 80 g. of oil or more a day to a high rate amongst the 27 men who recorded less than 60 g. a

Dayton, 1969

A Controlled Clinical Trial of a Diet High in Unsaturated Fat in Preventing Complications of Atherosclerosis

By Seymour Dayton, M.D., Morton Lee Pearce, M.D., Sam Hashimoto, M.S., Wilfrid J. Dixon, Ph.D., and Uwamie Tomiyasu, M.D.

Choice of Diet and Mode of Food Service

The circumstances of this trial—in particular the fact that most of the subjects were not highly motivated toward self-deprivation—rendered it mandatory that both diets be highly palatable by conventional criteria. It appeared on culinary grounds that a staff skilled in dietetics, with some industrial help on certain food products, could achieve a diet closely simulating the conventional institutional diet if, and only if, the total amount of dietary fat remained nearly unchanged. This restriction led to a decision to test a replacement of the saturated animal fats and hydrogenated shortenings of the conventional diet by equal quantities of unsaturated fat in the form of vegetable oils in the experimental diet. Because of uncertainty at the start of the trial about the importance of dietary cholesterol content, this was decreased as a secondary modification. A pilot study demonstrated that a varied and palatable diet could be developed in line with these specifications and that it was acceptable to most potential subjects, whereas low-fat diets were rejected forthwith. The diet chosen for study offered the incidental advantage that if it were ultimately found to be of value, it might be adopted by the general public more readily than would a diet requiring gastronomic sacrifice.

Most persons in the Domicile and all subjects in this study ate in a single large facility with one kitchen and two dining rooms. The food was served *ad libitum*, cafeteria style, with the two groups of subjects separated physically from each other and from men not on the study. To minimize errors in food preparation and service, cooking and serving containers were color-coded.

Since the participants had access to the community as well as to a canteen, total adherence to the study diet was the exception. Because rigid adherence could not be enforced, the level of adherence was monitored. Each man in the Home, including those not on the study, was issued a meal ticket of distinctive color which was punched at each meal. The punched ticket served as a record of meal attendance. This system also assured that each man remained on his assigned diet. All participants in the study were personally known to the dietitians and food service workers, who were thus further able to minimize deviations from prescribed diet within the dining room.

Diets

The control diet was a conventional food pattern containing 40% fat calories, mostly of animal origin. It was similar to the regular diet but not identical to it. The design of the experimental diet involved substitution of vegetable oils for about two-thirds of the animal fat, total fat content being kept around 40%. An attempt was made to stabilize the iodine value of the mixed fat in the control diet at 55 and that in the experimental diet at 100. Multiple vegetables oils were used, including corn, soybean, safflower, and cottonseed, the choice in an individual instance being largely pragmatic.

Because the potential importance of restricting dietary cholesterol intake was unclear at the time the study was begun, and because rigorous restriction of cholesterol-containing foods seemed likely to violate the goal of palatability, a compromise was arrived at by restriction of egg yolks to seven per week in the experimental diet. Largely because of this restriction and the absence of butterfat from the experimental diet, it was substantially lower in cholesterol than was the control ration.

Vegetable oils were incorporated into the experimental diet in the form of filled milk,* imitation ice cream, "unsaturated" margarine, special sausage products, and filled cheeses. Vegetable oils were used liberally in cooking and baking. Meat fat was minimized by the use of specially trimmed lean cuts. Further dietetic details are given in a separate publication.[7]

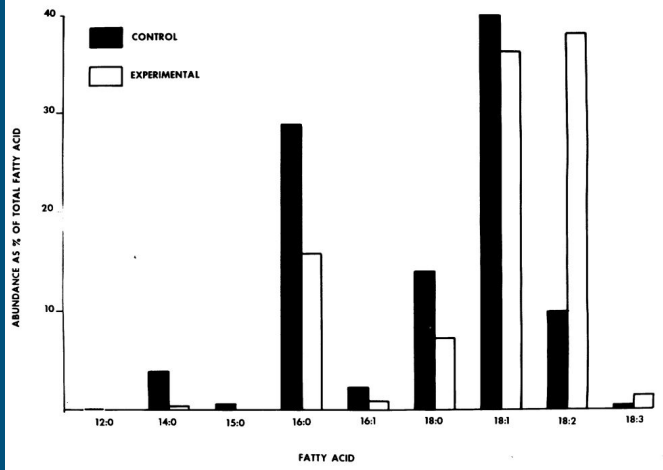


Figure 2

Fatty acids in dietary fat. The data are means of 19 eight-week collections analyzed at intervals during the study. Fatty acids are identified by chain length and number of double bonds.

Table 16

Composition of Diets

	Control	Experimental	*P*
Total daily calories†	2,496 ± 159	2,496 ± 122	
Protein (g/day)†	96.3 ± 8.8	97.4 ± 8.5	> 0.05*
Fat (g/day)†	111.2 ± 9.1	107.9 ± 7.3	< 0.001*
Fat calories (% of total)†	40.1 ± 2.2	38.9 ± 1.9	< 0.001*
Iodine value of fat†	53.5 ± 3.5	102.4 ± 4.6	< 0.001*
Cholesterol (mg/1,000 cal)‡	262	146	< 0.01**
Cholesterol (mg/day)‡	653	365	< 0.01**
β-sitosterol (mg/day)‡	< 50	215	< 0.01**

* By *t*-test.

** By sign test, using paired values.

† Mean ± SD of 412 to 427 one-week pooled collections.

‡ Mean of 19 analyses, each representing a four- to ten-week pool, weighted as to collection period.

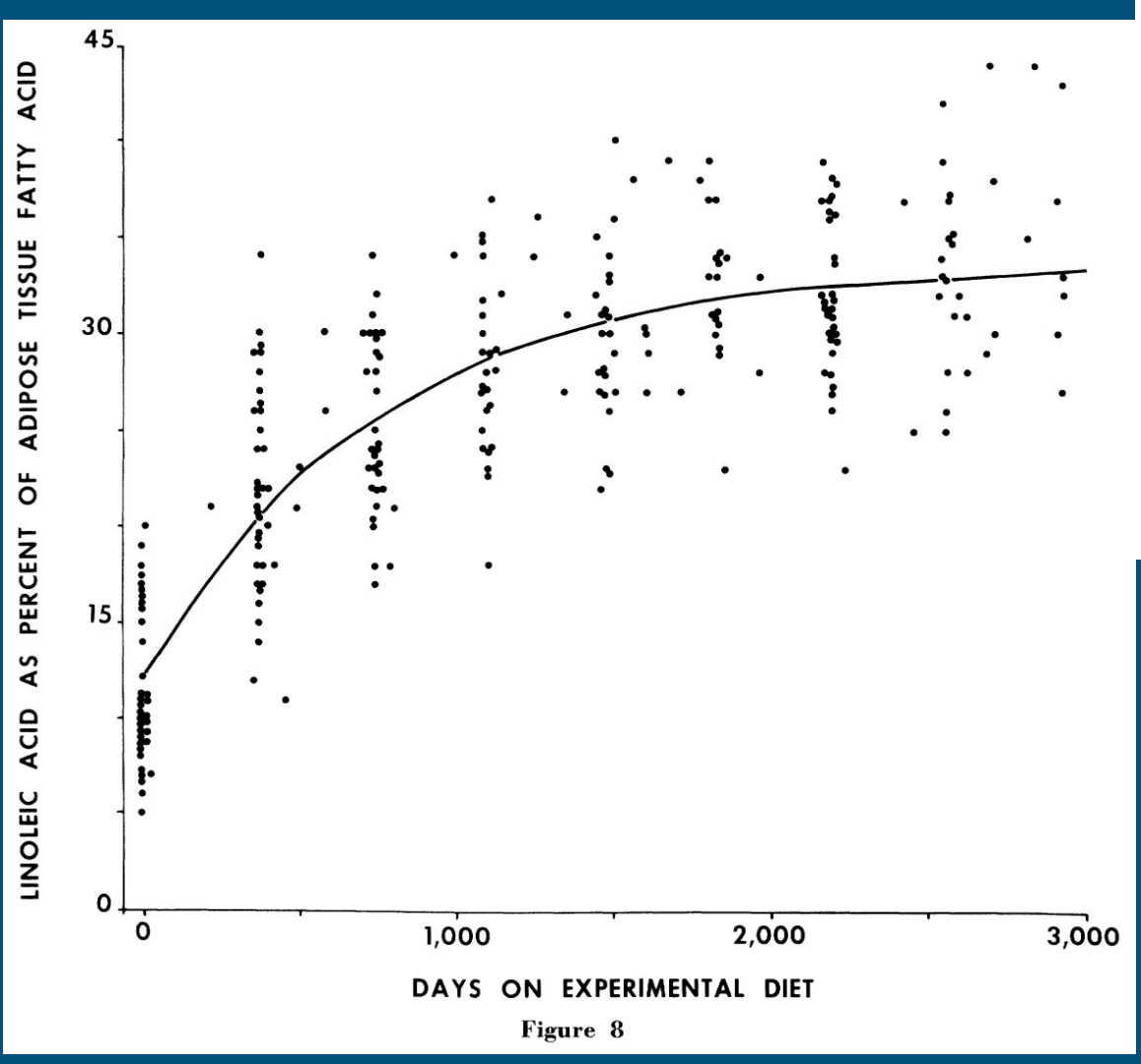


Figure 8

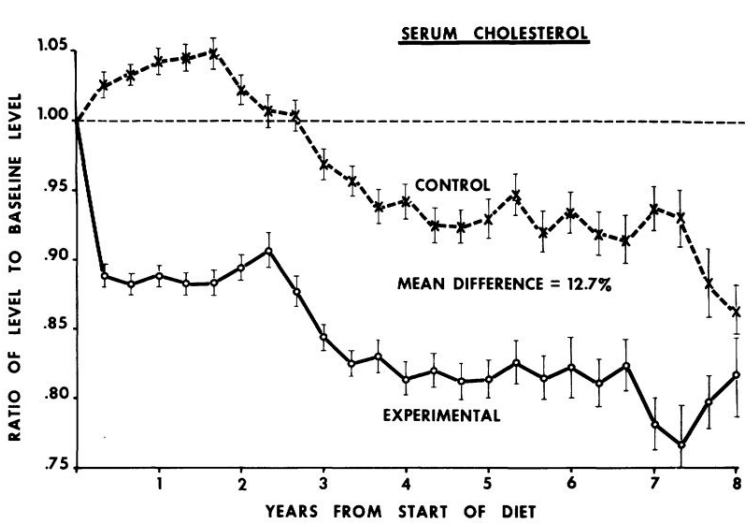


Figure 5

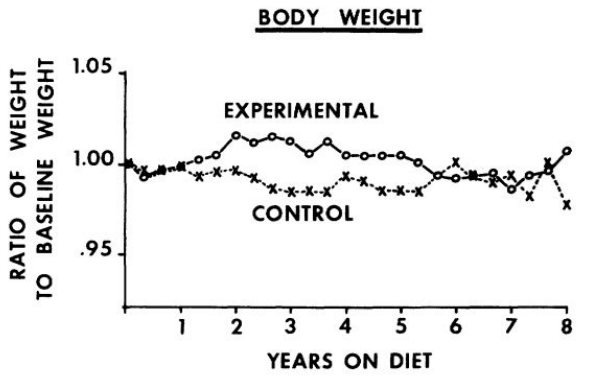


Figure 4

Mean body weights during the study, by diet.

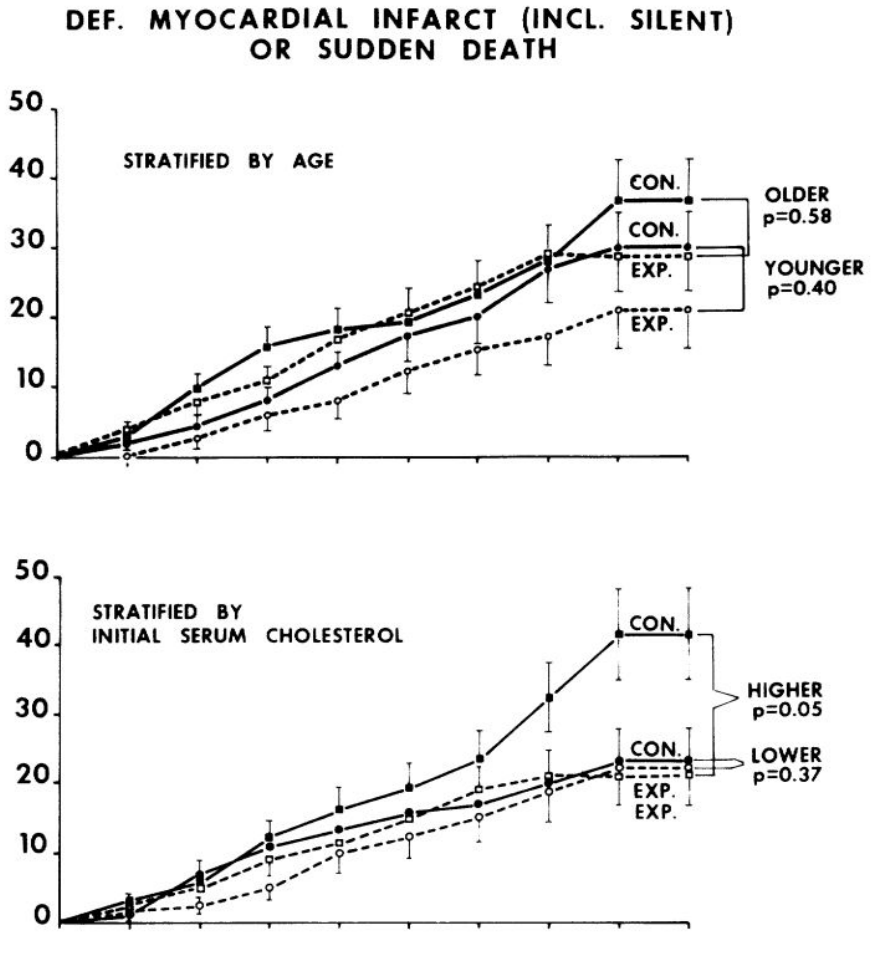
Table 23

Summary Tabulation of Primary and Secondary End Points ("Hard" Events)

Type of event	Number of events			Number of men
	Fatal*	Nonfatal	Total	
Definite myocardial infarction, by ECG only				
Control	0	4	4	4
Experimental	0	9	9	9
Definite, overt myocardial infarction				
Control	23	24	47	40
Experimental	23	10	33	27
Sudden death due to coronary heart disease				
Control	27		27	27
Experimental	18		18	18
Definite cerebral infarction				
Control	9	16	25	22
Experimental	3	10	13	13
Ruptured aneurysm				
Control	5	0	5	5
Experimental	2	0	2	2
Amputation				
Control	3	2	5	5
Experimental	0	7	7	5
Miscellaneous				
Control	3	3	6	6
Experimental	2	1	3	2
Total				
Control	70	49	119	96†
Experimental	48	37	85	66†
Chi^2 on totals	4.45			6.63
P	< 0.05			0.01

* Cases in which the event was either the sole cause or a partial cause of death.

† Because a number of subjects had multiple events in these categories, this figure is smaller than that obtained by totaling the column.



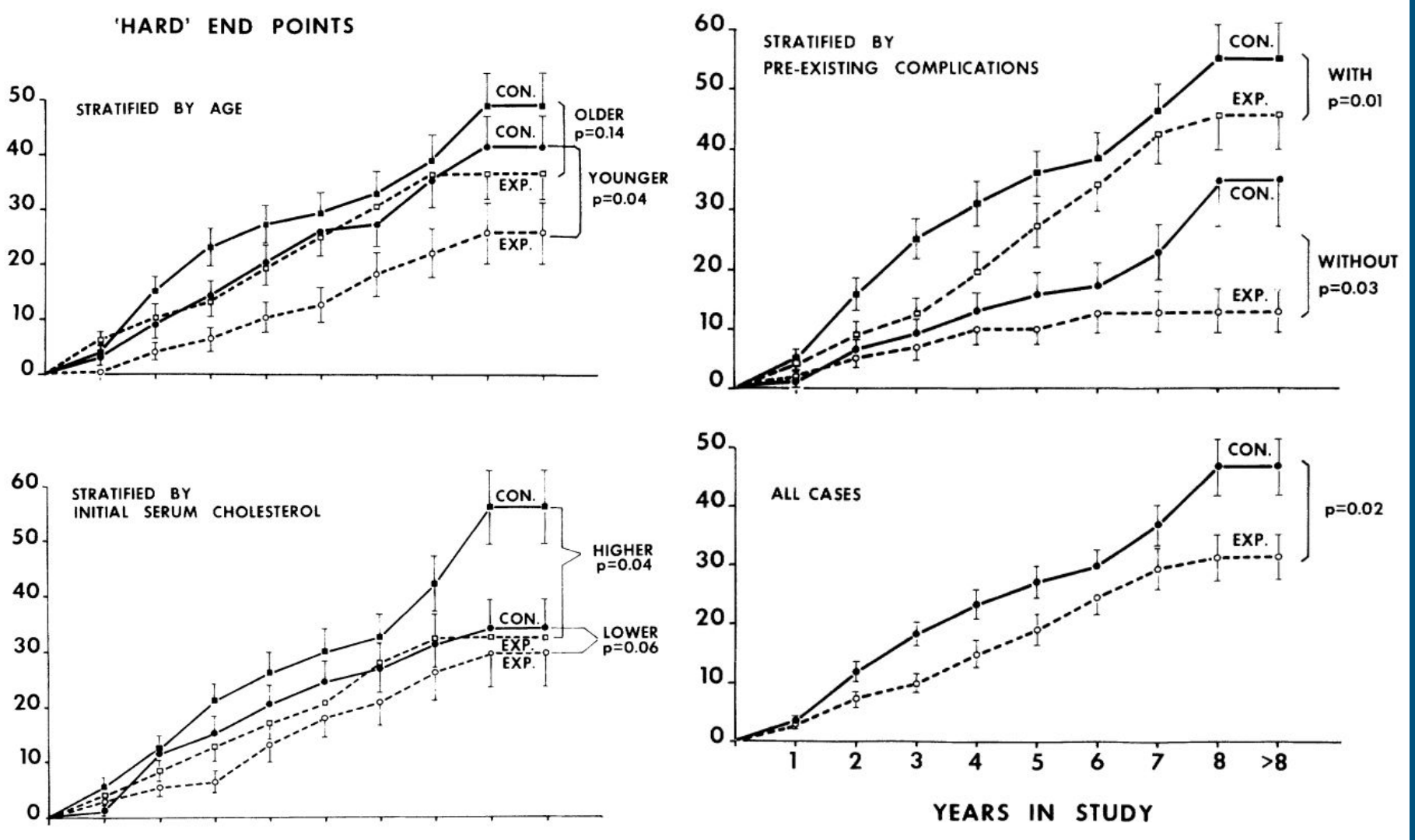

'HARD' END POINTS
STRATIFIED BY AGE
CON.
CON.
EXP.
EXP.
OLDER
p=0.14
YOUNGER
p=0.04
STRATIFIED BY
PRE-EXISTING COMPLICATIONS
CON.
EXP.
CON.
EXP.
WITH
p=0.01
WITHOUT
p=0.03
STRATIFIED BY
INITIAL SERUM CHOLESTEROL
CON.
CON.
EXP.
EXP.
HIGHER
p=0.04
LOWER
p=0.06
ALL CASES
CON.
EXP.
p=0.02
0
10
20
30
40
50
60
1
2
3
4
5
6
7
8
>8
YEARS IN STUDY

Table 27

Summary Tabulation of Deaths by Category

Category	Number of cases	
	Control	Experimental
Due to acute atherosclerotic event (sole cause)	60	39
Mixed causes, including acute atherosclerotic event	10	9
Due to atherosclerotic complication without acute event	1	2
Mixed causes, including atherosclerotic complication without acute event	10	7
Other cause	71	85
Uncertain cause	25	32
Total	177	174

Table 30

Incidence Rates for Major Categories of Events After Stratification of the Study Population by Baseline Serum Cholesterol Level

	Cumulative incidence rates					
	Four-year		Eight-year		*P* for curve*	*P* for eight-year incidence†
	Con.	Exp.	Con.	Exp.		
Sudden death						
Low cholesterol‡	0.07	0.06	0.12	0.11	0.76	>0.8
High cholesterol§	0.05	0.05	0.22	0.06	0.08	<0.02
Definite myocardial infarct (overt or silent)						
Low cholesterol	0.10	0.05	0.17	0.16	0.41	>0.8
High cholesterol	0.12	0.10	0.30	0.21	0.67	>0.2
Definite cerebral infarct						
Low cholesterol	0.06	0.04	0.07	0.06	0.34	>0.6
High cholesterol	0.07	0.03	0.17	0.06	0.20	$0.1 > P > 0.05$
Sudden death or Definite myocardial infarct or Definite cerebral infarct						
Low cholesterol	0.20	0.12	0.31	0.28	0.08	>0.6
High cholesterol	0.23	0.16	0.54	0.28	0.01	<0.001
All "hard" end points						
Low cholesterol	0.20	0.13	0.34	0.30	0.06	>0.5
High cholesterol	0.26	0.17	0.56	0.32	0.04	<0.005
Fatal atherosclerotic events						
Low cholesterol	0.11	0.07	0.21	0.17	0.31	>0.4
High cholesterol	0.14	0.09	0.29	0.18	0.15	<0.05

* Computed by the method of Forsythe and Frey,[28] comparing the control (Con.) group incidence curve with the experimental (Exp.) group incidence curve.

† Computed by *t*-test. At four years none of the incidence rates showed significant differences between control and experimental groups.

‡ Baseline serum cholesterol ≤233 mg/dl.

§ Baseline serum cholesterol > 233 mg/dl.

Table 31

Rates for Combined Incidence of Sudden Death, Definite Myocardial Infarction (Silent or Overt), and Definite Cerebral Infarction by Quartiles of Initial Serum Cholesterol Level

Quartile	Four-year incidence		Eight-year incidence		*P* for eight-year incidence*
	Con.	Exp.	Con.	Exp.	
Lowest	0.14	0.11	0.24	0.25	N.S.
Second	0.26	0.13	0.37	0.30	N.S.
Third	0.20	0.15	0.54	0.27	< 0.025
Highest	0.27	0.18	0.53	0.27	< 0.05

*By *t*-test. None of the four-year incidence figures revealed significant differences between the control (Con.) and experimental (Exp.) groups. N.S. = not significant.

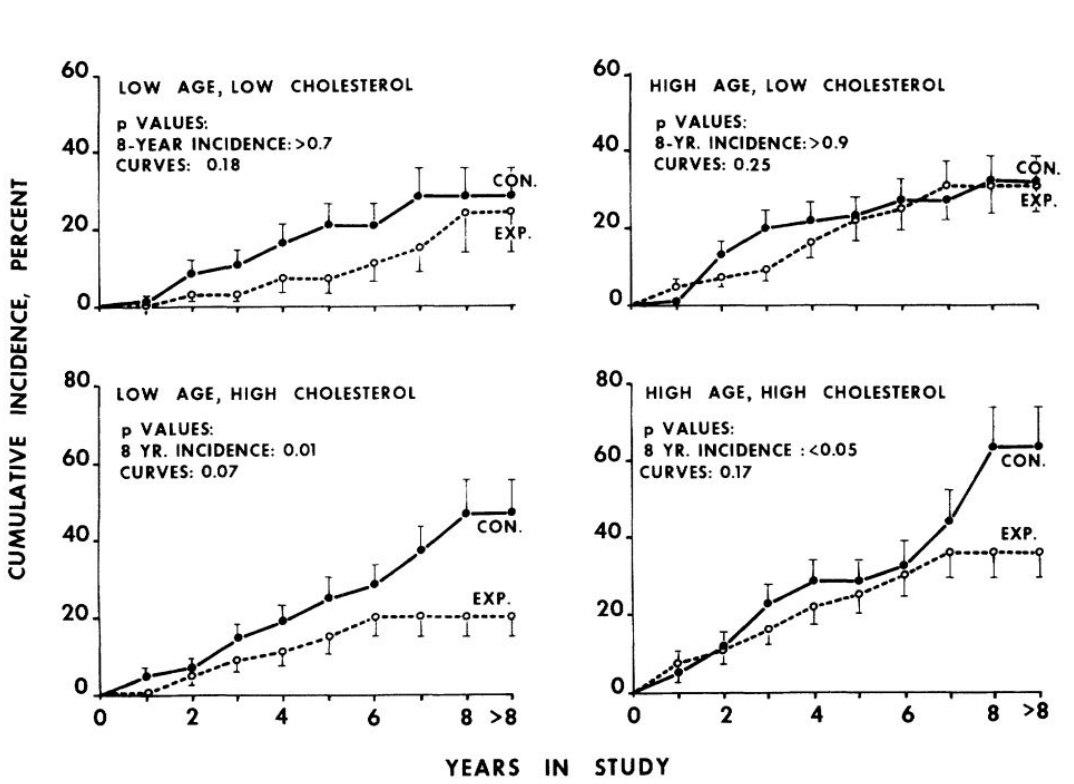


Figure 15

Cumulative combined incidence of sudden death due to coronary heart disease (C.H.D.), definite myocardial infarction (silent or overt), and definite cerebral infarction, after factorial stratification by age at entry and baseline serum cholesterol concentration. Vertical lines are standard errors of the incidence rates. P values were computed by the method of Forsythe and Frey.[28] CON. = control; EXP. = experimental.

LETTERS TO THE EDITOR | VOLUME 295, ISSUE 7644, P473-474, FEBRUARY 28, 1970

DIET AND ATHEROSCLEROSIS

Seymour Dayton • MortonLee Pearce

TABLE I—NUMBERS AND INCIDENCE-RATES OF MAJOR END-POINTS, STRATIFIED BY CIGARETTE-SMOKING HABITS AT ENTRY INTO THE TRIAL

Cigarette use at entry into study	Control group		Experimental group	
	No. of subjects	Incidence* per 100 man-years	No. of subjects	Incidence* per 100 man-years
Less than 10 cigarettes per day:				
No. of men in subgroup	166	..	164	..
S.D. or M.I.	25	2·45	21	2·02
S.D., M.I., or C.I.	32	3·13	25	2·40
Any " hard " end-point†	32	3·13	27	2·60
Fatal atherosclerotic events	20	1·95	18	1·73
10–20 cigarettes per day:				
No. of men in subgroup	129	..	173	..
S.D. or M.I.	22	2·56	20	1·76
S.D., M.I., or C.I.	30	3·49	21	1·85
Any " hard " end-point	34	3·95	25	2·20
Fatal atherosclerotic events	26	3·02	19	1·67
More than 20 cigarettes per day:				
No. of men in subgroup	70	..	45	..
S.D. or M.I.	13	2·86	5	1·70
S.D., M.I., or C.I.	17	3·73	6	2·04
Any " hard " end-point	20	4·39	6	2·04
Fatal atherosclerotic events	16	3·51	6	2·04
Not known:				
No. of men in subgroup	57	..	42	..
S.D. or M.I.	5	1·24	6	1·95
S.D., M.I., or C.I.	8	1·99	8	2·60
Any " hard " end-point	10	2·48	8	2·60
Fatal atherosclerotic events	8	1·99	5	1·62
All subjects:				
No. of men in group	422	..	424	..
S.D. or M.I.	65	2·37	52	1·87
S.D., M.I., or C.I.	87	3·18	60	2·16
Any " hard " end-point	96	3·51	66	2·38
Fatal atherosclerotic events	70	2·55	48	1·73

* A man with more than one event in the category cited was counted once only.

† Includes those events cited in the preceding footnote, plus the following: amputation of an extremity due to ischæmic gangrene, ruptured aneurysm, intestinal infarction.

S.D. = sudden death due to ischæmic heart-disease.

M.I. = definite myocardial infarction (overt or silent).

C.I. = definite cerebral infarction.

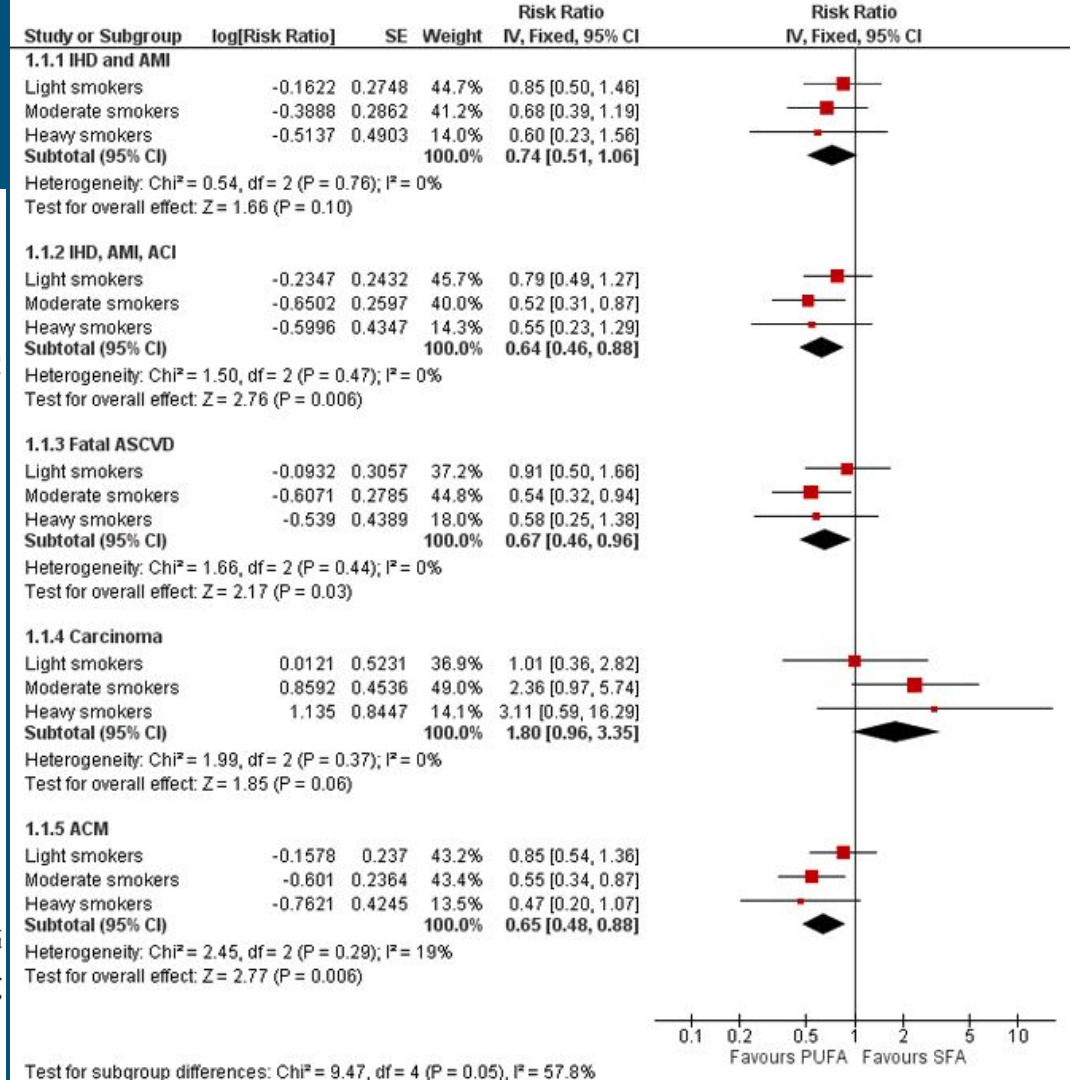


TABLE V—ADHERENCE TO DIET IN PATIENTS WITH FATAL CARCINOMA DURING THE DIET PHASE*

Adherence (%)	Control group	Experimental group
0–10	2	10
10–20	1	2
20–30	1	3
30–40	0	0
40–50	3	3
50–60	3	3
60–70	0	4
70–80	2	2
80–90	4	1
90–100	1	3
..	17	31

* Adherence, calculated from attendance records, is expressed as a percentage of the maximum number of meals which could have been taken in the study dining-hall.

$\chi^2 = 10{\cdot}26$; $P > 0{\cdot}3$.

TABLE VI—ADHERENCE TO DIET IN THE TOTAL STUDY POPULATION

Adherence (%)	Control group	Experimental group
0–10	82	120
10–20	47	46
20–30	31	42
30–40	21	30
40–50	42	23
50–60	40	33
60–70	32	32
70–80	42	37
80–90	50	31
90–100	35	30
..	422	424

$\chi^2 = 21{\cdot}78$; $P < 0{\cdot}01$.

ORIGINAL ARTICLES | VOLUME 297, ISSUE 7697, P464-467, MARCH 06, 1971

INCIDENCE OF CANCER IN MEN ON A DIET HIGH IN POLYUNSATURATED FAT

Morton Lee Pearce • Seymour Dayton

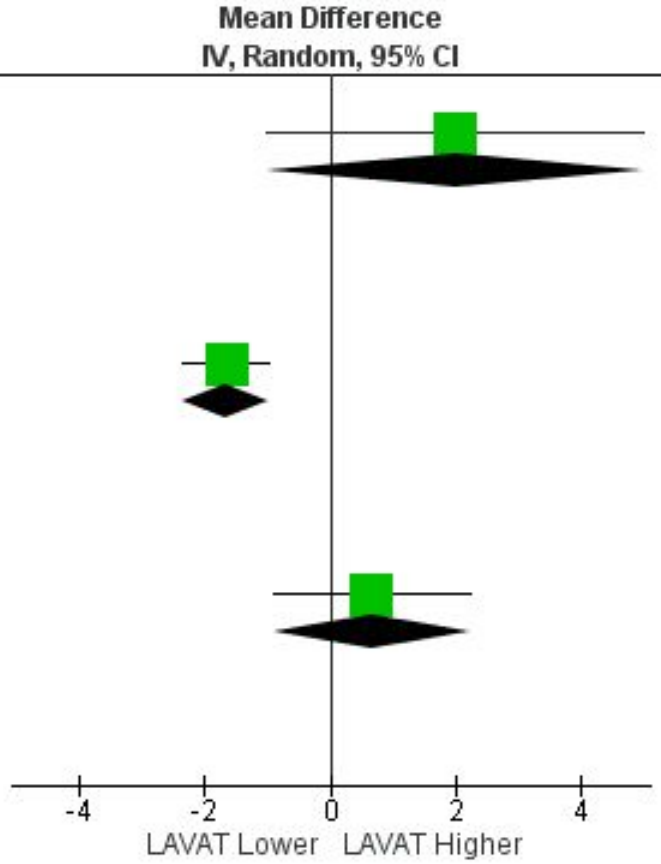
Published: March 06, 1971 • DOI: https://doi.org/10.1016/S0140-6736(71)91086-5

Many of the cancer deaths in the experimental group were among those who did not adhere closely to the diet. This reduces the possibility that the feeding of polyunsaturated oils was responsible for the excess carcinoma mortality observed in the experimental group. However, there were significantly more low adherers in the entire experimental group than in the controls (table VI). In both groups, the numbers of cancer deaths among the various adherence strata are compatible with random distribution (table V). A high incidence among high adherers would be expected if some constituent of the experimental diet were contributing to cancer fatality.

Baseline tissue LA in LA Veterans compared to Navajo Indians, Inuit, and Tsimane

Study or Subgroup	LAVAT Mean	LAVAT SD	LAVAT Total	Traditional Mean	Traditional SD	Traditional Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 Navajo								
Navajo	10.9	3.5	240	8.9	3.71	6	100.0%	2.00 [-1.00, 5.00]
Subtotal (95% CI)			**240**			**6**	**100.0%**	**2.00 [-1.00, 5.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.31 (P = 0.19)								
1.1.2 Inuit								
Inuit	10.9	3.5	240	12.56	3.07	129	100.0%	-1.66 [-2.35, -0.97]
Subtotal (95% CI)			**240**			**129**	**100.0%**	**-1.66 [-2.35, -0.97]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.71 (P < 0.00001)								
1.1.3 Tsimane								
Tsimane	10.9	3.5	240	10.23	4.56	35	100.0%	0.67 [-0.90, 2.24]
Subtotal (95% CI)			**240**			**35**	**100.0%**	**0.67 [-0.90, 2.24]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.83 (P = 0.40)								

Test for subgroup differences: Chi² = 11.46, df = 2 (P = 0.003), I² = 82.5%



Special Article | 1 November 1963

Coronary Heart Disease Among the Navajo Indians

HUGH S. FULMER, M.D., RICHARD W. ROBERTS, M.D.

Author, Article and Disclosure Information

https://doi.org/10.7326/0003-4819-59-5-740

TABLE 17. Adipose Tissue Analyses

		Myristic	Palmitic	Palmitoleic	Stearic	Oleic	Linoleic
				%			
Navajo on a traditional diet	1	4.1	21.3	9.9	5.5	46.0	6.0
	2	2.8	21.8	9.9	5.3	43.2	6.8
	3	1.6	18.3	13.4	1.5	50.8	8.4
	4	1.7	18.4	13.2	2.0	51.4	9.0
	5	2.6	23.5	9.3	6.6	49.0	5.4
	6	4.1	18.2	10.2	3.3	49.7	9.3
	7	2.1	12.6	12.3	3.9	52.8	9.6
	8	2.5	21.2	7.4	7.2	47.9	7.3
	9	2.5	20.5	9.5	3.3	49.5	10.1
	Average	2.7	19.5	10.6	4.3	48.9	8.0
Navajo on a modern diet	1	1.8	22.2	7.6	4.3	53.5	10.5
	2	3.7	22.2	11.7	3.4	47.8	8.9
	3	2.6	26.8	6.2	5.4	48.4	10.1
	Average	2.7	23.7	8.5	4.4	49.9	9.8
Rockefeller Institute Normals—Average		3.3	19.5	6.9	4.2	46.3	11.4

A 6-year cohort and descriptive epidemiologic study in the Many Farms Navajo Indian population has revealed only 4 cases of coronary heart disease in 508 adults 30 years old or older. The incidence is significantly low when an appropriate age and sex matched segment is compared to the Framingham population, whose people have undergone intensive study for coronary heart disease.

Fatty acid patterns in human adipose tissue

JULES HIRSCH | *The Rockefeller Institute, New York City*

TABLE 1. *Per Cent Fatty Acid Composition of Human Adipose Tissue in Seven Studies*

Fatty Acid	Cramer & Brown (1943)	Hirsch et al. (1960)	Gellhorn & Marks (1961)	Scott et al. (1962)	Hegsted et al. (1962)	Dayton et al. (1962)	Heffernan (1963)
12:0*	0.5	0.7	0.4	0.6	0.5	1	1.1
14:0	3.5	3.3	2.4	4.1	3.6	2	4.7
14:1	0.4	0.6				1	
16:0	25.0	19.5	24.6	25.0	24.6	21	23.8
16:1	6.4	6.9	5.6	6.3	6.1	7	5.7
18:0	7.0	4.2	6.0	4.3	6.7	6	5.6
18:1	45.9	46.7	49.9	50.2	50.3	52	52.4
18:2	9.6	11.4	9.5	9.5	7.9	9	6.7
20:4	0.7	0.2					
Other C20	1.2	1.6					

TABLE 6. *Adipose Composition of Vegetarians**

Fatty Acid	Random American Diet	Seventh Day Adventists (9)	Navajo Indians on Traditional Diet (6)	Navajo Indians on Western Diet (3)	Trappist Monks (6)
14:0	3.3	1.1	2.6	2.7	3.2
16:0	19.5	13.9	19.1	23.7	20.9
16:1	6.9	4.4	10.3	8.5	6.4
18:0	4.2	2.2	4.4	4.4	4.1
18:1	46.3	48.8	50.0	49.9	47.0
18:2	11.4	26.2	8.4	9.8	13.5

FULL LENGTH ARTICLE | VOLUME 181, ISSUE 2, P353-362, AUGUST 01, 2005

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Adipose tissue triglyceride fatty acids and atherosclerosis in Alaska Natives and non-Natives

Joe McLaughlin • John Middaugh • Donald Boudreau • ... Steve Parry • Richard Tracy • William Newman • Show all authors

DOI: https://doi.org/10.1016/j.atherosclerosis.2005.01.019

Table 1
Comparison of differences in atherosclerosis risk factors, extent of atherosclerotic raised lesions (percentage of surface area involved), and proportions (mass percentage) of adipose tissue triglyceride fatty acids between Alaska Natives and non-Natives

	Alaska Native			Non-Native			*P*-value
	n	Value	S.E.M.[a]	*n*	Value	S.E.M.[a]	
Atherosclerosis risk factors							
Mean age (years)	130	37.05	1.47	115	39.92	1.38	0.159
Age range		9–85			8–81		
Sex (male, female)	130	92, 38		115	88, 27		0.311
Mean total serum cholesterol (mg/dL)	101	225.85	7.45	95	213.92	8.08	0.278
Mean HDL-cholesterol (mg/dL)	91	67.90	2.77	88	53.11	2.48	<0.001
Percentage of smokers (thiocyanate ≥ 90 micromoles/L)	97	25 (24/73)	0.04	93	49 (46/47)	0.05	<0.001
Percentage with hyperglycemia (glycated HGb ≥ 8%)	124	10 (13/111)	0.03	112	12 (13/99)	0.03	0.784
Percentage with hypertension (estimated MBP ≥ 110)	123	11 (14/109)	0.03	112	9 (10/102)	0.03	0.537
Mean body mass index	128	24.27	0.49	113	24.35	0.42	0.909
Raised lesions (percentage of total surface)							
Thoracic aorta	130	9.00	1.73	115	12.39	1.90	0.189
Abdominal aorta	130	16.39	2.41	115	32.71	3.32	<0.001
Left anterior descending coronary artery	126	16.00	2.31	113	31.49	3.00	<0.001
Right coronary artery	126	13.65	2.24	114	28.31	3.07	<0.001
Saturated fatty acids (SFA) (mass%)							
14:0	129	2.76	0.06	115	3.11	0.08	<0.001
16:0	129	23.01	0.36	115	23.89	0.33	0.077
18:0	129	6.51	0.13	115	6.90	0.15	0.046
Total	129	32.60	0.44	115	34.32	0.47	0.008
Monounsaturated fatty acids (MUFA) (mass%)							
14:1	129	0.27	0.01	115	0.28	0.01	0.449
16:1	129	5.23	0.14	115	4.26	0.13	<0.001
18:1	129	43.01	0.32	115	42.77	0.31	0.594
20:1	129	0.93	0.04	115	0.68	0.02	<0.001
Total	129	49.44	0.39	115	47.99	0.37	0.008
Polyunsaturated fatty acids (PUFA) (mass%)							
ω-6							
18:2 Linoleic acid	129	12.56	0.27	115	13.27	0.26	0.065
20:2	129	1.48	0.06	115	1.36	0.05	0.116
20:3	129	0.24	0.01	115	0.24	0.01	0.729
20:4 Arachadonic acid (AA)	129	0.17	0.01	115	0.20	0.01	0.004
Total long-chain ω-6[b]	129	1.89	0.06	115	1.81	0.06	0.336
Total ω-6	129	14.45	0.26	115	15.07	0.26	0.093

Fatty acid composition in the mature milk of Bolivian forager-horticulturalists: controlled comparisons with a US sample

Melanie A. Martin*, William D. Lassek†, Steven J.C. Gaulin*, Rhobert W. Evans†, Jessica G. Woo‡, Sheela R. Geraghty§, Barbara S. Davidson¶, Ardythe L. Morrow¶, Hillard S. Kaplan and Michael D. Gurven***

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Table 2. Mean saturated, trans, monounsaturated, and polyunsaturated fatty acid content of Tsimane and Cincinnati milk*

Fatty acid % wt/wt	Population	Mean + SD	Median	Interquartile range	Significance q value
n-6 Polyunsaturated FA					
18:2n-6 (LA)	Tsimane	10.23 ± 4.56	9.31	5.45	<0.001
	Cincinnati	18.88 ± 5.10	18.09	6.04	

Dependence of human milk essential fatty acids on adipose stores during lactation

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J C Martin, P Bougnoux, A Fignon, V Theret, J M Antoine, F Lamisse, C Couet ✉

The American Journal of Clinical Nutrition, Volume 58, Issue 5, November 1993, Pages 653–659,
https://doi.org/10.1093/ajcn/58.5.653
Published: 01 November 1993 **Article history** ▾

TABLE 2
Fatty acid composition of milk and white adipose tissue samples on days 5 and 30 postpartum*

	Milk		White adipose tissue	
Fatty acids	Day 5	Day 30	Day 5	Day 30
	% †			
SFA				
16:0	24.99 ± 1.93	23.30 ± 2.95	19.47 ± 2.06	19.33 ± 1.59
18:0	6.82 ± 0.94	7.67 ± 1.37	3.36 ± 0.74	3.24 ± 0.62
Others‡	10.73 ± 2.17	14.50 ± 3.76	4.13 ± 0.69	4.35 ± 0.85
Total	42.54 ± 3.59	45.47 ± 5.72	26.96 ± 3.19	26.92 ± 2.52
MUFA				
16:1§	2.84 ± 0.60	2.64 ± 0.60	7.49 ± 1.26	7.65 ± 1.27
18:1§	35.22 ± 2.03	33.06 ± 4.01	45.41 ± 2.54	45.38 ± 2.38
Others‖	1.22 ± 0.25	0.87 ± 0.34	1.30 ± 0.20	1.34 ± 0.19
Total	39.28 ± 2.35	36.58 ± 4.16	54.19 ± 3.35	54.37 ± 2.94
PUFA				
18:2n−6§	12.20 ± 2.84	12.68 ± 5.00	14.55 ± 3.00	14.60 ± 2.88
18:3n−3	0.69 ± 0.19	0.59 ± 0.20	0.47 ± 0.10	0.46 ± 0.06
Others¶	2.99 ± 0.89	1.82 ± 0.36	1.32 ± 0.40	1.30 ± 0.26
Total	15.88 ± 3.30	15.09 ± 5.29	16.34 ± 3.19	16.36 ± 3.00

* $\bar{x}$ ± SD; n = 24. SFA, saturate
acids; PUFA, polyunsaturated fatty ac
† Percent of total area; unidentifie
‡ Includes 10:0, 12:0, 14:0, 15:0,
§ Includes *trans* isomers.
‖ Includes 14:1, 20:1, 22:1, and 24
¶ Sum of the n−6 and n−3 long-c

and mature milk. Linoleate contents of body stores of triglycerides contribute to explaining interindividual variations of the linoleate content in both colostrum and mature milk. this was not the case for α-linolenic acid, whatever the stage of lactation studied. The absence of any precursor-product relationship between

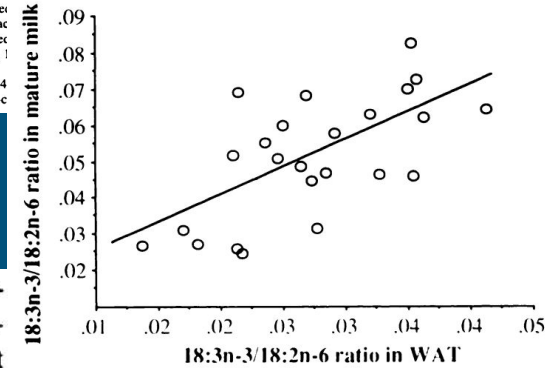

FIG 2. Relationship of the ratio of 18:3n−3 to 18:2n−6 between human mature milk and white adipose tissue (WAT). Solid line: linear-regression fit. n = 24.

FULL LENGTH ARTICLE | VOLUME 2, ISSUE 2, P73-77, JULY 01, 1983

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Breast milk and adipose tissue fatty acid composition in relation to maternal dietary intake

D. Heldenberg • O. Levtov • N. Eckstein • L. Barns • R. Getter • I. Tamir • Show footnotes

DOI: https://doi.org/10.1016/0261-5614(83)90036-5

confirm this. It seems much more likely that the main source of C-18:2 in human milk is FA released from AT. Therefore short-term dietary modifications did not result in a concommitant change in human milk C-18:2 concentration.

Table 1 Fatty acid relative concentrations (g/100g) (mean ± S.D.) of Adipose Tissue and Breast Milk Triglyceride

	n	10:0*	12:0	14:0	16:0	16:1	18:0	18:1	18:2
Adipose Tissue	23	—**	—**	2.3± 0.9	21.0± 2.2	5.0± 1.2	4.3± 1.8	42.8± 3.1	24.6± 3.5
Colostrum	23	—**	2.6± 1.1	5.7± 1.5	25.1± 1.9	2.9± 0.7	7.3± 1.2	37.1± 2.6	19.1± 3.0 $p<0.001$***
Breast Milk									
2 wk	20	1.8± 0.5	7.5± 2.3	6.6± 2.0	20.9± 2.2	3.0± 0.9	6.4± 1.1	32.8± 3.3	21.0± 3.5 $p<0.005$***
6 wk	8	1.8± 0.4	6.5± 2.0	5.4± 1.3	19.3± 1.4	2.9± 0.6	5.9± 1.2	34.8± 2.1	23.2± 2.7

* First number indicates carbon atom chain length, second number shows number of double bonds.
** Less than 1%.
*** Significance of difference from AT. Student's t-test.

Table 2 Dietary intake of linoleic acid (mean and range) and human milk relative concentration (g/100g/(mean and range)

		*DIET**	Breast Milk	TG	Fatty	Acids				
		Linoleic acid g/24 hours	C-10:0**	C-12:0	C-14:0	C-16:0	C-16:1	C-18:0	C-18:1	C-18:2
Group A $n = 4$	Normal	19.9 (14.0-22.5)	1.7 (0.8-2.4)	5.8 (1.7-7.9)	4.8 (2.4-5.8)	20.0 (17.5-21.6)	2.9 (2.1-3.9)	4.9 (3.7-5.8)	37.1 (32.4-44.2)	22.6 (20.6-25.5)
	High	79.0 (71.0-98.0)	1.4 (1.0-2.0)	4.8 (2.4-7.3)	4.5 (3.0-6.6)	21.4 (18.2-24.6)	3.1 (1.5-3.9)	4.9 (3.9-6.2)	35.1 (30.0-40.2)	24.8 (19.9-28.0)
Group B $n = 3$	Normal	17.4 (13.5-22.5)	1.4 (1.0-1.8)	5.4 (3.2-8.5)	4.7 (3.2-6.6)	18.4 (17.0-19.9)	2.8 (2.2-3.1)	6.8 (6.0-8.1)	35.9 (33.3-39.0)	24.5 (22.5-26.4)
	Low	3.8 (1.5-5.4)	1.0 (0.8-1.3)	3.2 (1.7-4.7)	3.1 (2.4-3.8)	18.6 (17.0-20.7)	3.0 (2.3-3.5)	4.1 (3.7-4.7)	41.7 (39.1-44.2)	25.2 (22.1-28.5)

* Isocaloric exchange of PU fat for saturated Fat.
** First number indicates carbon atom chain length, second number shows number of double bonds.

Park, 2021

Open Access Article

Causal Effects of Serum Levels of n-3 or n-6 Polyunsaturated Fatty Acids on Coronary Artery Disease: Mendelian Randomization Study

by Sehoon Park [1,2], Soojin Lee [3], Yaerim Kim [4], Yeonhee Lee [3], Min Woo Kang [5], Kwangsoo Kim [6], Yong Chul Kim [5], Seung Seok Han [5,7], Hajeong Lee [5,7], Jung Pyo Lee [7,8,9], Kwon Wook Joo [5,7,8], Chun Soo Lim [7,8,9], Yon Su Kim [1,5,7,8] and Dong Ki Kim [5,7,8,*]

Table 3. Allele-score based Mendelian randomization results in the UK Biobank data for MI outcome.

Genetically Predicted PUFA Level by Allele–Scores (1 Standard Deviation Increase)	Main Analysis [a]		Sensitivity Analysis Adjusted for Phenotypical Covariates [b]	
	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
n-3 PUFAs				
Eicosapentaenoic acid	0.973 (0.956–0.991)	0.003	0.969 (0.949–0.989)	0.002
Docosapentaenoic acid	1.027 (1.009–1.046)	0.004	1.029 (1.008–1.050)	0.006
Docosahexaenoic acid	1.000 (0.982–1.018)	0.986	1.003 (0.982–1.023)	0.804
n-6 PUFAs				
Linoleic acid	0.975 (0.957–0.992)	0.005	0.967 (0.947–0.987)	0.001
Gamma-linolenic acid	1.022 (1.003–1.040)	0.020	1.028 (1.007–1.049)	0.009
Dihomo-gamma-linolenic acid	0.972 (0.955–0.990)	0.002	0.969 (0.950–0.989)	0.003
Arachidonic acid	1.027 (1.009–1.046)	0.004	1.034 (1.013–1.056)	0.001
Adrenic acid	1.004 (0.986–1.022)	0.672	1.008 (0.987–1.029)	0.458

PUFA = polyunsaturated fatty acids; OR = odds ratio; CI = confidence interval; MI = myocardial infarction. All allele scores were scaled to a one standard deivation increase. [a] The logistic regression model was adjusted for age, sex, and the first 10 principal components of the genetic information. [b] The phenotypical hypertension, diabetes mellitus, obesity, dyslipidemia medication history, smoking, laboratory values for low-density lipoprotein, high-density lipoprotein, and triglycerides were added to the main model.

Li, 2020

Am J Clin Nutr. 2020 Jul; 112(1): 150–167. PMCID: PMC7326588
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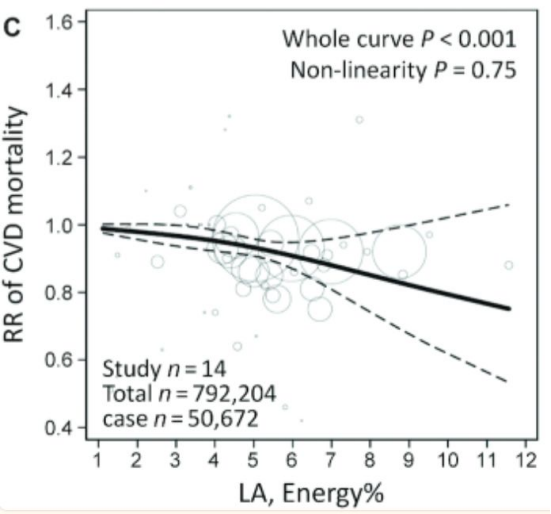
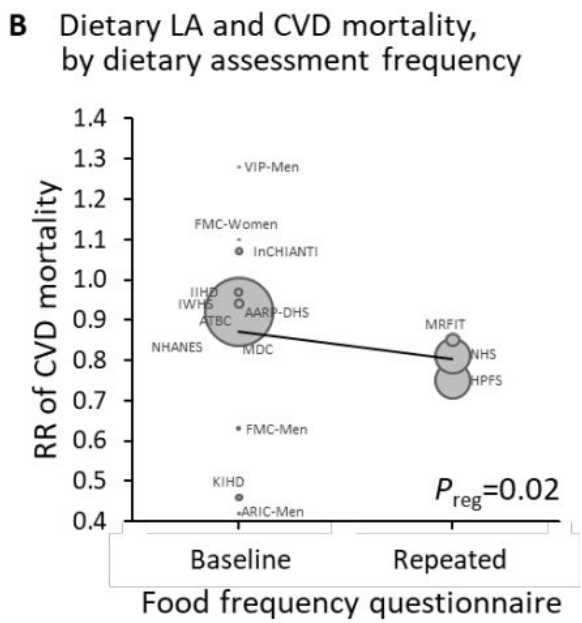
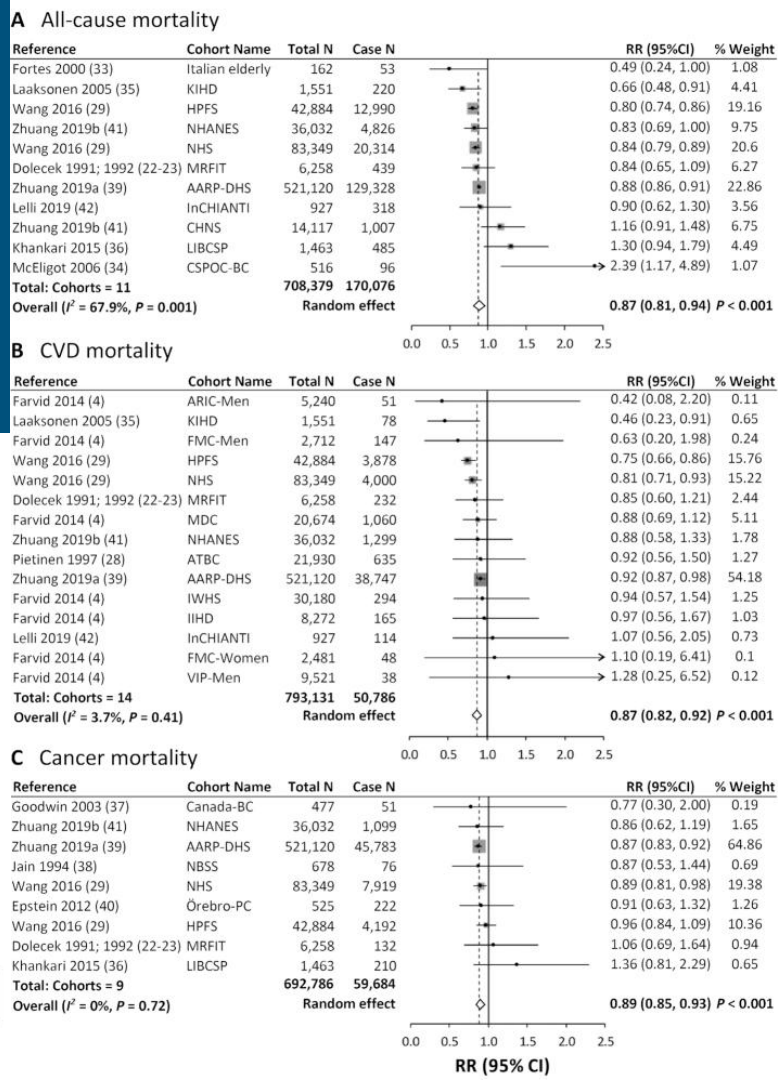
Dietary intake and biomarkers of linoleic acid and mortality: systematic review and meta-analysis of prospective cohort studies

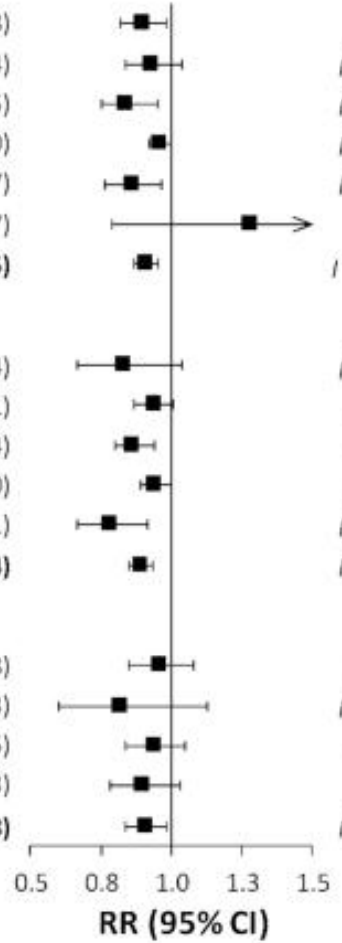
Jun Li, Marta Guasch-Ferré, Yanping Li, and Frank B Hu





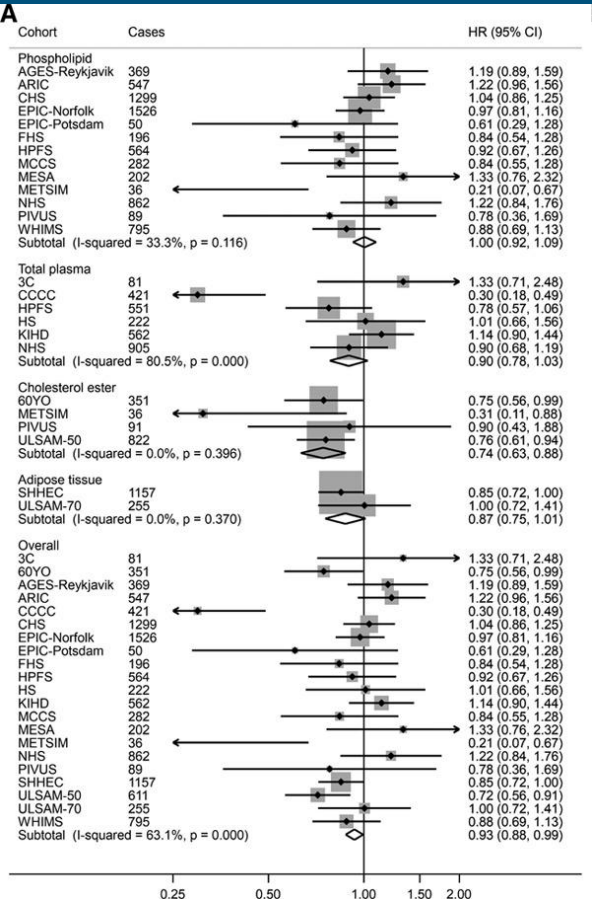


Mortality Outcome /Tissue types	Studies	Participants	Events	RR (95% CI)	Heterogeneity
All-cause mortality					
Adipose Tissue	1	853	605	0.90 (0.82, 0.98)	-
Phospholipids	4	4,276	2,390	0.93 (0.84, 1.04)	I^2 =40.6%; *P* =0.15
Cholesteryl esters	3	6,078	1,503	0.84 (0.75, 0.95)	I^2 =60.2%; *P* =0.06
Erythrocytes	4	13,404	3,311	0.96 (0.92, 1.00)	I^2 =22.7%; *P* =0.28
Total Serum or Plasma	3	4,813	1,712	0.86 (0.76, 0.97)	I^2 =42.4%; *P* =0.18
Whole blood	1	956	237	1.28 (0.79, 2.07)	-
All Tissue types combined	**16**	**30,380**	**9,758**	**0.91 (0.87, 0.95)**	I^2 =64.1%, *P* <0.001
CVD mortality					
Adipose Tissue	2	5,244	559	0.83 (0.67, 1.04)	I^2 =65.6%; *P* =0.09
Phospholipids	6	23,854	2,724	0.94 (0.87, 1.01)	I^2 =0%; *P* =0.72
Cholesteryl esters	5	7,115	827	0.86 (0.80, 0.94)	I^2 =0%; *P* =0.41
Erythrocytes	3	12,260	1,289	0.94 (0.89, 1.00)	I^2 =0%; *P* =0.87
Total Serum or Plasma	4	8,348	1,093	0.78 (0.67, 0.91)	I^2 =34.5%; *P* =0.21
All Tissue types combined	**20**	**56,821**	**6,492**	**0.89 (0.85, 0.94)**	I^2 =28.9%, *P*= 0.11
Cancer mortality					
Phospholipids	2	3,115	519	0.96 (0.85, 1.08)	I^2 =0%; *P* =0.44
Cholesteryl esters	3	5,590	383	0.82 (0.60, 1.13)	I^2 =70.7%; *P* =0.03
Erythrocytes	2	9,001	608	0.94 (0.84, 1.05)	I^2 =0%; *P* =0.97
Total Serum or Plasma	1	2,480	317	0.90 (0.78, 1.03)	-
All Tissue types combined	**7** [1]	**19,863**	**1,719**	**0.91 (0.84, 0.98)**	I^2 =26.3%, *P*= 0.23

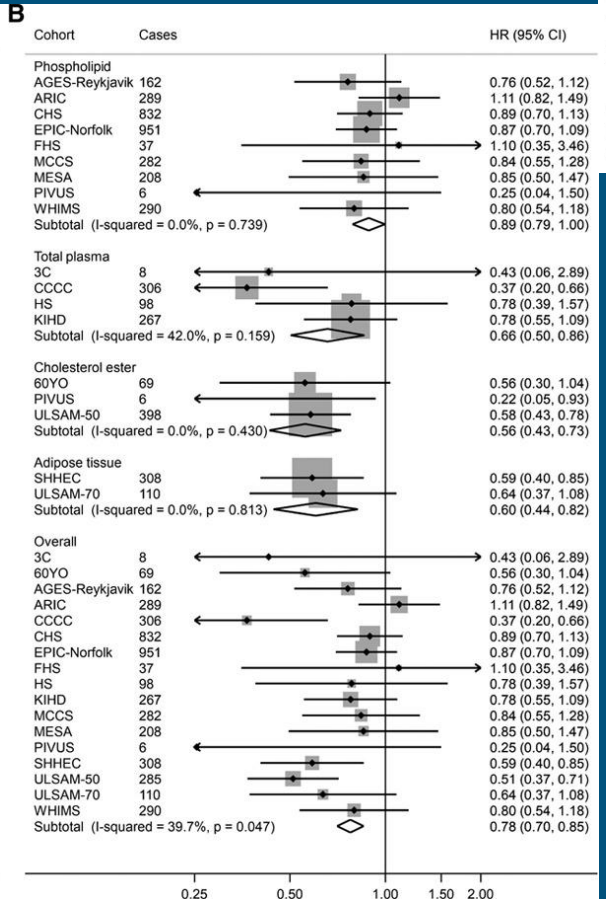


Marklund, 2019

CVD



CVD mortality



Biomarkers of Dietary Omega-6 Fatty Acids and Incident Cardiovascular Disease and Mortality

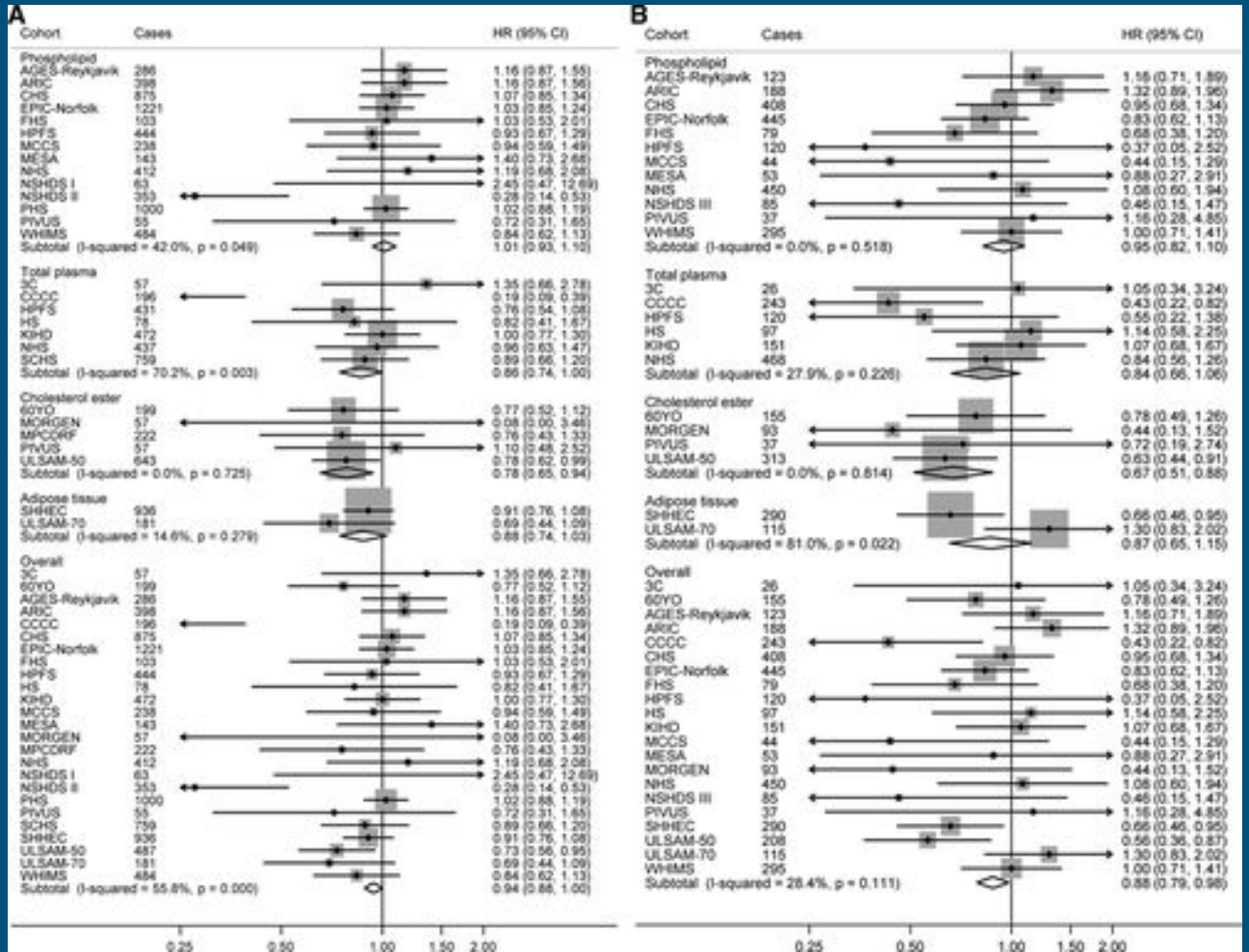
An Individual-Level Pooled Analysis of 30 Cohort Studies

Matti Marklund ✉, Jason H.Y. Wu, Fumiaki Imamura, Liana C. Del Gobbo, Amanda Fretts, Janette de Goede, Peilin Shi, Nathan Tintle, Maria Wennberg, Stella Aslibekyan, Tzu-An Chen, … See all authors

Originally published 11 Apr 2019 | https://doi.org/10.1161/CIRCULATIONAHA.118.038908 | Circulation. 2019;139:2422–2436

CHD

Ischemic stroke



Arachidonic acid

CVD

CVD mortality

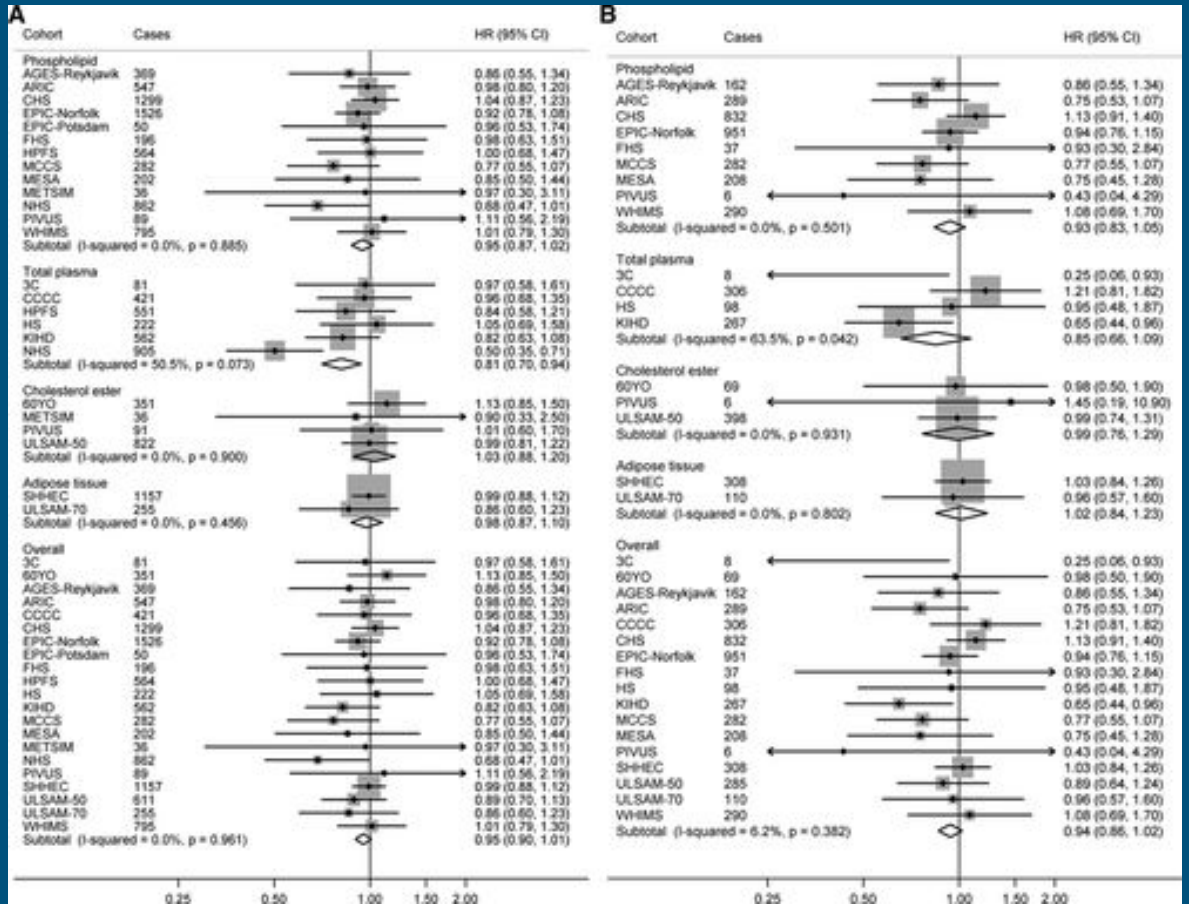


Table 2. Risk of Incident CVD According to Objective Biomarker Levels of Linoleic Acid (18:2n6) and Arachidonic Acid (20:4n6) in 30 Pooled Prospective Cohort Studies

Outcome	Biomarker	Studies, n	Cases, n	Multivariable-Adjusted Hazard Ratio (95% CI) per Interquintile Range*	
				Linoleic Acid	Arachidonic Acid
Total CVD	Phospholipid	14	6853	1.00 (0.92–1.09)	0.95 (0.87–1.03)
	Total plasma	6	2742	0.90 (0.78–1.03)	0.81 (0.70–0.94)
	Cholesterol esters	4	1300	0.74 (0.63–0.88)	1.03 (0.88–1.20)
	Adipose tissue	2	1412	0.87 (0.75–1.01)	0.98 (0.87–1.10)
	Overall†	21	10477	0.93 (0.88–0.99)	0.95 (0.90–1.01)
CVD mortality	Phospholipid	9	3057	0.89 (0.79–1.00)	0.93 (0.83–1.05)
	Total plasma	4	679	0.66 (0.50–0.86)	0.85 (0.66–1.09)
	Cholesterol esters	3	473	0.56 (0.43–0.73)	0.99 (0.76–1.29)
	Adipose tissue	2	418	0.60 (0.44–0.82)	1.02 (0.84–1.23)
	Overall†	17	4508	0.78 (0.70–0.85)	0.94 (0.86–1.02)
Total CHD	Phospholipid	14	6075	1.01 (0.93–1.10)	0.96 (0.90–1.03)
	Total plasma	7	2430	0.86 (0.74–1.00)	0.86 (0.74–1.01)
	Cholesterol esters	5	1178	0.78 (0.65–0.94)	1.02 (0.85–1.23)
	Adipose tissue	3‡	3255	0.88 (0.74–1.03)	1.10 (0.98–1.23)
	Overall†	26‡	11857	0.94 (0.88–1.00)	0.99 (0.94–1.04)
Ischemic stroke	Phospholipid	12	2327	0.95 (0.82–1.10)	0.98 (0.85–1.13)
	Total plasma	6	1105	0.84 (0.66–1.06)	0.93 (0.73–1.18)
	Cholesterol esters	4	598	0.67 (0.51–0.88)	1.13 (0.89–1.43)
	Adipose tissue	2	405	0.87 (0.65–1.15)	0.91 (0.74–1.11)
	Overall†	21	3705	0.88 (0.79–0.98)	0.99 (0.90–1.10)

Farvid, 2014

Circulation
Volume 130, Issue 18, 28 October 2014; Pages 1568-1578
https://doi.org/10.1161/CIRCULATIONAHA.114.010236

ORIGINAL ARTICLE

Dietary Linoleic Acid and Risk of Coronary Heart Disease: A Systematic Review and Meta-Analysis of Prospective Cohort Studies

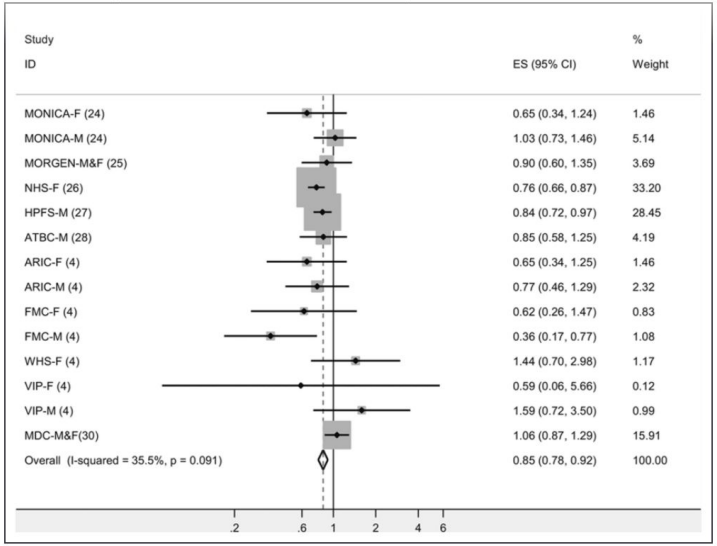


Figure 2. Dietary intake of linoleic acid and relative risk of total coronary heart disease events (highest category versus lowest category). The relative risk was pooled by using fixed-effects meta-analysis. ARIC indicates Atherosclerosis Risk in Communities; ATBC, Alpha-Tocopherol and Beta-Carotene Cancer Prevention; CI, confidence interval; ES, effect size; F, female; FMC, Finnish Mobile Clinic Health; HPFS, Health Professional Follow-Up Study; M, male; MDC, Malmo Diet and Cancer Cohort; MONICA, Multinational Monitoring of Trends and Determinations in Cardiovascular Disease; MORGEN, Monitoring Project on Risk Factors for Chronic Diseases; NHS, Nurses' Health Study; VIP, Västerbotten Intervention Program; and WHS, Women's Health Study.

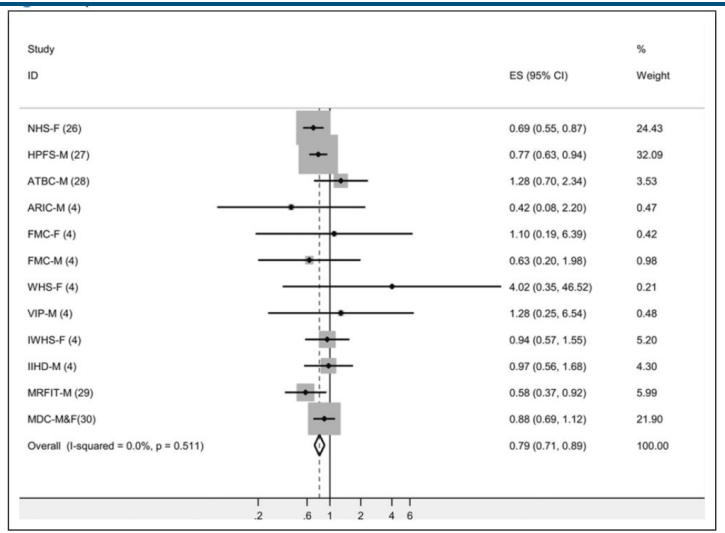


Figure 3. Dietary intake of linoleic acid and relative risk of coronary heart disease deaths (highest category versus lowest category). The relative risk was pooled by using fixed-effects meta-analysis. ARIC indicates Atherosclerosis Risk in Communities; ATBC, Alpha-Tocopherol and Beta-Carotene Cancer Prevention; CI, confidence interval; ES, effect size; F, female; FMC, Finnish Mobile Clinic Health; HPFS, Health Professional Follow-Up Study; IIHD, Israeli Ischemic Heart Disease; IWHS, Iowa Women's Health Study; M, male; MDC, Malmo Diet and Cancer Cohort; MRFIT, Multiple Risk Factor Intervention Trial; NHS, Nurses' Health Study; VIP, Västerbotten Intervention Program; and WHS, Women's Health Study.

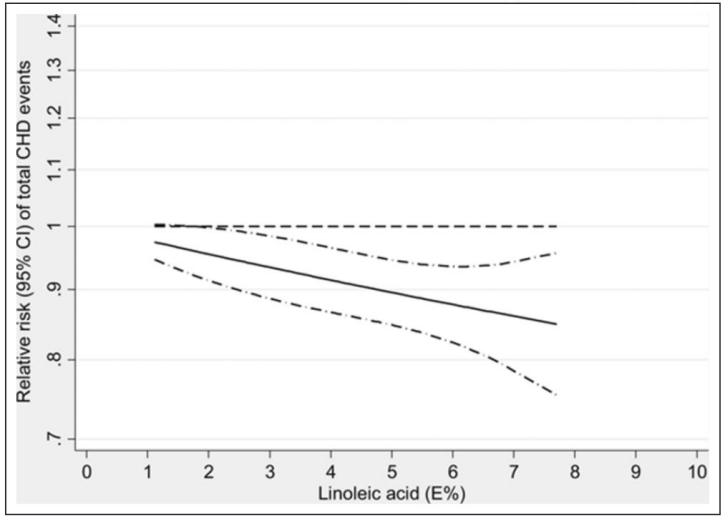


Figure 4. Dose–response analysis for the curvilinear association between dietary intake of linoleic acid and total coronary heart disease events. *P*=0.91 for nonlinearity relationship, indicating a linear relationship. %E indicates percent of energy.

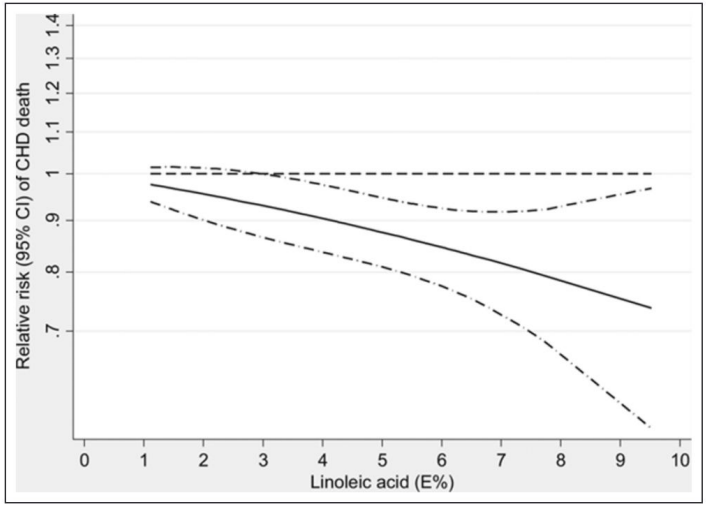


Figure 5. Dose–response analysis for the curvilinear association between dietary intake of linoleic acid and coronary heart disease deaths. *P*=0.72 for nonlinearity relationship, indicating a linear relationship. %E indicates percent of energy.

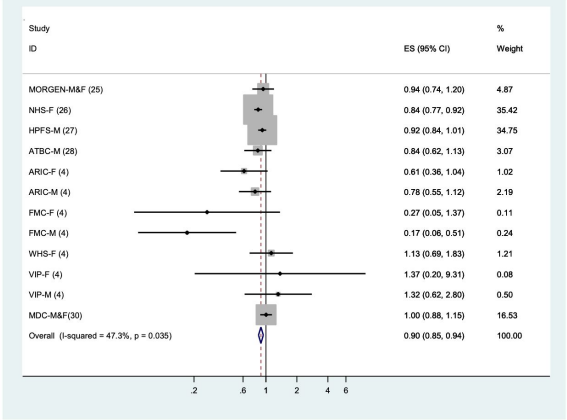


Figure S1. Two-stage dose-response meta-analysis of substituting each 5% energy from linoleic acid for 5% energy from carbohydrates and relative risk of total coronary heart disease events. The relative risk was pooled by using fixed effects meta-analysis.

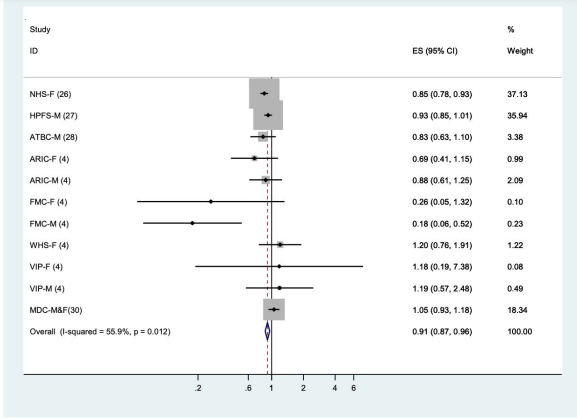


Figure S2. Two-stage dose-response meta-analysis of substituting each 5% energy from linoleic acid for 5% energy from saturated fat and relative risk of total coronary heart disease events. The relative risk was pooled by using fixed effects meta-analysis.

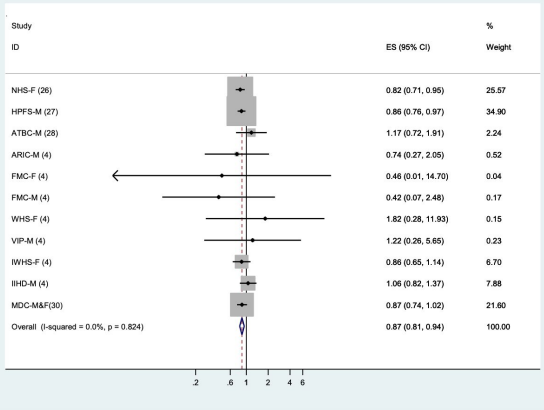


Figure S3. Two-stage dose-response meta-analysis of substituting each 5% energy from linoleic acid for 5% energy from carbohydrates and relative risk of coronary heart disease deaths. The relative risk was pooled by using fixed effects meta-analysis.

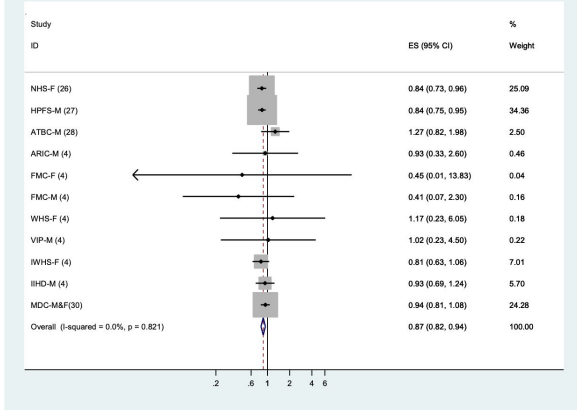


Figure S4. Two-stage dose-response meta-analysis of substituting each 5% energy from linoleic acid for 5% energy from saturated fat and relative risk of coronary heart disease deaths. The relative risk was pooled by using fixed effects meta-analysis.

Laaksonen, 2005

January 24, 2005

Prediction of Cardiovascular Mortality in Middle-aged Men by Dietary and Serum Linoleic and Polyunsaturated Fatty Acids

David E. Laaksonen, MD, PhD, MPH; Kristiina Nyyssönen, PhD; Leo Niskanen, MD, PhD; et al

» Author Affiliations | Article Information

Arch Intern Med. 2005;165(2):193-199. doi:10.1001/archinte.165.2.193

Table 3. Relative Risks of Cardiovascular Death According to Dietary Fatty Acid Intake Categorized Into Thirds*

Dietary Fatty Acid Intake in Thirds, Median (Range)	Model 1	Model 2	Model 3	Model 4
Dietary linoleic acid intake (g/d, energy adjusted)				
6.5 (2.2-7.7)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
8.9 (7.7-10.3)	0.64 (0.39-1.06)	0.73 (0.43-1.22)	0.73 (0.43-1.23)	0.74 (0.43-1.27)
12.9 (10.4-52.3)	0.39 (0.21-0.71)	0.49 (0.26-0.92)	0.46 (0.24-0.90)	0.46 (0.23-0.91)
P for trend	.01	.02	.02	.03
Dietary α-linolenic acid intake (g/d, energy adjusted)				
1.1 (0.4-1.3)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
1.5 (1.3-1.7)	1.09 (0.65-1.83)	1.18 (0.70-1.99)	1.15 (0.67-1.99)	1.16 (0.66-2.02)
2.0 (1.7-4.7)	0.58 (0.32-1.06)	0.65 (0.36-1.18)	0.63 (0.33-1.19)	0.63 (0.33-1.21)
P for trend	.08	.18	.15	.18
Dietary polyunsaturated fat intake (g/d, energy adjusted)				
8.8 (4.1-10.2)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
11.7 (10.2-13.4)	0.62 (0.37-1.04)	0.67 (0.40-1.13)	0.69 (0.41-1.18)	0.78 (0.45-1.34)
16.3 (13.4-57.1)	0.38 (0.20-0.70)	0.46 (0.24-0.86)	0.44 (0.22-0.85)	0.45 (0.23-0.90)
P for trend	.01	.01	.01	.02

*Data are given as relative risk (95% confidence interval) of cardiovascular death (n = 78). Cox proportional hazards regression analyses: model 1, adjusted for age and year of examination; 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 α-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.

Table 4. Relative Risks of Cardiovascular Death According to Serum Fatty Acid Proportions Categorized Into Thirds*

Serum Fatty Acid Proportion in Thirds, Median (Range), %	Model 1	Model 2	Model 3	Model 4
Esterified linoleic acid proportions				
24 (11-26)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
28 (26-30)	0.82 (0.48-1.41)	0.95 (0.54-1.65)	1.00 (0.56-1.72)	1.20 (0.66-2.10)
32 (30-43)	0.42 (0.21-0.80)	0.48 (0.24-0.93)	0.51 (0.24-1.04)	0.59 (0.28-1.23)
P for trend	.01	.04	.08	.22
Esterified n-6 fatty acid proportions				
31 (16-33)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
35 (33-36)	0.64 (0.37-1.10)	0.74 (0.42-1.32)	0.79 (0.44-1.42)	0.99 (0.55-1.80)
38 (36-49)	0.37 (0.19-0.72)	0.42 (0.22-0.83)	0.46 (0.23-0.95)	0.51 (0.25-1.07)
P for trend	.003	.01	.04	.10
Esterified α-linolenic acid proportions				
0.6 (0.0-0.7)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
0.8 (0.7-0.9)	0.52 (0.28-0.97)	0.52 (0.28-0.97)	0.53 (0.28-0.99)	0.66 (0.34-1.28)
1.0 (0.9-1.7)	0.77 (0.44-1.37)	0.84 (0.47-1.50)	0.86 (0.47-1.55)	1.19 (0.63-2.26)
P for trend	.49	.52	.57	.61
Esterified polyunsaturated fatty acid proportions				
37 (22-39)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
40 (39-42)	0.56 (0.32-0.96)	0.66 (0.38-1.17)	0.72 (0.40-1.30)	0.84 (0.45-1.54)
44 (42-54)	0.25 (0.12-0.50)	0.30 (0.15-0.62)	0.32 (0.15-0.70)	0.36 (0.16-0.79)
P for trend	<.001	.001	.004	.01

*Data are given as relative risk (95% confidence interval) of cardiovascular death (n = 69). See Table 3 for an explanation of the models.

Wang, 2016

JAMA Internal Medicine | Original Investigation

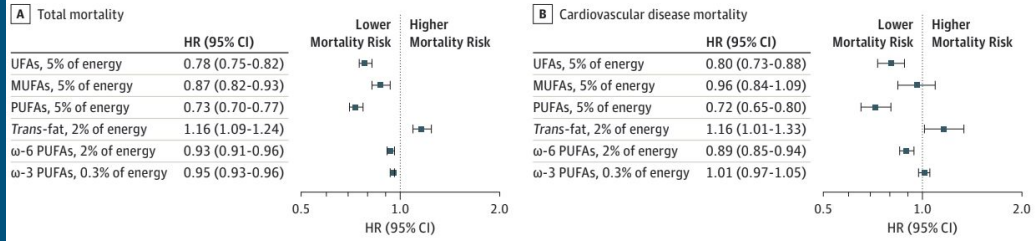
Association of Specific Dietary Fats With Total and Cause-Specific Mortality

Dong D. Wang, MD, MSc; Yanping Li, PhD; Stephanie E. Chiuve, ScD; Meir J. Stampfer, MD, DrPH; JoAnn E. Manson, MD, DrPH; Eric B. Rimm, ScD; Walter C. Willett, MD, DrPH; Frank B. Hu, MD, PhD

Table 3. Associations Between Dietary ω-6 and ω-3 PUFA Intake and Total Mortality (Comparison Is Isocaloric Substitution for Total Carbohydrates)

	Quintile of Dietary Fatty Acid Intake					*P* Value for Trend	HR (95% CI)[a]
	1	2	3	4	5		
ω-6 PUFA Intake							
Total ω-6 PUFA							
NHS							
Median, % of energy	3.4	4.3	4.9	5.5	6.7	NA	NA
No. of deaths	4124	4346	4158	3897	3789	NA	NA
HPFS							
Median, % of energy	3.7	4.5	5.1	5.8	6.9	NA	NA
No. of deaths	2874	2679	2622	2477	2338	NA	NA
Pooled[b]							
Age-adjusted model	1 [Reference]	0.89 (0.86-0.92)	0.85 (0.83-0.88)	0.80 (0.77-0.83)	0.75 (0.73-0.78)	<.001	0.84 (0.82-0.86)
MV-adjusted model[c]	1 [Reference]	0.96 (0.93-0.99)	0.93 (0.90-0.97)	0.88 (0.84-0.92)	0.85 (0.81-0.89)	<.001	0.90 (0.88-0.93)
Linoleic acid							
NHS							
Median, % of energy	3.3	4.2	4.8	5.4	6.5	NA	NA
No. of deaths	4165	4358	4148	3896	3747	NA	NA
HPFS							
Median, % of energy	3.6	4.4	5.0	5.6	6.7	NA	NA
No. of deaths	2910	2670	2569	2508	2333	NA	NA
Pooled[b]							
Age-adjusted model	1 [Reference]	0.90 (0.87-0.93)	0.86 (0.83-0.89)	0.81 (0.78-0.84)	0.74 (0.71-0.76)	<.001	0.82 (0.81-0.84)
MV-adjusted model[c]	1 [Reference]	0.97 (0.93-1.00)	0.92 (0.89-0.96)	0.88 (0.84-0.91)	0.82 (0.79-0.86)	<.001	0.88 (0.86-0.91)

Figure 2. Multivariable Hazard Ratios (HRs) of Mortality by Isocaloric Substitution of Specific Types of Fatty Acid for Saturated Fatty Acids



Zhuang, 2019

Dietary Fats in Relation to Total and Cause-Specific Mortality in a Prospective Cohort of 521 120 Individuals With 16 Years of Follow-Up

Pan Zhuang, Yu Zhang, Wei He, Xiaoqian Chen, Jingnan Chen, Lilin He, Lei Mao, Fei Wu and Jingjing Jiao

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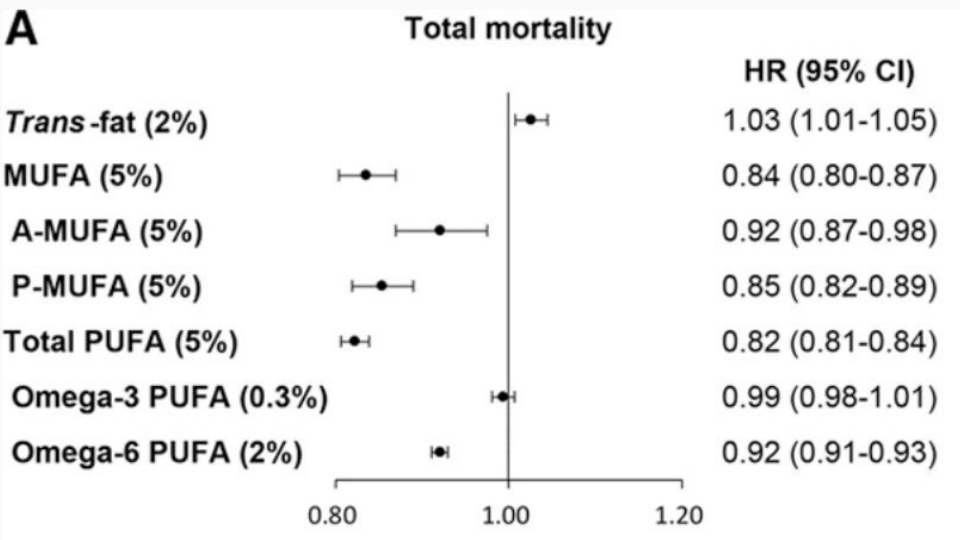
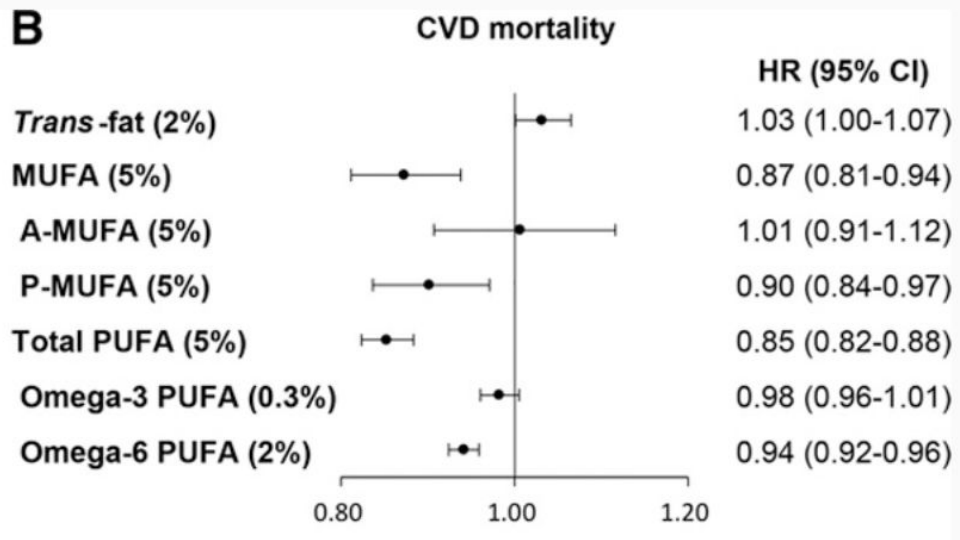
Circulation Research. 2019;124:757–768





Kim, 2020

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Original article

Association between dietary fat intake and mortality from all-causes, cardiovascular disease, and cancer: A systematic review and meta-analysis of prospective cohort studies

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[c] Departments of Nutrition and Epidemiology, Harvard TH Chan School of Public Health, Boston, MA, USA

Table 2
Summary of pooled relative risks (RR) of mortality from all-causes, CVD, and cancer for total and specific types of fat intake.

	Highest *versus* lowest				% of energy increment from fat				
	No. of studies	RR (95% CI)	I^2 (%)	*P* value	% of energy	No. of studies	RR (95% CI)	I^2 (%)	*P* value
All-cause mortality									
Total fat	8	0.89 (0.81–0.99)	82.3	<0.001	5	6	0.99 (0.98–1.00)	67.5	0.002
Saturated fat	11	1.03 (0.94–1.13)	90.4	<0.001	5	10	1.02 (1.00–1.05)	83.1	<0.001
Monounsaturated fat	10	0.94 (0.89–0.99)	61.2	0.003	5	8	0.98 (0.97–0.99)	36.8	0.11
Polyunsaturated fat	11	0.88 (0.81–0.94)	84.7	<0.001	5	9	0.93 (0.89–0.97)	83.7	<0.001
Trans-fat	5	1.11 (1.02–1.21)	80.8	0.001	1	6	1.06 (1.01–1.10)	89.5	<0.001
CVD mortality									
Total fat	9	0.95 (0.85–1.07)	51.3	0.02	5	7	1.00 (0.99–1.01)	48.3	0.04
Saturated fat	11	1.02 (0.92–1.12)	78.2	<0.001	5	10	1.03 (1.00–1.07)	76.1	<0.001
Monounsaturated fat	11	0.94 (0.88–1.01)	47.1	0.03	5	9	0.99 (0.96–1.01)	53.1	0.01
Polyunsaturated fat	11	0.95 (0.89–1.02)	64.2	0.001	5	9	0.95 (0.91–0.98)	59.1	0.004
Trans-fat	6	1.14 (1.02–1.26)	46.6	0.1	1	7	1.06 (1.02–1.11)	50.8	0.05
Cancer mortality									
Total fat	5	1.00 (0.88–1.14)	69.2	0.003	5	4	1.00 (0.99–1.01)	50.9	0.07
Saturated fat	7	1.09 (1.00–1.18)	73.2	<0.001	5	6	1.04 (1.02–1.06)	58.8	0.02
Monounsaturated fat	7	0.98 (0.93–1.03)	35.8	0.13	5	6	0.99 (0.98–1.00)	11.8	0.34
Polyunsaturated fat	7	0.92 (0.89–0.95)	13.0	0.33	5	6	0.96 (0.94–0.99)	41.9	0.10
Trans-fat	3	0.97 (0.91–1.03)	46.1	0.17	1	3	0.99 (0.98–1.00)	0.0	0.37

CVD, cardiovascular disease.

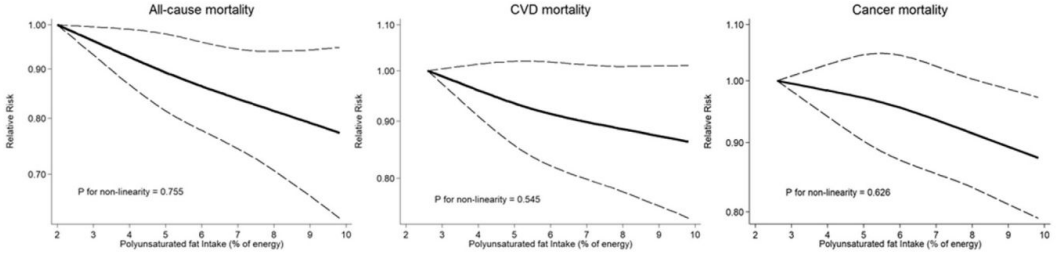


Fig. 4. Pooled dose–response association between dietary polyunsaturated fat and mortality from all-causes, CVD, and cancer. Solid lines represent relative risk (RR), dashed lines represent 95% confidence intervals.

Zhang, 2021

Research article | Open Access | Published: 15 April 2021

Cooking oil/fat consumption and deaths from cardiometabolic diseases and other causes: prospective analysis of 521,120 individuals

Yu Zhang, Pan Zhuang, Fei Wu, Wei He, Lei Mao, Wei Jia, Yiju Zhang, Xiaoqian Chen & Jingjing Jiao

BMC Medicine **19**, Article number: 92 (2021) | Cite this article

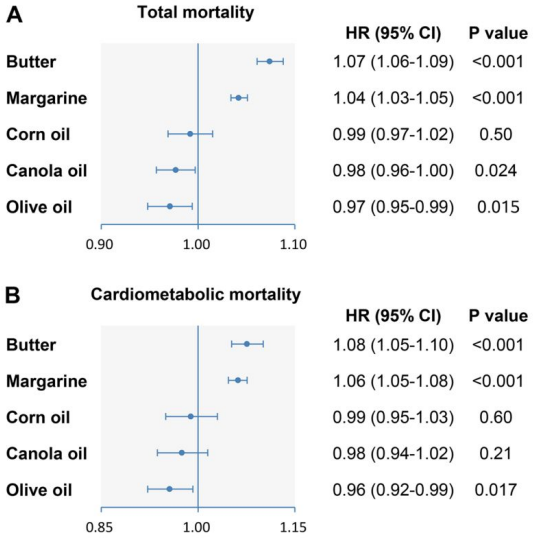


Fig. 1 Multivariable-adjusted hazard ratios of total and cardiometabolic mortality for 1-tablespoon/day increment in cooking oil/fat consumption. Forest plots show the multivariable HRs of total (**a**) and cardiometabolic (**b**) mortality associated with 1-tablespoon/day increment in butter, margarine, corn oil, canola oil, and olive oil consumption. HRs were adjusted for age, sex, BMI, race, education, marital status, household income, smoking, alcohol, vigorous physical activity, usual activity at work, perceived health condition, history of heart disease, stroke, diabetes, and cancer at baseline, Healthy Eating Index-2015, total energy intake, and consumption of remaining oils where appropriate (butter, margarine, lard, corn oil, canola oil, olive oil, and other vegetable oils). Horizontal lines represent 95% CIs

Table 2 HRs (95% CIs) of all-cause mortality according to cooking oil/fat consumption

	Categories of individual cooking oil/fat consumption				
	Non-consumers	T1	T2	T3	*P* trend
Butter					
Median intake (IQR)	0	1.0 (0.4–2.0)	5.5 (4.2–6.9)	13.7 (10.7–18.8)	
Death cases/*n*	75,826/303,987	15,792/72,377	17,915/72,378	19,795/72,378	
Person-years	4,262,749	1,030,708	1,014,202	999,439	
Model 1[a]	1.00	0.88 (0.86–0.89)	1.02 (1.00–1.03)	1.14 (1.13–1.16)	< 0.001
Model 2[b]	1.00	0.96 (0.94–0.97)	1.04 (1.02–1.06)	1.12 (1.10–1.14)	< 0.001
Model 3[c]	1.00	0.98 (0.96–1.00)	1.05 (1.03–1.06)	1.09 (1.07–1.11)	< 0.001
Margarine					
Median intake (IQR)	0	2.4 (0.9–4.0)	9.3 (7.4–11.4)	20.6 (16.7–26.6)	
Death cases/*n*	32,633/134,374	29,070/128,915	32,583/128,916	35,042/128,915	
Person-years	1,888,086	1,829,523	1,804,411	1,785,077	
Model 1[a]	1.00	0.90 (0.89–0.92)	1.01 (0.99–1.02)	1.08 (1.06–1.09)	< 0.001
Model 2[b]	1.00	0.94 (0.92–0.95)	0.99 (0.97–1.00)	1.00 (0.99–1.02)	< 0.001
Model 3[c]	1.00	0.99 (0.97–1.01)	1.03 (1.01–1.05)	1.07 (1.05–1.09)	< 0.001
Corn oil					
Median intake (IQR)	0	0.4 (0.2–0.5)	1.1 (0.8–1.4)	3.4 (2.4–5.5)	
Death cases/*n*	98,499/399,360	9400/40586	10,240/40,587	11,189/40,587	
Person-years	5,605,569	574,055	567,538	559,935	
Model 1[a]	1.00	0.95 (0.93–0.97)	1.03 (1.01–1.05)	1.12 (1.10–1.14)	< 0.001
Model 2[b]	1.00	0.96 (0.94–0.98)	0.99 (0.97–1.01)	1.02 (1.00–1.04)	0.21
Model 3[c]	1.00	0.97 (0.94–0.99)	0.98 (0.96–1.00)	0.99 (0.97–1.01)	0.092
Canola oil					
Median intake (IQR)	0	0.4 (0.2–0.5)	1.0 (0.8–1.3)	3.2 (2.3–5.3)	
Death cases/*n*	95,507/376,913	10,571/48,069	11,129/48,069	12,121/48,069	
Person-years	5,269,352	684,537	680,475	672,733	
Model 1[a]	1.00	0.88 (0.86–0.89)	0.91 (0.89–0.92)	0.98 (0.96–0.99)	< 0.001
Model 2[b]	1.00	0.94 (0.93–0.96)	0.96 (0.94–0.97)	0.97 (0.95–0.99)	< 0.001
Model 3[c]	1.00	0.98 (0.95–1.00)	0.97 (0.95–0.99)	0.97 (0.95–0.99)	< 0.001
Olive oil					
Median intake (IQR)	0	0.4 (0.3–0.5)	1.2 (0.9–1.5)	3.8 (2.6–6.2)	
Death cases/*n*	91,948/353,766	11,878/55,784	12,386/55,785	13,116/55,785	
Person-years	4,930,793	796,402	793,033	786,869	
Model 1[a]	1.00	0.85 (0.84–0.87)	0.87 (0.86–0.89)	0.91 (0.89–0.93)	< 0.001
Model 2[b]	1.00	0.94 (0.92–0.96)	0.96 (0.94–0.98)	0.97 (0.95–0.99)	< 0.001
Model 3[c]	1.00	0.96 (0.94–0.99)	0.97 (0.95–0.98)	0.96 (0.95–0.98)	< 0.001

Margarine contains *trans*-fat, a well-documented risk factor for arterial calcification and coronary heart disease [26], and has a negative impact on plasma lipid profiles in both healthy individuals and patients with hypercholesterolemia [27]. Our findings were consistent with a recent meta-analysis, showing a positive association of *trans*-fat with all-cause and CVD mortality [28]. The observed association of margarine intake with modestly higher diabetes mortality was in line with a European multi-center study [29]. In addition, higher incidence of asthma onset was contributed by the intake of margarine [30], supporting our finding of elevated RD mortality. Compared with tub/soft margarine, our secondary analysis showed that stick margarine consumption turned to be much stronger for its positive association with AD mortality, which could be explained by higher *trans*-fat content (15–21%) [31] and supported by previous evidence suggesting a negative effect of *trans*-fat on dementia [32]. Taken together, our results suggest the importance of restricting intake of *trans*-fat containing margarines to decrease the incidence of cardiometabolic diseases.

Table 3 HRs (95% CIs) of CVD and diabetes mortality according to cooking oil/fat consumption

	Categories of individual cooking oil/fat consumption				
	Non-consumers	T1	T2	T3	*P* trend
Cardiovascular disease mortality					
Butter					
Death cases/*n*	23,406/303,987	4623/72,377	5213/72,378	5505/72,378	
Model 1[a]	1.00	0.83 (0.80–0.86)	0.96 (0.93–0.99)	1.04 (1.01–1.07)	< 0.001
Model 2[b]	1.00	0.93 (0.90–0.96)	1.02 (0.99–1.05)	1.07 (1.04–1.11)	< 0.001
Model 3[c]	1.00	0.96 (0.93–1.00)	1.04 (1.01–1.08)	1.08 (1.05–1.12)	< 0.001
Margarine					
Death cases/*n*	9305/134,374	8630/128,915	9901/128,916	10,911/128,915	
Model 1[a]	1.00	0.93 (0.90–0.96)	1.06 (1.03–1.09)	1.17 (1.14–1.21)	< 0.001
Model 2[b]	1.00	0.95 (0.92–0.98)	1.02 (0.99–1.05)	1.04 (1.01–1.07)	< 0.001
Model 3[c]	1.00	1.01 (0.97–1.04)	1.06 (1.02–1.09)	1.10 (1.06–1.14)	< 0.001
Corn oil					
Death cases/*n*	29,443/399,360	2830/40,586	3068/40,587	3406/40,587	
Model 1[a]	1.00	0.97 (0.93–1.01)	1.03 (0.99–1.07)	1.14 (1.10–1.18)	< 0.001
Model 2[b]	1.00	0.99 (0.96–1.03)	1.00 (0.97–1.04)	1.02 (0.99–1.06)	0.22
Model 3[c]	1.00	1.01 (0.96–1.05)	0.99 (0.95–1.03)	1.00 (0.96–1.03)	0.78
Canola oil					
Death cases/*n*	28,520/376,913	3149/48,069	3362/48,069	3716/48,069	
Model 1[a]	1.00	0.89 (0.85–0.92)	0.93 (0.89–0.96)	1.01 (0.97–1.04)	0.70
Model 2[b]	1.00	0.96 (0.92–1.00)	0.97 (0.94–1.01)	0.97 (0.94–1.01)	0.080
Model 3[c]	1.00	0.99 (0.95–1.04)	0.98 (0.94–1.02)	0.97 (0.94–1.00)	0.052
Olive oil					
Death cases/*n*	27,962/353,766	3377/55,784	3578/55,785	3830/55,785	
Model 1[a]	1.00	0.81 (0.78–0.84)	0.84 (0.81–0.87)	0.88 (0.85–0.91)	< 0.001
Model 2[b]	1.00	0.92 (0.89–0.96)	0.95 (0.92–0.98)	0.95 (0.92–0.98)	0.002
Model 3[c]	1.00	0.93 (0.89–0.97)	0.95 (0.92–0.99)	0.95 (0.92–0.99)	0.001

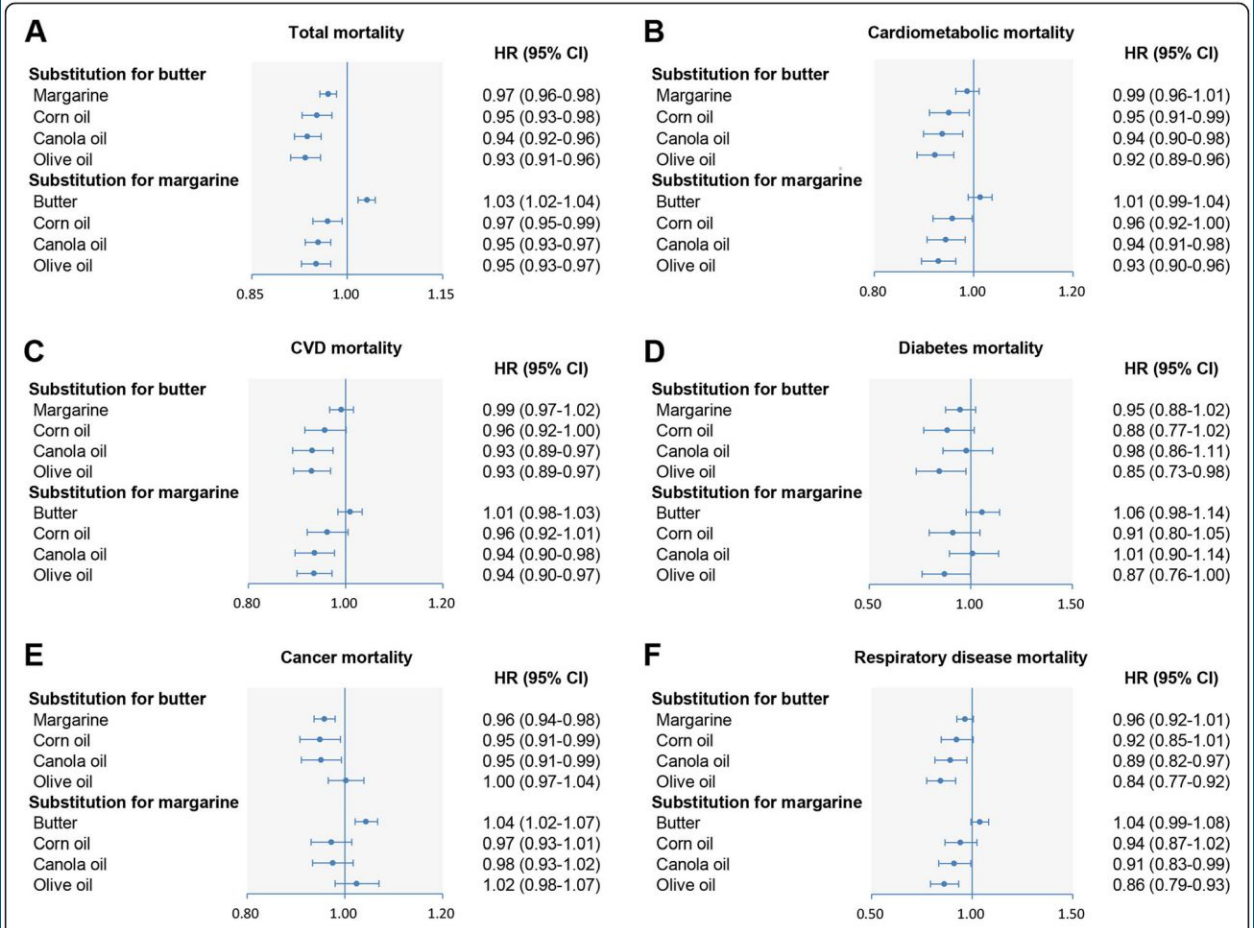


Fig. 3 Multivariable-adjusted hazard ratios of total and cause-specific mortality by substitution of 1 tablespoon/day individual cooking oils/fats for butter and margarine. Forest plots show the multivariable HRs of total and cause-specific mortality associated with substitution of 1 tablespoon/day individual cooking oils/fats for equivalent amounts of butter and margarine. HRs were adjusted for age, sex, BMI, race, education, marital status, household income, smoking, alcohol, vigorous physical activity, usual activity at work, perceived health condition, history of heart disease, stroke, diabetes, and cancer at baseline, Healthy Eating Index-2015, and total energy intake. Horizontal lines represent 95% CIs

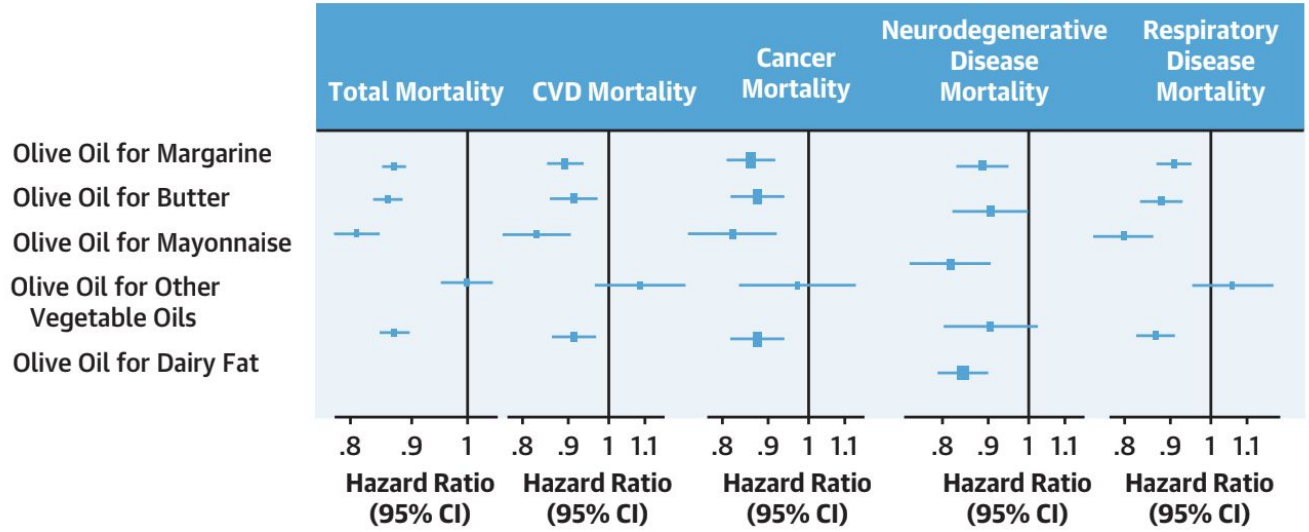
Guasch-Ferre, 2021

Curr Dev Nutr. 2021 Jun; 5(Suppl 2): 1036. PMCID: PMC8181296
Published online 2021 Jun 7. doi: 10.1093/cdn/nzab053_029

Consumption of Total Olive Oil and Risk of Total and Cause-Specific Mortality in US Adults

Marta Guasch-Ferre, Yanping Li, Walter Willett, Qi Sun, Laura Sampson, Jordi Salas-Salvado, Miguel Ángel Martinez-Gonzalez, Meir Stampfer, and Frank Hu

FIGURE 1 **Mortality Associated With Olive Oil Substituted for Other Fats**



HR (95% CI) for mortality substituting 10 g of olive oil for equivalent amount of other fats. Model was adjusted for age, ethnicity, ancestry, married, living alone, smoking status, alcohol intake, physical, family history of diabetes, myocardial infarction or cancer, multivitamin use, aspirin use, in women postmenopausal status and menopausal hormone use, energy intake, body mass index, red meat, fruits and vegetables, nuts, soda, whole grains, and the intake of trans fat, and mutually adjusted for the intake of other types of fat. Results were pooled using a pooled dataset and stratifying by cohort and time period. CVD = cardiovascular disease.

SACN Report, 2019

Table S1: Summary table of the evidence on the relationship between saturated fats and health outcomes, intermediate markers and risk factors

Outcome	Reduced intake of saturated fats		Saturated fats substitution with PUFA		Saturated fats substitution with MUFA		Saturated fats substitution with carbohydrates		Saturated fats substitution with proteins	
	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence	Direction of effect/ association	Strength of evidence
Cardiovascular diseases (RCTs)										
CVD mortality	-	Adequate	-	Adequate	n/a	Insufficient	-	Limited	-	Limited
CVD events	↓	Adequate	↓	Adequate	n/a	Insufficient	-	Limited	-	Limited
CHD mortality	-	Adequate	-	Adequate	n/a	Insufficient	-	Limited	-	Limited
CHD events	↓	Moderate	↓	Moderate	n/a	Insufficient	-	Moderate	-	Moderate
Strokes	-	Adequate	n/a	Insufficient	n/a	No evidence	-	Limited	-	Limited
Peripheral vascular disease	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Cardiovascular diseases (PCS)										
CVD mortality	-	Adequate	↓	Limited[1]	n/a	No evidence	n/a	Insufficient	n/a	No evidence
CVD events	-	Adequate	n/a	No evidence	n/a	No evidence	n/a	Insufficient	n/a	No evidence
CHD mortality	↓	Moderate[2]	↓	Moderate	-	Limited	-	Adequate	n/a	No evidence
CHD events	↓	Moderate[2]	↓	Moderate	↑	Limited	↑	Adequate	n/a	No evidence
Strokes	-	Adequate[3,4]	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence
Peripheral vascular disease	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence	n/a	No evidence

Mensink, 2016

Lipid or lipoprotein	Unit	Change per 1% of energy replaced			No[1]
		PUFA → Carb	PUFA → SFA	PUFA → MUFA	
ΔTotal cholesterol	mmol/L	0.019	0.066	0.016	177/74
95% CI[2]		0.013 to 0.025	0.060 to 0.073	0.011 to 0.022	
P-value		<0.001	<0.001	<0.001	
ΔLDL cholesterol	mmol/L	0.019	0.058	0.012	165/69
95% CI		0.012 to 0.025	0.052 to 0.064	0.007 to 0.017	
P-value		<0.001	<0.001	<0.001	
ΔHDL cholesterol	mmol/L	–0.005	0.005	0.003	163/68
95% CI		–0.007 to –0.004	0.004 to 0.007	0.001 to 0.004	
P-value		<0.001	<0.001	<0.001	
ΔTriglyceride	mmol/L	0.020	0.010	0.006	172/72
95% CI		0.016 to 0.024	0.006 to 0.014	0.003 to 0.009	
P-value		<0.001	<0.001	<0.001	
ΔTotal to HDL cholesterol ratio		0.032	0.034	0.005	159/66
95% CI		0.025 to 0.039	0.027 to 0.041	0.000 to 0.011	
P-value		<0.001	<0.001	0.053	
ΔLDL to HDL cholesterol ratio		0.024	0.035	0.004	161/67
95% CI		0.017 to 0.031	0.028 to 0.041	–0.001 to 0.009	
P-value		<0.001	<0.001	0.104	
ΔTriglyceride to HDL cholesterol ratio		0.018	0.004	0.003	161/67
95% CI		0.014 to 0.022	0.001 to 0.008	0.000 to 0.006	
P-value		<0.001	0.026	0.040	
ΔApoA-I	mg/dL	–1.8	6.3	3.4	104/42
95% CI		–4.0 to 0.3	3.9 to 8.7	1.6 to 5.3	
P-value		0.097	<0.001	0.001	
ΔApoB	mg/dL	5.7	10.3	1.8	102/41
95% CI		3.3 to 8.1	7.7 to 12.8	–0.2 to 3.8	
P-value		<0.001	<0.001	0.074	

Effects of saturated fatty acids on serum lipids and lipoproteins: a systematic review and regression analysis

Citation
Mensink, Ronald P. & World Health Organization. (2016).
Effects of saturated fatty acids on serum lipids and lipoproteins: a systematic review and regression analysis. World Health Organization.
https://apps.who.int/iris/handle/10665/246104

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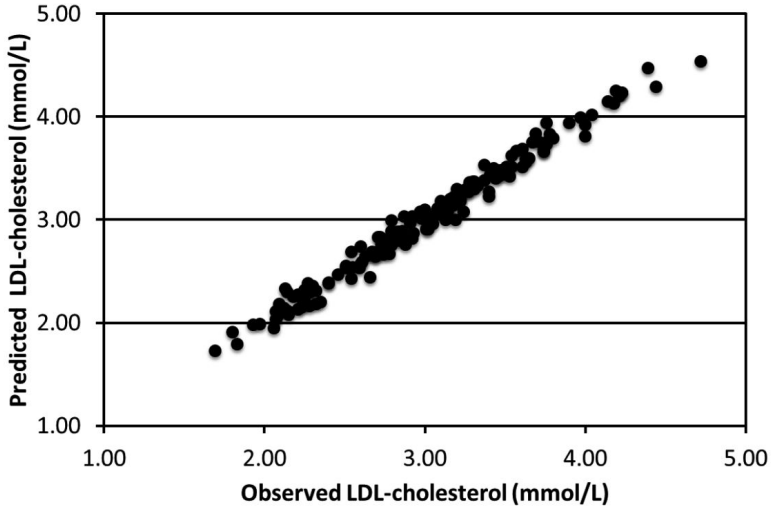
ANNEX 5.

Relationship between observed and predicted serum LDL cholesterol concentrations

Each point refers to one of the 165 diets from the 69 studies as used for the calculations in regression model 1 (see **Section 2.2.4 and Table 2**). "Predicted" values were calculated as the intrinsic level of the group under study plus the predicted change induced by their experimental diet



Amiri, 2020

SYSTEMATIC REVIEWS AND META-ANALYSES | VOLUME 30, ISSUE 12, P2133-2145, NOVEMBER 27, 2020

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The effects of Canola oil on cardiovascular risk factors: A systematic review and meta-analysis with dose-response analysis of controlled clinical trials

Mojgan Amiri [1] • Hamidreza Raeisi-Dehkordi [1] • Nizal Sarrafzadegan • Scott C. Forbes
Amin Salehi-Abargouei • Show footnotes

Published: June 18, 2020 • DOI: https://doi.org/10.1016/j.numecd.2020.06.007 Check for updates

Table 1- The effect of CO versus other edible oils on cardio-metabolic markers; all analyses were conducted using random effects model.

		Meta-analysis		Heterogeneity			Publication bias		Dose-response analysis	
Metabolic markers	**No. of trials / participants**	**WMD (95%CI)**	**P for effect**	**Q statistic**	**P value**	**I^2 (%)**	**Egger's test**	**Begg's test**	**Coefficient**	**P value**
Blood lipid markers										
TC (mmol/l)[1]	37/ 1637	-0.27 (-0.38, -0.17)	<0.001	479.93	<0.001	92.5	0.488	0.628	-0.031	<0.001
TG (mmol/l)	37/ 1647	-0.02 (-0.06, 0.01)	0.210	157.61	<0.001	77.2	0.035	0.917	-0.008	0.006
HDL-C (mmol/l)	36/ 1644	-0.01 (-0.02, 0.0)	0.055	56.34	0.013	37.9	0.938	0.577	-0.001	0.082
LDL-C (mmol/l)	35/ 1569	-0.23 (-0.33, -0.14)	<0.001	399.52	<0.001	91.5	0.350	0.989	-0.021	<0.001
LDL/HDL	10/ 526	-0.21 (-0.34, -0.08)	0.002	11.8	0.225	23.7	0.376	0.858	-0.018	0.003
TC/HDL	15/ 753	-0.13 (-0.21, -0.06)	<0.001	15.97	0.315	12.3	0.604	0.276	-0.021	0.002
VLDL (mmol/l)	14/ 404	-0.001 (-0.05, 0.04)	0.876	36.95	<0.001	64.8	0.988	1	-0.004	0.275
HDL-2 (mmol/l)	6/ 202	0.04 (-0.05, 0.14)	0.338	26.50	<0.001	81.1	0.780	0.707	0.004	0.182
HDL-3 (mmol/l)	6/ 202	-0.03 (-0.11, 0.05)	0.461	61.17	<0.001	91.8	0.793	0.452	-0.007	0.003
HDL-TG (mmol/l)	7/ 217	0.00 (-0.01, 0.01)	0.826	10.31	0.011	41.8	0.238	0.230	0.001	0.467
LDL-TG (mmol/l)	8/ 325	-0.01 (-0.04, 0.01)	0.244	27.26	<0.001	74.3	0.284	0.711	0.0005	0.624
VLDL-TG(mmol/l)	8/ 325	0.06 (-0.03, 0.14)	0.191	3.47	0.061	48	0.815	1	-0.006	0.439
Apo A-1 (g/l)	17/ 811	0.01 (-0.02, 0.04)	0.353	40.66	0.001	60.7	0.957	0.967	-0.0001	0.904
Apo B (g/l)	14/ 736	-0.03 (-0.06, -0.01)	0.012	27.11	0.012	52	0.614	1	-0.004	0.023
Lp (a) (mg/dl)	8/ 262	2.8 (-3.96, 9.56)	0.326	1.09	0.993	0	0.246	0.348	0.172	0.750
Apo B /Apo A-1	6/ 405	-0.02 (-0.03, -0.01)	0.024	3.84	0.573	0	0.910	0.707	-0.0007	0.210

Table 4- The effect of CO versus saturated fat intake on different metabolic markers; all analyses were conducted using random effects.

		Meta-analysis		Heterogeneity			Publication bias	
	no. of trials / participants	Weighted mean difference (95%CI)	P for effect	Q statistic	P value	I^2 (%)	Egger's test	Begg's test
Blood lipid markers								
TC (mmol/l) [1]	11/ 233	-0.59 (-0.80, -0.38)	<0.001	192.30	<0.001	94.8	0.044	0.072
TG (mmol/l)	11/ 233	-0.08 (-0.15, -0.01)	0.043	57.57	<0.001	82.6	0.110	0.243
HDL-C (mmol/l)	10/ 218	-0.01 (-0.04, 0.01)	0.306	10.94	0.28	17.7	0.254	0.371
LDL-C (mmol/l)	10/ 218	-0.49 (-0.70, -0.28)	<0.001	203.58	0	95.6	0.001	0.016
LDL/HDL	3/ 62	-0.46 (-0.98, 0.07)	0.087	7.91	0.019	74.7	-	-
TC/HDL	5/ 105	-0.29 (-0.54, -0.04)	0.025	5.35	0.253	25.2	-	-
VLDL (mmol/l)	4/ 77	-0.04 (-0.11, 0.04)	0.350	4.94	0.176	39.2	-	-
HDL-2 (mmol/l)	3/ 58	0.07 (-0.10, 0.24)	0.427	25.74	<0.001	92.2	-	-
HDL-3 (mmol/l)	3/ 58	-0.06 (-0.23, 0.10)	0.452	52.48	<0.001	96.2	-	-
HDL-TG (mmol/l)	2/ 39	-0.01 (-0.02, 0.01)	0.374	0.3	0.582	0	-	-
LDL-TG (mmol/l)	2/ 39	-0.04 (-0.11, 0.03)	0.234	3.36	0.067	70.2	-	-
VLDL-TG(mmol/l)	2/ 39	-0.18 (-0.44, 0.08)	0.171	0	1	0	-	-
Apo A-1 (g/l)	4/ 77	-0.03 (-0.08, 0.01)	0.158	4.22	0.239	28.8	-	-
Apo B (g/l)	4/ 77	-0.09 (-0.16, -0.02)	0.008	7.19	0.066	58.3	-	-
Lp (a) (mg/dl)	4/ 77	1.98 (-1.39, 5.35)	0.250	0.66	0.883	0	-	-
Apo B /Apo A-1	2/ 43	-0.04 (-0.12, 0.04)	0.302	1.95	0.162	48.8	-	-

Ference, 2017

ESC European Society of Cardiology
European Heart Journal (2017) **38**, 2459–2472
doi:10.1093/eurheartj/ehx144

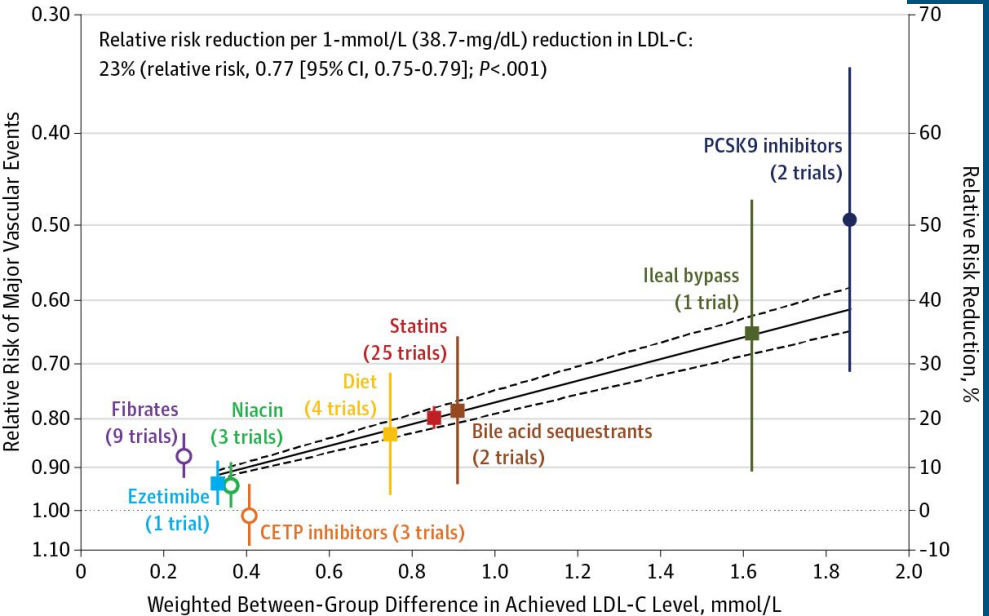
Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel

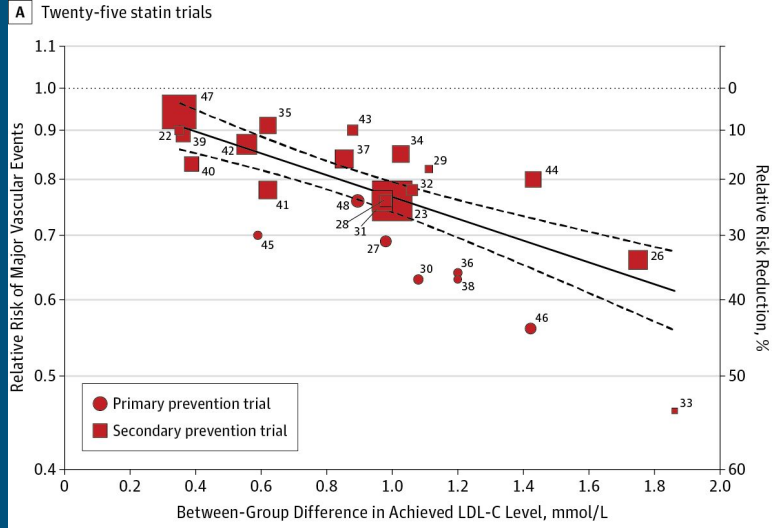
Table 1 **Criteria for causality: low-density lipoprotein (LDL) and atherosclerotic cardiovascular disease (ASCVD)**

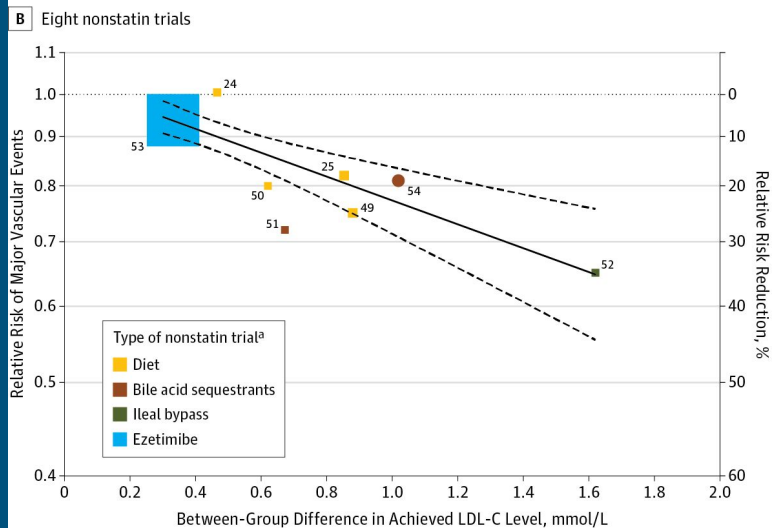
Criterion (modified from reference[5])	Evidence grade	Summary of the evidence (references)
1. Plausibility	1	LDL and other apolipoprotein (apo) B-containing lipoproteins (very low-density lipoprotein their remnants, intermediate-density lipoprotein and lipoprotein(a)) are directly implicated in the initiation and progression of ASCVD; experimentally induced elevations in plasma LDL and other apoB-containing lipoproteins lead to atherosclerosis in all mammalian species studied.[2,5–12]
2. Strength	1	Monogenic and polygenic-mediated lifelong elevations in LDL lead to markedly higher lifetime risk.[13–20,27–31,40,43]
3. Biological gradient	1	Monogenic lipid disorders, prospective cohort studies, Mendelian randomization studies, and randomized intervention trials uniformly demonstrate a dose-dependent, log-linear association between the absolute magnitude of exposure to LDL and risk of ASCVD[13–22,27–36,38–40,42–47]
4. Temporal sequence	1	Monogenic lipid disorders and Mendelian randomization studies demonstrate that exposure to elevated LDL precedes the onset of ASCVD[13–20,27–31,40,43]
5. Specificity	1	Mendelian randomization studies and randomized intervention trials both provide unconfounded randomized evidence that LDL is associated with ASCVD independent of other risk factors[28,31–33,40,43]
6. Consistency	1	Over 200 studies involving more than 2 million participants with over 20 million person-years of follow-up and more than 150 000 cardiovascular events consistently demonstrate a dose-dependent, log-linear association between the absolute magnitude of exposure to LDL and risk of ASCVD[13–22,27–36,38–40,42–47]
7. Coherence	1	Monogenic lipid disorders, prospective cohort studies, Mendelian randomization studies, and randomized intervention trials all show a dose-dependent, log-linear association between the absolute magnitude of exposure to LDL and risk of ASCVD[15–18,21,22,28,30–32,35,36,43,44,47]
8. Reduction in risk with intervention	1	More than 30 randomized trials involving over 200 000 participants and 30 000 ASCVD events evaluating therapies specifically designed to lower LDL (including statins, ezetimibe, and PCSK9 inhibitors) consistently demonstrate that reducing LDL cholesterol (LDL-C) reduces the risk of ASCVD events proportional to the absolute reduction in LDL-C[32–34,38,39,42,45–47]

Criteria are graded by a modification of the quality criteria adopted by the European Society of Cardiology system.
For reference, see http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/Guidelinesdevelopment/Writing-ESC-Guidelines (31 January 2017).
These are defined as follows:
Class 1: Evidence and/or general agreement that the criterion for causality is fulfilled.
Class 2: Conflicting evidence and/or a divergence of opinion about whether the criterion indicated causality.
Class 3: Evidence or general agreement that the criterion for causality is not fulfilled.

Furthermore, in the Lipid Research Clinics Coronary Primary Prevention Trial, treatment with the bile acid sequestrant cholestyramine reduced LDL-C by 0.7 mmol/L and reduced the relative risk of cardiovascular death or MI by 19%.[45] Similarly, in the Program on Surgical Control of Hyperlipidemia (POSCH) study, ileal bypass surgery reduced LDL-C by 1.85 mmol/L and reduced the relative risk of cardiovascular death or MI by 35%.[46] In both trials, the observed risk reduction was consistent with the proportional risk reduction per unit lower LDL-C observed during treatment with a statin or with combined statin and ezetimibe therapy (*Figure 2*). Indeed, in a recent meta-analysis of 49 studies including 312 175 participants and 39 645 major vascular events that compared the effects of 9 different types of lipid-lowering therapies, nearly all of these therapeutic approaches to lowering LDL-C were associated with a consistent 20–25% proportional reduction in vascular events per millimole per litre reduction in LDL-C.[47] These findings are in line with those from the Mendelian randomization studies and demonstrate that the clinical benefit of lowering LDL-C appears to be independent of the mechanism by which LDL-C is lowered (*Figure 3*).







Borén, 2020

Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel

Jan Borén, M John Chapman ✉, Ronald M Krauss, Chris J Packard, Jacob F Bentzon, Christoph J Binder, Mat J Daemen, Linda L Demer, Robert A Hegele, Stephen J Nicholls ... Show more
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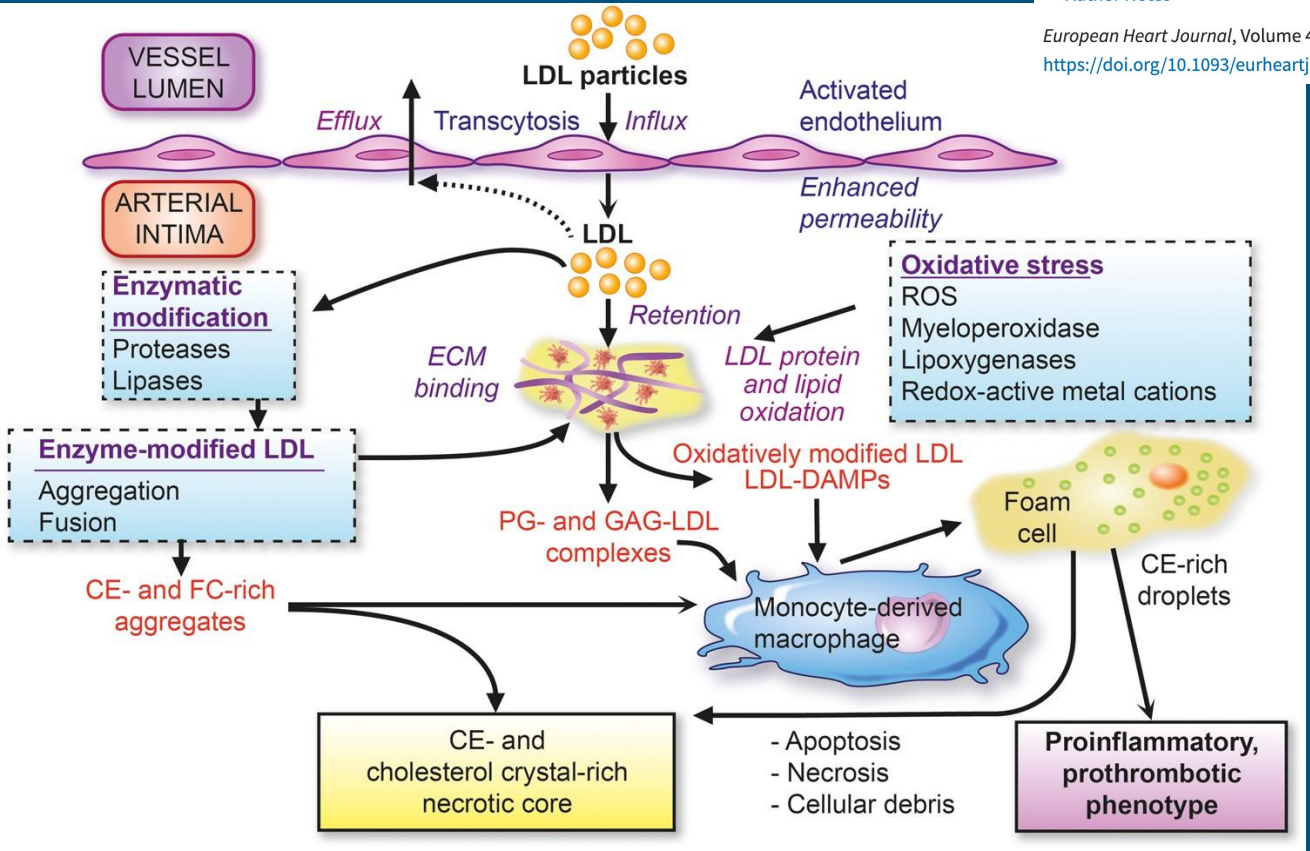
European Heart Journal, Volume 41, Issue 24, 21 June 2020, Pages 2313–2330,
https://doi.org/10.1093/eurheartj/ehz962



Low-density lipoprotein as the primary driver of atherogenesis

All LDL particles exert atherogenicity to variable degrees, which can be influenced by the proteome, lipidome, proteoglycan binding, aggregability, and oxidative susceptibility.[64,96,97] The atherogenic actions of LDL in arterial tissue have multiple origins. Broadly, these encompass:

(1) Formation of macrophage-derived foam cells upon phagocytic uptake of aggregated LDL particles, or LDL in which lipid and/or protein components have undergone covalent modification, triggering uptake by scavenger receptors. Aggregation may occur by non-enzymatic or enzymatically induced mechanisms. Oxidation of lipids (phospholipids, cholesteryl esters, and cholesterol) or apoB100 can occur enzymatically (e.g. by myeloperoxidase) or non-enzymatically (e.g. by reactive oxygen species liberated by activated endothelial cells or macrophages).

(2) Release of bioactive proinflammatory lipids (e.g. oxidized phospholipids) or their fragments (e.g. short-chain aldehydes) subsequent to oxidation, which may exert both local and systemic actions.

(3) Formation of extracellular lipid deposits, notably cholesterol crystals, upon particle denaturation.

(4) Induction of an innate immune response, involving damage-associated molecular patterns (DAMPs, notably oxidation-specific epitopes and cholesterol crystals). Damage-associated molecular patterns promote recruitment of immuno-inflammatory cells (monocyte-macrophages, neutrophils, lymphocytes, and dendritic cells) leading to local and potentially chronic inflammation that can induce cell death by apoptosis or necrosis, thereby contributing to necrotic core formation.

(5) Induction of an adaptive immune response subsequent to covalent modification of apoB100 by aldehydes or apoB100 degradation with the activation of antigen-specific T-cell responses and antibodies.[114–118]

Beyond LDL, additional apoB-containing lipoproteins (<70 nm diameter) can exacerbate the atherogenic process; these include Lp(a) (which is composed of apo(a) covalently linked to the apoB of LDL and is a major carrier of proinflammatory oxidized phospholipids) and cholesterol-enriched remnant particles metabolically derived from TGRL.[6,7,11,13,26,119] Whereas the classic TG-poor LDL requires modification for efficient uptake by arterial macrophages, remnant particles are taken up by members of the LDL receptor family in their native state.[107,120] There is also evidence that LPL-mediated hydrolysis of TG from incoming remnant particles enhances the inflammatory response of arterial macrophages,[121,122] and that the internalization of remnants induces lysosomal engorgement and altered trafficking of lipoprotein cholesterol within the cell,[123] thus inducing endoplasmic reticulum stress and activation of apoptosis disproportionate to the cholesterol cargo delivered.

Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel

Jan Borén, M John Chapman ✉, Ronald M Krauss, Chris J Packard, Jacob F Bentzon, Christoph J Binder, Mat J Daemen, Linda L Demer, Robert A Hegele, Stephen J Nicholls ... Show more

Author Notes

European Heart Journal, Volume 41, Issue 24, 21 June 2020, Pages 2313–2330,
https://doi.org/10.1093/eurheartj/ehz962

All LDL particles exert atherogenicity to variable degrees, which can be influenced by the proteome, lipidome, proteoglycan binding, aggregability, and oxidative susceptibility.[64,96,97] The atherogenic actions of LDL in arterial tissue have multiple origins. Broadly, these encompass:

Review > Curr Opin Lipidol. 2004 Feb;15(1):19-24.
doi: 10.1097/00041433-200402000-00005.

Associations of low density lipoprotein particle composition with atherogenicity

Aaron T Lada [1], Lawrence L Rudel

Affiliations + expand

PMID: 15166804 DOI: 10.1097/00041433-200402000-00005

Other than size, compositional factors can alter the susceptibility of LDL particles to oxidation. Enrichment of LDL particles with n-6 polyunsaturated fatty acids leads to an increased susceptibility of LDL to oxidation in vitro [68]. However, the increased susceptibility to in-vitro oxidation of n-6 fatty acid-enriched LDL has not been shown to be associated with an increased CHD risk. Typically, a reduction in CHD susceptibility results when polyunsaturated fatty acids are more abundant [69–71]. Studies have shown that enrichment with n-3 fatty acids lead to decreased LDL oxidation [72] – a finding confirmed in a recent study [73], which showed that n-3-enriched LDL was less susceptible to oxidation and led to decreased apoptosis in macrophages. In addition, the enrichment of LDL with monounsaturated fatty acids is usually associated with decreased in-vitro oxidation compared with LDL enriched with n-6 polyunsaturated fatty acids [68,74]. However, data from animal studies suggest that monounsaturated fatty acids are more atherogenic than n-6 polyunsaturated fatty acids [75–77]. In summary, the available data do not consistently support an association between the susceptibility of LDL particles to in-vitro measures of oxidation and CHD risk. The validity of the argument that sdLDL are more atherogenic because of an increased tendency to undergo in-vitro oxidation is questioned.

Factors affecting retention of low-density lipoprotein in the artery wall

Subendothelial accumulation of LDL at lesion-susceptible arterial sites is mainly due to selective retention of LDL in the intima, and is mediated by interaction of specific positively charged amino acyl residues (arginine and lysine) in apoB100 with negatively charged sulfate and carboxylic acid groups of arterial wall proteoglycans.[49] Genetic alteration of either the proteoglycan-binding domain of apoB100 or the apoB100-binding domain of arterial wall proteoglycans greatly reduces atherogenesis.[49,50] Thus, the atherogenicity of LDL is linked to the ability of its apoB100 moiety to interact with arterial wall proteoglycans,[50,51] a process influenced by compositional changes in both the core and surface of the LDL particle. For example, enrichment of human LDL with cholesteryl oleate enhances proteoglycan-binding and atherogenesis.[52] In addition, apoE, apoC-III, and serum amyloid A increase the affinity of LDL for arterial wall proteoglycans.[49,53–55]

Responses elicited by low-density lipoprotein retained in the artery wall

Retention and subsequent accumulation of LDL in the artery wall triggers a number of events that initiate and propagate lesion development.[21,50] Due to the local microenvironment of the subendothelial matrix, LDL particles are susceptible to oxidation by both enzymatic and non-enzymatic mechanisms, which leads to the generation of oxidized LDL (oxLDL) containing several bioactive molecules including oxidized phospholipids.[129,130] Oxidized LDL, in turn, initiates a sterile inflammatory response by activating endothelial cells to up-regulate adhesion molecules and chemokines that trigger the recruitment of monocytes—typically inflammatory Ly6C^{hi} monocytes—into the artery wall.[131] The importance of oxidized phospholipids in the inflammatory response of the vascular wall has been demonstrated through the transgenic expression of an oxidized phospholipid-neutralizing single-chain antibody, which protected atherosclerosis-prone mice against lesion formation.[132] Newly recruited monocytes differentiate into macrophages that can further promote the oxidation of LDL particles, which are then recognized and internalized by specific scavenger receptors giving rise to cholesterol-laden foam cells.[133] Several other modifications of retained LDL, including enzymatic degradation or aggregation, have also been shown to promote its uptake by macrophages. Macropinocytosis of native LDL may also contribute to this process.[134,135]

After 20 weeks, 231 mice were perfusion-fixed. Seven aortas were not analysed for technical reasons. The remaining 224 aortas were analysed with the *en face* procedure[13]. The extent of atherosclerosis correlated with the plasma concentration of human apoB100 in all groups (Fig. 2). However, transgenic mice expressing proteoglycan-binding-defective LDL ($R,K_{3359–3369} \rightarrow S,A$, 6-GBSM, and $K_{3363} \rightarrow E$ LDL) had significantly less atherosclerosis than mice expressing wild-type control or $W_{4369} \rightarrow Y$ LDL (Table 3)

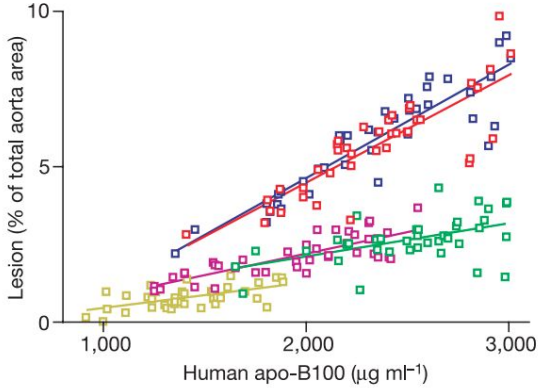


Figure 2 Effect on aorta of an atherogenic diet in transgenic mice. The data shows the correlation between the percentage of total aortic surface area covered by lesions and the plasma concentration of human apoB100 in transgenic mice fed an atherogenic diet for 20 weeks. Recombinant control LDL (red) and $W_{4369} \rightarrow Y$ LDL (blue), both with normal proteoglycan binding. Proteoglycan-binding-defective $R,K_{3359–3369} \rightarrow S,A$ LDL (pink), $K_{3363} \rightarrow E$ LDL (light green), and 6-GBSM LDL (dark green). The percentage of total aortic surface area covered by lesions in mice expressing the recombinant LDL were 5.7 ± 1.5, 5.8 ± 1.7, 2.1 ± 0.66, 0.81 ± 0.36 or 2.7 ± 0.72, respectively (mean ± s.d.).

Published: 13 June 2002

Subendothelial retention of atherogenic lipoproteins in early atherosclerosis

Kristina Skålén, Maria Gustafsson, Ellen Knutsen Rydberg, Lillemor Mattsson Hultén, Olov Wiklund, Thomas L. Innerarity & Jan Borén ✉

Nature **417**, 750–754 (2002) | Cite this article

Mouse LDL often contain apoE, but apoB100 is the sole apolipoprotein on human LDL. Thus, bridging molecules are probably less important than a direct interaction between apoB100 and proteoglycans for subendothelial retention of atherogenic lipoproteins in humans. Retained lipoproteins can directly or indirectly provoke all known features of early lesions and, by stimulating local synthesis of proteoglycans, can accelerate further retention and aggregation[3]. Thus, atherosclerosis is initiated by subendothelial retention of atherogenic lipoproteins. □

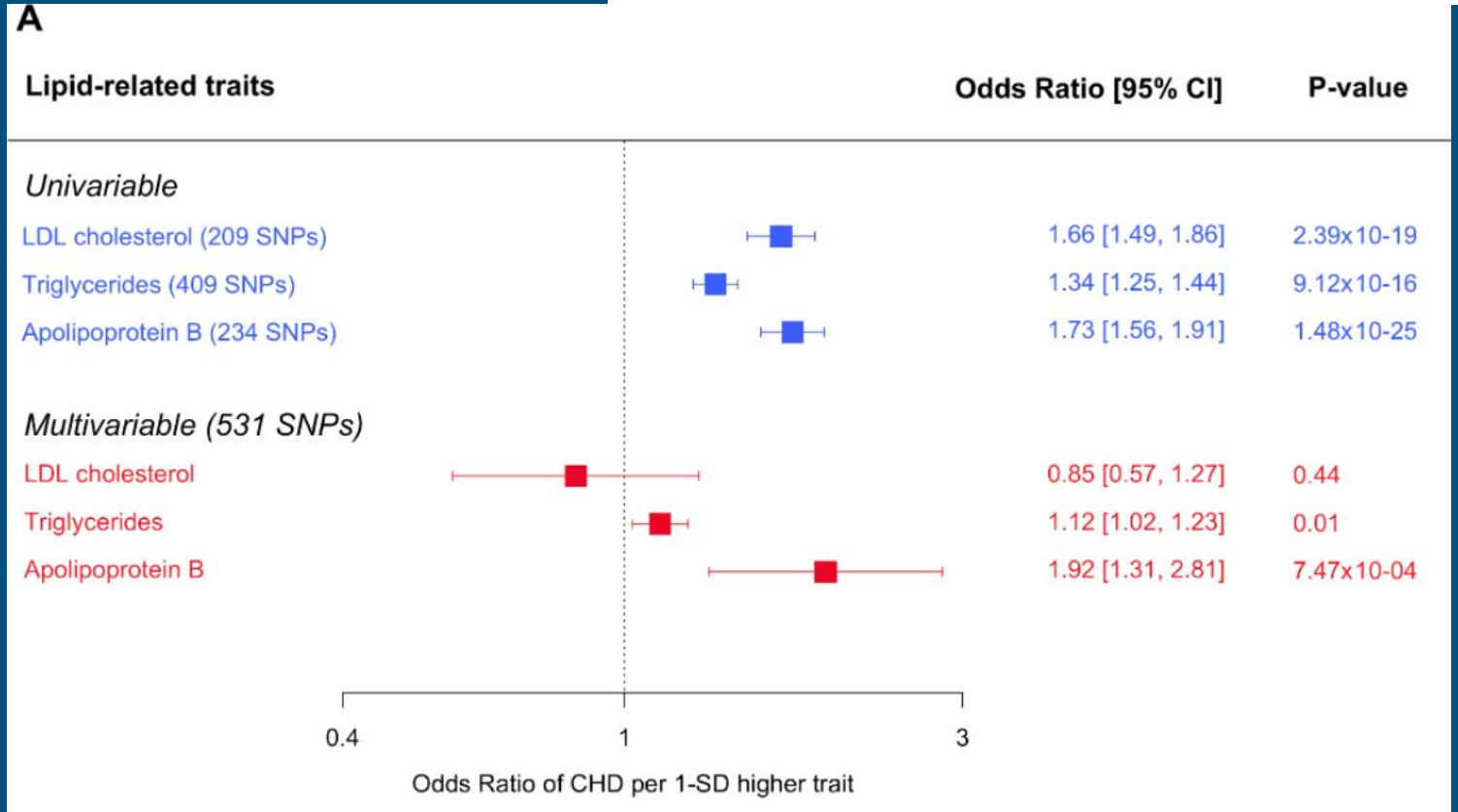
To verify that the differences in atherogenicity were due solely to different affinities for arterial proteoglycans, we performed several control experiments. First, we analysed the formation of conjugated dienes in $R,K_{3359–3369} \rightarrow S,A$ LDL and recombinant control LDL after copper-stimulated oxidation[14]. The lag phase for the formation of conjugated dienes in $R,K_{3359–3369} \rightarrow S,A$ LDL and recombinant control LDL was 79 ± 6 and 74 ± 8 min, respectively, and the maximal rate of conjugated dienes formed was 6.1 ± 0.5 and 5.8 ± 0.4 molecules $min^{-1} \times$ LDL particle, respectively (mean ± s.d.; $n = 3$). Thus, proteoglycan-binding-defective LDL were as susceptible to oxidation as recombinant control LDL.

Richardson, 2020

Evaluating the relationship between circulating lipoprotein lipids and apolipoproteins with risk of coronary heart disease: A multivariable Mendelian randomisation analysis

Tom G. Richardson, Eleanor Sanderson, Tom M. Palmer, Mika Ala-Korpela, Brian A. Ference, George Davey Smith, Michael V. Holmes

Published: March 23, 2020 • https://doi.org/10.1371/journal.pmed.1003062



Schwingshackl, 2021

Research

Evaluating agreement between bodies of evidence from randomised controlled trials and cohort studies in nutrition research: meta-epidemiological study

BMJ 2021 ; 374 doi: https://doi.org/10.1136/bmj.n1864 (Published 15 September 2021)
Cite this as: *BMJ* 2021;374:n1864

The number of primary studies contributing to the 97 diet-disease outcome pairs ranged from 1 to 64 (median 6) for BoE from randomised controlled trials, and from 1 to 68 (median 7) for BoE from cohort studies (overall >950 trials and >750 cohort studies). The total number of participants ranged from 56 to 211957 for BoE from randomised controlled trials, and from 2563 to 1797670 for BoE from cohort studies. Of the identified 97 diet-disease outcome pairs, 83 were included in the meta-analysis (71 binary, 12 continuous). We could not include 14 diet-disease outcome pairs in the meta-analysis (reasons in supplementary table 6).

Similarities

Of 97 diet-disease outcome pairs, none was rated as more or less identical, 57 (59%) were similar but not identical, and 40 (41%) were broadly similar. Interventions or exposures rated as broadly similar accounted for most PI/ECO dissimilarities overall (n=17/40; 42.5%). Of 83 diet-disease outcome pairs included in the meta-analysis, 57 (69%) were similar but not identical and 26 (31%) were broadly similar. Interventions or exposures rated as broadly similar accounted for most PI/ECO dissimilarities overall (n=17/26; 65%). Supplementary table 13 shows additional information.

Beyerbach, 2022

Evaluating Concordance of Bodies of Evidence from Randomized Controlled Trials, Dietary Intake, and Biomarkers of Intake in Cohort Studies: A Meta-Epidemiological Study Get access

Jessica Beyerbach, Julia Stadelmaier, Georg Hoffmann, Sara Balduzzi, Nils Bröckelmann, Lukas Schwingshackl

Advances in Nutrition, Volume 13, Issue 1, January 2022, Pages 48–65,
https://doi.org/10.1093/advances/nmab095
Published: 02 September 2021 **Article history**

Quantitative concordance: Using the second definition (calculated as z-score), 88%, 69%, and 90% of the diet-disease associations were quantitatively concordant comparing BoE_{RCTs} vs. $BoE_{CSs\ dietary\ intake}$, BoE_{RCTs} vs. $BoE_{CSs\ biomarkers}$ and comparing both BoE from CSs, respectively **(Table 3)**. 65% (32/49) of the diet-disease association were quantitatively concordant considering all three BoE simultaneously.

Conclusion

Our findings suggest that BoE from RCTs and CSs are often quantitatively concordant. Prospective SRs in nutrition research should include whenever possible BoE from RCTs, and CSs on dietary intake and biomarker of intake to provide the whole picture for an investigated diet-disease association.

Moorthy, 2013

Findings. In 23 out of 34 associations the summary findings from meta-analyses of epidemiological studies and of RCTs were in the same direction. In 6 of 23 associations, meta-analyses of epidemiological studies and of RCTs had statistically significant findings. In the remaining 11 out of 34 assocations, meta-analyses of epidemiological studies and of RCTs had summaries pointing in opposite directions. In 12 out of 34 associations the summary findings of epidemiological studies were statistically significantly different from those of RCTs, in 6 out of 12 point estimates were in the same direction, and in the other 6 in opposing directions. Despite the variation in the size and the connectivity of the citation graphs across the examined associations, we find no evidence of association between quantitative metrics of the citation graphs and the probability that the two research designs have concordant or discordant findings (using various definitions of concordance or discordance).

Review

Concordance Between the Findings of Epidemiological Studies and Randomized Trials in Nutrition: An Empirical Evaluation and Citation Analysis: Nutritional Research Series, Vol. 6 [Internet]

Denish Moorthy [1], Mei Chung [1], Jounghee Lee [1], Winifred W Yu [1], Joseph Lau [1], Thomas A Trikalinos [1]

Table 2. Qualitative and quantitative concordance of effects in epidemiological studies and RCTs

ID	Direction of Effect (Epi)	Significance (Epi)	Direction of Effect (RCT)	Significance (RCT)	Qualitative Concordance (1st definition)	z-Score	p-Value	Quantitative Concordance (2nd definition)	Quantitative Concordance (3rd definition)
1	Decreasing	Not sign	Decreasing	Not sign	Unclear	0.22	0.83	Not discordant	Not discordant
2	Decreasing	Sign	Decreasing	Not sign	Unclear	-0.91	0.36	Not discordant	Not discordant
3	Increasing	Not sign	Decreasing	Not sign	Unclear	1.36	0.18	Not discordant	Not discordant
4	Increasing	Not sign	Increasing	Not sign	Unclear	0.08	0.94	Not discordant	Not discordant
5	Decreasing	Not sign	Increasing	Not sign	Unclear	-1.50	0.13	Not discordant	Not discordant
6	Decreasing	Sign	Increasing	Not sign	Unclear	-1.54	0.12	Not discordant	Not discordant
7	Decreasing	Sign	Increasing	Not sign	Unclear	-3.08	0.00	Discordant	Discordant
8	Decreasing	Sign	Increasing	Not sign	Unclear	-2.00	0.05	Discordant	Discordant
9	Increasing	Not sign	Increasing	Not sign	Unclear	0.00	1.00	Not discordant	Not discordant
10	Increasing	Not sign	Increasing	Not sign	Unclear	0.00	1.00	Not discordant	Not discordant
11	Increasing	Not sign	Decreasing	Not sign	Unclear	1.20	0.23	Not discordant	Not discordant
12	Decreasing	Not sign	Decreasing	Not sign	Unclear	0.13	0.89	Not discordant	Not discordant
13	Decreasing	Sign	Decreasing	Sign	Concordant	2.52	0.01	Discordant	Not discordant
14	Decreasing	Sign	Decreasing	Not sign	Unclear	0.65	0.51	Not discordant	Not discordant
15	Decreasing	Sign	Increasing	Not sign	Unclear	-2.48	0.01	Discordant	Discordant
16	Decreasing	Not sign	Decreasing	Not sign	Unclear	-1.15	0.25	Not discordant	Not discordant
17	Decreasing	Sign	Decreasing	Not sign	Unclear	-2.08	0.04	Discordant	Not discordant
18	Decreasing	Sign	Decreasing	Not sign	Unclear	-0.98	0.33	Not discordant	Not discordant
19	Decreasing	Sign	Decreasing	Not sign	Unclear	-1.64	0.10	Not discordant	Not discordant
20	Increasing	Not sign	Increasing	Not sign	Unclear	-0.37	0.71	Not discordant	Not discordant
21	Decreasing	Not sign	Decreasing	Not sign	Unclear	-0.31	0.75	Not discordant	Not discordant
22	Increasing	Not sign	Increasing	Not sign	Unclear	0.00	1.00	Not discordant	Not discordant
23	Decreasing	Sign	Decreasing	Sign	Concordant	-2.07	0.04	Discordant	Not discordant
24	Decreasing	Sign	Decreasing	Sign	Concordant	2.14	0.03	Discordant	Not discordant
25	Decreasing	Sign	Increasing	Not sign	Unclear	-2.19	0.03	Discordant	Discordant
26	Decreasing	Sign	Increasing	Not sign	Unclear	-2.79	0.01	Discordant	Discordant
27	Decreasing	Not sign	Decreasing	Not sign	Unclear	0.22	0.83	Not discordant	Not discordant
28	Increasing	Not sign	Decreasing	Not sign	Unclear	1.46	0.14	Not discordant	Not discordant
29	Decreasing	Not sign	Increasing	Not sign	Unclear	-2.06	0.04	Discordant	Discordant
30	Decreasing	Sign	Decreasing	Sign	Concordant	-1.56	0.12	Not discordant	Not discordant
31	Decreasing	Sign	Decreasing	Not sign	Unclear	-1.13	0.26	Not discordant	Not discordant
32	Decreasing	Sign	Decreasing	Not sign	Unclear	-2.41	0.02	Discordant	Not discordant
33	Decreasing	Sign	Decreasing	Sign	Concordant	3.06	0.00	Discordant	Not discordant
34	Decreasing	Sign	Decreasing	Sign	Concordant	0.95	0.34	Not discordant	Not discordant

Note: Sign = statistically significant at the 0.05 level

Cui, 2021

Review

Validity of the food frequency questionnaire for adults in nutritional epidemiological studies: A systematic review and meta-analysis

Qi Cui, Yang Xia, Qijun Wu, Qing Chang, **Kaijun Niu** & **Yuhong Zhao**

Published online: 14 Sep 2021

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Table 2. Pooled effect estimates (95% CI) and heterogeneity of the correlation coefficients between FFQs and 24-hour recalls for energy and macronutrients.

	Crude			Energy-adjusted			De-attenuated		
Nutrients	Correlation coefficient	N	I^2	Correlation coefficient	N	I^2	Correlation coefficient	N	I^2
Energy	0.473 (0.415, 0.526)	61	94.0	N/A	N/A	N/A	0.493 (0.439, 0.544)	34	87.5
Carbohydrate	0.473 (0.432, 0.512)	60	86.2	0.454 (0.409, 0.497)	44	83.2	0.549 (0.502, 0.593)	41	87.1
Protein	0.404 (0.369, 0.438)	61	77.9	0.357 (0.313, 0.399)	45	78.8	0.549 (0.502, 0.593)	43	83.2
Fat	0.437 (0.394, 0.480)	55	86.6	0.424 (0.375, 0.469)	44	85.0	0.503 (0.451, 0.551)	39	87.7
Plant fat	0.234 (0.157, 0.307)	4	9.4	0.244 (-0.01, 0.468)	2	88.1	0.480 (0.221, 0.675)	2	89.0
Trans-fat	0.282 (0.099, 0.447)	3	68.0	0.266 (0.163, 0.364)	3	70.1	0.497 (0.451, 0.540)	2	0
Cholesterol	0.402 (0.357, 0.446)	39	76.7	0.385 (0.341, 0.428)	32	74.3	0.489 (0.435, 0.538)	27	81.3
Sugar	0.498 (0.387, 0.595)	8	81.2	0.512 (0.438, 0.580)	7	56.4	0.644 (0.534, 0.732)	6	80.3
Starch	0.427 (0.334, 0.512)	1	N/A	0.376 (0.279, 0.466)	1	N/A	0.772 (0.724, 0.813)	1	N/A
Alcohol	0.721 (0.670, 0.765)	17	83.1	0.742 (0.688, 0.788)	12	80.5	0.735 (0.649, 0.802)	8	87.6
Water	0.472 (0.401, 0.536)	6	0	0.435 (0.354, 0.509)	3	0	0.492 (0.320, 0.633)	1	N/A
Fiber	0.435 (0.395, 0.473)	50	76.2	0.449 (0.405, 0.491)	40	81.9	0.483 (0.432, 0.531)	34	84.3
Soluble fiber	0.472 (0.141, 0.708)	2	89.3	0.528 (0.488, 0.566)	3	0	0.620 (0.534, 0.694)	2	74.7
Insoluble fiber	0.481 (0.403, 0.551)	4	70.1	0.478 (0.414, 0.538)	3	0	0.555 (0.449, 0.647)	3	84.5
MUFA	0.377 (0.324, 0.428)	31	74.1	0.390 (0.339, 0.440)	27	80.3	0.517 (0.429, 0.595)	24	93.9
PUFA	0.316 (0.266, 0.363)	34	69.4	0.343 (0.290, 0.392)	27	77.4	0.411 (0.338, 0.481)	26	89.8
SFA	0.427 (0.380, 0.472)	41	78.5	0.461 (0.407, 0.512)	33	85.9	0.536 (0.472, 0.594)	31	91.0
Linoleic acid	0.357 (0.244, 0.459)	4	60.9	0.377 (0.323, 0.427)	3	13.0	0.626 (0.467, 0.746)	2	93.6
Linolenic acid	0.465 (0.122, 0.708)	3	91.9	0.329 (0.254, 0.400)	3	47.7	0.500 (0.404, 0.585)	2	77.0
Oleic acid	0.491 (0.289, 0.650)	2	89.8	0.317 (0.265, 0.366)	2	0	0.481 (0.393, 0.560)	2	71.5
EPA	N/A	N/A	N/A	0.479 (0.315, 0.615)	2	91.6	0.578 (0.535, 0.618)	1	N/A
DHA	N/A	N/A	41.6	0.474 (0.350, 0.581)	2	85.5	0.610 (0.491, 0.707)	1	N/A
TFA	0.410 (0.205, 0.580)	1	N/A	N/A	N/A	N/A	0.459 (0.262, 0.619)	1	N/A
n-3 fatty acid	N/A	N/A	N/A	0.330 (0.242, 0.413)	1	N/A	0.463 (0.361, 0.554)	2	74.5
Caffeine	0.770 (0.676, 0.840)	2	81.5	0.772 (0.665, 0.849)	2	85.4	0.787 (0.709, 0.846)	2	76.5
Lycopene	0.220 (0.093, 0.341)	1	N/A	0.192 (0.062, 0.314)	1	N/A	0.277 (0.152, 0.394)	1	N/A
Cryptoxanthin	0.375 (0.257, 0.482)	1	N/A	0.394 (0.278, 0.499)	1	N/A	0.571 (0.476, 0.653)	1	N/A
Daidzein	0.500 (0.307, 0.654)	1	N/A	0.520 (0.331, 0.669)	1	N/A	0.632 (0.471, 0.752)	1	N/A
Genistein	0.380 (0.165, 0.560)	1	N/A	0.420 (0.212, 0.592)	1	N/A	0.551 (0.370, 0.693)	1	N/A

N, number of studies; CI, confidence interval; I^2, inconsistency index; N/A, not available.

Table 3. Pooled effect estimates (95% CI) and heterogeneity of the correlation coefficients between FFQs and food records for energy and macronutrients.

	Crude			Energy-adjusted			De-attenuated		
Nutrients	Correlation coefficient	N	I^2	Correlation coefficient	N	I^2	Correlation coefficient	N	I^2
Energy	0.397 (0.356, 0.437)	55	74.4	N/A	N/A	N/A	0.412 (0.304, 0.511)	17	92.4
Carbohydrate	0.434 (0.386, 0.479)	52	82.5	0.492 (0.452, 0.531)	37	78.6	0.564 (0.504, 0.620)	22	88.4
Protein	0.347 (0.318, 0.375)	55	44.2	0.364 (0.330, 0.396)	41	60.8	0.455 (0.409, 0.498)	21	69.8
Fat	0.374 (0.341, 0.407)	50	57.4	0.423 (0.393, 0.451)	38	57.0	0.498 (0.450, 0.542)	20	75.4
Plant fat	0.355 (0.207, 0.487)	5	55.6	0.373 (0.220, 0.507)	2	0	0.181 (-0.16, 0.489)	1	N/A
Trans-fat	0.278 (-0.09, 0.583)	2	82.8	0.560 (0.375, 0.701)	1	N/A	0.104 (-0.10, 0.303)	1	N/A
Cholesterol	0.408 (0.359, 0.455)	35	69.5	0.428 (0.385, 0.469)	29	69.4	0.498 (0.438, 0.553)	15	80.3
Sugar	0.490 (0.419, 0.556)	13	57.5	0.543 (0.473, 0.606)	8	69.9	0.618 (0.525, 0.697)	2	84.5
Starch	0.408 (0.343, 0.469)	6	33.5	0.400 (0.345, 0.451)	5	0	N/A	N/A	N/A
Alcohol	0.735 (0.683, 0.780)	27	90.7	0.704 (0.656, 0.747)	20	89.7	0.792 (0.741, 0.834)	7	88.2
Water	0.536 (0.373, 0.667)	2	0	0.461 (0.359, 0.552)	3	69.8	0.438 (0.339, 0.527)	3	67.5
Fiber	0.367 (0.323, 0.408)	45	66.1	0.486 (0.444, 0.526)	35	76.3	0.542 (0.488, 0.591)	19	81.8
Soluble fiber	0.380 (0.312, 0.446)	5	19.1	0.496 (0.435, 0.551)	8	59.0	0.544 (0.478, 0.605)	6	59.2
Insoluble fiber	0.396 (0.330, 0.458)	5	14.1	0.527 (0.470, 0.580)	8	58.6	0.575 (0.507, 0.637)	6	65.4
MUFA	0.372 (0.329, 0.413)	34	62.5	0.389 (0.350, 0.426)	29	64.5	0.423 (0.360, 0.482)	14	77.5
PUFA	0.351 (0.300, 0.399)	34	72.3	0.345 (0.305, 0.383)	28	63.6	0.400 (0.347, 0.450)	14	66.4
n-3 PUFA	0.272 (0.214, 0.329)	7	0	0.323 (0.283, 0.363)	10	50.0	0.418 (0.344, 0.486)	6	59.0
n-6 PUFA	0.247 (0.162, 0.329)	6	43.5	0.335 (0.274, 0.393)	9	49.7	0.370 (0.260, 0.471)	5	78.2
SFA	0.464 (0.423, 0.502)	38	67.0	0.480 (0.444, 0.515)	33	68.8	0.529 (0.481, 0.575)	17	73.9
Linoleic acid	0.384 (0.156, 0.573)	4	79.9	0.321 (0.123, 0.494)	3	65.8	0.532 (0.458, 0.598)	1	N/A
Linolenic acid	0.505 (0.126, 0.756)	3	93.3	0.312 (0.039, 0.541)	2	82.6	0.551 (0.480, 0.616)	1	N/A
Oleic acid	0.358 (0.276, 0.435)	3	5.2	0.454 (0.380, 0.521)	2	0	0.542 (0.469, 0.607)	1	N/A
EPA	0.373 (0.192, 0.529)	3	48.6	0.255 (0.100, 0.397)	2	0	0.512 (0.210, 0.724)	1	N/A
DHA	0.367 (0.155, 0.547)	3	61.7	0.240 (0.084, 0.384)	2	0	0.462 (0.147, 0.692)	1	N/A
TFA	0.298 (0.231, 0.363)	3	0	0.415 (0.236, 0.566)	3	85.9	0.544 (0.463, 0.615)	2	0
n-3 fatty acid	0.173 (0.040, 0.299)	2	0	N/A	N/A	N/A	0.162 (-0.04, 0.355)	1	N/A
n-6 fatty acid	0.331 (0.010, 0.589)	2	72.1	N/A	N/A	N/A	N/A	N/A	N/A
Caffeine	0.498 (0.120, 0.749)	4	93.7	0.524 (0.114, 0.781)	3	94.6	0.734 (0.581, 0.836)	2	81.1
Lycopene	0.327 (0.237, 0.411)	6	47.4	0.329 (0.247, 0.405)	6	37.5	0.529 (0.408, 0.630)	2	52.8
Cryptoxanthin	0.220 (-0.05, 0.463)	2	90.3	0.428 (0.309, 0.533)	4	85.6	0.459 (0.354, 0.553)	5	82.8
Daidzein	0.565 (0.407, 0.690)	3	81.7	0.601 (0.544, 0.653)	5	61.1	0.677 (0.611, 0.734)	4	69.2
Genistein	0.554 (0.400, 0.678)	3	80.4	0.594 (0.537, 0.645)	5	59.6	0.658 (0.601, 0.708)	4	56.6

N, number of studies; CI, confidence interval; I^2, inconsistency index; N/A, not available.

We found that the validity correlation of FFQs on energy and most nutrient intake ranged approximately from 0.4 to 0.7 and from 0.3 to 0.6 for 24HRs and FRs, which were used as reference methods in healthy adults, respectively. The results indicated that an FFQ was a valid tool to measure the overall dietary intake in epidemiological studies. Subsequently, it is recommended that the sample size, the characteristics of reference methods, and the actual situation of the study should be considered comprehensively when designing the validation study. Moreover, the results of the subgroup analyses showed that FFQs with a self-administered mode, more items, and shorter reference period improved the validity correlations. Furthermore, the use of FFQs may result in an overestimation of dietary consumption compare to reference methods (e.g., FRs and 24HRs). In comparison to other dietary assessment methods, FFQs can be less accurate in estimating daily nutrient intake. Thus, FFQs should be used with caution for individual dietary guidance.

Table 4. Pooled effect estimates (95% CI) and heterogeneity of standardized mean differences for energy and macronutrients.

	24-hour recall				Food record			
Nutrients	SMD[a]	N	I^2	P_z	SMD[a]	N	I^2	P_z
Energy	0.287 (0.262, 0.313)	54	96.5	<0.001	0.073 (0.040, 0.106)	57	96.9	<0.001
Carbohydrate	0.430 (0.404, 0.457)	52	96.9	<0.001	0.106 (0.074, 0.139)	56	97.4	<0.001
Protein	0.342 (0.315, 0.369)	51	96.7	<0.001	0.051 (0.020, 0.083)	57	95.2	<0.01
Fat	0.111 (0.083, 0.138)	50	98.2	<0.01	−0.084 (−0.117, −0.052)	55	94.9	<0.001
Plant fat	−0.194 (−0.293, −0.096)	4	99.4	0.736	−0.177 (−0.272, −0.083)	9	96.4	<0.001
Trans-fat	0.283 (0.208, 0.358)	4	97.5	0.082	0.386 (0.192, 0.579)	3	88.0	<0.001
Cholesterol	0.288 (0.252, 0.325)	33	95.3	<0.001	−0.184 (−0.223, −0.144)	39	93.6	<0.001
Sugar	0.242 (0.144, 0.339)	7	95.0	0.559	0.409 (0.348, 0.469)	14	80.1	<0.001
Starch	0.390 (0.235, 0.546)	1	N/A	<0.001	0.262 (0.184, 0.340)	6	96.3	<0.001
Alcohol	0.092 (0.035, 0.149)	16	96.5	0.833	−0.002 (−0.042, 0.039)	31	72.8	0.938
Water	0.220 (0.121, 0.318)	5	96.1	0.158	0.127 (0.039, 0.215)	5	94.1	<0.01
Fiber	0.450 (0.416, 0.483)	43	97.3	<0.001	0.078 (0.041, 0.115)	50	96.3	<0.001
Soluble fiber	0.707 (0.623, 0.792)	2	99.2	0.434	−0.200 (−0.267, −0.133)	9	94.0	<0.001
Insoluble fiber	0.726 (0.650, 0.802)	3	99.1	0.326	−0.351 (−0.419, −0.284)	9	96.4	<0.001
MUFA	0.451 (0.412, 0.491)	29	95.8	<0.001	0.076 (0.038, 0.113)	38	95.8	<0.001
PUFA	0.449 (0.411, 0.487)	31	93.7	<0.001	0.038 (0.001, 0.075)	38	94.0	0.045
n-3 PUFA	N/A	N/A	N/A	N/A	−0.091 (−0.156, −0.027)	10	96.0	<0.01
n-6 PUFA	N/A	N/A	N/A	N/A	−0.029 (−0.094, 0.036)	9	92.4	0.379
SFA	0.250 (0.215, 0.286)	35	94.1	<0.001	0.070 (0.034, 0.106)	43	94.4	<0.001
Linoleic Acid	0.759 (0.680, 0.838)	4	97.0	0.013	−0.179 (−0.297, −0.062)	4	93.5	<0.01
Linolenic Acid	0.180 (0.103, 0.257)	3	92.1	0.222	−0.163 (−0.287, −0.04)	3	98.6	0.010
Oleic acid	0.641 (0.560, 0.722)	2	95.9	<0.01	0.100 (−0.022, 0.223)	3	98.2	0.108
EPA	0.288 (0.216, 0.359)	3	99.3	0.308	−0.387 (−0.57, −0.203)	4	89.3	<0.001
DHA	0.459 (0.388, 0.530)	3	99.1	0.112	−0.395 (−0.581, −0.21)	4	93.3	<0.001
TFA	N/A	N/A	N/A	N/A	0.147 (0.044, 0.250)	4	97.6	<0.01
n-3 fatty acid	0.691 (0.601, 0.781)	1	N/A	N/A	−0.022 (−0.213, 0.168)	2	95.0	0.820
n-6 fatty acid	N/A	N/A	N/A	N/A	−0.393 (−0.643, −0.143)	1	N/A	<0.01
Caffeine	0.044 (−0.076, 0.164)	2	0	0.470	0.054 (−0.065, 0.174)	4	97.9	0.371
Daidzein	N/A	N/A	N/A	N/A	0.261 (0.189, 0.334)	6	0	<0.001
Genistein	N/A	N/A	N/A	N/A	0.239 (0.166, 0.311)	6	0	<0.001
Lycopene	0.095 (−0.089, 0.280)	1	N/A	0.312	−0.135 (−0.225, −0.044)	4	90.6	<0.01
Cryptoxanthin	0.138 (−0.047, 0.323)	1	N/A	0.143	0.276 (0.207, 0.345)	6	95.1	<0.001

SMD, standardized mean difference; CI, confidence interval; N, No. of studies; I^2, inconsistency index; P_z, P for Z test; N/A, not available.
[a]SMDs were calculated by means of nutrient intakes from FFQ minus that from reference methods.

Da Silva, 2017

RESEARCH PAPER

Using the method of triads in the validation of a food frequency questionnaire to assess the consumption of fatty acids in adults

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Table 4 Validation coefficients to the profile of total fatty acids, estimated by the food-frequency questionnaire (FFQ), 24-h food record (R24h) and biomarkers, in 152 adult individuals, Viçosa, 2014

	Validation coefficients		
Nutrients	FFQ ρQT	R24h ρBT	Biomarker ρRT
Total lipids (g)	0.84	0.18	0.42
Saturated fatty acids (g)	1.32	0.07	0.32
Saturated fatty acids (% total fat)	0.28	1.04	0.06
Monounsaturated fatty acids (g)	1.39	0.11	0.25
Linoleic acid (g)	0.27	0.07	1.49
Linoleic acid (% total fat)	0.31	1.12	0.12
Linolenic acid (g)	0.38	0.10	0.90
Linolenic acid (% total fat)	0.45	0.11	0.41

ρQT, validation coefficient of food-frequency questionnaire; ρBT, validation coefficient of the reference method (R24h); ρRT, validation coefficient of biomarker.

In Table 4, the FFQ was considered as the adequate dietary method for estimating the ingestion of total fat, linolenic and linoleic acids based on the validation coefficients. High (≥0.6) validation coefficients were found for total fat (0.84) estimated by the FFQ and for linolenic acid (0.90) estimated by the biomarker.

The validation was considered moderate for linolenic acid (g, %) and linoleic acid (%), both estimated by the FFQ.

Table 5 Classification of 152 participants (*n*) in tertiles of consumption of fatty acids and biomarkers between the means of dietary survey methods, Viçosa, 2014

	FFQ and R24h		FFQ and biomarkers		R24h and biomarkers	
Nutrients	Same tertile	Opposite tertiles	Same tertile	Opposite tertiles	Same tertile	Opposite tertiles
Total lipids (g)	72	22	65	14	62	12
Saturated fatty acids (g)	75	25	68	18	65	15
Saturated fatty acids (% total fat)	74	24	63	11	67	17
Monounsaturated fatty acids (g)	72	22	70	20	66	16
Linoleic acid (g)	73	23	29	6	32	10
Linoleic acid (% total fat)	74	24	101	0	101	0
Linolenic acid (g)	80	30	29	10	29	13
Linolenic acid (% total fat)	69	19	100	0	101	0

FFQ, food-frequency questionnaire; R24h, 24-h food record.

Table 5 presents the joint classification of fatty acid consumption estimation (percentage of individuals classified in the same tertile) among the methods investigated. High concordance between FFQ and R24h is confirmed for all nutrients assessed. The concordance analysis between biomarkers and FFQ or R24h confirmed that the linolenic and linoleic acids presented greater concordance because they showed a greater number of individuals in the same tertile.

Bowman, 2011

› Alzheimer Dis Assoc Disord. Jan-Mar 2011;25(1):49-57. doi: 10.1097/WAD.0b013e3181f333d6.

Reliability and validity of food frequency questionnaire and nutrient biomarkers in elders with and without mild cognitive impairment

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Affiliations + expand

PMID: 20856100 PMCID: PMC3042482 DOI: 10.1097/WAD.0b013e3181f333d6

In MCI 12 of the 26 correlation coefficients generated between FFQ and plasma were positive in linear direction (Table 2, MCI). By comparison, 17 of the 26 nutrients had coefficients of the appropriate direction in NIE, and 7 of these 17 did reach significance (Table 2, NIE). The calorie-and-multivariate adjusted models had no apparent advantage over the crude model that was unadjusted for energy intake and other variables (Table 2, Calorie adjusted, Multivariate-adjusted).

Pearson correlation coefficients between plasma and FFQ nutrient estimates by cognitive status*

		Crude			Calorie-adjusted[1]			Multivariate-adjusted[2]		
		Total	MCI	NIE	Total	MCI	NIE	Total	MCI	NIE
Vitamin	Ascorbic acid	.32	.15	.52*	.32	.15	.52*	.30	.09	.51
	Alpha-tocopherol	.17	.15	.10	.17	.15	.10	.11	.21	−.04
	Gamma-tocopherol	−.21	−.20	−.02	−.16	−.20	−.02	−.15	−.37	−.04
	Lutein + zeaxanthin	.48**	−.19	.72**	.47**	−.19	.72**	.37*	−.35	.76**
	Beta-cryptoxanthin	.41**	−.11	.72**	.41**	−.11	.72**	.35*	−.15	.64*
	Alpha-carotene	.49**	.43	.65**	.49**	.43	.65**	.49**	.44	.73**
	Beta-carotene	.43**	.45	.48*	.43**	.35	.49*	.34*	.22	.71**
	Lycopene	.12	−.01	.23	.12	.01	.23	.08	.06	.06
	Vitamin B6	−.08	.05	−.28	.01	.09	−.20	.01	.12	−.18
	Folate	.04	−.25	.39	−.08	.04	−.28	−.10	.04	−.29
	Vitamin B12	.19	.10	.28	.04	−.25	.39	.14	−.07	.42
	Vitamin D	.32	.15	.52*	.19	.10	.28	.16	.18	.13
Mineral	Copper	.12	−.15	.28	.12	−.15	.28	.06	−.14	.23
	Iron	.02	.11	−.04	.02	.13	−.04	.07	.02	.26
	Magnesium	−.35*	−.52*	−.19	−.35*	−.52*	−.19	−.36*	−.54*	−.17
	Selenium	−.33*	−.41	−.13	−.33*	−.41	−.13	−.32	−.50	−.14
	Zinc	.01	.09	−.19	.01	.09	−.19	.05	.21	−.20
Lipid	PUFA, total	.10	−.06	.30	.10	−.06	.30	.00	−.07	−.09
	MUFA, total	−.15	−.10	−.15	−.15	−.10	−.14	−.07	.05	.03
	SFA, total	−.13	−.04	−.32	−.13	−.04	−.32	−.11	.01	−.42
	Linoleic acid	.09	−.05	.23	.07	−.05	.23	−.07	−.16	−.14
	Arachidonic acid	.01	−.05	.10	−.01	−.05	.10	.03	−.01	.14
	Alpha-linolenic acid	.15	.23	.03	.15	.23	.03	.14	.23	−.12
	EPA	.39*	.22	.43	.39*	.22	.43	.39*	.38	.41

		Crude			Calorie-adjusted[1]			Multivariate-adjusted[2]		
		Total	MCI	NIE	Total	MCI	NIE	Total	MCI	NIE
	DHA	.39*	.04	.65**	.39*	.04	.65**	.38*	.06	.66**
	Cholesterol[3]	−.06	−.19	.07	−.06	−.20	.07	−.05	−.13	.01

Vyas, 2020

CORRESPONDENCE | VOLUME 137, P141, DECEMBER 15, 2020

Translation of Cardiovascular Animal Models to Human Randomized Trials

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All data are available from the authors upon request. We searched MEDLINE (Supplementary Table 1) to identify cardiovascular animal models studying the efficacy of any intervention for any cardiovascular condition and published in the year 2010 (to allow for 10 years of subsequent translation to human trials). To be eligible, each animal study had to show evidence of benefit for an intervention for cardiovascular disease. For each animal study, we conducted a separate literature search to identify analogous human randomized trials in MEDLINE, EMBASE, Cochrane Library, NIH Clinical Trials and Web of Science. If at least one positive trial was available, translation was deemed “positive”.

Our literature search identified a total of 121 animal studies published in 78 different journals (Supplementary Figure). The median length of follow-up for animal experiments was 21 days (interquartile range [IQR]: 2-56). The median number of experimental animals used was 29 (IQR: 19-53). Most studies had major methodological deficiencies including lack of randomization, lack of blinding and failure to report sample size calculations (Figure). Overall, translation was positive for 25 studies (20.7%; Supplementary Table 2). Neurovascular disease models were predictive of a lack of translation (odds ratio 0.08, 95% CI 0.01 to 0.59).

Waters, 2020

EDITORIAL | VOLUME 32, ISSUE 2, P136-138, FEBRUARY 01, 2021

PDF [230 KB] Figures

How often do highly promising cancer biology discoveries translate into effective treatments?

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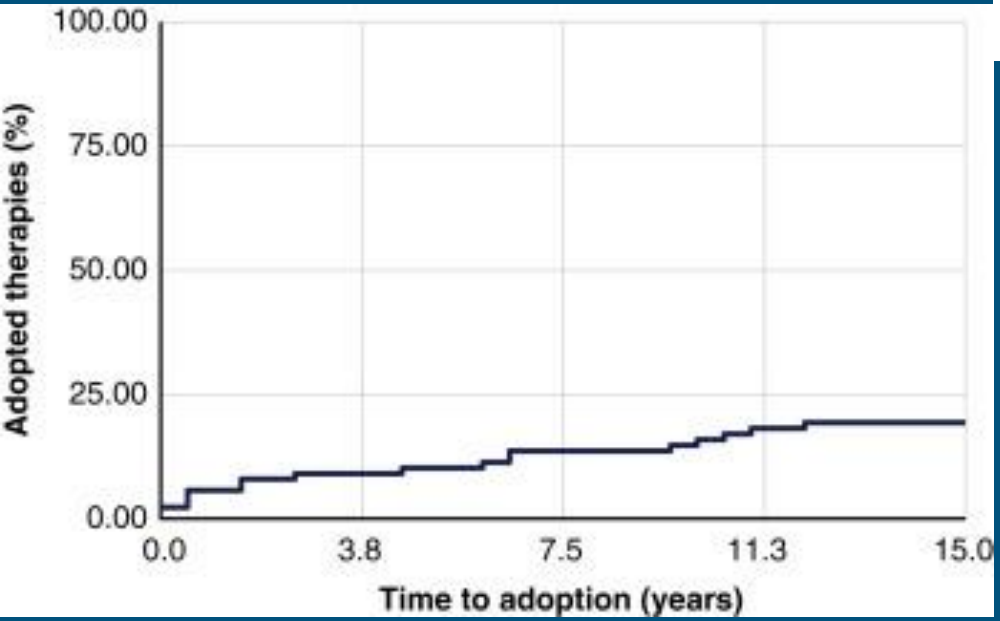
Less than 20% (19.3%) of cancer science discoveries touted as breakthrough, landmark, groundbreaking, or highly promising translated into clinical therapy or practice with a median follow-up of 15 years.



Wong, 2019

Estimation of clinical trial success rates and related parameters

Chi Heem Wong, Kien Wei Siah, Andrew W Lo ✉

Biostatistics, Volume 20, Issue 2, April 2019, Pages 273–286, https://doi.org/10.1093/biostatistics/kxx069

Published: 31 January 2018 **Article history** ▾

Table 1. *Comparison of the results of our article with previous publications using data from January 1, 2000, to October 31, 2015. We computed this using the algorithm shown in Fig. S5 in the Supplementary Material, which traces drug development programs and calculates the proportion of programs that advance from one phase to another*

	This study—all indications (industry)				This study—lead indications (industry)		Thomas *and others* (2016)—all indications		Hay *and others* (2014)—all indications		Hay *and others* (2014)—lead indications		DiMasi *and others* (2010)—lead indications	
Method	Path-by-Path		Phase-by-Phase		Path-by-Path		Phase-by-Phase		Phase-by-Phase		Phase-by-Phase		Phase-by-Phase	
	$POS_{i,i+1}$	$POS_{i,APP}$	$POS_{i,i+1}$	$POS_{i,APP}$	$POS_{i,i+1}$	$POS_{i,APP}$	$POS_{i,i+1}$	$POS_{i,APP}$	$POS_{i,i+1}$	$POS_{i,APP}$	$POS_{i,i+1}$	$POS_{i,APP}$	$POS_{i,i+1}$	$POS_{i,APP}$
Phase 1 to 2	66.4%	13.8%	38.8%	6.9%	75.8%	21.6%	63.2%	9.6%	64.5%	10.4%	66.5%	15.3%	71.0%	19.0%
Phase 2 to 3	48.6%	21.0%	38.2%	28.8%	55.6%	26.4%	30.7%	15.2%	32.4%	16.2%	39.5%	23.1%	45.0%	26.8%
Phase 3 to APP	59.0%	59.0%	59.0%	59.0%	67.7%	67.7%	49.6%	49.6%	50.0%	50.0%	58.4%	58.4%	60.0%	59.5%
Phase 1 to APP		13.8%		6.9%		21.6%		9.6%		10.4%		15.3%		19.0%
Number of drugs	15 102						Unknown		5820		4736		1316	
Years of source data (time-span)	2000–2015 (16 years)						2006–2015 (10 years)		2003–2011 (9 years)				1993–2009 (17 years)	
Number of companies	5764						1103		835				50	

Table 2. *The POS by therapeutic group, using data from January 1, 2000, to October 31, 2015. We computed this using the path-by-path method. SE denotes the standard error*

All indications (industry)								
	Phase 1 to Phase 2		Phase 2 to Phase 3			Phase 3 to Approval		Overall
Therapeutic group	Total paths	$POS_{1,2}$, % (SE, %)	Total paths	$POS_{2,3}$, % (SE, %)	$POS_{2,APP}$, % (SE, %)	Total paths	$POS_{3,APP}$, % (SE, %)	POS, % (SE, %)
Oncology	17 368	57.6 (0.4)	6533	32.7 (0.6)	6.7 (0.3)	1236	35.5 (1.4)	3.4 (0.2)
Metabolic/ Endocrinology	3589	76.2 (0.7)	2357	59.7 (1.0)	24.1 (0.9)	1101	51.6 (1.5)	19.6 (0.7)
Cardiovascular	2810	73.3 (0.8)	1858	65.7 (1.1)	32.3 (1.1)	964	62.2 (1.6)	25.5 (0.9)
CNS	4924	73.2 (0.6)	3037	51.9 (0.9)	19.5 (0.7)	1156	51.1 (1.5)	15.0 (0.6)
Autoimmune/ Inflammation	5086	69.8 (0.6)	2910	45.7 (0.9)	21.2 (0.8)	969	63.7 (1.5)	15.1 (0.6)
Genitourinary	757	68.7 (1.7)	475	57.1 (2.3)	29.7 (2.1)	212	66.5 (3.2)	21.6 (1.6)
Infectious disease	3963	70.1 (0.7)	2314	58.3 (1.0)	35.1 (1.0)	1078	75.3 (1.3)	25.2 (0.8)
Ophthalmology	674	87.1 (1.3)	461	60.7 (2.3)	33.6 (2.2)	207	74.9 (3.0)	32.6 (2.2)
Vaccines (Infectious Disease)	1869	76.8 (1.0)	1235	58.2 (1.4)	42.1 (1.4)	609	85.4 (1.4)	33.4 (1.2)
Overall	41 040	66.4 (0.2)	21 180	48.6 (0.3)	21.0 (0.3)	7532	59.0 (0.6)	13.8 (0.2)
All without oncology	23 672	73.0 (0.3)	14 647	55.7 (0.4)	27.3 (0.4)	6296	63.6 (0.6)	20.9 (0.3)

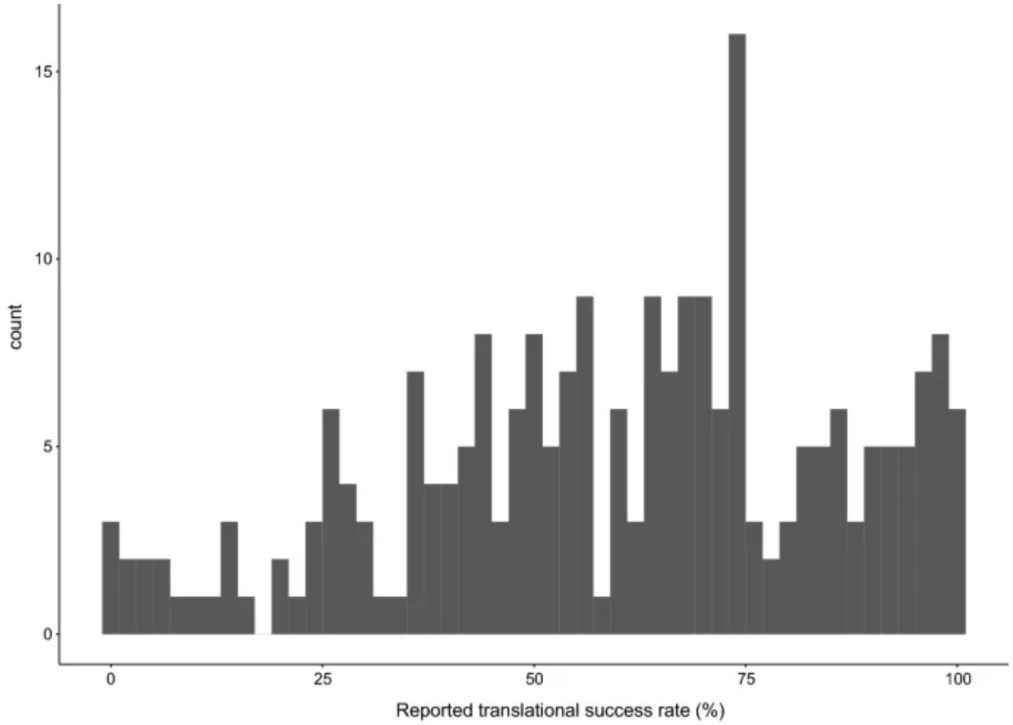
Lead indications (Industry)

	Phase 1 to Phase 2		Phase 2 to Phase 3			Phase 3 to Approval		Overall
Therapeutic group	Total paths	$POS_{1,2}$, % (SE, %)	Total paths	$POS_{2,3}$, % (SE, %)	$POS_{2,APP}$, % (SE, %)	Total paths	$POS_{3,APP}$, % (SE, %)	POS, % (SE, %)
Oncology	3107	78.7 (0.7)	1601	53.9 (1.2)	13.1 (0.8)	431	48.5 (2.4)	11.4 (0.7)
Metabolic/ Endocrinology	2012	75.2 (1.0)	1273	57.0 (1.4)	26.4 (1.2)	535	62.8 (2.1)	21.3 (1.0)
Cardiovascular	1599	71.1 (1.1)	1002	64.9 (1.5)	34.1 (1.5)	473	72.3 (2.1)	26.6 (1.2)
CNS	2777	75.0 (0.8)	1695	54.5 (1.2)	24.1 (1.0)	648	63.0 (1.9)	19.3 (0.9)
Autoimmune/ Inflammation	2900	78.9 (0.8)	1862	48.7 (1.2)	24.3 (1.0)	659	68.6 (1.8)	20.3 (0.9)
Genitourinary	568	73.4 (1.9)	382	59.2 (2.5)	31.9 (2.4)	176	69.3 (3.5)	25.3 (2.0)
Infectious Disease	2186	74.6 (0.9)	1326	58.0 (1.4)	34.3 (1.3)	594	76.6 (1.7)	26.7 (1.1)
Ophthalmology	437	89.0 (1.5)	302	57.6 (2.8)	30.5 (2.6)	124	74.2 (3.9)	30.7 (2.7)
Vaccines (Infectious Disease)	881	75.8 (1.4)	567	57.1 (2.1)	40.4 (2.1)	269	85.1 (2.2)	31.6 (1.7)
Overall	16 467	75.8 (0.3)	10 010	55.6 (0.5)	26.4 (0.4)	3909	67.7 (0.7)	21.6 (0.4)
All without oncology	13 360	75.8 (0.4)	8409	55.9 (0.5)	29.0 (0.5)	3478	70.0 (0.8)	23.4 (0.4)

Leenaars, 2019

The range of published translational success rates is 0% to 100%. A histogram of all published translational success rates is provided in Fig. 2.

Fig. 2



Review | Open Access | Published: 15 July 2019

Animal to human translation: a systematic scoping review of reported concordance rates

Cathalijn H. C. Leenaars ✉, Carien Kouwenaar, Frans R. Stafleu, André Bleich, Merel Ritskes-Hoitinga, Rob B. M. De Vries & Franck L. B. Meijboom

Journal of Translational Medicine **17**, Article number: 223 (2019) | Cite this article

Perrin, 2014

Conclusion

The diseases that infants, children, and youth experience, including those responsible for substantial hospitalization, have changed dramatically over the past half century. A wider array of vaccines has markedly decreased many previously fatal infections as well as others that caused enough morbidity to lead to hospitalization. With advances in medical care, mortality rates began stabilizing for many severe, rare conditions around 1980, although since then other more common conditions have greatly increased in prevalence, out of proportion to changes in the occurrence of rare conditions. The differential epidemiology in these groups of conditions calls for a system of regionalized care for rare, complex conditions, based mainly in pediatric hospitals, and decentralized care for the common conditions, with the bulk of care delivered and received in primary care settings. ■

By James M. Perrin, L. Elizabeth Anderson, and Jeanne Van Cleave

The Rise In Chronic Conditions Among Infants, Children, And Youth Can Be Met With Continued Health System Innovations

DOI: 10.1377/hlthaff.2014.0832
HEALTH AFFAIRS 33,
NO. 12 (2014): 2099–2105

Su, 2017

Food & Function

PAPER

View Article Online
View Journal

Check for updates

Cite this: DOI: 10.1039/c7fo00433h

Dietary linoleic acid intake and blood inflammatory markers: a systematic review and meta-analysis of randomized controlled trials†

Hang Su, Ruijie Liu, Ming Chang, Jianhua Huang and Xingguo Wang*

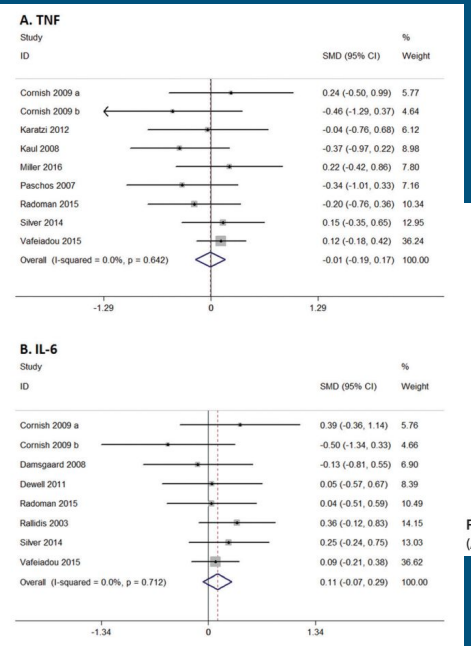


Fig. 2 Effect of increasing dietary LA intake on the blood concentrations of TNF (A) and IL-6 (B).

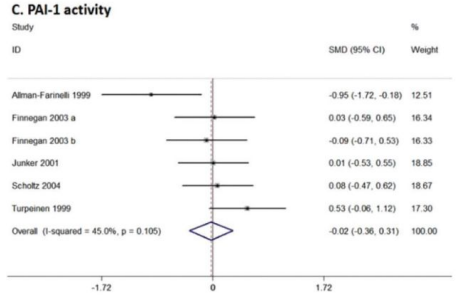
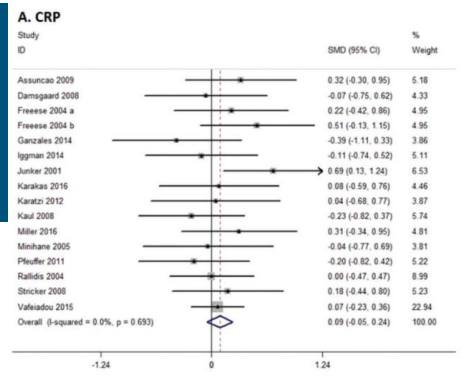


Fig. 3 Effect of increasing dietary LA intake on the blood levels of CRP (A), fibrinogen (B) and PAI-1 activity (C).



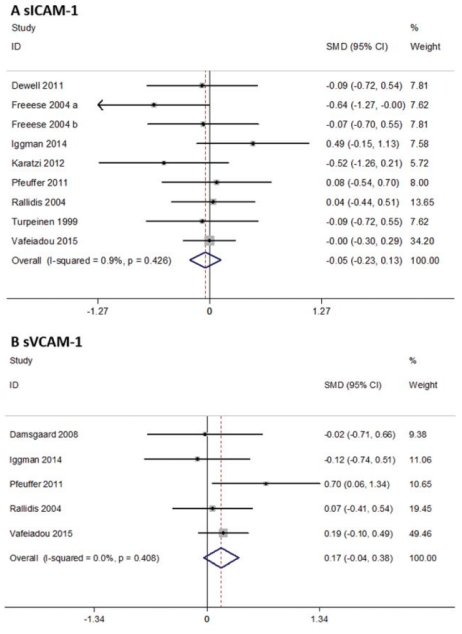
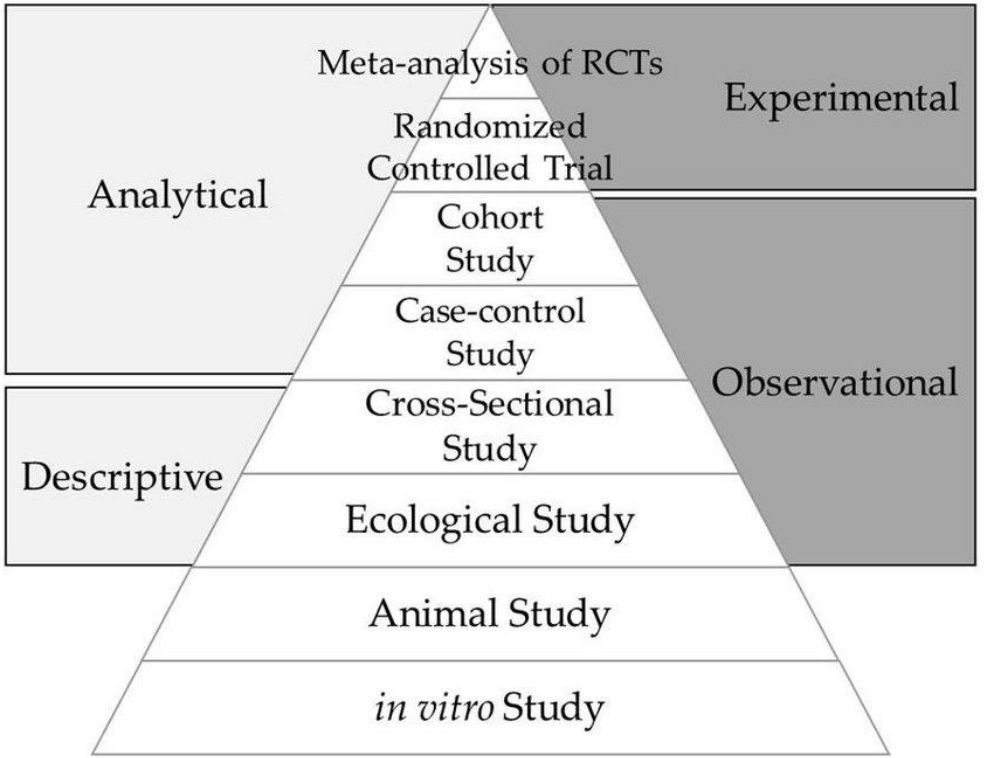


Fig. 4 Effect of increasing dietary LA intake on the blood concentrations of sICAM-1 (A) and sVCAM-1 (B).

Tucker’s References

And my rebuttals

Woolsey, 1948



Public Health Reports

Vol. 63 • SEPTEMBER 24, 1948 • *No. 39*

Statistical Studies of Heart Diseases

II. Important Factors in Heart Disease Mortality Trends

By THEODORE D. WOOLSEY and I. M. MORIYAMA, *Biostatisticians*
Public Health Service

Ryle, 1949

THE NATURAL HISTORY OF CORONARY DISEASE

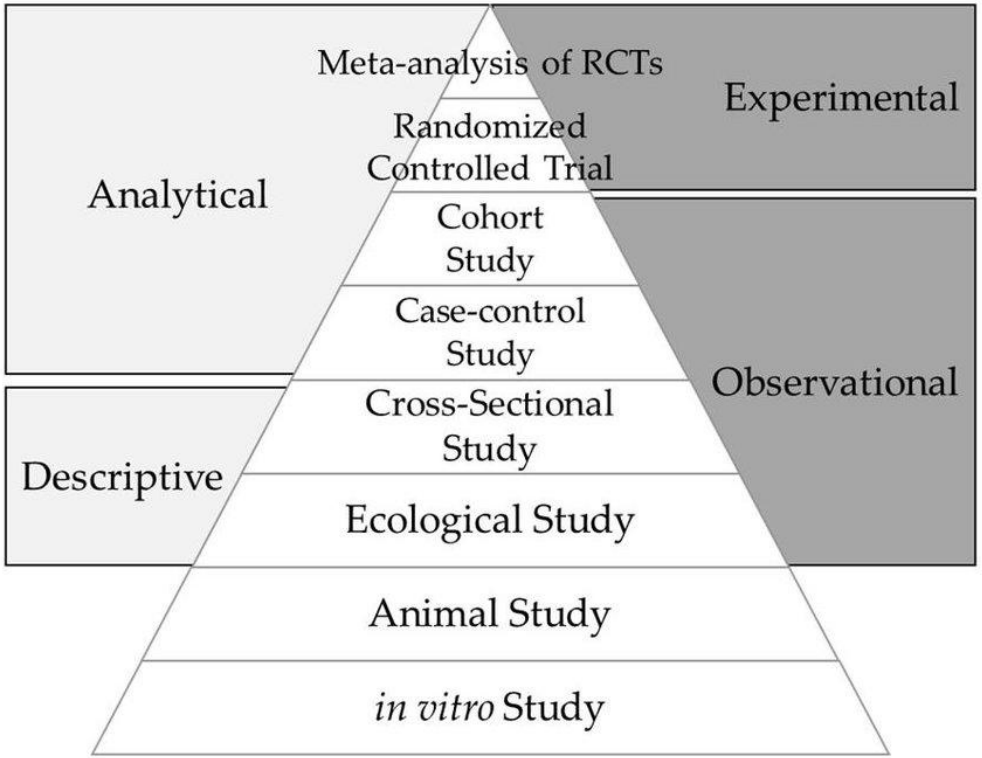
A CLINICAL AND EPIDEMIOLOGICAL STUDY

BY

JOHN A. RYLE AND W. T. RUSSELL

From the Institute of Social Medicine, Oxford

Received June 12, 1949



Preventive Medicine
Volume 26, Issue 4, July 1997, Pages 447-450

Regular Article

Trends in Cigarette Smoking in the United States ☆

Lawrence Garfinkel [a, 1]

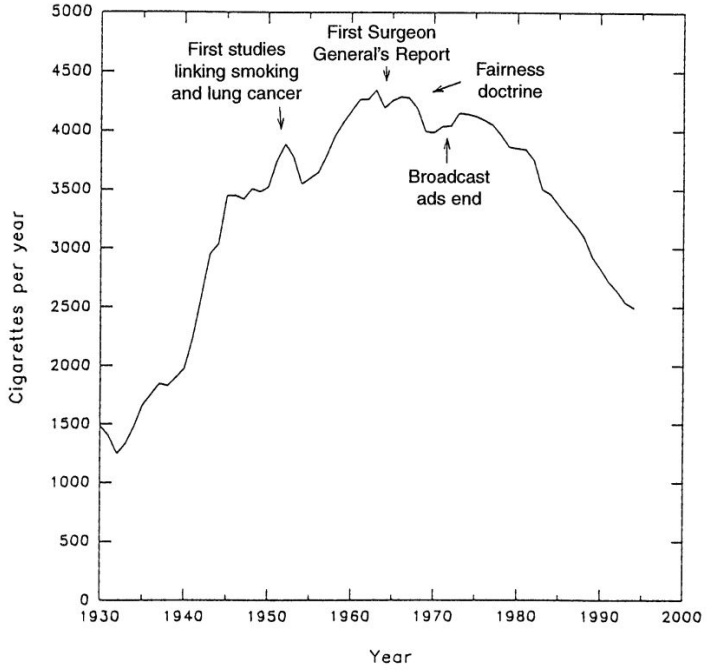
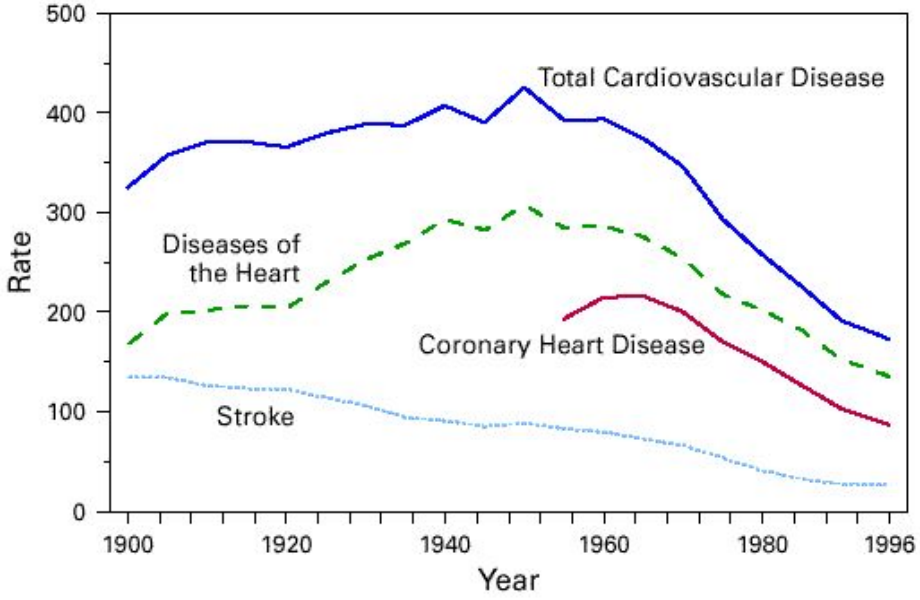


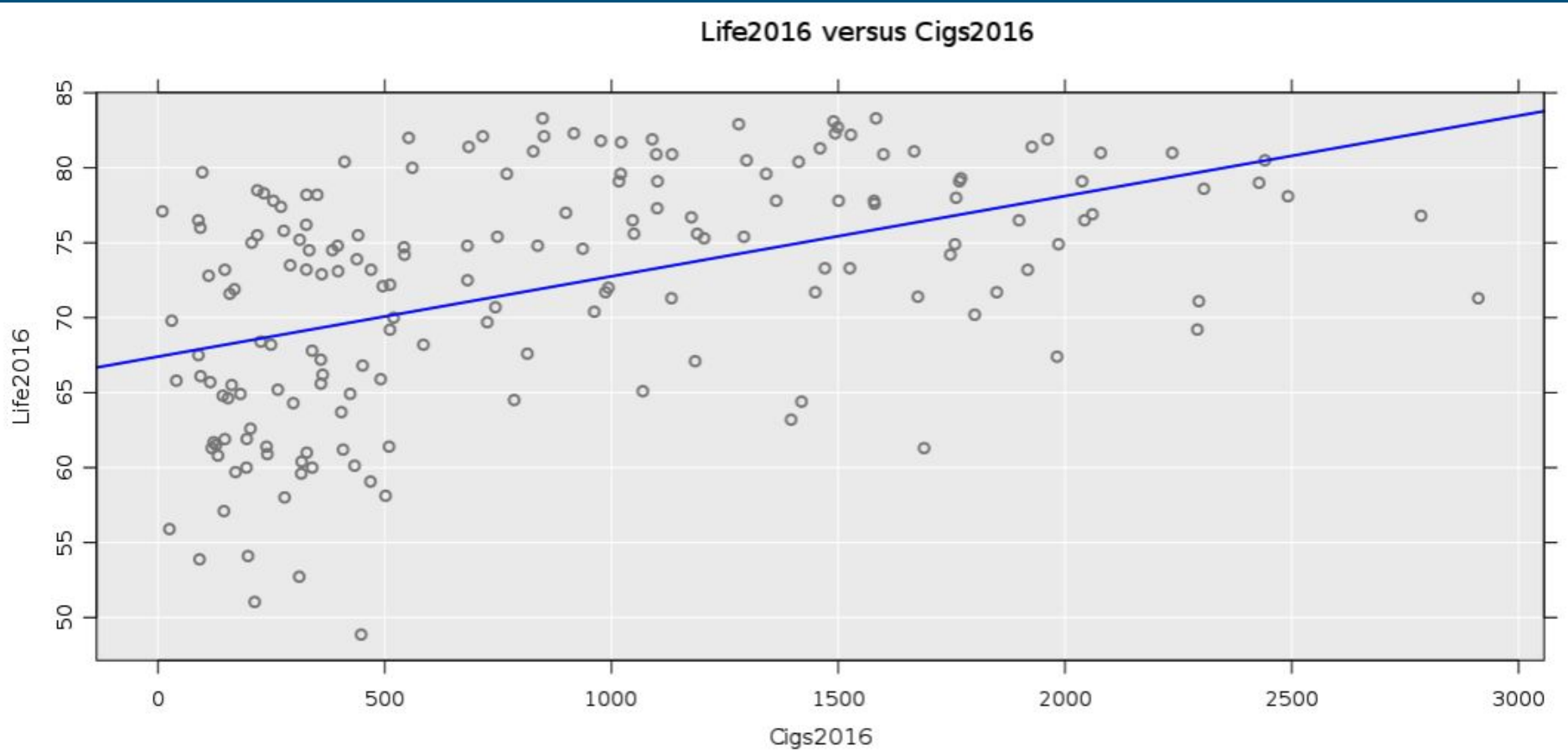
FIG. 1. Cigarette consumption per capita in adults age 18 and older, United States, 1930–1994. Source: Ref. [*26*].

FIGURE 1. Age-adjusted death rates* for total cardiovascular disease, diseases of the heart, coronary heart disease, and stroke,† by year — United States, 1900–1996



*Per 100,000 population, standardized to the 1940 U.S. population.
†Diseases are classified according to *International Classification of Diseases* (ICD) codes in use when the deaths were reported. ICD classification revisions occurred in 1910, 1921, 1930, 1939, 1949, 1958, 1968, and 1979. Death rates before 1933 do not include all states. Comparability ratios were applied to rates for 1970 and 1975.

Source: Adapted from reference 1; data provided by the National Heart, Lung and Blood Institute, National Institutes of Health.


Life2016 versus Cigs2016
Life2016
Cigs2016
50
55
60
65
70
75
80
85
0
500
1000
1500
2000
2500
3000

Lee, 1964

Geographic Pathology of Myocardial Infarction*

Part I. Myocardial Infarction in Orientals and Whites in the United States

Kyu Taik Lee, Richard Nail, Laurence A. Sherman *and* Michael Milano

Part II. Myocardial Infarction in Orientals in Korea and Japan

Kyu Taik Lee, Carl Deden, Hideshge Imai, Fairfield Goodale *and* Sang Chul Nam

Part III. Myocardial Infarction in Africans in Africa and Negroes and Whites in the United States

Kyu Taik Lee, Fairfield Goodale, R. Foster Scott *and* Eric S. Snell

Part IV. Measurement of Amount of Coronary Arteriosclerosis in Africans, Koreans, Japanese and New Yorkers

Kyu Taik Lee, Assaad S. Daoud, John Jarmolych, Louis Jakovic *and* Rudolfo Florentin
Albany, New York

TABLE V

Autopsy Data Pertaining to Occurrence Rate of Myocardial Infarction from Uganda, Nigeria and New Orleans, La.*

Age	Sex	Uganda Negro			Nigeria Negro			New Orleans Negro			New Orleans White		
		No. c̄ M.I.	No. of Autops.	% c̄ M.I.	No. c̄ M.I.	No. of Autops.	% c̄ M.I.	No. c̄ M.I.	No. of Autops.	% c̄ M.I.	No. c̄ M.I.	No. of Autops.	% c̄ M.I.
20–29	M	0	(1004)	0	1	(79)	1	0	(17)	0	1	(9)	11
	F	0	(175)	0	0	(111)	0	0	(21)	0	0	(10)	0
30–39	M	0	(1219)	0	0	(82)	0	3	(35)	9	3	(23)	13
	F	0	(235)	0	0	(77)	0	2	(60)	3	1	(21)	5
40–49	M	0	(760)	0	1	(56)	2	5	(75)	7	9	(55)	16
	F	0	(120)	0	0	(32)	0	10	(105)	10	4	(37)	11
50–59	M	1	(453)	0.2	0	(61)	0	24	(153)	16	28	(129)	22
	F	0	(60)	0	0	(21)	0	12	(144)	8	11	(56)	20
60–69	M	0	(198)	0	0	(39)	0	22	(149)	15	36	(148)	24
	F	0	(29)	0	0	(8)	0	31	(149)	21	24	(89)	27
70+	M	0	(71)	0	0	(8)	0	32	(141)	23	71	(210)	34
	F	0	(12)	0	0	(2)	0	30	(130)	23	54	(159)	34

* The period covered in this study for Nigeria is 1959–1961 and for New Orleans, 1957–1959. For Uganda the majority of the autopsies from 1946–1959 are included, but a substantial number were of unknown age and were excluded (none of unknown age had myocardial infarction). This table is based on studies in Ref. 17 and 18.

Perrin, 2014

Conclusion

The diseases that infants, children, and youth experience, including those responsible for substantial hospitalization, have changed dramatically over the past half century. A wider array of vaccines has markedly decreased many previously fatal infections as well as others that caused enough morbidity to lead to hospitalization. With advances in medical care, mortality rates began stabilizing for many severe, rare conditions around 1980, although since then other more common conditions have greatly increased in prevalence, out of proportion to changes in the occurrence of rare conditions. The differential epidemiology in these groups of conditions calls for a system of regionalized care for rare, complex conditions, based mainly in pediatric hospitals, and decentralized care for the common conditions, with the bulk of care delivered and received in primary care settings. ■

By James M. Perrin, L. Elizabeth Anderson, and Jeanne Van Cleave

The Rise In Chronic Conditions Among Infants, Children, And Youth Can Be Met With Continued Health System Innovations

DOI: 10.1377/hlthaff.2014.0832
HEALTH AFFAIRS 33,
NO. 12 (2014): 2099–2105

CHD in Cultures Consuming Traditional Diet

Special Article | 1 November 1963

Coronary Heart Disease Among the Navajo Indians

HUGH S. FULMER, M.D., RICHARD W. ROBERTS, M.D.

Author, Article and Disclosure Information

https://doi.org/10.7326/0003-4819-59-5-740

TABLE 17. Adipose Tissue Analyses

		Myristic	Palmitic	Palmitoleic	Stearic	Oleic	Linoleic
				%			
Navajo on a traditional diet	1	4.1	21.3	9.9	5.5	46.0	6.0
	2	2.8	21.8	9.9	5.3	43.2	6.8
	3	1.6	18.3	13.4	1.5	50.8	8.4
	4	1.7	18.4	13.2	2.0	51.4	9.0
	5	2.6	23.5	9.3	6.6	49.0	5.4
	6	4.1	18.2	10.2	3.3	49.7	9.3
	7	2.1	12.6	12.3	3.9	52.8	9.6
	8	2.5	21.2	7.4	7.2	47.9	7.3
	9	2.5	20.5	9.5	3.3	49.5	10.1
	Average	2.7	19.5	10.6	4.3	48.9	8.0
Navajo on a modern diet	1	1.8	22.2	7.6	4.3	53.5	10.5
	2	3.7	22.2	11.7	3.4	47.8	8.9
	3	2.6	26.8	6.2	5.4	48.4	10.1
	Average	2.7	23.7	8.5	4.4	49.9	9.8
Rockefeller Institute Normals—Average		3.3	19.5	6.9	4.2	46.3	11.4

A 6-year cohort and descriptive epidemiologic study in the Many Farms Navajo Indian population has revealed only 4 cases of coronary heart disease in 508 adults 30 years old or older. The incidence is significantly low when an appropriate age and sex matched segment is compared to the Framingham population, whose people have undergone intensive study for coronary heart disease.

Bull World Health Organ. 1964; 31(3): 321–335.

Myocardial disease in a rural population in Jamaica*

J. Fodor, W. E. Miall, K. L. Standard, Z. Fejfar, and K. L. Stuart

TABLE 9

THE PREVALENCE OF MYOCARDIAL DISEASE, LAWRENCE TAVERN, 1962

Population	Myocardial disease				No myocardial disease	Total
	Angina only	ECG changes only	Angina + ECG changes	Total (and %)		
Females:						
35-44 years	7	5	—	12(12.5)	84	96
45-54 years	6	4	6	16(17.8)	74	90
55-64 years	7	7	1	15(16.1)	78	93
Total	20	16	7	43(15.4)	236	279
35-44 years	9	2	1	12(13.3)	78	90
45-54 years	4	4	1	9(10.0)	81	90
55-64 years	9	2	4	15(16.9)	74	89
Total	22	8	6	36(13.4)	233	269

FULL LENGTH ARTICLE | VOLUME 166, ISSUE 2, P351-357,
FEBRUARY 01, 2003

Low incidence of cardiovascular disease among the Inuit—what is the evidence?

Peter Bjerregaard • T. Kue Young • Robert A. Hegele

DOI: https://doi.org/10.1016/S0021-9150(02)00364-7

Table 3
Mortality from cardiovascular diseases among the Inuit in Canada and Alaska in the 1990s

	Indigenous	All	Ratio	CI (95%)
Cerebrovascular disease				
Nunavik, Canada, 1995–1997[a]	200	48	4.13	1.07–10.68
Nunavut, Canada	not available	–	–	–
Alaska Natives, 1993–1998[b]	36	27	1.36	1.17–1.57
Alaska Inuit[c]	not available	–	–	–
IHD				
Nunavik, Canada	not available	–	–	–
Nunavut, Canada, 1995–1997[a]	40	136	0.29	0.06–0.87
Alaska Natives, 1993–1998[b]	79	79	0.99	0.88–1.11
Alaska Inuit, 1990–1998[b,c]	70	82	0.85	0.74–0.96

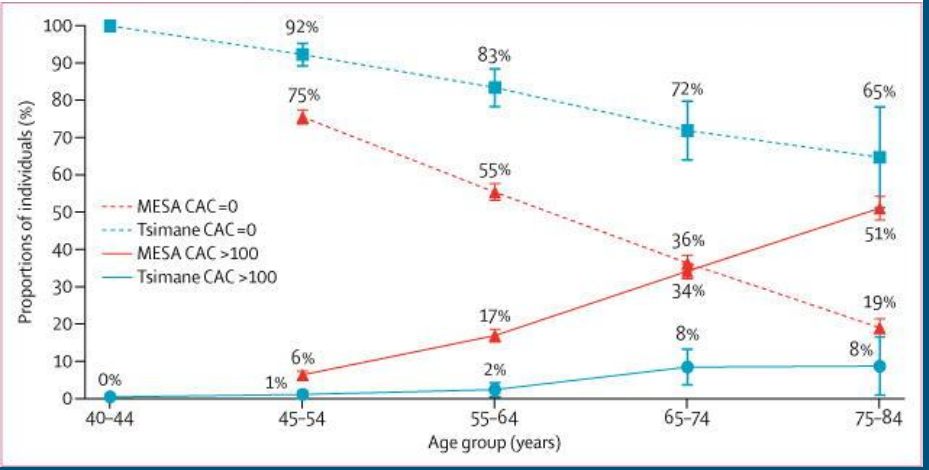
Adjusted to different standard populations.
[a] Adjusted to the Canadian population 1991.
[b] Adjusted to the US population 1940.
[c] Six census areas with predominantly Inuit population.

5. Conclusion

Mortality from stroke is similar or probably higher among the Inuit than among other western populations. The evidence for a low mortality from IHD is fragile and rests on unreliable mortality statistics. If present, it seems not to be associated with a low prevalence of general atherosclerosis. The life style of the Inuit is rapidly changing towards an increased cardiovascular risk factor profile [52]. Physical activity declines, obesity is widespread, the reliance on imported food increases, and the smoking rates are alarmingly high. We may still obtain a picture of the determinants of the traditional Inuit cardiovascular disease and mortality pattern by studying the life style of the elders in an historical perspective and following their disease and mortality pattern over the coming years, but time is running out. In a few years from now we may not be able to find out why the Inuit were protected against IHD–if ever they were.

Lancet. Author manuscript; available in PMC 2018 Jul 3.
PMCID: PMC6028773
Published in final edited form as:
NIHMSID: NIHMS976319
Lancet. 2017 Apr 29; 389(10080): 1730–1739.
PMID: 28320601
Published online 2017 Mar 17. doi: 10.1016/S0140-6736(17)30752-3

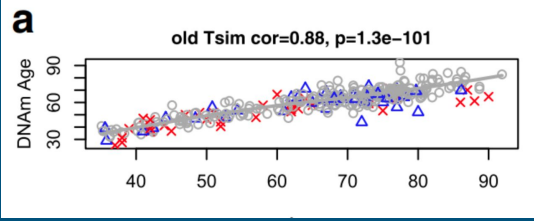
Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study



Genome Biol. 2016; 17: 171.
PMCID: PMC4980791
Published online 2016 Aug 11. doi: 10.1186/s13059-016-1030-0
PMID: 27511193

An epigenetic clock analysis of race/ethnicity, sex, and coronary heart disease

Steve Horvath,[✉#1,2] Michael Gurven,[#3] Morgan E. Levine,[1] Benjamin C. Trumble,[3] Hillard Kaplan,[4] Hooman Allayee,[5] Beate R. Ritz,[6] Brian Chen,[7] Ake T. Lu,[1] Tammy M. Rickabaugh,[8] Beth D. Jamieson,[8] Dianjianyi Sun,[9] Shengxu Li,[9] Wei Chen,[9] Lluis Quintana-Murci,[10] Maud Fagny,[11] Michael S. Kobor,[12] Philip S. Tsao,[13,14] Alexander P. Reiner,[15] Kerstin L. Edlefsen,[16] Devin Absher,[#17] and Themistocles L. Assimes[#13]



JAMA Netw Open. 2019 Dec; 2(12): e1918270.
PMCID: PMC6991216
Published online 2019 Dec 27. doi: 10.1001/jamanetworkopen.2019.18270
PMID: 31880790

Atherosclerosis in 16th-Century Greenlandic Inuit Mummies

L. Samuel Wann, MD,[✉1] Jagat Narula, MD, PhD,[2] Ron Blankstein, MD,[3] Randall C. Thompson, MD,[4] Bruno Frohlich, PhD,[5] Caleb E. Finch, PhD,[6] and Gregory S. Thomas, MD, MPH[7]

This cases series presents evidence for the presence of calcified plaques in the mummified remains of 3 young Inuit individuals living 500 years ago, suggesting the presence of atherosclerosis despite their vigorous lifestyle and marine-based diet. While we cannot know the incidence of ancient ischemic events, cardiovascular deaths were rare among mid 20th century Inuit people, similar to contemporary Amazonian Tsimane people, who have low-grade atherosclerosis and low incidence of cardiovascular death.[7,8,9] The etiologic complexity of atherosclerosis confounds identification of single factors, such as ω-3 fatty acids, as causal or protective. Other factors may include environmental smoke,[10] which is produced by indoor fires used by Inuit and many other ancient peoples who also incurred atherosclerosis.

ATHEROSCLEROSIS IN THE MASAI

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GEORGE V. MANN, ANNE SPOERRY, MARGARETE GARY, DEBRA JARASHOW

American Journal of Epidemiology, Volume 95, Issue 1, January 1972, Pages 26–37,
https://doi.org/10.1093/oxfordjournals.aje.a121365

Published: 01 January 1972 **Article history** ▾

Mann, G. V. (Vanderbilt Univ. School of Medicine, Nashville, Tenn. 37203), A. Spoerry, M. Gray, and D. Jarashow. Atherosclerosis in the Masai. *Am J Epidemiol* 95: 26–37, 1972.—The hearts and aortae of 50 Masai men were collected at autopsy. These pastoral people are exceptionally active and fit and they consume diets of milk and meat. The intake of animal fat exceeds that of American men. Measurements of the aorta showed extensive atherosclerosis with lipid infiltration and fibrous changes but very few complicated lesions. The coronary arteries showed intimal thickening by atherosclerosis which equaled that of old U.S. men. The Masai vessels enlarge with age to more than compensate for this disease. It is speculated that the Masai are protected from their atherosclerosis by physical fitness which causes their coronary vessels to be capacious.

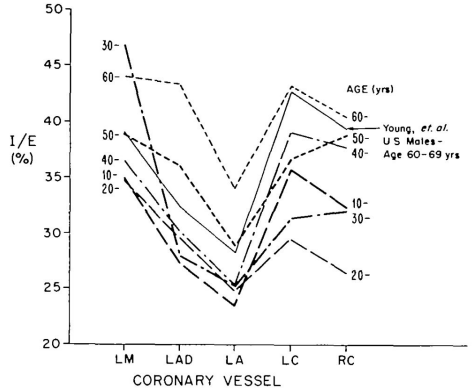

FIGURE 7. Masai coronary arteries—intimal thickness by site and age. The coronary vessels are: LM, left main; LAD, left anterior descending; LA, left anterior; LC, left circumflex; RC, right. Young's U.S. data are shown as the solid line. I/E = intimal area/area within external lamina.

ARTICLES | VOLUME 381, ISSUE 9873, P1211-1222, APRIL 06, 2013

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Atherosclerosis across 4000 years of human history: the Horus study of four ancient populations

Prof Randall C Thompson, MD • Prof Adel H Allam, MD • Guido P Lombardi, MD • L Samuel Wann, MD • M Linda Sutherland, MD • James D Sutherland, MD • et al. Show all authors

Published: March 11, 2013 • DOI: https://doi.org/10.1016/S0140-6736(13)60598-X • Check for updates

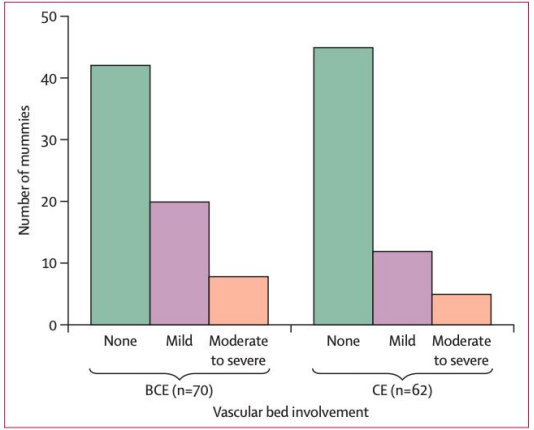


***Figure 3*: Severity of atherosclerosis in mummies from before the common era (BCE) and the common era (CE)**
None=no vessel involvement. Mild=one to two vascular beds affected. Moderate to severe=three to five vascular beds affected.

In conclusion, atherosclerosis was common in four preindustrial populations, including a preagricultural hunter-gatherer population, and across a wide span of human history. It remains prevalent in contemporary human beings. The presence of atherosclerosis in premodern human beings suggests that the disease is an inherent component of human ageing and not characteristic of any specific diet or lifestyle.

Atherosclerosis in mummified human remains from Vilnius, Lithuania (18th–19th centuries AD): A computed tomographic investigation

Correction(s) for this article

Dario Piombino-Mascali, Rimantas Jankauskas, Algirdas Tamošiūnas, Ramūnas Valančius
... See all authors

First published: 20 June 2014 | https://doi.org/10.1002/ajhb.22578 | Citations: 10

TABLE 1. Vessel atherosclerosis in the three investigated mummies

Location	VD3: adult male	VD9: adult female	VD12: adult male
Carotid	Definite	Definite	Definite
Coronary	Definite	Definite	Definite
Aortic	Definite	Definite	Definite
Iliac or femoral	Definite	Definite	Definite
Popliteal or tibial	–	Definite	Definite

VD, Vilnius Dominicans.

TABLE 2. Valve calcifications in the three investigated mummies

Location	VD3: adult male	VD9: adult female	VD12: adult male
Aortic valve leaflets	Definite	–	Definite
Mitral valve anulus	Definite	Definite	–
Mitral valve leaflets	–	–	–

VD, Vilnius Dominicans.

CONCLUSIONS

As it is today in modern Lithuanians, atherosclerosis was also present in historic Vilnans. While genetic factors may have played a role in the premature development of the disease, historical and bioanthropological evidence suggests that diet and the environment might have also been determinants. European mummies from the medieval and modern periods represent valuable paleopathological material for further investigations of this condition, combining ethnographic, documentary, and biomedical data. It would therefore be beneficial to extend this research to a wider sample of preserved bodies, such as Hungarian, Polish, and Italian mummies, to better evaluate the natural history of this disease.

ACKNOWLEDGMENTS

We are most grateful to Daumantas Liekis, curator of the crypt, for advocating and supporting the project, to embalmer Danas Jankauskas for logistical assistance and

Verschuren, 1995

Table 2.—Cutoff Points and Mean Serum Total Cholesterol Level (mmol/L [mg/dL]) to Baseline Cholesterol Quartile per Cohort and Calculated Dilution Factor

	Cholesterol Quartile	Northern Europe	United States	Southern Europe Inland	Southern Europe Mediterranean	Serbia	Japan
1	Range	<5.60 [216]	<5.40 [209]	<4.55 [176]	<4.40 [170]	<3.65 [142]	<3.65 [141]
	Mean baseline (SD)	5.00 (0.50) [193 (19)]	4.85 (0.50) [187 (19)]	4.00 (0.45) [155 (17)]	3.95 (0.40) [152 (16)]	3.30 (0.35) [127 (13)]	3.20 (0.35) [124 (14)]
	Mean 5-y follow-up (SD)	5.55 (0.95) [214 (36)]	5.15 (0.80) [200 (31)]	4.75 (0.85) [183 (33)]	4.60 (0.80) [179 (32)]	4.10 (0.80) [159 (32)]	Not available
2	Range	5.60-6.40 [216-248]	5.40-6.05 [209-235]	4.55-5.15 [176-200]	4.40-5.05 [170-196]	3.65-4.15 [142-160]	3.65-4.15 [141-161]
	Mean baseline (SD)	6.00 (0.25) [233 (9)]	5.75 (0.20) [223 (8)]	4.90 (0.20) [189 (7)]	4.75 (0.20) [184 (7)]	3.95 (0.15) [152 (5)]	3.90 (0.15) [151 (6)]
	Mean 5-y follow-up (SD)	6.25 (0.75) [241 (30)]	5.85 (0.70) [227 (27)]	5.45 (0.80) [210 (32)]	5.15 (0.70) [199 (28)]	4.70 (0.85) [182 (33)]	Not available
3	Range	6.45-7.30 [249-282]	6.10-6.90 [236-267]	5.20-5.90 [201-229]	5.10-5.80 [197-224]	4.15-4.75 [161-183]	4.20-4.85 [162-187]
	Mean baseline (SD)	6.90 (0.45) [266 (18)]	6.50 (0.25) [252 (9)]	5.55 (0.20) [215 (8)]	5.45 (0.20) [210 (8)]	4.45 (0.20) [173 (7)]	4.50 (0.20) [175 (7)]
	Mean 5-y follow-up (SD)	6.80 (0.85) [264 (33)]	6.40 (0.70) [247 (27)]	5.90 (0.85) [228 (33)]	5.60 (0.75) [217 (29)]	5.10 (0.80) [197 (31)]	Not available
4	Range	>7.30 [282]	>6.90 [267]	>5.90 [229]	>5.80 [224]	>4.75 [183]	>4.85 [187]
	Mean baseline (SD)	8.30 (0.95) [321 (37)]	7.75 (0.85) [300 (33)]	6.70 (0.07) [260 (28)]	6.60 (0.75) [256 (29)]	5.35 (0.60) [207 (23)]	5.50 (0.55) [212 (21)]
	Mean 5-y follow-up (SD)	7.80 (1.15) [302 (44)]	7.20 (1.05) [279 (41)]	6.70 (1.10) [260 (43)]	6.55 (1.05) [254 (41)]	5.80 (1.00) [224 (39)]	Not available
	Cholesterol difference between the lowest and highest quartiles						
	Baseline	3.30 [128]	2.90 [113]	2.70 [105]	2.70 [104]	2.05 [80]	2.25 [88]
	5-y follow-up	2.25 [88]	2.05 [79]	2.00 [77]	1.95 [75]	1.70 [65]	Not available
	Dilution factor	1.45	1.43	1.36	1.39	1.23	Not available

July 12, 1995

Serum Total Cholesterol and Long-term Coronary Heart Disease Mortality in Different Cultures

Twenty-five—Year Follow-up of the Seven Countries Study

W. M. Monique Verschuren, MSc; David R. Jacobs, PhD; Bennie P. M. Bloemberg, PhD; et al

» Author Affiliations

JAMA. 1995;274(2):131-136. doi:10.1001/jama.1995.03530020049031

Table 3.—Crude and Adjusted Relative Risks (95% Confidence Interval) per Cholesterol Quartile for Each Cohort

Cohort	Cholesterol Quartile 1 (Low)	2	3	4 (High)	χ^2 Trend *P*
Northern Europe					
Crude	1.0	1.18 (0.90-1.55)	1.45 (1.12-1.89)	2.16 (1.69-2.76)	<.001
Adjusted*	1.0	1.11 (0.84-1.45)	1.34 (1.03-1.74)	2.03 (1.59-2.59)	<.001
United States					
Crude	1.0	1.22 (0.89-1.68)	1.50 (1.11-2.04)	2.74 (2.07-3.63)	<.001
Adjusted	1.0	1.09 (0.79-1.51)	1.39 (1.03-1.89)	2.34 (1.77-3.11)	<.001
Southern Europe, Inland					
Crude	1.0	1.24 (0.86-1.79)	1.55 (1.10-2.18)	1.65 (1.17-2.33)	<.01
Adjusted	1.0	1.21 (0.84-1.74)	1.50 (1.06-2.12)	1.52 (1.07-2.15)	<.01
Southern Europe, Mediterranean					
Crude	1.0	1.12 (0.62-2.00)	1.51 (0.87-2.61)	2.30 (1.38-3.82)	<.001
Adjusted	1.0	1.03 (0.57-1.85)	1.35 (0.78-2.33)	1.66 (0.98-2.80)	<.05
Serbia					
Crude	1.0	1.57 (0.76-3.27)	2.17 (1.10-4.30)	2.17 (1.07-4.38)	<.05
Adjusted	1.0	1.43 (0.69-2.96)	1.88 (0.94-3.73)	1.86 (0.92-3.76)	≥.05
Japan					
Crude	1.0	1.46 (0.61-3.50)	0.82 (0.30-2.26)	1.13 (0.45-2.86)	≥.05
Adjusted	1.0	1.51 (0.60-3.84)	0.89 (0.31-2.57)	1.13 (0.42-3.02)	≥.05

*Adjusted for age, systolic blood pressure, and cigarette smoking.

Okuyama, 1996

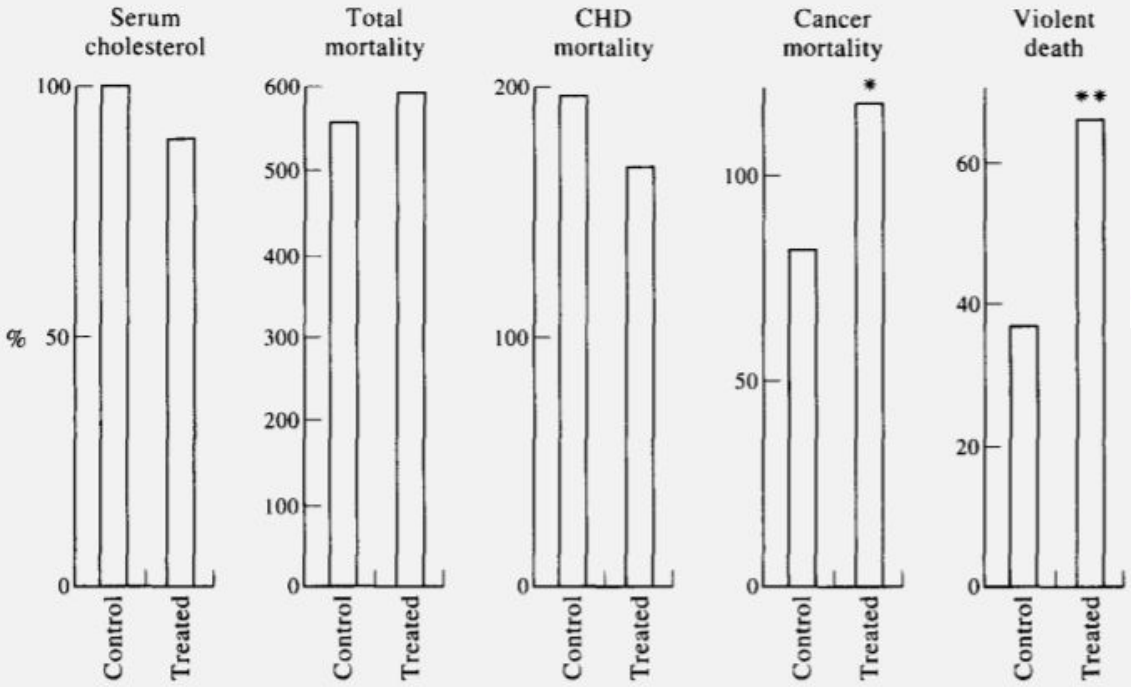


Fig. 8. Summary of intervention trials for the prevention of coronary heart disease by Muldoon *et al.*[293] The intervention trials included Los Angeles Veterans Administration study (1968), Minnesota coronary survey (1975), World Health Organization study (1978), Colestipol–Upjohn study (1978), Lipid Research Clinics coronary primary prevention trial (1984) and Helsinki heart study (1987). Serum cholesterol is shown as percentage of the control, and mortalities for the intervention ($n = 12\,457$) and control ($n = 12\,390$) group are summarized. The violent death includes those from accident, violence, trauma and suicide. Data taken from Muldoon *et al.*[293]

ELSEVIER

Progress in Lipid Research

Volume 35, Issue 4, December 1996, Pages 409-457

Dietary fatty acids — The n-6n-3 balance and chronic elderly diseases. Excess linoleic acid and relative n-3 deficiency syndrome seen in Japan

Harumi Okuyama, Tetsuyuki Kobayashi, Shiro Watanabe

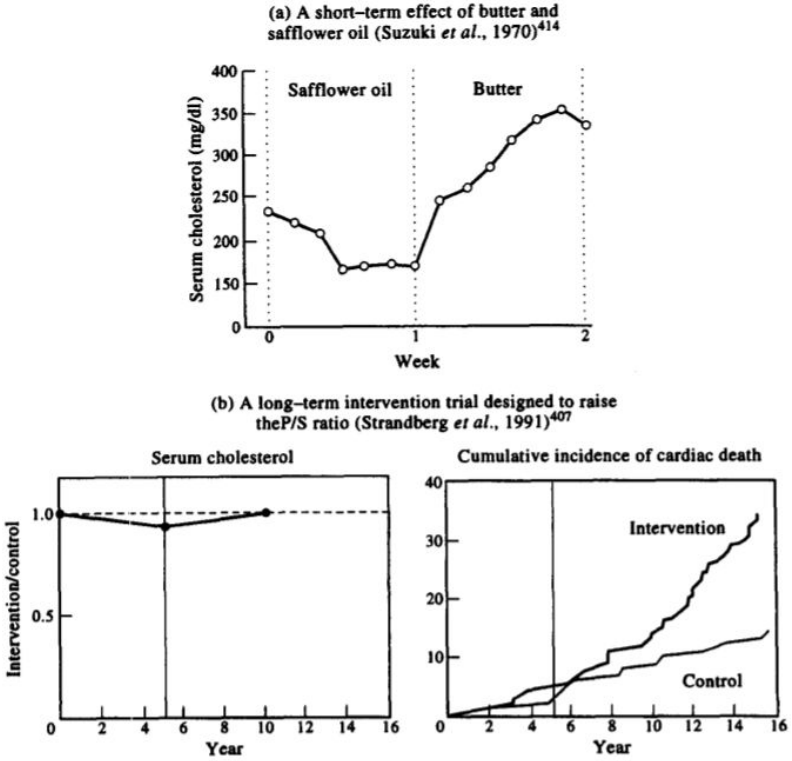


Fig. 7. Effect of animal fat and high-LA vegetable oil on plasma cholesterol and cardiac death — a short-term and long-term intervention trial. (a). A short-term effect of butter and safflower oil (Suzuki *et al.*)[414] (b). A long-term intervention trial designed to raise the P/S ratio (Strandberg *et al.*).[407]

The 15 year study in Finland reported by Strandberg *et al.*[281,407] is particularly interesting. When typical nutritional recommendations were made to decrease the intake of animal fats and high-cholesterol foods and to increase LA in the form of soft margarine, plasma cholesterol was not affected after 10 years. The incidences of cardiac and total death were not much different for up to 10 years, but the mortalities from coronary heart diseases (CHD) and all causes at 15 years were 2.4- and 1.4-fold higher in the treated group than in the control group, respectively (Fig. 7). Although hypotensive and hypocholesterolemic drugs were used for the initial 5 years, the proportions of subjects using these drugs were similarly low at 10 years, and the differences in the mortalities increased significantly after 10 years. Therefore, we suggest that it is not the drugs used but the nutritional factors (i.e. increased LA) that increased the incidence of CHD.

October 18, 1985

Multifactorial Primary Prevention of Cardiovascular Diseases in Middle-aged Men

Risk Factor Changes, Incidence, and Mortality

Tatu A. Miettinen, MD; Jussi K. Huttunen, MD; Vesa Naukkarinen, MD; et al

» Author Affiliations

JAMA. 1985;254(15):2097-2102. doi:10.1001/jama.1985.03360150073027

The subjects in the intervention group met one of the investigators every fourth month during the follow-up period of five years. During the first visit, oral and written dietary instructions were given to all participants. They were advised to reduce the intake of calories, saturated fat, cholesterol, alcohol, and sugar and to increase that of polyunsaturated fats (mainly soft margarine), fish, chicken, veal, and vegetables. A program to increase physical activity was given to every participant, and antismoking advice was given individually to all smokers. During the subsequent face-to-face visits, the participants were repeatedly given advice on diet, weight reduction, smoking cessation, and physical exercise. Serum lipid levels, blood pressure, and body weight were measured at each visit. Serum electrolyte values, blood glucose level, urinalysis, and ECG were determined when indicated.

If the blood pressure and serum lipid values were still above the target levels after four months of the trial, or if these values were found to be above the target level in two consecutive visits during the study, the drug therapy was initiated as follows. Blood pressure treatment was

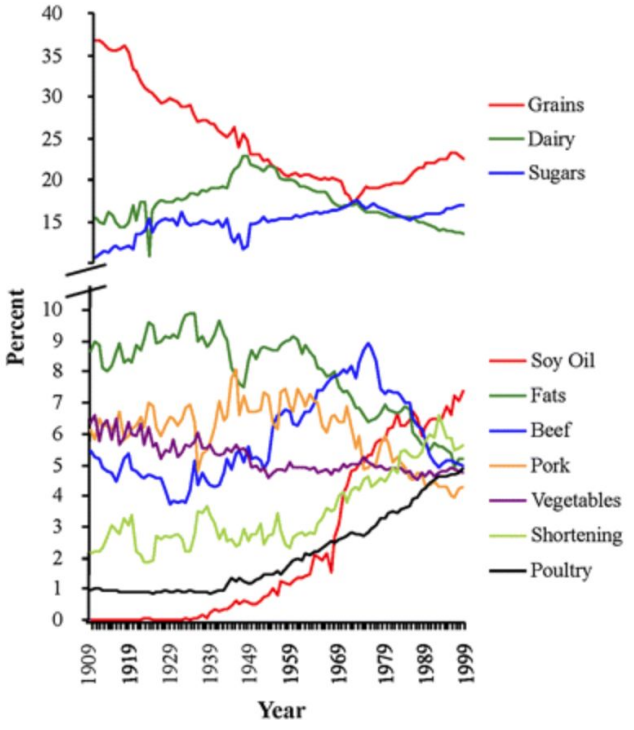
Blasbalg, 2011

TABLE 2
Estimated annual per capita consumption of foods in 1909 and 1999

Food category	Availability 1909	Availability 1999	Percentage difference
	kg		
Oils	0.7	14.7	2051
Soybean	0.01	11.6	116,300
Canola[1]	0.01	0.8	16,700
Peanut[2]	0.01	0.7	7000
Palm	0.01	0.2	1800
Corn	0.1	0.8	550
Olive	0.1	0.7	500
Coconut	0.04	0.23	475
Safflower[3]	0.04	0.05	25
Cottonseed	0.4	0.31	−21
Sunflower[4]	0.1	0.08	−27
Sesame[5]	0.07	0.05	−29
Fats	17.9	18.2	1.7
Margarine	0.3	3.6	1038
Beef tallow	0.5	2.1	371
Shortening	3.3	9	170
Butter	8.1	2.2	−73
Lard	5.8	1.3	−77
Poultry	7.8	43.2	454
Nuts	1.5	3.8	155
Shellfish	1	2.1	114
Sugars	38.3	71.9	88
Spice	4.5	7.2	63
Fruit	78.4	105.1	34
Finfish	4	4.6	16
Beef	34.6	34.7	0.4
Game	1.4	1.3	−2.7
Eggs	16.1	14.9	−7.3
Pork	28.3	24.4	−14
Dairy	143.8	121.8	−15
Vegetables	187.8	138.1	−27
Grains	135.9	92.2	−32
Legumes	6	3.9	−36
Lamb	2.7	0.5	−81

TABLE 3
Major sources of calories

Food category	Percentage contribution 1909	Percentage contribution 1999	Percentage difference
Soybean oil	0.006	7.38	123,810
Poultry	0.94	4.94	426
Spice	0.22	0.85	277
Oils	0.44	1.55	250
Shellfish	0.06	0.15	163
Shortening	2.17	5.67	161
Nuts	0.65	1.62	149
Sugars	10.64	16.95	59
Fruit	2.52	3.36	33
Game	0.12	0.12	0
Beef	5.46	4.98	−9
Eggs	1.56	1.4	−10
Dairy	15.44	13.54	−12
Finfish	0.47	0.39	−16
Vegetables	6.35	4.75	−25
Pork	6.18	4.28	−31
Grains	36.75	22.43	−39
Fats	8.63	5.22	−39
Legumes	0.98	0.35	−64
Lamb	0.42	0.07	−83
Total	100	100	—



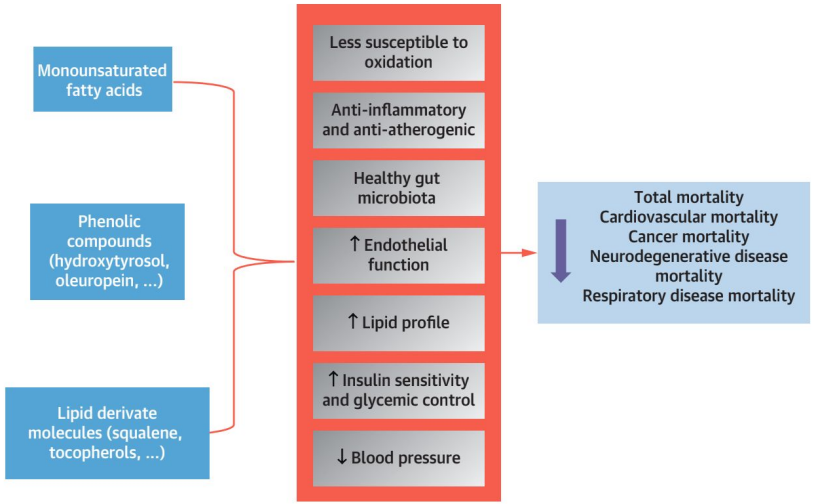
USDA Loss-Adjusted Data

Average daily per capita calories from the U.S. food availability, adjusted for spoilage and other waste

Year	Meat, eggs, and nuts	Dairy	Fruit	Vegetables	Flour and cereal products**	Added fats and oils and dairy fats*	Sugar and sweeteners (Added)	Total
1970	509	250	71	135	410	346	333	2,054
1971	516	251	73	133	404	342	335	2,054
1972	515	249	69	133	399	353	339	2,057
1973	486	247	72	133	411	357	340	2,046
1974	503	241	73	128	406	349	329	2,028
1975	494	240	76	132	416	351	318	2,025
1976	516	241	77	132	430	367	335	2,099
1977	512	240	78	132	417	353	342	2,074
1978	506	239	78	127	427	364	339	2,079
1979	501	237	77	130	431	372	342	2,089
1980	496	233	83	127	437	372	335	2,084
1981	501	231	79	126	437	370	334	2,079
1982	495	234	81	129	436	372	328	2,076
1983	505	238	88	131	438	387	333	2,120
1984	509	242	85	131	448	402	340	2,157
1985	518	246	86	134	476	424	352	2,236
1986	515	247	89	136	490	431	347	2,256
1987	511	249	91	134	513	427	359	2,284
1988	517	245	89	135	526	433	363	2,308
1989	508	241	91	136	521	413	358	2,268
1990	501	241	88	136	541	411	369	2,287
1991	504	241	87	143	543	419	370	2,307
1992	512	241	91	142	551	433	378	2,347
1993	509	237	93	146	567	453	386	2,392
1994	514	240	94	146	571	443	394	2,402
1995	512	239	91	146	567	434	401	2,388
1996	509	237	93	150	588	424	403	2,404
1997	508	236	94	146	589	427	413	2,412
1998	521	235	95	143	582	425	416	2,419
1999	538	238	98	146	586	444	423	2,472
2000*	534	237	94	146	596	537	415	2,561
2001	530	236	92	146	584	548	410	2,546
2002	546	237	91	141	573	577	408	2,574
2003	547	237	92	146	575	575	394	2,566
2004	554	238	92	143	570	573	395	2,566
2005	546	238	90	137	571	573	396	2,551
2006	550	237	89	139	580	571	387	2,554
2007	548	237	89	138	589	584	377	2,562
2008	534	234	86	131	586	594	378	2,543
2009	527	237	84	126	580	551	363	2,469
2010	526	235	86	130	581	575	367	2,501

Guasch-Ferré, 2022

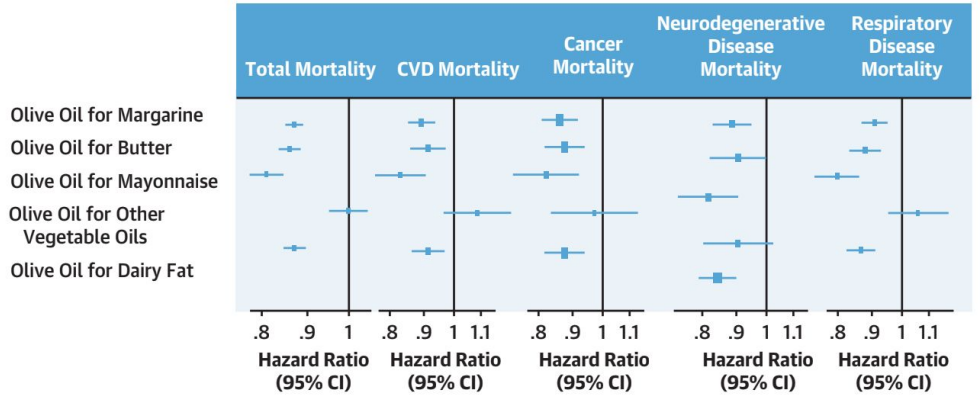
CENTRAL ILLUSTRATION Potential Mechanisms for Olive Oil Intake and Mortality



Guasch-Ferré, M. et al. J Am Coll Cardiol. 2022;79(2):101-112.

Olive oil is high in bioactive compounds and has been associated with lower risk of total and cause-specific mortality in 2 prospective cohorts including 92,383 U.S. men and women followed-up for up to 28 years. Potential mechanisms of these associations include olive oil being less susceptible to oxidation; having anti-inflammatory and antiatherogenic properties; and improving oxidative stress, endothelial function, lipid profile, insulin sensitivity, and blood pressure. ↑ = improvement; ↓ = worsening.

FIGURE 1 Mortality Associated With Olive Oil Substituted for Other Fats



HR (95% CI) for mortality substituting 10 g of olive oil for equivalent amount of other fats. Model was adjusted for age, ethnicity, ancestry, married, living alone, smoking status, alcohol intake, physical, family history of diabetes, myocardial infarction or cancer, multivitamin use, aspirin use, in women postmenopausal status and menopausal hormone use, energy intake, body mass index, red meat, fruits and vegetables, nuts, soda, whole grains, and the intake of trans fat, and mutually adjusted for the intake of other types of fat. Results were pooled using a pooled dataset and stratifying by cohort and time period. CVD = cardiovascular disease.

Goldstein, 1979

Proc Natl Acad Sci U S A. 1979 Jan; 76(1): 333–337.
doi: 10.1073/pnas.76.1.333
PMCID: PMC382933
PMID: 218198

Binding site on macrophages that mediates uptake and degradation of acetylated low density lipoprotein, producing massive cholesterol deposition

Joseph L. Goldstein, Y. K. Ho, Sandip K. Basu, and Michael S. Brown

The physiologic significance, if any, of the acetyl-LDL uptake system in macrophages *in vivo* is not yet known. However, the demonstration that uptake of acetyl-LDL through this binding site leads to massive cellular deposition of cholesterol raises the possibility that this receptor may be responsible for the accumulation of LDL-derived cholesteryl esters in macrophages and other scavenger cells that occurs throughout the body in patients with familial hypercholesterolemia. Support for this hypothesis will require the demonstration that native LDL can be converted in the body into a form that is recognized by the acetyl-LDL binding site. Although *in vivo* acetylation of plasma LDL seems unlikely at this point, some chemical or physical alteration of LDL occurring in plasma or interstitial fluid may make it susceptible to recognition by the macrophage binding site.

Steinberg, 1989

MECHANISMS OF DISEASE

FRANKLIN H. EPSTEIN, M.D., *Editor*

BEYOND CHOLESTEROL

Modifications of Low-Density Lipoprotein That Increase Its Atherogenicity

DANIEL STEINBERG, M.D., PH.D.,
SAMPATH PARTHASARATHY, PH.D.,
THOMAS E. CAREW, PH.D., JOHN C. KHOO, PH.D.,
AND JOSEPH L. WITZTUM, M.D.

ELEVATED LDL LEVELS AND THE FATTY STREAK — A HYPOTHESIS INVOLVING OXIDATIVE MODIFICATION

These newer findings about the properties of oxidized LDL, together with the information available from experimental pathology and cell biology of the macrophage, make it possible to propose a hypothesis about the development of the fatty-streak lesion that is based solely on the presence of elevated plasma LDL levels plus the oxidative modification of LDL within the artery wall.[64] This hypothesis is constructed on four potentially atherogenic effects of oxidized LDL (Fig. 2): chemotactic activity, facilitating the recruitment of circulating monocytes; inhibition of the migration of macrophages from within the artery back to the plasma compartment; enhanced uptake of LDL by macrophages through the acetyl LDL receptor, leading to the generation of foam cells; and cytotoxicity, possibly facilitating the entry of LDL or monocytes in the early stages and leading to frank endothelial denudation later.

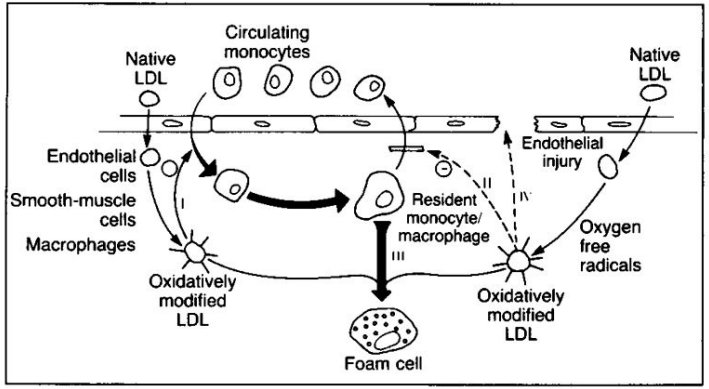


Figure 2. Four Mechanisms by Which the Oxidation of LDL (Catalyzed by Endothelial Cells, Smooth-Muscle Cells, or Macrophages) May Contribute to Atherogenesis.

Mechanisms are the recruitment of circulating monocytes by means of the chemotactic factor present in oxidized LDL, but absent in native LDL (I); inhibition by oxidized LDL of the motility of resident macrophages and therefore of their ability to leave the intima (II); enhanced rate of uptake of oxidized LDL by resident macrophages, leading to the generation of foam cells (III); cytotoxicity of oxidized LDL, leading to loss of endothelial integrity (IV). Reproduced from Quinn et al.[55] with the permission of the publisher.

Does Oxidation of LDL Occur in Vivo?

For several reasons, it seems that the oxidation of LDL probably occurs not in the circulation but within the artery wall. First, even if oxidized LDL were generated in the plasma, it would be swept up within minutes by the liver.[24,40,65] Second, oxidation is inhibited by plasma and so probably requires the favorable conditions of a sequestered microenvironment. An analogy may be made to the manner in which immunologic killer cells act on their victims, by creating a microenvironment between themselves and the target. In that microenvironment, between the plasma membranes of aggressor and victim, the concentrations of toxic factors can be very high indeed. By analogy, the LDL molecule in the subendothelial space may find itself from time to time trapped in a space between cells where antioxidant levels are low.

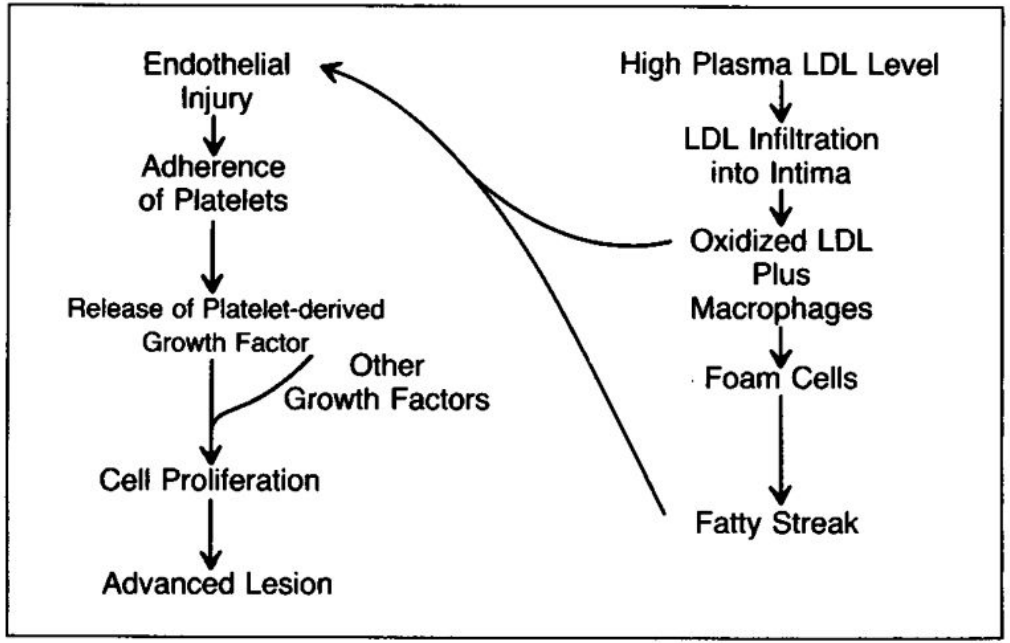


Figure 3. Postulated Linkage between the Lipid-Infiltration Hypothesis and the Endothelial-Injury Hypothesis.

Witztum, 1991

Overview of the concept of oxidative modification of LDL

There can be no doubt now that there is a continuum of increasing risk for complications of atherosclerosis when plasma cholesterol levels exceed ~ 160–180 mg/dl. Many types of experimental and clinical evidence substantiate the "cholesterol hypothesis." Many primary and secondary prevention trials, including the recent angiographic trials (CLAS and FATS) document that reduction of plasma cholesterol is as powerful as has been predicted in slowing the progression and clinical expression of coronary atherosclerosis. However, the cellular and molecular mechanisms linking hypercholesterolemia to atherogenesis and its sequelae remain unclear.

If lowering of LDL is efficacious in ameliorating the atherogenic process, why then should one bother to understand the mechanisms? Simply because lowering LDL will not be a total solution. Although it may be true that if cholesterol levels were reduced to < 150 mg/dl there would be little if any coronary artery disease (CAD),[1] it is not likely that this will occur any time soon. At any given level of LDL there is great variability in

Research Article Free access | 10.1172/JCI115499

Role of oxidized low density lipoprotein in atherogenesis.

J L Witztum and D Steinberg

Published December 1, 1991 - More info

Evidence for the presence in vivo of Ox-LDL

The evidence for the presence in vivo of Ox-LDL has been reviewed elsewhere in some detail and will not be elaborated extensively (1, 2). It should be noted that to date the evidence for the presence of Ox-LDL is confined to atherosclerotic tissue. Immunocytochemical techniques have demonstrated the presence in arterial lesions, but not in normal arteries, of epitopes found in Ox-LDL. LDL extracted from arterial lesions

We have assumed that the oxidative modification occurs primarily in the intima, in microdomains sequestered from the many plasma antioxidants. We have reasoned that significant degrees of oxidative modification of LDL do not take place in plasma because of its high antioxidant content. Furthermore, our in vivo studies in guinea pigs showed that even very slight degrees of oxidation of LDL (not sufficient to increase in vitro uptake in macrophages) nevertheless led to more rapid removal of the LDL from plasma, presumably by scavenger receptors present on sinusoidal cells of the liver (2). However, plasma LDL could undergo limited degrees of oxidation, that would have no consequences while still in the vascular space; yet, when such LDL entered the intima, it might then be "primed" for more rapid oxidative modification mediated by cells. In fact, there are numerous reports in the literature sug-

Thus, we now can understand how hyperlipoproteinemia could of itself be a sufficient basis for initiating the atherosclerotic process in all its manifestations, including the cellular proliferation and matrix deposition. As recently shown in vitro, components of oxidized lipid can also stimulate collagen gene expression, at least in fibroblasts (51). Thus, there could be a link between matrix formation and oxidation as well. As already mentioned, many additional factors undoubtedly affect the rate and extent of lesion progression at any level of hyperlipoproteinemia and much remains to be learned in this connection. Finally, we can now see that the accumulation of lipid per se, while certainly contributing to the plaque and the narrowing of the vessel's lumen, nevertheless need not be directly contributing in a major way to the early "pathogenesis" of the fatty streak. The damage may be done primarily by oxidized LDL (or its oxidation products) before or coincident with the delivery of lipid to arterial cells.

Factors potentially affecting the oxidation of LDL in vivo

While evidence continues to accumulate supporting an important role for oxidative modification in atherogenesis, ultimately a clinical test of this hypothesis in man will be needed to demonstrate that inhibition of oxidation of LDL will inhibit the atherogenic process. To design effective clinical trials, one must understand those factors responsible for LDL oxidation in vivo. Conceptually, one can group such factors into two classes: first, those intrinsic to LDL, i.e., compositional and structural factors increasing or decreasing susceptibility of a given LDL to oxidation; and second, those extrinsic to LDL, i.e., factors in plasma or tissues that promote or inhibit oxidation of LDL (Table II).

Reaven, 1993

The results demonstrate quite clearly that the fatty acids in LDL that are most readily oxidized are 18:2 and 20:4. Oxidation of 18:1 also occurs, but to a lesser extent. Furthermore, the oxidation of 18:1 generates a relatively stable product, which, unlike polyunsaturated fatty acids, can generate only trace amounts of reactive aldehydes. Linoleic acid comprises from 35 to 50% of the total fatty acids in LDL and nearly 90% of the polyunsaturated fatty acids. The high content of 18:2 in LDL, its great abundance in the LDL core, and its capacity to easily undergo oxidation generating a wide array of reactive aldehydes and other products give this fatty acid a key role in LDL peroxidation. This study demonstrates that changes in dietary fatty acids can significantly alter LDL fatty acid composition in mildly hypercholesterolemic subjects. These are the individuals likely to benefit the most from dietary intervention. By decreasing the ratio of 18:2 to 18:1 in their LDL, it becomes less susceptible to in vitro oxidation and modification. It remains to be demonstrated that more practical diets can lead to similar findings and that this form of dietary intervention can slow or inhibit the development of atherosclerosis. Nevertheless, this study supports the concept that replacement of saturated fat with monounsaturated fat may reduce the risk for coronary artery disease both by lowering LDL levels and by decreasing the susceptibility of the LDL to oxidative modification.

> J Clin Invest. 1993 Feb;91(2):668-76. doi: 10.1172/JCI116247.

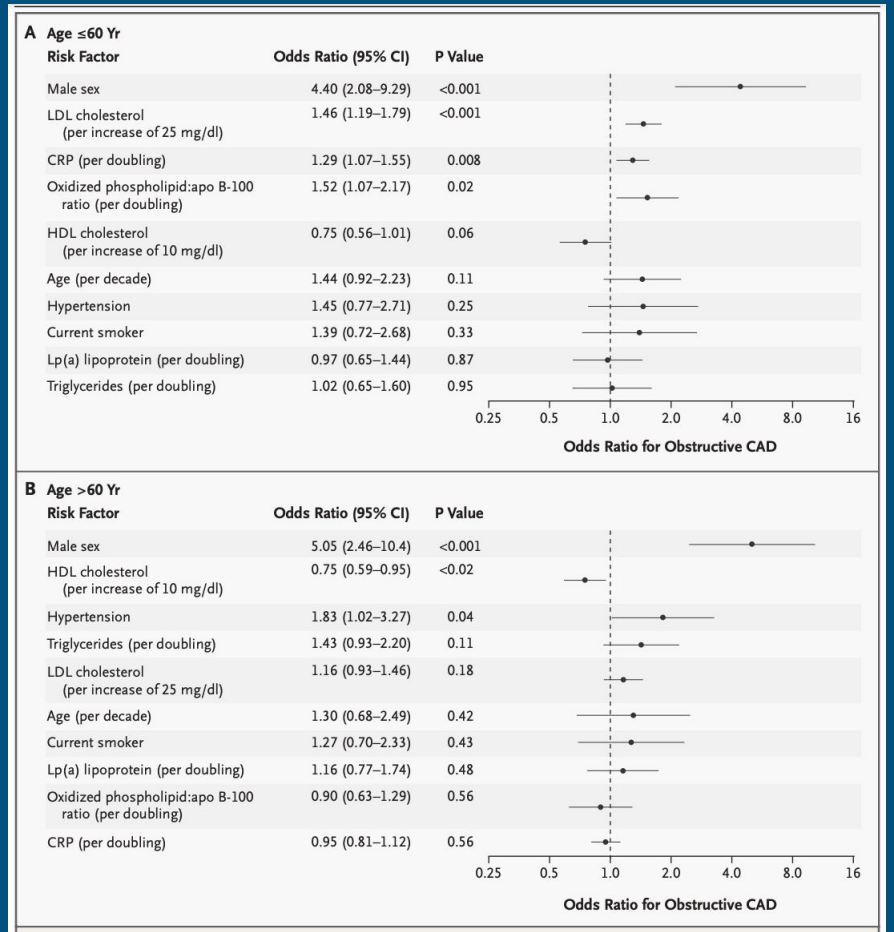
Effects of oleate-rich and linoleate-rich diets on the susceptibility of low density lipoprotein to oxidative modification in mildly hypercholesterolemic subjects

P Reaven [1], S Parthasarathy, B J Grasse, E Miller, D Steinberg, J L Witztum

Affiliations + expand

PMID: 8432867 PMCID: PMC288008 DOI: 10.1172/JCI116247

Tsimikas, 2005



A Age ≤60 Yr

Risk Factor	Odds Ratio (95% CI)	P Value
Male sex	4.40 (2.08–9.29)	<0.001
LDL cholesterol (per increase of 25 mg/dl)	1.46 (1.19–1.79)	<0.001
CRP (per doubling)	1.29 (1.07–1.55)	0.008
Oxidized phospholipid:apo B-100 ratio (per doubling)	1.52 (1.07–2.17)	0.02
HDL cholesterol (per increase of 10 mg/dl)	0.75 (0.56–1.01)	0.06
Age (per decade)	1.44 (0.92–2.23)	0.11
Hypertension	1.45 (0.77–2.71)	0.25
Current smoker	1.39 (0.72–2.68)	0.33
Lp(a) lipoprotein (per doubling)	0.97 (0.65–1.44)	0.87
Triglycerides (per doubling)	1.02 (0.65–1.60)	0.95

0.25 0.5 1.0 2.0 4.0 8.0 16

Odds Ratio for Obstructive CAD

B Age >60 Yr

Risk Factor	Odds Ratio (95% CI)	P Value
Male sex	5.05 (2.46–10.4)	<0.001
HDL cholesterol (per increase of 10 mg/dl)	0.75 (0.59–0.95)	<0.02
Hypertension	1.83 (1.02–3.27)	0.04
Triglycerides (per doubling)	1.43 (0.93–2.20)	0.11
LDL cholesterol (per increase of 25 mg/dl)	1.16 (0.93–1.46)	0.18
Age (per decade)	1.30 (0.68–2.49)	0.42
Current smoker	1.27 (0.70–2.33)	0.43
Lp(a) lipoprotein (per doubling)	1.16 (0.77–1.74)	0.48
Oxidized phospholipid:apo B-100 ratio (per doubling)	0.90 (0.63–1.29)	0.56
CRP (per doubling)	0.95 (0.81–1.12)	0.56

0.25 0.5 1.0 2.0 4.0 8.0 16

Odds Ratio for Obstructive CAD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oxidized Phospholipids, Lp(a) Lipoprotein, and Coronary Artery Disease

Sotirios Tsimikas, M.D., Emmanouil S. Brilakis, M.D., Elizabeth R. Miller, B.S., Joseph P. McConnell, Ph.D., Ryan J. Lennon, M.S., Kenneth S. Kornman, Ph.D., Joseph L. Witztum, M.D., and Peter B. Berger, M.D.

Wu, 2006

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Vol. 48, No. 5, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.03.057

Atherosclerosis

Is Plasma Oxidized Low-Density Lipoprotein, Measured With the Widely Used Antibody 4E6, an Independent Predictor of Coronary Heart Disease Among U.S. Men and Women?

Tianying Wu, MD, PhD,* Walter C. Willett, MD, DrPh,*†‡ Nader Rifai, PhD,‖ Iris Shai, PhD,* JoAnn E. Manson, MD, DrPh,†‡§ Eric B. Rimm, ScD*†‡

Boston, Massachusetts

Table 4. OxLDL in Comparison With Mutually Adjusted ApoB or Total/HDL Cholesterol Ratio in Multivariate Models

	Mutually Adjusted Marker 1			Mutually Adjusted Marker 2		
	Marker	RR (95% CI)	p_{LRT}	Marker	RR (95% CI)	p_{LRT}
Men	OxLDL	1.31 (0.67–2.57) p for linear trend = 0.3	0.5	ApoB	2.80 (1.44–5.44) p for linear trend = 0.0003	0.004
	OxLDL	1.70 (0.93–3.13) p for linear trend = 0.03	0.1	Total/HDL cholesterol ratio	2.82 (1.48–5.38) p for linear trend = 0.0001	0.002
Women	OxLDL	1.75 (0.77–4.01) p for linear trend = 0.1	1.0	ApoB	2.67 (1.09–6.53) p for linear trend = 0.02	0.06
	OxLDL	1.17 (0.51–2.68) p for linear trend = 0.3	0.2	Total/HDL cholesterol ratio	4.30 (1.76–10.52) p for linear trend = 0.0004	0.002

Multivariates included: body mass index, physical activity, alcohol consumption, history of high blood pressure, high cholesterol and diabetes, family history of myocardial infarction, and use of aspirin. The p value of the likelihood ratio test (LRT) is for adding the corresponding marker to the model; it compares the model with corresponding marker with the model without the corresponding marker with 4 def. Each marker is added to the model in quintiles with 4 dummy variables.

RR = relative risk in the highest compared with the lowest quintile of each marker; Ox = oxidized; other abbreviations as in Tables 1 to 3.

Obesity, the metabolic syndrome, and oxidized LDL

Paul Holvoet

The American Journal of Clinical Nutrition, Volume 83, Issue 6, June 2006, Page 1438,
https://doi.org/10.1093/ajcn/83.6.1438

Published: 01 June 2006

Knopp and Paramsothy concluded that the study by Weinbrenner et al showed an increase in immunologically detected epitopes of lipid peroxides in the LDLs of persons with abdominal obesity. However, Weinbrenner et al measured circulating concentrations of oxidized LDL with an enzyme-linked immunosorbent assay procedure that uses the monoclonal antibody 4E6 (Mercodia AB, Uppsala, Sweden). Because this antibody was developed in my laboratory (3), I would like to correctly describe the characteristics of this monoclonal antibody. It is directed against a conformational epitope in the apolipoprotein B-100 moiety of LDL that is generated as a consequence of the substitution of ≥60 lysine residues of apolipoprotein B-100 with aldehydes. This number of substituted lysines corresponds to the minimum number required for scavenger-mediated uptake of oxidized LDL. Substituting aldehydes can be produced by peroxidation of lipids of LDL, which results in the generation of oxidized LDL. However, lipid peroxidation is not required. Indeed, aldehydes that are released by endothelial cells under oxidative stress or by activated platelets may also induce the oxidative modification of apolipoprotein B-100 in the absence of peroxidation of lipids of LDL.

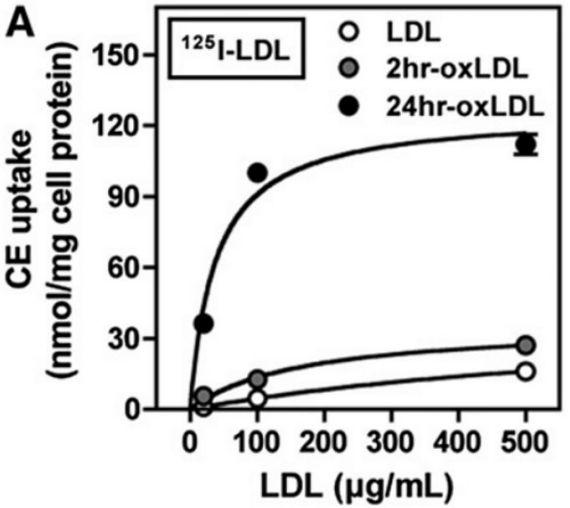
J Lipid Res. 2014 Aug;55(8):1648-56. doi: 10.1194/jlr.M044644. Epub 2014 Jun 2.

Minimally oxidized LDL inhibits macrophage selective cholesteryl ester uptake and native LDL-induced foam cell formation

Jason M Meyer [1], Ailing Ji [2], Lei Cai [2], Deneys R van der Westhuyzen [2]

Affiliations + expand

PMID: 24891335 PMCID: PMC4109759 DOI: 10.1194/jlr.M044644



Carmena, 1996

Atherosclerosis
Volume 125, Issue 2, 6 September 1996, Pages 243-255

Research paper

Effect of olive and sunflower oils on low density lipoprotein level, composition, size, oxidation and interaction with arterial proteoglycans

Rafael Carmena [a], Juan F. Ascaso [a], Germán Camejo [b, c], Gregorio Varela [d], Eva Hurt-Camejo [c], JoséM. Ordovas [e], José Martinez-Valls [a], Monica Bergström [b], Boel Wallin [b]

Table 2
Fat and antioxidant content of the diets during the two experimental periods

Parameter	Sunflower seed oil	Olive oil
SFA, g/d (% daily energy)	18.4 ± 2.5 (6.8)	19.0 ± 3.3 (6.9)
MUFA, g/d (% daily energy)	30.0 ± 4.4 (10.9)	59.0 ± 6.3 (21.6)
PUFA, g/d (% daily energy)	36.6 ± 4.6 (13.3)	11.1 ± 1.4 (4.7)
Total fat, g/d (% daily energy)	85.0 (31)	89.6 (30.5)
Total MUFA + PUFA g/d (% daily energy)	66.6 (24.2)	70.6 (25.6)
Vitamin E, mg/d	27.0 ± 3.7	9.1 ± 1.4
Beta-carotenes, μg/d	6540.0 ± 705.0	4179.0 ± 795.4
Vitamin C, mg/d	261.9 ± 64.9	120.0 ± 60.6

Values are means ± SD (% contribution to total daily energy)

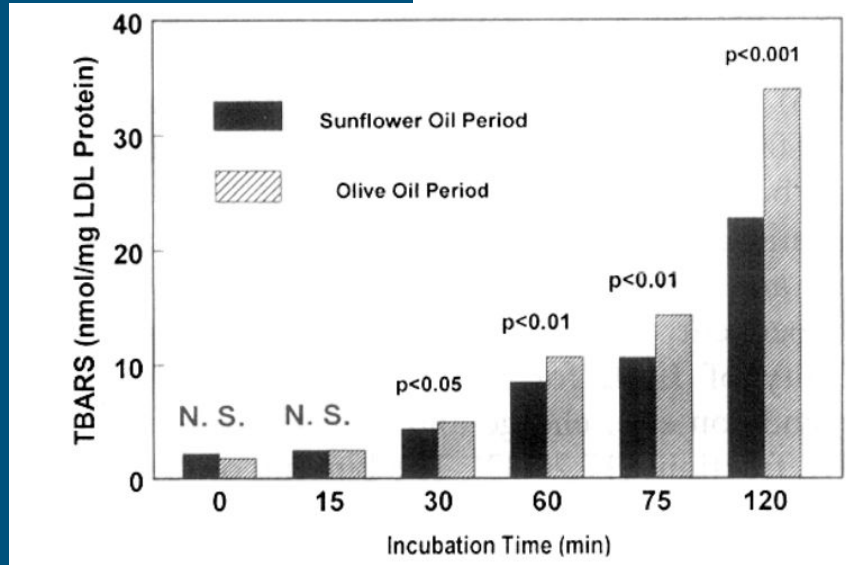


Fig. 1. Kinetics of copper-catalyzed oxidation of LDL isolated at the end of the sunflower and olive oil dietary periods.

Palomäki, 2010

Research | Open Access | Published: 01 December 2010

Effects of dietary cold-pressed turnip rapeseed oil and butter on serum lipids, oxidized LDL and arterial elasticity in men with metabolic syndrome

Ari Palomäki, Hanna Pohjantähti-Maaroos ✉, Marja Wallenius, Päivi Kankkunen, Heikki Aro, Sari Husgafvel, Juha-Matti Pihlava & Kalevi Oksanen

Lipids in Health and Disease **9**, Article number: 137 (2010) | Cite this article

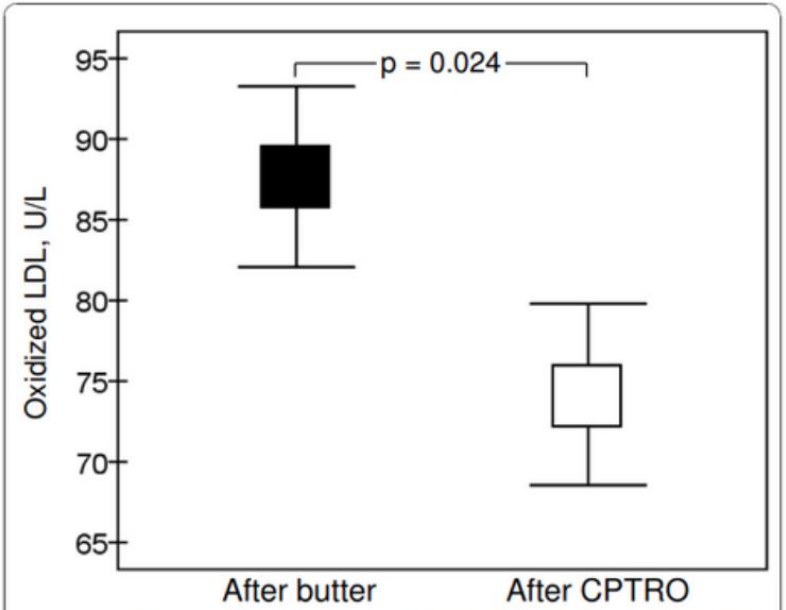


Figure 2 Plasma concentration of oxidized LDL at the end of fat supplementation periods. OxLDL was 87.7 ± 5.6 U/L after the butter and 74.2 ± 5.6 U/L after the CPTRO (cold-pressed turnip rapeseed oil) period (p = 0.024).

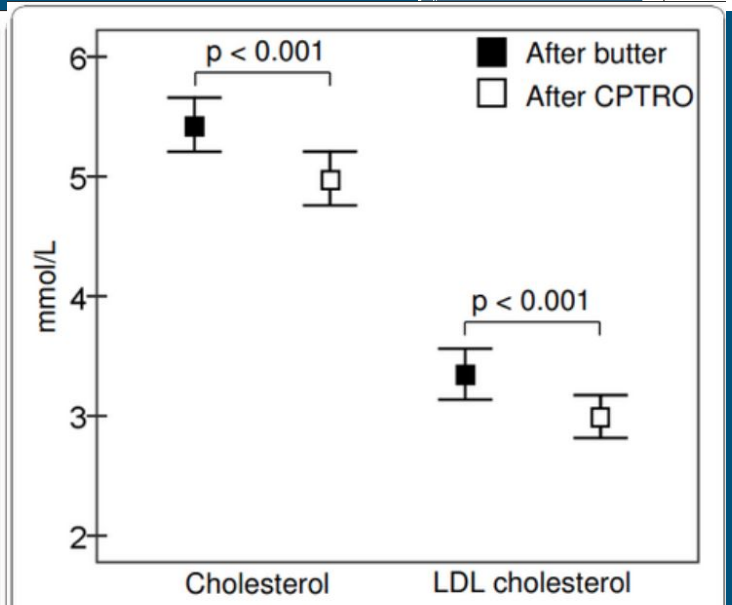


Figure 3 Concentrations of total and LDL cholesterol. Total cholesterol was 5.43 ± 0.23 mmol/L at the end of the butter and 4.98 ± 0.23 mmol/L at the end of the CPTRO (cold-pressed turnip rapeseed oil) period (p < 0.001). LDL cholesterol was 3.35 ± 0.21 mmol/L and 3.00 ± 0.18 mmol/L, respectively (p < 0.001).

Tsouli, 2006

Measurement of OxLDL levels

Plasma levels of OxLDL were measured by a competitive enzyme-linked immunosorbent assay using a specific murine monoclonar antibody (4E6) according to the instructions provided by the manufacturer (Mersodia, Uppsala, Sweden). The specificity of this method was studied by performing the assay in five different plasma samples in which 5 or 15 ng of protein of native LDL or $OxLDL_D$ was added exogenously. Intra-assay and interassay coefficients of variation of the assay were 6.0% and 7.0%, respectively.

RESEARCH ARTICLE | VOLUME 47, ISSUE 10, P2208-2214,
Journal of Lipid Research
PDF [128 KB] Figures

Autoantibody titers against OxLDL are correlated with Achilles tendon thickness in patients with familial hypercholesterolemia

Sofia G. Tsouli • Dimitrios N. Kiortsis • Evangelia S. Lourida • ... Maria I. Argyropoulou • Moses Elisaf
Alexandros D. Tselepis • Show all authors

Open Access • DOI: https://doi.org/10.1194/jlr.M600109-JLR200

OxLDL levels

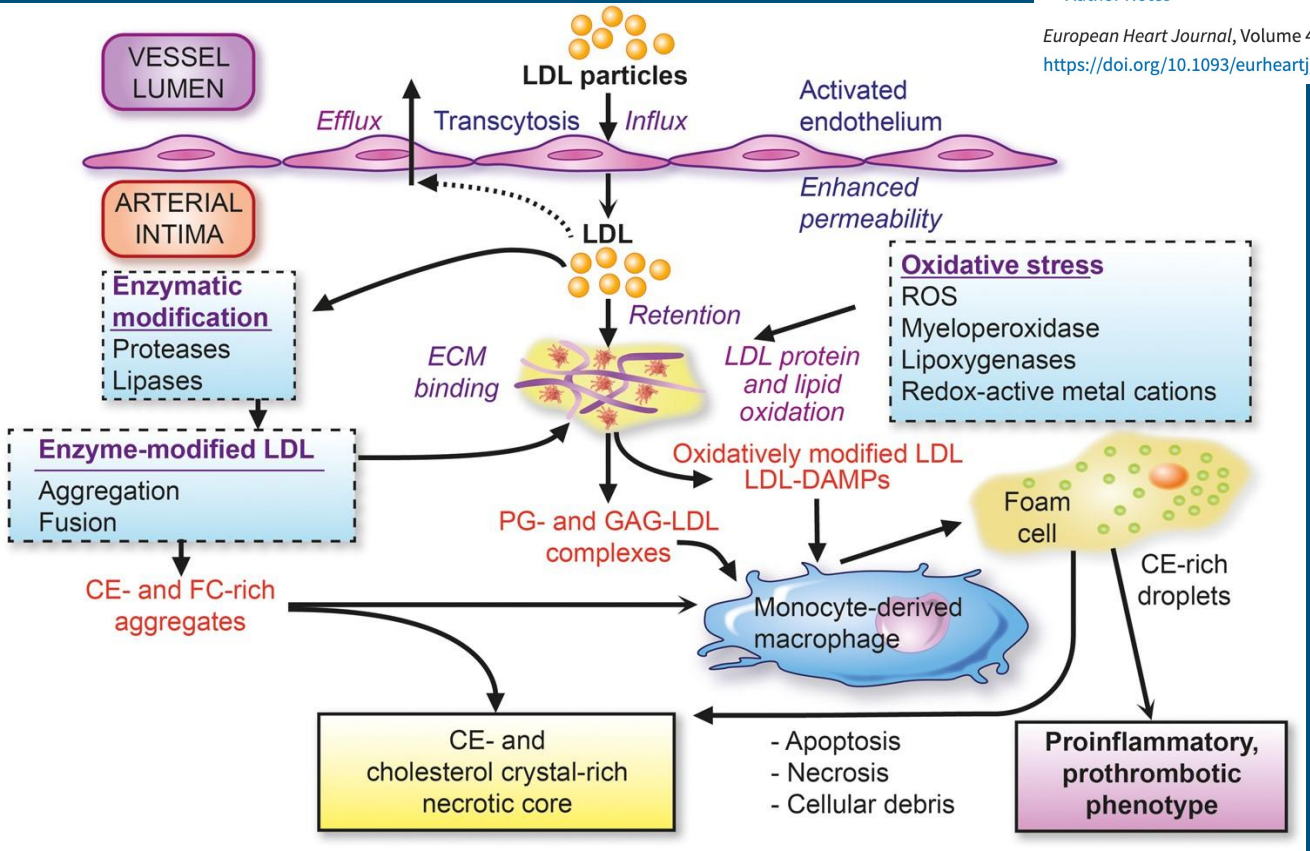
FH patients exhibited significantly higher plasma OxLDL levels than controls. The ratio of OxLDL to apoB-100 (i.e., the proportion of oxidized apoB-100 to total apoB-100) was also significantly higher in FH patients compared with controls (Table 1). OxLDL was positively correlated with total cholesterol ($r = 0.48$, $P = 0.004$), LDL-cholesterol ($r = 0.471$, $P = 0.005$), and apoB-100 ($r = 0.653$, $P = 0.001$).

Borén, 2020

Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel

Jan Borén, M John Chapman ✉, Ronald M Krauss, Chris J Packard, Jacob F Bentzon, Christoph J Binder, Mat J Daemen, Linda L Demer, Robert A Hegele, Stephen J Nicholls ... Show more
Author Notes

European Heart Journal, Volume 41, Issue 24, 21 June 2020, Pages 2313–2330,
https://doi.org/10.1093/eurheartj/ehz962



Low-density lipoprotein as the primary driver of atherogenesis

All LDL particles exert atherogenicity to variable degrees, which can be influenced by the proteome, lipidome, proteoglycan binding, aggregability, and oxidative susceptibility.[64,96,97] The atherogenic actions of LDL in arterial tissue have multiple origins. Broadly, these encompass:

(1) Formation of macrophage-derived foam cells upon phagocytic uptake of aggregated LDL particles, or LDL in which lipid and/or protein components have undergone covalent modification, triggering uptake by scavenger receptors. Aggregation may occur by non-enzymatic or enzymatically induced mechanisms. Oxidation of lipids (phospholipids, cholesteryl esters, and cholesterol) or apoB100 can occur enzymatically (e.g. by myeloperoxidase) or non-enzymatically (e.g. by reactive oxygen species liberated by activated endothelial cells or macrophages).

(2) Release of bioactive proinflammatory lipids (e.g. oxidized phospholipids) or their fragments (e.g. short-chain aldehydes) subsequent to oxidation, which may exert both local and systemic actions.

(3) Formation of extracellular lipid deposits, notably cholesterol crystals, upon particle denaturation.

(4) Induction of an innate immune response, involving damage-associated molecular patterns (DAMPs, notably oxidation-specific epitopes and cholesterol crystals). Damage-associated molecular patterns promote recruitment of immuno-inflammatory cells (monocyte-macrophages, neutrophils, lymphocytes, and dendritic cells) leading to local and potentially chronic inflammation that can induce cell death by apoptosis or necrosis, thereby contributing to necrotic core formation.

(5) Induction of an adaptive immune response subsequent to covalent modification of apoB100 by aldehydes or apoB100 degradation with the activation of antigen-specific T-cell responses and antibodies.[114–118]

Beyond LDL, additional apoB-containing lipoproteins (<70 nm diameter) can exacerbate the atherogenic process; these include Lp(a) (which is composed of apo(a) covalently linked to the apoB of LDL and is a major carrier of proinflammatory oxidized phospholipids) and cholesterol-enriched remnant particles metabolically derived from TGRL.[6,7,11,13,26,119] Whereas the classic TG-poor LDL requires modification for efficient uptake by arterial macrophages, remnant particles are taken up by members of the LDL receptor family in their native state.[107,120] There is also evidence that LPL-mediated hydrolysis of TG from incoming remnant particles enhances the inflammatory response of arterial macrophages,[121,122] and that the internalization of remnants induces lysosomal engorgement and altered trafficking of lipoprotein cholesterol within the cell,[123] thus inducing endoplasmic reticulum stress and activation of apoptosis disproportionate to the cholesterol cargo delivered.

Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel

Jan Borén, M John Chapman ✉, Ronald M Krauss, Chris J Packard, Jacob F Bentzon, Christoph J Binder, Mat J Daemen, Linda L Demer, Robert A Hegele, Stephen J Nicholls ... Show more

Author Notes

European Heart Journal, Volume 41, Issue 24, 21 June 2020, Pages 2313–2330,
https://doi.org/10.1093/eurheartj/ehz962

All LDL particles exert atherogenicity to variable degrees, which can be influenced by the proteome, lipidome, proteoglycan binding, aggregability, and oxidative susceptibility.[64,96,97] The atherogenic actions of LDL in arterial tissue have multiple origins. Broadly, these encompass:

Review > Curr Opin Lipidol. 2004 Feb;15(1):19-24.
doi: 10.1097/00041433-200402000-00005.

Associations of low density lipoprotein particle composition with atherogenicity

Aaron T Lada [1], Lawrence L Rudel

Affiliations + expand

PMID: 15166804 DOI: 10.1097/00041433-200402000-00005

Other than size, compositional factors can alter the susceptibility of LDL particles to oxidation. Enrichment of LDL particles with n-6 polyunsaturated fatty acids leads to an increased susceptibility of LDL to oxidation in vitro [68]. However, the increased susceptibility to in-vitro oxidation of n-6 fatty acid-enriched LDL has not been shown to be associated with an increased CHD risk. Typically, a reduction in CHD susceptibility results when polyunsaturated fatty acids are more abundant [69–71]. Studies have shown that enrichment with n-3 fatty acids lead to decreased LDL oxidation [72] – a finding confirmed in a recent study [73], which showed that n-3-enriched LDL was less susceptible to oxidation and led to decreased apoptosis in macrophages. In addition, the enrichment of LDL with monounsaturated fatty acids is usually associated with decreased in-vitro oxidation compared with LDL enriched with n-6 polyunsaturated fatty acids [68,74]. However, data from animal studies suggest that monounsaturated fatty acids are more atherogenic than n-6 polyunsaturated fatty acids [75–77]. In summary, the available data do not consistently support an association between the susceptibility of LDL particles to in-vitro measures of oxidation and CHD risk. The validity of the argument that sdLDL are more atherogenic because of an increased tendency to undergo in-vitro oxidation is questioned.

Factors affecting retention of low-density lipoprotein in the artery wall

Subendothelial accumulation of LDL at lesion-susceptible arterial sites is mainly due to selective retention of LDL in the intima, and is mediated by interaction of specific positively charged amino acyl residues (arginine and lysine) in apoB100 with negatively charged sulfate and carboxylic acid groups of arterial wall proteoglycans.[49] Genetic alteration of either the proteoglycan-binding domain of apoB100 or the apoB100-binding domain of arterial wall proteoglycans greatly reduces atherogenesis.[49,50] Thus, the atherogenicity of LDL is linked to the ability of its apoB100 moiety to interact with arterial wall proteoglycans,[50,51] a process influenced by compositional changes in both the core and surface of the LDL particle. For example, enrichment of human LDL with cholesteryl oleate enhances proteoglycan-binding and atherogenesis.[52] In addition, apoE, apoC-III, and serum amyloid A increase the affinity of LDL for arterial wall proteoglycans.[49,53–55]

Responses elicited by low-density lipoprotein retained in the artery wall

Retention and subsequent accumulation of LDL in the artery wall triggers a number of events that initiate and propagate lesion development.[21,50] Due to the local microenvironment of the subendothelial matrix, LDL particles are susceptible to oxidation by both enzymatic and non-enzymatic mechanisms, which leads to the generation of oxidized LDL (oxLDL) containing several bioactive molecules including oxidized phospholipids.[129,130] Oxidized LDL, in turn, initiates a sterile inflammatory response by activating endothelial cells to up-regulate adhesion molecules and chemokines that trigger the recruitment of monocytes—typically inflammatory Ly6C^{hi} monocytes—into the artery wall.[131] The importance of oxidized phospholipids in the inflammatory response of the vascular wall has been demonstrated through the transgenic expression of an oxidized phospholipid-neutralizing single-chain antibody, which protected atherosclerosis-prone mice against lesion formation.[132] Newly recruited monocytes differentiate into macrophages that can further promote the oxidation of LDL particles, which are then recognized and internalized by specific scavenger receptors giving rise to cholesterol-laden foam cells.[133] Several other modifications of retained LDL, including enzymatic degradation or aggregation, have also been shown to promote its uptake by macrophages. Macropinocytosis of native LDL may also contribute to this process.[134,135]

After 20 weeks, 231 mice were perfusion-fixed. Seven aortas were not analysed for technical reasons. The remaining 224 aortas were analysed with the *en face* procedure[13]. The extent of atherosclerosis correlated with the plasma concentration of human apoB100 in all groups (Fig. 2). However, transgenic mice expressing proteoglycan-binding-defective LDL ($R,K_{3359–3369} \rightarrow S,A$, 6-GBSM, and $K_{3363} \rightarrow E$ LDL) had significantly less atherosclerosis than mice expressing wild-type control or $W_{4369} \rightarrow Y$ LDL (Table 3)

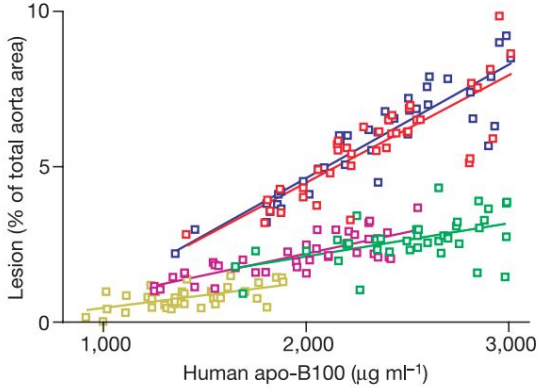


Figure 2 Effect on aorta of an atherogenic diet in transgenic mice. The data shows the correlation between the percentage of total aortic surface area covered by lesions and the plasma concentration of human apoB100 in transgenic mice fed an atherogenic diet for 20 weeks. Recombinant control LDL (red) and $W_{4369} \rightarrow Y$ LDL (blue), both with normal proteoglycan binding. Proteoglycan-binding-defective $R,K_{3359–3369} \rightarrow S,A$ LDL (pink), $K_{3363} \rightarrow E$ LDL (light green), and 6-GBSM LDL (dark green). The percentage of total aortic surface area covered by lesions in mice expressing the recombinant LDL were 5.7 ± 1.5, 5.8 ± 1.7, 2.1 ± 0.66, 0.81 ± 0.36 or 2.7 ± 0.72, respectively (mean ± s.d.).

Published: 13 June 2002

Subendothelial retention of atherogenic lipoproteins in early atherosclerosis

Kristina Skålén, Maria Gustafsson, Ellen Knutsen Rydberg, Lillemor Mattsson Hultén, Olov Wiklund, Thomas L. Innerarity & Jan Borén ✉

Nature **417**, 750–754 (2002) | Cite this article

Mouse LDL often contain apoE, but apoB100 is the sole apolipoprotein on human LDL. Thus, bridging molecules are probably less important than a direct interaction between apoB100 and proteoglycans for subendothelial retention of atherogenic lipoproteins in humans. Retained lipoproteins can directly or indirectly provoke all known features of early lesions and, by stimulating local synthesis of proteoglycans, can accelerate further retention and aggregation[3]. Thus, atherosclerosis is initiated by subendothelial retention of atherogenic lipoproteins. □

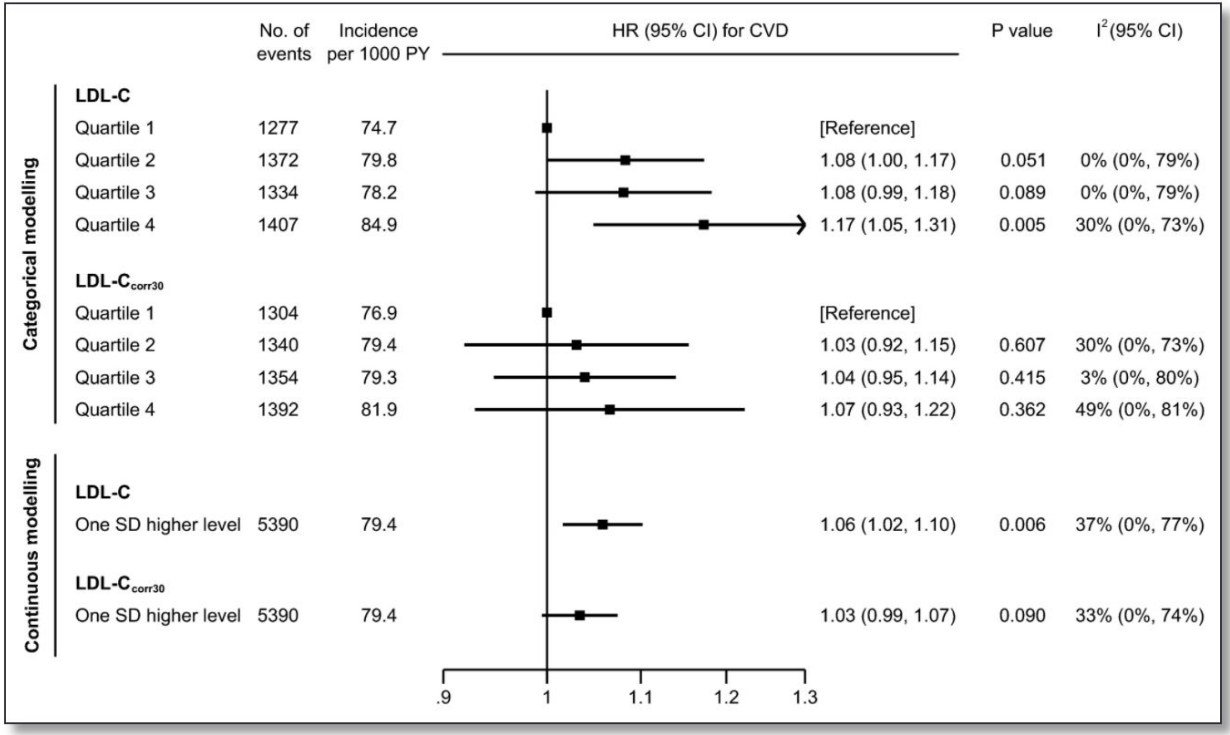
To verify that the differences in atherogenicity were due solely to different affinities for arterial proteoglycans, we performed several control experiments. First, we analysed the formation of conjugated dienes in $R,K_{3359–3369} \rightarrow S,A$ LDL and recombinant control LDL after copper-stimulated oxidation[14]. The lag phase for the formation of conjugated dienes in $R,K_{3359–3369} \rightarrow S,A$ LDL and recombinant control LDL was 79 ± 6 and 74 ± 8 min, respectively, and the maximal rate of conjugated dienes formed was 6.1 ± 0.5 and 5.8 ± 0.4 molecules $min^{-1} \times$ LDL particle, respectively (mean ± s.d.; $n = 3$). Thus, proteoglycan-binding-defective LDL were as susceptible to oxidation as recombinant control LDL.

Willeit, 2020

Low-Density Lipoprotein Cholesterol Corrected for Lipoprotein(a) Cholesterol, Risk Thresholds, and Cardiovascular Events

Peter Willeit, Calvin Yeang, Patrick M. Moriarty, Lena Tschiderer, Stephen A. Varvel, Joseph P. McConnell and Sotirios Tsimikas

Originally published 23 Nov 2020 | https://doi.org/10.1161/JAHA.119.016318 | Journal of the American Heart Association. 2020;9:e016318



Deleanu, 2016

Profiles of Fatty Acids and the Main Lipid Peroxidation Products of Human Atherogenic Low Density Lipoproteins

MARIANA DELEANU[1,2], GABRIELA M. SANDA[1], CAMELIA S. STANCU[1], MONA E. POPA[2], ANCA V. SIMA[1]*
[1] "Nicolae Simionescu" Institute for Cellular Biology and Pathology of the Romanian Academy, 8 B.P. Hasdeu Str, 050568, Bucharest, Romania
[2] University of Agronomical Sciences and Veterinary Medicine Bucharest, Faculty of Biotechnology, 59 Marasti Blvd., 011464, Bucharest, Romania

Results and discussions

It is well known that the high saturated fat intake generates high serum lipids levels and the development of atherosclerosis. The analysis of serum and tissue FA distribution was included in population studies on CVD and their risk factors [26].

The ω-3 FA, EPA (1.16±0.23, $p<0.001$) and DHA (1.71±0.54, $p<0.001$) were totally reduced, being transformed in peroxidation products (fig. 1).

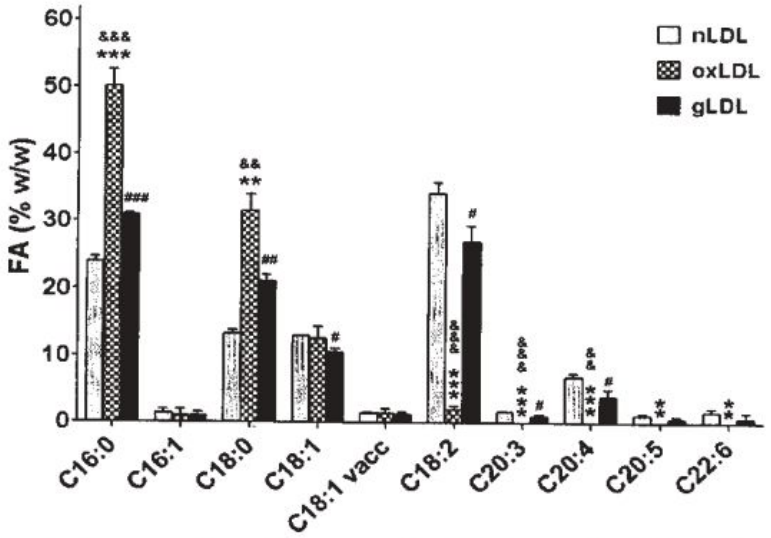


Fig. 1. Composition of fatty acids (FA) in oxidized low density poproteins (oxLDL) and glycated low density lipoproteins (gLDL) compared to native low density lipoproteins (nLDL). The data are expressed as mean ± SD; n=3 samples for each

Kothapalli, 2020

FULL LENGTH ARTICLE | VOLUME 162, 102183, NOVEMBER 01, 2020

PDF [1 MB] Figures

Polyunsaturated fatty acid biosynthesis pathway and genetics. implications for interindividual variability in prothrombotic, inflammatory conditions such as COVID-19☆,☆☆,★,★★

Kumar S.D. Kothapalli • Hui Gyu Park • J. Thomas Brenna

Published: September 30, 2020 • DOI: https://doi.org/10.1016/j.plefa.2020.102183 • Check for upda

HUFA for any individual. We predict that fast desaturators (insertion allele at rs66698963; major haplotype in Europeans) are predisposed to higher risk and pathological responses to SARS-CoV-2 could be reduced with high dose omega-3 HUFA.

Put another way, only 2 ways are known to increase circulating DHA status in humans: 1) consume (preformed) DHA, or 2) lower dietary LA.

Park, 2021

Open Access Article

Causal Effects of Serum Levels of n-3 or n-6 Polyunsaturated Fatty Acids on Coronary Artery Disease: Mendelian Randomization Study

by Sehoon Park [1,2], Soojin Lee [3], Yaerim Kim [4], Yeonhee Lee [3], Min Woo Kang [5], Kwangsoo Kim [6], Yong Chul Kim [5], Seung Seok Han [5,7], Hajeong Lee [5,7], Jung Pyo Lee [7,8,9], Kwon Wook Joo [5,7,8], Chun Soo Lim [7,8,9], Yon Su Kim [1,5,7,8] and Dong Ki Kim [5,7,8,*]

Table 3. Allele-score based Mendelian randomization results in the UK Biobank data for MI outcome.

Genetically Predicted PUFA Level by Allele–Scores (1 Standard Deviation Increase)	Main Analysis [a]		Sensitivity Analysis Adjusted for Phenotypical Covariates [b]	
	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
n-3 PUFAs				
Eicosapentaenoic acid	0.973 (0.956–0.991)	0.003	0.969 (0.949–0.989)	0.002
Docosapentaenoic acid	1.027 (1.009–1.046)	0.004	1.029 (1.008–1.050)	0.006
Docosahexaenoic acid	1.000 (0.982–1.018)	0.986	1.003 (0.982–1.023)	0.804
n-6 PUFAs				
Linoleic acid	0.975 (0.957–0.992)	0.005	0.967 (0.947–0.987)	0.001
Gamma-linolenic acid	1.022 (1.003–1.040)	0.020	1.028 (1.007–1.049)	0.009
Dihomo-gamma-linolenic acid	0.972 (0.955–0.990)	0.002	0.969 (0.950–0.989)	0.003
Arachidonic acid	1.027 (1.009–1.046)	0.004	1.034 (1.013–1.056)	0.001
Adrenic acid	1.004 (0.986–1.022)	0.672	1.008 (0.987–1.029)	0.458

PUFA = polyunsaturated fatty acids; OR = odds ratio; CI = confidence interval; MI = myocardial infarction. All allele scores were scaled to a one standard deivation increase. [a] The logistic regression model was adjusted for age, sex, and the first 10 principal components of the genetic information. [b] The phenotypical hypertension, diabetes mellitus, obesity, dyslipidemia medication history, smoking, laboratory values for low-density lipoprotein, high-density lipoprotein, and triglycerides were added to the main model.

Griffin, 2008

Problems with the dietary ratio of n-6/n-3 PUFAs

The ratio of n-6/n-3 PUFAs does have a number of inherent problems that were concisely reviewed by William Harris at a recent workshop at the UK Food Standards Agency [9]. Firstly, the ratio makes no distinction between ALA and the metabolically more active EPA/DHA. Secondly, all ratios suffer from the fact that the components can change in different directions or not at all to produce a higher or lower ratio. In terms of n-6 and n-3 PUFAs, this has produced considerable variation in the physiological response to a decrease in the ratio that has confounded the interpretation of intervention studies. Finally, there is an underlying premise that the ratio balances bad and good elements of n-3/n-6 PUFAs, primarily because eicosanoids derived from the principal membrane n-6 PUFA, arachidonic acid, are metabolically more potent in promoting inflammation, platelet aggregation, and immune and vascular reactivity than those derived from LC n-3 PUFAs [12,13]. It follows from this idea that high or increased intakes of dietary linoleic acid as the dietary precursor of arachidonic acid should increase membrane arachidonic acid and exert adverse effects on CVD when there is epidemiological evidence to suggest that the opposite is true, and that both linoleic acid and ALA exert favourable effects on CVD risk [14–16]. Moreover, not only do patients with CVD have low tissue arachidonic acid status, but also there is no relationship between dietary linoleic acid and tissue membrane arachidonic acid in humans [17•,18]. This evidence conflicts with the widely held view, and recent cross-cultural evidence [19•], that dietary n-6 PUFAs, chiefly linoleic acid, exerts adverse effects on cardiovascular health, mediated through tissue arachidonic acid.

NUTRITION AND METABOLISM: EDITED BY PAUL NESTEL AND RONALD MENSINK

How relevant is the ratio of dietary n-6 to n-3 polyunsaturated fatty acids to cardiovascular disease risk? Evidence from the OPTILIP study

Griffin, Bruce A

Author Information

Current Opinion in Lipidology: February 2008 - Volume 19 - Issue 1 - p 57-62
doi: 10.1097/MOL.0b013e3282f2e2a8

Conclusion

The OPTILIP study set out to determine the optimal ratio of n-6/n-3 PUFAs in the UK diet but inadvertently succeeded in establishing the irrelevance of this dietary ratio and reaffirming the benefits of LC n-3 PUFAs. The stable isotope tracer study by Goyens *et al.* [22••] arrived at the same conclusion on the value of the ratio of n-6/n-3 PUFAs, and also produced evidence to suggest that the conversion of ALA to LC n-3 PUFAs could be enhanced by decreasing and increasing the absolute amounts sof dietary linoleic acid and ALA respectively. The ratio of n-6/n-3 PUFAs might be dead, but the question of how linoleic acid and ALA influence the conversion of ALA, especially under pathophysiological conditions, is still very much alive.

Taha, 2014

FULL LENGTH ARTICLE | VOLUME 90, ISSUE 5, P151-157,
MAY 01, 2014

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Dietary omega-6 fatty acid lowering increases bioavailability of omega-3 polyunsaturated fatty acids in human plasma lipid pools

Ameer Y. Taha • Yewon Cheon • Keturah F. Faurot • ... Joseph R. Hibbeln • Amit Ringel • Christopher E. Ramsden • Show all authors

Published: March 26, 2014 • DOI: https://doi.org/10.1016/j.plefa.2014.02.003 • Check for updates

4.5. Conclusion

In conclusion, 12 weeks of dietary LA lowering increased concentrations of n-3 PUFAs in plasma esterified and unesterified lipids, and a combination of dietary LA lowering with concurrent increases in EPA and DHA further increased circulating n-3 PUFA levels and reduced esterified AA and other n-6 PUFA concentrations in a patient population with chronic headaches.

Archer, 2015

SPECIAL ARTICLE | VOLUME 90, ISSUE 7, P911-926, JULY 01, 2015

PDF [419 KB] Figures Save

The Inadmissibility of What We Eat in America and NHANES Dietary Data in Nutrition and Obesity Research and the Scientific Formulation of National Dietary Guidelines

Edward Archer, PhD • Gregory Pavela, PhD • Carl J. Lavie, MD

Published: June 09, 2015 • DOI: https://doi.org/10.1016/j.mayocp.2015.04.009

THE VALIDITY OF HUMAN MEMORY AND RECALL AS INSTRUMENTS FOR THE GENERATION OF SCIENTIFIC DATA

Overview

The use of M-BMs requires faith in the belief that human perception, memory, and recall are accurate and reliable instruments for the generation of scientific data. Nevertheless, more than 80 years of research demonstrates that this belief is patently false.[50,58,70,90] The discrepancy between objective reality and human memory is well established,[48,91] and the limitations of recall are widely acknowledged in disciplines outside of nutrition and obesity.[47-49,69,70,92] In fact, the scientific study and analysis of memory would be impossible if it were not for the inherent fallibility of memory.[49] Bartlett[93] presented the first empirical evidence that the human memory is not a literal, accurate, or precise reproduction of past events. During the ensuing 80 years, research has clearly demonstrated that the encoding of memories[69,91] and subsequent recall depend on constructive and reconstructive processes (eg, imagination)[48,69,53] that are susceptible to errors, distortions, omissions, complete fabrications, false reports, and illusions.[50,58,69,70,90]

Bowman, 2011

› Alzheimer Dis Assoc Disord. Jan-Mar 2011;25(1):49-57. doi: 10.1097/WAD.0b013e3181f333d6.

Reliability and validity of food frequency questionnaire and nutrient biomarkers in elders with and without mild cognitive impairment

Gene L Bowman [1], Jackilen Shannon, Emily Ho, Maret G Traber, Balz Frei, Barry S Oken, Jeffery A Kaye, Joseph F Quinn

Affiliations + expand

PMID: 20856100 PMCID: PMC3042482 DOI: 10.1097/WAD.0b013e3181f333d6

In MCI 12 of the 26 correlation coefficients generated between FFQ and plasma were positive in linear direction (Table 2, MCI). By comparison, 17 of the 26 nutrients had coefficients of the appropriate direction in NIE, and 7 of these 17 did reach significance (Table 2, NIE). The calorie-and-multivariate adjusted models had no apparent advantage over the crude model that was unadjusted for energy intake and other variables (Table 2, Calorie adjusted, Multivariate-adjusted).

Pearson correlation coefficients between plasma and FFQ nutrient estimates by cognitive status*

		Crude			Calorie-adjusted[1]			Multivariate-adjusted[2]		
		Total	MCI	NIE	Total	MCI	NIE	Total	MCI	NIE
Vitamin	Ascorbic acid	.32	.15	.52*	.32	.15	.52*	.30	.09	.51
	Alpha-tocopherol	.17	.15	.10	.17	.15	.10	.11	.21	−.04
	Gamma-tocopherol	−.21	−.20	−.02	−.16	−.20	−.02	−.15	−.37	−.04
	Lutein + zeaxanthin	.48**	−.19	.72**	.47**	−.19	.72**	.37*	−.35	.76**
	Beta-cryptoxanthin	.41**	−.11	.72**	.41**	−.11	.72**	.35*	−.15	.64*
	Alpha-carotene	.49**	.43	.65**	.49**	.43	.65**	.49**	.44	.73**
	Beta-carotene	.43**	.45	.48*	.43**	.35	.49*	.34*	.22	.71**
	Lycopene	.12	−.01	.23	.12	.01	.23	.08	.06	.06
	Vitamin B6	−.08	.05	−.28	.01	.09	−.20	.01	.12	−.18
	Folate	.04	−.25	.39	−.08	.04	−.28	−.10	.04	−.29
	Vitamin B12	.19	.10	.28	.04	−.25	.39	.14	−.07	.42
	Vitamin D	.32	.15	.52*	.19	.10	.28	.16	.18	.13
Mineral	Copper	.12	−.15	.28	.12	−.15	.28	.06	−.14	.23
	Iron	.02	.11	−.04	.02	.13	−.04	.07	.02	.26
	Magnesium	−.35*	−.52*	−.19	−.35*	−.52*	−.19	−.36*	−.54*	−.17
	Selenium	−.33*	−.41	−.13	−.33*	−.41	−.13	−.32	−.50	−.14
	Zinc	.01	.09	−.19	.01	.09	−.19	.05	.21	−.20
Lipid	PUFA, total	.10	−.06	.30	.10	−.06	.30	.00	−.07	−.09
	MUFA, total	−.15	−.10	−.15	−.15	−.10	−.14	−.07	.05	.03
	SFA, total	−.13	−.04	−.32	−.13	−.04	−.32	−.11	.01	−.42
	Linoleic acid	.09	−.05	.23	.07	−.05	.23	−.07	−.16	−.14
	Arachidonic acid	.01	−.05	.10	−.01	−.05	.10	.03	−.01	.14
	Alpha-linolenic acid	.15	.23	.03	.15	.23	.03	.14	.23	−.12
	EPA	.39*	.22	.43	.39*	.22	.43	.39*	.38	.41

		Crude			Calorie-adjusted[1]			Multivariate-adjusted[2]		
		Total	MCI	NIE	Total	MCI	NIE	Total	MCI	NIE
	DHA	.39*	.04	.65**	.39*	.04	.65**	.38*	.06	.66**
	Cholesterol[3]	−.06	−.19	.07	−.06	−.20	.07	−.05	−.13	.01

Ioannidis, 2018

September 11, 2018

The Challenge of Reforming Nutritional Epidemiologic Research

John P. A. Ioannidis, MD, DSc[1]

» Author Affiliations

JAMA. 2018;320(10):969-970. doi:10.1001/jama.2018.11025

Proponents of the status quo of nutritional epidemiology point to occasional small trials with surrogate or metabolic outcomes (eg, lipids, diabetes, composite end points) whose results agree with epidemiologic findings. However, these small trials often have selective reporting bias similar to that of nutritional epidemiology.

In recent updated meta-analyses of prospective cohort studies, almost all foods revealed statistically significant associations with mortality risk.[1] Substantial deficiencies of key nutrients (eg, vitamins), extreme overconsumption of food, and obesity from excessive calories may indeed increase mortality risk. However, can small intake differences of specific nutrients, foods, or diet patterns with similar calories causally, markedly, and almost ubiquitously affect survival?

Assuming the meta-analyzed evidence from cohort studies represents life span–long causal associations, for a baseline life expectancy of 80 years, eating 12 hazelnuts daily (1 oz) would prolong life by 12 years (ie, 1 year per hazelnut),[1] drinking 3 cups of coffee daily would achieve a similar gain of 12 extra years,[2] and eating a single mandarin orange daily (80 g) would add 5 years of life.[1] Conversely, consuming 1 egg daily would reduce life expectancy by 6 years, and eating 2 slices of bacon (30 g) daily would shorten life by a decade, an effect worse than smoking.[1] Could these results possibly be true? Authors often use causal language when reporting the findings from these studies (eg, "optimal consumption of risk-decreasing foods results in a 56% reduction of all-cause mortality").[1] Burden-of-disease studies and guidelines endorse these estimates. Even when authors add caveats, results are still often presented by the media as causal.

Reforming Nutritional Epidemiologic Research

To the Editor The Viewpoint by Dr Ioannidis[1] discussed the need for reform of nutritional epidemiologic research. We were surprised by the "nonexpert" calculations of gain or loss in life expectancy using data from our meta-analysis.[2] We presented the findings in our meta-analysis as relative risks (RRs). Ioannidis calculated from those RRs the number of years of life gained or lost by consumption of a number of foods. Such calculations are not in line with statistical methodology and should not be used in a scientific debate about diet-disease associations and potential implications. An RR of 2 does not mean a shorter life expectancy of 40 years or an RR of 4 a shorter life expectancy of 60 years. An RR of 0.5 does not generate a life expectancy of 120 years or an RR of 0.85 a life expectancy of 92 years, a 12-year increase in life expectancy for 1 serving of nuts daily as calculated by Ioannidis. In the article, more misleading calculations of this type were done using other examples from our publication, but we would like to point out that heavy smoking, with an RR of 2.38 to 2.66,[3] would result in a life expectancy of only about 35 years (assuming a life expectancy of 80 years), or a loss of life-years of 45 years according to the calculations of Ioannidis.

Such misinterpretations are not helpful to initiate a debate. We acknowledge that nutrition research has to deal with complex issues. Nutritional epidemiology intends to explain disease occurrence by dietary factors and has to address this complexity by continuously improving the methodology. We see progress over the past years but also note that more rigorous, hypothesis-driven conduct and interpretation of nutritional epidemiologic studies together with integration of biological knowledge might be helpful for this scientific discipline.

Young and Karr, 2011

We ourselves carried out an informal but comprehensive accounting of 12 randomised clinical trials that tested observational claims – see Table 1. The 12 clinical trials tested 52 observational claims. They all confirmed no claims in the direction of the observational claims. We repeat that figure: 0 out of 52. To put it another way, 100% of the observational claims failed to replicate. In fact, five claims (9.6%) are statistically significant in the clinical trials *in the opposite direction* to the observational claim. To us, a false discovery rate of over 80% is potent evidence that the observational study process is not in control. The problem, which has been recognised at least since 1988, is systemic.

Deming, data and observational studies

A process out of control and needing fixing

S. Stanley Young, Alan Karr

First published: 25 August 2011 | https://doi.org/10.1111/j.1740-9713.2011.00506.x
Citations: 106

ID no.	*Pos.*	*Neg.*	*No. of claims*	*Treatment(s)*	*Reference*
1	0	1	3	Vit E, beta-carotene	*NEJM* 1994; **330:** 1029-1035
2	0	3	4	Hormone Replacement Ther.	*JAMA* 2003; **289:** 2651–2662, 2663–2672, 2673–2684
3	0	1	2	Vit E, beta-carotene	*JNCI* 2005; **97:** 481-488
4	0	0	3	Vit E	*JAMA* 2005; **293:** 1338-1347
5	0	0	3	Low Fat	*JAMA*. 2006; **295:** 655-666
6	0	0	3	Vit D, Calcium	*NEJM* 2006; **354:** 669-683
7	0	0	2	Folic acid, Vit B6, B12	*NEJM* 2006; **354:** 2764-2772
8	0	0	2	Low Fat	*JAMA* 2007; **298:** 289–298
9	0	0	12	Vit C, Vit E, beta-carotene	*Arch Intern Med* 2007; **167:** 1610-1618
10	0	0	12	Vit C, Vit E	*JAMA* 2008; **300:** 2123-2133
11	0	0	3	Vit E, Selenium	*JAMA* 2009; **301:** 39-51
12	0	0	3	HRT + Vitamins	*JAMA* 2002; **288:** 2431-2440
Totals	0	5	52		

Schwingshackl, 2021

Research

Evaluating agreement between bodies of evidence from randomised controlled trials and cohort studies in nutrition research: meta-epidemiological study

BMJ 2021 ; 374 doi: https://doi.org/10.1136/bmj.n1864 (Published 15 September 2021)
Cite this as: *BMJ* 2021;374:n1864

The number of primary studies contributing to the 97 diet-disease outcome pairs ranged from 1 to 64 (median 6) for BoE from randomised controlled trials, and from 1 to 68 (median 7) for BoE from cohort studies (overall >950 trials and >750 cohort studies). The total number of participants ranged from 56 to 211957 for BoE from randomised controlled trials, and from 2563 to 1797670 for BoE from cohort studies. Of the identified 97 diet-disease outcome pairs, 83 were included in the meta-analysis (71 binary, 12 continuous). We could not include 14 diet-disease outcome pairs in the meta-analysis (reasons in supplementary table 6).

Similarities

Of 97 diet-disease outcome pairs, none was rated as more or less identical, 57 (59%) were similar but not identical, and 40 (41%) were broadly similar. Interventions or exposures rated as broadly similar accounted for most PI/ECO dissimilarities overall (n=17/40; 42.5%). Of 83 diet-disease outcome pairs included in the meta-analysis, 57 (69%) were similar but not identical and 26 (31%) were broadly similar. Interventions or exposures rated as broadly similar accounted for most PI/ECO dissimilarities overall (n=17/26; 65%). Supplementary table 13 shows additional information.

Beyerbach, 2022

Evaluating Concordance of Bodies of Evidence from Randomized Controlled Trials, Dietary Intake, and Biomarkers of Intake in Cohort Studies: A Meta-Epidemiological Study Get access

Jessica Beyerbach, Julia Stadelmaier, Georg Hoffmann, Sara Balduzzi, Nils Bröckelmann, Lukas Schwingshackl

Advances in Nutrition, Volume 13, Issue 1, January 2022, Pages 48–65,
https://doi.org/10.1093/advances/nmab095
Published: 02 September 2021 **Article history**

Quantitative concordance: Using the second definition (calculated as z-score), 88%, 69%, and 90% of the diet-disease associations were quantitatively concordant comparing BoE_{RCTs} vs. $BoE_{CSs\ dietary\ intake}$, BoE_{RCTs} vs. $BoE_{CSs\ biomarkers}$ and comparing both BoE from CSs, respectively **(Table 3)**. 65% (32/49) of the diet-disease association were quantitatively concordant considering all three BoE simultaneously.

Conclusion

Our findings suggest that BoE from RCTs and CSs are often quantitatively concordant. Prospective SRs in nutrition research should include whenever possible BoE from RCTs, and CSs on dietary intake and biomarker of intake to provide the whole picture for an investigated diet-disease association.

Moorthy, 2013

Findings. In 23 out of 34 associations the summary findings from meta-analyses of epidemiological studies and of RCTs were in the same direction. In 6 of 23 associations, meta-analyses of epidemiological studies and of RCTs had statistically significant findings. In the remaining 11 out of 34 assocations, meta-analyses of epidemiological studies and of RCTs had summaries pointing in opposite directions. In 12 out of 34 associations the summary findings of epidemiological studies were statistically significantly different from those of RCTs, in 6 out of 12 point estimates were in the same direction, and in the other 6 in opposing directions. Despite the variation in the size and the connectivity of the citation graphs across the examined associations, we find no evidence of association between quantitative metrics of the citation graphs and the probability that the two research designs have concordant or discordant findings (using various definitions of concordance or discordance).

Review

Concordance Between the Findings of Epidemiological Studies and Randomized Trials in Nutrition: An Empirical Evaluation and Citation Analysis: Nutritional Research Series, Vol. 6 [Internet]

Denish Moorthy [1], Mei Chung [1], Jounghee Lee [1], Winifred W Yu [1], Joseph Lau [1], Thomas A Trikalinos [1]

Table 2. Qualitative and quantitative concordance of effects in epidemiological studies and RCTs

ID	Direction of Effect (Epi)	Significance (Epi)	Direction of Effect (RCT)	Significance (RCT)	Qualitative Concordance (1st definition)	z-Score	p-Value	Quantitative Concordance (2nd definition)	Quantitative Concordance (3rd definition)
1	Decreasing	Not sign	Decreasing	Not sign	Unclear	0.22	0.83	Not discordant	Not discordant
2	Decreasing	Sign	Decreasing	Not sign	Unclear	-0.91	0.36	Not discordant	Not discordant
3	Increasing	Not sign	Decreasing	Not sign	Unclear	1.36	0.18	Not discordant	Not discordant
4	Increasing	Not sign	Increasing	Not sign	Unclear	0.08	0.94	Not discordant	Not discordant
5	Decreasing	Not sign	Increasing	Not sign	Unclear	-1.50	0.13	Not discordant	Not discordant
6	Decreasing	Sign	Increasing	Not sign	Unclear	-1.54	0.12	Not discordant	Not discordant
7	Decreasing	Sign	Increasing	Not sign	Unclear	-3.08	0.00	Discordant	Discordant
8	Decreasing	Sign	Increasing	Not sign	Unclear	-2.00	0.05	Discordant	Discordant
9	Increasing	Not sign	Increasing	Not sign	Unclear	0.00	1.00	Not discordant	Not discordant
10	Increasing	Not sign	Increasing	Not sign	Unclear	0.00	1.00	Not discordant	Not discordant
11	Increasing	Not sign	Decreasing	Not sign	Unclear	1.20	0.23	Not discordant	Not discordant
12	Decreasing	Not sign	Decreasing	Not sign	Unclear	0.13	0.89	Not discordant	Not discordant
13	Decreasing	Sign	Decreasing	Sign	Concordant	2.52	0.01	Discordant	Not discordant
14	Decreasing	Sign	Decreasing	Not sign	Unclear	0.65	0.51	Not discordant	Not discordant
15	Decreasing	Sign	Increasing	Not sign	Unclear	-2.48	0.01	Discordant	Discordant
16	Decreasing	Not sign	Decreasing	Not sign	Unclear	-1.15	0.25	Not discordant	Not discordant
17	Decreasing	Sign	Decreasing	Not sign	Unclear	-2.08	0.04	Discordant	Not discordant
18	Decreasing	Sign	Decreasing	Not sign	Unclear	-0.98	0.33	Not discordant	Not discordant
19	Decreasing	Sign	Decreasing	Not sign	Unclear	-1.64	0.10	Not discordant	Not discordant
20	Increasing	Not sign	Increasing	Not sign	Unclear	-0.37	0.71	Not discordant	Not discordant
21	Decreasing	Not sign	Decreasing	Not sign	Unclear	-0.31	0.75	Not discordant	Not discordant
22	Increasing	Not sign	Increasing	Not sign	Unclear	0.00	1.00	Not discordant	Not discordant
23	Decreasing	Sign	Decreasing	Sign	Concordant	-2.07	0.04	Discordant	Not discordant
24	Decreasing	Sign	Decreasing	Sign	Concordant	2.14	0.03	Discordant	Not discordant
25	Decreasing	Sign	Increasing	Not sign	Unclear	-2.19	0.03	Discordant	Discordant
26	Decreasing	Sign	Increasing	Not sign	Unclear	-2.79	0.01	Discordant	Discordant
27	Decreasing	Not sign	Decreasing	Not sign	Unclear	0.22	0.83	Not discordant	Not discordant
28	Increasing	Not sign	Decreasing	Not sign	Unclear	1.46	0.14	Not discordant	Not discordant
29	Decreasing	Not sign	Increasing	Not sign	Unclear	-2.06	0.04	Discordant	Discordant
30	Decreasing	Sign	Decreasing	Sign	Concordant	-1.56	0.12	Not discordant	Not discordant
31	Decreasing	Sign	Decreasing	Not sign	Unclear	-1.13	0.26	Not discordant	Not discordant
32	Decreasing	Sign	Decreasing	Not sign	Unclear	-2.41	0.02	Discordant	Not discordant
33	Decreasing	Sign	Decreasing	Sign	Concordant	3.06	0.00	Discordant	Not discordant
34	Decreasing	Sign	Decreasing	Sign	Concordant	0.95	0.34	Not discordant	Not discordant

Note: Sign = statistically significant at the 0.05 level

McShane, 2019 & Amrhein, 2019

Abandon Statistical Significance

Blakeley B. McShane, David Gal, Andrew Gelman, Christian Robert & Jennifer L. Tackett

Pages 235-245 | Received 30 Oct 2017, Accepted 06 Sep 2018, Published online: 20 Mar 2019

Download citation https://doi.org/10.1080/00031305.2018.1527253 Check for updates

Scientists rise up against statistical significance

Valentin Amrhein, Sander Greenland, Blake McShane and more than 800 signatories call for an end to hyped claims and the dismissal of possibly crucial effects.

Valentin Amrhein, Sander Greenland & Blake McShane

Statology, 2020

Absolute value of *r*	Strength of relationship
r < 0.25	No relationship
0.25 < r < 0.5	Weak relationship
0.5 < r < 0.75	Moderate relationship
r > 0.75	Strong relationship

JANUARY 22, 2020 BY ZACH

What is Considered to Be a "Strong" Correlation?

The correlation between two variables is considered to be strong if the absolute value of *r* is greater than **0.75**. However, the definition of a "strong" correlation can vary from one field to the next.

Medical

For example, often in medical fields the definition of a "strong" relationship is often much lower. If the relationship between taking a certain drug and the reduction in heart attacks is $r = \mathbf{0.3}$, this might be considered a "weak positive" relationship in other fields, but in medicine it's significant enough that it would be worth taking the drug to reduce the chances of having a heart attack.

In summary:

- As a rule of thumb, a correlation greater than 0.75 is considered to be a "strong" correlation between two variables.
- However, this rule of thumb can vary from field to field. For example, a much lower correlation could be considered strong in a medical field compared to a technology field. It's best to use domain specific expertise when deciding what is considered to be strong.
- When using a correlation to describe the relationship between two variables, it's useful to also create a scatterplot so that you can identify any outliers in the dataset along with a potential nonlinear relationship.

Baum, 2012

ORIGINAL ARTICLE | VOLUME 6, ISSUE 3, P216-234, MAY 01, 2012

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Fatty acids in cardiovascular health and disease: A comprehensive update

Seth J. Baum, MD, FNLA • Penny M. Kris-Etherton, PhD, RD • Walter C. Willett, MD, DrPH • ...
Jay Whelan, PhD, MPH • Christopher E. Ramsden, MD, USPHS • Robert C. Block, MD, MPH •
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Published: April 16, 2012 • DOI: https://doi.org/10.1016/j.jacl.2012.04.077

The science regarding the biological effects of fatty acids is complex and constantly evolving (Fig. 1). The long-chain PUFAs most often studied include LA, ALA, arachidonic acid (AA; 20:4 n-6), EPA (20:5 n-3), and DHA (22:6 n-3).[3] An important point in Figure 1 is that with dietary conditions typical of developed countries, the conversions of LA to AA and ALA to EPA occur to minimal extents in humans. Previously, it was believed that the conversion of LA to AA and ALA to EPA represented processes wherein there was intense competition for the enzymes of elongation and desaturation.[4] However, it is now believed that there is minimal forward conversion of these PUFAs to longer and more unsaturated fats. Instead, retroconversion, ie, the small increase in EPA when DHA is fed, may be more consequential. This retroconversion may or may not be attributable to actual enzymatic production of EPA from DHA.[5] It is possible that DHA feeding liberates, or otherwise facilitates, the transfer of EPA from noncirculating depots into the blood. Tracer studies are needed to test the retroconversion hypothesis.

Results from a recent pooled analysis of large cohort studies indicated that, when compared calorie-for-calorie, there was a statistically significant greater relative risk for CHD with carbohydrate versus SFA (Fig. 2).[12] When the comparison was made between n-6 PUFA and SFA, PUFA intake was associated with a statistically significant lower CHD risk. This result was similar to the original Nurses' Health Study, ie, that the relation of SFA intake to CHD risk depended on the comparator.

In conclusion, available evidence suggests that increasing intake of LA correlates with reduced CHD risk. However, because of the theoretical potential for LA to be converted to AA leading to putative increased production of potentially damaging eicosanoids, additional research that supports current dietary recommendations for PUFA would resolve the lingering controversy about their health benefits.

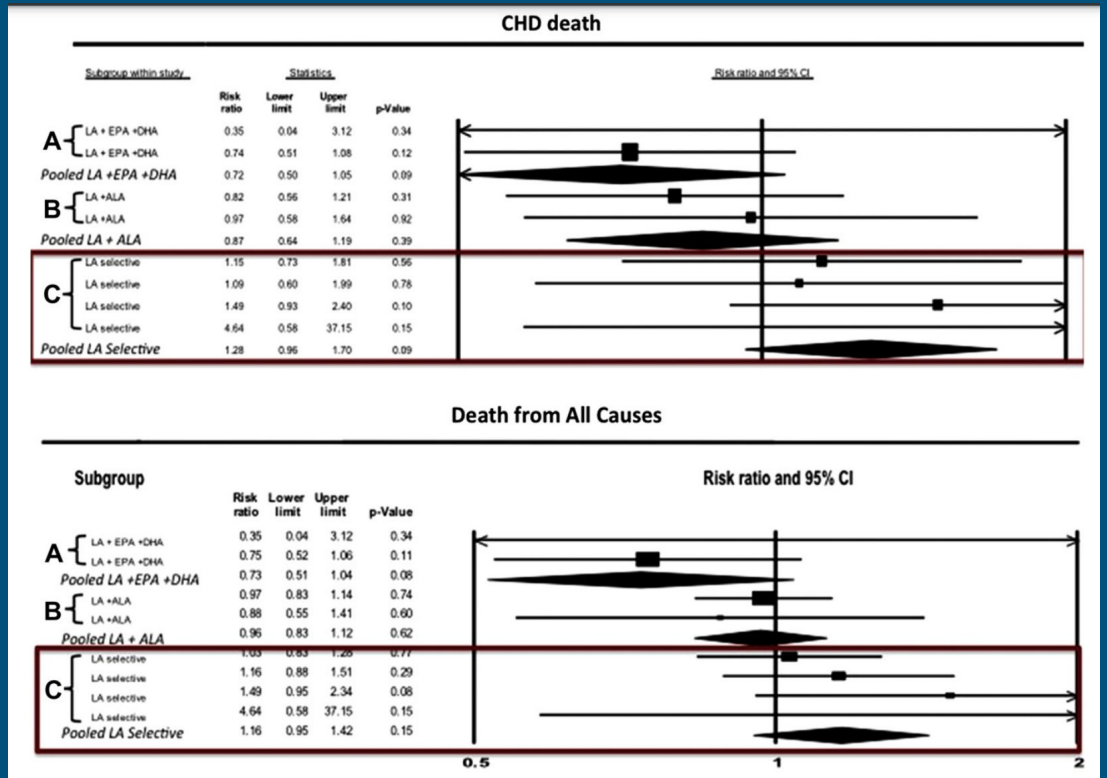
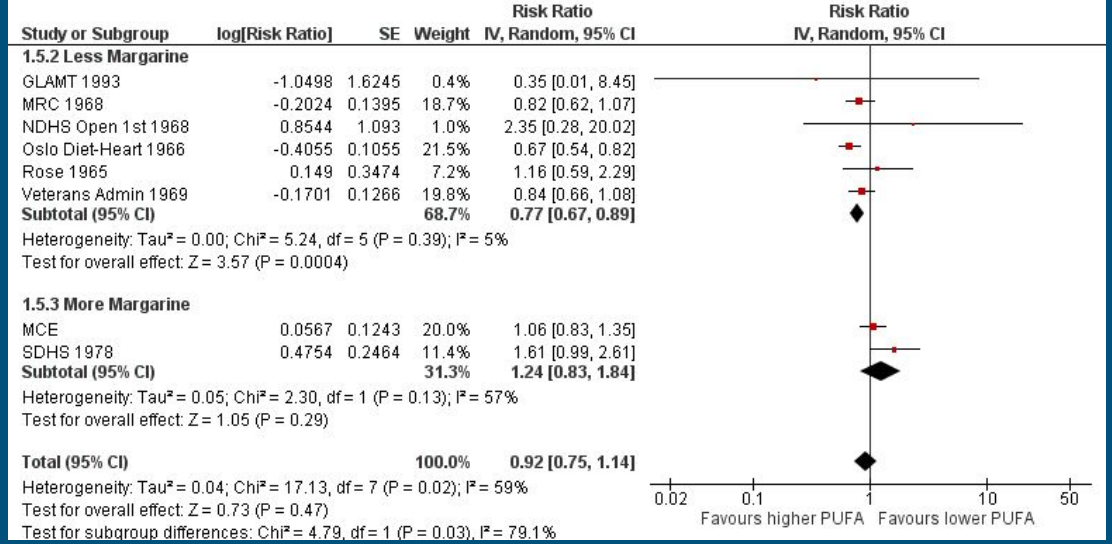
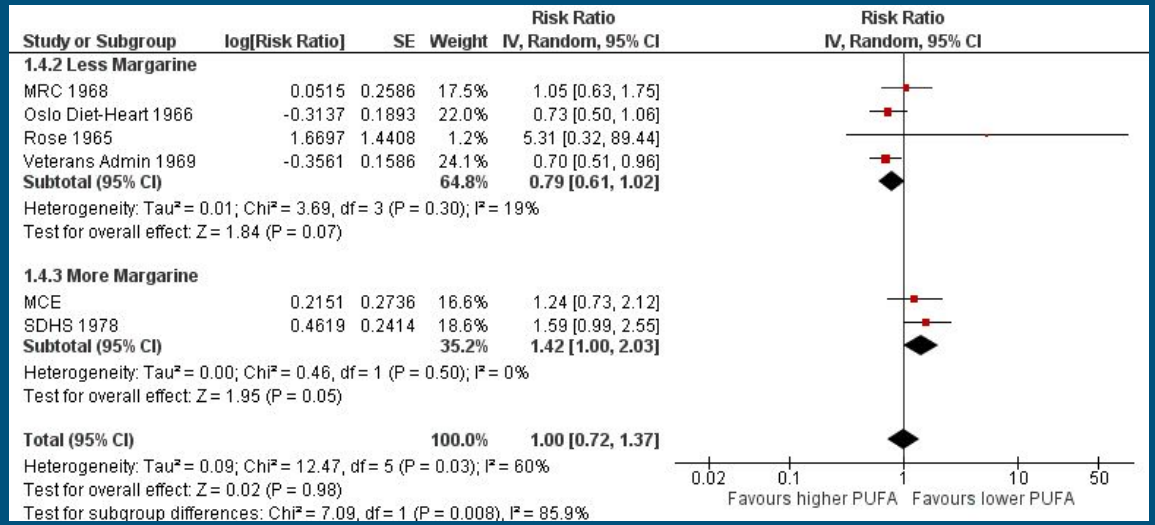


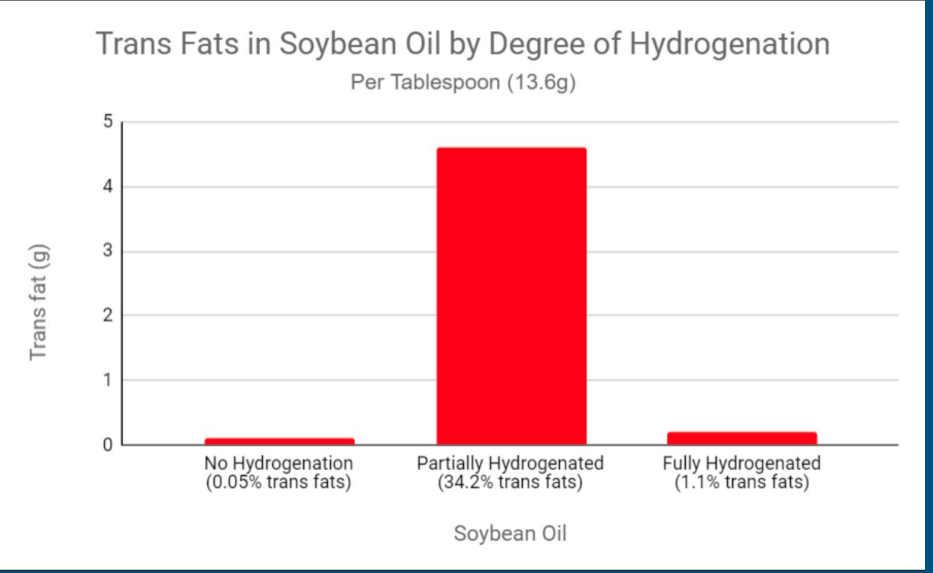
Figure 8 Forest plots of CHD death and death from all causes from a meta-analysis of randomized controlled trials in which dietary

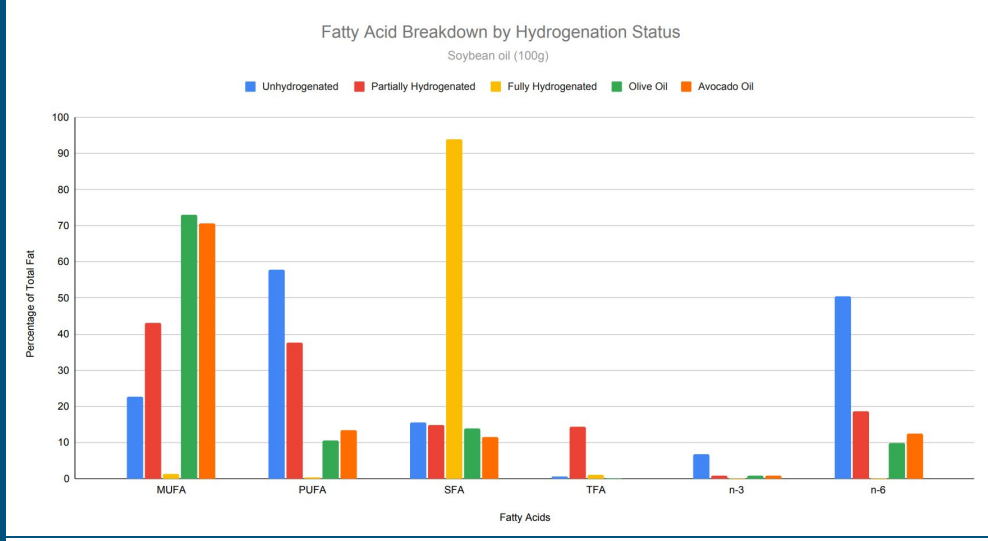
CVD events

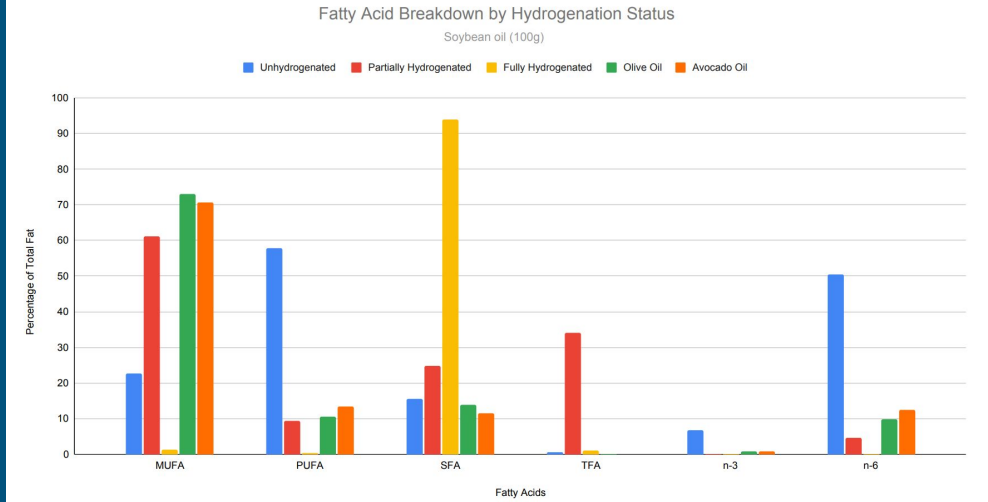


CVD mortality




Trans Fats in Soybean Oil by Degree of Hydrogenation
Per Tablespoon (13.6g)
Trans fat (g)
5
4
3
2
1
0
No Hydrogenation
(0.05% trans fats)
Partially Hydrogenated
(34.2% trans fats)
Fully Hydrogenated
(1.1% trans fats)
Soybean Oil


Fatty Acid Breakdown by Hydrogenation Status
Soybean oil (100g)
Unhydrogenated
Partially Hydrogenated
Fully Hydrogenated
Olive Oil
Avocado Oil
Percentage of Total Fat
100
90
80
70
60
50
40
30
20
10
0
MUFA
PUFA
SFA
TFA
n-3
n-6
Fatty Acids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MUFA
PUFA
SFA
TFA
n-3
n-6
Fatty Acids

It should be noted that although the aforementioned comparisons were with carbohydrates, not all carbohydrates are the same in terms of composition and relationship with clinical end points. Approximately one-half of the calories in the United States diet are from carbohydrates; the majority in the forms of sugar, refined starch, and starch from potatoes. Therefore, any comparisons with carbohydrates in epidemiologic studies are inherently comparisons with unhealthful choices. In a recent study by Jakobsen et al[16] in which they compared different forms of carbohydrates with SFAs, high glycemic index carbohydrates were more strongly associated with risk of CHD than was SFA intake. However, low- or medium-glycemic index carbohydrates, compared with SFAs, were not associated with increased risk.

Thus, the relationship of SFA intake to CVD risk is complex and depends to a great degree on the comparator. The available evidence suggests that replacing SFA with MUFA and PUFA may be beneficial while replacing SFA with carbohydrate may not lower risk or may increase risk if the replacement is with high glycemic index forms of carbohydrate.

Intake of carbohydrates compared with intake of saturated fatty acids and risk of myocardial infarction: importance of the glycemic index

FREE

Marianne U Jakobsen ✉, Claus Dethlefsen, Albert M Joensen, Jakob Stegger, Anne Tjønneland, Erik B Schmidt, Kim Overvad

The American Journal of Clinical Nutrition, Volume 91, Issue 6, June 2010, Pages 1764–1768,
https://doi.org/10.3945/ajcn.2009.29099

TABLE 3
Hazard ratios (HRs) for myocardial infarction per 5% increment of energy intake from carbohydrates with low–glycemic index (low-GI), medium-GI, or high-GI values and a concomitant lower energy intake from saturated fatty acids[1]

	All participants		Women		Men	
Tertiles of dietary GI[2]	Median dietary GI (80% central range)	HR (95% CI)	Median dietary GI (80% central range)	HR (95% CI)	Median dietary GI (80% central range)	HR (95% CI)
Carbohydrates with low-GI values (first tertile)	82 (77, 85)	0.88 (0.72, 1.07)	80 (75, 82)	1.17 (0.80, 1.71)	84 (79, 86)	0.83 (0.65, 1.04)
Carbohydrates with medium-GI values (second tertile)	88 (86, 90)	0.98 (0.80, 1.21)	85 (84, 87)	0.80 (0.54, 1.18)	89 (87, 91)	1.08 (0.84, 1.38)
Carbohydrates with high-GI values (third tertile)	93 (91, 98)	1.33 (1.08, 1.64)	91 (88, 96)	1.10 (0.75, 1.63)	94 (92, 98)	1.34 (1.04, 1.71)

de Lorgeril, 1994

ARTICLES | VOLUME 343, ISSUE 8911, P1454-1459, JUNE 11, 1994

Save

Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease

M de Lorgeril, MD • S Renaud, PhD • P Salen, BSc • I Monjaud, BSc • N Mamelle, PhD • J.L Martin, MSc • et al.

Show all authors

Published: June 11, 1994 • DOI: https://doi.org/10.1016/S0140-6736(94)92580-1

Foods	Control n = 192	Experimental n = 219	p
Bread	145 (7)	167 (6)	0 01
Cereals	99 4 (11)	94 0 (10)	0 22
Legumes	9 9 (3 0)	19 9 (4 3)	0 07
Vegetables	288 (12)	316 (10)	0 07
Fruits	203 (12)	251 (12)	0 007
Delicatessen	13 4 (2 4)	6 4 (1 5)	0 01
Meat	60 4 (5 5)	40 8 (5 0)	0 009
Poultry	52 8 (6 0)	57 8 (5 0)	0 42
Cheese	35 0 (2 6)	32 2 (2 0)	0 25
Butter and cream	16 6 (1 6)	2 8 (0 6)	< 0 001
Margarine	5 1 (0 6)	19 0 (1 0)	< 0 001
Oil	16 5 (0 9)	15 7 (0 8)	0 65
Fish	39 5 (5 7)	46 5 (5 6)	0 16

Results in g/day. Mean (SEM). Delicatessen = ham, sausage, and offal.

Table 5: **Intake of the main foodstuffs after 1 to 4-years follow-up in the 2 groups**

	Experimental group—(weeks)				At 1 to 4 years follow up*		
	0 n = 210	8 n = 228	52 n = 243	104 n = 145	Control n = 192	Experimental n = 219	p
Total calories	2062 (43)	1964 (37)	1944 (32)	1991 (43)	2140 (45)	1928 (32)	<0 001
Proteins (g)	17 2 (0 3)	17 1 (0 2)	17 0 (0 3)	17 2 (0 3)	16 5 (0 3)	17 2 (0 3)	0 12
Comprising—% calories							
Total lipids	30 7 (0 6)	28 6 (0 5)	29 2 (0 5)	30·0 (0 6)	32 7 (0 7)	30 5 (0 5)	0 008
Saturated fats	10·5 (0 3)	7 1 (0 2)	7 7 (0 2)	7 9 (0 3)	11 7 (0 4)	8 3 (0 2)	<0 001
18:1 (n-9)	9 0 (0·2)	12 2 (0 2)	12 6 (0 3)	12 9 (0 3)	10 3 (0 3)	12 9 (0 3)	<0 001
18:2 (n-6)	5.8 (0·2)	3 6 (0 1)	3 5 (0 1)	3 6 (0 1)	5 3 (0 2)	3 6 (0 1)	<0 001
18:3 (n-3)	0 24 (0 01)	0 76 (0 03)	0 77 (0 03)	0 80 (0 04)	0 27 (0 02)	0 81 (0 03)	<0 001
Alcohol	5 1 (0 4)	5 0 (0 4)	5 5 (0 4)	4 9 (0 5)	6 4 (0·5)	5 5 (0 4)	0 19
P/S ratio	0 78 (0 04)	0·77 (0 03)	0 70 (0 03)	0·73 (0 03)	0 69 (0 07)	0 65 (0·06)	0·59
Ascorbic acid (mg)	120 5 (4 6)	129 1 (5 4)	118 6 (4 1)	125 0 (5 5)	101 7 (4 7)	115 8 (4 2)	0 02
Alpha-tocopherol (mg)	13 9 (0·5)	11 9 (0 3)	11 7 (0 3)	11 6 (0 4)	12 9 (0 5)	11 6 (0 3)	0 02
Cholesterol (mg)	333 (16)	252 (14)	219 (11)	237 (14)	318 (15)	217 (11)	<0 001

*Evaluation of controls done only June 1992 to March 1993 so as not to influence diètary habits of the control group earlier in the study, compared to the experimental groups evaluated during the same period. Mean (SE). P/S = polyunsaturated/saturated fat.

Table 3: **Nutrient daily intake in the experimental group at different periods, and in control and experimental groups at the same period of follow-up**

Fatty Acids	BL %	Con %	Int %	BL (g)	Con (g)	Int (g)	Con Δ	Int Δ	BG Δ	X Δ
Calories	2062	2140	1928	2062	2140	1928	1.04	0.94	0.90	1.11
Total Fat	30.7	32.7	30.5	73.0	77.8	65.3	1.07	0.90	0.84	1.19
SFA	10.5	11.7	8.3	24.1	27.8	17.8	1.16	0.74	0.64	1.56
18:1	9.0	10.3	12.9	20.6	24.5	27.6	1.19	1.34	1.13	1.13
18:2	5.8	5.3	3.6	13.3	12.6	7.7	0.95	0.58	0.61	1.63
18:3	0.2	0.3	0.8	0.5	0.6	1.8	1.17	3.27	2.80	2.80
Alcohol	5.1	6.4	5.8	15.0	19.6	16.1	1.30	1.07	0.82	1.22

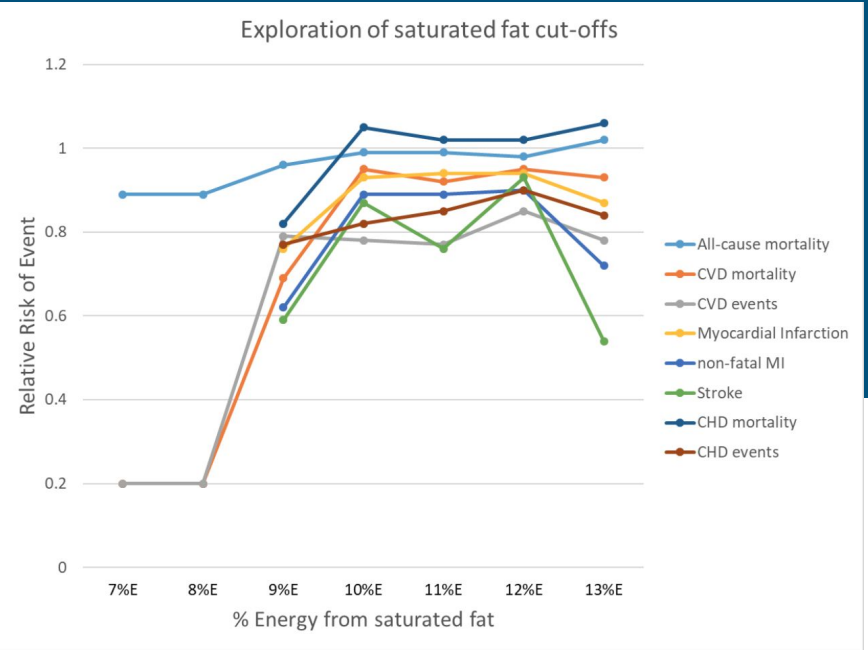


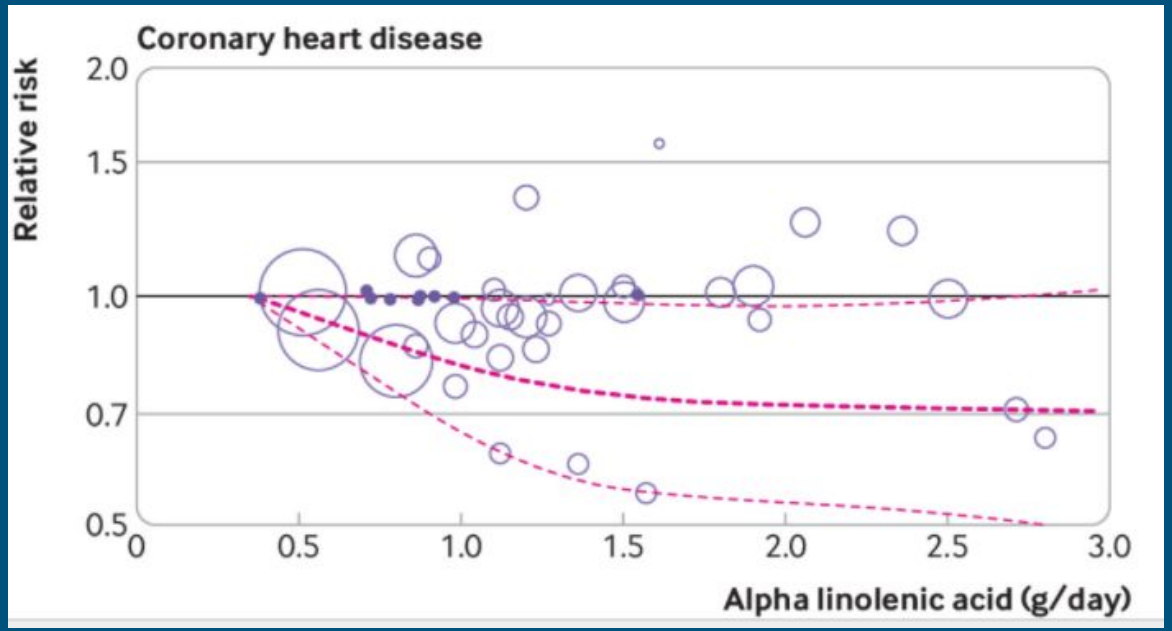
Table 4. Meta-regression of effects of SFA reduction on cardiovascular events

Regression factor	No. of studies	Constant	Coefficient (95% CI)	P value	Proportion of between study variation explained
Change in SFA as %E	8	0.01	0.05 (-0.03 to 0.13)	0.16	89%
Change in SFA as % of control	8	0.26	0.01 (-0.01 to 0.03)	0.14	89%
Baseline SFA as %E	8	0.68	-0.06 (-0.15 to 0.04)	0.19	81%
Change in TC, mmol/L	12	0.03	0.69 (0.05 to 1.33)	0.04	99%
Change in PUFA as %E	5	-0.01	-0.02 (-0.08 to 0.03)	0.25	100%
Change in MUFA as %E	5	-0.26	-0.03 (-0.14 to 0.09)	0.50	-87%
Change in CHO as %E	7	-0.11	-0.00 (-0.05 to 0.05)	0.92	-273%
Change in total fat intake as %E	9	-0.17	-0.01 (-0.03 to 0.01)	0.28	100%
Gender*	13	-0.17	-0.14 (-0.63 to 0.35)	0.55	-13%
Study duration	13	-0.47	0.00 (-0.01 to 0.02)	0.76	-24.8%
CVD risk at baseline**	13	-0.44	0.03 (-0.48 to 0.55)	0.89	-39%

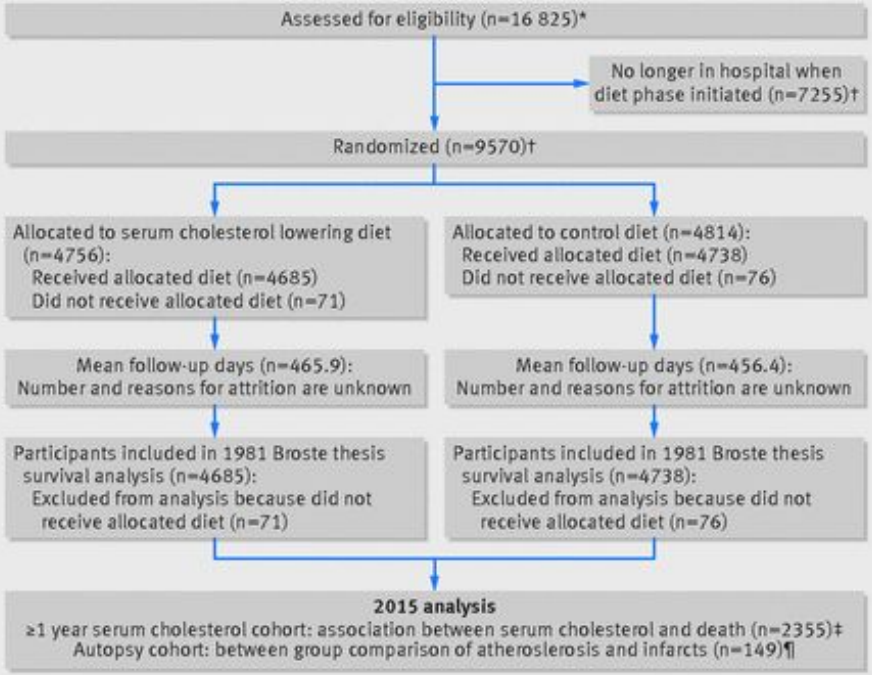
Research

Dietary intake and biomarkers of alpha linolenic acid and risk of all cause, cardiovascular, and cancer mortality: systematic review and dose-response meta-analysis of cohort studies

BMJ 2021 ; 375 doi: https://doi.org/10.1136/bmj.n2213 (Published 14 October 2021)
Cite this as: *BMJ* 2021;375:n2213



Ramsden, 2016



Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968-73)

BMJ 2016 ; 353 doi: https://doi.org/10.1136/bmj.i1246 (Published 12 April 2016)
Cite this as: *BMJ* 2016;353:i1246

Power and sample size considerations

The recovered documents did not contain a traditional sample size calculation. This was likely because of the lack of a prespecified primary endpoint. We did recover multiple power calculations with different endpoints and assumptions, which provide ranges for adequate sample sizes. For example, based on epidemiological associations between serum cholesterol and coronary heart disease events in non-randomized cohorts, the MCE investigators applied the Cornfield equation [risk = k(serum cholesterol)^{n}] to predict that between 2490 and 11 645 participants would be required to "obtain a difference in 5 years significant at the 95% confidence level" with $\alpha=\beta=0.05$.[19] Based on the rate of strictly defined deaths from coronary heart disease observed during the MCE observational phase, and the elimination of all participants staying in the hospital less than a year, the estimated duration of the experiment required to assess the efficacy of the intervention was 3.6 years (with $\alpha=\beta=0.05$).[20] These calculations were made to allow 95% power; typical β used in randomized controlled trials today is 0.20, which allows for 80% power.

Test of effect of lipid lowering by diet on cardiovascular risk. The Minnesota Coronary Survey.

I D FrantzJr, E A Dawson, P L Ashman, L C Gatewood, G E Bartsch, K Kuba and E R Brewer

Originally published 1 Jan 1989 | https://doi.org/10.1161/01.ATV.9.1.129 | Arteriosclerosis: An Official Journal of the American Heart Association, Inc.. 1989;9:129–135

Table 4. Primary End-points (Acute and Silent Myocardial Infarctions and Sudden Deaths)

Time in hospital (yrs)	Men		Women		Total	
	Treatment	Control	Treatment	Control	Treatment	Control
<1	81.9(42)	88.0(47)	55.6(35)	27.6(16)	67.4 (77)	56.6 (63)
≥1	13.9(27)	14.8(27)	15.5(27)	17.4(31)	14.7 (54)	16.1 (58)
≥2	8.8(14)	11.4(17)	11.3(16)	10.5(15)	10.0 (30)	11.0 (32)
≥3	4.3 (5)	7.0 (8)	8.9(10)	4.3 (5)	6.6 (15)	5.6 (13)
≥4	1.2 (1)	1.3 (1)	1.3 (1)	0.0 (0)	1.3 (2)	0.6 (1)
Total	28.1(69)	31.4(74)	26.2(62)	19.9(47)	27.2(131)	25.7(121)

These data include people of all ages. Values are the rates per 1000 person-years with numbers of persons in parentheses.

Table 6, in which the analysis is confined to persons on diet for at least 2 years and in the age groups chosen for recent drug trials, shows some favorable trends, but the numbers are far too small to achieve statistical significance.

Table 6. Trends in Persons on Diets More than 2 Years

	Events	
	Acute MI, sudden death, and silent MI	All deaths
Ages 35 to 39		
Men		
Treatment group	5.4(4)	5.4(4)
Control group	9.8(7)	7.0(5)
Women		
Treatment group	3.2(2)	9.8(6)
Control group	6.6(4)	6.6(4)
Ages 45 to 55 years		
Men		
Treatment group	0.0(0)	6.1(2)
Control group	16.7(6)	11.1(4)
Women		
Treatment group	3.8(1)	3.8(1)
Control group	14.2(4)	14.2(4)

Values are events or deaths per 1000 person-years with numbers of persons in parentheses.
MI=myocardial infarction.

Dietary Fats and Cardiovascular Disease: A Presidential Advisory From the American Heart Association

Frank M. Sacks, Alice H. Lichtenstein, Jason H.Y. Wu, Lawrence J. Appel, Mark A. Creager, Penny M. Kris-Etherton, Michael Miller, Eric B. Rimm, Lawrence L. Rudel, Jennifer G. Robinson, ... See all authors
and On behalf of the American Heart Association

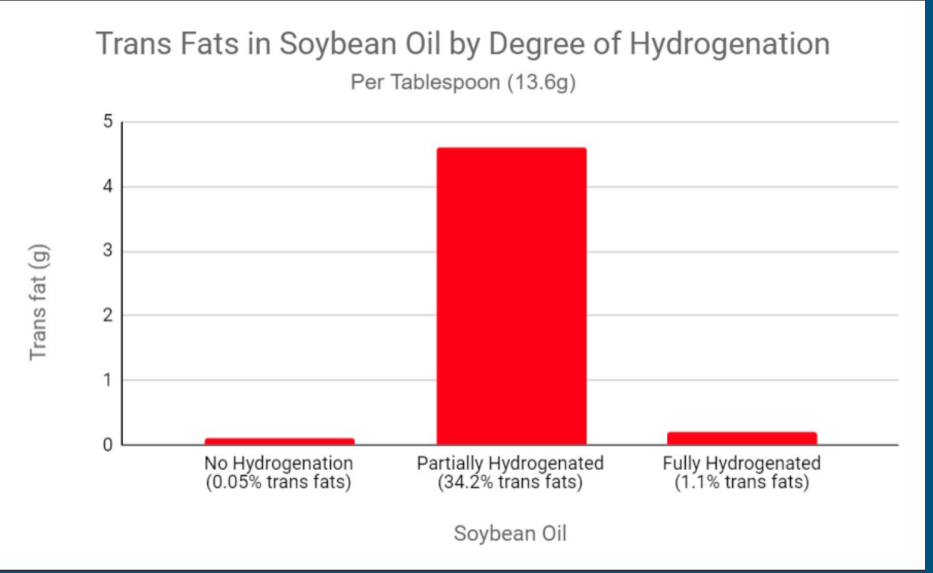
Originally published 15 Jun 2017 | https://doi.org/10.1161/CIR.0000000000000510 | Circulation. 2017;136:e1–e23

Table 2 Predicted and observed changes in serum cholesterol in intervention and control groups

	Observed dietary changes*		Serum cholesterol % changes	
	LA (% change)	SFA (% change)	Predicted based on Keys equation†	Observed in MCE (n=2355)‡
Intervention diet	288	−51	−18.1%	−13.8% (SD 13.0%), P<0.001
Control diet	38	-1	−1.1%	−1.0% (SD 14.5%), P<0.001

LA=linoleic acid; SFA=saturated fat.
*Changes from baseline hospital diet calculated from 1975 abstract, with LA estimated by multiplying total polyunsaturated fatty acids by 0.9.
†ΔChol=1.3(2ΔS−ΔP) where S and P are percentage of calories from saturated and polyunsaturated fatty acids, respectively
‡Percent change in serum cholesterol concentration calculated for each individual in cohort that received diet for one year or more. P values from paired *t* test comparing concentrations before and after randomization.

The Minnesota Coronary Survey[34] compared high polyunsaturated with high saturated fat diets in patients hospitalized for mental illness. The participants were given the assigned diets only when they were patients in the hospital. Because hospitalization for mental illness became less common and less prolonged after the study started, as a national trend, the patients received the assigned diets intermittently, contrary to the intent of the researchers, and for a much shorter time than planned. The researchers originally enrolled 9570 participants in the trial and intended to study them for at least 3.6 years to be able to adequately test the effect of the diets. However, the trend toward outpatient treatment of mental illness resulted in ≈75% of the participants being discharged from inpatient care during the first year of the study. Only about half the remaining patients stayed in the study for at least 3 years. The average duration was only 384 days. The incidence of CHD events was similar in the 2 groups, 25.7 and 27.2 per 1000 person-years in the control and polyunsaturated fat groups, respectively. A recent reanalysis of this trial restricted to the participants who remained in the trial for at least 1 year also found no significant differences in CHD events or CHD deaths.[39] We excluded this trial from the core group because of the short duration, large percentage of withdrawals from the study, and intermittent treatment, which is not relevant to clinical practice. Another concern is the use of lightly hydrogenated corn oil margarine in the polyunsaturated fat diet. This type of margarine contains *trans* linoleic acid, the type of *trans* fatty acid most strongly associated with CHD.[40]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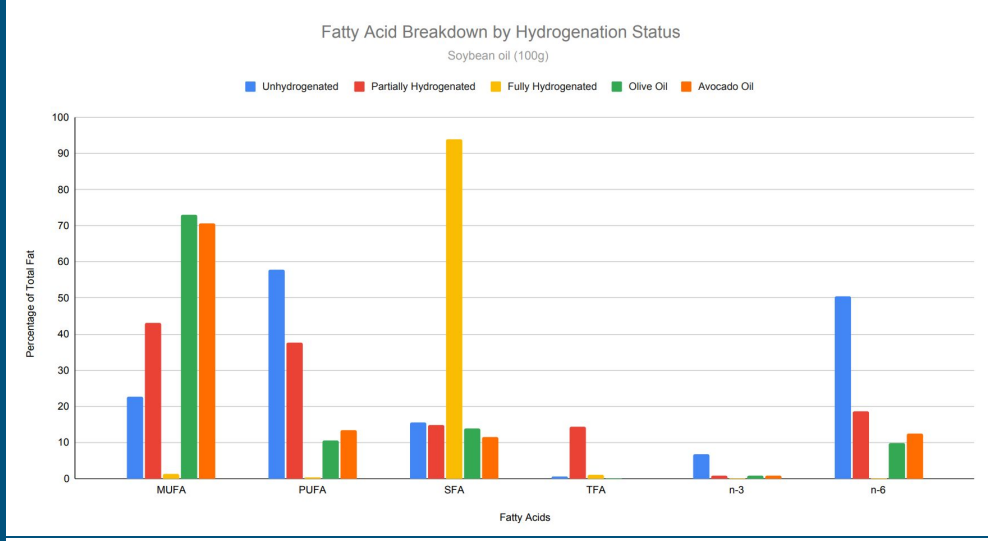
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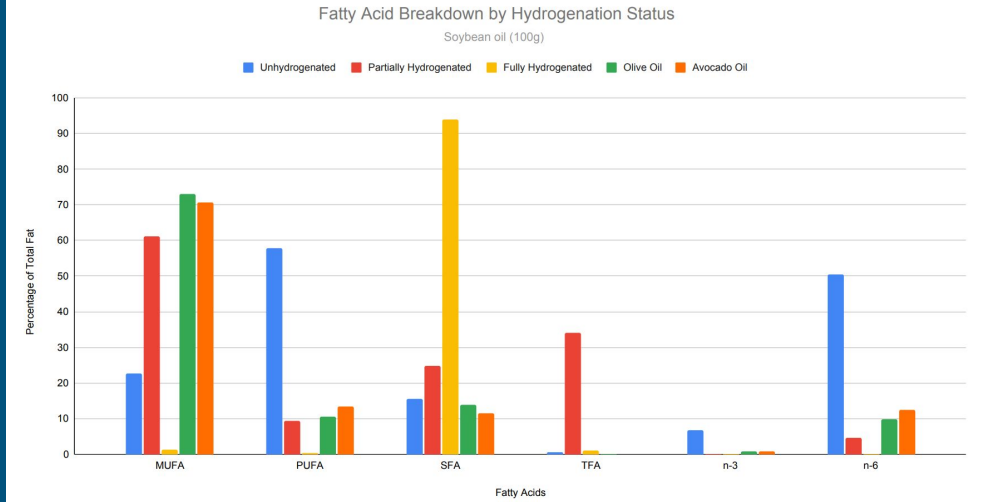
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Fatty Acids

Zock, 1992

Clinical Trial > J Lipid Res. 1992 Mar;33(3):399-410.

Hydrogenation alternatives: effects of trans fatty acids and stearic acid versus linoleic acid on serum lipids and lipoproteins in humans

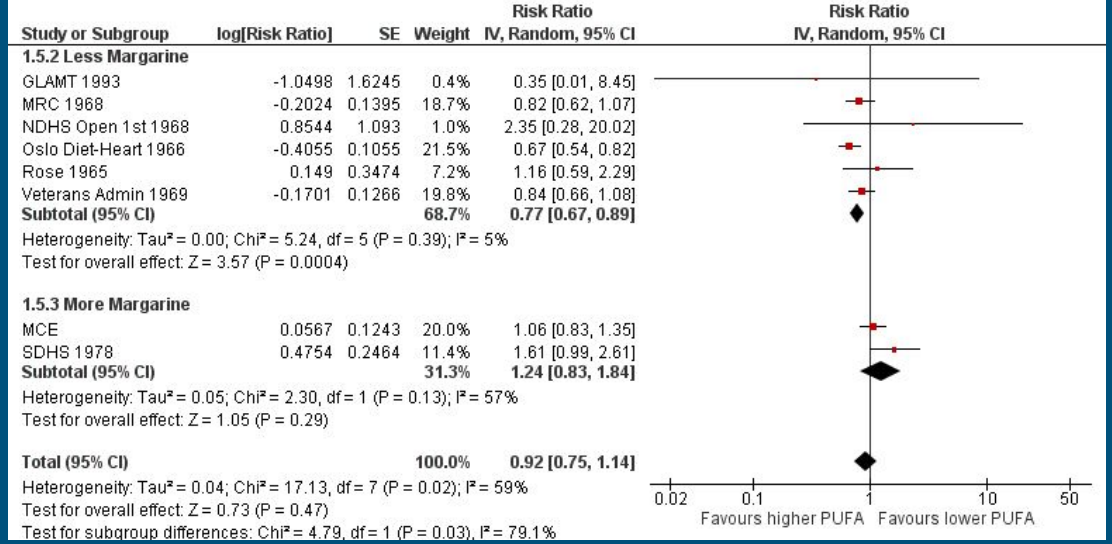
P L Zock [1], M B Katan

TABLE 3. Fatty acid composition of serum cholesteryl esters at the end of the three dietary periods

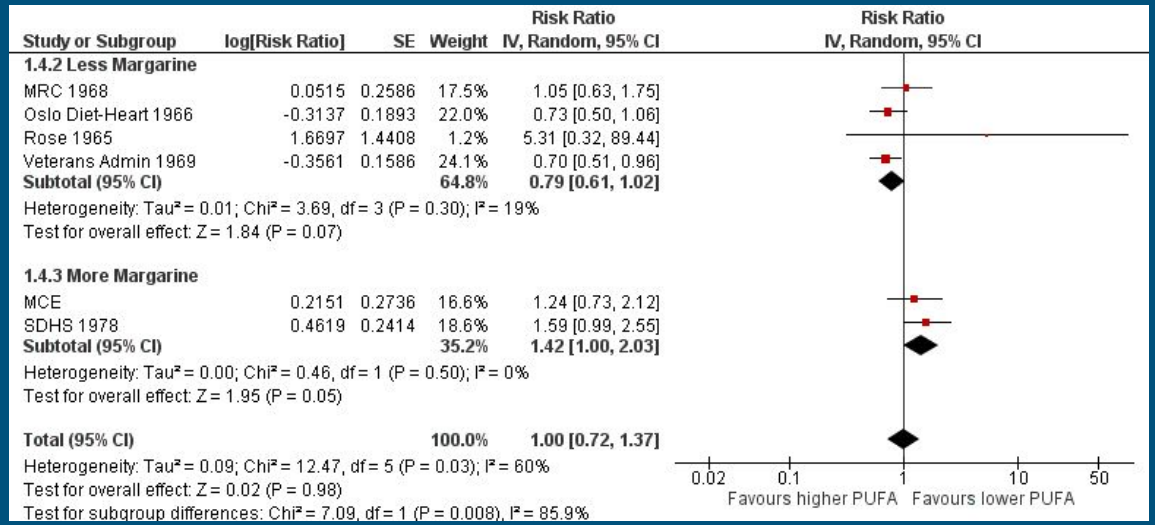
Fatty Acid	Linoleate-Diet	Stearate-Diet	*Trans*-Diet
		g per 100 g of fatty acids	
C14:0	2.71 ± 0.85	2.29 ± 1.18	2.52 ± 1.05
C16:0[a]	8.75 ± 0.55	8.37 ± 0.64	9.10 ± 0.64
C16:1[a]	1.72 ± 0.77	1.97 ± 0.72	2.52 ± 0.62
C18:0	0.77 ± 0.11	1.74 ± 0.38[b]	0.87 ± 0.29
cis-C18:1[a]	15.06 ± 1.57[b]	20.16 ± 1.44	20.62 ± 1.40
Trans-C18:1	0.13 ± 0.18	0.12 ± 0.19	0.94 ± 0.30[b]
Cis,cis-C18:2[a]	61.01 ± 3.92[b]	54.41 ± 3.23	52.84 ± 3.35
C20:4	6.36 ± 1.36	6.79 ± 1.32	6.42 ± 1.05
Other	3.51 ± 0.98	4.16 ± 0.81	4.17 ± 0.81

Values are means ± SD. The 26 men and 30 women consumed each diet for 3 weeks each, in random order.
[a]Significantly different between each of the diets, $P < 0.02$.
[b]Significantly different from both other diets, $P < 0.0001$.

CVD events



CVD mortality

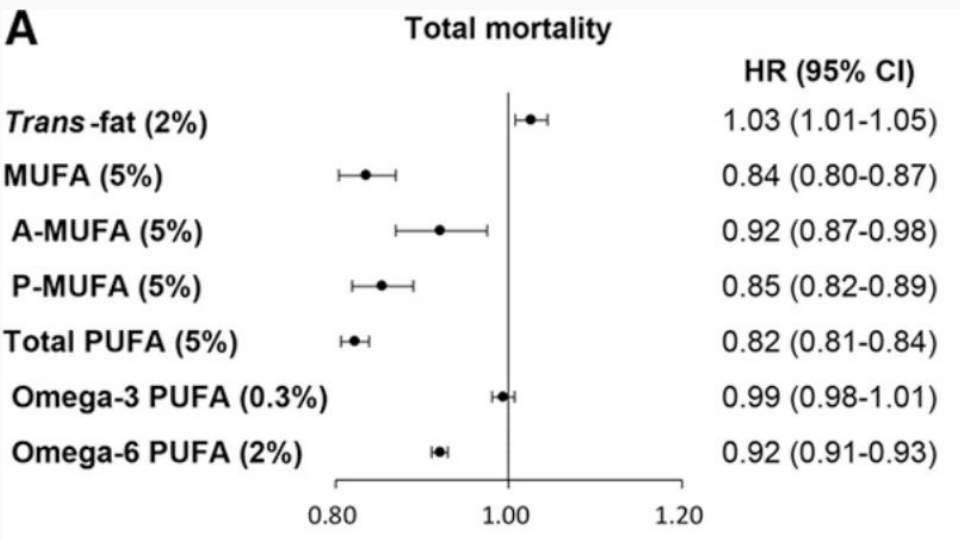


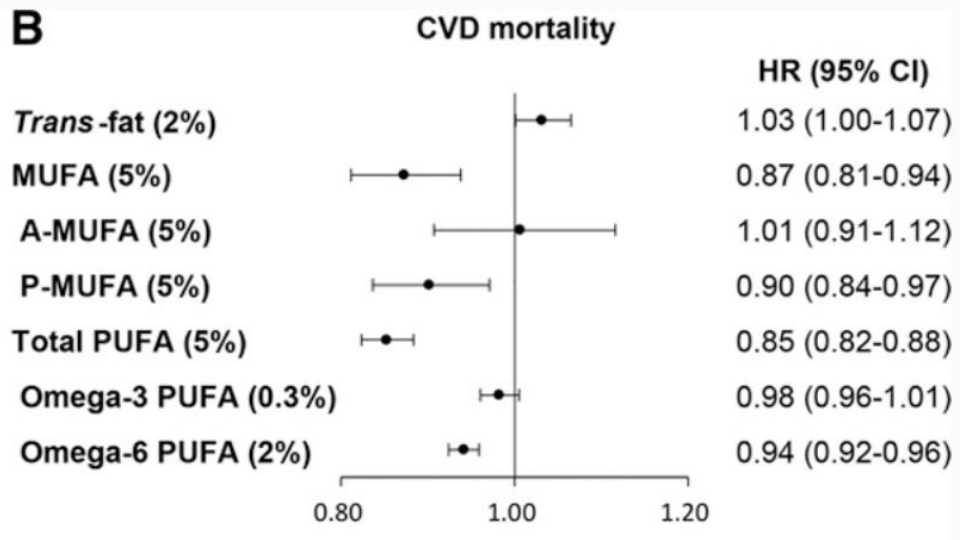
Zhuang, 2019

Dietary Fats in Relation to Total and Cause-Specific Mortality in a Prospective Cohort of 521 120 Individuals With 16 Years of Follow-Up

Pan Zhuang, Yu Zhang, Wei He, Xiaoqian Chen, Jingnan Chen, Lilin He, Lei Mao, Fei Wu and Jingjing Jiao

Originally published 14 Jan 2019 |
https://doi.org/10.1161/CIRCRESAHA.118.314038 |
Circulation Research. 2019;124:757–768

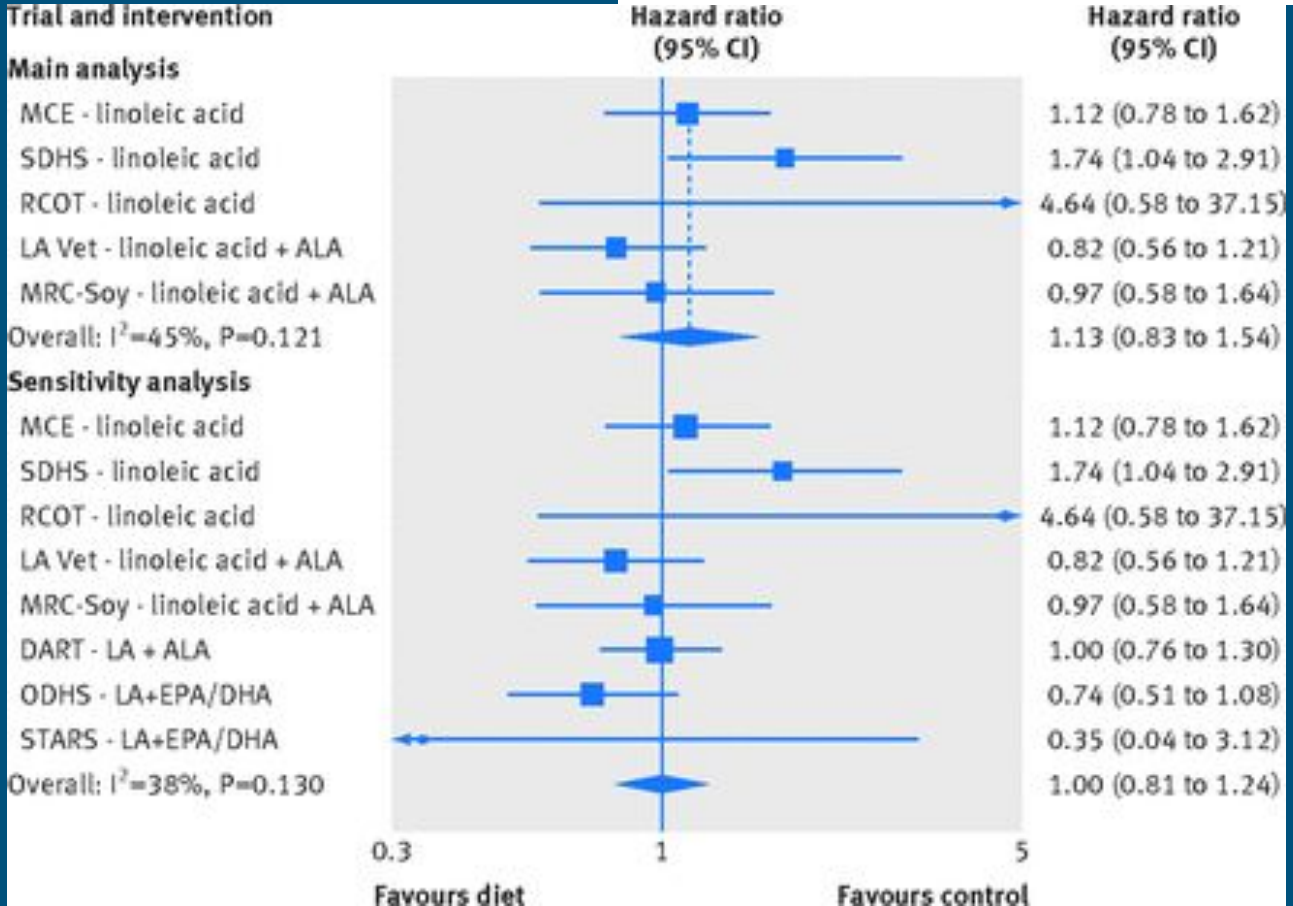




Ramsden, 2016

Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968-73)

BMJ 2016 ; 353 doi: https://doi.org/10.1136/bmj.i1246 (Published 12 April 2016)
Cite this as: *BMJ* 2016;353:i1246



Ramsden, 2013

Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis

BMJ 2013 ; 346 doi: https://doi.org/10.1136/bmj.e8707 (Published 05 February 2013)
Cite this as: *BMJ* 2013;346:e8707

Diet intervention

The intervention group received instructions to increase their PUFA intake to about 15% of food energy, and to reduce their intake of SFA and dietary cholesterol to less than 10% of food energy and 300 mg per day, respectively.[10] To achieve these targets, intervention participants were provided with liquid safflower oil and safflower oil polyunsaturated margarine ("Miracle" brand, Marrickville Margarine). Liquid safflower oil was substituted for animal fats, common margarines and shortenings in cooking oils, salad dressings, baked goods, and other products, and was also taken as a supplement. Safflower oil polyunsaturated margarine was used in place of butter and common margarines. Safflower oil is a concentrated source of n-6 LA (table 1)[9] and contains no other reported PUFAs. Therefore, the intervention oil selectively increased n-6 LA without a concurrent increase in n-3 PUFAs; this LA selective PUFA intervention will be referred to as the LA intervention.

However, Dr Robert Grenfell, National Cardiovascular Health Director at the Heart Foundation said that the new research from the 1966 study is "misguided" because it is not based on a healthy group of people.

"This was not a study in a healthy population, but a study in a small group of unhealthy middle aged men," Dr Grenfell said.

"In the 60s and 70s margarine still contained trans fats – which we now know are extremely harmful to heart health. Replacing saturated fat with a product that was high in trans fat would never be recommended now," Dr Grenfell added.

Meanwhile, the Deputy Chairman of the Sydney University Nutrition Research Foundation, Bill Shrapnel, agreed that the study was not objective because margarine no longer contains the trans fatty acids it did at the time of the trials.

"When this study began, Miracle margarine contained approximately 15 per cent trans fatty acids, which have the worst effect on heart disease risk of any fat. The adverse effect of the intervention in this study was almost certainly due to the increase in trans fatty acids in the diet," Mr Shrapnel said.

"Recent, well conducted studies indicate that replacing saturated fat with polyunsaturated fats lowers heart disease risk and this is widely accepted," Mr Shrapnel added.

Dietary Fats and Cardiovascular Disease: A Presidential Advisory From the American Heart Association

Frank M. Sacks, Alice H. Lichtenstein, Jason H.Y. Wu, Lawrence J. Appel, Mark A. Creager, Penny M. Kris-Etherton, Michael Miller, Eric B. Rimm, Lawrence L. Rudel, Jennifer G. Robinson, ... See all authors
and On behalf of the American Heart Association

Originally published 15 Jun 2017 | https://doi.org/10.1161/CIR.0000000000000510 | Circulation. 2017;136:e1–e23

The Sydney Heart Study[35] was unique among the diet trials on CVD because a margarine high in *trans* unsaturated fat was a major component of the diet for participants assigned to the high polyunsaturated diet. When this trial was conducted, there was little recognition of the harms of *trans* unsaturated fat in partially hydrogenated vegetable oils, so the researchers inadvertently tested substitution of saturated with an even more atherogenic *trans* fat. As predicted from current knowledge about *trans* unsaturated fat, CVD events were higher in the experimental group. If anything, this trial confirmed the results of observational studies that also report higher CVD risk from results from regression models in which *trans* unsaturated fat replaced saturated fat.[41,42] We did not include this trial in our evaluation of the effects of lowering dietary saturated fat because *trans* fats are not recommended[3,13] and are being eliminated from the food supply.[43]

Rose, 1965

Br Med J. 1965 Jun 12; 1(5449): 1531–1533.
doi: 10.1136/bmj.1.5449.1531

Corn Oil in Treatment of Ischaemic Heart Disease

G. A. Rose, W. B. Thomson, and R. T. Williams

TABLE I.—*Characteristics of Patients at Entry to Trial in the Three Treatment Groups*

	Treatment Group		
	Control	Olive Oil	Corn Oil
Total No. of patients	26	26	28
Mean age at entry (years)	58·8	55·0	52·6
„ body weight (kg.)	71·8	71·4	75·9
„ serum cholesterol (mg./100 ml.)	253	262	263
History of angina only	*5*	*4*	*4*
Resting E.C.G. normal	0	3	2
„ „ abnormal	5	1	2
History of infarction	*21*	*22*	*24*
1 infarct only	17	17	20
2 or more infarcts	4	5	4
Resting E.C.G. normal	1	4	3
„ „ abnormal	20	18	21
Diastolic B.P. ⩽90 mm.	9	14	13
„ „ >90 mm.	12	8	11
No exertional dyspnoea	9	7	15
Exertional dyspnoea	12	15	9
No heart failure	14	15	19
Heart failure*	7	7	5

* Jugular venous congestion *or* oedema *or* basal fine rales.

TABLE V.—*Progress of Patients*

	0–6 Months			6–12 Months			12–18 Months			18–24 Months		
	Control	Olive	Corn	Control	Olive	Corn	Control	Olive	Corn	Control	Olive	Corn
Major cardiac events:												
Sudden death	—	1	2	—	—	—	1	1	1	—	—	—
Fatal infarction	—	—	1	—	1	1	—	—	—	—	—	—
Definite infarction, non-fatal	2	2	1	—	—	—	1	1	2	—	1	—
Probable infarction, non-fatal	1	1	—	—	—	—	1	—	4	—	1	—
Total	3	4	4	0	1	1	3	2	7	0	2	0
"Other significant cardiac pain"	3	1	2	1	—	1	1	1	—	—	—	—
Removed from trial for other complications	—	—	—	—	1*	1‡	—	1†	1†	—	—	—
Lost to follow-up	—	1	—	1	—	1	1	1	—	—	1	—
Proportion in trial and free of major cardiac events, as percentage of those not removed from trial for other complications nor lost to follow-up	88	84	86	88	79	81	75	68	52	75	57	52

* Gangrene. † Diabetes mellitus. ‡ Pulmonary embolism.

Hooper, 2018

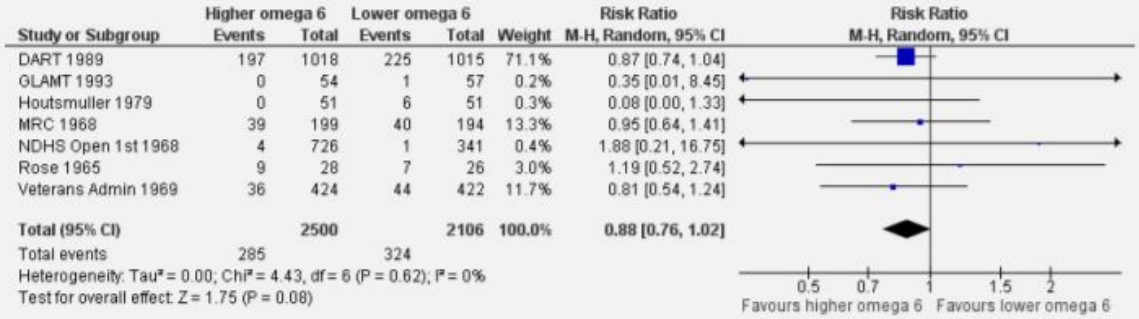
Cochrane Database of Systematic Reviews | Review - Intervention

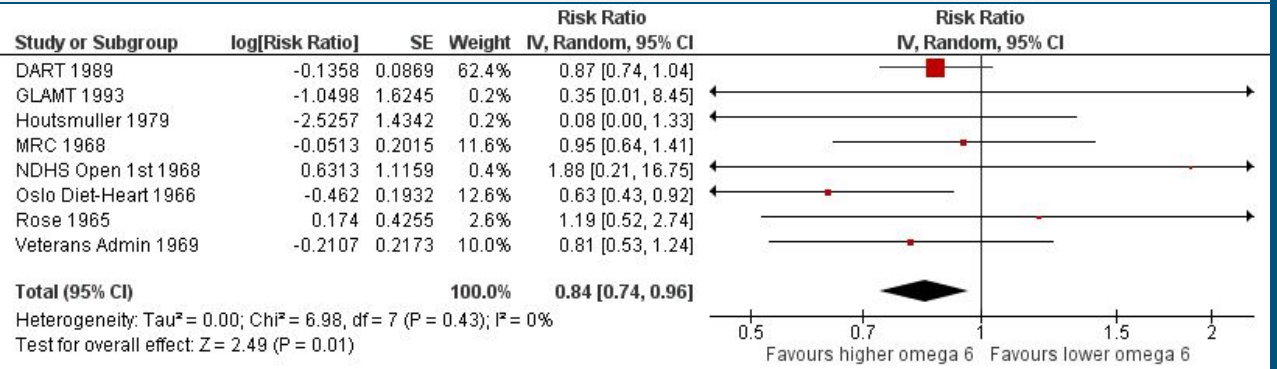
Omega-6 fats for the primary and secondary prevention of cardiovascular disease

Lee Hooper, Lena Al-Khudairy, Asmaa S Abdelhamid, Karen Rees, Julii S Brainard, Tracey J Brown, Sarah M Ajabnoor, Alex T O'Brien, Lauren E Winstanley, Daisy H Donaldson, Fujian Song, Katherine HO Deane
Authors' declarations of interest

Version published: 18 July 2018 Version history
https://doi.org/10.1002/14651858.CD011094.pub3

Figure 5. Forest plot of comparison: 2 Secondary outcomes - higher omega-6 vs lower omega-6, outcome: 2.1 Myocardial infarction (MI), overall.





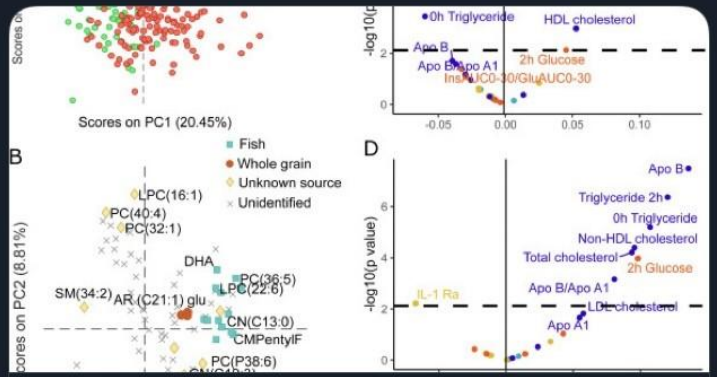
21 CVD mortality - subgroup by baseline omega-6 Show forest plot	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
21.1 ≥ 8% E from n-6	1	133	Risk Ratio (M-H, Random, 95% CI)	4.93 [0.24, 100.70]
21.2 5% to < 8% E from n-6	2	2491	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.05, 1.66]
21.3 < 5% E from n-6	1	846	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.51, 0.96]
21.4 Baseline n-6 not reported	3	549	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.38, 2.34]
44 CHD events - subgroup by baseline omega-6 Show forest plot	7	3997	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.66, 1.17]
44.1 ≥ 8% E from n-6	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
44.2 5% to < 8% E from n-6	2	2491	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.68, 2.01]
44.3 < 5% E from n-6	1	846	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.56, 1.04]
44.4 Baseline omega 6 not reported	4	660	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.31, 1.47]
38 CHD events - subgroup by LA or GLA Show forest plot	7	3997	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.66, 1.17]
38.1 Mainly LA	6	3886	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.66, 1.19]
38.2 GLA supplements	1	111	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.45]

31 Body weight, kg Show forest plot	4	358	Mean Difference (IV, Random, 95% CI)	-3.12 [-12.60, 6.36]
32 Body mass index, kg/m^2 Show forest plot	1	371	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.56, 0.16]
33 Fat weight, kg Show forest plot	1	30	Mean Difference (IV, Random, 95% CI)	-7.70 [-14.60, -0.80]

Simon Hill MSc, BSc (Hons) @th... · 6h

Hey Tucker are you suggesting the results of this study are not meaningful? If so, why?

Specific trial link that they're talking about below:



clinicalnutritionjournal.com

Analysis of the SYSDIET Healthy Nordic Diet randomized trial based on...

1 1

Tucker Goodrich

@TuckerGoodrich

Replying to @theproof

Not meaningful, no. Short-term, just markers, the usual nonsense.

"The scores of metabolites characterizing the diets associated with outcomes related with cardio-metabolic risk."