Appendix: Supplementary material [posted as supplied by author]
Part 1: MCE supporting materials and historical context

Tribute to Dr. Ivan Frantz in leading the Minnesota Coronary Experiment team

Reared on Margarine and to the Tune of Spinning Ultracentrifuges: A Son's Recollections of Ivan D. Frantz, Jr. During the Early Days of Lipid Research

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As the youngest son of Ivan and Veronica Frantz, I was born in Minneapolis, MN in 1958 at the University of Minnesota Hospitals. My father spent long days in his laboratory at the Variety Club Heart Hospital on East River Road. In the evening he would sit at the dining room table, a yellow pad in front of him, armed with a pencil, an eraser and sharpener, and an array of papers and files. He hand wrote his drafts, and as he did, the entire table would jostle. He had impeccable cursive, having won awards in school for his penmanship. On weekends he would take me down to the laboratory, pushing back a heavy wooden door with his name on it, revealing an exciting world filled with the sound of spinning ultracentrifuges. He showed me the miracle of separating lipid fractions with Percoll gradients, and the evolving techniques of electrophoresis. On crisp autumn Saturdays we would stop in before the Minnesota Gopher football game, and if we were lucky he would make a stellar New England clam chowder in a beaker over a Bunsen burner.

My father was a brilliant, yet humble man. His goal was to do the best science possible, and to promote public health through efforts to develop sufficient understanding of factors driving cardiovascular disease to permit informed intervention. He did not seek the spotlight. In the early days of lipid research, computers were in their infancy. As computing evolved and became an important tool for research, he taught himself computer languages, including Fortran and Cobol. He rarely took vacation, and when he did always brought along things to work on.

As I reflect on the evolution of thought regarding diet and cardiovascular risk, and having sifted through thousands of files from my father's basement that pertained to his passionate pursuit of lipid research, I think about what my father would have thought of the additional analyses so painstakingly conducted by Dr. Chris Ramsden and colleagues and reported in the accompanying manuscript.

In the first paragraph of a short paper published in Atherosclerosis in 1977 regarding treatment of hyperlipidemia, my father sounded a cautionary note: "Several of the more effective methods of treating hyperlipidemias were discovered by accident. In some cases the mode of action remains unknown. As

long as this state of ignorance persists, one must harbor some misgivings that, despite a satisfying fall in blood lipid concentrations, the treatment may be doing more harm than good [1]." In that paper, he closed by noting the remarkable Japanese fishermen who had a lifelong diet low in cholesterol and saturated fat, and wondering whether that lifelong approach was likely to be greater than what could be achieved by dietary modifications later in life.

He performed small crossover studies of the effects of various diets on lipid lowering in healthy college students, trying to understand whether the partially hydrogenated soybean oil favored by food manufacturers was as effective as corn or unhydrogenated soy oil in lipid lowering. The partially hydrogenated oil did lower cholesterol, but not as much as the other oils, and had less effect on triglycerides [2].

The campaign to undertake large clinical trials of dietary modification took many years to come to fruition. It was necessary to convince those responsible for public health that such trials were not only worth the expense, but also feasible. Therefore my father undertook preliminary studies to prove feasibility [3]. The Minnesota Coronary Survey thus was many years in the making, from its roots in epidemiology of cardiovascular disease, to development of analytical techniques capable of measuring lipid levels reproducibly, to designing the clinical trials and convincing the necessary policy stewards and funding agencies that such trials could and should be carried out. Completing the MCS was an enormous effort on the part of many individuals, including the subjects who agreed to participate. My father would praise the whole team for their efforts in making the work possible. The entire lipid research team at the U of M was passionate about what they were trying to accomplish. Accordingly the disappointment when the overall study results were negative must have been profound. My father officially had retired from the U of M in 1984, though it was hard to see any major difference in his work ethic as an Emeritus Professor in the years after that, culminating in the publication of the MCS study results in 1989 when he was 74 years old.

If he were alive today, I know my father would have been delighted that the data he had devoted his career to making possible had been painstakingly revisited in order to shed additional light on the frustratingly paradoxical results. Science is a never ending search for the truth, including the need to revise hypotheses, to explain unexpected results, and to apply that knowledge for the betterment of the human race.

Table A. Full cohort and pre-specified subgroups of the Minnesota Coronary Experiment

(Sub)groups	Key Considerations
Full cohort	With >9,400 participants, the full MCE population was easily the largest randomized controlled diet-heart trial testing whether replacement of SFA with vegetable oil rich in LA reduced the risk of CHD and death.
Women	The MCE is the only diet-heart trial to evaluate clinical effects in women after random assignment to either serum cholesterol lowering diet or control diet. Since CHD manifests later in women than men, the expanded age range of the MCE population was considered a unique opportunity to assess clinical efficacy of the diet in women.
Men	Men were considered a subgroup likely to establish benefit of the serum cholesterol lowering diet, due to higher incidence of CHD than women.
≥ age 65	The MCE is the larger of only two RCTs testing the clinical effects of a serum cholesterol-lowering diet in individuals older than 65. Analyses of this high-risk subgroup were planned but not reported.
< age 65	Participants <65 were considered a population that was likely to see benefit from the serum cholesterol lowering diet.
Primary prevention (No EKG evidence of prior myocardial infarction)	The majority of MCE participants (about 95%) did not have EKG evidence of a current or prior myocardial infarction (no pathological Q wave) at randomization.
Secondary prevention (EKG evidence of prior myocardial infarction)	In the grant proposal, MCE investigators reported that the presence of a pathological Q wave on EKG upon entry into the pre-randomization observational phase was associated with an increased risk of a subsequent event by a factor of 2.6 [4]. Analyses of this high-risk subgroup were planned but not reported.
Participants consuming study diets for ≥1 year	MCE investigators hypothesized that the effects of the serum cholesterol lowering diet would take substantial time to manifest. A special emphasis was placed on participants who were exposed to study diets for ≥ 1 year, in terms of serum cholesterol measurements, sample size calculations, and subgroup analyses [4-6].
Autopsy cohort	MCE investigators hypothesized that participants randomized to the serum cholesterol lowering diet would have less advanced coronary, aortic and cerebrovascular atherosclerosis and fewer myocardial infarcts and strokes at autopsy.

Table references[4-12]. Abbreviations: CHD, coronary heart disease; EKG, electrocardiogram.

Recovery and validation of MCE data and study materials

We recovered raw data from the Minnesota Coronary Experiment (MCE) stored on two 9-track magnetic tapes ('tape 2' and 'tape 4') (see **fig A** below), using similar methods as we previously employed to recover missing Sydney Diet Heart Study (see the web appendix of [13]). Technical expertise in data recovery and conversion was provided by John Svee (Data Conversion Resource, Inc., Aurora, Colorado, USA). Computer Logics software was used to read the raw tape to disk via a pertec interface with 9-track equipment attached to Windows 98 boxes in pure DOS mode. Tape 2 contained data written to tape on the 327th day of 1988. The raw MCE 'tape 2' data was split into 2 logical files with standard zero-length separation blocks between files. These data were stored on the tape in fixed length American Standard Code for Information Interchange (ASCII) text files. Tape 4 contained data written to tape on the 183rd day of 1985. We determined that it was written using Kronos operating system, version 53. This Kronos data was found to be expressed in 6-bit, rather than standard 8-bit characters. The data format and the exact character conversion table code (Table B-2 on page 106 from [14]) were identified and translated by trial and error, ultimately resulting in readable ASCII characters which were found to represent a related series of punched cards. Each "record" of punched card data ended in a series of ":" characters. These were translated from the original varying number of colon characters per line into PC record marks (character 13 + character 10). Next these punch card records were programmatically assembled into fixed length ASCII text records. This file of 57,664 records was split into three files representing Type D sub-records (MCE data collection form 011, see Appendix Section VI.), Type R sub-records (MCE form 02) and Type X sub-records (MCE forms 02/11).

In addition to the tape processing, Data Conversion Resource was used to post-process the results of numerous scanned data summary tables on green-bar paper. This process took the scanned documents translated via OCR and corrected for various OCR errors such as numeral "5" resulting as ":S" and so forth. These fully converted and corrected documents were triple-verified to ensure accuracy of character recognition. For further validation, each of the recovered MCE datasets were compared to each other and to data reported in the 1989 study publication [8], the 1981 Master's Thesis [9], and the 1975 conference proceedings [10-12], as well as numerous other recovered MCE documents and data sources. After validation, data elements from all sources were merged into a master file in a format suitable for statistical analysis.

Paper autopsy files were recovered for 149 of the 295 MCE participants who underwent autopsy. Each manila autopsy file folder contained completed carbon copies of MCE data forms 08 (Coronary Artery Atherosclerosis), 09 (Classification of Myocardial Infarcts), and 10 (Classification of Aorta), but did not contain missing data for Atherosclerosis of Brain (Form 12) or Circle of Willis (Form 13). Recovered autopsy data were entered into spreadsheets matching the MCE study forms in a blinded manner, and triple-verified for accuracy.

We also recovered an extensive collection of FORTRAN coding sheets authored by Dr. Ivan Frantz, which outlined the analysis plans for autopsy materials and other aspects of the study. Autopsy-related coding sheets included the original, extensive plans for analyses of myocardial infarcts, coronary atherosclerosis, aortic atherosclerosis, and cerebrovascular atherosclerosis, arteriosclerosis and infarcts according to treatment group, and stratified by gender, age and time on study diets.

We also found evidence that all autopsy-related data was stored on a 9-track magnetic tape (Tape #380, written on 12/12/1974) entitled 'Autopsy-stones'. Despite an extensive search, we have not yet been able to recover this tape.

fig A: Recovered 9-track magnetic "tape 4" with MCE data

Table B. Intervention start dates and diet duration in the seven MCE hospitals

Hospital	Observational Start date	Observational Duration (months)	Diet start date	Diet duration (months)
Willmar	9/1/1966	24	11/6/1968	56
Hastings	9/1/1966	26	1/14/1969	54
Fergus Falls	9/1/1966	27	2/11/1969	53
St. Peter	9/1/1966	31	5/15/1969	49
Oak Terrace Nursing Home	2/1966	40	6/2/1969	49
Moose Lake	9/1/1966	37	10/1/1969	45
Anoka	9/1/1966	42	2/16/1970	41

Chemical compositions of the intervention and control diets in the seven MCE hospitals

All samples included

CHEMICAL ANALYSIS OF THREE WEEK FOOD COLLECTION -- CONTROL AND TREATMENT DIETS

MAY 12, 1971 - JUNE 1, 1971

		TOT CAL	PROT GMS	FAT GMS	FAT %CAL	CHO GMS	CHOL MGMS	POLY %	POLY %CAL	SAT %	SAT %CAL	MONO %	MONO %CAL	OTHER %	OTHER %CAL	TOT FA %		P:S
ANOKA	CONTROL	2688	93.9	116.9	39.2	314.9	458	17.8	7.00	40.5	15.84	41.5	16.28	.2	.07	100.5	39.36	.55
ANOKA	TREATMENT	2792	95.4	129.1	41.6	312.2	150	44.1	18.33	19.3	8.03	36.5	15.18	.0	.02	99.8	41.46	2.29
FERGUS FALLS	CONTROL	2292	101.9	106.7	41.8	231.0	560	10.1	4.14	52.0	21.75	37.0	15.49	.9	.39	100.3	41.88	.20
FERGUS FALLS	TREATMENT	2162	99.6	99.3	41.3	217.5	195	36.1	14.95	26.8	11.06	36.9	15.21	.2	.09	100.0	41.31	1.35
HASTINGS	CONTROL	2244	75.4	103.3	41.4	253.2	402	11.9	4.93	50.7	20.98	36.8	15.23	.7	.27	99.7	41.27	.23
HASTINGS	TREATMENT	2247	76.3	99.5	39.8	261.4	111	42.1	16.79	21.4	8.53	36.1	14.38	.4	.15	100.0	39.85	1.97
MOOSE LAKE	CONTROL	2307	85.2	85.4	33.4	299.5	421	13.3	4.41	46.2	15.52	39.3	13.09	1.2	.39	100.1	33.45	.29
MOOSE LAKE	TREATMENT	2490	87.0	98.1	35.5	314.6	158	36.0	12.76	25.5	9.06	38.3	13.58	.2	.06	100.0	35.47	1.43
OAK TERRACE	CONTROL	2000	78.6	79.6	35.6	242.4	460	11.7	4.16	49.0	17.36	39.1	14.02	.3	.09	100.0	35.62	.24
OAK TERRACE	TREATMENT	2097	81.9	90.2	38.7	239.4	151	32.5	12.58	27.0	10.48	40.3	15.58	.2	.06	100.0	38.70	1.29
ST. PETER	CONTROL	2338	88.8	110.4	42.5	247.1	487	20.6	8.71	41.4	17.72	37.8	15.99	.3	.11	100.0	42.53	.62
ST. PETER	TREATMENT	2377	87.6	112.8	42.7	252.7	236	32.8	14.00	28.7	12.29	38.3	16.37	.2	.08	100.0	42.73	1.41
WILLMAR	CONTROL	2473	91.2	112.6	41.0	273.7	389	16.8	6.87	43.7	18.00	38.6	15.76	.9	.36	100.0	40.99	.40
WILLMAR	TREATMENT	2432	90.8	108.4	40.1	273.4	278	37.8	15.20	26.7	10.71	35.3	14.12	.2	.07	99.9	40.05	1.42

Cal=calories; GMS=grams; %CAL= percentage of food energy; MGMS=milligrams; CHO= carbohydrates; CHOL=dietary cholesterol; POLY=polyunsaturated fatty acids; SAT=saturated fatty acids; MONO=monounsaturated fatty acids; TOT FA=total fatty acids; P:S=polyunsaturated to saturated fatty acid ratio.

Table C: Classification of fatal and non-fatal events in the MCE

Event code	Diagnostic category
01	Acute myocardial infarction, autopsied
02	Acute myocardial infarction, not autopsied
03	Sudden cardiac death (cardiac arrest)
04	CHD death (other)
05	Acute myocardial infarction, non-fatal
06	Acute stroke, non-fatal
07	Acute CHD illness, non-fatal
08	Silent myocardial infarction (EKG only)
09	All other deaths
10	Stroke, fatal

Ascertainment and coding of fatal and non-fatal events

Fatal and non-fatal events were assigned specific International classification of diseases codes [5] by the PI under masked conditions based on evaluation of hospital chart and autopsy findings and, when necessary, consultation with the attending physician. Each event was later assigned to one of ten categories of MCE coded events (**table C**). To ensure masking was not compromised by the anticipated between-group differences in follow-up serum cholesterol, the PI did not have access to serum cholesterol measures [7].

The MCE team also paid close attention to the overall death rate in both groups since “atherosclerosis may contribute to many deaths in which no actual fresh myocardial infarct or coronary occlusion has occurred” [7], and “deaths attributed to pneumonia or other causes could be related ultimately to coronary events” [7].

Table D: Important MCE data that remain missing

Unanswered Questions	MCE Hypotheses	Data reported	Missing data	Why these data are important
Full cohort and pre-specified subpopulations				
Did the serum cholesterol lowering diet alter risk for CHD events and deaths in patients with pre-existing CHD (secondary prevention)?	The diet is likely to be protective in this high-risk population	392 randomized subjects had a pathological Q wave on initial EKG	CVD events and deaths were not reported for this high-risk population	This MCE subgroup is the second largest secondary prevention RCT cohort with provision of LA-rich vegetable oil in place of SFA (without co-provision of EPA+DHA). The Sydney Diet Heart Study (n=458) is the largest such cohort.
Did the serum cholesterol lowering diet alter risk for CHD events and deaths in participants 65 years of age and older?	Effects in older adults are unknown. "Even a clear negative result in older subjects would be of great practical significance" [7]	Life table analysis [9] shows substantial increased risk of death (without statistics).	CVD events were not reported. It is not clear if the increased risk of death in treatment group was statistically significant.	The MCE is the larger of only two RCT to test whether replacing SFA with vegetable oil rich in LA alters the risk of CHD and death in older adults.
Associations between changes in serum cholesterol and CVD events and deaths				
Was the degree of serum cholesterol lowering related to risk of CHD events and CHD deaths?	The degree of serum cholesterol lowering is likely to be inversely associated with risk of CHD events	No data reported. We recovered all serum cholesterol data.	CHD and CVD events for all subjects with serum cholesterol data	The MCE is the largest RCT to test whether the serum cholesterol lowering effects of replacing SFA with vegetable oil rich in LA alters the risk of CHD.
Post-mortem analyses				
Did the serum cholesterol-lowering diet reduce the progression of atherosclerosis in the Circle of Willis (brain) or the risk of stroke?	The diet is likely to reduce strokes and atherosclerotic progression	No data reported	Postmortem cerebrovascular atherosclerosis and infarct data for all 295 autopsies (Tape #380, 12/12/1974)	Only postmortem human data looking at the role of diet-induced serum cholesterol lowering, or of increasing LA in place of SFA, on cerebral atherosclerosis or ischemic stroke.
Did the serum cholesterol-lowering diet reduce the progression of aortic or coronary atherosclerosis or myocardial infarction?	The diet is likely to reduce myocardial infarcts and atherosclerotic progression	Recovered aortic and coronary atherosclerosis data and myocardial infarct data for 149 subjects	Postmortem coronary, aortic atherosclerosis and myocardial infarct data for 146 of 295 completed autopsies (MCE Tape #380)	Only postmortem human data looking at the role of diet-induced cholesterol lowering, or of increasing LA in place of SFA, on aortic or coronary atherosclerosis or myocardial infarcts (MI). Analysis of recovered data (partial dataset) found more MI, and a signal toward increased coronary atherosclerosis in the cholesterol lowering diet group.
New hypotheses to explain unfavorable study results				
Did the serum cholesterol-lowering diet have adverse effects in subpopulations known to have increased linoleic acid oxidation (eg, alcoholics, heavy smokers, older adults)?	Hypothesis proposed to help explain unfavorable results of the Sydney Diet Heart Study [13]	No data reported	Smoking status, alcoholic diagnosis and other diagnostic coding	In the Sydney Diet Heart Study, there was significant effect modification by drinking status; heavy drinkers (HR 2.89; p=0.03) and smokers (HR 2.09; p=0.03) who were randomized to the high LA intervention fared poorly [13]

Table E: Serum cholesterol lowering according to diet adherence in the MCE

Meals attended	Intervention			Control			Combined groups		
	n	mean	sd	n	mean	sd	n	mean	sd
>98%	390	-18.0	10.7	379	-2.8	13.6	769	-10.5	14.4
>90-98%	433	-14.3	12.8	451	-1.0	14.7	884	-7.5	15.3
>70-90%	258	-10.7	12.5	238	0.6	15.8	496	-5.2	15.3
≤70%	98	-2.9	15.4	108	1.6	13.3	206	-0.6	14.5
Total	**1179**	**-13.8**	**13.0**	**1176**	**-1.0**	**14.5**	**2355**	**-7.4**	**15.2**

Data are from the ≥1 year serum cholesterol cohort. Values are for average change in serum cholesterol from baseline.

Table F: Characteristics of the MCE autopsy cohort (n=149)

	Intervention		**Control**		t-Test
	Mean (SD)	n	Mean (SD)	n	p-value
Age at randomization, years	71.1 (11.9)	76	67.8 (14.1)	73	0.127
Systolic blood pressure, mmHg	127 (22.9)	75	128 (19.8)	68	0.829
Diastolic blood pressure, mmHg	77 (13.4)	75	75.1 (11.5)	68	0.363
Serum Cholesterol, mg/dL	214 (50)	69	206 (65)	62	0.403
Serum Triglycerides, mg/dL	109 (39.7)	69	113 (70.5)	62	0.699
BMI	23.6 (4.5)	69	23.2 (3.6)	61	0.617
Diet exposure in days	345 (272)	76	352 (312)	73	0.886
% Missed meals†	3.4 (5.4)	69	3.7 (7.0)	62	0.788
% Male	60.5 (49.2)	76	68.5 (46.8)	73	0.313

†Average percentage of missed meals throughout the full study period

Table G: Association between serum cholesterol and risk of infarct and atherosclerosis in the MCE autopsy cohort

	Intervention				Control				Both Groups			
	n	**Coef†**	**95% CI**	**p-value**	**n**	**Coef†**	**95% CI**	**p-value**	**n**	**Coef†**	**95% CI**	**p-value**
Coronary atherosclerosis score	64	-1.75	(-3.88, 0.38)	0.09	59	-0.24	(-2.27, 1.80)	0.78	123	-0.51	(-1.89, 0.87)	0.40
Aortic atherosclerosis score	61	0.10	(-0.23, 0.43)	0.49	56	-0.12	(-0.49, 0.26)	0.47	117	-0.02	(-0.33, 0.28)	0.85
	n	**OR‡**	**95% CI**	**p-value**	**n**	**OR‡**	**95% CI**	**p-value**	**n**	**OR‡**	**95% CI**	**p-value**
Myocardial infarcts	65	0.98	(0.56, 1.72)	0.96	59	1.02	(0.52, 1.99)	0.95	124	1.19	(0.84, 1.69)	0.34

†Coefficients are change in atherosclerosis score for each 30 mg/dL *decrease* in average serum cholesterol. Based on linear regressions for atherosclerosis score as a function of average follow-up serum cholesterol, adjusted for baseline serum cholesterol, age, BMI, gender, adherence to the diet, and systolic blood pressure, and clustering within hospital.

‡ Odds ratio for each 30 mg/dL *decrease* in average serum cholesterol. Based on logistic regressions for having at least one infarct as a function of average follow-up serum cholesterol, adjusted for baseline serum cholesterol, age, BMI, gender, adherence to the diet, and systolic blood pressure.

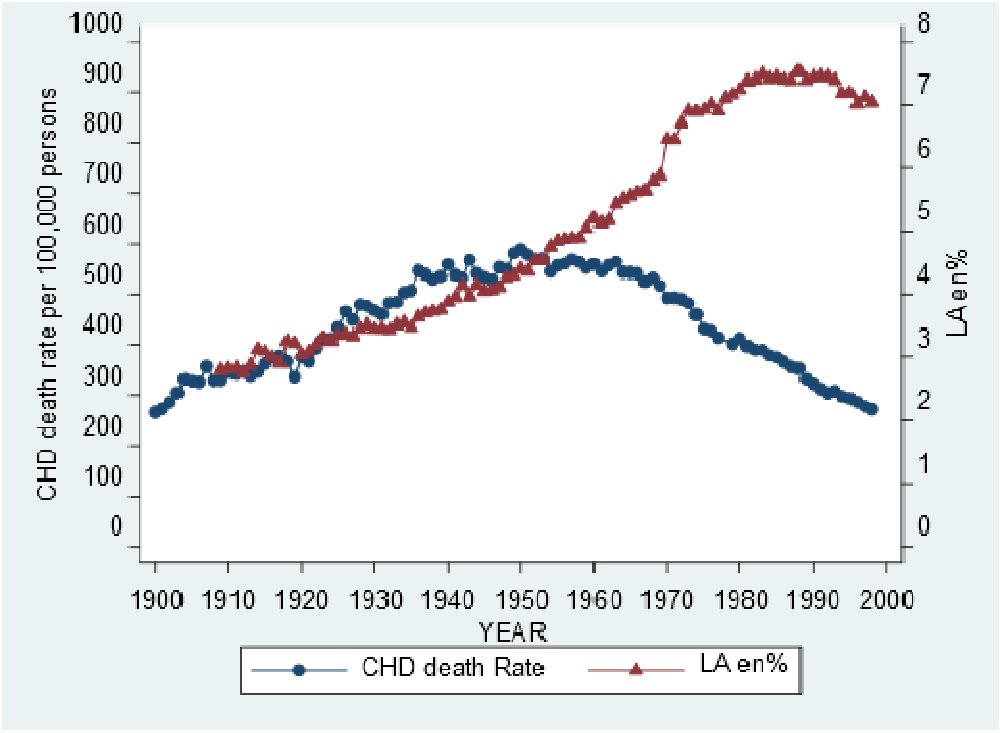

Fig B: Ecological association between change in LA and CHD mortality in the United States in the 20th century

Ecological associations between LA and CHD mortality are subject to many important confounders. Notable confounders in the 1909-1960 interval include diagnostic bias due to increasing availability of electrocardiograms, increased health care access, and growing appreciation for the presence of coronary heart disease. Notable confounders in the 1960–2000 interval include public health initiatives (eg, major declines in smoking & secondhand smoke exposure, widespread access to defibrillators and ambulances), and major advances in medications (eg, aspirin, antihypertensives, statins) and surgical treatments (e.g., coronary artery bypass graft, angioplasty).

†Mean annual LA intakes are estimated from USDA economic disappearance data and expressed as a percentage of food energy [15]; ‡CHD mortality data downloaded from [16].

Abbreviations: CHD, coronary heart disease; LA, linoleic acid; en%, percentage of energy from foods.

Ecological associations between LA intake and CHD mortality have been cited as support for the diet-heart hypothesis[17]. However, these associations are subject to many important confounders and wholly dependent on the timeframe selected (**fig B**). For example, the steep rise in per capita LA intake between 1909 and 1960 in the United States was accompanied by a steep rise in CHD mortality. By contrast, the comparatively modest increase in dietary LA between 1960 and 2000 coincided with a steep decline in CHD mortality. Drawing a causal inference from this latter interval requires disregarding both the rise in CHD, and many potential dominant confounders (see legend of **fig B**). It is also notable that the majority of the increase in per capita LA intake in the United States occurred before 1961, when serum cholesterol lowering dietary advice was initiated.

Table H: Linoleic acid contents of nuts, seeds, and vegetable oils

Whole food or extracted oil	LA content (g/100g)
Corn	0.5
Corn Oil	53.5
Soybeans	10.8
Soybean Oil	51.0
Sunflower Seeds	23.1
Sunflower Oil†	65.7
Cottonseed Oil	51.5
Canola Oil	19.0
Almonds	12.3
Pecans	20.6

LA, linoleic acid. Fatty acid contents of oils vary to some extent by season, latitude, and other conditions. USDA National Nutrient Database numbers: corn 11167, corn oil 04518, soybeans 16111, soybean oil 04044, sunflower seeds 12036, sunflower oil 04506, cottonseed oil 04502, canola oil 04582, almonds 12061, pecans 12142[18].†Varieties of sunflower oil with lower LA content are commercially available.

Part 2

Systematic review & meta-analysis of RCTs that replaced SFA with LA rich vegetable oil

Effects of Replacing Saturated Fat with Vegetable Oils Rich in Linoleic Acid on Coronary Heart Disease Mortality: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

ABSTRACT

Background

A key component of dietary guidelines has long been to replace saturated fat (SFA) with vegetable oils (e.g., corn oil, safflower oil, soybean oil) that are rich in linoleic acid (LA). This advice is based on the traditional diet-heart hypothesis prediction that replacement of SFA with LA decreases coronary heart disease (CHD) and all-cause mortality by reducing serum LDL and total cholesterol.

Objective

To conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) that specifically tested whether replacement of SFA with LA-rich vegetable oil decreases CHD mortality and all-cause mortality.

Methods

Studies published in English from 1950 to Sept. 2015 were identified through systematic searches of PubMed, EMBASE, and CINAHL, hand-searching of related publications, grey literature sources, and contact with study investigators and family members of deceased investigators to identify potentially unpublished trials and endpoints. Studies were included if they randomly assigned individual participants to a diet intervention that provided vegetable oil rich in linoleic acid in place of saturated fat compared to a usual care control diet, reported deaths from CHD or all-causes, and were not confounded by unequal intensity of major concomitant dietary or medical interventions. Study quality and bias assessment included the following: random sequence generation; adequacy of allocation concealment; adequacy of blinding of participants and personnel; adequacy of blinding of outcome assessments; selective reporting; systematic differences in between-group care; and study-specific sources of potential bias. All review stages were conducted independently by two investigators. Pooled hazard ratios (HR) were calculated using inverse-variance weighted random-effects meta-analysis.

Results

Of 1270 publications initially identified, only five RCTs were included in the main analysis representing 10,808 participants, 324 deaths attributed to CHD, and 1,001 deaths from all-causes. The mean change in serum cholesterol in the course of these trials ranged from 7.8 to 13.8% lower in the intervention vs. control groups. In meta-analyses, these cholesterol-lowering interventions showed no evidence of benefit on CHD mortality (HR 1.13; 95% CI 0.83, 1.54) or all-cause mortality (HR 1.07; 95% CI 0.90, 1.27). There was evidence of statistical heterogeneity in both magnitude and direction of effect for the CHD mortality (I^2: 45.1%; Tau^2: 0.0534) and all-cause mortality (I^2: 38.8%; Tau^2: 0.0132). In sensitivity analyses including additional 3 RCTs that were confounded by provision of n-3 EPA+DHA and other major diet changes, and/or relied on advice only (with modest diet changes) null results were noted for both CHD mortality (HR 1.00; 95% CI 0.81, 1.24; I^2: 37.5%;) and all-cause mortality (HR 1.00; 95% CI 0.87, 1.15; I^2: 34%). Reasons for heterogeneity of the pooled HR among the eight studies were explored; neither the dose of LA nor differences in between-group cholesterol lowering helped explain the heterogeneity.

Conclusions

Available RCT evidence demonstrates that replacement of SFA with LA-rich vegetable oil effectively lowers serum cholesterol, but does not support the hypothesis that this translates to lower risk of death from CHD or all-causes.

INTRODUCTION

The traditional diet-heart hypothesis predicts that replacing dietary SFA with vegetable oils rich in LA will reduce CHD events and deaths by lowering serum cholesterol. Advice to replace SFA with LA-rich vegetable oils (e.g., corn oil, sunflower oil, safflower oil, cottonseed oil, or soybean oil) has been a cornerstone of dietary guidelines for the past half-century (**see main paper, Figure 10**). However, the lack of supporting RCT evidence for such advice has been a source of controversy.[13, 19] Several diet-heart meta-analyses have been published, but they have not specifically examined the effects of replacing SFA with LA-rich vegetable oils. For example, a meta-analysis by Hooper et al [20] included RCTs that lowered SFA but did not distinguish between trials that replaced SFA with LA-rich oils, from those that replaced total and saturated fat with carbohydrates, and also included RCTs that markedly increased dietary EPA+DHA alongside LA. Similarly, Mozaffarian et al [21] included RCTs that markedly increased dietary EPA+DHA from seafood and cod liver oil, among other diet changes (e.g. sugar restriction, increase in fiber). EPA and DHA are not present in vegetable oils and are reported to influence CHD pathogenesis by mechanisms independent of cholesterol lowering. Therefore, it is not clear whether the results of previous meta-analyses are driven by 1) reductions in SFA, 2) replacement of SFA with LA-rich vegetable oil, 3) or to increases in EPA+DHA. The objective of this systematic review and meta-analysis is to determine whether RCTs that *specifically* replaced SFA with LA-rich vegetable oil(s) provide evidence to support the traditional diet-heart hypothesis.

METHODS

We followed the PRISMA (www.prisma-statement/org) guidelines[22] throughout the design, implementation, analysis, and reporting of this systematic review and meta-analysis.

Data sources

A protocol for this systematic review and meta-analysis has not been registered. A search was conducted using three major databases: the National Library of Medicine's PubMed, EMBASE, and CINAHL. We used search terms utilized by other investigators (2010) (**table I**).[21] Published meta-analyses and reviews were examined for additional peer-reviewed articles not discovered through database searches.[19-21] The search strategy focused on retrieval of articles from the peer-reviewed medical literature, reference lists of systematic reviews, meta-analyses, individual trials, grey literature sources, and, based on our previous work, also included extensive contact with study investigators and family members of deceased investigators to identify unpublished data.

Table I. PubMed Search Terms, 25 September 2015

("Fatty Acids, Omega-6"[Mesh] OR "unsaturated fatty acid"[tiab] OR "unsaturated fatty acids"[tiab] OR "unsaturated fat"[tiab] OR "unsaturated fats"[tiab] OR "polyunsaturated fatty acid"[tiab] OR "polyunsaturated fatty acids"[tiab] OR "polyunsaturated fat"[tiab] OR "polyunsaturated fats"[tiab] OR "omega-6"[tiab] OR "linoleic"[tiab] OR "octadecadienoic acid"[tiab] OR "safflower oil"[tiab] OR "sesame oil"[tiab] OR "soybean oil"[tiab] OR "soyabean oil"[tiab] OR "corn oil"[tiab]) AND ("cardiovascular diseases"[Mesh] OR "cardiovascular disease"[tiab] OR "cardiovascular diseases"[tiab] OR "heart disease"[tiab] OR "heart diseases"[tiab] OR "myocardial infarction"[tiab] OR "myocardial infarctions"[tiab] OR "heart attack"[tiab] OR "heart attacks"[tiab] OR "sudden death"[tiab] OR "sudden deaths"[tiab] OR "coronary syndrome"[tiab]) NOT ("Case Reports"[Publication Type] OR "stroke"[tiab] OR "strokes"[tiab] OR "cerebrovascular accident"[tiab] OR "cerebrovascular accidents"[tiab] OR "Fatty Acids, Omega-3"[Mesh] OR "omega-3"[tw] OR "n-3"[tw]) AND ((Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp]) AND "humans"[MeSH Terms] AND "adult"[MeSH Terms])

Study selection and data extraction

Included in the main analysis were all serum cholesterol-lowering RCTs with a publication in English that (a) randomly assigned individual participants, (b) provided an LA-rich vegetable oil intervention in place of SFA, compared to a usual care control diet, (c) were not confounded by the addition of large quantities of n-3 EPA and DHA or by other major concomitant interventions (e.g., complex diet pattern changes) or unequal intensity of medical management (e.g., smoking cessation advice or blood pressure control), and (d) reported deaths due to CHD or all causes. Hence, RCTs that provided large quantities of n-3 EPA and DHA, or provided advice only without provision of LA rich oils were excluded from the main analysis, as were studies with only biochemical or intermediate endpoints. Sensitivity analyses included diet-heart RCTs that also provided large quantities of n-3 EPA and DHA or provided advice only without provision of an LA-rich study oil, but otherwise met the inclusion and exclusion criteria for the main analysis.

All review stages were conducted independently by two investigators. Studies were screened based on an inspection of their titles and/or abstracts. Methods papers were carefully examined to determine key elements of the dietary interventions. Duplicate publications and abstracts from the same study were reviewed to examine consistency and to glean additional information about design and study outcomes but were otherwise not considered. Reviews and commentaries were not considered. Studies with a primary focus on medication evaluation were also excluded.

Data extracted from the studies included the number of trial participants in the experimental and control diets as well as deaths from coronary heart disease (CHD) and all causes by intervention group. Also extracted were hazard ratios where available along with the maximum follow-up time for each study. Additionally included were the fatty acid composition of the study oils and other aspects of the study

diets. The change in total cholesterol by group assignment was calculated for each study. Also noted was whether the sample populations were institutionalized or free living and whether the study target was secondary prevention of CHD (e.g., population recruited from post-infarction population) or a population with and without CHD at baseline.

Bias Assessment

Risk of bias was assessed for individual studies and included the following study characteristics: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessments; 5) selective reporting; 6) systematic differences in between-group medical care; and 7) study-specific sources of potential bias. Two investigators rated the risk of bias independently and resolved any discrepancies with discussion.

Statistical Analysis

We calculated pooled risk estimates (hazard ratios with 95% confidence intervals and p-values) for CHD death and all-cause mortality for the five RCTs that met inclusion criteria (main analysis) and again including Oslo Diet Heart Study, the St. Thomas Atherosclerosis Regression Study, and the Diet and Re-infarction Trial in sensitivity analysis. When hazard ratios were not available, they were estimated by calculating risk ratios. Results of random effects models are reported using the Dersimonian and Laird inverse-variance weighting method [23] . Between-study heterogeneity was assessed with the I^2 statistic along with an estimate of between-study variance (Tau-squared) and stratification by study oil. Publication bias was assessed by visual inspection of a funnel plot of the treatment effect versus standard error. Because there was some evidence of imbalance in the funnel plot, in a sensitivity analyses, estimates were examined using a trim and fill procedure and excluding the small Rose Corn Oil Trial. Potential sources of heterogeneity were explored using stratified fixed effects meta-analysis (for type of PUFAs) and inverse variance weighted meta-regressions (for between-group cholesterol reduction and increases in dietary linoleic acid).

Statistical analyses were performed using Stata version 13.1 (Stata Corporation, College Station, TX, 2009) with a two-tailed alpha set at 0.05.

Results

The searches returned a total of 1260 articles, 301 of which were duplicate articles or additional articles on the same study (**fig C 3**). Ten additional articles were identified through review articles. Most screened studies were excluded because they were supplement-only studies, they were drug interventions, or they only reported biochemical endpoints. Others were observational studies, commentaries, genetic studies, trial design studies, studies to develop dietary measures, or compliance reports. Particular attention was given to the 60 studies reporting dietary interventions (**table J**).

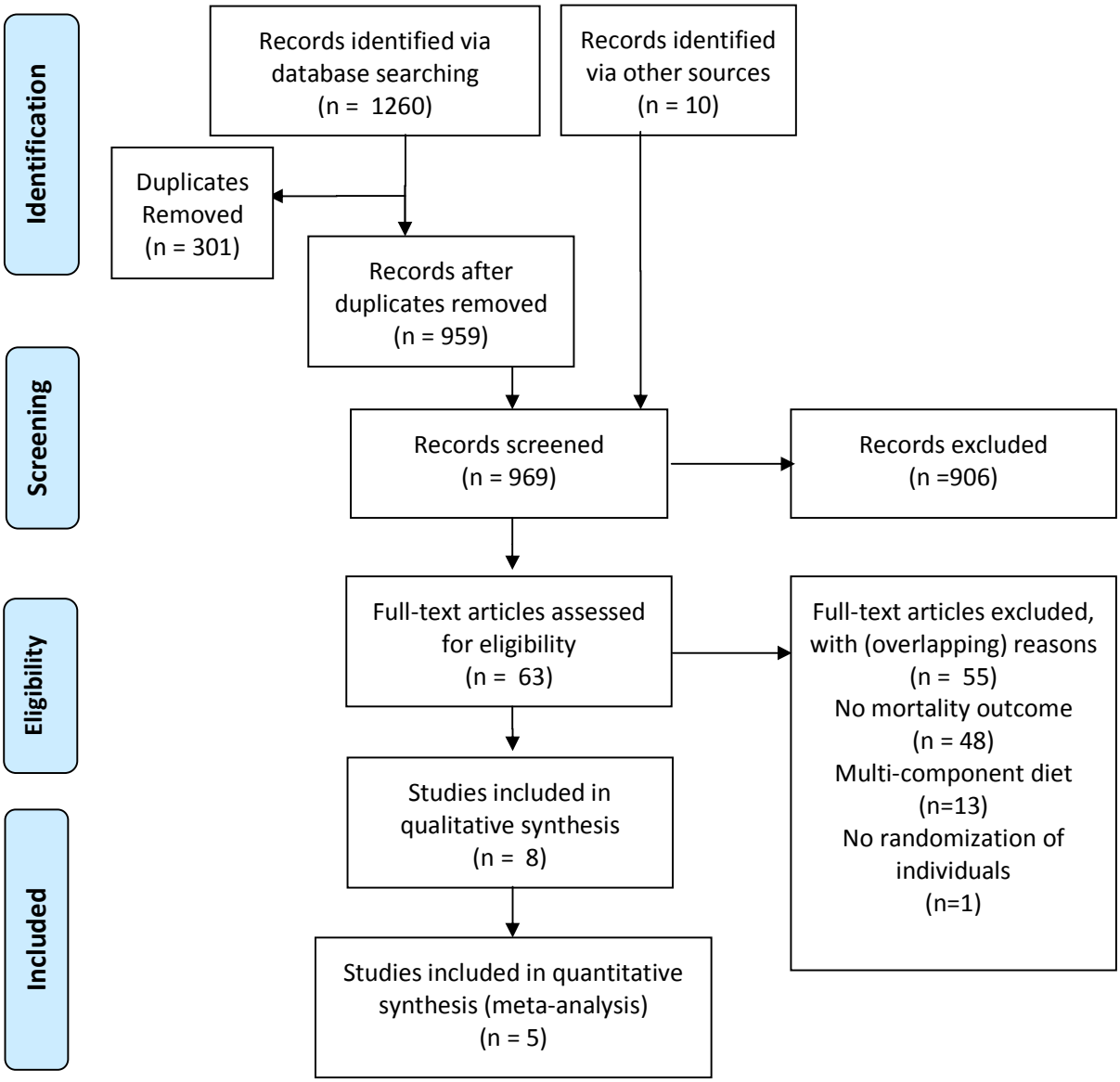

Fig C. PRISMA diagram: Study screening and eligibility

Table J. Characteristics of the 60 excluded dietary intervention studies

First author or Study Name, primary aim	Dietary interventions	Concomitant interventions	Mortality outcome
1. Finnish Mental Hospital Study (FMHS)[24-26] Effects of diets on mortality	Participants were not randomized. Crossover study of two hospitals (one control, one intervention) (see p. 47)	Higher exposure to cardiotoxic drug thioridazine in control	CHD mortality
2. Lyon Diet Heart Study [27-29] Secondary prevention of CHD death	Multiple between-group differences in diet Did not substitute LA-rich oil in place of SFA	No between-group imbalance	CHD mortality Non-fatal infarction
3.THIS-DIET[30] Secondary prevention of CHD events and death	Multiple between-group differences in diet Did not substitute LA-rich oil in place of SFA	No between-group imbalance	Composite outcome: all-cause + CHD deaths, MI, CHD, HF or stroke
4. Indo-Mediterranean Diet-Heart Study [31] Secondary prevention of CHD events and death	Multiple between-group differences in diet Did not substitute LA-rich oil in place of SFA	No between-group imbalance	Fatal and non-fatal MI, SCD, composite events.
5. Indian Diet Heart Study[32] Secondary prevention of CHD events and death	Multiple between-group differences in diet	No between-group imbalance	Fatal and non-fatal MI, SCD
6. Women's Health Initiative[33] (Howard) Secondary prevention of CHD events and death	Multiple between-group differences in diet Did not substitute LA-rich oil in place of SFA	None	Non-fatal MI, CHD death, CABG/PCI, composite CHD
7. Droste [34] Effects of diet on cerebral blood flow	Multiple between-group differences in diet Did not substitute LA-rich oil in place of SFA	Between-group imbalance in lifestyle change recommendations	None
8. Korhonen [35] Effects of diets on blood pressure	Multiple between-group differences in diet	No between-group imbalance	None
9. Esposito[36] In metabolic syndrome, effects of diet on endothelial function and inflammatory markers	Multiple between-group differences in diet Did not substitute LA-rich oil in place of SFA	No between-group imbalance	None
10. RESMENA [37-40] In metabolic syndrome, effect on body composition and oxidative stress	Multiple between-group differences in diet Did not substitute LA-rich oil in place of SFA	None	None
11. Castañer [41] Effects of diets on gene expression	Multiple between-group differences in diet Did not substitute LA-rich oil in place of SFA	None	None

First author or Study Name, primary aim	Dietary interventions	Concomitant interventions	Mortality outcome
12. OmniHeart [42, 43] Effects of diets on CHD risk factors in metabolic syndrome	High vs. low CHO diet Did not substitute LA-rich oil in place of SFA	None	None
13. Lichtenstein [44] Effects of diets on CHD risk factors in hypercholesterolemia	AHA Step 2 diet vs. usual Western Unspecified PUFA	None	None
14. Mangravite[45, 46] Effects of diets on CHD risk factors	High vs. low SFA: CHO vs. beef Did not substitute LA-rich oil in place of SFA	None	None
15. Lecerf[47] Effects of diets on lipid profile in hypercholesterolemia	SFA replaced with MUFA & mixed n-3/n-6 PUFA Multiple between-group differences in diet	None	None
16. Nielsen[48] Effects of diets on lipid oxidation in hypercholesterolemia	Canola vs. olive. vs. sunflower oil feeding Did not substitute LA-rich oil in place of SFA	None	None
17. Goyens[49] Effects of diets on CHD risk markers in older adults	ALA vs. EPA/DHA rich diet Did not substitute LA-rich oil in place of SFA	None	None
18. Azadbakht[50] Effects of diets on CHD risk factors in Type 2 diabetics	Multiple between-group differences in diet Did not substitute LA-rich oil in place of SFA	None	None
19. Raatz[51] Effects of diets on lipid metabolites in postmenopausal women	High fat vs. low fat diet Did not substitute LA-rich oil in place of SFA	None	None
20. Moore[52] Effects of diets on CHD risk factors	High/low LA+/- high/low n-3 diets Did not substitute LA-rich oil alone in place of SFA	None	None
21. Zhang[53] Effects of diets on lipid profile in hypercholesterolemia	Fatty fish substituted for pork/chicken/beef Did not substitute LA-rich oil in place of SFA	None	None
22. Madigan[54] Effects of diets on lipid profile in Type 2 diabetes	LA-rich vs. Oleic acid-rich diet Did not substitute LA-rich oil in place of SFA	None	None
23. Minihane[55] Effects of diets on lipids and insulin in Asian Indians	Moderate vs. high n-6:n-3 PUFA diet Did not substitute LA-rich oil in place of SFA	None	None
24. Singer[56] Effects of dietary oils on CHD risk factors in hypertensive men	Oleic vs. LA-rich vs. ALA-rich oils Did not substitute LA-rich oil in place of SFA	None	None

First author or Study Name, primary aim	Dietary interventions	Concomitant interventions	Mortality outcome
25. Puska[57-59] Effects of diets on blood pressure	Two levels of increased PUFA substituted for SFA	None	None
26. TRANSLinE Study [60-62] Effect of diets on CHD risk factors	High vs. low TFA Did not substitute LA-rich oil in place of SFA	None	None
27. Han[63] Effect of diets on cytokines and cellular immune markers	SFA vs. TFA vs. Soy oil	None	None
28. Beltsville Human Nutrition Center lipid studies[64-66]	Stearic acid, oleic acid feeding studies Did not substitute LA-rich oil in place of SFA	None	None
29. Dyerberg[67] Effects of diets on CHD risk factors	TFA vs. n-3 PUFA Did not substitute LA-rich oil in place of SFA	None	None
30. Sanders[68] Effects of diets on lipids/hemostasis	n-6 vs n-3 PUFA vs. SFA	None	None
31. RISCK trial[69] Effects of diets on insulin sensitivity and CHD risk factors	Multiple between-group differences in diet Did not substitute LA-rich oil in place of SFA	None	None
32. Gustafsson[70] Effects of diets on lipids	Diets with P/S ratios of 1.3 and 0.7	None	None
33. Erkkilä[71] Effects of diets on lipids	Lean vs. fatty fish vs. meats Did not substitute LA-rich oil in place of SFA	None	None
34. Kondo[72] Effects of diets on endothelial function	Fish vs. control diet Did not substitute LA-rich oil in place of SFA	None	None
35. Lindqvist[73] Effects of diet on CHD biomarkers	Fish vs. control diet Did not substitute LA-rich oil in place of SFA	None	None
36. Williams[74] Effects of diets on serum lipids	MUFA vs. control Did not substitute LA-rich oil in place of SFA	None	None
37. Lithander[75] Effect of diets on adiponectin	High vs low SFA:UFA diet Did not substitute LA-rich oil in place of SFA	None	None
38. Mclaughlin[76] Effects of diets on CVD risk factors	High vs. low CHO in calorie restricted diets Did not substitute LA-rich oil in place of SFA	None	None
39. Muzio[77] Effects of diets on CHD risk factors in metabolic syndrome	High vs. low CHO in calorie restricted diets Did not substitute LA-rich oil in place of SFA	None	None

First author or Study Name, primary aim	Dietary interventions	Concomitant interventions	Mortality outcome
40. Raff[78, 79] Effects of diets on CHD risk factors	CLA vs. Control fat Did not substitute LA-rich oil in place of SFA	None	None
41. Rivellese[80] Effects of diets on CVD risk factors	Mixed FA and CHO dietary changes Did not substitute LA-rich oil in place of SFA	None	None
42. LIPGENE study[81-88] Effects of diets in metabolic syndrome	Hi MUFA vs. SFA vs. CHO Did not substitute LA-rich oil in place of SFA	None	None
43. Rasmussen[89] Effects of diets on CVD risk factors	MUFA vs. SFA Did not substitute LA-rich oil in place of SFA	None	None
44. Zhao[90, 91] Effects of diets on vascular inflammation in hypercholesterolemia	ALA vs. LA vs. SFA diets Did not substitute LA-rich oil in place of SFA	None	None
45. Nigam[92] Effects of diets on NAFLD	Olive or canola oil substituted for usual cooking oil—neither is LA-rich	None	None
46. OPTLIP[93] Effects of diets on insulin sensitivity	4 diets altering n-6:n-3 ratios Did not substitute LA-rich oil in place of SFA	None	None
47. Insull[94] Effects of diets on lipids	Partially hydrogenated soybean, corn, sunflower oils; Did not substitute LA-rich oil in place of SFA	None	None
48. Annuzzi[95] Effects of diets on CHD risk markers in metabolic syndrome	n-3 +/- polyphenols vs. control Did not substitute LA-rich oil in place of SFA	None	None
49. de Roos[96, 97] Effects of diets on CHD risk markers	TFA vs. SFA Did not substitute LA-rich oil in place of SFA	None	None
50. Jenkins[98] Effects of diets on CHD risk markers	MUFA VS. SFA Did not substitute LA-rich oil in place of SFA	None	None
51. Foley[99] Effects of diets on lipids	MUFA vs. PUFA vs. SFA	None	None
52. SYSDIMET[100] (de Mello) Effects of diets on endothelial function in metabolic syndrome	Multiple between-group differences in diet	None	None
53. Fuentes[101] Effects of diets on endothelial function	SFA vs. MUFA vs. n-6+n-3 PUFA Did not substitute LA-rich oil in place of SFA	None	None
54. Fuentes[102] Effects of diets on endothelial function	SFA vs. Mediterranean vs. low TF/SFA diet Did not substitute LA-rich oil in place of SFA	None	None

First author or Study Name, primary aim	Dietary interventions	Concomitant interventions	Mortality outcome
55. WISH-CARE[103] (Vasquez) Effects of fish consumption on lipids in metabolic syndrome	White fish vs. no fish Did not substitute LA-rich oil in place of SFA	None	None
56. Houtsmuller [104] Effects of LA vs. SFA margarine on diabetic micro- & macro-angiopathy	Linoleic acid-rich intervention vs. 'saturated margarine' intervention (35%E as SFA). Comparison group with unrealistic amount of SFA (35%E) exclusively from 'saturated margarine'; No usual care control group	None	None
57. Borchgrevink[105] Secondary prevention of CHD mortality	Linseed oil (ALA) vs corn oil (LA) in place of other oils ; no SFA control group	None	CHD and all-cause mortality; CVD events
58. Ashton [106] Effects of diets on lipids/insulin in healthy males	Low fat, high carbohydrate diet vs. high oleic sunflower oil (MUFA) Did not substitute LA-rich oil in place of SFA	None	None
59. Teng [107] Effects of diets on inflammatory markers	Partially hydrogenated soybean oil vs. high oleic palm oil vs. palm stearin Did not substitute LA-rich oil in place of SFA	None	None
60. Christiansen [108] Effect of diets on DM markers/lipids among diabetics	SFA vs. MUFA vs TFA (trans MUFA) Did not substitute LA-rich oil in place of SFA	None	None

Abbreviations: ALA = alpha linolenic acid; CABG/PCI = coronary artery bypass surgery/percutaneous coronary intervention; CHD = coronary heart disease; CHO = carbohydrate; LA = linoleic acid; MI = myocardial infarction; MUFA = mono-unsaturated fatty acid; PUFA = poly-unsaturated fatty acid; SCD = sudden cardiac death; SFA = saturated fatty acid; TF = total fat; TFA = trans fatty acid.

RCTs included in the main analysis

Only five RCTs met our inclusion criteria: the Minnesota Coronary Experiment (MCE) [8-12, 109], the Sydney Diet Heart Study (SDHS) [13, 110-113], the Rose Corn Oil Trial (RCOT) [114], the Los Angeles Veterans study (LA Vet) [115-122], and the Medical Research Council Soy study (MRC Soy) [123, 124] (**table K**). These are the five known RCTs that randomly assigned individual participants to a diet intervention that provided vegetable oil rich in linoleic acid in place of saturated fat compared to a usual care control diet, reported deaths from CHD or all-causes, and had no between-group differences in major concomitant interventions. Compared to control groups, all five intervention groups lowered serum cholesterol (mean range from 8 to 14% lower). They represent a total of 10,808 individuals (5,413 in the intervention diet groups and 5,395 in the control diet group), 324 CHD deaths (169 intervention, 155 control), and 1,001 deaths from all causes (515 intervention, 486 control). Maximum follow-up ranged from 2 years to 7 years.

RCTs included in sensitivity analyses

Three additional RCTs were included in a sensitivity analysis: the Oslo Diet Heart Study (ODHS), the St. Thomas Atherosclerosis Regression Study (STARS), and the Diet and Re-infarction Trial (DART) (**table K**). These diet-heart trials, which randomly assigned individual participants and reported CHD deaths and all-cause mortality, have been included in previous meta-analyses on this topic. However, two of these trials were confounded by unequal application of other dietary factors, and another achieved only a very modest change in dietary LA without provision of study oils.

ODHS

The ODHS has often been represented as a test of the replacement of SFA with an LA-rich vegetable oil (soybean oil). However, in addition to soybean oil, the intervention group received a very large dose (≈5 grams per day) of n-3 EPA+DHA from provision of sardines canned in cod liver oil, and was advised to restrict sugar intake and to replace refined carbohydrates with less processed selections [125-127]. Since EPA+DHA (and sugar) are reported to influence CHD risk by mechanisms independent of serum cholesterol lowering, it is not possible to determine which intervention components were responsible for study results.

STARS

STARS [128-130] has often been represented as a test of the replacement of SFA with an LA-rich vegetable oil. However, unequal administration of multiple dietary factors do not allow for determination of the effects of LA. For example, the STARS intervention group received advice (and some study foods) to: (1) reduce total fat and SFA; (2) increase n-6 and n-3 polyunsaturated fatty acids, (3) avoid processed [128] foods, and (4) increase dietary fiber (especially the soluble fiber polygalacturonate) [129]. While this intervention had only a very modest (non-statistically significant) increase in n-6 LA (+1.6%E) [128], it doubled EPA+DHA from (100 to 210 mg per day), lowered total fat by 27%, and increased fiber by 53%. Given these multifaceted changes, the very modest increase in LA likely accounted for only a small fraction of the observed 12.2% serum cholesterol lowering achieved. Taken together, this study design provides little insight into whether replacement of SFA with LA rich vegetable oils can reduce CHD and death. Nevertheless, since other meta-analyses on this topic included STARS, we include it here in sensitivity analysis.

DART

The DART 'fat advice' intervention group achieved only a very modest reduction in serum cholesterol (-4%), and only modestly increased *total* polyunsaturated fatty acids, without providing study oils or reporting the specific n-6 and n-3 content of such increases. Given these limitations, it is not clear how much the DART results can be expected to help determine whether replacement of SFA with LA-rich oil

reduces risk of CHD and death (the traditional diet heart hypothesis) [131-136]. Nevertheless, since other meta-analyses on this topic included DART, we include it here a sensitivity analysis.

The eight RCTs in the sensitivity analysis represent a total of 13,328 individuals (6664 in each diet group) with a total of 609 CHD deaths (304 in the treatment, 305 in the control group) and 1,315 deaths from all causes (668 treatment, 657 control).

Exclusion of the Finnish Mental Hospital Study (FMHS)

The FMHS has been included in some previous meta-analyses of RCTs [21]. However, the FMHS is not suitable for inclusion because patients were assigned by hospital and were not randomized as individual patients, among other critical limitations (Reviewed in [109, 137]). For example, there was disproportionate exposure to the cardiotoxic drug thioridazine in one (control) study arm. The FMHS was a 12-year crossover study that assigned two hospitals (Hospital N and Hospital K) of mostly schizophrenic patients (77% in K and 69% in N) in 1959 to either a soybean oil based serum cholesterol-lowering diet (N) or the usual hospital diet (K) for 6 years. After this initial 6-year phase, diets were switched so that Hospital N patients received the Hospital N usual diet and Hospital K patients received a soybean oil diet. Issues related to within-hospital diet exposures at crossover in 1965 also confounded this unusual design. For example, study populations were ‘rejuvenated by discarding the six oldest annual cohorts and admitting six new annual cohorts on the younger end of the age range’ in 1965 [26].

Bias Assessment

All studies included in both the main and sensitivity analyses were parallel-group randomized controlled trials with blinded outcome assessment and no apparent systematic between-group differences in medical care (**tables K and L**). The possibility of selective reporting has been documented for both the SDHS[13] and, in this report, the MCE. Potential sources of bias in the five RCTs included the main analysis are summarized in **tables K and L**.

In the MCE and SDHS, the intervention groups replaced major sources of SFA (e.g. animal fats, common hard margarines, shortenings) with both LA-rich vegetable oils and polyunsaturated soft margarines. Since polyunsaturated margarines contain some trans fatty acids (TFA), it has been speculated that the unfavorable results of these trials could be due to TFA (http://www.bmj.com/content/346/bmj.e8707/rr/629609). However, upon careful examination of the intervention diets and the control diets in these RCTs, it becomes clear that between-group differences in TFA are an exceedingly unlikely explanation for these unfavorable findings (reviewed in http://www.bmj.com/content/346/bmj.e8707/rr/631590). For example, the liquid vegetable oils and polyunsaturated margarines provided to the intervention groups displaced substantial amounts of common hard margarines, shortenings and other TFA-rich foods that were present in the control diets (see Limitations section in the main paper).

The RCOT was small (n=84), and we only used two of the three randomized groups (corn oil group (n=28) and control diet group (n=26)).

The baseline and control diets in the LA Veterans Study were rich in hydrogenated oils [121] and contained ≤0.1%E α-linolenic acid (ALA). This extraordinarily low (deficient?) level of ALA is rare in modern diets and is unlikely to be achieved without extensive hydrogenation. Since the intervention increased n-3 ALA to more normative levels (0.7%E), the results of this study may be confounded by one group experiencing recovery from a deficient state.

Potential sources of bias in the three RCTs included in the sensitivity analysis are described above.

Table K. Characteristics of randomized controlled trials that replaced SFA with LA-rich vegetable oil(s)

Trial	Population	Group	CHD deaths	All-cause deaths	Total sample	Provided LA-rich oil in place of SFA	Confounded by EPA+DHA	Reduction in serum cholesterol‡	Maximum follow-up time
Studies included in primary analysis†									
Minnesota Coronary [8-12, 109]	Institutionalized Men & Women with and without CHD	Intervention	61	269	4541	Yes	No	-13.8%	≤ 4.5 years
		Control	54	248	4516				
Sydney Diet-Heart [13, 110-113]	Ambulatory Men with CHD	Intervention	36	39	221	Yes	No	-7.8%	≤ 7 years
		Control	24	28	237				
Rose Corn Oil [114]	Ambulatory Men with CHD	Intervention	5	5	28	Yes	No	-11.8%	≤ 2 years
		Control	1	1	26				
Los Angeles Veterans [115-122]	Institutionalized Men with and without CHD	Intervention	42	174	424	Yes	No	-12.7%	≤ 8 years
		Control	51	178	422				
Medical Research Council Soy [123, 124]	Ambulatory Men with CHD	Intervention	25	28	199	Yes	No	-13.3%	≤ 7 years
		Control	25	31	194				
Studies included in sensitivity analysis only									
Oslo Diet-Heart [125-127]	Ambulatory Men with CHD	Intervention	37	41	206	Yes	Yes (5 g/day)	-13.9%	≤ 5 years
		Control	50	55	206				
St. Thomas Atherosclerosis [128-130]	Ambulatory Men with CHD	Intervention	1	1	27	No	Yes (doubled from 100 to 210 mg/day)	-12.2%	≤ 3 years
		Control	3	3	28				
Diet and Re-infarction Trial [131-136]	Ambulatory Men with CHD	Intervention	35	111	1018	No	No	-4%	≤ 2 years
		Control	47	113	1015				

†The Finnish Mental Hospital Study (FMHS) has been included in some previous meta-analyses of RCT [21]. However, the FMHS is not suitable for inclusion because patients were assigned by hospital and not randomized as individual patients, and the cardiotoxic medication thioridazine was used disproportionately in one study arm [13, 109]. ‡Reports the between-group difference in the change in cholesterol over the course of the trial. Abbreviations: CHD, coronary heart disease; LA, linoleic acid; SFA, saturated fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid

Table L. Risk of bias and methodological quality and assessments for included randomized controlled trials

RCT	Random sequence generation	Allocation concealment	Blinding of participants & personnel	Selective reporting	Systematic between-group differences in medical care	Other potential bias	Increased dietary LA?	Concurrent increase in n-3 ALA and/or EPA+DHA	Achieved serum cholesterol reduction
Studies included in main analysis									
MCE [8-12, 109]	Low	Low	Double-blind	Moderate ‡	Low	Low	Yes (+8.5%E)	No	Yes (-13.8%)
SDHS [13, 110-113]	Low	Low	Blinded outcome assessment	Moderate ‡	Low	Low	Yes (+7.1%E)	No	Yes (-7.8%)
RCOT [114]	Low	Low	Blinded outcome assessment	Low	Low	Small trial with 3 study groups	Yes (+≈14%E)	No	Yes (-11.8%)
LA Vet [115-122]	Low	Low	Double-blind	Low	Low	Control diet high in hydrogenated oils and n-3 deficient (<0.1%E n-3 ALA)	Yes (+10.0%E)	Yes (+0.6%E ALA)	Yes (-12.7%)
MRC Soy [123, 124]	Low	Low	Blinded outcome assessment	Low	Low	Low	Yes (+≈15%E)	Yes, (+≈2%E ALA)	Yes (-13.3%)
Studies included in sensitivity analysis only									
ODHS [125-127]	Low	Low	Blinded outcome assessment	Low	Low	Treatment group reduced sugar, low quality carbohydrates. Control diet very high in partially hydrogenated fish oil.	Yes (+12.3%E)	Yes¶ (+≈5g/d of n-3 EPA+ DHA)	Yes (-13.9%)
STARS [128-130]	Low	Low	Blinded outcome assessment	Low	Low	Small trial with 3 study groups. Run-in phase with cholestyramine. Low-fat diet, increased soluble fiber.	Very modest (+1.6%E) §	Doubled EPA+DHA (from 100mg to 210mg per day)	Yes § (-12.2%)
DART [131-136]	Low	Low	Blinded outcome assessment	Low	Low	Advice only, modest diet changes	Modest (total PUFA +2.8%E) ‖	Unknown	Very modest (-4%) ‖

'Low' refers to low risk of bias, 'moderate' refers to moderate risk of bias

‡ Recovered data included in 2013 and 2015 publications ¶ Massive dose of EPA+DHA due to provision of sardines canned in cod liver oil;

§ STARS had very modest increase LA (+1.6%E), which is predicted to account for only a very small amount of serum cholesterol lowering that was achieved.

‖ DART had modest increase in total PUFA (+2.8%E) and modest reduction in serum cholesterol (-4%).

Abbreviations: MCE, Minnesota Coronary Experiment; SDHS, Sydney Diet Heart Study; RCOT, Rose Corn Oil Trial; LA Vet, Los Angeles Veterans Trial; MRC-Soy, Medical Research Council Soybean Oil Trial; ODHS, Oslo Diet Heart Study; STARS, St Thomas Atherosclerosis Regression Study. DART, Diet and Reinfarction Trial; LA, linoleic acid; ALA, alpha-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; PUFA, total polyunsaturated fatty acids

Meta-analysis

For the CHD mortality outcome, the main analysis resulted in a pooled hazard ratio of 1.13 (95% CI: 0.83, 1.54) with evidence of moderate heterogeneity in both magnitude and direction of effect **(fig D**: I-squared = 45.1%; Tau-squared: 0.0534). The all-cause mortality analysis resulted in similar findings (HR 1.07 (0.90, 1.27); (I-squared of 38.8%; Tau-squared of 0.0132) (**fig E**).

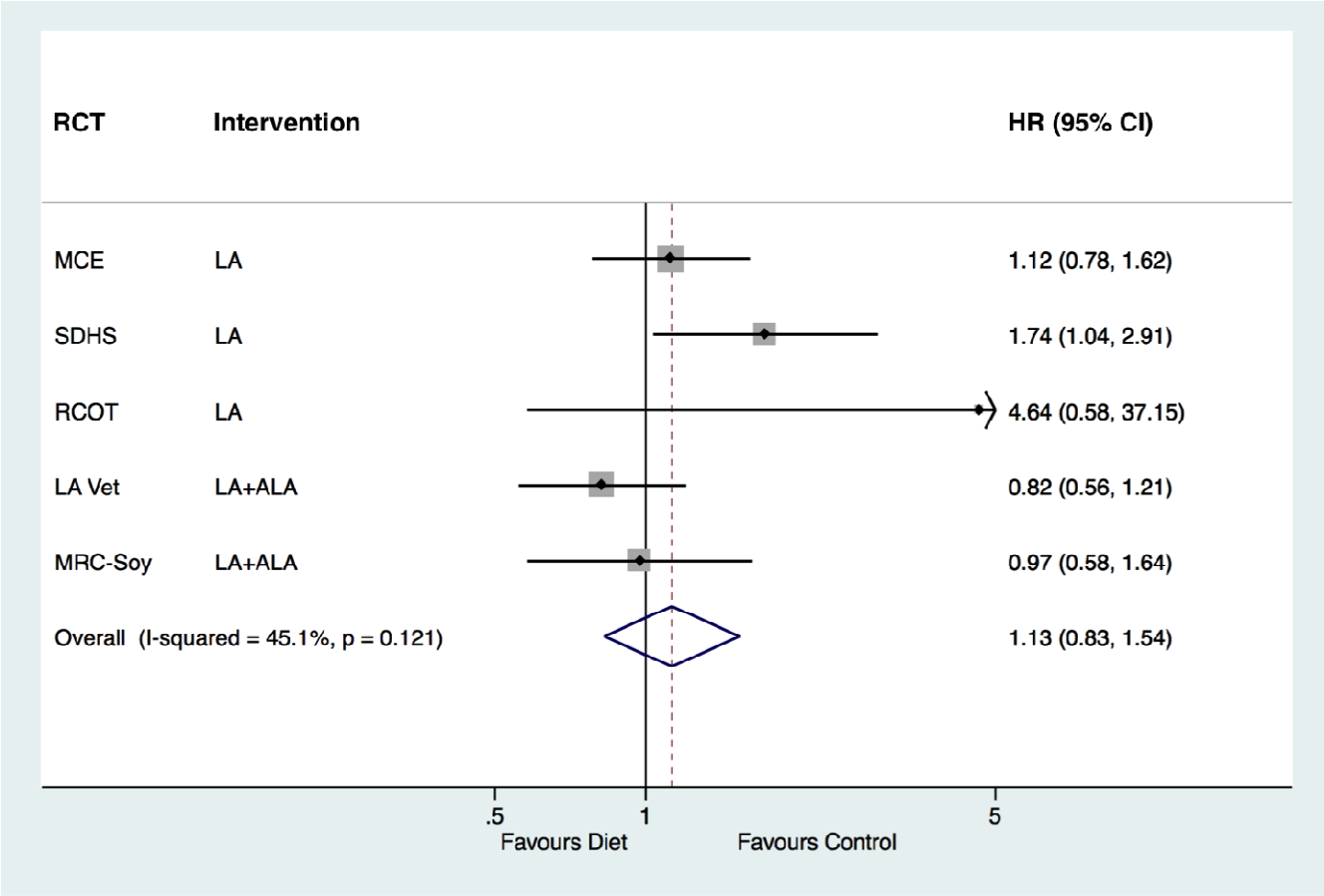

Fig D. CHD mortality in RCTs providing vegetable oils rich in LA (without added n-3 EPA+DHA) in place of SFA (main analysis)

Results are based on random-effects models. Risk ratios were substituted for hazard ratios where the latter were unavailable. Abbreviations: MCE, Minnesota Coronary Experiment; SDHS, Sydney Diet Heart Study; RCOT, Rose Corn Oil Trial; LA Vet, Los Angeles Veterans Trial; MRC-Soy, Medical Research Council Soybean Oil Trial; LA, linoleic acid; SFA, saturated fatty acids.

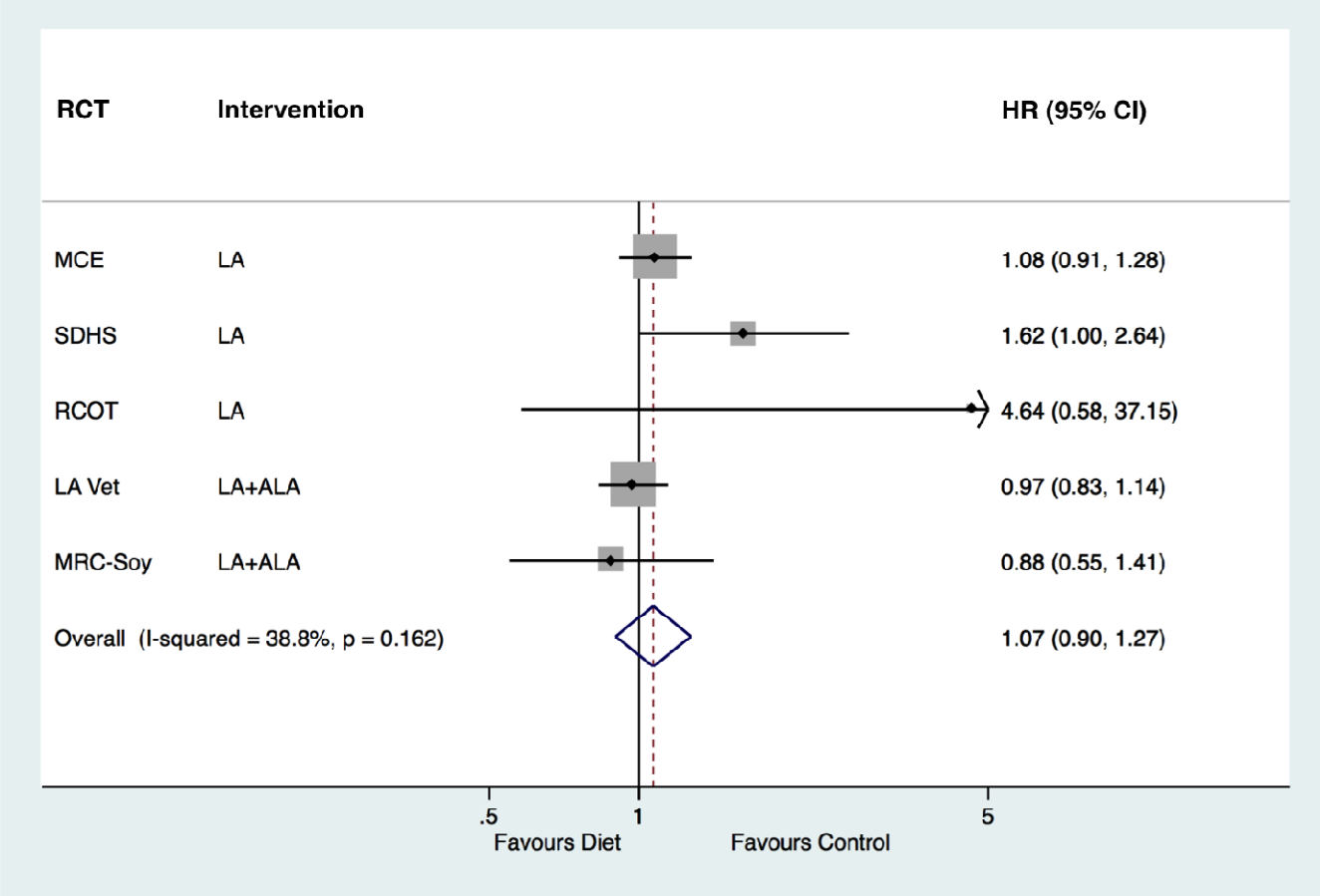

Fig E. All-cause mortality in RCTs providing vegetable oils rich in LA (without added n-3 EPA+DHA) in place of SFA (main analysis)

Results are based on random-effects models. Risk ratios were substituted for hazard ratios where the latter were unavailable. Abbreviations: MCE, Minnesota Coronary Experiment; SDHS, Sydney Diet Heart Study; RCOT, Rose Corn Oil Trial; LA Vet, Los Angeles Veterans Trial; MRC-Soy, Medical Research Council Soybean Oil Trial; LA, linoleic acid; ALA, alpha-linolenic acid; SFA, saturated fatty acids.

Publication bias analysis

Funnel plot inspection of the five RCTs in the main analysis suggested the possibility of publication bias with the Rose Corn Oil Trial an outlier (**fig F**). Thus, a trim and fill analysis was performed, filling in the presumed missing study, along with analyses excluding the small Rose Corn Oil Trial. These sensitivity analyses had minimal influence on pooled HR estimates. For the CHD mortality outcome, the filled, pooled HR was 1.10 (95% CI: 0.79, 1.52). The estimate with the Rose Corn Oil Trial removed was very similar: pooled HR 1.09 (95% CI: 0.81, 1.46). Heterogeneity remained evident with an I-squared of 44.5%. The pooled hazard ratio for all-cause mortality without the Rose Corn Oil Trial was 1.05 (95% CI: 0.90, 1.23) with comparable heterogeneity (I-squared 34.0%).

With the inclusion of the three additional diet-heart trials that provided large quantities of n-3 EPA and DHA, or provided advice only without provision of a study oil that was rich in LA, there was no suggestion

of publication bias (**fig G**). The pooled hazard ratio for CHD mortality (see **fig H**) was 1.00 (95% CI: 0.81, 1.24; I-squared: 37.5%) and for all-cause mortality 1.00 (95% CI: 0.87, 1.15; I-squared: 34.1%) (**fig I**).

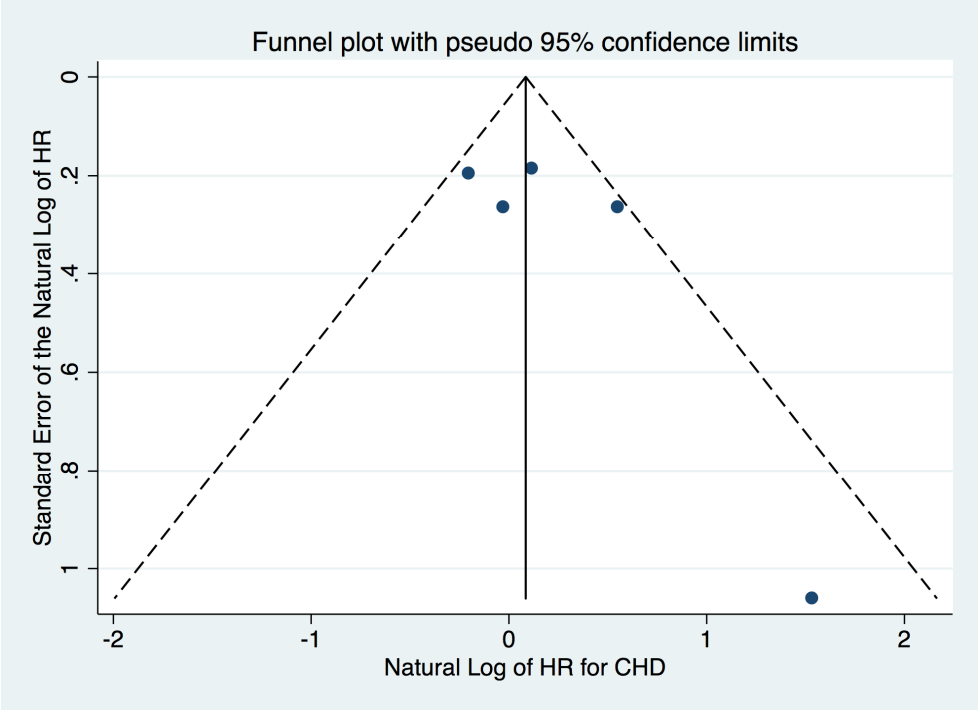

Fig F. Funnel plot for CHD mortality in five RCTs providing LA-rich oils in place of SFA
Funnel plots of treatment effect versus standard error (on the natural log scale) for CHD mortality showed some evidence of skew, raising a concern about potential publication bias. Removal of the Rose Corn Oil Trial mitigated this concern.

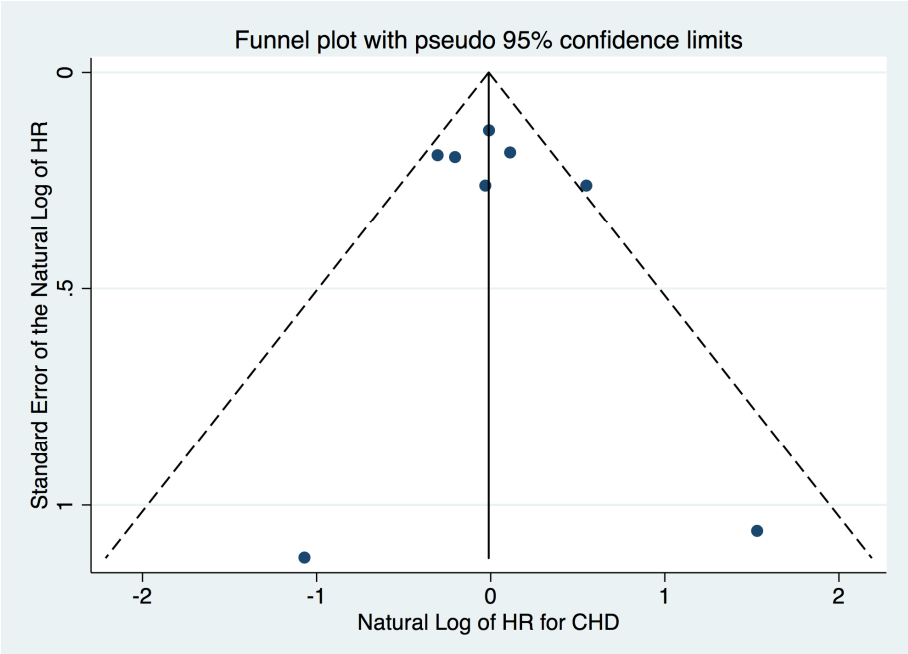

Fig G. Funnel plot for CHD mortality in eight RCTs with oil provision or advice to replace SFA with LA-rich oils, with or without confounding by n-3 EPA+DHA

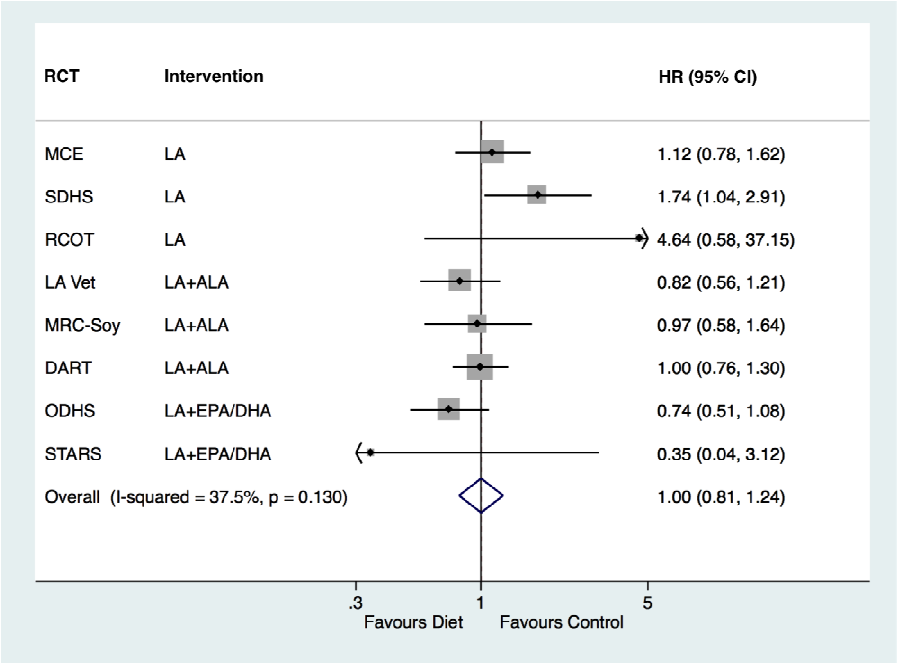

Fig H. CHD mortality in eight RCTs with provision or advice to replace SFA with LA-rich oils, with or without confounding by n-3 EPA+DHA (sensitivity analysis)

Abbreviations: MCE, Minnesota Coronary Experiment; SDHS, Sydney Diet Heart Study; RCOT, Rose Corn Oil Trial; LA Vet, Los Angeles Veterans Trial; MRC-Soy, Medical Research Council Soy Oil Trial. DART, Diet and Reinfarction Trial; ODHS, Oslo Diet Heart Study; STARS, St Thomas Atherosclerosis Regression Study. LA, linoleic acid; ALA, α-linolenic acid; SFA, saturated fat.

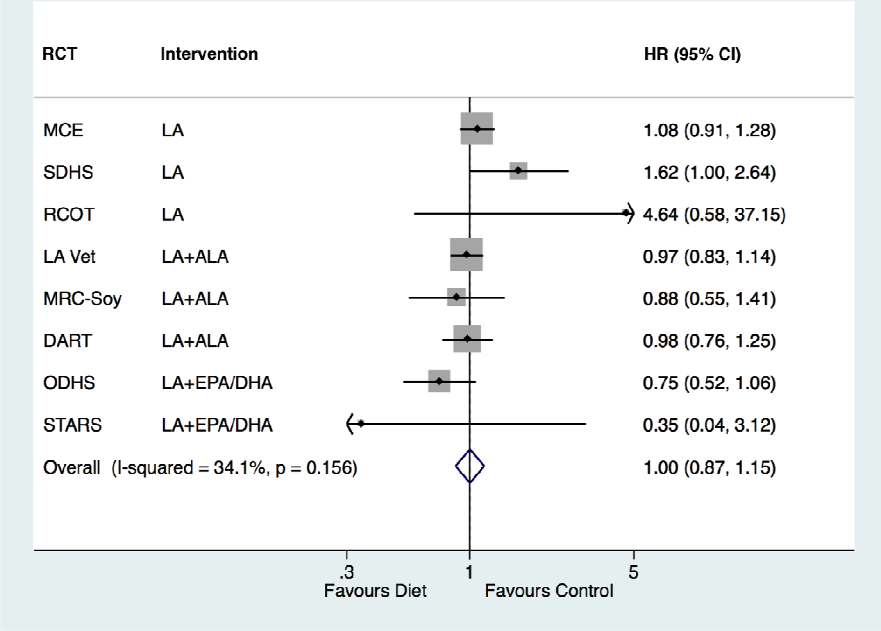

Fig I. All-cause mortality in eight RCTs with provision or advice to replace SFA with LA-rich oils, with or without confounding by n-3 EPA+DHA (sensitivity analysis)

Abbreviations: MCE, Minnesota Coronary Experiment; SDHS, Sydney Diet Heart Study; RCOT, Rose Corn Oil Trial; LA Vet, Los Angeles Veterans Trial; MRC-Soy, Medical Research Council Soy Oil Trial. DART, Diet and Reinfarction Trial; ODHS, Oslo Diet Heart Study; STARS, St Thomas Atherosclerosis Regression Study. LA, linoleic acid; ALA, α-linolenic acid; SFA, saturated fat.

Heterogeneity Exploration

We explored the following potential sources of heterogeneity for CHD mortality in the eight RCTs: (1) the n-6 and n-3 fatty acid compositions of intervention vs. control diets; (2) the doses of n-6 LA provided/achieved in the intervention group; and (3) the degree of serum cholesterol lowering achieved in the intervention group compared to control. Three RCTs increased n-6 LA only, three others increased both n-6 LA and n-3 ALA, and two others increased both n-6 LA and n-3 EPA+DHA. Heterogeneity between groups was statistically significant (p=0.03; I^2 =37.5%) with no evidence for heterogeneity within either the LA+ALA or LA+EPA/DHA groups (I^2 = 0%). Evidence for heterogeneity in the LA only group persisted (I^2 =37.5%), but was related to the magnitude rather than the direction of the effect. The pooled HR for CHD mortality for the studies providing LA alone was 1.33 (0.99, 1.79) compared to 0.94 (0.77, 1.15) for studies with LA+ALA and 0.72 (0.50, 1.05) for studies providing LA+EPA/DHA (**fig J**).

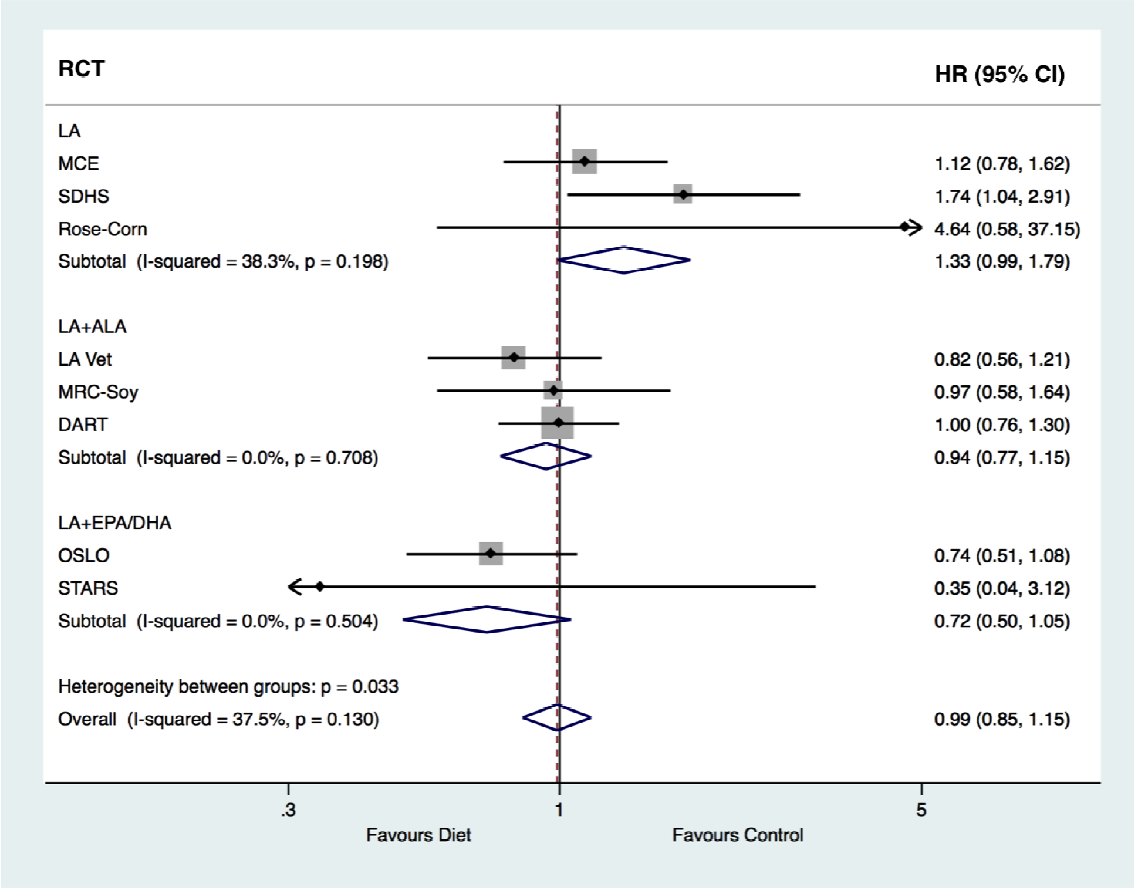

Fig J. CHD mortality in eight RCTs with provision or advice to replace SFA with LA-rich oils, with or without confounding by n-3 EPA+DHA, stratified by n-6 and n-3 fatty acid content (sensitivity analysis)*

*fixed effects estimates

Abbreviations: MCE, Minnesota Coronary Experiment; SDHS, Sydney Diet Heart Study; RCOT, Rose Corn Oil Trial; LA Vet, Los Angeles Veterans Trial; MRC-Soy, Medical Research Council Soybean Oil Trial. DART, Diet and Reinfarction Trial; ODHS, Oslo Diet Heart Study; STARS, St Thomas Atherosclerosis Regression Study.

Meta-regression analyses explored heterogeneity in the CHD mortality HR due to between-group cholesterol lowering and the magnitude of the increase in LA in the intervention groups. Across the eight studies, every one-unit decrease in between-group cholesterol lowering was non-significantly associated with a 2% increase in the HR (1.02; 95% CI: 0.95, 1.10). This model performed poorly compared with the model without between-group cholesterol lowering with a residual I^2 of 42% and an adjusted R^2 of -107%. Similar null findings are noted when the change in LA (%E) is examined (HR 1.02; 95% CI: 0.95, 1.10; residual I^2 42%; adjusted R^2 of -76%), suggesting that neither the magnitude of serum cholesterol lowering nor the dose of LA help to explain the heterogeneity among the trials.

Effects on composite CHD endpoints non-fatal myocardial infarction

The traditional diet-heart hypothesis predicts that replacement of SFA with LA-rich vegetable oils will reduce the risk of *both* non-fatal and fatal CHD events, however, our meta-analysis does not include non-fatal CHD event data. Unfortunately, several critical deficiencies in the collection and reporting of non-fatal CHD events in these RCTs make it unfeasible to reliably estimate risk of composite CHD or non-fatal events. For example, one of the five RCTs in the main analysis (the SDHS) did not report non-fatal CHD events [113]. Another RCT (the MCE) reported only a composite outcome and did not distinguish between soft endpoints (e.g. routine follow-up EKG suggestive of silent/asymptomatic myocardial infarction), and hard endpoints of acute non-fatal myocardial infarction (MI) and CHD deaths [8].

Aware of these limitations, we performed exploratory sensitivity analyses of the composite endpoint (MI plus CHD death) and non-fatal MI alone (**figs K and L**, respectively). For the MCE, we estimated non-fatal MI by subtracting deaths attributed to "Cardiac Arrest, Heart Block" (making the assumptions that "Cardiac Arrest, Heart Block" is essentially comparable to "Sudden cardiac deaths" and that all MIs were non-fatal). There was no indication of benefit from the replacement of SFA with LA-rich vegetable oils using either composite MI plus CHD death or non-fatal MI as outcomes. For the composite outcome of MI plus CHD mortality, there was a pooled hazard ratio of 1.07 (95% CI: 0.80, 1.41). For the non-fatal MI outcome, there was a pooled hazard ratio of 0.94 (95% CI: 0.73, 1.21).

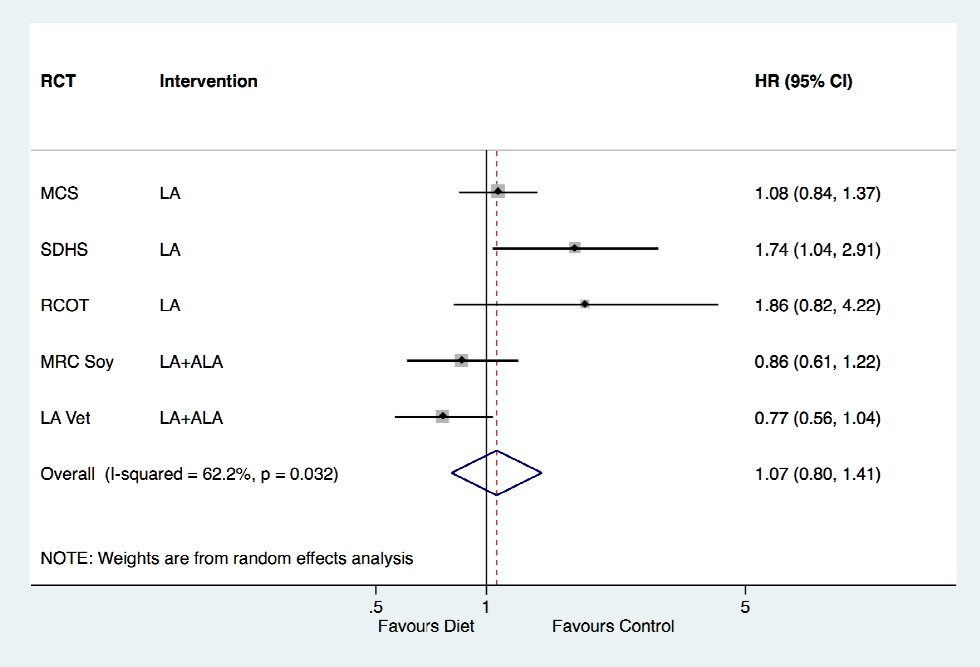

Fig K. Composite endpoint (myocardial infarcts plus CHD mortality) in RCTs providing vegetable oils rich in LA (without added n-3 EPA+DHA) in place of SFA (sensitivity analysis)

Abbreviations: MCE, Minnesota Coronary Experiment; SDHS, Sydney Diet Heart Study; RCOT, Rose Corn Oil Trial; LA Vet, Los Angeles Veterans Trial; MRC-Soy, Medical Research Council Soybean Oil Trial. DART, Diet and Reinfarction Trial; ODHS, Oslo Diet Heart Study; STARS, St Thomas Atherosclerosis Regression Study.

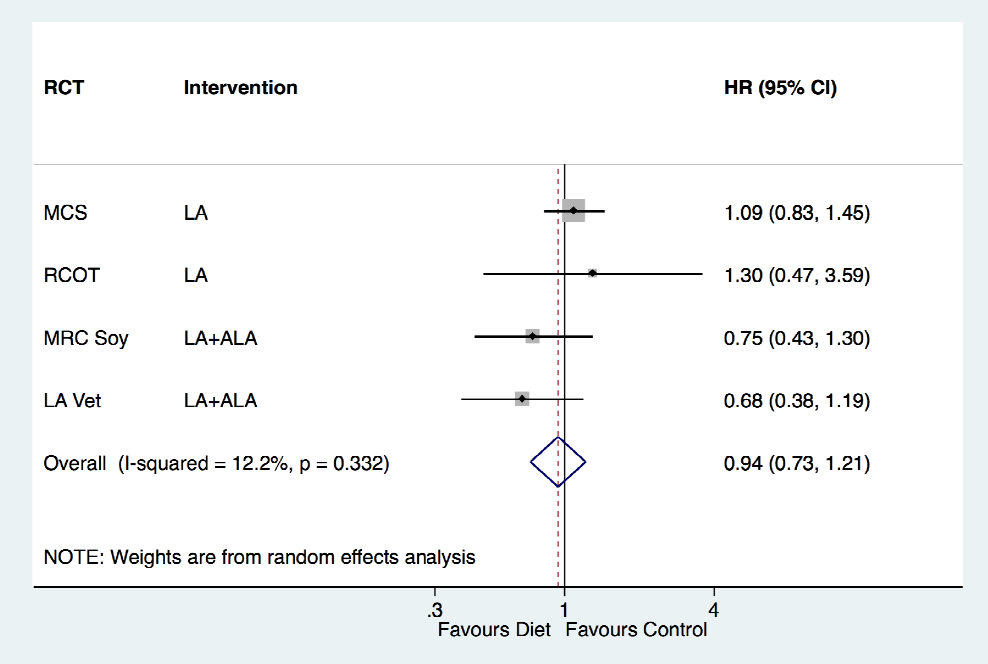

Fig L. Non-fatal myocardial infarcts in RCTs providing vegetable oils rich in LA (without added n-3 EPA+DHA) in place of SFA (sensitivity analysis)

Abbreviations: MCE, Minnesota Coronary Experiment; SDHS, Sydney Diet Heart Study; RCOT, Rose Corn Oil Trial; LA Vet, Los Angeles Veterans Trial; MRC-Soy, Medical Research Council Soybean Oil Trial. DART, Diet and Reinfarction Trial; ODHS, Oslo Diet Heart Study; STARS, St Thomas Atherosclerosis Regression Study.

DISCUSSION

Summary of Evidence

In our main meta-analyses, based on the five RCTs that provided LA-rich vegetable oil in place of SFA, we found no evidence for reductions in either CHD mortality or all-cause mortality. This conclusion was unchanged after sensitivity analyses that either 1) included RCTs that offered advice only or that, in addition to LA sources, also provided n-3 EPA and DHA, or 2) included composite or non-fatal endpoints. However, evidence of moderate heterogeneity weakens the conclusions we can make about the CHD mortality findings and their ability to translate into recommendations for the population. Exploratory analyses suggest that neither the between-group differences in serum cholesterol lowering nor the doses of LA provided help to explain this heterogeneity.

Limitations

The small number of RCTs that have tested the traditional diet-heart hypothesis replacing SFA with LA-rich vegetable oil is an important limitation of our meta-analysis. Remarkably, only five diet-heart RCTs have specifically tested whether provision of an LA-rich vegetable oil in place of SFA reduced risk of CHD death or all-cause mortality. The fact that the MCE accounted for about 80% of all randomized participants in these trials highlights the paucity of causal RCT evidence supporting the traditional diet heart hypothesis and the importance of the MCE in assessing the evidence base for LA-rich interventions. Even with inclusion of advice-only RCTs (with only modest diet changes and other limitations) and RCTs confounded by provision of large quantities of n-3 EPA+DHA in sensitivity analyses, MCE still accounted for 68% of all randomized participants. The small number of RCTs, coupled with differences in methodological quality and design, and population characteristics of the individual RCTs (**tables K and L**) (reviewed in [13, 109]) indicate that more research is needed in this area before evidence-based recommendations can be supported.

Conclusion

Available RCT evidence demonstrates that replacement of SFA with LA-rich vegetable oil effectively lowers serum cholesterol, but does not support the hypothesis that this translates to lower risk of death from CHD or all-causes.

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