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All PUFAs Are Not Created Equal: Absence of CHD Benefit Specific to Linoleic Acid in Randomized Controlled Trials and Prospective Observational Cohorts

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Advice to maintain or increase consumption of the omega-6 polyunsaturated fatty acid (n–6 PUFA) linoleic acid (LA) should be derived from interventional and observational trials evaluating the specific effects of dietary LA, rather than effects of n–3 PUFAs or total PUFAs. Failure to make a clear distinction among PUFA species may result in inadvertently attributing health effects of n–3 PUFAs to linoleic acid. Pooled analyses of randomized controlled trials (RCTs) of clinical CHD events [1] and intermediate risk factors [2] and pooled analyses of nonrandomized prospective observational trials of clinical CHD events [3] are often cited as providing strong concordant evidence [1, 4] that LA is cardioprotective. These pooled analyses [1–3] form the primary basis for recent population-wide advice to maintain or increase n–6 PUFA [5–7]. However, total PUFA rather than n–6 LA, was defined as the independent variable for statistical calculations in all three pooled analyses [1–3] (table 1), then interpreted as attributable to LA [4–8]. In this paper we: (1) establish that a clear distinction was not made between n–3 and n–6 PUFAs in pooled analyses of randomized and nonrandomized trials (tables 2, 3), (2) report whether a clear distinction was made between n–3 and n–6 PUFAs in each individual trial before pooling, (3) assess strengths and limitations of randomized and nonrandomized study designs for disentangling respective intakes of n–6 and n–3 PUFA species, and (4) highlight the necessity of making a clear distinction between PUFA species for interpreting the results of clinical trials and formulating dietary guidelines.

Randomized Controlled Trials of Clinical CHD Outcomes

Individual RCTs, and two meta-analyses of RCTs evaluating clinical CHD outcomes [1, 9] have been recently cited as providing ‘the most convincing data about the benefits of omega-6 PUFAs [7]. Here we evaluate these studies for their selective evaluation of LA.

Gordon Meta-Analysis of Cholesterol-Lowering and Mortality

The Gordon meta-analysis [9], which found a 24% reduction in CHD events, intended to evaluate the effects of cholesterol-lowering diets in general rather than the effects of n–6 LA, total PUFAs or any other PUFA species. Five of the six pooled RCTs lowered cholesterol with mixed PUFA dietary interventions containing substantial quantities of n–3 ALA [10–12] and/ or EPA+DHA [10, 13], alongside n–6 LA. The remaining RCT [14]

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lowered cholesterol by reducing total fat and saturated fat intake, but did not increase n–6 or n–3 PUFA intake. Therefore, Gordon's meta-analysis did not evaluate the specific effects of n–6 PUFAs on CHD risk. Despite this limitation, the analysis was featured in the 2009 AHA Advisory [5] and was later cited as providing convincing [6, 7] evidence for benefits if n–6 PUFAs. A letter to the editor [15, see Appendix 1] challenging the validity of representing Gordon's meta-analysis as evidence of benefits of n–6 PUFAs was not published by *Circulation*, which allowed no letters in response to the 2009 AHA Advisory. The letter was instead posted alongside other critiques and an AHA Advisory response on the AHA website [16], where it is not indexed in PubMed.

Mozaffarian et al. Meta-Analysis of Total PUFAs and CHD Risk (March 2010)

The Mozaffarian et al. [1] meta-analysis similarly does not provide data specific for the role of LA, rather this analysis included seven RCTs that increased 'polyunsaturated fat in place of saturated fat' and found CHD risk reduction of about 10% per 5 en% increase in total PUFA intake. Mozaffarian et al. [1] concluded that their findings have 'immediate implications' for dietary recommendations and that the present World Health Organization recommended upper limit of 10 en% as PUFA [17] may need to be increased. Importantly, however, five of the seven analyzed trials substantially increased both n–6 LA and n–3 ALA [10–12] and/or EPA + DHA [10, 13], while another did not provide specific PUFA composition data [18]. The Oslo Diet Heart Study (ODHS) [10] was included but is not a specific evaluation of LA or soybean oil as the intervention actually provided 'considerable quantities of Norwegian sardines canned in cod liver oil' [10] to the experimental group, along with instructions to substitute fish, shellfish and whale for meat and eggs. Oslo experimental dieters consumed more than 25-times average U.S. EPA + DHA intake [19] (about 5 g/day [10]), and nearly 5-times average USA ALA intake [19] (2.7 en% [10]). Therefore, it is not necessarily valid to attribute the CHD benefits in the ODHS to n–6 LA.

The Minnesota Coronary Survey [20, 21] (n = 9,057) was the only RCT included in the Mozaffarian et al. [1] meta-analysis that increased n–6 LA without concurrently increasing n–3 PUFAs. This RCT found no indication of benefit, and a signal toward increased risk of CHD in women (RR 1.31; 95% CI 0.90–1.90; p = 0.16). Two other RCTs that specifically increased n–6 LA by providing safflower and/or corn oil were not analyzed by Mozaffarian et al. [1]. In the Rose Corn Oil Trial [22] (n = 54), experimental dieters consuming an extra 14.9 en% as n–6 LA from corn oil had a 4.64-fold increase in risk for both CHD death and death from all causes (RR 4.64; 95% CI 0.58, 37.15; p = 0.15). In the Sydney Diet Heart Study (SDHS) [23], consumption of safflower oil and safflower oil polyunsaturated margarine produced a 49% increased risk of death from all causes (RR 1.49; 95% CI 0.95, 2.34; p = 0.08). The unfavorable SDHS results were not represented in the Mozaffarian et al. meta-analysis because CHD events and CHD deaths were not reported by group. However, the vast majority of total deaths in the combined groups were attributed to CHD (91%) and CVD (96%). Exclusion of these two n–6-specific PUFA trials and lack of a clear distinction between PUFA species precluded an evaluation of the specific effects of n–6 LA. Despite these critical limitations, the Mozaffarian et al. [1] meta-analysis has been considered decisive [4] and convincing [7] evidence for CHD benefits of n–6 LA.

Ramsden et al. Meta-Analysis of n–6-Specific and Mixed PUFA RCTs (December 2010)

In order to more accurately assess the specific effects of n–6 LA on CHD outcomes, Ramsden et al. [24] evaluated the effects of dietary interventions that increased n–6 LA with specificity (n–6-specific PUFA RCTs) separately from those that substantially increased both n–6 LA and n–3 ALA [10–12] and/or EPA+DHA [10, 13] (mixed n–3/n–6 PUFA

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RCTs). The specific study oils and PUFA compositions of dietary interventions were ascertained by searching both published literature and public records (e.g. research grant applications, original protocols, study progress reports, scientific proceedings from national conferences, library special collections). This extensive search identified previously unappreciated data, allowing a more precise evaluation of the CHD effects of the n–6 PUFA LA.

Importantly, mixed n–3/n–6 PUFA and n–6-specific PUFA dietary interventions were found to have significantly different effects on risk of nonfatal MI + CHD death ($p = 0.02$); mixed n–3/n–6 PUFA interventions showed clear benefit, while n–6-specific PUFA interventions actually tended to increase the risks of both CHD and death from all causes. In a pooled analysis of four datasets with 1,706 participants, mixed n–3/n–6 PUFA diets reduced the risk of nonfatal MI + CHD death by 22% (RR = 0.78; 95% CI 0.65,0.93; $p = 0.005$). The four n-6 specific PUFA datasets (n = 9,569) showed no indication of benefit and a signal toward harm; however, only 3 of these 4 datasets reported nonfatal MI + CHD death. A pooled analysis of these three n–6-specific PUFA datasets with CHD outcomes (n = 9,057) resulted a nonsignificant 13% increase in risk of nonfatal MI + CHD death (RR = 1.13; 95% CI 0.84, 1.53; $p = 0.43$). This nonsignificant increase in CHD may underestimate the potential harm of n–6 PUFAs because it does not capture the 49% increased risk of death from the fourth n–6-specific PUFA dataset, the SDHS. Each of the four n–6-specific PUFA datasets (n = 9,569) reported total deaths from all causes; pooled analysis found that consumption of n–6 PUFAs in place of trans and saturated fatty acids resulted in an increased risk of death that approached statistical significance, when analyzed independently (RR 1.16; 95% CI 0.95–1.42; $p = 0.15$) or in comparison to mixed n–3/n–6 PUFA dietary interventions ($p = 0.055$). Based on these findings Ramsden et al. [24] concluded that (1) a clear distinction should be made between n–6 and n–3 PUFAs in future publications, research, and public health advisories, and (2) advice to maintain or increase n–6 PUFAs should be reconsidered because adherence is unlikely to provide the intended benefits, and may actually increase the risks of CHD and death.

Jakobsen et al. Pooled Analysis 11 Nonrandomized Prospective Observational Trials

Evidence from trials evaluating PUFAs in general may not necessarily be informative for evaluating the specific effects of LA. The Jakobsen et al. [3] pooled analysis of 11 prospective cohort observational studies found a 13% reduction in CHD risk for every 5 en % increase in PUFAs, which is considered to be concordant with the 10% risk reduction reported by Mozaffarian et al., and the predicted 9% risk reduction attributed to LDL-cholesterol lowering [1, 2, 4]. At first glance, the Jakobsen et al. [3] results produce an apparent discrepancy with the lack of benefit, and signal toward harm, from n–6-specific PUFAs in the Ramsden et al. [24] meta-analysis of RCTs. Indeed, the Jakobsen et al. [3] results have been cited as evidence that ‘refutes the hypotheses that omega-6 polyunsaturated fatty acids increase heart disease risk’ [4]. However, Jakobsen et al. [3] defined the dietary exposure variable as ‘[total] PUFAs; including both n–3 and n–6 fatty acids, also known as omega-3 and omega-6 fatty acids; primarily n–6 linoleic acid’ (table 1). By defining the exposure variable as the sum of all PUFAs, rather than specifying n–6 PUFAs or n–6 LA, Jakobsen et al. [3] did not attempt to disentangle the separate intakes of different PUFA species (i.e. LA, ALA, EPA+DHA). Because the independent effects of n–6 LA and n–3 ALA, EPA and DHA were not evaluated, it is not necessarily valid to attribute the modest reported benefits to n–6 LA.

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Making a Distinction between LA and ALA in Observational Trials: The Nurses Health Study and Health Professionals Follow-Up Study

Critical to the interpretation of prospective observational cohorts is validation of food frequency questionnaires (FFQs) to accurately estimate the absolute intakes of LA and ALA by predicting adipose tissue composition, and to selectively disentangle the respective intakes of LA and ALA. The two largest observational cohorts that were pooled in the Jakobsen et al. [3] analysis, the Nurses Health Study (NHS) [25, 26] and Health Professional Follow-up Study (HPFS) [27, 28], did attempt to evaluate the respective intakes and CHD effects of n–6 LA and n–3 ALA via periodic administration of semi-quantitative FFQs. Here we will carefully evaluate the ability of the semi-quantitative FFQs used in the NHS and HPFS to capture: (1) the absolute intakes of LA and ALA, and (2) the data necessary to disentangle the respective intakes of LA and ALA.

80,082 NHS participants completed baseline FFQs in 1980 [25]. Follow-up FFQs were administered in 1984, 1986, 1990, 1994 and 1998 (table 4); 43,757 HPFS participants completed the corresponding baseline FFQ in 1986 [27]. Follow-up questionnaires were administered in 1990, 1994 and 1998. The questionnaires from both studies are available online (http://www.channing.harvard.edu/nhs/questionnaires/index.shtml and http://www.hsph.harvard.edu/hpfs/hpfs_qx.htm).

Absolute Intakes of LA and ALA

The revised 131-item FFQ that was used in the latter two-thirds of the NHS (1986, 1990, 1994, 1998) was found to provide ‘weak-to-moderate’ [29] associations between single FFQ estimates of dietary intakes of LA and ALA and adipose tissue LA (r = 0.23–0.35) and ALA (r = 0.25–0.33), respectively, in a subset of 140 participants, when each fatty acid is expressed as a percentage of total fat rather than caloric intake [29]. These associations are on the low end of the spectrum of correlation coefficients in comparison to published results for other FFQs (range: r = 0.22–0.58), and are also substantially weaker than associations obtained using multiple 24-hour recall data (r = 0.70–0.71), as reviewed by Hodson et al. [30]. The corresponding associations were not reported for the shorter 61-item 1980 FFQ used to collect NHS baseline data or for the intermediate 116-item FFQ used in 1984 (http://www.channing.harvard.edu/nhs/questionnaires/index.shtml). The 1980 FFQ did not capture any specific types or brands of oils (table 4). The 1984 FFQ included only one question about name brand and type of cooking oil ‘usually use[d]’ at home (table 4). Therefore, it is reasonable to assume that the first two NHS FFQs provide less accurate estimates of absolute LA and ALA consumption than the ‘weak to moderate’ associations reported for the 1986 FFQ [29]. We agree with the author’s statement that more data on the relation between dietary LA and ALA and adipose tissue LA and ALA are needed for validation [29].

An advantage of the HPFS is the use of the more detailed 131-item FFQ throughout [27] (http://www.hsph.harvard.edu/hpfs/hpfs_qx.htm). This FFQ provided weak associations between dietary LA (estimated by a single FFQ) and adipose tissue LA (r = −0.01 to 0.10 (unadjusted), r = 0.08–0.21 (adjusted for total caloric intake), but was stronger after adjustment for percentage of total fat (r = 0.37–0.48) [31]. Relationships between estimated dietary n–3 ALA and adipose ALA have not been reported.

Disentangling Respective Intakes of LA and ALA in Packaged Foods

An inherent challenge in using a FFQ to disentangle the respective intakes of LA and ALA is that both of these linked PUFAs are present in highly variable amounts in apparently

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similar food items (table 5). Critically, the NHS and HPFS FFQs did not specify name brands of packaged foods. Hence, similar food-items were assigned identical nutrient compositions despite widely divergent absolute and relative contents of LA and ALA (table 5). For example, vinaigrette salad dressing was assigned the same nutrient composition whether it contained soybean oil (LA 50 vs. ALA 7 g/100 g), canola oil (LA 20 vs. ALA 9 g/100 g), or corn oil (LA 54 vs. ALA 1 g/100 g) (table 5). Indeed, some commercial salad dressings and other packaged food items list 'safflower and/or sunflower and/or canola oil', or simply 'vegetable oil' on package labels, making it impossible to characterize the PUFA composition without laboratory testing. The same imprecision and potential for misclassification of LA and ALA exists for crackers, cookies, breads, potato chips/corn chips, mayonnaise, pizza, and other packaged food products (table 5).

Disentangling Respective Intakes of LA and ALA when Dining Away from Home

NHANES Survey data indicate that Americans consume about 38% of total dietary PUFAs outside the home [32]. However, the NHS and HPFS FFQs (table 4) do not inquire about, and therefore have no means of identifying, the specific oils used in cooking, salad dressings and other foods prepared away from home. Therefore, the NHS and HPFS did not capture the data necessary to disentangle LA and ALA intake for at least 38% of total PUFA consumption.

Disentangling Respective Intakes of LA and ALA in Home-Prepared Meals and Snacks

The 61-item 1980 NHS FFQ, which did not identify specific oils or name brands of relevant food items (table 4), provided baseline data for the finding that dietary n–6 LA is associated with lower CHD risk in the NHS [25, 33]. The revised 116-item 1984 NHS FFQ did not capture specific name brands for the three reported main sources of ALA (mayonnaise, oil and vinegar salad dressing, and margarine) [26] (table 4), but provided baseline data for the finding that dietary n–3 ALA is associated with lower risk of fatal CHD in the NHS. The revised 131-item 1986 FFQ, which was used for follow-up in the NHS and for the duration of the HPFS, did not capture name brands or the specific oils used in shortenings, mayonnaises, salad dressings or packaged foods (table 4).

All of the FFQs used in the HPFS, and the latter 4 of 6 FFQs used in the NHS (1986, 1990, 1994, 1998), asked participants to specify the brand and type of cooking oil and margarine that were 'usually use(d)' at home (table 4). There is a possibility of bias as the 1990, 1994 and 1998 questionnaires prompted participants by listing a single highly advertised brand for vegetable oil, e.g. 'Mazola Corn Oil' (1990 and 1998) or 'Wesson Corn Oil' (1994), and margarine, e.g. 'Promise Extra Light' (1990) or 'Land-O-Lakes Country Morning Blend Light' (1994) or 'Parkay Corn Oil Spread' (1998). This all-or-nothing classification approach also makes the assumption that the same brand cooking oil and/or margarine specified in the FFQ was the only such product consumed in each household over the entire period between FFQs. Hence, there is potential for misclassification of LA and ALA when other oils and margarines were used but not reported.

Specific Findings Generated from Limited Observational Data

We have shown here that the FFQs administered in the NHS and HPFS provide reasonable estimates of total 18-carbon PUFA consumption (i.e. LA + ALA). However, these FFQs have the potential to misclassify these two linked PUFA species in all food categories, especially in packaged food items and in foods eaten away from home. Misclassification of

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LA and ALA in individual participants prohibits accurate estimation of the independent effects of either variable. Although the NHS reported associations for the LA to ALA ratio and the risk of fatal CHD [26], the precise methodology used to estimate the absolute and relative intakes of LA and ALA from these limited data has not been published. Despite these critical limitations, the NHS and HPFS have reported associations between CHD risk and each of these highly covariate dietary variables for which specific individuation has not been established.

Strengths and Limitations of Nonrandomized Observational Trials and Randomized Controlled Trials for Evaluating the Specific Effects of LA and ALA

Observational Trials

Nonrandomized prospective cohort observational trials have several important strengths for assessing the effects of total PUFAs on CHD risk. Self-reported dietary exposure variables produced from FFQs provide a cost-effective means for gathering data over long periods of time and across wide ranges of nutrient intakes. The FFQs used in the NHS and HPFS may provide reasonable estimates of total 18-carbon PUFAs (i.e. LA + ALA). However, we have shown here that these FFQs have limited ability to disentangle the respective intakes of LA and ALA in individual participants. Therefore, published reports of the effects of individual PUFA species from nonrandomized observational cohorts should be interpreted with considerable caution. A more general limitation of the observational study design is the potential for residual confounding due to incomplete adjustment for healthy behaviors that were not measured or accounted for in risk models. In a meta-analysis of RCTs, good adherence to study medication (or placebo) was associated with significantly better health outcomes; good adherers randomized to medications of placebo had equivalent 44% lower risk of death [34], compared to those who were less adherent. This ‘healthy adherer effect’ has been confirmed to have a stronger relationship to outcome than the actual treatment in many diseases [35, 36].

Healthy Observer Effect?

Observational trials may be confounded by a similar ‘healthy observer effect’, where those who observe officially endorsed health practices have a lower risk of disease and death. Since Americans have been repeatedly advised to substitute vegetable oils for animal fats since 1961 [19, 37], a ‘healthy observer effect’ could account for some or all of the observed inverse association between dietary PUFAs and CHD risk in observational cohorts.

A similar ‘healthy observer effect’ may help explain the discrepant relationships between hormone replacement therapy (HRT) use and risk of CHD seen in observational cohorts and RCTs. Although HRT use was consistently associated with reduced CHD risk in individual cohorts and a pooled analysis of 16 observational cohorts [38, 39], it caused significant increases in CHD and death in a large RCT [40, 41].

Randomized Controlled Trials

The most important strength of RCTs is the random allocation of individuals to a treatment or control group. This process theoretically generates populations with equivalent baseline characteristics, thereby eliminating bias due to the ‘healthy adherer effect’ and other unmeasured potential confounders. Controlled dietary interventions also allow for the provision of specific study oils and foods with known nutrient compositions. Therefore, RCTs provide the opportunity to make specific changes in dietary intakes of n–6 and n–3 PUFA species, and to measure these intakes more precisely. The meta-analysis by Ramsden

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et al. [24] included three n–6-specific PUFA RCTs (4 datasets; 9,569 participants) that selectively increased the n–6 PUFA LA by replacing animal fats and hydrogenated oils with safflower and/or corn oil [20, 22, 23]. This type of controlled design allows for a more accurate evaluation of the specific effects of n–6 LA (as a replacement for saturated and trans fatty acids) compared to nonrandomized designs. However, the considerable resources required for an RCT often result in smaller sample sizes and shorter duration of follow-up than observational studies. Furthermore, the generalizability of RCT findings to other populations and less extreme nutrient intakes is not always clear. Therefore, randomized and nonrandomized study designs provide complementary information as long as the exposure variables are well-defined and comparable. RCTs and observational trials both provide complementary data on the effects of *total* PUFAs on CHD. However, we have shown here that only RCTs provide sufficient data to evaluate the specific effects of the n–6 PUFA LA.

Conclusion

Dietary advice to specifically increase n–6 LA has not been based on data that specifically evaluates dietary LA. We have shown here that the prospective observational cohorts put forth as evidence for CHD benefits of n–6 LA have limited ability to disentangle respective intakes and effects of n–6 LA and n–3 ALA using FFQ data. A pooled analysis of four RCT datasets provides the most appropriate data to evaluate the specific CHD effects of increasing LA in place of saturated and trans fatty acids. This analysis found no benefit, and a relatively consistent signal toward harm from selectively increasing LA. We conclude that evidence from RCTs and prospective observational cohorts, the top two tiers of evidence-based medicine, does not support current population-wide advice to maintain or increase consumption of the n–6 PUFA LA.

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Table 1

Defining the independent variable in pooled analyses cited as concordant evidence for CHD benefits of n–6 PUFAs

Pooled analysis	Outcome	Defining the independent variable	Exposure variable(s)	Mixed PUFA[1] or n–6-specific[2]
Mozaffarian et al. [1], Meta-analysis of RCTs	nonfatal MIs + CHD death	'[total] PUFA consumption as a replacement for SFA'	LA + ALA +/− EPA+DHA	mixed n–3 + n–6
Mensink et al. [2], meta-analysis of RCTs	LDL-cholesterol	'total PUFAs may be considered to equal the n–6 PUFAs with 18 carbon atoms (linoleic acid plus some α-linolenic acid)'	LA + ALA	mixed n–3 + n–6
Jakobsen et al. [3], pooled analysis of 11 observational cohorts,	CHD events + CHD death	'[total] PUFAs; including both n–3 and n–6 fatty acids, also known as omega-3 and omega-6 fatty acids; primarily n–6 linoleic acid'	LA + ALA + EPA+DHA	mixed n–3 + n–6

[1] Mixed PUFA indicates dietary interventions that substantially increased both n–3 and n–6 PUFAs, or exposure variables that include both n–3 and n–6 PUFAs.

[2] n–6-specific indicates interventions that increased n–6 linoleic acid without a concurrent increase in n–3 PUFAs. None of the pooled analyses in table 1 defined the independent variable as n–6 linoleic acid or even n–6 PUFAs. Therefore, none evaluated the specific effects of n–6 linoleic acid.

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Table 2

General characteristics of 8 randomized controlled dietary intervention trials that substituted PUFAs for saturated and trans fatty acids

Study	Total n	Oil	Controlled variable(s)[1]	Mixed n–3/n–6[2] or n–6-specific[3]	Published outcome(s)
MRC soy	393	soybean oil	LA + ALA	mixed n–3/n–6	nonfatal MI, CHD death, all cause mortality
Oslo Diet – heart	412	soybean and cod liver oil	LA + ALA EPA+DHA	mixed n–3/n–6	nonfatal MI, CHD death, all cause mortality
STARS	55	unspecified	LA + EPA+DHA	mixed n–3/n–6	nonfatal MI, CHD death, all cause mortality
LA veterans	846	corn and soybean oil	LA + ALA	mixed n–3/n–6	nonfatal MI, CHD death, all cause mortality
Rose corn	54	corn oil	LA	n–6-specific	nonfatal MI, CHD death, all cause mortality
Sydney Diet –heart	458	safflower oil	LA	n–6-specific	all cause mortality
Minnesota CS (men)	4,393	corn oil	LA	n–6-specific	nonfatal MI, CHD death, all cause mortality
Minnesota CS (women)	4,664	corn oil	LA	n–6-specific	nonfatal MI, CHD death, all cause mortality

MRC = Medical Research Council; STARS = St. Thomas Atherosclerosis Regression Study; DART = Diet and Re-infarction Trial; CS = Coronary Survey.

[1] PUFAs replaced a combination of trans and saturated fats in all 8 datasets.

[2] Mixed PUFA indicates dietary interventions that substantially increased both n–3 and n–6 PUFAs.

[3] n–6-specific indicates interventions that increased n–6 linoleic acid without a concurrent increase in n–3 PUFAs.

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Table 3

Characteristics of 11 nonrandomized observational trials that assessed PUFA intake

	Total, n	% of participants	% of events	Dietary intake assessment[#]	Dietary exposure variable(s)
NHSa	81,415	23.6	7.0	FFQ (61-item)	total PUFAs[2]
NHSb	61,706	17.9	12.2	FFQ (131-item)	total PUFAs[2]
HPFS	41,754	12.1	22.3	FFQ (131-item)	total PUFAs[2]
WHS[1]	37,272	10.8	2.7	FFQ	total PUFAs
IWHS	30,180	8.8	5.2 (fatal CHD)	FFQ	total PUFAs
AHS	22,642	6.6	3.9	FFQ	total PUFAs
ATBC[1]	21,141	6.1	24.5	FFQ	total PUFAs
VIP	20,076	5.8	2.8	FFQ	total PUFAs
ARIC	11,721	3.4	6.9	FFQ	total PUFAs
IIHD	8,272	2.4	2.9 (fatal CHD)	FFQ	linoleic acid (ALA not assessed) [42]
FMC	5,193	1.5	8.5	Diet history	total PUFAs
GPS	3,324	1.0	2.4 [43]	7-day-weighed food record	PUFAs (unspecified)
Pooled total	344,696	100			

NHSa = Nurses Health Study 1980 baseline; NHSb = Nurses Health Study 1986 baseline; HPFS = Health Professionals Follow-up Study; IWHS = Iowa Women's Health Study; AHS = Adventist Health Study; ATBC = Alpha Tocopherol and Beta Carotene Cancer Prevention Study; VIP = Vasterbotten Intervention Program; ARIC = Atherosclerosis Risk and Community Study; IIHD = Israeli Ischemic Heart Disease Study; FMC = Finnish Mobile Clinic Health Study; GPS = Glostrup Population Study; FFQ = Food Frequency Questionnaire.

[1] Indicates randomized controlled trial.

[2] The NHS and HPFS reported LA and ALA intakes and estimated their respective effects (table 4).

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Table 4

Food frequency questionnaires in the Nurse Health Study and Health Professionals Follow-up Study

FFQ Year	Name brand veg-etable oils identified?	Name brand margarines identified?	Name brand shortenings identified?	Name brand mayonnaise identified?	Name brand salad dressings identified?	Comments
NHS 1980[1] (61-item)	no	no	no	no	no	No specific name-brand questions
NHS and HPFS 1984[2] (116-item)	partial	no	no	no	no	What type of fat do you usually use for frying and sautéing?[4] What type of fat do you usually use for baking?[4] What form of margarine do you usually use? (e.g. tub or stick) What type of cooking oil do you usually use? (specify type and brand)
NHS and HPFS 1986[3] (131-item)	partial	partial	no	no	no	Kind of fat most often used at home for baking[4] Kind of fat most often used at home for frying and sautéing[4] What form of margarine do you usually use? (brand and type) Usual type of cooking oil: (brand and type)
NHS and HPFS 1990[3]	partial	partial	No	No	No	What type of fat do you usually use for frying and sautéing at home?[4] What type of fat do you usually use for baking at home?[4] What form of margarine do you usually use? (e.g. Promise Extra Light) What type of cooking oil do you usually use at home? (e.g. Mazola Corn Oil)
NHS and HPFS 1994[3]	partial	partial	no	no	no	What kind of fat is usually used for frying and sautéing at home?[4] What kind of fat is usually used for baking at home?[4] What form of margarine do you usually use? (e.g. Land O'Lakes Country Morning Blend Light) What type of cooking oil do you usually use at home (e.g. Wesson Corn Oil)?

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FFQ Year	Name brand vegetable oils identified?	Name brand margarines identified?	Name brand shortenings identified?	Name brand mayonnaise identified?	Name brand salad dressings identified?	Comments
NHS and HPFS 1998[3]	partial	partial	no	no	no	What kind of fat is usually used for frying and sautéing at home?[4,5] What kind of fat is usually used for baking at home?[4] What form of margarine do you usually use? (e.g. Parkay Corn Oil Spread) What type of cooking oil do you usually use at home? (e.g. Mazola Corn Oil)?

NHS = Nurses Health Study; HPFS = Health Professionals Follow-up Study.

[1]The 61-item 1980 NHS FFQ that provided baseline data for a published report that dietary n–6 LA is associated with lower CHD risk [26] did not identify specific oils or name brands of food items.

[2]The revised 116-item 1984 NHS FFQ that provided baseline data for a published report that dietary ALA is associated with lower risk of fatal CHD did not capture specific name brands for the 3 reported primary sources of ALA (mayonnaise, oil and vinegar salad dressing, and margarine).

[3]The revised 131-item 1986 FFQ, which did not capture name brands or specific oils used in shortenings, mayon-naises, or salad dressings or packaged foods (table 5), was used throughout the HPFS.

[4]Indicates a question regarding generic fat sources (e.g. real butter, margarine, vegetable oil, vegetable shortening, lard), without identifying specific name brands or specific oils in ingredient lists.

[5]The 1998 FFQ is the first year listing olive oil as an option for the fat ‘usually used’ for cooking at home. None of the 1980, 1984, 1986, 1990, or 1994 FFQs include olive oil as an option for cooking.

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Table 5

Markedly different absolute and relative amounts of LA and ALA in different brands of apparently similar food items

Food item	USDA# or brand name	Vegetable oil in product	LA[1] (g/100 g fat)	ALA[1] (g/100 g fat)	FFQ discriminates ALA and LA
Cooking oil – 1	Wesson®	corn oil	54	1	partial[2]
Cooking oil – 2	Crisco®	soybean	50	7	partial[2]
Cooking oil – 3	Wesson®/Crisco®	canola	20	9	partial[2]
Margarine – 1	Saffola®	safflower	75	0	partial[2]
Margarine – 2	Pride Zero Trans Whipped Spread®	soybean	50	7	partial[2]
Margarine – 3	Canoleo®	canola	20	9	partial[2]
Salad dressing – 1	Kraft® Seven Seas Red Wine Vinaigrette Dressing	canola	20	9	no
Salad dressing – 2	Wish Bone® Salad Dressing, Robusto Italian	soybean	50	7	no
Salad dressing – 3	Hain® Mayo	safflower	75	0	no
Mayonnaise – 1	Kraft Fat Free® NDB# 04013	fat free	0	0	no
Mayonnaise – 2	Hellman's Real®	soybean	50	7	no
Mayonnaise – 3	Hellman's Canola Cholesterol free®	canola	20	9	no
Shortening – 1	Shortening NDB No: 04546	cottonseed	54	0	no
Shortening – 2	Crisco All-Vegetable®	soybean	50	7	no
Cracker – 1	Haddar® Light Whole Wheat Matzos	no added fat	0	0	no
Cracker – 2	Old London® Sesame Melba Toast	canola	20	9	no
Cracker – 3	Nabisco® Multigrain Saltine Keebler®	soybean	50	7	no
Cracker – 4	Hain Wheatettes®	safflower	75	0	no
Chips – 1	Lay's Kettle-Cooked®	canola	20	9	no
Chips – 2	Kettle Brand® Krinkle Cut™	safflower	75	0	no

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Food item	USDA# or brand name	Vegetable oil in product	LA[1] (g/100 g fat)	ALA[1] (g/100 g fat)	FFQ discriminates ALA and LA
	Potato Chips Sea Salt				
Chips – 3	Fritos®	corn	54	0	no
Pizza – 3	Papa John's®	vegetable	17[3]	2[3]	no
Pizza – 5	Amy's®	high oleic sunflower/olive	4[3]	3[3]	no
Pizza – 6	Amy's®	high oleic safflower/olive	6[3]	3[3]	no
Pizza – 7	Newman's Own®	corn/olive	14[3]	3[3]	no
Pizza – 8	Rossini's® Gourmet Vegan	soybean	20[3]	3[3]	
Restaurant oil – 1	NDB # 01003	clarified butter	2	1.4	no
Restaurant oil – 2	NDB # 04645	canola, deep frying	9	1.0	no
Restaurant oil – 3	NDB # 04644	canola for salads and light frying	19	6.3	no
Restaurant oil – 4	NDB # 04643	canola for salads and light frying	18	6.4	no
Restaurant oil – 5	NDB # 04653	soy, clear fry	39	3.8	no
Restaurant oil – 6	NDB # 04650	soy, light frying	51	6.9	no
Restaurant oil – 7	NDB # 04042	peanut, for salad or cooking	32	0	no
Restaurant oil – 8	NDB # 04584	high oleic sunflower	3.6	0.2	no
Restaurant oil – 9	NDB # 04060	sunflower	39.8	0.2	no
Restaurant oil – 10	NDB # 04060	palm and palm kernel	3.2	0	no

NDB = USDA Nutrient Database. Different brands of salad dressings, mayonnaises, margarines, shortenings, vegetable oils, chips, crackers and other packaged foods contain markedly different absolute and relative amounts of LA and ALA.

[1] Grams of LA and ALA per 100 g of total fat in the primary oil in the ingredient list unless otherwise specified.

[2] See table 4.

[3] Estimated from USDA data.

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