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Differential effects of adulterated versus unadulterated forms of linoleic acid on cardiovascular health

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Abstract

According to the classic “diet-heart” hypothesis, high dietary intake of saturated fats and cholesterol combined with low intake of polyunsaturated fats can increase levels of serum cholesterol and lead to the development of atherogenic plaques and ultimately cardiovascular disease. Recently, the beneficial health effects of omega 6 polyunsaturated fatty acids, particularly linoleic acid (LA), on cardiovascular health have been called into question with some scientists suggesting that consumption of LA should be reduced in Westernized countries. The focus of this critical review is on the controversy surrounding the effects of dietary intake of LA on cardiovascular health. Specifically, we critically examine the effects of both unadulterated and adulterated forms of LA on cardiovascular health outcomes based on findings from epidemiological studies and randomized controlled trials. Additionally, we address common concerns surrounding dietary intake of LA regarding its relationship with arachidonic acid, the ratio of omega 6 to omega 3 fatty acids, and its relationship with inflammation. Our critical review indicates that unadulterated forms of LA are cardio-protective and should be consumed as part of a healthy diet. In contrast, abundant evidence now indicates that adulterated forms of LA, predominantly hydrogenated vegetable oils, are atherogenic and should not be considered part of a healthy diet. The ability to adulterate the natural omega 6 fatty acid, LA, has contributed to mixed findings regarding the effects of this fatty acid on cardiovascular health. Thus, it is critical that the source of LA be taken into account when drawing conclusions about the physiological effects of this fatty acid. The findings of the present review are in line with current dietary recommendations of the American Heart Association.

Many chronic diseases are now recognized to be directly related to an individual’s dietary intake. Dietary fatty acids in particular have been implicated in the development of cardiovascular disease (CVD), the leading cause of death in developed countries[1,2]. According to the classic “diet-heart” hypothesis, high dietary intake of saturated fats and cholesterol combined with low intake of polyunsaturated fatty acids (PUFAs) can increase levels of serum cholesterol. This leads to the development of atherogenic plaques and ultimately cardiovascular diseases. Based on this hypothesis and findings from epidemiological studies dating back to the 1950s, many experts have recommended consumption of diets relatively low in saturated fats but higher in mono-unsaturated and polyunsaturated fats. In line with these recommendations, dietary intake of PUFAs, especially linoleic acid (LA), have been associated with substantially lower risk of CVDs in

large-scale longitudinal studies, such as the Nurses' Health Study[3], as well as number of randomized controlled trials (RCTs)[4–14]. Recent comprehensive reviews have also concluded that both omega 6 and omega 3 fatty acids reduce risk of heart diseases, and that the ratio of these fatty acids is "not useful and can be misleading."[15] Despite these findings and conclusions from recent reviews, there remains significant controversy over the health benefits/risks associated with dietary intake of LA, the primary omega 6 fatty acid[16]. Specifically, the beneficial health effects of LA on cardiovascular health outcomes have recently been called into question, with some scientists suggesting that consumption of LA should be reduced in Westernized countries[17].

The present controversy and divergent conclusions drawn by leading experts about the potential health benefits and risks associated with LA intake appears to be due to few factors. First, the effects of unadulterated (natural) forms of LA (e.g., sunflower oil) versus adulterated (chemically altered) forms of LA (e.g., hydrogenated vegetable oil) have not been distinguished when evaluating the effects of this fatty acid on cardiovascular risk factors and outcomes. Thus, previous studies and reviews of the literature may have come to disparate conclusions about the health benefits/risks associated with dietary intake of LA due to the form of LA used (i.e., adulterated versus unadulterated). Given the mounting evidence indicating adulterated fats, predominantly hydrogenated oils, commonly known as trans fats, are atherogenic[3,15], it is critical to distinguish between the effects of unadulterated versus adulterated forms of LA to understand the true effect of this fatty acid on cardiovascular health. A better understanding of the health effects of the different forms of LA on cardiovascular health is both urgent and important given that LA is currently the predominant PUFA in Westernized diets[16], and adulterated forms of LA are present in a large variety of foods consumed on a regular basis[18].

The focus of this brief review is on the controversy surrounding the effects of dietary LA on cardiovascular health. Specifically, we critically examine the effects of both unadulterated and adulterated forms of LA on cardiovascular health outcomes based on findings from epidemiological studies and RCTs. In this regard, we detail the potential confounding effects of the form of LA consumed in the conclusions drawn by previous authors regarding the health benefits and risks of dietary intake of LA on cardiovascular outcomes. We also review evidence addressing three common concerns regarding the potential adverse effects of dietary intake of LA on cardiovascular health: linoleic acid converts to arachidonic acid, ratio of omega 6 to omega 3 fatty acids is critical for health, and high intake of omega 6 fatty acids promotes inflammation.

In the sections below, we review the differential effects of unadulterated (natural) forms of LA versus adulterated (chemically altered) forms on cardiovascular health. Since LA is the primary omega 6 PUFA in many vegetable oils, we have used findings from studies that have examined the effects of vegetable oils with high LA content on cardiovascular health as a surrogate for LA in the studies reviewed below.

1. Effects of unadulterated forms of LA on cardiovascular health

The beneficial effect of PUFAs on cardiovascular health is supported by findings from recent meta-analyses and comprehensive reviews, as well as a recent position statement by the American Heart Association (AHA). For example, a recent meta-analysis of RCTs examining the effects of dietary LA on CVD risk[19] found that there was a 10% reduction in risk for CVD for each 5% increase in energy intake from PUFAs. In the trials included in this meta-analysis, the average weighted PUFA consumption was approximately 15% of total energy intake in the intervention groups and 5% of total energy intake in the control groups. Additionally, the authors of a recent review[20] of the effects of PUFA intake on cardiovascular health concluded that "the body of data supports the recommendation for n-6 PUFA intake above 5%, and ideally about 10% of total energy." In their most recent statement[21], the AHA has also supported the beneficial effects of PUFAs on cardiovascular health: "The AHA supports omega 6 PUFA intake of at least 5% to 10% of energy in the context of other AHA lifestyle and dietary recommendations. To reduce omega-6 PUFA intakes from their current levels would be more likely to increase than to decrease risk for coronary heart disease (CHD)." Thus, the findings of the three comprehensive reviews described above suggest that greater risk reductions may be obtained from consuming a higher intake of PUFAs (i.e., 10% to 15% of total energy intake) than is currently recommended in many countries (i.e., 4% to 5% of total energy intake). Table 1 summarizes the results of 12 studies[4–14,22] in which dietary intake of natural-unadulterated forms of LA were associated with reductions in cardiovascular risk factors.

Another method that can be used to determine the effects of LA on cardiovascular health is to examine the relation between both dietary and serum levels of LA with cardiovascular and total mortality. Using this approach, the evidence strongly supports a protective effect of dietary intake of unadulterated forms of LA. For example, a large-scale, prospective cohort study of 1,551 middle-aged men found that cardiovascular mortality was inversely related to both dietary intake of LA and serum esterified LA levels[22]. Specifically, men with energy adjusted dietary intake of LA and PUFA in the upper third tertile had lower levels of CVD than men with intake in the lower third, after adjustment for age. Serum levels of LA were also inversely associated with overall mortality levels. Thus, this large-scale trial found a strong inverse association between both dietary intake of LA with CVD mortality and serum levels of LA with total mortality. Another community-based prospective trial examined the association of individual serum esterified fatty acids in relation to both cardiovascular and total mortality[23]. Similar to the findings of the large-scale study mentioned above, the proportion of serum esterified LA was inversely related to both cardiovascular and total mortality. In contrast, serum fatty acids associated with saturated fat intake were positively related to both cardiovascular and total mortality. Taken together, the findings of both of these longitudinal cohort studies suggest that both dietary intake of LA and endogenous levels of this fatty acid, which are directly related to dietary intake, are cardio-protective and inversely related to CVD and total mortality.

The findings described above are further supported by a study conducted by Wolfe and colleagues in primates which was specifically designed to test the hypothesis that diets enriched with n-6 polyunsaturated fat would decrease levels of coronary artery

atherosclerosis compared to diets enriched with saturated fat[24]. To test this hypothesis, African green monkeys were fed an atherogenic diet (0.8 mg cholesterol/K) throughout their lives which allowed for quantification of atherosclerosis following death at three different time points (i.e., ages 16, 32, and 60 months). The only difference in the diets was that one diet contained a high amount of saturated fats whereas the other consisted of omega 6 polyunsaturated fats derived from safflower oil. The primary findings of this study were that animals fed the polyunsaturated fat diet had significantly less coronary artery atherosclerosis than the animals fed the saturated fat diet. Moreover, the average coronary artery intimal area in the animals fed the polyunsaturated fat diet was one fourth the size of the coronary artery intimal area of the animals fed the saturated fat diet. Additionally, the average size of the largest coronary intimal lesion in animals fed the polyunsaturated diet was one fifth the size of the animals fed the saturated fat diet. The findings of this study demonstrate that dietary interventions with omega 6 polyunsaturated fats reduce the development of atherosclerosis in primates, providing further support that PUFAs have cardio-protective effects in humans.

2. Effects of adulterated forms of LA on cardiovascular outcomes

In contrast to recent findings indicating polyunsaturated fats containing unadulterated forms of LA reduce risk of CVD, a growing body of evidence indicates that adulterated (chemically altered) forms of LA (e.g., partially hydrogenated vegetable oils) have adverse effects on cardiovascular health[7,14,15]. These adulterated forms of omega 6 polyunsatured fats, commonly known as trans fats, entered the mainstream diet approximately three decades ago. Trans fats are isomers of unsaturated fatty acids that contain at least one nonconjugated double bond in the trans configuration[25]. Trans fats are primarily composed of hydrogenated or partially-hydrogenated vegetable oils. Once hydrogenation occurs, the unsaturated oil is chemically altered into a trans fat, a fat that is less fluid and has a higher melting point. This process appears to chemically alter the fatty acid in such a manner that dietary consumption increases rather than decreases CVD risk. Unfortunately, trans fats and adulterated forms of LA are present in a wide variety of foods commonly consumed[18]. Specifically, major sources of adulterated forms of LA frequently consumed in Westernized diets include: (1) hydrogenated oils (trans fats), (2) high allergenic oils, (3) genetically modified (GMO) foods, (4) fried and oxidized foods, (5) solvent extracted cooking oils, and (6) conventional meat products. Table 2 summarizes findings from epidemiological studies and RCTs on the relationship between intake of adulterated forms of LA with CVD risk factors[13,26–29].

RCTs have also specifically examined the impact of adding or substituting adulterated forms of LA in place of unadulterated forms on cardiovascular health suggest that adulterated forms of LA have adverse health effects. For example, a study conducted by Zock and Katan[14] used a multiple, cross-over design to compare the effects of dietary intake of unadulterated LA [(cis,cis-C18:2(n-6)] and its hydrogenation products elaidic [trans-C18:1(n-9)] and stearic acid (C18:0) on serum lipoprotein levels in humans. A total of 56 healthy, normolipemic individuals (26 men and 30 women) participated in this trial. Each participant was instructed to consume one of three experimental diets, in random order, for three weeks each. The linoleate-diet provided 12.0% of total energy intake as LA, 2.8% as

stearic acid, and 0.1% as trans fatty acids. The stearate-diet supplied 3.9% energy as LA, 11.8% stearic acid, and 0.3% trans fatty acids. The trans-diet provided 3.8% energy as LA, 3.0% stearic acid, and 7.7% as monounsaturated trans fatty acids, largely elaidic acid [(trans-C18:1(n-9)]. Other nutrients were held constant across all diets. The primary findings of this trial were that the hydrogenated fatty acid diets significantly increased low-density lipoprotein cholesterol (LDL-C) levels and significantly decreased high-density lipoprotein cholesterol (HDL-C) levels relative to the unadulterated LA diet (all $P < 0.001$). Thus, the findings of this study strongly suggest that consumption of chemically altered forms of LA, (i.e., stearic or trans fatty acids) has adverse effects on serum cholesterol levels, in comparison to unadulterated forms of LA.

A more recent study conducted by Vega-López *et al*[13] utilized a double-blind, cross-over design to assess the effect of substituting corn oil for partially-hydrogenated soybean oil in 30 postmenopausal women with elevated LDL-C concentrations. The participants were randomly assigned to one of two 35-day diets during which either corn oil or partially-hydrogenated soybean oil was added to their diet with each oil contributing two-thirds of the total fat content of the diet. The diets were adjusted to sustain baseline body weight and did not differ besides the type of oil incorporated in the food. The primary findings of this study were that the corn oil enriched diet significantly reduced fasting total cholesterol, LDL-C, and VLDL-C relative to the partially-hydrogenated soybean oil enriched diet. In addition, the corn oil diet significantly lowered Apo B, lipoprotein (a) and sdLDL-cholesterol compared to the partially-hydrogenated soybean oil diet. These findings indicate that partially-hydrogenated soybean oil, which contains adulterated forms of LA, adversely affected a number of CVD risk factors in comparison to corn oil, which contains unadulterated forms of LA.

Another method used to determine the effects of dietary intake of adulterated form of LA is to examine the relation between biomarkers of trans fat intake and trans isomers of LA with CVD risk. For example, a study by Lemaitre *et al*[30] examined the association of trans fatty acid intake with risk of primary cardiac arrest, based on analyses of red blood cell membrane level of trans fatty acids, in a population-based, case-control study. A total of 179 individuals, aged 25–74 years, were selected out of a hospital cardiac care unit from 1988 to 1999, and 285 control participants were randomly selected from the community, matched to the cases according to sex and age. Selected participants did not have previously diagnosed heart disease and were not taking omega 3 fish oil supplements. The primary findings of this study were that higher levels of trans fatty acids found in the red blood cell membranes were associated with a 1.5 times increase in the risk of primary cardiac arrest even after controlling for lifestyle and medical risk factors. Additionally, higher levels of trans isomers of LA found in the blood were associated with a three-fold increase in risk of primary cardiac arrest. Thus, the findings of this study suggest that dietary intake of total trans fatty acids is associated with an increased risk of primary cardiac arrest among patients with CVD, and dietary intake of adulterated forms of LA (i.e., trans isomers of LA) further increase CVD risk.

In a more recent study, Lemaitre *et al*[30] examined the associations of plasma phospholipid trans fatty acids with fatal ischemic heart disease and sudden cardiac death. Between the

years of 1992 and 1998, a total of 214 cases of fatal myocardial infarction and CHD death were collected from men and women, age 65 years and older, from the Cardiovascular Health Study cohort. Control subjects (n = 214) were randomly selected and matched to the cases in terms of prevalent cardiovascular disease, timing of the blood draw, and demographics. Participants were excluded if they died in nursing homes or if they used fish oil supplements at the time of the blood draw. Blood samples were collected to assess the plasma phospholipid fatty acids. The results of this study were that, after controlling for known CVD risk factors, higher levels of plasma phospholipid trans isomers of LA were associated with higher risk of fatal ischemic heart disease (odds ratio = 1.68). Higher levels of trans isomers of LA were associated with a two-fold higher risk of sudden cardiac death. Thus, the findings of this study strongly suggest that dietary intake of trans isomers of LA increase risk of sudden cardiac death and fatal ischemic heart disease.

The findings described above, as well as the studies presented in Tables 1 and 2, strongly suggest that adulterated and unadulterated forms of LA have differential effects on cardiovascular health. These findings highlight the importance of carefully evaluating the form of LA consumed when drawing conclusions about the effects of this fatty acid on cardiovascular health. As noted above, some previous reviews[17] and studies[31,32] have not separated the form of LA used in dietary interventions when evaluating the effects of this fatty acid on cardiovascular health. Based on the evidence reviewed above, we believe that the failure to distinguish between the effects of adulterated versus unadulterated forms of LA on cardiovascular health has led to incorrect conclusions that dietary intake of LA increases CVD risk[17]. Rather, the appropriate conclusion is that dietary intake of adulterated (chemically altered) forms of LA increase CVD risk, but dietary intake of unadulterated (natural) forms of LA decreases CVD risk. Given that many adults currently consume adulterated forms of LA[18], the need to understand the effects of chemically altering this fatty acid on cardiovascular health is both urgent and important.

3 Other notable concerns related to dietary intake of LA

3.1. LA converts to arachidonic acid

A major concern with dietary intake of LA is that it increases serum plasma levels of arachidonic acid, with subsequent generation of excessive amounts of pro-inflammatory eicosanoids. In a recent systematic review[33], Rett and Whelan investigated whether LA converts to arachidonic acid. Based on data obtained from 36 articles containing over 4,300 participants, dietary intake of LA was not associated with serum or plasma phospholipid levels of arachidonic acid. When dietary LA levels were increased up to six-fold, no significant changes in arachidonic acid levels were observed. Similarly, decreasing dietary intake of LA by up to 90% was not associated with changes in arachidonic acid levels in the phospholipid levels of serum or plasma. Thus, this systemic review found no support for the frequently cited concern that increasing dietary LA increases tissue levels of arachidonic acid. In contrast, dietary intake of gamma-LA (GLA) and arachadonic acid were both found to increase serum and plasma phospholipid levels of arachidonic acid[33].

Consistent with the findings of this review described above, Liou and Innis[34] found that changing the dietary content of LA from 1% to 4% to 10% in a randomized crossover study

in men had little or no effect on the content of arachidonic acid in plasma phospholipids;however, the direction of change observed indicated that higher dietary intake of LA was associated with lower tissue levels of arachidonic acid. Previous population-based studies have also found relatively minor changes in tissue levels of arachidonic acid in response to increases in dietary LA content from 4% to 10%[35]. Thus, the current body of evidence strongly suggests that dietary intake of LA does not significantly increase levels of arachidonic acid within the body.

3.2 Ratio of omega 6 to omega 3 fatty acids

Some scientists have recently argued that the ratio of the omega 6 to omega 3 fatty acids is critical for cardiovascular health, as well as overall health[17,36]. As noted above, recent comprehensive reviews by leading experts have challenged this view, and have concluded that both omega 6 and omega 3 fatty acids reduce risk of heart disease, and that the ratio of these fatty acids is “not useful and can be misleading.”[15] These experts have argued that the ratio of omega 6 to omega 3 not useful or important because both types of PUFAs are essential and reduce risk of heart disease.

Findings to date seem to support such conclusions. For example, an epidemiological study by Pischon *et al*[37] examined whether high intake of omega 6 fatty acids would reduce the known health promoting effects of omega 3 fatty acids. This large-scale study included 405 healthy men and 454 healthy women. As expected, intake of omega 3 fatty acids was inversely associated with pro-inflammatory markers. this association was not present among participants reporting low intake of omega 6 fatty acids, but there was a strong inverse relation between omega 3 intake and pro-inflammatory markers among participants reporting high intake of omega 6 fatty acids. Thus, the findings of this study strongly suggest that omega 6 fatty acids do not inhibit the beneficial effects of omega 3 fatty acids, and that the combination of both fatty acids leads to the greatest reduction in levels of inflammation.

In a recent large scale, longitudinal study (n=25,639), Khaw *et al*[38] assessed the relationship between various serum phospholipid fatty acid concentrations and the incidence of CHD over a mean of 13 years. The major findings were that phospholipid content of saturated fatty acids was positively associated with CHD risk, whereas the phospholipid content of omega-6 polyunsaturated fatty acids, specifically LA and arachidonic acid, were associated with lower levels of CHD risk. Noteworthy, omega 3 concentrations were not significantly associated with CHD. Thus, the findings of this large-scale trial indicate that the beneficial effects of LA on reduction in CHD risk are independent of the effects of omega 3 fatty acids on CHD.

3.3 LA increases levels of inflammation

Some scientists have suggested that high intakes of LA can increase levels of inflammation through a pathway that is independent of arachidonic acid accumulation in tissues[36]. To date, no evidence exists to support the proposition that unadulterated forms of LA are pro-inflammatory in the range of current diets. In contrast, there is increasing evidence that LA has anti-inflammatory properties. For example, Ferrucci *et al*[39] measured the relationship between plasma PUFAs and circulating inflammatory markers in a cross-sectional study of

1,123 participants aged 20 to 93 years. LA composed three-quarters of the plasma n-6 PUFAs, but no correlation was found between total physiological levels of this fatty acid with pro-inflammatory markers. Participants in the lowest quartile of plasma total n-6 PUFAs, however, had the highest levels of pro-inflammatory markers and the lowest levels of the anti-inflammatory markers. Thus, the findings of this epidemiological study indicate that low levels of n-6 PUFAs, rather than high levels, are associated with higher levels of pro-inflammatory markers.

In a more recent epidemiological study, Petersson et al (2008) [40] examined the relation between fatty acid composition and low grade inflammation levels over 20 years in 767 middle-age Swedish men. Low grade inflammation was assessed by C-reactive protein (CRP) levels in the present study, and the relation between fatty acid composition in serum cholesterol esters at age 50 and CRP concentrations at age 70 was investigated using a regression model. At the end of this 20 year longitudinal study, CRP concentrations were inversely associated with the proportion of LA in serum cholesterol esters. There was a positive association, however, with the proportion of saturated fat in serum cholesterol esters. Thus, a fatty acid composition represented by a low intake of LA was associated with elevated levels of systemic inflammation, as measured by CRP concentrations, and this association was independent of weight status and insulin resistance.

In a recent RCT, Bjermo *et al*[41] investigated the effects of a high PUFA diet on systemic inflammation in 67 abdominally obese subjects. Participants were randomly assigned to a 10-week isocaloric diet high in unadulterated n-6 PUFAs (PUFA diet) or high in saturated fatty acid mainly from butter (SFA diet), without altering the macronutrient intake. Following the dietary intervention, levels of the TNF receptor-2 and IL-1 receptor antagonist concentrations were significantly lower during the PUFA diet, as compared to the SFA diet, whereas levels of insulin were significantly higher following the SFA diet. Moreover, compliant participants (defined by change in serum LA), had significant reductions in the insulin, total/HDL-C ratio, LDL-C, and triglycerides during the PUFA diet than during the SFA diet. Thus, the findings of this RCT provide further evidence that a high n-6 PUFA intake does not cause any signs of inflammation or oxidative stress and may lead to reductions in the expression of specific pro-inflammatory markers (i.e., TNF-α and IL-1).

In another recent study, Asp *et al*[4] used a randomized, crossover design to study the effects of conjugated LA and unadulterated high linoleic safflower oil supplementation on glycemic indices, blood lipids, and inflammation in 55 post-menopausal obese women with type 2 diabetes. Participants were administered either 8 gof conjugated LA or high linoleic safflower oil daily for 16 week periods, separated by a 4-week washout period. No changes in dietary intake or physical activity were recommended. Following 16 weeks of treatment, supplementation with high linoleic safflower oil significantly reduced levels of CRP, an established marker of systemic inflammation, and significantly improved indices of insulin sensitivity. In contrast, supplementation with conjugated LA had no effect on these inflammatory and metabolic parameters. Noteworthy, levels of serum LA were increased following high linoleic safflower use, while no change was observed when participants consumed conjugated LA. Thus, the findings of this study provide further support that

unadulterated forms of LA are not pro-inflammatory, but rather reduce systemic inflammation when consumed at levels in line with current dietary recommendations.

4 Conclusions

Our critical review indicates that natural unadulterated forms of LA have significant cardiovascular benefits and should be consumed as part of a healthy diet. In contrast, adulterated forms of LA are atherogenic and therefore should be avoided. Given the consistent findings regarding the adverse effects of adulterated fats on cardiovascular health outcomes, it is critical to consider the source and form of LA when drawing conclusions about its effects on cardiovascular health. We strongly recommend that future studies using LA clarify the form, namely, unadulterated versus adulterated, of the fatty acid being tested to avoid further controversies. There is little evidence to support the ratio of omega 3 to omega 6 fatty acids as being critical for cardiovascular health benefits. Rather, both omega 3 and 6 polyunsaturated fats appear to have independent cardiovascular health benefits with high levels of both fatty acids being associated with the low levels of inflammation. Furthermore, there is very little evidence demonstrating dietary intake of LA is associated with increased levels of inflammation. On the contrary, high dietary intake of natural unadulterated LA is associated with reductions in inflammation and CVD risk. Thus, the findings of the present review are in line with recent reviews, as well as current dietary recommendations of the AHA, and suggest that increasing intake of natural-unadulterated forms of LA provides cardiovascular health benefits.

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Table 1

Effect of Unadulterated Linoleic Acid on Cardiovascular Outcomes in Human Studies

Author	*n*	Study Design	Intervention Period	Source	% LA of Total Fatty Acids	% LA of Total Energy Intake	Control	Effect on Cardiovascular Health	Study Finding
Zock & Katan (1992)	56	RCT	21 d	Margarine high in LA & high-LA sunflower oil	61.9%	12.0%	Stearic acid & elaidic acid (*trans* fatty acids)	Positive	Decreased LDL-C & Increased HDL-C
Kris-Etherton et al (1993)	18	RCT	26 d	Soybean oil	N/A	17.8%	Stearic acid, oleic acid, & myristic acid	Positive	Decreased LDL-C & increased HDL-C (relative to the stearic & myristic acids
Thijssen & Mensink (2005)	45	RCT	35 d	A mixture of palm oil, safflower oil, olive oil, cocoa butter, & high-oleic acid sunflower oil	43.9%	9.3%	Stearic acid & oleic acid	Neutral	No significant differences were found
Hunter et al (2000)	9	RCT	14 d	Blended oil with diet	36.5%	N/A	Stearic acid & oleic acid	Positive	Increased anti-aggregatory prostaglandin E1 binding to platelet membranes
Mensink et al (1992)	56	RCT	21 d	Sunflower oil	N/A	12.0%	Stearic acid & *trans*-monounsaturates	Positive	Decreased median Lp(a) levels (relative to the *trans* diet)
Thijssen et al (2005)	45	RCT	35 d	Not identified	23.2%	9.3%	Stearic acid & oleic acid	Positive	Ex vivo platelet aggregation time was favorably prolonged & the mean platelet volume of the subjects increased (relative to the stearic acid)
Hunter et al (2001)	6	RCT	14 d	Blended oil that contained stearic, oleic, & linoleic acid	36.5%	N/A	Stearic acid & oleic acid	Positive	Increased activated factor VII at 3 h after consumption (relative to the stearic acid)
Laaksonen et al (2005)	1551	Cross-sectional	N/A	Dietary Linoleic Acid	N/A	N/A	N/A	Positive	Reduced the risk of cardiovascular death
Asp et al (2011)	55	RCT	112 d	Safflower oil	78.4%	9.8%	Conjugated linoleic acid	Positive	Decreased HbA1c & C-reactive protein; Increased QUICKI; Increased HDL-C
Becker et al (1983)	12	RCT	28 d	Corn oil & Olive oil	45.7%	N/A	High monounsaturat ed fat & high saturated fat	Positive	Lowered LDL- to HDL-cholesterol ratios
Derr et al (1993)	18	RCT	26 d	Soybean oil	48.7%	17.8%	Stearic acid	Positive	Hypocholesterolemic effect
Laine et al (1982)	24	Case-control	70 d	Corn oil & soy oil	59.8%; 53.2%	N/A	Hydrogenated soy oil & palm oil	Positive	Decreased total plasma cholesterol & LDL-C

Author	*n*	Study Design	Intervention Period	Source	% LA of Total Fatty Acids	% LA of Total Energy Intake	Control	Effect on Cardiovascular Health	Study Finding
Vega-Lopez et al (2009)	30	RCT	35 d	Corn oil	N/A	N/A	Partially hydrogenated soybean oil	Positive	Decreased fasting total cholesterol, LDL-C, sdLDL-C, VLDL-C, Lp(a), Apo B, & concentrations
Rodenas et al (2005)	14	Case-control	28 d	Olive oil & Sunflower oil	N/A	10.0%	Oleic acid	Positive	Decreased serum total cholesterol, phospholipids, apo AII, apo B, LDL fraction, & 10 yr cardiovascular risk

LA: linoleic acid; RCT: randomized controlled trial; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; Lp (a): lipoprotein (a); VLDL-C: very low-density lipoprotein cholesterol; HbA1c: hemoglobin A1c; QUICKI: quantitative insulin sensitivity check index.

Table 2

Effect of Hydrogenated Linoleic Acid on Cardiovascular Outcomes in Human Studies

Author	*n*	Study Design	Intervention Period	Source	% LA of Total Fatty Acids	% LA of Total Energy	Control	Effect on Cardiovascular Health	Study Finding
Lemaitre et al (2006)	5888	Case-control	N/A	Partially hydrogenated safflower oil and cottonseed oil	N/A	N/A	N/A	Negative	Increased risk for fatal ischemic heart disease
Matthan et al (2004)	8	RCT	35 d	Partially hydrogenated soybean oil	N/A	N/A	Unsaturated & saturated fats	Negative	Decreased HDL-C levels; Increased apoA-I fractional catabolic rate
Mauger et al (2003)	36	RTC	35 d	Partially hydrogenated soybean oil	N/A	N/A	N/A	Negative	Increased sdLDL-C levels & serum triaglycerol concentration
Vega-Lopez et al (2006)	15	RCT	35d	Partially hydrogenated soybean oil	N/A	7.22%	Soybean oil, palm oil, & canola oil	Negative	Elevated concentrations of LDL-C and apoB
Vega-Lopez et al (2009)	30	RCT	35d	Partially hydrogenated soybean oil	N/A	N/A	Corn oil	Negative	Resulted in higher concentrations of sdLDL, RemLC, triglyceride, HDL-C, and adiponectin.

LA: linoleic acid; RCT: randomized controlled trial; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.