Cardiovascular disease risk of dietary stearic acid compared with trans, other saturated, and unsaturated fatty acids: a systematic review1–4

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ABSTRACT

Background: High stearic acid (STA) soybean oil is a trans-free, oxidatively stable, non-LDL-cholesterol-raising oil that can be used to replace trans fatty acids (TFAs) in solid fat applications.

Objective: The objective was to assess the cardiovascular health effects of dietary STA compared with those of trans, other saturated, and unsaturated fatty acids.

Design: We reviewed epidemiologic and clinical studies that evaluated the relation between STA and cardiovascular disease (CVD) risk factors, including plasma lipids and lipoproteins, hemostatic variables, and inflammatory markers.

Results: In comparison with other saturated fatty acids, STA lowered LDL cholesterol, was neutral with respect to HDL cholesterol, and directionally lowered the ratio of total to HDL cholesterol. STA tended to raise LDL cholesterol, lower HDL cholesterol, and increase the ratio of total to HDL cholesterol in comparison with unsaturated fatty acids. In 2 of 4 studies, high-STA diets increased lipoprotein(a) in comparison with diets high in saturated fatty acids. Three studies showed increased plasma fibrinogen when dietary STA exceeded 9% of energy (the current 90th percentile of intake is 3.5%). Replacing industrial TFAs with STA might increase STA intake from 3.0% (current) to 4.0% of energy and from 4% to 5% of energy at the 90th percentile. One-to-one substitution of STA for TFAs showed a decrease or no effect on LDL cholesterol, an increase or no effect on HDL cholesterol, and a decrease in the ratio of total to HDL cholesterol.

Conclusions: TFA intake should be reduced as much as possible because of its adverse effects on lipids and lipoproteins. The replacement of TFA with STA compared with other saturated fatty acids in foods that require solid fats beneficially affects LDL cholesterol, the primary target for CVD risk reduction; unsaturated fats are preferred for liquid fat applications. Research is needed to evaluate the effects of STA on emerging CVD risk markers such as fibrinogen and to understand the responses in different populations. Am J Clin Nutr 2010;91:46–63.

INTRODUCTION

This review examined the scientific literature regarding the health effects of dietary stearic acid (STA, 18:0), a possible replacement for trans fatty acids (TFA), particularly in foods that require solid fats (eg, spreads, margarines, baking shortenings, and baked goods). It also compared the effects of STA with other saturated fatty acids, such as palmitic acid (16:0), and with unsaturated fatty acids [oleic (18:1) and linoleic (18:2) acids].

Dietary guidelines released by major health professional organizations and many government agencies worldwide recommend that TFA intake from industrial sources be as low as possible (reviewed by Hunter; 1). In response, the food industry is working on ways to eliminate or greatly reduce TFAs in food products. Current efforts focus on 4 technological options: 1) modification of the hydrogenation process, 2) use of interesterification, 3) use of fractions high in solids from natural oils, and 4) use of trait-enhanced oils (1). All 4 technologies can be used to make fats for solid fat applications. Challenges to the food industry in replacing TFA in foods are to develop formulation options that provide equivalent functionality, are economically feasible, and do not greatly increase saturated fatty acid content.

An American Heart Association conference in 2006 recognized that the reduction of TFA in the food supply is a complex issue that must consider both intended and unintended consequences related to nutrition and public health. A key conclusion of the conference was that both TFAs from industrial sources and cholesterol-raising saturated fatty acids should be reduced (2).

High-STA soybean oil, now under development by agricultural and food-processing companies, is a trans-free, oxidatively stable, non-LDL-cholesterol-raising (3) oil (compared with oils high in palmitic, myristic, and lauric acids) for potential replacement of TFAs and cholesterol-raising saturated fatty acids in solid fat applications (baked goods, shortenings, and margarines). High polyunsaturated fatty acid (PUFA) and mono-unsaturated fatty acid (MUIFA) oils (eg, soybean, sunflower, and canola) are acceptable replacements for TFAs for frying and ingredient use, but do not provide the needed functionality in the specified applications. Some foods require specific textural characteristics for consumer acceptability, for example, flaky pie crusts or crunchy crackers that are uniquely provided by...
solid fats and not by unsaturated fats. It is important to recognize that not all fats serve the same purposes in foods. Because of recommendations to decrease trans and saturated fats, there is a need to find suitable solid fat substitutes that do not increase CVD risk. A fat high in STA is a candidate, but its safety must be assured. Our review comprehensively evaluated the safety of STA beyond reporting effects of high-STA diets on plasma lipid and lipoprotein concentrations. In particular, we assessed dose-response relations between dietary STA amounts and concentrations of LDL and HDL cholesterol and the ratio of total cholesterol (TC) to HDL cholesterol (TC/HDL-cholesterol ratio). We evaluated the changes in these lipoproteins and in the TC/HDL-cholesterol ratio when STA replaces cholesterol-raising saturated fatty acids, MUFA, or PUFA in the diet. We also evaluated effects of high-STA diets on hemostatic factors and markers of inflammation. In addition, we projected an increase in intake of STA if STA were a substitute for TFAs, and we assessed the effects of substituting STA for TFAs in the diet.

METHODS

A comprehensive literature review was conducted by using Medline (www.pubmed.org), The Cochrane Library (www.cochrane.org), Biological Abstracts, and Commonwealth Agricultural Bureau (www.cabi.org) databases to evaluate the health effects of STA. The following key words were used in the search: STA, stearate, saturated fat/saturated fatty acids, and trans fat/ trans fatty acid. The search included abstracts of articles published from January 1957 to May 2008. A total of 226 studies were identified in our literature search. The article eligibility criteria used in the present review are described by the Food and Drug Administration (4, 5). These criteria included English language experimental and observational human studies that evaluated the effects of STA-rich fats on the major endpoints assessed for cardiovascular disease (CVD). The studies reviewed used different sources of STA, including fats naturally high in STA and interesterified (randomized) fats high in STA. Other criteria included the following: the study had to have had a control treatment [a diet high in saturated fatty acids, high in carbohydrate, a baseline (habitual) diet, or high in MUFAs or PUFAs]; a feeding period of ≥2 wk; and experimental diets that were well-defined. Endpoints included effects on concentrations of plasma lipids, lipoproteins, hemostatic factors, and markers of inflammation. A total of 32 experimental studies met our criteria and are incorporated into our tables and/or discussion.

Excluded studies (ie, not meeting our criteria) included those in which the participants were younger than 18 y, <8 subjects completed the study, the duration of the study was <2 wk, the subjects consumed self-selected diets, there was no control diet, isotores were used, there were no dietary fatty acid analyses, there were no CVD-related endpoint measurements, and no information was provided about the control for body weight, physical activity, and carbohydrate, protein, or cholesterol intakes between treatment groups.

Regression analyses were performed by including all selected studies. Regression coefficients were calculated for relations between changes in lipoprotein measures (high-STA diet treatment minus control for LDL cholesterol, HDL cholesterol, and TC/HDL-cholesterol ratio) and changes in dietary fatty acids (STA; sum of lauric (12:0), myristic (14:0), and palmitic acids (LMP); total MUFA (ΔMono, mostly oleic acid); and total PUFA (ΔPoly, mostly linoleic acid). The dietary changes in STA (ΔSTA; amount of STA in the high-STA treatment minus the amount of STA in the control treatment), ΔLMP, ΔMono, and ΔPoly were independent variables in the model. The comparisons between a high-STA diet and a high-saturated (LMP) diet and between a high-STA diet and a high-MUFA or high-PUFA diet yielded 20, 8, or 4 sets of data points, respectively. Including ΔSTA and ΔLMP or ΔSTA and the change in individual fatty acids in the same regression model resulted in high variance inflation factors (>10), which are used to measure the effect of collinearity among the variables in a regression model. Univariate regression thus was used to calculate regression coefficients for the lipoprotein measures when saturated fatty acids (LMP), MUFA, or PUFA were replaced by STA in the diet. Multivariate regression was used to calculate regression coefficients when STA was replaced by saturated fatty acids, MUFA, or PUFA.

In the univariate regression model, we calculated regression coefficients for comparisons between a high-STA diet and high-LMP, ΔMUFA, or ΔPUFA diets. The estimated coefficient indicated the change of one lipoprotein measure (eg, LDL cholesterol) when each 1% of energy as LMP, MUFA, or PUFA was replaced by STA. In the multivariate regression model, adjustments were made for between-study differences, such as age, sex, body mass index, and within-study differences in cholesterol intake between diets. Regression coefficients for ΔLMP, ΔMono, or ΔPoly were estimated by the least-squares regression method. The appropriateness of the regression model was tested by residue analysis. Outlier detection was checked by Cook’s Distance as described by Mensink et al (6). Effects of changes in dietary STA on lipoprotein measures were visualized by scatter plots. Data were plotted by using Prism 5.01 (GraphPad Software Inc, La Jolla, CA). Statistical analyses were performed by using MiniTAB version 15 (MiniTAB Inc, State College, PA).

STEARIC ACID IN THE FOOD SUPPLY

We estimated the current average consumption of STA by the US population to be 3.0% of energy, based on data from the National Health and Nutrition Examination Survey (NHANES) 2005–2006 (7). Similar estimates were reported by Kris-Etherton et al (2.9% of energy) (8) and by Allison et al (3.2% of energy) (9). Using data presented by Allison et al (9), we estimated the 90th percentile of STA intake to be 3.5% of energy. Of the saturated fatty acids consumed in the United States, STA ranks second (25.8% of total saturated fatty acid intake) to palmitic acid (56.3% of total saturated fatty acid intake) (10). The intake of STA in 14 European countries (11) has been estimated to range from about 1.8% to 4.4% of energy. The midpoint of this range (3.1% of energy) is similar to the average intake reported for the US population (7–9).

Sources of dietary STA include 1) meat, poultry, fish, eggs, and dairy products (60%); 2) grains, vegetables, fruit, sweets, and all others prepared with fats (30%), and 3) fats and oils (10%). Fats naturally rich in STA (shown with typical amounts of STA expressed as a percentage of total fatty acids) include beef tallow (19%), lard (14%), butterfat (12%), cocoa butter

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(34%), and sheanut oil (39%). Dietary saturated fatty acids, including STA, provide energy, are structural components of cell membranes, and contribute desirable texture and palatability to foods in the diet.

HUMAN STUDIES RELATING DIETARY SATURATED FATS AND STEARIC ACID TO RISK OF CORONARY HEART DISEASE

Epidemiologic studies

We found 21 epidemiologic studies that reported associations between the intake of saturated fatty acids and the risk of CHD (12–32). Many, but not all, of these studies have reported a positive association between the intake of total saturated fatty acids and the risk of CHD or with coronary events, particularly when relative risks between the highest and lowest categories of intake were considered. In these studies, STA was included as part of total saturated fatty acids. Among these studies, total saturated fatty acid intakes ranged from 4% to 25% of energy. Only 3 of the 21 studies (12, 16, 17) attempted to examine the intake of individual saturated fatty acids, including STA. The range of STA intakes, reported for 2 of these 3 studies (16, 17), was 2.3–4.9% of energy. These 3 studies are discussed below.

Kromhout et al (12) reported the results of 25-y mortality from CHD in the Seven Countries Study. This study, initiated by Keys et al in 1958 (33), considered the intake between individual fatty acids and dietary cholesterol in relation to CHD risk in 12,763 middle-aged men in 16 cohorts in 7 countries. Average total saturated fatty acid intakes ranged from 4% to 23% of energy. Among the individual saturated fatty acids, average intakes of lauric and myristic acids were most strongly correlated with the average total serum cholesterol concentration (r > 0.8, P < 0.001). Intakes of palmitic acid and STA were less correlated (r = 0.60–0.62, P < 0.05).

A strong positive association was observed between 25-y death rates from CHD and average intakes of total saturated fatty acids (sum of lauric, myristic, palmitic, and STA; r > 0.8, P < 0.001). The authors concluded that total dietary saturated fatty acids (including STA as part of the total) are important determinants of differences in population rates of CHD death. On the other hand, an independent effect of STA on serum cholesterol could not be examined because the average intake of STA was strongly associated with the average intakes of lauric, myristic, and palmitic acids. This confounding situation was difficult to control and prevented a definitive conclusion from being drawn about CVD risk associated with dietary STA.

The study by Watts et al (16) measured the progression of coronary artery disease (CAD) in 50 hypercholesterolemic men receiving a lipid-lowering diet or usual care (St Thomas’ Atherosclerosis Regression Study). Progression of CAD over 39 mo was measured by a decrease in the width of coronary segments on angiography. Dietary energy, saturated fat, and STA intakes were significantly lower in the lipid-lowering diet group than in the usual care group. Watts et al (16) found that progression of CAD was highly correlated with the intakes of palmitic acid, STA, palmitoleic acid (16:1), and elaidic (trans-18:1) acid (P < 0.001). After adjustment for age, weight, blood pressure, smoking, plasma total (or LDL) cholesterol, and treatment group, the best predictors of change in width of coronary segments were STA and elaidic acid, the intakes of these fatty acids being closely correlated with each other (r = 0.77, P < 0.001). This suggested that progression of CAD in men is strongly related to intakes of both long-chain saturated and trans unsaturated fatty acids. The reported independent association of STA and CAD was suggested to relate to the procoagulant properties of STA (eg, activating factor VIIc or increasing platelet aggregation).

The third study that examined the effects of individual saturated fatty acids, including STA, and their food sources in relation to risk of CHD was conducted by Hu et al (17). This study was part of the Nurses’ Health Study, a prospective cohort study of 80,082 women aged 34–59 y established in 1976. Median saturated fatty acid intakes (assessed by a food-frequency questionnaire) ranged from 9.5% to 17.2% of energy, and STA intakes, from 2.6 to 4.9% of energy. In multivariate analyses controlling for age, smoking, and other covariates, intakes of short- to medium-chain saturated fatty acids [butyric (4:0), caproic (6:0), caprylic (8:0), and capric acids (10:0)] were not significantly associated with the risk of CHD. In contrast, intakes of longer-chain saturated fatty acids (lauric, myristic, palmitic, and STA) each were separately associated with a 9–24% increase in risk.

The multivariate relative risk (RR) for a 1% energy increase from STA (adjusted for intakes of MUFA, trans fat, protein, fiber, cholesterol, and total energy) was 1.19 (P < 0.02). Similar adjustments to the individual RR values for 1% energy increases from lauric, myristic, and palmitic acids caused these RR values to become nonsignificant. In addition, when the RR value for STA was further adjusted for the sum of lauric, myristic, and palmitic acids, the association of STA with CHD risk became nonsignificant. When all long-chain saturated fatty acids (12:0–18:0) were summed, the RR for a 5% increase in energy intake was associated with a modest increase in risk (RR = 1.29, P < 0.05). These results are less robust but consistent with the finding of Kromhout et al (12) of a strong positive association between 25-y mortality from CHD and intake of total saturated fatty acids. Kromhout et al (12), unlike Hu et al (17), did not adjust for confounders (eg, for trans fat, fiber, total energy, and alcohol intakes; history of CHD; and aspirin use) in determining correlations between intakes of individual fatty acids and CHD mortality. In addition, Hu et al (17) noted that their ability to distinguish among the individual saturated fatty acids was limited by their high intercorrelations [also noted by Kromhout et al (12) and Watts et al (16)] because their predominant sources were the same foods.

Although many epidemiologic studies have shown an association between saturated fatty acid intake and CHD risk, 8 studies reported no association between saturated fatty acid intake and coronary deaths (34–41). Possible explanations for this finding included reports that all subjects were consuming a high-saturated-fat diet (34) and that all subjects were middle-aged smokers eating a high-fat diet (35). In the latter case, subjects with a family history of CHD might have reduced their saturated fatty acid intake either before or during the study. Another reason why saturated fatty acids may not have been associated with CHD risk is because they raise HDL cholesterol compared with carbohydrate and thus do not change the ratio of LDL to HDL cholesterol (6). In contrast, substitution of PUFAs for saturated fatty acids has been associated with a reduced risk (6).
In summary, intake of total saturated fatty acids (including STA as part of the total) has been shown to be positively associated with the risk of CHD or with a major coronary event in many but not all studies. One study (16) reported an association between the intake of STA and the progression of CAD, which was independent of plasma cholesterol. Another study that reported an independent association of STA on increasing CHD risk (17) found that the association became nonsignificant after adjustment for the sum of the intakes of lauric, myristic, and palmitic acids. An independent association of STA on increasing CHD risk has not been shown to date because the average intake of STA has been strongly associated with the intakes of lauric, myristic, and palmitic acids.

Clinical trials reporting changes in plasma lipid and lipoprotein concentrations

The Institute of Medicine (IOM) report of the National Academies (3) points out that, based on epidemiologic evidence, long-chain saturated fatty acids are associated with an increased CHD risk because of their hypercholesterolemic effects compared with unsaturated fatty acids and carbohydrate. A positive linear relation between serum total and LDL-cholesterol concentrations and risk of CHD or CHD mortality was reported as was a positive linear trend between the intake of TFA and the ratio of LDL cholesterol to HDL cholesterol. Results from clinical studies cited in the IOM report (3) show a positive linear relation between intake of total saturated fatty acids and LDL-cholesterol concentrations, based on meta-analyses conducted by Mensink and Katan (42), Hegsted et al (43), and Clarke et al (44). Importantly, the IOM report (3) also cited controlled studies (eg, 45) showing that STA differed in its effect on blood cholesterol concentrations, having a neutral effect compared with the other long-chain saturated fatty acids.

A more recent meta-analysis of 60 controlled clinical trials (6) showed that STA, when substituted for carbohydrate, has a neutral effect on total and LDL cholesterol, whereas lauric, myristic, and palmitic acids all have a hypercholesterolemic effect. The authors of this meta-analysis (6) suggested that CHD risk is reduced most effectively when TFA and saturated fatty acids are replaced by cis unsaturated fatty acids.

We assessed 22 human trials in which changes in serum LDL cholesterol, HDL cholesterol, triglycerides, and lipoprotein(a) [Lp(a)] were measured after feeding diets high in STA (45–66) (Table 1). Two of these trials were follow-up experiments in which Lp(a) concentrations were reported (47, 53) after previous measurements of LDL cholesterol, HDL cholesterol, and triglycerides (46, 52). The 20 feeding trials listed in Table 1 are grouped according to 4 control diets: high in saturated fatty acids, high in carbohydrate, baseline (habitual), and high in unsaturated fatty acids. Some studies in Table 1 are listed ≥2 times if these studies included ≥2 control comparisons. Within each control treatment, the studies are listed in order of decreasing amount of dietary STA. The duration of the studies varied between 14 and 40 d. Amounts of STA in the high-STA diets ranged from 4% to 17% of energy. Nearly all of the studies used conventional food diets except for 2 (45, 54), which used liquid-formula diets.

Most studies did not report TC/HDL-cholesterol ratios, so we calculated the ratios from the mean values of TC and HDL cholesterol presented. Because each treatment had only one corresponding TC/HDL-cholesterol ratio, it was not possible to conduct statistical analyses to determine whether the ratio for an STA treatment was significantly different from that of a control treatment. Accordingly, we have used the terms directional increase or directional decrease to indicate that a TC/HDL-cholesterol ratio for one treatment was higher or lower than that for a comparative treatment.

Effects of STA compared with other saturated fatty acids

Of the 20 studies in Table 1, 14 compared a high-STA diet (4–17% of energy) with a control diet high in saturated fatty acids (palmitic, myristic, or lauric acids, or butterfat) (Table 1A). Eight of these studies reported decreases in LDL cholesterol after the high-STA diet (45, 50, 52, 54–56, 60, 62), and 6 found no significant change in LDL cholesterol (48, 51, 57, 61, 63, 64). Two studies (60, 62) reported a decrease in LDL cholesterol compared with one saturated fatty acid treatment, but no significant change or an increase compared with a second saturated fatty acid treatment. Six of the 14 studies in Table 1A reported decreases in HDL cholesterol after the high-STA diet (48, 50–52, 57, 62), and 8 reported no changes (45, 54–56, 60, 61, 63, 64) in HDL cholesterol. Considering triglyceride concentrations, one study showed an increase (48) and one a decrease (50) after the high-STA diet. The remaining 12 studies showed no significant change in TG after the high-STA diet. Nine of 14 studies found an independent association of STA on increasing CHD risk because of their hypercholesterolemic effects compared with unsaturated fatty acids and carbohydrate. Of the 8 palmitic acid studies, treatments with myristic acid alone (52) were included. The latter study (52) reported a decrease in LDL cholesterol, and the former study (60) reported no change in LDL cholesterol. The remaining 6 studies in Table 1A used a saturated fatty acid mixture (eg, butterfat, dairy fat, or a combination of lauric, myristic, and palmitic acids), which did not permit comparison of the high-STA diet with individual saturated fatty acids. Of the 8 palmidic acid studies, 2 showed changes (decreases) in HDL cholesterol after the high-STA diet (52, 57), and 2 showed directional increases (of uncertain significance) in the TC/HDL-cholesterol ratio (56, 57). None of these showed effects on triglyceride concentrations.

In summary, considering studies in which effects of STA were compared with those of the individual saturated fatty acids palmitic, myristic, and lauric acids in 8 studies are presented in Table 1A. All 8 studies included a high–palmitic acid diet as a control treatment. Of these studies, the high-STA diet resulted in decreased LDL-cholesterol concentrations in 4 studies (45, 52, 56, 60) and no significant change in LDL cholesterol in 4 other studies (57, 61, 63, 64). In 2 of the 8 palmitic acid studies, treatments with myristic acid alone (60) or in combination with lauric acid (52) were included. The latter study (52) reported a decrease in LDL cholesterol, and the former study (60) reported no change in LDL cholesterol. The remaining 6 studies in Table 1A used a saturated fatty acid mixture (eg, butterfat, dairy fat, or a combination of lauric, myristic, and palmitic acids), which did not permit comparison of the high-STA diet with individual saturated fatty acids. Of the 8 palmidic acid studies, 2 showed changes (decreases) in HDL cholesterol after the high-STA diet (52, 57), and 2 showed directional increases (of uncertain significance) in the TC/HDL-cholesterol ratio (56, 57). None of these showed effects on triglyceride concentrations.
<table>
<thead>
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<th>Study</th>
<th>Study population</th>
<th>Period</th>
<th>STA</th>
<th>Control</th>
<th>ΔLDL-C</th>
<th>ΔHDL-C</th>
<th>ΔTG</th>
<th>ΔTC/HDL-C ratio</th>
<th>ΔLP(a)</th>
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<td>A: Control diet high in saturated fatty</td>
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<td>acids (palmitic acid, myristic acid, or</td>
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<td>Bonanome and Grundy, 1988 (45)</td>
<td>11 men (4 with CHD history)</td>
<td>21</td>
<td>17.2</td>
<td>PA</td>
<td>21.5^2</td>
<td>5.5^1</td>
<td>0.7^†</td>
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<td>35</td>
<td>14.1</td>
<td>PA</td>
<td>1.6^1</td>
<td>0.9^1</td>
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<td>1.0^†</td>
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<td>15 men, normocholesterolemic</td>
<td>21</td>
<td>13.7</td>
<td>PA</td>
<td>26.4^4</td>
<td>13.1^3</td>
<td>4.1^†</td>
<td>10.2^†</td>
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<td>Tholstrup et al, 1995 (53)</td>
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<td>21</td>
<td>13.7</td>
<td>NR</td>
<td>29.0^1</td>
<td>27.7^3</td>
<td>5.4^†</td>
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<td>Denke and Grundy, 1991 (54)</td>
<td>10 men (2 with history of CHD)</td>
<td>21</td>
<td>13.2</td>
<td>Butterfat</td>
<td>9.9^6</td>
<td>0.0^1</td>
<td>3.2^†</td>
<td>8.4^†</td>
<td>NR</td>
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<td>Snook et al, 1999 (60)</td>
<td>18 women, normocholesterolemic</td>
<td>35</td>
<td>12.8</td>
<td>PA</td>
<td>13.7^6</td>
<td>1.5^†</td>
<td>20.0^†</td>
<td>10.8^†</td>
<td>NR</td>
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<tr>
<td>Sundram et al, 2007 (51)</td>
<td>30 men and women, normocholesterolemic</td>
<td>28</td>
<td>12.5</td>
<td>Palm olein</td>
<td>3.9^†</td>
<td>9.1^5</td>
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<td>26</td>
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<td>Butterfat</td>
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<td>16.3^†</td>
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<td>35</td>
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<td>LMP</td>
<td>13.6^7</td>
<td>3.8^†</td>
<td>12.5^†</td>
<td>12.9^†</td>
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<td>49 women and 31 men, normocholesterolemic</td>
<td>35</td>
<td>9.3</td>
<td>Dairy fat</td>
<td>9.1^6</td>
<td>11.3^5</td>
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<td>21.1^†</td>
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<td>40</td>
<td>7.3</td>
<td>PA</td>
<td>6.1^6</td>
<td>11.1^1</td>
<td>0.0^1</td>
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<td>28</td>
<td>7.3</td>
<td>PA</td>
<td>7.9^1</td>
<td>9.3^6</td>
<td>16.0^†</td>
<td>1.0^†</td>
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<td>28</td>
<td>6.6</td>
<td>PA</td>
<td>6.0^1</td>
<td>3.5^1</td>
<td>4.3^1</td>
<td>1.8^†</td>
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<td>4.6</td>
<td>Butter oil/grapeseed oil (90:10)</td>
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<td>9.1^2</td>
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<td>9 men, normocholesterolemic</td>
<td>21</td>
<td>4.3</td>
<td>PA</td>
<td>6.5^2</td>
<td>7.8^2</td>
<td>5.5^†</td>
<td>15.5^†</td>
<td>NR</td>
</tr>
<tr>
<td>B: Control diet high in carbohydrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nestel et al, 1998 (61)</td>
<td>15 men and women, hypercholesterolemic</td>
<td>35</td>
<td>14.1</td>
<td>Low-fat diet (CHO)</td>
<td>0.6^†</td>
<td>0.0^1</td>
<td>8.0^†</td>
<td>1.2^†</td>
<td>NR</td>
</tr>
<tr>
<td>Judd et al, 2002 (48)</td>
<td>50 men, normocholesterolemic</td>
<td>35</td>
<td>10.9</td>
<td>CHO</td>
<td>1.5^†</td>
<td>3.3^1</td>
<td>10.6^†</td>
<td>4.8^†</td>
<td>NR</td>
</tr>
<tr>
<td>Kris-Etherton et al, 1994 (49)</td>
<td>42 men, normocholesterolemic</td>
<td>27</td>
<td>5.0</td>
<td>CHO</td>
<td>2.3^†</td>
<td>4.2^6</td>
<td>12.2^6</td>
<td>2.6^†</td>
<td>NR</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>Period</th>
<th>STA</th>
<th>Control</th>
<th>ΔLDL-C</th>
<th>ΔHDL-C</th>
<th>ΔTG</th>
<th>ΔTC/HDL-C ratio</th>
<th>ΔLp(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>C: Control diet was a baseline (habitual) diet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snook et al, 1999 (60)</td>
<td>18 women, normocholesterolemic</td>
<td>35</td>
<td>12.8</td>
<td>Baseline</td>
<td>7.2↓</td>
<td>2.2↓</td>
<td>3.0↓</td>
<td>2.4↓</td>
<td>NR</td>
</tr>
<tr>
<td>Schwab et al, 1996 (57)</td>
<td>12 women, normocholesterolemic</td>
<td>28</td>
<td>7.3</td>
<td>Baseline</td>
<td>0.0</td>
<td>8.7↓</td>
<td>16.8↓</td>
<td>4.7↑</td>
<td>NR</td>
</tr>
<tr>
<td>Kelly et al, 2001 (63)</td>
<td>13 men, normocholesterolemic</td>
<td>28</td>
<td>6.6</td>
<td>Baseline</td>
<td>11.9↓</td>
<td>10.7↓</td>
<td>4.3↑</td>
<td>0.8↑</td>
<td>NR</td>
</tr>
<tr>
<td>Kelly et al, 2002 (64)</td>
<td>9 men, normocholesterolemic</td>
<td>21</td>
<td>4.3</td>
<td>Baseline</td>
<td>10.9↓</td>
<td>6.6↑</td>
<td>3.7↑</td>
<td>11.3↓</td>
<td>NR</td>
</tr>
<tr>
<td>D: Control diet high in unsaturated fatty acids (oleic acid or linoleic acid)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bonanome and Grundy, 1988 (45)</td>
<td>11 men (4 with CHD history)</td>
<td>21</td>
<td>17.2</td>
<td>OL</td>
<td>7.5↓</td>
<td>8.8↓</td>
<td>5.8↑</td>
<td>4.8↑</td>
<td>NR</td>
</tr>
<tr>
<td>Denke and Grundy, 1991 (54)</td>
<td>10 men (2 with history of CHD)</td>
<td>21</td>
<td>13.2</td>
<td>OL</td>
<td>5.5↑</td>
<td>0.0</td>
<td>17.5↑</td>
<td>5.4↑</td>
<td>NR</td>
</tr>
<tr>
<td>Hunter et al, 2000 (59)</td>
<td>9 men, normocholesterolemic</td>
<td>14</td>
<td>13.0</td>
<td>OL</td>
<td>11.3↑</td>
<td>8.9↑</td>
<td>36.9↑</td>
<td>3.2↑</td>
<td>NR</td>
</tr>
<tr>
<td>Zock and Katan, 1992 (46)</td>
<td>30 women and 26 men, normocholesterolemic</td>
<td>21</td>
<td>11.8</td>
<td>LA</td>
<td>8.1↑</td>
<td>7.7↓</td>
<td>5.9↑</td>
<td>9.8↑</td>
<td>NR</td>
</tr>
<tr>
<td>Mensink et al, 1992 (47)</td>
<td>30 women and 26 men, normocholesterolemic</td>
<td>21</td>
<td>11.8</td>
<td>LA</td>
<td>6.0↑</td>
<td>4.1↓</td>
<td>9.5↑</td>
<td>7.8↑</td>
<td>NR</td>
</tr>
<tr>
<td>Kris-Etherton et al, 1993 (55)</td>
<td>14 men, normocholesterolemic</td>
<td>26</td>
<td>11.4</td>
<td>OL</td>
<td>11.8↑</td>
<td>8.1↓</td>
<td>3.6↑</td>
<td>18.3↑</td>
<td>NR</td>
</tr>
<tr>
<td>Judd et al, 2002 (48)</td>
<td>50 men, normocholesterolemic</td>
<td>35</td>
<td>10.9</td>
<td>OL</td>
<td>22.7↑</td>
<td>1.7↓</td>
<td>19.2↑</td>
<td>21.4↑</td>
<td>NR</td>
</tr>
<tr>
<td>Thijssen and Mensink, 2005 (58)</td>
<td>27 women and 18 men, normocholesterolemic</td>
<td>35</td>
<td>7.7</td>
<td>OL</td>
<td>5.2↑</td>
<td>6.8↑</td>
<td>29.2↑</td>
<td>11.4↑</td>
<td>NR</td>
</tr>
<tr>
<td>Berry et al, 2007 (66)</td>
<td>16 men, normocholesterolemic</td>
<td>21</td>
<td>7.7 (unrandomized)</td>
<td>OL</td>
<td>12.6↑</td>
<td>5.4↑</td>
<td>20.4↑</td>
<td>15.1↑</td>
<td>NR</td>
</tr>
<tr>
<td>Louheranta et al, 1998 (65)</td>
<td>15 women, normocholesterolemic</td>
<td>28</td>
<td>6.6</td>
<td>OL</td>
<td>3.8↑</td>
<td>0.7↑</td>
<td>2.5↑</td>
<td>3.4↑</td>
<td>NR</td>
</tr>
</tbody>
</table>

Changes in plasma lipid and lipoprotein concentrations (compared with control treatments) after subjects consumed high-STA diets for 14 to 40 d. The table is divided into 4 subgroups according to control treatment [saturated fatty acids, high carbohydrate (CHO), baseline (habitual), or unsaturated fatty acids]. The studies in each subgroup are listed in order of decreasing amounts of dietary STA. Four studies included 2 different amounts of dietary STA. Several studies are listed in ≥2 subgroups because ≥2 control comparisons were possible [eg, the study by Judd et al (48) had high saturated fatty acid, high CHO, and high unsaturated fatty acids comparisons]. ΔLDL-C, change in LDL cholesterol; ΔHDL-C, change in HDL cholesterol; ΔTG, change in triglycerides; ΔTC/HDL-C ratio, change in total cholesterol/HDL-C ratio; ΔLp(a), change in lipoprotein(a); OL, oleic acid; LA, linoleic acid; PA, palmitic acid; ML, myristic and lauric acids; MY, myristic acid; LMP, lauric, myristic, and palmitic acids; LEAR, lowerucic acid rapeseed oil; ↑, increase compared with control; ↓, decrease compared with control; NR, not reported; CHD, coronary heart disease.

1 Changes in plasma lipid and lipoprotein concentrations (compared with control treatments) after subjects consumed high-STA diets for 14 to 40 d. The table is divided into 4 subgroups according to control treatment [saturated fatty acids, high carbohydrate (CHO), baseline (habitual), or unsaturated fatty acids]. The studies in each subgroup are listed in order of decreasing amounts of dietary STA. Four studies included 2 different amounts of dietary STA. Several studies are listed in ≥2 subgroups because ≥2 control comparisons were possible [eg, the study by Judd et al (48) had high saturated fatty acid, high CHO, and high unsaturated fatty acids comparisons]. ΔLDL-C, change in LDL cholesterol; ΔHDL-C, change in HDL cholesterol; ΔTG, change in triglycerides; ΔTC/HDL-C ratio, change in total cholesterol/HDL-C ratio; ΔLp(a), change in lipoprotein(a); OL, oleic acid; LA, linoleic acid; PA, palmitic acid; ML, myristic and lauric acids; MY, myristic acid; LMP, lauric, myristic, and palmitic acids; LEAR, lowerucic acid rapeseed oil; ↑, increase compared with control; ↓, decrease compared with control; NR, not reported; CHD, coronary heart disease.

2-7 Significantly different from control treatment: 2P < 0.005, 3P < 0.001, 4P < 0.025, 5P < 0.002, 6P < 0.05, 7P < 0.01.
neutral effects of dietary STA compared with cholesterol-raising saturated fatty acids were shown previously (3, 6).

**Effects of STA compared with dietary carbohydrate and with baseline diets**

Effects of STA compared with dietary carbohydrate were evaluated in 3 studies (48, 49, 61; Table 1B). All 3 studies reported no significant change in LDL cholesterol after a high-STA diet compared with a high-carbohydrate (low fat) treatment and no consistent effect on the TC/HDL-cholesterol ratio. In the study by Judd et al (48), the high-carbohydrate treatment resulted in a significant 3% decrease in HDL cholesterol compared with the high-STA diet. The study by Kris-Etherton et al (49) reported an increase in HDL cholesterol after healthy male subjects were fed a milk chocolate bar daily that provided 42 g saturated fat (17 g STA) compared with males fed a high-carbohydrate snack (a fig bar or Graham crackers plus juice). These results are consistent with the meta-analyses reported by Mensink and Katan (42) and Mensink et al (6), which showed a neutral effect of STA on LDL cholesterol when compared with dietary carbohydrate.

After a high-STA diet compared with a baseline (habitual) diet (Table 1C), 3 studies reported a 7–12% decrease in LDL cholesterol (60, 63, 64), and 1 study reported no significant change (57). One study (63) also reported a significant decrease in the HDL-cholesterol concentration. There was no consistent effect on the TC/HDL-cholesterol ratio.

Overall, the results showed that dietary STA had no effect on LDL cholesterol compared with a diet high in carbohydrate (low in total fat) and decreased LDL cholesterol in 3 of 4 studies compared with a baseline (habitual) diet.

**Effects of STA compared with unsaturated fatty acids**

Eight studies compared the effects of a high-STA diet with those of a control diet high in oleic acid (45, 48, 54, 55, 58, 59, 65, 66) (Table 1D). Substituting STA for oleic acid resulted in significant increases in LDL cholesterol in 3 of these studies (48, 54, 55), a decrease in HDL cholesterol in 1 study (48), and an increase in triglyceride in 2 studies (48, 54). The other studies (45, 58, 59, 65, 66) reported no significant changes in LDL cholesterol, HDL cholesterol, or triglycerides as a result of substituting STA for oleic acid. Directional increases in the TC/HDL-cholesterol ratio were seen in 6 of the 8 studies. The study by Denke and Grundy (54) reported an increase in LDL cholesterol after a beef-fat diet (7.6% of energy as STA), but no change in LDL cholesterol after a cocoa butter diet (13.2% of energy as STA). Four studies compared feeding a high-STA diet with a control diet high in linoleic acid (46, 55, 58, 59) (Table 1D). Substituting STA for linoleic acid increased LDL cholesterol in 2 studies (46, 55), decreased HDL cholesterol in 1 study (46), increased triglycerides in 2 studies (46, 55), and directionally increased the TC/HDL-cholesterol ratio in all 4 studies.

Collectively, as shown in Table 1D, when STA replaced oleic acid or linoleic acid, LDL cholesterol increased 5–24% in 4 of 9 studies but did not change in 5 other studies. HDL cholesterol decreased 4–7% in 2 studies but did not change in 7 others. Triglycerides increased 10–37% in 4 studies but did not change in 5 others. The effects reported for linoleic acid tended to be consistent, whereas for oleic acid they were more variable. However, only a small number of studies (9) have made such comparisons. Seven of 9 studies showed a directional increase in the TC/HDL-cholesterol ratio after a high-STA diet compared with the unsaturated fatty acid diet. This suggests that unsaturated fatty acids had a more favorable effect on the ratio than did STA. Overall, oleic or linoleic acids have beneficial effects on LDL cholesterol and HDL cholesterol compared with STA.

**Effects of STA on Lp(a)**

Lp(a) is an emerging marker of CHD risk (67). Lp(a) measurements were made in only 4 of the 20 studies listed in Table 1. Mensink et al (47) [an extension of the study by Zock and Katan (46)] and Louheranta et al (65) reported no significant change in Lp(a) concentrations after feeding a high-STA diet compared with a high–linoleic acid or high–oleic acid control diet. In contrast, Aro et al (50) and Tholstrup et al (53) observed increased Lp(a) concentrations of 8% and 34%, respectively, after feeding a high-STA diet compared with control diets high in saturated fatty acids. On the other hand, a study by Clevéden et al (68) reported that a diet high in cholesterol-raising saturated fatty acids decreased Lp(a) compared with a diet high in oleic acid. In addition, Ginsberg et al (69) reported an increase in Lp(a) after consumption of a Step I diet that was low in saturated fat. Thus, the Lp(a)-raising effect of STA compared with saturated fatty acids reported by Aro et al (50) and Tholstrup et al (53) might have been due to the Lp(a)-lowering effect of saturated fatty acids rather than an Lp(a)-raising effect of STA. The available data considering changes in Lp(a) concentrations with dietary STA are limited, and further studies are needed to evaluate the effects of STA on Lp(a).

**Effects of interesterification**

Among the studies listed in Table 1, 9 of 20 used high-STA diets in which the high-STA fat was produced by interesterification (45, 46, 48, 50, 51, 61–63, 66), ie, STA was enriched at the sn-2 position of the triglyceride molecule, thereby enhancing its absorption (70). The use of interesterified fats in these studies did not result in any consistent changes in LDL-cholesterol, HDL-cholesterol, Lp(a), or triglyceride concentrations compared with
TABLE 2
Univariate regression coefficients (and 95% CIs) for mean changes (Δ) in plasma LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), and the ratio of total cholesterol to HDL-C (TC/HDL-C ratio) when stearic acid (STA), constituting 1% of dietary energy, isocalorically replaced lauric, myristic, and palmitic acids (LMP); cis-monounsaturated fatty acids; or cis-polyunsaturated fatty acids.

<table>
<thead>
<tr>
<th>Dietary fatty acids (% of energy) replaced by STA</th>
<th>ΔLDL-C mmol/L</th>
<th>P</th>
<th>ΔHDL-C mmol/L</th>
<th>P</th>
<th>ΔTC/HDL-C ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔLMP</td>
<td>-0.036</td>
<td>0.034</td>
<td>-0.006</td>
<td>0.305</td>
<td>-0.008</td>
<td>0.668</td>
</tr>
<tr>
<td>-0.069, 0.003</td>
<td></td>
<td></td>
<td>-0.018, 0.006</td>
<td></td>
<td>-0.044, 0.03</td>
<td></td>
</tr>
<tr>
<td>ΔMonounsaturated</td>
<td>-0.035</td>
<td>0.201</td>
<td>-0.01</td>
<td>0.171</td>
<td>-0.001</td>
<td>0.971</td>
</tr>
<tr>
<td>-0.095, 0.025</td>
<td></td>
<td></td>
<td>-0.026, 0.005</td>
<td></td>
<td>-0.045, 0.043</td>
<td></td>
</tr>
<tr>
<td>ΔPolyunsaturated</td>
<td>0.034</td>
<td>0.758</td>
<td>-0.013</td>
<td>0.235</td>
<td>0.065</td>
<td>0.432</td>
</tr>
<tr>
<td>-0.381, 0.45</td>
<td></td>
<td></td>
<td>-0.045, 0.02</td>
<td></td>
<td>-0.22, 0.351</td>
<td></td>
</tr>
</tbody>
</table>

1 Regression coefficients were calculated for changes in lipoprotein measures (high-STA treatment minus control to obtain ΔLDL-C, ΔHDL-C, and ΔTC/HDL-C ratio) in relation to changes in amounts of dietary fatty acids (treatment minus control) reported in Table 1, A and D. A P value <0.05 was considered statistically significant.

Effects of univariate regression analyses on LDL cholesterol, HDL cholesterol, and the TC/HDL-cholesterol ratio

Changes in LDL cholesterol (high-STA treatment minus control) from studies presented in Table 1, A or D have been plotted against changes in dietary STA amount (treatment minus control) when STA was substituted for cholesterol-raising saturated fatty acids (20 data points), for MUFAs (8 data points), or for PUFAs (4 data points) (Figure 1). Substituting STA for cholesterol-raising saturated fatty acids indicated that the LDL-cholesterol concentration decreases as dietary STA increases. In the univariate analysis, interpreted as cholesterol-raising saturated fatty acids being replaced by STA, there was a significant reduction in LDL cholesterol with increasing STA amount. The univariate regression coefficient for this relation was −0.036 (P = 0.034) (Table 2). This regression coefficient suggests that for each 1% of energy increase in STA, when substituted for cholesterol-raising saturated fatty acids, the LDL-cholesterol concentration could decrease by 0.036 mmol/L. This modifies the traditionally accepted view that dietary STA is cholesterol-neutral to the view that dietary STA is LDL-cholesterol lowering, when compared with other saturated fatty acids, such as palmitic acid. It should be noted, however, that because the selected control diets were designed to substitute other saturated fatty acids (primarily lauric, myristic, and palmitic acids) for STA, the LDL cholesterol reduction associated with the replacement of other saturated fatty acids with STA could have been due to a combination of simultaneously decreasing amounts of other saturated fatty acids and increasing STA.

Changes in LDL cholesterol when STA was substituted for MUFAs or for PUFAs also are shown in Figure 1. The directional decrease in LDL cholesterol associated with the substitution of STA for MUFAs was not statistically significant. Also, the directional increase in LDL cholesterol associated with the substitution of STA for PUFAs was not statistically significant. The corresponding univariate regression coefficients were not statistically significant (Table 2). This lack of significance in these 2 relations may have been related to there being fewer data points, ie, fewer studies considering effects of STA substituted for MUFAs or PUFAs.

Similar graphs have plotted changes in HDL cholesterol and changes in the TC/HDL-cholesterol ratio (Figures 2 and 3, respectively) against changes in dietary STA, when STA was substituted for cholesterol-raising saturated fatty acids, MUFAs, or PUFAs. Both figures indicate nonsignificant changes in either HDL cholesterol (Figure 2) or in the TC/HDL-cholesterol ratio (Figure 3) when STA replaced cholesterol-raising saturated fatty acids, MUFAs, or PUFAs. After univariate analysis, substituting STA for cholesterol-raising saturated fatty acids, MUFAs, or PUFAs resulted in nonsignificant changes in both HDL cholesterol and in the TC/HDL-cholesterol ratio with increasing STA amount (Table 2).

It is important to point out that Figures 1–3 each contain 32 data points, 20 of which were taken from the 14 studies in Table 1A and 12 of which were taken from the 9 studies in Table 1D.

FIGURE 2. Changes (Δ) in HDL cholesterol (ΔHDL-C) [high stearic acid (STA) treatment minus control, expressed as mmol/L] plotted against changes in dietary STA amount [treatment minus control, expressed as % of energy (%en)] when STA was substituted for cholesterol-raising saturated fatty acids (Sat), monounsaturated fatty acids (MUFAs), or polyunsaturated fatty acids (PUFAs). The graph was prepared from data presented in Table 1, A and D.
Each point represents the difference between a high-STA diet and one control diet. Of the 14 studies in Table 1A, 3 (52, 60, 62) included 2 different control treatments (eg, palmitic acid and myristic acid diets), 1 (54) included 2 different combinations of STA and a butterfat control treatment, and 1 (55) included 3 such combinations. This accounts for 20 data points from 14 studies.

**Effects of multivariate regression analyses on LDL cholesterol, HDL cholesterol, and the TC/HDL-cholesterol ratio**

In the multivariate analysis, interpreted as STA being replaced by cholesterol-raising saturated fatty acids, there was a significant increase in LDL cholesterol with increasing amount of these saturated fatty acids. The multivariate regression coefficient for this relation was 0.043 ($P < 0.001$) (Table 3). This regression coefficient suggests that for each 1% of energy increase in cholesterol-raising saturated fatty acids, when substituted for STA, the LDL-cholesterol concentration would increase by 0.043 mmol/L.

Also, after multivariate analysis, there were small but significant increases in both HDL cholesterol and in the TC/HDL-cholesterol ratio as dietary STA increased. On the other hand, replacement of STA by MUFAs or PUFAs did not result in significant changes in either HDL cholesterol or in the TC/HDL-cholesterol ratio by multivariate analysis (Table 3).

**Comparison of our regression analyses with those of Mensink et al**

Mensink et al (6), in their meta-analysis, reported that replacing dietary carbohydrates isoenergetically with saturated fatty acids resulted in increases in LDL cholesterol and HDL cholesterol. These relations had positive regression coefficients of 0.032 and 0.010, respectively. Similarly, we found that replacing STA with cholesterol-raising saturated fatty acids raised LDL cholesterol and HDL cholesterol. Our relations had positive multivariate regression coefficients of 0.043 and 0.009, respectively (Table 3). Our results are similar to those of Mensink et al (6), but clearly show a dose-response relation for reducing LDL-cholesterol concentrations as dietary STA increased (Figure 1). Mensink et al (6) further reported significant decreases in LDL cholesterol after replacing carbohydrates with MUFAs or PUFAs (regression coefficients of –0.009 and –0.019, respectively) and significant increases in HDL cholesterol after replacing carbohydrates with MUFAs and PUFAs (regression coefficients of 0.008 and 0.006, respectively). On the other hand, we found no significant relations after the replacement of STA with MUFAs or PUFAs, perhaps because we had many fewer studies to consider (8 studies for MUFAs and 4 for PUFAs) than did Mensink et al (43 studies).

In summary, our univariate analyses indicated that when cholesterol-raising saturated fatty acids were replaced by STA, there was a significant reduction in LDL-cholesterol concentration but no changes in HDL cholesterol or in the TC/HDL-cholesterol ratio with an increasing dietary STA amount. Multivariate analyses indicated that when STA was replaced by cholesterol-raising saturated fatty acids, there were significant increases in LDL cholesterol, HDL cholesterol, and in the TC/HDL-cholesterol ratio with increasing amounts of these saturated fatty acids. Univariate analyses for replacement of either MUFAs or PUFAs by STA resulted in no significant changes in LDL cholesterol, HDL cholesterol, or the TC/HDL-cholesterol ratio. Similarly, multivariate analyses for replacement of STA by MUFAs or PUFAs resulted in no significant changes in LDL cholesterol, HDL cholesterol, or the TC/HDL-cholesterol ratio.

**TABLE 3**

Multivariate regression coefficients (and 95% CIs) for mean changes ($\Delta$) in plasma LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), and the ratio of total cholesterol to HDL-C (TC/HDL-C ratio) when stearic acid (STA), constituting 1% of dietary energy, isocalorically replaced lauric, myristic, and palmitic acids (LMP); cis-monounsaturated fatty acids; or cis-polyunsaturated fatty acids

<table>
<thead>
<tr>
<th>Dietary fatty acids (%) of energy</th>
<th>$\Delta$LDL-C</th>
<th>$P$</th>
<th>$\Delta$HDL-C</th>
<th>$P$</th>
<th>$\Delta$TC/HDL-C ratio</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmol/L</td>
<td></td>
<td>mmol/L</td>
<td></td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td>ALMP</td>
<td>0.043</td>
<td>&lt;0.001</td>
<td>0.009</td>
<td>0.001</td>
<td>0.015</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td>(0.028, 0.057)</td>
<td></td>
<td>(0.005, 0.013)</td>
<td></td>
<td>(0.001, 0.03)</td>
<td></td>
</tr>
<tr>
<td>AMonounsaturated</td>
<td>0.005</td>
<td>0.686</td>
<td>0.004</td>
<td>0.381</td>
<td>-0.018</td>
<td>0.129</td>
</tr>
<tr>
<td></td>
<td>(-0.02, 0.03)</td>
<td></td>
<td>(-0.004, 0.012)</td>
<td></td>
<td>(-0.043, 0.007)</td>
<td></td>
</tr>
<tr>
<td>APolysaturated</td>
<td>-0.02</td>
<td>0.222</td>
<td>0.001</td>
<td>0.874</td>
<td>-0.026</td>
<td>0.074</td>
</tr>
<tr>
<td></td>
<td>(-0.051, 0.011)</td>
<td></td>
<td>(-0.009, 0.011)</td>
<td></td>
<td>(-0.055, 0.002)</td>
<td></td>
</tr>
</tbody>
</table>

1 Multivariate regression analysis was used to represent the replacement of STA by other fatty acids (ALMP, AMonounsaturated, or APolysaturated). A $P$ value <0.05 was considered statistically significant.
Coagulation and fibrinolysis

**Formation of fibrin**

\[
\text{Prothrombin} \quad \downarrow \quad \text{FVIIc / FVIIa + TF} \quad \downarrow \\
\text{F1 + F2} \quad \downarrow \\
\text{Thrombin} \quad \downarrow \\
\text{Fibrinogen} \quad \rightarrow \quad \text{Fibrin} \quad \rightarrow \quad \text{Fibrin degradations products} \quad \uparrow \\
\text{t-PA} \quad \rightarrow \quad \text{Plasmin} \quad \uparrow \\
\text{PAI-1} \\
\]

**Fibrinolysis**

Dissolution of fibrin

**FIGURE 4.** Key steps in the formation of blood clots (coagulation) or the dissolution of blood clots (fibrinolysis). The variables investigated in the studies reported in this article included fibrinogen, factor VII coagulant activity (FVIIc), activated factor VII (FVIIa), prothrombin fragments 1 and 2 (F1 + F2), tissue plasminogen activator (t-PA), and plasminogen activator inhibitor type 1 (PAI-1). Tissue factor (TF) was not investigated in these studies. This figure was reported in Tholstrup (71) and was adapted with permission from *Lipids.*

Clinical trials reporting changes in plasma hemostatic (blood clotting) factors and markers of inflammation

Hemostatic variables affect either the formation of blood clots (coagulation) or the dissolution of blood clots (fibrinolysis). The key steps in these processes are outlined in Figure 4 [adapted from Tholstrup (1)]. Fibrin (the clot) is formed by a stepwise process in which prothrombin is first converted to thrombin. This reaction is stimulated by factor VII, which exists in 2 forms: factor VII coagulant activity (FVIIc) and activated factor VII (FVIIa). FVIIc is a measure of the amount of zymogen (inactive form of the protein). FVIIa is normally ∼1% of total factor VII (71) and stimulates conversion of prothrombin to thrombin. Prothrombin fragments 1 and 2 (F1 + F2) also are produced in this reaction. Thrombin promotes the conversion of fibrinogen to fibrin. Elevated plasma concentrations of fibrinogen, FVIIc, and FVIIa, and F1 + F2 have been associated with an increased risk of developing CHD because they increase the risk of clot formation [reviewed by Tholstrup (71)]. A recent meta-analysis (72) reports moderately strong associations between plasma fibrinogen concentrations and the risk of CHD, stroke, other vascular mortality, and nonvascular mortality in a wide range of circumstances.

Regarding the breakdown of blood clots, the primary initiator of fibrinolysis is tissue plasminogen activator (t-PA), which when bound to fibrin activates the conversion of plasminogen to plasin. Plasin, in turn, cleaves fibrin and breaks up the clot. Low concentrations of t-PA may increase the risk of subsequent CHD. However, the major regulator of fibrinolysis is plasminogen activator inhibitor type 1 (PAI-1), which blocks the conversion of t-PA to plasminogen. High PAI-1 concentrations have been associated with an increased CHD risk [reviewed by Tholstrup (71)].

Systemic inflammation is involved with a variety of neurologic and degenerative conditions and is considered a nonlipid risk factor for CHD, insulin resistance, diabetes, and heart failure. Low-grade systemic inflammation can be measured in blood with the inflammatory marker C-reactive protein (CRP). Other plasma markers of inflammation include the proinflammatory cytokine interleukin-6 (IL-6) and adhesion molecules (eg, selectins). Elevated plasma concentrations of markers of inflammation have been proposed to be strong predictors of CVD (73-76).

We found 10 studies in which changes in plasma hemostatic factors and markers of inflammation were measured after feeding diets high in STA for 14 to 40 d (52, 59, 63-65, 77-81). The

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**TABLE 4**

Effects of dietary stearic acid (STA) on hemostatic factors and markers of inflammation (change compared with control)

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>Period</th>
<th>STA</th>
<th>Control</th>
<th>ΔFibrinogen</th>
<th>ΔFVIIc</th>
<th>ΔCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladbjerg et al, 1995 (79)</td>
<td>15 men, normocholesterolemic</td>
<td>21</td>
<td>13.7</td>
<td>ML</td>
<td>10.5†2</td>
<td>14.7†2</td>
<td>7.1†</td>
</tr>
<tr>
<td>Baer et al, 2004 (77)</td>
<td>50 men, normocholesterolemic</td>
<td>35</td>
<td>10.9</td>
<td>OL</td>
<td>5.5†4</td>
<td>NR</td>
<td>160†</td>
</tr>
<tr>
<td>Mutanen and Aro, 1997 (78)</td>
<td>49 women and 31 men, normocholesterolemic</td>
<td>35</td>
<td>9.3</td>
<td>Dairy fat</td>
<td>4.3†4</td>
<td>NR</td>
<td>5.2†</td>
</tr>
<tr>
<td>Hunter et al, 2000 (59)</td>
<td>9 men, normocholesterolemic</td>
<td>14</td>
<td>13.0</td>
<td>OL</td>
<td>3.6†</td>
<td>5.1†</td>
<td>NR</td>
</tr>
<tr>
<td>Thijssen et al, 2005 (80)</td>
<td>27 women and 18 men, hypercholesterolemic</td>
<td>35</td>
<td>7.7</td>
<td>LA</td>
<td>0.0</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Louheranta et al, 1998 (65)</td>
<td>15 women, normocholesterolemic</td>
<td>28</td>
<td>6.8</td>
<td>OL</td>
<td>3.0†</td>
<td>1.2†</td>
<td>NR</td>
</tr>
<tr>
<td>Kelly et al, 2001 (63)</td>
<td>13 men, normocholesterolemic</td>
<td>28</td>
<td>6.6</td>
<td>PA</td>
<td>4.2†</td>
<td>7.6†</td>
<td>NR</td>
</tr>
</tbody>
</table>

† Changes in 2 hemostatic (blood clotting) factors and one plasma marker of inflammation (compared with control treatments) after subjects consumed high-STA diets for 14 to 35 d. The first 3 studies listed reported significant increases in fibrinogen concentrations. The last 4 studies found no significant increases in fibrinogen concentrations. Otherwise, the studies are listed in order of decreasing amounts of dietary STA. One study (Baer et al; 77) included 2 amounts of dietary STA: ΔFVIIc, change in factor VII coagulant activity; ΔCRP, change in C-reactive protein concentration; OL, oleic acid; LA, linoleic acid; PA, palmitic acid; ML, myristic and lauric acids; NR, not reported; †, increase compared with control; ††, decrease compared with control.

2,4 Significantly different from control treatment: ††P < 0.01, †††P < 0.05.
Thromboxane A2 tends to increase platelet aggregation, whereas PAI-1, and platelet aggregation. In these studies included fibrinogen, FVIIc, FVIIa, F1 + F2, t-PA, ranged from 4% to 14% of energy. Hemostatic factors measured in these studies used conventional-food diets with STA amounts that ranged from 4% to 14% of energy. Hunter et al (59, 63, 65, 80). In contrast, in 3 other studies, fibrinogen concentrations increased 4.0–10.5% after feeding a high-STA diet (77–79). Tholstrup, whose research group reported the 10.5% increase (79), suggested that this increase may be biologically insignificant, but recommended that this result be investigated further (71). Baer et al (77), on the other hand, speculated that the 5.5% increase in fibrinogen concentration they observed after their high-STA diet (10.9% of energy) might represent an increased CHD risk. However, after an intermediate-STA diet (6.9% of energy), which also provided TFA (4.2% of energy), they found no significant change in fibrinogen concentration. A high trans diet (8.3% of energy) had no significant effect on fibrinogen concentration compared with the oleic acid control diet.

FVIIc decreased nearly 15% in 1 study (79) and 7.6% in another study (63), but showed no change in 3 other studies (59, 65, 78) (Table 4). Hunter et al (59) found no changes in either FVIIa concentration or FVIIag concentrations after 2 wk of feeding a high-STA diet (13% of energy) compared with a high–oleic acid diet. On the other hand, Bladbjerg et al (79) reported an 11% decrease in FVIIag concentrations as well as a 10% decrease in F1 + F2 after 3 wk of feeding a diet with 13.7% of energy as STA compared with a diet high in myristic plus lauric acid (3.5% of energy as myristic acid and 10.7% of energy as lauric acid). In addition, 4 of the 7 studies listed in Table 4 reported measuring concentrations of t-PA and PAI-1 after feeding high-STA diets (9.3–14% of energy) for 14 to 35 d (52, 59, 78, 80). No significant changes were seen in these measures compared with the control treatments.

No significant changes in platelet aggregation (in response to agonist ADP) were reported in 2 studies that compared the effects of high-STA diets and control diets (59, 64). Blair et al (81) reported that consumption of a high-STA diet (7.3% of energy) for 4 wk did not affect in vivo thromboxane A2 or prostacyclin biosynthesis. Thromboxane A2 tends to increase platelet aggregation, whereas prostacyclin tends to reduce platelet aggregation.

The inflammatory marker CRP was measured in 2 studies after the consumption of high-STA diets (77, 79). Baer et al (77) found no significant change in CRP concentration after feeding STA at either 6.9% or 10.9% of energy compared with either an oleic acid control diet or a high-carbohydrate control diet for 5 wk. In contrast, a high–trans fat diet (8% of energy as TFAs) increased CRP concentrations 4.8-fold compared with the oleic acid control diet and 3.4-fold compared with the high-carbohydrate diet. Bladbjerg et al (79) also found no significant change in CRP after 3 wk of feeding a high-STA diet (14% of energy) compared with a diet high in myristic and lauric acids (3.5% and 10.7% of energy, respectively).

Baer et al (77) measured concentrations of 2 additional markers of inflammation, IL-6 and E-selectin, after feeding STA at either 6.9% or 10.9% of energy. IL-6 concentrations did not change significantly after the moderate-STA (6.9% of energy) diet compared with the oleic acid or high-carbohydrate diets. On the other hand, after the higher-STA (10.9% of energy) diet, IL-6 concentrations increased 55% compared with the oleic acid diet but did not change significantly compared with the high-carbohydrate diet. E-selectin concentrations increased significantly by 7.2% and 8.2% after the 6.9% and 10.9% of energy STA diets, respectively, compared with the oleic acid diet. E-selectin concentrations, however, did not change significantly compared with the high-carbohydrate diet. There is epidemiologic evidence suggesting that IL-6 and E-selectin are associated with an increased risk of coronary disease (75, 82–87); however, there are reports of no association (76, 88–90). On the other hand, there is evidence that the risk of type 2 diabetes is associated with elevated plasma concentrations of IL-6 (91–96) and of E-selectin (97–102).

In summary, it appears that diets with high amounts of STA (certainly up to 9% of energy and perhaps as high as 14% of energy) fed for up to 40 d may have little or no detrimental effects on thrombogenic risk. Effects of feeding high amounts of STA on fibrinogen were inconsistent, with no change reported in 4 studies and increases reported in 3 other studies. However, the increase in fibrinogen concentration was seen only after feeding STA at an amount of >9% of energy, which is well above the current 90th percentile of intake (3.5% of energy). Thus, moderate increases in intake of STA up to around the 90th percentile would not be expected to have adverse effects on the normal blood clotting process or on dissolution of blood clots. High amounts of STA (6.9–14% of energy) had no effect on the inflammatory marker CRP in the 2 studies in which it was measured. On the other hand, one study reported increases in E-selectin concentration after feeding STA at 6.9% or 10.9% of energy and an increase in IL-6 after feeding STA at 10.9% of energy. Additional research is needed to determine the effects of STA on IL-6 and E-selectin and on other inflammatory cytokines.

Postprandial effects of stearic acid on blood lipids and lipoproteins

It is important to evaluate the postprandial effects of dietary fatty acids on lipids and lipoproteins because an increased risk of atherosclerosis and CVD has been associated with an impaired clearance of triglyceride-rich chylomicron remnants (103). Underlying mechanisms that account for this include an increase in the formation of small, dense LDL particles and a concomitant decrease in HDL cholesterol [reviewed by Roche and Gibney (103)]. Moreover, as noted by O’Keefe and Bell (104), an increase in postprandial chylomicron remnants and free fatty acids increase oxidative stress and inflammation, as well as endothelial dysfunction (ie, vasoconstriction), and possibly potentiate adverse effects of postprandial hyperglycemia. Collectively, this sequelae of physiologic events contributes to an increase in CVD risk burden. Also, concomitant with these responses to postprandial hyperlipidemia (and hyperglycemia) are untoward effects in hemostatic factors that increase the risk of atherothrombosis (see next section). Thus, any dietary factor that affects the postprandial response has the potential to increase or decrease CVD risk.

Single meals high in STA have been used to assess postprandial effects of STA. Relevant studies are summarized below. In these studies the high amount of STA ranged from 13% to 26% of energy. In general, plasma triglyceride concentrations peaked between 2 and 4 h after single meals high a particular fatty acid,
irrespective of whether the fatty acid was saturated (STA, palmitic acid, or myristic acid) or unsaturated [oleic, linoleic, or a combination of linoleic and \(\alpha\)-linolenic acids (18:3)]

Sanders et al (105) reported that the increase in serum triglyceride concentration was lower after consumption of STA as a structured triglyceride [Salatrim (Cultor Food Science, Ardsley, NY); STA randomly distributed among positions of the triglyceride] compared with STA as cocoa butter (STA primarily in positions 1 and 3 of the triglyceride). This difference in triglyceride response may have been due to reduced digestibility and/or a higher amount of short-chain fatty acids in this structured triglyceride and also to the higher amount of STA in that meal (20.4% of energy compared with 14% of energy in the cocoa butter meal).

Hunter et al (106) found that a meal containing STA (13% of energy), in an amount similar to that used by Sanders et al (105; 14% of energy), also resulted in no significant differences in plasma postprandial triglyceride responses from meals high in STA, oleic acid, or linoleic acid. On the other hand, in studies with meals containing higher amounts of STA (19–26% of energy), plasma triglyceride responses to the high-STA meals were lower than those from meals containing high amounts of unsaturated fatty acids (oleic, linoleic, or a combination of linoleic and \(\alpha\)-linolenic acids) along with a low amount of STA (2–4% of energy) (107–110). Comparing effects of meals high in either STA or myristic acid, Tholstrup et al (111, 112), reported a tendency to lower chylomicron triglycerides 2 h after the STA meal, probably because of a lower and slower absorption. After 4 h, both STA and myristic acid appeared to be equally absorbed. Muesing et al (113) found that the plasma triglyceride increase after a meal containing corn oil (96%; 1.7% of energy as STA) was twice that after a meal containing beef tallow (48%; 18.5% of energy as STA).

In summary, studies involving single meals high in STA generally have shown reduced triglyceride concentrations compared with meals high in other long-chain saturated and unsaturated fatty acids. These reduced responses are consistent with reduced absorption rates and amounts of STA compared with those of most other dietary fatty acids. None of the studies we reviewed reported measurements of amounts or clearance rates of chylomicron remnants. Overall, high-STA diets did not demonstrate any unusual postprandial responses that might be associated with CVD risk.

Postprandial effects of stearic acid on hemostatic factors

Postprandial triglyceridermia is of clinical concern because it triggers a procoagulant state that involves disturbances in coagulation and fibrinolysis due to increased concentrations of FVIIa (procoagulant effect) and PAI-1 (antifibrinolytic effect) (reviewed by Duttaroy; 114). The magnitude of the hemostatic metabolic perturbations induced by postprandial increases in triglycerides and glucose are a function of the increase in plasma triglycerides and glucose and the extent to which these elevations are sustained. The adverse effects of postprandial triglycerideremia on hemostasis are further reason to evaluate the effects that individual fatty acids (and other dietary factors) have on this physiologic system that affects CVD risk.

Effects of single meals high in STA (13–26% of energy) on hemostatic factors are summarized below. Hemostatic factors considered included FVIIc, FVIIa, FIIlag, F1 + F2, t-PA, and PAI-1. None of these hemostatic factors responded to single meals high in STA in a manner suggestive of a potential risk of CVD.

Five studies (105, 106, 109, 110, 115) measured plasma FVIIc and FVIIa activities after feeding single meals high in STA or single meals high in one or more other fatty acids, including oleic, elaidic, linoleic, and palmitic acids and medium-chain triglycerides. FVIIc and FVIIa activities increased or were unchanged after all of the test meals, irrespective of the fatty acid enriched in the meal. In all cases, the increases in FVIIc or FVIIa after the high-STA meals were less than or equal to the increases seen after meals high in one of the other fatty acids. Two studies (105, 106) also measured FIIlag activity, and found no differences in this measure after meals high in either STA, oleic acid, or linoleic acid.

Considering other hemostatic factors, Sanders et al (105) found that t-PA activity increased and PAI-1 activity decreased after test meals high in either STA or oleic acid. In contrast, Hunter et al (106) reported no significant differences in t-PA activity, PAI-1 activity, or F1 + F2 concentrations after single meals moderately high in STA, oleic acid, or linoleic acid. A study by Tholstrup et al (112) found no evidence of an acute prothrombotic effect of meals high in either STA or myristic acid. Both fats reduced platelet aggregation (induced by either collagen or ADP) compared with fasting values, and the degree of platelet aggregation was not different between the STA and myristic acid fats. In summary, studies in which single meals provided up to 26% of energy from STA have shown no evidence of adverse effects on cardiovascular health based on the hemostatic risk factors evaluated.

PROJECTED INCREASED INTAKE OF STEARIC ACID BY THE US POPULATION

The current consumption of STA in the US diet is \(\approx 3.0\%\) of total energy (7). The lowest practical intake of TFAs in the US diet is \(\approx 1\%\) of energy, because this amount allows for the relatively small amounts of TFA contributed by meat and dairy products and also by deodorization of fats and oils (116). Considering that STA could be a useful substitute for TFA in many food applications, the question of how much STA would increase in the diet if it were a substitute for TFA has been addressed by 2 groups (8, 117).

One report (8) that estimated the increase in STA as a replacement for TFA was based on the assumption that STA is the sole fatty acid substitute for TFA. This is likely an overestimate because multiple substitutes for partially hydrogenated oils that contain TFA will be included according to availability, cost, taste, and functionality. Using NHANES 1999–2000 data, the average \(\text{trans}\) fat intake by males of all ages (consuming 2666 kcal/d) is 6.1 g/d, or 2.03% of total energy. Because \(\approx 50\%\) of this amount (ie, 1% of energy from TFA), could be substituted by STA (the remaining 1% being the nonsubstitutable amount from meat and dairy products), Kris-Etherton et al (8) concluded that a one-for-one substitution (on a % energy basis) with STA would increase total STA intake by 3 g/d to 3.7% of energy. This value is close to the current estimated 90th percentile of intake of STA, which is 3.5% of energy (9).

A recent study by DiRienzo et al (117) estimated the effect on fatty acid intake in the US if a high-STA, low–\(\alpha\)-linolenic acid
TABLE 5

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Period</th>
<th>TC/HDL-C Δ</th>
<th>LDL-C Δ</th>
<th>HDL-C Δ</th>
<th>TG Δ</th>
<th>Lp(a) Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zock and Katan, 1992 (46); 30 women and 26 men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mensink et al, 1992 (47)</td>
<td>normocholesterolemic (moderate STA/TFA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mensink et al, 1992 (47)</td>
<td>normocholesterolemic (high STA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mensink et al, 1992 (47)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:**

- **Δ** indicates the change from TFA to STA diet.
- **% of energy** indicates the percentage of energy contributed by the fatty acid.
- **NR** indicates not reported.

**Results:**

- The intake of palmitic acid remained unchanged. Use of HSLL as a substitute for partially hydrogenated soybean oils (HSLL) were substituted for partially hydrogenated soybean oils used in baked foods, shortenings, fried foods, and margarines (including spreads). Using NHANES data from 1999 to 2002, baseline and 90th percentile intakes of 5 fatty acids and total TFAs were determined after substituting HSLL for 100% of the partially hydrogenated soybean oil used in these 4 food categories. Use of HSLL was reported to increase STA intake from a baseline amount of 3.0% of energy [identical to the US average intake of 3.0% (7)] to 3.7–4.5% of energy at the mean and to 4.3–5.4% of energy at the 90th percentile, with a concomitant decrease in TFA intake from 2.5% to 0.9% of energy at the mean and from 3% to 0.9% of energy at the 90th percentile. The intake of palmitic acid remained unchanged. Thus, use of HSLL as a substitute for partially hydrogenated soybean oils was predicted to result in changes in fatty acid intake consistent with current dietary recommendations.

- We believe that a new 90th percentile of STA intake would not greatly exceed 5% of energy. This is because the primary use of a high-STA oil would likely be restricted to solid fat applications. In addition, many spread products and at least one household shortening currently are marketed in trans-free versions without the use of higher-STA oils. Assuming 100% market penetration of high-STA oils into applications that previously used partially hydrogenated oils, the 90th percentile of intake of STA (4.3–5.4% of energy) is still below the 9.3% of energy level that was associated with an increase in fibrinogen concentration in one study (78; Table 4). Higher amounts of dietary STA (10.9% and 13.7% of energy) also resulted in increased fibrinogen concentrations (77, 79). The use of STA in some of these formulations could benefit not only through fat reduction but also could reduce cholesterol-raising saturated fatty acids in these products.

- Although 9.3% of energy was the lowest amount of dietary STA at which an unfavorable effect was seen in a controlled trial, we cannot exclude the possibility that unfavorable effects could occur at lower amounts. A small effect that is not statistically significant in a clinical trial could well have relevant health effects at the population level.

- In summary, increased amounts of dietary STA, as the result of replacing TFAs, would not be expected to have unfavorable effects on cardiovascular health. This is because one-for-one replacement of TFAs by STA might increase the intake of STA to 3.7–4.5% of energy (8, 117). Although this range exceeds somewhat the current 90th percentile of intake of STA, 3.5% of energy (9), most studies that fed much higher amounts of STA, namely 7–14% of energy for up to 35 d (45, 49, 52, 55, 57–60, 62, 64, 77), did not find adverse effects on blood lipid or lipoprotein concentrations or on most hemostatic factors. An unfavorable effect on fibrinogen concentrations did not occur until the amount of dietary STA exceeded 9% of energy (78). Although the preponderance of evidence indicates that dietary STA has a neutral effect on plasma lipids, lipoproteins, and hemostatic factors, it may be helpful to undertake a longer-term feeding study at the newly established 90th percentile of intake to confirm expected effects on these measures.

**REPLACING DIETARY TRANS FATTY ACIDS WITH STEARIC ACID**

Four studies assessed the effect of substituting STA for TFA in the diet (46, 48, 50, 51). Key study design aspects and results are...
shown in Table 5. These studies involved between 30 and 80 subjects who consumed diets high in either STA or TFA for 21 to 35 d. The subjects then switched to the other diet (high in either STA or TFA, respectively) for an equivalent period of time.

Three studies (46, 48, 50) involved roughly a one-to-one substitution of STA for TFA on a percentage of energy basis (Table 5). This was determined by calculating the changes in TFA and STA amounts (ΔTFA and ΔSTA) between the corresponding diets. For example, ΔTFA = (amount of TFA in high-TFA diet) – (amount of TFA in high-STA diet). Similarly, ΔSTA = (amount of STA in high-STA diet) – (amount of STA in high-TFA diet). CRP, C-reactive protein; IL-6, interleukin-6; FVIIc, factor VII coagulant activity; t-PA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor type-1; †, increase compared with control; ‡, decrease compared with control; NR, not reported.

Effects of replacement of TFAs by STA on hemostatic factors (Table 6). These changes were assessed in 2 follow-up studies (Table 6; 77, 78). Baer et al (77) analyzed blood samples for hemostatic factors and markers of inflammation that were originally collected for the study by Judd et al (48). Baer et al (77) found that substituting 4% STA for a similar amount of TFAs resulted in no significant change in fibrinogen concentration, but there was a large (79%) decrease in CRP concentration. Substituting 8% STA for a similar amount of TFAs resulted in a significant 4% increase in fibrinogen concentration and no effect on CRP. These substitutions of STA for TFAs also resulted in no significant changes in IL-6 concentration, but a significant decrease in E-selectin concentration.

TABLE 6
Effects of substituting dietary stearic acid (STA) for trans fatty acids (TFAs) on hemostatic factors and markers of inflammation (change from TFA to STA diet)†

<table>
<thead>
<tr>
<th>Study</th>
<th>ΔTFA</th>
<th>ΔSTA</th>
<th>ΔFibrinogen</th>
<th>ΔCRP</th>
<th>ΔIL-6</th>
<th>ΔE-selectin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baer et al, 2004 (77)</td>
<td>4.1 ‡</td>
<td>4.1 †</td>
<td>0.4 (NS)</td>
<td>79 ‡</td>
<td>4.3 (NS)</td>
<td>6.3 (NS)</td>
</tr>
<tr>
<td>(same study population and period</td>
<td>8.0  ‡</td>
<td>8.1 †</td>
<td>4.4 ‡</td>
<td>46 ‡</td>
<td>4.3 (NS)</td>
<td>5.4 (NS)</td>
</tr>
<tr>
<td>as Judd et al, 2002; 48</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mutanen and Aro, 1997 (78)</td>
<td>8.3 ‡</td>
<td>6.7 †</td>
<td>0.3 (NS)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>(same study population and period</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>as Aro et al, 1997; 50</td>
<td></td>
<td></td>
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</tbody>
</table>

† Changes (Δ) in dietary TFA and STA were calculated from reported amounts of TFA and STA in the corresponding diets. For example, ΔTFA = (amount of TFA in high-TFA diet) – (amount of TFA in high-STA diet). Similarly, ΔSTA = (amount of STA in high-STA diet) – (amount of STA in high-TFA diet). CRP, C-reactive protein; IL-6, interleukin-6; FVIIc, factor VII coagulant activity; t-PA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor type-1; †, increase compared with control; ‡, decrease compared with control; NR, not reported.

TABLE 7
Effects of dietary stearic acid (STA) on plasma glucose and insulin concentrations (change compared with control)†

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>Period</th>
<th>Amount of STA</th>
<th>Control fat</th>
<th>ΔGlucose</th>
<th>ΔInsulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sundram et al, 2007 (51)</td>
<td>30 men and women, normocholesterolemic</td>
<td>28</td>
<td>12.5</td>
<td>Palm olein</td>
<td>18.7 †</td>
<td>21.6 †</td>
</tr>
<tr>
<td>Berry et al, 2007 (66)</td>
<td>16 men, normocholesterolemic</td>
<td>21</td>
<td>7.2 (randomized shea butter)</td>
<td>High oleic sunflower oil</td>
<td>2.1 †</td>
<td>5.2 †</td>
</tr>
<tr>
<td>Louheranta et al, 1998 (65)</td>
<td>15 women, normocholesterolemic</td>
<td>28</td>
<td>6.8</td>
<td>High oleic acid</td>
<td>0.0</td>
<td>4.2 †</td>
</tr>
<tr>
<td>Finley et al, 1994 (118)</td>
<td>19 men and 17 women, normocholesterolemic</td>
<td>7</td>
<td>12.3 or 12.8 (Salatrim; Nabisco Foods Group, East Hanover, NJ)</td>
<td>Hydrogenated coconut oil</td>
<td>1.6 †</td>
<td>NR</td>
</tr>
</tbody>
</table>

† Changes (Δ) in plasma glucose and insulin concentrations in healthy human subjects after the consumption of diets high in STA (7–13% of energy) for ≤28 d. †, increase compared with control; ‡, decrease compared with control; NR, not reported.

‡ Significantly different from control treatment, P < 0.001.
The study by Sundram et al (51) and 3 other studies (65, 66, 118) investigated possible changes in plasma glucose and insulin concentrations after feeding a high-STA diet (7–13% of energy) for 7 to 28 d. Relevant details are outlined in Table 7. The preponderance of evidence (65, 66, 118) reported no significant changes in either plasma glucose or insulin concentrations after feeding diets with up to 13% of energy as STA for 7 to 28 d. Baer et al (77) informed us that, in his study (77), fasting plasma glucose and insulin concentrations were not significantly different after feeding high-STA diets (10.9% or 6.9% of energy) compared with saturated or unsaturated control diets (DJ Baer, unpublished observations, 2009).

In contrast, Sundram et al (51) found that feeding a diet that provided 12.5% of energy from STA for 28 d resulted in a 19% increase in plasma glucose concentration and a 22% decrease in plasma insulin concentration compared with a palm olein diet. The increased plasma glucose and decreased insulin concentration after Sundram et al’s high-STA diet (51) might be explained by insulin resistance in the study subjects. However, Sundram et al (51) did not report testing their subjects for insulin resistance or glucose tolerance. Three other studies (65, 66, 118) and one personal communication involving similarly high-STA diets did not report decreases in plasma glucose concentrations. Further research is needed to clarify whether high dietary amounts of STA may have unfavorable effects on plasma glucose and insulin.

In summary, these studies support the safety of a one-to-one substitution of STA for TFAs at reasonable amounts of intake with little or no adverse effects to be expected on plasma lipid or lipoprotein concentrations or on concentrations of most hemicratic factors. Because there is some evidence of adverse effects, especially at high intakes, further research is warranted evaluating the safety of STA in all population groups in the United States. Unsaturated fatty acids can replace TFAs in some applications (eg, frying fats); however, the sole use of unsaturated fats is unsuitable in food applications requiring food structure provided by solid fats (eg, spreads, margarines, and shortenings).

LIMITATIONS OF OUR REVIEW

Our review evaluated the current literature on STA and CVD risk factors. As is apparent, there is a substantive evidence base that focuses mainly on endpoints related to CVD risk. Inherent to a comprehensive literature review such as ours is the reality that there are many different considerations: the study designs used, fats tested high in a specific fatty acid (ie, STA), population groups assessed, and endpoints evaluated. Moreover, other possible endpoints could be important in determining the role of STA in CVD risk that need to be considered as the science evolves. An example of this is new research that suggests possible adverse effects of high intakes of STA and palmitic acid on stearoyl-CoA desaturase activity, the enzyme that catalyzes the conversion of STA to oleic acid. Stearoyl-CoA desaturase has been implicated in the promotion of lipogenesis and the development of obesity and disorders of lipid metabolism (119). Instances such as this underscore the importance of comprehensively evaluating the safety of any new fat or foods introduced into the food system.

One limitation of the literature is that most of the subjects were of European descent and were mainly young and healthy. This is important because other populations may differ with respect to insulin resistance and insulin-secreting capacity and thus respond differently to macronutrient intake.

SUGGESTIONS FOR FURTHER RESEARCH

The safety and nutritional evaluation of any new oil should take into account not only the STA amount but also the overall fatty acid profile, intended use, and potential nutritional effect on the population’s diet to ensure that intakes are within the range that previous research has shown to be safe. Such evaluations should routinely be part of the assessment of any new or modified food product and should not be unique to a high-STA oil.

Possible adverse metabolic effects of STA on variables such as Lp(a), fibrinogen, IL-6, E-selectin, glucose, and insulin should be studied further. Long-term feeding studies will clarify the effects of STA on these and other metabolic factors. In addition, we recommend consideration of other possible markers to assess the potential risk of increased STA intake. One such marker could be the enzyme stearoyl-CoA desaturase, which may play a role in the development of obesity and disorders of lipid metabolism.

CONCLUSIONS

We conclude that STA is a reasonable substitute for TFAs and cholesterol-raising saturated fatty acids for solid fat applications, eg, baked goods, shortenings, spreads, and margarines. On the basis of available evidence, we believe that such a substitution is not likely to adversely affect CVD risk. Diets high in STA (eg, up to 11% of energy fed for up to 40 d) appear to have favorable effects on plasma LDL-cholesterol concentrations and directionally favorable effects on the TC/HDL-cholesterol ratio compared with cholesterol-raising saturated fatty acids (eg, palmitic acid) and with TFA. LDL cholesterol decreased as dietary STA increased in a statistically significant dose-response relation. Compared with unsaturated fatty acids (oleic and linoleic acids), high-STA diets tend to increase both LDL cholesterol and the TC/HDL-cholesterol ratio because of the independent LDL-cholesterol and the TC/HDL-cholesterol ratio–lowering effects of MUFAs and PUFAs. Dietary STA had neutral or lowering effects on HDL cholesterol compared with either saturated or unsaturated fatty acids. Small increases in Lp(a) concentrations after high-STA diets have been reported in 2 studies, whereas no effect on Lp(a) was observed in 2 other studies. Most hemostatic factors (eg, FVIIc, FVIIa, FVIIag, t-PA, PAI-1, and platelet aggregation) appear not to be affected by high-STA diets. Increases in fibrinogen concentrations were reported in 3 studies after feeding diets in which STA exceeded 9% of energy, which is well above the 90th percentile of intake (currently at ≈3.5% of energy). Substitution of TFAs by STA would likely not increase intakes of STA above 4–5% of energy. CRP did not change in 2 studies in which it was evaluated. Ten studies involving single meals high in STA (up to 26% of energy) did not report responses associated with increased CVD risk. Three of 4 studies reported no effect of high-STA diets on plasma glucose and insulin concentrations. One-to-one replacement of dietary TFAs by STA in 3 studies consistently decreased or did not change LDL-cholesterol concentrations and either increased or did not change HDL-cholesterol concentrations.

For solid fat applications, STA would be an excellent substitute for TFAs and cholesterol-raising saturated fatty acids.
CARDIOVASCULAR SAFETY OF DIETARY STEARIC ACID 61

Unsaturated fats are unsuitable for solid fat applications for functionality reasons but are suitable for liquid fat applications, such as frying.

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