

REVIEW ARTICLE

MEDICAL PROGRESS

Trans Fatty Acids and Cardiovascular Disease

Dariusz Mozaffarian, M.D., M.P.H., Martijn B. Katan, Ph.D.,
Alberto Ascherio, M.D., Dr.P.H., Meir J. Stampfer, M.D., Dr.P.H.,
and Walter C. Willett, M.D., Dr.P.H.

TRANS FATS, UNSATURATED FATTY ACIDS WITH AT LEAST ONE DOUBLE bond in the trans configuration (Fig. 1), are formed during the partial hydrogenation of vegetable oils, a process that converts vegetable oils into semi-solid fats for use in margarines, commercial cooking, and manufacturing processes. From the perspective of the food industry, partially hydrogenated vegetable oils are attractive because of their long shelf life, their stability during deep-frying, and their semisolidity, which can be customized to enhance the palatability of baked goods and sweets. The average consumption of industrially produced trans fatty acids in the United States is 2 to 3 percent of total calories consumed.¹ Major sources of trans fats are deep-fried fast foods, bakery products, packaged snack foods, margarines, and crackers (Table 1). Naturally occurring trans fats are consumed in smaller amounts (about 0.5 percent of total energy intake) in meats and dairy products from cows, sheep, and other ruminants; these trans fats are produced by the action of bacteria in the ruminant stomach.

The Food and Drug Administration (FDA) ruled that, effective January 1, 2006, the nutrition labels for all conventional foods and supplements must indicate the content of trans fatty acids.² This ruling represents the first substantive change to food labeling since the requirement for the listing of basic per-serving nutritional information was added in 1990. The Department of Agriculture made a limited intake of trans fatty acids a key recommendation of the new food-pyramid guidelines,³ subsequent to the recommendations of the Dietary Guidelines Advisory Committee that the consumption of trans fatty acids be kept below 1 percent of total energy intake.⁴ The New York City Department of Health and Mental Hygiene has asked 20,000 restaurants and 14,000 food suppliers to eliminate partially hydrogenated oils from kitchens and to provide foods and food products that are free of industrially produced trans fatty acids.⁵ Denmark has enacted, and Canada is considering, legislation to eliminate industrially produced trans fats from food supplies.^{6,7}

Each of these actions was prompted by evidence that consumption of trans fatty acids increases the risk of coronary heart disease (CHD). This article reviews the evidence of physiological and cellular effects of trans fatty acids, the relations between the intake of trans fat and CHD, sudden death from cardiac causes, and diabetes; and the feasibility and potential implications of reducing or eliminating the consumption of trans fatty acids from partially hydrogenated vegetable oils in the United States.

From the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, and the Departments of Nutrition and Epidemiology, Harvard School of Public Health — all in Boston (D.M., A.A., M.J.S., W.C.W.); and the Division of Human Nutrition, Wageningen University, and Wageningen Center for Food Sciences — both in Wageningen, the Netherlands (M.B.K.). Address reprint requests to Dr. Mozaffarian at the Harvard School of Public Health, 665 Huntington Ave., Bldg. 2, Rm. 315, Boston, MA 02115, or at dmozaffa@hsph.harvard.edu.

N Engl J Med 2006;354:1601-13.

Copyright © 2006 Massachusetts Medical Society.

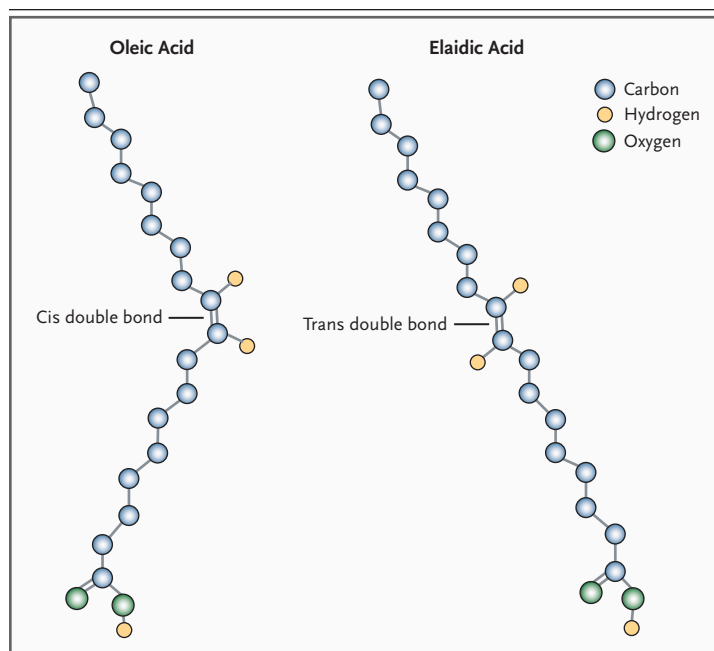


Figure 1. Structure of Cis and Trans Fatty Acids.

Both oleic acid and elaidic acid are 18-carbon fatty acids with a single double bond. However, oleic acid has a cis double bond (hydrogen atoms are on the same side of the bond), which causes a bend or kink in the fatty acid chain, whereas elaidic acid has a trans double bond (hydrogen atoms are on opposite sides of the bond), which straightens the fatty acid chain. The trans bond imparts a structure more similar to that of saturated fats, altering the physiological properties and effects of the fatty acid. In elaidic acid, the double bond occurs at the ninth carbon atom (*trans*-18:1n-9). Partially hydrogenated oils contain mixtures of isomers in which the trans bond may occur anywhere between the 4th and the 10th carbon; smaller amounts of isomers with a second trans double bond (*trans, trans*-18:2) are also present.

PHYSIOLOGICAL EFFECTS OF TRANS FATTY ACIDS

SERUM LIPIDS

The main effects of trans fatty acids on serum lipid levels have been evaluated in controlled dietary trials. The effect on serum lipid levels of isocaloric replacement of saturated fat or cis unsaturated fats with trans fat was calculated from a meta-analysis of 12 randomized, controlled trials of trans fatty acid consumption published through November 2005 (Fig. 2). These data were derived from 524 subjects in 39 separate study groups or study periods⁸⁻¹⁹ with the use of previously described methods²⁰ (Mensink R, Maastricht University: personal communication) and established effects of saturated and cis unsaturated fats on serum lipid levels.²⁰ As compared with the consumption of an equal number of

calories from saturated or cis unsaturated fats, the consumption of trans fatty acids raises levels of low-density lipoprotein (LDL) cholesterol, reduces levels of high-density lipoprotein (HDL) cholesterol, and increases the ratio of total cholesterol to HDL cholesterol, a powerful predictor of the risk of CHD.²¹ Trans fats also increase the blood levels of triglycerides as compared with the intake of other fats,²⁰ increase levels of Lp(a) lipoprotein,²² and reduce the particle size of LDL cholesterol,²³ each of which may further raise the risk of CHD. Thus, trans fatty acids have markedly adverse effects on serum lipids. Although these effects would be expected to increase the risk of CHD, the relation between the intake of trans fats and the incidence of CHD reported in prospective studies has been greater than that predicted by changes in serum lipid levels alone,^{20,22} suggesting that trans fatty acids may also influence other risk factors for CHD.

SYSTEMIC INFLAMMATION

Recent evidence indicates that trans fats promote inflammation. In women, greater intake of trans fatty acids was associated with increased activity of the tumor necrosis factor (TNF) system; among those with a higher body-mass index, greater intake of trans fatty acids was also associated with increased levels of interleukin-6 and C-reactive protein.²⁴ In a study of overweight women, greater intake of trans fat was again associated with increased activity of the TNF system and increased levels of interleukin-6 and C-reactive protein.²⁵ In patients with established heart disease, membrane levels of trans fatty acids (a biomarker of the dietary intake of trans fats) were independently associated with activation of systemic inflammatory responses, including substantially increased levels of interleukin-6, TNF- α , TNF receptors, and monocyte chemoattractant protein 1.²⁶

Inflammatory effects have also been reported in randomized, controlled trials. In patients with hypercholesterolemia, the production of interleukin-6 and TNF- α by cultured mononuclear cells was greater after one month of a soybean-margarine diet (6.7 percent of energy from trans fatty acids) than after one month of a soybean-oil diet (0.6 percent of energy from trans fatty acids); the production of interleukin-1 β was not significantly affected.²⁷ In another trial, five weeks of a diet in which 8 percent of energy intake was from trans fatty acids, as compared with oleic acid, increased

plasma levels of interleukin-6 and C-reactive protein.²⁸ In these trials, the inflammatory effects of trans fatty acids did not differ significantly from those of saturated fat.^{27,28}

Because the presence of inflammation is an independent risk factor for atherosclerosis, sudden death from cardiac causes, diabetes, and heart failure,²⁹⁻³² the inflammatory effects of trans fats may account in part for their effects on cardiovascular health. For example, on the basis of the positive association between C-reactive protein levels and the risk of cardiovascular disease,³³ the difference in C-reactive protein levels seen with a median intake of trans fat of 2.1 percent, as compared with 0.9 percent, of the total energy intake²⁵ would correspond to an increase in risk of approximately 30 percent.

ENDOTHELIAL-CELL FUNCTION

Several studies suggest that trans fats cause endothelial dysfunction. After adjustment for other risk factors, greater intake of trans fatty acids was associated with increased levels of several markers of endothelial dysfunction, including soluble intercellular adhesion molecule 1, soluble vascular-cell adhesion molecule 1, and E-selectin.²⁵ This observed increase in E-selectin levels was similar to findings in a randomized trial when oleic acid or carbohydrate was replaced isocalorically with trans fat.²⁸ In another trial, consumption of trans fatty acids impaired endothelial function, as reflected by a reduction in brachial artery flow-mediated vasodilatation by 29 percent, as compared with intake of saturated fat.³⁴

OTHER EFFECTS

Trans fatty acids may influence other risk factors for cardiovascular disease. In controlled trials, consumption of trans fat reduced the activity of serum paraoxonase,³⁵ an enzyme that is closely associated with HDL cholesterol, and impaired the postprandial activity of tissue plasminogen activator.³⁶ Trials evaluating the effects of the consumption of trans fatty acids on insulin sensitivity have shown variable results.^{18,37-41} Such variability may be due to differences in the population or the measure of insulin resistance examined and may depend on the duration of intake (short-term trials may not detect an effect). Further investigation is needed to elucidate the possible effects of trans fatty acids on these and other physiological pathways.

POTENTIAL MOLECULAR MECHANISMS

Far from being inert carriers of calories, fatty acids are powerful modulators of cell function, altering membrane fluidity and responses of membrane receptors by means of their incorporation into the phospholipids in cellular membranes.⁴²⁻⁴⁴ Fatty acids also bind to and modulate nuclear receptors that regulate gene transcription, such as peroxisome-proliferator-activated receptors, liver X receptor, and sterol regulatory element-binding protein-1.⁴⁵ Fatty acids may also directly or indirectly modulate metabolic and inflammatory responses of the endoplasmic reticulum.⁴⁶ By means of such effects, trans fatty acids may thereby affect the function and responses of many types of cells (Fig. 3).

Trans fats appear to affect lipid metabolism through several pathways. *In vitro*, trans fatty acids alter the secretion, lipid composition, and size of apolipoprotein B-100 (apoB-100) particles produced by hepatic cells.^{47,48} Such alteration is paralleled in studies in humans by decreased rates of LDL apoB-100 catabolism,⁴⁹ reductions in the size of LDL cholesterol particles,²³ increased rates of apoA-I catabolism,⁴⁹ and changes in serum lipid levels.^{20,22} Trans fatty acids also increase the cellular accumulation and the secretion of free cholesterol and cholesterol esters by hepocytes *in vitro*.⁴⁷ In humans, the consumption of trans fat increases plasma activity of cholesteryl ester transfer protein,⁵⁰ the main enzyme for the transfer of cholesterol esters from HDL to LDL and very-low-density lipoprotein (VLDL) cholesterol. This increased activity may explain decreases in the levels of HDL and increases in the levels of LDL and VLDL cholesterol seen with intake of trans fatty acids.^{20,22}

The cellular mechanisms relating trans fats to inflammatory pathways and other, nonlipid pathways are not well established. Monocytes and macrophages, endothelial cells, and adipocytes may each play a role. Trans fatty acids modulate monocyte and macrophage responses in humans, increasing the production by monocytes of TNF- α and interleukin-6²⁷ and possibly also levels of monocyte chemoattractant protein 1.²⁶ Trans fats also affect vascular function. Trans fats have been shown to increase circulating biomarkers of endothelial dysfunction^{25,28} and to impair nitric oxide-dependent arterial dilatation.³⁴ Trans fatty

Table 1. Typical Trans Fatty Acid Content of Foods Produced or Prepared with Partially Hydrogenated Vegetable Oils in the United States.

Type of Food	Trans Fatty Acid Content*			
	g/Typical Serving	g/100 g	% of Total Fatty Acids	% of Daily Energy Intake for 2000-kcal Diet
Fast or frozen foods				
French fries†	4.7–6.1	4.2–5.8	28–36	2.1–2.7
Breaded fish burger‡	5.6	3.4	28	2.5
Breaded chicken nuggets‡	5.0	4.9	25	2.3
French fries, frozen†	2.8	2.5	30	1.3
Enchilada‡	2.1	1.1	12	0.9
Burrito‡	1.1	0.9	12	0.5
Pizza†	1.1	0.5	9	0.5
Packaged snacks				
Tortilla (corn) chips†	1.6	5.8	22	0.7
Popcorn, microwave†	1.2	3.0	11	0.5
Granola bar‡	1.0	3.7	18	0.5
Breakfast bar‡	0.6	1.3	15	0.3
Bakery products				
Pie†	3.9	3.1	28	1.8
Danish or sweet roll†	3.3	4.7	25	1.5
Doughnuts†	2.7	5.7	25	1.2
Cookies†	1.8	5.9	26	0.8
Cake†	1.7	2.7	16	0.8
Brownie†	1.0	3.4	21	0.5
Muffin†	0.7	1.3	14	0.3

acids also influence fatty acid metabolism of adipocytes, resulting in reduced triglyceride uptake, reduced esterification of newly synthesized cholesterol, and increased production of free fatty acids.⁵¹ The effects of adiposity on the relations between intake of trans fat and circulating interleukin-6 and C-reactive protein levels suggest that the inflammatory effects of trans fats may be partially mediated by adipose tissue.²⁴ In studies of animals, the consumption of trans fat alters the expression in adipocytes of genes for peroxisome-proliferator-activated receptor- γ , resistin, and lipoprotein lipase,⁵² compounds with central roles in the metabolism of fatty acids and glucose.⁴⁵ Thus, there are several possible mechanisms whereby trans fats may affect both lipid and nonlipid risk factors for cardiovascular disease. Each of these pathways warrants additional investigation, particularly the potential influence of trans fatty acids on nuclear receptors, membrane receptors, and membrane fluidity.

INTAKE OF TRANS FAT AND CARDIOVASCULAR DISEASE

In our opinion, conducting randomized long-term trials to test the effects of trans fat intake on the incidence of cardiovascular events would be unethical, given the adverse effects of trans fats on serum lipid levels and inflammation. Therefore, in addition to short-term randomized trials of intermediate end points, carefully performed observational studies provide a reasonable approach for evaluating the effects of trans fat on cardiovascular health.

CHD

On a per-calorie basis, trans fats appear to increase the risk of CHD more than any other macronutrient, conferring a substantially increased risk at low levels of consumption (1 to 3 percent of total energy intake).^{22,53-55} In a meta-analysis of four prospective cohort studies involving nearly 140,000

Table 1. (Continued.)

Type of Food	Trans Fatty Acid Content*			
	g/Typical Serving	g/100 g	% of Total Fatty Acids	% of Daily Energy Intake for 2000-kcal Diet
Margarines				
Vegetable shortening†	2.7§	19.2	19	1.2§
Hard (stick)†	0.9–2.5	6.2–16.8	15–23	0.4–1.1
Soft (tub)†	0.3–1.4	1.9–10.2	5–14	0.1–0.6
Other				
Pancakes†	3.1	2.0	21	1.4
Crackers†	2.1	7.1	34	0.9
Tortillas†	0.5	1.8	25	0.2
Chocolate bar†	0.2	0.6	2	0.1
Peanut butter†	0.1	0.4	1	0.05

* Values are based on national brands that contain partially hydrogenated vegetable oils and that were sold in the United States in 2002. These same foods will contain little or no trans fatty acids if produced or prepared with other fats or oils, such as unhydrogenated vegetable oils or fully (not partially) hydrogenated vegetable oils. Very small amounts of trans fatty acids (less than 2 percent) may be formed during deodorization of vegetable oil, a process unrelated to partial hydrogenation. Dairy and meat products from cows, sheep, and other ruminants contain small amounts (1 to 8 percent of total fatty acids) of naturally occurring trans fatty acids produced by the action of bacteria in the ruminant stomach. Data are from the Harvard Food Composition Database.

† For french fries and margarines, the top national brands were analyzed individually for fatty acid composition with the use of gas chromatography (Harvard Biomarker Laboratory, Dr. Hannia Campos); the ranges are shown. For the other foods, the top national brands were combined into one sample for analysis. The proportion of the total sample that each brand constituted was determined by the brand's percent market share in the national marketplace, as determined from market-share and consumption statistics (TableBase, Responsive Database Services) and from Harvard cohort pilot consumption data representing a national sample.

‡ The contents and types of partially hydrogenated oils were determined from recipe information (Harvard Food Composition Database, based on packaging and USDA sources), and the trans fatty acid content of these oils was calculated on the basis of gas-chromatography analysis of similar foods. For the fast or frozen foods, the trans fat content of the oils was calculated from the fatty acid composition of the oils in french fries; for granola bars, from a mix of partially hydrogenated soybean oil and household vegetable shortening; and for breakfast bars, from household vegetable shortening.

§ Values are per tablespoon (given that there is no typical serving size).

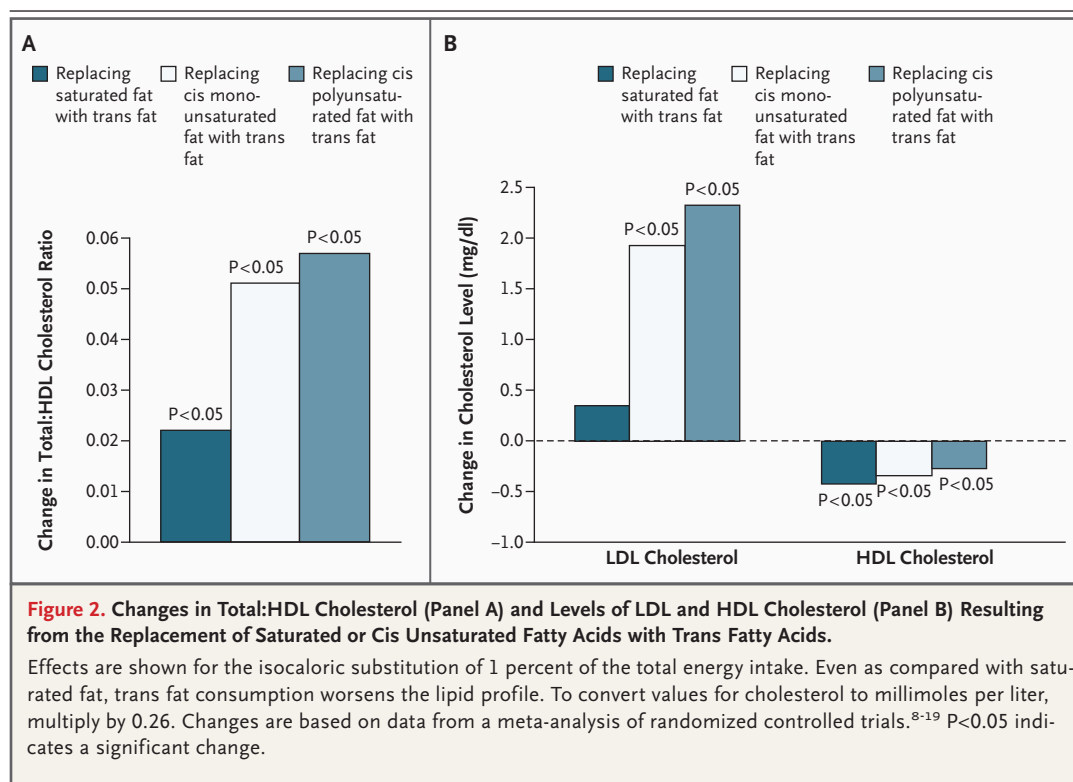
subjects,⁵³⁻⁵⁶ including updated analyses from the two largest studies, a 2 percent increase in energy intake from trans fatty acids was associated with a 23 percent increase in the incidence of CHD (pooled relative risk, 1.23; 95 percent confidence interval, 1.11 to 1.37; $P < 0.001$) (Fig. 4).

The relation between trans fatty acid levels in adipose tissue, a biomarker of the dietary intake of trans fats, and the risk of nonfatal myocardial infarction has also been evaluated in three retrospective case-control studies⁵⁸⁻⁶⁰ (Fig. 4). The addition of these studies to the meta-analysis increased the magnitude of the association between trans fatty acids and the risk of CHD (pooled relative risk in prospective and retrospective studies, 1.29; 95 percent confidence interval, 1.11 to 1.49; $P < 0.001$). Clifton et al. showed that the positive association between levels of trans fat in adipose tissue and the risk of nonfatal myocardial infar-

tion was mitigated after 1996, when trans fats were eliminated from margarines sold in Australia and trans fat levels decreased in both case patients and controls.⁶⁰

SUDDEN DEATH FROM CARDIAC CAUSES

Some data suggest that trans fatty acids may increase the risk of sudden death from cardiac causes. In a study that compared adipose tissue obtained at autopsy from 66 patients with sudden death from cardiac causes with that obtained from 286 healthy age- and sex-matched controls, levels of trans fat were not found to be associated with sudden death from cardiac causes.⁶¹ In contrast, in a larger, community-based case-control study (179 cases), levels of trans fatty acids in erythrocyte membranes were associated with an increase in the risk of sudden cardiac death (odds ratio for interquintile range, 1.47; 95 percent confidence



interval, 1.01 to 2.13), after adjustment for other risk factors.⁶² When different trans-isomers were evaluated separately, the increased risk appeared to be related to the 18-carbon isomers (*trans*-18:1 and especially *trans*-18:2); similar isomer-specific relations were seen in studies evaluating systemic inflammation.²⁴⁻²⁶ After adjustment for the levels of other membrane fatty acids, higher *trans*-18:2 levels were associated with a tripling of the risk of sudden death from cardiac causes (odds ratio for interquintile range, 3.05; 95 percent confidence interval, 1.71 to 5.44).⁶²

DIABETES

Three prospective studies have investigated the relation between the intake of trans fatty acids and the incidence of diabetes. Consumption of trans fat was not significantly associated with the risk of diabetes in two of these studies — among male health professionals⁶³ and among women in Iowa.⁶⁴ However, the intake of trans fatty acids was significantly related to the risk of diabetes among 84,941 female nurses who were followed for 16 years and in whom self-reported diabetes was validated and information on dietary intake

was periodically updated.⁶⁵ After adjustment for other risk factors, trans fat intake was positively associated with the incidence of diabetes (P<0.001 for trend), with a risk 39 percentage points greater in the highest quintile (relative risk, 1.39; 95 percent confidence interval, 1.23 to 1.56) than in the lowest quintile.

What might account for the different results of these studies? The intake of trans fat was relatively low among the male health professionals (overall median intake was 1.3 percent of energy, equal to the median intake in the lowest quintile among the nurses)⁵⁵; the smaller range of intake may have limited the ability to detect a difference in the risk of diabetes. In the Iowa cohort, a validation study suggested that the self-reported diagnosis of diabetes was incorrect in 36 percent of subjects, and diet was assessed only at baseline and may have changed over time.⁶⁴ Misclassification of both the exposure and outcome variables would bias the results toward a null association. Alternatively, the intake of trans fat may not be an important risk factor for new-onset diabetes; additional studies are needed. Molecular mechanisms that might account for an effect of trans fatty acids on the

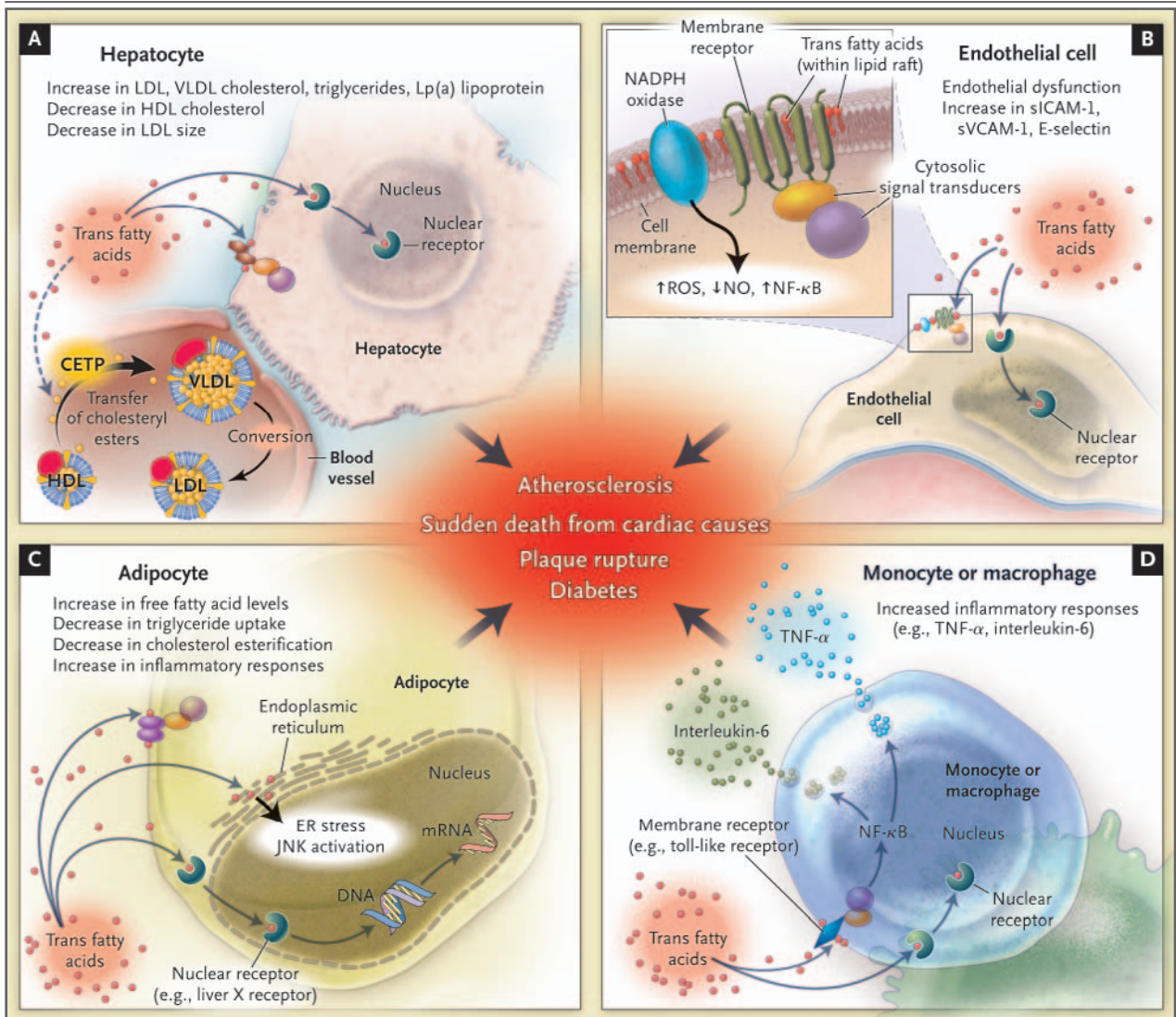


Figure 3. Potential Physiological Effects of Trans Fatty Acids.

Changes in hepatocyte production, secretion, and catabolism of lipoproteins, together with effects on plasma cholesteryl ester transfer protein (CETP), probably account for adverse effects of trans fatty acids on serum lipid levels (Panel A). The effect on CETP is probably not direct but mediated through effects on membrane or nuclear receptors (dashed line). Trans fatty acids also alter fatty acid metabolism and, possibly, inflammatory responses of adipocytes. In addition, nitric oxide-dependent endothelial dysfunction and increased levels of circulating adhesion molecules (soluble intercellular adhesion molecule 1 [sICAM-1] and soluble vascular-cell adhesion molecule 1 [sVCAM-1]) are seen with trans fat intake. Trans fatty acids also modulate monocyte and macrophage activity (Panel D), as manifested by increased production of inflammatory mediators. Each of these effects has been seen in controlled studies in humans and may, individually or in concert, increase the risk of atherosclerosis, plaque rupture, sudden death from cardiac causes, and diabetes. The subcellular mechanisms for these effects are not well established, but they may be mediated by effects on membrane receptors that localize with and are influenced by specific membrane phospholipids (Panel B), such as endothelial nitric oxide (NO) synthase or toll-like receptors; by direct binding of trans fatty acids to nuclear receptors regulating gene transcription, such as liver X receptor (Panel C); and by direct or indirect effects on endoplasmic reticulum (ER) responses, such as activation of Jun N-terminal kinase (JNK). Such hypothesized subcellular pathways — which have been shown to exist for other fatty acids — require further investigation. TNF-α denotes tumor necrosis factor α, ROS reactive oxygen species, NF-κB nuclear factor κB, and mRNA messenger RNA.

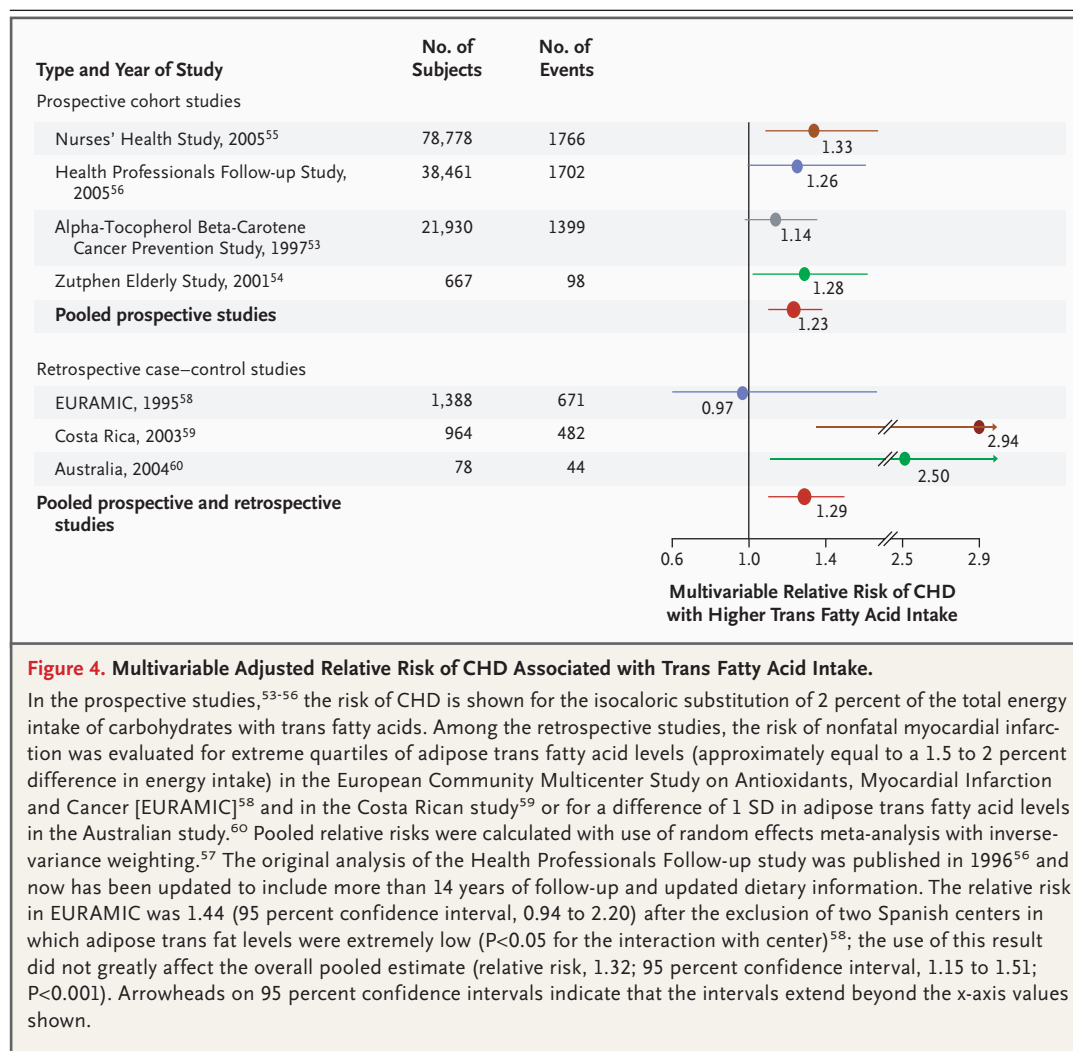


Figure 4. Multivariable Adjusted Relative Risk of CHD Associated with Trans Fatty Acid Intake.

In the prospective studies,⁵³⁻⁵⁶ the risk of CHD is shown for the isocaloric substitution of 2 percent of the total energy intake of carbohydrates with trans fatty acids. Among the retrospective studies, the risk of nonfatal myocardial infarction was evaluated for extreme quartiles of adipose trans fatty acid levels (approximately equal to a 1.5 to 2 percent difference in energy intake) in the European Community Multicenter Study on Antioxidants, Myocardial Infarction and Cancer [EURAMIC]⁵⁸ and in the Costa Rican study⁵⁹ or for a difference of 1 SD in adipose trans fatty acid levels in the Australian study.⁶⁰ Pooled relative risks were calculated with use of random effects meta-analysis with inverse-variance weighting.⁵⁷ The original analysis of the Health Professionals Follow-up study was published in 1996⁵⁶ and now has been updated to include more than 14 years of follow-up and updated dietary information. The relative risk in EURAMIC was 1.44 (95 percent confidence interval, 0.94 to 2.20) after the exclusion of two Spanish centers in which adipose trans fat levels were extremely low ($P < 0.05$ for the interaction with center)⁵⁸; the use of this result did not greatly affect the overall pooled estimate (relative risk, 1.32; 95 percent confidence interval, 1.15 to 1.51; $P < 0.001$). Arrowheads on 95 percent confidence intervals indicate that the intervals extend beyond the x-axis values shown.

incidence of diabetes are not well established, but evidence of effects of trans fatty acids on metabolism in adipocytes⁵² and on systemic inflammation²⁴⁻²⁸ suggests plausible pathways.

TRANS FATTY ACIDS FROM RUMINANTS

Most trans fats in the U.S. diet are produced industrially during the partial hydrogenation of vegetable oils. However, smaller amounts are present in dairy products and in meat from cows, sheep, and other ruminants, produced by bacteria in their stomachs. The predominant trans-isomer in ruminants is vaccenic acid, from which conjugated linolenic acid (another trans fatty acid) can be formed. It is possible to change the trans fatty acid content of ruminant products to some degree

by altering the animals' feed,⁶⁶ although levels of trans fat in milk and meats are already relatively low (1 to 8 percent of total fats).

In fact, most efforts have focused on increasing, rather than decreasing, the levels of conjugated linolenic acid in ruminant products, owing to its hypothesized health benefits for humans. However, the evidence of such benefits is inconclusive. For example, dietary trials indicate that consumption of conjugated linolenic acid reduces insulin sensitivity, increases lipid peroxidation, and has mixed effects on markers of inflammation and immune function.^{40,41,67,68}

Of four prospective studies evaluating the relation between the intake of trans fatty acids from ruminants and the risk of CHD, none identified a significant positive association, whereas three identified nonsignificant trends toward an in-

verse association.^{53,54,69,70} The absence of a higher risk of CHD associated with the intake of trans fatty acids from ruminants as compared with the intake of industrially produced trans fatty acids may be due to lower levels of intake (typically less than 0.5 percent of total energy intake), different biologic effects (ruminant and industrial trans fats share some, but not all, isomers), or the presence of other factors in dairy and meat products that balance any effects of the small amount of trans fats they contain. Although each of these potential explanations deserves further investigation, the sum of the current evidence suggests that the public health implications of consuming trans fats from ruminant products are relatively limited.

REDUCING INTAKE OF TRANS FATTY ACIDS

OPTIMAL LEVELS

To determine the optimal level of intake for a nutrient, both the risks and benefits should be considered. Given the adverse effects of trans fatty acids on serum lipid levels, systemic inflammation, and possibly other risk factors for cardiovascular disease and the positive associations with the risk of CHD, sudden death from cardiac causes, and possibly diabetes, the potential for harm is clear. The evidence and the magnitude of adverse health effects of trans fatty acids are in fact far stronger on average than those of food contaminants or pesticide residues, which have in some cases received considerable attention.⁷¹ Furthermore, trans fats from partially hydrogenated oils have no intrinsic health value above their caloric value. Thus, from a nutritional standpoint, the consumption of trans fatty acids results in considerable potential harm but no apparent benefit. In addition, adverse effects are seen even at low levels of intake: 1 to 3 percent of total energy intake, or approximately 20 to 60 calories (2 to 7 g) for a person consuming 2000 calories per day. Thus, complete or near-complete avoidance of industrially produced trans fats — consumption of less than 0.5 percent of the total energy intake — may be necessary to avoid adverse effects and would be prudent to minimize health risks.

CONSUMERS' CHOICES

The intake of trans fat can be reduced by consumers' decisions to choose foods free of trans

fatty acids, assisted by advice from health care providers about how to avoid the main foods containing trans fats (Table 1). Physicians and other health care providers can also support institutional changes to reduce the use of trans fat in food services at schools, hospitals, and other work sites.

The amounts of trans fat in foods can vary widely depending on the content of partially hydrogenated oils, with some foods containing little or no trans fatty acids and other, similar foods containing high levels.⁷² The mandatory specification of trans fat content on the nutrition labels of foods² should facilitate the avoidance of trans fatty acids, but only if consumers read the labels and base their decisions on what they read. However, the producers of foods that contain less than 500 mg of trans fatty acids per serving will be allowed to list the content of trans fatty acids as 0 on the packaging, so even consumers who read the labels might unwittingly consume substantial amounts of trans fats in multiple servings (for example, several pats of margarine or several cookies per day). Inspection of the ingredients list for the content of partially hydrogenated oils will be the only way to identify these foods. (Fully hydrogenated oils are typically listed simply as "hydrogenated" and do not contain trans fatty acids.) More important, food labels are not obligatory (and are rarely seen) in restaurants, bakeries, and many other retail food outlets. Avoidance of trans fats at these sites will depend on consumers' knowledge of the type and quantity of oils used in food preparation. Acquiring this knowledge is a potentially daunting but important task, because as trans fatty acids are increasingly eliminated from packaged foods, most trans fats will be consumed from food obtained at these sites.

INDUSTRY ALTERNATIVES

Trans fat intake could also be reduced if food manufacturers and restaurants choose to use alternatives to partially hydrogenated oils. To maximize health benefits, such alternatives should be low in both trans and saturated fats. Although concerns have been raised that decreasing the use of partially hydrogenated oils would increase the cost of certain foods and reduce their palatability, recent experience in European countries suggests that such concerns are overstated.^{6,73-75}

For example, in 2004, Denmark mandated that

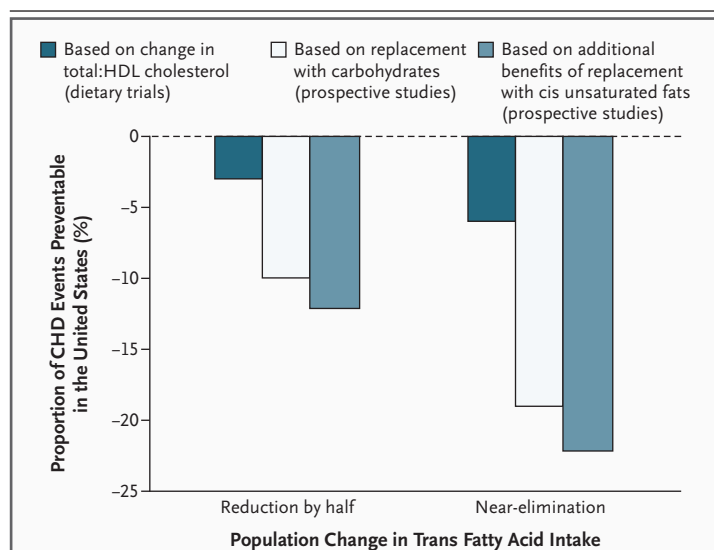


Figure 5. Estimated Effects of Reducing the Consumption of Industrially Produced Trans Fatty Acids on the Incidence of CHD (Nonfatal Myocardial Infarction or Death from CHD) in the United States.

Population attributable risks were calculated for a reduction by approximately half in the percent of energy intake (from 2.1 percent to 1.1 percent) or the near-elimination (from 2.1 percent to 0.1 percent) of trans fatty acid intake. Three effects were estimated: based on the effects of isocaloric replacement of trans fats with cis mono- or polyunsaturated fats (averaged effect) on the ratio of total to HDL cholesterol in controlled trials (as shown in Fig. 2) and the relation of this ratio to the incidence of CHD²¹; based on the reported relation of trans fatty acid intake, substituted for carbohydrate intake, with the incidence of CHD in a pooled analysis of prospective studies (as shown in Fig. 4); and based on the additional potential benefits if trans fats were replaced with cis mono- or polyunsaturated fats (averaged effect), as calculated from the pooled analysis of the prospective studies and the difference in relative risk resulting from trans fats being replaced by carbohydrates as compared with cis unsaturated fats in updated 2005 analyses from two cohorts.^{55,56}

all oils and fats used in locally made or imported foods must contain less than 2 percent industrially produced trans fatty acids. This legislation essentially eliminated the use of partially hydrogenated vegetable oils in Denmark.⁶ Comparisons of foods before and after the legislation demonstrated that partially hydrogenated oils were replaced mostly with cis unsaturated fatty acids in soft margarines, packaged snacks, and fast foods, with some saturated fatty acids from tropical oils or fully hydrogenated vegetable oils used in certain cookies and bakery products.⁶ Overall, the consumption of saturated fat did not increase. Both government and industry representatives agreed that these changes did not appreciably affect the quality, cost, or availability of food.^{6,73,74} Thus, french fries and chicken nuggets from U.S.

fast-food restaurants located in Denmark contain virtually no trans fatty acids, whereas the same foods in the United States contain 5 to 10 g of trans fatty acids per serving (as discussed by Stender et al. elsewhere in this issue of the *Journal*⁷⁵). In Norway, Finland, and the Netherlands, cooperative efforts between government agencies and food industries have also resulted in substantial reductions in the use and consumption of trans fat without notable increases in the cost of foods or reductions in the quality or availability of foods.⁷⁶

Some food manufacturers in the United States have voluntarily reduced their use of partially hydrogenated vegetable oils.^{77,78} Many products that contained trans fatty acids in the past are now available in formulations that are free of trans fatty acids. The mandated labeling of trans fat content² may provide an additional impetus for such changes. It has been noted that the FDA acknowledges the potential harm of consumption of any amount of industrially produced trans fat, yet it also maintains that partially hydrogenated oils are basically safe.⁷⁹ A petition to the FDA calls for a removal of partially hydrogenated oils from the “generally regarded as safe” category⁸⁰ — that is, “generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use.”⁸¹ Doing so would effectively eliminate the consumption of industrially produced trans fatty acids in the United States. On the basis of experience in Europe, substantial reduction in the use of partially hydrogenated oils appears to be a feasible goal in the United States and could be effected through either legislation or voluntary efforts by food manufacturers.

POTENTIAL BENEFITS OF REDUCING INTAKE

We calculated the potential effect of reducing the intake of industrially produced trans fatty acids on the incidence of CHD in the United States (Fig. 5). On the basis of the predicted changes in total and HDL cholesterol levels alone (Fig. 2),²¹ a meaningful proportion of CHD events (3 to 6 percent) would be averted. However, we believe that this reduction is an underestimate, since trans fats may also influence the risk of CHD through other mechanisms, such as inflammatory or endothelial effects. On the basis of reported relations between trans fat intake and CHD events in prospective studies (Fig. 4), which may account

more satisfactorily for the total effects of trans fatty acids, 10 to 19 percent of CHD events in the United States could be averted by reducing the intake of trans fat. Thus, given the 1.2 million annual myocardial infarctions and deaths from CHD in the United States,⁸² near-elimination of industrially produced trans fats might avert between 72,000 (6 percent) and 228,000 (19 percent) CHD events each year.

These estimates are based on the replacement of trans fats with carbohydrates. In practice, however, trans fats in partially hydrogenated oils would most commonly be replaced with unhydrogenated (cis) unsaturated fats,⁶ which may have additional potential benefits as compared with carbohydrates. If such additional potential benefit is considered, greater proportions of CHD events (12 to 22 percent) might be averted (Fig. 5). Partial hydrogenation also largely destroys α -linolenic acid, the plant-based n-3 fatty acid. Although the cardiovascular benefits of α -linolenic acid are not established conclusively,⁸³ the replacement of partially hydrogenated fats with unhydrogenated oils containing α -linolenic acid (such as soybean oil) may further reduce the risk of CHD by increasing the population intake of n-3 fatty acids.

CONCLUSIONS

On the basis of evidence from in vitro experimental studies, dietary trials, and prospective obser-

vational studies, the consumption of trans fatty acids from partially hydrogenated oils provides no apparent nutritional benefit and has considerable potential for harm. Although the elimination of partially hydrogenated oils from foods may be challenging for restaurants and food manufacturers in the United States, experience in other countries indicates that such fats can largely be replaced by cis unsaturated fats without increasing the cost or reducing the quality or availability of foods. Health care providers should advise consumers about how to minimize the intake of trans fats, consumers should recognize and avoid products containing trans fats and restaurants and food manufacturers should choose to use alternative fats in food production and preparation. These steps should help reduce the consumption of trans fatty acids, possibly resulting in substantial health benefits such as averting thousands of CHD events each year in the United States.

Supported by a grant (K08-HL-075628) from the National Heart, Lung, and Blood Institute, National Institutes of Health. The Wageningen Center for Food Sciences is an alliance of major Dutch food companies, Maastricht University, TNO Nutrition and Food Research, and Wageningen University and Research Center, with financial support from the Dutch government.

No potential conflict of interest relevant to this article was reported.

We are indebted to Dr. Ronald Mensink for providing updated meta-analysis results, to Dr. Peter Clifton for providing risk estimates from his published study, and to the organizers of and participants in the First International Symposium on Trans Fatty Acids and Health (Copenhagen, September 11–13, 2005) for informative discussions and international perspectives on trans fatty acids and cardiovascular health.

REFERENCES

- Allison DB, Egan SK, Barraj LM, Caughman C, Infante M, Heimbach JT. Estimated intakes of trans fatty and other fatty acids in the US population. *J Am Diet Assoc* 1999;99:166-74.
- Food and Drug Administration. FDA acts to provide better information to consumers on trans fats. 2005. (Accessed March 17, 2006, at <http://www.fda.gov/oc/initiatives/transfat/>.)
- Department of Health and Human Services, Department of Agriculture. Dietary guidelines for Americans 2005. (Accessed March 17, 2006, at <http://www.health.gov/dietaryguidelines/dga2005/document/>.)
- Dietary Guidelines Advisory Committee. Nutrition and your health: dietary guidelines for Americans: 2005 Dietary Guidelines Advisory Committee report. Washington, D.C.: Department of Agriculture, 2005. (Accessed March 17, 2006, at <http://www.health.gov/dietaryguidelines/dga2005/report/>.)
- Health department asks restaurateurs and food suppliers to voluntarily make an oil change and eliminate artificial trans fat. Press release of the New York City Department of Health and Mental Hygiene, New York, August 10, 2005. (Accessed March 17, 2006, at <http://www.nyc.gov/html/doh/html/pr/pr083-05.shtml>.)
- Leth T, Bysted A, Erendah-Mikkelsen A. The effect of the regulation on trans fatty acid content in Danish food. First International Symposium on Trans Fatty Acids and Health, Rungstedgaard, Denmark, September 11–13, 2005. abstract.
- Health Canada. Government response to the interim recommendations of the Trans Fat Task Force. 2005. (Accessed March 17, 2006, at http://www.hc-sc.gc.ca/fn-an/nutrition/gras-trans-fats/government_response_reponse_gouvernement_e.html.)
- Laine DC, Snodgrass CM, Dawson EA, Ener MA, Kuba K, Frantz ID Jr. Lightly hydrogenated soy oil versus other vegetable oils as a lipid-lowering dietary constituent. *Am J Clin Nutr* 1982;35:683-90.
- Mensink RP, Katan MB. Effect of dietary trans fatty acids on high-density and low-density lipoprotein cholesterol levels in healthy subjects. *N Engl J Med* 1990;323:439-45.
- Zock PL, Katan MB. Hydrogenation alternatives: effects of trans fatty acids and stearic acid versus linoleic acid on serum lipids and lipoproteins in humans. *J Lipid Res* 1992;33:399-410.
- Judd JT, Clevidence BA, Muesing RA, Wittes J, Sunkin ME, Podczasy JJ. Dietary trans fatty acids: effects on plasma lipids and lipoproteins of healthy men and women. *Am J Clin Nutr* 1994;59:861-8.
- Almendingen K, Jordal O, Kierulf P, Sandstad B, Pedersen JI. Effects of partially hydrogenated fish oil, partially hydrogenated soybean oil, and butter on serum lipoproteins and Lp[a] in men. *J Lipid Res* 1995;36:1370-84.

13. Aro A, Jauhiainen M, Partanen R, Salminen I, Mutanen M. Stearic acid, trans fatty acids, and dairy fat: effects on serum and lipoprotein lipids, apolipoproteins, lipoprotein(a), and lipid transfer proteins in healthy subjects. *Am J Clin Nutr* 1997; 65:1419-26.
14. Judd JT, Baer DJ, Clevidence BA, et al. Effects of margarine compared with those of butter on blood lipid profiles related to cardiovascular disease risk factors in normolipemic adults fed controlled diets. *Am J Clin Nutr* 1998;68:768-77.
15. Muller H, Jordal O, Kierulff P, Kirkhus B, Pedersen JI. Replacement of partially hydrogenated soybean oil by palm oil in margarine without unfavorable effects on serum lipoproteins. *Lipids* 1998;33:879-87.
16. Lichtenstein AH, Ausman LM, Jalbert SM, Schaefer EJ. Effects of different forms of dietary hydrogenated fats on serum lipoprotein cholesterol levels. *N Engl J Med* 1999;340:1933-40.
17. de Roos N, Schouten E, Katan M. Consumption of a solid fat rich in lauric acid results in a more favorable serum lipid profile in healthy men and women than consumption of a solid fat rich in trans-fatty acids. *J Nutr* 2001;131:242-5.
18. Lovejoy JC, Smith SR, Champagne CM, et al. Effects of diets enriched in saturated (palmitic), monounsaturated (oleic), or trans (elaidd) fatty acids on insulin sensitivity and substrate oxidation in healthy adults. *Diabetes Care* 2002;25:1283-8.
19. Judd JT, Baer DJ, Clevidence BA, Kris-Etherton P, Muesing RA, Iwano M. Dietary cis and trans monounsaturated and saturated FA and plasma lipids and lipoproteins in men. *Lipids* 2002;37:123-31.
20. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr* 2003; 77:1146-55.
21. Stampfer MJ, Sacks FM, Salvini S, Willett WC, Hennekens CH. A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. *N Engl J Med* 1991;325:373-81.
22. Ascherio A, Katan MB, Zock PL, Stampfer MJ, Willett WC. Trans fatty acids and coronary heart disease. *N Engl J Med* 1999;340:1994-8.
23. Mauger JF, Lichtenstein AH, Ausman LM, et al. Effect of different forms of dietary hydrogenated fats on LDL particle size. *Am J Clin Nutr* 2003;78:370-5.
24. Mozaffarian D, Pischon T, Hankinson SE, et al. Dietary intake of trans fatty acids and systemic inflammation in women. *Am J Clin Nutr* 2004;79:606-12.
25. Lopez-Garcia E, Schulze MB, Meigs JB, et al. Consumption of trans fatty acids is related to plasma biomarkers of inflammation and endothelial dysfunction. *J Nutr* 2005;135:562-6.
26. Mozaffarian D, Rimm EB, King IB, Lawler RL, McDonald GB, Levy WC. Trans fatty acids and systemic inflammation in heart failure. *Am J Clin Nutr* 2004;80:1521-5.
27. Han SN, Leka LS, Lichtenstein AH, Ausman LM, Schaefer EJ, Meydani SN. Effect of hydrogenated and saturated, relative to polyunsaturated, fat on immune and inflammatory responses of adults with moderate hypercholesterolemia. *J Lipid Res* 2002;43:445-52.
28. Baer DJ, Judd JT, Clevidence BA, Tracy RP. Dietary fatty acids affect plasma markers of inflammation in healthy men fed controlled diets: a randomized crossover study. *Am J Clin Nutr* 2004;79:969-73.
29. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002;105:1135-43.
30. Albert CM, Ma J, Rifai N, Stampfer MJ, Ridker PM. Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. *Circulation* 2002;105:2595-9.
31. Pickup JC. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. *Diabetes Care* 2004; 27:813-23.
32. Vasan RS, Sullivan LM, Roubenoff R, et al. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. *Circulation* 2003;107: 1486-91.
33. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000;342:836-43.
34. de Roos NM, Bots ML, Katan MB. Replacement of dietary saturated fatty acids by trans fatty acids lowers serum HDL cholesterol and impairs endothelial function in healthy men and women. *Arterioscler Thromb Vasc Biol* 2001;21:1233-7.
35. de Roos NM, Schouten EG, Scheek LM, van Tol A, Katan MB. Replacement of dietary saturated fat with trans fat reduces serum paraoxonase activity in healthy men and women. *Metabolism* 2002;51:1534-7.
36. Muller H, Seljeflot I, Solvoll K, Pedersen JI. Partially hydrogenated soybean oil reduces postprandial t-PA activity compared with palm oil. *Atherosclerosis* 2001; 155:467-76.
37. Louheranta AM, Turpeinen AK, Vidgren HM, Schwab US, Uusitupa MI. A high-trans fatty acid diet and insulin sensitivity in young healthy women. *Metabolism* 1999;48:870-5.
38. Christiansen E, Schnider S, Palmvig B, Tauber-Lassen E, Pedersen O. Intake of a diet high in trans monounsaturated fatty acids or saturated fatty acids. Effects on postprandial insulinemia and glycemia in obese patients with NIDDM. *Diabetes Care* 1997;20:881-7.
39. Lichtenstein AH, Erkkila AT, Larmache B, Schwab US, Jalbert SM, Ausman LM. Influence of hydrogenated fat and butter on CVD risk factors: remnant-like particles, glucose and insulin, blood pressure and C-reactive protein. *Atherosclerosis* 2003;171:97-107.
40. Riserus U, Smedman A, Basu S, Vessby B. Metabolic effects of conjugated linoleic acid in humans: the Swedish experience. *Am J Clin Nutr* 2004;79:1146S-8S.
41. Moloney F, Yeow TP, Mullen A, Nolan JJ, Roche HM. Conjugated linoleic acid supplementation, insulin sensitivity, and lipoprotein metabolism in patients with type 2 diabetes mellitus. *Am J Clin Nutr* 2004;80:887-95.
42. Clandinin MT, Cheema S, Field CJ, Garg ML, Venkatraman J, Clandinin TR. Dietary fat: exogenous determination of membrane structure and cell function. *FASEB J* 1991;5:2761-9.
43. Feller SE, Gawrisch K. Properties of docosahexaenoic-acid-containing lipids and their influence on the function of rhodopsin. *Curr Opin Struct Biol* 2005; 15:416-22.
44. Roach C, Feller SE, Ward JA, Shaikh SR, Zerouga M, Stillwell W. Comparison of cis and trans fatty acid containing phosphatidylcholines on membrane properties. *Biochemistry* 2004;43:6344-51.
45. Vanden Heuvel JP. Diet, fatty acids, and regulation of genes important for heart disease. *Curr Atheroscler Rep* 2004; 6:432-40.
46. Hotamisligil GS. Role of endoplasmic reticulum stress and c-Jun NH2-terminal kinase pathways in inflammation and origin of obesity and diabetes. *Diabetes* 2005;54:Suppl 2:S73-S78.
47. Dashti N, Feng Q, Freeman MR, Gandhi M, Franklin FA. Trans polyunsaturated fatty acids have more adverse effects than saturated fatty acids on the concentration and composition of lipoproteins secreted by human hepatoma HepG2 cells. *J Nutr* 2002;132:2651-9.
48. Mitmesser SH, Carr TP. Trans fatty acids alter the lipid composition and size of apoB-100-containing lipoproteins secreted by HepG2 cells. *J Nutr Biochem* 2005;16:178-83.
49. Matthan NR, Welty FK, Barrett PH, et al. Dietary hydrogenated fat increases high-density lipoprotein apoA-I catabolism and decreases low-density lipoprotein apoB-100 catabolism in hypercholesterolemic women. *Arterioscler Thromb Vasc Biol* 2004;24:1092-7.
50. van Tol A, Zock PL, van Gent T, Scheek LM, Katan MB. Dietary trans fatty acids increase serum cholesteryl ester transfer protein activity in man. *Atherosclerosis* 1995;115:129-34.

51. Matthan NR, Cianflone K, Lichtenstein AH, Ausman LM, Jauhiainen M, Jones PJ. Hydrogenated fat consumption affects acylation-stimulating protein levels and cholesterol esterification rates in moderately hypercholesterolemic women. *J Lipid Res* 2001;42:1841-8.
52. Saravanan N, Haseeb A, Ehtesham NZ, Ghafoorunissa X. Differential effects of dietary saturated and trans-fatty acids on expression of genes associated with insulin sensitivity in rat adipose tissue. *Eur J Endocrinol* 2005;153:159-65.
53. Pietinen P, Ascherio A, Korhonen P, et al. Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Am J Epidemiol* 1997;145:876-87.
54. Oomen CM, Ocke MC, Feskens EJ, van Erp-Baart MA, Kok EJ, Kromhout D. Association between trans fatty acid intake and 10-year risk of coronary heart disease in the Zutphen Elderly Study: a prospective population-based study. *Lancet* 2001; 357:746-51.
55. Oh K, Hu FB, Manson JE, Stampfer MJ, Willett WC. Dietary fat intake and risk of coronary heart disease in women: 20 years of follow-up of the Nurses' Health Study. *Am J Epidemiol* 2005;161:672-9.
56. Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer M, Willett WC. Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States. *BMJ* 1996; 313:84-90.
57. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
58. Aro A, Kardinaal AF, Salminen I, et al. Adipose tissue isomeric trans fatty acids and risk of myocardial infarction in nine countries: the EURAMIC study. *Lancet* 1995;345:273-8.
59. Baylin A, Kabagambe EK, Ascherio A, Spiegelman D, Campos H. High 18:2 trans-fatty acids in adipose tissue are associated with increased risk of nonfatal acute myocardial infarction in Costa Rican adults. *J Nutr* 2003;133:1186-91.
60. Clifton PM, Keogh JB, Noakes M. Trans fatty acids in adipose tissue and the food supply are associated with myocardial infarction. *J Nutr* 2004;134:874-9.
61. Roberts TL, Wood DA, Riemersma RA, Gallagher PJ, Lampe FC. Trans isomers of oleic and linoleic acids in adipose tissue and sudden cardiac death. *Lancet* 1995;345:278-82.
62. Lemaitre RN, King IB, Raghunathan TE, et al. Cell membrane trans-fatty acids and the risk of primary cardiac arrest. *Circulation* 2002;105:697-701.
63. van Dam RM, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Dietary patterns and risk for type 2 diabetes mellitus in U.S. men. *Ann Intern Med* 2002;136:201-9.
64. Meyer KA, Kushi LH, Jacobs DR Jr, Folsom AR. Dietary fat and incidence of type 2 diabetes in older Iowa women. *Diabetes Care* 2001;24:1528-35.
65. Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 2001;345:790-7.
66. Lock AL, Bauman DE. Modifying milk fat composition of dairy cows to enhance fatty acids beneficial to human health. *Lipids* 2004;39:1197-206.
67. Smedman A, Vessby B, Basu S. Isomer-specific effects of conjugated linoleic acid on lipid peroxidation in humans: regulation by alpha-tocopherol and cyclooxygenase-2 inhibitor. *Clin Sci (Lond)* 2004;106:67-73.
68. Nugent AP, Roche HM, Noone EJ, Long A, Kelleher DK, Gibney MJ. The effects of conjugated linoleic acid supplementation on immune function in healthy volunteers. *Eur J Clin Nutr* 2005;59:742-50.
69. Jakobsen MU, Overvad K, Dyerberg J, Heitmann BL. Intake of ruminant trans fatty acids and risk of coronary heart disease. *Am J Clin Nutr* (in press).
70. Willett WC, Stampfer MJ, Manson JE, et al. Intake of trans fatty acids and risk of coronary heart disease among women. *Lancet* 1993;341:581-5.
71. Hites RA, Foran JA, Carpenter DO, Hamilton MC, Knuth BA, Schwager SJ. Global assessment of organic contaminants in farmed salmon. *Science* 2004; 303:226-9.
72. Innis SM, Green TJ, Halsey TK. Variability in the trans fatty acid content of foods within a food category: implications for estimation of dietary trans fatty acid intakes. *J Am Coll Nutr* 1999;18:255-60.
73. Nielsen K. Is the quality and cost of food affected if industrially produced trans fatty acids are removed? First International Symposium on Trans Fatty Acids and Health, Rungstedgaard, Denmark, September 11-13, 2005. abstract.
74. Jensen HG. Labelling of trans fatty acid content in food, regulations, and what limits pros et cons — the Danish view. First International Symposium on Trans Fatty Acids and Health, Rungstedgaard, Denmark, September 11-13, 2005. abstract.
75. Stender S, Dyerberg J, Astrup A. High levels of trans fat in popular fast foods. *N Engl J Med* 2006;354:1650-2.
76. Aro A. The scientific basis for TFA regulations — is it sufficient? A personal view. In: Abstracts of the First International Symposium on Trans Fatty Acids and Health, Rungstedgaard, Denmark, September 11-13, 2005. abstract.
77. Products containing zero grams of trans fats. Dallas: Frito-Lay, July 7, 2005. (Accessed March 17, 2006, at http://www.fritolay.com/fl/flstore/cgi-bin/ProdDetEv_Cat_351852_NavRoot_306_ProdID_352020.htm.)
78. Oreo takes on a new twist with new varieties that contain zero grams of trans fat per serving. News release of Kraft Foods, East Hanover, N.J., April 6, 2004. (Accessed March 17, 2006, at <http://164.109.46.215/newsroom/04062004.html>.)
79. As serious as a heart attack. *New York Times*. June 25, 2005:A14. (Accessed March 17, 2006, at <http://www.nytimes.com>.)
80. Petition for rulemaking to revoke the authority for industry to use partially hydrogenated vegetable oils in foods. Washington, D.C.: Center for Science in the Public Interest, May 18, 2004. (Accessed March 17, 2006, at http://cspinet.org/new/pdf/trans_fat_petition_may_18.pdf.)
81. Food and Drug Administration, Center for Food Safety and Nutrition. Frequently asked questions about GRAS. (Accessed March 17, 2006, at <http://vm.cfsan.fda.gov/~dms/grasguid.html>.)
82. Heart disease and stroke statistics — 2004 update. Dallas: American Heart Association, 2005.
83. Mozaffarian D. Does alpha-linolenic acid intake reduce the risk of coronary heart disease? A review of the evidence. *Altern Ther Health Med* 2005;11:24-30.

Copyright © 2006 Massachusetts Medical Society.

POWERPOINT SLIDES OF JOURNAL FIGURES AND TABLES

At the *Journal's* Web site, subscribers can automatically create PowerPoint slides of *Journal* figures and tables. Click on a figure or table in the full-text version of any article at www.nejm.org, and then click on PowerPoint Slide for Teaching. A PowerPoint slide containing the image, with its title and reference citation, can then be downloaded and saved.