Health effects of \textit{trans} fatty acids\textsuperscript{1–3}

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\textbf{ABSTRACT} \textit{trans} Fatty acids are formed during the process of partial hydrogenation in which liquid vegetable oils are converted to margarine and vegetable shortening. Concern has existed that this process may have adverse consequences because natural essential fatty acids are destroyed and the new artificial isomers are structurally similar to saturated fats, lack the essential metabolic activity of the parent compounds, and inhibit the enzymatic desaturation of linoleic and linolenic acid. In the past 50 years a series of metabolic studies has provided unequivocal evidence that \textit{trans} fatty acids increase plasma concentrations of low-density-lipoprotein cholesterol and reduce concentrations of high-density-lipoprotein (HDL) cholesterol relative to the parent natural fat. In these same studies, \textit{trans} fatty acids increased the plasma ratio of total to HDL cholesterol nearly twofold compared with saturated fats. On the basis of these metabolic effects and the known relation of blood lipid concentrations to risk of coronary artery disease, we estimate conservatively that 30,000 premature deaths/y in the United States are attributable to consumption of \textit{trans} fatty acids. Epidemiologic studies, although not conclusive on their own, are consistent with adverse effects of this magnitude or even larger. Because there are no known nutritional benefits of \textit{trans} fatty acids and clear adverse metabolic consequences exist, prudent public policy would dictate that their consumption be minimized and that information on the \textit{trans} fatty acid content of foods be available to consumers.

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\textbf{KEY WORDS} \textit{trans} Fatty acids, fatty acids, coronary artery disease, myocardial infarction

\textbf{INTRODUCTION}

Naturally occurring unsaturated fats contain double bonds that are nearly all in the \textit{cis} configuration, and these occur most commonly in certain positions in the aliphatic chain. Enzymes involved in fatty acids synthesis have evolved to recognize these natural fatty acids with a high degree of specificity. Changes in the fatty acid composition of the diet can have major effects on several critical physiologic processes because the number and position of double bonds influence the function and metabolism of fatty acids, including their incorporation into phospholipids and their transformation into prostaglandins and other eicosanoids. Through human evolution, oleic acid, linoleic acid, linolenic acid, and the long-chain \textit{n–3} fatty acids from fish oils constituted almost all of the unsaturated fat in the food supply. The only appreciable sources of \textit{trans} isomers were dairy fat and the meat of ruminants, whose stomachs contain bacterial isomerases capable of converting the double bonds of polyunsaturated fats in plants to a \textit{trans} configuration.

At the turn of the century a dramatic change in the fatty acid composition of the food supply of industrialized countries occurred when a process was discovered to convert liquid oils into solid or semisolid fats (1). In this process, known as partial hydrogenation, oils are heated in the presence of nickel or other metal catalysts and exposed to hydrogen gas. This process causes some double bonds to be saturated while others are changed to a \textit{trans} configuration (geometric isomerism) or are shifted to a new position in the aliphatic chain (positional isomerism). The end products of partial hydrogenation typically contain >20 new isomers of oleic and linoleic acids; these artificial fatty acids may make up to 40% or more of the total fat (2). Altering the conditions of partial hydrogenation allows the creation of different fats that are used in the manufacture of margarine, fats for deep frying, or shortenings for baking.

During the course of this century, the production of partially hydrogenated vegetable oils increased steadily because of their low cost, long shelf life, and suitability for commercial frying. By about 1910, the per capita production of margarine and vegetable shortening in the United States was already >4 kg/y. Various forms of partially hydrogenated vegetable oils have replaced beef tallow, butter, and lard in homes and in many commercial applications, largely for economic and perceived (but undocumented) health benefits. Despite the continuing displacement of animal fats by partially hydrogenated fats in the United States, per capita consumption of \textit{trans} fatty acids from vegetable sources declined slightly from a peak of \textit{\sim}2.2% of energy in the 1960s to \textit{\sim}2.1% in the mid-1980s. This resulted largely from a reduction in the degree of hydrogenation to retain more of the original polyunsaturated fats. Thus, polyunsaturated fat increased greatly over this period. Data on consumption of \textit{trans} fatty acids in other countries are sparse. In the United Kingdom, consumption was \textit{\sim}6% of total fat (\textit{\sim}2.3% of energy) in the 1980s, and similar values have been reported from Sweden and Germany (3). Consumption of \textit{trans} fatty acids has increased in the Indian subcontinent, where

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partially hydrogenated vegetable oils (vanaspathi) are replacing the traditional ghee (clarified butter). It is likely that production and consumption of these products are increasing widely throughout the developing world as populations move from relying on subsistence agriculture to being urban societies dependent on a commercial food supply.

METABOLIC EFFECTS

For decades concerns have existed that trans fatty acids may have adverse physiologic effects because they are structurally similar to saturated fats, lack the essential metabolic activity of the parent compounds, and inhibit the enzymatic desaturation of linoleic and linolenic acid (4). Much less attention has been paid to the cis isomers of oleic and linoleic acid, which also interfere with the metabolism of the parent compounds and may be elongated and desaturated to eicosanoids of unusual structure (5, 6). A comprehensive report issued in 1985 did not find clear evidence of adverse effects of trans fat, but did indicate the need for further research (2).

In the past decade, new metabolic studies have provided unequivocal evidence that the partial hydrogenation of vegetable oil creates fatty acids that adversely affect plasma lipid concentrations relative to the natural oil. In a rigorous trial conducted in Holland by Mensink and Katan (7), trans fatty acids at 10% of energy in the diet increased low-density-lipoprotein (LDL) cholesterol and decreased high-density-lipoprotein (HDL) cholesterol when substituted for oleic acid. In contrast, saturated fats increased LDL but did not decrease HDL cholesterol when compared with oleic acid. The adverse effect of trans fatty acids on the ratio of total to HDL cholesterol was about twice that of saturated fats. These results, obtained at trans fatty acid intakes well above the average intake in most populations, were later confirmed in trials of diets containing 7.7% (8), 6% (9), and 3% (9) of energy as trans. Similar effects of trans fatty acids on LDL and HDL cholesterol have also been reported in men with mild hypercholesterolemia (10). When the effect of trans fatty acids and saturated fats on the ratio of total to HDL cholesterol are plotted against the percentage of energy contributed, there appears to be a linear dose-response relation, with the slope for trans fatty acids being nearly twice that of saturated fats (the absolute blood lipid concentrations for Figure 1 are shown in Table 1).

Moreover, in each of these individual studies in which these fats were compared, the adverse effect of trans fatty acids was significantly worse than that of saturated fat (7–9) as assessed by the ratio of total to HDL cholesterol. When the effects of trans fatty acids on LDL and HDL cholesterol were summarized separately, as in Figure 1, significant adverse effects were seen for both (for LDL, $\beta = 0.39 \text{ mmol} \cdot \text{L}^{-1} \cdot \%$ of energy$^{-1}$, 95% CI = 0.028, 0.050, $P = 0.001$; for HDL, $\beta = -0.012 \text{ mmol} \cdot \text{L}^{-1} \cdot \%$ of energy$^{-1}$, 95% CI = -0.015, -0.009, $P = 0.02$). In another metabolic study conducted in Asia, not included in the above summary, trans fatty acids at 7% of energy markedly increased LDL and reduced HDL relative to both oleic acid and saturated fat (13). In addition to having clear adverse effects on HDL cholesterol, intake of trans fatty acids increased plasma concentrations of lipoprotein(a), another putative risk factor for coronary artery disease (CAD), in two of three randomized trials (10, 14).

A common assertion is that trans fat reduces blood cholesterol concentrations compared with saturated fat (15). However, this is highly misleading because trans fat does so primarily by reducing HDL cholesterol, which cannot be construed as a desirable effect. For example, in the study of Mensink and Katan (7), trans fat at 10% of energy reduced total serum cholesterol by 6% compared with saturated fat, but this was mainly due to a 12% reduction in HDL cholesterol.

Although it seems likely that the effects on blood cholesterol fractions are not the same for all the trans isomers, there are no data on the relative potency of individual compounds. In two of the above experiments (7, 9), the trans diet contained a mixture of cis and trans isomers similar to that of commercially available margarine; in the others (8, 10), elaidic acid (9t-18:1, the trans isomer of oleic acid) contributed most of the total trans fatty acids.

FIGURE 1. Change in the ratio of total to HDL cholesterol by percentage of energy from trans fatty acids (●) and saturated fat (○) compared with natural unsaturated fat (for trans fat, $\beta = 0.059, P < 0.001$; for saturated fat, $\beta = 0.029, P = 0.10$; test for differences in slopes, $P = 0.03$). Data are from Judd et al (9), Zock and Katan (8), and Mensink and Katan (7). * $P < 0.005$, ** $P < 0.0001$. Figure adapted from reference 11.

EPIDEMIOLOGIC STUDIES

The prediction, based on the metabolic studies, that intake of partially hydrogenated fats increases the risk of coronary disease has been supported by several epidemiologic investigations. Intake of partially hydrogenated fats has paralleled the rise in CAD mortality in the United States and other countries (16). Also, among the seven countries studied by Keys and his colleagues, average intake of trans fatty acids, assessed by analysis of replicate food sample, was strongly associated with regional incidence of CAD (17). More detailed investigations that allow for the control of individual risk factors are desirable because many other variables besides dietary fat composition differ among countries and may account for at least some of the difference in CAD incidence.

Direct associations have been reported between concentrations of trans isomers in adipose tissue and risk of death from myocardial infarction (18) and between plasma concentrations of trans fatty acids and the presence of atherosclerosis (19). In the above investigations, however, other dietary factors that may affect the risk of CAD were not considered. This limitation was addressed in the Nurses’ Health Study (20), a longitudinal study of ~90 000 US women. In that investigation, women in the highest quintile of intake of trans fatty acids

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from partially hydrogenated vegetable fats at baseline (median intake = 3.2% of total energy) had a 35% higher risk of coronary disease than women in the lowest quintile (median = 1.3% of total energy), after standard cardiovascular risk factors were adjusted for. The association remained significant after further adjustment for intake of other types of fat, cholesterol, vitamins, and fiber. The positive association was limited to trans fatty acids from partially hydrogenated vegetable fat. The association was stronger when women who had changed their consumption of margarine during the past 10 years were excluded, suggesting that the association was not due simply to a switch to margarine by women with a suspicion of preclinical coronary disease. Also, the positive association with intake of trans fatty acids was due to high consumption of cookies and white bread, as well as a higher intake of margarine, indicating that the association was not simply the result of healthier behavior by women with a perceived higher risk of CAD. A positive association between intake of trans fatty acids and risk of myocardial infarction was also observed in a case-control study among men and women (21); the dose-response findings suggested a possible J-shaped relation, but a formal statistical test indicated that the data did not depart significantly from linearity. In both studies the risk was quantitatively higher than predicted by the effect of trans fatty acids on blood LDL and HDL concentrations, which is compatible with the suggestion that trans fatty acids may have other adverse physiologic effects perhaps mediated by lipoprotein(a) or a prothrombotic mechanism.

Two recent studies have been published that were interpreted by some as refuting an association between intake of trans fatty acids and risk of CAD (22, 23). The study of Roberts et al (23), based on adipose fatty acid analysis of only 66 cases of sudden death and matched control subjects, was simply too small to be informative. This can be appreciated by the fact that the 95% CIs for the relative risks in highest quintiles of both 18:1 trans (0.18, 1.83) and 18:2 trans (0.85, 2.84) easily included the relative risks seen in the Nurses’ Health Study. In this small study, neither diabetes nor hypertension was significantly associated with outcome, which would lead no reasonable person to conclude that they were not causes of coronary disease. In the EURAMIC study, a case-control study of nonfatal myocardial infarction that also sampled adipose tissue for fatty acid analysis, the Spanish centers had by far the lowest concentrations of trans fatty acids (22). Inasmuch as Spain also has very low CAD rates, this is certainly compatible with a causal relation. When the outlying Spanish data were appropriately excluded, the adjusted relative risk of CAD was 1.44 (95% CI: 0.94, 2.20) in the highest versus the lowest quartile of trans fat. Although not quite statistically significant, this was almost identical to the relative risk of 1.47 seen for the Nurses’ Health Study. As the authors concluded, these findings do not exclude the possibility that trans fatty acids have a significant effect on risk of CAD; indeed, the data tend to support such a relation.

In a report from the Framingham Heart Study (24), consumption of margarine was significantly associated with risk of future CAD, although use of butter was not.

**ESTIMATION OF DEATHS ATTRIBUTABLE TO TRANS FATTY ACIDS**

Although confounding by unmeasured factors remains a possible explanation of the results of the epidemiologic investigations, the combined evidence from metabolic and epidemiologic studies strongly supports a causal interpretation. We have elsewhere estimated that current intake of partially hydrogenated fats may account for > 30,000 deaths from CAD per year in the United States (25). This estimation was based only on the effect of trans fatty acids on blood concentrations of total and HDL cholesterol from metabolic studies and on the relation of the blood total-to-HDL cholesterol ratio to risk of CAD repeatedly documented in many studies. By this method, we calculated that ~7% of CAD deaths were attributable to trans fatty acid consumption; multiplying this by the ~500,000 CAD deaths that occur annually in the United States yields > 30,000 deaths. We have also estimated the number of deaths due only to the effects of trans fatty acids on LDL cholesterol with the use of a summary of the metabolic studies shown in Figure 1 to estimate the change in LDL corresponding to 2% of energy from trans fatty acids. This gives an estimate of 16,000 deaths annually. All of these are conservative estimates for several reasons: they assumed only 2% of energy from trans fatty acids for the population average, which is probably low; the relation between plasma total to HDL cholesterol and CAD risk is based on only one blood sample per subject, which will substantially underestimate the magnitude of association; and
we have not taken into account other possible adverse effects of partially hydrogenated fats, including effects on lipoprotein(a) or thrombotic tendency. Independent of our calculation, Grundy (26) estimated that 8% of premature CAD deaths in the United States can be attributed to consumption of trans fatty acids, which is very much in line with our estimate of 7%. Oil industry representatives have argued that causation can only be proven by randomized trials (27), but these would be unethical and logistically unfeasible and will almost surely never be conducted. Because there are no known nutritional benefits of partially hydrogenated fats and well-documented adverse metabolic effects, there appears to be no justification for adding these synthetic substances to the food supply.

PUBLIC HEALTH APPROACH TO REDUCING INTAKE OF trans FATTY ACIDS

Some have argued that dietary advice should still focus on lowering intake of total fat, maintaining that a decrease in fat intake will also cause a decrease in saturated and trans fats consumption (12). However, reducing total fat intake is not likely to be the most effective way to reduce trans fatty acids consumption. During the past decade in the United States, total fat intake has declined from 38% to 34% of energy, with only minor changes in trans fatty acid consumption. Much greater reductions can be achieved by changing manufacturing processes and specific food choices. Also, this contention ignores the possibility that trans fatty acids may have a worse effect (on a per-unit basis) than saturated fat, as suggested by the effects on the ratio of total to HDL cholesterol in metabolic studies.

At present, individuals who desire to reduce their blood cholesterol may see their efforts hampered by an increased consumption of trans fatty acids as a result of choosing foods low in saturated fat. This paradox is already a consequence of food labeling regulations in the United States and Canada, which do not require manufacturers to reveal the trans content of their products and allow labeling of products as “low in saturated fat” and “low in cholesterol” regardless of their trans fatty acid content. This policy provides a strong incentive to replace saturated fats with partially hydrogenated fats, and products with these labels are, in fact, those with the highest amounts of trans fatty acids (28). In a meta-analysis comparing the effects of various margarines and butter on blood lipids, Zock and Katan (29) found that the saturated fat content of margarines was unrelated to the ratio of total to HDL cholesterol. However, the trans fat content of margarines was strongly associated with the total-to-HDL cholesterol ratio and margarines with high trans fat content were similar to butter. These data provide independent confirmation of the relations described in Figure 1. In the United States, even moderate consumption of foods rich in trans fatty acids may increase consumption to 5% of energy, a level that would be predicted to negate the benefits of a reduction in 10% of energy from saturated fat (25, 30). Finally, average consumption data ignore the fact that a substantial proportion of the population consumes high amounts of trans fatty acids. For example, consumption may be ≥ 27 g/d in the United Kingdom for individuals with a diet high in fat, with hydrogenated fish oils as the major source (31). A working group of WHO/FAO reviewed the health effects of trans fatty acids and concluded that high intakes of trans fatty acids are undesirable and their consumption should be reduced (32). Although the US food industry has resisted change (15), the major European margarine and oil manufacturers have acknowledged the adverse effects of trans fat and have eliminated or greatly reduced amounts in margarines (33). From the changes in margarine alone, it was estimated that rates for CAD would be reduced by 5%. If such changes were made in the United States, this would reduce premature deaths by ~25 000/y.

Without greater availability of information on the trans fatty acid content of foods, health-conscious consumers are likely to be particularly mislead by claims of “low saturated fat” and “cooked in vegetable oil,” as those products may contain up to 35% trans fatty acids. Prudent dietary advice should aim to reduce specifically the amount of both saturated and trans fatty acids. This can be achieved by using vegetable oils in their natural, unhydrogenated form for frying, baking, and at the table and avoiding animal fats and commercial products baked or fried in hydrogenated fats, which include most fried fast foods, brands of potato and tortilla chips, donuts, crackers, cookies, and other bakery items. It is difficult to argue that consumers should not be allowed to make informed choices, which would require that food labels indicate the amount of trans fatty acids and that special labels be created for fast foods and other products with very high trans fatty acid contents and that are presently exempt from labeling requirements.

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REFERENCES