

Intake of *trans* fatty acids and risk of coronary heart disease among women

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Trans isomers of fatty acids, formed by the partial hydrogenation of vegetable oils to produce margarine and vegetable shortening, increase the ratio of plasma low-density-lipoprotein to high-density-lipoprotein cholesterol, so it is possible that they adversely influence risk of coronary heart disease (CHD). To investigate this possibility, we studied dietary data from participants in the Nurses' Health Study.

We calculated intake of *trans* fatty acids from dietary questionnaires completed by 85 095 women without diagnosed CHD, stroke, diabetes, or hypercholesterolaemia in 1980. During 8 years of follow-up, there were 431 cases of new CHD (non-fatal myocardial infarction or death from CHD). After adjustment for age and total energy intake, intake of *trans* isomers was directly related to risk of CHD (relative risk for highest vs lowest quintile 1.50 [95% CI 1.12-2.00], p for trend=0.001). Additional control for established CHD risk factors, multivitamin use, and intakes of saturated fat, monounsaturated fat, and linoleic acid, dietary cholesterol, vitamins E or C, carotene, or fibre did not change the relative risk substantially. The association was stronger for the 69 181 women whose margarine consumption over the previous 10 years had been stable (1.67 [1.05-2.66], p for trend=0.002). Intakes of foods that are major sources of *trans* isomers (margarine, cookies [biscuits], cake, and white bread) were each significantly associated with higher risks of CHD.

These findings support the hypothesis that consumption of partially hydrogenated vegetable oils may contribute to occurrence of CHD.

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Introduction

Trans isomers of fatty acids are formed when liquid vegetable oils are partially hydrogenated to form margarine and shortening. These processed vegetable fats, which many people use instead of animal fats containing saturated fat and cholesterol because of health concerns, contain between 5% and more than 30% of the isomers.¹ *Trans* isomers contribute to the hardness of the products; the carbon moieties on the two sides of a double bond provide a straight, closely packed configuration, whereas the *cis* isomers found in natural vegetable oils have a bent configuration.² *Trans* fatty acids are also formed in the rumen of cattle and make up about 5% of dairy and beef fat;³ however, the predominant isomer is structurally distinct from those derived from vegetable oils. *Trans* isomers are estimated to

constitute 5-6% of dietary fat consumed in the USA,⁴ but the proportion varies widely, depending on food choices.

There has been concern for some time that a high intake of *trans* isomers could adversely affect risk of coronary heart disease (CHD),⁵ partly because the straight configuration resembles that of saturated fats. Also, since many *trans* isomers are derived from the naturally occurring *cis*, *cis*-linoleic acid, a precursor of prostaglandins, they could have various effects on platelet activity and other important functions. Some, but not all, studies have shown moderate rises in serum total cholesterol with *trans* isomers.²

The 1985 review by the Federation of American Societies for Experimental Biology concluded that available laboratory evidence was not sufficient to implicate *trans* fatty acids as a cause of CHD; however, further investigation was recommended.⁴ Concern has been heightened by reports that replacement of naturally occurring fatty acid with *trans* isomers can increase concentrations of low-density-lipoprotein (LDL) cholesterol⁶⁻⁸ (and J. Judd, unpublished) and lipoprotein(a),^{8,9} and lower concentrations of high-density-lipoprotein (HDL) cholesterol^{6,7} (and J. Judd, unpublished).

To investigate whether a higher intake of *trans* isomers is associated with an increased risk of CHD, we studied dietary data collected in 1980 from participants in the Nurses' Health Study in relation to subsequent risk of CHD.

Subjects and methods

The Nurses' Health Study began in 1976, when 121 700 US female registered nurses completed questionnaires about their medical history, including previous cardiovascular disease, diabetes, hypertension, high serum cholesterol concentrations, and parental myocardial infarction.¹⁰ We also included questions on menopausal status, the use of postmenopausal hormones, cigarette smoking, height, and weight. Every 2 years, follow-up questionnaires were sent so that information could be updated and newly diagnosed major illnesses identified. In 1980 we collected data on usual dietary intake by means of a semiquantitative food frequency questionnaire developed and validated specifically for this study.^{11,12} We identified 61 foods that allowed maximum discrimination among intakes of total, saturated, and monounsaturated fats, linoleic acid (the most abundant polyunsaturated fat), cholesterol, *trans* fatty acids, and other nutrients. For each food, a commonly used unit or portion size (eg, one egg or one slice of bread) was specified, and the subject was

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TABLE I—RELATION OF POTENTIAL CHD RISK FACTORS TO ENERGY-ADJUSTED *TRANS*-FATTY-ACID INTAKE IN 1980*

	Quintile of <i>trans</i> -fatty-acid intake				
	1 (n = 16 768)	2 (n = 17 112)	3 (n = 17 067)	4 (n = 17 123)	5 (n = 17 025)
Mean intake of <i>trans</i> fatty acids (g/day)	2.4	3.2	3.9	4.5	5.7
% of group					
Current smokers	28	29	29	28	30
History of hypertension	16	14	14	14	14
Parental MI before 60 yr	14	14	14	14	14
Current postmenopausal hormone use	9	9	8	8	7
Vigorous exercise \geq 1 wk	50	46	43	41	35
Multivitamin use	42	36	33	31	28
Mean					
BMI (kg/m ²)	23.8	24.1	24.1	24.2	24.3
Saturated fat (g/day)	23.2	28.1	29.4	30.1	28.0
Monounsaturated fat (g/day)	21.7	27.3	29.8	31.7	31.3
Linoleic acid (g/day)	5.8	6.5	7.3	8.2	9.5
Cholesterol (mg/day)	326	341	340	337	308
Carotene (IU/day)	10 048	8479	7779	7067	6185
Dietary fibre (g/day)	19.3	17.5	16.3	15.4	14.0

*Directly age-standardised to distribution of whole cohort.
MI = myocardial infarction. BMI = body-mass index.

asked how often on average during the previous year she had consumed that amount. Nine responses were possible, ranging from "never" to "six or more times per day". For each food, we also asked whether intake had greatly increased or greatly decreased over the past 10 years. We asked about the type of margarine usually used (stick or tub) and types of fat used for frying, baking, and at the table. The intake of *trans* fatty acids and of other nutrients was calculated by multiplying the consumption frequency of each unit of food by the nutrient content of the specified portions. Values for total *trans* isomer contents of foods were based on analyses by Enig et al¹¹ and Slover, et al.¹³ We included all *trans* isomers of 18-carbon fatty acids. We divided the total intake of *trans* isomers into intakes from vegetable fat and from animal sources. Data for other dietary variables were obtained mainly from US Department of Agriculture sources.¹⁴ We adjusted nutrient values for total energy intake by regression analysis.¹² The adjustment for total energy intake is analogous to the isocaloric conditions used in feeding experiments to assess the effects of specific nutrients. For comparison with other data, we also calculated *trans*-fatty-acid intake as a percentage of total energy intake.

To assess the validity of our measure of *trans*-fatty-acid intake, we compared the intake calculated from a version of the dietary questionnaire used in a case-control study of breast cancer with the proportion of *trans* fatty acids in aspirates of adipose tissue measured by gas-liquid chromatography.¹⁵ Among 115 female controls, *trans* isomers made up 4.4% of adipose fatty acids and 5.8% of calculated fatty-acid intake. The correlation between calculated intake and measured amounts in adipose tissue was 0.51.

After up to four mailings, 98 464 women returned the 1980 dietary questionnaire. We excluded women who left ten or more food items blank, those who had implausibly high or low scores for total food intake, and those with previous diagnoses of angina, myocardial infarction, or stroke. Women reporting high serum cholesterol or diabetes were excluded because these disorders

increase the risk of CHD and could have caused women to change their diets. The final 1980 baseline population consisted of 85 095 women.

The study endpoint was incidence of CHD, defined as non-fatal myocardial infarction or death from CHD. Women who reported a non-fatal myocardial infarction on a follow-up questionnaire were asked for permission to review their medical records; the diagnosis was considered confirmed if WHO criteria (symptoms plus either rises in cardiac enzymes or diagnostic electrocardiographic changes)¹⁶ were satisfied. Myocardial infarctions that required hospital admission and for which confirmatory information was obtained by interview or letter, but for which no medical records were obtainable, were designated as probable (16%). Fatal CHD endpoints were initially ascertained by reports of family members and the National Death Index and documented by medical and death records;¹⁷ mortality follow-up was more than 98% complete. Medical records were reviewed by physicians unaware of questionnaire data.

Women were grouped in quintiles of intake of energy-adjusted *trans* fatty acids and other nutrients as calculated from the 1980 questionnaire. We also classified women according to their responses for individual foods. For most foods, we had to combine adjacent categories of responses in the original questions to provide sufficient women in a group; all such combining was done before analysis.

Proportional hazards models were used to estimate the relative risks (with 95% CI) of CHD associated with various intakes of *trans* fatty acids and other nutrients, with simultaneous adjustment for other risk factors. Follow-up for a subject was stopped at the time of death, myocardial infarction, or on May 31, 1988, whichever was first. Tests of trend across increasing quintiles of *trans*-fatty-acid intake were done by treating the five quintiles as a continuous variable and assigning the median intake for the quintile as its value. All *p* values are two tailed.

TABLE II—RELATIVE RISK OF CHD ACCORDING TO ENERGY-ADJUSTED INTAKE OF *TRANS*-FATTY ACIDS

	Relative risk (95% CI) in quintile					<i>p</i> (for trend)
	1	2	3	4	5	
No of cases	80	89	70	86	106	
Person-years follow-up	130 345	133 057	132 898	133 439	132 260	
Relative risk with adjustment for:						
Age only	1.0	1.15 (0.85-1.56)	1.03 (0.74-1.42)	1.16 (0.85-1.59)	1.50 (1.12-2.00)	0.001
Age and smoking	1.0	1.15 (0.85-1.56)	1.02 (0.74-1.42)	1.17 (0.86-1.60)	1.45 (1.08-1.94)	0.002
Standard risk factors*	1.0	1.12 (0.82-1.52)	0.97 (0.71-1.36)	1.12 (0.82-1.54)	1.35 (1.00-1.82)	0.009
Standard risk factors plus lipids†	1.0	1.15 (0.83-1.59)	1.03 (0.72-1.48)	1.22 (0.83-1.78)	1.57 (1.05-2.34)	0.002
Standard risk factors, lipids, and use of multivitamins	1.0	1.12 (0.81-1.55)	0.99 (0.69-1.43)	1.16 (0.80-1.70)	1.47 (0.98-2.20)	0.006

*Age, smoking, body-mass index, hypertension, alcohol intake, menopausal status, postmenopausal oestrogen use, energy intake, family history of myocardial infarction before age 60 yr.

†Intake of saturated fat, monounsaturated fat, and linoleic acid.

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TABLE III—RELATIVE RISK OF CHD IN RELATION TO ENERGY-ADJUSTED *TRANS*-FATTY-ACID INTAKE AMONG WOMEN WITHOUT CHANGE IN MARGARINE CONSUMPTION 1970-80*

	RR (95% CI) in quintile					p
	1	2	3	4	5	
Total <i>trans</i> isomers	1.0	1.23 (0.50-1.79)	1.11 (0.79-1.68)	1.36 (0.89-2.09)	1.67 (1.05-2.66)	0.002
Isomers from vegetable fats	1.0	1.43 (1.00-2.04)	1.11 (0.74-1.66)	1.39 (0.91-2.13)	1.78 (1.12-2.83)	0.009
Isomers from animal fats	1.0	0.76 (0.51-1.12)	0.69 (0.43-1.10)	0.55 (0.31-0.96)	0.59 (0.30-1.17)	0.230

*356 cases among 69 181 women, adjusted for age, smoking, body-mass index, hypertension, alcohol intake, menopausal status, postmenopausal oestrogen use, energy intake, dietary lipids, family history of myocardial infarction before age 60 yr, and multivitamin use.

Results

Among the 85 095 women followed for up to 8 years, there were 431 cases of CHD (324 non-fatal myocardial infarctions and 107 deaths from CHD) during 661 996 person-years of follow-up. The mean daily intake of total *trans* fatty acids in 1980 was 4.0 (SD 1.9) g or 5.8 (1.8)% of dietary fat. Median daily energy-adjusted *trans*-fatty-acid intake ranged from 2.4 g in the lowest quintile to 5.7 g in the highest (table I). Of the *trans*-isomer intake, 60% was from processed vegetable fats and 40% from animal sources, primarily beef and dairy fat.

Prevalence of current smoking, history of hypertension, parental myocardial infarction, and current postmenopausal oestrogen use did not vary significantly with intake of total *trans* fatty acids (table I). Although women with higher intakes of *trans* isomers tended to exercise less, their mean body-mass index was only slightly higher than that of women with lower intakes. As expected, intake of *trans* fatty acids was strongly associated with intake of other types of fat, especially monounsaturated fat and linoleic acid. These strong associations result partly from the inclusion of both *cis* and *trans* isomers in the calculations of monounsaturated fat and linoleic acid, as is standard practice. Intakes of carotene and dietary fibre and use of multivitamins were inversely associated with *trans*-fatty-acid consumption. In similar analyses for vegetable and animal sources of *trans* isomers, current cigarette smoking was less prevalent in the groups with higher consumption of vegetable sources but increased with higher intake of animal sources (lowest vs highest quintile, 31% vs 28% for vegetable sources and 25% vs 34% for animal sources). As expected, intakes of

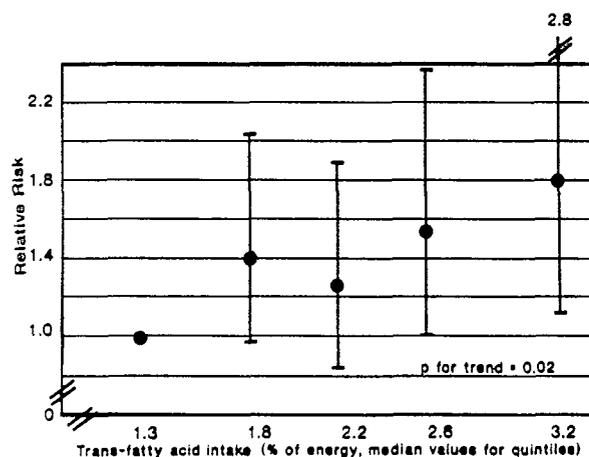
cholesterol and saturated fat were associated positively with animal *trans*-isomer intake and negatively with vegetable *trans*-isomer intake. Other variables were similarly related to intakes of animal and vegetable sources of *trans* isomers, except that the inverse relation with fibre intake was largely limited to animal sources.

When adjusted for age and total energy intake, intake of *trans* fatty acids was associated with a higher risk of CHD; the relative risk for the highest versus the lowest quintile was 1.50 (95% CI 1.12-2.00, *p* for trend = 0.001; table II). Adjustment for cigarette smoking, the strongest CHD risk factor in these data, decreased the relative risk only slightly. Further adjustment for other established CHD risk factors again slightly lowered the relative risk, but the trend with increasing intake remained significant.

The inclusion of other dietary fats in the analysis is very important because *trans*-isomer intake was strongly correlated with intake of monounsaturated fat and linoleic acid, both potentially protective against CHD. Additional adjustments individually for intake of monounsaturated fat or linoleic acid tended to increase the relative risk associated with intake of *trans* isomers. When linoleic acid, monounsaturated fat, and saturated fat were all added simultaneously to the model with established risk factors, the association between *trans*-isomer intake and CHD risk was a little stronger than that without these dietary lipids. Inclusion of multivitamin use, which was associated with lower risk of CHD, in the model with established risk factors and dietary lipids slightly reduced the association with *trans* isomers, but the trend remained significant. The 50% excess risk of CHD among women in the highest quintile of *trans*-isomer intake did not change appreciably and the tests for trends remained significant with further adjustments individually for intakes of carotene, vitamin E including supplements, vitamin C including supplements, dietary fibre, or cholesterol (data not shown). The inclusion of a term for vigorous physical activity did not affect the relative risks.

Because the relation of *trans*-fatty-acid intake to incidence of CHD could be distorted by alteration of diet in women who suspected they were at higher risk, we excluded at baseline those with previous angina, myocardial infarction, stroke, diabetes, or hypercholesterolaemia. To investigate further the possibility that some women might have suspected early, undiagnosed symptoms of CHD and thus substituted margarine for butter intake, we did an analysis excluding women who in 1980 reported that their margarine intake had greatly changed in previous 10 years (table III).

The association of *trans*-isomer intake with risk of CHD was somewhat stronger in this analysis; after adjustment for established risk factors and dietary lipids the relative risk (highest vs lowest quintile of *trans*-isomer intake) was 1.67 (95% CI 1.05-2.66). When intake of *trans* fatty acids was expressed as a percentage of total energy intake rather than adjusted for total energy intake by regression analysis, there was a similar significant relation (figure).



Relative risk of CHD by *trans*-fatty-acid intake as percentage of total energy.

Analysis for 69 181 women who in 1980 reported no change in margarine intake in previous 10 years. Relative risks from proportional hazards model controlling for age, standard risk factors, dietary lipids, and multiple vitamin use.

TABLE IV—INTAKE OF SPECIFIC FOODS IN RELATION TO RISK OF CHD AMONG 85 095 WOMEN*

	Relative risk (95% CI)						p (trend)
	< 1 per month	1-4 per month	2-4 per wk	5-6 per wk to 1 per day	2-3 per day	≥ 4 per day	
Margarine (teaspoon; 5 ml)	1.0	0.83 (0.50-1.38)	1.03 (0.71-1.50)	1.07 (0.80-1.42)	1.03 (0.77-1.38)	1.66 (1.10-2.49)	0.02
Beef, pork, lamb (main dish)	1.0	1.16 (0.59-2.26)	0.95 (0.48-1.86)	1.22† (0.61-2.43)	0.86
Cookie (1)	1.0	1.05 (0.81-1.36)	1.02 (0.75-1.39)	1.49 (1.09-2.04)	1.55† (1.02-2.34)	..	0.007
White bread (1 slice)	1.0	0.85 (0.59-1.24)	1.07 (0.78-1.47)	1.26 (0.96-1.66)	1.43† (1.08-1.90)	..	0.003

*From separate proportional hazards models, controlling for age, time period, body-mass index, alcohol intake, smoking, menopausal status, postmenopausal hormone use, family history of myocardial infarction before age 60 yr, history of hypertension, multivitamin use.
†Includes remaining frequency categories

The possibility that early symptoms of incipient CHD distorted the relation was further examined by dividing the follow-up into two 4-year periods (1980-84 and 1984-88). Positive trends with intake of *trans* isomers in 1980 were seen in both periods, but the association was slightly stronger during the second period (highest vs lowest quintile, relative risk = 1.55 for 1980-84 and 2.34 for 1984-88 in analyses adjusted for established risk factors and dietary lipids).

Trans fatty acids formed in the partial hydrogenation of vegetable oils differ structurally from those found in fat from ruminants; we therefore examined these sources separately in relation to risk of CHD (table III). The positive overall association was entirely accounted for by partially hydrogenated vegetable fats. By contrast, a non-significant inverse association was observed for *trans* isomers from animal fats.

To elucidate these relations further we identified the foods that contributed most to differences in total *trans*-isomer intake among study participants. By stepwise regression with energy-adjusted total *trans*-isomer intake as the dependent variable, each food was entered as a predictor variable. The four most important determinants were margarine, beef, pork, or lamb as a main dish, cookies (biscuits), and white bread (total $r^2 = 0.82$). We then examined each food in relation to risk of CHD by including them in models with control for age and other CHD risk factors (table IV). Women who ate four or more teaspoons of margarine (20 ml) per day were at higher risk of CHD (relative risk 1.66 [1.10-2.49]) than women who ate margarine less than once per month (p for trend = 0.02). When we examined associations for margarine in tub form or stick form separately, similar positive trends were seen for both (data not shown). Consumption of beef, pork, or lamb as a main dish was not significantly related to risk. However, consumption of cookies and white bread was significantly associated with higher risk of CHD. Intake of butter, not an important source of *trans* isomers, was not significantly associated with risk of CHD.

Discussion

In this large prospective cohort study we observed a positive association between intake of *trans* isomers of fatty acids and risk of CHD that was not accounted for by known risk factors, including other measured dietary variables. The positive association with total intake of *trans* isomers was due to intake of partially hydrogenated vegetable fats rather than isomers from ruminant sources.

One reason for concern that *trans*-isomer intake may increase the risk of CHD has been that consumption has greatly increased since the beginning of the century, at the same time as a major rise in CHD mortality.¹⁸ Since the mid 1960s, mortality from CHD has declined, as has intake of *trans* isomers as a percentage of total vegetable fat intake;¹⁸

the average absolute intake is also likely to have declined because both the *trans*-isomer composition of all fats produced in the USA⁴ and total fat intake per person¹⁹ decreased during this time. The reductions in intake are due largely to shifts towards softer margarines, which tend to have higher *cis*, *cis*-linoleic acid and lower *trans*-isomer content, and less hydrogenation of vegetable shortenings.²⁰ Our most recent analyses indicate that the *trans*-isomer content of margarines in the USA ranges between 7% and 24% of fatty acids, and that of vegetable shortening is about 15% (F. Slacks, personal communication). Also, production of partially hydrogenated cooking oils stopped in 1985-88. Although the intake of *trans* isomers generally followed the rise and subsequent decline of CHD in the USA during this century,¹⁸ data on time trends are difficult to interpret because many other factors vary simultaneously. In 1989-90 the US fast-food industry largely changed from use of beef tallow (3-5% *trans* isomers) to partially hydrogenated vegetable fats (about 30% *trans* isomers).²⁰ Thus, we found that the *trans*-isomer content of french fried potatoes from McDonald's and Burger King restaurants was between 24% and 35% of fatty acids. Pressures to avoid beef tallow and tropical oils are resulting in the substitution of partially hydrogenated vegetable fats in other products too.

In the only previous analytical study of *trans*-fatty-acid intake and risk of CHD the *trans*-isomer content of adipose fat was higher in people who died from ischaemic heart disease than among people dying from other causes.²¹ However, the study design did not allow for the control of other CHD risk factors. Moreover, in the part of the UK where that study took place, such isomers are largely derived from partially hydrogenated marine oils used for margarine. Although replication of that finding and ours is important, it may be complicated by the major changes in the processing of vegetable fats that have occurred over the past few years.

Although epidemiological data are limited, metabolic studies have contributed to concern about potential adverse effects of *trans* fatty acids on risk of CHD. Effects of *trans* isomers on total serum cholesterol varied in fourteen studies of this relation.² Mensink and Katan⁶ randomly allocated subjects 10% of energy as natural monounsaturated fat (oleic acid), saturated fat, or *trans* fatty acids (primarily elaidic acid, the main isomer in hydrogenated vegetable oils). The *trans* isomers increased LDL-cholesterol and decreased HDL-cholesterol while only slightly raising total cholesterol. After 3 weeks, the ratio of total to HDL cholesterol was significantly higher on the *trans*-fatty-acid diet than on the other diets. The results of a study in which *trans* isomers comprising 7.7% of energy were substituted for linoleic acid⁷ were similar, and in a third trial *trans* isomers increased LDL without a significant effect on HDL.⁸ In vitro, elaidic acid, but not oleic acid, increases the transfer of cholesteryl esters from HDL to LDL,²² which

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may account for these findings. *Trans* isomers seem to increase plasma lipoprotein(a) concentrations.^{8,9}

Trans fatty acids are closely related structurally to linoleic acid, and thus could interfere with important biological functions. *Trans* isomers may influence essential-fatty-acid metabolism by impairing the activity of $\Delta 6$, $\Delta 5$ desaturase, thus reducing the amount of arachidonic acid available, by interfering with other steps in the synthesis of eicosanoids from essential-fatty-acid precursors, and by becoming incorporated into membrane phospholipids and altering physical structure and function.²³ In vitro, collagen-induced platelet aggregation is inhibited less by *trans* than by *cis* isomers;²⁴ thrombogenesis may therefore be increased.

Our data on consumption of specific foods in relation to risk of CHD show that the association with *trans*-isomer intake is not derived from a single food or eating pattern; the use of margarine (as opposed to butter) is regarded by many as healthy eating behaviour. By contrast, consumption of cookies and white bread is widely considered less healthy. We found no association between red meat intake and CHD despite the fact that positive responses to this question were strongly associated with colon cancer risk.²⁵ This lack of association could be due to the distinct structure of the primary *trans* isomer in ruminant fat, *trans*-vaccenic acid, which has a double bond in the 11 as opposed to the 9 position in elaidic acid, the main *trans* isomer in partially hydrogenated vegetable oils.³ In human fibroblast cultures, elaidic acid inhibits $\Delta 6$ desaturase and fatty-acid synthesis to a greater degree than does *trans*-vaccenic acid.²⁶ On the other hand, the *trans*-isomer content of beef fat is low and most of the fatty acids are monounsaturated; these compounds have beneficial effects on blood lipids²⁷ and the susceptibility of LDL-cholesterol to oxidative modification.²⁸

Many sources of potential bias are limited by the prospective nature of this study. Nevertheless, it is possible that women with high intakes of *trans* isomers were at increased risk of CHD for other unknown reasons. A higher intake of animal sources of *trans* isomers was related to a general pattern of unhealthy behaviours, whereas it was the intake of vegetable sources that was associated with higher risk of CHD. We do not have evidence that the observed association is due to a general relation with less health-conscious behaviour. More direct data on the relation of intake of *trans* fatty acids and risk of CHD might be obtained from a randomised trial, but this does not seem feasible. Thus, findings from controlled metabolic studies, which indicate potentially adverse effects of these isomers, as well as other observational studies, will be important. Our study cannot distinguish the influence of the many specific isomers formed by the partial hydrogenation of vegetable oils, which include *cis* isomers with the double bonds in altered positions as well as various *trans*-isomers. Although this study included only women, the fact that blood lipids are related to intake of *trans* isomers similarly in men and in women suggests that the findings are likely to apply to men too.

Our findings must add to concern that the practice of partially hydrogenating vegetable oils to produce solid fats may have reduced the anticipated benefits of substituting these oils for highly saturated fats, and instead contributed to the occurrence of CHD.

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REFERENCES

- Enig MG, Pallansch LA, Sampugna J, Keeney M. Fatty acid composition of the fat in selected food items with emphasis on *trans* components. *J Am Oil Chem Soc* 1983; 60: 1788-94.
- Emken EA. Nutrition and biochemistry of *trans* and positional fatty acid isomers in hydrogenated oils. *Amu Rev Nutr* 1984; 4: 339-76.
- Parodi PW. Distribution of isomeric octadecenoic fatty acids in milk fat. *J Dairy Sci* 1976; 59: 1870-73.
- Senti FR, ed. Health aspects of dietary *trans* fatty acids: August 1985. Bethesda: Federation of American Societies for Experimental Biology, 1988.
- Kummerow FA. Nutrition imbalance and angiotoxins as dietary risk factors in coronary heart disease. *Am J Clin Nutr* 1979; 32: 58-83.
- Mensink RPM, 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.
- Nestel P, Noakes M, Belling B, et al. Plasma lipoprotein and Lp[a] changes with substitution of elaidic acid for oleic acid in the diet. *J Lipid Res* 1992; 33: 1029-36.
- Mensink RP, Zock PL, Katan MB, Hornstra G. Effect of dietary *cis* and *trans* fatty acids on serum lipoprotein [a] levels in humans. *J Lipid Res* 1992; 33: 1493-501.
- Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease. *N Engl J Med* 1991; 325: 756-62.
- Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semi-quantitative food frequency questionnaire. *Am J Epidemiol* 1985; 122: 51-65.
- Willett WC. Nutritional epidemiology. New York: Oxford University Press, 1989.
- Slover HT, Thompson RH Jr, Davis CS, Merola GV. Lipids in margarines and margarine-like foods. *J Am Oil Chem Soc* 1985; 62: 775-86.
- Department of Agriculture. Agricultural handbook no 8 series. Composition of foods—raw, processed, and prepared. Washington, DC: Government Printing Office, 1963-88.
- London SJ, Sacks FM, Caesar J, Stampfer MJ, Siguel E, Willett WC. Fatty acid composition of subcutaneous adipose tissue and diet in postmenopausal US women. *Am J Clin Nutr* 1991; 54: 340-45.
- WHO. IHD registers: report of the fifth working group. Copenhagen: WHO, 1971.
- Stampfer MJ, Willett WC, Speizer FE, et al. Test of the National Death Index. *Am J Epidemiol* 1984; 119: 837-39.
- Booyens J, Louwrens CC. The Eskimo diet: prophylactic effects ascribed to the balanced presence of natural *cis* unsaturated fatty acids and the absence of unnatural *trans* and *cis* isomers of unsaturated fatty acids. *Med Hypoth* 1986; 21: 387-408.
- Stephan AM, Wald NJ. Trends in individual consumption of dietary fat in the United States, 1920-1984. *Am J Clin Nutr* 1990; 52: 457-69.
- Hunter JE, Applewhite TH. Reassessment of *trans* fatty acid availability in the US diet. *Am J Clin Nutr* 1991; 54: 363-69.
- Thomas LH, Winter JA, Scott RG. Concentration of 18:1 and 16:1 transunsaturated fatty acids in the adipose body tissue of decedents dying of ischemic heart disease compared with controls: analysis by gas liquid chromatography. *J Epidemiol Commun Health* 1983; 37: 16-21.
- Lagrost L. Differential effects of *cis* and *trans* fatty acid isomers, oleic and elaidic acids, on the cholesteryl ester transfer protein activity. *Biochim Biophys Acta* 1992; 1124: 159-62.
- Kinsella JE, Bruckner G, Mai J, Shimp J. Metabolism of *trans* fatty acids with emphasis on the effects of *trans*, *trans*-octadecadienoate on lipid composition, essential fatty acids, and prostaglandins: an overview. *Am J Clin Nutr* 1981; 34: 2307-18.
- Peacock LIL, Wahl KWJ. Isomeric *cis* and *trans* fatty acids and porcine platelet reactivity to collagen *in vitro*. *Biochem Soc Trans* 1988; 16: 291.
- Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. *N Engl J Med* 1990; 323: 1664-72.
- Rosenthal MD, Whitehurst MC. Selective effects of isomeric *cis* and *trans* fatty acids on fatty acyl D9 and D6 desaturation by human skin fibroblasts. *Biochim Biophys Acta* 1983; 753: 450-59.
- Mensink RP, Katan MB. Effect of monounsaturated fatty acids versus complex carbohydrates on high-density lipoproteins in healthy men and women. *Lancet* 1987; i: 122-25.
- Parthasarathy S, Khoo JC, Miller E, Barnett J, Witztum JL, Steinberg D. Low density lipoprotein rich in oleic acid is protected against oxidative modification: implications for dietary prevention of atherosclerosis. *Proc Natl Acad Sci USA* 1990; 87: 3894-98.

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