

DIETARY FAT INTAKE AND THE RISK OF CORONARY HEART DISEASE
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BERNARD A. ROSNER, Ph.D., CHARLES H. HENNEKENS, M.D., AND WALTER C. WILLETT, M.D.**ABSTRACT**

Background The relation between dietary intake of specific types of fat, particularly trans unsaturated fat, and the risk of coronary disease remains unclear. We therefore studied this relation in women enrolled in the Nurses' Health Study.

Methods We prospectively studied 80,082 women who were 34 to 59 years of age and had no known coronary disease, stroke, cancer, hypercholesterolemia, or diabetes in 1980. Information on diet was obtained at base line and updated during follow-up by means of validated questionnaires. During 14 years of follow-up, we documented 939 cases of non-fatal myocardial infarction or death from coronary heart disease. Multivariate analyses included age, smoking status, total energy intake, dietary cholesterol intake, percentages of energy obtained from protein and specific types of fat, and other risk factors.

Results Each increase of 5 percent of energy intake from saturated fat, as compared with equivalent energy intake from carbohydrates, was associated with a 17 percent increase in the risk of coronary disease (relative risk, 1.17; 95 percent confidence interval, 0.97 to 1.41; $P=0.10$). As compared with equivalent energy from carbohydrates, the relative risk for a 2 percent increment in energy intake from trans unsaturated fat was 1.93 (95 percent confidence interval, 1.43 to 2.61; $P<0.001$); that for a 5 percent increment in energy from monounsaturated fat was 0.81 (95 percent confidence interval, 0.65 to 1.00; $P=0.05$); and that for a 5 percent increment in energy from polyunsaturated fat was 0.62 (95 percent confidence interval, 0.46 to 0.85; $P=0.003$). Total fat intake was not significantly related to the risk of coronary disease (for a 5 percent increase in energy from fat, the relative risk was 1.02; 95 percent confidence interval, 0.97 to 1.07; $P=0.55$). We estimated that the replacement of 5 percent of energy from saturated fat with energy from unsaturated fats would reduce risk by 42 percent (95 percent confidence interval, 23 to 56; $P<0.001$) and that the replacement of 2 percent of energy from trans fat with energy from unhydrogenated, unsaturated fats would reduce risk by 53 percent (95 percent confidence interval, 34 to 67; $P<0.001$).

Conclusions Our findings suggest that replacing saturated and trans unsaturated fats with unhydrogenated monounsaturated and polyunsaturated fats is more effective in preventing coronary heart disease in women than reducing overall fat intake. (N Engl J Med 1997;337:1491-9.)

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LOW-FAT, high-carbohydrate diets have been widely recommended as a way to reduce the risk of coronary heart disease because populations with low intakes of saturated and total fat tend to be at low risk and because saturated fat increases low-density lipoprotein (LDL) cholesterol levels.¹ However, low-fat, high-carbohydrate diets also reduce high-density lipoprotein (HDL) cholesterol levels and raise fasting levels of triglycerides.² Because low levels of HDL cholesterol and high levels of triglycerides independently increase risk, the value of replacing fat in general with carbohydrates has been questioned.³ Replacing saturated fat and trans unsaturated fat with unhydrogenated unsaturated fats has clear beneficial effects on blood lipids² and thus provides an alternative strategy for reducing the risk of coronary heart disease.

The results of prospective epidemiologic investigations of dietary fat and coronary disease have been inconsistent. A significant positive association between saturated fat and disease was found in two studies,^{4,5} but not in others.⁶⁻¹¹ A significant inverse association between polyunsaturated-fat intake and the risk of disease was found in only one study.⁹ The interpretation of these findings is complicated by the small size of the studies, inadequate dietary assessment, incomplete adjustment for energy intake, failure to account for trans isomers of unsaturated fats, and lack of control for other types of fat.¹² Repeated measurements of dietary components were rarely obtained during follow-up. Moreover, previous research on the relation of dietary fat to the risk of coronary disease has focused primarily on men.^{4-11,13-15}

We previously reported on the relation of dietary intake of trans unsaturated fat to the incidence of coronary disease among women in the Nurses' Health Study over an eight-year period.¹⁶ The present analyses extend those findings to a total of 14 years of follow-up to examine the effect of total dietary fat and specific major types of fat and to estimate the effects of substituting carbohydrates or unsaturated fat for saturated fat and trans unsaturated fat.

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METHODS

The Nurses' Health Study Cohort

The Nurses' Health Study was established in 1976, when 121,700 female nurses who were then 30 to 55 years of age completed a mailed questionnaire on their medical history and lifestyle. Every two years, follow-up questionnaires have been sent to obtain up-to-date information on risk factors and to identify newly diagnosed diseases. In 1980, a 61-item food-frequency questionnaire was included to assess dietary intake of specific fats and other nutrients. In 1984, the dietary questionnaire was expanded to include 116 items. Similar questionnaires were used to obtain current information on diet in 1986 and 1990.

After up to four mailings, 98,462 women returned the 1980 diet questionnaire. We excluded those with 10 or more blank items, those with implausibly high or low scores for total food or energy intake (<500 kcal or >3500 kcal per day), and those with previously diagnosed cancer, angina, myocardial infarction, stroke, or other cardiovascular diseases. Women reporting high serum cholesterol levels or diabetes were excluded from the present analyses because these disorders are associated with coronary heart disease and also could have caused women to change their diets. The final 1980 base-line population consisted of 80,082 women; over 90 percent responded to the subsequent biennial questionnaires and about 80 percent completed the food-frequency questionnaires during follow-up.

The Semiquantitative Food-Frequency Questionnaires

A detailed description of the food-frequency questionnaires and documentation of their reproducibility and validity have been published elsewhere.¹² A common unit or portion size for each food (e.g., one egg or one slice of bread) was specified, and participants were asked how often, on average, they had consumed that amount of the item during the previous year. The nine responses ranged from "never or less than once per month" to "six or more times per day." We also inquired about types of fat or oil used for frying, for baking, and at the table and the type of margarine usually used (stick or tub in 1980 and 1984 and brand and type in 1986 and 1990).

Nutrient intake was computed by multiplying the frequency of consumption of each food by the nutrient content of the specified portion, taking into account the type of fat used in preparation. Values for the amounts of dietary fats and other nutrients in the foods were obtained from the Harvard University Food Composition Database (completed on November 22, 1993), derived from Department of Agriculture sources¹⁷ and supplemented with information from manufacturers. Values for total trans isomer contents of foods were based on analyses by Enig et al.¹⁸ and Slover et al.¹⁹ We included all trans isomers of 18-carbon unsaturated fatty acids. The polyunsaturated fat for which data are reported in this study was the n-6 polyunsaturated fat linoleic acid (comprising 81 percent of total polyunsaturated fat in this population).

Both the original and the revised questionnaires provided a reasonable measure of total and specific types of fat when compared with four one-week dietary records (correlation coefficients for total and specific types of fat assessed by the dietary records and the food-frequency questionnaires ranged from 0.46 to 0.58 for the 1980 questionnaire and from 0.48 to 0.68 for the longer questionnaire used in 1984, 1986, and 1990).¹² The correlation between the calculated dietary intake of trans unsaturated fatty acids and the proportion of trans unsaturated fatty acids in adipose tissue was 0.51.²⁰

Identification of Cases of Coronary Heart Disease

The primary end point for this study was nonfatal myocardial infarction or fatal coronary disease occurring after the return of the 1980 questionnaire but before June 1, 1994. We sought to review the medical records of all women for whom such events

were reported. Records were reviewed by study physicians who had no knowledge of the women's risk-factor status as reported on their questionnaires. Myocardial infarction was confirmed if it met the World Health Organization's criteria — that is, symptoms plus either diagnostic electrocardiographic changes or elevated levels of cardiac enzymes.²¹ Infarctions that required hospital admission and for which confirmatory information was obtained by interview or letter, but for which no medical records were available, were designated as probable (17 percent). We included all confirmed and probable cases in our analyses because the results were the same when we analyzed only the confirmed cases after excluding probable cases.

Deaths were identified from state vital records and the National Death Index or reported by the women's next of kin or the postal system. Follow-up for the deaths was over 98 percent complete. Fatal coronary disease was considered to have occurred if there was fatal myocardial infarction confirmed by hospital records or on autopsy or if coronary disease was listed as the cause of death on the death certificate, if it was the underlying and most plausible cause, and if evidence of previous coronary disease was available.

Statistical Analysis

Person-time for each participant was calculated from the date of return of the 1980 questionnaire to the first end point, death, or June 1, 1994. Women who had reported having cardiovascular disease or cancer on previous questionnaires were excluded from subsequent follow-up; thus, each participant could contribute only one end point, and the cohort at risk included only those who remained free of both a cardiovascular end point and cancer at the beginning of each two-year follow-up interval.

Women were divided into five roughly equal groups according to quintiles for the percentage of energy obtained from each type of fat. Incidence was calculated by dividing the number of events by the person-time of follow-up in each quintile. For each type of fat, the relative risk was computed as the rate in a specific quintile divided by that in the group with the lowest intake, with adjustment for five-year age categories. In multivariate nutrient-density models,¹² we simultaneously included energy intake, the percentages of energy derived from protein and specific types of fat, and other potentially confounding variables. We also considered dietary fats as continuous variables. The coefficients from these models can be interpreted as the estimated effect of substituting a specific percentage of energy from fat for the same percentage of energy from carbohydrates. When estimating the effects of substituting one type of fat for another, using the difference in coefficients from the same model, we calculated the percentage reductions in risk and their 95 percent confidence intervals.¹² To estimate the effects of substituting unhydrogenated unsaturated fat for saturated fat or trans unsaturated fat, the model included saturated fat, trans unsaturated fat, and the sum of monounsaturated and polyunsaturated fats.

In order to represent long-term dietary patterns of individual subjects as accurately as possible, we used pooled logistic regression²² to model the incidence of coronary disease in relation to the cumulative average fat intake from all available dietary questionnaires up to the start of each two-year follow-up interval. For example, the incidence of coronary disease from 1980 through 1984 was related to the fat intake reported on the 1980 questionnaire, and incidence from 1984 through 1986 was related to the average intake reported on the 1980 and 1984 questionnaires. Because changes in diet after the development of intermediate end points such as angina, hypercholesterolemia, diabetes, and hypertension may confound the associations between diet and disease,²³ we stopped updating information on diet at the beginning of the interval during which those intermediate end points developed in an individual subject. We also conducted analyses relating incidence to fat intake as reported on the base-line (1980) dietary questionnaire. Nondietary covariates, including age, cigarette smoking, body-mass index (defined as the weight in kilograms divided by the square of the height in meters), postmeno-

pausal hormone use, consumption of alcohol, multivitamin use, and use of vitamin E supplements, were updated every two years. Aspirin use was assessed in 1980, 1982, 1984, and 1988. Whether the women engaged in vigorous exercise was assessed in 1980. All reported P values are two-sided.

RESULTS

During 1,057,269 person-years of follow-up from 1980 through 1994, we documented 658 nonfatal infarctions and 281 deaths from coronary heart disease. The dietary intakes of specific types of fat tended to be positively correlated with one another (Table 1), partly because of shared food sources, but the degree of correlation was high only between saturated and monounsaturated fats. The intake of each type of fat at base line was inversely associated with the consumption of folate, fiber, and alcohol, use of multivitamin and vitamin E supplements, and vigorous exercise (Table 2).

In age-adjusted analyses, a higher total fat intake was significantly associated with increased risk (Table 3). However, the association virtually disappeared in the multivariate analysis, primarily because of confounding by smoking, but also in part because of adjustment for alcohol use, vigorous exercise, and vitamin E supplementation. Adjustment for body-

TABLE 1. MEAN INTAKE AND CORRELATION OF SPECIFIC TYPES OF DIETARY FAT AT BASE LINE IN 1980.

VARIABLE	SATURATED FAT	MONO-UNSATURATED FAT	POLY-UNSATURATED FAT	TRANS UN-SATURATED FAT
Mean intake (% of energy)	15.6	16.0	4.3	2.2
Pearson correlation coefficient				
Correlation				
Saturated fat	1.0	—	—	—
Monounsaturated fat	0.81	1.0	—	—
Polyunsaturated fat	0.01	0.30	1.0	—
Trans unsaturated fat	0.30	0.55	0.59	1.0

mass index had no further effect. When total fat was entered into the multivariate model as a continuous variable, the relative risk was 1.02 (95 percent confidence interval, 0.97 to 1.07; $P=0.55$) for an increase of 5 percent in energy obtained from total fat, as compared with the equivalent energy obtained from carbohydrates.

TABLE 2. BASE-LINE CHARACTERISTICS AND RISK FACTORS FOR CORONARY HEART DISEASE ACCORDING TO THE INTAKE OF SPECIFIC TYPES OF FAT AT BASE LINE IN 1980.*

VARIABLE	SATURATED FAT			MONOUNSATURATED FAT			POLYUNSATURATED FAT			TRANS UNSATURATED FAT		
	INTER-LOWEST	INTER-MEDIATE	HIGHEST	INTER-LOWEST	INTER-MEDIATE	HIGHEST	INTER-LOWEST	INTER-MEDIATE	HIGHEST	INTER-LOWEST	INTER-MEDIATE	HIGHEST
mean value												
Age — yr	47	46	46	47	46	46	47	46	45	47	46	45
Body-mass index	24	24	24	24	24	24	24	24	24	24	24	24
Alcohol — g/day	9	6	5	9	7	4	10	6	5	10	6	4
Cholesterol — mg/1000 kcal/day	183	210	245	187	211	243	214	216	203	218	213	206
Folate — μ g/day†	434	358	306	442	363	298	398	359	340	450	352	303
Vitamin B ₆ — mg/day‡	3	3	3	4	3	3	3	3	3	4	3	2
Fiber — g/day	17	13	10	17	13	11	14	13	13	16	13	12
percent of women												
Parental history of myocardial infarction before 65 yr	20	20	20	21	20	20	20	20	20	20	20	20
Current smoking	27	27	33	27	27	32	32	27	28	28	28	30
History of hypertension	15	14	13	15	14	14	16	14	13	14	14	14
Multivitamin use	37	34	31	38	34	30	36	34	32	41	33	27
Vitamin E supplement use	16	12	11	16	12	11	13	12	13	19	11	9
Vigorous exercise‡	50	45	40	51	45	40	49	45	41	53	45	37
Regular aspirin use§	45	47	46	45	47	46	45	47	47	44	48	47
Current estrogen-replacement therapy (postmenopausal women only)	15	15	15	15	15	16	16	15	15	16	15	14

*Values have been adjusted for age. The women were divided into five groups for each type of fat according to quintiles for dietary intake. "Lowest" denotes the first quintile, "intermediate" the third quintile, and "highest" the fifth quintile.

†The values for folate and vitamin B₆ include multivitamin supplements.

‡Vigorous exercise was defined as vigorous exercise one or more times per week.

§Regular aspirin use was defined as aspirin use one or more times per week.

TABLE 3. RELATIVE RISK OF CORONARY HEART DISEASE ACCORDING TO QUINTILES OF SPECIFIC TYPES OF DIETARY FAT, DIETARY CHOLESTEROL, AND KEYS SCORE.*

VARIABLE†	QUINTILE					P FOR TREND
	1	2	3	4	5	
Total fat						
Intake (% of energy)	29.1	33.9	37.1	40.6	46.1	
RR (95% CI)						
Age-adjusted	1.0	1.02 (0.83–1.26)	1.08 (0.88–1.32)	0.99 (0.80–1.23)	1.30 (1.07–1.58)	0.02
Multivariate	1.0	0.91 (0.74–1.13)	1.01 (0.82–1.25)	1.03 (0.83–1.27)	1.04 (0.83–1.28)	0.50
Animal fat						
Intake (% of energy)	17.4	21.6	25.1	29.2	36.4	
RR (95% CI)						
Age-adjusted	1.0	0.97 (0.78–1.19)	0.96 (0.78–1.19)	1.05 (0.86–1.30)	1.30 (1.06–1.58)	0.001
Multivariate	1.0	1.01 (0.81–1.26)	0.89 (0.70–1.12)	1.13 (0.90–1.41)	1.17 (0.92–1.48)	0.05
After additional adjustment for vegetable and trans unsaturated fats	1.0	0.97 (0.78–1.21)	0.82 (0.64–1.04)	1.01 (0.79–1.27)	0.97 (0.74–1.26)	0.55
Vegetable fat						
Intake (% of energy)	5.4	8.8	11.2	13.5	17.2	
RR (95% CI)						
Age-adjusted	1.0	0.87 (0.72–1.06)	0.88 (0.73–1.07)	0.93 (0.76–1.13)	0.82 (0.67–1.01)	0.12
Multivariate	1.0	0.85 (0.70–1.04)	1.03 (0.84–1.25)	0.90 (0.73–1.12)	0.79 (0.63–1.00)	0.09
After additional adjustment for animal and trans unsaturated fats	1.0	0.82 (0.67–1.01)	0.96 (0.78–1.20)	0.82 (0.64–1.04)	0.67 (0.51–0.88)	0.009
Saturated fat						
Intake (% of energy)	10.7	12.8	14.3	16.0	18.8	
RR (95% CI)						
Age-adjusted	1.0	0.97 (0.79–1.20)	1.00 (0.81–1.24)	1.11 (0.91–1.37)	1.38 (1.13–1.68)	<0.001
Multivariate	1.0	0.91 (0.73–1.14)	0.90 (0.72–1.12)	1.12 (0.90–1.38)	1.16 (0.93–1.44)	0.04
After additional adjustment for mono-unsaturated, polyunsaturated, and trans unsaturated fats	1.0	0.87 (0.68–1.11)	0.85 (0.65–1.11)	1.05 (0.79–1.40)	1.07 (0.77–1.48)	0.37
Monounsaturated fat						
Intake (% of energy)	11.0	13.1	14.6	16.3	19.3	
RR (95% CI)						
Age-adjusted	1.0	1.03 (0.83–1.27)	1.18 (0.96–1.44)	1.15 (0.93–1.41)	1.30 (1.07–1.59)	0.004
Multivariate	1.0	1.08 (0.87–1.34)	1.05 (0.84–1.30)	1.12 (0.90–1.39)	1.18 (0.95–1.46)	0.14
After additional adjustment for saturated, polyunsaturated, and trans unsaturated fats	1.0	1.11 (0.86–1.43)	1.05 (0.79–1.41)	1.03 (0.74–1.43)	0.95 (0.64–1.39)	0.57
Polyunsaturated fat						
Intake (% of energy)	2.9	3.9	4.6	5.3	6.4	
RR (95% CI)						
Age-adjusted	1.0	0.92 (0.76–1.11)	0.92 (0.76–1.12)	0.91 (0.74–1.10)	0.89 (0.73–1.09)	0.28
Multivariate	1.0	0.99 (0.82–1.20)	0.97 (0.79–1.18)	0.93 (0.76–1.15)	0.83 (0.67–1.02)	0.07
After additional adjustment for saturated, monounsaturated, and trans unsaturated fats	1.0	0.94 (0.77–1.14)	0.88 (0.71–1.14)	0.81 (0.65–1.03)	0.68 (0.53–0.88)	0.003
Trans unsaturated fat						
Intake (% of energy)	1.3	1.7	2.0	2.4	2.9	
RR (95% CI)						
Age-adjusted	1.0	1.07 (0.86–1.32)	1.21 (0.98–1.49)	1.21 (0.99–1.49)	1.34 (1.09–1.64)	0.002
Multivariate	1.0	1.07 (0.86–1.33)	1.10 (0.89–1.37)	1.13 (0.91–1.39)	1.27 (1.03–1.56)	0.02
After additional adjustment for saturated, monounsaturated, and polyunsaturated fats	1.0	1.09 (0.87–1.37)	1.16 (0.91–1.47)	1.24 (0.96–1.60)	1.53 (1.16–2.02)	0.002
Cholesterol						
Intake (% of energy)	132	163	188	217	273	
RR (95% CI)						
Age-adjusted	1.0	1.16 (0.95–1.43)	1.09 (0.88–1.33)	1.08 (0.88–1.33)	1.12 (0.91–1.38)	0.49
Multivariate	1.0	1.19 (0.96–1.47)	1.14 (0.91–1.42)	1.32 (1.06–1.65)	1.25 (0.99–1.58)	0.07
After additional adjustment for saturated, monounsaturated, polyunsaturated, and trans unsaturated fats	1.0	1.15 (0.93–1.43)	1.08 (0.87–1.36)	1.24 (0.99–1.56)	1.17 (0.92–1.50)	0.24
Keys score‡						
Intake (% of energy)	35.7	41.8	46.6	52.1	61.1	
RR (95% CI)						
Age-adjusted	1.0	1.09 (0.88–1.36)	1.06 (0.85–1.32)	1.31 (1.07–1.61)	1.32 (1.08–1.63)	0.002
Multivariate	1.0	1.09 (0.87–1.37)	1.16 (0.93–1.44)	1.35 (1.09–1.68)	1.27 (1.02–1.60)	0.01

*Values for intake are medians for each quintile, computed as the cumulative updated average (see the Methods section). RR denotes relative risk, and CI confidence interval.

†The multivariate models included the following: age (5-year categories); time period (7 periods); body-mass index (5 categories); cigarette smoking (never, past, and current smoking of 1 to 14, 15 to 24, and ≥25 cigarettes per day); menopausal status (premenopausal, postmenopausal without hormone-replacement therapy, postmenopausal with past hormone-replacement therapy, and postmenopausal with current hormone-replacement therapy); parental history of myocardial infarction before 65 years of age; multivitamin use; vitamin E supplement use; alcohol consumption (4 categories); history of hypertension; aspirin use (none, 1 to 6 times per week, ≥7 times per week, and dose unknown); vigorous exercise ≥1 time per week; percentage of energy from protein; and total energy intake. Dietary cholesterol was also included in models for total and specific fats.

‡Keys score = 1.26(2S - P) + 1.5(√C), where S and P are the percentages of total energy from saturated and polyunsaturated fats, respectively, and C is the daily cholesterol intake in milligrams per 1000 kcal. Higher scores indicate higher projected changes in serum cholesterol (milligrams per deciliter).

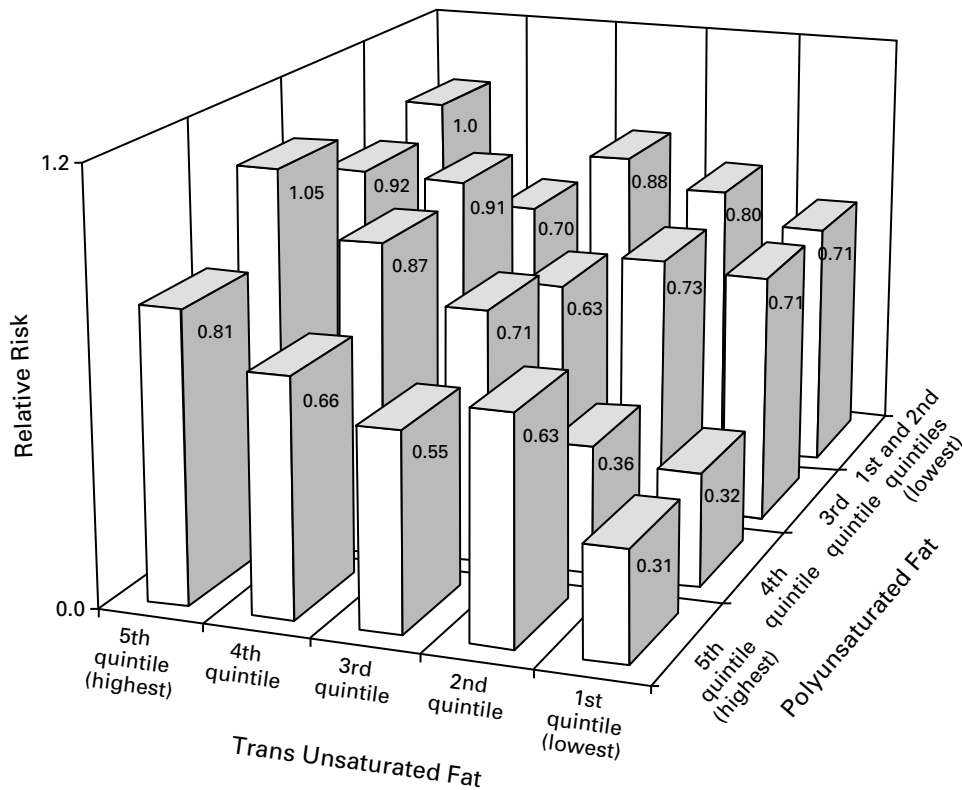


Figure 1. Multivariate Relative Risk of Coronary Heart Disease According to Dietary Intake of Trans Unsaturated and Polyunsaturated Fats.

The first and second quintiles for polyunsaturated-fat intake were combined to provide a sufficient number of women in each of the categories. The relative risks have been adjusted for age, time interval, body-mass index, cigarette smoking, menopausal status, parental history of premature myocardial infarction, use of multivitamins, use of vitamin E supplements, alcohol consumption, history of hypertension, aspirin use, physical activity, percentage of energy obtained from protein, saturated fat, and monounsaturated fat, dietary cholesterol, and total energy intake. The reference group for all comparisons was the women with the highest intake of trans unsaturated fat and the lowest intake of polyunsaturated fat.

The intakes of animal fat, saturated fat, monounsaturated fat, and trans unsaturated fat and the Keys score (which measures the projected change in the serum cholesterol concentration due to changes in the intakes of specific fats and cholesterol)²⁴ were each associated with an increased risk of disease in age-adjusted analyses (Table 3). After multivariate adjustment, all associations were attenuated, largely because of control for smoking, but the trends remained significant for trans unsaturated fats and the Keys score.

Because major food sources of monounsaturated fat in the United States (beef, dairy fats, and partially hydrogenated vegetable oil) can also have a high saturated, trans unsaturated, or polyunsaturated fat content, we included all four types simultaneously in our multivariate analyses (Table 3). In the adjusted analyses, the overall direction of the association for monounsaturated fat reversed, and there was a slight trend toward decreasing risk from the second to the

fifth quintiles with respect to monounsaturated-fat intake. Because an important source of polyunsaturated fat as well as trans unsaturated fat is partially hydrogenated vegetable oil, the associations for both polyunsaturated and trans unsaturated fats in this multivariate analysis became stronger. When these two fats were examined in combination (Fig. 1), risk was the lowest among those who had the lowest intake of trans unsaturated fat and the highest intake of polyunsaturated fat (e.g., those who consumed unhydrogenated soybean or corn oil instead of hard margarine) (relative risk, 0.31; 95 percent confidence interval, 0.11 to 0.88; $P=0.01$).

Next, we treated the percentages of total energy obtained from specific types of fat as continuous variables, with adjustment for the intake of other types (Table 4). We observed positive associations between the incidence of coronary heart disease and the intake of saturated fat ($P=0.10$) and trans unsaturated fat ($P<0.001$) and inverse associations

TABLE 4. MULTIVARIATE RELATIVE RISK OF CORONARY HEART DISEASE ASSOCIATED WITH INCREASES IN THE PERCENTAGE OF ENERGY FROM SPECIFIC TYPES OF FAT AND INCREASES IN DIETARY CHOLESTEROL.*

VARIABLE	UPDATED DIETARY INFORMATION		BASE-LINE DIETARY INFORMATION ONLY	
	RR (95% CI)	P VALUE	RR (95% CI)	P VALUE
Saturated fat (each increase of 5% of energy)	1.17 (0.97–1.41)	0.10	1.14 (0.97–1.34)	0.12
Monounsaturated fat (each increase of 5% of energy)	0.81 (0.65–1.00)	0.05	0.84 (0.70–1.01)	0.06
Polyunsaturated fat (each increase of 5% of energy)	0.62 (0.46–0.85)	0.003	0.74 (0.55–1.00)	0.05
Trans unsaturated fat (each increase of 2% of energy)	1.93 (1.43–2.61)	<0.001	1.62 (1.23–2.13)	<0.001
Cholesterol (each increase of 200 mg/1000 kcal)	1.12 (0.91–1.40)	0.29	1.07 (0.88–1.30)	0.50

*The multivariate models included the variables listed in Table 3. Intakes of specific types of fat and cholesterol were entered into the model simultaneously, so that the effects of fats were compared with those of an equivalent amount of energy from carbohydrates. RR denotes relative risk, and CI confidence interval.

with monounsaturated fat ($P=0.05$) and polyunsaturated fat ($P=0.003$). These associations did not differ significantly between current smokers and nonsmokers. The positive association for dietary cholesterol intake was not significant, whether we used the linear values or the square root of cholesterol intake in the analysis. The analyses using only base-line diet yielded qualitatively similar but somewhat weaker results (Table 4). Using the model for updated dietary information in Table 4, we estimated the effects of various isocaloric dietary substitutions on the risk of coronary disease (Fig. 2). Replacing 5 percent of energy from saturated fat with energy from unsaturated fats was associated with a 42 percent lower risk (95 percent confidence interval, 23 to 56 percent; $P<0.001$), and replacing 2 percent of energy from trans unsaturated fat with energy from unhydrogenated, unsaturated fats was associated with a 53 percent lower risk (95 percent confidence interval, 34 to 67 percent; $P<0.001$).

To examine further the relation of different types of fat to the risk of coronary disease, we included simultaneously in a multivariate model the intake of vegetable fats and that of animal fats, while controlling for the intake of trans unsaturated fat and other potentially confounding variables. The use of more vegetable fat was associated with a reduced risk (relative risk, 0.84 for each increase of 5 percent of energy, 95 percent confidence interval, 0.76 to 0.94; $P=0.001$), and animal fat had no significant association with disease (relative risk, 0.98 for each increase of 5 percent of energy; 95 percent confidence interval, 0.92 to 1.03; $P=0.40$).

In further analyses, control for diabetes and hypercholesterolemia diagnosed during follow-up in the multivariate model did not materially alter the results. An analysis in which only the most recent dietary data were included yielded qualitatively similar results. The results were also similar when we excluded events that occurred during the first four years of follow-up in order to avoid changes in diet

that may have been due to the presence of preclinical conditions and when we excluded participants who failed to complete any one of the dietary questionnaires during follow-up. Because of the strong correlation between the intakes of saturated and monounsaturated fats, we conducted an analysis in which we eliminated monounsaturated fat from the model; the associations for other fats were only slightly weakened.

DISCUSSION

In this large, prospective study of women, we found that a higher dietary intake of saturated fat and trans unsaturated fat was associated with an increased risk of coronary disease, whereas a higher intake of monounsaturated and polyunsaturated fats was associated with a decreased risk. Because of the opposite effects of different fats on incidence, total fat intake was not significantly related to the risk of coronary disease. The observed relation for saturated fat was much weaker than that predicted by international comparisons,¹ suggesting that the international analysis is seriously confounded by other lifestyle factors.³ However, our findings are consistent with the small-to-negligible effect predicted by metabolic studies of the relation of diet and blood lipid levels. For example, Krauss et al.²⁵ have estimated that replacing 4 percent of energy from saturated fat with an equivalent amount of energy from carbohydrates would reduce the rate of coronary disease by about 5 percent. If changes in HDL cholesterol are also considered, however, no effect would be anticipated.¹¹ As predicted by metabolic studies,² the replacement of saturated fat or trans unsaturated fat by cis (unhydrogenated) unsaturated fats was associated with larger reductions in risk than an isocaloric replacement by carbohydrates. In addition, dietary fats may contribute to risk through other mechanisms — for example, by influencing platelet aggregability, changing the threshold for ventricular fibrillation, or affecting sensitivity to insulin.¹²

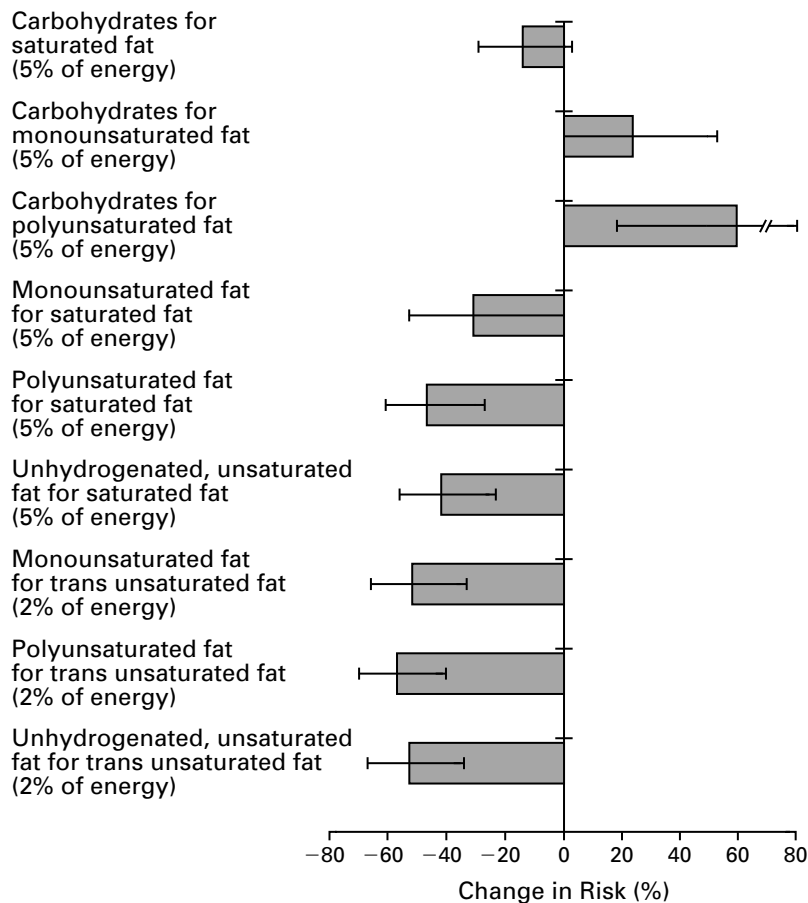


Figure 2. Estimated Percent Changes in the Risk of Coronary Heart Disease Associated with Isocaloric Substitutions of One Dietary Component for Another. The I bars represent 95 percent confidence intervals.

We observed a positive association, albeit not a statistically significant one, between dietary cholesterol intake and the risk of coronary disease. Metabolic studies suggest that the effect of dietary cholesterol on serum total cholesterol and LDL cholesterol levels in humans is considerably less strong than that of saturated fat.²⁶ A significant positive association between dietary cholesterol and coronary disease was observed in some studies,^{4,9} but not in others.^{10,11,15,27} In a pooled analysis²⁸ of four studies,^{4-6,9} the relative risk of coronary disease was 1.30 (95 percent confidence interval, 1.10 to 1.50) for an increase of 200 mg of dietary cholesterol per 1000 kcal of total energy intake; the 95 percent confidence interval includes our estimate.

The inverse association between the dietary intake of polyunsaturated fat and the incidence of coronary disease is consistent with the results of numerous metabolic studies that showed strong cholesterol-lowering effects of vegetable oils rich in linoleic acid when they were substituted for saturated fat in the

diet.¹ Also, diets high in polyunsaturated fat have been more effective than low-fat, high-carbohydrate diets in lowering total serum cholesterol as well as the incidence of coronary disease.²⁹

Epidemiologic data on monounsaturated fat are sparse. Two prospective studies found that the risk of coronary disease increased with higher intakes of monounsaturated fat in younger but not in older participants.^{15,27} However, neither study adjusted for the intake of other types of fat. In our analyses, after adjustment for the intake of other fats, monounsaturated-fat intake was inversely associated with risk. In metabolic studies, replacing carbohydrates with monounsaturated fat raises HDL cholesterol levels without affecting LDL cholesterol² and may also improve insulin sensitivity.³⁰ In addition, monounsaturated fat is resistant to oxidative modification.³¹ Ecologic correlations also suggest that the dietary intake of monounsaturated fat is inversely associated with total mortality and mortality due to coronary disease.³²

The positive association of coronary heart disease

with the intake of trans unsaturated fat is consistent with the results of most previous studies.³³ The concentration of trans unsaturated fatty acids in adipose tissue was not significantly associated with the risk of myocardial infarction in the European Antioxidant Myocardial Infarction and Cancer (EURAMIC) study³⁴ or with sudden death from cardiac causes in a small case-control study in the United Kingdom.³⁵ However, the 95 percent confidence intervals for the relative risks in the highest categories of consumption of trans unsaturated fatty acids in both studies were very wide and included our estimate of relative risk. Also in the EURAMIC study, after the exclusion of an outlier area (Spain), the relative risk for the highest versus the lowest category of dietary intake of trans unsaturated fats was close to ours (1.44; 95 percent confidence interval, 0.94 to 2.20).

Trans unsaturated fat from foods may adversely affect the risk of coronary disease by raising LDL cholesterol levels and lowering HDL cholesterol levels,³⁶ increasing Lp(a) lipoprotein levels,³⁶ raising triglyceride levels,³⁶ and interfering with essential-fatty-acid metabolism.³⁷ Hence, it is not surprising that the relative risks in this and other studies are larger than would be predicted solely on the basis of the effect of trans unsaturated fatty acids on blood lipids.³³ Imprecise dietary measurement and residual confounding have been suggested as alternative explanations for the observed positive associations.³⁸ However, errors in measuring dietary intake could have accounted for a lack of association, but not for the presence of an association.³⁹ In this study, we obtained repeated measurements of dietary intake in an attempt to reduce errors. As expected, the analyses using repeated measures yielded stronger effects of trans unsaturated fat on the incidence of coronary disease than those that included only the base-line measures.

To account for the effects of potential confounding by lifestyle factors, we adjusted for a multitude of dietary and nondietary risk factors. The multivariate-adjusted relative risk of coronary disease associated with the consumption of trans unsaturated fat was similar to the age-adjusted relative risk, suggesting that confounding by lifestyle factors had only a small effect. On the other hand, the intake of other fats had more important confounding effects, which actually strengthened the association of trans unsaturated fat with coronary disease. In addition, adjustment for intermediate end points such as hypercholesterolemia and diabetes did not materially alter the association, suggesting that confounding by precursors of coronary disease was minimal. Perhaps people with newly diagnosed intermediate end points such as angina might switch from butter to margarine, a change that could increase their intake of trans unsaturated fat and thus artificially produce an elevated risk. However, our data did not support this

speculation, since women who had intermediate end points actually tended to reduce their intakes of trans unsaturated fat. For example, from 1980 to 1984, the mean intake of trans unsaturated fat declined 13 percent among women in whom angina developed, as compared with 8 percent among women who did not have angina.

Food-consumption patterns in the United States have shifted considerably in the past decade.⁴⁰ In our study, total fat intake as a percentage of energy intake declined by about 19 percent from 1980 to 1990. Because we incorporated updated dietary information, our analyses took into account changes over time in dietary habits and food composition. Although the conclusions drawn from the analyses were qualitatively similar whether they were based on base-line or updated dietary information, the associations were somewhat stronger in the updated analyses, indicating the advantage of using the repeated measurements.

Our data provide evidence in support of the hypothesis that a higher dietary intake of saturated fat and trans unsaturated fat is associated with an increased risk of coronary disease, whereas a higher intake of monounsaturated and polyunsaturated fats is associated with reduced risk. These findings reinforce evidence from metabolic studies that replacing saturated fat and trans unsaturated fat in the diet with unhydrogenated monounsaturated and polyunsaturated fats favorably alters the lipid profile, but that reducing overall fat intake has little effect.

Supported by research grants (HL24074, HL34594, CA40356, and DK 46200) and a nutrition training grant (T32DK07703) from the National Institutes of Health.

We are indebted to the participants in the Nurses' Health Study for their continuing outstanding level of cooperation; to Al Wing, Mark Shneyder, Gary Chase, Karen Corsano, Lisa Dunn, Barbara Egan, Lori Ward, and Jill Arnold for their unfailing help; to Alberto Ascherio and Alicja Wolk for helpful comments; and to Frank E. Speizer, principal investigator of the Nurses' Health Study, for his support.

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CORRECTION

Dietary Fat Intake and the Risk of Coronary Heart Disease in Women

To the Editor: In their report on the relation between dietary fat intake and coronary heart disease in women, Hu et al. (Nov. 20 issue)¹ present data suggesting that there is no relation between fat intake and body-mass index. Specifically, in Table 2 of the article, describing base-line characteristics and risk factors according to four fat categories (saturated, monounsaturated, polyunsaturated, and trans unsaturated), each showing the lowest, intermediate, and highest quintiles of intake, the body-mass index is 24 in all 12 cells. Furthermore, the percentage of subjects reporting vigorous exercise in all four fat categories is uniformly lowest among women in the highest quintile of fat intake and highest among women in the lowest quintile of fat intake. Thus, the table indicates that women with low fat intakes and high levels of exercise have the same body-mass index as women with high fat intakes and low levels of exercise. This raises the possibility that the method of assessing diet or exercise may be flawed. The data as presented also support the need for caution in drawing interventional conclusions from cross-sectional observational data. This is particularly so given the low risk of coronary heart disease (27 deaths per 100,000 per year) in the group of women studied, who were all nurses, as compared with the overall risk in the population of women in the United States (rates of death from heart disease among white women 45 to 64 years of age in the United States: 62.5 and 51.0 per 100,000 per year, respectively, in 1985 and 1989²).

The authors also compare the effects of the replacement of 5 percent of calories from saturated fat with the replacement of 2 percent of calories from trans unsaturated fat, concluding that the former would lead to a 42 percent reduction in the risk of coronary heart disease and the latter a 53 percent reduction. It may be that calorie for calorie trans unsaturated fat exerts a greater effect on risk than saturated fat. However, whereas replacement of 5 percent of calories from saturated fat represents a 32 percent reduction in saturated fat intake (the mean being 15.6 percent in their population) and is feasible, replacement of 2 percent of calories from trans unsaturated fat implies a near-total (91 percent) removal of trans unsaturated fats from the diet (mean intake, 2.2 percent), which is not practically achievable. It would have been of interest to compare one-third reductions of both; in such a comparison, the effect of a feasible reduction in saturated fat intake would presumably outweigh the effect of a feasible reduction in trans unsaturated fat intake.

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To the Editor: Before the findings of Hu et al. can be considered valid, some limitations of such studies should be noted.

Studies with double-labeled water have demonstrated that estimates of energy consumption, of which fat is a major contributor, are rather inaccurate and biased. In the validation studies,¹ correlations for various fats ranged from 0.46 to 0.68 — that is, only 22 to 46 percent of the variance is explained. The inability to detect a clear effect of saturated fat and dietary cholesterol suggests the limited reliability of the data on these components, since metabolic studies have demonstrated that they have a major role in modifying serum lipid levels.²

It is well established that populations consuming low-fat diets have low low-density lipoprotein and high-density lipoprotein (HDL) levels and that mortality from coronary heart disease is also low. Triglyceride levels are not abnormally high. The elevation in triglycerides observed in experimental studies has been shown to be temporary.³ Also, the clinical significance of the lower HDL levels observed with low-fat diets has been questioned.⁴

The range of total fat intake recorded in these studies is limited and has little relevance to the protective effect of really low fat diets. It will probably be agreed, however, that within these limits, the composition of dietary fat, rather than the level, is of primary importance.

Although high levels of trans fats are clearly undesirable, we should not throw out the baby with the bath water by disparaging all margarines. Tub margarines offer important sources of polyunsaturated fatty acids with minimal amounts of trans acids.

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To the Editor: Hu et al. reported that total dietary fat intake in the Nurses' Health Study was not associated with the risk of coronary heart disease. This conclusion rests on the assumption that the food-frequency questionnaire generates accurate estimates of total fat intake for all subjects. However, it is widely accepted that there is bias toward the underestimation of food intake in dietary surveys,¹ and it is disappointing that the paper does not address this problem.

Hu et al. cite a book as providing evidence of the validity of the food-frequency questionnaire. The book refers to a 1985 study by Willett and colleagues² that validated the food-frequency questionnaire by comparing it with four one-week diet records collected over a period of one year in 173 subjects. Thus, validation depended on the assumption that because the two methods agree, each gives valid results. However, diet records have since been shown to underestimate energy intake as compared with measured energy expenditure.³ Furthermore, the reported mean energy intakes in 1985 in repeated food-frequency questionnaires (1418 and 1371 kcal) and diet records (1620 kcal)² were substantially less than the measured energy expenditure in 123 women of similar ages (2366 kcal).¹

The adjustment for total energy intake in the multivariate analysis would only compensate for underreporting if all macronutrients were equally underreported. However, evidence is accumulating of the differential reporting of foods and macronutrients.⁴ The situation is exacerbated because the probability of underestimation is greater in women than men,⁵ increases as body-mass index increases,⁴ and tends to be subject-specific and not eliminated by repeated measures.⁴ Since obesity is a known risk factor for coronary heart disease, women at higher risk for coronary heart disease (those with a high body-mass index) are more likely to have differentially reported foods and macronutrients. Although as Hu et al. state, "errors in measuring dietary intake could have accounted for a lack of association, but not the presence of an association," bias can both remove and create associations.

Have the authors considered repeating their analysis after excluding women who reported physiologically improbable food intakes? This can be done using cutoff limits for energy intake below which a woman of a given age and body weight could not live a normal lifestyle.¹ If the conclusions remain unchanged, they will rest on a sounder foundation.

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The authors reply:

To the Editor: Ockene and Nicolosi's inference about the three-dimensional relation among fat intake, physical activity, and body-mass index from the two-dimensional data in Table 2 is inappropriate; the more active women were actually leaner. Ockene and Nicolosi incorrectly characterize our prospective study as "cross-sectional." They also question the generalizability of the findings, but there is no reason to believe that the biologic effect of dietary fat on coronary risk differs between nurses and other women. Finally, a large reduction in trans fat is not as difficult as Ockene and Nicolosi think. Trans fat is the result of food-processing methods that can be changed. Today, most European margarines are free of trans fat, and the consumption of these products can, as Hegsted notes, have important health benefits.

Hegsted repeats the common misconception that the triglyceride-raising and HDL-depressing effects of a low-fat, high-carbohydrate diet are transient. This notion is not supported by a meta-analysis of 27 trials, lasting from 14 to 91 days,¹ or a recent large 1-year study.² Also, there is no evidence that the HDL-lowering effect of a low-fat diet is benign; the population comparisons cited by Hegsted are intractably confounded by major differences in physical activity and body fat.

Hegsted and Johnson et al. were concerned about potential bias in our measurement of diet, including the possibility of an underestimation of total energy intake, citing the validation study of our first questionnaire. The mean energy intake assessed by the revised questionnaire used since 1984 was 1844 kcal,³ a reasonable estimate for women of this age. Even if energy is underestimated, this would not affect our results, because we adjusted for both total energy intake

and body-mass index. Also, in several analyses, underreporting of the percentage of calories from fat was not related to obesity.^{4,5} Furthermore, the relation of total fat intake to the risk of coronary disease did not differ between obese and nonobese women. Our analyses already excluded women with energy intakes outside the range of 500 to 3500 kcal per day. Following the suggestion of Johnson et al., we calculated the ratio of reported caloric intake to predicted caloric intake for each participant using their age and weight. Excluding women with the greatest likelihood for underreporting (the lowest quintile of the ratio) did not change the result (relative risk for total fat [5 percent of energy], 1.02; 95 percent confidence interval, 0.96 to 1.09). The use of four dietary assessments over a period of 14 years was a unique strength of this study, which substantially dampens the likelihood of measurement error and variation due to true changes over time.

In Table 3 of our paper, the unit for cholesterol intake was incorrect. The correct unit is milligrams per 1000 kcal per day.

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