Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women[1–3]

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See corresponding editorial on page 951.

ABSTRACT

Background: Metabolic studies suggest that saturated fatty acids differ in their effects on blood lipids.

Objective: The objective was to examine the associations between intakes of individual saturated fatty acids and their food sources in relation to the risk of coronary heart disease (CHD).

Design: This was a prospective cohort study of 80 082 women in the Nurses' Health Study aged 34–59 y. Subjects had no known cardiovascular disease, cancer, hypercholesterolemia, or diabetes, and completed validated food-frequency questionnaires in 1980.

Results: During 14 y of follow-up, we documented 939 incident cases of major CHD events. In multivariate analyses in which age, smoking, and other covariates were controlled for, intakes of short- to medium-chain saturated fatty acids (4:0–10:0) were not significantly associated with the risk of CHD. In contrast, intakes of longer-chain saturated fatty acids (12:0–18:0) were each separately associated with a small increase in risk. The multivariate RR for a 1% energy increase from stearic acid was 1.19 (95% CI: 1.02, 1.37). The ratio of polyunsaturated to saturated fat was strongly and inversely associated with CHD risk (multivariate RR for a comparison of the highest with the lowest deciles: 0.58; 95% CI: 0.41, 0.83; P for trend < 0.0001). Conversely, higher ratios of red meat to poultry and fish consumption and of high-fat to low-fat dairy consumption were associated with significantly greater risk.

Conclusion: A distinction between stearic acid and other saturated fats does not appear to be important in dietary advice to reduce CHD risk, in part because of the high correlation between stearic acid and other saturated fatty acids in typical diets. *Am J Clin Nutr* 1999;70:1001–8.

KEY WORDS Coronary heart disease, women, saturated fat, foods, dietary fat, Nurses' Health Study, stearic acid

INTRODUCTION

Migration studies and international comparisons suggest a strong positive association between saturated fat intake and risk of coronary heart disease (CHD) (1, 2). In metabolic studies, diets high in saturated fat and low in polyunsaturated fat increase blood cholesterol concentrations (3, 4). However, different classes of saturated fatty acids can have different effects on plasma lipid and lipoprotein concentrations (5). Specifically, saturated fatty acids with 12–16 carbon atoms tend to increase plasma total and LDL-cholesterol concentrations, whereas stearic acid (18:0) does not have a cholesterol-raising effect compared with oleic acid (18:1). However, 18:0 may lower HDL and increase lipoprotein(a) [Lp(a)] concentrations (6). Among the cholesterol-raising saturated fatty acids, myristic acid (14:0) appears to be more potent than lauric acid (12:0) or palmitic acid (16:0) (5, 7), but the data are not entirely consistent (8).

The differential effects of specific saturated fats on plasma lipids and lipoproteins imply that these fats may have different effects on the risk of CHD. So far, epidemiologic studies have assessed only the association of the risk of CHD with total saturated fatty acids; to our knowledge, no data are available regarding the associations between individual saturated fatty acids and the risk of CHD. Recently, we reported a modest positive association between saturated fat intake and the risk of CHD in women participating in the Nurses' Health Study (9). The present analysis examines in detail the relations of intake of specific saturated fatty acids and their major food sources with the incidence of CHD during 14 y of follow-up.

SUBJECTS AND METHODS

The Nurses' Health Study cohort was established in 1976 when 121 700 female registered nurses aged 30–55 y and residing in 11 large US states provided detailed information on their medical history and lifestyle characteristics (10). Every 2 y,

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[2] Supported by research grants HL24074, HL34594, CA40356, and DK 46200 and nutrition training grant T32DK07703 from the National Institutes of Health.

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Received March 11, 1999.

Accepted for publication July 14, 1999.

follow-up questionnaires have been sent to update information on potential risk factors and to identify newly diagnosed cases of CHD and other diseases.

In 1980, a 61-item food-frequency questionnaire was included to assess intakes of specific fats and other nutrients. In 1984, the food-frequency questionnaire was expanded to include 116 food items. Similar questionnaires were used to update dietary intakes in 1986 and 1990. The primary change in the revised questionnaire was the creation of individual questions about groups of nutritionally similar food items that had been collapsed into single items on the more compressed original questionnaire. The reproducibility and validity of the food-frequency questionnaires were described in detail elsewhere (11, 12). In validation studies among subsamples of the main study, correlation coefficients between energy-adjusted saturated fat intakes derived from the 61-item and 116-item food-frequency questionnaires and from multiple, 1-wk dietary records (after within-person variation in the diet records was accounted for) were 0.65 and 0.68, respectively (L Sampson, E Rimm, M Stampfer, B Rosner, W Willett, unpublished observations, 1997).

To calculate intakes of specific saturated fatty acids and other nutrients, a commonly used unit or portion size for each food (eg, one egg or one slice of bread) was specified and the participant was asked how often on average during the previous year she had consumed that amount. Nine responses were possible, ranging from "never" to "≥6 times/d." Nutrient intakes were computed by multiplying the frequency of consumption of each unit of food by the nutrient content of the specified portions. Composition values for individual saturated fatty acids and other nutrients were obtained from US Department of Agriculture sources (13).

After up to 4 mailings, 98 462 women returned the 1980 dietary questionnaire. We excluded those who left ≥10 items blank, those with implausibly low or high scores for total food or energy intake [ie, <2094 kJ (500 kcal) or >14 650 kJ (3500 kcal)/d], and those with previously diagnosed cancer, angina, myocardial infarction, stroke, or other cardiovascular diseases. Women reporting high serum cholesterol concentrations or diabetes were excluded because these disorders are associated with a risk of CHD and also could have caused the women to change their diets. The final 1980 baseline population consisted of 80 082 women.

Ascertainment of endpoint

The primary endpoint for this study was nonfatal myocardial infarction or fatal coronary disease occurring after the return of the 1980 questionnaire but before 1 June 1994. We sought to review medical records for all such reports. Records were reviewed by study physicians with no knowledge of the subjects' self-reported risk factor status. Myocardial infarction was confirmed by using World Health Organization criteria: symptoms plus either diagnostic electrocardiographic changes or elevated cardiac enzymes (14). 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%). We included all confirmed and probable cases in our analyses because results were the same after probable cases were excluded.

Deaths were identified from state vital records and the National Death Index or were reported by next of kin or the postal system; follow-up for deaths was >98% complete (15). Fatal coronary disease was defined as fatal myocardial infarction if this was confirmed by hospital records or autopsy, or if coronary disease was listed as the cause of death on the death certificate and there was evidence of previous coronary disease. CHD cases were designated as presumed if the underlying cause on the death certificate was CHD but no records were available; these cases constituted ≈14.7% of fatal CHD cases. Analyses limited to confirmed cases yielded similar results, although with less precision. We also included sudden death within 1 h of the onset of symptoms in women with no other plausible cause of death (other than coronary disease); these cases constituted ≈12.3% of fatal CHD cases.

Data analysis

Person-years (the number of persons studied times the number of years of follow-up) for each participant were calculated from the date of return of the 1980 questionnaire to the date of the first CHD event, death, or 1 June 1994, whichever came first. Women were divided into quintiles according to the percentage of energy from each type of saturated fatty acid. Incidence rates were calculated by dividing the number of events by person-years of follow-up in each quintile. The relative risk (RR) was computed as the rate in a specific category of fat intake divided by that in the lowest quintile, with adjustment by 5-y age categories. In multivariate models using pooled logistic regression (16), we simultaneously included intakes of total energy, dietary cholesterol, protein, and fiber, and percentages of energy from saturated fat, monounsaturated fat, polyunsaturated fat, and *trans* fat, in addition to other potential confounding variables. In such models, the coefficient for a specific type of fat can be interpreted as an estimate of the effect of that fat compared with the same energy from carbohydrates (17). For analyses of food consumption in relation to the risk of CHD, we calculated composite scores for red meat, poultry and fish, low-fat dairy products, and high-fat dairy products and classified women into quintiles of these scores; median values for each quintile were used to test for a linear trend.

Because intakes of individual saturated fatty acids were highly correlated because of shared food sources, we did not enter all the specific saturated fatty acids into the model simultaneously. To distinguish 18:0 from other long-chain saturates, we entered the intake of 18:0 and the sum of 12:0, 14:0, and 16:0 into the model simultaneously. Because of a high correlation between 18:0 and 16:0 as a result of shared food sources, we also calculated 18:0 intakes, adjusted for 16:0 and other saturates, using the regression method that has been described for energy adjustment (17). We then conducted analyses using adjusted 18:0 intakes.

To reduce within-subject variation and best represent long-term dietary intakes, we used repeated measures of diet in the analyses (9). In particular, the incidence of CHD was related to the cumulative average of individual saturated fatty acids from all available questionnaires up to the start of each 2-y follow-up interval in a pooled logistic model. Because changes in diet after the development of intermediate endpoints such as angina, hypercholesterolemia, and diabetes may confound the diet-disease associations (18), we stopped updating the diet at the beginning of the time interval during which individuals developed those intermediate endpoints. Most covariates were updated biennially, including age (5-y category), time period (7 periods), body mass index (5 categories), cigarette smoking (never, past, and current smoking of 1–14, 15–24, and ≥25 cigarettes/d), menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone

TABLE 1
Individual saturated fatty acid intakes over time in the Nurses' Health Study[1]

	4:0–10:0	12:0	14:0	16:0	18:0	Total
			% of energy			
1980	0.69 ± 0.35	0.25 ± 0.10	1.38 ± 0.46	8.57 ± 2.00	4.01 ± 1.04	15.58 ± 3.60
1984	0.59 ± 0.28	0.23 ± 0.16	1.06 ± 0.36	6.54 ± 1.32	3.00 ± 0.70	12.45 ± 2.60
1986	0.57 ± 0.28	0.23 ± 0.15	1.02 ± 0.35	6.14 ± 1.31	2.77 ± 0.69	11.65 ± 2.60
1990	0.49 ± 0.24	0.24 ± 0.16	0.88 ± 0.33	5.92 ± 1.32	2.73 ± 0.74	10.63 ± 2.55
P for time trend	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

[1] $\bar{x}$ ± SD.

TABLE 2
Top 5 contributors to specific saturated fatty acids in the diet based on data from the 1984 food-frequency questionnaire[1]

4:0	6:0	8:0	10:0	12:0	14:0	16:0	18:0	Total saturated fat
Hard cheese [31]	Hard cheese [27]	Hard cheese [28]	Hard cheese [22]	Coffee whitener [18]	Hard cheese [20]	Beef as main dish [15]	Beef as main dish [16]	Beef as main dish [13]
Low-fat milk [13]	Butter [16]	Low-fat milk [15]	Butter [11]	Hard cheese [15]	Beef [11]	Hard cheese [10]	Hard cheese [9]	Hard cheese [11]
Whole milk [11]	Low-fat milk [13]	Whole milk [13]	Low-fat milk [11]	Low-fat milk [10]	Low-fat milk [8]	Beef as sandwich [5]	Beef as sandwich [6]	Beef as sandwich [5]
Ice cream [10]	Whole milk [12]	Ice cream [11]	Whole milk [10]	Whole milk [9]	Butter [8]	Hamburger [5]	Hamburger [6]	Hamburger [5]
Butter [9]	Ice cream [10]	Coffee whitener [7]	Ice cream [10]	Butter [9]	Whole milk [7]	Eggs [3]	Chocolate [5]	Low-fat milk [4]

[1] Percentage of absolute intake in brackets.

replacement, and postmenopausal with current hormone replacement), parental history of myocardial infarction before age 60 y, multivitamin use, vitamin E supplement use, and alcohol consumption (0, 0–4, 5–14, and ≥15 g/d). Aspirin use (none, 1–6/wk, ≥7/wk, and dose unknown) was assessed in 1980, 1982, 1984, and 1988 and regular vigorous exercise was assessed in 1980.

RESULTS

Individual saturated fatty acid intakes, except for 12:0, declined over time in this cohort (**Table 1**). At baseline, 16:0 accounted for ≈55% of total saturated fatty acid intakes and 18:0 accounted for ≈16%. The primary contributors to 16:0 and 18:0 intakes in our cohort included beef as a main dish, cheese, beef as a sandwich or mixed dish, and hamburgers (**Table 2**). Other saturated fatty acids, including short- to medium-chain saturated fatty acids (4:0–10:0), 12:0, and 14:0 were primarily from dairy products. Because of shared food sources, the correlations among specific saturated fatty acids were high (**Table 3**). From 1980 to 1994, the average intake of beef as a main dish decreased from 51.12 to 22.72 g/d (1.8 to 0.8 oz/d), the average intake of butter decreased from 2.45 to 1.05 g/d (0.49 to 0.21 pats/d), and the average intake of whole milk decreased from 63.44 to 17.08 g/d (0.26 to 0.07 glasses/d).

Women with high saturated fat intakes were more likely to smoke, less likely to exercise, and less likely to take multivitamin and vitamin E supplements (**Table 4**). Saturated fat intake was positively correlated with intakes of other fatty acids, especially monounsaturated fat and dietary cholesterol, and inversely correlated with intakes of alcohol and fiber.

RRs of CHD according to quintiles of individual saturated fatty acid intakes are shown in **Table 5**. Because of very low intakes of 12:0 and high correlations between 12:0 and 14:0, we combined the data for 12:0 and 14:0 in the analysis. There was no significant association between intakes of short- and medium-chain saturated fatty acids (4:0–10:0) in age-adjusted or multivariate analyses. After adjustment for age, there were trends toward a higher risk with higher intakes of 12:0 plus 14:0, 16:0, and 18:0. However, the associations were substantially attenuated after adjustment for smoking and other nondietary covariates. Adjustment for other dietary variables further attenuated these RRs.

RRs of CHD from analyses in which saturated fatty acids were treated as continuous variables are shown in **Table 6**. In the multivariate analyses with adjustment for both nondietary and dietary variables, the RRs for a 1% increase in energy intake were 0.97 (95% CI: 0.90, 1.05) for 4:0–10:0 and 1.12 (0.97, 1.31) for the sum of 12:0 and 14:0. When 14:0 was examined separately, the RR was 1.11 (0.91, 1.34). The RRs for a 1% increase in energy were 1.07 (0.98, 1.17) for 16:0 and 1.19 (1.02, 1.37) for 18:0. The association for 18:0 became nonsignificant after further adjustment for the sum of 12:0 and 16:0, but the point estimate of the RR did not change. When all long-chain saturated

TABLE 3
Pearson correlation coefficients between individual saturated fatty acids as reported (% of energy intake) on the 1984 food-frequency questionnaire[1]

	4:0–10:0	12:0	14:0	16:0	18:0
4:0–10:0	1.0				
12:0	0.57	1.0			
14:0	0.94	0.61	1.0		
16:0	0.53	0.32	0.73	1.0	
18:0	0.43	0.36	0.66	0.92	1.0

[1] Correlations were similar for other years.

TABLE 4
Relation of potential coronary heart disease risk factors (adjusted for age) to saturated fat (12:0–18:0) intakes in 1980[1]

	Quintiles of 12:0–18:0 intake					
	1 (9.5; <10.6)[2]	2 (11.4; 10.7–12.1)	3 (12.8; 12.2–13.6)	4 (14.5; 13.7–15.5)	5 (17.2; >15.5)	*P* for trend
Current smokers (%)	27	27	27	29	33	<0.0001
History of hypertension (%)	15	14	14	14	14	0.0004
Parental MI before age 60 y (%)	20	20	20	20	20	0.51
Current hormone use among postmenopausal women (%)	16	18	15	17	16	0.004
Vigorous exercise ≥1/wk (%)	50	47	45	43	40	<0.0001
Multivitamin use (%)	37	35	33	33	31	<0.0001
Vitamin E supplement use (%)	16	13	12	11	11	<0.0001
Aspirin use ≥1/wk (%)	45	47	48	47	46	<0.0001
Age (y)	46.7 ± 7.3[3]	45.9 ± 7.2	45.6 ± 7.2	45.5 ± 7.0	45.6 ± 7.0	<0.0001
Alcohol (g/d)	8.7 ± 13.7	7.4 ± 11.3	6.5 ± 9.8	5.8 ± 8.9	4.8 ± 7.6	<0.0001
BMI (kg/m^2)	23.9 ± 4.2	24.1 ± 4.2	24.2 ± 4.4	24.3 ± 4.4	24.4 ± 4.5	<0.0001
Monounsaturated fat (% of energy)	11.4 ± 2.5	14.3 ± 2.0	16.0 ± 2.0	17.7 ± 2.1	20.4 ± 2.8	<0.0001
Polyunsaturated fat (% of energy)	4.9 ± 1.6	5.3 ± 1.6	5.4 ± 1.6	5.4 ± 1.5	5.3 ± 1.5	<0.0001
trans Fat (% of energy)	1.9 ± 0.8	2.2 ± 0.7	2.3 ± 0.7	2.4 ± 0.7	2.5 ± 0.6	<0.0001
Dietary cholesterol (mg/MJ)	44.4 ± 19.4	48.5 ± 17.7	50.4 ± 17.2	53.3 ± 17.4	57.3 ± 19.4	<0.0001
Fiber (g/d)	17.1 ± 6.1	14.5 ± 4.2	13.5 ± 3.7	12.3 ± 3.3	10.5 ± 3.1	<0.0001

[1] n = 80 990. MI, myocardial infarction.
[2] Median intakes and ranges as percentages of energy.
[3] $\bar{x}$ ± SD.

TABLE 5
Relative risks (RR) and 95% CIs of coronary heart disease according to quintiles of intakes of individual saturated fatty acids

	Quintiles of intake					
	1 (low)	2	3	4	5 (high)	*P* for trend
4:0–10:0						
Median (% of energy)	0.87	1.18	1.39	1.62	2.00	—
Range (% of energy)	<1.05	1.05–1.29	1.30–1.50	1.51–1.77	>1.77	
Age-adjusted RR	1.0	0.84 (0.69, 1.03)	0.76 (0.62, 0.93)	0.71 (0.57, 0.870)	1.03 (0.85, 1.25)	0.99
Multivariate RR[1]	1.0	0.96 (0.79, 1.17)	0.88 (0.72, 1.09)	0.80 (0.65, 0.99)	1.07 (0.89, 1.30)	0.78
Adjusted for dietary variables[2]	1.0	0.95 (0.78, 1.17)	0.86 (0.70, 1.06)	0.77 (0.62, 0.95)	1.00 (0.82, 1.21)	0.60
12:0 + 14:0[3]						
Median (% of energy)	0.98	1.24	1.45	1.69	2.14	
Range (% of energy)	<1.13	1.13–1.34	1.35–1.56	1.57–1.87	>1.87	
Age-adjusted RR	1.0	0.97 (0.78, 1.20)	0.98 (0.79, 1.22)	1.28 (1.05, 1.57)	1.50 (1.23, 1.83)	0.0001
Multivariate RR[1]	1.0	1.00 (0.81, 1.24)	0.96 (0.78, 1.20)	1.14 (0.93, 1.39)	1.15 (0.94, 1.40)	0.07
Adjusted for dietary variables[2]	1.0	0.97 (0.78, 1.21)	0.92 (0.73, 1.15)	1.06 (0.85, 1.33)	1.05 (0.83, 1.32)	0.46
16:0						
Median (% of energy)	5.82	6.93	7.75	8.70	10.31	
Range (% of energy)	<6.46	6.46–7.34	7.35–8.19	8.20–9.34	9.33–20.45	
Age-adjusted RR[1]	1.0	0.81 (0.65, 1.01)	1.05 (0.85, 1.30)	1.46 (1.20, 1.78)	1.71 (1.40, 2.08)	0.0001
Multivariate RR[1]	1.0	0.78 (0.62, 0.97)	0.92 (0.75, 1.13)	1.10 (0.91, 1.35)	1.09 (0.89, 1.33)	0.04
Adjusted for dietary variables[2]	1.0	0.70 (0.55, 0.91)	0.83 (0.63, 1.10)	1.02 (0.74, 1.39)	1.03 (0.71, 1.50)	0.45
18:0						
Median values (% of energy)	2.61	3.17	3.60	4.09	4.91	
Range (% of energy)	<2.93	2.93–3.39	3.40–3.82	3.82–4.42	>4.42	
Age-adjusted RR	1.0	1.12 (0.90, 1.39)	1.17 (0.94, 1.46)	1.76 (1.43, 2.16)	1.97 (1.61, 2.42)	0.0001
Multivariate RR[1]	1.0	1.05 (0.84, 1.31)	1.02 (0.82, 1.27)	1.30 (1.06, 1.60)	1.24 (1.01, 1.53)	0.009
Adjusted for dietary variables[2]	1.0	0.99 (0.77, 1.28)	0.96 (0.72, 1.28)	1.23 (0.90, 1.68)	1.16 (0.81, 1.66)	0.30
Sum of 12:0–18:0						
Median intake (% of energy)	9.5	11.4	12.8	14.5	17.2	
Ranges (% of energy)	<10.6	10.7–12.1	12.2–13.6	13.7–15.5	>15.5	
Age-adjusted RR	1.0	0.89 (0.72, 1.11)	1.07 (0.86, 1.32)	1.50 (1.23, 1.83)	1.79 (1.47, 2.18)	0.0001
Multivariate RR[1]	1.0	0.87 (0.69, 1.08)	0.93 (0.75, 1.16)	1.14 (0.94, 1.40)	1.14 (0.93, 1.39)	0.03
Adjusted for dietary variables[2]	1.0	0.82 (0.64, 1.05)	0.87 (0.66, 1.14)	1.05 (0.78, 1.43)	1.04 (0.72, 1.48)	0.47

[1] Model included age (5-y category), time period (7 periods), BMI (5 categories), cigarette smoking (never, past, and current smoking of 1–14, 15–24, and ≥25 cigarettes/d), menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, and postmenopausal with current hormone replacement), parental history of myocardial infarction before age 60 y, vitamin E supplement use, alcohol consumption (4 categories), history of hypertension, aspirin use (none, 1–6/wk, ≥7/wk, and dose unknown), and vigorous exercise ≥1 time/wk (yes or no).
[2] Adjusted for intakes of monounsaturated fat, polyunsaturated fat, *trans* fat, protein, dietary cholesterol, dietary fiber, and total energy.
[3] These fatty acids were combined because of the very small amount of 12:0 in the diet and the similar food sources for the 2 fatty acids.

TABLE 6
Relative risks (RR) and 95% CIs of coronary heart disease for intakes of individual saturated fatty acids and the ratio of polyunsaturated to saturated fats (P:S) modeled as continuous variables

	RR (95% CI)	*P*
4:0–10:0 (1% of energy)		
Age-adjusted RR	1.07 (0.93, 1.23)	0.34
Multivariate RR[1]	1.07 (0.94, 1.23)	0.30
Adjusted for dietary variables[2]	0.97 (0.90, 1.05)	0.45
12:0 + 14:0 (1% of energy)		
Age-adjusted RR	1.41 (1.25, 1.59)	<0.0001
Multivariate RR[1]	1.14 (1.01, 1.29)	0.03
Adjusted for dietary variables[2]	1.12 (0.97, 1.31)	0.13
16:0 (1% of energy)		
Age-adjusted RR	1.12 (1.09, 1.16)	<0.0001
Multivariate RR[1]	1.03 (0.99, 1.07)	0.14
Adjusted for dietary variables[2]	1.07 (0.98, 1.17)	0.16
18:0 (1% of energy)		
Age-adjusted RR	1.30 (1.21, 1.39)	<0.0001
Multivariate RR[1]	1.09 (1.02, 1.17)	0.02
Adjusted for dietary variables[2]	1.19 (1.02, 1.37)	0.02
Further adjusted for the sum of 12:0–16:0	1.19 (0.98, 1.46)	0.09
12:0–18:0 (5% of energy)		
Age-adjusted RR	1.45 (1.31, 1.61)	<0.0001
Multivariate RR[1]	1.10 (1.00, 1.23)	0.05
Adjusted for dietary variables[2]	1.29 (1.00, 1.66)	0.05
P:S (each 0.2-unit increase)		
Age-adjusted RR	0.72 (0.66, 0.79)	<0.0001
Multivariate RR[1]	0.89 (0.82, 0.97)	0.01
Adjusted for dietary variables[2]	0.79 (0.70, 0.89)	<0.0001

[1] Model included age (5-y category), time period (7 periods), BMI (5 categories), cigarette smoking (never, past, and current smoking of 1–14, 15–24, and ≥25 cigarettes/d), menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, and postmenopausal with current hormone replacement), parental history of myocardial infarction before age 60 y, vitamin E supplement use, alcohol consumption (4 categories), history of hypertension, aspirin use (none, 1–6/wk, ≥7/wk, and dose unknown), and vigorous exercise ≥1 time/wk (yes or no).

[2] Adjusted for intakes of monounsaturated fat, *trans* fat, protein, fiber, cholesterol, and total energy.

fatty acids (12:0–18:0) were summed, the RR for a 5% increase in energy intake was 1.29 (1.00, 1.66) ($P = 0.05$).

To distinguish the effects of 18:0 intakes from intakes of other saturated fatty acids, despite the high correlations, we computed residuals for 18:0 by regressing 18:0 intakes on intakes of 16:0, the sum of 12:0 and 14:0, and short- to medium-chain saturates. The variation in 18:0 intake, independent of other saturated fatty acids, represented by this residual was 0.4% of energy for the 10th–90th percentiles. The RR for a 1% increase in energy intake from the 18:0 residuals was 1.22 (0.98, 1.54).

We also examined the association between the ratio of polyunsaturated fat (which itself was strongly inversely related to risk) to saturated fat (ie, the sum of 12:0–18:0) and the risk of CHD (Table 5). After adjustment for age, smoking, other nondietary variables, and intakes of monounsaturated fat, *trans* fat, protein, and total energy, a higher ratio was associated with a significantly lower risk of CHD (RR: 0.79; 0.70, 0.89) for each 0.2-unit increment in the ratio. When the ratio was treated as a categorical variable (**Figure 1**), the multivariate RRs across deciles of the ratio (the median values ranged from 0.23 to 0.72 from the lowest to the highest deciles) were 1.0 (reference), 0.92, 0.90, 0.87, 0.94, 0.81, 0.68, 0.72, 0.58, and 0.58 (0.41, 0.83).

Using the multivariate model including the sum of 12:0–18:0 in Table 6 after adjustment for dietary variables, we estimated the effects of isoenergetic replacement of saturated fats with carbohydrates or unsaturated fats on the risk of CHD. Replacement of 5% of energy from the sum of 12:0–18:0 fatty acids with energy from carbohydrate would reduce the risk by 22% (0–40%); replacement of 5% of energy from monounsaturated and polyunsaturated fatty acids with energy from carbohydrate would reduce the risk by 42% (6–65%) and 50% (30–64%), respectively.

Because beef and dairy products were the main sources of saturated fatty acids, we examined the associations between intakes of red meat (beef, pork, or lamb as a main dish; beef as a sandwich or mixed dish; hamburger; hot dog; processed meat; and bacon) and high-fat dairy products (whole milk, hard or cream cheese, ice cream, and butter) and the risk of CHD (**Table 7**). For the purpose of comparison, we also analyzed the associations between intakes of poultry and fish and low-fat dairy products (skim or low-fat milk, yogurt, and cottage cheese) and the risk of CHD. After adjustment for age, consumption of red meat and high-fat dairy products was associated with an increased risk of CHD, whereas consumption of poultry and fish and low-fat dairy products was associated with a lower risk. These associations were substantially attenuated in multivariate analyses and became nonsignificant, but the direction of the associations remained unchanged. The ratio of red meat to poultry and fish consumption was more strongly associated with the risk. Similarly, the ratio of high-fat to low-fat diary product consumption was positively associated with the risk of CHD. Among the dairy products, whole-milk consumption was associated with a significantly increased risk of CHD. The multivariate RRs across categories of intake of whole milk [almost never, <244 g/wk (1 glass/wk), 488–1464 g/wk (2–6 glasses/wk), 244 g/d (1 glass/d), and ≥488 g/d (2 glasses/d)] were 1.0, 1.20, 1.17, 1.48, and 1.67 (1.14, 1.90; P for trend < 0.0001). In contrast, a greater consumption of skim milk was associated with a nonsignificantly lower risk of CHD; corresponding RRs across categories of intake were 1.0, 0.83, 0.77, 0.89, and 0.78 (0.63, 0.96; P for trend = 0.09).

DISCUSSION

To our knowledge, this is the first epidemiologic study that examined the role of specific saturated fatty acids in relation to the risk of CHD. We found that a higher dietary intake of long-chain saturated fatty acids, including 12:0, 14:0, 16:0, and 18:0, was associated with an increased risk of CHD, whereas intake of short- to medium-chain saturated fatty acids (4:0–10:0) was not. Higher consumption of red meat and high-fat dairy products, the main sources of saturated fatty acids in the diet, was also associated with greater risk. In contrast, higher consumption of poultry and fish and low-fat dairy products was associated with a lower risk.

Because all individual long-chain saturated fatty acids (12:0, 14:0, 16:0, and 18:0) were associated with a small increase in risk, collectively, these fatty acids were associated with a modest increased risk, an effect that was distinct from that of the short- to medium-chain fatty acids. We did not find evidence that the

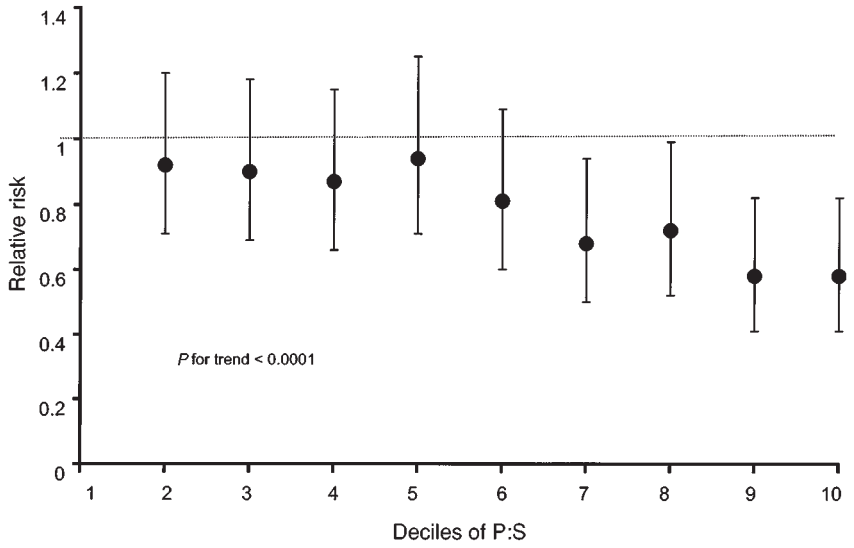

FIGURE 1. Multivariate relative risks of coronary heart disease according to deciles of the ratio of polyunsaturated to saturated fat (12:0–18:0) (P:S). Median values across the deciles were 0.23, 0.29, 0.34, 0.38, 0.42, 0.45, 0.49, 0.54, 0.60, and 0.72. Values were adjusted for age (5-y category), time period (7 periods), body mass index (5 categories), cigarette smoking (never, past, and current smoking of 1–14, 15–24, and ≥25 cigarettes/d), menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, and postmenopausal with current hormone replacement), parental history of myocardial infarction before age 60 y, vitamin E supplement use, alcohol consumption (4 categories), history of hypertension, aspirin use (none, 1–6/wk, ≥7/wk, and dose unknown), vigorous exercise ≥1 time/wk (yes or no), and intakes of monounsaturated fat, *trans* fat, protein, cholesterol, fiber, and total energy.

relation between 18:0 and risk of CHD was weaker than the associations of other saturated fats with CHD risk. However, our ability to distinguish among the types of saturated fats was limited by their high intercorrelations because their predominant sources were the same foods. This not only creates a high degree of statistical collinearity, but also suggests that distinguishing among specific types of saturated fat may not be of practical importance in dietary advice. Nevertheless, because of collinearity, our study could not address the effect of the addition of substantial amounts of purified 18:0 to the diet.

Most metabolic studies have shown that medium-chain saturated fatty acids with 8–10 carbons do not raise plasma cholesterol concentrations (19), although a recent study suggested the opposite (20). On the other hand, 12:0, 14:0, and 16:0 do increase total, LDL-, and HDL-cholesterol concentrations (7). Yu et al (19) reviewed 15 metabolic studies and found that 14:0 was more hypercholesterolemic than were the other fatty acids. More recent studies, however, showed no increase in total or LDL cholesterol when 14:0 was substituted for 16:0 (21), but did show an increase in HDL cholesterol when 14:0 was substituted for 16:0 or 18:1 (22).

Although 18:0 has little effect on total and LDL-cholesterol concentrations compared with carbohydrate, it may lower HDL cholesterol compared with monounsaturated or polyunsaturated fatty acids, and the HDL-lowering effect of 18:0 was particularly strong among women (19). Aro et al (6) reported recently that compared with a diet rich in dairy fat (rich in 14:0 and 16:0), 18:0 reduced LDL concentrations but also reduced HDL concentrations. Thus, the ratios of LDL to HDL and of apolipoprotein B to apolipoprotein A-I were not affected significantly. In addition, 18:0 increased Lp(a) concentrations (6) and may activate factor VII (23) and impair fibrinolysis (24). Overall, evidence from recent metabolic studies, similar to our data, does not appear to support making a distinction between 18:0 and other saturated fatty acids when giving dietary advice for reducing CHD risk. In addition to the well-known effects on CHD risk of LDL cholesterol, the overall adverse effects of long-chain saturated fatty acids on CHD risk observed in this study may be in part related to postprandial responses to these fatty acids. Weintraub et al (25) found that postprandial triacylglycerol concentrations were highest for a diet rich in saturated fat, lowest for a diet rich in n−3 polyunsaturated fat, and intermediate for a diet rich in n−6 polyunsaturated fat.

The observed relation between saturated fatty acid intake and risk of CHD was much weaker than that predicted by international comparisons (2). A major problem with the international comparisons was serious confounding by lifestyle variables such as physical activity and obesity and other aspects of diet such as fiber intake. Our results are consistent with the possibility that the proportional increase in plasma HDL-cholesterol concentration produced by saturated fatty acids somewhat compensates for its adverse effect on LDL-cholesterol concentrations. Finally, we found a strong inverse association between the ratio of polyunsaturated to saturated fat and the risk of CHD. This result is consistent with findings from dietary intervention trials in which substitution of polyunsaturated for saturated fat without a reduction in the total fat content of the diet substantially reduced the risk of CHD (26, 27).

In conclusion, a distinction between 18:0 and other saturated fats in dietary advice to reduce CHD risk does not appear to be important, in part because of the high correlation between 18:0 and other saturated fats in typical diets. However, these data do suggest that replacement of long-chain saturated fat with polyunsaturated fat is likely to reduce substantially the risk of CHD. Our results also support recommendations to substitute

TABLE 7
Relative risks (RR) and 95% CIs of coronary heart disease according to quintiles of intakes of red meat, white meat, and high-fat and low-fat dairy products[1]

	Quintiles of intake						
	1	2	3	4	5	*P* for trend	RR for 1 serving/d
Red meat							
Median intake (servings/d)	0.42	0.77	0.95	1.25	1.78	—	—
Range of intake	≤0.59	0.60–0.85	0.86–1.13	1.14–1.50	>1.50	—	—
Age-adjusted RR	1.0	1.08	1.08	1.25	1.61	<0.0001	1.43 (1.35, 1.65)
Multivariate RR[2]	1.0	1.02	0.95	1.03	1.15	0.35	1.09 (0.91, 1.30)
Poultry and fish							
Median intake (servings/d)	0.21	0.28	0.43	0.57	0.88	—	—
Range of intake	≤0.21	0.22–0.32	0.33–0.49	0.50–0.68	>0.68	—	—
Age-adjusted RR	1.0	0.83	0.65	0.62	0.62	<0.0001	0.51 (0.38, 0.67)
Multivariate RR[2]	1.0	0.92	0.88	0.80	0.85	0.06	0.76 (0.56, 1.02)
Ratio of red meat to poultry and fish							
Age-adjusted RR	1.0	1.07	1.32	1.51	1.91	<0.0001	—
Multivariate RR[2]	1.0	1.00	1.13	1.20	1.32	0.001	—
High-fat dairy products							
Median intake (servings/d)	0.28	0.62	1.00	1.50	2.93	—	—
Range of intake	≤0.50	0.51–0.85	0.86–1.22	1.22–2.04	>2.04	—	—
Age-adjusted RR	1.0	0.85	0.87	0.98	1.22	0.001	1.12 (1.05, 1.20)
Multivariate RR[2]	1.0	0.97	0.93	1.02	1.08	0.33	1.04 (0.96, 1.12)
Low-fat dairy products							
Median intake (servings/day)	0.05	0.28	0.65	1.13	2.28	—	—
Range of intake	≤0.13	0.14–0.43	0.44–0.89	0.90-1.43	>1.43	—	—
Age adjusted RR	1.0	0.70	0.53	0.54	0.56	<0.0001	0.80 (0.73, 0.87)
Multivariate RR[2]	1.0	0.84	0.77	0.77	0.82	0.11	0.93 (0.85, 1.02)
Ratio of high-fat to low-fat dairy products							
Age-adjusted RR	1.0	0.82	0.93	1.29	1.68	<0.0001	—
Multivariate RR[2]	1.0	0.87	0.94	1.17	1.27	0.0004	—

[1] Red meat is the composite score of the following foods: beef, pork, or lamb as a main dish; beef as a sandwich or mixed dish; hamburger; hot dog; processed meat; and bacon. High-fat dairy products include whole milk, hard or cream cheese, ice cream, and butter. Low-fat dairy products include skim or low-fat milk, yogurt, and cottage cheese.

[2] Adjusted for age (5-y category), time period (7 periods), body mass index (5 categories), cigarette smoking (never, past, and current smoking of 1–14, 15–24, and ≥25 cigarettes/d), menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, and postmenopausal with current hormone replacement), parental history of myocardial infarction before age 60 y; vitamin E supplement use, alcohol consumption (4 categories), history of hypertension, aspirin use (none, 1–6/wk, ≥7/wk, and dose unknown), vigorous exercise ≥1/wk (yes or no), and total energy intake. Red meat, white meat, and high-fat and low-fat dairy products were entered into the multivariate models simultaneously.

poultry and fish and low-fat dairy products for red meat and high-fat dairy products to reduce the risk of CHD.

We are indebted to the participants in the Nurses' Health Study for their continuing outstanding level of cooperation and to Al Wing, Mark Shneyder, Gary Chase, Karen Corsano, Lisa Dunn, Barbara Egan, Lori Ward, and Jill Arnold for their unfailing help.

REFERENCES

1. Kato H, Tillotson J, Nichamen MZ, Rhoads GG, Hamilton HB. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: serum lipids and diet. Am J Epidemiol 1973;97:372–85.
2. Keys A. Seven countries: a multivariate analysis of death and coronary heart disease. Cambridge, MA: Harvard University Press, 1980.
3. Hegsted DM, McGandy RB, Myers ML, Stare FJ. Quantitative effects of dietary fat on serum cholesterol in man. Am J Clin Nutr 1965;17:281–95.
4. Keys A, Parlin RW. Serum cholesterol response to changes in dietary lipids. Am J Clin Nutr 1966;19:175–81.
5. Kris-Etherton PM, Yu S. Individual fatty acid effects on plasma lipids and lipoproteins: human studies. Am J Clin Nutr 1997; 65(suppl):1628S–44S.
6. Aro A, Jauhiainen M, Partanen R, Salminen I, Mutanen M. Stearic acid, *trans* fatty acids, and dairy fat: effects on serum and lipoprotein lipids, apolipoproteins, lipoprotein(a), and lipid transfer proteins in healthy subjects. Am J Clin Nutr 1997;65: 1419–26.
7. Katan MB, Zock PL, Mensink RP. Dietary oils, serum lipoproteins, and coronary heart disease. Am J Clin Nutr 1995;61(suppl): 1368S–73S.
8. Temme E, Mensink RP, Hornstra G. Comparison of the effects of diets enriched in lauric, palmitic, or oleic acids on serum lipids and lipoproteins in healthy women and men. Am J Clin Nutr 1996; 63:897–903.
9. Hu FB, Stampfer MJ, Manson JE, et al. Dietary fat intake and risk of coronary heart disease in women. N Engl J Med 1997; 337:1491–9.
10. Colditz GA, Manson JE, Hankinson SE. The Nurses' Health Study: 20-year contribution to the understanding of health among women. J Womens Health 1997;6:49–62.
11. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51–65.
12. Willett WC, Sampson L, Browne ML, et al. The use of a self-administered questionnaire to assess diet four years in the past. Am J Epidemiol 1988;127:188–99.

13. US Department of Agriculture. Composition of foods—raw, processed, and prepared, 1963–1991. Agricultural handbook nos. 8–1 to 8–21. Washington, DC: US Government Printing Office, 1992.
14. Rose GA, Blackburn H. Cardiovascular survey methods. World Health Organ Monogr Ser 1982;58.
15. Stampfer MJ, Willett WC, Speizer FE, et al. Test of the National Death Index. Am J Epidemiol 1984;119:837–9.
16. D'Agostino RB, Lee ML, Belanger AJ, Cupples LA, Anderson K, Kannel WB. Relation of pooled logistic regression to time dependent Cox regression analysis: The Framingham Heart Study. Stat Med 1990;9:1501–15.
17. Willett WC. Nutritional epidemiology. 2nd ed. New York: Oxford University Press, 1998.
18. Shekelle RB, Stamler J, Paul O, Shryock AM, Liu S, Lepper M. Dietary lipids and serum cholesterol level: change in diet confounds the cross-sectional association. Am J Epidemiol 1982;115:506–14.
19. Yu S, Derr J, Etherton TD, Kris-Etherton PM. Plasma cholesterol-predictive equations demonstrate that stearic acid is neutral and monounsaturated fatty acids are hypocholesterolemic. Am J Clin Nutr 1995; 61:1129–39.
20. Cater NB, Heller HJ, Denke MA. Comparison of the effects of medium-chain triacylglycerols, palm oil, and high oleic acid sunflower oil on plasma triacylglycerol fatty acids and lipid and lipoprotein concentrations in humans. Am J Clin Nutr 1997;65:41–5.
21. Tholstrup T, Marckmann P, Jespersen J, Vessby B, Jart A, Sandstrom B. Effect on blood lipids, coagulation, and fibrinolysis of a fat high in myristic acid and a fat high in palmitic acid. Am J Clin Nutr 1994; 60:919–25.
22. Zock P, de Vries J, Katan M. Impact of myristic acid versus palmitic acid on plasma lipids and lipoprotein levels in healthy women and men. Arterioscler Thromb 1994;60:919–25.
23. Mitropoulos KA, Miller GJ, Martin JC, Reeves BEA, Cooper J. Dietary fat induces changes in factor VII coagulant activity through effects on plasma free stearic acid concentration. Arterioscler Thromb 1994;14:214–22.
24. Furguson JC, Mackay N, McNicol GP. Effect of feeding fat on fibrinolysis, Stypven time, and platelet aggregation in Africans, Asians, and Europeans. J Clin Pathol 1970;23:580–5.
25. Weitraub MS, Zechner R, Brown A, Eisenberg S, Breslow JL. Dietary polyunsaturated fats of the ω-6 and ω-3 series reduce postprandial lipoprotein levels. Chronic and acute effects of fat saturation on postprandial lipoprotein metabolism. J Clin Invest 1988;82:1884–93.
26. Dayton S, Pearce ML, Goldman H. Controlled trial of a diet high in unsaturated fat for prevention of atherosclerotic complications. Lancet 1968;16:1060–2.
27. Turpeinen O, Karvonen MJ, Pekkarinen M, Miettinen M, Elosuo R, Paavilainen E. Dietary prevention of coronary heart disease: The Finnish Mental Hospital Study. Int J Epidemiol 1979;8:99–118.