American Journal of Epidemiology
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Vol. 145, No. 10
Printed in U.S.A.

Intake of Fatty Acids and Risk of Coronary Heart Disease in a Cohort of Finnish Men

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

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The relation of intakes of specific fatty acids and the risk of coronary heart disease was examined in a cohort of 21,930 smoking men aged 50–69 years who were initially free of diagnosed cardiovascular disease. All men participated in the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study and completed a detailed and validated dietary questionnaire at baseline. After 6.1 years of follow-up from 1985–1988, the authors documented 1,399 major coronary events and 635 coronary deaths. After controlling for age, supplement group, several coronary risk factors, total energy, and fiber intake, the authors observed a significant positive association between the intake of *trans*-fatty acids and the risk of coronary death. For men in the top quintile of *trans*-fatty acid intake (median = 6.2 g/day), the multivariate relative risk of coronary death was 1.39 (95% confidence interval (CI) 1.09–1.78) (p for trend = 0.004) as compared with men in the lowest quintile of intake (median = 1.3 g/day). The intake of omega-3 fatty acids from fish was also directly related to the risk of coronary death in the multivariate model adjusting also for *trans*-saturated and *cis*-monounsaturated fatty acids (relative risk (RR) = 1.30, 95% CI 1.01–1.67) (p for trend = 0.06 for men in the highest quintile of intake compared with the lowest). There was no association between intakes of saturated or *cis*-monounsaturated fatty acids, linoleic or linolenic acid, or dietary cholesterol and the risk of coronary deaths. All the associations were similar but somewhat weaker for all major coronary events. *Am J Epidemiol* 1997;145:876–87.

cardiovascular diseases; diet; fats; lipids; mortality

Prospective studies addressing associations between dietary fats and the risk of coronary heart disease have failed to provide consistent evidence to support or refute the classical diet-heart hypothesis, which predicts adverse effects of dietary saturated fat and cholesterol and a beneficial effect of polyunsaturated fat intake (1, 2). However, many of these studies were small or used inadequate methods of dietary assessment, which could explain a failure to find associations. The evidence on *trans*-fatty acid intake in the etiology of coronary heart disease is controversial. *trans*-Fatty acids were associated with a higher risk of coronary heart disease in some epidemiologic studies (3–5), while some others have found no clear association (6, 7). Although an inverse association between fish consumption and the risk of coronary death has been seen in several prospective studies (8–12), other studies have failed to find an association (13–16). Of the three studies also reporting omega-3 fatty acid intake from fish (11, 15, 16), only one found an inverse association (11).

Received for publication February 26, 1996, and accepted for publication January 8, 1997.

Abbreviations: CI, confidence interval; ICD, *International Classification of Diseases*; RR, relative risk.

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MATERIALS AND METHODS

Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study was a randomized, double-blind, placebo-controlled primary prevention trial undertaken to determine whether supplementation with alpha-tocopherol, beta-carotene, or both would reduce the incidence of lung cancer in male smokers. The rationale, design, and methods of the study as well as the characteristics of the participants have been previously described in detail (17). The main results indi-

cated no reduction in lung cancer incidence after 5–8 years of dietary supplementation with either alpha-tocopherol or beta-carotene (18).

Participants were male smokers recruited from the total male population in 14 geographic areas in southwestern Finland from the respondents to a postal survey (n = 224,377) in 1985–1988. To be eligible, they had to be 50–69 years of age, to smoke five or more cigarettes per day at entry, and to give written informed consent. The exclusion criteria included a history of cancer or other serious disease limiting participation; use of vitamin E, vitamin A, or beta-carotene supplements in excess of predefined doses; and treatment with anticoagulant agents.

After these exclusions, 29,133 men were randomized into one of four supplementation regimens: alpha-tocopherol alone (daily dose of 50 mg), beta-carotene alone (20 mg), alpha-tocopherol and beta-carotene, or placebo. Follow-up continued for 5–8 years (median = 6.1 years), until death or April 30, 1993.

Diet was assessed at baseline using a self-administered, modified diet history method (19). This questionnaire was satisfactorily completed by 27,111 participants (93 percent). We excluded men who reported at baseline any prior diagnosis of myocardial infarction, angina, stroke, or diabetes (n = 4,346). We also excluded men with typical exercise-related chest pain (Rose classes 1 and 2) as well as men with missing data on cardiovascular risk factors (n = 835). After these exclusions, 21,930 men remained for the present analyses.

Baseline measurements

At baseline, the men provided information on general background characteristics and medical, smoking, and occupational history. Educational level was categorized as less than 7 years of school, 7–11 years, and more than 11 years. The frequency of leisure time physical activity (at least slightly strenuous activity for a minimum of 30 minutes at a time) was categorized as less than once a week, once or twice per week, or three or more times per week. Height and weight were measured, and the body mass index was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured from the right arm with a mercury sphygmomanometer under standardized conditions. The lower of two measurements at least 1 minute apart was recorded. Serum samples were collected and stored at −70°C for later analysis. Serum total and high density lipoprotein cholesterol levels were determined enzymatically (CHOD-PAP method; Boehringer Mannheim, New York, New York) (20). High density lipoprotein cholesterol was measured after precipitation of very low density and low density lipoproteins with dextran sulfate-magnesium chloride (21).

Dietary assessment

The diet questionnaire included 276 food items and mixed dishes and a portion size picture booklet of 122 photographs of foods, each with 3–5 different portion sizes. Each subject was asked to report the usual frequency of consumption and the usual portion size of foods during the previous 12 months. The frequencies were reported as the number of times per month, week, or day. At the first visit, the questionnaire together with the picture booklet was given to the subject to be completed at home. At the second baseline visit 2 weeks later, the questionnaire was returned and a nurse checked and completed it, spending on average 30 minutes interviewing the man about possible discrepancies.

The type of fat used on bread, which is an important carrier of fat in the Finnish diet, was asked by the brand name of the product. In order to have the type of fat used in cooking as correct as possible, the questionnaire included a question on where the main meals (lunch and dinner) were mostly eaten (at home, outside home, or both) and what type of fat was used in cooking. This information was used in the recipes of the mixed dishes.

The fatty acid content of foods was based on the analyses of 77 individual fatty acids or fatty acid isomers in Finnish foods carried out at the Department of Food Chemistry, University of Helsinki (22, 23). These analyses covered, for example, all commercially available brand names of fats (butter, butter-oil mixtures, margarines, oils). As a measure of *trans*-fatty acid intake, we included all *trans* isomers of 16- to 22-carbon fatty acids ($C_{16:1}$, $C_{18:1}$, $C_{18:2}$, $C_{20:1}$, and $C_{22:1}$). Omega-3 fatty acids from fish were defined as omega-3 polyunsaturated fatty acids of 20- and 22-carbon atoms. The intakes of lauric, myristic, and palmitic acids were combined, because these saturated fatty acids increase more the serum concentration of low density lipoprotein cholesterol than stearic acid.

The dietary method was validated in a pilot study carried out among 190 men prior to the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (19). The men completed the questionnaire first and then kept 24 days of food records spread over 6 months as the reference method. They filled in the questionnaire again at the end. The energy-adjusted correlations between the first or the second dietary questionnaire and the food records were 0.45/0.59 for total triglycerides, 0.64/0.75 for saturated fatty acids, 0.52/0.54 for *cis*-monounsaturated fatty acids, 0.71/0.76 for polyunsaturated fatty acids, 0.68/0.76 for li-

noleic acid, 0.55/0.63 for linolenic acid, 0.62/0.73 for *trans*-fatty acids, and 0.42/0.43 for omega-3 fatty acids from fish.

Ascertainment of endpoints

The endpoints of this study were major coronary events and coronary death. The major coronary events (n = 1,399) comprised the first nonfatal myocardial infarction (alive on day 28 from the onset of the attack) during the study (n = 818) or death due to coronary heart disease (n = 581). Data on nonfatal myocardial infarction were obtained from the National Hospital Discharge Register. Men who had a hospital discharge diagnosis with *International Classification of Diseases* (ICD), Eighth Revision, code 410.00 or 410.99 through December 31, 1986, or ICD, Ninth Revision, code 410.00 or 410.99 since January 1, 1987, were considered to be having an acute myocardial infarction. Deaths were identified through the Central Population Register. The death certificates were reviewed by one study physician, and a coronary death was assigned when coronary heart disease was described as the underlying cause of death (ICD, Ninth Revision, codes 410–414). In addition, the validity of the diagnosis of major coronary events was evaluated in 408 cases for whom all relevant information on the attack was collected from hospitals and pathology departments (24). The cases were reviewed according to the MONICA criteria (25), and 94 percent of them were then diagnosed as either definite or possible myocardial infarctions. Fifty-four men survived their first myocardial infarction but died from coronary heart disease during the study. These men were included in both major coronary events and coronary deaths. Thus, there are 635 coronary deaths in the analysis of associations between the intake of specific fatty acids and coronary mortality.

Statistical analysis

Participants contributed follow-up time from the date of randomization until an end point, death, or April 30, 1993. Men were grouped into quintiles of energy-adjusted intakes of nutrients as calculated from the dietary questionnaire. All nutrients were log-transformed before the energy adjustment, which was done by the residual method (26).

Proportional hazards models were used to estimate the relative risks (with 95 percent confidence intervals) of coronary heart disease associated with intakes of specific fatty acids, with simultaneous adjustment for age and supplementation group first and then for cardiovascular risk factors. Adjustment for supplementation group was done because the main results of the trial showed fewer deaths due to coronary heart disease among participants receiving alpha-tocopherol than among those not receiving alpha-tocopherol but more coronary deaths among recipients of beta-carotene than among those not receiving beta-carotene (18). Tests for the linearity of the trend were done by treating the energy-adjusted values of nutrients as continuous variables in the proportional hazards model. All p values are two tailed. The main analyses were corrected for measurement errors in assessing diet using the method developed by Prentice (27). The main analyses were also repeated in the placebo group of the trial cohort.

RESULTS

The number of cigarettes per day, years of smoking, blood pressure, body mass index, and serum total cholesterol were directly associated with the risk of both major coronary events and coronary deaths, whereas high density lipoprotein cholesterol, education, and physical activity were inversely related to the risk of coronary heart disease. Alcohol was inversely but nonsignificantly associated with all coronary events but had a u-shaped relation with coronary deaths. There was no association between energy intake and the risk of coronary heart disease. Fiber intake was inversely related to the risk of coronary heart disease.

After adjusting for age and supplementation group, we found that the only fatty acids that had a significant relation to the risk of major coronary event were *trans*-fatty acids (table 1). The relative risk comparing the highest quintile with the lowest was 1.19 (95 percent CI 1.00–1.41) (p for trend = 0.06). Adjustment for several cardiovascular risk factors slightly attenuated the relation (RR = 1.14, 95 percent CI 0.96–1.35) (p for trend = 0.16). Saturated, *cis*-monounsaturated or polyunsaturated fatty acids were not associated with the risk of coronary heart disease.

The intake of *trans*-fatty acids was also significantly associated with the risk of coronary death (table 2). The relative risk was 1.38 (95 percent CI 1.08–1.76) (p for trend = 0.006) for men in the highest quintile of intake compared with the lowest in the model adjusting for age and supplementation group. Further adjustment for coronary risk factors and fiber did not appreciably change the association (RR = 1.39, 95 percent CI 1.09–1.78) (p for trend = 0.004). Again, no significant associations between the intake of other fatty acids and the risk of coronary death were found in the model adjusting for age and supplementation group. However, in the multivariate models, there were significant inverse associations between coronary death

and the intake of saturated fatty acids and a positive association for polyunsaturated fatty acids and linoleic acid (p for trend both < 0.05). Further adjustment for serum total and high density lipoprotein cholesterol did not change the associations.

We examined these associations further in simultaneous models (table 3). After adjustment for the other fatty acids, the association between intakes of saturated fatty acids and linoleic acid and coronary death became nonsignificant. There was an inverse association between the intake of linolenic acid and the risk of coronary death; the relative risk between the extreme quintiles was 0.75 (95 percent CI 0.52–1.10) (p for trend = 0.05), but there was no significant association with *cis*-monounsaturated fatty acids. We observed a positive association between omega-3 fatty acid intake from fish and coronary death; the relative risk was 1.30 (95 percent CI 1.01–1.67) (p for trend = 0.06) for men in the highest quintile of intake compared with those in the lowest quintile. Consumption of fish was more weakly related to the risk of coronary death. The relative risk of coronary death in the highest quintile of fish intake was 1.12 (95 percent CI 0.88–1.43) (p for trend = 0.07) in the univariate model and 1.12 (95 percent CI 0.87–1.45) (p for trend = 0.09) in the multivariate model.

Adjustment for vitamin E, vitamin C, and beta-carotene did not change the results for saturated fatty acids or linoleic acid. However, the inverse association between coronary death and the intake of *cis*-monounsaturated fatty acids became stronger (RR between the extreme quintiles = 0.73, 95 percent CI 0.56–0.95) (p for trend = 0.06). This was also seen for linolenic acid (RR = 0.71, 95 percent CI 0.49–1.02) (p for trend = 0.07). The direct association with omega-3 fatty acids from fish remained similar (RR = 1.29, 95 percent CI 1.01–1.65) (p for trend = 0.07).

We examined the possible associations between the intake of *trans*-fatty acids and selected coronary heart disease risk factors as well as other dietary factors (table 4). There were no differences in age, smoking, body mass index, serum cholesterol, high density lipoprotein cholesterol, blood pressure, education, or physical activity across quintiles of *trans*-fatty acid intake. Intakes of saturated fatty acids and cholesterol were lowest in men in the lowest and highest quintile of *trans*-fatty acid intake, whereas the intake of polyunsaturated fatty acids and vitamin E increased with the intake of *trans*-fatty acids. There were no substantial differences in the intakes of dietary fiber, beta-carotene, or vitamin C. Alcohol intake was highest in the lowest quintile of *trans*-fatty acid intake. Men in the highest quintile of *trans*-fatty acid intake avoided butter almost completely (median = 5.2 g/day) but consumed considerable amounts of margarine (median = 49.6 g/day). *trans*-Fatty acid intake was not related to red meat or fish intake.

The relative risks of coronary death for total *trans*-fatty acids, elaidic acid, and *trans* isomers from vegetable and animal origin are shown in table 5. The results were almost identical for total *trans*-fatty acids, elaidic acid, and *trans* isomers from vegetable fats, whereas no association was seen between coronary death and *trans*-fatty acids from animal origin. Further adjustment for the intakes of saturated fat, linoleic acid, and cholesterol slightly increased the relative risks, although the confidence intervals also widened because of collinearity, especially with linoleic acid (the correlation between the energy-adjusted intakes of *trans*-fatty acids and linoleic acid was 0.81).

The association between *trans*-fatty acid intake as a percentage of energy and the risk of coronary death was also significant. The relative risk comparing the highest with the lowest quintile of intake was 1.43 (95 percent CI 1.12–1.84) (p for trend = 0.004). However, as can be seen in figure 1, the association is produced by the highest quintile of intake.

The analyses were repeated in the placebo group of the trial cohort, and they showed similar results. For example, the relative risk of coronary death for men in the highest quintile of *trans*-fatty acid intake compared with the lowest was 1.28 (95 percent CI 0.77–2.12). The confidence intervals are larger because of the smaller number of cases.

We used the data from the validation study to correct for the measurement error in estimating nutrient intakes. When the uncorrected relative risk of coronary death for an increment of 2 g of omega-3 fish fatty acids was 1.55 (95 percent CI 1.03–2.35) in the same model as in table 2, with the measurement error correction for intakes of energy, alcohol, dietary fiber, and omega-3 fatty acids from fish, the relative risk was 4.42 (95 percent CI 1.58–12.31). The uncorrected relative risk for an increment of 5 g of *trans*-fatty acids was 1.34 (95 percent CI 1.23–1.46) in the same basic model, and the corrected relative risk was 2.21 (95 percent CI 1.68–2.91). For comparison, the uncorrected relative risk for an increment of 5 g of saturated fatty acids was 0.96 (95 percent CI 0.95–0.98), and the corrected relative risk was 0.90 (95 percent CI 0.87–0.94).

DISCUSSION

In this large cohort of middle-aged men, we found no clear association between the intake of saturated fatty acids, linoleic acid, or cholesterol and the risk of coronary heart disease. *trans*-Fatty acid intake was

positively associated with the risk of coronary death. We found no support for the hypothesized inverse association between the intake of omega-3 fatty acids from fish and the risk of coronary heart disease; if anything, a positive association with coronary death was supported. Fish intake was less strongly related to the higher risk of major coronary events or coronary death. Inverse associations between the intakes of *cis*-monounsaturated fatty acids and linolenic acid and coronary death were also suggested.

Failure to demonstrate predicted associations could be due to random misclassification of dietary exposures, which tends to attenuate existing associations. Based on the validation study, the measurement error in all the specific fatty acids except for omega-3 fatty acids from fish seemed to be of about the same magnitude. Correlations between the intakes of fatty acids based on the dietary questionnaire and the food records were all between 0.62 and 0.76, but the correlation for omega-3 fatty acids from fish was 0.42. With this degree of validity together with the size of the study, we should have been able to detect important associations.

Compared with the previously reported cohorts, men in our study had a diet high in saturated fatty acids and cholesterol and low in polyunsaturated fatty acids, and they were all smokers. Their serum cholesterol level was also high compared with most other populations (median = 6.1 mmol/liter). One explanation for the lack of association between saturated fat intake and coronary heart disease is that men at high risk for coronary heart disease (e.g., family history)

TABLE 1. Relative risk (RR) of major coronary event by energy-adjusted quintiles of fatty acid intake, Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study during 6-year follow-up from 1985–1988

Quintile (intakes as medians)	Total triglycerides				Saturated fatty acids			
	Intake (g)	Cases/ person-years	Age-adjusted RR*	Multivariate RR†	Intake (g)	Cases/ person-years	Age-adjusted RR	Multivariate RR
1	83.2	268/24,961	1.00	1.00	34.7	283/25,353	1.00	1.00
2	94.7	274/25,523	0.99 (0.84–1.17)‡	0.95 (0.80–1.12)	43.3	254/25,347	0.89 (0.75–1.05)	0.87 (0.73–1.03)
3	102.4	278/25,486	1.01 (0.85–1.19)	0.94 (0.79–1.12)	50.3	250/25,853	0.84 (0.71–1.00)	0.82 (0.69–0.97)
4	110.1	277/25,414	0.99 (0.83–1.17)	0.88 (0.74–1.05)	57.4	307/25,346	1.03 (0.87–1.21)	0.95 (0.80–1.13)
5	121.6	302/25,586	1.05 (0.89–1.24)	0.87 (0.73–1.05)	67.5	305/25,271	0.99 (0.84–1.16)	0.87 (0.73–1.03)
p for trend			0.303	0.295			0.672	0.189
	C_{12}-C_{16} saturated fatty acids				*cis*-Monounsaturated fatty acids			
	Intake (g)	Cases/ person-years	Age-adjusted RR	Multivariate RR	Intake (g)	Cases/ person-years	Age-adjusted RR	Multivariate RR
1	21.7	283/25,393	1.00	1.00	26.0	286/24,995	1.00	1.00
2	27.1	257/25,372	0.90 (0.76–1.06)	0.88 (0.74–1.04)	29.5	268/25,454	0.92 (0.78–1.08)	0.88 (0.75–1.04)
3	31.5	252/25,632	0.85 (0.72–1.01)	0.83 (0.69–0.98)	31.8	273/25,515	0.95 (0.81–1.12)	0.89 (0.75–1.06)
4	35.8	296/25,334	0.99 (0.84–1.17)	0.91 (0.77–1.08)	34.1	297/25,355	1.04 (0.89–1.23)	0.95 (0.80–1.13)
5	42.2	311/25,240	1.01 (0.86–1.18)	0.88 (0.74–1.04)	37.8	275/25,651	0.96 (0.81–1.13)	0.82 (0.69–0.99)
p for trend			0.644	0.184			0.658	0.186
	Oleic acid				*trans*-Fatty acids			
	Intake (g)	Cases/ person-years	Age-adjusted RR	Multivariate RR	Intake (g)	Cases/ person-years	Age-adjusted RR	Multivariate RR
1	22.7	278/24,997	1.00	1.00	1.3	244/24,675	1.00	1.00
2	25.8	288/25,449	1.02 (0.87–1.20)	0.98 (0.82–1.15)	1.7	288/25,241	1.13 (0.95–1.34)	1.10 (0.93–1.31)
3	27.8	270/25,407	0.97 (0.82–1.15)	0.92 (0.77–1.09)	2.0	268/25,675	1.02 (0.86–1.22)	0.97 (0.82–1.16)
4	29.8	291/25,456	1.05 (0.89–1.24)	0.95 (0.80–1.13)	2.7	297/25,675	1.14 (0.96–1.34)	1.07 (0.90–1.28)
5	33.1	272/25,661	0.98 (0.83–1.16)	0.84 (0.70–1.01)	6.2	302/25,703	1.19 (1.00–1.41)	1.14 (0.96–1.35)
p for trend			0.629	0.223			0.055	0.158
	Polyunsaturated fatty acids				Linoleic acid			
	Intake (g)	Cases/ person-years	Age-adjusted RR	Multivariate RR	Intake (g)	Cases/ person-years	Age-adjusted RR	Multivariate RR
1	6.6	283/24,863	1.00	1.00	4.4	294/24,832	1.00	1.00
2	8.0	280/25,437	1.00 (0.85–1.18)	1.01 (0.85–1.19)	5.6	265/25,409	0.92 (0.78–1.09)	0.92 (0.78–1.09)
3	9.6	290/25,346	1.08 (0.91–1.27)	1.09 (0.92–1.29)	6.9	288/25,407	1.04 (0.88–1.22)	1.05 (0.89–1.24)
4	12.5	251/25,650	0.93 (0.79–1.11)	0.97 (0.81–1.15)	9.6	260/25,623	0.94 (0.79–1.11)	0.97 (0.82–1.15)
5	20.7	295/25,674	1.09 (0.93–1.29)	1.11 (0.94–1.31)	17.6	292/25,699	1.04 (0.89–1.23)	1.06 (0.90–1.25)
p for trend			0.524	0.470			0.544	0.481

Table 1 continues

TABLE 1. Continued

Quintile (intakes as medians)	Linolenic acid				Omega-3 fish fatty acids			
	Intake (g)	Cases/ person-years	Age-adjusted RR	Multivariate RR	Intake (g)	Cases/ person-years	Age-adjusted RR	Multivariate RR
1	0.9	303/24,808	1.00	1.00	0.2	284/25,538	1.00	1.00
2	1.2	277/24,345	0.93 (0.79–1.09)	0.94 (0.80–1.11)	0.3	263/25,630	0.94 (0.79–1.11)	0.94 (0.80–1.12)
3	1.5	280/25,714	0.96 (0.81–1.13)	0.99 (0.84–1.17)	0.4	280/25,460	1.01 (0.85–1.19)	1.03 (0.87–1.21)
4	1.9	274/25,471	0.95 (0.81–1.13)	1.01 (0.86–1.20)	0.5	274/25,390	0.98 (0.83–1.16)	1.02 (0.86–1.20)
5	2.5	265/25,632	0.94 (0.80–1.11)	0.96 (0.80–1.14)	0.8	298/24,952	1.10 (0.94–1.30)	1.15 (0.97–1.35)
p for trend			0.716	0.911			0.298	0.119

	Cholesterol			
	Intake (mg)	Cases/ person-years	Age-adjusted RR	Multivariate RR
1	390	290/25,196	1.00	1.00
2	477	258/25,463	0.88 (0.75–1.04)	0.86 (0.72–1.02)
3	543	282/25,394	0.96 (0.81–1.13)	0.91 (0.77–1.08)
4	621	273/25,421	0.92 (0.78–1.09)	0.87 (0.73–1.03)
5	768	296/25,496	1.01 (0.86–1.18)	0.93 (0.79–1.10)
p for trend			0.255	0.813

* Adjusted for age (5-year categories) and treatment group.
† Adjusted further for smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7–11, >11 years), and physical activity (<1, 1–2, >2 times per week).
‡ Numbers in parentheses, 95% confidence interval.

had reduced their saturated fat intake. Unfortunately, we did not collect data on family history of coronary heart disease. It could also be argued that men at high risk reduced their intake of saturated fat during the study. Since we do not have repeated measurements on everybody in the study, this possibility cannot be examined. However, the mean serum cholesterol level remained the same throughout the study in an annual subsample of about 700 men (different men each time). We also excluded men with angina pectoris at baseline and, thus, excluded the possibility that men could have changed their diet because of symptoms.

One could argue that maybe the range of saturated fat intake was not large enough to detect an association with coronary risk. The median intake was 11 percent of energy in the lowest quintile and 21.9 percent of energy in the highest quintile. The median intake of polyunsaturated fatty acids in these quintiles of saturated fat intake was 5.3 percent of energy and 2.3 percent of energy in the highest, and that of cholesterol was 168 mg/1,000 kcal versus 214 mg/1,000 kcal. When these ranges are used in the Keys equation (28), the expected change in serum cholesterol would be 42 mg/100 dl (1.09 mmol/liter). If we assume that a reduction in total serum cholesterol of 0.6 mmol/liter will cause a 24 percent decrease in the risk of coronary heart disease (29), the predicted decrease in the risk of coronary death should have been 44 percent. However, the dietary questionnaire probably exaggerates the true range of intakes of all nutrients. Based on our validation study (19) where we used 24 days of food records as the reference method, the range was, in fact, 57 percent narrower for saturated fatty acids, 82 percent narrower for polyunsaturated fatty acids, and 79 percent narrower for dietary cholesterol intake. After correcting for this difference, the expected change in serum total cholesterol would be 0.77 mmol/liter, and the estimated decrease in the risk of coronary death would be 31 percent. Thus, we should have been able to detect such an association had it existed.

A positive association between saturated fat intake and the risk of coronary heart disease has been found in five cohort studies: among men of Japanese ancestry in Hawaii (30), among men of Irish descent in Boston and Ireland (31), among younger men in the Framingham Study (32), among male Israeli civil servants (33), and among male health professionals in the United States (34). No significant associations were found in several other cohort studies (35–40) but, with the exception of the Western Electric Study (36), these had limited power because of their small size (35, 38–40) or inadequate dietary assessment (37, 38).

Cholesterol intake was associated with an increased risk of coronary death in the Honolulu Heart Study (30), the Ireland-Boston Diet-Heart Study (31), and the Western Electric Study (41). In the Health Professionals Follow-up Study, cholesterol intake was asso-

ciated with an increased risk of death from coronary heart disease, but, as with saturated fat, the association was largely explained by fiber intake (34). No significant associations were found in other cohort studies (31, 35, 37–39). The intake of polyunsaturated fatty acids was inversely associated with the risk of coronary heart disease in some (11, 34–36) but not in all (30, 31, 37, 38, 42) cohort studies.

The hypothesis that frequent intake of fish is protective of coronary heart disease has recently been challenged by three recent prospective studies. Among US male health professionals, increasing fish intake from one to two servings per week to five to six servings did not substantially reduce the risk of coronary heart disease (16). Among Finnish men living in the eastern lake area, a high intake of nonfatty freshwater fish and the consequent accumulation of mercury in the body were associated with an excess risk of myocardial infarction as well as death from coronary heart disease, cardiovascular disease, and all causes combined (43). The authors speculated that the underlying mechanism is the promotion of lipid peroxidation by mercury. The men in our study do not live in the same area and have access to both seawater and lake fish. Our results concerning a possible harmful effect of omega-3 fatty acids do not support the hypothesis that increasing the intake of omega-3 fish fatty acids or fish protects against coronary heart disease. As pointed out recently by Kromhout et al. (12), it could be that the possible protective effect of fish can only be detected in populations where a large proportion do not eat fish at all, as was the case in their

TABLE 2. Relative risk (RR) of coronary death by energy-adjusted quintiles of fatty acid intake, Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study during 6-year follow-up from 1985–1988

Quintile (intakes as medians)	Total triglycerides				Saturated fatty acids			
	Intake (g)	Cases/ person-years	Age-adjusted RR*	Multivariate RR†	Intake (g)	Cases/ person-years	Age-adjusted RR	Multivariate RR
1	83.2	123/25,455	1.00	1.00	34.7	138/25,827	1.00	1.00
2	94.7	133/25,961	1.04 (0.81–1.33)‡	1.05 (0.82–1.35)	43.3	113/25,818	0.81 (0.63–1.04)	0.80 (0.63–1.03)
3	102.4	122/25,972	0.96 (0.75–1.23)	0.96 (0.74–1.25)	50.3	116/26,083	0.79 (0.62–1.01)	0.77 (0.60–1.00)
4	110.1	125/25,900	0.95 (0.74–1.22)	0.91 (0.70–1.18)	57.4	135/25,869	0.90 (0.71–1.14)	0.83 (0.65–1.07)
5	121.6	132/26,100	0.97 (0.76–1.24)	0.85 (0.65–1.12)	67.5	133/25,790	0.83 (0.66–1.06)	0.73 (0.56–0.95)
p for trend			0.894	0.349			0.329	0.044
	C_{12}–C_{16} saturated fatty acids				*cis*-Monounsaturated fatty acids			
	Intake (g)	Cases/ person-years	Age-adjusted RR	Multivariate RR	Intake (g)	Cases/ person-years	Age-adjusted RR	Multivariate RR
1	21.7	138/25,873	1.00	1.00	26.0	151/25,455	1.00	1.00
2	27.1	112/25,842	0.80 (0.62–1.02)	0.79 (0.61–1.02)	29.5	113/25,939	0.73 (0.57–0.93)	0.72 (0.57–0.93)
3	31.5	114/26,087	0.77 (0.60–0.99)	0.76 (0.59–0.98)	31.8	120/25,986	0.80 (0.63–1.02)	0.77 (0.60–0.99)
4	35.8	135/25,836	0.90 (0.71–1.14)	0.84 (0.65–1.07)	34.1	121/25,925	0.81 (0.64–1.03)	0.76 (0.59–0.98)
5	42.2	136/25,751	0.85 (0.67–1.08)	0.74 (0.57–0.96)	37.8	130/26,084	0.88 (0.69–1.11)	0.77 (0.59–1.00)
p for trend			0.349	0.045			0.504	0.145
	Oleic acid				*trans*-Fatty acids			
	Intake (g)	Cases/ person-years	Age-adjusted RR	Multivariate RR	Intake (g)	Cases/ person-years	Age-adjusted RR	Multivariate RR
1	22.7	149/25,437	1.00	1.00	1.3	109/25,070	1.00	1.00
2	25.8	124/25,959	0.82 (0.65–1.04)	0.81 (0.63–1.03)	1.7	122/25,756	1.05 (0.81–1.36)	1.05 (0.81–1.36)
3	27.8	113/25,901	0.77 (0.60–0.98)	0.74 (0.58–0.96)	2.0	136/26,112	1.14 (0.88–1.47)	1.12 (0.87–1.45)
4	29.8	122/25,996	0.83 (0.65–1.05)	0.77 (0.60–1.00)	2.7	111/26,265	0.92 (0.71–1.20)	0.90 (0.69–1.18)
5	33.1	127/26,095	0.87 (0.69–1.11)	0.76 (0.59–0.99)	5.6	157/26,186	1.38 (1.08–1.76)	1.39 (1.09–1.78)
p for trend			0.581	0.213			0.006	0.004
	Polyunsaturated fatty acids				Linoleic acid			
	Intake (g)	Cases/ person-years	Age-adjusted RR	Multivariate RR	Intake (g)	Cases/ person-years	Age-adjusted RR	Multivariate RR
1	6.6	140/25,320	1.00	1.00	4.4	146/25,301	1.00	1.00
2	8.0	119/25,916	0.88 (0.69–1.12)	0.92 (0.72–1.18)	5.6	115/25,863	0.83 (0.65–1.06)	0.87 (0.68–1.11)
3	9.6	127/25,887	0.99 (0.78–1.26)	1.06 (0.83–1.36)	6.9	121/25,947	0.92 (0.72–1.17)	0.99 (0.78–1.27)
4	12.5	102/26,092	0.80 (0.62–1.04)	0.90 (0.69–1.17)	9.6	106/26,094	0.81 (0.63–1.04)	0.91 (0.70–1.17)
5	20.7	147/26,173	1.15 (0.91–1.45)	1.27 (1.00–1.61)	17.6	147/26,183	1.11 (0.88–1.40)	1.22 (0.97–1.55)
p for trend			0.156	0.034			0.141	0.032

Table 2 continues

TABLE 2. Continued

Quintile (intakes as medians)	Linolenic acid				Omega-3 fish fatty acids			
	Intake (g)	Cases/ person-years	Age-adjusted RR	Multivariate RR	Intake (g)	Cases/ person-years	Age-adjusted RR	Multivariate RR
1	0.9	149/25,277	1.00	1.00	0.2	126/26,032	1.00	1.00
2	1.2	127/25,821	0.89 (0.70–1.12)	0.94 (0.74–1.20)	0.3	114/26,081	0.93 (0.72–1.19)	0.93 (0.72–1.20)
3	1.5	124/26,226	0.90 (0.71–1.14)	0.98 (0.77–1.25)	0.4	120/25,950	0.98 (0.77–1.26)	0.98 (0.76–1.27)
4	1.9	122/25,961	0.90 (0.71–1.15)	1.03 (0.81–1.32)	0.5	130/25,855	1.06 (0.83–1.35)	1.07 (0.83–1.37)
5	2.5	113/26,103	0.97 (0.68–1.12)	0.99 (0.76–1.28)	0.8	145/25,470	1.23 (0.97–1.56)	1.24 (0.97–1.58)
p for trend			0.423	0.770			0.130	0.118

	Cholesterol			
	Intake (mg)	Cases/ person-years	Age-adjusted RR	Multivariate RR
1	390	132/25,716	1.00	1.00
2	477	123/25,839	0.93 (0.73–1.19)	0.90 (0.71–1.16)
3	543	115/25,904	0.86 (0.67–1.10)	0.81 (0.63–1.05)
4	621	126/25,934	0.93 (0.73–1.19)	0.86 (0.67–1.11)
5	768	139/25,995	1.04 (0.82–1.32)	0.92 (0.72–1.18)
p for trend			0.214	0.767

* Adjusted for age (5-year categories) and treatment group.
† Adjusted further for smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7–11, >11 years), and physical activity (<1, 1–2, >2 times per week).
‡ Numbers in parentheses, 95% confidence interval.

elderly cohort where 40 percent avoided fish. Our situation in Finland, however, is exceptional because of the high mercury content of local freshwater fish. Thus, further analyses using biomarkers of mercury exposure are needed also in this cohort to resolve this issue.

trans-Fatty acids increase serum low density lipoprotein cholesterol and decrease high density lipoprotein cholesterol when they constitute 3–10 percent of energy (44–46). *trans*-Fatty acids have also been found to increase blood levels of Lp[a], a likely risk factor of coronary heart disease, in several metabolic studies (45, 47). In a large prospective study among US nurses (3), women in the highest quintile of *trans*-fatty acid intake had a 40–50 percent higher risk of coronary heart disease compared with women in the lowest quintile. Similar findings were seen in a case-control study primarily among men (4). A positive association between plasma *trans*-fatty acids and the degree of atherosclerosis was observed in a cross-sectional angiographic study (5). In a multicenter case-control study involving eight European countries and Israel (the EURAMIC Study), no significant overall association was found between the $C_{18:1}$ *trans*-fatty acid content of adipose tissue and the risk of first myocardial infarction (6). However, *trans*-fatty acid levels were by far the lowest in the Spanish center, where coronary heart disease rates are also much lower. After excluding these outlying values, the relative risk for the highest quartile (RR = 1.44) was

TABLE 3. Relative risk of coronary death by energy-adjusted quintiles of selected fatty acid intakes in simultaneous models, Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study during 6-year follow-up from 1985–1988

Quintile (intakes as medians)	Saturated fatty acids, multivariate model* adjusting also for *trans*-, *cis*-mono and linoleic acid	*cis*-Monounsaturated fatty acids adjusting also for *trans*-saturated and linoleic acid	Linoleic acid adjusted also for *trans*-, *cis*-monounsaturated and saturated fatty acids	Linolenic acid adjusted also for *trans*-, *cis*-monounsaturated and saturated fatty acids	Omega-3 fish fatty acids adjusted also for *trans*-saturated and *cis*-monounsaturated fatty acids
1	1.00	1.00	1.00	1.00	1.00
2	0.90 (0.68–1.18)†	0.71 (0.55–0.92)	0.89 (0.69–1.15)	0.95 (0.74–1.21)	0.94 (0.73–1.22)
3	0.92 (0.67–1.26)	0.76 (0.58–1.00)	1.04 (0.79–1.37)	0.94 (0.71–1.24)	1.01 (0.78–1.30)
4	1.04 (0.72–1.48)	0.76 (0.57–1.03)	0.90 (0.65–1.26)	0.87 (0.63–1.20)	1.10 (0.86–1.42)
5	0.93 (0.60–1.44)	0.79 (0.56–1.10)	0.92 (0.56–1.50)	0.75 (0.52–1.10)	1.30 (1.01–1.67)
p for trend	0.909	0.429	0.674	0.050	0.056

* Adjusted for age (5-year categories), treatment group, smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber (quintiles), education (<7, 7–11, >11 years), and physical activity (<1, 1–2, >2 times per year).
† Numbers in parentheses, 95% confidence interval.

TABLE 4. Relation of energy-adjusted *trans*-fatty acid intake to selected coronary heart disease risk factors, as well as intake of nutrients and foods at baseline,* Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, 1985–1988

Quintile of *trans*-fatty acid intake	Median daily intake of *trans*-fatty acids (g)	Medians of							
		Age (years)	Smoking (years)	No. of cigarettes/day	Body mass index (kg/m²)	Serum cholesterol (mmol/liter)	HDL cholesterol† (mmol/liter)	Systolic BP† (mmHg)	Diastolic BP (mmHg)
1	1.3	56.4	36.8	19.6	26.2	6.1	1.1	140	88
2	1.7	56.6	36.5	19.6	25.8	6.2	1.1	140	88
3	2.0	57.0	37.1	19.8	25.6	6.3	1.1	139	87
4	2.7	56.9	36.9	19.6	25.6	6.2	1.1	139	87
5	5.6	56.2	36.9	20.0	26.0	6.0	1.1	140	88

	% of group		Median daily intake of							
	Education (>11 years)	Physical activity (>2 times per week)	Energy (kcal)	Triglycerides (g)	Saturated fatty acids (g)	*cis*-Mono-unsaturated fatty acids (g)	Poly-unsaturated fatty acids (g)	Linoleic acid (g)	Linolenic acid (g)	Omega-3 fish fatty acids (g)
1	11.1	20.5	2,657	88.1	43.9	29.1	8.9	6.4	1.5	0.4
2	9.7	17.6	2,794	101.2	53.4	31.7	8.6	6.1	1.4	0.4
3	8.8	17.3	2,844	110.2	60.1	33.4	8.6	6.0	1.3	0.4
4	10.9	17.9	2,770	101.0	57.8	33.5	10.1	7.4	1.5	0.4
5	13.6	19.6	2,673	100.2	38.1	30.3	19.7	16.6	2.2	0.4

	Median daily intake of									
	Cholesterol (mg)	Dietary fiber (g)	Alcohol (g)	Beta-carotene (mg)	Vitamin C (mg)	Vitamin E (mg)	Butter (g)	Margarine (g)	Red meat (g)	Fish (g)
1	517	24.5	16.9	1.75	102	9.7	35.7	5.4	60.4	34.2
2	574	25.0	12.6	1.75	101	9.5	44.2	8.9	63.4	32.8
3	599	24.4	10.0	1.71	96	9.4	51.2	10.2	62.9	31.3
4	584	23.3	9.6	1.70	93	10.6	43.9	17.3	60.7	30.6
5	465	24.6	10.9	1.67	96	17.8	5.1	49.4	56.3	32.2

* Directly age standardized to distribution of whole cohort.
† HDL cholesterol, high density lipoprotein cholesterol; BP, blood pressure.

similar to that observed with coronary deaths in this study. Furthermore, there was a positive association between the adipose tissue *trans*-fatty acid concentration and the risk of first myocardial infarction in the Finnish and Norwegian centers. In a small population case-control study in the United Kingdom, no evidence of an association between adipose tissue *trans*-fatty acids and the risk of sudden cardiac death (n = 66) was found (7). However, because of the small sample size, the confidence interval included the relative risk that we observed.

The average *trans*-fatty acid intake varies from 2 to 10 g/day (equivalent to about 1–4 percent of energy) in different countries in Europe (6), and the estimates vary from 3–5 g based on dietary assessment to 8 g based on Food Balance Sheets in the United States (48–50). Compared with these, the median *trans*-fatty acid intake in our cohort, 2.0 g/day or 0.95 percent of energy, is low. The intake exceeded 2 percent of energy only in the highest quintile of intake, which could explain why the risk of coronary heart disease was not elevated in the lower quintiles. The median intake of *trans*-fatty acids was 2.2 percent of energy in the Nurses' Health Study and 3.2 percent in the fifth quintile (3).

The *trans*-fatty acid content of Finnish margarines used in the 1980s varied from 0 to 17 percent of total fatty acids (22). The *trans*-fatty acid content of hard margarines was generally lower (2.7–13 percent) because of their content of animal fats than that of soft margarines, which ranged from 15 to 17 percent, except for one brand that contained none. The main reason for high *trans*-fatty acid intake in our study was primarily due to heavy use of soft margarines. In the Finnish food pattern, bread has traditionally been the main carrier of butter or margarine as is evident also in our study population of middle-aged men. Besides margarines, there are no other important sources of *trans*-fatty acids in the Finnish diet, which explains the generally low intake compared with many other countries. Based on a national dietary survey carried out in 1992, the average *trans*-fatty acid intake was about 2 g/day, which is about 1 percent of energy (51).

In conclusion, the results of this cohort study support the hypothesis that a high intake of *trans*-fatty acids increased the risk of coronary heart disease,

TABLE 5. Relative risk (RR) of coronary death by energy-adjusted quintiles of *trans*-fatty acid intake, Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study during 6-year follow-up from 1985–1988

Quintile (intakes as medians)	Total *trans*-fatty acids			Elaidic acid		
	Intake (g)	Age-adjusted RR*	Multivariate RR†	Intake (g)	Age-adjusted RR	Multivariate RR
1	1.8	1.00	1.00	1.3	1.00	1.00
2	2.4	1.05 (0.81–1.36)‡	1.05 (0.81–1.36)	1.7	1.04 (0.80–1.34)	1.03 (0.80–1.34)
3	2.9	1.14 (0.88–1.47)	1.12 (0.87–1.45)	2.0	1.07 (0.83–1.38)	1.04 (0.80–1.34)
4	3.5	0.92 (0.71–1.20)	0.90 (0.69–1.18)	2.7	0.92 (0.70–1.19)	0.90 (0.69–1.18)
5	6.2	1.38 (1.08–1.76)	1.39 (1.09–1.78)	5.6	1.35 (1.06–1.73)	1.37 (1.07–1.75)
p for trend		0.006	0.004		0.004	0.002
	Vegetable *trans*-fatty acids			Animal *trans*-fatty acids		
	Intake (g)	Age-adjusted RR	Multivariate RR	Intake (g)	Age-adjusted RR	Multivariate RR
1	0.1	1.00	1.00	0.6	1.00	1.00
2	0.4	0.84 (0.66–1.07)	0.87 (0.68–1.11)	1.1	0.98 (0.76–1.26)	0.97 (0.75–1.25)
3	0.8	0.72 (0.56–0.93)	0.77 (0.60–1.01)	1.5	0.96 (0.75–1.24)	0.91 (0.70–1.19)
4	1.6	0.88 (0.69–1.12)	0.94 (0.73–1.20)	1.9	1.00 (0.78–1.28)	0.90 (0.69–1.17)
5	5.1	1.15 (0.91–1.44)	1.23 (0.97–1.55)	2.5	1.03 (0.80–1.31)	0.83 (0.62–1.11)
p for trend		0.009	0.004		0.857	0.035

* Adjusted for age (5-year categories) and treatment group.
† Adjusted further for smoking, body mass index, blood pressure, intakes of energy, alcohol, and fiber, education (<7, 7–11, >11 years), and physical activity (<1, 1–2, >2 times per week).
‡ Numbers in parentheses, 95% confidence interval.

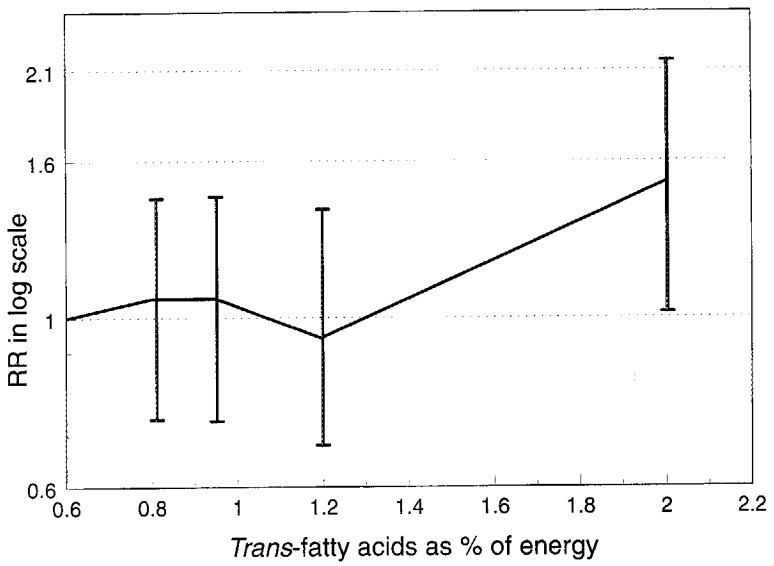

FIGURE 1. Association between *trans*-fatty acid intake as a percentage of energy and the relative risk (RR) of death from coronary heart disease in a model adjusting for smoking, body mass index, blood pressure, education, physical activity, and intakes of total energy, alcohol, and fiber, Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study during 6-year follow-up from 1985–1988. Bars, confidence interval.

especially coronary death. However, residual confounding by unmeasured factors cannot be totally excluded. In contrast to some previous studies, we could not observe any protective effect of omega-3 fish fatty acids; rather, intake of these fatty acids was associated with a higher risk of coronary death. Since the intake of fish was not associated with coronary heart disease, however, a firm conclusion regarding this result cannot be drawn. The selective nature of this cohort (middle-aged, smoking men eating a diet high in fat) warrants relatively cautious extrapolation to other populations.

ACKNOWLEDGMENTS

This study was supported by contract N01-CN-45165 from the National Cancer Institute and a fellowship from the Academy of Finland.

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