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Dietary Fat Intake and Risk of Coronary Heart Disease in Women: 20 Years of Follow-up of the Nurses' Health Study

Kyungwon Oh[1], Frank B. Hu[1,2,3], JoAnn E. Manson[2,3,4], Meir J. Stampfer[1,2,3], and Walter C. Willett[1,2,3]

[1] Department of Nutrition, Harvard School of Public Health, Boston, MA.
[2] Department of Epidemiology, Harvard School of Public Health, Boston, MA.
[3] The Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.
[4] Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.

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The authors examined the associations of dietary fat and specific types of fat with risk of coronary heart disease (CHD) among 78,778 US women initially free of cardiovascular disease and diabetes in 1980. They documented 1,766 incident CHD cases (including 1,241 nonfatal myocardial infarctions and 525 CHD deaths) during 20 years of follow-up. Polyunsaturated fat intake was inversely associated with CHD risk (multivariate relative risk (RR) for the highest vs. the lowest quintile = 0.75, 95% confidence interval (CI): 0.60, 0.92; $p_{trend} = 0.004$), whereas *trans*-fat intake was associated with an elevated risk of CHD (RR = 1.33, 95% CI: 1.07, 1.66; $p_{trend} = 0.01$). The associations between intakes of polyunsaturated fat and *trans*-fat with CHD risk were most evident among women younger than age 65 years (for polyunsaturated fat, RR = 0.66, 95% CI: 0.50, 0.85; $p_{trend} = 0.002$ and for *trans*-fat, RR = 1.50, 95% CI: 1.13, 2.00; $p_{trend} = 0.01$). The inverse association between polyunsaturated fat intake and CHD risk was strongest among women whose body mass index was $\geq$25 kg/m^2. Findings continue to support an inverse relation between polyunsaturated fat intake and CHD risk, particularly among younger or overweight women. In addition, *trans*-fat intake was associated with increased risk of CHD, particularly for younger women.

coronary disease; fatty acids; risk factors

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; RR, relative risk.

The results of prospective epidemiologic studies have in general suggested relations between specific types of fat and risk of coronary heart disease (CHD), but no relation with total fat (1–5). These findings are consistent with the effects of dietary fats on blood lipids in controlled feeding studies (6) and the limited randomized trials examining CHD endpoints (7). In several studies, risk factors (in particular, blood lipids) for CHD incidence have been attenuated with advancing age (8–11). Body mass index (BMI) is strongly associated with risk of CHD and is a major determinant of insulin resistance (12, 13). The metabolic responses to dietary fat are strongly modified by underlying insulin resistance (14), but whether the relations between fat intake and risk of CHD are modified by BMI and other risk factors has not been examined in detail.

We previously reported the relations of dietary total fat and specific types of fat with risk of CHD over a 14-year period (1). In the present study, we extended this follow-up to 20 years. We hypothesized that the relations between specific types of fat and risk of CHD are stronger among younger women. Dietary measurements were made repeatedly to reduce the impact of errors in dietary assessment and to account for changes in diet over time.

Correspondence to Dr. Walter C. Willett, Department of Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115 (e-mail: wwillett@hsph.harvard.edu).

TABLE 1. Characteristics and risk factors for coronary heart disease according to intake of specific types of fat* in 1990, Nurses' Health Study, United States

	Saturated fat		Monounsaturated fat		Polyunsaturated fat		*Trans*-fat	
	1	5	1	5	1	5	1	5
Age (years)	57	55	57	55	57	55	57	55
Body mass index (kg/m^2)	24	24	24	24	24	25	24	24
Current smoking (%)	14	23	15	22	20	18	16	19
Physical activity (hours/week)†	3.6	2.9	3.7	2.9	3.3	3.0	3.8	2.7
History of hypertension (%)	15	16	15	16	16	15	15	16
Parental history of MI‡ (%)	20	19	20	19	20	20	20	19
Current hormone use (%)	31	25	29	26	26	30	30	25
Aspirin use (%)	51	45	51	46	46	54	50	49
Multivitamin use (%)	34	23	35	23	29	28	36	23
Total energy (kcal/day)	1,698	1,721	1,684	1,715	1,672	1,764	1,676	1,758
Cholesterol (mg/day)	200	244	203	240	219	223	216	222
Protein (g/day)	75	76	76	76	76	74	78	73
Dietary fiber (g/day)	21	18	21	18	20	19	21	18
Alcohol (g/day)	6.5	4.3	6.4	4.1	6.8	4.3	7.1	3.5

* 1, lowest quintile; 5, highest quintile.
† Hours spent engaging in moderate to vigorous exercise/week.
‡ MI, myocardial infarction.

MATERIALS AND METHODS

Population

The Nurses' Health Study was initiated in 1976 when 121,700 female registered nurses aged 30–55 years completed a mailed questionnaire about their lifestyle factors and medical history, including previous cardiovascular disease, cancer, diabetes, hypertension, and high cholesterol levels. Follow-up questionnaires have been sent to these women every 2 years to update information and identify newly diagnosed major illnesses. A food frequency questionnaire was first administered in 1980. In this analysis, we included participants who returned the 1980 questionnaire and excluded those who left 10 or more food items blank or whose total energy intake was implausible (n = 5,579), and those who had a history of cardiovascular disease (angina, myocardial infarction, stroke, other cardiovascular disease; n = 1,645), cancer (n = 3,610), diabetes (n = 1,410), or hypercholesterolemia (n = 4,269) before June 1, 1980; women may have changed their diet because of the presence of these conditions. After these exclusions, data on 78,778 women remained in the analysis.

Ascertainment of diet

A detailed description of our food frequency questionnaire and documentation of its reproducibility and validity were published earlier (1). In 1980, we collected information on usual diet by using a food frequency questionnaire including 61 foods. For each food, a commonly used unit or portion size was specified, and each woman was asked how often, on average, she had consumed that quantity during the previous year. Nine responses were possible, ranging from "almost never" to "six or more times per day." In 1984, the dietary questionnaire was expanded to include 116 items. Similar questionnaires were used to update dietary information in 1986, 1990, 1994, and 1998. Daily intake of fat and fatty acids was calculated by multiplying the frequency of consumption of each item by its nutrient content and summing the nutrient contributions of all foods on the basis of US Department of Agriculture food composition data (15), taking into account types of margarine and fats used in cooking and baking. The questionnaire provided a reasonable measure of total and specific types of fat when compared with multiple dietary records; correlation coefficients between intakes from the 1986 questionnaire and 1986 dietary records were 0.57 for total fat, 0.68 for saturated fat, 0.48 for polyunsaturated fat, and 0.58 for monounsaturated fat (16). The correlation between *trans*-fat intake according to the food frequency questionnaire and the composition of *trans*-fat in adipose tissue was 0.51 (17), and total fat intake has also been validated by using differences in blood fasting triglyceride levels (18).

Ascertainment of CHD

The endpoint was nonfatal myocardial infarction or fatal CHD that occurred after the 1980 questionnaire was returned but before June 1, 2000. We requested permission to review medical records of women who reported having a nonfatal myocardial infarction on a follow-up questionnaire. These records were reviewed by physicians without their knowledge of the participant's exposure status. Myocardial infarction was confirmed if it met the criteria of the

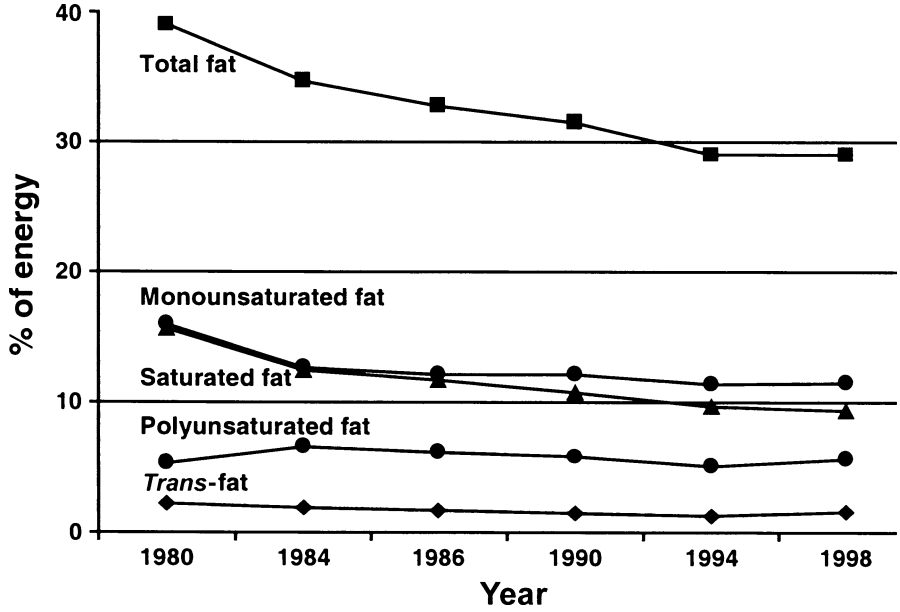

FIGURE 1. Trends in intakes of total fat and specific types of fat over time in the Nurses' Health Study, United States, 1980–2000.

World Health Organization based on symptoms plus either diagnostic electrocardiographic changes or elevated cardiac enzyme concentrations, which have been described in detail elsewhere (1). Myocardial infarctions that necessitated 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 (24 percent).

Deaths were identified from the National Death Index, next of kin, or the US postal system. Using all sources combined, we estimated that follow-up for the deaths was more than 98 percent complete (19). Fatal CHD was defined as fatal if it was confirmed by hospital records or autopsy or if CHD was listed as the cause of death on the death certificate and was the underlying and most plausible cause, and if evidence of previous CHD was available.

Statistical analyses

For each study participant, person-years of follow-up were counted from the date of returning the 1980 questionnaire to the date of CHD diagnosis; the date of death; or June 1, 2000, whichever occurred first. Women were grouped in quintiles according to the percentage of energy obtained from each type of fat. For each type of fat, the relative risk was computed as the rate for a specific quintile divided by that for the group with the lowest intake. We used Cox proportional hazards modeling (the PROC PHREG procedure) for all multivariate analyses (SAS Institute, Inc., Cary, North Carolina). To best represent the participants' long-term dietary patterns during follow-up, we used a cumulative average method based on all available measurements of diet up to the beginning of each 2-year interval (1). For example, for women, dietary data from the 1980 questionnaire were used to predict CHD incidence between June 1980 and June 1984, the average of the 1980 and 1984 dietary intake was used to predict CHD incidence between June 1984 and 1986, and so on. Other nondietary covariates were updated every 2 years. In addition, when examining the effect of isocaloric substitution of dietary fat for carbohydrate, we used multivariate nutrient-density models that simultaneously included energy intake, percentage of energy derived from protein, and other potentially confounding variables (1). Tests for trends were conducted by assigning the median value to each quintile and modeling this value as a continuous variable. In addition, we conducted analyses stratified by age and BMI to assess effect modification by these variables and tested the significance of the interaction with a likelihood ratio test. The continuous measure of cumulative average of linoleic acid intake was used to fit a restricted cubic spline model and to obtain a smooth representation of the relative risk as a function of linoleic acid intake.

RESULTS

Among the 78,778 women followed up for 20 years, we documented 1,766 incident cases of CHD (1,241 nonfatal myocardial infarctions and 525 CHD deaths). Women were grouped in quintiles according to intakes of specific types of fat (table 1). In 1990, the midpoint of the 20 years of follow-up, women with a high intake of each type of fat were younger, had a lower prevalence of physical activity and multivitamin use, and consumed less dietary fiber and alcohol. The distributions of race (mostly White; 94 percent) and lipid-lowering medication use (8 percent in 1996 and 12 percent in 1998) did not differ by intakes of specific types of fat (data not shown).

TABLE 2. Relative risks of coronary heart disease according to intake of specific types of dietary fat, Nurses' Health Study, United States, 1980–2000

	Quintile					p_{trend}
	1 (lowest)	2	3	4	5 (highest)	
Total fat						
Median (% of energy)	28.3	32.6	35.6	38.7	44.0	
Age-adjusted RR*	1	0.97	1.02	1.17	1.26	0.001
95% CI*		0.84, 1.12	0.88, 1.18	1.01, 1.35	1.07, 1.47	
Multivariate† RR	1	0.94	0.91	0.98	0.92	0.49
95% CI		0.81, 1.08	0.79, 1.06	0.84, 1.15	0.77, 1.09	
Saturated fat						
Median (% of energy)	10.1	11.9	13.3	14.8	17.6	
Age-adjusted RR	1	1.05	1.16	1.35	1.52	<0.0001
95% CI		0.91, 1.21	1.00, 1.34	1.16, 1.56	1.30, 1.79	
Multivariate‡ RR	1	0.94	0.96	1.01	0.97	0.93
95% CI		0.80, 1.11	0.79, 1.16	0.81, 1.26	0.73, 1.27	
Monounsaturated fat						
Median (% of energy)	10.6	12.5	13.8	15.3	18.0	
Age-adjusted RR	1	1.01	1.11	1.18	1.30	0.0003
95% CI		0.87, 1.16	0.96, 1.28	1.02, 1.37	1.11, 1.53	
Multivariate‡ RR	1	0.94	0.95	0.91	0.82	0.19
95% CI		0.79, 1.11	0.78, 1.17	0.72, 1.16	0.62, 1.10	
Polyunsaturated fat						
Median (% of energy)	4.1	5.0	5.6	6.3	7.4	
Age-adjusted RR	1	0.93	0.81	0.83	0.80	0.002
95% CI		0.81, 1.07	0.70, 0.94	0.72, 0.97	0.69, 0.94	
Multivariate‡ RR	1	0.98	0.83	0.84	0.75	0.004
95% CI		0.84, 1.14	0.70, 0.99	0.70, 1.02	0.60, 0.92	
Trans-fat						
Median (% of energy)	1.3	1.6	1.9	2.2	2.8	
Age-adjusted RR	1	1.11	1.31	1.24	1.39	<0.0001
95% CI		0.96, 1.28	1.14, 1.52	1.07, 1.44	1.19, 1.63	
Multivariate‡ RR	1	1.08	1.29	1.19	1.33	0.01
95% CI		0.92, 1.26	1.09, 1.53	0.99, 1.44	1.07, 1.66	

* RR, relative risk; CI, confidence interval.

† Adjusted for age (continuous), body mass index (five categories), smoking (never, past, current 1–14, 15–24, ≥25 cigarettes/day), alcohol intake (four categories), parental history of myocardial infarction, history of hypertension, menopausal status and hormone use, aspirin use (five categories), multivitamin use, vitamin E supplement use, physical activity (hours/week, five categories), and energy, protein, and cholesterol intake (quintiles).

‡ Adjusted for the variables cited above and intakes of saturated, monounsaturated, polyunsaturated, and *trans*-fat; α-linolenic acid; marine n-3 fatty acids; cereal fiber; and fruits and vegetables (quintiles).

From 1980 to 1998, the average intake of total fat decreased from 39.0 percent to 29.0 percent, saturated fat intake decreased from 15.6 percent to 9.4 percent, monounsaturated fat intake decreased from 16.0 percent to 11.5 percent, and *trans*-fat intake decreased from 2.2 percent to 1.6 percent. Polyunsaturated fat intake increased from 5.3 percent to 5.6 percent (figure 1).

In age-adjusted analyses, total fat intake was significantly associated with increased risk of CHD (table 2). However, in the multivariate analyses, the association was attenuated and was not significant. For specific types of fat, intakes of saturated fat, monounsaturated fat, polyunsaturated fat, and *trans*-fat were each significantly associated with risk of CHD in age-adjusted analyses. When we incorporated all types of fat, including n-3 fatty acids, in the same model, so that the relative risks represent substitution of carbohydrate with the same percentage of energy from each type of fat, greater polyunsaturated fat intake was significantly

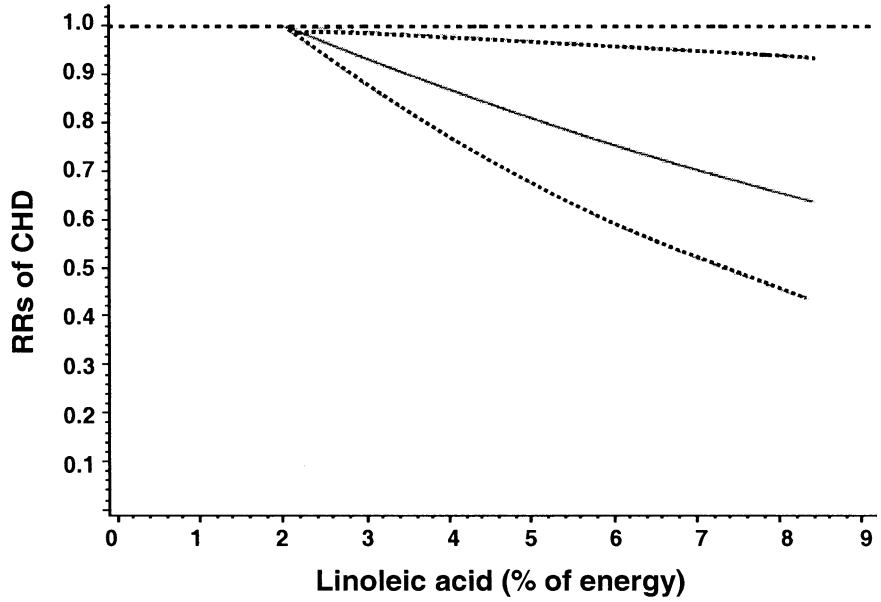

FIGURE 2. Spline regression model of the relative risks (RRs) of coronary heart disease (CHD) according to linoleic acid intake in the Nurses' Health Study, United States, 1980–2000. Relative risks were adjusted for the variables listed as multivariate in table 2. Solid line, point estimates; dotted lines, 95% confidence interval.

associated with lower risk of CHD (relative risk (RR) = 0.75, 95 percent confidence interval (CI): 0.60, 0.92; p_{trend} = 0.004), and *trans*-fat intake was significantly positively associated with risk of CHD (RR = 1.33, 95 percent CI: 1.07, 1.66; p_{trend} = 0.01). A similar inverse association was observed between linoleic acid (the major polyunsaturated fat) intake and risk of CHD; the relative risks for linoleic acid were 1 (referent), 1.02, 0.91, 0.87, and 0.77 (95 percent CI: 0.62, 0.95); p_{trend} = 0.01. In a spline regression analysis, the relation between linoleic acid intake and risk of CHD appeared linear over the range of intake in this cohort (5th and 95th percentiles = 2.8 percent and 7.0 percent of energy, respectively) (figure 2). Intakes of saturated fat and monounsaturated fat were not statistically significant predictors of CHD when adjusted for nondietary and dietary risk factors. However, the ratio of polyunsaturated fat to saturated fat was inversely associated with risk of CHD; the relative risks for the ratio of polyunsaturated fat to saturated fat were 1 (referent), 1.11, 1.04, 0.91, and 0.87 (95 percent CI: 0.72, 1.05), p_{trend} = 0.01.

The relation between specific types of fat and risk of CHD differed by age and BMI category (table 3). A strong inverse association between polyunsaturated fat intake and risk of CHD was found among women younger than age 65 years (RR = 0.66, 95 percent CI: 0.50, 0.85; p_{trend} = 0.002) but not among those aged 65 years or older (test for interaction = 0.03). Likewise, *trans*-fat intake was most strongly related to risk of CHD among women younger than age 65 years (RR = 1.50, 95 percent CI: 1.13, 2.00; p_{trend} = 0.01), although the interaction was not significant; p = 0.58). Intakes of total fat, saturated fat, and monounsaturated fat had no clear relation to CHD regardless of age group (data not shown). Polyunsaturated fat intake was more strongly associated with risk of CHD among women whose BMI was $\geq$25 kg/m^2 (RR = 0.63, 95 percent CI: 0.47, 0.84; p_{trend} = 0.002, test for interaction = 0.26), whereas *trans*-fat intake was more clearly associated with risk of CHD among women whose BMI was <25 kg/m^2 (RR = 1.53, 95 percent CI: 1.09, 2.15; p_{trend} = 0.02, test for interaction = 0.17). Little relation between intakes of total fat, saturated fat, and monounsaturated fat and risk of CHD was found across these strata (data not shown).

DISCUSSION

In this 20-year follow-up, as in our earlier analyses, we found that a higher intake of polyunsaturated fat was associated with a decreased risk of CHD, whereas a higher intake of *trans*-fat was associated with an increased risk of CHD, independent of other dietary factors and cardiovascular risk factors. In addition, the relations of polyunsaturated fat and *trans*-fat intake with CHD risk were stronger among women younger than age 65 years. Because of opposing effects of specific types of fat, total fat intake as a percentage of energy was not significantly related to risk of CHD.

Polyunsaturated fat, both n-6 and n-3 classes, has been proposed to reduce the risk of CHD through its beneficial effects on blood lipids, insulin sensitivity, inhibition of thrombosis, and the threshold for ventricular fibrillation (20). Our results are consistent with those of the Western Electric Study (3). However, the results of other studies have been inconsistent; two studies showed slightly inverse trends with risk of CHD (21, 22), but other trials did not

TABLE 3. Relative risks* of coronary heart disease according to intakes of specific types of fat, stratified by age and body mass index, Nurses' Health Study, United States, 1980–2000

	Quintile					p_{trend}
	1 (lowest)	2	3	4	5 (highest)	
Age (years)						
<65 (n = 1,111)						
Polyunsaturated fat						
RR†	1	0.87	0.68	0.74	0.66	0.002
95% CI†		0.72, 1.05	0.55, 0.85	0.59, 0.93	0.50, 0.85	
Trans-fat						
RR	1	1.20	1.35	1.37	1.50	0.01
95% CI		0.97, 1.48	1.08, 1.70	1.07, 1.75	1.13, 2.00	
≥65 (n = 655)						
Polyunsaturated fat						
RR	1	1.22	1.18	1.08	0.96	0.60
95% CI		0.94, 1.59	0.89, 1.57	0.78, 1.49	0.66, 1.39	
Trans-fat						
RR	1	0.94	1.22	0.96	1.15	0.49
95% CI		0.74, 1.19	0.94, 1.58	0.71, 1.31	0.80, 1.66	
Body mass index (kg/m^2)						
<25 (n = 752)						
Polyunsaturated fat						
RR	1	1.08	0.84	0.92	0.91	0.43
95% CI		0.86, 1.36	0.65, 1.10	0.69, 1.23	0.67, 1.26	
Trans-fat						
RR	1	1.28	1.42	1.48	1.53	0.02
95% CI		1.00, 1.62	1.09, 1.86	1.11, 1.99	1.09, 2.15	
≥25 (n = 1,014)						
Polyunsaturated fat						
RR	1	0.90	0.81	0.78	0.63	0.002
95% CI		0.73, 1.11	0.65, 1.02	0.60, 1.00	0.47, 0.84	
Trans-fat						
RR	1	0.94	1.21	1.02	1.19	0.26
95% CI		0.76, 1.16	0.97, 1.51	0.79, 1.31	0.88, 1.60	

* Adjusted for the variables listed as multivariate in table 2.
† RR, relative risk; CI, confidence interval.

show apparent relations (23, 24). Although there have been concerns that high intake of linoleic acid (n-6) might have adverse effects on CHD risk (25), we observed a linear inverse relation within the range of intakes in this population. In another recent report, linoleic acid intake was inversely related to risk of coronary artery disease, although this relation did not attain statistical significance (26), and, in a population with higher intakes (average 10 percent of energy), high adipose linoleic acid level was not associated with increased risk of CHD (27).

Trans-fat can contribute to increased risk of CHD by adversely influencing blood lipids, including concentrations of low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, and lipoprotein(a); low density lipoprotein particle size; endothelial function; insulin resistance; and thrombosis (20, 28, 29). Positive associations between intake of *trans*-fat and risk of CHD were seen in many studies (1, 2, 4, 5). In a meta-analysis, Oomen et al. (2) estimated that the pooled relative risk of CHD associated with a difference of 2 percent of energy in *trans*-fat was 1.25 (95 percent CI: 1.11, 1.40). The stronger association in the Nurses' Health Study may relate to the younger age of this population and the repeated measurement of diet.

The observed relations in this analysis were consistent with previous findings in our cohort (1) but somewhat weaker. Dietary patterns in the United States have changed during the last 20 years, as has the composition of many

processed foods. In our study, total fat intake decreased by 26 percent from 1980 to 1998. Intakes of saturated fat, monounsaturated fat, and *trans*-fat decreased by 40 percent, 28 percent, and 27 percent, respectively, while polyunsaturated fat intake increased by 6 percent during this period. Improvements in diet during follow-up may have contributed to the weaker relations between dietary fat and the risk of CHD. Hu et al. (30) also reported a substantial decline in CHD incidence in this cohort due to changes in dietary intake and other risk factors.

In this analysis, these associations of polyunsaturated fat and *trans*-fat intake with risk of CHD appeared to be stronger among women younger than age 65 years, which would also lead to weaker associations as the population ages. In many (8–11) but not all (31, 32) studies, prediction of CHD by blood lipids, smoking, and BMI has declined with advancing age. Pekkanen et al. (33) pointed out that the decline in blood cholesterol levels and the associated high CHD mortality in the elderly might be caused by other factors, such as an increased prevalence of chronic disease or a decline in health status or metabolic changes associated with aging. Because dietary fat may affect risk of CHD in part by influencing blood lipids, an attenuated relation between blood lipids and CHD risk in the elderly might in part explain why the observed associations between dietary fatty acids and CHD risk was stronger among women younger than age 65 years. In addition, the inverse relation of polyunsaturated fat intake to CHD risk did not differ in analyses stratified by menopausal status and hormone use (data not shown).

Obesity, the major determinant of insulin resistance and hyperinsulinemia, is strongly associated with risk of CHD (12, 13). We found that polyunsaturated fat intake appeared to be most clearly related to risk of CHD among women with a higher BMI, and *trans*-fat intake was related to risk of CHD among women with a lower BMI in this study, although the tests for interaction were not statistically significant. This result was consistent with a previous report of a stronger association between polyunsaturated fat intake and diabetes risk among overweight or obese women in our cohort (34). It is possible that polyunsaturated fat may have contributed to a lower risk of CHD by improving both blood lipid levels and insulin resistance in overweight women, whereas *trans*-fat may have influenced risk of CHD mainly by its adverse effects on blood lipid levels, which could be more clearly seen among women with less insulin resistance. However, the observed differences by BMI could also be due to chance, and further studies are needed to clarify these relations. A limitation of our study is that we did not measure blood lipid levels, which could be useful in determining whether the effects of dietary fats on CHD risk are mediated by blood lipid levels. Although evidence is strong that linoleic acid can reduce the risk of CHD, concerns have been raised that higher intakes might increase the risk of cancers. However, in our cohort studies (35–37), we found no evidence that higher intakes of polyunsaturated fat or linoleic acid were associated with increased risks of breast, colon, and ovarian cancer, and a recent meta-analysis reported that high intake of linoleic acid was not related to the risks of breast, colorectal, or prostate cancer (38).

In summary, our results provide evidence that high intake of *trans*-fat increases the risk of CHD in women, and they suggest that the effects are stronger among younger women. Our findings also support a benefit of polyunsaturated fat intake, at least up to approximately 7 percent of energy, in preventing CHD, particularly among women who are younger or overweight.

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