Dietary fat intake and risk of type 2 diabetes in women[1–3]

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ABSTRACT

Background: The long-term relations between specific types of dietary fat and risk of type 2 diabetes remain unclear.

Objective: Our objective was to examine the relations between dietary fat intakes and the risk of type 2 diabetes.

Design: We prospectively followed 84 204 women aged 34–59 y with no diabetes, cardiovascular disease, or cancer in 1980. Detailed dietary information was assessed at baseline and updated in 1984, 1986, and 1990 by using validated questionnaires. Relative risks of type 2 diabetes were obtained from pooled logistic models adjusted for nondietary and dietary covariates.

Results: During 14 y of follow-up, 2507 incident cases of type 2 diabetes were documented. Total fat intake, compared with equivalent energy intake from carbohydrates, was not associated with risk of type 2 diabetes; for a 5% increase in total energy from fat, the relative risk (RR) was 0.98 (95% CI: 0.94, 1.02). Intakes of saturated or monounsaturated fatty acids were also not significantly associated with the risk of diabetes. However, for a 5% increase in energy from polyunsaturated fat, the RR was 0.63 (0.53, 0.76; $P < 0.0001$) and for a 2% increase in energy from *trans* fatty acids the RR was 1.39 (1.15, 1.67; $P = 0.0006$). We estimated that replacing 2% of energy from *trans* fatty acids isoenergetically with polyunsaturated fat would lead to a 40% lower risk (RR: 0.60; 95% CI: 0.48, 0.75).

Conclusions: These data suggest that total fat and saturated and monounsaturated fatty acid intakes are not associated with risk of type 2 diabetes in women, but that *trans* fatty acids increase and polyunsaturated fatty acids reduce risk. Substituting nonhydrogenated polyunsaturated fatty acids for *trans* fatty acids would likely reduce the risk of type 2 diabetes substantially. *Am J Clin Nutr* 2001;73:1019-26.

KEY WORDS Dietary fat, polyunsaturated fat, *trans* fatty acids, type 2 diabetes, risk, women

See corresponding editorial on page 1001.

INTRODUCTION

Excess body fat resulting from an imbalance between energy intake and physical activity is the primary risk factor for type 2 diabetes (1, 2), but a role for dietary fat has also been hypothesized. However, the long-term effects of specific types of dietary fatty acids on insulin resistance and risk of type 2 diabetes remain unclear (3). Beneficial effects of diets high in monounsaturated (4, 5) and polyunsaturated (6) fatty acids relative to low-fat, high-carbohydrate diets on glucose control and insulin sensitivity have been reported, but these effects have not been seen universally (7, 8). Short-term studies documented adverse effects of *trans* fatty acid intakes on serum lipoprotein profiles (9, 10) and insulin sensitivity (11).

Epidemiologic data on dietary fats and risk of type 2 diabetes are sparse. One cross-sectional analysis reported a positive association of saturated fatty acid intake with insulin concentrations but an inverse association with polyunsaturated fatty acid intake (12). Two prospective studies that evaluated the incidence of type 2 diabetes reported no association between total dietary fat (13, 14) or specific types of fatty acids and risk of diabetes (14). However, these findings were limited by inadequate dietary assessment, a small number of endpoints, and incomplete control of confounding. In particular, these analyses did not adjust one type of fatty acid for the other, which is important because they tend to be intercorrelated (15) and may have opposing effects.

We previously reported an inverse relation of vegetable fat intake to 6-y incidence of diabetes in a large cohort of men (16), as did the Nurses' Health Study (17, 18). In the present analysis, which is based on 14 y of follow-up in the Nurses' Health Study, we examined in detail specific types of dietary fatty acids in relation to risk of type 2 diabetes. Dietary measurements were made repeatedly to reduce errors in dietary assessment and to account for changes in eating behaviors and food consumption over time. In addition, we used multivariate modeling to assess the long-term independent effects of major types of dietary fatty acids by mutually adjusting intakes of specific types of fatty acids for each other.

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SUBJECTS AND METHODS

Study population

The Nurses' Health Study is a longitudinal investigation of diet and lifestyle factors in relation to incidence of chronic diseases in 121 700 US female registered nurses aged 30–55 y at enrollment. The cohort was assembled in 1976 when the participants returned a mailed questionnaire about known and suspected risk factors for cancer and cardiovascular disease (19). In 1980 we assessed dietary intakes of specific types of fat and other nutrients by using a 61-item semiquantitative food-frequency questionnaire (20). In 1984 an expanded food-frequency questionnaire (116 food items) was mailed to cohort members; similar questionnaires were used to update dietary information in 1986 and 1990. For the present analysis, we used information from respondents (98 462 women aged 34–59 y) to the 1980 questionnaire. We excluded participants who did not satisfy the a priori criteria of a daily energy intake between 2092 and 14 644 kJ/d (500 and 3500 kcal/d) and those who left >10 of the 61 items on the dietary questionnaire blank. In addition, we excluded women who reported on the 1980 or a previous questionnaire a diagnosis of diabetes and those who reported cancer, myocardial infarction, angina, stroke, and coronary artery surgery because they may have modified their diet after the diagnosis. The remaining 84 204 women were followed for diabetes incidence during the subsequent 14 y (1980–1994). The follow-up rates for type 2 diabetes were 98% of the total potential person-years of follow-up. The protocol of the study was approved by the Institutional Review Board at Brigham and Women's Hospital.

Dietary assessment

We used validated semiquantitative food-frequency questionnaires to assess the participants' diets. Full descriptions of the food-frequency questionnaire in its abbreviated (61 items, 1980) and expanded (116–136 items, 1984 and on) forms, the procedures for calculating nutrient intakes, and data on reproducibility and validity in this cohort were previously reported (21–23). A common unit or portion size for each food (eg, one egg or one slice of bread) was specified and participants were asked how often on average during the previous year they had consumed that amount. The 9 responses ranged from "never or less than once per month" to "six or more times per day." Detailed information about types of fat or oil used for frying, baking, and at the table and the type of margarine usually used was collected: stick or tub in 1980 and 1984 and brand and type in 1986 and 1990. Composition values for dietary fats and other nutrients were obtained from the Harvard University Food Composition Database, derived from US Department of Agriculture sources (24) and supplemented with manufacturer's information. Food-composition data are continuously updated to account for changes in food processing and improved analytic methods. Values in 1980 for the total *trans* isomer fatty acid contents of foods were based on analyses by Enig et al (25) and Slover et al (26) and were updated by using data from the US Department of Agriculture, food manufacturers, and analyses of commonly used margarines, shortenings, and baked products at the Harvard School of Public Health (Department of Nutrition, Boston). We included all *trans* isomers of 18-carbon fatty acids. The most important determinants of *trans* fatty acids at baseline in the Nurses' Health Study were margarine; beef, pork, or lamb as a main dish; cookies (biscuits); and white bread (15). All of these food items were assessed at baseline and updated in 1984, 1986, and 1990. The polyunsaturated fat intakes reported in this study include only linoleic acid, which accounted for 81% of the total polyunsaturated fatty acid intake in our cohort. Nutrient intake was computed by multiplying the frequency of consumption of each food by the nutrient content of the specified portions, taking into account the type of fat used in preparation, including the brand, type, and year of margarine use.

Both the original and revised questionnaires provide a reasonable measure of total and specific types of fat intakes when compared with multiple 1-wk diet records; correlation coefficients for total and specific types of fat assessed by dietary records and food-frequency questionnaires ranged from 0.46 to 0.58 for the abbreviated 1980 questionnaire and from 0.48 to 0.68 for the expanded questionnaire (27). The correlation coefficient between calculated dietary intake of *trans* fatty acids and the proportion of *trans* fatty acids in adipose tissue was 0.51 (28).

Measurement of nondietary factors

In 1980 participants provided information on their weight and smoking status. We updated this information every 2 y during follow-up. The validity of self-reported weight in this cohort was previously reported (r = 0.96 between self-reported and measured weight) (29). The level of physical activity in metabolic equivalents per week was estimated based on the self-reported duration per week of various forms of exercise, with each activity weighted by its intensity level (30) according to information collected via the questionnaires at baseline, 1986, and 1992. In 1982 participants provided information on the history of diabetes in first-degree relatives.

Follow-up and ascertainment of cases

On the baseline and follow-up questionnaires that were mailed every 2 y (from 1980 to 1994), we inquired about whether diabetes had been newly diagnosed. When a diagnosis of diabetes mellitus was reported on a follow-up questionnaire, participants were asked to complete a supplementary questionnaire to confirm the report and to ascertain the date of diagnosis and details of the diagnostic tests, presenting symptoms, and medications. After women with type 1 and gestational diabetes only were excluded, the diagnosis of type 2 diabetes was established if one or more of the following criteria were met: *1*) one or more classic symptoms (excessive thirst, polyuria, weight loss, and pruritus) plus a fasting plasma glucose concentration ≥7.78 mmol/L (140 mg/dL) or a random plasma glucose concentration ≥11.11 mmol/L (200 mg/dL), *2*) ≥2 elevated plasma glucose concentrations on different occasions (fasting ≥7.78 mmol/L, random ≥11.11 mmol/L, or ≥11.11 mmol/L after ≥2 h of oral-glucose-tolerance testing) in the absence of symptoms, or *3*) treatment with medication for hypoglycemia (insulin or oral hypoglycemic agents). These criteria correspond to those proposed in 1979 by the National Diabetes Data Group (31) and the World Health Organization in 1985 (32). The high validity of self-reported diabetes in this cohort on the supplementary questionnaire was previously documented and the diagnosis was confirmed by a review of medical records in 98% of cases (17). In 1997 the fasting plasma glucose concentration indicative of type 2 diabetes was lowered (≥7.0 mmol/L, or 126 mg/dL) on the basis of the American Diabetes Association's recommendation (33). In the current analyses, we used the previous criterion because at the time the follow-up was conducted, the National

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TABLE 1
Baseline characteristics and risk factors for diabetes according to the intake of specific types of fat at baseline

	Polyunsaturated fat			*trans* Fat		
	Lowest quintile	Intermediate quintile	Highest quintile	Lowest quintile	Intermediate quintile	Highest quintile
Age (y)	48 ± 7[1]	46 ± 7	45 ± 7	47 ± 7	46 ± 7	46 ± 7
BMI (kg/m^2)	24 ± 4	24 ± 4	24 ± 5	24 ± 4	24 ± 4	24 ± 5
Alcohol (g/d)	10 ± 14	6 ± 10	5 ± 8	10 ± 14	6 ± 9	4 ± 7
Cholesterol (mg·MJ^{-1}·d^{-1})	51.2 ± 17.9	51.6 ± 18.4	48.3 ± 20.1	51.9 ± 24.1	50.9 ± 16.7	49.2 ± 16.7
Folate from diet (μg/d)	284 ± 122	257 ± 103	234 ± 90	313 ± 124	251 ± 96	216 ± 81
Fiber (g/d)	14 ± 6	13 ± 5	13 ± 4	16 ± 6	13 ± 4	12 ± 4
Saturated fat (% of energy)	15 ± 4	16 ± 3	15 ± 3	13 ± 4	16 ± 3	16 ± 3
Monounsaturated fat (% of energy)	14 ± 4	16 ± 4	17 ± 3	12 ± 3	16 ± 3	18 ± 3
Polyunsaturated fat (% of energy)	2 ± 0.4	4 ± 0.2	7 ± 1	3 ± 2	4 ± 1	6 ± 2
trans Fat (% of energy)	2 ± 0.5	2 ± 0.5	3 ± 0.8	1 ± 0.3	2 ± 0.1	3 ± 0.5
Family history of diabetes (%)	19	18	18	18	18	19
Current smoking (%)	32	27	28	28	28	30
Vigorous exercise ≥1/wk (%)	48	45	42	53	43	37
Currently receiving estrogen replacement therapy, postmenopausal women only (%)	19	19	18	19	19	17

[1] $\bar{x}$ ± SD.

Diabetes Data Group and World Health Organization definitions were the standard. Also, use of a stricter definition of type 2 diabetes can minimize false-positive results and thus enhance the validity of the observed associations (34). Deaths were identified from state vital records and the National Death Index or were reported by next of kin and the postal system; mortality follow-up was 98% complete (15).

Statistical analysis

For each participant, person-time of follow-up was counted from the date of return of the 1980 questionnaire to the date of diabetes diagnosis, to the time of return of the most recent follow-up questionnaire, or to 1 June 1994, whichever came first. Women with diabetes or cancer as indicated on a previous questionnaire were excluded from subsequent follow-up; thus, the cohort at risk included only those who remained free from diabetes or cancer at the beginning of every 2-y follow-up interval.

Women were divided into quintiles by percentage of energy from each type of fatty acid; incidence rates were calculated by dividing the number of events by person-time of follow-up in each quintile. To reduce within-subject variation and best represent the long-term diet, we used pooled logistic regression (35) to model the cumulative average of fat intake from all available dietary questionnaires up to the start of each 2-y follow-up interval in relation to diabetes incidence. During the next 2 y, for example, the fat intake from the 1980 questionnaire was related to disease incidence during the 1980–1982 and 1982–1984 time intervals and the average fat intake from the 1980 and 1984 questionnaires was related to incidence during 1984–1986. Because changes in diet after development of hypercholesterolemia, hypertension, angina, myocardial infarction, coronary artery surgery, or stroke may confound the diet-disease associations (36), we stopped updating dietary information at the beginning of the time interval during which individuals developed these endpoints.

In multivariate nutrient-density models (27), we simultaneously included energy intake, percentages of energy from protein and specific fatty acids, and other potential confounding variables. The nondietary covariates included seven 2-y time periods, age in 5-y categories, body mass index [BMI: weight (in kg) divided by the square of the height (in m) in 11 categories], smoking status (never, past, and current smoking classified into 3 categories on the basis of the number of cigarettes smoked/d: 1–14, 15–24, and ≥25), alcohol consumption (g/d in 4 categories), physical activity (metabolic equivalents/wk in 5 categories), and history of diabetes in a first-degree relative. We tested for significant monotonic trends across quintiles of fat intake by assigning each participant the median value for the category and modeling this value as a continuous variable. All *P* values are two-sided.

We evaluated the effects of specific types of fatty acids by expressing them as a percentage of total energy (nutrient density) and including them in models as continuous variables. When all types of fats, protein, and alcohol are included simultaneously, the coefficients from these nutrient-density models can be interpreted as the effect of exchanging energy from a specific fat for the same amount of energy from carbohydrates. We also estimated the effects of substituting one type of fat for another, using the difference between coefficients from the same model (27).

RESULTS

During 14 y of follow-up, we documented 2507 incident cases of type 2 diabetes. As previously reported (15), intakes of specific types of fat at baseline tended to correlate with one another. Intake of saturated fat correlated with intakes of monounsaturated fat (r = 0.81) and *trans* fat (r = 0.30) but not with intake of polyunsaturated fat (r = 0.01). Intake of monounsaturated fat was correlated with intakes of *trans* fat (r = 0.55) and polyunsaturated fat (r = 0.30). Intake of polyunsaturated fat was correlated with that of *trans* fat (r = 0.58). The high correlation between monounsaturated and saturated fatty acids was due to shared sources of these fats (ie, dairy products and beef). As described elsewhere (15), BMI was not appreciably associated with total or specific types of dietary fat. Women with a higher intake of *trans* fat were more likely to smoke, were less likely to engage in regular physical activity, and had lower intakes of alcohol and folate (**Table 1**). Women with a higher intake of polyunsaturated fat were less likely to smoke, less likely to engage in regular exercise, and also had lower intakes of alcohol and folate. Women who consumed

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TABLE 2
Relative risks (and 95% CIs) of type 2 diabetes according to quintiles of intake of specific types of dietary fat and fatty acids[1]

Variable	Quintile 1	2	3	4	5	*P* for trend
Total fat	28.9	33.9	37.2	40.6	46.1	
Age- and BMI-adjusted	1.0	0.90 (0.78, 1.02)	1.07 (0.95, 1.22)	1.07 (0.94, 1.21)	1.12 (0.99, 1.27)	0.006
Multivariate	1.0	0.87 (0.77, 1.00)	1.01 (0.88, 1.15)	0.97 (0.85, 1.10)	0.97 (0.85, 1.11)	0.96
Animal fat	17.3	21.6	25.0	29.2	36.4	
Age- and BMI-adjusted	1.0	0.94 (0.82, 1.08)	1.12 (0.98, 1.28)	1.25 (1.09, 1.42)	1.36 (1.20, 1.55)	<0.0001
Multivariate	1.0	0.90 (0.80, 1.06)	1.08 (0.93, 1.24)	1.17 (1.02, 1.35)	1.25 (1.08, 1.45)	<0.0001
Further adjustment for vegetable and *trans* fats	1.0	0.88 (0.76, 1.02)	1.00 (0.86, 1.15)	1.02 (0.88, 1.19)	0.97 (0.82, 1.15)	0.71
Vegetable fat	5.3	8.7	11.1	13.5	17.2	
Age- and BMI-adjusted	1.0	0.88 (0.79, 0.99)	0.73 (0.64, 0.82)	0.74 (0.66, 0.84)	0.72 (0.64, 0.82)	<0.0001
Multivariate	1.0	0.88 (0.78, 0.99)	0.71 (0.63, 0.81)	0.71 (0.62, 0.81)	0.68 (0.59, 0.78)	<0.0001
Further adjustment for animal and *trans* fats	1.0	0.85 (0.75, 0.96)	0.67 (0.59, 0.77)	0.65 (0.56, 0.76)	0.60 (0.51, 0.71)	<0.0001
SFA	10.7	12.8	14.3	16.0	18.8	
Age- and BMI-adjusted	1.0	1.03 (0.90, 1.18)	1.07 (0.94, 1.22)	1.21 (1.06, 1.37)	1.27 (1.12, 1.44)	<0.0001
Multivariate	1.0	1.00 (0.87, 1.15)	1.01 (0.88, 1.15)	1.10 (0.96, 1.26)	1.11 (0.97, 1.28)	0.05
Further adjustment for MUFAs, PUFAs, and *trans* fats	1.0	0.97 (0.83, 1.12)	0.96 (0.81, 1.14)	1.03 (0.86, 1.24)	0.99 (0.80, 1.21)	0.98
MUFA	10.9	13.1	14.6	16.3	19.3	
Age- and BMI-adjusted	1.0	1.08 (0.95, 1.23)	1.12 (0.98, 1.28)	1.15 (1.01, 1.31)	1.29 (1.14, 1.47)	<0.0001
Multivariate	1.0	1.05 (0.92, 1.20)	1.05 (0.92, 1.21)	1.05 (0.92, 1.21)	1.13 (0.99, 1.39)	0.07
Further adjustment for SFAs, PUFAs, and *trans* fats	1.0	1.07 (0.91, 1.25)	1.05 (0.88, 1.26)	1.02 (0.83, 1.25)	1.06 (0.84, 1.33)	0.51
PUFA	2.9	3.4	4.1	4.8	6.2	
Age- and BMI-adjusted	1.0	0.90 (0.79, 1.01)	0.83 (0.73, 0.93)	0.84 (0.75, 0.95)	0.87 (0.77, 0.99)	0.02
Multivariate	1.0	0.90 (0.80, 1.01)	0.82 (0.73, 0.93)	0.82 (0.72, 0.94)	0.85 (0.75, 0.97)	0.009
Further adjustment for SFAs, MUFAs, and *trans* fats	1.0	0.86 (0.76, 0.97)	0.77 (0.67, 0.88)	0.75 (0.65, 0.86)	0.75 (0.65, 0.88)	0.0002
trans Unsaturated fat	1.3	1.7	2.0	2.4	2.9	
Age- and BMI-adjusted	1.0	1.11 (0.97, 1.26)	1.16 (1.02, 1.32)	1.10 (0.97, 1.26)	1.26 (1.11, 1.43)	0.002
Multivariate	1.0	1.08 (0.95, 1.23)	1.11 (0.98, 1.27)	1.04 (0.91, 1.19)	1.15 (1.01, 1.32)	0.09
Further adjustment for SFAs, MUFAs, and PUFAs	1.0	1.12 (0.97, 1.29)	1.18 (1.02, 1.37)	1.14 (0.97, 1.34)	1.31 (1.10, 1.56)	0.02
Cholesterol	131	163	188	217	273	
Age- and BMI-adjusted	1.0	1.00 (0.87, 1.15)	1.12 (0.98, 1.28)	1.21 (1.06, 1.38)	1.32 (1.16, 150)	<0.0001
Multivariate	1.0	1.04 (0.90, 1.20)	1.18 (1.02, 1.37)	1.29 (1.12, 1.49)	1.42 (1.23, 1.65)	<0.0001
Further adjustment for SFAs, MUFAs, PUFAs, and *trans* fats	1.0	1.02 (0.88, 1.18)	1.16 (1.00, 1.34)	1.25 (1.08, 1.45)	1.36 (1.17, 1.59)	<0.0001

[1] Values are medians and were computed as a percentage of energy (except for cholesterol; mg/d) by quintile as the cumulative updated average. Age- and BMI-adjusted models included age (5-y categories) and BMI (11 categories). SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid. The multivariate models included age (5-y categories), time period (7 periods), BMI (11 categories), cigarette smoking (never, past, or current smoking of 1–14, 15–24, and ≥25 cigarettes/d), parental history of diabetes, alcohol consumption (4 categories), physical activity (metabolic equivalents/wk: 5 categories), percentage of energy from protein, and total energy intake. Dietary cholesterol was also included in models for total and specific fats.

both higher amounts of polyunsaturated fat and lower amounts of *trans* fat tended to eat less stick margarine and use more liquid vegetable oils, especially salad-dressing products.

In age- and BMI-adjusted analyses, higher total fat intake was weakly related to greater risk of diabetes (**Table 2**). In multivariate analyses controlling for known risk factors, total fat intake was no longer significantly associated with diabetes risk; adjustments for physical activity and alcohol intake largely accounted for the reduction in relative risk (RR). In age- and BMI-adjusted and multivariate analyses, vegetable fat was associated with reduced risk of diabetes. When animal and vegetable fats were both included in the same model with intake of *trans* fatty acids and known risk factors, animal fat was not associated with diabetes risk (Table 1).

Saturated and monounsaturated fatty acid intakes were each associated with an increased risk of diabetes in age- and BMI-adjusted analyses, but, in multivariate analyses including all major types of fatty acids, these associations were greatly attenuated. In contrast, polyunsaturated fatty acid intake was inversely associated with diabetes risk in all analyses.

Intakes of *trans* fatty acids was positively associated with risk of diabetes in age- and BMI-adjusted analyses. This association was slightly attenuated after adjustment for known risk factors but became stronger after other types of fat were controlled for. In addition, we examined the joint effect of polyunsaturated fatty acid and *trans* fatty acid intakes. The RR for the combination of a low *trans* fatty acid quintile and a high polyunsaturated fatty acid quintile compared with the opposite extreme was 0.66 (95%

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TABLE 3
Multivariate relative risk (RR) of type 2 diabetes associated with increases in the percentage of energy from specific types of fat or fatty acids and dietary cholesterol[1]

Model	RR	95% CI	*P*
Model 1			
Saturated fat (5% increase in energy)	0.97	(0.86, 1.10)	0.68
Monounsaturated fat (5% increase in energy)	1.05	(0.91, 1.20)	0.52
Polyunsaturated fat (5% increase in energy)	0.63	(0.53, 0.76)	<0.0001
trans Unsaturated fat (2% increase in energy)	1.39	(1.15, 1.67)	0.0006
Cholesterol (23.9-mg/MJ increase)[2]	1.12	(1.05, 1.19)	0.0003
Model 2			
Animal fat (5% increase in energy)	0.98	(0.95, 1.02)	0.35
Vegetable fat (5% increase in energy)	0.79	(0.74, 0.84)	<0.0001
Model 3			
Total fat (5% increase in energy)	0.98	(0.94, 1.02)	0.24

[1] The multivariate models included age (5-y categories), time period (7 periods), BMI (11 categories), cigarette smoking (never, past, or current smoking of 1–14, 15–24, and ≥25 cigarettes/d), parental history of diabetes, alcohol consumption (4 categories), physical activity (metabolic equivalents/wk: 5 categories), percentage of energy from protein, and total energy intake.

[2] 23.9 mg/MJ = 100 mg/1000 kcal.

CI: 0.49, 0.93; $P < 0.0001$). Dietary cholesterol was positively associated with diabetes risk in all analyses (Table 2).

Because polyunsaturated fat intake in these analyses included only linoleic acid (the primary n−6 fatty acid), we also examined the relation of marine n−3 fatty acids (eicosapentaenoic acid plus docosahexaenoic acid) to risk of diabetes. In a multivariate model that also included the major types of fat, the RRs for increasing quintiles of marine n−3 fatty acids were 1.0 (reference), 1.00 (95% CI: 0.88, 1.13), 0.93 (0.81, 1.06), 0.97 (0.84, 1.12), and 0.80 (0.67, 0.95); the *P* for the trend was 0.02. Because intakes of both n−6 and marine n−3 fatty acids were inversely associated with risk of diabetes, the ratio of n−6 to n−3 fatty acids was not significantly related to risk of diabetes.

To examine further the relations between different dietary fats and risk of diabetes, we also modeled the percentages of energy from specific types of fatty acids or sources of fat (animal or vegetable) as continuous variables, adjusting one type of fat for another and for known risk factors. In this model, a 5% increase in energy from vegetable fat was associated with a reduced risk of diabetes, whereas a similar increase in energy from animal fat was not associated with risk. Saturated and monounsaturated fatty acid intakes were not significantly related to diabetes risk when compared with an equivalent amount of energy from carbohydrate (**Table 3**). When included in the model with other types of fat, a 2% increase in energy from *trans* fatty acids was associated with a significantly increased risk; each increase of 23.9 mg dietary cholesterol/MJ (100 mg/1000 kcal) was associated with a 12% increased risk (Table 2).

We also estimated the effect of various isoenergetic dietary substitutions on the risk of diabetes (**Figure 1**). Replacing 5% of energy from polyunsaturated fatty acids with the same amount of energy from carbohydrates was associated with a 58% greater risk of diabetes (RR: 1.58; 95% CI: 1.31, 1.90; $P < 0.0001$). Replacing 5% of energy from saturated fatty acids with energy from polyunsaturated fatty acids was associated with a 35% lower risk (0.65; 0.54, 0.78; $P < 0.0001$). Replacing 2% of energy from *trans* fatty acids with carbohydrate was associated with a 28% lower risk (0.72; 0.60, 0.87; $P < 0.001$), but replacing *trans* fatty acids with polyunsaturated fatty acids was associated with a 40% lower risk (0.60; 0.48, 0.75; $P < 0.0001$).

We evaluated the possibility that the associations between different types of dietary fat and diabetes risk might be modified by major nondietary risk factors. The observed inverse association with polyunsaturated fatty acid intake did not appreciably differ across categories of BMI, physical activity, alcohol consumption, or family history of diabetes. However, the positive associations with *trans* fatty acids and cholesterol were observed most clearly among overweight and less physically active women (**Table 4**). In an analysis excluding women with either reported hypercholesterolemia or hypertension at baseline, the association

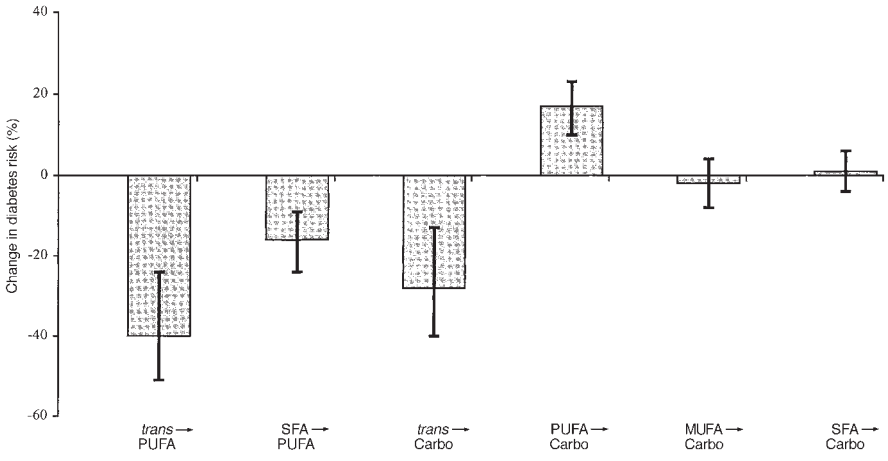

FIGURE 1. Estimated changes in risk of type 2 diabetes associated with isoenergetic substitutions of 2% of energy. Associations were adjusted for the same covariates as in Table 2. *trans*, *trans* fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; Carbo, carbohydrates; MUFA, monounsaturated fatty acids. The arrows indicate substitution of the second fat listed for the first fat listed. Bars represent 95% CIs.

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TABLE 4
Relative risks (RR) of type 2 diabetes associated with increases in the percentage of energy from specific types of dietary fatty acids and dietary cholesterol according to major risk factors[1]

	Polyunsaturated fat (5% increase in energy)			*trans* Unsaturated fat (2% increase in energy)			Cholesterol (23.9-mg/MJ increase)[2]		
Risk factor	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
BMI (kg/m^2)									
<25 (*n* = 267)	0.75	(0.43, 1.31)	0.31	0.76	(0.44, 1.32)	0.33	1.04	(0.84, 1.28)	0.74
25–30 (*n* = 665)	0.51	(0.35, 0.74)	0.0004	1.28	(0.89, 1.86)	0.18	1.01	(0.89, 1.56)	0.91
>30 (*n* = 1213)	0.68	(0.52, 0.88)	0.004	1.31	(1.00, 1.72)	0.05	1.15	(1.07, 1.25)	0.0005
Physical activity level (METS/wk)									
1st and 2nd quintile (*n* = 1237)	0.58	(0.44, 0.76)	0.0001	1.82	(1.39, 2.38)	0.0001	1.16	(1.03, 1.26)	0.0006
3rd to 5th quintile (*n* = 1234)	0.69	(0.53, 0.89)	0.005	1.05	(0.88, 1.37)	0.71	1.08	(0.99, 1.18)	0.07
Alcohol consumption									
Nondrinker (*n* = 1054)	0.77	(0.58, 1.02)	0.07	1.11	(0.83, 1.48)	0.43	1.08	(0.98, 1.19)	0.12
0.1–5.00 mg/d (*n* = 634)	0.43	(0.29, 0.64)	0.0001	1.60	(1.10, 2.34)	0.01	1.15	(1.02, 1.30)	0.02
>5.0 mg/d (*n* = 315)	0.52	(0.31, 0.87)	0.01	1.61	(0.94, 2.74)	0.08	1.17	(1.01, 1.35)	0.04
Family history of diabetes									
Yes (*n* = 920)	0.62	(0.45, 0.85)	0.003	1.51	(1.10, 2.06)	0.01	1.13	(1.02, 1.24)	0.02
No (*n* = 1574)	0.64	(0.51, 0.81)	0.0002	1.35	(1.07, 1.70)	0.01	1.12	(1.03, 1.20)	0.006

[1] The multivariate models included age (5-y categories), time period (7 periods), BMI (11 categories), cigarette smoking (never, past, or current smoking of 1–14, 15–24, and ≥25 cigarettes/d), parental history of diabetes, alcohol consumption (4 categories), physical activity (metabolic equivalents/wk: 5 categories), percentage of energy from protein, and total energy intake. Intakes of specific types of fat and cholesterol were entered into the model simultaneously so that the effects of fats were compared with those of an equivalent amount of energy from carbohydrates. METS, metabolic equivalents.

[2] 23.9 mg/MJ = 100 mg/1000 kcal.

with intakes of polyunsaturated fatty acids (for 5% of energy: 0.64; 0.50, 0.82) and *trans* fatty acids (for 2% of energy: 1.37; 1.08, 1.74) were similar to those in the overall population.

DISCUSSION

In this large prospective study of women, we found no association between total fat intake and risk of type 2 diabetes after controlling for known risk factors. However, polyunsaturated fatty acid intake was associated with a substantial reduction in risk, and *trans* fatty acids and dietary cholesterol were associated with increased risk. We estimated that replacing 5% of energy from saturated fatty acid with energy from polyunsaturated fatty acid was associated with a 35% lower risk and that replacing 2% of energy from *trans* fatty acids with polyunsaturated fatty acid was associated with a 40% lower risk. Because the average intake of *trans* fatty acids from partially hydrogenated vegetable oils is ≈3% of energy in the United States (37, 38), our data suggest that the incidence of type 2 diabetes could be reduced by ≥40% if these oils were consumed in their original, unhydrogenated form.

Epidemiologic data on dietary fat and risk of diabetes are sparse and most of these studies are limited by incomplete control of potential confounding variables. Cross-sectional analyses have reported positive associations with saturated and monounsaturated fatty acids (12, 39) and an inverse association with polyunsaturated fatty acid intake (12). Two previous prospective studies, a 12-y follow-up study of 1462 women in Sweden (13) and a 25-y follow-up of 841 men in the Zutphen Study (14), found no significant associations between total dietary fat or specific types of fat and risk of diabetes. However, these studies were small and did not adjust simultaneously for other types of fats.

Our results regarding the lack of association with total fat and the inverse association with vegetable fat intake are also consistent with recently reported findings in a large prospective study of men (16). These findings are also consistent with earlier analyses in the Nurses' Health Study involving shorter follow-up periods (17, 18), but in the present study none of the specific types of fatty acids were significantly associated with risk of diabetes. However, our previous analyses with shorter follow-up periods did not include the mutual adjustment of one type of fatty acid for other types. Because some food sources of polyunsaturated fat, such as margarines, are also important sources of *trans* fatty acids, and because they have opposing effects, simultaneous control for the major type of fat appears to be essential to assess their independent effects. The importance of this multivariate modeling approach was previously documented for coronary heart disease (15, 40). The relative risk associated with polyunsaturated fatty acid intake adjusted for known risk factors was similar to that obtained in the age- and BMI-adjusted analysis, suggesting that confounding by lifestyle variables was only minor. However, intakes of other fats had more important confounding effects; adjustment for them strengthened the inverse association for polyunsaturated fatty acid intake and the positive association for *trans* fatty acids.

Imprecise dietary measurement and residual confounding are possible alternative explanations for some of the observed associations. However, errors in dietary assessment measures might have accounted for a lack of association but not the reverse (41). Notably, although simultaneous adjustments for other specific types of fat strengthened our findings, qualitatively similar associations were seen in analyses adjusted for age and BMI only. The repeated dietary measurements made in this study were advantageous because they allowed for fewer measurement errors and for changes in behavioral dietary patterns and food composition over time to be assessed (15, 40). On the basis of baseline dietary data from 1980 only, the associations with polyunsaturated (5% of energy) and *trans* (2% of energy) fatty acids were much weaker.

The inverse association with polyunsaturated fatty acid intake in the present analysis is consistent with the findings of a 6-y metabolic study in 102 diabetic patients that compared isoenergetic diets with different amount of linoleic acid [1.3 compared

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with 4.8 g/MJ, or 5.3 compared with 20 g/1000 kcal]. At the end of follow-up, there was a significant improvement in the results of oral-glucose-tolerance tests in the group that consumed the linoleic acid–enriched diet (6). A 30-wk crossover study by Heine et al (8) of 14 diabetic patients compared the long-term effects on lipoproteins of isoenergetic diets with a high ratio and those with a low ratio of polyunsaturated to saturated fatty acids (10% compared with 3% of energy intake from polyunsaturated fatty acids, respectively). The group that consumed the diet with a high ratio had an increased insulin response (assessed by in vitro binding of labeled insulin to red blood cells) and improved insulin sensitivity (indicated by a higher metabolic clearance response). However, there were no significant difference in insulin concentrations or glucose control between the 2 groups.

One proposed mechanism for the effect of polyunsaturated fatty acids on insulin sensitivity comes from observations that the fatty acid composition of cell membranes, which reflects the fatty acid composition of the diet (42), modulates insulin action; a greater saturated fatty acid content of membrane phospholipids increases insulin resistance (43). In animal models, diets enriched with polyunsaturated fatty acids enhance peripheral glucose utilization (44).

The positive association between risk of type 2 diabetes and *trans* fatty acid intake observed in our analysis is consistent with most previous studies in humans and animals, which indicate a wide variety of adverse metabolic effects on lipoprotein metabolism (10, 45) and insulin sensitivity (11, 46). In diabetic patients who consumed diets enriched with *trans* fatty acids (20% of energy) or saturated fatty acids (20% of energy) for 6 wk, the postprandial insulin response increased by 59% and 77%, respectively, compared with the effects of an isoenergetic diet with 20% of energy from nonhydrogenated monounsaturated fatty acids (11). In a preliminary report, a single meal high in *trans* fatty acids caused a reduction in insulin sensitivity (46). Although the mechanisms involved in the long-term effect of *trans* fatty acid intakes on insulin metabolism remain unclear, in vitro studies suggest a differential effect of *trans* compared with *cis* fatty acids on the regulation of insulin secretion: *trans* fatty acids potentiate glucose-stimulated insulin secretion more than do *cis*-isomers of identical chain length (47).

In a recent meta-analysis, the association between intake of *trans* fatty acids and risk of coronary heart disease in prospective studies was stronger than that predicted by the adverse effects of *trans* fatty acid intake on LDL and HDL cholesterol alone (10). The present findings suggest that this may be explained in part by disorders in carbohydrate metabolism related to higher intake of *trans* fatty acids. The positive association we observed between cholesterol intake and risk of type 2 diabetes has not been reported in other populations and requires confirmation.

In our study, the positive associations with *trans* fatty acid intakes and dietary cholesterol were observed primarily in obese and less physically active women. Although these subgroup findings need confirmation, we speculate that the effects of dietary *trans* fatty acids and cholesterol are not sufficient to cause diabetes, but in the presence of underlying insulin resistance may increase the probability of developing clinical disease. Nevertheless, the issue of multiple comparison should be considered because we looked at several dietary fatty acids simultaneously in the present analyses.

These data suggest that total fat and saturated and monounsaturated fatty acid intakes are not importantly associated with risk of type 2 diabetes in women but that dietary *trans* fatty acids increase and dietary polyunsaturated fatty acids reduce the risk. Thus, substitution of nonhydrogenated polyunsaturated fatty acids for *trans* fatty acids in the diet is likely to reduce the risk of type 2 diabetes substantially.

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