Dietary Fat and Incidence of Type 2 Diabetes in Older Iowa Women

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OBJECTIVE — To examine the associations between reported intakes of dietary fat and incident type 2 diabetes.

RESEARCH DESIGN AND METHODS — We studied the relation between dietary fatty acids and diabetes in a prospective cohort study of 35,988 older women who initially did not have diabetes. Diet was assessed with a food frequency questionnaire at baseline, and 1,890 incident cases of diabetes occurred during 11 years of follow-up.

RESULTS — After adjusting for age, smoking, alcohol consumption, BMI, waist-to-hip ratio, physical activity, demographic factors, and dietary magnesium and cereal fiber, diabetes incidence was negatively associated with dietary polyunsaturated fatty acids, vegetable fat, and *trans* fatty acids and positively associated with ω-3 fatty acids, cholesterol, and the Keys score. After simultaneous adjustment for other dietary fat, only vegetable fat remained clearly related to diabetes risk. Relative risks across quintiles of vegetable fat intake were 1.00, 0.90, 0.87, 0.84, and 0.82 ($P = 0.02$). Diabetes risk was also inversely related to substituting polyunsaturated fatty acids for saturated fatty acids and positively correlated to the Keys dietary score.

CONCLUSIONS — These data support an inverse relation between incident type 2 diabetes and vegetable fat and substituting polyunsaturated fatty acids for saturated fatty acids and cholesterol.

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Although a low-fat diet is recommended for diabetic and nondiabetic patients (1), findings from epidemiological studies on the association of total dietary fat with type 2 diabetes or insulin sensitivity have been inconsistent (2–8). Metabolic and epidemiological studies suggest that dietary fat subtypes may be relevant to diabetes pathophysiology. Specific dietary fatty acids may influence the development of diabetes by modifying the phospholipid composition of cell membranes, which in turn may alter the function of the insulin receptor (9,10).

While controlling for dietary and nondietary factors, we examined the relation between baseline intake of total dietary fat and dietary fat subtypes and the development of type 2 diabetes over 11 years of follow-up in the Iowa Women's Health Study.

RESEARCH DESIGN AND METHODS

— The Iowa Women's Health Study is a prospective cohort study of older Iowa women. In January 1986, a random sample of 99,826 women aged 55–69 years who had a valid Iowa driver's license were mailed a 16-page questionnaire and asked to participate. The study sample consisted of the 41,836 women who returned the baseline questionnaire. Respondents had a lower mean BMI (0.4 kg/m^2 less), were 3 months older, and were more likely to live in counties that were rural and less affluent than nonrespondents (11).

Women were excluded from analysis if they reported implausibly high (>5,000 kcal) or low (<600 kcal) energy intakes, left ≥30 items blank on the food-frequency questionnaire, or had diabetes at baseline. Women were considered to have diabetes at baseline if they responded "yes" or "don't know" to one of the following questions: *1*) have you ever been told by a doctor that you have sugar diabetes? and *2*) have you ever taken insulin or pills for sugar diabetes (or to lower blood glucose)? After exclusions, 35,988 women remained eligible for the study.

Data collection

The baseline questionnaire included questions on known or suspected risk factors for diabetes, such as age, BMI, waist-to-hip ratio (WHR), physical activity, alcohol consumption, and smoking history. BMI was calculated from weight and height measurements provided by the participants. WHR was calculated as the average of two measurements taken by the participant's spouse or friend using a paper tape measure that was included with the questionnaire (12). The women reported their frequency of moderate (e.g., golf and long walks) and vigorous (e.g., swimming and aerobics) physical activity. Pack-years of smoking were calculated from information on the intensity and duration of cigarette smoking. Alcohol consumption was assessed with a food frequency questionnaire that queried the participants' typical intakes of wine, beer, and spirits. In addition, the participants provided information on their marital status, educational attainment, residence, and use of hormone replacement therapy.

The principal dietary exposure of interest was intake of fat, including cholesterol and the Keys score. In addition to total dietary fat, we analyzed saturated, polyunsaturated, monounsaturated, *trans* fatty acids, long-chain ω-3 fatty acids, and

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Abbreviations: IGT, impaired glucose tolerance; RR, rate ratio; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Distribution of baseline risk factors for diabetes according to energy-adjusted* dietary fat intake among 35,988 Iowa women, 1986–1997*

Quintiles of intake:	Total fat		Saturated fatty acids		Poly-unsaturated fatty acids		Mono-unsaturated fatty acids		Long-chain ω-3 fatty acids		*Trans* fatty acids		Cholesterol		Animal fat		Vegetable fat	
	1	5	1	5	1	5	1	5	1	5	1	5	1	5	1	5	1	5
Mean																		
Age (years)	61.9	61.1	61.9	61.1	61.6	61.5	61.8	61.1	61.6	61.4	61.6	61.6	62.0	61.1	61.9	61.0	61.5	61.5
BMI (kg/m^2)	26.2	27.2	26.1	27.0	26.6	26.9	26.2	27.2	26.4	27.4	26.4	26.8	25.9	27.7	26.0	27.3	26.9	26.6
WHR	0.830	0.840	0.829	0.839	0.836	0.834	0.830	0.840	0.837	0.833	0.830	0.838	0.831	0.841	0.829	0.840	0.837	0.834
Percent																		
Never drinker	49.2	57.8	48.2	57.3	53.4	51.6	48.9	58.7	59.2	49.6	47.3	59.6	52.7	55.2	50.2	56.9	51.9	54.6
High-school graduate	83.3	79.9	83.5	78.6	80.5	83.3	84.0	80.0	79.2	84.0	84.4	80.3	82.6	79.9	83.5	78.9	80.7	83.3
High physical activity	33.8	18.6	33.0	19.0	27.0	24.3	35.8	17.3	21.5	31.8	36.4	17.3	27.2	24.0	30.6	20.0	28.8	21.1
Current smoker	12.9	20.4	13.0	21.1	15.3	16.2	12.6	19.7	15.6	14.2	14.5	16.1	14.5	17.3	13.8	19.0	15.2	16.8
Never used hormone replacement therapy	60.2	63.1	58.6	64.3	63.6	59.1	59.5	63.8	62.2	59.7	58.2	63.4	58.8	63.8	58.2	64.6	63.5	59.2
Currently married	74.4	81.0	75.2	80.2	77.5	77.4	74.5	81.7	78.5	75.8	76.6	77.2	74.9	79.5	73.7	82.6	79.2	75.4
Urban residence (>10,000 population)	38.9	28.9	39.1	28.9	31.4	36.9	39.3	28.7	30.2	37.6	39.1	31.3	38.4	29.0	40.5	26.1	29.9	37.6
Correlation coefficient																		
Total fat	1.0		0.82		0.47		0.96		−0.16		0.50		0.35		0.67		0.40	
Saturated fatty acids			1.0		−0.03		0.70		−0.20		0.25		0.40		0.86		−0.06	
Polyunsaturated fatty acids					1.0		0.43		0.06		0.33		−0.07		−0.23		0.86	
Monounsaturated fatty acids							1.0		−0.19		0.62		0.29		0.60		0.43	
Long-chain ω-3 fatty acids									1.0		−0.23		0.20		−0.07		−0.11	
Trans fatty acids											1.0		−0.05		0.08		0.52	
Cholesterol													1.0		0.58		−0.30	
Animal fat															1.0		−0.42	
Vegetable fat																	1.0	

*Adjusted for total energy intake according to the methods of Willett and Stampfer (19).

animal and vegetable fat. The Keys score, which correlates changes in fatty acid intake with changes in serum cholesterol, was calculated as $1.26\,(2S - P) + (Z)^{1/2}$, where S = percent of energy from saturated fat, P = percent of energy from polyunsaturated fat, and Z = dietary cholesterol in mg/1,000 kcal (13). A higher Keys score corresponds to higher relative intake of saturated fat and cholesterol and a lower relative intake of polyunsaturated fat. We also examined several foods and food groups high in dietary fats, including total meat, red meat, eggs, nuts, and olive oil salad dressing.

A 127-item food-frequency questionnaire similar to that used in the 1984 Nurses' Health Study was used to assess typical food intake over the previous year (14). The validity of the food-frequency questionnaire was evaluated by comparing nutrient values determined from the questionnaire with values estimated from the average of five 24-h dietary recall surveys in 44 study participants (15). Energy-adjusted Pearson's correlation coefficients were 0.62, 0.59, 0.62, 0.43, and 0.21 for total fat, saturated fat, monounsaturated fat, polyunsaturated fat, and cholesterol, respectively. Correlation coefficients were not calculated for other fat variables.

Diabetes incidence was determined by an affirmative response to the following question, which was on all of the follow-up mailed surveys: "Since baseline or respective follow-up, were you diagnosed for the first time by a doctor as having sugar diabetes?" During 11 years of follow-up, 1,890 women reported incident diabetes in the four follow-up surveys administered in 1987 (n = 344), 1989 (n = 331), 1992 (n = 466), and 1997 (n = 749). Response rates for the four follow-up surveys were 91, 89, 86, and 79%, respectively.

A validation study of self-reported diabetes was conducted on 85 cohort participants in 1988 after the first follow-up survey. Subjects tended to over-report having diabetes; of 44 women who reported having diabetes at baseline, 28 (64%) were confirmed as having diabetes by their physician. All 41 women who reported not having diabetes at baseline were confirmed as not having diabetes (16).

Statistical analysis

For women who did not report a diagnosis of diabetes, person-time-at-risk was

calculated from baseline to the date of the last completed follow-up survey. For women who reported a diagnosis of diabetes, person-time was calculated as the sum of the known disease-free period and half of the period during which the diagnosis was made. Mortality status was determined annually through linkage with the State Health Registry of Iowa or, in the case of nonrespondents and emigrants from Iowa, via the National Death Index.

Nutrient intakes were adjusted for total energy through the residual method (17) and divided into quintiles. Trend analyses weighted each category of dietary intake by the median intake for that category. Cox proportional hazards regression models provided estimates of rate ratios (RRs). The SAS package was used (18); all *P* values were two-sided.

To examine the independent effects of specific fat subtypes, we simultaneously adjusted for all fat subtypes. Because we adjusted for dietary protein, the regression coefficients are an estimate of the effect of substituting a specific fat subtype for carbohydrates in the diet. We further examined substituting one fat subtype for another by including total fat and all fat subtypes except the subtype for which we substituted (19).

RESULTS — The distributions of several known risk factors for diabetes and correlation coefficients among dietary fat variables are presented in Table 1. Women in the highest category of saturated, monounsaturated, *trans* fatty acids, and animal fat had a higher BMI and WHR, but they consumed less alcohol and engaged in less physical activity. For cholesterol, these relations were similar but not as pronounced. The risk-factor differences among categories of polyunsaturated and ω-3 fatty acids and vegetable fat were not extreme. Overall, 99% of the population was non-Hispanic white and 95% were of Protestant or Catholic religious faith; these distributions did not vary according to fat intake. Positive correlations were evident between total and saturated fat, total and monounsaturated fat, animal and saturated fat, and vegetable and polyunsaturated fat.

After adjusting for nondietary factors in a multivariate regression analysis, total dietary fat, saturated fatty acids, and monounsaturated fatty acids were not related to incident diabetes (Table 2). Animal fat, cholesterol, the Keys score, and ω-3 fatty acids were positively correlated to diabetes. Comparing the highest with the lowest levels of intake, animal fat was associated with a 20% increase in incident diabetes (RR 1.19 and 95% CI 1.02–1.39). Comparing the highest with the lowest quintiles of intake, diabetes incidence increased with dietary cholesterol intake and the Keys score (1.24, 1.07–1.43) and (1.27, 1.08–1.49), respectively. There were inverse relations with polyunsaturated fatty acids and *trans* fatty acids and vegetable fat. Relative risks among quintiles of intake were 1.0, 0.93, 0.90, 0.84, and 0.87 ($P = 0.03$) and 1.0, 0.88, 0.84, 0.81, and 0.78 ($P = 0.0007$) for polyunsaturated fatty acids and vegetable fat, respectively.

We further adjusted for dietary magnesium and cereal fiber (Table 2), both of which were inversely related to diabetes incidence in this population (20). After this adjustment, animal fat was no longer related to diabetes risk ($P = 0.24$). Also attenuated were relations with dietary cholesterol and the Keys score. Comparing the highest to the lowest category of intake, the RRs for cholesterol and the Keys score were 1.17 (95% CI 1.01–1.37) and 1.17 (0.99–1.38), respectively.

After simultaneous adjustment for other dietary fat subtypes, vegetable fat remained clearly associated with type 2 diabetes (Table 3). Relative risks across quintiles of vegetable fat intake were 1.00, 0.90, 0.87, 0.84, and 0.82 ($P = 0.02$), and they did not change appreciably after further adjustment for vitamin E. When we substituted polyunsaturated fatty acids for saturated fatty acids and vegetable fat for animal fat, we found that they were inversely related to diabetes risk. RRs across polyunsaturated fat intake were 1.0, 0.92, 0.89, 0.83, and 0.84 ($P = 0.02$). Comparing the highest to the lowest category of vegetable intake, the RR was 0.78 (95% CI 0.67–0.91).

We analyzed foods and food groups that contribute to fat intake. Total meat intake was positively correlated to diabetes risk. Relative risks across categories of intake were 1.0, 1.04, 1.07, 1.15, and 1.35 ($P = 0.0004$). After adjustment for vegetable fat and dietary cholesterol, magnesium, and cereal fiber, the relative risks across categories of intake were 1.0, 1.01, 1.02, 1.06, and 1.19 ($P = 0.07$). Eggs were also positively correlated to diabetes risk, with RRs across categories of intake of 1.0, 1.01, 1.11, and 1.21 ($P = 0.02$). This relation was eliminated after the adjustment for dietary cholesterol ($P = 0.99$). Foods high in vegetable fat, such as nuts, olive oil dressing, and margarine were not clearly related to diabetes risk.

There was no evidence in these data for modification of the relation between vegetable fat and diabetes by BMI. The relative risks for increasing vegetable fat intake roughly indicated a 20% reduction in diabetes when comparing the highest and lowest tertiles of vegetable fat in both the lowest and highest BMI tertiles. Similarly, we did not find support for effect modification by physical activity, alcohol consumption, or vitamin E intake.

CONCLUSIONS — Data from this prospective study of older women indicate that the composition of dietary fat may play a role in the development of type 2 diabetes. After adjusting for potential confounding variables and animal fat, we found an inverse relation between vegetable fat and incident type 2 diabetes. Polyunsaturated fatty acid was inversely related to diabetes risk when substituted for saturated fatty acid, and the Keys dietary score was positively correlated to diabetes.

There was no relation between dietary fat and diabetes in several prospective studies, which was consistent with our findings (5–8). Among 1,462 Swedish women, the mean intake of total dietary fat (based on a diet history) did not differ for women who did and did not go on to develop diabetes (7). The percent of energy derived from fat did not differ among Pima Indian women who developed diabetes compared with those who remained disease free (6).

However, other prospective studies have shown a positive correlation between diabetes and total dietary fat. Among subjects with impaired glucose tolerance (IGT), total dietary fat (assessed by 24-h recall) predicted conversion to diabetes within 1–3 years (21). In two cohorts of the Seven Countries Study, the percent of energy from fat predicted diabetes and was positively correlated to postload glucose levels after 20 years of follow-up (22).

Results from cross-sectional studies have been similarly mixed. A positive correlation between insulin sensitivity, derived from postload insulin and glucose measurements, and total dietary fat, which was reported by Lovejoy and DiGi-

Table 2—*Multivariate-adjusted relative risks of incident diabetes across quintiles of dietary fat variables among 35,988 Iowa women, 1986–1992*

Variable	Quintile of Intake					*P* for trend
	1	2	3	4	5	
Total dietary fat						
Median intake (g/day)	55.7	56.1	60.1	66.8	86.6	
Cases	332	351	380	387	440	
Relative risk* (95% CI)	1.00	1.04 (0.88–1.21)	1.01 (0.86–1.18)	1.02 (0.87–1.19)	1.04 (0.89–1.21)	0.69
Relative risk† (95% CI)	1.00	1.00 (0.85–1.17)	0.95 (0.81–1.11)	0.93 (0.79–1.10)	0.89 (0.75–1.05)	0.11
Saturated fatty acids						
Median intake (g/day)	19.3	19.2	20.4	23.2	31.8	
Cases	313	342	386	432	417	
Relative risk* (95% CI)	1.00	1.07 (0.91–1.26)	1.10 (0.94–1.30)	1.16 (1.00–1.36)	1.11 (0.95–1.29)	0.14
Relative risk† (95% CI)	1.00	1.05 (0.89–1.24)	1.06 (0.90–1.25)	1.10 (0.94–1.29)	1.00 (0.85–1.18)	0.91
Polyunsaturated fatty acids						
Median intake (g/day)	8.9	9.2	10.4	12.2	16.6	
Cases	412	372	369	351	386	
Relative risk* (95% CI)	1.00	0.93 (0.80–1.08)	0.90 (0.78–1.05)	0.84 (0.73–0.98)	0.87 (0.75–1.00)	0.03
Relative risk† (95% CI)	1.00	0.94 (0.81–1.08)	0.91 (0.78–1.06)	0.85 (0.73–0.99)	0.88 (0.76–1.02)	0.05
Monounsaturated fatty acids						
Median intake (g/day)	20.4	20.9	22.7	25.7	33.8	
Cases	336	354	378	368	454	
Relative risk* (95% CI)	1.00	1.01 (0.86–1.18)	1.05 (0.90–1.23)	0.95 (0.81–1.11)	1.06 (0.91–1.23)	0.58
Relative risk† (95% CI)	1.00	0.99 (0.84–1.16)	1.01 (0.86–1.19)	0.90 (0.76–1.06)	0.96 (0.82–1.13)	0.48
Long-chain ω-3 fatty acids						
Median intake (g/day)	0.03	0.09	0.13	0.20	0.39	
Cases	387	360	358	345	440	
Relative risk* (95% CI)	1.00	0.97 (0.83–1.12)	0.99 (0.85–1.16)	0.97 (0.83–1.13)	1.15 (1.00–1.33)	0.02
Relative risk† (95% CI)	1.00	0.98 (0.84–1.14)	1.01 (0.87–1.18)	0.99 (0.85–1.15)	1.20 (1.03–1.39)	0.006
Trans fatty acids						
Median intake	2.2	2.4	2.8	3.5	5.2	
Cases	363	388	379	360	400	
Relative risk* (95% CI)	1.00	1.01 (0.87–1.18)	0.93 (0.80–1.09)	0.86 (0.74–1.01)	0.88 (0.76–1.03)	0.03
Relative risk† (95% CI)	1.00	0.99 (0.85–1.15)	0.90 (0.77–1.05)	0.82 (0.70–0.97)	0.83 (0.70–0.97)	0.004
Cholesterol						
Median intake (mg/day)	185	201	237	281	382	
Cases	325	301	368	402	494	
Relative risk* (95% CI)	1.00	0.87 (0.74–1.03)	1.07 (0.91–1.25)	1.10 (0.94–1.28)	1.24 (1.07–1.43)	0.0001
Relative risk† (95% CI)	1.00	0.86 (0.73–1.01)	1.04 (0.89–1.22)	1.06 (0.91–1.24)	1.17 (1.01–1.37)	0.002
Keys score						
Median	31.4	37.4	41.6	46.0	53.2	
Cases	283	346	400	422	439	
Relative risk* (95% CI)	1.00	1.14 (0.97–1.34)	1.21 (1.03–1.42)	1.25 (1.07–1.46)	1.27 (1.08–1.49)	0.002
Relative risk† (95% CI)	1.00	1.12 (0.95–1.32)	1.17 (1.00–1.37)	1.19 (1.01–1.39)	1.17 (0.99–1.38)	0.06
Animal fat						
Median intake (g/day)	29.1	29.8	33.7	40.4	56.8	
Cases	317	344	364	416	449	
Relative risk* (95% CI)	1.00	1.08 (0.92–1.27)	1.08 (0.92–1.27)	1.17 (1.01–1.37)	1.19 (1.02–1.39)	0.01
Relative risk† (95% CI)	1.00	1.06 (0.90–1.25)	1.04 (0.89–1.23)	1.12 (0.95–1.31)	1.09 (0.93–1.28)	0.24
Vegetable fat						
Median intake (g/day)	18.6	20.2	23.7	29.2	41.7	
Cases	434	377	358	349	372	
Relative risk* (95% CI)	1.00	0.88 (0.76–1.02)	0.84 (0.73–0.98)	0.81 (0.69–0.94)	0.78 (0.68–0.91)	0.0007
Relative risk† (95% CI)	1.00	0.86 (0.76–1.03)	0.85 (0.73–0.99)	0.81 (0.70–0.95)	0.79 (0.68–0.92)	0.001

*Proportional hazards regression models were adjusted for age, total energy, WHR (quintiles: <0.762, 0.763–0.805, 0.806–0.848, 0.849–0.901, >0.901), BMI (quintiles: <22.7, 22.7–24.8, 24.9–27.0, 27.1–30.2, >30.2), physical activity (four levels each for frequency of vigorous and moderate activity: never or rarely, a few times a year, from a few times a month to about once a week, or 2 times a week or more), cigarette smoking (none, 1–19 pack-years, 20–39 pack-years or ≥40 pack-years), alcohol consumption (none, <4 g per day, from 4–10 g per day, or ≥10 g per day), education (no high school diploma, high school diploma, college or vocational school but no degree, or college degree), marital status (currently married, never married, separated or divorced, or widowed), residential area (farm, rural or small town with population up to 2,499, town of population from 2,500–10,000 or city or town with population >10,000), and hormone replacement therapy (current, former, or never). †Additionally adjusted for energy-adjusted dietary magnesium (quintiles) and cereal fiber (quintiles).

Table 3—*Multivariate-adjusted* relative risks of incident diabetes across quintiles of dietary fat variables among 35,988 Iowa women, 1986–1992*

	Quintile of Intake					
Variable	1	2	3	4	5	*P* for trend
Saturated fatty acids						
Relative risk† (95% CI)	1.00	1.06 (0.89–1.27)	1.07 (0.89–1.29)	1.11 (0.91–1.36)	0.95 (0.76–1.19)	0.71
Polyunsaturated fatty acids						
Relative risk† (95% CI)	1.00	0.94 (0.81–1.09)	0.93 (0.79–1.08)	0.88 (0.74–1.03)	0.90 (0.75–1.07)	0.19
Relative risk‡ (95% CI)	1.00	0.92 (0.79–1.07)	0.89 (0.76–1.04)	0.83 (0.71–0.98)	0.84 (0.71–0.98)	0.02
Monounsaturated fatty acids						
Relative risk† (95% CI)	1.00	0.99 (0.83–1.19)	1.03 (0.84–1.27)	0.93 (0.74–1.18)	1.02 (0.78–1.34)	0.93
Long-chain ω-3 fatty acids						
Relative risk† (95% CI)	1.00	0.97 (0.83–1.12)	0.99 (0.84–1.15)	0.94 (0.80–1.10)	1.11 (0.94–1.30)	0.14
Trans fatty acids						
Relative risk† (95% CI)	1.00	1.01 (0.86–1.19)	0.94 (0.79–1.12)	0.88 (0.73–1.06)	0.92 (0.75–1.11)	0.20
Cholesterol						
Relative risk† (95% CI)	1.00	0.84 (0.71–1.00)	1.02 (0.86–1.22)	1.03 (0.87–1.23)	1.11 (0.92–1.33)	0.07
Animal fat						
Relative risk§ (95% CI)	1.00	1.04 (0.88–1.22)	0.97 (0.82–1.15)	0.99 (0.83–1.18)	0.89 (0.73–1.07)	0.18
Vegetable fat						
Relative risk§ (95% CI)	1.00	0.90 (0.78–1.04)	0.87 (0.75–1.01)	0.84 (0.72–0.98)	0.82 (0.70–0.97)	0.02
Relative risk‖ (95% CI)	1.00	0.88 (0.76–1.02)	0.84 (0.72–0.97)	0.81 (0.6–0.94)	0.78 (0.67–0.91)	0.001

*All models included variables listed in Table 2, reference 2 and dietary protein (quintiles); †model included saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, *trans* fatty acids, ω-3 fatty acids, and cholesterol (quintiles); ‡model included total fat, monounsaturated fatty acids, *trans* fatty acids, and ω-3 fatty acids quintiles; §model included vegetable fat and animal fat (quintiles); ‖model included total fat (quintiles).

rolamo (23), was apparent only before adjusting for BMI. Two other studies also found no association with fasting insulin after accounting for BMI (24,25), whereas another study (26) found that total fat was unrelated to fasting insulin in univariate and multivariate analyses. In contrast, several studies (27–30) found a positive correlation between total dietary fat and fasting or postprandial insulin (independent of BMI) or a negative correlation with insulin sensitivity (34).

Our findings are consistent with some, but not all, prospective epidemiological studies that have examined subtypes of dietary fatty acids. In one study, vegetable fat and polyunsaturated fatty acids were inversely related to incident type 2 diabetes among lean women but not among obese women (31); saturated fatty acids, monounsaturated fatty acids, and animal fats were not related to diabetes. Although statistically nonsignificant, the RRs (0.85 among women and 0.83 among men comparing the highest with the lowest quintile of vegetable fat consumption) for incident diabetes reported in two studies by Salmeron and colleagues (32,33) were strikingly similar to ours for vegetable fat. Incident diabetes and conversion to diabetes were positively correlated to saturated fat and unrelated to polyunsaturated fat in two other follow-up studies (21,22). These findings are more in line with those from most cross-sectional studies, in which saturated fat was positively correlated to fasting insulin (24,26–29) or area under the insulin curve (34) and inversely related to insulin sensitivity (34). The findings for polyunsaturated fatty acids from these studies were more varied, showing inverse (34), positive (27), and no correlation (25,28,29,34) with insulin concentrations or sensitivity.

The inverse relationship between diabetes and vegetable fat remained after adjustment for other dietary fat, but that for polyunsaturated fatty acids did not. Likewise, Salmeron and colleagues (32,33) reported no association between polyunsaturated fatty acids and diabetes. When the highest to the lowest quintiles of polyunsaturated fatty acid intake were compared, the adjusted relative risks for diabetes were 0.97 in women and 1.01 in men. Vegetable fat includes fats found in nonanimal sources, including fruits and vegetables, grains, nuts, and oils. It is possible that vegetable fat represents the combination of several potentially healthful fat subtypes, including polyunsaturated fatty acids and monounsaturated fatty acids, from vegetable sources. Furthermore, although we considered several dietary factors that have been hypothesized to relate to diabetes risk, such as vitamin E, cereal fiber, and magnesium, vegetable fat will be highly correlated with any number of additional nutrients that we did not include, which may influence diabetes risk.

Although polyunsaturated fatty acids were not related to diabetes after adjusting for all other fatty acids, a true inverse relation is possible. It may be argued that dietary factors are so highly correlated that a high degree of attenuation is inevitable with simultaneous adjustment for dietary factors. When substituted for saturated fatty acids in the diet, polyunsaturated fatty acids were inversely related to diabetes, whereas the Keys score was positively correlated to diabetes. These findings are consistent with data from a 10-year follow-up study of middle-aged men who did and did not develop type 2 diabetes (35). Men who did develop type 2 diabetes had a higher proportion of saturated fatty acids and a lower proportion of linoleic acid in serum cholesterol esters, which in part reflects dietary fatty acid composition, than men who did not de-

velop type 2 diabetes (35). A cross-sectional study of 45 subjects found no relationship between insulin sensitivity and the ratio of dietary polyunsaturated fatty acids to saturated fatty acids (23).

Feeding studies support a positive correlation between monounsaturated fatty acid intake and insulin sensitivity (36–39). In our study population, monounsaturated fatty acid consumption was more highly correlated with saturated and animal fat consumption (correlation coefficients 0.70 and 0.62, respectively) than with polyunsaturated and vegetable fat consumption (correlation coefficients 0.43 and 0.29, respectively). This may limit our ability to isolate the effects of individual fats; it underscores the importance of the specific dietary characteristics of studied populations. Such correlations will be somewhat population-specific; they may have contributed to the positive associations between monounsaturated fat and incident diabetes (22), to the progression to diabetes from IGT (21), and to fasting insulin (27,28) in some studies, but the inverse relation with insulin sensitivity (34) appears in other studies.

In our study, diabetes was positively correlated to dietary cholesterol and the Keys score. Similarly, Feskens et al. (22) found a positive correlation between dietary cholesterol and 20-year diabetes incidence in two Seven Countries Study cohorts. Conversely, two cross-sectional studies found no association between dietary cholesterol and fasting or postprandial insulin (26,34). It is unclear how dietary cholesterol may affect diabetes incidence, and our findings should be interpreted with caution, particularly because the association was attenuated after adjustment for other dietary fat variables.

Dietary cholesterol is related to serum cholesterol levels to some extent (40), and it is possible that changes in serum cholesterol explain the association between dietary cholesterol and diabetes risk (40). Our findings for the Keys score are consistent with the finding that the Keys dietary score indicates positive changes in serum cholesterol predicted by positive changes in dietary cholesterol and saturated fatty acids and negative changes in polyunsaturated fatty acids (13). In two other studies, the univariate or age-adjusted rate of incident diabetes was 50% greater in the highest than in the lowest category of serum cholesterol, although the estimate from only one study was statistically significant (5,8). However, it is difficult to distinguish the relations between the Keys score and serum cholesterol from the relation between the Keys score and saturated and polyunsaturated fatty acid intake, for which the evidence of an association with diabetes is far more compelling.

Differential intakes of dietary fat subtypes may affect diabetes risk by modifying the fatty acid composition of the phospholipid membrane, which may play a role in blood glucose regulation through effects on insulin secretion, insulin receptor properties, and glucose transport. Borkman et al. (41) reported significant inverse relations between fasting serum insulin and the content of ω-3 and ω-6 fatty acids within skeletal-muscle phospholipids. Compared with saturated fatty acids, polyunsaturated fatty acids appear to enhance insulin secretion (42), and saturated fatty acids have been shown to decrease insulin binding to receptors and to impair glucose transport (9).

Error in the measurement of diet, diabetes, and covariates in this study may have limited our ability to obtain accurate relative-risk estimates. Random measurement error in dietary exposures most frequently attenuates risk estimates (43). Of particular interest is the potential for misclassification of *trans* fatty acid intake that resulted from temporal changes in the consumption and manufacturing patterns of *trans* fatty acids in the U.S. during the 1980s, when many consumers switched to soft, reduced *trans* fat margarine and industry ceased the partial hydrogenation of household salad and cooking oils (44). These changes could have resulted in a large misclassification of *trans* fatty acid intake in our population.

The validation study correlation coefficient for cholesterol was quite low (0.21). This did not prevent us from detecting an association between cholesterol and diabetes, but it may reflect a degree of random error in this variable that prevented us from detecting a truly larger magnitude of association. Our validation sample was quite small ($n = 44$), and it is possible that our sample was aberrant; correlations for other fat variables were similar to those obtained in another large study of women, in which the correlation coefficient for cholesterol was 0.61 (14).

Incident cases of diabetes were ascertained by self-report. Our validation study (see above) suggested that participants over-reported diabetes compared with physician diagnoses (16). This is consistent with findings from one study (45) in which 29 of 44 (66%) positive reports of diabetes were validated with medical records. Nonvalidated positive reports may nonetheless reflect some level of diabetes. One study found that several persons with nonvalidated positive reports of diabetes had some history of glycosuria (46). Thus, nondiabetic concentrations of blood glucose may not be entirely benign, and women who falsely reported a diagnosis of diabetes may still have some level of underlying disease, such as IGT. This possibility is supported by the change in the diagnostic criteria for diabetes to lower levels of fasting glucose (47). The ascertainment of diabetes in the present study was sensitive enough to confirm associations with other risk factors for diabetes (i.e., weight [16], physical activity [48], and dietary fiber [20]) obtained from studies with validated diabetes. Assuming that the error in diabetes ascertainment was independent and nondifferential, present findings would only be strengthened by more accurate ascertainment of disease.

Dietary fat may contribute to the etiology of type 2 diabetes. After adjusting for nondietary and dietary covariates, we found that vegetable fat was inversely related to incident diabetes in this population of older Iowa women. In addition, substituting polyunsaturated fatty acids for saturated fatty acids appeared to reduce the rate of diabetes.

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