Dietary Fat and Meat Intake in Relation to Risk of Type 2 Diabetes in Men

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OBJECTIVE — To examine dietary fat and meat intake in relation to risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS — We prospectively followed 42,504 male participants of the Health Professionals Follow-Up Study who were aged 40–75 years and free of diagnosed diabetes, cardiovascular disease, and cancer in 1986. Diet was assessed by a validated food frequency questionnaire and updated in 1990 and 1994. During 12 years of follow-up, we ascertained 1,321 incident cases of type 2 diabetes.

RESULTS — Intakes of total fat (multivariate RR for extreme quintiles 1.27, CI 1.04–1.55, *P* for trend = 0.02) and saturated fat (1.34, 1.09–1.66, *P* for trend = 0.01) were associated with a higher risk of type 2 diabetes. However, these associations disappeared after additional adjustment for BMI (total fat RR 0.97, CI 0.79–1.18; saturated fat 0.97, 0.79–1.20). Intakes of oleic acid, *trans*-fat, long-chain n-3 fat, and α-linolenic acid were not associated with diabetes risk after multivariate adjustment. Linoleic acid was associated with a lower risk of type 2 diabetes in men <65 years of age (RR 0.74, CI 0.60–0.92, *P* for trend = 0.01) and in men with a BMI <25 kg/m^2 (0.53, 0.33–0.85, *P* for trend = 0.006) but not in older and obese men. Frequent consumption of processed meat was associated with a higher risk for type 2 diabetes (RR 1.46, CI 1.14–1.86 for ≥5/week vs. <1/month, *P* for trend <0.0001).

CONCLUSIONS — Total and saturated fat intake were associated with a higher risk of type 2 diabetes, but these associations were not independent of BMI. Frequent consumption of processed meats may increase risk of type 2 diabetes.

Diabetes Care **25:417–424, 2002**

Migration studies and analyses of secular trends indicate that adoption of a "Western lifestyle" is strongly associated with type 2 diabetes (1). Obesity and lack of physical activity are known to be major determinants (2,3), but evidence also suggests that dietary factors play a role in the development of type 2 diabetes (4). A major characteristic of Western diets is a high intake of animal fat and meat.

Animal studies suggest that the type of fat in the diet may affect insulin sensitivity by changing the fatty acid composition of membrane lipids. A higher proportion of unsaturated fat may improve insulin signaling by increasing membrane fluidity (5). Consistent with this mechanism, the proportion of unsaturated fat in skeletal muscle membrane lipids was positively associated with insulin sensitivity in humans (6). Several studies of hyperinsulinemia and hyperglycemia suggested a detrimental effect of saturated fat (7–12) and a beneficial effect of polyunsaturated fat (8,13). However, other studies did not confirm these results (14–16). Lack of adjustment for confounding by other dietary and nondietary risk factors may have contributed to the inconsistencies in findings. Alternatively, the apparently divergent results observed in different populations may be real because the effects of dietary fat may vary with population characteristics, such as age, BMI, and physical activity, that are associated with insulin sensitivity (17–19).

Few studies have examined the possible role of n-3 fatty acids (9,12,20–22) or *trans*-fat (21,22) in the development of type 2 diabetes. Previously, we reported that *trans*-fat was positively associated and polyunsaturated fat inversely associated with risk of type 2 diabetes in women (21). Meat intake was associated with a higher risk of diagnosed diabetes in a study in Seventh-Day Adventists (23), but it has never been examined in detail.

In 6 years of follow-up in this cohort of male health professionals, we did not observe significant associations between major types of fat and risk of type 2 diabetes (24). In the present report, we extended this analysis to 12 years of follow-up; used repeated dietary assessments, stratified by age, BMI, and physical activity; and examined intake of *trans*-fat, specific polyunsaturated fats, and meats in relation to risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS

The Health Professionals Follow-up Study started in 1986, when 51,529 male health professionals (dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, and podiatrists) completed a detailed mailed questionnaire on medical history, diet, and other potential risk factors for major diseases. The participants lived in all 50 U.S. states, were predominantly white, and were 40–75 years of age in 1986. We excluded from the analysis 1,595 men who did not satisfy the a priori criteria of a reported

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Received for publication 28 December 2000 and accepted in revised form 6 December 2001.

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

daily energy intake between 3.3 and 17.6 MJ (800 and 4,200 kcal) and blank responses for <70 of 131 food items on the diet questionnaire (<5% had >11 blanks). We also excluded men who reported diabetes, cardiovascular disease (myocardial infarction, angina pectoris, coronary artery surgery, or stroke), or cancer (except nonmelanoma skin cancer) at baseline because diagnosis of these diseases may affect diet or reporting of diet. After exclusions, 42,504 men remained and were followed for incidence of type 2 diabetes during the subsequent 12 years (1986–1998). Every 2 years, questionnaires were mailed to the members of the cohort to update information on exposures and to identify new cases of type 2 diabetes and other diseases. The follow-up rate as a proportion of the total potential person-years of follow-up was ~97% for nonfatal events. Deaths were reported by family members, coworkers, or postal authorities or were identified through systematic searches of the National Death Index.

Dietary assessment

To assess dietary intake, we used a 131-item semiquantitative food frequency questionnaire in 1986 and again in 1990 and 1994 to update dietary information. For each food, a commonly used unit or portion size was specified, and participants were asked to indicate for each food how often, on average, they had consumed the amount specified during the past year. Nine responses were possible, ranging from "never or less than once a month" to "six or more times per day." The questionnaire also included questions about the types of fat commonly used for cooking and at the table, and there was an open-ended section for foods that were not listed. We computed nutrient intakes by multiplying the consumption frequency of each food used by the nutrient content in the specified portion. Values for the nutrient amounts in foods were obtained from the Harvard University Food Composition database, derived from U.S. Department of Agriculture sources (25), and supplemented with information from manufacturers and published literature.

The validity and reproducibility of the food-frequency questionnaire was assessed among 127 participants of this cohort (26). The Pearson correlation coefficients for intake measured by two 1-week diet records and by the food-frequency questionnaire, adjusted for week-to-week variation in the diet records, were 0.67 for total fat, 0.75 for saturated fat, 0.68 for monounsaturated fat (primarily oleic acid), 0.37 for polyunsaturated fat (primarily linoleic acid), and 0.76 for cholesterol. These correlations ranged from 0.56 (chicken, turkey without skin) to 0.83 (processed meats) for meat consumption (27). Intake of fatty acids (as a proportion of total fat) estimated by the questionnaire was also compared with the proportions of fats in adipose tissue (28). The Spearman correlation was 0.49 for the long-chain n-3 fatty acid eicopentaenoic acid and 0.29 for *trans*-fat. Because the correlation between the proportion of polyunsaturated fat in adipose tissue and estimates of intake from the questionnaire (Spearman $r = 0.50$) and from diet records ($r = 0.47$) were similar, measurement error in the diet record probably contributed to the relatively low correlation between the questionnaire and the diet record estimate.

Ascertainment of type 2 diabetes

We mailed a supplementary questionnaire on symptoms, diagnostic tests, and medication to all men who reported a diagnosis of diabetes on any of the biennial follow-up questionnaires ($n = 2056$). Confirmation of diabetes required at least one of the following: *1*) an elevated plasma glucose concentration (fasting plasma glucose ≥7.8 mmol/l, random plasma glucose ≥11.1 mmol/l, and/or plasma glucose ≥11.1 mmol/l after ≥2 h during an oral glucose tolerance test), plus at least one classic symptom (excessive thirst, polyuria, weight loss, or hunger); *2*) at least two elevated plasma glucose concentrations on different occasions; or *3*) treatment with insulin or oral hypoglycemic medication. Men who reported to have type 1 diabetes on the supplementary questionnaire were excluded. These criteria are consistent with those proposed by the World Health Organization in 1985 (29). We did not use the diabetes classification of the American Diabetes Association (30) because the large majority of the cases of diabetes in this study occurred before these criteria were published. The validity of our assessment of type 2 diabetes was verified with medical records in a subsample of 71 participants of the cohort. A physician blinded to the information on the supplementary questionnaire reviewed the records according to the diagnostic criteria. Of the 71 participants who were classified as having type 2 diabetes, 12 had incomplete records, e.g., absent laboratory data ($n = 2$) or only one set of laboratory data ($n = 9$). Among the remaining 59 subjects, the classification of type 2 diabetes was confirmed in 57 (97%). One patient denied having diabetes, and one lacked evidence of diabetes in his submitted records.

Assessment of nondietary exposure

Weight, smoking status, and physical activity were assessed in 1986 and on each biennial follow-up questionnaire. Participants provided information on age, diagnosis of hypertension and hypercholesterolemia, and height in 1986 and on family history of diabetes in 1987. A family history of type 2 diabetes was considered to be present if at least one of the first-degree relatives had a diagnosis of diabetes after 30 years of age. Physical activity (in MET hours per week) was based on reported time spent on various activities, weighting each activity by its intensity level (31). The validity of self-reported weight (32) and physical activity (31) in this cohort has been reported previously.

Statistical analysis

Analyses adjusted for age and energy intake were based on incidence rates of type 2 diabetes, using person-months of follow-up. Participants contributed follow-up time from the return of the 1986 questionnaire until diagnosis of type 2 diabetes, death, or the end of the study period. Relative risks were calculated by dividing the incidence rate of type 2 diabetes among men in each category of intake by the rate in the lowest category. The Mantel-Haenzel estimator was used to adjust for age (across 5-year categories) and total energy intake (33); linear trends were tested with the Mantel Extension test (34).

We used pooled logistic regression analyses with 2-year intervals to estimate multivariate-adjusted RRs for each category of intake as compared with the lowest category. With short time intervals and low rates of events, this approach gives results very similar to Cox proportional hazards analyses (35). Participants who died or were diagnosed with diabetes

Table 1—*Baseline characteristics of the study population by quintiles of fat intake

	Saturated fat		*Trans*-fat		Linoleic acid		Long-chain n-3 fat	
Quintile of intake:	Q1	Q5	Q1	Q5	Q1	Q5	Q1	Q5
Age (years)	54.5	53.0	54.3	53.4	54.4	53.3	52.5	54.8
BMI (kg/m^2)	24.6	26.0	24.9	25.6	25.3	25.5	25.5	25.4
Physical activity (MET/week)†	27.7	15.9	27.2	16.4	22.2	19.5	16.8	25.1
Current smokers (%)	5.7	14.3	6.4	11.5	11.3	8.6	11.6	7.4
Family history of diabetes (%)	19.3	20.2	19.8	19.5	18.7	19.9	18.6	21.3
Hypertension (%)	20.7	17.9	19.9	18.0	20.0	18.8	17.5	20.8
Hypercholesterolemia (%)	16.1	6.5	13.3	8.6	9.8	11.2	7.2	14.4
Total energy intake (kcal/day)	1,891	2,079	1,863	2,126	1,959	2,002	1,976	1,929
Alcohol intake (g/day)	14.4	8.3	13.8	8.2	14.7	9.0	10.9	10.7
Cereal fiber intake (g/day)	7.7	4.4	7.0	5.4	6.0	5.7	5.7	6.1
Magnesium intake (mg/day)	406	315	415	309	363	356	328	386

*Standardized to the age distribution of the total study population (except for age); quintiles were based on energy percentage of fat intakes, except for quintiles of long chain n-3 fat, which were based on intake in mg/day adjusted for energy intake with the residual method; Q1 = lowest quintile, Q5 = highest quintile. †MET hours per week (one metabolic equivalent is the energy expended at rest).

during a 2-year cycle were censored at the end of that 2-year period and were not entered in any subsequent 2-year cycle.

To reduce within-subject variation and best represent long-term diet, we used the cumulative average of dietary intakes from all available dietary questionnaires up to the start of each 2-year follow-up interval (36); the 1986 intake was used for the follow-up between 1986 and 1990; the average of the 1986 and 1990 intake was used for the follow-up between 1990 and 1994; and the average of the 1986, 1990, and 1994 intake was used for the follow-up between 1994 and 1998. We stopped updating diet at the beginning of the time interval during which individuals developed hypertension, hypercholesterolemia, cancer (except nonmelanoma skin cancer), or cardiovascular diseases (myocardial infarction, coronary artery surgery, stroke, or angina pectoris) because changes in diet after development of these end points may confound the relationship between diet and diabetes (36). To reduce residual confounding, the same cumulative updating approach was used for physical activity and alcohol intake, using the information from all the available assessments. BMI and smoking status were also updated during follow-up, using the most recent data for each 2-year interval. The results were essentially the same in analyses relating diet in 1986 to incidence of type 2 diabetes between 1992 and 1998.

Categorical variables were included in the models as binary indicator variables. We tested for linear trends across categories of dietary intake by assigning each participant the median value for the category and modeling this value as a continuous variable. In addition, we conducted analyses with dietary intake and potential confounders (age, BMI, and physical activity) modeled as continuous variables. Tests for statistical interaction were conducted by including cross-product terms of continuous variables in a multivariate logistic regression model. All *P* values are two-sided.

RESULTS — Table 1 shows baseline characteristics of the cohort members according to quintile of fat intake. Men with higher intakes of saturated fat had a higher BMI, a lower level of physical activity, and were more likely to smoke cigarettes and less likely to have hypercholesterolemia. The cross-sectional association with hypercholesterolemia probably reflects changes in diet after diagnosis. Furthermore, a higher intake of saturated fat was associated with lower intakes of alcohol, cereal fiber, and magnesium. Similar associations were observed for intake of oleic acid (the predominant monounsaturated fat in the diet), *trans*-fat, and total fat. Characteristics differed less according to intake of linoleic acid (the predominant polyunsaturated fat in the diet) and α-linolenic acid. High intakes of long-chain n-3 fatty acids were associated with a healthier lifestyle.

During 466,508 person-years of follow-up, we ascertained 1,321 cases of type 2 diabetes. In the age-and energy-adjusted analyses, intakes of total fat, saturated fat, oleic acid, and *trans*-fat were associated with an increased risk of type 2 diabetes (Table 2). These associations were attenuated after additional adjustment for other risk factors, particularly magnesium and cereal fiber intake. Intakes of total fat (RR for extreme quintiles 1.27, 95% CI 1.04–1.55, *P* for trend = 0.02) and saturated fat (1.34, 1.09–1.66, *P* for trend = 0.01) remained significantly associated with risk of type 2 diabetes, but these associations disappeared after further adjustment for BMI. Intakes of linoleic acid, *trans*-fat, α-linolenic acid, and long-chain n-3 fat were not appreciably associated with risk of type 2 diabetes in any of the models (Table 2). In addition, no association with risk of type 2 diabetes was observed for animal fat (RR 1.12, 95% CI 0.91–1.38, *P* for trend = 0.22), vegetable fat (0.89, 0.74–1.06, *P* for trend = 0.08), cholesterol (1.12, 0.92–1.35, *P* for trend = 0.11), and the ratio of n-3 to n-6 polyunsaturated fat (1.10, 0.92–1.31, *P* for trend = 0.73) after multivariate adjustment (the final model described in the legend for Table 2 was used). The results were similar when fat intakes and covariables (dietary intakes, age, physical activity, and BMI) were modeled as continuous variables (total fat RR 1.04, 95% CI 0.99–1.10 for an isoenergetic substitution replacing 5% of energy from nonfat with fat) and when intakes of saturated fat, oleic acid, linoleic acid, and *trans*-fat were modeled simultaneously. Also, the associations were essentially the same if only symptomatic

Table 2—*Relative risk of type 2 diabetes by quintiles of dietary fats*

	Quintile of intake					*P* for trend
	1 (low)	2	3	4	5 (high)	
Total fat						
Median (E%)	24	29	32	35	39	
Age- and energy-adjusted RR*	1	1.22 (1.00–1.48)	1.63 (1.35–1.96)	1.58 (1.31–1.91)	1.88 (1.56–2.25)	<0.0001
Multivariate RR†	1	1.19 (0.98–1.45)	1.56 (1.30–1.88)	1.49 (1.23–1.80)	1.63 (1.35–1.96)	<0.0001
Further adjustment for diet‡	1	1.10 (0.90–1.34)	1.37 (1.13–1.66)	1.24 (1.02–1.51)	1.27 (1.04–1.55)	0.02
Further adjustment for diet and BMI§	1	0.99 (0.81–1.21)	1.14 (0.94–1.39)	1.00 (0.82–1.22)	0.97 (0.79–1.18)	0.63
Saturated fat						
Median (E%)	7.6	9.6	11	12	14	
Age- and energy-adjusted RR*	1	1.51 (1.24–1.84)	1.66 (1.37–2.02)	2.06 (1.70–2.50)	2.01 (1.66–2.44)	<0.0001
Multivariate RR†	1	1.47 (1.21–1.79)	1.58 (1.30–1.92)	1.90 (1.57–2.29)	1.74 (1.43–2.11)	<0.0001
Further adjustment for diet‡	1	1.36 (1.11–1.66)	1.38 (1.13–1.69)	1.57 (1.29–1.92)	1.34 (1.09–1.66)	0.01
Further adjustment for diet and BMI§	1	1.20 (0.98–1.46)	1.12 (0.92–1.38)	1.22 (1.00–1.49)	0.97 (0.79–1.20)	0.47
Oleic acid						
Median (E%)	8.0	10	11	12	14	
Age- and energy-adjusted RR*	1	1.23 (1.02–1.49)	1.49 (1.24–1.79)	1.66 (1.38–1.99)	1.63 (1.35–1.96)	<0.0001
Multivariate RR†	1	1.23 (1.02–1.49)	1.46 (1.21–1.75)	1.59 (1.32–1.91)	1.47 (1.22–1.77)	<0.0001
Further adjustment for diet‡	1	1.13 (0.93–1.37)	1.27 (1.05–1.53)	1.32 (1.09–1.60)	1.15 (0.94–1.40)	0.12
Further adjustment for diet and BMI§	1	1.02 (0.84–1.24)	1.09 (0.90–1.32)	1.09 (0.90–1.33)	0.93 (0.76–1.14)	0.53
Linoleic acid						
Median (E%)	3.5	4.4	4.9	5.6	6.8	
Age- and energy-adjusted RR*	1	1.05 (0.88–1.24)	1.09 (0.92–1.29)	1.13 (0.96–1.34)	0.98 (0.83–1.17)	0.90
Multivariate RR†	1	1.06 (0.89–1.27)	1.12 (0.94–1.33)	1.14 (0.96–1.35)	0.95 (0.79–1.13)	0.60
Further adjustment for diet‡	1	1.04 (0.88–1.24)	1.09 (0.92–1.30)	1.10 (0.93–1.31)	0.92 (0.77–1.10)	0.39
Further adjustment for diet and BMI§	1	0.99 (0.83–1.18)	1.03 (0.86–1.23)	1.06 (0.89–1.26)	0.89 (0.74–1.06)	0.27
Trans-fat						
Median (E%)	0.7	1.0	1.3	1.5	2.0	
Age- and energy-adjusted RR*	1	1.20 (1.00–1.44)	1.24 (1.04–1.49)	1.33 (1.11–1.59)	1.39 (1.16–1.67)	0.0004
Multivariate RR†	1	1.17 (0.98–1.41)	1.22 (1.02–1.46)	1.28 (1.07–1.53)	1.28 (1.07–1.53)	0.009
Further adjustment for diet‡	1	1.06 (0.89–1.28)	1.05 (0.87–1.27)	1.06 (0.87–1.28)	1.02 (0.84–1.24)	1.00
Further adjustment for diet and BMI§	1	0.95 (0.79–1.15)	0.93 (0.77–1.12)	0.91 (0.75–1.11)	0.90 (0.74–1.10)	0.33
α-Linolenic acid						
Median (mg/day)	321	396	458	533	671	
Age- and energy-adjusted RR*	1	1.06 (0.89–1.26)	1.18 (0.99–1.40)	1.16 (0.97–1.38)	1.15 (0.96–1.37)	0.12
Multivariate RR†	1	1.07 (0.90–1.28)	1.16 (0.97–1.37)	1.11 (0.94–1.33)	1.05 (0.88–1.26)	0.64
Further adjustment for diet‡	1	1.07 (0.90–1.28)	1.15 (0.96–1.36)	1.10 (0.92–1.31)	1.01 (0.85–1.20)	0.93
Further adjustment for diet and BMI§	1	1.03 (0.86–1.23)	1.10 (0.92–1.31)	1.00 (0.84–1.20)	0.93 (0.78–1.11)	0.27
Long-chain n-3 fatty acids						
Median (mg/day)	80	155	250	350	570	
Age- and energy-adjusted RR*	1	0.98 (0.83–1.16)	0.88 (0.74–1.05)	0.95 (0.81–1.13)	0.88 (0.74–1.04)	0.13
Multivariate RR†	1	1.01 (0.85–1.20)	0.91 (0.77–1.09)	0.99 (0.83–1.17)	0.90 (0.75–1.07)	0.20
Further adjustment for diet‡	1	1.03 (0.87–1.22)	0.95 (0.79–1.13)	1.05 (0.89–1.25)	1.01 (0.84–1.20)	0.91
Further adjustment for diet and BMI§	1	1.01 (0.85–1.19)	0.95 (0.79–1.13)	1.05 (0.88–1.25)	1.01 (0.84–1.21)	0.81

Data are RR (95% CI), unless otherwise indicated. Quintiles were based on energy percentage of fat intakes, except for quintiles of α-linolenic acid and long-chain n-3 fat, which were based on intake in milligrams per day adjusted for energy intake with the residual method. *RRs (95% CI) adjusted for age (5-year categories) and total energy intake (quintiles); †adjusted for age (5-year categories), total energy intake (quintiles), time period (6 periods), physical activity (quintiles of METs), cigarette smoking (never, past, and current smoking of 1–14, 15–24, and ≥25 cigarettes/day), alcohol consumption (0, 0.1–4, 5–14, 15–29, and ≥30 g/day), hypercholesterolemia (yes/no), hypertension (yes/no), and family history of type 2 diabetes (yes/no); ‡multivariate model with additional adjustment for intake (quintiles) of cereal fiber and magnesium; §multivariate model with additional adjustment for intake (quintiles) of cereal fiber and magnesium and BMI (<23.0, 23.0–23.9, 24.0–24.9, 25.0–26.9, 27.0–28.9, 29.0–30.9, 31.0–32.9, 33.0–34.9, and ≥35 kg/m^2).

(*n* = 810) or only asymptomatic (*n* = 511) cases were studied as an end point.

We also conducted analyses with stratification for age, BMI, and physical activity. Greater intake of linoleic acid was significantly associated with a lower risk of diabetes among men younger than 65 years (RR 0.74, 95% CI 0.60–0.92 for highest versus lowest quintile, *P* for trend = 0.01) and among nonoverweight men (0.53, 0.33–0.85, *P* for trend = 0.006) (Table 3). Modeled as a continuous variable, the RR associated with a 5% of energy higher linoleic acid intake was 0.80 (95% CI 0.62–1.03) among men

Table 3—*Relative risk of type 2 diabetes according to linoleic acid intake, stratified by BMI and age

	Quintiles of linoleic acid intake					
	1 (low)	2	3	4	5 (high)	*P* for trend
Age (years)						
<65 (n = 866)	1	0.85 (0.68–1.05)	0.93 (0.76–1.15)	0.86 (0.70–1.07)	0.74 (0.60–0.92)	0.01
≥65 (n = 449)	1	1.34 (0.99–1.82)	1.22 (0.89–1.68)	1.57 (1.16–2.12)	1.22 (0.89–1.68)	0.16
BMI (kg/m^2)						
<25.0 (n = 207)	1	0.98 (0.66–1.46)	0.81 (0.53–1.24)	0.82 (0.54–1.25)	0.53 (0.33–0.85)	0.006
25.0–29.9 (n = 677)	1	0.93 (0.73–1.20)	1.08 (0.85–1.38)	1.07 (0.84–1.36)	0.95 (0.74–1.22)	0.90
≥30.0 (n = 398)	1	1.00 (0.72–1.40)	1.07 (0.77–1.49)	1.17 (0.84–1.62)	0.95 (0.68–1.33)	0.94

Data are RR (95% CI). *RRs (95% CI) were adjusted for age (5-year categories), total energy intake (quintiles), time period (6 periods), physical activity (quintiles of METs), cigarette smoking (never, past, and current smoking of 1–14, 15–24, and ≥25 cigarettes/day), alcohol consumption (0, 0.1–4, 5–14, 15–29, and ≥30 g/day), hypercholesterolemia (yes/no), hypertension (yes/no), family history of type 2 diabetes (yes/ no), intake (quintiles) of cereal fiber and magnesium, and BMI (<23.0, 23.0–23.9, 24.0–24.9, 25.0–26.9, 27.0–28.9, 29.0–30.9, 31.0–32.9, 33.0–34.9, ≥35 kg/m^2), except for the stratifying variables (in the BMI-stratified analysis, categories of BMI in the multivariate model were: <23.0, 23–23.9, and 24.0–24.9 for BMI <25 kg/m^2; 25.0–26.9 and 27.0–29.9 for BMI 25–30 kg/m^2; 30.0–32.9, 33.0–34.9, and ≥35.0 for BMI ≥30 kg/m^2: in the age-stratified analysis, categories of age in the multivariate model were: <45, 45–49, 50–54, 55–59, and 60–64 for age <65 years; and 65–69 and ≥70 for age ≥65 years). In the BMI-stratified analysis, BMI at baseline was used for stratification and adjustment. The total number of subjects is <1,321 because of missing values.

<65 years of age and 0.49 (0.29–0.83) among nonoverweight men. The interaction terms for age and linoleic acid intake (P = 0.03) and for BMI and linoleic acid intake (P = 0.05) were statistically significant. No other significant associations were observed within strata of age, BMI, or physical activity.

Meat was a major contributor to total fat intake in this population. In 1986, 19% of total fat was from unprocessed red meat, 7% from poultry, and 5% from processed meat. After adjustment for risk factors and intake of cereal fiber and magnesium, men who consumed processed meat at least five times a week had a RR for type 2 diabetes of 1.46 (95% CI 1.14–1.86, P for trend <0.0001), as compared with men who consumed processed meats less than once a month (Table 4). In a model with continuous variables, the RR for a one-serving-per-day higher intake of processed meat was RR 1.34 (95% CI 1.17–1.53). Furthermore, the association was essentially the same if only symptomatic or only asymptomatic cases were studied as an end point.

Consumption of unprocessed red meat (RR 1.05, 95% CI 0.85–1.30 for highest vs. lowest quintile) and of poultry (1.12, 0.95–1.32) was not substantially associated with risk for type 2 diabetes. Of

Table 4—*Relative risk of type 2 diabetes according to processed meat consumption*

	Frequency of consumption (servings)					*P* for trend
	<1/month	1–3/month	1/week	2–4/week	≥5/week	
Total processed meat						
Cases/person-years	114/61,065	278/113,393	251/104,561	443/131,701	234/55,472	
Age- and energy-adjusted RR*	1	1.36 (1.10–1.70)	1.43 (1.14–1.79)	2.02 (1.62–2.52)	2.77 (2.11–3.65)	<0.0001
Multivariate RR†	1	1.13 (0.90–1.41)	1.04 (0.82–1.30)	1.35 (1.08–1.68)	1.46 (1.14–1.86)	<0.0001
Bacon						
Cases/person-years	403/166,812	398/160,277	276/81,115	234/56,084		
Age- and energy-adjusted RR*	1	1.08 (0.94–1.24)	1.48 (1.26–1.74)	1.75 (1.47–2.09)		<0.0001
Multivariate RR†	1	0.96 (0.83–1.10)	1.19 (1.01–1.40)	1.33 (1.11–1.58)		0.0002
Hot dogs						
Cases/person-years	421/181,810	557/191,817	221/61,186	97/22,973		
Age- and energy-adjusted RR*	1	1.32 (1.16–1.50)	1.78 (1.50–2.11)	2.02 (1.59–2.55)		<0.0001
Multivariate RR†	1	1.14 (1.00–1.30)	1.27 (1.07–1.51)	1.26 (1.00–1.60)		0.03
Other processed meats						
Cases/person-years	245/110,404	399/161,400	294/91,407	375/100,222		
Age- and energy-adjusted RR*	1	1.17 (1.00–1.38)	1.63 (1.37–1.94)	1.88 (1.58–2.25)		<0.0001
Multivariate RR†	1	0.95 (0.81–1.12)	1.12 (0.94–1.34)	1.18 (0.99–1.41)		0.01

Total processed meat includes bacon, hot dogs, and other processed meats (e.g. sausage, salami, and bologna). The total number of cases is <1,321 and the total number of person-years <466,508 because of missing values. *RRs (95% CI) adjusted for age (5-year categories) and total energy intake (quintiles); †RR adjusted for age (5-year categories), total energy intake (quintiles), time period (6 periods), physical activity (quintiles of METs), cigarette smoking (never, past, and current smoking of 1–14, 15–24, and ≥25 cigarettes/day), alcohol consumption (0, 0.1–4, 5–14, 15–29, and ≥30 g/day), hypercholesterolemia (yes/no), hypertension (yes/no), family history of type 2 diabetes (yes/no), intake (quintiles) of cereal fiber and magnesium, and BMI (<23.0, 23.0–23.9, 24.0–24.9, 25.0–26.9, 27.0–28.9, 29.0–30.9, 31.0–32.9, 33.0–34.9, and ≥35 kg/m^2).

the eight questionnaire items on meat and poultry consumption, only consumption of the three processed meat items (Table 4) and hamburgers (RR 1.27, 95% CI 0.99–1.62 for ≥2/week versus <1/month) was appreciably associated with diabetes risk. Consumption of beef, lamb, or pork as a main dish or a mixed dish; chicken or turkey with or without skin; or major nonmeat sources of fat (high-fat dairy and nuts) was not substantially associated with risk of type 2 diabetes.

CONCLUSIONS — In this large prospective study of men with 12 years of follow-up, intake of total and saturated fat was associated with a higher risk of type 2 diabetes, but these associations disappeared after further adjustment for BMI. Oleic acid, *trans*-fat, long-chain n-3 fat, and α-linolenic acid were not appreciably associated with risk of type 2 diabetes after multivariate adjustment. Intake of linoleic acid was inversely associated with risk of type 2 diabetes in men <65 years of age and men with a BMI <25 kg/m^2 but not in older and obese participants. Frequent consumption of processed meat was associated with an increased risk of type 2 diabetes.

The prospective design and high rate of follow-up in this study minimizes the possibility of recall bias or bias caused by loss of follow-up. Furthermore, the extensive information on potential confounders and the large study size allowed us to examine confounding and effect modification in detail. Self-reported diabetes was confirmed by a supplementary questionnaire, and validation with medical records indicated that reporting of diabetes was accurate in this medically knowledgeable population. Some underdiagnosis of diabetes is likely because screening for blood glucose was not feasible, given the size of the cohort. However, as compared with the general population, the degree of underdiagnosis was probably smaller in this cohort of health professionals with ready access to medical care. Moreover, underascertainment of cases, if not associated with exposure, would not be expected to affect the RR estimates (33). We also considered the possibility that dietary factors were associated with the likelihood to be screened for diabetes. However, when we restricted the analyses to symptomatic cases or to asymptomatic cases, the findings were essentially the same, arguing against presence of surveillance bias.

In contrast to findings in the present study and two large cohorts of women (21,22), earlier studies observed an association between intake of saturated (7,9,37) or total fat (9,38) with glucose intolerance. In our study, the association between these fats and type 2 diabetes was attenuated after adjustment for other lifestyle factors and intake of cereal fiber and magnesium. Hence, residual confounding caused by incomplete control for physical activity (7,9) or other dietary factors (37, 38) may have affected the results in earlier studies. We observed a modest increase in risk of type 2 diabetes with a higher intake of fat (primarily saturated fat), but this association disappeared after controlling for BMI. The increased risk associated with fat intake before adjustment for BMI could possibly represent an effect of dietary fat on risk of diabetes mediated by body fatness. However, the association between fat intake and diabetes risk before adjustment for BMI reflected a cross-sectional association between fat intake and BMI that is also plausibly caused by confounding. Specifically, confounding by health consciousness may create an association between fat intake and BMI: persons who strive to be lean and restrain energy intake because they believe it to be healthy may also consume a lower-fat diet because they have been told that is healthy. It is widely recognized that inferences about the effect of dietary fat on body fatness should be based on data from randomized intervention trials, rather than observational studies (39,40). Whether total fat intake has an important effect on body fatness is controversial (39,40). Finally, random measurement error may have attenuated the observed associations between fat intake and risk of type 2 diabetes.

Analyses in subgroups increase the probability of chance findings. However, our finding of an inverse association between intake of linoleic acid and risk of type 2 diabetes among younger and leaner men agrees with findings in two cohorts of women (21,22). Furthermore, Vessby et al. (41) reported that men who developed type 2 diabetes during a 10-year period had a lower proportion of linoleic acid in their serum cholesterol esters at baseline. Some (8,13) but not all (14–16) cross-sectional studies with questionnaire-assessed diet have suggested that polyunsaturated fat intake was inversely associated with hyperglycemia or hyperinsulinemia. Our findings suggest that differences in body fatness or age between the study populations may have contributed to differences in findings for polyunsaturated fat. The large decreases in insulin sensitivity associated with advanced age and obesity (17,18) may have obscured a more modest effect of linoleic acid intake on insulin sensitivity.

A positive association between *trans*-fat intake and risk of type 2 diabetes was observed in the Nurses' Health Study (21), but not in the Iowa Women's Health Study or the present study (22). Possibly, differences in the amount of *trans*-fat consumed in these studies may explain this difference in results (e.g., the median intake at baseline was 1.2% of energy in the present study vs. 2.2% in the nurses). Adverse effects of *trans*-fat on postprandial hyperinsulinemia have been observed at high levels of intake (42).

Few studies have examined the association between meat consumption and risk of type 2 diabetes. In a study of Seventh-Day Adventists, total meat consumption was associated with a higher prevalence of type 2 diabetes and with a higher incidence of diabetes as mentioned on death certificates (23). Furthermore, consumption of processed meat, but not of other meats, was positively associated with risk of type 2 diabetes in the Nurses' Health Study, after adjustment for BMI, prior weight change, and alcohol and energy intake (43). Because nitrites are commonly used for the preservation of meats, processed meats are a major source of nitrites in the diet (44). Nitrosamines can be formed in foods or the stomach by interaction of nitrites with amines from the meat, and nitrosamines have been detected in processed meats such as sausages and bacon (45). Some nitrosamines are known to be β-cell toxins (46), and consumption of foods with a high content of nitrites and nitrosamines was positively associated with risk of type 1 diabetes in several populations (47–49). The relevance of nitrosamines for type 2 diabetes is less clear, but low doses of the nitrosamide streptozotocin in combination with dietary-induced insulin resistance resulted in metabolic characteristics in mice that are very similar to type 2 diabetes in humans (50). Still, the observed association between processed meat intake and type 2 diabetes may reflect another unidentified lifestyle factor or components of meats other than nitrites and ni-

trosamines. Further study of the possible long-term effects of processed meat intake and other sources of nitrosamines on glucose homeostasis is warranted.

In conclusion, total and saturated fat intake was associated with a higher risk of type 2 diabetes, but these associations were not independent of BMI. Nevertheless, because type 2 diabetes is a heterogeneous disease, we cannot exclude the possibility that the association with dietary fat is different for specific subtypes of the disease, which we did not identify. Our findings contribute to the evidence that higher intakes of linoleic acid may reduce risk of type 2 diabetes, especially among leaner and younger men. Frequent consumption of processed meats may increase risk of type 2 diabetes.

Acknowledgments— This study was supported by research grant CA-55075 and HL-35464 from the National Institutes of Health. F.B.H. was partly supported by a research award from the American Diabetes Association.

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