

A Prospective Study of Red Meat Consumption and Type 2 Diabetes in Middle-Aged and Elderly Women

The Women's Health Study

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OBJECTIVE — The aim of this study was to prospectively assess the relation between red meat intake and incidence of type 2 diabetes.

RESEARCH DESIGN AND METHODS — Over an average of 8.8 years, we evaluated 37,309 participants in the Women's Health Study aged ≥ 45 years who were free of cardiovascular disease, cancer, and type 2 diabetes and completed validated semiquantitative food frequency questionnaires in 1993.

RESULTS — During 326,876 person-years of follow-up, we documented 1,558 incident cases of type 2 diabetes. After adjusting for age, BMI, total energy intake, exercise, alcohol intake, cigarette smoking, and family history of diabetes, we found positive associations between intakes of red meat and processed meat and risk of type 2 diabetes. Comparing women in the highest quintile with those in the lowest quintile, the multivariate-adjusted relative risks (RRs) of type 2 diabetes were 1.28 for red meat (95% CI 1.07–1.53, $P < 0.001$ for trend) and 1.23 for processed meat intake (1.05–1.45, $P = 0.001$ for trend). Furthermore, the significantly increased diabetes risk appeared to be most pronounced for frequent consumption of total processed meat (RR 1.43, 95% CI 1.17–1.75 for ≥ 5 /week vs. < 1 /month, $P < 0.001$ for trend) and two major subtypes, which were bacon (1.21, 1.06–1.39 for ≥ 2 /week vs. < 1 /week, $P = 0.004$ for trend) and hot dogs (1.28, 1.09–1.50 for ≥ 2 /week vs. < 1 /week, $P = 0.003$ for trend). These results remained significant after further adjustment for intakes of dietary fiber, magnesium, glycemic load, and total fat. Intakes of total cholesterol, animal protein, and heme iron were also significantly associated with a higher risk of type 2 diabetes.

CONCLUSIONS — Our data indicate that higher consumption of total red meat, especially various processed meats, may increase risk of developing type 2 diabetes in women.

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The adoption of a “western diet” characterized by high intakes of red and processed meat as well as other components, including refined grain products, snacks, sweets, French fries, and pizza, is believed to contribute to the epidemic of type 2 diabetes in the world (1). A diet high in red meat has long been

suspected as an important and independent contributor to risk of type 2 diabetes. This hypothesis was first generated based on the evidence from ecologic and migrant studies (2,3) and subsequently supported by several cross-sectional and prospective studies of dietary patterns and diabetes (4–6).

Since the Seventh Day Adventists Study first reported a positive association between total meat intake and risk of type 2 diabetes in a population with a large proportion of vegetarians (7), few studies have specifically assessed this relation between meat consumption and incidence of diabetes. Of note, two recent cohort studies in U.S. men and women observed a significant association between frequent consumption of processed meat and an increased risk of type 2 diabetes (8,9). However, because of scarce data, it is unclear whether these observed positive associations are consistent in other cohorts. Furthermore, it remains uncertain whether the adverse association of red meat or processed meat consumption with diabetes risk is mediated through its high fat content, protein, or some other specific components produced from certain cooking or processing practices such as nitrates and nitrites.

Therefore, we prospectively investigated the associations of red and processed meat and various subtypes of each, and type of major nutrients, with the incidence of type 2 diabetes in the Women's Health Study (WHS), comprised of a large cohort of U.S. women.

RESEARCH DESIGN AND METHODS

The WHS is a randomized, double-blind, placebo-controlled trial designed to evaluate the balance of benefits and risks of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer (10). We randomized a total of 39,876 female health professionals aged ≥ 45 years who were free of coronary heart disease,

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Abbreviations: ADA, American Diabetes Association; SFFQ, semiquantitative food frequency questionnaire; WHS, Women's Health Study.

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

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stroke, and cancer (other than nonmelanoma skin cancer). Of them, 98% provided detailed information about their diet, completing a 131-item semiquantitative food frequency questionnaire (SFFQ) in 1993 (10). We excluded individuals with >70 items left blank in their SFFQ and with energy intake outside the range of 2,514 kJ (600 kcal) and 14,665 kJ (3,500 kcal), with reported diabetes at baseline, and with completed data on meat consumption, which left 37,309 women for the analysis. This study has been conducted according to the ethical guidelines of Brigham and Women's Hospital. Written informed consent was obtained from all participants.

Assessment of meat intake

For each food, a commonly used unit or portion size was specified, and each participant was asked how often she had consumed that amount, on average, over the previous year. Nine possible responses ranging from "never" to "six or more times per day" were recorded. Intake of each meat item was calculated by multiplying the intake frequency of individual items in those food categories by their weights, estimated from the specified portion size. Nutrient intakes were computed by multiplying the frequency of consumption of each unit of food from the SFFQ by the nutrient content of the specified portion size according to food composition tables from the Harvard Food Composition Database (11). Each nutrient was adjusted for total energy using the residual method (12). Red meat intake was considered to be the sum of hamburger, beef, or lamb as a main dish, pork as a main dish, beef, pork, or lamb as a sandwich or mixed dish, and all processed meat. Total processed meat was considered to be the sum of hot dogs, bacon, and other processed meat. Other processed meat included sausage, salami, and bologna. This SFFQ has demonstrated reasonably good validity as a measure of long-term average dietary intakes in women (13). The correlations between the SFFQ and two 1-week diet records were 0.48–0.68 for total and specific types of fat intakes, 0.35–0.45 for meat, and 0.33–0.53 for processed meat (13,14).

Ascertainment of type 2 diabetes

The status of type 2 diabetes was evaluated at baseline, and women with a history of diagnosed diabetes were excluded.

Thereafter, all of the participants were asked annually whether and when they had been diagnosed with diabetes since completing the previous questionnaire. Two complementary approaches have been used to confirm self-reported type 2 diabetes in the WHS. First, we attempted to contact 473 women with self-reported diabetes who provided a blood sample as part of a nested case-control study of diabetes, to verify the self-reported diagnosis (15). Using the American Diabetes Association (ADA) diagnostic criteria (16), the self-reported diagnosis of diabetes was confirmed in 406 (91%) of 446 women who responded via telephone interview (15). Second, a random sample of 147 women with self-reported diabetes was mailed a supplemental diabetes questionnaire, also using the ADA criteria to parallel the telephone interview. Among 136 respondents, 124 (91%) women were classified as having type 2 diabetes by the supplemental questionnaire. In addition, 113 of the 124 women gave permission to contact their primary care physician. Ninety-seven of the 113 physicians responded, of whom 90 provided adequate information to apply the ADA criteria. For these 90 women, 89 (99%) were confirmed to have type 2 diabetes on the basis of the combined information from the supplemental questionnaire and physician information. Thus, we believe that self-reported type 2 diabetes is valid in the WHS.

Data analysis

We first categorized intakes of red and processed meats into quintiles of intake. We also categorized meat consumption by aggregating nine possible responses from SFFQ into four categories for red meat and total processed meat (<1/week, 1/week, 2–4/week, \geq 5/week). Subtype of red meat and processed meat were categorized into three categories (<1/week, 1/week, \geq 2/week). We calculated the incidence rates of type 2 diabetes for each category of baseline meat intake by dividing the number of incident cases by the person-years of follow-up from 1993 to 2003. After testing the proportional hazard assumption, we used Cox proportional hazards models to estimate the rate ratios (described as relative risks [RRs]) and 95% CIs of developing type 2 diabetes for each category of meat item compared with the lowest category. The initial model was adjusted for age and total en-

ergy intake. In multivariate models, we adjusted for age (continuous), BMI (continuous), total energy intake (quintiles), smoking status (current, past, and never), exercise (rarely/never, <1/week, 1–3/week, and \geq 4/week), alcohol intake (rarely/never, 1–3 drinks/month, 1–6 drinks/week, \geq 1 drink/day), and family history of diabetes (yes/no) and then further adjusted for dietary factors, including intakes of dietary fiber (quintiles), glycemic load (quintiles), total fat (quintiles), and magnesium (quintiles). Tests of linear trend across increasing categories of intake were conducted by assigning the medians of intakes in quintiles treated as a continuous variable. A likelihood ratio test was used to assess the significance of interaction terms. We also did separate analyses for intakes of type of fat, protein, dietary heme iron, and total iron. All statistical analyses were conducted using SAS (version 8.0; SAS Institute, Cary, NC).

RESULTS— At baseline in 1993, the differences comparing the highest intake to the lowest intake among 37,309 women were ~10-fold in total red meat intake (Table 1). High consumers of red meat tended to be current smokers and less likely to exercise, use postmenopausal hormones, or use supplements of multivitamins than those who rarely consumed red meat. Women with higher intake of red meat also had a higher BMI and were more likely to have a history of hypertension and a family history of diabetes. Furthermore, total red meat intake was positively associated with total energy intake, intakes of all fatty acids, cholesterol, and protein but inversely associated with dietary carbohydrate, fiber, magnesium intakes, and glycemic load. Similar associations were observed for total meat and processed meat.

During an average of 8.8 years of follow-up (326,876 person-years), we documented 1,558 incident cases of type 2 diabetes. In the age- and energy-adjusted models, total red meat and processed meat were significantly associated with an increased risk of type 2 diabetes (Table 2). After adjusting for age, total energy intake, BMI, smoking, alcohol intake, physical activity, and family history of diabetes, these associations were attenuated but remained statistically significant for red meat and processed meat (RRs comparing two extreme quintiles 1.28,

Table 1—Baseline characteristics among 37,309 women according to intakes of total meat, red meat, and processed meat comparing highest quintile (Q5) to lowest quintile (Q1) in the WHS

Quintile of intake	Total meat		Red meat		Processed meat	
	Q1	Q5	Q1	Q5	Q1	Q5
Median intake (servings/day)	0.63	2.27	0.13	1.42	0	0.56
Age (years)	54.6 ± 7.5	53.5 ± 6.7	54.3 ± 7.2	53.5 ± 6.8	54.0 ± 7.0	54.0 ± 7.1
Smoking (%)						
Current	11.4	15.3	7.97	18.8	7.65	20.8
Never	51.3	51.5	51.5	50.3	53.6	47.2
Past	37.4	33.2	40.5	30.9	38.8	32.0
Exercise (%)						
Rarely/never	36.5	40.7	30.0	47.0	30.7	46.7
<1/week	17.2	22.5	15.8	22.2	16.2	22.3
1–3/week	32.2	29.2	36.0	25.1	36.1	25.1
≥4/week	14.2	7.65	18.2	5.74	17.0	5.95
Alcohol consumption (%)						
Rarely never	49.2	45.9	46.5	48.2	45.2	46.3
1–3 drinks/month	12.8	12.4	13.3	12.2	13.4	12.3
1–6 drinks/week	28.7	31.3	30.9	29.3	31.8	30.2
≥1 drink/day	9.29	10.4	9.33	10.3	9.67	11.2
Postmenopausal hormone use (%)						
Never	46.0	49.3	46.4	50.2	46.1	49.4
Past	10.7	10.8	10.3	10.9	9.60	11.5
Current	43.4	40.0	43.3	39.0	44.3	39.1
Mean BMI (kg/m ²)	24.8 ± 4.3	27.1 ± 5.5	24.7 ± 4.3	27.0 ± 5.5	24.9 ± 4.4	26.9 ± 5.5
Multivitamin use (%)	31.6	27.4	34.0	25.1	32.2	25.9
History of hypertension (%)	22.4	29.1	22.2	28.2	22.0	29.5
History of high cholesterol (%)	26.4	27.3	28.1	26.0	28.0	25.6
Family history of diabetes (%)	23.7	27.5	24.1	26.9	23.6	27.1
Diet (adjusted for total energy)						
Total calorie (kcal/day)	1,333	2,236	1,458	2,127	1,569	1,989
Carbohydrate (g/day)	248	200	248	199	239	206
Total fat (g/day)	52.7	62.7	48.4	66.1	50.7	64.6
Saturated fat (g/day)	18.0	21.4	16.0	23.0	16.9	22.4
Monounsaturated fat (g/day)	19.4	23.7	17.4	25.3	18.5	24.6
Polyunsaturated fat (g/day)	10.7	11.5	10.6	11.5	10.5	11.7
Trans fatty acid (g/day)	2.12	2.43	1.72	2.74	1.80	2.69
Cholesterol (mg/day)	173	267	186	259	199	254
Proteins (g/day)	69.6	89.9	78.9	83.2	82.0	79.5
Fiber (g/day)	21.2	17.4	22.7	16.2	21.8	16.6
Magnesium (mg/day)	355	325	377	305	369	308
Glycemic load*	187	150	185	151	178	157

Data are means ± SD unless otherwise indicated. All covariate values are according to the quintiles of total red meat consumption. All the means of nutrients are energy adjusted. *Glycemic load was defined as an indicator of blood glucose induced by an individual's total carbohydrate intake. Each unit of glycemic load represents the equivalent of 1 g of carbohydrate from white bread.

95% CI 1.07–1.53, *P* for trend < 0.001 for red meat and 1.23, 1.05–1.45, *P* for trend = 0.001 for processed meat). Additional adjustment for dietary fiber, glycemic load, magnesium intake, and total fat intake did not change these significant results. As compared with the lowest quintile of intake, the multivariate-adjusted RRs of type 2 diabetes across increasing quintiles were 1.00, 0.90, 1.07, 1.08, and 1.24 for red meat intake (*P* = 0.005 for

trend) and 1.00, 0.96, 0.95, 1.08, and 1.19 for total processed meat intake (*P* for trend = 0.007).

The multivariate-adjusted RRs when frequency of red meat and processed meat consumption were modeled as four categories (<1/week, 1/week, 2–4/week, and ≥5/week) were 1.00, 1.15, 1.08, and 1.29, respectively (*P* = 0.01 for trend), for red meat and 1.00, 1.05, 1.20, and 1.43 for total processed meat (*P* < 0.001

for trend). After further adjustment for nutrient factors, only total processed meat intake remained significantly associated with diabetic risk. As major items of processed meat, bacon and hot dogs also showed consistently positive associations with risk of type 2 diabetes (Table 3). Comparing women who consumed ≥2/week to those who consumed <1/week, the multivariate-adjusted RRs of type 2 diabetes after controlling for dietary nu-

trients were 1.17 (95% CI 1.02–1.35, $P = 0.02$ for trend) for bacon and 1.24 (1.05–1.45, $P = 0.02$ for trend) for hot dogs. Subtypes of red meat appeared to increase diabetes risk in the multivariate models, but 95% CIs were wider and included the null.

Finally, we found significantly positive associations for dietary intakes of cholesterol, animal protein, and heme iron, which are the primary constituents of red meat (Table 4). The multivariate-adjusted RRs comparing two extreme quintiles were 1.35 for cholesterol (95% CI 1.11–1.64, $P = 0.003$ for trend), 1.44 for animal protein (1.16–1.78, $P = 0.001$ for trend), and 1.46 for heme iron (1.20–1.78, $P < 0.0001$ for trend).

CONCLUSIONS — In this large prospective study, we found that a higher consumption of red meat, especially total processed meat, was associated with an increased risk of developing type 2 diabetes in middle-aged and older U.S. women, independent of known diabetes risk factors.

The prospective design and high follow-up rates in our study minimized the possibility of selection bias or recall bias. As any measurement errors from baseline SFFQ were unlikely to be related to subsequent diabetes end points, misclassification of dietary assessment would most likely be nondifferential and would have attenuated the true associations. Thus, our observed associations may not be explained by such errors and were, on the contrary, somewhat conservative. Our results were also less likely to be influenced by misclassification of type 2 diabetes because of a high accuracy of self-reported diabetes as assessed by our validation study. Moreover, because we adjusted for age, BMI, and other important risk factors for type 2 diabetes, the residual confounding due to these known factors was probably modest.

Our findings are consistent with recent evidence from both the Health Professionals Follow-Up Study of male health professionals and the Nurses' Health Study II of younger and middle-aged U.S. women (8,9). Processed meat appeared entirely responsible for the elevated diabetes risk associated with total red meat in these two large cohort studies (8,9).

Red meat, especially processed meat, contains certain types of preservatives, additives, or other chemicals arising from

Table 2—RR of type 2 diabetes according to consumption of red meat and total processed meat in the WHS

	Frequency of consumption					P for trend	Quintiles of intake					P for trend
	<1 time/week	1 time/week	2–4 times/week	≥5 times/week	1 (lowest)		2	3	4	5 (highest)		
Red meat												
Median intake, servings/day	0.03	0.20	0.42	1.06	—	0.13	0.40	0.57	0.86	1.42	—	
Cases/person-years	69/22,694	110/30,284	502/128,806	877/145,092	—	225/64,742	229/63,204	299/69,244	322/64,146	483/65,541	—	
Age, energy adjusted	1.00	1.20 (0.89–1.62)	1.30 (1.01–1.68)	2.03 (1.58–2.60)	<0.0001	1.00	1.06 (0.88–1.28)	1.29 (1.08–1.54)	1.53 (1.28–1.83)	2.24 (1.88–2.66)	<0.0001	
Multivariate model 1*	1.00	1.15 (0.85–1.57)	1.08 (0.83–1.40)	1.29 (0.99–1.67)	0.01	1.00	0.89 (0.74–1.08)	1.07 (0.90–1.28)	1.09 (0.91–1.31)	1.28 (1.07–1.53)	<0.001	
Multivariate Model 2†	1.00	1.16 (0.85–1.58)	1.09 (0.83–1.43)	1.25 (0.94–1.67)	0.07	1.00	0.90 (0.74–1.10)	1.07 (0.88–1.30)	1.08 (0.89–1.33)	1.24 (1.00–1.54)	0.005	
Total processed meat												
Median intake, servings/day	0	0.14	0.43	0.92	—	0	0.07	0.13	0.21	0.56	—	
Cases/person-years	55/150,891	457/97,859	395/60,827	136/14,119	—	309/86,704	246/64,187	172/41,203	384/72,400	432/59,202	—	
Age, energy adjusted	1.00	1.27 (1.12–1.44)	1.74 (1.52–1.98)	2.49 (2.05–3.03)	<0.0001	1.00	1.07 (0.91–1.27)	1.17 (0.97–1.41)	1.48 (1.27–1.72)	1.98 (1.70–2.30)	<0.0001	
Multivariate model 1*	1.00	1.05 (0.92–1.19)	1.20 (1.05–1.38)	1.43 (1.17–1.75)	<0.001	1.00	0.96 (0.81–1.14)	0.96 (0.79–1.16)	1.11 (0.95–1.29)	1.23 (1.05–1.45)	0.001	
Multivariate model 2†	1.00	1.03 (0.91–1.18)	1.17 (1.01–1.36)	1.38 (1.11–1.71)	0.003	1.00	0.96 (0.81–1.14)	0.95 (0.78–1.15)	1.08 (0.91–1.27)	1.19 (1.00–1.42)	0.007	

Data are RR (95% CI). *Multivariate model 1: adjusted for age (continuous), BMI (continuous), total energy intake (quintiles), smoking (current, past, and never), exercise (frequently/never, <1 time/week, 1–3 times/week, and ≥4 times/week), alcohol use (rarely/never, 1–3 drinks/month, 1–6 drinks/week, and ≥1 drink/day), and family history of diabetes (yes/no). †Multivariate model 2: model 1 with additional adjustment for dietary intakes of fiber intake (quintiles), glycemic load (quintiles), magnesium (quintiles), and total fat (quintiles).

Table 3—RR of type 2 diabetes according to subtypes of red meat and processed meat in the WHS

	Frequency of consumption			P for trend
	<1 time/week	1 time/week	≥2 times/week	
Red meat				
Beef or lamb as a main dish				
Cases/person-years	199/52,840	482/106,678	858/163,127	
Age, energy adjusted	1.00	1.19 (1.01–1.41)	1.35 (1.15–1.58)	<0.0001
Multivariate model 1*	1.00	1.07 (0.91–1.27)	1.15 (0.98–1.35)	0.07
Multivariate model 2†	1.00	1.07 (0.90–1.27)	1.12 (0.94–1.33)	0.22
Pork as a main dish				
Cases/person-years	391/91,050	620/135,719	544/99,043	
Age, energy adjusted	1.00	1.05 (0.93–1.20)	1.23 (1.07–1.41)	0.002
Multivariate model 1*	1.00	0.98 (0.86–1.12)	1.10 (0.95–1.26)	0.16
Multivariate model 2†	1.00	0.97 (0.85–1.11)	1.06 (0.92–1.23)	0.36
Beef, pork, or lamb as a sandwich or mixed dish				
Cases/person-years	163/44,245	411/95,201	971/184,184	
Age, energy adjusted	1.00	1.17 (0.98–1.41)	1.40 (1.18–1.66)	<0.0001
Multivariate model 1*	1.00	1.07 (0.89–1.29)	1.15 (0.96–1.37)	0.09
Multivariate model 2†	1.00	1.06 (0.88–1.28)	1.12 (0.93–1.34)	0.21
Hamburgers				
Cases/person-years	174/53,936	511/123,780	867/147,174	
Age, energy adjusted	1.00	1.29 (1.09–1.53)	1.81 (1.54–2.14)	<0.0001
Multivariate model 1*	1.00	1.10 (0.92–1.31)	1.18 (1.00–1.41)	0.04
Multivariate model 2†	1.00	1.09 (0.91–1.30)	1.15 (0.95–1.38)	0.14
Processed meat				
Bacon				
Cases/person-years	690/173,840	497/96,981	364/54,876	
Age, energy adjusted	1.00	1.27 (1.14–1.43)	1.59 (1.40–1.81)	<0.0001
Multivariate model 1*	1.00	1.12 (0.99–1.26)	1.21 (1.06–1.39)	0.004
Multivariate model 2†	1.00	1.10 (0.97–1.24)	1.17 (1.02–1.35)	0.02
Hot dogs				
Cases/person-years	811/202,195	522/95,147	215/27,736	
Age, energy adjusted	1.00	1.35 (1.21–1.51)	1.84 (1.58–2.15)	<0.0001
Multivariate model 1*	1.00	1.08 (0.96–1.21)	1.28 (1.09–1.50)	0.003
Multivariate model 2†	1.00	1.06 (0.94–1.19)	1.24 (1.05–1.45)	0.02
Other processed meats‡				
Cases/person-years	580/144,224	494/108,859	480/72,486	
Age, energy adjusted	1.00	1.13 (1.00–1.27)	1.60 (1.41–1.81)	<0.0001
Multivariate model 1*	1.00	0.91 (0.80–1.03)	1.12 (0.99–1.28)	0.13
Multivariate model 2†	1.00	0.89 (0.78–1.01)	1.07 (0.93–1.23)	0.43

Data are RR (95% CI); *Multivariate model 1: adjusted for age (continuous), BMI (continuous), total energy intake (quintiles), smoking (current, past, and never), exercise (rarely/never, <1 time/week, 1–3 times/week, and ≥4 times/week), alcohol use (rarely/never, 1–3 drinks/month, 1–6 drinks/week, and ≥1 drink/day), and family history of diabetes (yes/no). †Multivariate model 2: model 1 with additional adjustment for dietary intakes of fiber intake (quintiles), glycemic load (quintiles), magnesium (quintiles), and total fat (quintiles). ‡Other processed meats include sausage, salami, and bologna.

meat preparation, including preservation, packaging, and cooking. These compounds include nitrates and nitrites added in meat processing as well as a variety of heterocyclic amines and polycyclic aromatic hydrocarbons formed in red meat, especially when cooked well done (17). These compounds can be converted to N-nitrosamines (17), which were found to be toxic to pancreatic β-cell (18). Consumption of foods with a high content of nitrites and nitrosamines has

been associated with type 1 diabetes (19–21). Also, advanced glycation and lipoxidation end products produced during the cooking or processing of meat have been associated with insulin resistance and diabetes-related complications in animal models (22) and human subjects (23,24). Therefore, such specific compounds mainly present in processed meat might largely explain the observed significant association between processed meat intake and type 2 diabetes.

Nevertheless, red meat is also a major source for saturated fat, cholesterol, animal protein, and heme iron. It has been shown that certain types of fat from red meat may play a major role in the development of type 2 diabetes (9,25). As noted in a recent review, epidemiological evidence for the relevance of dietary fats and risk of type 2 diabetes seem to be inconsistent (25). The present study did not show any positive associations between intakes of saturated fat or *trans* fatty

Table 4—RR of type 2 diabetes according to quintiles of nutrient intake in the WHS

	Quintile of intake					P for trend
	1 (lowest)	2	3	4	5 (highest)	
Saturated fat						
Median intake (g/day)	13.8	17.1	19.4	21.8	25.8	
Cases/person-years	231/65,587	268/65,503	301/65,758	337/65,285	421/64,743	
Age, energy adjusted	1.00	1.17 (0.98–1.39)	1.31 (1.10–1.55)	1.48 (1.26–1.76)	1.90 (1.62–2.23)	<0.0001
Multivariate model 1*	1.00	0.96 (0.80–1.14)	1.04 (0.87–1.24)	1.01 (0.85–1.20)	1.10 (0.93–1.31)	0.14
Multivariate model 2†	1.00	0.95 (0.76–1.18)	0.94 (0.73–1.21)	0.85 (0.64–1.13)	0.89 (0.66–1.21)	0.49
Monounsaturated fat						
Median intake (g/day)	15.1	18.9	21.4	24.0	27.9	
Cases/person-years	242/65,355	242/65,631	305/65,635	343/65,275	426/64,980	
Age, energy adjusted	1.00	0.99 (0.83–1.18)	1.25 (1.06–1.48)	1.41 (1.20–1.67)	1.79 (1.52–2.09)	<0.0001
Multivariate model 1*	1.00	0.91 (0.76–1.09)	1.06 (0.89–1.26)	1.10 (0.93–1.30)	1.14 (0.97–1.35)	0.02
Multivariate model 2†	1.00	1.01 (0.77–1.32)	1.11 (0.80–1.55)	1.17 (0.81–1.70)	1.27 (0.85–1.91)	0.20
n-3 polyunsaturated fat§						
Median intake (g/day)	0.95	1.17	1.34	1.54	1.88	
Cases/person-years	283/66,108	299/63,856	301/66,863	322/63,488	353/66,562	
Age, energy adjusted	1.00	1.08 (0.92–1.27)	1.03 (0.88–1.21)	1.16 (0.99–1.36)	1.21 (1.04–1.42)	0.009
Multivariate model 1*	1.00	1.08 (0.92–1.28)	1.04 (0.88–1.23)	1.11 (0.95–1.31)	1.09 (0.93–1.28)	0.28
Multivariate model 2†	1.00	1.09 (0.92–1.29)	1.06 (0.89–1.25)	1.13 (0.96–1.34)	1.10 (0.93–1.30)	0.30
n-6 polyunsaturated fat‡						
Median intake (g/day)	7.35	9.12	10.5	12.0	14.5	
Cases/person-years	260/64,953	302/65,430	315/65,293	331/65,409	350/65,791	
Age, energy adjusted	1.00	1.14 (0.97–1.35)	1.19 (1.01–1.40)	1.24 (1.06–1.46)	1.31 (1.12–1.54)	0.001
Multivariate model 1*	1.00	1.06 (0.90–1.26)	1.12 (0.95–1.32)	1.09 (0.92–1.28)	1.03 (0.87–1.21)	0.90
Multivariate model 2†	1.00	1.06 (0.89–1.26)	1.09 (0.91–1.31)	1.04 (0.86–1.25)	0.95 (0.78–1.16)	0.39
trans fatty acid						
Median intake (g/day)	1.12	1.64	2.09	2.65	3.66	
Cases/person-years	226/65,788	294/64,637	306/65,305	347/66,054	385/65,093	
Age, energy adjusted	1.00	1.34 (1.13–1.59)	1.38 (1.16–1.63)	1.54 (1.31–1.83)	1.76 (1.49–2.08)	<0.001
Multivariate model 1*	1.00	1.21 (1.01–1.44)	1.13 (0.95–1.35)	1.15 (0.96–1.37)	1.14 (0.96–1.35)	0.47
Multivariate model 2†	1.00	1.21 (1.00–1.46)	1.09 (0.89–1.33)	1.07 (0.87–1.32)	1.03 (0.83–1.28)	0.44
Cholesterol						
Median intake (mg/day)	147	188	219	253	309	
Cases/person-years	219/65,594	258/65,688	303/65,546	333/65,315	445/64,733	
Age, energy adjusted	1.00	1.19 (0.99–1.42)	1.39 (1.17–1.66)	1.54 (1.30–1.83)	2.13 (1.81–2.51)	<0.0001
Multivariate model 1*	1.00	1.06 (0.89–1.28)	1.18 (0.99–1.41)	1.13 (0.95–1.34)	1.33 (1.12–1.57)	0.001
Multivariate model 2†	1.00	1.09 (0.90–1.31)	1.21 (1.00–1.47)	1.15 (0.95–1.40)	1.35 (1.11–1.64)	0.003
Animal fat						
Median intake (g/day)	19.7	26.0	30.4	35.2	43.1	
Cases/person-years	238/65,645	237/65,740	304/65,547	346/65,228	433/64,715	
Age, energy adjusted	1.00	1.00 (0.84–1.20)	1.30 (1.10–1.54)	1.49 (1.27–1.76)	1.90 (1.62–2.23)	<0.0001
Multivariate model 1*	1.00	0.93 (0.77–1.11)	1.03 (0.87–1.23)	1.08 (0.91–1.28)	1.17 (0.99–1.38)	0.01
Multivariate model 2†	1.00	0.94 (0.78–1.15)	1.05 (0.86–1.29)	1.08 (0.87–1.34)	1.13 (0.90–1.43)	0.16
Vegetable fat						
Median intake (g/day)	16.9	22.0	25.9	30.2	37.3	
Cases/person-years	286/64,927	294/65,311	326/65,460	317/65,535	335/65,644	
Age, energy adjusted	1.00	1.01 (0.86–1.19)	1.12 (0.95–1.31)	1.08 (0.92–1.27)	1.14 (0.98–1.34)	0.07
Multivariate model 1*	1.00	0.97 (0.83–1.15)	1.10 (0.94–1.30)	1.04 (0.89–1.23)	0.94 (0.80–1.11)	0.59
Multivariate model 2†	1.00	0.98 (0.82–1.16)	1.08 (0.90–1.28)	0.98 (0.81–1.18)	0.85 (0.70–1.03)	0.08
Animal protein						
Median intake (g/day)	39.8	50.5	57.8	65.3	77.3	
Cases/person-years	233/65,541	290/65,512	306/65,415	352/65,274	377/65,133	
Age, energy adjusted	1.00	1.25 (1.05–1.48)	1.33 (1.12–1.58)	1.55 (1.31–1.83)	1.70 (1.44–2.00)	<0.0001
Multivariate model 1*	1.00	1.19 (1.00–1.42)	1.24 (1.04–1.48)	1.34 (1.13–1.59)	1.27 (1.08–1.51)	0.004
Multivariate model 2†	1.00	1.24 (1.03–1.48)	1.33 (1.10–1.60)	1.48 (1.21–1.79)	1.44 (1.16–1.78)	0.001

Continued

Table 4—Continued

	Quintile of intake					P for trend
	1 (lowest)	2	3	4	5 (highest)	
Vegetable protein						
Median intake (g/day)	17.1	20.2	22.5	24.9	29.2	
Cases/person-years	393/64,754	284/65,550	320/65,746	314/65,403	247/65,423	
Age, energy adjusted	1.00	0.70 (0.60–0.82)	0.79 (0.68–0.92)	0.77 (0.66–0.89)	0.61 (0.52–0.71)	<0.0001
Multivariate model 1*	1.00	0.80 (0.68–0.93)	0.95 (0.82–1.11)	0.92 (0.79–1.07)	0.82 (0.69–0.97)	0.10
Multivariate model 2†	1.00	0.84 (0.71–0.99)	1.03 (0.86–1.23)	1.01 (0.83–1.23)	0.91 (0.73–1.14)	0.83
Heme iron						
Median intake (mg/day)	0.59	0.84	1.02	1.22	1.55	
Cases/person-years	216/65,859	265/63,533	290/67,652	349/65,284	438/64,548	
Age, energy adjusted	1.00	1.29 (1.07–1.54)	1.33 (1.12–1.59)	1.67 (1.41–1.98)	2.17 (1.84–2.55)	<0.0001
Multivariate model 1*	1.00	1.18 (0.98–1.42)	1.13 (0.95–1.36)	1.30 (1.09–1.55)	1.41 (1.19–1.67)	<0.0001
Multivariate model 2†	1.00	1.20 (1.00–1.45)	1.17 (0.97–1.41)	1.35 (1.12–1.63)	1.46 (1.20–1.78)	<0.0001
Total iron						
Median intake (mg/day)	10.0	11.8	13.7	18.0	33.8	
Cases/person-years	304/65,405	365/65,431	353/65,076	267/65,450	269/65,514	
Age, energy adjusted	1.00	1.17 (1.00–1.36)	1.11 (0.95–1.30)	0.83 (0.70–0.98)	0.86 (0.73–1.02)	0.001
Multivariate model 1*	1.00	1.18 (1.01–1.38)	1.14 (0.97–1.34)	0.99 (0.83–1.17)	1.03 (0.87–1.22)	0.37
Multivariate model 2†	1.00	1.24 (1.05–1.45)	1.23 (1.04–1.46)	1.09 (0.90–1.31)	1.13 (0.93–1.37)	0.94

Data are RR (95% CI). *Multivariate model 1: adjusted for age (continuous), BMI (continuous), total energy intake (quintiles), smoking (current, past, and never), exercise (rarely/never, <1 time/week, 1–3 times/week, and ≥4 times/week), alcohol use (rarely/never, 1–3 drinks/month, 1–6 drinks/week, and ≥1 drink/day), and family history of diabetes (yes/no). †Multivariate model 2: model 1 with additional adjustment for dietary intakes of fiber intake (quintiles), glycemic load (quintiles), magnesium (quintiles), and total fat (quintiles). ‡n-3 polyunsaturated fat included 18:3, 20:5, 22:5, and 22:6 while n-6 fat included 18:2 and 20:4 fatty acids.

acid and risk of type 2 diabetes. Likewise, we found no evidence of decreased risk of diabetes with increased intake of mono-unsaturated or polyunsaturated fatty acids or vegetable fat. However, cholesterol intake tended to be positively related to an elevated risk of diabetes. Cholesterol intake from red meat may thus explain, at least in part, the observed association between red meat intake and type 2 diabetes.

Recently, body iron overload has been postulated to promote insulin resistance and increase type 2 diabetes risk (26–30). However, the positive association between heme iron intake and type 2 diabetes should be interpreted with caution because the high correlation between red meat intake and heme iron intake substantially limited our statistical capability to separate the independent effect of heme iron from other components of red meat. The lack of association between total iron intake and risk of type 2 diabetes might reflect the fact that body iron status is not well regulated by intakes of total dietary iron or heme iron.

Our study has several limitations. First, we cannot completely exclude the possibilities of residual confounding from unmeasured or incompletely measured underlying lifestyle factors even though we have adjusted for many major risk fac-

tors for type 2 diabetes. Second, participants might change their diets after developing some diseases. However, these associations persisted when we carried out secondary analyses after excluding participants who had a history of hypertension or high cholesterol levels, which allows for elimination of dietary change related to these diagnoses. Third, because of a high degree of statistical collinearity, our ability to reliably distinguish the effect of red meat from intakes of its major components such as animal fat, animal protein, and heme iron was limited. Fourth, limited variation of intakes for each subtype of total red meat or other processed meat in our cohort could lead to insufficient statistical power to detect significant association. Finally, we were also unable to assess levels of specific chemicals added or produced in different food preparation methods and thus could not address the relationship between these specific chemicals and diabetic risk.

In conclusion, our study indicates that higher consumption of total red meat, especially various processed meats, may increase risk of developing type 2 diabetes in women. However, the underlying mechanisms by which consumption of red meat or processed meat influence type 2 diabetes

risk are still not well understood and require further investigation.

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References

1. Himsworth HP: Diet and the incidence of diabetes mellitus. *Clin Sci* 2:117–148, 1935
2. Kawate R, Yamakido M, Nishimoto Y, Bennett PH, Hamman RF, Knowler WC: Diabetes mellitus and its vascular complications in Japanese migrants on the Island of Hawaii. *Diabetes Care* 2:161–170, 1979
3. Pratley RE: Gene-environment interactions in the pathogenesis of type 2 diabetes mellitus: lessons learned from the Pima Indians. *Proc Nutr Soc* 57:175–181, 1998
4. Gittelsohn J, Wolever TM, Harris SB, Harris-Giraldo R, Hanley AJ, Zinman B: Specific patterns of food consumption and preparation are associated with diabetes and obesity in a Native Canadian community. *J Nutr* 128:541–547, 1998
5. Williams DE, Prevost AT, Whichelow MJ, Cox BD, Day NE, Wareham NJ: A cross-sectional study of dietary patterns with

- glucose intolerance and other features of the metabolic syndrome. *Br J Nutr* 83: 257–266, 2000
6. van Dam RM, Rimm EB, Willett WC, Stampfer MJ, Hu FB: Dietary patterns and risk for type 2 diabetes mellitus in U.S. men. *Ann Intern Med* 136:201–209, 2002
 7. Snowdon DA, Phillips RL: Does a vegetarian diet reduce the occurrence of diabetes? *Am J Public Health* 75:507–512, 1985
 8. Schulze MB, Manson JE, Willett WC, Hu FB: Processed meat intake and incidence of type 2 diabetes in younger and middle-aged women. *Diabetologia* 46:1465–1473, 2003
 9. van Dam RM, Willett WC, Rimm EB, Stampfer MJ, Hu FB: Dietary fat and meat intake in relation to risk of type 2 diabetes in men. *Diabetes Care* 25:417–424, 2002
 10. Buring JE, Hennekens CH: The Women's Health Study: summary of the study design. *J Myocard Ischemia* 4:27–29, 1992
 11. Watt BK, Merrill AL: *Composition of Foods: Raw, Processed, Prepared, 1963–1992*. Washington, DC, U.S. Govt. Printing Office, 1993 (Dept. of Agriculture handbook no. 8)
 12. Willett WC, Stampfer MJ: Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol* 124:17–27, 1986
 13. Willett WC: *Nutritional Epidemiology*. New York, Oxford University Press, 1998
 14. Feskanih D, Rimm EB, Giovannucci EL, Colditz GA, Stampfer MJ, Litin LB, Willett WC: Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. *J Am Diet Assoc* 93:790–796, 1993
 15. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM: C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 286:327–334, 2001
 16. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
 17. Lijinsky W: N-nitroso compounds in the diet. *Mutat Res* 443:129–138, 1999
 18. LeDoux SP, Woodley SE, Patton NJ, Wilson GL: Mechanisms of nitrosourea-induced β -cell damage: alterations in DNA. *Diabetes* 35:866–872, 1986
 19. Dahlquist GG, Blom LG, Persson LA, Sandstrom AI, Wall SG: Dietary factors and the risk of developing insulin dependent diabetes in childhood. *BMJ* 300: 1302–1306, 1990
 20. Virtanen SM, Jaakkola L, Rasanen L, Ylonen K, Aro A, Lounamaa R, Akerblom HK, Tuomilehto J: Nitrate and nitrite intake and the risk for type 1 diabetes in Finnish children: Childhood Diabetes in Finland Study Group. *Diabet Med* 11: 656–662, 1994
 21. Helgason T, Jonasson MR: Evidence for a food additive as a cause of ketosis-prone diabetes. *Lancet* 2:716–720, 1981
 22. Hofmann SM, Dong HJ, Li Z, Cai W, Altomonte J, Thung SN, Zeng F, Fisher EA, Vlassara H: Improved insulin sensitivity is associated with restricted intake of dietary glycoxidation products in the db/db mouse. *Diabetes* 51:2082–2089, 2002
 23. Peppia M, Goldberg T, Cai W, Rayfield E, Vlassara H: Glycotoxins: a missing link in the “relationship of dietary fat and meat intake in relation to risk of type 2 diabetes in men.” *Diabetes Care* 25:1898–1899, 2002
 24. Vlassara H, Cai W, Crandall J, Goldberg T, Oberstein R, Dardaine V, Peppia M, Rayfield EJ: Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy. *Proc Natl Acad Sci U S A* 99:15596–15601, 2002
 25. Hu FB, van Dam RM, Liu S: Diet and risk of type II diabetes: the role of types of fat and carbohydrate. *Diabetologia* 44:805–817, 2001
 26. Tuomainen TP, Nyysönen K, Salonen R, Tervahauta A, Korpela H, Lakka T, Kaplan GA, Salonen JT: Body iron stores are associated with serum insulin and blood glucose concentrations: population study in 1,013 eastern Finnish men. *Diabetes Care* 20:426–428, 1997
 27. Fernandez-Real JM, Ricart-Engel W, Arroyo E, Balanca R, Casamitjana-Abella R, Cabrero D, Fernandez-Castaner M, Soler J: Serum ferritin as a component of the insulin resistance syndrome. *Diabetes Care* 21:62–68, 1998
 28. Hua NW, Stoohs RA, Facchini FS: Low iron status and enhanced insulin sensitivity in lacto-ovo vegetarians. *Br J Nutr* 86: 515–519, 2001
 29. Ford ES, Cogswell ME: Diabetes and serum ferritin concentration among U.S. adults. *Diabetes Care* 22:1978–1983, 1999
 30. Jiang R, Manson JE, Meigs JB, Ma J, Rifai N, Hu FB: Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. *JAMA* 291:711–717, 2004