Original Investigation

Changes in Red Meat Consumption and Subsequent Risk of Type 2 Diabetes Mellitus
Three Cohorts of US Men and Women

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IMPORTANCE Red meat consumption has been consistently associated with an increased risk of type 2 diabetes mellitus (T2DM). However, whether changes in red meat intake are related to subsequent T2DM risk remains unknown.

OBJECTIVE To evaluate the association between changes in red meat consumption during a 4-year period and subsequent 4-year risk of T2DM in US adults.

DESIGN AND SETTING Three prospective cohort studies in US men and women.

PARTICIPANTS We followed up 26 357 men in the Health Professionals Follow-up Study (1986-2006), 48 709 women in the Nurses' Health Study (1986-2006), and 74 077 women in the Nurses' Health Study II (1991-2007). Diet was assessed by validated food frequency questionnaires and updated every 4 years. Time-dependent Cox proportional hazards regression models were used to calculate hazard ratios with adjustment for age, family history, race, marital status, initial red meat consumption, smoking status, and initial and changes in other lifestyle factors (physical activity, alcohol intake, total energy intake, and diet quality). Results across cohorts were pooled by an inverse variance–weighted, fixed-effect meta-analysis.

MAIN OUTCOMES AND MEASURES Incident T2DM cases validated by supplementary questionnaires.

RESULTS During 1 965 824 person-years of follow-up, we documented 7540 incident T2DM cases. In the multivariate-adjusted models, increasing red meat intake during a 4-year interval was associated with an elevated risk of T2DM during the subsequent 4 years in each cohort (all $P < .001$ for trend). Compared with the reference group of no change in red meat intake, increasing red meat intake of more than 0.50 servings per day was associated with a 48% (pooled hazard ratio, 1.48; 95% CI, 1.37-1.59) elevated risk in the subsequent 4-year period, and the association was modestly attenuated after further adjustment for initial body mass index and concurrent weight gain (1.30; 95% CI, 1.21-1.41). Reducing red meat consumption by more than 0.50 servings per day from baseline to the first 4 years of follow-up was associated with a 14% (pooled hazard ratio, 0.86; 95% CI, 0.80-0.93) lower risk during the subsequent entire follow-up through 2006 or 2007.

CONCLUSIONS AND RELEVANCE Increasing red meat consumption over time is associated with an elevated subsequent risk of T2DM, and the association is partly mediated by body weight. Our results add further evidence that limiting red meat consumption over time confers benefits for T2DM prevention.

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Red meat consumption has been consistently related to an elevated risk of type 2 diabetes mellitus (T2DM). For example, 3 recent meta-analyses[1-3] of prospective cohort studies reported positive associations. However, most previous studies measured red meat consumption only at baseline with limited follow-up information. In real life, a person's eating behavior changes over time, and secular trends in red meat intake are also changing dramatically across the globe.[4] Because a measurement at a single time point does not capture the variability of red meat intake during follow-up, it is important to evaluate whether changes in red meat intake over time alter the risk of developing T2DM. Therefore, we analyzed data from 3 Harvard cohort studies: the Health Professionals Follow-up Study (HPFS), the Nurses' Health Study (NHS), and the Nurses' Health Study II (NHS II), in which we collected repeated measurements of red meat intake every 4 years, as well as other dietary components, lifestyle factors, and medical history with up to 20 years of follow-up. These repeated measures and long duration of follow-up allow us to investigate the association between dynamic changes in red meat intake and subsequent risk of T2DM. We conducted 2 sets of change analysis. In the first analysis, we examined 4-year change in red meat intake in relation to T2DM incidence in the next 4 years of follow-up. In the second analysis, to examine long-term effects of meat intake on T2DM, we analyzed changes in red meat intake from baseline to the first 4-year follow-up with T2DM incidence in the subsequent 12 (NHS II) and 16 (NHS and HPFS) years of follow-up.

Methods

Study Population

The HPFS was initiated in 1986 when 51 529 US male health professionals, aged 40 to 75 years, returned a baseline questionnaire about detailed medical history, as well as lifestyle and usual diet. The NHS consists of 121 700 registered female nurses, aged 30 to 55 years, who completed a baseline questionnaire about lifestyle and medical history in 1976. The NHS II, established in 1989, comprises 116 671 younger female registered nurses, aged 25 to 42 years, who responded to a baseline questionnaire similar to that of the NHS. Detailed descriptions of the cohorts have been introduced elsewhere.[3,5] In all cohorts, questionnaires were administered at baseline and biennially thereafter to collect and update information on lifestyle practices (eg, smoking and physical activity) and the occurrence of new-onset diseases. The cumulative follow-up of the 3 cohorts exceeds 90% of potential person-times.

In the current analysis, we used 1986 for the HPFS and NHS and 1991 for the NHS II as the baseline when we assessed detailed information on diet and lifestyle factors. Because we used the changes in red meat consumption every 4 years as the exposure to predict the subsequent 4-year T2DM risk, we excluded men and women who had a history of diabetes mellitus (including type 1 diabetes mellitus, T2DM, and gestational diabetes), cardiovascular disease, or cancer 4 years after baseline (ie, 1990 for the HPFS and NHS and 1995 for the NHS II). In addition, we excluded participants who left more than 10 blank food items on the baseline food frequency questionnaire (FFQ), reported unusual total energy intake levels (ie, <800 or >4200 kcal/d for men and <500 or >3500 kcal/d for women), or did not report meat consumption. After exclusions, data from 26 357 HPFS men, 48 709 NHS women, and 74 077 NHS II women were available. Participants who were excluded because of missing baseline FFQ data were similar in age and body mass index (BMI) compared with those included in the analysis (data not shown). The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and the Harvard School of Public Health.

Assessment of Meat Consumption

Dietary information, collected by a validated FFQ in 1986 for the HPFS and NHS and in 1991 for the NHS II, was updated every 4 years with similar FFQs. In all FFQs, we asked participants how often, on average, they consumed each food of a standard portion size. Frequency responses ranged from never or less than once per month to 6 or more times per day. Questionnaire items on unprocessed red meat (85 g or 3 oz) included beef, pork, or lamb as main dish; hamburger; and beef, pork, or lamb as a sandwich or mixed dish. Items on processed red meat included bacon (2 slices, 13 g), hot dogs (1 hot dog, 45 g), and sausage, salami, bologna, and other processed red meats (1 piece, 28 g). The reproducibility and validity of FFQs have been demonstrated in detail elsewhere.[6-8] Correlation coefficients between FFQs and multiple diet records ranged from 0.38 to 0.70 for various red meat items.[7]

Assessment of Covariates

In the follow-up questionnaires, we obtained updated information on risk factors for T2DM, such as body weight, cigarette smoking, physical activity, and a history of hypertension and hypercholesterolemia. We also ascertained menopausal status and postmenopausal hormone use in women. Alcohol intake was asked on the FFQ and updated every 4 years. We also collected information on a family history of T2DM, race, and marital status. To assess overall diet quality, we calculated a diet score based on the 2010 Alternative Healthy Eating Index,[9] which was designed to reflect food choices and nutrients associated with reduced noncommunicable disease risk. For the current analysis, we constructed the Alternative Healthy Eating Index score without the meat and alcohol components because they were included separately in the models.

Assessment of T2DM

Incident T2DM cases were identified by self-report on the main questionnaires every 2 years and confirmed by a validated supplementary questionnaire regarding symptoms, diagnostic tests, and treatment. The diagnosis was confirmed if at least 1 of the following was reported according to the National Diabetes Data Group[10] criteria: (1) 1 or more classic symptoms (excessive thirst, polyuria, weight loss, or hunger) plus fasting glucose levels 140 mg/dL or higher or random glucose levels 200 mg/dL or higher (to convert to millimoles per liter, multiply by 0.0555), (2) at least 2 elevated glucose concentrations on different occasions (fasting glucose levels ≥140 mg/dL, random glucose levels ≥200 mg/dL, and/or concentrations ≥200 mg/dL after 2 hours or more by oral glucose tolerance testing) in the

absence of symptoms, or (3) treatment with hypoglycemic medication (insulin or oral hypoglycemic agent). For cases diagnosed in 1998 and later, the fasting glucose threshold was lowered to 126 mg/dL according to the American Diabetes Association[11] criteria.

The validity of the supplementary questionnaire for the diagnosis of T2DM has been documented previously: of 59 cases in the HPFS and 62 cases in the NHS confirmed by supplementary questionnaires, 57 (97%) and 61 (98%) cases, respectively, were reconfirmed by medical records.[12,13] In another substudy to assess the prevalence of undiagnosed T2DM cases in the NHS, only 1 of 200 randomly selected women had elevated fasting glucose or fructosamine levels barely above the diagnostic cutoffs.[14] We excluded false-positive cases and included only incident cases confirmed by the supplemental questionnaires.

Statistical Analysis

We calculated each individual's person-years from the date of returning the baseline questionnaire to the date of T2DM diagnosis, death, or the end of the follow-up (January 31, 2006, for the HPFS; June 30, 2006, for the NHS; and June 30, 2007, for the NHS II), whichever came first. We used change in red meat consumption updated every 4 years as a time-varying exposure, and time-dependent Cox proportional hazards regression was used to estimate the hazard ratio (HR) for T2DM risk in the subsequent 4 years. For example, we used changes in red meat consumption between the 1986 and 1990 questionnaires to predict T2DM risk from 1990 through 1994, changes between the 1990 and 1994 questionnaires to predict T2DM risk from 1994 through 1998, and so forth. In the multivariate analysis, in addition to age and calendar time, we simultaneously controlled for various potential confounding factors, including race (white or nonwhite), family history of T2DM (yes or no), marital status (with spouse, yes or no; updated every 4 years), history of hypertension and hypercholesterolemia (yes or no; updated every 4 years), and simultaneous changes in other lifestyle factors: smoking status (never to never, never to current, past to past, past to current, current to past, current to current, or missing indicator), as well as initial and changes (all in quintiles) in alcohol intake, physical activity, total energy intake, and diet quality (Alternative Healthy Eating Index score). In the NHS and NHS II, we also adjusted for postmenopausal status and menopausal hormone use. It has been reported that increasing red meat consumption was related to weight gain in the 3 cohorts[5]; therefore, body weight and weight gain could be mediators. We adjusted for initial BMI (calculated as weight in kilograms divided by height in meters squared) (<23, 23-24.9, 25-29.9, 30-34.9, and ≥35) and changes in body weight (quintiles) in each 4-year period as time-varying covariates in an additional model. We also analyzed processed and unprocessed red meat separately.

In the second analysis, to examine long-term effects of red meat intake on T2DM, we analyzed changes in intake from baseline to the first 4-year follow-up and T2DM incidence in the subsequent follow-up years. Specifically, we used changes in red meat consumption between 1986 and 1990 to predict T2DM risk from 1990 through 2006 for the NHS and HPFS, as well as between 1991 and 1995 to predict T2DM risk from 1995 through 2007 for the NHS II.

To minimize missing values during follow-up, we replaced them with carried-forward values for continuous variables and added a missing indicator for categorical variables. Stratified analyses were performed a priori by initial BMI categories (<30.0 and ≥30.0), and the interaction was tested by including cross-product terms in the models. An inverse variance–weighted, fixed-effect meta-analysis was used to combine the results across cohorts because no significant heterogeneity was found.

We conducted a series of sensitivity analyses to test the robustness of our results: we stopped updating the dietary information after self-report of incident cardiovascular disease or cancer during the follow-up, censored participants when they did not answer FFQs during the follow-up, and used a multiple imputation procedure with 20 rounds of imputation and included all covariates to account for missing dietary and covariate data. All analyses were performed using SAS software, version 9.2 (SAS Institute), at a 2-tailed *P* value of .05.

Results

We documented 7540 incident T2DM cases during the follow-up (1561 in the HPFS, 3482 in the NHS, and 2497 in the NHS II). **Table 1** describes the distribution of baseline characteristics according to change in total red meat consumption. Compared with people with relatively stable intake, individuals who decreased or increased their intake were generally younger, had higher BMI levels, had a lower diet quality score, and were more likely to be smokers. Those who decreased intake were also more likely to report a diagnosis of hypertension or hypercholesterolemia. As expected, increasing red meat intake was related to concurrent weight gain, increases in total energy intake, and decreases in diet quality scores, while the associations with decreasing red meat intake were in the opposite direction.

Table 2 shows the HRs of T2DM according to changes in total red meat consumption. Compared with individuals whose intake remained relatively stable in each 4-year period, those who increased their red meat intake were at elevated risks (*P* < .001 in all 3 cohorts): increasing red meat intake of more than 0.50 servings per day was associated with a 48% (pooled HR, 1.48; 95% CI, 1.37-1.59) elevated risk in the subsequent 4-year period, and the association was modestly attenuated after further adjustment for initial BMI and concurrent weight gain (pooled HR, 1.30; 95% CI, 1.21-1.41). A moderate increase (0.15-0.50 servings per day) in red meat intake was also associated with an elevated risk: the corresponding pooled HRs were 1.21 (95% CI, 1.13-1.30) and 1.15 (95% CI, 1.07-1.23) before and after adjustment for initial BMI and concurrent weight gain, respectively. The associations were greater for processed than for unprocessed red meat (eTable 1 in Supplement).

No significant decreased T2DM risk was found with a reduction of red meat intake within a 4-year period (Table 2). However, when we used reduction in red meat consumption from baseline to the first 4-year follow-up as the exposure to predict future risk of T2DM during the entire follow-up (instead of just the subsequent 4 years), we observed that a reduction of red meat intake of more than 0.50 servings per day was associated with a 14% (pooled HR, 0.86; 95% CI, 0.80-

Table 1. Characteristics According to Baseline 4-Year Changes in Total Red Meat Intake

Variable	Changes in Frequency of Red Meat Consumption (Categories in Servings per Day)[a]				
	Decrease		No Change or Relatively Stable (±0.14)	Increase	
	Moderate to Large (>0.50)	Small to Moderate (0.15-0.50)		Small to Moderate (0.15-0.50)	Moderate to Large (>0.50)
Health Professional Follow-up Study					
No. of participants	6145	5427	6728	4484	3573
Initial red meat intake, servings per day	1.93 (0.89)	1.17 (0.62)	0.73 (0.63)	0.89 (0.62)	1.07 (0.67)
Age, y	55.9 (8.9)	56.2 (9.1)	56.6 (9.2)	56.0 (9.1)	55.9 (9.0)
Initial BMI	25.6 (3.1)	25.2 (3.0)	24.9 (2.9)	25.2 (2.9)	25.6 (3.2)
Weight change, kg	0.23 (3.8)	0.54 (3.4)	0.68 (3.3)	0.95 (3.4)	1.20 (3.6)
Initial physical activity, MET-h/wk	19.6 (29.3)	22.3 (30.6)	24.3 (30.9)	22.4 (32.8)	19.1 (26.3)
Changes in physical activity, MET-h/wk	−0.8 (33.5)	−0.4 (32.4)	−0.8 (32.0)	−1.3 (33.2)	−0.9 (34.0)
Initial alcohol intake, g/d	12.3 (16.0)	11.8 (15.2)	10.2 (13.8)	12.0 (15.6)	12.3 (16.3)
Changes in alcohol intake, g/d	−1.8 (9.7)	−1.5 (9.2)	−1.0 (8.5)	−1.1 (9.0)	−0.7 (10.1)
White race, %	96.0	95.9	95.3	96.4	95.7
Marital status, with spouse, %	89.2	89.7	89.6	89.6	88.5
Current smoker, %	7.8	6.7	5.9	8.1	11.1
Hypertension, %	16.6	15.7	14.3	14.8	15.1
High cholesterol, %	25.0	20.6	19.6	16.4	15.6
Family history of T2DM, %	21.3	20.3	20.6	20.1	20.9
Total energy intake, kcal/d	2251 (603)	2004 (571)	1858 (558)	1914 (571)	2009 (592)
Change in total energy intake, kcal/d	−361 (488)	−158 (440)	−47 (438)	61 (439)	278 (504)
AHEI score	46.6 (9.5)	49.2 (9.9)	51.8 (10.5)	50.1 (10.5)	47.8 (10.2)
Change in AHEI score	2.2 (8.4)	0.5 (8.1)	−0.3 (8.0)	−1.0 (8.1)	−1.5 (8.2)
Nurses' Health Study					
No. of participants	11 401	10 965	12 841	8450	5052
Initial red meat intake, servings per day	1.70 (0.69)	1.04 (0.49)	0.71 (0.49)	0.77 (0.48)	0.87 (0.49)
Age, y	55.6 (7.1)	55.8 (7.1)	56.3 (7.0)	56.0 (7.1)	55.4 (7.1)
Initial BMI	25.2 (4.8)	24.9 (4.4)	24.6 (4.3)	24.9 (4.4)	25.4 (4.8)
Weight change, kg	0.6 (5.0)	1.0 (4.5)	1.2 (4.5)	1.5 (4.5)	1.9 (4.9)
Initial physical activity, MET-h/wk	12.9 (18.3)	14.1 (20.1)	15.8 (22.8)	15.0 (22.3)	13.1 (18.2)
Changes in physical activity, MET-h/wk	1.5 (15.2)	1.5 (15.5)	1.3 (16.3)	1.1 (15.9)	1.2 (15.6)
Initial alcohol intake, g/d	6.5 (11.0)	6.3 (10.4)	6.3 (10.5)	6.4 (10.7)	6.5 (11.5)
Changes in alcohol intake, g/d	−1.4 (6.7)	−1.1 (6.2)	−1.0 (6.4)	−0.9 (6.4)	−0.6 (6.6)
White race, %	98.2	98.1	98.2	98.5	98.0
Marital status, with spouse, %	94.8	94.4	93.4	94.4	94.9
Current smoker, %	17.2	15.7	14.1	16.5	19.6
Hypertension, %	22.4	21.9	21.7	22.6	24.1
High cholesterol, %	35.8	35.5	33.9	30.9	28.8
Family history of T2DM, %	29.0	27.9	28.0	28.3	29.0
Menopausal status and postmenopausal hormone use, %					
Premenopausal	32.1	31.1	28.6	30.5	33.5
Postmenopausal + never users	27.5	27.3	27.7	26.9	26.4
Postmenopausal + past users	13.5	13.8	14.5	14.0	13.2
Postmenopausal + current users	24.8	25.9	27.3	26.7	24.5
Missing information	2.2	1.8	2.0	1.9	2.4
Total energy intake, kcal/d	1990 (519)	1759 (492)	1646 (488)	1678 (493)	1750 (506)
Change in total energy intake, kcal/d	−273 (442)	−80 (396)	26 (390)	137 (398)	320 (443)
AHEI score	45.6 (9.4)	47.7 (9.8)	49.6 (10.2)	48.2 (10.1)	46.9 (9.8)
Change in AHEI score	1.8 (8.6)	0.7 (8.3)	−0.3 (8.0)	−0.8 (8.1)	−1.5 (8.4)
Nurses' Health Study II					
No. of participants	16 532	18 900	21 667	10 954	6024
Initial red meat intake, servings per day	1.61 (0.66)	0.92 (0.45)	0.60 (0.63)	0.69 (0.47)	0.78 (0.48)
Age, y	40.1 (4.6)	40.3 (4.6)	40.3 (4.6)	40.0 (4.7)	39.8 (4.7)

(continued)

Table 1. Characteristics According to Baseline 4-Year Changes in Total Red Meat Intake (continued)

Variable	Changes in Frequency of Red Meat Consumption (Categories in Servings per Day)[a]				
	Decrease		No Change or Relatively Stable (±0.14)	Increase	
	Moderate to Large (>0.50)	Small to Moderate (0.15-0.50)		Small to Moderate (0.15-0.50)	Moderate to Large (>0.50)
Initial BMI	25.0 (5.4)	24.3 (4.9)	23.9 (4.7)	24.4 (5.1)	25.2 (5.6)
Weight change, kg	2.6 (6.1)	2.9 (5.8)	3.2 (5.7)	3.9 (6.0)	4.7 (6.8)
Initial physical activity, MET-h/wk	18.6 (24.0)	20.2 (25.6)	23.5 (30.6)	20.3 (26.5)	18.9 (24.9)
Changes in physical activity, MET-h/wk	−1.1 (20.8)	−1.7 (21.1)	−2.8 (23.2)	−2.5 (21.8)	−3.1 (21.3)
Initial alcohol intake, g/d	3.0 (6.0)	3.2 (6.0)	3.2 (6.0)	3.2 (6.1)	3.0 (6.2)
Changes in alcohol intake, g/d	0.2 (4.4)	0.3 (4.4)	0.5 (4.5)	0.5 (4.6)	0.5 (4.9)
White race, %	96.9	97.3	96.9	96.9	96.4
Marital status, with spouse, %	86.8	85.9	81.6	83.5	83.2
Current smoker, %	11.4	10.0	9.2	10.6	13.2
Hypertension, %	9.5	8.1	8.1	9.1	10.4
High cholesterol, %	21.3	19.7	19.3	21.3	23.3
Family history of T2DM, %	36.5	34.9	33.4	34.2	36.1
Menopausal status and postmenopausal hormone use, %					
Premenopausal	90.9	91.6	91.3	91.0	90.3
Postmenopausal + never users	0.5	0.4	0.5	0.4	0.5
Postmenopausal + past users	0.7	0.7	0.7	0.9	0.8
Postmenopausal + current users	5.9	5.4	5.4	5.7	6.3
Missing information	2.1	2.0	2.0	2.0	2.1
Total energy intake, kcal/d	2045 (537)	1773 (503)	1659 (508)	1674 (504)	1730 (512)
Change in total energy intake, kcal/d	−255 (481)	−46 (432)	69 (439)	236 (441)	476 (488)
AHEI score	41.7 (8.8)	44.0 (9.1)	46.1 (9.7)	44.4 (9.5)	43.3 (9.4)
Change in AHEI score	1.9 (7.9)	0.6 (7.8)	−0.2 (7.9)	−0.6 (7.9)	−1.6 (8.0)

Abbreviations: AHEI, Alternate Healthy Eating Index; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MET, metabolic equivalent of task; T2DM, type 2 diabetes mellitus.

[a] Values are presented as mean (SD) unless noted otherwise.

0.93) and 10% (pooled HR, 0.90; 95% CI, 0.83-0.97) lower risk before and after adjustment for initial BMI plus concurrent weight gain, respectively (**Table 3**).

The **Figure** and eTable 2 (in Supplement) show results based on the initial and subsequent 4-year intake of red meat. Compared with stable low-level consumers (<2 servings per week; reference group), individuals who increased their red meat intake from low to high levels had an almost 2-fold risk (pooled HR, 1.99; 95% CI, 1.53-2.58). The pooled HR was 1.37 (95% CI, 1.22-1.53) for stable, moderate-level consumers; rose to 1.87 (1.65-2.12) for those who increased their intake from moderate to high levels; and decreased to 1.19 (1.02-1.38) in individuals who reduced their intake from moderate to low levels. Compared with the reference group, the pooled HR was 2.10 (95% CI, 1.87-2.37) for stable high-level consumers and decreased to 1.69 (1.49-1.92) and 1.78 (1.40-2.27) for those who reduced intake from high to moderate or low levels 4 years later, respectively. All estimates were attenuated after adjustment for initial BMI and concurrent weight changes (eTable 2 in Supplement).

We observed a significant interaction between initial BMI and changes in red meat intake in relation to the risk of T2DM (eTable 3 in Supplement). Compared with stable consumption, increasing intake of more than 0.50 servings per day within a 4-year period was associated with a 65% (pooled HR, 1.65; 95% CI, 1.48-1.84) elevated risk of developing T2DM in the subsequent 4-year interval among nonobese individuals, while the corresponding pooled HR was 1.14 (95% CI, 1.02-1.27) among obese individuals.

The results were robust in various sensitivity analyses: compared with stable red meat consumption, the pooled HR was 1.38 (95% CI, 1.28-1.49) for increasing red meat intake more than 0.50 servings per day within a 4-year period when we stopped updating dietary information after self-reported cardiovascular disease or cancer (eTable 4 in Supplement), 1.45 (95% CI, 1.34-1.57) when we censored participants without dietary information during follow-up (eTable 5 in Supplement), and 1.41 (95% CI, 1.30-1.52) when we used the multiple imputation method for the missing data during the follow-up (eTable 6 in Supplement). Again, all estimates were modestly attenuated after adjustment for initial BMI and concurrent weight changes.

Discussion

In these 3 large prospective cohorts of US men and women, 4-year increases in red meat consumption were positively associated with subsequent 4-year risk of T2DM, independent of initial red meat intake and changes in other lifestyle factors, including overall diet quality and body weight. This association was observed for unprocessed and processed red meat. Decreasing red meat intake was not associated with an acute but rather a prolonged reduced risk of T2DM.

Table 2. Type 2 Diabetes Mellitus According to Updated 4-Year Changes in Total Red Meat Intake[a]

Variable	Changes in Frequency of Red Meat Consumption (Categories in Servings per Day)[b]					P Value for Trend[c]
	Decrease		No Change or Relatively Stable (±0.14)	Increase		
	Moderate to Large (>0.50)	Small to Moderate (0.15-0.50)		Small to Moderate (0.15-0.50)	Moderate to Large (>0.50)	
HPFS						
Cases/person-years	336/69 097	255/74 221	458/133 862	248/60 190	264/44 372	
Multivariate model 1[d]	1.06 (0.89-1.27)	0.92 (0.78-1.09)	1 [Reference]	1.21 (1.03-1.43)	1.59 (1.34-1.88)	<.001
Multivariate model 2[e]	1.08 (0.90-1.29)	0.94 (0.80-1.12)	1 [Reference]	1.20 (1.01-1.41)	1.48 (1.25-1.75)	.001
NHS						
Cases/person-years	658/128 173	770/168 022	1061/246 411	587/117 130	406/62 021	
Multivariate model 1[d]	0.90 (0.80-1.01)	0.96 (0.87-1.06)	1 [Reference]	1.16 (1.05-1.28)	1.36 (1.21-1.53)	<.001
Multivariate model 2[e]	0.95 (0.84-1.07)	0.98 (0.89-1.08)	1 [Reference]	1.10 (0.99-1.21)	1.22 (1.08-1.38)	<.001
NHS II						
Cases/person-years	466/141 889	433/179 136	682/296 201	452/146 734	464/98 366	
Multivariate model 1[d]	1.00 (0.87-1.15)	0.98 (0.86-1.11)	1 [Reference]	1.30 (1.15-1.47)	1.55 (1.37-1.76)	<.001
Multivariate model 2[e]	1.04 (0.90-1.19)	0.98 (0.86-1.11)	1 [Reference]	1.20 (1.06-1.36)	1.31 (1.16-1.49)	<.001
Pooled[f]						
Multivariate model 1[d]	0.96 (0.89-1.04)	0.96 (0.89-1.03)	1 [Reference]	1.21 (1.13-1.30)	1.48 (1.37-1.59)	<.001
Multivariate model 2[e]	1.00 (0.92-1.09)	0.97 (0.91-1.04)	1 [Reference]	1.15 (1.07-1.23)	1.30 (1.21-1.41)	<.001

Abbreviations: HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; NHS II, Nurses' Health Study II; T2DM, type 2 diabetes mellitus.

[a] Data are based on 20 years of follow-up (1986-2006) in the HPFS, 20 years of follow-up (1986-2006) in the NHS, and 16 years of follow-up (1991-2007) in the NHS II. The exposure was change in red meat intake in each 4-year period, and the outcome was the incidence of T2DM in the subsequent 4 years.

[b] Values are presented as hazard ratios (95% CI) unless noted otherwise.

[c] *P* value for trend was derived from tests of linear trend across categories of changes in red meat consumption by treating the median value of each category as a continuous variable.

[d] Adjusted for age, initial red meat intake (quintiles), race (white or nonwhite), marital status (with spouse, yes or no), family history of T2DM (yes or no), history of hypertension (yes or no), history of hypercholesterolemia (yes or no), and simultaneous changes in other lifestyle factors: smoking status (never to never, never to current, past to past, past to current, current to past, current to current, or missing indicator) and initial and changes (all in quintiles) in alcohol intake, physical activity, total energy intake, and diet quality (Alternative Healthy Eating Index). In the NHS and NHS II, postmenopausal status and menopausal hormone use were also included.

[e] Model 1 plus initial body mass index (calculated as weight in kilograms divided by height in meters squared) (<23, 23-24.9, 25-29.9, 30-34.9, and ≥35) and weight change (quintiles) during the 4-year period.

[f] The results across the 3 cohorts were pooled using an inverse variance–weighted, fixed-effect meta-analysis.

Three meta-analyses of prospective cohort studies have reported a positive association between red meat intake and T2DM.[1-3] However, most previous studies evaluated the relationship between meat intake at baseline and T2DM risk with limited information during follow-up. Because individuals' eating behaviors may change over time,[4] a single time measurement may not capture the variability of red meat intake during follow-up. To our knowledge, this study is the first to investigate the association between changes in red meat intake and subsequent T2DM risk. Our results are largely consistent with previous reports but extend the findings to suggest that increasing red meat intake is followed by an elevated risk of T2DM in a short-term (4 years) and long-term (12-16 years) period.

Our previous analysis[3] in the 3 cohorts found that red meat intake was associated with an increased risk of T2DM. However, that analysis did not consider changes in red meat intake. An important finding from our analysis is that both initial (data not shown, but results were similar to our previous study[3]) and changes in red meat intake were independently related to an elevated risk of T2DM. Joint analysis of initial and subsequent 4-year intake of red meat confirmed that consistent high intake was related to a greater risk of T2DM compared with a consistent low level, and this risk rose quickly and substantially (almost 2-fold) when increasing intake from low to high levels. Changing from high to low levels did not completely mitigate the increased risk within 4 years for people with initial high red meat intake; however, the analysis of change during the first 4 years in relation to T2DM during the entire follow-up period suggests that reducing red meat intake still has a long-term benefit. The absence of a short-term reduction in the risk of T2DM may be the result of higher-risk patients (those with lipid disorders, hypertension, or other cardiometabolic risk factors) being most likely to be counseled by their health care providers to reduce red meat consumption.

In the current study, adjustment for BMI modestly attenuated the association between red meat intake and T2DM risk, which suggests that it may be partly mediated through obesity and weight gain. In the 3 Harvard cohorts[5] and a large European cohort,[15] red meat intake was positively associated with future risk of weight gain. Furthermore, we observed a significant interaction with initial BMI, and the association was much stronger among nonobese compared with obese people. This is consistent with the recent EPIC-InterAct study in European populations,[16] although that study used only baseline information. It is possible that obese individuals are already at a high risk of T2DM because of their body weight and higher initial red meat intake (data not shown), and increasing red meat intake has only a modestly deleterious effect on the relative scale. However, the absolute risk associated with red meat intake among obese individuals is much greater, and thus limiting their red meat intake is still beneficial.

Table 3. Type 2 Diabetes Mellitus During 12 (NHS II) and 16 Years (NHS and HPFS) of Follow-up, According to Initial 4-Year Changes in Total Red Meat Categories[a]

Variable	Changes in Frequency of Red Meat Consumption (Categories in Servings per Day)[b]					*P* Value for Trend[c]
	Decrease		No Change or Relatively Stable (±0.14)	Increase		
	Moderate to Large (>0.50)	Small to Moderate (0.15-0.50)		Small to Moderate (0.15-0.50)	Moderate to Large (>0.50)	
HPFS						
Cases/person-years	410/88 993	320/79 063	326/98 626	277/64 893	274/50 940	
Multivariate model 1[d]	0.91 (0.77-1.09)	1.06 (0.90-1.24)	1 [Reference]	1.24 (1.05-1.47)	1.40 (1.17-1.66)	<.001
Multivariate model 2[e]	0.94 (0.78-1.11)	1.06 (0.90-1.25)	1 [Reference]	1.22 (1.03-1.44)	1.30 (1.09-1.55)	<.001
NHS						
Cases/person-years	894/168 326	769/162 814	840/191 145	585/125 816	455/73 919	
Multivariate model 1[d]	0.82 (0.73-0.91)	0.92 (0.83-1.01)	1 [Reference]	1.03 (0.92-1.14)	1.25 (1.11-1.41)	<.001
Multivariate model 2[e]	0.86 (0.77-0.97)	0.91 (0.83-1.01)	1 [Reference]	0.98 (0.88-1.09)	1.12 (1.00-1.27)	.002
NHS II						
Cases/person-years	658/191 832	579/220 505	592/253 202	397/127 237	303/69 634	
Multivariate model 1[d]	0.90 (0.79-1.03)	0.95 (0.84-1.07)	1 [Reference]	1.21 (1.06-1.38)	1.34 (1.16-1.55)	<.001
Multivariate model 2[e]	0.93 (0.82-1.07)	0.97 (0.86-1.09)	1 [Reference]	1.12 (0.99-1.28)	1.16 (1.01-1.34)	.01
Pooled[f]						
Multivariate model 1[d]	0.86 (0.80-0.93)	0.95 (0.89-1.02)	1 [Reference]	1.13 (1.05-1.21)	1.31 (1.21-1.42)	<.001
Multivariate model 2[e]	0.90 (0.83-0.97)	0.96 (0.89-1.03)	1 [Reference]	1.07 (0.99-1.15)	1.17 (1.08-1.27)	<.001

Abbreviations: See Table 2.

[a] Data are based on 20 years of follow-up (1986-2006) in the HPFS, 20 years of follow-up (1986-2006) in the NHS, and 16 years of follow-up (1991-2007) in the NHS II. The exposure was change in red meat intake in the baseline 4-year period (1986-1990 in the HPFS and NHS, and 1991-1995 in the NHS II), and the outcome was the incidence of T2DM in the subsequent follow-up years (1990-2006 in the HPFS and NHS, and 1995-2007 in the NHS II).

[b] Values are presented as hazard ratios (95% CI) unless noted otherwise.

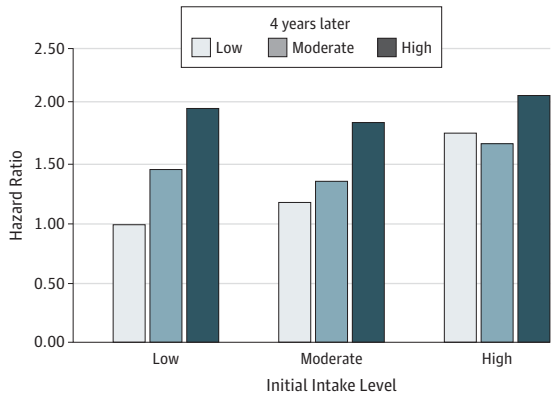
[c] See footnote c in Table 2.

[d] See footnote d in Table 2.

[e] See footnote e in Table 2.

[f] See footnote f in Table 2.

Figure. Hazard Ratios of Type 2 Diabetes According to Updated 4-Year Changes in Total Red Meat Intake



Low intake level was defined as less than 2 servings per week; moderate intake, 2 to 6 servings per week; and high intake, 7 or more servings per week. The reference group (hazard ratio, 1.00) was the low intake level at both the initial and the 4-year follow-up visits. The results across the 3 cohorts were pooled using an inverse variance–weighted, fixed-effect meta-analysis. See the Statistical Analysis section for an explanation of the analysis.

Since our study is observational in nature, causality cannot be inferred. Randomized clinical trials may better address the causal relationship between red meat and T2DM but may not be feasible. Our "change-to-risk" analysis capitalizes on repeated measurements and long-term follow-up. Our analysis approach is, to some extent, a natural experiment, in which individuals choose to change their diet and lifestyles without investigator-initiated interventions, and thus the results may be more externally generalizable to the real world compared with a well-controlled laboratory setting. We do not know the underlying reasons why people increased or decreased their red meat intake. Some people may decrease intake because of health concerns, particularly if they are at high risk of cardiovascular disease. This may explain the lack of association between reduced red meat intake and T2DM risk in the subsequent 4 years. The analysis using the initial 4-year change in red meat intake as the exposure, however, showed a significantly decreased risk during the subsequent long-term follow-up, suggesting that it may take longer for the benefits of reducing red meat intake to manifest.

The strengths of the current study include a large sample size, high follow-up rates, and repeated assessments of dietary and lifestyle variables during a long period. Therefore, our cohorts are among the few studies able to investigate changes in red meat intake and subsequent risk of T2DM. The consistency of the results across all 3 cohorts indicates that our findings are unlikely due to chance.

We are also aware of several limitations. First, our study populations primarily consisted of white educated US adults. Although the homogeneity of socioeconomic status helps reduce confounding, it may potentially limit generalizability. Second, some measurement errors in dietary assessment are inevitable. However, in a prospective study design, measurement errors are more likely to attenuate associations toward the null. Third, the FFQs were administered every 4 years, and we do not know exactly when the changes in red meat intake occurred within that 4-year period. Last, changes in red meat intake may be a marker of lifestyle changes, but we have simultaneously adjusted for initial and

changes in multiple diet and lifestyle factors, and the previous analysis[5] suggested a modest correlation among changes in different dietary and behavioral factors. However, residual and unmeasured confounding from other lifestyle behaviors is still possible.

In conclusion, in these 3 cohorts of US adults, increases in red meat intake within a 4-year period were associated with a higher risk of T2DM in the subsequent 4-year interval. In addition, a reduction in red meat intake was associated with a lower incidence of T2DM during a subsequent long-term follow-up. Our results confirm the robustness of the association between red meat and T2DM and add further evidence that limiting red meat consumption over time confers benefits for T2DM prevention.

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Invited Commentary

Oxygen-Carrying Proteins in Meat and Risk of Diabetes Mellitus

William J. Evans, PhD

The article by Pan et al[1] confirms previous observations that the consumption of so-called red meat is associated with an increased risk of type 2 diabetes mellitus (T2DM). While previous studies have been cross-sectional in nature, the present study demonstrated that a relatively short-term (4-year) increase in red meat consumption is associated with subsequent risk, even in individuals who initially consumed low amounts of red meat. The authors demonstrated that consuming more red meat is also associated with weight gain, and a statistical adjustment for change in body weight attenuates but does not eliminate the risk, indicating that increased weight is not the only cause of a greater risk of T2DM associated with red meat consumption. The data in this article are valuable for those considering strategies to decrease the risk of developing T2DM.

The designation of meat according to its "redness" does not provide an adequate description of the category of meat exam-