Original Investigation

Association of Specific Dietary Fats With Total and Cause-Specific Mortality

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IMPORTANCE Previous studies have shown distinct associations between specific dietary fat and cardiovascular disease. However, evidence on specific dietary fat and mortality remains limited and inconsistent.

OBJECTIVE To examine the associations of specific dietary fats with total and cause-specific mortality in 2 large ongoing cohort studies.

DESIGN, SETTING, AND PARTICIPANTS This cohort study investigated 83 349 women from the Nurses' Health Study (July 1, 1980, to June 30, 2012) and 42 884 men from the Health Professionals Follow-up Study (February 1, 1986, to January 31, 2012) who were free of cardiovascular disease, cancer, and types 1 and 2 diabetes at baseline. Dietary fat intake was assessed at baseline and updated every 2 to 4 years. Information on mortality was obtained from systematic searches of the vital records of states and the National Death Index, supplemented by reports from family members or postal authorities. Data were analyzed from September 18, 2014, to March 27, 2016.

MAIN OUTCOMES AND MEASURES Total and cause-specific mortality.

RESULTS During 3 439 954 person-years of follow-up, 33 304 deaths were documented. After adjustment for known and suspected risk factors, dietary total fat compared with total carbohydrates was inversely associated with total mortality (hazard ratio [HR] comparing extreme quintiles, 0.84; 95% CI, 0.81-0.88; $P < .001$ for trend). The HRs of total mortality comparing extreme quintiles of specific dietary fats were 1.08 (95% CI, 1.03-1.14) for saturated fat, 0.81 (95% CI, 0.78-0.84) for polyunsaturated fatty acid (PUFA), 0.89 (95% CI, 0.84-0.94) for monounsaturated fatty acid (MUFA), and 1.13 (95% CI, 1.07-1.18) for *trans*-fat ($P < .001$ for trend for all). Replacing 5% of energy from saturated fats with equivalent energy from PUFA and MUFA was associated with estimated reductions in total mortality of 27% (HR, 0.73; 95% CI, 0.70-0.77) and 13% (HR, 0.87; 95% CI, 0.82-0.93), respectively. The HR for total mortality comparing extreme quintiles of ω-6 PUFA intake was 0.85 (95% CI, 0.81-0.89; $P < .001$ for trend). Intake of ω-6 PUFA, especially linoleic acid, was inversely associated with mortality owing to most major causes, whereas marine ω-3 PUFA intake was associated with a modestly lower total mortality (HR comparing extreme quintiles, 0.96; 95% CI, 0.93-1.00; $P = .002$ for trend).

CONCLUSIONS AND RELEVANCE Different types of dietary fats have divergent associations with total and cause-specific mortality. These findings support current dietary recommendations to replace saturated fat and *trans*-fat with unsaturated fats.

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Health effects of different types of dietary fats have been a long-standing research topic of interest for decades.[1] Vast literature clearly indicates that specific types of dietary fat have distinct effects on the risk for cardiovascular disease (CVD), and replacing saturated fats with unsaturated fats and avoidance of *trans*-fat is widely recommended.[1-4] However, a recent meta-analysis[5] concluded that dietary polyunsaturated fatty acids (PUFAs) or saturated fatty acids (SFAs) had no significant associations with the risk for coronary heart disease (CHD), but failed to specify the macronutrient to which saturated fat was compared; by default this component consists largely of refined starch and sugar in Western diets.[6,7] In addition, existing evidence, especially from relatively small clinical trials, regarding the effects of ω-3 PUFAs on total and cause-specific mortality remains inconsistent.[8,9] The health benefits of ω-6 PUFA intake are still contentious; concern has been raised over the hypothesized proinflammatory and prothrombotic effects of ω-6 PUFA.[10] The evidence of an association of industrially produced *trans*-fatty acids (TFAs) and the risk for CHD is well established,[11] although little data are available on TFA intake and mortality.

Numerous controlled metabolic trials have documented the effects of dietary fatty acids on blood lipid levels.[3,12] However, these fatty acids also influence other mechanistic pathways such as insulin resistance, endothelial function, electrophysiologic phenomena, carcinogenesis, and systemic inflammation.[9,13,14] In addition to CVD, various dietary fatty acids have been associated with incidence of other major chronic diseases, including type 2 diabetes, cancer, multiple sclerosis, and respiratory diseases, in prospective cohort studies.[15-18] To address the role of dietary fats in overall health, analysis of total and cause-specific mortality as outcomes would be informative. Therefore, we prospectively examined the associations of specific dietary fats with total and cause-specific mortality in 2 large ongoing prospective cohort studies, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). The many repeated dietary assessments in the cohorts provided a unique assessment of diet during multiple decades. Also, these assessments allowed us to estimate the consequences of isocalorically replacing one type of fat with another, thus describing the choices we make on a daily basis and providing a basis for dietary guidelines.

Key Points

Question What are the long-term associations between dietary intake of specific fats and mortality?

Findings In this cohort study that included 126 233 participants followed up for as long as 32 years, higher intakes of saturated fat and *trans*-fat were associated with increased mortality, whereas higher intakes of polyunsaturated (PUFA) and monounsaturated (MUFA) fatty acids were associated with lower mortality. Replacing 5% of energy from saturated fats with equivalent energy from PUFA and MUFA was associated with reductions in total mortality of 27% and 13%, respectively.

Meaning These findings support current dietary recommendations to replace saturated fat and *trans*-fat with unsaturated fat.

Methods

Study Population

The NHS is a prospective cohort study of 121 700 registered female nurses aged 30 to 55 years in 1976; 92 468 participants responded to the semiquantitative food frequency questionnaire (SFFQ) in 1980. The HPFS is a prospective cohort study of 51 529 male health care professionals aged 40 to 75 years in 1986. The baseline of this analysis was defined as 1980 for the NHS and 1986 for the HPFS. Both cohorts have been followed up via biennial mailed questionnaires that inquire about lifestyle risk factors and other exposures of interest, as well as newly diagnosed diseases. We also collected information on race, marital status, and family history of major chronic diseases. The cumulative follow-up of both cohorts exceeds 90% of potential person-time. The study was approved by the human research committees at the Harvard T. H. Chan School of Public Health and the Brigham and Women's Hospital. The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and the Harvard School of Public Health, with participants' consent implied by the return of the questionnaires.

We excluded participants who had a history of diabetes, CVD, or cancer; who did not provide information on dietary fat intake; or who reported implausible SFFQ data (total energy intake <800 or >4200 kcal/d for men and <600 or >3500 kcal/d for women) at baseline (eTable 1 in the Supplement). After exclusions, the analytical population consisted of 83 349 women and 42 884 men.

Dietary Assessment

Dietary information was collected with SFFQs.[19,20] In each SFFQ, we asked how often, on average, the participant had consumed a specified portion size of each food during the preceding year. The number of listed foods was 61 in 1980 and was expanded to 116 to 150 in 1984 and thereafter; additional frequently used foods were reported in an open-ended section. We also collected detailed information on the type of fat or oil used in food preparation and the brand or type of margarines on the SFFQ. Fatty acid and other nutrient values were calculated based on the Harvard University Food Composition Table,[21] which is updated regularly using external publications and direct analysis of fatty acids in commonly used margarines and processed foods to take into account changes in manufacturing. We calculated mean daily nutrient and total energy intakes by multiplying the frequency of consumption of each item by its nutrient content and summing the products across all foods, taking into account the specific brand and type of margarines and the types of fat used in food preparation. The assessment of specific types of fat has been validated by comparison with multiple weighed 1-week dietary records and with fatty acid measurements in adipose tissue and plasma.[19,20,22-24]

The correlations between energy-adjusted intakes assessed by the 1986 questionnaire and the mean of diet records collected in 1980 and 1986, corrected for variation in the records, were 0.67 for total fat, 0.70 for SFAs, 0.69 for monounsaturated fatty acids (MUFAs), and 0.64 for PUFAs.[19,20] Correlations increased when the mean of 3 SFFQs (1980, 1984, and 1986) was used; for example, for SFAs the correlation was 0.95.[19,20] The correlations between dietary fatty acid intake assessed by the SFFQ and the composition of fatty acids in adipose tissue were 0.51 for TFAs, 0.35 for linoleic acid, and 0.48 for marine ω-3 PUFAs in women,[22] and 0.29 for TFAs, 0.48 for linoleic acid, and 0.47 for eicosapentaenoic acid in men. Alcohol intake was also estimated from the SFFQs.

In the NHS, dietary questionnaires used in this analysis were completed in 1980, 1984, 1986, and then every 4 years, for a total of 9 assessments. In the HPFS, dietary questionnaires were completed in 1986 and then every 4 years for a total of 7 assessments.

Ascertainment of Death

We performed systematic searches of the vital records of states and of the National Death Index, supplemented by reports from family members or postal authorities. More than 98% of the deaths in each cohort were identified.[25] A physician reviewed death certificates and medical records to classify the cause of death according to the *International Classification of Diseases, Eighth Revision* and *Ninth Revision* (eTable 2 in the Supplement).

Statistical Analysis

Data were analyzed from September 18, 2014, to March 27, 2016. The percentages of energy intake from total fat and specific dietary fats were calculated as cumulative means to the start of each 2- or 4-year follow-up interval to best represent long-term dietary intake and dampen within-person variation. We categorized participants into quintiles of intake levels. Person-years of follow-up were calculated from baseline to the earliest of time of death, loss to or unavailability for follow-up, or the end of follow-up. The last date of follow-up was defined as June 30, 2012, for the NHS and January 31, 2012, for the HPFS.

Cox proportional hazards regression models were applied to estimate hazard ratios (HRs) and their 95% CIs of mortality by comparing participants in each quintile with those in the lowest quintile. To quantify a linear trend, we assigned the median within each quintile and modeled this variable continuously; the Wald test was used for statistical significance. In addition to including percentages of energy from total and specific fat as quintiles, we also included them as continuous terms in the multivariable models.

For multivariable analyses, we built isocaloric substitution models that simultaneously included energy intake, the percentages of energy derived from protein, and specific types of fat and other potentially confounding variables. The coefficients from these models can be interpreted as the estimated effect of substituting a certain percentage of energy from fat for equivalent energy from carbohydrates.

For repeatedly measured covariates, we included their updated values as time-varying variables in the model. To minimize missing covariates, we replaced missing data with the last valid values. The covariates had very few missing values after the replacement. In addition, we included missing indicators for the remaining missing covariates in the model.

To evaluate the effect of substituting specific types of fat for saturated fat, we treated intake as a continuous variable and calculated the difference in coefficients. Because we hypothesized that the effects of total and specific ω-3 PUFAs might be more acute, we conducted an additional analysis using the most recent data on ω-3 PUFAs at the beginning of each biennial follow-up.

We conducted sensitivity analyses to test the robustness of our findings. To address concern that chronic disease occurrence in the years that preceded diagnosis may influence dietary behavior, we conducted lagged analyses by excluding the first 4 years of follow-up data and adding a 4-year lag period between assessment of dietary fat intake and each follow-up period. To address the possibility that our findings may be explained by underlying overall dietary pattern, we further adjusted for overall dietary pattern score (the Alternate Healthy Eating Index-2010 score[26] minus component scores for fatty acids). To minimize the influence of hypertension and hypercholesterolemia on our results, we performed additional analysis by excluding participants who reported hypertension and hypercholesterolemia at baseline. An inverse-variance–weighted, fixed-effect meta-analysis was used to combine the results across the cohorts. All analyses were performed using SAS software (version 9.2; SAS Institute Inc), at a 2-tailed *P* value of .05.

Results

Population Characteristics

During 32 years of follow-up in the NHS (2 464 852 person-years), we documented 20 314 deaths; during 26 years of follow-up in the HPFS (975 102 person-years), we documented 12 990 deaths (total, 33 304 deaths in 3 439 954 person-years of follow-up). At baseline, participants with higher SFA and MUFA intakes had higher body mass indexes and higher levels of total energy and dietary cholesterol intake, but were less likely to be physically active, to use multivitamin and vitamin E supplements, and to report histories of hypercholesterolemia and hypertension (**Table 1**). The prevalence of current smoking was higher among men with higher SFA and MUFA intakes. Women with higher intakes of SFA, PUFA, and MUFA were generally older.

Total Mortality

Although total fat intake was positively associated with total mortality in age-adjusted models, an inverse association became apparent after adjusting for other potential confounding variables ($P < .001$ for trend) (**Table 2** and eTable 3 in the Supplement). When substituted for total carbohydrates, a higher intake of SFA was associated with a slightly higher total mortality (HR comparing extreme quintiles, 1.08; 95% CI,

Table 1. Age-Adjusted Characteristics of Men and Women Across Quintiles of Fatty Acid Intake at Baseline[a]

	Quintile of Saturated Fat Intake			Quintile of Polyunsaturated Fat Intake			Quintile of Monounsaturated Fat Intake		
Characteristic	1	3	5	1	3	5	1	3	5
NHS (1980)									
Fatty acid intake, % of energy	8.0	11.9	17.9	3.8	5.6	7.9	8.9	12.9	18.7
Age, y	48.2	46.5	45.9	47.2	45.8	45.1	47.9	46.3	45.8
BMI	23.6	24.2	24.4	24.2	24.4	24.3	23.9	24.2	24.4
Alcohol intake, g/d	10.0	8.0	5.4	8.3	5.4	4.5	9.4	7.6	5.4
Total energy intake, kcal/d	1380	1467	1631	1553	1591	1552	1410	1495	1633
Protein intake, % of energy	18.1	18.6	19.4	19.5	19.0	18.1	19.2	18.6	19.4
Carbohydrate intake, % of energy	53.6	45.8	34.7	40.4	38.1	37.3	51.4	44.6	34.0
Cholesterol intake, mg/d	218	275	360	322	337	308	246	290	360
Physical activity, MET-h/wk	17.9	15.5	13.1	15.2	13.5	12.2	18.5	14.9	12.8
Current smoking, %	26.7	26.6	29.7	30.0	27.1	29.4	26.5	27.4	29.5
Premenopausal, %	55.2	55.9	56.3	55.8	56.2	56.5	55.0	56.4	56.1
Current menopausal hormone use, %	8.4	8.2	8.3	8.5	8.5	7.9	8.6	8.3	8.4
Multivitamin use, %	65.4	59.8	58.3	59.9	57.6	58.4	64.2	58.5	57.9
Aspirin use, %	42.3	46.4	47.4	45.7	47.4	47.9	43.1	46.8	47.3
Vitamin E use, %	86.3	82.7	80.0	81.1	81.4	82.3	85.6	81.7	80.5
Family history, %									
Myocardial infarction	8.4	8.9	8.8	8.6	9.3	8.8	8.5	8.7	8.9
Diabetes	27.3	28.1	28.5	27.9	28.5	28.2	27.6	26.3	28.9
Cancer	15.1	13.9	14.0	14.0	14.3	13.9	14.6	14.2	14.1
Hypercholesterolemia, %	8.3	5.6	4.5	5.2	5.3	5.9	7.0	5.0	4.8
Hypertension, %	17.0	16.3	14.9	16.5	15.5	14.0	17.3	15.6	15.1
HPFS (1986)									
Fatty acid intake, % of energy	6.8	10.3	14.2	4.1	5.8	8.1	8.4	12.1	15.7
Age, y	54.2	53.1	52.5	53.6	52.8	53.1	53.7	52.8	53.1
BMI	24.5	25.4	26.0	25.3	25.5	25.5	24.8	25.5	26.0
Alcohol intake, g/d	14.5	12.4	8.7	14.7	11.1	9.0	14.5	12.0	8.1
Total energy intake, kcal/d	1878	1986	2068	1983	2008	1978	1873	2000	2088
Protein intake, % of energy	18.2	18.4	18.8	18.1	18.7	18.5	18.4	18.4	18.8
Carbohydrate intake, % of energy	55.6	47.7	41.4	50.4	46.6	43.4	54.9	46.9	40.0
Cholesterol intake, mg/d	212	287	366	286	311	298	226	303	362
Physical activity, MET-h/wk	29.4	21.5	17.1	22.5	21.2	20.4	27.7	21.1	16.7
Current smoking, %	5.6	8.4	13.7	11.3	9.1	8.7	6.7	9.7	13.2
Multivitamin use, %	69.7	63.1	57.6	62.4	61.8	62.5	68.5	61.7	58.6
Aspirin use, %	26.5	26.7	26.1	26.5	26.6	27.0	26.7	26.4	26.7
Vitamin E use, %	30.2	21.0	16.1	20.4	19.4	22.3	27.2	20.0	16.8
Family history, %									
Myocardial infarction	36.1	31.0	29.7	31.6	31.2	32.6	34.8	31.6	30.8
Diabetes	19.6	19.6	20.8	19.6	20.7	20.9	20.3	19.8	20.5
Cancer	32.7	34.2	33.9	32.7	35.1	35.1	33.6	34.6	34.4
Hypercholesterolemia, %	17.2	10.1	7.0	9.4	10.1	11.6	14.3	9.6	8.2
Hypertension, %	21.3	20.0	18.2	20.0	19.2	19.4	20.9	20.0	18.3

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent tasks; NHS, Nurses' Health Study.

[a] Unless otherwise indicated, data are expressed as means. All variables except age were age standardized.

1.03-1.14; $P < .001$ for trend). For TFA intake, a significant positive association with total mortality was observed (HR comparing extreme quintiles, 1.13; 95% CI, 1.07-1.18; $P < .001$ for trend). Intakes of PUFA and MUFA were inversely associated with total mortality (**Figure 1** and eTable 4 in the Supplement); HRs comparing extreme quintiles were 0.81 (95% CI, 0.78-0.84) for PUFA and 0.89 (95% CI, 0.84-0.94) for MUFA ($P < .001$ for trend for both). The inverse association between total PUFA and mortality was mainly driven by linoleic acid, as illustrated by their high correlation (correlation coefficient, 0.99; eTable 5 in the Supplement). The corresponding HR for linoleic acid intake was 0.82 (95% CI, 0.79-0.86; $P < .001$

Table 2. Associations Between Total and Specific Types of Fat Intake and Total Mortality (Comparison Is Isocaloric Substitution for Total Carbohydrates)

	Quintile of Dietary Fatty Acid Intake					*P* Value for Trend	HR (95% CI)[a]
	1	2	3	4	5		
Total fat intake							
NHS							
Median, % of energy	25.4	30.0	33.2	36.6	42.2	NA	NA
No. of deaths	5852	4625	4069	3386	2382	NA	NA
HPFS							
Median, % of energy	23.8	28.3	31.3	34.2	38.4	NA	NA
No. of deaths	2698	2604	2647	2605	2436	NA	NA
Pooled[b]							
Age-adjusted model	1 [Reference]	1.03 (1.00-1.07)	1.13 (1.09-1.16)	1.19 (1.15-1.23)	1.29 (1.24-1.34)	<.001	1.09 (1.08-1.10)
MV-adjusted model[c]	1 [Reference]	0.95 (0.92-0.99)	0.96 (0.92-0.99)	0.91 (0.88-0.95)	0.84 (0.81-0.88)	<.001	0.95 (0.94-0.96)
Saturated fat intake							
NHS							
Median, % of energy	8.2	10.2	11.8	13.5	16.5	NA	NA
No. of deaths	5660	4729	4217	3376	2332	NA	NA
HPFS							
Median, % of energy	7.1	9.0	10.2	11.5	13.5	NA	NA
No. of deaths	2606	2662	2602	2548	2572	NA	NA
Pooled[b]							
Age-adjusted model	1 [Reference]	1.16 (1.12-1.19)	1.32 (1.27-1.36)	1.45 (1.40-1.50)	1.71 (1.65-1.78)	<.001	1.45 (1.42-1.48)
MV-adjusted model[c]	1 [Reference]	1.04 (1.00-1.08)	1.09 (1.05-1.14)	1.09 (1.04-1.14)	1.08 (1.03-1.14)	<.001	1.08 (1.04-1.11)
Unsaturated fat intake							
NHS							
Median, % of energy	14.2	16.8	18.7	20.6	23.8	NA	NA
No. of deaths	6024	4589	3864	3285	2552	NA	NA
HPFS							
Median, % of energy	13.7	16.3	18.0	19.7	22.3	NA	NA
No. of deaths	2760	2666	2657	2488	2419	NA	NA
Pooled[b]							
Age-adjusted model	1 [Reference]	0.98 (0.95-1.01)	1.02 (0.98-1.05)	1.02 (0.99-1.05)	1.03 (0.99-1.07)	.03	1.02 (1.00-1.04)
MV-adjusted model[c]	1 [Reference]	0.89 (0.86-0.92)	0.85 (0.82-0.88)	0.80 (0.77-0.83)	0.76 (0.72-0.79)	<.001	0.85 (0.83-0.87)
Polyunsaturated fat intake							
NHS							
Median, % energy	4.2	5.0	5.6	6.3	7.5	NA	NA
No. of deaths	4423	4380	3997	3829	3685	NA	NA
HPFS							
Median, % of energy	4.4	5.2	5.8	6.5	7.7	NA	NA
No. of deaths	2872	2633	2513	2545	2427	NA	NA
Pooled[b]							
Age-adjusted model	1 [Reference]	0.91 (0.88-0.94)	0.85 (0.82-0.88)	0.81 (0.78-0.84)	0.73 (0.70-0.75)	<.001	0.62 (0.59-0.65)
MV-adjusted model[c]	1 [Reference]	0.97 (0.94-1.00)	0.91 (0.87-0.94)	0.87 (0.84-0.91)	0.81 (0.78-0.84)	<.001	0.73 (0.69-0.77)
Monounsaturated fat intake							
NHS							
Median, % of energy	9.4	11.4	12.8	14.4	17.2	NA	NA
No. of deaths	6241	4769	3789	3191	2324	NA	NA
HPFS							
Median, % of energy	8.9	10.8	12.1	13.3	15.3	NA	NA
No. of deaths	2748	2637	2622	2598	2385	NA	NA
Pooled[b]							
Age-adjusted model	1 [Reference]	1.05 (1.02-1.08)	1.10 (1.06-1.14)	1.17 (1.13-1.21)	1.22 (1.17-1.26)	<.001	1.16 (1.13-1.19)
MV-adjusted model[c]	1 [Reference]	0.95 (0.92-0.99)	0.93 (0.89-0.97)	0.93 (0.89-0.98)	0.89 (0.84-0.94)	<.001	0.90 (0.87-0.94)

(continued)

Table 2. Associations Between Total and Specific Types of Fat Intake and Total Mortality (Comparison Is Isocaloric Substitution for Total Carbohydrates) (continued)

	Quintile of Dietary Fatty Acid Intake					*P* Value for Trend	HR (95% CI)[a]
	1	2	3	4	5		
Trans-fat intake							
NHS							
Median, % of energy	0.9	1.2	1.5	1.9	2.5	NA	NA
No. of deaths	5747	5158	4268	3099	2042	NA	NA
HPFS							
Median, % of energy	0.7	1.0	1.2	1.4	1.9	NA	NA
No. of deaths	2511	2642	2683	2698	2456	NA	NA
Pooled[b]							
Age-adjusted model	1 [Reference]	1.31 (1.27-1.35)	1.49 (1.44-1.54)	1.63 (1.57-1.69)	1.73 (1.66-1.80)	<.001	2.31 (2.20-2.43)
MV-adjusted model[c]	1 [Reference]	1.11 (1.07-1.15)	1.14 (1.10-1.19)	1.15 (1.10-1.20)	1.13 (1.07-1.18)	<.001	1.16 (1.09-1.24)

Abbreviations: HPFS, Health Professional Follow-up Study; HR, hazard ratio; MV, multivariable; NA, not applicable; NHS, Nurses' Health Study.

[a] Indicates hazard ratio of total mortality of substituting 5% of energy intake from total fatty acids, saturated fatty acids, unsaturated fatty acids, polyunsaturated fatty acids, and monounsaturated fatty acids and 2% of energy from *trans*-fatty acids for the same energy from total carbohydrates.

[b] Results for NHS and HPFS from the multivariable model were combined using the fixed-effects model.

[c] Adjusted for age (in months), white race (yes vs no), marital status (with spouse, yes or no), body mass index (<23.0, 23.0-24.9, 25.0-29.9, 30.0-34.9, or ≥35.0 [calculated as weight in kilograms divided by height in meters squared]), physical activity (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9, or ≥27.0 h of metabolic equivalent tasks per week), smoking status (never, past, current 1-14 cigarettes/d, current 15-24 cigarettes/d, or current ≥25 cigarettes/d), alcohol consumption (women: 0, 0.1-4.9, 5.0-14.9, or ≥15.0 g/d; men: 0, 0.1-4.9, 5.0-29.9, or ≥30.0 g/d), multivitamin use (yes vs no), vitamin E supplement use (yes vs no), current aspirin use (yes vs no), family history of myocardial infarction (yes vs no), family history of diabetes (yes vs no), family history of cancer (yes vs no), history of hypertension (yes vs no), history of hypercholesterolemia (yes vs no), intakes of total energy and dietary cholesterol (quintiles), percentage of energy intake from dietary protein (quintiles), and menopausal status and hormone use in women (premenopausal, postmenopausal never users, postmenopausal past users, or postmenopausal current users). All models, except total fat intake, also included percentages of energy intake from remaining fatty acids (saturated, polyunsaturated, and monounsaturated and *trans*-fatty acids, all in quintiles).

for trend) (**Table 3** and eTable 6 in the Supplement). Intake of total ω-3 PUFA was associated with modestly lower total mortality, which was mainly driven by the inverse association of marine ω-3 PUFAs (docosahexaenoic acid and eicosapentaenoic acid) with total mortality. The HRs comparing extreme quintiles were 0.95 (95% CI, 0.91-0.99; *P* = .03 for trend) for total ω-3 PUFAs and 0.96 (95% CI, 0.93-1.00; *P* = .002 for trend) for marine ω-3 PUFAs. The inverse associations became stronger in continuous analyses and when recent intakes of total and marine ω-3 PUFAs were used (eTable 7 in the Supplement); HRs comparing extreme quintiles were 0.91 (95% CI, 0.87-0.95) and 0.90 (95% CI, 0.87-0.93; *P* < .001 for trend for both) for recent intakes of total and marine ω-3 PUFAs, respectively. The ω-6:ω-3 ratio was not significantly associated with total mortality (*P* = .29 for trend). The associations for total and specific types of fat remained largely unchanged in sensitivity analyses (eTables 8-10 in the Supplement).

Cause-Specific Mortality

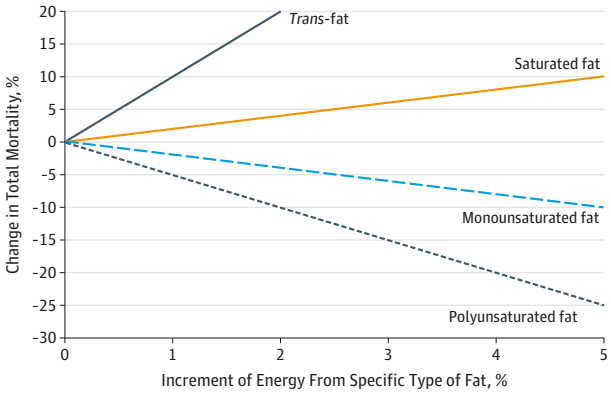
Intake of SFA, when substituted for total carbohydrates, was not significantly associated with CVD mortality (*P* = .17 for trend across quintiles; eTable 11 in the Supplement), whereas TFA intake was associated with a 20% higher CVD mortality across quintiles (HR, 1.20; 95% CI, 1.08-1.33; *P* < .001 for trend). Intake of PUFA was inversely associated with CVD mortality (*P* < .001 for trend). We observed an inverse association, primarily in women, between MUFA intake and CVD mortality (*P* = .01 for trend). Among specific PUFAs, linoleic acid intake was most strongly related to a lower risk for CVD mortality (*P* < .001 for trend) (eTable 12 in the Supplement).

Dietary intake of SFA, when substituted for total carbohydrates, was associated with slightly higher cancer mortality (HR comparing extreme quintiles, 1.07; 95% CI, 0.98-1.17; *P* = .02 for trend), whereas PUFA intake, especially linoleic acid intake, was associated with modestly lower cancer mortality (HR comparing extreme quintiles of PUFA intake, 0.93; 95% CI, 0.87-0.99; *P* = .02 for trend) (eTables 13 and 14 in the Supplement). Other major subclasses of dietary fat generally were not associated with cancer mortality except that α-linolenic acid intake was associated with a slightly elevated risk for cancer mortality (eTables 13 and 14 in the Supplement). However, this association was not significant when recent α-linolenic acid intake was analyzed (eTable 7 in the Supplement). We observed inverse associations of PUFA and MUFA intakes and strong positive associations of TFA intake with neurodegenerative (eTable 15 in the Supplement) and respiratory (eTable 16 in the Supplement) disease mortality. Higher SFA intake was associated with a substantial increase of mortality due to respiratory disease (HR comparing extreme quintiles, 1.56; 95% CI, 1.30-1.87; *P* < .001 for trend). Among major PUFAs, ω-3 PUFA intake, primarily α-linolenic acid, was inversely associated with neurodegenerative disease mortality (eTable 17 in the Supplement). Marine ω-3 PUFA intake was inversely associated with respiratory disease mortality (eTable 18 in the Supplement). Sensitivity analyses minimally changed these results for cause-specific mortality (eTables 8-10 in the Supplement).

Fat Substitution Analysis

Figure 2 shows that replacing 5% of energy from SFAs with the same energy from PUFAs and MUFAs was associated with an

Figure 1. Change in Total Mortality Associated With Increases in the Percentage of Energy From Specific Types of Fat



Multivariable hazard ratios of total mortality associated with replacing the percentage of energy from total carbohydrates by the same energy from specific types of fat ($P < .001$ for trend for all) were used. The model was adjusted for age (in months), white race (yes vs no), marital status (with spouse, yes or no), body mass index (<23.0, 23.0-24.9, 25.0-29.9, 30.0-34.9, or ≥35.0 [calculated as weight in kilograms divided by height in meters squared]), physical activity (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9, or ≥27.0 h of metabolic equivalent tasks per week), smoking status (never, past, current 1-14 cigarettes/d, current 15-24 cigarettes/d, or current ≥25 cigarettes/d), alcohol consumption (women: 0, 0.1-4.9, 5.0-14.9, or ≥15.0 g/d; men: 0, 0.1-4.9, 5.0-29.9, or ≥30.0 g/d), multivitamin use (yes vs no), vitamin E supplement use (yes vs no), current aspirin use (yes vs no), family history of myocardial infarction (yes vs no), family history of diabetes (yes vs no), family history of cancer (yes vs no), history of hypertension (yes vs no), history of hypercholesterolemia (yes vs no), intakes of total energy and dietary cholesterol (quintiles), percentage of energy intake from dietary protein (quintiles), menopausal status and hormone use in women (premenopausal, postmenopausal never users, postmenopausal past users, or postmenopausal current users), and percentage of energy from the remaining specific types of fat (saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, and *trans*-fatty acids, all modeled as continuous variables). Results for the Nurses' Health Study and Health Professional Follow-up Study from the multivariable model were combined using the fixed-effects model.

estimated reduction in total mortality of 27% (HR, 0.73; 95% CI, 0.70-0.77) and 13% (HR, 0.87; 95% CI, 0.82-0.93), respectively (eTable 19 in the Supplement). Replacing SFAs with the same energy from PUFAs was associated with a lower risk for mortality due to CVD, cancer, and neurodegenerative disease. Replacement of 5% of energy from SFAs with 5% of energy from MUFAs was associated with a 29% estimated reduction in neurodegenerative disease mortality (HR, 0.71; 95% CI, 0.57-0.88) (eTable 19 in the Supplement).

Discussion

In 2 large cohorts with many repeated measures of diet and a long duration of follow-up, we found that higher intakes of PUFA and MUFA were associated with lower mortality, whereas higher intakes of SFA and TFA were associated with increased mortality. Although the modest positive association between SFA intake and mortality suggests small health benefits of replacing SFAs with total carbohydrates, replacing SFAs with MUFAs and/or PUFAs was associated with a significantly lower risk for total and cause-specific mortality due to several major chronic diseases. Dietary intake of total fat, compared with total carbohydrates, was inversely associated with total mortality. However, the association between total fat intake and mortality largely depends on specific types of fat. Intake of linoleic acid, the most abundant ω-6 PUFA, showed strong inverse associations with total and most cause-specific mortality, without any evidence of detrimental effects. A higher ω-6:ω-3 PUFA ratio was not associated with increased mortality, but with a slightly lower CVD and cancer mortality.

Previous data on the associations between different types of ω-6 PUFA intake and total mortality have been limited. Concordant with our findings, 2 prospective cohort studies using circulating biomarkers[27,28] found a lower total mortality associated with higher serum concentrations of ω-6 PUFA. Evidence from clinical trials also supported a protective effect of soybean oil with a higher ω-6:ω-3 PUFA ratio on CHD risk.[29,30] Contrary to our findings, a recent reanalysis of the Sydney Diet Heart Study,[31] a secondary prevention trial, reported a significant increase in total mortality in participants assigned to an intervention consisting of higher ω-6 PUFA intake. However, that study was very small (n = 221) and of short duration (39 months) and included only individuals with existing CVD, and the intervention likely reduced ω-3 PUFA intake. In addition, the results may have been confounded by *trans*-fat in the special margarines used for the intervention that were high in linoleic acid levels.[6]

We observed a modest inverse association between marine ω-3 PUFA intake and total mortality. Previously, prospective cohorts in generally healthy populations yielded mixed results,[32-36] whereas most randomized clinical trials found nonsignificant effects of fish oil supplementation on total mortality.[9,37] The significant inverse association between intake of ω-3 PUFAs and death due to neurodegenerative diseases has not, to our knowledge, been previously reported.

We found a significant inverse association between MUFA intake and total mortality. In contrast, previous studies[2,38,39] generally reported nonsignificant or even positive associations with MUFA. This discordance might be owing to the strong correlations between MUFA and SFA, because animal fats are major sources of both types of fats in most Western diets, and between MUFA and TFA, because partial hydrogenation produces both. In our 2 cohorts, the correlation between MUFA and SFA decreased during the follow-up, and the major food sources of MUFA have shifted from animal-sourced to plant-sourced foods over time (eTable 20 in the Supplement); thus we had greater power to differentiate the association of MUFA with mortality. Consistent with our analysis, the major source of MUFA in Mediterranean populations, olive oil, has been associated with a substantially lower total mortality.[38] Important benefits of MUFA from plant sources have also been supported by the Prevención con Dieta Mediterránea (PREDIMED) trial,[40,41] in which the addition of olive oil and nuts, also high in MUFA levels, reduced the incidence of CVD and diabetes.

Compared with overall carbohydrates, higher SFA intake was associated with a slight increase in total mortality, but not significantly associated with CVD mortality. The lack of the

Table 3. Associations Between Dietary ω-6 and ω-3 PUFA Intake and Total Mortality (Comparison Is Isocaloric Substitution for Total Carbohydrates)

	Quintile of Dietary Fatty Acid Intake					*P* Value for Trend	HR (95% CI)[a]
	1	2	3	4	5		
ω-6 PUFA Intake							
Total ω-6 PUFA							
NHS							
Median, % of energy	3.4	4.3	4.9	5.5	6.7	NA	NA
No. of deaths	4124	4346	4158	3897	3789	NA	NA
HPFS							
Median, % of energy	3.7	4.5	5.1	5.8	6.9	NA	NA
No. of deaths	2874	2679	2622	2477	2338	NA	NA
Pooled[b]							
Age-adjusted model	1 [Reference]	0.89 (0.86-0.92)	0.85 (0.83-0.88)	0.80 (0.77-0.83)	0.75 (0.73-0.78)	<.001	0.84 (0.82-0.86)
MV-adjusted model[c]	1 [Reference]	0.96 (0.93-0.99)	0.93 (0.90-0.97)	0.88 (0.84-0.92)	0.85 (0.81-0.89)	<.001	0.90 (0.88-0.93)
Linoleic acid							
NHS							
Median, % of energy	3.3	4.2	4.8	5.4	6.5	NA	NA
No. of deaths	4165	4358	4148	3896	3747	NA	NA
HPFS							
Median, % of energy	3.6	4.4	5.0	5.6	6.7	NA	NA
No. of deaths	2910	2670	2569	2508	2333	NA	NA
Pooled[b]							
Age-adjusted model	1 [Reference]	0.90 (0.87-0.93)	0.86 (0.83-0.89)	0.81 (0.78-0.84)	0.74 (0.71-0.76)	<.001	0.82 (0.81-0.84)
MV-adjusted model[c]	1 [Reference]	0.97 (0.93-1.00)	0.92 (0.89-0.96)	0.88 (0.84-0.91)	0.82 (0.79-0.86)	<.001	0.88 (0.86-0.91)
Arachidonic acid							
NHS							
Median, % of energy	0.05	0.06	0.07	0.09	0.11	NA	NA
Deaths, No.	5809	4329	3648	3419	3109	NA	NA
HPFS							
Median, % of energy	0.05	0.06	0.07	0.09	0.11	NA	NA
No. of deaths	2644	2595	2519	2546	2686	NA	NA
Pooled[b]							
Age-adjusted model	1 [Reference]	1.00 (0.97-1.04)	0.98 (0.94-1.01)	1.00 (0.97-1.03)	0.97 (0.94-1.01)	.14	0.89 (0.76-1.03)
MV-adjusted model[c]	1 [Reference]	0.99 (0.96-1.03)	0.94 (0.90-0.97)	0.94 (0.91-0.98)	0.90 (0.85-0.94)	<.001	0.58 (0.47-0.73)
ω-3 PUFA Intake							
Total ω-3 PUFA							
NHS							
Median, % of energy	0.48	0.57	0.63	0.72	0.88	NA	NA
No. of deaths	4132	3786	3875	4090	4431	NA	NA
HPFS							
Median, % of energy	0.46	0.57	0.65	0.75	0.94	NA	NA
No. of deaths	2441	2548	2645	2644	2712	NA	NA
Pooled[b]							
Age-adjusted model	1 [Reference]	0.89 (0.86-0.92)	0.86 (0.83-0.89)	0.82 (0.79-0.85)	0.66 (0.64-0.69)	<.001	0.77 (0.75-0.78)
MV-adjusted model[c]	1 [Reference]	0.99 (0.96-1.03)	1.00 (0.97-1.04)	1.02 (0.98-1.06)	0.95 (0.91-0.99)	.03	0.97 (0.94-0.99)
α-Linolenic acid							
NHS							
Median, % of energy	0.41	0.48	0.53	0.59	0.70	NA	NA
No. of deaths	4274	3800	3831	3839	4570	NA	NA
HPFS							
Median, % of energy	0.38	0.45	0.50	0.56	0.68	NA	NA
No. of deaths	2398	2431	2544	2700	2917	NA	NA

(continued)

Table 3. Associations Between Dietary ω-6 and ω-3 PUFA Intake and Total Mortality (Comparison Is Isocaloric Substitution for Total Carbohydrates) (continued)

	Quintile of Dietary Fatty Acid Intake					*P* Value for Trend	HR (95% CI)[a]
	1	2	3	4	5		
Pooled[b]							
Age-adjusted model	1 [Reference]	0.96 (0.92-0.99)	0.96 (0.93-1.00)	0.93 (0.90-0.96)	0.79 (0.76-0.81)	<.001	0.79 (0.77-0.82)
MV-adjusted model[c]	1 [Reference]	1.00 (0.96-1.03)	1.04 (1.00-1.08)	1.03 (0.99-1.07)	0.99 (0.95-1.03)	.80	0.98 (0.94-1.02)
Marine ω-3 fatty acids (DHA+EPA)							
NHS							
Median, % of energy	0.03	0.05	0.08	0.12	0.21	NA	NA
No. of deaths	3725	4123	4247	4019	4200	NA	NA
HPFS							
Median, % of energy	0.04	0.08	0.12	0.18	0.31	NA	NA
No. of deaths	2558	2655	2635	2490	2652	NA	NA
Pooled[b]							
Age-adjusted model	1 [Reference]	0.98 (0.94-1.01)	0.94 (0.91-0.98)	0.86 (0.83-0.89)	0.74 (0.71-0.76)	<.001	0.67 (0.64-0.70)
MV-adjusted model[c]	1 [Reference]	1.04 (1.00-1.07)	1.05 (1.02-1.09)	1.03 (0.99-1.07)	0.96 (0.93-1.00)	.002	0.93 (0.89-0.98)
ω-6:ω-3 ratio							
NHS							
Median, % of energy	5.5	6.7	7.6	8.4	9.9	NA	NA
No. of deaths	4070	4316	4275	4147	3506	NA	NA
HPFS							
Median, % of energy	5.5	6.9	7.9	8.9	10.8	NA	NA
No. of deaths	2968	2782	2642	2432	2166	NA	NA
Pooled[b]							
Age-adjusted model	1 [Reference]	1.11 (1.07-1.15)	1.15 (1.11-1.19)	1.18 (1.14-1.22)	1.18 (1.14-1.23)	<.001	1.03 (1.03-1.04)
MV-adjusted model[c]	1 [Reference]	1.04 (1.01-1.08)	1.02 (0.99-1.06)	1.02 (0.98-1.06)	0.99 (0.95-1.03)	.29	1.00 (0.99-1.00)

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HPFS, Health Professional Follow-up Study; HR, hazard ratio; MV, multivariable; NA, not applicable; NHS, Nurses' Health Study; PUFA, polyunsaturated fatty acid.

[a] Indicates hazard ratio of total mortality of substituting 2% of energy from total ω-6 PUFA and linoleic acid and 0.3% of energy from total ω-3 PUFA, arachidonic acid, α-linolenic acid, and marine ω-3 fatty acids, for the same energy from total carbohydrates, as well as hazard ratio of total mortality for every 1-unit increment in ω-6:ω-3 ratio.

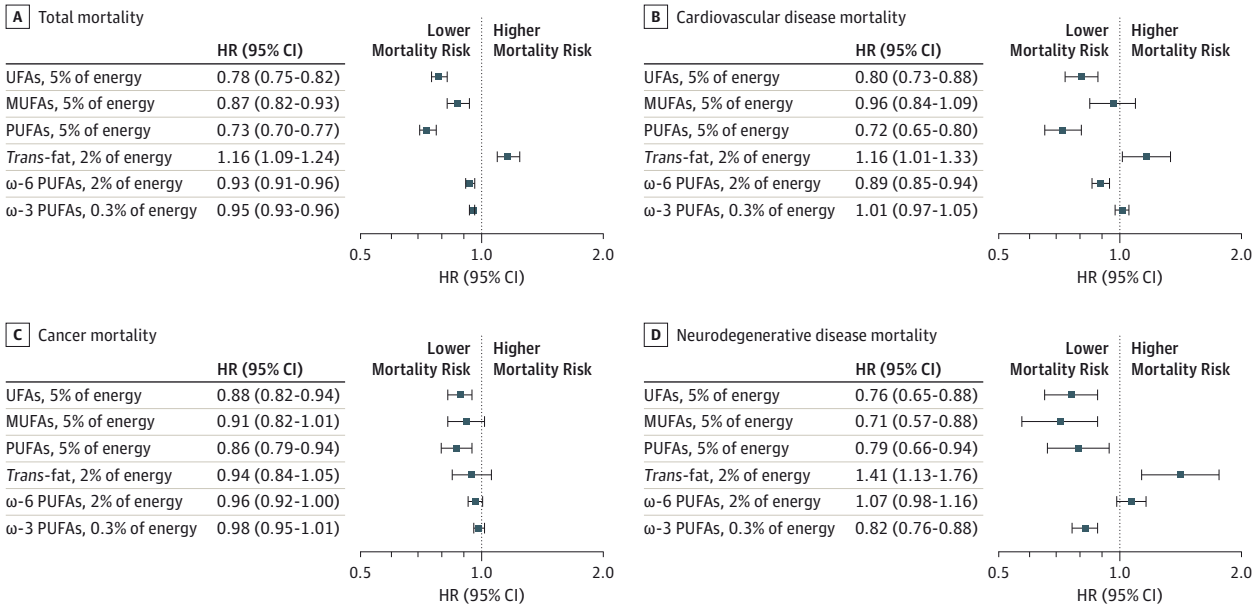
[b] Results for NHS and HPFS from the multivariable model were combined using the fixed-effects model.

[c] Adjusted for age (in months), white race (yes vs no), marital status (with spouse, yes or no), body mass index (<23.0, 23.0-24.9, 25.0-29.9, 30.0-34.9, or ≥35.0 [calculated as weight in kilograms divided by height in meters squared]), physical activity (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9, or ≥27.0 h of metabolic equivalent tasks per week), smoking status (never, past, current 1-14 cigarettes/d, current 15-24 cigarettes/d, or current ≥25 cigarettes/d), alcohol consumption (women: 0, 0.1-4.9, 5.0-14.9, or ≥15.0 g/d; men: 0, 0.1-4.9, 5.0-29.9, or ≥30.0 g/d), multivitamin use (yes vs no), vitamin E supplement use (yes vs no), current aspirin use (yes vs no), family history of myocardial infarction (yes vs no), family history of diabetes (yes vs no), family history of cancer (yes vs no), history of hypertension (yes vs no), history of hypercholesterolemia (yes vs no), intakes of total energy and dietary cholesterol (quintiles), percentage of energy intake from dietary protein (quintiles), and menopausal status and hormone use in women (premenopausal, postmenopausal never users, postmenopausal past users, or postmenopausal current users). All models also included percentages of energy intake from remaining fatty acids (saturated fatty acids, PUFAs, monounsaturated fatty acids, *trans*-fatty acids, ω-6 PUFAs, ω-3 PUFAs, linoleic acid, arachidonic acid, α-linolenic acid, and marine ω-3 fatty acids, all in quintiles).

association with CVD is expected because the major sources of carbohydrates in a typical Western diet are highly processed foods with large amounts of refined starch and sugar, providing a high glycemic load that can increase CVD risk independent of SFA.[7,42,43] In our substitution analyses, replacing SFA with unsaturated fatty acids was associated with a substantially lower risk for total and CVD mortality. These findings were generally consistent with evidence from previous studies.[2,44-46] However, a recent meta-analysis[5] concluded that specific types of fat, including saturated, monounsaturated, or polyunsaturated, had no significant effect on the risk for CHD. Another meta-analysis[47] also reported nonsignificant associations of SFA intake with total and CVD mortality and CHD incidence. However, most studies included in these meta-analyses did not explicitly model the effects of macronutrient substitution and did not specify the comparison source of energy for the type of fat under scrutiny, which limits the interpretations of these findings.[6,44] Our analyses provide strong evidence that using PUFAs and/or MUFAs as the replacement nutrients for SFAs can confer substantial health benefits, whereas replacing SFAs with total carbohydrates has little effect on CVD mortality. However, the effects of replacement by carbohydrates may depend in part on the quality of the carbohydrates.[7]

Data on specific types of dietary fat and non-CVD mortality are sparse. We observed no major effects of most types of

Figure 2. Multivariable Hazard Ratios (HRs) of Mortality by Isocaloric Substitution of Specific Types of Fatty Acid for Saturated Fatty Acids



The model was adjusted for age (in months), white race (yes vs no), marital status (with spouse, yes or no), body mass index (<23.0, 23.0-24.9, 25.0-29.9, 30.0-34.9, or ≥35.0 [calculated as weight in kilograms divided by height in meters squared]), physical activity (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9, or ≥27.0 h of metabolic equivalent tasks per week), smoking status (never, past, current 1-14 cigarettes/d, current 15-24 cigarettes/d, or current ≥25 cigarettes/d), alcohol consumption (women: 0, 0.1-4.9, 5.0-14.9, or ≥15.0 g/d; men: 0, 0.1-4.9, 5.0-29.9, or ≥30.0 g/d), multivitamin use (yes vs no), vitamin E supplement use (yes vs no), current aspirin use (yes vs no), family history of myocardial infarction (yes vs no), family history of diabetes (yes vs no), family history of cancer (yes vs no), history of hypertension (yes vs no), history of hypercholesterolemia (yes vs no), intakes of total energy and dietary cholesterol (quintiles), percentage of energy intake from dietary protein (quintiles), menopausal status and hormone use in women (premenopausal, postmenopausal never users, postmenopausal past users, or postmenopausal current users), and percentage of energy from remaining fatty acids (saturated fatty acids, polyunsaturated fatty acids [PUFAs], monounsaturated fatty acids [MUFAs], *trans*-fatty acids, ω-6 PUFAs, ω-3 PUFAs, linoleic acid, arachidonic acid, α-linolenic acid, and marine ω-3 fats, all modeled as continuous variables). Results for the Nurses' Health Study and Health Professional Follow-up Study from the multivariable model were combined using the fixed-effects model. UFA indicates unsaturated fatty acid; and error bars, 95% CI.

dietary fat on cancer mortality, although a modest inverse association with linoleic acid was observed. Our findings of an inverse association between a higher intake of PUFAs, primarily α-linolenic acid, and lower mortality due to neurodegenerative diseases are consistent with limited evidence on the incidence of major neurodegenerative diseases, including Alzheimer disease,[48] amyotrophic lateral sclerosis,[15] and Parkinson disease,[49] in prospective cohorts. Finally, we observed a positive association between saturated and *trans*-fat intakes and respiratory disease mortality, but an inverse association with PUFAs. These findings are novel and therefore require confirmation in further studies.

Our results have several limitations. First, reverse causation is a possible explanation for our findings, because people with chronic disease and poor health might change their habitual diet. However, we excluded participants with known major chronic diseases at baseline. Also, those persons concerned about a serious illness might change toward a diet generally perceived to be healthier, which would not explain our findings. In addition, our findings remained largely unchanged when we excluded the first 4 years of follow-up or added a 4-year lag period between dietary assessment and each follow-up period. Second, because our study was observational in nature, causality cannot be established. However, our results were largely consistent with results from existing observational studies and randomized clinical trials on diet and CVD-related outcomes. Third, although we adjusted for many potential confounders, residual confounding could not be ruled out. Fourth, measurement errors are inevitable in estimates of food and nutrient intakes. However, our adjustment for energy intake and use of prospectively collected, cumulative mean intake using many repeated dietary assessments reduced the impact of measurement errors.[19,20] The strengths of the present study include the large sample size, high rates of follow-up, and repeated assessments of dietary and lifestyle variables during a long period.

Conclusions

We found that different types of dietary fats have divergent associations with total and cause-specific mortality. Replacement of saturated fats with unsaturated fats can confer substantial health benefits and should continue to be a key message in dietary recommendations. These findings also support the elimination of partially hydrogenated vegetable oils, the primary source of *trans*-fatty acids.

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Study concept and design: Wang, Hu.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Wang, Willett.
Critical revision of the manuscript for important intellectual content: All authors.
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REFERENCE

1. Willett WC. Dietary fats and coronary heart disease. *J Intern Med*. 2012;272(1):13-24.

2. Jakobsen MU, O'Reilly EJ, Heitmann BL, et al. Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. *Am J Clin Nutr*. 2009;89(5):1425-1432.

3. Hu FB, Stampfer MJ, Manson JE, et al. Dietary fat intake and the risk of coronary heart disease in women. *N Engl J Med*. 1997;337(21):1491-1499.

4. Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans. *Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans, 2010, to the Secretary of Agriculture and the Secretary of Health and Human Services*. Washington, DC: Agricultural Research Service; 2010.

5. Chowdhury R, Warnakula S, Kunutsor S, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. *Ann Intern Med*. 2014;160(6):398-406.

6. Willett WC, Stampfer MJ, Sacks FM. Association of dietary, circulating, and supplement fatty acids with coronary risk. *Ann Intern Med*. 2014;161(6):453.

7. Li Y, Hruby A, Bernstein AM, et al. Saturated fats compared with unsaturated fats and sources of carbohydrates in relation to risk of coronary heart disease: a prospective cohort study. *J Am Coll Cardiol*. 2015;66(14):1538-1548.

8. Harris WS. Are n-3 fatty acids still cardioprotective? *Curr Opin Clin Nutr Metab Care*. 2013;16(2):141-149.

9. Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. *J Am Coll Cardiol*. 2011;58(20):2047-2067.

10. Harris WS, Shearer GC. Omega-6 fatty acids and cardiovascular disease: friend, not foe? *Circulation*. 2014;130(18):1562-1564.

11. Mozaffarian D, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Trans fatty acids and cardiovascular disease. *N Engl J Med*. 2006;354(15):1601-1613.

12. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr*. 2003;77(5):1146-1155.

13. Micha R, Mozaffarian D. Saturated fat and cardiometabolic risk factors, coronary heart disease, stroke, and diabetes: a fresh look at the evidence. *Lipids*. 2010;45(10):893-905.

14. Larsson SC, Kumlin M, Ingelman-Sundberg M, Wolk A. Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. *Am J Clin Nutr*. 2004;79(6):935-945.

15. Fitzgerald KC, O'Reilly EJ, Falcone GJ, et al. Dietary ω-3 polyunsaturated fatty acid intake and risk for amyotrophic lateral sclerosis. *JAMA Neurol*. 2014;71(9):1102-1110.

16. Wu JH, Micha R, Imamura F, et al. Omega-3 fatty acids and incident type 2 diabetes: a systematic review and meta-analysis. *Br J Nutr*. 2012;107(suppl 2):S214-S227.

17. Giovannucci E, Rimm EB, Colditz GA, et al. A prospective study of dietary fat and risk of prostate cancer [published correction appears in *J Natl Cancer Inst*. 2013;105(13):994]. *J Natl Cancer Inst*. 1993;85(19):1571-1579.

18. Astorg P. Dietary n-6 and n-3 polyunsaturated fatty acids and prostate cancer risk: a review of epidemiological and experimental evidence. *Cancer Causes Control*. 2004;15(4):367-386.

19. Willett WC. Food frequency methods. In: *Nutritional Epidemiology*. 3rd ed. New York, NY: Oxford University Press; 2013:40.

20. Willett WC. Reproducibility and validity of food-frequency questionnaires. In: *Nutritional Epidemiology*. 3rd ed. New York, NY: Oxford University Press; 2013:40.

21. Harvard T. H. Chan School of Public Health Nutrition Department. Food composition table. https://regepi.bwh.harvard.edu/health/nutrition/. Posted January 15, 2015. Accessed March 8th, 2015.

22. London SJ, Sacks FM, Caesar J, Stampfer MJ, Siguel E, Willett WC. Fatty acid composition of subcutaneous adipose tissue and diet in postmenopausal US women. *Am J Clin Nutr*. 1991;54(2):340-345.

23. Hunter DJ, Rimm EB, Sacks FM, et al. Comparison of measures of fatty acid intake by subcutaneous fat aspirate, food frequency questionnaire, and diet records in a free-living population of US men. *Am J Epidemiol*. 1992;135(4):418-427.

24. Sun Q, Ma J, Campos H, Hankinson SE, Hu FB. Comparison between plasma and erythrocyte fatty acid content as biomarkers of fatty acid intake in US women. *Am J Clin Nutr*. 2007;86(1):74-81.

25. Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the National Death Index and Equifax Nationwide Death Search. *Am J Epidemiol*. 1994;140(11):1016-1019.

26. Chiuve SE, Fung TT, Rimm EB, et al. Alternative dietary indices both strongly predict risk of chronic disease. *J Nutr*. 2012;142(6):1009-1018.

27. Wu JH, Lemaitre RN, King IB, et al. Circulating omega-6 polyunsaturated fatty acids and total and cause-specific mortality: the Cardiovascular Health Study. *Circulation*. 2014;130(15):1245-1253.

28. Warensjö E, Sundström J, Vessby B, Cederholm T, Risérus U. Markers of dietary fat quality and fatty acid desaturation as predictors of total and cardiovascular mortality: a population-based prospective study. *Am J Clin Nutr*. 2008;88(1):203-209.

29. Controlled trial of soya-bean oil in myocardial infarction. *Lancet*. 1968;2(7570):693-699.

30. Leren P. The Oslo Diet-Heart Study: eleven-year report. *Circulation*. 1970;42(5):935-942.

31. Ramsden CE, Zamora D, Leelarthaepin B, et al. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. *BMJ*. 2013;346:e8707.

32. Folsom AR, Demissie Z. Fish intake, marine omega-3 fatty acids, and mortality in a cohort of postmenopausal women. *Am J Epidemiol*. 2004;160(10):1005-1010.

33. Virtanen JK, Voutilainen S, Rissanen TH, et al. Mercury, fish oils, and risk of acute coronary events and cardiovascular disease, coronary heart disease, and all-cause mortality in men in eastern Finland. *Arterioscler Thromb Vasc Biol*. 2005;25(1):228-233.

34. Yuan JM, Ross RK, Gao YT, Yu MC. Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. *Am J Epidemiol*. 2001;154(9):809-816.

35. Bell GA, Kantor ED, Lampe JW, Kristal AR, Heckbert SR, White E. Intake of long-chain ω-3 fatty acids from diet and supplements in relation to mortality. *Am J Epidemiol*. 2014;179(6):710-720.

36. Mozaffarian D, Lemaitre RN, King IB, et al. Plasma phospholipid long-chain ω-3 fatty acids and total and cause-specific mortality in older adults: a cohort study. *Ann Intern Med*. 2013;158(7):515-525.

37. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. *JAMA*. 2012;308(10):1024-1033.

38. Schwingshackl L, Hoffmann G. Monounsaturated fatty acids, olive oil and health status: a systematic review and meta-analysis of cohort studies. *Lipids Health Dis*. 2014;13:154.

39. Virtanen JK, Mursu J, Tuomainen TP, Voutilainen S. Dietary fatty acids and risk of coronary heart disease in men: the Kuopio Ischemic Heart Disease Risk Factor Study. *Arterioscler Thromb Vasc Biol*. 2014;34(12):2679-2687.

40. Estruch R, Ros E, Salas-Salvadó J, et al; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med*. 2013;368(14):1279-1290.

41. Salas-Salvadó J, Bulló M, Estruch R, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. *Ann Intern Med*. 2014;160(1):1-10.

42. Hu FB. Are refined carbohydrates worse than saturated fat? *Am J Clin Nutr*. 2010;91(6):1541-1542.

43. Jakobsen MU, Dethlefsen C, Joensen AM, et al. Intake of carbohydrates compared with intake of saturated fatty acids and risk of myocardial infarction: importance of the glycemic index. *Am J Clin Nutr*. 2010;91(6):1764-1768.

44. Farvid MS, Ding M, Pan A, et al. Dietary linoleic acid and risk of coronary heart disease: a systematic review and meta-analysis of prospective cohort studies. *Circulation*. 2014;130(18):1568-1578.

45. Chiuve SE, Rimm EB, Sandhu RK, et al. Dietary fat quality and risk of sudden cardiac death in women. *Am J Clin Nutr*. 2012;96(3):498-507.

46. Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. *PLoS Med*. 2010;7(3):e1000252.

47. de Souza RJ, Mente A, Maroleanu A, et al. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. *BMJ*. 2015;351:h3978.

48. Otaegui-Arrazola A, Amiano P, Elbusto A, Urdaneta E, Martínez-Lage P. Diet, cognition, and Alzheimer's disease: food for thought. *Eur J Nutr*. 2014;53(1):1-23.

49. de Lau LM, Bornebroek M, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM. Dietary fatty acids and the risk of Parkinson disease: the Rotterdam Study. *Neurology*. 2005;64(12):2040-2045.