Dietary Fats in Relation to Total and Cause-Specific Mortality in a Prospective Cohort of 521 120 Individuals With 16 Years of Follow-Up

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Rationale: **Evidence linking saturated fat intake with cardiovascular health is controversial. The associations of unsaturated fats with total and cardiovascular disease (CVD) mortality remain inconsistent, and data about non-CVD mortality are limited.**

Objective: **To assess dietary fat intake in relation to total and cause-specific mortality.**

Methods and Results: **We analyzed data of 521 120 participants aged 50 to 71 years from the National Institutes of Health-American Association of Retired Persons Diet and Health Study with 16 years of follow-up. Intakes of saturated fatty acids (SFAs), trans-fatty acids, monounsaturated fatty acids (MUFAs), and polyunsaturated fatty acids (PUFAs) were assessed via food frequency questionnaires. Hazard ratios and 95% CIs were estimated using the Cox proportional hazards model. Overall, 129 328 deaths were documented during 7.3 million person-years of follow-up. In the replacement of carbohydrates, multivariable-adjusted hazard ratios of total mortality comparing extreme quintiles were 1.29 (95% CI, 1.25–1.33) for SFAs, 1.03 (1.00–1.05) for trans-fatty acids, 0.98 (0.94–1.02) for MUFAs, 1.09 (1.06–1.13) for animal MUFAs, 0.94 (0.91–0.97) for plant MUFAs, 0.93 (0.91–0.95) for PUFAs, 0.92 (0.90–0.94) for marine omega-3 PUFAs, 1.06 (1.03–1.09) for α-linolenic acid, 0.88 (0.86–0.91) for linoleic acid, and 1.10 (1.08–1.13) for arachidonic acid. CVD mortality was inversely associated with marine omega-3 PUFA intake (*P* trend <0.0001), whereas it was positively associated with SFA, trans-fatty acid, and arachidonic acid intake. Isocalorically replacing 5% of the energy from SFAs with plant MUFAs was associated with 15%, 10%, 11%, and 30% lower total mortality, CVD, cancer, and respiratory disease mortality, respectively. Isocaloric replacement of SFA with linoleic acid (2%) was associated with lower total (8%), CVD (6%), cancer (8%), respiratory disease (11%), and diabetes mellitus (9%) mortality.**

Conclusions: **Intakes of SFAs, trans-fatty acids, animal MUFAs, α-linolenic acid, and arachidonic acid were associated with higher mortality. Dietary intake of marine omega-3 PUFAs and replacing SFAs with plant MUFAs or linoleic acid were associated with lower total, CVD, and certain cause-specific mortality.**

Clinical Trial Registration: **URL: http://www.clinicaltrials.gov. Unique identifier: NCT00340015. (*Circ Res*. 2019;124:757-768. DOI: 10.1161/CIRCRESAHA.118.314038.)**

Key Words: cardiovascular diseases ■ diet ■ epidemiology ■ fatty acids ■ mortality

Dietary fats, mainly triglycerides from both animal- and plant-derived foods, are traditionally considered as unhealthy components. Nonetheless, researches over the past few decades have recognized that different types of fats have divergent effects on cardiovascular health.[1] Therefore, current dietary guidelines recommend limiting the intake of saturated fatty acids (SFAs) and trans-fatty acids (TFAs), while increasing unsaturated fatty acids (UFAs) for the replacement of SFAs on the basis of vast literature.[2] Unfortunately, accumulating evidence from recent epidemiological and clinical studies is challenging this time-honored dietary strategy.

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Typically, conclusions from recent meta-analyses have not supported the association of SFAs with total mortality, cardiovascular disease (CVD), or diabetes mellitus mortality.[3–5] Associations of polyunsaturated fatty acids (PUFAs) with mortality also conflict. Inconsistent results were reported for

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Novelty and Significance

What Is Known?

- There is little direct evidence to support prevailing dietary guidelines that recommend replacing saturated fat with unsaturated fat for overall health and longevity.
- Previous small-scale studies report conflicting results about the associations of specific dietary fats with total and cardiovascular disease (CVD) mortality.
- Little is known about associations between specific dietary fats and mortality from non-CVD causes.

What New Information Does This Article Contribute?

- Intake of dietary saturated fat, trans-fat, monounsaturated fatty acids (MUFAs) from animal sources, α-linolenic acid, and arachidonic acid are associated with higher mortality, whereas the intake of polyunsaturated fatty acids (PUFAs), linoleic acid, and marine omega-3 PUFAs are associated with lower mortality.
- Replacing saturated fat with plant MUFAs or linoleic acid is associated with lower all-cause mortality and mortality from certain causes, including CVD, cancer, respiratory disease, diabetes mellitus, and Alzheimer disease.

Evidence linking specific dietary fat intake with total and CVD mortality is controversial, and data on non-CVD mortality are limited. In this large prospective cohort, we found that intake of saturated fat, trans-fat, animal MUFAs, α-linolenic acid, and arachidonic acid was associated with higher mortality. The intake of marine omega-3 PUFAs and replacement of saturated fat with plant MUFAs or linoleic acid were associated with lower total, CVD, and certain cause-specific mortality. These findings support current dietary recommendations that highlight eliminating trans-fat intake and replacing saturated fat with MUFAs and PUFAs. Our findings also suggest that the consumption of MUFAs from plant-based sources and PUFAs from foods rich in linoleic acid or marine omega-3 PUFAs may be beneficial for general health and for decreasing the risk of several chronic diseases.

Nonstandard Abbreviations and Acronyms

A-MUFA	animal MUFA
AA	arachidonic acid
AARP	formerly known as the American Association for Retired Persons
AD	Alzheimer disease
ALA	α-linolenic acid
BMI	body mass index
CHD	coronary heart disease
CLD	chronic liver disease
CVD	cardiovascular disease
HDL	high-density lipoprotein
HPFS	Health Professionals Follow-Up Study
HR	hazard ratio
LA	linoleic acid
LDL	low-density lipoprotein
MUFA	monounsaturated fatty acid
P-MUFA	plant MUFA
PUFA	polyunsaturated fatty acid
RD	respiratory disease
SFA	saturated fatty acid
TFA	trans-fatty acid
UFA	unsaturated fatty acid.

omega-3 PUFA intake in relation to mortality.[6–8] The association of α-linolenic acid (ALA) intake with mortality was inconsistent with that of marine omega-3 PUFA intake.[7,9,10] Public concerns have increasingly been highlighted for linking higher omega-6/omega-3 ratios with the prevalence of various chronic disorders.[11,12] Additionally, the different roles of specific omega-6 PUFAs, such as linoleic acid (LA) and arachidonic acid (AA), are poorly understood. Although substituting SFAs with UFAs and especially PUFAs is recommended, it is unclear which types of PUFAs should be considered. Intake of monounsaturated fatty acids (MUFAs) has been reported to improve blood lipid profiles, inflammatory factors, and typical CVD risk factors in clinical trials, but little evidence showed MUFA consumption in relation to lower CVD mortality in observational studies,[13–15] which failed to specify the source of MUFAs. Unlike SFAs and PUFAs that are primary from animal-based and plant-based sources, respectively, MUFAs can be consumed from both sources and exert notable health effects. The adverse effect of TFA intake on coronary heart disease (CHD) has been proven,[16] whereas data on mortality are lacking. In addition, the associations of dietary fats with respiratory disease (RD), diabetes mellitus, and Alzheimer disease (AD) mortality remain unclear.

The present study assessed the relationships of specific fats with total and cause-specific mortality among 521 120 participants in the National Institutes of Health-American Association of Retired Persons (AARP) Diet and Health Study, which is the largest prospective study to date with a long-term follow-up duration. We hypothesized that individual types of dietary fats determine their associations with mortality in the general population.

Methods

Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the Division of Cancer Epidemiology & Genetics from National Cancer Institute at linda.liao@nih.gov (Linda Liao).

Study Population

We used data from the National Institutes of Health-AARP Diet and Health Study, which is a large prospective cohort consisting of 617 119 AARP members aged 50 to 71 years and enrolled between 1995 and 1996.[17] The participants were from 6 US states (CA, FL, LA, NJ, NC, and PA) and 2 metropolitan areas (Atlanta, GA and Detroit, MI) and provided written informed consent. At baseline, comprehensive questionnaires were mailed to AARP members to collect data on demographic, lifestyle, and diet information. Among 567 169 individuals who completed and returned the baseline questionnaire, this study excluded duplicate records, proxy responders, withdrawals, those who moved or died before entry, those with null person-years of follow-up, or those

who reported implausible total energy intake at baseline. Finally, a total of 521 120 participants (306 365 men and 214 755 women) were selected (Online Figure I). The Special Studies Institutional Review Board of the National Cancer Institute approved this study.

Dietary Assessment

Diet data were assessed using a validated 124-item food frequency questionnaire at baseline, which was developed as the Diet History Questionnaire at National Cancer Institute.[17] The participants were asked about their consumption frequency of each food item with a prespecified portion size by the nutrient content over the previous year. The USDA 1994 to 1996 Continuing Survey of Food Intakes by Individuals[18] were used to calibrate Diet History Questionnaire data and calculate the daily intake of dietary fats, including SFAs, MUFAs, TFAs, PUFAs, omega-3 PUFAs (marine omega-3 PUFAs and ALA), and omega-6 PUFAs (LA and AA), as well as proteins and carbohydrates. We also separated MUFAs into plant-based MUFAs (P-MUFAs) and animal-based MUFAs (A-MUFAs) according to the food sources. In a substudy of AARP members using 2 nonconsecutive 24-hour dietary recalls, estimated correlations between true and food frequency questionnaire-reported intakes of 29 food groups were mostly 0.5 or greater.[19] In another Diet History Questionnaire validation study, estimated correlations between nutrient intakes and practical intakes ranged from 0.4 to 0.8.[20] For instance, the adjusted correlation coefficient was 0.76 in men and 0.69 in women for SFAs, 0.71 in men and 0.62 in women for MUFAs, and 0.53 in men and 0.56 in women for PUFAs.[20] Total energy intake was also calculated based on the Continuing Survey of Food Intakes by Individual. However, energy intake is underestimated by food frequency questionnaires because of a limited number of foods.

Data on other demographic and lifestyle factors including race, weight, height, marital status, education, physical activity, smoking, and alcohol consumption were also collected.[17]

Follow-Up and Deaths Ascertainment

The duration of follow-up was calculated from the baseline (1995 or 1996) to the time of death or the end of follow-up (December 31, 2011), whichever was earlier. The participants were followed periodically by linkage to the National Change of Address database maintained by the US Postal Service, while the vital status was confirmed by annual linkage to the Social Security Administration Death Master File. The complete follow-up rate for mortality exceeded 99% in this cohort study. The causes of death were then obtained from follow-up searches of the National Death Index Plus and classified into 22 categories according to the ninth and tenth revision codes of the *International Classification of Diseases Ninth Revision* and *Tenth Revision* (*ICD-9* and *ICD-10*; Online Table I).

Statistical Analysis

Dietary fats were expressed as percentages of total energy (energy is 9 kcal/g for fatty acids) by the nutrient density method,[21] a widely used approach in epidemiological analyses to address the correlations between nutrient intakes and total calorie intake and largely cancel out the correlated measurement errors between them. The data were divided into quintiles for the entire cohort study. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs by considering follow-up person-years as the time metric and the first categories of intakes as the references. Tests for trends were performed by assigning median values to corresponding categories of intakes as continuous variables. The change of mortality associated with a fixed 1-SD increase of specific dietary fat intake (% of energy) was also assessed.

Four stepwise models were established to adjust for covariates of known or suspected risk factors for death. Model 1 was adjusted for age and sex. Model 2 was also adjusted for race, marital status, body mass index (BMI), education, household income, smoking status, physical activity, and alcohol consumption. Model 3 was further adjusted for history of hypertension, history of hypercholesterolemia, perceived health condition, history of heart disease, stroke, diabetes mellitus, and cancer at baseline, multi-vitamin use, aspirin use, and hormones use for women. The final multivariable model 4 was additionally adjusted for dietary factors, including total energy intake and energy intake from proteins and other remaining fatty acids (SFAs, MUFAs, PUFAs, and TFAs). The regression coefficient for the specific dietary fats in model 4 can be interpreted as the estimated effect of substituting the fat for the same percentage of energy from carbohydrates. The model for cancer mortality was additionally adjusted for family history of cancer.

We evaluated the effect of replacing SFAs with other types of fats by establishing isocaloric substitution models that simultaneously included total energy intake and percentages of energy from proteins, carbohydrates, and all fats except SFAs. By leaving SFAs out of the model, regression coefficients of the other fats could be interpreted as estimated effects of replacing SFAs with specific fats while leaving other fatty acids unchanged. Subgroup analyses were conducted and stratified by age, sex, BMI, hypertension, and hypercholesterolemia. *P* values for interactions were estimated by the likelihood ratio test.

We also conducted a supplemental analysis that further included energy intake from the carbohydrates in the model to evaluate the associations when fats were not compared with other macronutrients. Several sensitivity analyses were performed by (1) addressing the potential residual confounding by measuring variables using the propensity-score adjustment[22]; (2) further adjusting for the Healthy Eating Index-2015 to test whether the findings could be explained by the overall dietary patterns; (3) excluding those with extreme BMI (<18.5 or >40 kg/m^2); (4) excluding those with heart disease, stroke, cancer, and diabetes mellitus at baseline; (5) excluding the initial 5 years of follow-up; and (6) ending the follow-up at 2004 (mid point, 8 years of follow-up).

All of the statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). Two-sided *P* values <0.05 were considered as statistically significant.

Results

Population Characteristics

Baseline characteristics by quintiles of dietary fat intake are shown in Table 1. The participants with higher intakes of SFAs, MUFAs, and PUFAs were more likely to be fatter, be current smokers, have hypercholesterolemia, diabetes mellitus and fair or poor health status, and have lower levels of household income and education. However, they were less likely to exercise more, use multivitamins and aspirin, and report a history of heart disease. The participants with higher consumption of MUFAs and SFAs were more likely to be younger, be male and white, and have lower prevalence of hypertension, while higher prevalence of hypertension was observed among those with higher intake of PUFAs. Intakes of SFAs, MUFAs, and PUFAs were positively associated with total energy intake but inversely related to alcohol consumption.

Dietary Fats and Total Mortality

During a follow-up of 16 years (7 307 097 person-years), 129 328 deaths (85 037 in the men and 44 291 in the women) were documented. Dietary intakes of SFAs and TFAs were both positively associated with total mortality in age- and sex-adjusted analyses (*P* trend <0.0001) and also in multivariable-adjusted models 2 to 4 (Table 2). When substituting for carbohydrates (model 4), the multivariable HRs (95% CIs) comparing the highest quintile to the lowest quintile of SFA and TFA intakes were 1.29 (1.25–1.33; *P* trend <0.0001) and 1.03 (1.00–1.05; *P* trend=0.0062), respectively. The PUFA intake was strongly and inversely associated with the total mortality in the fully adjusted model 4 (*P* trend <0.0001). Each 1-SD increment of energy from PUFAs was related to a 2% lower total mortality (Figure 1). Although no significant association

Table 1. Characteristics of the Participants (N=521 120) by Quintiles of Dietary Fat Intakes in the NIH-AARP Diet and Health Study

	Quintile of SFA Intake			Quintile of PUFA Intake			Quintile of MUFA Intake		
Characteristics	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5
Range (% of energy)	≤6.9	8.5–10.0	≥11.8	≤5.2	6.3–7.3	≥8.6	≤8.7	10.6–12.2	≥14.0
Age, y	63.2*	62.8	62.6	62.8	62.8	62.9	63.0	62.9	62.6
Male, %	55.2	59.3	61.5	59.8	60.7	52.9	53.2	58.9	63.8
Race, %									
White	89.6	91.6	93.9	90.8	92.6	91.0	90.3	91.9	92.8
Black	4.3	3.9	2.7	3.2	3.3	4.6	3.8	3.7	3.6
Hispanic	2.2	1.9	1.3	2.6	1.6	1.4	2.3	1.8	1.3
Asian	2.2	1.1	0.5	1.6	1.0	1.3	1.9	1.1	0.8
BMI, kg/m^2	25.1	26.6	27.1	25.8	26.5	26.6	25.3	26.5	27.3
Married, %	65.7	70.0	67.2	65.0	70.3	67.0	63.4	69.4	71.3
College graduate or postgraduate, %	45.7	38.9	32.6	42.0	39.6	34.6	45.2	39.6	31.8
Current smoker, %	6.7	10.4	19.7	10.6	11.1	14.0	7.4	10.9	17.8
Physical activity, ≥5 times/wk (%)	27.4	17.6	14.1	23.1	18.5	16.6	27.0	17.8	14.2
Annual household income (USD)†	50 632	48 328	47 240	49 925	49 056	47 083	50 893	48 920	46 127
History of hypercholesterolemia, %	22.6	26.1	29.7	25.8	26.1	26.5	24.3	26.8	27.4
History of hypertension, %	24.3	23.8	21.6	23.3	23.4	23.5	23.9	23.5	22.8
Heart disease, %	18.8	13.3	10.8	15.4	13.8	12.9	17.3	13.1	12.5
Stroke, %	2.1	2.0	2.2	2.2	2.0	2.2	2.1	2.0	2.3
Cancer, %	8.9	9.0	9.2	8.9	8.9	9.4	9.1	8.9	9.1
Diabetes mellitus, %	6.1	9.4	11.5	6.2	9.1	12.2	6.0	8.6	13.3
Fair or poor health, %	10.6	12.7	15.9	11.8	12.4	15.0	10.4	12.1	16.9
First-degree relatives with cancer, %	49.4	50.1	49.9	48.8	50.4	50.2	49.1	50.3	50.0
Replacement hormones use, %	24.6	21.8	18.6	20.8	21.0	24.8	25.3	22.0	18.0
Currently using multivitamins, %	60.6	55.8	50.9	58.2	55.8	52.9	60.8	56.0	49.8
Daily use of aspirin in the past 12 mo, %	18.7	14.4	12.0	16.1	14.8	13.5	17.7	14.4	13.1
Daily dietary intake									
Total energy, kcal/d	1545.1	1683.4	1874.5	1638.8	1704.8	1697.1	1546.7	1685.1	1860.3
Alcohol from alcoholic drinks, g/d	2.6	1.9	1.3	2.9	1.9	1.2	2.5	2.0	1.1
Total protein (% of energy)	14.7	15.5	15.5	14.9	15.7	14.9	14.9	15.4	15.5
Total fat (% of energy)	20.5	30.6	38.6	21.2	30.2	38.0	20.3	30.3	39.7
SFAs (% of energy)	5.8	9.2	13.2	6.9	9.3	10.5	5.9	9.3	12.1
MUFAs (% of energy)	7.5	11.7	14.4	7.9	11.5	14.3	7.3	11.4	15.3
TFAs (% of energy)	1.3	2.1	2.4	1.4	2.1	2.5	1.2	2.1	2.8
PUFAs (% of energy)	5.2	7.1	7.5	4.5	6.8	9.8	4.8	6.8	8.9
Omega-3 PUFAs (% of energy)	0.6	0.7	0.8	0.5	0.7	1.0	0.5	0.7	0.8
ALA (% of energy)	0.5	0.6	0.7	0.4	0.6	0.9	0.5	0.6	0.8
Marine omega-3 PUFAs (% of energy)‡	0.04	0.04	0.04	0.03	0.04	0.04	0.04	0.04	0.04
Omega-6 PUFAs (% of energy)	4.6	6.4	6.7	3.9	6.0	8.8	4.2	6.1	8.0
LA (% of energy)	4.5	6.3	6.6	3.9	6.0	8.8	4.1	6.0	7.9
AA (% of energy)	0.04	0.05	0.05	0.04	0.05	0.05	0.03	0.05	0.06
Omega-6/omega-3 ratio	8.2	9.0	8.4	7.7	8.8	9.3	7.8	8.7	9.4

AA indicates arachidonic acid; ALA, α-linolenic acid; BMI, body mass index; LA, linoleic acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; Q, quintile; SFA, saturated fatty acid; and TFA, trans-fatty acid.

*Data are medians or percentages.

†Household income in 1999.

‡Marine omega-3 PUFA intake was calculated by the sum of eicosapentaenoic acid and docosahexaenoic acid.

Table 2. Associations of Specific Dietary Fat Intake With Total Mortality

	Quintiles of Dietary Fat Intake					*P* Trend
	Q1	Q2	Q3	Q4	Q5	
SFAs						
Range (% of energy)	≤6.89	6.89–8.50	8.50–9.98	9.98–11.78	≥11.78	
Median intake (% of energy)	5.79	7.74	9.23	10.80	13.24	
No. of deaths, n (%)	22 578 (21.7)	23 493 (22.5)	25 258 (24.2)	26 975 (25.9)	31 024 (29.8)	
Model 1*	1.00	1.07 (1.05–1.08)	1.16 (1.14–1.18)	1.27 (1.24–1.29)	1.52 (1.49–1.55)	<0.0001
Model 2†	1.00	1.02 (1.01–1.04)	1.07 (1.05–1.09)	1.10 (1.08–1.12)	1.18 (1.16–1.20)	<0.0001
Model 3‡	1.00	1.04 (1.02–1.06)	1.09 (1.07–1.11)	1.14 (1.12–1.16)	1.24 (1.22–1.26)	<0.0001
Model 4§	1.00	1.08 (1.06–1.10)	1.15 (1.12–1.18)	1.19 (1.16–1.22)	1.29 (1.25–1.33)	<0.0001
PUFAs						
Range (% of energy)	≤5.20	5.20–6.27	6.27–7.29	7.29–8.64	≥8.64	
Median intake (% of energy)	4.46	5.77	6.77	7.88	9.82	
No. of deaths, n (%)	25 502 (24.5)	24 981 (24.0)	25 494 (24.5)	25 943 (24.9)	27 408 (26.3)	
Model 1*	1.00	0.98 (0.96–1.00)	0.99 (0.98–1.01)	1.02 (1.00–1.04)	1.11 (1.09–1.13)	<0.0001
Model 2†	1.00	0.98 (0.96–1.00)	0.98 (0.97–1.00)	0.99 (0.97–1.01)	1.02 (1.00–1.04)	0.0098
Model 3‡	1.00	0.99 (0.97–1.00)	0.99 (0.97–1.01)	0.99 (0.97–1.01)	1.01 (0.99–1.03)	0.12
Model 4§	1.00	0.97 (0.95–0.99)	0.95 (0.93–0.97)	0.94 (0.92–0.96)	0.93 (0.91–0.95)	<0.0001
MUFAs						
Range (% of energy)	≤8.73	8.73–10.62	10.62–12.23	12.23–14.03	≥14.03	
Median intake (% of energy)	7.33	9.75	11.43	13.07	15.34	
No. of deaths, n (%)	23 020 (22.1)	23 682 (22.7)	25 011 (24.0)	26 852 (25.8)	30 763 (29.5)	
Model 1*	1.00	1.04 (1.02–1.06)	1.10 (1.08–1.12)	1.20 (1.18–1.22)	1.42 (1.40–1.45)	<0.0001
Model 2†	1.00	1.00 (0.99–1.02)	1.02 (1.00–1.04)	1.05 (1.03–1.07)	1.12 (1.10–1.14)	<0.0001
Model 3‡	1.00	1.02 (1.00–1.04)	1.04 (1.02–1.06)	1.08 (1.06–1.10)	1.14 (1.12–1.16)	<0.0001
Model 4§	1.00	0.98 (0.95–1.00)	0.96 (0.93–0.99)	0.96 (0.93–0.99)	0.98 (0.94–1.02)	0.72
A-MUFAs						
Range (% of energy)	≤4.19	4.19–5.43	5.43–6.56	6.56–7.92	≥7.92	
Median intake (% of energy)	3.32	4.85	5.98	7.18	8.98	
No. of deaths, n (%)	22 864 (21.9)	23 825 (22.9)	24 987 (24.0)	26 950 (25.9)	30 702 (29.5)	
Model 1*	1.00	1.06 (1.04–1.08)	1.13 (1.11–1.15)	1.26 (1.24–1.28)	1.50 (1.47–1.53)	<0.0001
Model 2†	1.00	1.03 (1.01–1.05)	1.06 (1.04–1.08)	1.12 (1.10–1.14)	1.19 (1.16–1.21)	<0.0001
Model 3‡	1.00	1.04 (1.02–1.06)	1.07 (1.05–1.09)	1.14 (1.12–1.16)	1.22 (1.20–1.24)	<0.0001
Model 4§	1.00	1.02 (1.00–1.04)	1.03 (1.00–1.05)	1.06 (1.03–1.09)	1.09 (1.06–1.13)	<0.0001
P-MUFAs						
Range (% of energy)	≤3.49	3.49–4.51	4.51–5.54	5.54–6.92	≥6.92	
Median intake (% of energy)	2.83	4.02	5.01	6.15	8.13	
No. of deaths, n (%)	25 474 (24.4)	24 954 (23.9)	25 130 (24.1)	25 951 (24.9)	27 819 (26.7)	
Model 1*	1.00	0.97 (0.95–0.99)	0.97 (0.95–0.99)	1.00 (0.99–1.02)	1.07 (1.05–1.09)	<0.0001
Model 2†	1.00	0.97 (0.95–0.98)	0.95 (0.93–0.96)	0.96 (0.94–0.98)	0.97 (0.96–0.99)	0.035
Model 3‡	1.00	0.98 (0.96–0.99)	0.95 (0.94–0.97)	0.97 (0.95–0.98)	0.97 (0.95–0.99)	0.0031
Model 4§	1.00	0.97 (0.95–0.99)	0.94 (0.92–0.96)	0.95 (0.92–0.97)	0.94 (0.91–0.97)	0.0004
TFAs						
Range (% of energy)	≤1.41	1.41–1.81	1.81–2.20	2.20–2.73	≥2.73	

(*Continued*)

Table 2. Continued

	Quintiles of Dietary Fat Intake					*P* Trend
	Q1	Q2	Q3	Q4	Q5	
Median intake (% of energy)	1.14	1.62	2.00	2.43	3.20	
No. of deaths, n (%)	22 675 (21.8)	24 159 (23.2)	25 546 (24.5)	27 268 (26.2)	29 680 (28.5)	
Model 1*	1.00	1.07 (1.05–1.09)	1.14 (1.12–1.16)	1.22 (1.20–1.24)	1.31 (1.29–1.34)	<0.0001
Model 2†	1.00	1.02 (1.00–1.04)	1.04 (1.02–1.06)	1.06 (1.04–1.08)	1.09 (1.07–1.11)	<0.0001
Model 3‡	1.00	1.02 (1.00–1.04)	1.04 (1.02–1.06)	1.06 (1.04–1.08)	1.08 (1.06–1.10)	<0.0001
Model 4§	1.00	1.00 (0.98–1.02)	1.00 (0.98–1.02)	1.01 (0.99–1.03)	1.03 (1.00–1.05)	0.0062

A-MUFA indicates animal-based MUFA; BMI, body mass index; HR, hazard ratio; MUFA, monounsaturated fatty acid; P-MUFA, plant-based MUFA; PUFA, polyunsaturated fatty acid; Q, quintile; SFA, saturated fatty acid; and TFA, trans-fatty acid.

*Adjusted for age and sex.

†Additionally adjusted for BMI (in kg/m^2; <18.5, 18.5–25, 25–30, 30–35, ≥35, or missing), race (white, black, Hispanic/Asian/Pacific Islander/American Indian/Alaskan native, or unknown/missing), education (less than high school, high school graduate, some college, college graduate, or unknown/missing), marital status (married/living as married or widowed/divorced/separated/never married/unknown), household income (quintiles), smoking (never smoked, quit, ≤20 cigarettes a day, quit, >20 cigarettes a day, currently smoking, ≤20 cigarettes a day, currently smoking, >20 cigarettes a day, or unknown), alcohol (0, 0.1–4.9, 5.0–29.9, or ≥30 g/day), and physical activity (never/rarely, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, ≥5 times/wk, or unknown/missing).

‡Additionally adjusted for history of hypertension (yes or no), history of hypercholesterolemia (yes or no), perceived health condition (excellent, very good, good, fair, or poor), history of heart disease (yes or no), stroke (yes or no), diabetes mellitus (yes or no), and cancer (yes or no) at baseline, multi-vitamin use (never, <1 time/wk, 1–3 times/wk, 4–6 times/wk, or every day), aspirin use (no, monthly, weekly, daily, or missing), and hormones use (never, <5 y, 5–9 y, ≥10 y, or unknown) for women.

§Further adjusted for intake of total energy, percentages of energy intake from protein, and remaining fatty acids where appropriate (SFAs, PUFAs, P-MUFAs, A-MUFAs, and TFAs, all in quintiles). Comparison is an isocaloric substitution for total carbohydrates in this model.

of MUFA intake with total mortality was observed in the final model, lower total mortality was present when MUFAs were not compared with other macronutrients (Online Table VII). About MUFAs from different sources, A-MUFA intake was correlated with a higher total mortality (*P* trend <0.0001), whereas P-MUFA intake was inversely associated with total mortality (*P* trend=0.0004; model 4). HR (95% CI) comparing the highest versus lowest quintile was 1.09 (1.06–1.13) for A-MUFAs and 0.94 (0.91–0.97) for P-MUFAs (Table 2).

For specific PUFAs, distinctive associations were observed when comparing carbohydrates (model 4; Table 3). Total omega-3 PUFA intake was related to higher total mortality and mainly ascribed to the positive association of ALA intake (HR comparing the highest versus lowest quintile: 1.06; 95% CI, 1.03–1.09; *P* trend <0.0001), whereas marine omega-3 PUFA intake was associated with lower total mortality (HR: 0.92; 95% CI, 0.90–0.94; *P* trend <0.0001). The inverse association of total omega-6 PUFA intake with the total mortality was mainly driven by LA intake (HR: 0.88; 95% CI, 0.86–0.91; *P* trend <0.0001). In contrast, each 1-SD increment of energy from the AA intake was related to 4% higher total mortality (Figure 1). In addition, the omega-6/omega-3 ratio was associated with lower total mortality (*P* trend=0.0002).

Dietary Fats and Cause-Specific Mortality

SFA intake was associated with higher CVD, cancer, RD, diabetes mellitus, infections, and chronic liver disease mortality after multivariable adjustment (Online Table III), while TFA intake was related to higher CVD and RD mortality. Notably, each 1-SD increment of energy from SFAs was related to a 7% higher CVD mortality (Figure 1). A-MUFA intake was correlated with higher CVD, RD, and kidney disease mortality while P-MUFA intake was related to lower CVD mortality. In contrast, total PUFA intake was associated with lower CVD, cancer, infections, and chronic liver disease mortality.

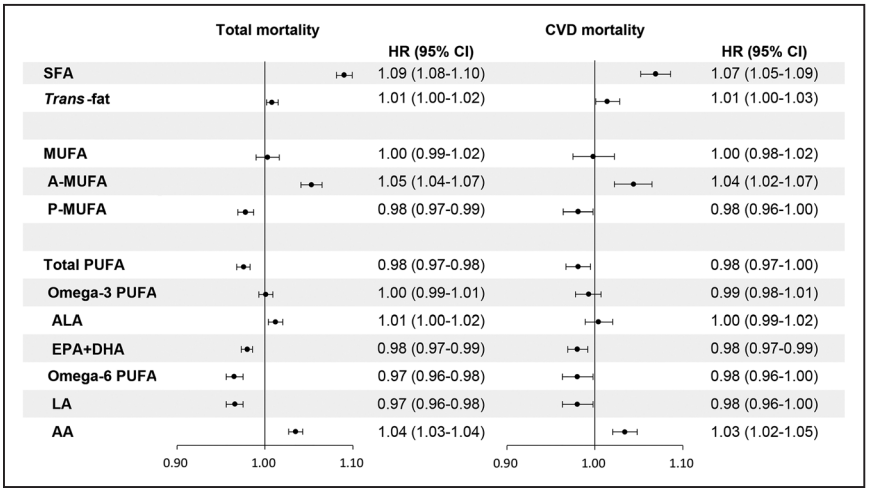

Figure 1. Multivariable hazards ratios (HRs) (95% CIs) of total and cardiovascular disease (CVD) mortality for 1-SD increment in specific types of dietary fat intake compared with total carbohydrates. Forest plots show the multivariable HRs of total and CVD mortality associated with 1-SD increment of specific types of dietary fats intakes. Horizontal lines represent 95% CIs. A-MUFA indicates animal MUFA; AA, arachidonic acid; ALA, α-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MUFA, monounsaturated fatty acid; P-MUFA, plant MUFA; PUFA, polyunsaturated fatty acid; and SFA, saturated fatty acid.

Table 3. Associations of Omega-3 and Omega-6 PUFA Intake With Total Mortality

	Quintiles of Dietary Fat Intake					*P* Trend
	Q1	Q2	Q3	Q4	Q5	
Total omega-3 PUFAs						
Range (% of energy)	≤0.54	0.54–0.63	0.63–0.73	0.73–0.87	≥0.87	
Median intake (% of energy)	0.47	0.59	0.68	0.79	1.00	
No. of deaths, n (%)	26 121 (25.1)	25 259 (24.2)	25 593 (24.6)	26 056 (25.0)	26 299 (25.2)	
Model 1*	1.00	0.96 (0.95–0.98)	0.98 (0.96–0.99)	1.01 (0.99–1.02)	1.04 (1.02–1.06)	<0.0001
Model 2†	1.00	0.99 (0.97–1.01)	1.00 (0.99–1.02)	1.03 (1.01–1.04)	1.03 (1.01–1.05)	<0.0001
Model 3‡	1.00	1.00 (0.98–1.02)	1.01 (1.00–1.03)	1.03 (1.01–1.05)	1.04 (1.02–1.06)	<0.0001
Model 4§	1.00	0.99 (0.97–1.01)	1.00 (0.98–1.02)	1.02 (1.00–1.04)	1.02 (1.00–1.05)	0.026
α-Linolenic acid						
Range (% of energy)	≤0.48	0.48–0.58	0.58–0.67	0.67–0.80	≥0.80	
Median intake (% of energy)	0.42	0.53	0.62	0.73	0.93	
No. of deaths, n (%)	25 560 (24.5)	25 042 (24.0)	25 761 (24.7)	26 113 (25.1)	26 852 (25.8)	
Model 1*	1.00	0.98 (0.96–1.00)	1.01 (1.00–1.03)	1.04 (1.02–1.06)	1.09 (1.07–1.11)	<0.0001
Model 2†	1.00	0.99 (0.98–1.01)	1.01 (1.00–1.03)	1.02 (1.01–1.04)	1.04 (1.03–1.06)	<0.0001
Model 3‡	1.00	1.00 (0.99–1.02)	1.03 (1.01–1.05)	1.04 (1.02–1.06)	1.06 (1.04–1.08)	<0.0001
Model 4§	1.00	1.00 (0.98–1.02)	1.02 (1.00–1.05)	1.04 (1.01–1.06)	1.06 (1.03–1.09)	<0.0001
Marine omega-3 PUFAs						
Range (% of energy)	≤0.021	0.021–0.033	0.033–0.048	0.048–0.075	≥0.075	
Median intake (% of energy)	0.01	0.03	0.04	0.06	0.10	
No. of deaths, n (%)	28 562 (27.4)	26 531 (25.5)	25 917 (24.9)	24 993 (24.0)	23 325 (22.4)	
Model 1*	1.00	0.93 (0.92–0.95)	0.92 (0.90–0.93)	0.88 (0.87–0.90)	0.81 (0.80–0.83)	<0.0001
Model 2†	1.00	0.98 (0.96–1.00)	0.99 (0.97–1.01)	0.98 (0.96–1.00)	0.95 (0.94–0.97)	<0.0001
Model 3‡	1.00	0.97 (0.96–0.99)	0.98 (0.96–1.00)	0.96 (0.94–0.98)	0.92 (0.91–0.94)	<0.0001
Model 4§	1.00	0.97 (0.95–0.99)	0.97 (0.96–0.99)	0.95 (0.93–0.97)	0.92 (0.90–0.94)	<0.0001
Total omega-6 PUFAs						
Range (% of energy)	≤4.57	4.57–5.56	5.56–6.49	6.49–7.73	≥7.73	
Median intake (% of energy)	3.90	5.09	6.01	7.03	8.81	
No. of deaths, n (%)	25 510 (24.5)	24 906 (23.9)	25 386 (24.4)	26 056 (25.0)	27 470 (26.4)	
Model 1*	1.00	0.98 (0.96–0.99)	0.99 (0.97–1.01)	1.02 (1.01–1.04)	1.11 (1.09–1.13)	<0.0001
Model 2†	1.00	0.98 (0.96–0.99)	0.98 (0.96–0.99)	0.99 (0.97–1.01)	1.01 (0.99–1.03)	0.020
Model 3‡	1.00	0.98 (0.97–1.00)	0.98 (0.96–1.00)	0.99 (0.97–1.01)	1.00 (0.99–1.02)	0.31
Model 4§	1.00	0.96 (0.94–0.98)	0.93 (0.91–0.95)	0.91 (0.89–0.94)	0.89 (0.86–0.92)	<0.0001
Linoleic acid						
Range (% of energy)	≤4.53	4.53–5.50	5.50–6.44	6.44–7.67	≥7.67	
Median intake (% of energy)	3.85	5.04	5.96	6.98	8.75	
No. of deaths, n (%)	25 541 (24.5)	24 886 (23.9)	25 413 (24.4)	26 060 (25.0)	27 428 (26.3)	
Model 1*	1.00	0.97 (0.96–0.99)	0.99 (0.97–1.01)	1.02 (1.00–1.04)	1.10 (1.08–1.12)	<0.0001
Model 2†	1.00	0.97 (0.96–0.99)	0.98 (0.96–0.99)	0.99 (0.97–1.01)	1.01 (0.99–1.03)	0.047
Model 3‡	1.00	0.98 (0.96–1.00)	0.98 (0.96–1.00)	0.99 (0.97–1.01)	1.00 (0.98–1.02)	0.45
Model 4§	1.00	0.95 (0.93–0.97)	0.93 (0.90–0.95)	0.91 (0.88–0.93)	0.88 (0.86–0.91)	<0.0001
Arachidonic acid						
Range (% of energy)	≤0.031	0.031–0.042	0.042–0.053	0.053–0.067	≥0.067	

(*Continued*)

Table 3. Continued

	Quintiles of Dietary Fat Intake					*P* Trend
	Q1	Q2	Q3	Q4	Q5	
Median intake (% of energy)	0.02	0.04	0.05	0.06	0.08	
No. of deaths, n (%)	25 734 (24.7)	25 457 (24.4)	25 506 (24.5)	25 591 (24.6)	27 040 (25.9)	
Model 1*	1.00	0.99 (0.98–1.01)	1.02 (1.00–1.03)	1.05 (1.04–1.07)	1.17 (1.15–1.19)	<0.0001
Model 2†	1.00	1.00 (0.98–1.02)	1.02 (1.00–1.04)	1.04 (1.02–1.06)	1.10 (1.08–1.12)	<0.0001
Model 3‡	1.00	0.99 (0.98–1.01)	1.01 (0.99–1.02)	1.02 (1.00–1.04)	1.06 (1.04–1.08)	<0.0001
Model 4§	1.00	1.01 (0.99–1.03)	1.03 (1.01–1.05)	1.05 (1.03–1.08)	1.10 (1.08–1.13)	<0.0001
Omega-6/omega-3 ratio						
Range (% of energy)	≤7.43	7.43–8.29	8.29–9.08	9.08–10.14	≥10.14	
Median intake (% of energy)	6.77	7.89	8.67	9.54	11.14	
No. of deaths, n (%)	25 019 (24.0)	24 863 (23.9)	25 781 (24.7)	26 112 (25.1)	27 553 (26.4)	
Model 1*	1.00	0.99 (0.97–1.01)	1.03 (1.01–1.05)	1.04 (1.02–1.06)	1.10 (1.08–1.11)	<0.0001
Model 2†	1.00	0.97 (0.95–0.99)	0.98 (0.97–1.00)	0.97 (0.95–0.99)	0.97 (0.96–0.99)	0.0066
Model 3‡	1.00	0.97 (0.96–0.99)	0.98 (0.97–1.00)	0.96 (0.95–0.98)	0.95 (0.94–0.97)	<0.0001
Model 4§	1.00	0.98 (0.96–0.99)	0.99 (0.97–1.01)	0.97 (0.95–0.99)	0.96 (0.94–0.98)	0.0002

HR indicates hazard ratio; PUFA, polyunsaturated fatty acid; and Q, quintile.

*Adjusted for age and sex.

†Additionally adjusted for BMI (in kg/m^2; <18.5, 18.5–25, 25–30, 30–35, ≥35, or missing), race (white, black, Hispanic/Asian/Pacific Islander/American Indian/Alaskan native, or unknown/missing), education (less than high school, high school graduate, some college, college graduate, or unknown/missing), marital status (married/living as married or widowed/divorced/separated/never married/unknown), household income (quintiles), smoking (never smoked, quit, ≤20 cigarettes a day, quit, >20 cigarettes a day, currently smoking, ≤20 cigarettes a day, currently smoking, >20 cigarettes a day, or unknown), alcohol (0, 0.1–4.9, 5.0–29.9, or ≥30 g/day), and physical activity (never/rarely, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, ≥5 times/wk, or unknown/missing).

‡Additionally adjusted for history of hypertension (yes or no), history of hypercholesterolemia (yes or no), perceived health condition (excellent, very good, good, fair, or poor), history of heart disease (yes or no), stroke (yes or no), diabetes mellitus (yes or no), and cancer (yes or no) at baseline, multi-vitamin use (never, <1 time/wk, 1–3 times/wk, 4–6 times/wk, or every day), aspirin use (no, monthly, weekly, daily, or missing), and hormones use (never, <5 y, 5–9 y, ≥10 y, or unknown) for women.

§Further adjusted for intake of total energy, percentages of energy intake from protein, and remaining fatty acids where appropriate (SFAs, PUFAs, P-MUFAs, A-MUFAs, and TFAs, all in quintiles). Comparison is an isocaloric substitution for total carbohydrates in this model.

For specific PUFAs, marine omega-3 PUFA intake was associated with lower CVD, cancer, RD, AD, and chronic liver disease mortality, whereas ALA intake was associated with higher cancer and RD mortality (Online Table IV). Intake of LA, the most abundant omega-6 PUFA, was related to lower CVD, cancer, diabetes mellitus, infections, and kidney disease mortality. However, AA intake was associated with higher CVD, cancer, and RD mortality (Online Table V). Lower cancer and diabetes mellitus mortality but higher AD mortality was observed with the elevation of the omega-6/omega-3 ratio (Online Table VI).

Substitution Analyses

Figure 2 shows total and major chronic diseases mortality by isocaloric replacement of SFAs with specific fats. In the substitution model, a 5% replacement of energy from SFAs with MUFAs was associated with a 16% lower total mortality, a 13% lower CVD mortality, an 11% lower cancer mortality, and a 32% lower RD mortality. Replacing energy from SFAs with P-MUFAs was related to similar reductions in total, CVD, cancer, and RD mortality. However, a 2% isocaloric replacement of energy from SFAs with TFAs was associated with a 3% higher total and CVD mortality, a 9% higher RD mortality, and a 17% higher AD mortality. Isocalorically substituting 2% of energy from SFAs with omega-6 PUFAs was associated with an 8% lower total mortality, a 6% lower CVD mortality, an 8% lower cancer mortality, an 11% lower RD mortality, and a 9% lower diabetes mellitus mortality, which was mainly driven by LA (Online Table VIII). A 0.3% replacement of energy from SFAs with omega-3 PUFAs was associated with a 12% lower AD mortality.

Subgroup Analyses

In the subgroup analyses, significant interactions for specific fats in relation to total mortality were observed when the analyses were stratified by sex, BMI, baseline hypercholesterolemia, and hypertension (Online Table IX). Notably, we observed a stronger positive association of SFA intake and negative associations of LA, marine omega-3 PUFA, and total PUFA intake with total mortality in the men than in the women. The positive associations of SFA and A-MUFA intakes in relation to total mortality were more pronounced among the nonobese participants than the obese participants, while positive associations of TFA intake with total mortality were observed only in the participants with BMI ≥30, hypercholesterolemia, and hypertension. In addition, the inverse association of marine omega-3 PUFA intake with total mortality was restricted to the nonobese subjects. The positive associations of A-MUFAs, ALA, and AA intakes were more

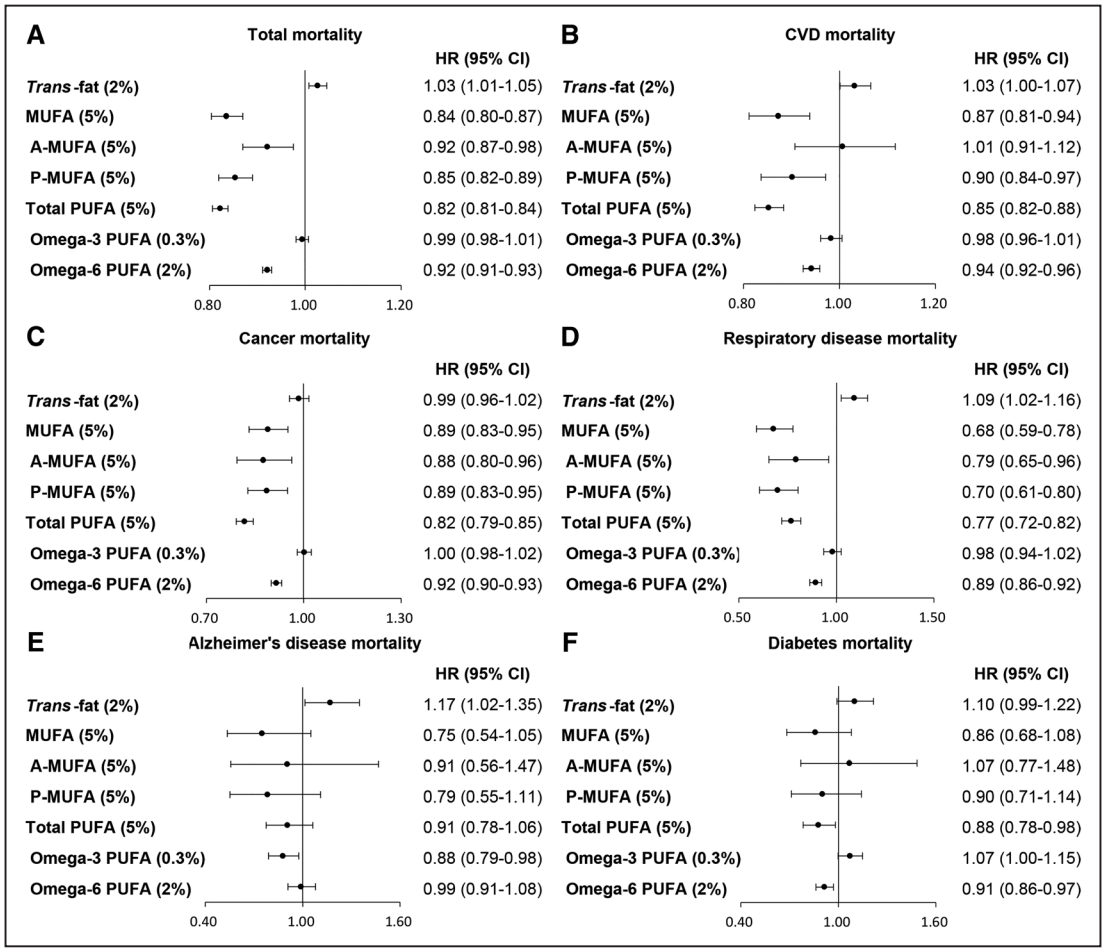

Figure 2. Multivariable hazards ratios (HRs) (95% CIs) of total and cause-specific mortality by isocaloric substitution of saturated fatty acids (SFAs) with specific dietary fats. Forest plots show the multivariable HRs of (**A**) total, (**B**) cardiovascular disease (CVD), (**C**) cancer, (**D**) respiratory disease (RD), (**E**) Alzheimer disease (AD), and (**F**) diabetes mellitus mortality associated with isocalorically replacing the percentage of energy from SFAs by specific types of dietary fats (5% of energy for monounsaturated fatty acids [MUFAs] and polyunsaturated fatty acids [PUFAs], 2% for trans-fats and omega-6 PUFAs, and 0.3% for omega-3 PUFAs). Horizontal lines represent 95% CIs.

pronounced among the nonhypertensive participants than the hypertensive subjects.

Sensitivity Analyses

The significant associations of specific dietary fats with total and cause-specific mortality remained similar after further adjusting for a propensity score or Healthy Eating Index-2015 (Online Tables X and XI), excluding the first 5 years of follow-up, the participants with extreme BMI, or those with CVD, cancer, and diabetes mellitus at baseline (Online Tables XII through XIV), or shortening the follow-up duration to 8 years (Online Table XV).

Discussion

This large prospective cohort study found consistent associations of SFA, A-MUFA, and TFA intake with higher total and certain cause-specific mortality. In contrast, the participants with higher intake of P-MUFAs, marine omega-3 PUFAs, and LA or lower intake of ALA and AA had lower total mortality and certain cause-specific mortality. To the best of our knowledge, this is the largest prospective study that investigated the associations between specific dietary fats and mortality among the general population with a long-term duration of follow-up (16 years on average).

Our results of SFA intake in relation to higher total mortality and CVD mortality are consistent with those of a recent US Nurses' Health Study and HPFS (Health Professionals Follow-Up Study),[8] Japanese Takayama Study,[23] and other prior studies[24,25] but are inconsistent with those showing inverse associations.[26,27] Compared with findings reporting SFA intake with a narrow range and a limited sample size, the current study provided a wide range of SFA intake (<7% and >12% of energy from SFAs among the lowest and the highest quintiles of participants, respectively) and enough cases of deaths (129 328 deaths) to underscore the association of SFA intake with higher mortality. Similarly, the current results of TFA intake in relation to higher total mortality and CVD mortality are in agreement with those of a recent meta-analysis.[3] TFA consumption has also recently been linked to an increased risk of fatty liver,[28] peripheral artery disease,[29] cardiometabolic risk factors,[30] and decreased leucocyte telomere length.[31] Interestingly, we found that the relationship between TFA intake and total mortality was mainly driven by the positive association with RD mortality, which needs to be further confirmed.

Because of common major sources of animal fats in Western diets, total MUFA intake was strongly correlated with

SFA intake (Spearman coefficient 0.80, $P<0.0001$, Online Table II), which may obscure the association with MUFAs. The relationships between MUFA intake and CHD risk were dependent on the food sources of MUFAs in that A-MUFA intake was associated with a higher CHD risk whereas P-MUFA intake tended to be associated with a lower CHD risk.[32] Additionally, a recent meta-analysis showed that the inverse associations of MUFA intake with total mortality and CVD mortality were mainly driven by the intake of olive oils, the major plant source of MUFAs in the Mediterranean diet.[33] We also found that A-MUFA intake was associated with a higher risk of total mortality and CVD mortality while P-MUFA intake was associated with a lower risk, underscoring the role of food sources in the health effects of MUFA intake. We also observed reductions in the risk of cancer and RD mortality when replacing SFAs with MUFAs, especially with P-MUFAs, which are more practical. Previous epidemiological studies have shown the protective effects of MUFAs on colorectal and breast cancer.[34,35] About RD, a Western diet containing SFAs and TFAs was related to a higher risk of chronic obstructive pulmonary disease, whereas MUFA intake might ameliorate this disorder via relieving postprandial inflammation.[36]

Omega-3 PUFAs may have protective effects on inflammation-driven chronic diseases, including CVD, cancer, RD, AD, and chronic liver disease.[37] Their supplements as valid nutraceuticals could reduce blood triglycerides with no clinically significant effects on LDL (low-density lipoprotein)-Cholesterol and HDL (high-density lipoprotein)-Cholesterol, although a meta-analysis concluded no protective effect on cardiovascular outcomes including cardiac death.[38] Accumulative evidence supported the secondary prevention of CHD in patients with prior CHD.[39] Our findings are in line with other cohort studies showing inverse associations of marine omega-3 PUFA intake with CVD, cancer, and AD mortality.[6,40,41] However, little evidence or inconsistent results supported our findings of inverse associations between marine omega-3 PUFA intake with total mortality and RD mortality.[6,7,42]

The physiological effects of ALA mainly stem from its conversion into marine omega-3 PUFAs, but the conversion rates are limited and sex-dependent.[43] The current study showed that ALA intake was associated with higher cancer mortality, which was in line with previous Nurses' Health Study and HPFS research.[8] However, the findings of ALA intake in relation to higher total mortality and RD mortality still warrant further evidence from prospective studies and randomized controlled trials. Nonetheless, the observed health risk of ALA may be ascribed to the presence of trans-ALA in food. Because of the nature of its unsaturated structure, ALA is 12 to 15 times more easily to be converted into transforms than LA and up to 40% of ALA can be present as trans isomers.[44]

Strong inverse associations of LA intake with risk of death from CVD, cancer, diabetes mellitus, and infections were observed, which were consistent with several general population-based prospective studies,[8,45,46] but were not supported by a recent meta-analysis showing no reductions in total and CVD mortality when substituting SFAs with LA.[47] Furthermore, the inverse association with CVD mortality was not in accordance with a positive association in CVD patients.[48] This inconsistent result may be ascribed to the use of margarine as the source of LA containing TFAs before trans-fat use was phased out in the last decade. The current study found an inverse association of LA intake with mortality from diabetes mellitus, which was in line with a previous meta-analysis demonstrating an inverse relationship between omega-6 PUFA biomarkers and the prevalence of type 2 diabetes mellitus.[49] However, the current findings of an inverse association of LA intake with cancer and infections mortality warrant further elucidation.

In contrast, AA intake was associated with higher total mortality, CVD, cancer, and RD mortality. Although it is a derivative of LA, excess AA intake may induce proinflammatory and prothrombotic effects, and thereby underlies pathophysiological changes.[50,51] Using biomarkers of AA in adipose tissue, previous studies showed positive associations with myocardial infarction[52] and CVD mortality.[53] However, these biomarkers may be not related to dietary intake of AA. Because AA intake was weakly correlated with SFA intake (Spearman coefficient 0.28, $P<0.0001$, Online Table II), our results of strong associations of AA intake with higher mortality promote public concerns.

About the composition of PUFA intake, we found the omega-6/omega-3 ratio was associated with lower total mortality, cancer mortality, and diabetes mellitus mortality but higher AD mortality. Because the associations appeared largely different between marine omega-3 PUFA and ALA intake and also between LA and AA intake, the omega-6/omega-3 ratio may not be a robust biomarker for associating mortality compared with specific omega-3 and omega-6 PUFAs. Similarly, the dietary recommendations of substituting SFAs with PUFAs should preferably refer to specific PUFAs.

Our subgroup analyses showed more prominent associations of SFAs, PUFAs, LA, and marine omega-3 PUFA intake with total mortality in men than in women, which may be because of sexual dimorphism in the metabolism of PUFA[43] and other sex-dependent lifestyle factors. Compared with the healthy participants, the obese, hypercholesterolemic, or hypertensive subjects had weaker or stronger associations with mortality. Future mechanistic work is needed to characterize the role of specific dietary fat intake among these patients with a high risk of CVD.

The strengths of the current study include the prospective design, large population size (129 328 deaths among 521 120 participants), and long duration of the 16-year follow-up, which substantially reduce the change of reverse causality and enables subgroup analyses. The broad ranges of dietary fat intake allow us to comprehensively assess the effects of fats at different intake levels. We also excluded participants with CVD, cancer, and diabetes mellitus at baseline, or initial 5 years of follow-up to further reduce the effect of reverse causality and observed similar results in sensitivity analyses.

This study had several limitations. First, despite full adjustment for acknowledged confounders, we could not exclude the possibility of residual or unmeasured confounding. Second, the causality could not be established due to the observational study setting. Third, measurement errors may be still present in the analyses although the portion size of food was specified in the food frequency questionnaires. Finally, only a single measurement for dietary intake was conducted at baseline, but the long-term dietary patterns appear to

be nearly unchanged. Despite the potential time-dependent changes in dietary patterns, strong significant associations existed with a shorter duration of follow-up, indicating this is unlikely to have resulted in appreciable errors. Nonetheless, we could not capture the potential changes in the fat content of specific foods, especially for trans-fat, which has been largely reduced. Hence, even if the patterns of food were constant, the intake of trans-fat decreased dramatically, dampening the apparent risk.

In conclusion, this study observed the detrimental effects of SFAs, TFAs, A-MUFAs, ALA, and AA intake on total mortality and other certain cause-specific mortality. Higher intake of marine n-3 PUFAs was associated with lower total mortality, CVD, cancer, RD, and AD mortality. Isocalorically replacing SFAs with P-MUFAs or LA was associated with lower total mortality, CVD, cancer, and RD mortality. These findings support the recent dietary guidelines from the US Department of Agriculture, which recommend eliminating TFA intake from processed foods such as fried foods, crackers, and margarine, and replacing SFAs (mainly from red meats) with MUFAs and PUFAs. Furthermore, our results suggest that the consumption of MUFAs from plant-based sources and PUFAs from foods rich in LA and marine omega-3 PUFAs should be encouraged for general health and the control of various chronic diseases.

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Disclosures

None.

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