Dietary fat intake and risk of cardiovascular disease and all-cause mortality in a population at high risk of cardiovascular disease[1]

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ABSTRACT

Background: Dietary fat quality and fat replacement are more important for cardiovascular disease (CVD) prevention than is total dietary fat intake.

Objective: The aim was to evaluate the association between total fat intake and fat subtypes with the risk of CVD (myocardial infarction, stroke, or death from cardiovascular causes) and cardiovascular and all-cause death. We also examined the hypothetical effect of the isocaloric substitution of one macronutrient for another.

Design: We prospectively studied 7038 participants at high CVD risk from the PREvención con DIeta MEDiterránea (PREDIMED) study. The trial was conducted from 2003 to 2010, but the present analysis was based on an expanded follow-up until 2012. At baseline and yearly thereafter, total and specific fat subtypes were repeatedly measured by using validated food-frequency questionnaires. Time-dependent Cox proportional hazards models were used.

Results: After 6 y of follow-up, we documented 336 CVD cases and 414 total deaths. HRs (95% CIs) for CVD for those in the highest quintile of total fat, monounsaturated fatty acid (MUFA), and polyunsaturated fatty acid (PUFA) intake compared with those in the lowest quintile were 0.58 (0.39, 0.86), 0.50 (0.31, 0.81), and 0.68 (0.48, 0.96), respectively. In the comparison between extreme quintiles, higher saturated fatty acid (SFA) and *trans*-fat intakes were associated with 81% (HR: 1.81; 95% CI: 1.05, 3.13) and 67% (HR: 1.67; 95% CI: 1.09, 2.57) higher risk of CVD. Inverse associations with all-cause death were also observed for PUFA and MUFA intakes. Isocaloric replacements of SFAs with MUFAs and PUFAs or *trans* fat with MUFAs were associated with a lower risk of CVD. SFAs from pastries and processed foods were associated with a higher risk of CVD.

Conclusions: Intakes of MUFAs and PUFAs were associated with a lower risk of CVD and death, whereas SFA and *trans*-fat intakes were associated with a higher risk of CVD. The replacement of SFAs with MUFAs and PUFAs or of *trans* fat with MUFAs was inversely associated with CVD. This trial was registered at www.controlled-trials.com as ISRCTN 35739639. *Am J Clin Nutr* 2015;102:1563–73.

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INTRODUCTION

The reduction in the intake of dietary fat has traditionally been recommended by health institutions (1). However, dietary fat quality has been recognized as being even more important than the total amount of fat for the prevention of cardiovascular disease (CVD)[14] and death (2, 3). In general, *trans*-fat intake from partially hydrogenated vegetable oils is associated with adverse effects on health, and its consumption has been recommended to be reduced to a minimum (4). In addition, CVD risk can also be reduced by decreasing the intake of SFAs and replacing them with a combination of PUFAs and MUFAs (2). The findings from the PREvención con DIeta MEDiterránea (PREDIMED) study, a randomized primary-prevention nutrition trial, in individuals at high CVD risk (5), showed that Mediterranean diets (MedDiets), which were high in MUFAs and PUFAs [because they were supplemented with extra-virgin olive oil (EVOO) or nuts] and low in SFAs and *trans* fat, were effective for the prevention of clinical events of CVD compared with a low-fat control diet (5).

Because of the controversy in the findings of multiple studies, the research in the field has questioned if there is really a positive association between SFAs and CVD, as traditionally speculated (6). Moreover, the results on the relation between the intake of other fat subtypes, CVD, and death are still inconsistent (4, 6–8). Previous studies were conducted in apparently healthy individuals, and data on the role of fat subtypes and the risk of CVD in high-risk patients are limited. For instance, although MUFA intake is reported to be beneficial for preventing several CVD risk factors (e.g., high HDL cholesterol, low blood pressure, and improved inflammatory status), there is not enough available evidence supporting a reduction in the risk of clinical events of CVD or death by MUFA consumption (3, 4).

Recently, researchers have focused not only on total SFA intake but also on the subtypes of SFAs, their food sources, what dietary patterns these foods are part of, and by which foods they are replaced. In fact, food sources contain different amounts and proportions of SFAs, such as myristic, lauric, and stearic acids, which can have differential effects on blood lipids and inflammation, and therefore on CVD risk (9). Although the associations between SFA consumption from different food sources and the incidence of CVD were investigated previously in the Multi-Ethnic Study of Atherosclerosis (9), these associations have not been investigated in a population at high CVD risk with the use of repeated measurements of intake. Furthermore, the relation of these different sources of SFAs with all-cause mortality has never been reported.

In the present prospective study, we hypothesized that MUFAs and PUFAs are associated with a lower risk of CVD and death, whereas SFAs and *trans* fat are associated with a higher risk. We examined the association between intakes of the major types of fatty acids and the risk of CVD, cardiovascular death, and all-cause death in a population at high CVD risk from the PREDIMED study. We also estimated the associations of hypothetic isocaloric substitutions of several dietary components and fat subtypes on the risk of CVD and death. Because more importance has been placed on the differences in the biological effects of fatty acids derived from different food sources (10), the association of SFA intake from different food sources and the risk of CVD and death was also explored.

METHODS

Study population

We used data from the PREDIMED trial as an observational prospective cohort study. The design and protocol of the PREDIMED study (http://www.predimed.es) have been detailed elsewhere (5, 11). The PREDIMED study was a large, multicenter, parallel-group randomized trial for the primary prevention of CVD. The participants were recruited from October 2003 until June 2009. Although the trial was completed in December 2010, the endpoints for the present analysis were based on an extended follow-up until June 2012 with the use of the same methods as those used during the trial to obtain updated information on CVD clinical events and death. Participants were men (aged 55–80 y) and women (aged 60–80 y) who were free of CVD at baseline but who were at high CVD risk because they had either type 2 diabetes or at least 3 of the following CVD risk factors: current smoking, hypertension, hypercholesterolemia, low HDL cholesterol, overweight/obesity, or family history of premature coronary heart disease. Exclusion criteria were the presence of any severe chronic illness, alcohol or drug abuse, a BMI (in kg/m^2) $\geq$40, and allergy or intolerance to olive oil or nuts (5). Participants were randomly assigned to receive: a MedDiet supplemented with EVOO oil (MedDiet+EVOO), a MedDiet supplemented with mixed nuts (MedDiet+nuts), or advice on a low-fat diet (control group). Several companies donated olive oil and nuts to the participants of both MedDiet interventions during the study. The trial was registered at http://www.controlled-trials.com (ISRCTN35739639). All participants provided written informed consent according to a protocol approved by the institutional review boards.

Dietary and other covariate assessment

At baseline and yearly during the follow-up, trained dietitians completed a semiquantitative food-frequency questionnaire (FFQ) in a face-to-face interview with the participants. This questionnaire has been validated in a population at high CVD risk from Spain; however, the questionnaire was not compared with objective measurements (12). Reproducibility and validity of the FFQ for total dietary fat, SFAs, MUFAs, and PUFAs estimated by the Pearson correlation (r) were 0.61, 0.67, 0.59, and 0.63, respectively. The intraclass correlation coefficients for reproducibility and validity were 0.75 and 0.63 for total fat, 0.81 and 0.68 for SFAs, 0.74 and 0.67 for MUFAs, and 0.77 and 0.60 for PUFAs. The FFQ included 137 food items, and frequencies of consumption of food items were reported on an incremental scale with 9 levels (never or almost never; 1–3 times/mo; 1, 2–4, and 5–6 times/wk; and 1, 2–3, 4–6, and >6 times/d). We used Spanish

[14] Abbreviations used: CVD, cardiovascular disease; EVOO, extra-virgin olive oil; FFQ, food-frequency questionnaire; MedDiet, Mediterranean diet; PREDIMED, PREvención con DIeta MEDiterránea; RCT, randomized controlled trial.

food-composition tables to estimate energy and nutrient intake (13). At baseline and yearly during the follow-up, a questionnaire on lifestyle variables, educational achievement, history of illnesses, and medication use was administered. Physical activity was assessed by using the validated Spanish version of the Minnesota Leisure-Time Physical Activity questionnaire (14). Participants were considered to be diabetic, hypercholesterolemic, or hypertensive if they had previously been diagnosed as such and/or if they were being treated with antidiabetic, cholesterol-lowering, or antihypertensive agents, respectively. Anthropometric and blood pressure measurements were taken by trained personnel. We used calibrated scales and a wall-mounted stadiometer to measure weight and height, respectively, with participants wearing light clothing and no shoes; waist circumference was measured midway between the lowest rib and the iliac crest by using an anthropometric tape; and we used a validated oscillometer (Omron HEM705CP) to measure blood pressure, in triplicate, with a 5-min interval between each measurement, and we recorded the mean of these 3 values.

Ascertainment of CVD and death

For the present analysis, we used the following 3 different endpoints: *1*) the primary endpoint of the PREDIMED trial, which is a composite of cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes); *2*) cardiovascular death; and *3*) all-cause death. The endpoint adjudication committee, whose members were blinded to treatment allocation, updated information on these endpoints once per year. The committee used different sources of information, as follows: *1*) yearly questionnaires and examinations for all participants, *2*) family physicians, *3*) comprehensive yearly review of medical records of all participants, and *4*) yearly consultation of the National Death Index. Medical records of deceased participants were requested, and the endpoint adjudication committee determined the cause of death and confirmed major events. This allowed us to assess mortality, regardless of attrition, and therefore mortality results were not affected by the drop-out rates.

Statistical analysis

Participants with total energy intakes less or more than predefined limits (800 and 4000 kcal/d for men and 500 and 3500 kcal/d for women) and those with missing information on the FFQ were excluded from the present analysis. To take advantage of the repeated measurements of the diet, we used yearly updated measures of total dietary fat and subtypes of fat intake using data from baseline to the last FFQ before the onset of disease or death. Participants were categorized into 5 groups according to quintiles of the percentage of energy obtained from total fat and each type of fat (MUFAs, PUFAs, SFAs, and *trans* fat). Baseline characteristics are presented according to extreme quintiles of total fat and subtypes of fat as means (±SDs) for quantitative traits and *n* (%) for categorical variables.

Follow-up time was calculated as the interval between the date of cardiovascular event, death, or end of follow-up (the date of the last visit or the last recorded clinical event of participants while still alive), whichever came first, and the date of random assignment. Time-dependent Cox regression models were used to assess the associations between yearly updated measures of total fat and subtypes of fat intake (classified in quintiles for the percentage of energy), CVD, and death during follow-up. HRs and their 95% CIs were calculated by using the lowest quintile as the reference category.

Multivariable model 1 for the total fat analysis was stratified by recruitment center and adjusted for age, sex, intervention group, updated total energy (kcal/d), alcohol intake (continuous, adding a quadratic term), updated quintiles of protein, and dietary cholesterol. Model 1 for specific subtypes of fat also included as covariates the other subtypes of fat. Model 2 was further adjusted for nondietary confounders and the following classical CVD risk factors: BMI, smoking status (never, former, or current smoker), educational level (primary education, secondary education, or academic/graduate), leisure-time physical activity (metabolic equivalent task minutes/d), baseline diabetes (yes or no), hypertension (yes or no), hypercholesterolemia (yes or no), family history of coronary heart disease (yes or no), use of antihypertensive medication (yes or no), use of oral antidiabetic agents (yes or no), and use of lipid-lowering drugs (yes or no). The estimated HRs can be interpreted as the estimated differences in risk of a lower energy intake from carbohydrates and a concomitant higher energy intake from total fat or subtypes of dietary fat.

To test for linear trend across successive categories, we replaced quintiles by the median intake for each quintile and modeled these values as a continuous variable. HRs and 95% CIs for CVD and all-cause death for a 5% energy increment for total and subtypes of dietary fat were also calculated.

We also estimated the associations of isocaloric substitutions of carbohydrates, MUFAs, and PUFAs for SFAs and *trans* fat by including both continuous variables in the same multivariable model, which also contained the same covariates as in the previous models. We used the difference between regression coefficients and their variances and covariances to derive the HRs and 95% CIs of the substitution analyses. We conducted these analyses both for all-cause death and CVD as outcomes.

In addition, we evaluated the association between SFA intake from different food sources (vegetable SFAs, dairy SFAs, SFAs from pastries, meat and processed-meat SFAs, and fish SFAs) and CVD and all-cause death using the same statistical models as in previous analysis. The estimated HRs of these models can be interpreted as the estimated differences in risk of a lower energy intake from a specific SFA food source and a concomitant higher energy intake from the rest of the SFA food sources, because SFA intake was not included as a covariate in the model.

Statistical tests were 2-sided, and $P < 0.05$ was considered to indicate significance. Analyses were performed by using Stata 12.1 (StataCorp).

RESULTS

Among the 7038 participants who were followed for a median of 6 y, we documented 336 cardiovascular events (myocardial infarction, stroke, or cardiovascular death), 102 cardiovascular deaths, and 414 total deaths. Individuals were grouped into quintiles of yearly updated measures of total fat and specific types of fat intake (**Table 1**). The mean age of participants at baseline was 67 y. The mean intake of total fat (percentage of energy) in the lowest quintile was 29.7% compared with 48.7% in the top quintile of total fat intake. Those participants with a high intake of total fat, SFAs, and *trans* fat were less physically active and

TABLE 1
Baseline characteristics according to quintile of updated measurements of specific types of fat and total fat intake[1]

		Total fat		MUFAs		PUFAs		SFAs		*trans* Fat	
	Total population	Q1	Q5	Q1	Q5	Q1	Q5	Q1	Q5	Q1	Q5
Participants, *n*	7038	1408	1407	1408	1407	1408	1407	1408	1407	1408	1407
Age, y	67 ± 6[2]	67 ± 6	67 ± 6	67 ± 6	67 ± 6	67 ± 6	67 ± 6	67 ± 6	67 ± 6	67 ± 6	67 ± 6*
Women, *n* (%)	4045 (57.5)	765 (54.3)	859 (61.0)*	792 (56.2)	872 (61.9)*	829 (58.9)	787 (55.9)	800 (56.8)	832 (59.1)	892 (63.3)	828 (58.8)*
BMI, kg/m^2	29.9 ± 3.8	29.7 ± 3.7	30.1 ± 4.0	29.9 ± 3.7	30.2 ± 3.9	30.1 ± 3.7	29.7 ± 3.8	29.6 ± 3.6	30.1 ± 3.8	29.6 ± 3.7	30.2 ± 3.9
Smoking habit, *n* (%)											
Never	4324 (61.4)	859 (61.0)	887 (63.0)	856 (60.8)	889 (63.1)	881 (62.5)	861 (61.1)	875 (62.1)	850 (60.4)	940 (66.7)	846 (60.1)*
Former	1734 (24.4)	342 (24.3)	327 (23.2)	364 (25.8)	326 (23.1)	320 (22.7)	356 (25.3)	335 (23.8)	341 (24.4)	303 (21.5)	357 (25.3)*
Current	980 (13.9)	207 (14.7)	193 (13.7)	188 (13.5)	192 (13.6)	207 (14.7)	190 (13.5)	198 (14.0)	216 (15.3)	165 (11.7)	204 (14.5)*
Intervention group, *n* (%)											
MedDiet + EVOO	2446 (34.7)	497 (35.3)	452 (32.1)*	477 (33.8)	496 (35.2)*	528 (37.5)	455 (32.3)*	496 (35.2)	486 (34.5)	494 (35.1)	488 (34.6)
MedDiet + nuts	2304 (32.7)	409 (29.0)	452 (32.1)*	419 (29.7)	455 (32.3)*	375 (26.6)	513 (34.4)*	442 (31.4)	456 (32.4)	456 (32.4)	470 (33.4)
Control group	2288 (32.5)	502 (35.6)	460 (32.7)	512 (36.3)	456 (32.4)	505 (35.8)	438 (31.2)	470 (33.4)	465 (33.0)	458 (32.5)	449 (31.9)
Education, *n* (%)											
Primary	5466 (77.6)	1140 (80.1)	1062 (75.4)*	1144 (81.2)	1059 (75.2)*	1107 (78.6)	1122 (79.7)	1119 (79.4)	1072 (76.1)	1140 (80.9)	1079 (76.7)
Secondary	1314 (18.6)	215 (15.2)	292 (20.7)*	219 (15.5)	302 (21.4)*	246 (17.4)	243 (17.2)	236 (16.7)	278 (19.7)	221 (15.7)	277 (16.7)
University/graduate	258 (3.6)	53 (3.7)	53 (3.7)	45 (3.2)	46 (3.3)	55 (3.9)	42 (2.9)	53 (3.7)	57 (4.0)	47 (3.3)	51 (3.6)
Physical activity, MET-min/d	233 ± 239	249 ± 262	214 ± 226*	249 ± 267	213 ± 204*	220 ± 226	246 ± 251*	247 ± 259	225 ± 244*	242 ± 237	220 ± 246*
Family history of CHD, *n* (%)	1731 (24.6)	355 (23.8)	329 (23.4)*	318 (22.6)	323 (22.9)	380 (26.9)	325 (23.1)	355 (25.2)	339 (24.0)	367 (26.0)	361 (25.6)
Diabetes, *n* (%)	3447 (48.9)	623 (44.2)	811 (57.6)*	745 (47.1)	787 (55.9)*	627 (44.5)	733 (52.1)*	581 (41.2)	806 (57.2)*	620 (44.0)	757 (53.8)*
Hypertension, *n* (%)	5815 (82.6)	1192 (84.6)	1128 (80.1)*	1189 (84.4)	1144 (81.3)	1196 (84.9)	1164 (82.7)	1185 (84.1)	1112 (79.0)*	1167 (82.8)	1139 (80.9)
Hypercholesterolemia, *n* (%)	5076 (72.2)	1101 (78.2)	935 (66.4)*	1067 (75.8)	938 (66.6)*	1020 (72.4)	1001 (71.4)	1122 (79.7)	930 (66.1)*	1079 (76.6)	943 (67.0)*
Oral antidiabetic agents, *n* (%)	2269 (32.2)	405 (28.7)	559 (39.7)*	432 (30.7)	544 (38.6)*	413 (29.3)	486 (34.5)	372 (26.4)	554 (39.3)*	407 (28.9)	510 (36.2)*
Antihypertensive agents, *n* (%)	5116 (72.7)	1030 (73.1)	1026 (72.9)	1032 (73.3)	1040 (73.9)	1045 (74.2)	1027 (72.9)	1047 (74.3)	970 (68.9)*	1034 (73.4)	1001 (71.1)
Lipid-lowering medication, *n* (%)	3395 (48.2)	736 (52.2)	638 (45.3)*	721 (51.2)	641 (45.5)*	672 (47.7)	687 (48.8)	768 (54.5)	594 (42.2)*	748 (53.1)	626 (44.5)*
Energy and nutrient intake											
Total energy intake, kcal/d	2238 ± 544	2254 ± 567	2161 ± 507*	2282 ± 557	2109 ± 472*	2175 ± 564	2314 ± 543*	2219 ± 563	2264 ± 552*	2128 ± 526*	2259 ± 535*
Cholesterol, mg/d	361.3 ± 123.3	327.1 ± 110.4	371.1 ± 131.7*	340.8 ± 116.8	350.3 ± 123.0*	340.9 ± 117.6	365.5 ± 125.5*	298.9 ± 95.9	417.7 ± 135.5*	300.3 ± 98.8	408.3 ± 139.5*
Carbohydrates, % of total energy	41.6 ± 7.1	50.2 ± 5.4	33.7 ± 4.2*	49.4 ± 5.8	34.6 ± 4.7*	47.1 ± 6.7	38.8 ± 6.6*	48.1 ± 6.5	36.5 ± 5.8*	44.4 ± 7.4	39.5 ± 6.6*
Protein, % of total energy	16.6 ± 2.8	16.9 ± 2.9	16.0 ± 2.6*	17.0 ± 2.9	15.7 ± 2.4*	17.1 ± 3.1	16.1 ± 2.6*	16.3 ± 2.9	16.9 ± 2.8*	16.4 ± 2.9	16.6 ± 2.7*
Total fat, % of total energy	39.3 ± 6.8	29.7 ± 3.0	48.7 ± 3.3*	30.8 ± 4.4	47.9 ± 3.9*	32.9 ± 5.2	42.9 ± 6.2*	32.4 ± 5.4	44.6 ± 5.5*	36.9 ± 7.3	41.7 ± 6.2*
MUFAs, % of total energy	19.6 ± 4.5	14.0 ± 2.3	25.4 ± 3.2*	13.4 ± 1.8	26.1 ± 2.4*	16.4 ± 3.3	19.7 ± 4.8*	16.0 ± 3.8	21.9 ± 4.3*	18.9 ± 4.9	20.1 ± 4.4*
PUFAs, % of total energy	6.2 ± 2.0	4.8 ± 1.5	7.5 ± 2.2*	5.8 ± 2.5	6.8 ± 1.7*	4.0 ± 0.47	9.4 ± 1.8*	5.8 ± 2.0	6.4 ± 1.9*	6.0 ± 2.0	6.3 ± 2.0*
SFAs, % of total energy	9.9 ± 2.2	7.8 ± 1.6	11.8 ± 2.0*	8.3 ± 2.0	11.3 ± 2.0*	9.2 ± 2.3	10.1 ± 2.0*	7.0 ± 0.8	13.2 ± 1.4*	8.1 ± 1.7	12.1 ± 2.1*
trans Fat, % of total energy	0.22 ± 0.14	0.17 ± 0.11	0.27 ± 0.16*	0.20 ± 0.13	0.24 ± 0.15*	0.21 ± 0.15	0.23 ± 0.15*	0.12 ± 0.07	0.37 ± 0.16*	0.07 ± 0.02	0.46 ± 0.12*
Dietary fiber, g/d	25.1 ± 8.6	28.9 ± 10.1	21.4 ± 6.3*	29.2 ± 10.10	21.4 ± 6.39*	25.7 ± 9.2	26.1 ± 8.9*	29.4 ± 10.7	21.9 ± 7.1*	27.0 ± 9.7	23.3 ± 7.6*
Alcohol, g/d	8.4 ± 14.3	10.8 ± 18.3	5.1 ± 9.0*	9.5 ± 16.8	5.6 ± 9.9*	9.5 ± 16.8	7.4 ± 12.4*	10.7 ± 18.3	6.5 ± 10.6*	7.4 ± 13.8	6.9 ± 11.0*

[1]All quintiles were included in the analyses. *P value <0.05 for comparisons between quintiles of dietary fat subtypes (Pearson's chi-square test for categorical variables or 1-factor ANOVA for continuous variables), as appropriate. CHD, coronary heart disease; EVOO, extra-virgin olive oil; MedDiet, Mediterranean Diet; MET-min, metabolic equivalent task minutes; Q, quintile.
[2]Mean ± SD (all such values).

TABLE 2
HRs (95% CIs) of cardiovascular disease and all-cause death according to quintile of updated measurements of total dietary fat and specific subtypes of dietary fat intake[1]

	Quintile					
	1 (lowest)	2	3	4	5 (highest)	*P*-trend
Cardiovascular disease						
Total fat						
Cases, *n* (%)	1408 (4.2)	1408 (3.7)	1407 (4.3)	1408 (4.1)	1407 (3.3)	
Median, % of energy	31.3	36.7	40.1	43.5	48.2	
Multivariable model 1	1 (Ref)	0.95 (0.68, 1.34)	0.89 (0.62, 1.26)	0.81 (0.55, 1.17)	0.65 (0.44, 0.98)	0.02
Multivariable model 2	1 (Ref)	0.94 (0.67, 1.32)	0.86 (0.60, 1.22)	0.75 (0.52, 1.08)	0.58 (0.39, 0.86)	<0.01
MUFAs						
Cases, *n* (%)	1408 (4.5)	1408 (3.9)	1408 (3.3)	1408 (4.4)	1407 (3.4)	
Median, % of energy	14.9	18.3	20.7	23.0	26.1	
Multivariable model 1	1 (Ref)	0.87 (0.61, 1.25)	0.63 (0.43, 0.94)	0.74 (0.50, 1.12)	0.52 (0.33, 0.84)	<0.01
Multivariable model 3	1 (Ref)	0.88 (0.61, 1.26)	0.66 (0.44, 0.98)	0.76 (0.50, 1.16)	0.50 (0.31, 0.81)	<0.01
PUFAs						
Cases, *n* (%)	1408 (4.8)	1408 (3.8)	1407 (3.7)	1408 (3.7)	1407 (3.5)	
Median, % of energy	4.2	5.3	6.1	7.2	9.0	
Multivariable model 1	1 (Ref)	0.78 (0.56, 1.08)	0.71 (0.51, 1.01)	0.73 (0.51, 1.04)	0.70 (0.50, 0.99)	0.08
Multivariable model 3	1 (Ref)	0.78 (0.56, 1.09)	0.72 (0.51, 1.02)	0.71 (0.51, 1.01)	0.68 (0.48, 0.96)	0.04
SFAs						
Cases, *n* (%)	1408 (2.9)	1408 (3.5)	1407 (4.2)	1408 (3.9)	1407 (4.9)	
Median, % of energy	6.9	8.4	9.4	10.5	12.2	
Multivariable model 1	1 (Ref)	1.46 (0.95, 2.24)	1.56 (0.98, 2.48)	1.49 (0.90, 2.47)	1.96 (0.90, 2.47)	0.03
Multivariable model 3	1 (Ref)	1.44 (0.94, 2.21)	1.48 (0.93, 2.35)	1.39 (0.84, 2.30)	1.81 (1.05, 3.13)	0.07
trans Fat						
Cases, *n* (%)	1408 (2.9)	1408 (2.9)	1408 (4.1)	1408 (4.5)	1407 (5.2)	
Median, % of energy	0.05	0.10	0.16	0.23	0.37	
Multivariable model 1	1 (Ref)	1.05 (0.70, 1.58)	1.43 (0.96, 2.14)	1.55 (1.05, 2.30)	1.76 (1.15, 2.70)	<0.01
Multivariable model 3	1 (Ref)	1.03 (0.68, 1.55)	1.41 (0.94, 2.10)	1.48 (0.99, 2.21)	1.67 (1.09, 2.57)	<0.01
All-cause death						
Total fat						
Cases, *n* (%)	1408 (6.3)	1408 (6.9)	1407 (5.3)	1408 (6.0)	1407 (6.0)	
Median, % of energy	31.3	36.7	40.2	43.5	48.2	
Multivariable model 1	1 (Ref)	1.04 (0.77, 1.40)	0.73 (0.53, 1.01)	0.80 (0.58, 0.82)	0.57 (0.40, 0.82)	<0.01
Multivariable model 2	1 (Ref)	1.02 (0.75, 1.37)	0.71 (0.51, 0.98)	0.75 (0.54, 1.05)	0.53 (0.37, 0.76)	<0.01
MUFAs						
Cases, *n* (%)	1408 (6.3)	1408 (6.1)	1407 (5.9)	1408 (5.4)	1407 (5.4)	
Median, % of energy	14.7	17.9	20.5	22.8	26.0	
Multivariable model 1	1 (Ref)	0.85 (0.62, 1.16)	0.78 (0.56, 1.08)	0.70 (0.49, 1.00)	0.64 (0.43, 0.95)	0.02
Multivariable model 2	1 (Ref)	0.86 (0.63, 1.17)	0.78 (0.56, 1.09)	0.69 (0.48, 0.99)	0.64 (0.43, 0.94)	0.01
PUFAs						
Cases, *n* (%)	1408 (8.1)	1408 (5.9)	1407 (5.9)	1408 (4.9)	1407 (4.4)	
Median, % of energy	4.2	5.3	6.2	7.2	9.0	
Multivariable model 1	1 (Ref)	0.72 (0.53, 0.97)	0.71 (0.52, 0.97)	0.56 (0.40, 0.78)	0.50 (0.35, 0.71)	<0.01
Multivariable model 2	1 (Ref)	0.73 (0.54, 0.99)	0.72 (0.53, 0.99)	0.56 (0.39, 0.80)	0.50 (0.35, 0.73)	<0.01
SFAs						
Cases, *n* (%)	1408 (5.0)	1408 (5.8)	1407 (5.7)	1408 (6.2)	1407 (6.6)	
Median, % of energy	6.9	8.3	9.4	10.5	12.1	
Multivariable model 1	1 (Ref)	1.20 (0.86, 1.68)	1.17 (0.82, 1.67)	1.22 (0.84, 1.77)	1.21 (0.81, 1.80)	0.47
Multivariable model 2	1 (Ref)	1.16 (0.83, 1.62)	1.12 (0.78, 1.61)	1.12 (0.78, 1.60)	1.08 (0.74, 1.58)	0.90
trans Fat						
Cases, *n* (%)	1408 (4.8)	1408 (5.9)	1407 (4.7)	1408 (6.4)	1407 (7.5)	
Median, % of energy	0.05	0.10	0.16	0.23	0.36	
Multivariable model 1	1 (Ref)	1.15 (0.83, 1.60)	0.90 (0.64, 1.29)	1.22 (0.87, 1.72)	1.38 (1.00, 1.94)	0.03
Multivariable model 2	1 (Ref)	1.11 (0.80, 1.54)	0.86 (0.59, 1.24)	1.13 (0.78, 1.64)	1.29 (0.87, 1.90)	0.12

[1]Time-dependent Cox regression models were used to assess the risk of cardiovascular disease and all-cause death by quintile of updated measurements of total dietary fat and dietary fat subtype intake. Multivariable model 1 was adjusted for age (y), sex, intervention group, yearly updated total energy intake (kcal/d), alcohol intake (continuous, adding a quadratic term), updated quintiles of fiber, protein intake, and dietary cholesterol for the total fat analysis. Model 1 for specific subtypes of fat also included as covariates the other subtypes of fat. Model 2 was further adjusted for nondietary variables and classical cardiovascular disease risk factors: BMI (kg/m^2), smoking status (never, former, or current smoker), educational level (primary education, secondary education, or academic/graduate), leisure-time physical activity (metabolic equivalent task minutes/d), baseline diabetes (yes or no), hypertension (yes or no), hypercholesterolemia (yes or no), family history of coronary heart disease (yes or no), use of antihypertensive medication (yes or no), use of oral antidiabetic agents (yes or no), and use of lipid-lowering drugs (yes or no). Extremes of total energy intake (>4000 or <800 kcal/d in men and >3500 or <500 kcal/d in women) were excluded. A major event was a composite of myocardial infarction, stroke, or death from cardiovascular causes. Ref, reference.

had a higher prevalence of diabetes. They also consumed more cholesterol and less dietary fiber and carbohydrates. The drop-out rate was 4.2% (3.0% in the MedDiet groups and 6.9% in the control group). The drop-out rates according to different quintiles of total fat were 8.7% in the first, 4.0% in the second, 3.3% in the third, 2.6% in the fourth, and 2.8% in the highest quintile. The drop-out distribution for quintiles of specific fat subtypes was similar to that of total fat.

Table 2 shows the RRs of CVD according to updated measurements of total dietary fat and specific subtypes of fat intake. The HRs represented the replacement of energy from total carbohydrates with the same percentage of energy from total fat and each type of fat. Total fat intake was significantly associated with a lower risk of CVD. In the fully adjusted model, compared with the lowest quintile (reference), the highest quintile of total fat intake was associated with a 42% lower CVD risk (HR: 0.58; 95% CI: 0.39, 0.86). For specific types of fat, MUFAs and PUFAs were also significantly associated with a lower risk of CVD (Table 2). On the contrary, higher intakes of SFA and *trans* fat were significantly associated with a higher risk of CVD after the model was adjusted for potential confounders.

Total fat intake was significantly associated with a lower risk of total death (Table 2). In the fully adjusted model, the risk of all-cause death was 47% lower in the top quintile compared with the reference (HR: 0.53; 95% CI: 0.37, 0.76). Inverse associations between the intake of MUFAs and PUFAs and total death were found. In the fully adjusted model, compared with the reference quintile, the HR (95% CI) for the top quintile of MUFAs was 0.64 (0.43, 0.94) and was 0.50 (0.35, 0.73) for PUFAs (P-trend < 0.01). *trans* Fat intake was significantly associated with a 38% higher risk of all-cause death in the multivariable model 1, but the association was attenuated in the fully adjusted model. SFAs were not significantly associated with all-cause death.

PUFA and MUFA intakes were also inversely associated with cardiovascular death (data not shown). The HR (95% CI) was 0.37 (0.18, 0.76) for participants in the highest quintile of PUFA intake compared with those in the reference quintile (P-trend < 0.01). For MUFAs, the corresponding HR was 0.78 (0.34, 0.97). SFA intake was associated with a greater risk of cardiovascular death in the age-adjusted and the multivariable model 1 (HR: 1.73; 95% CI: 1.10, 4.80); however, in the fully adjusted model, the association was nonsignificant. The respective HR for *trans* fat for individuals in the highest quintile was 1.53 (1.07, 2.18) in the fully adjusted model.

When we analyzed the association between SFAs from different food sources and CVD and all-cause death (**Table 3**), we observed that updated measurements of vegetable SFA intake (from oils, nuts, vegetables, margarine) tended to be associated with a 47% lower risk of CVD (P-trend = 0.06). Fish SFAs also tended to be inversely associated with CVD and death [HR (95% CI): 0.70 (0.46, 0.99) and 0.63 (0.39, 0.98), respectively], although the intake of this nutrient was low. SFAs from pastries and processed foods were associated with a higher risk of CVD (HR: 1.46; 95% CI: 1.01, 2.13; P-trend = 0.04). No significant associations were found for SFAs from dairy products or from meat and processed meat and CVD and all-cause death (Table 3).

Figure 1 shows the risk of all-cause death and CVD for a 5% energy increment from total and subtypes of dietary fat. A 5% energy increment from MUFAs and PUFAs was inversely associated with all-cause death and CVD. A 5% energy increment from SFAs was associated with a higher risk of CVD (HR: 1.35; 95% CI: 1.03, 1.73) but not death.

The associations of various isocaloric dietary substitutions on the risk of CVD and all-cause death are shown in **Figure 2**. The replacement of 5% of energy from SFAs with MUFAs or PUFAs was associated with 37% and 33% lower risks of CVD. The replacement of SFAs with PUFAs was associated with a 39% lower risk of all-cause death. The isocaloric dietary substitution of SFAs by carbohydrates was nonsignificant. The replacement of 1% of energy from *trans* fat with MUFAs was associated with 8% lower risk of CVD, and replacing *trans* fat with PUFAs was associated with 8% lower risk of all-cause death.

When using the cumulative average of dietary fat subtypes and total fat, the results were consistent with those reported for repeated measurements of intake. In addition, the results that used an intention-to-treat approach were also consistent with those from the primary analysis.

DISCUSSION

In this prospective study in individuals at high CVD risk, a higher dietary intake of total fat was associated with a lower risk of CVD, whereas a higher intake of SFAs and *trans* fat was associated with a greater risk. Higher intakes of MUFAs and PUFAs were both associated with a lower risk of CVD, cardiovascular death, and all-cause death. The isocaloric substitution of SFAs or *trans* fat with MUFAs or PUFAs was associated with a lower risk of CVD and death. In addition, we found that a higher intake of SFAs from pastries and processed food was associated with a higher risk of CVD. A new finding to highlight was that SFAs from vegetable and fish were associated with a lower risk of CVD. However, this last finding should be interpreted cautiously because the amount of SFAs from fish consumed in our population was small.

The observed benefit on CVD and death of replacing SFAs and *trans* fat with PUFAs or MUFAs found in our population is consistent with a pooled analysis of 11 cohorts (15) and a meta-analyses of >20 randomized controlled trials (RCTs) (16). PUFAs in place of SFAs were found to be associated with a lower risk of coronary heart disease and death in a pooled analysis of 11 prospective cohort studies (15). Another recent pooled analysis of 8 RCTs concluded that the coronary heart disease risk is lowered by 10% for every 5% intake of energy from PUFAs replacing SFAs (17). Even though the intake of MUFAs has been related to beneficial effects on health (18), there is still no unanimous rationale for MUFA recommendations (4). Our results showed inverse associations between MUFAs and CVD, all-cause death, and cardiovascular death. Of note, our population had a high intake of nuts and olive oil, which are common MUFA sources. A possible reduction in the risk of CVD and death was also found for the replacement of SFAs with MUFAs in previous studies (15, 16, 19). These data are in line with our results, in which we found that substituting SFA with MUFA intake was associated with a 37% lower risk of CVD. Dietary fats were an important part of the dietary intervention conducted in the trial. Therefore, we acknowledge that it is difficult to disentangle whether the associations found are driven by the specific intake of MUFAs and PUFAs or by the supplement foods provided (olive oil or mixed nuts) and the MedDiet intervention. Nevertheless, we adjusted the analysis for intervention

TABLE 3
HRs (95% CIs) of cardiovascular disease and all-cause death according to quintile of updated measurements of SFA subtypes[1]

	Quintile					
	1 (lowest)	2	3	4	5 (highest)	*P*-trend
Cardiovascular disease						
Vegetable SFAs (oils, nuts, bread, vegetables, rice, margarine, other)						
Median, % of energy	2.32	3.11	3.63	4.08	4.78	
Multivariable model 1	1 (Ref)	0.81 (0.56, 1.15)	0.68 (0.45, 1.03)	0.78 (0.49, 1.22)	0.58 (0.33, 0.99)	0.08
Multivariable model 2	1 (Ref)	0.78 (0.55, 1.12)	0.68 (0.45, 1.02)	0.76 (0.48, 1.19)	0.53 (0.30, 0.93)	0.06
Dairy SFAs						
Median, % of energy	0.55	1.36	2.11	2.98	4.50	
Multivariable model 1	1 (Ref)	0.84 (0.56, 1.27)	1.15 (0.78, 1.70)	0.98 (0.65, 1.49)	0.86 (0.54, 1.36)	0.64
Multivariable model 2	1 (Ref)	0.83 (0.56, 1.25)	1.15 (0.78, 1.71)	0.98 (0.65, 1.49)	0.83 (0.52, 1.31)	0.54
SFAs from pastries and other processed foods (cookies, donuts, bakery, sauces, pizza, other)						
Median, % of energy	0.04	0.25	0.58	1.07	1.86	
Multivariable model 1	1 (Ref)	1.16 (0.79, 1.70)	1.02 (0.69, 1.51)	1.34 (0.92, 1.95)	1.37 (0.94, 2.01)	0.07
Multivariable model 2	1 (Ref)	1.21 (0.83, 1.78)	1.09 (0.74, 1.63)	1.44 (0.99, 2.09)	1.46 (1.01, 2.13)	0.04
SFAs from meat, processed meats (sausages, hamburger, other), and eggs						
Median, % of energy	0.91	1.46	1.96	2.52	3.58	
Multivariable model 1	1 (Ref)	0.98 (0.66, 1.44)	0.95 (0.64, 1.42)	1.22 (0.81, 1.82)	1.19 (0.77, 1.84)	0.27
Multivariable model 2	1 (Ref)	0.99 (0.67, 1.46)	0.95 (0.64, 1.42)	1.22 (0.82, 1.83)	1.19 (0.77, 1.83)	0.28
Fish SFAs (includes seafood)						
Median, % of energy	0.20	0.32	0.43	0.62	0.91	
Multivariable model 1	1 (Ref)	0.92 (0.66, 1.29)	0.98 (0.70, 1.39)	0.92 (0.64, 1.32)	0.68 (0.45, 0.97)	0.12
Multivariable model 2	1 (Ref)	0.89 (0.64, 1.25)	0.97 (0.69, 1.36)	0.95 (0.66, 1.36)	0.70 (0.46, 0.99)	0.11
All-cause death						
Vegetable SFAs (oils, nuts, bread, vegetables, rice, margarine, other)						
Multivariable model 1	1 (Ref)	0.76 (0.48, 1.21)	0.65 (0.38, 1.11)	0.79 (0.44, 1.43)	0.67 (0.34, 1.31)	0.28
Multivariable model 2	1 (Ref)	0.75 (0.47, 1.20)	0.64 (0.37, 1.10)	0.81 (0.45, 1.43)	0.70 (0.35, 1.38)	0.34
Dairy SFAs						
Multivariable model 1	1 (Ref)	0.95 (0.56, 1.59)	1.37 (0.83, 2.27)	1.18 (0.68, 2.02)	1.47 (0.82, 2.62)	0.18
Multivariable model 2	1 (Ref)	0.94 (0.56, 1.57)	1.36 (0.82, 2.25)	1.16 (0.67, 1.99)	1.46 (0.82, 2.61)	0.19
SFAs from pastries and other processed foods (cookies, donuts, bakery, sauces, pizza, other)						
Multivariable model 1	1 (Ref)	0.80 (0.49, 1.29)	0.95 (0.59, 1.53)	1.04 (0.65, 1.66)	1.26 (0.80, 1.99)	0.13
Multivariable model 2	1 (Ref)	0.79 (0.49, 1.29)	0.96 (0.59, 1.53)	1.03 (0.64, 1.65)	1.22 (0.78, 1.93)	0.17
SFAs from meat, processed meats (sausages, hamburger, other), and eggs						
Multivariable model 1	1 (Ref)	0.92 (0.56, 1.52)	1.02 (0.61, 1.68)	1.32 (0.80, 2.19)	1.06 (0.61, 1.85)	0.67
Multivariable model 2	1 (Ref)	0.91 (0.55, 1.50)	1.00 (0.60, 1.65)	1.28 (0.77, 2.12)	1.02 (0.58, 1.78)	0.77
Fish SFAs (includes seafood)						
Multivariable model 1	1 (Ref)	0.76 (0.51, 1.14)	0.49 (0.30, 0.78)	0.67 (0.43, 1.05)	0.62 (0.38, 1.00)	0.10
Multivariable model 2	1 (Ref)	0.78 (0.52, 1.16)	0.50 (0.31, 0.81)	0.70 (0.45, 1.10)	0.63 (0.39, 0.98)	0.11

[1]Time-dependent Cox regression models were used to assess the risk of cardiovascular disease and all-cause death by quintile of updated measurements of subtypes of SFA intake. Multivariable model 1 was adjusted for age (y), sex, intervention group, yearly updated total energy (kcal/d), alcohol intake (continuous, adding a quadratic term), and quintiles of updated fiber, protein, carbohydrates, dietary cholesterol, and other subtypes of fat intake (MUFAs, PUFAs, and *trans* fat). Model 2 was further adjusted for nondietary variables and classical cardiovascular disease risk factors: BMI (kg/m^2), smoking status (never, former, or current smoker), educational level (primary education, secondary education, or academic/graduate), leisure-time physical activity (metabolic task equivalent minutes/d), baseline diabetes (yes or no), hypertension (yes or no), hypercholesterolemia (yes or no), family history of coronary heart disease (yes or no), use of antihypertensive medication (yes or no), use of oral antidiabetic agents (yes or no), use of lipid-lowering drugs (yes or no). Extremes of total energy intake (>4000 or <800 kcal/d in men and >3500 or <500 kcal/d in women) were excluded. A major event was a composite of myocardial infarction, stroke, and death from cardiovascular causes.

group to control for the effect of the intervention. In addition, in a further analysis, when stratifying the sample by intervention group we found similar results in the 3 intervention groups, suggesting that the results are independent of the intervention. Although dietary patterns and analysis of food items often tell us more about lifestyles than do single nutrients, it is important to investigate which individual nutrients within dietary patterns exert or amplify beneficial or detrimental effects on disease risk.

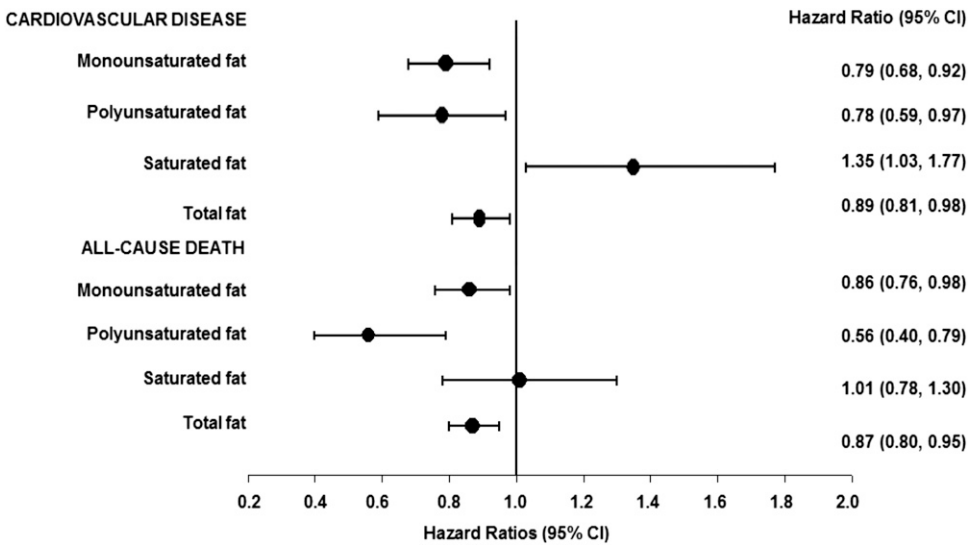

FIGURE 1 HRs (95% CIs) of all-cause death and cardiovascular disease for a 5% energy increment of total and subtypes of dietary fat. Multivariable time-dependent Cox regression models were adjusted for age (y), sex, intervention group, BMI (kg/m^2), smoking status (never, former, or current smoker), educational level (primary education, secondary education, or academic/graduate), leisure-time physical activity (metabolic equivalent task minutes/d), baseline diabetes (yes or no), hypertension (yes or no), hypercholesterolemia (yes or no), family history of coronary heart disease (yes or no), use of antihypertensive medication (yes or no), use of oral antidiabetic agents (yes or no), use of lipid-lowering drugs (yes or no), yearly updated total energy (kcal/d), alcohol intake (continuous, adding a quadratic term), and yearly updated fiber, protein, and dietary cholesterol for the total fat analysis. For specific subtypes of fat, the model also included as covariates the other subtypes of fat. All models were stratified by recruitment center. Extremes of total energy intake were excluded (n = 7038). The estimated RRs can be interpreted as the estimated differences in risk of a 5% lower energy intake from carbohydrate and a concomitant higher energy intake from total dietary fat and subtypes of dietary fat.

A higher intake of total fat in our population was associated with a lower risk of CVD and all-cause death. Of note, the greater proportion of total fat consumed in this population came from MUFAs and PUFAs, which have shown beneficial effects on health (20). On the contrary, and in accordance with the results of the Nurses' Health Study (21) and a recent prospective study in 58,672 Japanese individuals (22), total fat intake was not associated with cardiovascular death in the present study. In agreement with several other studies (7, 16, 19, 23), *trans*-fat intake was associated with a higher risk of CVD, and benefits of its replacement were also shown. Our results contribute to the convincing evidence on the benefits of decreasing the intake of

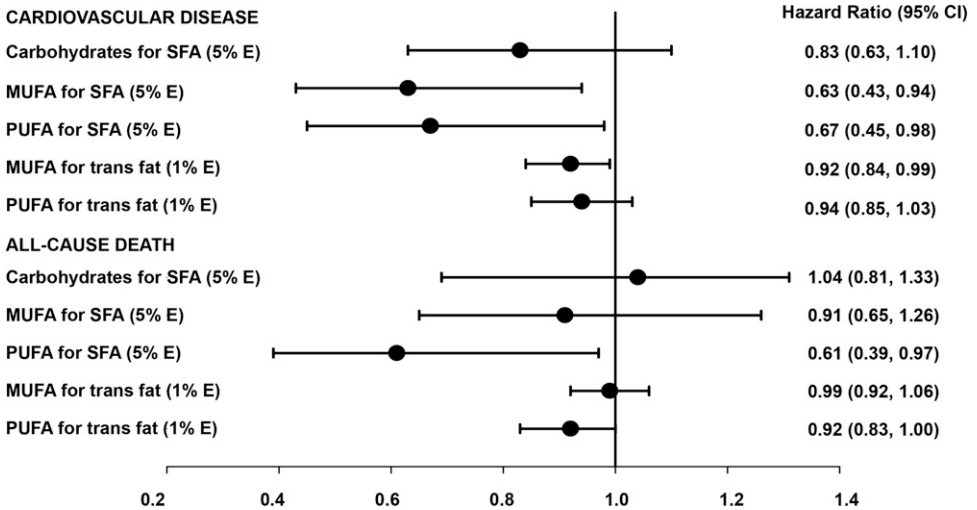

FIGURE 2 Estimated HRs (95% CIs) of all-cause death and cardiovascular disease associated with isocaloric substitutions of one dietary component for another. Multivariable time-dependent Cox regression models were adjusted for age (y), sex and intervention group, BMI (kg/m^2), smoking status (never, former, or current smoker), educational level (primary education, secondary education, or academic/graduate), leisure-time physical activity (metabolic equivalent task minutes/d), baseline diabetes (yes or no), hypertension (yes or no), hypercholesterolemia (yes or no), family history of coronary heart disease (yes or no), use of antihypertensive medication (yes or no), use of oral antidiabetic agents (yes or no), use of lipid-lowering drugs (yes or no), yearly updated total energy (kcal/d), alcohol intake (continuous, adding a quadratic term), and yearly updated fiber, protein, carbohydrates, dietary cholesterol, and other subtypes of fat intake. All models were stratified by recruitment center. Extremes of total energy intake were excluded (n = 7038). The estimated RRs can be interpreted as the estimated differences in risk of a 5% lower energy intake from SFAs or 1% lower energy from *trans* fat and a concomitant higher energy intake from carbohydrates, MUFAs, and PUFAs, respectively. E, energy.

trans fat to a minimum for its known adverse effects on health, particularly industrial hydrogenated *trans* fat (24, 25).

Substantial accruing evidence from meta-analyses indicates that the effects of the consumption of SFAs on CVD risk vary depending on the replaced nutrient (6, 15–17, 19). Most of the meta-analyses failed to show significant associations between the intake of SFAs and risk of CVD, stroke, or death (6, 19, 23). However, they were unable to consider the effects of replacing nutrients and the effects of different food sources of these SFAs (7, 8). Our results showed that increased consumption of SFAs was associated with a higher risk of CVD. But no associations with cardiovascular and total death were found. SFA intake was not associated with all-cause mortality and CVD mortality in a recent meta-analysis of 6 prospective cohort studies (23). Contrary to our study, in that meta-analysis (23) the replacement of SFAs or *trans* fat with other nutrients was not evaluated. We found a consistent reduction in the risk of both CVD and death when replacing the intake of SFAs with other dietary components such as MUFAs or PUFAs. No significant associations were found for the substitution of SFAs with total carbohydrates and CVD and death, probably because it is important to differentiate between carbohydrate types, such as legumes, whole grains, and refined sugars. These results are in accordance with the Scientific Report of the 2015 Dietary Guidelines for Americans Advisory Committee (3).

Because food sources contain different proportions of specific SFAs, which may have a different influence on CVD, we evaluated the associations of SFAs from several food sources. MUFAs mainly come from olive oil, PUFAs derive from nuts, and the amount of *trans* fatty acids consumed is very low in this elderly Mediterranean population at high CVD risk. As expected, we found that SFAs from pastries and processed foods were associated with a higher risk of CVD. Our findings are consistent with those from a large multiethnic cohort that evaluated the association of SFA consumption from different food sources and the incidence of CVD (9). In that study they found that dairy SFAs were associated with a lower CVD risk, but in our analysis SFAs from dairy products were not significantly associated with CVD and all-cause death. Perhaps the beneficial effects of dairy products on CVD are mainly attributed to other nutrients, such as calcium, potassium, peptides, and some vitamins, instead of only the type of SFA. Vegetable SFAs, mainly from vegetable oils, nuts, vegetables, and margarine, were inversely associated with CVD in our study. In the study by de Oliveira Otto et al. (9), no associations between plant SFAs and CVD were reported, but the SFA consumption of these food sources was quite low compared with our population. In addition, that study (9) comprised the US general population, whereas our study was conducted in Mediterranean individuals at high CVD risk. Inverse associations between fish SFAs and CVD were also found in our analysis. Because this approach is relatively new, further studies are needed to confirm these promising findings. It should be acknowledged that other dietary components in the food sources containing SFAs may have played a role in the observed associations, such as refined carbohydrates in pastries or salt in processed foods.

Several biological mechanisms underlie the aforementioned associations. First, MUFAs have beneficial effects on CVD risk factors. Scientific evidence has shown that MUFAs improve the lipid profile (4), decrease blood pressure, and modulate insulin resistance, endothelial function (26), and glycemic control (27). Second, PUFAs have been shown to exert antithrombotic and antiarrhythmic effects (especially n–3 fatty acids) and improve serum lipids, inflammation, blood pressure, endothelial function, and myocardial oxygen utilization (28–30), thus improving atherosclerosis pathways and consequently decreasing the risk of CVD. Third, evidence has suggested that SFAs increase LDL cholesterol, and therefore they can increase the risk of CVD (28, 31). The replacement of SFAs with PUFAs or MUFAs has been shown to decrease total and LDL cholesterol but had minimal effect on HDL cholesterol (32, 33). SFA replacement with PUFA and/or high-quality carbohydrates can reduce as well the risk of coronary heart disease (34). SFAs may also reduce insulin sensitivity, promote inflammation, and have adverse effects on vascular function (6), but this still remains to be elucidated. Moreover, consistent scientific evidence has shown that *trans* fat, regardless of its source, increases the ratio of plasma LDL to HDL cholesterol (24). Our results may help to highlight the importance of the quality of fat rather than total fat in the specific recommendations for individuals at high CVD risk and provide epidemiologic evidence for the current guidelines. Our study is the first, to our knowledge, to test the association between different SFA food sources on CVD and death in individuals at high CVD risk by using repeated measurements of dietary intake.

Limitations of the present study require discussion. First, because the method used for dietary assessment was an FFQ, measurement errors in total fat and subtypes of fat intake were inevitable. However, the FFQ used was validated, and the repeated measurements of dietary fat analyzed may provide a more robust approach to test associations than with only one-time assessment as an exposure. Although dropouts were different across categories of fat intake, it is unlikely that a differential attrition bias may have occurred and might provide an alternative explanation to our findings. Differences in attrition rates among categories of fat intake were therefore small in magnitude and not very likely to induce a relevant differential misclassification bias in the outcomes. Furthermore, the potential bias, if any, would be in the direction of an underestimation of the number of outcomes occurring in the lowest category of total fat intake, because there were more dropouts in the first quintile and we may have missed some cases of CVD in the dropouts. Finally, we estimated the hypothetical effect of isocaloric substitutions of dietary fat for another dietary component under causality of assumption. Strengths of the present study include its prospective design, the use of repeated dietary measurements during follow-up, the ability to control for potential confounders due to recording of comprehensive data, and the accurate and blind assessment of incident cases of CVD and death.

In summary, MUFAs and PUFAs were inversely associated with CVD and death, whereas SFAs and *trans* fat were associated with a higher risk of CVD in individuals at high CVD risk. Total dietary fat was associated with a lower risk of CVD and all-cause death. The replacement of SFAs with MUFAs or PUFAs or *trans* fat with PUFAs was associated with a lower risk of CVD. Finally, the consumption of SFAs from pastries and processed food was associated with a greater risk in high-risk individuals.

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