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ORIGINAL RESEARCH

Dietary Fatty Acids, Macronutrient Substitutions, Food Sources and Incidence of Coronary Heart Disease: Findings From the EPIC-CVD Case-Cohort Study Across Nine European Countries

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BACKGROUND: There is controversy about associations between total dietary fatty acids, their classes (saturated fatty acids [SFAs], monounsaturated fatty acids, and polyunsaturated fatty acids), and risk of coronary heart disease (CHD). Specifically, the relevance of food sources of SFAs to CHD associations is uncertain.

METHODS AND RESULTS: We conducted a case-cohort study involving 10 529 incident CHD cases and a random subcohort of 16 730 adults selected from a cohort of 385 747 participants in 9 countries of the EPIC (European Prospective Investigation into Cancer and Nutrition) study. We estimated multivariable adjusted country-specific hazard ratios (HRs) and 95% CIs per 5% of energy intake from dietary fatty acids, with and without isocaloric macronutrient substitutions, using Prentice-weighted Cox regression models and pooled results using random-effects meta-analysis. We found no evidence for associations of the consumption of total or fatty acid classes with CHD, regardless of macronutrient substitutions. In analyses considering food sources, CHD incidence was lower per 1% higher energy intake of SFAs from yogurt (HR, 0.93 [95% CI, 0.88–0.99]), cheese (HR, 0.98 [95% CI, 0.96–1.00]), and fish (HR, 0.87 [95% CI, 0.75–1.00]), but higher for SFAs from red meat (HR, 1.07 [95% CI, 1.02–1.12]) and butter (HR, 1.02 [95% CI, 1.00–1.04]).

CONCLUSIONS: This observational study found no strong associations of total fatty acids, SFAs, monounsaturated fatty acids, and polyunsaturated fatty acids, with incident CHD. By contrast, we found associations of SFAs with CHD in opposite directions dependent on the food source. These findings should be further confirmed, but support public health recommendations to consider food sources alongside the macronutrients they contain, and suggest the importance of the overall food matrix.

Key Words: coronary heart disease ■ dietary guidelines ■ nutritional epidemiology ■ primary prevention ■ saturated fat

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CLINICAL PERSPECTIVE

What Is New?

- In a large prospective cohort study including men and women with diverse diets across 9 European countries, there were no strong associations between dietary saturated fatty acids (SFAs) and coronary heart disease (CHD) incidence, or between the substitution of polyunsaturated or monounsaturated fatty acids for saturated fatty acids and CHD incidence.
- In contrast, there were differences in CHD risk when food sources of SFAs were considered, with a lower CHD incidence with consumption of SFAs from fermented dairy products (yogurt and cheese) and fish, but a higher CHD incidence with consumption of SFAs from red meat and butter.

What Are the Clinical Implications?

- The differential associations with CHD of SFAs from different food sources provide support for the adoption of a food-based translation of recommendations for saturated fat intake in dietary guidelines.
- The current findings are based on a large multicountry European study but should be further evaluated in diverse populations where macronutrient intakes, their food sources, and overall dietary patterns vary.

Nonstandard Abbreviations and Acronyms

EPIC	European Prospective Investigation into Cancer and Nutrition
GI	glycemic index
MUFA	monounsaturated fatty acid
PREDIMED	Prevención con Dieta Mediterránea
PUFA	polyunsaturated fatty acid
SFA	saturated fatty acid
TEI	total energy intake

The association of dietary fatty acids with coronary heart disease (CHD) is complex but important because of its enormous public health impact, because diet is a potentially modifiable factor. Most public health dietary guidelines recommend limiting saturated fatty acid (SFA) intake and replacing it with unsaturated fatty acids (specifically polyunsaturated fatty acids [PUFAs]) for the prevention of cardiovascular diseases (CVDs).[1–3] However, meta-analyses of underpinning randomized trials have drawn different conclusions on the benefits of such dietary modifications for CHD risk.[4–6] Although trials find beneficial effects of substituting PUFAs for SFAs on circulating lipids,[7] extrapolation of summary trial evidence to public health recommendations is challenging, because this does not take into account foods and nutrients correlated with SFA intakes in free-living populations. Observational data for longer-term CHD incidence are inconclusive and dominated by study of populations in the United States and Northern Europe,[8–10] whereas other cohorts that have investigated macronutrient substitutions have generally been unable to confirm their findings.[11–13] Further studies have not modeled the effects of macronutrient substitutions specifically for SFAs[14] or did not investigate CHD incidence as a separate outcome.[15,16] Consequently, the role of dietary fatty acids in CHD risk in various populations in Europe, with diverse intake levels and, importantly, food sources, remains uncertain. For example, emerging evidence suggests differing relevance of SFAs from different food sources to CHD,[17] but studies have yielded mixed results.[11–13,18–21]

Recent appraisals of the health effects of SFAs by the World Health Organization[1] and the UK Scientific Advisory Committee on Nutrition[2] have highlighted the need for further research on this topic. For example, considerable gaps in the understanding remain, including the role of monounsaturated fatty acids (MUFAs) as substitution nutrients for SFAs,[9,11,12,22,23] and lack of clarity on whether potential effects of substituting carbohydrates for SFAs on CHD risk depend on carbohydrate quality.[11,12,15,23–25]

To help address these uncertainties, we investigated associations between dietary fatty acids and incident CHD in a large pan-European prospective case-cohort study, the EPIC (European Prospective Investigation into Cancer and Nutrition)-CVD study. Our objectives were to examine (1) associations of dietary total fatty acids, SFAs, MUFAs, and PUFAs with first incident CHD; (2) the relevance of statistically modeled substitution of fatty acids for total carbohydrates, and of MUFAs, PUFAs, and carbohydrates, including by different levels of carbohydrate quality, for SFAs; and (3) associations of SFAs from various food sources with CHD incidence.

METHODS

Study Population

The EPIC-CVD study is a case-cohort study nested within EPIC, a prospective cohort including ~520 000 men and women recruited from 23 study centers in 10 European countries between 1992 and 2000.[26,27] Requests to access the supporting anonymized data may be made by qualified researchers trained in human participant confidentiality protocols by following the instructions at http://epic.iarc.fr/access/index.

php. In this study, we chose a case-cohort design in EPIC to enable efficient measurement of molecular factors (eg, biomarkers of metabolism, genetics) in a reference subcohort that serves as the comparator group for incidence of several different disease outcomes, including type 2 diabetes mellitus, CHD, stroke, and cancers. The case-cohort design has the advantages of temporal sequence and power of a cohort study (in that it involves the complete number of incident cases) with the measurement efficiency of a case-control study.[28] Among all participants with a stored blood sample (n=385 747), a total of 13 603 incident CHD cases were ascertained during follow-up, and a random subcohort of 18 249 center-stratified participants was selected irrespective of future disease status.[26,29] After excluding participants with prior history of myocardial infarction or stroke, missing follow-up data, non–first CHD events (where first event was not myocardial infarction), preexisting angina, missing covariates, and participants from Norway because of small sample size, a total of 16 730 random subcohort members and 10 529 participants with an incident CHD event (among whom 572 participants were in the subcohort, by design of a case-cohort study) were included in the analyses (Figure S1). The study complies with the Declaration of Helsinki. Ethical review boards of the cohorts approved the study protocol, and all participants provided written informed consent.[27]

Ascertainment of CHD

The primary outcome was first nonfatal or fatal CHD (*International Classification of Diseases, Ninth Edition* [*ICD-9*] codes 410–414 and *Tenth Edition* [*ICD-10*] codes I20–I25).[26] Nonfatal and fatal first CHD events were included as separate secondary outcomes in sensitivity analyses. Methods to ascertain incident CHD events in different centers included self-report, linkage with registries, review of medical records, or a combination of these. Suspected CHD was validated among all ascertained cases within centers, except in the Netherlands, United Kingdom, and Sweden, where validation was conducted among a sample of CHD events, and France, where no validation information was available. The last year of follow-up varied between 2003 and 2010 across centers. Nonfatal and fatal events occurring within 28 days of each other were considered a single fatal event. Follow-up data for each participant were censored at the time of a first CHD event or the end of the follow-up period, whichever occurred first.

Assessment of Dietary Intake

Habitual food consumption over the past year was assessed by center-specific food frequency questionnaires or diet histories, either self-administered or assessed in face-to-face interviews.[27] Validity of each dietary questionnaire was assessed in subgroups of participants within centers using a reference method of monthly 24-hour recalls or weighed food records.[30] In analyses comparing intakes based on the 2 instruments, correlation coefficients were between 0.31 and 0.87 for total fat (except they were lower in Greece, 0.09 in men and 0.26 in women), 0.39 to 0.84 for SFA, 0.28 to 0.89 for MUFA, and 0.26 to 0.89 for PUFA.[30] All dietary nutrient data were collected in a cohort-specific manner and standardized centrally within the EPIC consortium. The European Nutrient Database was established to facilitate comparability of the dietary exposures. The European Nutrient Database and estimation of food and nutrient intakes have been described in detail previously.[31] Mean dietary glycemic index (GI) was calculated using standardized methods.[32] Dietary total fatty acids were calculated as the sum of SFAs, MUFAs, and PUFAs. Total energy intake (TEI) was defined as daily energy from dietary fatty acids, carbohydrates, and protein from plant, animal, and mixed/unknown origin (in kilocalories). Alcohol was not considered a feasible substitution nutrient, and therefore was not included in the definition of TEI but was used as a model covariate.[9,14] Macronutrients were expressed as their relative contribution to TEI (%TEI). Dietary fiber and GI were energy adjusted with the residual method for analyses of associations with CHD. Dietary SFAs from the following food groups were expressed in %TEI: total dairy (excluding butter) and subtypes milk, yogurt/thick milk, and cheese; added fats and subtypes vegetable (plant) oils, butter, and margarine; total meat and subtypes red, processed, and poultry; cakes and biscuits; sugar and confectionary; cereals; eggs; condiments and sauces; fish; and nuts and seeds.

Assessment of Covariates

Lifestyle health behaviors, social factors, and medical history were assessed by country-specific questionnaires.[27] Height and weight were measured in most centers except EPIC-Oxford and France, where self-reported height and weight were used for most participants for whom measured values were not available.[27] Methods for measuring other vascular risk factors are detailed in the Table S1 legend.

Statistical Analysis

All analyses were performed using Stata version 14 (StataCorp College Station, TX). The percentage of individuals excluded because of missing values of baseline covariates among the study sample was <5%, and based on this we had prespecified to conduct a complete-case analysis. Baseline characteristics were summarized in the subcohort. We estimated Pearson

partial correlation coefficients (95% CIs) of dietary SFAs, MUFAs, and PUFAs with (1) all macronutrients, adjusted for age and sex and (2) foods, adjusted for age, sex, TEI, and body mass index, within the subcohort of each country, to allow for country-specific differences in confounding structures. We then applied the Fisher *z* transformation to these estimates and combined them across countries using random-effects meta-analysis. Skewed variables (PUFA, TEI, fiber, triglycerides, total cholesterol: high-density lipoprotein cholesterol [HDL-C] ratio, and C-reactive protein) were log-transformed where required. Mean (95% CI) vascular risk factors were calculated by subcohort quintiles of dietary fatty acids, adjusted for age, sex, and EPIC center using linear regression to estimate least squares means. In these analyses, no correction for multiple testing was prespecified, but we considered the direction, magnitude and precision (with 95% CIs), as well as consistency, of associations in the interpretation of our findings.

Modeling Associations with CHD

To account for the oversampling of incident CHD cases in a case-cohort study design, modified Cox proportional hazards models using Prentice weights were fitted to estimate hazard ratios (HRs) and 95% CIs of total fatty acids, SFAs, MUFAs, and PUFAs with CHD within countries, using age as the underlying time variable and stratifying baseline hazards by sex. To evaluate the effect of confounding on associations, we constructed 4 models with sequential adjustment for different types of potential confounding factors as follows: Model 1 (basic confounders) was adjusted for age at study entry, study center, and TEI (continuous). Model 2 additionally included lifestyle and socioeconomic characteristics: education (low, medium, high), smoking status (never, former, current), and physical activity (inactive, moderately inactive, moderately active, active). Model 3 additionally included dietary factors: dietary fiber (continuous), fruit and vegetable intake (continuous), and alcohol (0, 0–6, 6–12, 12–24, >24 g/d). Model 4 additionally included known cardiometabolic risk factors: body mass index (continuous), and preexisting diabetes mellitus, hypertension, and hyperlipidemia (self-reported, yes; no/unknown for each). To estimate combined HRs (95% CIs), country-specific results were pooled using random effects under the assumption that the associations varied by country because of differences in demographic and lifestyle characteristics, and assessment methods. We conducted univariate meta-analysis and also multivariate meta-analysis, which accounted for correlations between estimated HRs for all macronutrients and TEI (but not other covariates). Heterogeneity was assessed with the I^2 statistic. Associations were modeled across quintiles of exposures. After confirming no suggestion of nonlinearity (Table S2), we used the nutrient density model to evaluate the isocaloric substitution per 5%TEI from fatty acids (i.e., as continuous covariates) for any other energy source.[33]

In macronutrient-specific isocaloric substitution models, we modeled (1) substitution of 5%TEI from total fatty acids, and from SFAs, MUFAs, and PUFAs for 5%TEI from carbohydrates, and (2) substitution of 5%TEI from MUFAs, PUFAs, and carbohydrates for 5%TEI from SFAs, by including TEI and all macronutrients (i.e., total fatty acids or SFAs, MUFAs, and PUFAs; carbohydrates; protein from plant, animal, and unknown/mixed origin) in the models except the nutrient to be substituted for (i.e., carbohydrates or SFAs). In Models 3 and 4 (adjusting for fruit and vegetable intake), associations of carbohydrates should be interpreted as carbohydrates from food sources other than fruit and vegetables.

Testing for Effect Modification

To evaluate potential effect modification by carbohydrate quality, associations of substituting carbohydrates for SFAs were stratified by thirds of GI[32] (low: ≤54.4, medium: 54.4–57.5, and high: ≥57.5). Associations were also stratified to evaluate potential effect modification by biological differences (i.e., sex and age [by median, <52.4 versus ≥52.4 years]), plausibility of reported energy intake (suspected under-, plausible-, and over-reporting, defined by intake levels±2 SD of predicted total energy expenditure), and reverse causality (preexisting diabetes mellitus, hypertension, and/or hyperlipidemia). Statistical significance of interactions was evaluated with the *P* value of a cross-product term of effect modifiers and exposures. Countries with <10 CHD cases or noncases in exposure categories were excluded.

Food-Specific SFAs and CHD

First, we analyzed associations with CHD of SFAs (per 1%TEI) from primary food sources previously described in EPIC,[34] plus yogurt and red meat,[35,36] and poultry (main meat subtype consumed in EPIC). Second, associations of each food source were additionally adjusted for the sum of SFAs from all other foods. We estimated HRs of substituting macronutrient intakes (MUFAs, PUFAs, carbohydrates, and SFAs from other foods) for SFAs from selected SFA-rich foods. The selected foods were those where the SFA content showed evidence of association with CHD at $P<0.05$. Given their shared direction of association in our analyses, and the relatively low contribution of yogurt to SFA consumption (Table S3), SFAs from yogurt and cheese were combined into SFAs from fermented dairy products in macronutrient-specific substitution analyses to increase statistical power.

Ancillary Analyses

Heterogeneity among geographical regions (South: Greece, Italy, Spain, France; Central: the Netherlands, United Kingdom, Germany; North: Denmark, Sweden) was assessed with the I^2 statistic and tested against a χ^2 distribution. We also (1) investigated associations with fatal and nonfatal CHD separately, (2) excluded the first 2 years of follow-up to evaluate potential reverse causality, (3) excluded participants with extreme energy intakes (<500 or >3500 kcal/d for women; <800 or >4000 kcal/d for men), and (4) Winsorized top and bottom 1% of covariates to evaluate effects of extreme reporting. Because there are alternative approaches to energy adjustment than the nutrient density model we used, we repeated analyses of associations among dietary SFAs, MUFAs, and PUFAs with CHD using 2 further modeling approaches: (1) the nutrient residual model and (2) the energy partition model.[33] In the nutrient residual model, we evaluated associations per 10 energy-adjusted grams per day from a specific fatty acid to substitute for any other sources of energy; in the energy-partition model, we estimated the effect of adding 10 g/d (90 kcal/d) from a specific fatty acid to existing macronutrient intakes by adjusting for all other macronutrients but not for TEI. We conducted post hoc analyses, repeating primary analysis Model 4 pooling data from all countries together in 1-stage fixed-effects models, rather than country-specific 2-stage random-effects modeling, to evaluate similarity in results using these 2 different approaches. We also conducted calibration analyses by correcting observed HRs (95% CIs) from food-frequency questionnaire data for country-specific regression dilution ratios that were estimated among ~8% of participants with single 24-hour recall data available.

RESULTS

Baseline Characteristics

The median subcohort age was 52.4 years (interquartile range, 46.0–59.2 years), and 62% were women (Table 1). Diets varied by country; for instance, intake levels and ranges of dietary MUFAs were higher in Southern countries (Greece, Spain, and Italy) compared with the rest of Europe (Figure S2). Median (interquartile range) intakes were 35.0 (30.9–39.2) %TEI for total fatty acids, 14.0 (11.7–16.4) for SFAs, 14.1 (11.9–17.0) for MUFAs, and 5.5 (4.5–7.0) for PUFAs (Table 2). SFAs correlated positively with MUFAs and animal proteins, and inversely with carbohydrates and plant proteins (Table S4). Most vascular risk factors varied modestly across quintiles of fatty acids. Comparing top versus bottom SFA quintiles, triglycerides were 0.08 mmol/L higher, whereas non–HDL-C and total cholesterol:HDL-C ratios were similar (Table S1).

Dairy products, particularly cheese, contributed most to dietary SFAs in all countries (Table S3), whereas food sources of unsaturated fatty acids were diverse. For instance, vegetable oils contributed over 45% to dietary MUFAs in Southern European countries but <1% in Northern Europe, where meat was the predominant source of MUFAs (20.4%–31.4%) (results not shown). Positive correlations of foods with fatty acids reflected their fatty acid composition and contributions to fatty acid intakes (Figure S3), except the inverse correlation of total dairy with MUFAs, despite dairy being within the top 3 MUFA food sources in all EPIC countries. Inverse correlations were observed for cereal products (for SFAs and MUFAs), fruit and vegetables (SFAs), and butter (PUFAs).

Fatty Acids and CHD, and Effect Modification

Total fatty acids, SFAs, MUFAs, or PUFAs were not associated with incident CHD (Figure 1, Table S5, Figures S4 and S5). Substituting energy from total fatty acids, SFAs, MUFAs, or PUFAs for energy from carbohydrates was not associated with CHD (Figure 2). Similarly, substituting energy from MUFAs, PUFAs, or carbohydrates for energy from SFAs was not associated with CHD (Figure 3). There were some differences in associations among countries. For instance, substituting SFAs for carbohydrates was associated with a higher CHD incidence in France (HR, 2.99; 95% CI, 1.13–7.90), whereas there was no association in any other country or overall (pooled HR, 0.97; 95% CI, 0.87–1.09; I^2=42%; Figure 2). There was no evidence from an interaction test that the association varied by GI levels of diet (P for interaction=0.579; Table S6). There was no evidence for differences in associations between men and women, between different age groups, or by plausibility of energy reporting or by preexisting diabetes mellitus, hypertension, and hyperlipidemia (Tables S7 and S8).

Food Sources of SFAs and CHD

Each 1%TEI from SFAs from yogurt, cheese, and fish was associated with a 7% (HR, 0.93; 95% CI, 0.88–0.99; P=0.017), 2% (HR, 0.98; 95% CI, 0.96–1.00; P=0.018), and 13% (HR, 0.87; 95% CI, 0.75–1.00; P=0.048) lower CHD incidence, respectively (Table 3). In contrast, SFAs from red meat and butter, respectively, were associated with a 7% (HR, 1.07; 95% CI, 1.02–1.12; P=0.007) and 2% (HR, 1.02; 95% CI, 1.00–1.04; P=0.032) higher CHD incidence per 1%TEI. After adjusting for SFAs from other food sources, these HRs remained similar. Specific macronutrient substitutions for SFAs from food sources reflected these findings, including higher CHD incidence when substituting carbohydrates for SFAs from fermented dairy products

Table 1. Baseline Participant Characteristics in the Lowest (Q1) and Highest (Q5) Quintiles of Dietary Fatty Acid Intake (in Percent of Energy Intake) in the EPIC-CVD Case-Cohort Study Subcohort (n=16 730)*

		Total Fatty Acids		SFAs		MUFAs		PUFAs	
	All	Q1, n=3346	Q5, n=3346	Q1, n=3346	Q5, n=3346	Q1, n=3346	Q5, n=3346	Q1, n=3346	Q5, n=3346
Age, y	52.4 (46.0–59.2)	53.3 (47.5–59.8)	50.9 (43.6–58.5)	52.0 (45.5–58.5)	52.9 (47.2–59.8)	54.6 (49.6–60.3)	49.5 (42.9–56.8)	51.9 (45.1–58.9)	52.1 (45.6–59.4)
Women	10 414 (62.2)	2261 (67.6)	2016 (60.3)	2016 (60.3)	2070 (61.9)	2387 (71.3)	2029 (60.6)	2158 (64.5)	2089 (62.4)
Education									
None/primary	7154 (42.8)	1487 (44.4)	1497 (44.7)	1981 (59.2)	1062 (31.7)	1149 (34.3)	1914 (57.2)	1670 (49.9)	1408 (42.1)
Secondary	2531 (15.1)	500 (14.9)	506 (15.1)	404 (12.1)	562 (16.8)	570 (17.0)	501 (15.0)	539 (16.1)	459 (13.7)
Vocational/ university	7045 (42.1)	1359 (40.6)	1343 (40.1)	961 (28.7)	1722 (51.5)	1627 (48.6)	931 (27.8)	1137 (34.0)	1479 (44.2)
Physical activity									
Inactive	4084 (24.4)	797 (23.8)	1002 (29.9)	1071 (32.0)	709 (21.2)	605 (18.1)	1144 (34.2)	937 (28.0)	834 (24.9)
Moderately inactive	5614 (33.6)	1095 (32.7)	1093 (32.7)	1083 (32.4)	1154 (34.5)	1030 (30.8)	1123 (33.6)	1167 (34.9)	1082 (32.3)
Moderately active	3806 (22.7)	700 (20.9)	764 (22.8)	632 (18.9)	838 (25.0)	827 (24.7)	674 (20.1)	689 (20.6)	824 (24.6)
Active	3226 (19.3)	754 (22.5)	487 (14.6)	560 (16.7)	645 (19.3)	884 (26.4)	405 (12.1)	553 (16.5)	606 (18.1)
Smoking status									
Never	7912 (47.3)	1723 (51.5)	1449 (43.3)	1731 (51.7)	1374 (41.1)	1713 (51.2)	1587 (47.4)	1690 (50.5)	1550 (46.3)
Former	4425 (26.4)	934 (27.9)	834 (24.9)	845 (25.3)	913 (27.3)	982 (29.3)	730 (21.8)	838 (25.0)	911 (27.2)
Current	4393 (26.3)	689 (20.6)	1063 (31.8)	770 (23.0)	1059 (31.6)	651 (19.5)	1029 (30.8)	818 (24.4)	885 (26.4)
Current drinker	13 856 (82.8)	2619 (78.3)	2764 (82.6)	2429 (72.6)	2923 (87.4)	2748 (82.1)	2572 (76.9)	2612 (78.1)	2779 (83.1)
Alcohol intake, current drinkers, g/d	8.6 (2.5–21.3)	6.4 (1.8–17.2)	9.1 (2.8–22.3)	9.8 (2.1–25.5)	8.5 (2.8–19.5)	5.6 (1.7–13.9)	10.0 (2.4–25.3)	6.9 (1.7–20.8)	9.5 (3.0–22.0)
Menopausal status, women									
Premenopausal	3471 (20.7)	630 (18.8)	807 (24.1)	719 (35.7)	621 (30.0)	538 (22.5)	942 (46.4)	764 (35.4)	738 (35.3)
Perimenopausal	1687 (10.1)	363 (10.8)	309 (9.2)	256 (12.7)	414 (20.0)	401 (16.8)	226 (11.1)	318 (14.7)	347 (16.6)
Postmenopausal	5256 (31.4)	1268 (37.9)	900 (26.9)	1041 (51.6)	1035 (50.0)	1448 (60.7)	861 (42.4)	1076 (49.9)	1004 (48.1)
BMI, kg/m^2	25.7 (23.2–28.7)	25.7 (23.2–28.5)	26.1 (23.2–29.2)	26.8 (24.2–29.7)	24.8 (22.4–27.6)	25.2 (22.8–27.9)	26.9 (24.2–30.0)	25.6 (23.0–28.6)	25.9 (23.3–29.0)
Overweight, 25–30 kg/m^2	6654 (39.8)	1380 (41.2)	1301 (38.9)	1491 (44.6)	1164 (34.8)	1292 (38.6)	1432 (42.8)	1306 (39.0)	1307 (39.1)
Obesity, >30 kg/m^2	2919 (17.4)	550 (16.4)	678 (20.3)	768 (23.0)	424 (12.7)	458 (13.7)	830 (24.8)	582 (17.4)	655 (19.6)
Preexisting diabetes mellitus	514 (3.1)	134 (4.0)	119 (3.6)	158 (4.7)	74 (2.2)	118 (3.5)	119 (3.6)	88 (2.6)	139 (4.2)
Preexisting hypertension	3295 (19.7)	674 (20.1)	656 (19.6)	712 (21.3)	576 (17.2)	651 (19.5)	669 (20.0)	681 (20.4)	706 (21.1)
Preexisting hyperlipidemia	2465 (14.7)	604 (18.1)	464 (13.9)	826 (24.7)	284 (8.5)	454 (13.6)	640 (19.1)	555 (16.6)	550 (16.4)

(*Continued*)

Table 1. Continued

	All	Total Fatty Acids		SFAs		MUFAs		PUFAs	
		Q1, n=3346	Q5, n=3346	Q1, n=3346	Q5, n=3346	Q1, n=3346	Q5, n=3346	Q1, n=3346	Q5, n=3346
Country									
Greece	1201 (7.2)	14 (0.4)	931 (27.8)	242 (7.2)	99 (3.0)	5 (0.1)	1049 (31.4)	201 (6.0)	304 (9.1)
Spain	3639 (21.8)	730 (21.8)	679 (20.3)	1599 (47.8)	251 (7.5)	333 (10.0)	1407 (42.1)	868 (25.9)	846 (25.3)
Italy	1992 (11.9)	446 (13.3)	268 (8)	631 (18.9)	111 (3.3)	66 (2.0)	706 (21.1)	987 (29.5)	53 (1.6)
France	551 (3.3)	89 (2.7)	123 (3.7)	47 (1.4)	203 (6.1)	146 (4.4)	20 (0.6)	58 (1.7)	174 (5.2)
United Kingdom	1076 (6.4)	325 (9.7)	101 (3)	212 (6.3)	176 (5.3)	437 (13.1)	12 (0.4)	86 (2.6)	412 (12.3)
the Netherlands	1356 (8.1)	366 (10.9)	91 (2.7)	113 (3.4)	286 (8.5)	759 (22.7)	4 (0.1)	109 (3.3)	435 (13.0)
Germany	1995 (11.9)	303 (9.1)	381 (11.4)	132 (3.9)	657 (19.6)	407 (12.2)	36 (1.1)	166 (5.0)	540 (16.1)
Denmark	2005 (12.0)	488 (14.6)	162 (4.8)	204 (6.1)	466 (13.9)	539 (16.1)	27 (0.8)	306 (9.1)	214 (6.4)
Sweden	2915 (17.4)	585 (17.5)	610 (18.2)	166 (5.0)	1097 (32.8)	654 (19.5)	85 (2.5)	565 (16.9)	368 (11.0)

BMI indicates body mass index; EPIC-CVD, European Prospective Investigation into Cancer and Nutrition–Cardiovascular Disease; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; and SFAs, saturated fatty acids.
*All values are number (percent) or median (interquartile range).

(yogurt and cheese) and lower CHD incidence when substituting specific macronutrients for SFAs from red meat (Table S9).

Ancillary Analyses

There were some geographical differences in associations of SFAs ($P_{heterogeneity}$=0.029) and of PUFAs substituting for SFAs ($P_{heterogeneity}$=0.039), but none of the region-specific estimates were significant (eg, the HR for substituting PUFAs for SFAs was 0.84 [95% CI, 0.69–1.02] in Central Europe versus 1.17 [95% CI, 0.93–1.47] in the South) (Table S10). Investigating fatal or nonfatal CHD separately, excluding the first 2 years of follow-up, excluding extreme energy reporters, Winsorizing covariates, and 1-stage analysis did not materially change the results (Tables S11 and S12). Regression calibration analyses with 24-hour recall data made no difference to our findings (results not shown).

DISCUSSION

In this large pan-European observational study, total dietary fatty acids and their classes (SFAs, MUFAs, and PUFAs) were not associated with CHD, regardless of which other macronutrient was substituted for. By contrast, we observed directionally opposite associations of SFAs with CHD incidence depending on the food sources. For example, whereas consuming SFAs from fermented dairy products and fish was associated with lower CHD incidence, intake of SFAs from red meat and butter was associated with higher CHD incidence. These results suggest the importance of the overall food matrix alongside the consideration of the nutrient composition.

Findings in Context of Prior Evidence

To our knowledge, our study is the first to report on associations of dietary fatty acids and incident CHD across multiple regions in Europe with diverse diets,[27] allowing standardized investigation of various intake levels and food sources. Overall, SFA intake was high, with <12% of participants consuming less than the recommended upper limit of 10%TEI from SFAs.[2] Consistent with most previous evidence,[5,37,38] we observed essentially null associations of dietary fatty acids with CHD incidence in a random-effects meta-analysis when not considering the substitution nutrient. Our observation of null CHD association when substituting PUFAs for carbohydrates was consistent with results from the global PURE (Prospective Urban Rural Epidemiology) study, which involved participants from 18 countries in 5 continents.[14] However, our observed null association when substituting PUFAs for SFAs differed from studies of CHD based in the United States and Northern

Table 2. Baseline Dietary Characteristics in the Lowest (Q1) and Highest (Q5) Quintiles of Dietary Fatty Acid Intake (in Percent of Energy Intake) in the EPIC-CVD Case-Cohort Study Subcohort (n=16 730)

Dietary Factors	All Subcohort, n=16 730	Total Fatty Acids		SFAs		MUFAs		PUFAs	
		Q1, n=3346	Q5, n=3346	Q1, n=3346	Q5, n=3346	Q1, n=3346	Q5, n=3346	Q1, n=3346	Q5, n=3346
Total energy intake, kcal	1904 (1551–2343)	1754 (1423–2153)	2015 (1630–2474)	1789 (1447–2202)	2031 (1647–2474)	1738 (1417–2105)	1962 (1591–2420)	1897 (1512–2345)	1890 (1545–2327)
Fatty acids, %TEI									
Total	35.0 (30.9–39.2)	27.4 (25.1–28.8)	43.2 (41.5–45.7)	29.3 (25.6–33.6)	40.0 (37.6–43.0)	28.5 (25.8–30.6)	40.9 (37.7–44.7)	30.9 (27.3–35.2)	37.8 (34.2–41.7)
SFAs	14.0 (11.7–16.4)	10.9 (9.1–12.5)	16.7 (13.8–19.5)	9.7 (8.5–10.5)	18.7 (17.8–20.1)	12.4 (10.6–14.1)	13.0 (11.2–15.2)	12.9 (10.6–15.5)	14.0 (11.8–16.1)
MUFAs	14.1 (11.9–17.0)	10.4 (9.3–12.1)	18.9 (16.1–23.8)	14.2 (10.3–17.9)	14.8 (13.4–16.5)	10.2 (9.2–10.8)	21.1 (19.3–24.0)	13.9 (11.1–16.8)	13.9 (12.0–16.3)
PUFAs	5.5 (4.5–7.0)	4.6 (3.9–5.7)	6.3 (5.1–8.3)	5.1 (4.2–6.8)	5.7 (4.7–6.9)	5.4 (4.2–6.8)	5.2 (4.5–6.4)	3.9 (3.6–4.1)	8.9 (8.1–10.3)
MUFA:SFA ratio	0.9 (0.8–1.3)	0.9 (0.8–1.3)	1.1 (0.8–1.7)	1.5 (1.1–2.0)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	1.7 (1.4–2.0)	1.1 (0.8–1.4)	1.0 (0.9–1.2)
PUFA:SFA ratio	0.4 (0.3–0.5)	0.4 (0.3–0.6)	0.4 (0.3–0.5)	0.6 (0.4–0.7)	0.3 (0.2–0.4)	0.4 (0.3–0.6)	0.4 (0.3–0.5)	0.3 (0.2–0.4)	0.7 (0.5–0.8)
Protein, %TEI									
Total	18.0 (15.9–20.3)	18.1 (15.9–20.6)	17.3 (15.5–19.8)	19.1 (16.5–21.7)	17.1 (15.1–19.3)	17.8 (15.7–20.2)	18.5 (16.3–21.0)	17.8 (15.8–20.0)	18.0 (15.9–20.5)
Plant origin	5.4 (4.5–6.4)	6.2 (5.3–7.3)	5.0 (3.9–6.0)	6.8 (6.0–7.7)	4.3 (3.6–5.0)	5.8 (5.0–6.7)	5.8 (4.9–6.7)	5.6 (4.7–6.6)	5.5 (4.6–6.5)
Animal origin	11.1 (8.8–13.6)	10.4 (8.1–13.1)	11.1 (9–13.7)	11.1 (8.5–14.1)	11.1 (8.9–13.5)	10.3 (8.0–12.9)	11.7 (9.5–14.4)	10.8 (8.6–13.3)	10.9 (8.7–13.6)
Mixed origin	1.2 (0.6–2.0)	1.2 (0.6–1.9)	0.9 (0.4–1.7)	0.8 (0.3–1.4)	1.4 (0.8–2.2)	1.4 (0.8–2.1)	0.6 (0.3–1.2)	1.1 (0.5–1.8)	1.3 (0.6–2.1)
Carbohydrate, %TEI)	46.6 (42.1–51.1)	54.7 (51.9–57.7)	38.6 (35.7–41.4)	50.9 (45.9–55.8)	42.6 (38.9–45.8)	53.6 (50.4–57.0)	40.1 (36.5–43.6)	50.7 (46.3–55.0)	43.8 (39.6–47.7)
GI	56.0 (53.6–58.5)	56.5 (53.8–59.2)	55.2 (52.7–57.6)	57.0 (53.9–59.8)	55.7 (53.3–58.0)	56.0 (53.5–58.5)	55.3 (52.9–57.7)	56.2 (53.6–59.0)	55.8 (53.4–58.4)
Dietary fiber, g/d	21.8 (17.3–27.2)	23.6 (18.8–29.3)	20.1 (15.9–25.1)	24.2 (19.2–30.5)	19.4 (15.2–24.5)	23.1 (18.6–28.6)	21.8 (17.5–27.1)	21.4 (17.0–26.8)	22.0 (17.3–27.3)
Fruits and vegetables, g/d	396.9 (249.0–594.2)	436.8 (283.4–620.1)	448.8 (245.1–725.3)	542.6 (370.3–750.8)	275.7 (182.1–416.0)	392.5 (255.7–561.2)	602.7 (421.9–815.4)	435.5 (273.1–635.9)	396.6 (251.9–600.1)
Total dairy	275.7 (159.1–441.4)	299.7 (161.2–488.7)	239.7 (134.2–368.9)	213.4 (98.5–348.3)	333.3 (204.4–527.1)	358.2 (210.6–556.9)	214.8 (119.5–325.4)	302.1 (180.9–476.4)	252.4 (139.8–394.2)
Milk	155.3 (32.8–293)	178.6 (37.5–342.7)	109.3 (19.3–227.7)	150 (21.7–256.1)	156.3 (36.1–339.3)	200.0 (49.9–400.0)	121.4 (22.3–225.2)	176.4 (53.5–320.0)	139.5 (22.1–277.6)
Yogurt/thick fermented milk	26.3 (0–93.3)	35.7 (0.0–113.0)	17.9 (0.0–57.4)	8.3 (0.0–55.4)	35.7 (2.5–107.1)	53.8 (8.8–125.0)	13.4 (0.0–42.9)	21.4 (0.0–107.1)	21.4 (0.0–71.4)
Cheese	30 (14.6–54.2)	20.3 (8.1–37.6)	44.3 (22.1–77.1)	14.2 (2.6–29.2)	42.9 (23.2–75.5)	22.3 (10.9–40.1)	38.1 (13.5–70.8)	35.7 (15.9–62.6)	25.1 (11.4–45.4)
Added fats	29 (18.6–41.7)	18.3 (11.3–27.3)	44.5 (31.4–59.1)	26.9 (16.6–38.0)	33.6 (23.3–47.9)	18.3 (11.1–27.9)	42.4 (32.0–54.9)	24.6 (15.8–35.2)	33.1 (23.1–47.5)
Vegetable oils	6.8 (1.3–25.9)	4.6 (0.7–16.2)	24.2 (3.4–46.4)	23.1 (8.4–34.7)	2.6 (0.2–6.7)	2.3 (0.2–5.7)	38.6 (28.2–50.4)	15.7 (1.3–27.9)	7.9 (2.9–26.0)
Butter	0.0 (0.0–2.2)	0 (0.0–1.3)	0.0 (0.0–2.0)	0.0 (0.0–0.2)	1.4 (0.0–14.3)	0.2 (0.0–2.6)	0.0 (0.0–0.5)	0.1 (0.0–2.2)	0.0 (0.0–2.0)
Margarine	4 (0.1–20.6)	3.2 (0.0–12.8)	2.3 (0.0–20.8)	0.1 (0.0–3.7)	13.3 (1.2–34.9)	8.6 (1.3–20.0)	0.2 (0.0–2.0)	0.3 (0.0–4.2)	10.4 (0.3–26.0)
Meat	100.7 (67.6–140.3)	82.0 (54.1–115.4)	106.3 (72.0–153.3)	93.7 (60.3–134.2)	103.3 (71.4–144.6)	78.1 (50.3–112.0)	104.2 (70.6–151.4)	86.1 (57.2–121.9)	105.9 (68.7–148.9)
Red meat	39.3 (19.6–65.5)	30.8 (12.9–53.8)	44.1 (24.0–68.3)	33.7 (16.1–56.5)	38.1 (18.6–66.0)	31.5 (13.4–55.5)	45.1 (25.9–68.7)	33.4 (15.3–57.6)	39.3 (20.7–65.6)

(*Continued*)

Table 2. Continued

Dietary Factors	All Subcohort, n=16 730	Total Fatty Acids		SFAs		MUFAs		PUFAs	
		Q1, n=3346	Q5, n=3346	Q1, n=3346	Q5, n=3346	Q1, n=3346	Q5, n=3346	Q1, n=3346	Q5, n=3346
Processed meat	25.9 (12–47.5)	18.7 (9.0–33.4)	25.2 (5.0–55.8)	17.4 (6.5–35.1)	35.1 (19.0–60.3)	18.6 (9.0–32.9)	16.3 (2.6–39.6)	19.8 (8.6–36.2)	27.4 (11.1–52.2)
Poultry	16.1 (7.2–31.1)	15.6 (7.0–30.0)	18.3 (7.1–35.4)	23.7 (11.4–42.5)	10.3 (3.3–20.8)	11.1 (4.2–23.2)	24.4 (13.0–39.3)	15.7 (7.2–29.1)	16.4 (6.7–35.6)
Cakes and biscuits	27.9 (10.7–55.8)	21.4 (7.5–42.9)	25.4 (9.8–52.7)	14.1 (1.1–32.5)	37.4 (15.8–69.0)	24.5 (10.5–46.8)	19.2 (5.3–42.9)	26.1 (8.9–56.4)	25.9 (9.9–51.1)
Sugar and confectionary	29.5 (14.9–52.4)	29.3 (13.7–52.9)	23.1 (11.5–43.4)	20.0 (9.2–36.4)	36.2 (18.5–62.0)	33.3 (16.2–57.5)	20.0 (10.0–34.1)	31.5 (15.5–54.6)	24.4 (12.3–45.6)
Cereal and cereal products	197.0 (140.4–273.0)	216.2 (148.6–309.8)	172.7 (124.8–230.6)	228.7 (157.2–323.7)	170.4 (124.3–231.7)	195.9 (137.7–269.2)	194.7 (140.0–263.3)	218.2 (147.9–320.6)	184.6 (132.5–249.3)
Eggs and egg products	14.3 (6.9–24.8)	9.8 (3.6–21.0)	15.2 (7.4–27.7)	14.2 (6.1–26.0)	14.5 (6.6–25.6)	9.6 (3.6–20.8)	15.9 (8.0–28.4)	11.2 (4.4–20.6)	16.1 (8.2–27.4)
Condiments and sauces	13.2 (6.3–25.2)	10.1 (4.5–19.9)	16.2 (7.6–30.6)	10.5 (4.5–18.8)	16.4 (7.6–33.0)	11.4 (4.9–22.6)	11.4 (5.5–19.6)	8.3 (3.9–16.9)	17.8 (8.5–33.0)
Fish and shellfish	28.3 (14.7–50.6)	25.1 (11.8–47.3)	27.3 (14.8–49.8)	38.1 (18.5–69.0)	23.8 (12.3–41.7)	19.3 (8.8–39.2)	33 (18.7–62.4)	24.2 (12.5–43.8)	30.3 (14.2–55.4)
Nuts and seeds	0.6 (0–3.4)	0.3 (0.0–1.6)	1.3 (0.0–5.3)	0.2 (0.0–2.1)	0.7 (0.0–3.4)	0.7 (0.0–2.3)	0.3 (0.0–5.3)	0.2 (0.0–0.8)	1.6 (0.0–7.1)

All values are median (interquartile range). All food intakes are expressed as grams per day. %TEI indicates percentage of total energy intake; EPIC-CVD, European Prospective Investigation into Cancer and Nutrition–Cardiovascular Disease; GI, glycemic index; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; and SFAs, saturated fatty acids.

Europe reporting inverse associations.[8–10,23] This is in line with mixed findings from other studies in Europe, including a positive association with composite CVD in the UK Biobank study (with 10 724 CVD cases),[15] and an inverse association with composite CVD among Spanish adults from the PREDIMED (Prevención con Dieta Mediterránea) study (with 336 CVD cases).[16] The latter results are not directly comparable to our findings, because these were based on an observational follow-up of a randomized clinical trial among those at high CVD risk (PREDIMED study),[16] whereas our study was based in a general population. Because associations in UK Biobank and the PREDIMED study were with composite CVD only, it is unclear to what extent these are driven by CHD or other CVD subtypes such as stroke. Importantly, our results are consistent with a previous Dutch cohort reporting a null CHD association of substituting PUFAs for SFAs.[12]

Some meta-analyses of randomized trials,[4,5] but not all,[6] have reported a beneficial effect on CVD or CHD risk of substituting PUFAs for SFAs. In addition to these heterogeneous findings across trials, the types and quantities of SFA-rich foods consumed in trial participants may differ from those in free-living populations.[17] The potential inverse association with CHD of substituting PUFAs for SFAs from butter, but not fermented dairy, highlights the importance of considering the food source of the SFAs.

The relevance of substituting MUFAs for SFAs to CHD risk is largely unaccounted for in trials,[2] whereas observational studies of CHD have variously reported inverse,[23] null,[12] and positive[9–11] associations, potentially because of differences between plant- and animal-derived MUFAs.[22] Although substituting MUFAs for SFAs was associated with lower composite CVD incidence in the PREDIMED study,[16] there was no strong evidence for an association in UK Biobank (P=0.21).[15] In the present study, substituting MUFAs for SFAs was not associated with CHD. Data on plant- versus animal-derived MUFAs were not available. However, associations were consistently null across all European regions we studied, regardless of food sources being mainly plant based (vegetable oils) in Southern European centers and mainly animal based (dairy and meat) in the other centers.

Previous studies attempted to test whether a diet with low carbohydrate quality may weaken the association of SFA intakes with CHD risk.[12,23–25] However, we found no evidence for the potential effect modification caused by carbohydrate quality assessed by GI. The lack of effect modification could reflect multiple factors. Our GI measure for the multiple European populations was limited, because true GI values may have varied substantially among populations.[39] Moreover, GI as a marker of carbohydrate quality is limited, because it captures the effect of glucose only, not other

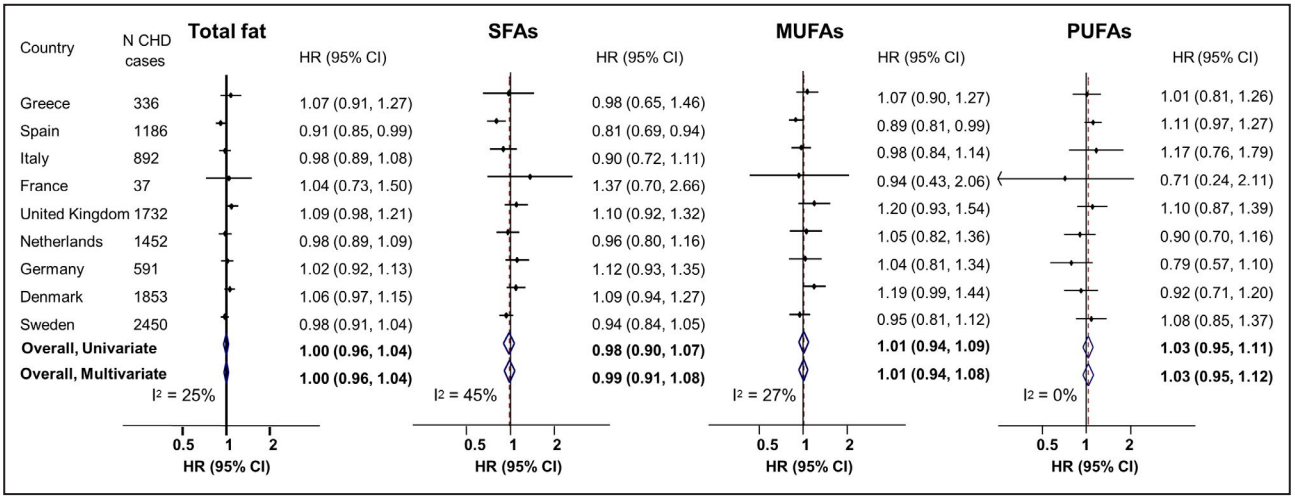

Figure 1. Associations of dietary consumption of each of total fat, saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), and polyunsaturated fatty acids (PUFAs) (all per 5% of total energy intake) with incidence of coronary heart disease (CHD) in the EPIC-CVD (European Prospective Investigation into Cancer and Nutrition–Cardiovascular Disease) study.

Hazard ratios (HRs) and 95% CIs for each 5% higher energy intake from total fat, SFAs, MUFAs, and PUFAs were analyzed within each country separately, with age as the underlying time variable and the baseline hazard stratified by sex. The multivariable-adjusted HR included adjustment for age at recruitment (years), center, energy intake (kcal/d), education (low, medium, high), smoking (never, former, current), physical activity (inactive, moderately inactive, moderately active, active), alcohol intake (0, 0–6, 6–12, 12–24, >24 g/d), dietary fiber (g/d, continuous), fruit and vegetable consumption (g/d, continuous), body mass index (kg/m^2, continuous), preexisting diabetes mellitus, hypertension, and hyperlipidemia. Country-specific HRs (95% CIs) were combined in univariate and multivariate random-effects meta-analyses to obtain pooled HRs and 95% CIs.

monosaccharides, and the effects of GI cannot be separated from fiber and sugar intake that vary by low- or high-GI foods. Further research is warranted to assess carbohydrate quality and the interaction with fat quality, for example, by using biomarkers for sugar intake. Potential nutritional biomarkers in urine or blood have been identified, and these can offer more precise objective assessment to complement the information from subjective dietary assessment for sugar consumption.[40] There is also a need to improve databases of sugar contents and GI values of diverse food products in diverse settings.[39]

Previous observational studies investigating SFAs from food sources with CHD are limited with inconsistent results. Specifically, the inverse association of SFAs from dairy, driven by yogurt and cheese in EPIC-CVD, is consistent with 2 smaller studies that included 1807[11] and 316[18] CHD cases, but not with other large studies reporting null associations.[12,13,19,20] Similarly, the higher CHD incidence associated with SFAs from red and total meat is consistent with some,[13,18] but not all studies.[11–13] Observational evidence of macronutrient-specific substitutions for fatty acids from different foods in relation to CHD is scarce, and focused on fats from total dairy and/or meat.[19,21] By contrast, our study modeled several specific macronutrient substitutions for SFAs from fermented dairy, butter, and red meat, finding opposite associations with CHD depending on SFA food sources and the substitution macronutrient.

Potential Explanations

The observed opposing associations of lower CHD incidence with SFAs from fermented dairy, and of higher CHD incidence with SFAs from red meat, may cancel each other out to create a null association for total SFA intake, highlighting the importance of considering the food sources of nutrients. A key mechanism proposed to link SFAs to increased CHD risk involves effects of dietary fatty acids on lipid metabolism, including low-density lipoprotein–raising effects of dietary SFAs.[1,7] It is possible that different food sources of fatty acids contributed to a lack of differences in non–HDL-C across total SFA intake levels, because meat and dairy consumption have opposite associations (positive and inverse, respectively) with plasma non–HDL-C in EPIC-CVD.[41] Although we cannot establish causality from these observational findings, consuming total fat and SFAs from cheese raised circulating low-density lipoprotein cholesterol concentrations less than consuming similar amounts of fatty acids from butter in trials,[42,43] and the effects of red meat consumption on circulating lipids depend on the comparison diet,[44] also pointing to the importance of the food matrix.

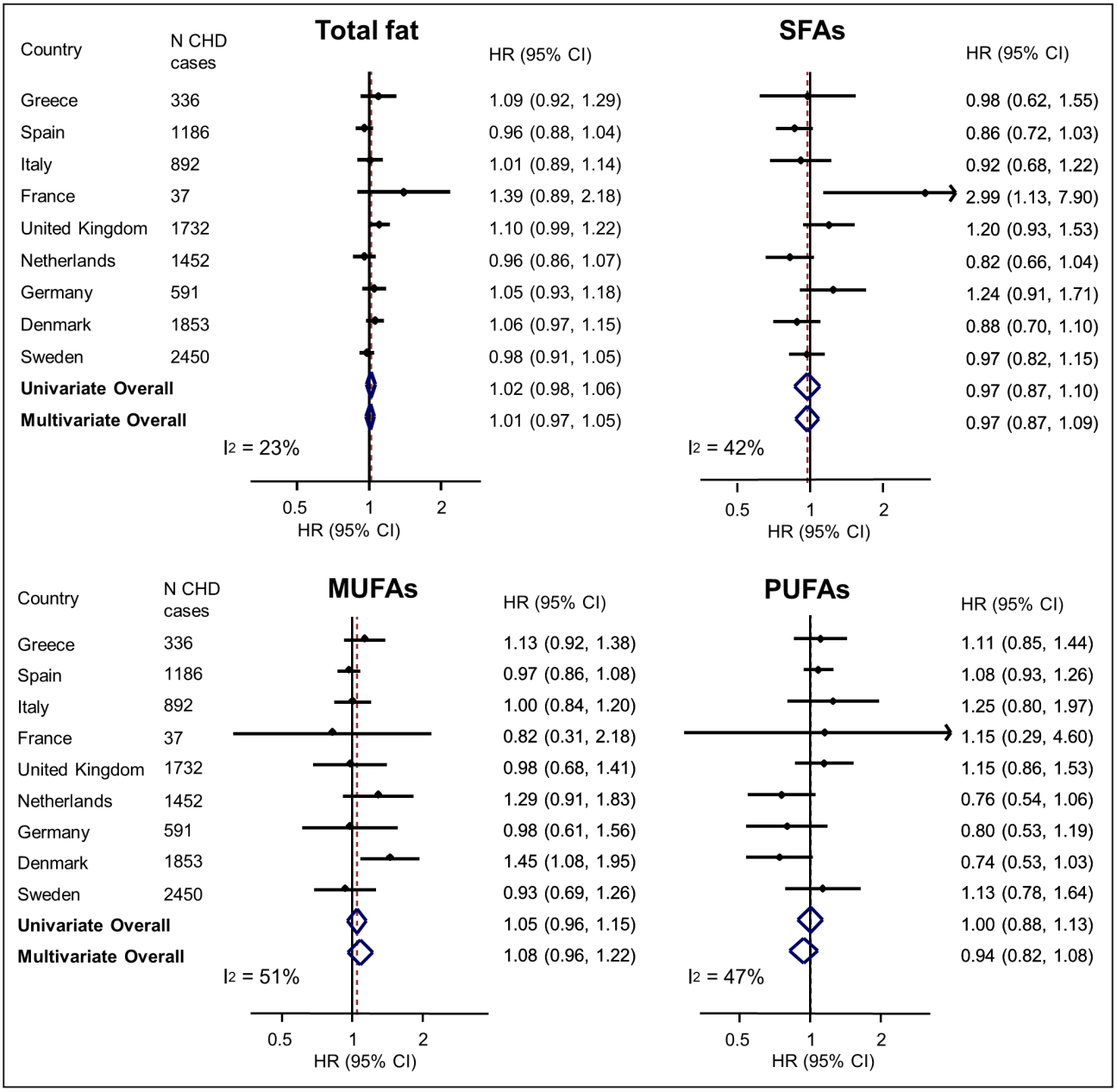

Figure 2. The associations with coronary heart disease (CHD) of substituting 5% energy intake from dietary fatty acids (total and classes) for 5% energy from carbohydrates in the EPIC-CVD (European Prospective Investigation into Cancer and Nutrition–Cardiovascular Disease) study.

Hazard ratios (HRs) and 95% CIs for each 5% higher energy intake from total fatty acids, saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), and polyunsaturated fatty acids (PUFAs), to substitute for 5% lower energy intake from carbohydrates, were analyzed within each country separately, with age as the underlying time variable and the baseline hazard stratified by sex. The multivariable-adjusted HR included adjustment for age at recruitment (years), center, energy intake (kcal/d), smoking (never, former, current), education (low, medium, high), physical activity (inactive, moderately inactive, moderately active, active), alcohol intake (0, 0–6, 6–12, 12–24, >24 g/d), dietary fiber, fruit, and vegetable consumption, body mass index, preexisting diabetes mellitus, hypertension and hyperlipidemia, and all macronutrients except the replacement nutrient (carbohydrates) (i.e., animal-derived protein, plant-derived protein, and mixed-origin protein), and total fat or, for specific fatty acid analysis, SFAs, MUFAs, and PUFAs. Country-specific HRs (95% CIs) were combined in univariate and multivariate random-effects meta-analyses to obtain pooled-effect estimates and 95% CIs.

Specific SFA isomer composition of different foods may contribute to their associations with CHD.[11,45] For instance, observational evidence suggests that odd-chain and even-chain SFAs are associated differently with CHD incidence,[37] and trial evidence indicates different directions of effect of different individual

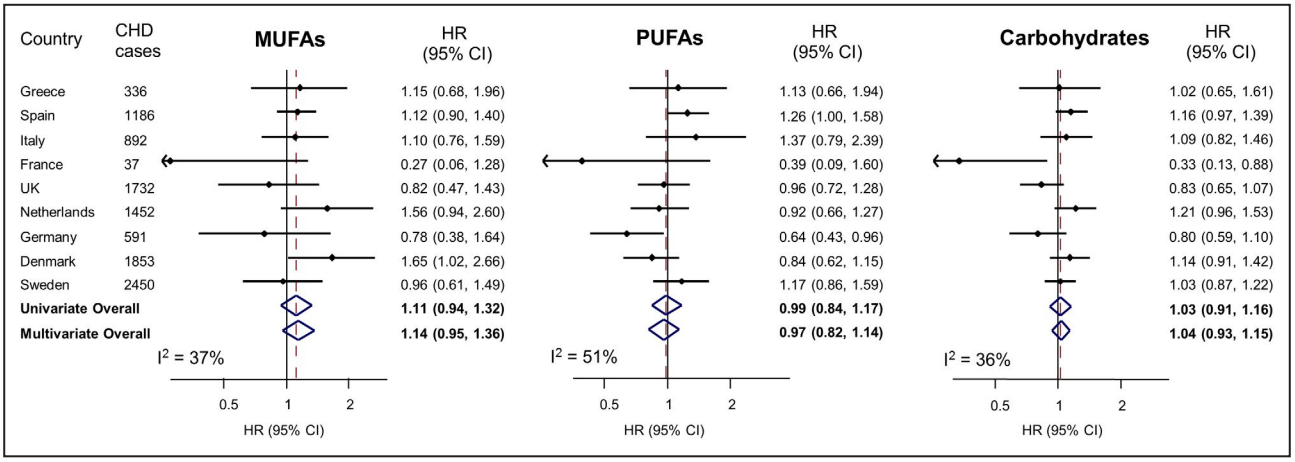

Figure 3. The associations with coronary heart disease (CHD) of substituting 5% energy intake from monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), or carbohydrates for 5% energy from saturated fatty acids (SFAs) in the EPIC-CVD (European Prospective Investigation into Cancer and Nutrition–Cardiovascular Disease) study.
Hazard ratios (HRs) and 95% CIs for each 5% higher energy intake from MUFAs, PUFAs and carbohydrates, to substitute for 5% lower energy intake from SFAs, were analyzed within each country separately, with age as the underlying time variable and the baseline hazard stratified by sex. The multivariable-adjusted HR included adjustment for age at recruitment (years), center, energy intake (kcal/d), education (low, medium, high), smoking (never, former, current), physical activity (inactive, moderately inactive, moderately active, active), alcohol intake (0, 0–6, 6–12, 12–24, >24 g/d), dietary fiber, fruit and vegetable consumption, body mass index, preexisting diabetes mellitus, hypertension, and hyperlipidemia, and all macronutrients except the replacement nutrient (SFAs) (i.e., MUFAs, PUFAs, carbohydrates, animal-derived protein, plant-derived protein, and mixed-origin protein). Country-specific HRs (95% CIs) were combined in univariate and multivariate random-effects meta-analysis to obtain pooled effect estimates and 95% CIs.

SFAs on serum lipids.[7] Thus, food-specific associations with CHD may be attributable to the different mix of individual SFA isomers and other fatty acids in addition to other nutrients and bio-active components in foods or by correlations with other foods or behaviors. Vitamin K, bioactive peptides generated during fermentation, and probiotics in yogurt may contribute to inverse associations of SFAs from fermented dairy products with CHD.[45] Equally, dietary SFAs, iron, phosphatidylcholine, L-carnitine, and advanced glycation end products may all contribute to mechanisms underlying positive associations of red meat, and hence SFAs from red meat in the current study, with CHD.[46] Although we have observed food-specific associations of SFAs with CHD, it is impossible to confirm within an observational study whether associations are specific to SFAs versus other constituents of those foods. Our finding of an inverse association of SFAs from fish, which contributes more to dietary PUFAs than to SFAs, further highlights the limited ability to separate potential effects of different nutrients within foods or to attribute causality specifically to SFAs from observed associations.

Strengths and Limitations

Strengths of the current study include the large sample size involving participants from 9 European countries with heterogeneous dietary habits[27] and comprehensive analyses addressing macronutrient-specific substitutions, potential effect modification by carbohydrate quality (GI), and associations of SFAs from different food sources.

The study's potential limitations merit consideration. Our principal findings were not highly significant, suggesting the need for further evaluation of this hypothesis in additional studies and in further populations. No standardized data were available across all EPIC-CVD countries to reliably investigate associations of n3- and n6-PUFAs, plant- versus animal-derived SFAs, MUFAs, or PUFAs, or of subtypes of carbohydrates (eg, sugar and starch), separately. Nutrient intake from nutritional supplements was not available. Our study included largely White participants, and our findings may therefore not be generalizable to other ethnic/racial groups. Our findings reflect associations among participants in an observational study, and therefore our report is based on self-reported dietary intakes and food sources of fatty acids in this study population, rather than causal effects of changes in fatty acid intake, which would require an experimental design. Our findings reflect associations within the range of dietary intake levels observed within our study population. It is possible that generalizability to other populations in different countries may be affected by differences in dietary patterns, risk factor profiles, and nutrient contents of food sources of SFAs (eg, fortification with micronutrients if such nutrients are causally related to CHD). Therefore, our findings should be further confirmed in other large-scale observational studies among diverse populations with different intake levels, and in intervention studies

Table 3. Associations With Coronary Heart Disease of Dietary SFAs From Different Food Sources (per 1%TEI), Without and With Adjustment for SFAs From Any Other Foods in the EPIC-CVD Case-Cohort Study

SFAs From Food Source	Contribution of Food to SFAs, %TEI*	Multivariable Adjustments†			Additional Adjustment for SFAs From Any Other Food Sources‡		
		HR (95% CI) per 1%TEI	*P* Value	I^2	HR (95% CI) per 1%TEI	*P* Value	I^2
Dairy products	4.4 (2.9–6.2)	0.98 (0.97–1.00)	0.027	0	0.99 (0.97–1.00)	0.060	1
Milk	0.7 (0.1–1.6)	1.01 (0.99–1.04)	0.239	0	1.01 (0.98–1.04)	0.464	0
Yogurt/thick fermented milk	0.1 (0.0–0.5)	0.93 (0.88–0.99)	0.017	0	0.93 (0.88–0.99)	0.016	0
Cheese	2.3 (1.2–4.0)	0.98 (0.96–1.00)	0.018	10	0.98 (0.96–0.99)	0.007	6
Added fats	2.7 (1.7–4.1)	1.02 (1.00–1.04)	0.018	23	1.02 (1.00–1.03)	0.061	5
Vegetable oils	0.5 (0.1–1.7)	1.03 (0.96–1.11)	0.426	0	1.01 (0.94–1.09)	0.804	0
Butter	0.0 (0.0–0.5)	1.02 (1.00–1.04)	0.032	4	1.02 (1.00–1.04)	0.058	3
Margarine	0.4 (0.0–1.9)	1.00 (0.97–1.03)	0.979	28	1.00 (0.98–1.03)	0.885	15
Meat	2.2 (1.4–3.2)	1.04 (1.01–1.08)	0.013	35	1.05 (1.00–1.09)	0.053	54
Red and processed	1.8 (1.1–2.9)	1.05 (1.01–1.09)	0.015	43	1.05 (1.00–1.10)	0.048	57
Red	0.7 (0.04–1.3)	1.07 (1.02–1.12)	0.007	15	1.07 (1.01–1.12)	0.020	26
Processed	0.8 (0.3–1.6)	1.03 (0.99–1.07)	0.150	16	1.04 (0.98–1.09)	0.196	44
Poultry	0.1 (0.1–0.3)	0.95 (0.80–1.13)	0.552	23	0.93 (0.80–1.08)	0.360	10
Cakes and biscuits	0.9 (0.4–1.8)	0.97 (0.94–1.00)	0.069	8	0.98 (0.94–1.01)	0.210	32
Sugar and confectionary	0.4 (0.1–0.9)	1.00 (0.96–1.03)	0.816	0	0.99 (0.96–1.03)	0.748	0
Cereal and cereal products	0.4 (0.3–0.6)	1.08 (0.93–1.25)	0.333	41	1.08 (0.93–1.25)	0.329	40
Egg and egg products	0.2 (0.1–0.4)	0.90 (0.79–1.04)	0.143	0	0.90 (0.78–1.03)	0.121	0
Condiments and sauces	0.2 (0.1–0.4)	0.97 (0.82–1.15)	0.725	54	0.95 (0.81–1.13)	0.596	52
Fish and shellfish	0.1 (0.1–0.3)	0.87 (0.75–1.00)	0.048	0	0.85 (0.74–0.99)	0.031	0
Nuts and seeds	0.0 (0.0–0.1)	0.82 (0.65–1.03)	0.089	36	0.83 (0.65–1.05)	0.111	37

%TEI indicates percentage of total energy intake; EPIC-CVD, European Prospective Investigation into Cancer and Nutrition–Cardiovascular Disease; HR, hazard ratio; and SFAs, saturated fatty acids.

*All values are median (interquartile range) in the overall subcohort (n=16 730).

†HRs and 95% CIs for each 1% higher energy intake from SFAs from each food group were analyzed within each country separately, with age as the underlying time variable and the baseline hazard stratified by sex. The multivariable-adjusted HR included adjustment for age at recruitment (years), center, energy intake (kcal/d), education (low, medium, high), smoking (never, former, current), physical activity (inactive, moderately inactive, moderately active, active), alcohol intake (0, 0–6, 6–12, 12–24, >24 g/d) dietary fiber (g/d, continuous), fruit and vegetable consumption (g/d, continuous), body mass index (kg/m^2, continuous), preexisting diabetes mellitus, hypertension, and hyperlipidemia. Country-specific HRs (95% CIs) were combined in a multivariate random-effects meta-analysis to obtain pooled-effect estimates and 95% CIs. The analysis included all 16 730 subcohort members and 10 529 coronary heart disease cases.

‡Additionally adjusted for the sum of SFAs (%TEI) from all other food sources.

when feasible, acknowledging that the latter may pose major challenges of logistics, cost, and adherence with interventional dietary regimes over the required period of time until end points develop. Despite overall null associations of dietary fatty acids with CHD in our study, there were some country-specific differences in associations. This may be explained by country-specific differences in food sources of dietary fatty acids, or residual confounding that might differ among country-specific study populations. For instance, the positive association of substituting SFAs for carbohydrates in France despite the overall null association in EPIC-CVD might be explained by specific dietary patterns and unique characteristics of this study population including all-women education professionals. Nevertheless, there was minimal heterogeneity in associations of SFAs from specific foods with CHD incidence, including of SFAs from dairy, red meat, processed meat, and butter, thus supporting the importance of considering the overall food matrix across all included countries. Despite adjusting for a range of potential confounders, we cannot exclude potential residual confounding from unmeasured factors such as from trans fats. However, trans fat intake has traditionally been lower across Western Europe (mean intake ~1%TEI) compared with North America (~4%TEI).[47] Moreover, our main findings relate to SFAs from foods containing ruminant trans fats, rather than the harmful industrial trans fats,[38] making it less likely that our conclusions on the importance of food sources of SFAs would have been materially affected by residual confounding from trans fats. Although we adjusted for self-reported preexisting hyperlipidemia, information on lipid-lowering drugs was not available. Hence, if the associations in our study populations were mediated by lipid levels, our findings could underestimate the true associations. Similarly,

although we adjusted for self-reported preexisting hypertension and diabetes mellitus, no information on relevant medication was available. By contrast, our study's use of single baseline measurements of multiple covariates, potentially with nonrandom measurement error, could have biased associations toward or away from the null, contributing to the overall null associations of fatty acids with CHD. Dietary questionnaires were validated, with estimated validity coefficients for total fat ranging from 0.31 to 0.89 across countries (except Greece: 0.09 in men, 0.26 in women).[30] This variation among countries may be related to differences in dietary reporting arising from cultural differences or dietary assessment methods as well as center-specific validation methods. Thus, we cannot exclude the possibility that the country-specific associations with CHD were influenced by different levels of validity of the measures of exposure among countries. Although our primary results were based on analyses of habitual diet captured by food-frequency questionnaire data, regression calibration analyses using 24-hour recall data available among a subset of participants did not change our overall findings or interpretation. We conducted a range of sensitivity analyses, suggesting that the study's principal results were robust to over- and underreporting of energy intake. Our current work focused on food-specific associations of SFAs only, based on prior evidence of differences in associations with CHD of dairy products[19,20,35,36] and meat,[35] 2 major food sources of SFAs. Future studies need to investigate how the overall food matrix affects CHD risk, ideally within causally informative designs.

Potential Public Health Implications

The observed opposing associations of SFAs from fermented dairy products versus SFAs from red meat suggest that the potential health effects of limiting SFAs in general, and by extension of substituting other macronutrients for SFAs, may be beneficial, neutral, or detrimental (assuming causality) depending on which specific changes in food consumption are made to limit or substitute for SFAs. Overall, shared food sources of SFAs, MUFAs, and PUFAs, their correlations, and food-specific associations of SFAs in the current study, whether or not causally attributable to fatty acids, emphasize the importance of considering the source foods, rather than macronutrients alone, when evaluating associations with disease risk. Our findings imply that recommendations to limit dietary SFAs and replace them with MUFAs or PUFAs for CHD prevention may not be guaranteed to achieve optimal health benefits without considering the food matrix from which fatty acids are consumed within populations. This study adds to growing evidence suggesting that future dietary guidelines for CHD prevention should consider the totality of evidence on nutrients, foods, and dietary patterns combined.

CONCLUSIONS

This epidemiological study found no strong evidence for associations of total dietary fatty acids, SFAs, MUFAs, and PUFAs with incident CHD, regardless of the substitution nutrients, within the range of intake in this European population. By contrast, we found associations of SFAs with CHD in opposite directions, dependent on the food source, suggesting the importance of the overall food matrix. These observational findings need to be further confirmed but support public health recommendations to consider food sources alongside the individual macronutrients they contain.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S12
Figure S1–S5

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SUPPLEMENTAL MATERIAL

Dietary fatty acids, macronutrient substitutions, food sources and incidence of coronary heart disease: findings from the EPIC-CVD case-cohort study across nine European countries

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Table S1. Baseline biomedical risk factors in lowest (Q1) and highest (Q5) quintiles of dietary total fatty acids, saturated, monounsaturated and polyunsaturated fatty acids (%TEI) in the EPIC-CVD case-cohort study subcohort, among a subset of participants with available biomarkers, adjusted for age, sex and study centre.

			Total fatty acids		SFAs		MUFAs		PUFAs	
		Subcohort	Q1 (≤29.9)	Q5 (≥40.2)	Q1 (≤11.2)	Q5 (≥17.1)	Q1 (≤11.3)	Q5 (≥18.0)	Q1 (≤4.3)	Q5 (≥7.5)
Lipids (mmol/l)*	**N**	16,013	3,219	3,197	3,261	3,137	3,208	3,282	3,246	3,218
	TC	5.94 (5.92, 5.95)	5.96 (5.94, 5.97)	5.91 (5.89, 5.93)	5.92 (5.90, 5.94)	5.94 (5.92, 5.96)	6.01 (5.99, 6.03)	5.88 (5.85, 5.90)	5.90 (5.88, 5.92)	5.95 (5.93, 5.97)
	HDL-C	1.49 (1.48, 1.49)	1.50 (1.50, 1.51)	1.47 (1.46, 1.47)	1.47 (1.47, 1.48)	1.50 (1.49, 1.51)	1.52 (1.51, 1.53)	1.45 (1.44, 1.46)	1.48 (1.47, 1.49)	1.50 (1.49, 1.50)
	Non HDL-C	4.45 (4.43, 4.47)	4.45 (4.44, 4.47)	4.44 (4.42, 4.47)	4.45 (4.43, 4.47)	4.44 (4.42, 4.46)	4.49 (4.47, 4.51)	4.42 (4.39, 4.45)	4.42 (4.40, 4.44)	4.46 (4.44, 4.48)
	Triglycerides †	1.15 (1.14, 1.16)	1.15 (1.14, 1.16)	1.12 (1.11, 1.14)	1.11 (1.09, 1.12)	1.19 (1.18, 1.20)	1.19 (1.18, 1.21)	1.06 (1.05, 1.07)	1.10 (1.09, 1.11)	1.15 (1.14, 1.16)
	TC:HDL-C ratio†	4.08 (4.06, 4.10)	4.05 (4.03, 4.07)	4.12 (4.10, 4.15)	4.10 (4.07, 4.12)	4.06 (4.03, 4.08)	4.04 (4.02, 4.07)	4.12 (4.09, 4.16)	4.07 (4.04, 4.09)	4.06 (4.04, 4.09)
Blood Pressure (mm Hg)*	**N**	12,696	2,597	2,490	1,905	2,826	2,897	2,002	2,484	2,395
	SBP	132.1 (131.8, 132.4)	132.2 (131.9, 132.6)	131 (130.5, 131.4)	131.4 (131, 131.8)	132.9 (132.5, 133.2)	132.4 (132.0, 132.7)	128.8 (128.3, 129.4)	131.3 (131, 131.7)	131.4 (131.1, 131.8)
	DBP	81.5 (81.3, 81.7)	81.1 (80.9, 81.3)	81.3 (81.1, 81.6)	81.2 (80.9, 81.4)	81.8 (81.6, 82.0)	80.8 (80.6, 81.0)	80.7 (80.3, 81.0)	81.4 (81.2, 81.6)	81.1 (80.9, 81.3)
CRP (mg/l) †	**N**	16,016	3,218	3,201	3,267	3,140	3,206	3,283	3,244	3,244
		1.16 (1.14, 1.17)	1.17 (1.15, 1.19)	1.14 (1.12, 1.17)	1.20 (1.18, 1.23)	1.11 (1.09, 1.13)	1.17 (1.14, 1.19)	1.18 (1.15, 1.21)	1.15 (1.13, 1.17)	1.15 (1.13, 1.17)
HbA1c (%)*	**N**	16,426	3,264	3,303	3,310	3,275	3,256	3,316	3,273	3,308
		5.52 (5.51, 5.53)	5.52 (5.51, 5.53)	5.56 (5.54, 5.57)	5.52 (5.51, 5.53)	5.53 (5.52, 5.54)	5.52 (5.51, 5.53)	5.54 (5.53, 5.56)	5.53 (5.52, 5.54)	5.50 (5.49, 5.52)

CRP, C-reactive protein; DBP, diastolic blood pressure; IQR, interquartile range; HDL-C, high-density lipoprotein cholesterol; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acid; SBP, systolic blood pressure; SFA, saturated fatty acid; TC, total cholesterol; CI, confidence interval; %TEI, percentage of total energy intake.
Systolic and diastolic blood pressure measurements: In most centres, systolic and diastolic blood pressure was measured in duplicate in sitting position.[26] Where available, we used the average of both measurements.
Biochemical measurements: Non-fasted blood samples obtained at baseline were stored at the International Agency for Research on Cancer (IARC) or local biobanks.[29]
Serum concentrations of total cholesterol (TC), HDL-Cholesterol (HDL-C), triglycerides and high-sensitivity C-reactive protein (CRP), and erythrocyte haemoglobin A1c

(HbA1c) were measured by Stichting Huisartsen Laboratorium (Etten-Leur; the Netherlands), using Cobas enzymatic assays (Roche Diagnostics, Mannheim, Germany) on a Roche/Hitachi Modular P Analyzer for all biomarkers except HbA1c, which was measured with a Tosoh-G8 HPLC (Tosoh Bioscience, Japan). [29]
Means (95% CIs) were estimated from multivariable linear regression, adjusted for age, sex and study centre, among participants in the overall subcohort with measured data on all presented lipids (n=16,013), SBP and DBP (n=12,696), CRP (n=16,016) and HbA1c (n=16,426).
* All values are means (95% CI), unless specified otherwise.
† Geometric means (95% CI).

Table S2. HRs (95% CIs) of CHD across quintiles of dietary total fat, saturated, monounsaturated and polyunsaturated fatty acid intake (%TEI) and tests for trend across categories: EPIC-CVD case-cohort study.

		Q1 (lowest intake)	Q2	Q3	Q4	Q5 (highest intake)	P for trend
Total fat	**Median (subcohort)**	27.4	31.8	35.0	38.3	44.0	
	HR (95% CI)	1.00 (ref)	0.97 (0.87, 1.08)	0.95 (0.86, 1.06)	0.92 (0.81, 1.05)	1.02 (0.89, 1.16)	0.859
SFA	**Median (subcohort)**	9.7	12.2	14.0	15.9	18.7	
	HR (95% CI)	1.00 (ref)	0.88 (0.79, 0.98)	0.87 (0.77, 0.98)	0.87 (0.74, 1.02)	0.86 (0.75, 0.99)	0.173
MUFA†		10.1	12.2	14.0	16.2	21.1	
	HR (95% CI)	1.00 (ref)	0.96 (0.86, 1.09)	0.99 (0.86, 1.13)	1.06 (0.85, 1.33)	0.98 (0.82, 1.19)	0.466
PUFA		3.9	4.7	5.6	6.7	9.0	
	HR (95% CI)	1.00 (ref)	0.98 (0.88, 1.09)	1.00 (0.86, 1.15)	0.99 (0.87, 1.13)	0.98 (0.87, 1.10)	0.920

CI, confidence interval; HR, hazard ratio; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.
Hazard ratios (HRs) and 95% confidence intervals (CIs) across quintiles of dietary SFAs, MUFAs and PUFAs, where quintiles were based on the overall subcohort, were analysed within each country separately, with age as the underlying time variable and the baseline hazard stratified by sex. Country-specific HRs (95% CIs) were combined in multivariate random-effects meta-analysis to obtain pooled effect estimates and 95% CIs. The multivariable-adjusted HR included adjustment for age at recruitment (years), centre, energy intake (kcal/day), education (low, medium, high), smoking (never, former, current), physical activity (inactive, moderately inactive, moderately active, active), alcohol intake (0, 0-6, 6-12, 12-13, >24 g/day), dietary fibre (g/day, continuous), fruit and vegetable consumption (g/day, continuous), body-mass index (kg/m^2, continuous), reported history of diabetes, hypertension and hyperlipidemia. P for trend was assessed by assigning participants the median dietary intake level in their respective quintile (based on the overall subcohort) and analysing as a continuous exposure.
† Greece was excluded in analysis of MUFA with CHD, because there were no CHD cases in the reference category (Q1)

Table S3. Contribution of food groups (%) to dietary saturated fatty acid intake (%TEI) in the EPIC-CVD case-cohort study subcohort.

		Subcohort (n=16,730)	Greece (n=1,201)	Spain (n=3,639)	Italy (n=1,992)	France (n=551)	UK (n=1,076)	Netherlands (n=1,356)	Germany (n=1,995)	Denmark (n=2,005)	Sweden (n=2,915)
Total SFAs from all foods (%TEI)		14.0 (11.7-16.4)	13.2 (11.6-14.9)	11.6 (9.6-13.8)	12.4 (10.7-14.2)	16.1 (13.7-18.4)	13.6 (11.7-15.7)	14.9 (13.1-16.7)	15.6 (13.7-17.7)	15.0 (12.9-16.9)	16.0 (14.0-18.3)
Dairy products		32.0 (22.6-42.3)	41.4 (31.8-50.2)	29.7 (16.6-43.2)	38.2 (29.4-47.4)	37.7 (27.8-46.4)	27.8 (20.3-36.6)	34.5 (26.6-43.9)	28.9 (21.1-37.4)	28.7 (20.1-37.8)	31.2 (23.6-39.3)
	Milk	4.8 (1.0-11.3)	4.6 (1.0-10.1)	9.1 (1.2-18.5)	3.8 (0.0-8.2)	0.3 (0.0-3.6)	10.5 (3.2-17.4)	6.6 (2.6-11.4)	1.4 (0.1-5.7)	4.2 (1.2-9.7)	4.7 (2.1-9.5)
	Yoghurt / thick fermented milk	0.9 (0.0-3.3)	1.7 (0.7-3.7)	0.0 (0.0-1.7)	0.3 (0.0-2.1)	1.3 (0.3-3.0)	0.3 (0.0-1.1)	0.6 (0.2-1.5)	2.1 (0.6-4.9)	1.6 (0.3-6.7)	1.9 (0.0-5.9)
	Cheese	17.0 (8.5-28.1)	30.5 (21.1-39.7)	10.6 (0.6-26.6)	30.4 (22.0-40.1)	25.8 (15.5-35.6)	10.8 (5.5-16.3)	19.2 (12.1-27.5)	13.5 (8.2-20.3)	14.7 (8.5-23.0)	15.2 (8.8-22.9)
Added fats		20.5 (13.5-29.4)	28.4 (22.9-35.1)	15.5 (10.4-22.6)	20.6 (15.9-26.4)	12.8 (7.3-19.6)	16.8 (10.5-25.1)	21.0 (14.9-29.3)	20.3 (13.5-28.8)	22.8 (13.0-31.7)	25.6 (17.0-36.3)
	vegetable oils*	3.3 (0.7-14.0)	25.2 (20.1-31.9)	13.4 (9.0-19.6)	16.3 (12.2-21.6)	2.2 (1.4-3.5)	2.7 (1.4-4.5)	1.2 (0.2-2.6)	1.7 (1.0-3.0)	0.7 (0.3-2.2)	0.0 (0.0-0.7)
	butter	0.1 (0.0-3.8)	0.1 (0.0-1.2)	0.0 (0.0-0.0)	1.0 (0.0.2-3)	5.9 (0.6-14.2)	0.6 (0-9.5.0)	4.7 (2.8-8.9)	8.2 (1.6-20.2)	0.0 (0.0-0.0)	0.0 (0.0-0.3)
	margarines	3.0 (0.1-13.5)	0.9 (0.1-3.4)	0.0 (0.0-0.6)	0.1 (0.0-0.2)	0.0 (0.0-2.3)	6.6 (2.0-12.5)	7.7 (3.7-13.0)	3.6 (0.8-8.8)	15.0 (5.5-26.2)	21.1 (13.2-31.3)
Meat		15.7 (10.1-23.2)	10.6 (7.8-14.3)	19.5 (12.4-29.2)	11.0 (7.6-15.3)	13.5 (9.4-18.8)	10.5 (6.3-15.5)	15.5 (10.9-21.4)	17.6 (11.1-24.5)	24.3 (18.6-31.0)	15.3 (10.7-20.8)
	red meat	5.2 (2.7-9.7)	7.3 (4.9-10.3)	4.4 (2.1-7.7)	4.2 (2.5-6.3)	6.0 (2.7-10.4)	4.2 (1.9-7.2)	8.3 (5.2-12.2)	2.8 (1.7-4.5)	15.8 (11.7-20.7)	4.4 (2.3-7.6)
	processed	6.1 (2.6-11.2)	0.3 (0.0-0.7)	8.5 (3.7-15.6)	3.8 (2.0-6.7)	4.8 (2.4-7.6)	4.5 (2.3-7.4)	5.1 (2.7-8.6)	12.9 (7.4-19.2)	5.9 (3.4-9.3)	7.6 (4.2-11.6)
	poultry	1.1 (0.4-2.3)	1.7 (1.0-3.0)	2.7 (1.4-5.0)	1.2 (0.6-2.2)	1.1 (0.2-2.1)	0.5 (0.2-1.2)	0.6 (0.3-1.2)	0.7 (0.4-1.4)	0.9 (0.5-1.6)	0.5 (0.0-1.4)
Cakes and biscuits		6.5 (2.7-12.7)	2.5 (1.1-4.4)	7.3 (0.0-20.0)	8.1 (3.7-14.3)	7.0 (3.2-11.7)	10.0 (5.7-16.9)	5.6 (3.1-8.8)	10.3 (5.4-16.6)	4.1 (2.0-7.8)	6.9 (3.8-11.3)
Sugar and confectionary		2.8 (0.7-6.1)	2.5 (0.6-5.0)	0.0 (0.0-1.1)	4.0 (1.8-7.5)	1.5 (0.2-7.0)	7.1 (3.5-12.9)	5.1 (2.9-8.1)	2.3 (1.0-5.0)	3.2 (1.8-6.0)	3.5 (1.7-6.6)
Cereal and cereal products		2.9 (1.9-4.5)	2.1 (1.5-2.9)	2.7 (1.7-4.1)	5.2 (3.2-7.7)	3.3 (2.2-4.6)	4.5 (2.7-7.4)	4.0 (2.9-5.3)	2.4 (1.6-3.7)	2.8 (2.0-3.8)	2.5 (1.8-3.5)
Egg and egg products		1.6 (0.8-2.8)	1.3 (0.8-2.0)	2.7 (1.5-4.5)	1.8 (1.1-2.7)	1.9 (1.1-3.1)	1.0 (0.5-2.1)	1.2 (0.7-2.0)	1.4 (0.7-2.2)	1.8 (1.1-3.1)	0.6 (0.2-1.8)
Condiments and sauces		1.1 (0.4-2.8)	1.9 (0.7-3.7)	0.5 (0.2-1.0)	0.6 (0.2-1.2)	4.9 (3.1-7.0)	2.6 (1.3-4.7)	1.0 (0.5-1.7)	1.9 (1.0-3.5)	1.6 (0.7-3.2)	1.8 (0.4-4.8)
Fish and shellfish		1.0 (0.4-2.0)	0.3 (0.2-0.6)	1.9 (0.9-3.5)	0.8 (0.4-1.4)	0.7 (0.4-1.2)	0.8 (0.3-1.4)	0.4 (0.1-0.8)	0.9 (0.4-1.6)	1.9 (1.1-3.1)	0.9 (0.3-2.0)
Nuts and seeds		0.1 (0.0-0.7)	0.8 (0.1-1.7)	0.0 (0.0-0.6)	0.0 (0.0-0.1)	0.6 (0.0-1.4)	0.4 (0.0-1.1)	1.3 (0.4-3.0)	0.2 (0.1-0.9)	0.2 (0.1-0.3)	0.0 (0.0-0.1)

SFAs, saturated fatty acids; %TEI, percentage of total energy intake.

All values are median (interquartile range), in %TEI (for total SFAs) or in % contribution to dietary SFA intakes (for foods).
* Includes all vegetable oils evaluated by country -specific dietary questionnaires, including olive oil where applicable.

Table S4. Pearson partial correlations (95% CI) in the EPIC-CVD case-cohort study subcohort (n=16,730).

	SFA	MUFA	PUFA	Carbohydrates	Animal protein	Plant protein	Total energy
SFA	1						
MUFA	0.54 (0.36, 0.68)	1					
PUFA	0.03 (-0.06, 0.11)	0.26 (-0.01, 0.51)	1				
Carbohydrates	-0.70 (-0.76, -0.63)	-0.79 (-0.85, -0.70)	-0.40 (-0.48, -0.32)	1			
Animal protein	0.23 (0.07, 0.37)	0.15 (0.05, 0.24)	0.03 (-0.07, 0.12)	-0.58 (-0.65, -0.50)	1		
Plant protein	-0.56 (-0.62, -0.48)	-0.32 (-0.42, -0.23)	0.00 (-0.08, 0.09)	0.42 (0.33, 0.50)	-0.34 (-0.43, -0.24)	1	
Total energy	0.20 (0.15, 0.25)	0.09 (0.01, 0.16)	0.05 (-0.01, 0.10)	-0.03 (-0.09, 0.03)	-0.16 (-0.22, -0.11)	-0.22 (-0.31, -0.13)	1

CI, confidence interval; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.
All macronutrients are expressed in % of total energy intake. Pearson partial correlations, adjusted for age and sex, were calculated in the subcohort of each country. Fisher's Z transformation was then used to transform country-specific correlation coefficients r (95% CIs) to obtain a normally distributed variable, i.e. using $z = 0.5*\ln((1+r)/1-r))$. Z-transformed correlation coefficients r (95% CIs) were subsequently pooled using random effects meta-analysis, and back-transformation was applied to obtain an overall correlation coefficient r (95% CI).

Table S5. HRs (95% CIs) of CHD and dietary total fatty acids, saturated, monounsaturated and polyunsaturated fatty acids (per 5 %TEI) with progressive adjustment for confounders in the EPIC-CVD case-cohort study.

	Model 1			Model 2			Model 3			Model 4		
	HR (95% CI)	**P**	**I^2**	**HR (95% CI)**	**P**	**I^2**	**HR (95% CI)**	**P**	**I^2**	**HR (95% CI)**	**P**	**I^2**
Total fatty acids	1.04 (0.99, 1.09)	0.083	63	1.01 (0.97, 1.06)	0.554	51	1.00 (0.97, 1.04)	0.779	18	1.00 (0.96, 1.04)	0.992	25
SFA	1.06 (0.97, 1.16)	0.205	68	1.00 (0.93, 1.08)	0.907	53	0.97 (0.90, 1.05)	0.411	42	0.99 (0.91, 1.08)	0.815	45
MUFA	1.10 (0.98, 1.22)	0.107	75	1.04 (0.95, 1.13)	0.382	57	1.03 (0.96, 1.10)	0.449	29	1.01 (0.94, 1.08)	0.806	27
PUFA	1.03 (0.93, 1.14)	0.567	36	1.03 (0.94, 1.12)	0.512	20	1.07 (0.99, 1.16)	0.074	2	1.03 (0.95, 1.12)	0.471	0

CI, confidence interval; HR, hazard ratio; SD, standard deviation; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.
Hazard ratios (HRs) and 95% confidence intervals (CIs) for each 5% higher contribution to total energy intake from dietary SFAs, MUFAs and PUFAs were analysed within each country separately, with age as the underlying time variable and the baseline hazard stratified by sex. Country-specific HRs (95% CIs) were combined in multivariate random-effects meta-analysis to obtain pooled effect estimates and 95% CIs. The multivariable-adjusted HR included adjustment for (model 1:) age at recruitment (years), centre, energy intake (kcal/day), (model 2:) education (low, medium, high), smoking (never, former, current), physical activity (inactive, moderately inactive, moderately active, active), alcohol intake (0, 0-6, 6-12, 12-13, >24 g/day), (model 3:) dietary fibre (g/day, continuous), fruit and vegetable consumption (g/day, continuous), (model 4:)), body-mass index (kg/m^2, continuous), reported history of diabetes, hypertension and hyperlipidemia.

Table S6. Associations with coronary heart disease of substituting 5% total energy intake from carbohydrates for 5% total energy from saturated fatty acids by thirds of energy-adjusted glycaemic index in the EPIC-CVD case-cohort study.

GI category (range energy-adjusted GI)	N cases/ N total	HR (95% CI)*	P	P interaction †
Low (34.2-54.4)	2,642 / 7,933	0.93 (0.79, 1.11)	0.430	0.579
Medium (54.4-57.5)	3,561 / 8,815	1.01 (0.80, 1.29)	0.904	
High (57.5-77.8)	4,289 / 9,353	1.21 (1.02, 1.43)	0.030	

HR, hazard ratio; CI, confidence interval; GI, glycaemic index;
Hazard ratios (HRs) and 95% confidence intervals (CIs) for each 5% higher contribution to total energy intake from dietary carbohydrates to substitute for 5% lower energy intake from SFAs among participants with low, medium and high glycaemic index were analysed within each country separately, with age as the underlying time variable and the baseline hazard stratified by sex. The multivariable-adjusted HR included adjustment for all macronutrients except SFA, i.e. MUFAs, PUFAs, carbohydrates, plant protein, animal protein and mixed-origin protein (all in %TEI), and centre, energy intake (kcal/day), education (low, medium, high), smoking (never, former, current), physical activity (inactive, moderately inactive, moderately active, active), alcohol intake (0, 0-6, 6-12, 12-13, >24 g/day), dietary fibre (g/day, continuous), fruit and vegetable consumption (g/day, continuous), body-mass index (kg/m^2, continuous), pre-existing diabetes, hypertension and hyperlipidemia.. Country-specific HRs (95% CIs) were combined in multivariate random-effects meta-analysis to obtain pooled effect estimates and 95% CIs. Low, medium and high GI were defined by thirds of the distribution in the overall subcohort. Not adjusting associations across strata of GI for fibre intake in strata-specific analyses did not affect the results.
* France was excluded from these analysis to aid model convergence. Age at recruitment was not included as covariate in these models to aid model convergence in country-specific analysis within GI strata – analysis including age at recruitment as covariate yielded similar results where models did converge.
† P-values for interaction: reported P-value is from the model including the interaction term between GI and carbohydrate intake and not adjusted for dietary fibre consumption, and meta-analysis of the interaction term only.

Table S7. Stratified analysis of dietary saturated, monounsaturated and polyunsaturated fatty acids (per 5%TEI) and CHD in the EPIC-CVD case-cohort study.

		SFAs			MUFAs			PUFAs		
Effect modifier		**HR (95% CI)**	**P**	**P interaction**	**HR (95% CI)**	**P**	**P interaction**	**HR (95% CI)**	**P**	**P interaction**
Sex*				NA/0.425			NA/0.075			NA/0.117
	Men	1.02 (0.94, 1.10)	0.708		1.04 (0.95, 1.14)	0.353		1.00 (0.90, 1.11)	0.980	
	Women (all)	0.92 (0.80, 1.06)	0.255		0.96 (0.87, 1.06)	0.395		1.08 (0.92, 1.26)	0.366	
	Women (mixed-sex centres)	0.95 (0.81, 1.12)	0.538	0.456	0.97 (0.87, 1.07)	0.514	0.100	1.15 (0.99, 1.34)	0.064	0.106
Age*				0.091/0.367†			0.749/0.4967†			0.480/0.161†
	<52.4	0.89 (0.75, 1.05)	0.155		0.98 (0.85, 1.13)	0.751		0.90 (0.70, 1.17)	0.442	
	≥52.4	1.01 (0.92, 1.11)	0.825		1.03 (0.95, 1.11)	0.432		1.04 (0.94, 1.15)	0.499	
Plausibility of self-reported energy intake*				NA/0.956			NA/0.557			NA/0.460
	Under	1.01 (0.89, 1.15)	0.845		1.06 (0.94, 1.19)	0.343		0.94 (0.80, 1.10)	0.446	
	Plausible	0.98 (0.85, 1.12)	0.731		1.03 (0.90, 1.18)	0.652		1.04 (0.92, 1.17)	0.536	
	Over	0.93 (0.67, 1.30)	0.683		1.07 (0.82, 1.40)	0.610		1.44 (0.91, 2.30)	0.122	
Pre-existing diabetes/ hypertension/ hyperlipidemia				NA/0.956			NA/0.975			NA/0.090
	No/unknown	0.99 (0.88, 1.13)	0.928		1.00 (0.92, 1.08)	0.965		0.99 (0.89, 1.10)	0.847	
	yes	1.00 (0.87, 1.15)	0.996		1.00 (0.91, 1.08)	0.918		1.11 (0.98, 1.26)	0.092	

CI, confidence interval; HR, hazard ratio; SFA, saturated fatty acid; %TEI, percentage contribution to total energy intake.

Hazard ratios (HRs) and 95% confidence intervals (CIs) for each 5% higher contribution to total energy intake from dietary SFAs, MUFAs and PUFAs by categories of potential effect modifiers were analysed, with age as the underlying time variable and the baseline hazard stratified by sex. The multivariable-adjusted HR included adjustment for age at recruitment, centre, energy intake (kcal/day), education (low, medium, high), smoking (never, former, current), physical activity (inactive, moderately inactive, moderately active, active), alcohol intake (0, 0-6, 6-12, 12-13, >24 g/day), dietary fibre (g/day, continuous), fruit and vegetable consumption (g/day, continuous), body-mass index (kg/m^2, continuous), reported history of diabetes, hypertension and hyperlipidemia.

* France was excluded from analysis of sex, age and energy reporting because <10 cases in at least one reference category.

† P-value for interaction, investigated with effect modifier modelled as continuous / categorical covariate in the models.

Table S8. Stratified analysis of associations with CHD of substituting 5% energy from monounsaturated fatty acids, polyunsaturated fatty acids, and carbohydrates for energy from SFAs in the EPIC-CVD case-cohort study.

		MUFAs			PUFAs			Carbohydrates		
Effect modifier		**HR (95% CI)**	**P**	**P interaction**	**HR (95% CI)**	**P**	**P interaction**	**HR (95% CI)**	**P**	**P interaction**
Sex *				0.0866			0.1319			0.9133
	Men	1.15 (0.94, 1.39)	0.173		0.90 (0.75, 1.08)	0.264		1.01 (0.90, 1.13)	0.918	
	Women (all)	1.11 (0.89, 1.39)	0.332		1.14 (0.93, 1.41)	0.214		1.08 (0.92, 1.28)	0.346	
	Women (mixed-sex centres)	1.06 (0.84, 1.36)	0.611	0.1161	1.15 (0.92, 1.44)	0.209	0.1222	1.05 (0.87, 1.27)	0.621	0.9308
Age *				0.8290/0.7333†			0.3383/0.1165†			0.2130/0.1759†
	<52.4	1.63 (1.19, 2.25)	**0.003**		0.93 (0.64, 1.35)	0.701		1.27 (1.07, 1.50)	**0.005**	
	≥52.4	1.09 (0.92, 1.29)	0.316		0.97 (0.83, 1.14)	0.740		1.00 (0.91, 1.10)	0.966	
Plausibility of self-reported energy intake *				0.6239			0.5984			0.8945
	Under reporting	1.12 (0.82, 1.52)	0.475		0.95 (0.71, 1.27)	0.731		1.03 (0.71, 1.27)	0.790	
	Plausible	1.24 (0.98, 1.57)	0.847		1.02 (0.82, 1.27)	0.847		1.08 (0.94, 1.25)	0.280	
	Over reporting	1.08 (0.64, 1.80)	0.779		1.55 (0.77, 3.13)	0.218		1.07 (0.74, 1.55)	0.710	
Pre-existing diabetes/ hypertension/ hyperlipidemia				0.9289			0.0594			0.1903
	No/unknown	1.00 (0.77, 1.30)	0.998		0.93 (0.76, 1.30)	0.426		0.99 (0.83, 1.17)	0.871	
	yes	1.11 (0.87, 1.43)	0.408		1.07 (0.80, 1.42)	0.656		1.01 (0.83, 1.21)	0.948	

CI, confidence interval; HR, hazard ratio; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; %TEI, percentage contribution to total energy intake.

Hazard ratios (HRs) and 95% confidence intervals (CIs) for each 5% higher contribution to total energy intake from dietary MUFAs, PUFAs and carbohydrates to substitute for 5% lower energy intake from dietary SFAs by categories of potential effect modifiers were analysed, with age as the underlying time variable and the baseline hazard stratified by sex. The multivariable-adjusted HR included adjustment for all macronutrients except SFA, i.e. MUFAs, PUFAs, carbohydrates, plant protein, animal protein and mixed-origin protein (all in %TEI), and age at recruitment, centre, energy intake (kcal/day), education (low, medium, high), smoking (never, former, current), physical activity (inactive, moderately inactive, moderately active, active), alcohol intake (0, 0-6, 6-12, 12-13, >24 g/day), dietary fibre (g/day, continuous), fruit and vegetable consumption (g/day, continuous), body-mass index (kg/m^2, continuous), reported history of diabetes, hypertension and hyperlipidemia.

* France was excluded from analysis of sex, age and energy reporting because <10 cases in at least one reference category.

† P-value for interaction, investigated with effect modifier modelled as continuous / categorical covariate in the models.

Table S9 Associations with CHD of substituting dietary monounsaturated fatty acids, polyunsaturated fatty acids, carbohydrates, and saturated fatty acids from other foods, for saturated fatty acids from fermented dairy products, red meat, or butter (per 5%TEI) in the EPIC-CVD case-cohort study.

Food-specific SFAs to be substituted for (↓5%TEI)	Macronutrient substituting for SFAs from food (↑5%TEI)	HR (95% CI)	P	I^2
SFAs from fermented dairy (yoghurt + cheese)	MUFAs	1.18 (1.00, 1.40)	0.055	26
	PUFAs	1.07 (0.90, 1.27)	0.446	42
	Carbohydrates	1.13 (1.02, 1.25)	0.023	17
	SFAs from other foods (not fermented dairy)	1.20 (1.02, 1.40)	0.028	55
SFAs from red meat	MUFAs	0.74 (0.52, 1.07)	0.108	24
	PUFAs	0.67 (0.47, 0.95)	0.026	36
	Carbohydrates	0.70 (0.51, 0.97)	0.032	29
	SFAs from other foods (not red meat)	0.70 (0.52, 0.93)	0.014	24
SFAs from butter	MUFAs	1.01 (0.82, 1.25)	0.896	26
	PUFAs	0.89 (0.76, 1.04)	0.158	25
	Carbohydrates	0.92 (0.81, 1.05)	0.222	19
	SFAs from other foods (not butter)	0.86 (0.76, 0.98)	0.019	18

Hazard ratios (HRs) and 95% confidence intervals (CIs) for each 5% higher energy intake from MUFAs, PUFAs and carbohydrates to substitute for 5% lower energy intake from saturated fatty acids (SFAs) from specific foods were analysed within each country separately, with age as the underlying time variable and the baseline hazard stratified by sex. The multivariable-adjusted HR included adjustment for age at recruitment (years), centre, energy intake (kcal/day), education (low, medium, high), smoking (never, former, current), physical activity (inactive, moderately inactive, moderately active, active), alcohol intake (0, 0-6, 6-12, 12-13, >24 g/day), dietary fibre (g/day, continuous), fruit and vegetable consumption (g/day, continuous), body-mass index (kg/m^2, continuous), reported history of diabetes, hypertension and hyperlipidemia, and for total MUFAs, PUFAs, carbohydrates, plant-derived, animal-derived and mixed-origin protein, and the sum of SFAs from all other foods, all per 5%TEI. Country-specific HRs (95% CIs) were combined in univariate and multivariate random-effects meta-analysis to obtain pooled effect estimates and 95% CIs. The analysis included all 16,730 subcohort members and 10,529 CHD cases.

Table S10. Associations of dietary fatty acids (total and classes) with incident CHD by region in the EPIC-CVD case-cohort study.

	Overall			South	Central	North	
	HR (95% CI)	P	I^2 (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	P for heterogeneity between regions
Intake of:							
Total fat[a]	1.00 (0.96, 2.04)	0.992	25 (0-65)	0.96 (0.91, 1.02)	1.03 (0.97, 1.09)	1.01 (0.96, 1.06)	0.192
SFAs[a]	0.99 (0.91, 1.08)	0.815	45 (0-75)	0.91 (0.79, 1.05)	1.06 (0.95, 1.18)	0.99 (0.93, 1.06)	**0.029**
MUFAs[a]	1.01 (0.94, 1.08)	0.806	27 (0-66)	0.96 (0.89, 1.04)	1.10 (0.95, 1.27)	1.06 (0.93, 1.19)	0.135
PUFAs[a]	1.03 (0.95, 1.12)	0.471	0 (0-65)	1.08 (0.97, 1.21)	0.95 (0.82, 1.11)	1.00 (0.84, 1.20)	0.400
Dietary SFAs to be substituted by:							
MUFAs[b]	1.14 (0.95, 1.36)	0.174	37 (0-71)	1.08 (0.88, 1.31)	1.03 (0.74, 1.45)	1.21 (0.88, 1.68)	0.808
PUFAs[b]	0.97 (0.82, 1.14)	0.680	51 (0-77)	1.17 (0.93, 1.47)	0.84 (0.69, 1.02)	1.00 (0.80, 1.25)	**0.039**
Carbohydrates[b]	1.04 (0.93, 1.15)	0.509	36 (0-71)	1.06 (0.91, 1.23)	0.94 (0.81, 1.10)	1.07 (0.94, 1.23)	0.441

CI, confidence interval; HR, hazard ratio; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.
South: Greece, Spain, Italy, France; Central: the Netherlands, United Kingdom, Germany; North: Denmark, Sweden.
[a]HR per 5% higher energy intake from exposure to substitute for energy from any other macronutrient source.
[b]HR (95% CI) per 5% higher energy intake from exposure to substitute 5% energy intake from SFA.
Hazard ratios (HRs) and 95% confidence intervals (CIs) were analysed within each country separately, with age as the underlying time variable and the baseline hazard stratified by sex. Country-specific HRs (95% CIs) were combined in multivariate random-effects meta-analysis to obtain pooled effect estimates and 95% CIs. The multivariable-adjusted HR included adjustment age at recruitment (years), centre, energy intake (kcal/day), education (low, medium, high), smoking (never, former, current), physical activity (inactive, moderately inactive, moderately active, active), alcohol intake (0, 0-6, 6-12, 12-13, >24 g/day), dietary fibre (g/day, continuous), fruit and vegetable consumption (g/day, continuous), body-mass index (kg/m^2, continuous), reported history of diabetes, hypertension and hyperlipidemia. In macronutrient-specific substitution analysis, models were additionally adjusted for all macronutrients except SFA, i.e. MUFAs, PUFAs, carbohydrates, plant protein, animal protein and mixed-origin protein (all in %TEI). P for heterogeneity between regions was obtained from fixed-effect meta-analysis by region. Region-specific HRs (95% CIs) were estimated by multivariate random-effects meta-analysis of country-specific effect estimates within each region.

Table S11. Associations of dietary fatty acids with CHD in the EPIC-CVD case-cohort study: sensitivity analyses

		Total fatty acids		SFAs		MUFAs		PUFAs	
	N cases / total	HR (95% CI)*	I^2 (95% CI)	HR (95% CI)*	I^2 (95% CI)	HR (95% CI)*	I^2 (95% CI)	HR (95% CI)*	I^2 (95% CI)
Fatal CHD†	1,614 / 17,688	1.01 (0.95, 1.08	0 (0-68)	1.00 (0.85, 1.16)	37 (0-72)	1.07 (0.94, 1.22)	0 (0-68)	1.00 (0.77, 1.29)	53 (0-79)
Non-fatal CHD†	8,878 / 24,592	1.00 (0.96, 1.04)	37 (0-72)	0.98 (0.90, 1.07)	46 (0-76)	1.00 (0.93, 1.08)	31 (0-69)	1.04 (0.95, 1.12)	0 (0-68)
Excluding the first 2 years of follow-up	9,479 / 25,637	0.99 (0.96, 1.03)	18 (0-60)	0.98 (0.89, 1.07)	48 (0-76)	0.99 (0.93, 1.06)	11 (0-52)	1.03 (0.95, 1.12)	1 (0-65)
Excluding extreme energy intake reporters‡	10,387 / 26,339	1.00 (0.96, 1.04)	38 (0-71)	0.99 (0.91, 1.08)	49 (0-76)	1.02 (0.93, 1.10)	42 (0-73)	1.02 (0.94, 1.11)	0 (0-65)

HR, hazard ratio; CHD, coronary heart disease; CI, confidence interval; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.

* HR (95% CI) per 5% higher energy intake from exposure to replace energy from any other macronutrient source.

† France was excluded from analyses of fatal and non-fatal CHD, because there were <10 incident fatal CHD cases. The incidence rates in the subcohort were 23.77 first non-fatal CHD events per 10,000 person-years, and 5.255 fatal CHD events per 10,000 person-years.

‡ Extreme energy intake was defined as total energy intake <500 or >3500 kcal/day for women, and <800 or >4000 kcal/day for men.

Hazard ratios (HRs) and 95% confidence intervals (CIs) were analysed within each country separately, with age as the underlying time variable and the baseline hazard stratified by sex. Country-specific HRs (95% CIs) were combined in multivariate random-effects meta-analysis to obtain pooled effect estimates and 95% CIs. The multivariable-adjusted HR included adjustment age at recruitment (years), centre, energy intake (kcal/day), education (low, medium, high), smoking (never, former, current), physical activity (inactive, moderately inactive, moderately active, active), alcohol intake (0, 0-6, 6-12, 12-13, >24 g/day), dietary fibre (continuous), fruit and vegetable consumption (continuous), body-mass index (continuous), reported history of diabetes, hypertension and hyperlipidemia.

Table S12. Associations of 5%TEI from monounsaturated fatty acids, polyunsaturated fatty acids, and carbohydrates to substitute for 5%TEI from saturated fatty acids with CHD in the EPIC-CVD case-cohort study: sensitivity analyses

		SFAs to be substituted by:					
		MUFAs		PUFAs		Carbohydrates	
	N cases / total	HR (95% CI)*	I^2 (95% CI)	HR (95% CI)*	I^2 (95% CI)	HR (95% CI)*	I^2 (95% CI)
Fatal CHD†	1,614 / 17,688	1.17 (0.89, 1.54)	1 (0-68)	0.98 (0.61, 1.57)	73 (45-87)	1.02 (0.86, 1.21)	18 (0-60)
Non-fatal CHD†	8,878 / 24,592	1.14 (0.96, 1.35)	28 (0-68)	1.00 (0.86, 1.16)	41 (0-74)	1.05 (0.96, 1.15)	24 (0-65)
Excluding the first 2 years of follow-up	9,479 / 25,637	1.14 (0.96, 1.36)	27 (0-66)	0.98 (0.82, 1.18)	54 (3-78)	1.05 (0.94, 1.16)	36 (0-71)
Excluding extreme energy intake reporters‡	10,387 / 26,339	1.14 (0.95, 1.36)	33 (0-69)	0.96 (0.81, 1.15)	54 (3-78)	1.03 (0.93, 1.14)	34 (0-70)
Winsorized covariates	10,529 / 26,687	1.11 (0.93, 1.33)	34 (0-70)	0.95 (0.80, 1.13)	54 (2-78)	1.02 (0.92, 1.13)	35 (0-70)
One-stage analyses§	10,529 / 26,687	1.03 (0.93, 1.16)	NA	1.02 (0.92, 1.13)	NA	1.01 (0.94, 1.08)	NA

HR, hazard ratio; CHD, coronary heart disease; CI, confidence interval; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; TEI, total energy intake.

* Hazard ratios (HRs) and 95% confidence intervals (CIs) per 5% higher energy intake from exposure to replace energy from SFAs, analysed within each country separately. Country-specific HRs (95% CIs) were combined in multivariate random-effects meta-analysis to obtain pooled effect estimates and 95% CIs. Models included age as underlying time variable and baseline hazards were stratified by sex. The multivariable-adjusted HR included adjustment age at recruitment (years), centre, energy intake (kcal/day), education (low, medium, high), smoking (never, former, current), physical activity (inactive, moderately inactive, moderately active, active), alcohol intake (0, 0-6, 6-12, 12-13, >24 g/day), dietary fibre (continuous), fruit and vegetable consumption (continuous), body-mass index (continuous), reported history of diabetes, hypertension and hyperlipidemia, and all macronutrients except SFA, i.e. MUFAs, PUFAs, carbohydrates, plant protein, animal protein and mixed-origin protein (all in %TEI).

† France was excluded from analyses of fatal and non-fatal CHD, because there were <10 incident fatal CHD cases, and in analyses of winsorized covariates to aid model convergence. The incidence rates in the subcohort were 23.77 first non-fatal CHD events per 10,000 person-years, and 5.255 fatal CHD events per 10,000 person-years.

‡ Extreme energy intake was defined as total energy intake <500 or >3500 kcal/day for women, and <800 or >4000 kcal/day for men.

§ In one-stage analyses, data from all countries were pooled together in one analysis model.

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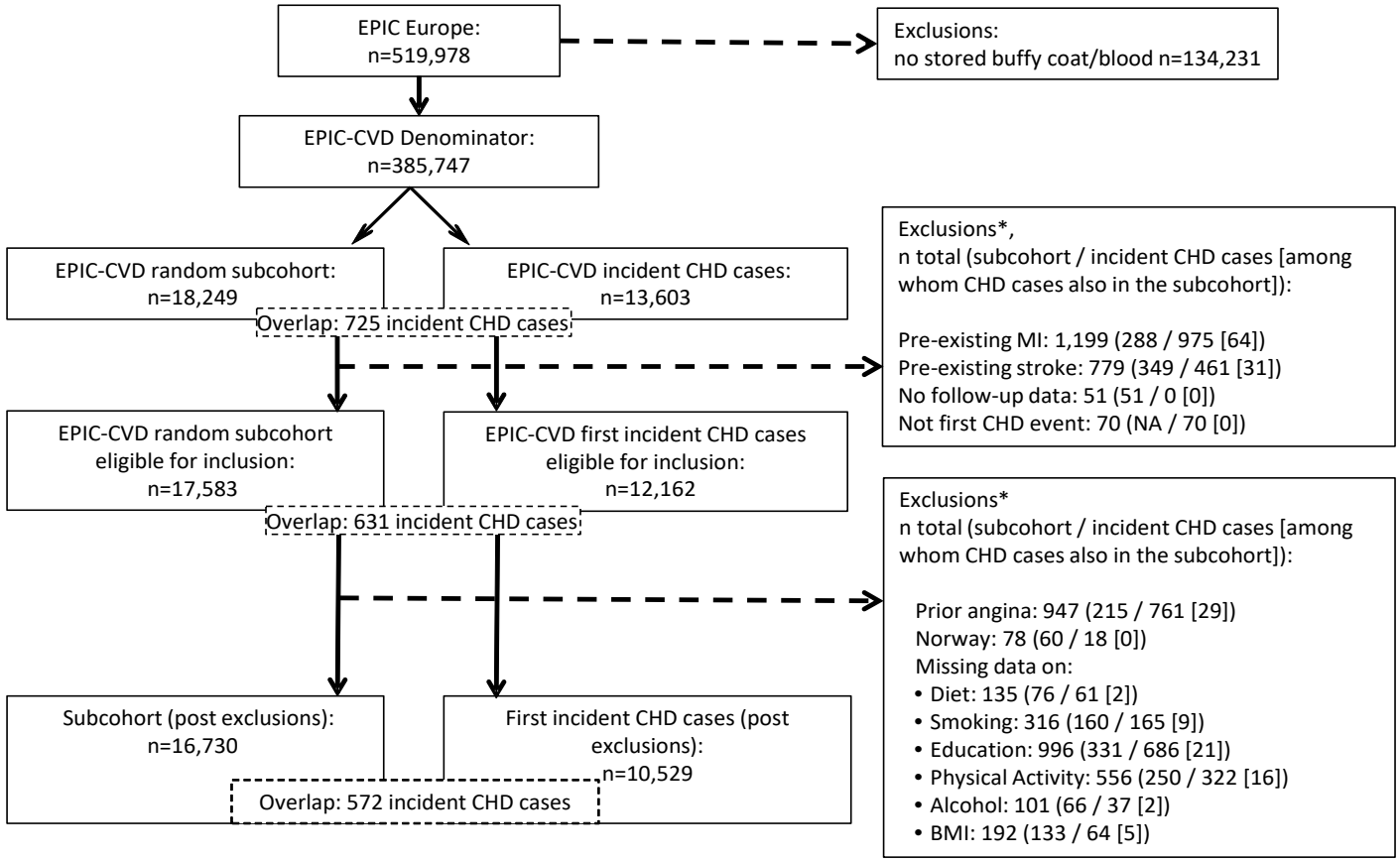
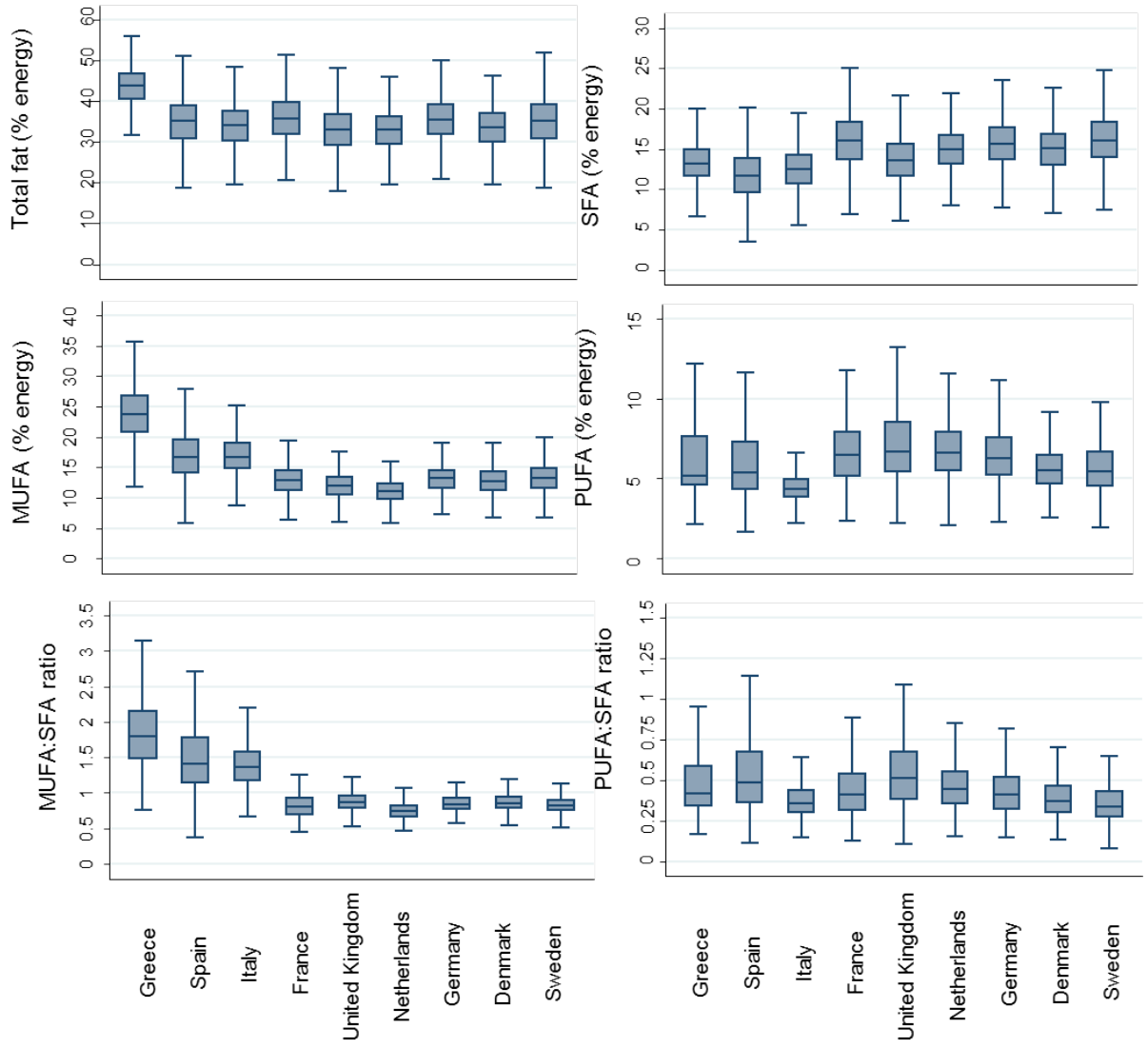
Figure S1. Number of participants included in analyses of the association of dietary fatty acids and incident coronary heart disease: EPIC-CVD case-cohort study.



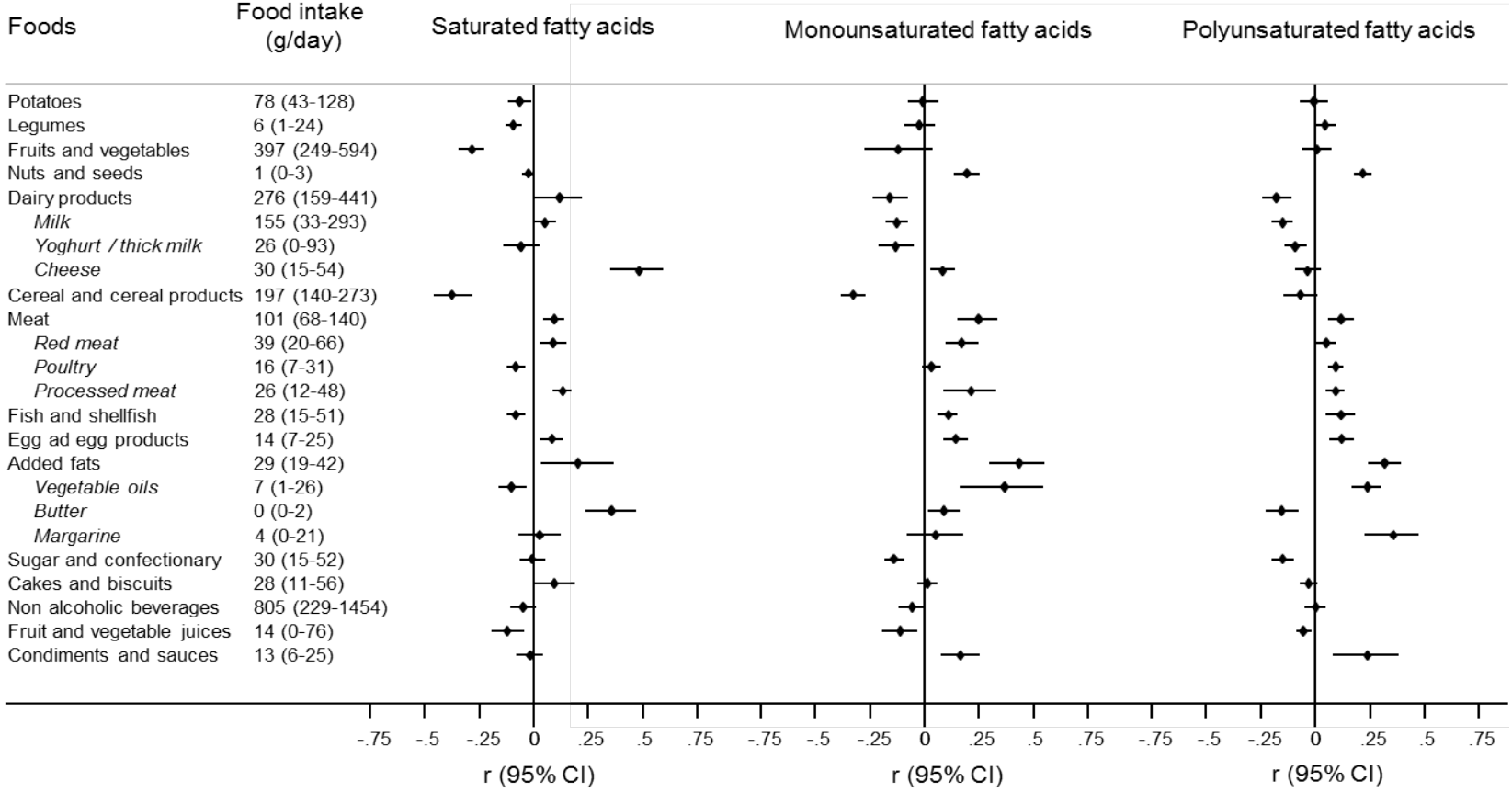
BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; EPIC, European Prospective Investigation into Cancer and Nutrition; MI, myocardial infarction;*The number of exclusions due to different causes within each box may overlap.
Norway was excluded due to small sample size.

Figure S2. Distribution of dietary fatty acid intake levels across countries in the EPIC-CVD case-cohort study subcohort (n=16,730).



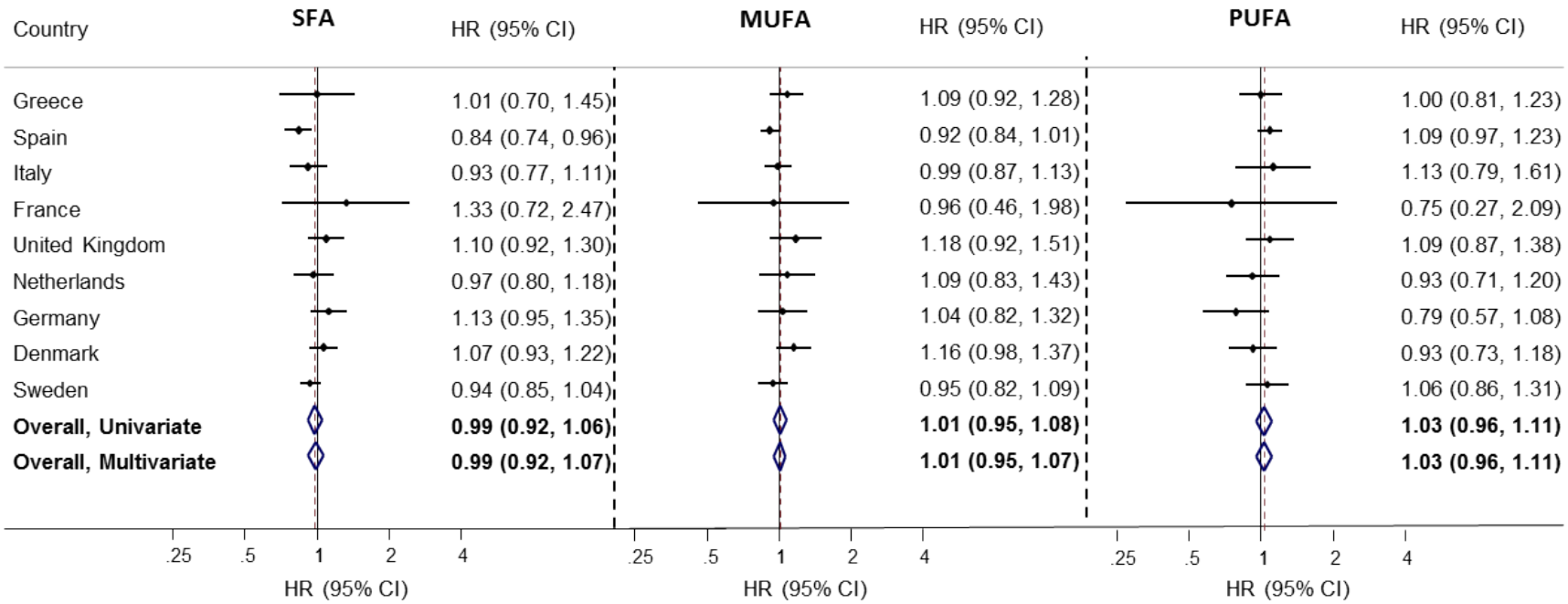
MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; SFAs, saturated fatty acids; Boxes present 25th percentile, median, 75th percentile, whiskers are the 25th percentile minus 1·5* the interquartile range (lower) and the 75th percentile plus 1·5*the interquartile range (upper). Fatty acids were expressed in percentage of total energy intake, and their distributions evaluated within the subcohort in each country.

Figure S3. Pearson partial correlation coefficients of dietary fatty acids with food groups in the EPIC-CVD case-cohort study subcohort (n=16,730).



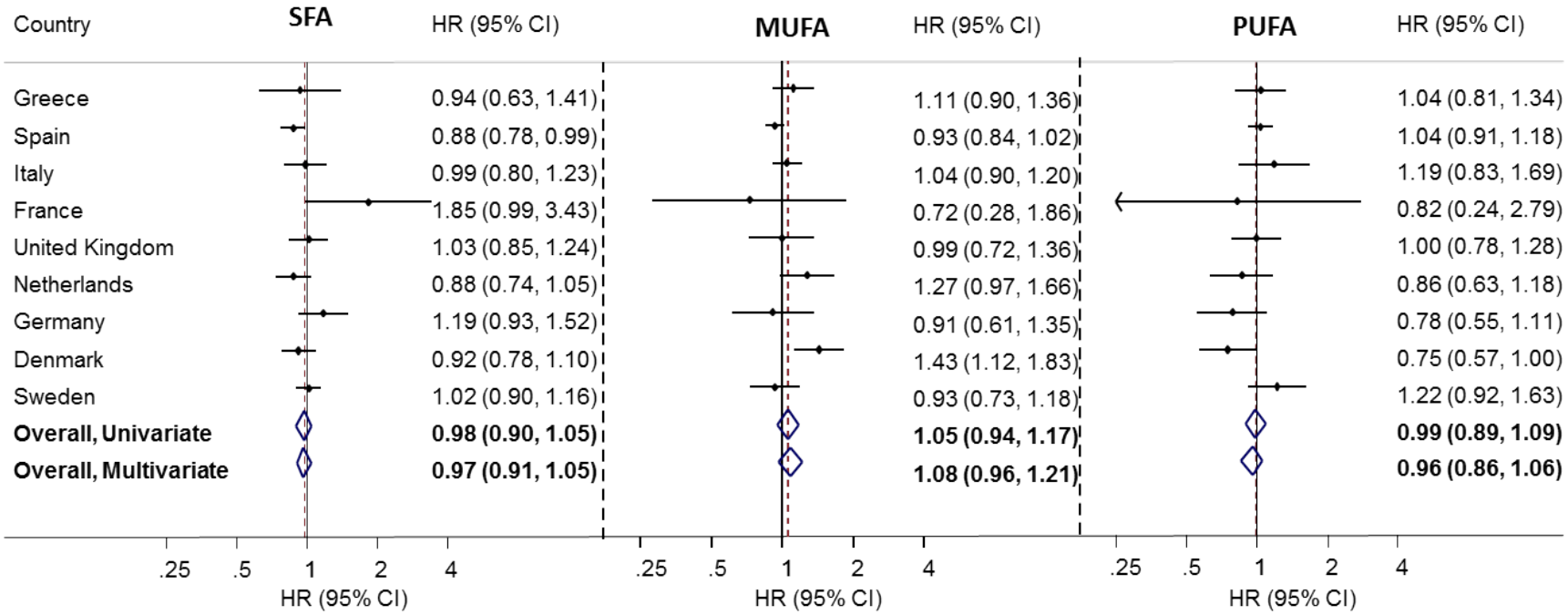
Food intake levels are presented in median (interquartile range). Country-specific correlations r (95% confidence interval [CI]) were adjusted for age, sex, energy intake and body mass index. Fisher's Z transformation was then used to transform country-specific correlation coefficients r (95% CIs) to obtain a normally distributed variable, i.e. using z = 0.5*ln((1+r)/1-r)). Z-transformed correlation coefficients r (95% CIs) were subsequently pooled using random effects meta-analysis, and back-transformation was applied to obtain an overall correlation coefficient r (95% CI). Dietary saturated, monounsaturated and polyunsaturated fatty acids were expressed in % total energy intake. Polyunsaturated fatty acids were log-transformed to normalize the distribution. Food group `vegetable oils` includes all vegetable oils evaluated by country -specific dietary questionnaires, including olive oil where applicable.

Figure S4. Associations with CHD of dietary saturated, monounsaturated and polyunsaturated fatty acids in the EPIC-CVD case-cohort study, analysed with the energy residual method.



Hazard ratios (HRs) and 95% confidence intervals (CIs) for each 10 energy-adjusted g/day higher intake from saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) were analysed within each country separately, with age as the underlying time variable and the baseline hazard stratified by sex. Country-specific HRs (95% CIs) were combined in univariate and multivariate random-effects meta-analysis to obtain pooled effect estimates and 95% CIs. The multivariable-adjusted HR included adjustment for age at recruitment (years), centre, energy intake (kcal/day), education (low, medium, high), smoking (never, former, current), physical activity (inactive, moderately inactive, moderately active, active), alcohol intake (0, 0-6, 6-12, 12-13, >24 g/day), dietary fibre (g/day, continuous), fruit and vegetable consumption (g/day, continuous), body-mass index (kg/m^2, continuous), reported history of diabetes, hypertension and hyperlipidaemia.

Figure S5. Associations with CHD of dietary saturated, monounsaturated and polyunsaturated fatty acids in the EPIC-CVD case-cohort study, analysed with the energy partition model.



Hazard ratios (HRs) and 95% confidence intervals (CIs) for each 10 g/day higher intake from saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) were analysed within each country separately, with age as the underlying time variable and the baseline hazard stratified by sex. Country-specific HRs (95% CIs) were combined in univariate and multivariate random-effects meta-analysis to obtain pooled effect estimates and 95% CIs. The multivariable-adjusted HRs included adjustment for age at recruitment (years), centre, education (low, medium, high), smoking (never, former, current), physical activity (inactive, moderately inactive, moderately active, active), alcohol intake (0, 0-6, 6-12, 12-13, >24 g/day), dietary fibre (g/day, continuous), fruit and vegetable consumption (g/day, continuous), body-mass index (kg/m^2, continuous), reported history of diabetes, hypertension and hyperlipidaemia, and SFAs, MUFAs, PUFAs, carbohydrates, . animal-derived protein, plant-derived protein, and mixed-origin protein (all per 10 g/day, included simultaneously in the model).