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Consumption of individual saturated fatty acids and the risk of myocardial infarction in a UK and a Danish cohort

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ABSTRACT

Background: The effect of individual saturated fatty acids (SFAs) on serum cholesterol levels depends on their carbon-chain length. Whether the association with myocardial infarction (MI) also differs across individual SFAs is unclear. We examined the association between consumption of individual SFAs, differing in chain lengths ranging from 4 through 18 carbons, and risk of MI.

Methods: We used data from 22,050 and 53,375 participants from EPIC-Norfolk (UK) and EPIC-Denmark, respectively. Baseline SFA intakes were assessed through validated, country-specific food frequency questionnaires. Cox regression analysis was used to estimate associations between intakes of individual SFAs and MI risk, for each cohort separately.

Results: During median follow-up times of 18.8 years in EPIC-Norfolk and 13.6 years in Denmark, respectively, 1204 and 2260 MI events occurred. Mean (±SD) total SFA intake was 13.3 (±3.5) en% in EPIC-Norfolk, and 12.5 (±2.6) en% in EPIC-Denmark. After multivariable adjustment, intakes of C12:0 (lauric acid) and C14:0 (myristic acid) inversely associated with MI risk in EPIC-Denmark (HR upper versus lowest quintile: 0.80 (95%CI: 0.66, 0.96) for both SFAs). Intakes in the third and fourth quintiles of C4:0–C10:0 also associated with lower MI risk in EPIC-Denmark. Moreover, substitution of C16:0 (palmitic acid) and C18:0 (stearic acid) with plant proteins resulted in a reduction of MI risk in EPIC-Denmark (HR per 1 energy%: 0.86 (95%CI: 0.78, 0.95) and 0.87 (95%CI: 0.79, 0.96) respectively). No such associations were found in EPIC-Norfolk.

Conclusion: The results from the present study suggest that the association between SFA and MI risk depends on the carbon chain-length of the SFA.

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1. Introduction

Limiting the intake of dietary saturated fatty acids (SFAs) is an important component of the dietary recommendations for the prevention of coronary heart disease (CHD) [1–4]. A high intake of SFAs, compared with carbohydrates is associated with higher serum LDL cholesterol concentrations [5], which is an established risk factor for CHD. However, the link between SFAs and CHD has been heavily debated for years now, because of inconsistent results from observational cohort studies [6–9].

One of the proposed explanations for the inconsistent findings in meta-analyses of these cohort studies is that the association between SFAs and CHD differs across types of SFAs, based on their carbon-atom chain lengths. A recent meta-analysis of 52 controlled trials showed that the effect of dietary SFA on serum cholesterol levels in humans differed depending on the chain-length [5]. Compared to carbohydrates, lauric acid (C12:0), myristic acid (C14:0) and palmitic acid (C16:0) increased LDL and HDL cholesterol, C12:0 improved the total to HDL cholesterol ratio, and stearic acid (C18:0) had neutral effects [5]. This suggests not all SFA may be equally harmful with respect to CHD development. Approaching SFAs as a whole in observational studies may therefore have obscured the association with CHD risk.

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Four previous prospective cohort studies [10–13] indeed observed differential associations with CHD when individual SFAs were separated in the analyses, but their findings are inconsistent. In the Nurses' Health Study (NHS) [10,13] and the Health Professional Follow-up Study (HPFS) [13], SFAs with chain lengths of 12 or more carbons were associated with a higher CHD risk. In the Rotterdam study, C16:0 was associated with an increased risk [12]. In the EPIC-NL cohort, the SFAs with chain lengths up to 10 carbons, as well as the odd-chain SFAs, pentadecylic acid (C15:0) and margaric acid (C17:0), were associated with a lower CHD risk [11].

Addressing the associations of individual SFAs with CHD risk in other populations will yield more insight into if and how individual SFAs associate with CHD risk. Therefore, the objective of this study was to investigate the association between individual SFAs and MI risk in a UK and a Danish cohort.

2. Methods

2.1. Study population

For the present study, we used data from EPIC-Norfolk (European Investigation into Cancer and Nutrition-Norfolk cohort), and from the Danish Diet, Cancer and Health cohort (further referred to as EPIC-Denmark). Both cohorts are part of the international multicentre EPIC study [14]. Detailed descriptions of the design and rationale of both cohorts can be found elsewhere [15,16]. In brief, the recruitment of both cohorts took place between 1993 and 1997. Participants for EPIC-Norfolk were recruited through 35 participating General Practices in the rural areas of Norfolk and market towns as well as the city of Norwich, in the United Kingdom [15]. A total of 25,639 men and women, aged 40 through 74 years, were enrolled in the study. Participants for EPIC-Denmark were selected from the Copenhagen and Aarhus areas in Denmark, and were identified through the Civil Registration System (CPR) [16]. Selection criteria were being born in Denmark, being between 50 and 64 years of age, and being free of cancer. A total of 57,053 men and women were enrolled.

All participants gave written informed consent before enrolment into the study, and ethical approval for the studies was obtained from the Norfolk and Norwich Hospital Ethics Committee (EPIC-Norfolk) and from the relevant Scientific Committees and the Danish Data Protection Agency (EPIC-Denmark).

We excluded participants who had a history of cancer (n = 1435 in EPIC-Norfolk; n = 574 in EPIC-Denmark), a history of cardiovascular disease (EPIC-Norfolk, n = 1045) or myocardial infarction (EPIC-Denmark, n = 900), had missing or incomplete dietary data (n = 547; n = 91), reported implausible energy intakes compared to their estimated basal metabolic rate (n = 266; n = 554), or had missing data on co-variables (n = 296; n = 1559), leaving 22,050 and 53,375 participants for analysis in EPIC-Norfolk and EPIC-Denmark, respectively.

2.2. Dietary assessment

Baseline dietary data were obtained through validated, country specific Food Frequency Questionnaires (FFQs), that allowed the participants to specify the food consumption frequency during the preceding year [17,18]. For each participant, the daily intakes of macro- and micronutrients were calculated using FETA [19], based on McCance & Widdowson's food composition tables [20–29] (Norfolk) or the software program FoodCalc [30] (EPIC-Denmark). Data on individual fatty acid intake were calculated based on the fatty acids supplement to the McCance & Widdowson's The Composition of Foods [31], or McCance and Widdowson's The Composition of Foods integrated dataset (CoF IDS) [32], and on the Danish food composition tables from 1996 [33].

The FFQs were both previously validated [34–36] against weighed records. The Norfolk FFQ was not validated for its ability to measure saturated fat, but for total fat, the correlation coefficient was 0.55 in women [34]. For the Danish FFQ, the correlation coefficients were 0.67 (men) and 0.48 (women) for total fat intake, and 0.46 (men) and 0.39 (women) for saturated fat intake [36].

For the present analyses, the intakes of individual saturated fatty acids (SFAs), and of all other macronutrients were expressed as percentages of total energy intake (en%). For both cohorts, we summed the intakes of butyric acid (C4:0) through capric acid (C10:0), because of very low intakes and because they are all derived from dairy food sources. For the same reasons, the intakes of C15:0 and C17:0 were also summed in EPIC-Norfolk. In EPIC-Denmark, C15:0 was analysed individually because no data on C17:0 intake were available. C12:0 through C14:0 and C12:0 through C18:0 were also analysed combined to facilitate comparison with a previous study [13]. Furthermore, for the Danish cohort, *trans* fatty acids intake was available only from ruminant sources, and was therefore left out of the analyses.

2.3. Outcome assessment

Information on vital status was obtained by flagging the participants for death certification at the United Kingdom Office of National Statistics (EPIC-Norfolk), and through linkage with The Danish National Patient Register [37] and The Danish Register of Causes of Death [38] (EPIC-Denmark). Information on hospital admissions in Norfolk and Denmark was obtained through linkage with the Norfolk Health Authority database (ENCORE), and the Danish National Patient Register, respectively.

The cause of death or hospital admission were coded according to the ninth revision of the International Classification of Diseases (ICD) for Norfolk, and according to the eight and tenth ICD revisions for Denmark. The outcome of interest in the present study was incident myocardial infarction (MI). This included both fatal and non-fatal events classified with codes 410–410.99 (ICD-8 and ICD-9) and I21.0–121.9 (ICD-10). In the Danish cohort also cardiac arrest cases (ICD-8 code: 427.27, and ICD-10 codes: I46.0–I46.9) were included if the arrest was considered to be of cardiac origin after validation. Follow up was up until 31 March 2015 (EPIC-Norfolk), and 31 December 2009 (EPIC-Denmark).

Follow-up rates were (very close to) 100% for both cohorts.

2.4. Assessment of other variables

Information on baseline non-dietary factors, including medical history, medication use, smoking status, alcohol use, education level and physical activity level, was obtained through general questionnaires. Smoking status was defined as never, former and current. Education level was categorized as none, 0 level, A level, and having a degree (Norfolk), or according to the number of years one attended school: 0–7 years, 8–10 years, >10 years (Denmark). Alcohol intake, as obtained from the FFQ, was expressed according to the following categories: none, 0–5, 5–15, 15–30, 30–45, and ≥45 g/d. Physical activity level was obtained using a validated questionnaire and expressed according to the Cambridge Physical Activity Index [39] into the following categories: active, moderately active, moderately inactive, and inactive. Height, weight and waist circumference were measured at the physical examination. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2), and divided into the following categories: <18.5, 18.5–23, 23–25, 25–30, 30–35, and ≥35 kg/m^2. Hypertension was defined as diastolic blood pressure > 90 mm/Hg, systolic blood pressure > 140 mm/Hg [40], use of antihypertensive medication or self-reported high blood pressure (UK), or self-reported hypertension (Denmark; yes/no/don't know). Hypercholesterolemia was defined as total cholesterol >6.5 mmol/L [41] or use of lipid lowering drugs at baseline (UK), or self-reported medical treatment or history hypercholesterolemia (Denmark; yes/no/don't know). Postmenopausal status was defined as having no cycle for >5 years (UK) or self-reported natural or surgical postmenopausal status (Denmark), and codes as yes/no/male. Hormone replacement therapy was categorized into current, former and never (UK), or use of hormones for menopause (Denmark; yes/no).

2.5. Data analysis

2.5.1. Main analysis

All analyses were performed separately per cohort. SFA intakes were dived into cohort specific quintiles. We calculated Pearson correlations for SFA intakes. We used Cox proportional Hazard regression analysis to calculate Hazard Ratios (HR) with 95% confidence intervals (CI) for the associations of SFAs with MI risk. In model 1, we adjusted HRs for age (continuous), sex (male/female), total energy intake (kcal, excluding alcohol), BMI (categories), education level (categories), physical activity level (categories), smoking status (categories), hypertension (UK yes/no; Denmark yes/no/don't know), alcohol intake (categories), use of post-menopausal hormones (UK current/former/never; Denmark yes/no) and in the UK also for aspirin use (yes/no), multivitamin use (yes/no) and family history of MI (yes/no). In model 2, we additionally adjusted for intakes of PUFA (en%), protein (en%), the sum of all other SFAs (en%), and trans fatty acids (UK only; en%). In model 3, we additionally adjusted for hypercholesterolemia (UK yes/no; Denmark yes/no/don't know) as possible intermediate of the relationship between SFA intakes and CHD [5]. We also adjusted for postmenopausal status (categories), to facilitate comparison with previous work [13]. P for trend was calculated by linearly including quartile specific median FA intake in the model. We examined the possibly non-linear relationships non-parametrically with restricted cubic splines [42], after limiting the analysis to participants from the SFA intake percentile 1 to 99. Tests for non-linearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms.

2.5.2. Additional analyses

Results for the main analysis (model 2) from the two cohorts were pooled with a random effects model. Additionally, we performed isocaloric substitution modelling by adjusting for co-variables in model 1, plus total energy (en%, excluding alcohol) and energy (en%) from PUFA, MUFA, protein (subdivided in plant and other protein), carbohydrates (UK; subdivided in starch carbohydrates and other carbohydrates) and SFA intakes. By leaving the intake of a particular SFA of interest out of the model, regression coefficients of other macronutrients could be interpreted as the effect of isocalorically replacing the SFA intake not in the model. We reported substitutions with PUFA, MUFA, plant protein and starch carbohydrates (UK) or total carbohydrates (Denmark).

To investigate if food sources of the SFA intakes contributed to the observed associations, we investigated the association between SFA from meat and total dairy and MI in both cohorts, and between SFA from cakes and cookies, cheese, hard fats and soft fats and MI in the UK cohort, after adjustment for co-variables in model 2.

We tested for possible interactions in our main analyses, for age, sex, BMI, physical activity and smoking by including an interaction term between the co-variable and SFA intakes to adjustment model 2. If this interaction term was statistically significant, stratified analyses were presented for this co-variable.

We checked the Cox proportional hazards assumption by visually inspecting log-log plots, and observed no deviation from the assumption.

We performed a series of sensitivity analyses for our main analysis. First, we repeated our analyses by ending the follow up after eight years, to examine whether the associations were different for a shorter follow up time. Second, to limit the possibility of reverse causation, we repeated the analyses after exclusion of the first two years of follow up. Thirdly, we repeated the analyses after exclusion of all participants who reported the use of lipid-lowering medication at baseline as this associates with both SFA intake and MI. Also, we repeated the analyses while adjusting for diabetes at baseline. Additionally, we examined the potential mediation by ratio of blood total cholesterol: HDL-cholesterol levels among a selection of EPIC-Norfolk participants (n = 19,974) by additionally adjusting for this ratio.

All statistical analyses were done using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Population characteristics

The mean (±SD) intakes per day of total SFA were 13.3 (±3.5) en%, and 12.5 (±2.6) en% in EPIC-Norfolk and EPIC-Denmark, respectively. In both cohorts the majority of SFA was represented by C16:0 (~52%), C18:0 (~22%) and C14:0 (~10%) (**Supplemental Fig. 1**). High correlations were observed for C4:0–C10:0 with C14:0, and with C15:0. Also, correlations between C16:0 and C18:0 were high (**Supplemental Table 1**).

Participants (in both cohorts) with higher intakes of energy from total SFA, as well as from all the individual SFAs (data not shown), were more often male, had a lower BMI, were less educated, more often a smoker, and less physically active. Moreover, higher intakes of SFA were associated with higher intakes of total energy, MUFA, *trans*-fat, and lower intakes of carbohydrates, fibre, vitamin C, and alcohol (Tables 1 and 2).

3.2. Association between individual SFAs and MI risk

During median follow-up times of 18.8 (IQR 17.4, 20.2) years in the UK and 13.6 (IQR 12.9, 14.3) years in Denmark, respectively, 1204 (5.5%) and 2260 (4.2%) MI events occurred.

Table 1
Baseline characteristics across quintiles of total SFA intake (en%) in EPIC-Norfolk.

Total SFA, en%	Q1	Q2	Q3	Q4	Q5
	8.5 (±1.3)	11 (±0.5)	12.5 (±0.4)	14.2 (±0.6)	17.6 (±2)
Participants (n)	4410	4410	4410	4410	4410
Age, y	58.3 (±8.7)	58.5 (±9.2)	58.4 (±9.3)	58.6 (±9.5)	59.7 (±9.4)
Male (%)	35	42	46	50	52
BMI, kg/m^2	26.5 (±4.0)	26.4 (±3.9)	26.3 (±3.8)	26.3 (±3.9)	26.0 (±3.9)
Waist circumference, cm	86.6 (±12.2)	87.8 (±12.2)	88.0 (±12.2)	88.9 (±12.5)	88.8 (±12.4)
Education level (%)					
None	33	35	36	37	39
Degree	14	14	13	12	12
Current smoker (%)	8	9	10	12	20
Physically inactive (%)	26	28	29	32	32
Physically active (%)	20	20	19	18	19
Systolic blood pressure, mm Hg	134.7 (±18.5)	135.4 (±18.4)	135.0 (±18.2)	135.3 (±18.1)	135.6 (±18.2)
Diastolic blood pressure, mm Hg	81.9 (±11.3)	82.5 (±11.2)	82.5 (±11.1)	82.8 (±11.2)	82.7 (±11.2)
Hypertension[a] (%)	15	15	13	12	12
Total cholesterol, mmol/L	6.1 (±1.2)	6.1 (±1.2)	6.2 (±1.2)	6.2 (±1.1)	6.3 (±1.2)
HDL-cholesterol, mmol/L	1.5 (±0.4)	1.4 (±0.4)	1.4 (±0.4)	1.4 (±0.4)	1.4 (±0.4)
LDL-cholesterol, mmol/L	3.9 (±1)	3.9 (±1)	4.0 (±1)	4.0 (±1)	4.1 (±1.1)
Triglycerides, mmol/L	1.7 (±1.1)	1.8 (±1.1)	1.8 (±1.1)	1.8 (±1.1)	1.8 (±1.1)
Hypercholesterolemia[b] (%)	34	31	33	32	35
Diabetes mellitus (%)	3	2	2	2	1
Family history of MI (%)	39	38	35	35	33
Postmenopausal (% among women)	36	33	32	29	30
HRT use (% among women)					
Current	24	23	21	17	19
Former	12	12	12	12	9
Supplement use (%)	58	53	47	42	37
Aspirin use (%)	7	6	6	6	4
Daily dietary intakes					
Alcohol, g	5 (1−13)	5 (1−11)	5 (1–11)	4 (1−10)	3 (1–10)
Energy, kcal	1787 (±502)	1987 (±555)	2087 (±581)	2155 (±617)	2229 (±642)
Fat, en%	25.7 (±4.1)	30.9 (±3.1)	33.6 (±3.1)	36.1 (±3.3)	39.7 (±4.0)
Sum of C4:0–C10:0, en%	0.3 (0.2–0.4)	0.4 (0.3–0.5)	0.5 (0.4–0.5)	0.5 (0.4–0.6)	0.7 (0.6–0.8)
Sum of C12:0–C14:0, en%	1.2 (0.9–1.4)	1.6 (1.4–1.7)	1.8 (1.6–2.0)	2.2 (1.9–2.4)	3.0 (2.6–3.4)
Sum of C15:0 & C17:0, en%	0.8 (0.7–0.9)	1.1 (1–1.2)	1.3 (1.2–1.4)	1.6 (1.4–1.7)	2.1 (1.9–2.4)
Sum of C12:0–C18:0, en%	8.1 (7.2–8.8)	10.1 (9.7–10.5)	11.5 (11.1–11.8)	12.9 (12.5–13.4)	15.4 (14.5–16.7)
C12:0, en%	0.3 (0.2–0.4)	0.4 (0.3–0.5)	0.5 (0.4–0.5)	0.5 (0.4–0.6)	0.7 (0.6–0.8)
C14:0, en%	0.8 (0.6–0.9)	1.1 (0.9–1.2)	1.3 (1.1–1.4)	1.5 (1.3–1.7)	2.1 (1.8–2.4)
C16:0, en%	4.8 (4.3–5.2)	5.9 (5.6–6.2)	6.6 (6.4–6.9)	7.4 (7.1–7.7)	8.6 (8.1–9.2)
C18:0, en%	1.9 (1.7–2.1)	2.4 (2.2–2.6)	2.7 (2.5–2.9)	3.0 (2.9–3.3)	3.6 (3.3–3.9)
Cis-MUFA, en%	7.6 (±1.6)	8.8 (±1.5)	9.4 (±1.6)	10.0 (±1.7)	10.5 (±1.8)
Cis-PUFA, en%	5.8 (±1.9)	6.2 (±2.1)	6.2 (±2.1)	5.9 (±2)	4.9 (±1.8)
Trans fatty acids, en%	1.0 (±0.4)	1.3 (±0.4)	1.5 (±0.5)	1.7 (±0.5)	1.9 (±0.6)
Carbohydrates, en%	55.4 (±6.9)	52.2 (±5.6)	50.3 (±5.3)	48.5 (±5.2)	45.5 (±5.5)
Starch carbohydrates, en%	25.6 (±5.8)	24.7 (±4.8)	23.9 (±4.3)	23.0 (±4.0)	21.6 (±4.1)
Protein, en%	18.3 (±3.4)	17.2 (±3.0)	16.5 (±2.8)	16.1 (±2.8)	15.4 (±2.7)
Plant protein, en%	6.5 (±1.5)	5.5 (±1.2)	5 (±1.1)	4.5 (±1.1)	4.1 (±1.1)
Cholesterol, mg	194 (±77)	244 (±87)	275 (±97)	310 (±109)	363 (±130)
Fibre, g	21 (±8)	20 (±6)	19 (±6)	18 (±6)	16 (±6)
Vitamin C, mg	149 (±72)	129 (±58)	120 (±53)	113 (±50)	105 (±49)

All values are means (±SD) or median (quartile 1–quartile 4), unless indicated otherwise.
[a] Defined as diastolic blood pressure >90 mm/Hg, systolic blood pressure > 140 mm/Hg, use of antihypertensive medication or self-reported high blood pressure.
[b] Defined as total cholesterol >6.5 mmol/L, or use of lipid-lowering drugs at baseline.

Table 2
Baseline characteristics across quintiles of total SFA intake (en%) in the Danish Diet Cancer and Health cohort.

Total SFA, en%	Q1	Q2	Q3	Q4	Q5
	8.8 (±1.2)	11.1 (±0.4)	12.5 (±0.4)	13.9 (±0.4)	16.2 (±1.3)
Participants (n)	10,675	10,675	10,675	10,675	10,675
Age, years	56.5 (±4.3)	56.5 (±4.3)	56.6 (±4.4)	56.7 (±4.4)	56.9 (±4.4)
Male (%)	42	47	49	50	50
BMI, kg/m^2	26.2 (±3.9)	26.2 (±4)	26.0 (±4)	25.9 (±4.1)	25.7 (±4.2)
Waist circumference, cm	88.1 (±12.4)	88.9 (±12.6)	88.7 (±12.4)	88.6 (±12.6)	88.4 (±13.1)
Years of education (%)					
7 years or less	30	31	32	34	36
8–10 years	47	47	46	46	44
>10 years	23	22	21	20	20
Current smoker (%)	26	30	33	36	45
Physically inactive (%)	10	10	10	11	13
Physically active (%)	35	35	35	35	33
Systolic blood pressure, mm Hg	141 (±21)	140 (±21)	140 (±20)	139 (±20)	138 (±20)
Diastolic blood pressure, mm Hg	84 (±11)	84 (±11)	83 (±10)	83 (±11)	82 (±11)
Hypertension (%)	20	17	16	14	13
Diabetes (%)	2.9	2.3	1.8	1.7	1.5
Postmenopausal status (% among women)[a]	78	76	78	78	80
HRT use (% among women)	29	30	29	29	28
Daily dietary intakes					
Alcohol, g	17 (7–40)	15 (7–35)	14 (7–32)	12 (6–23)	9 (3–17)
Energy, kcal	2190 (±590)	2302 (±616)	2377 (±645)	2430 (±674)	2451 (±705)
Sum of C4:0–C10:0, en%	0.6 (0.5–0.8)	0.9 (0.7–1.1)	1.1 (0.9–1.3)	1.3 (1.1–1.6)	1.7 (4.1–2.1)
Sum of C12:0–C14:0, en%	1.1 (0.9–1.2)	1.4 (1.2–1.5)	1.6 (1.4–1.8)	1.8 (1.7–2.0)	2.2 (2.0–2.5)
Sum of C12:0–C18:0, en%	8.2 (7.4–8.8)	9.9 (9.6–10.2)	11.1 (10.8–11.4)	12.2 (11.9–12.6)	13.9 (13.3–14.7)
C12:0, en%	0.2 (0.2–0.3)	0.3 (0.2–0.3)	0.3 (0.3–0.4)	0.4 (0.3–0.5)	0.5 (0.4–0.6)
C14:0, en%	0.8 (0.7–1)	1.1 (1–1.2)	1.3 (1.1–1.4)	1.4 (1.3–1.6)	1.7 (1.6–1.9)
C16:0, en%	4.9 (4.5–5.3)	5.9 (5.7–6.1)	6.5 (6.3–6.8)	7.1 (6.9–7.4)	8.0 (7.7–8.5)
C15:0, en%	0.1 (0–0.1)	0.1 (0.1–0.1)	0.1 (0.1–0.1)	0.1 (0.1–0.1)	0.1 (0.1–0.2)
C18:0, en%	2.1 (1.8–2.3)	2.5 (2.4–2.7)	2.8 (2.7–3)	3.1 (2.9–3.3)	3.5 (3.3–3.8)
MUFA, en%	8.7 (±1.7)	10.3 (±1.5)	11.2 (±1.5)	11.9 (±1.5)	12.8 (±1.7)
PUFA, en%	5.2 (±1.6)	5.6 (±1.5)	5.6 (±1.4)	5.6 (±1.3)	5.2 (±1.2)
Carbohydrates, en%	47.9 (±7.7)	44.7 (±6.1)	43.3 (±5.4)	42.1 (±5)	40.4 (±4.6)
Protein, en%	16.2 (±2.6)	16.5 (±2.5)	16.5 (±2.4)	16.6 (±2.3)	16.7 (±2.3)
Plant protein, en%	5.2 (±1.1)	4.7 (±0.8)	4.5 (±0.8)	4.3 (±0.7)	4.1 (±0.8)
Cholesterol, mg	351 (±156)	417 (±166)	450 (±174)	482 (±189)	514 (±214)
Fibre, g	23 (±8)	22 (±7)	21 (±7)	21 (±7)	19 (±6)

All values are means (±SD) or median (quartile 1–quartile 4), unless indicated otherwise.
[a] Natural or chirurgical menopause.

3.2.1. EPIC-Norfolk

After multivariable adjustment for lifestyle and dietary factors, a higher intake of the sum of C4:0–C10:0 (Q5 0.85, 95%CI 0.63, 1.14), C14:0 (Q5 0.78, 95%CI 0.55, 1.09), the sum of C15:0 and C17:0 (Q5 0.78, 95%CI 0.58, 1.06) and C18:0 (Q5 0.79, 95%CI 0.56, 1.13) were weakly associated with lower MI risk, but none of these associations were significant (Table 3). Further adjusting for hypercholesterolemia and menopausal status in model 3 did not affect associations (Table 3). Restricting follow-up to the first eight years strengthened the associations for the sum of C15:0 and C17:0 (Q5 0.57, 95% 0.34, 0.97), but otherwise did not change results. Excluding the first two years of follow-up, excluding lipid lowering drug users, adjusting for TC/HDL ratio (**Supplemental Table 2**), or adjusting for baseline diabetes (data not shown), did not change the conclusions. No evidence of a non-linear association between C4:0–C10:0 or C12:0–C18:0 and MI was found (**Supplemental Figs. 2 and 3**). There were no interactions for the intakes of C4:0–C10:0 and C12–C18:0 with sex, age, smoking, or BMI, whereas interaction by physical activity was suggested ($p = 0.01$) for intake of C12:0–C18:0, although no meaningful differences were found in stratified analyses (**Supplemental Table 3**).

In isocaloric substitution analyses (Table 4 and **Supplemental Table 4 – latter shows median intakes per SFA -**), no statistically significant associations were found with MI risk. Additional adjustment for hypercholesterolemia and menopausal status did not change the results of the substitution analyses (data now shown).

Intakes of SFA from dairy, meat, cakes and cookies, cheese, soft fats or hard fats were not associated with MI risk (**Supplemental Table 5**).

3.2.2. EPIC-Denmark

The multivariable adjusted HRs for the association of C4:0–C10:0 with MI risk in EPIC-Denmark, suggested an inverse association in especially quintile 3 and 4 when compared to quintile 1 (Q3 0.87, 95%CI 0.75, 1.00; Q4 0.81, 95% CI 0.69, 0.94) (Table 3). This non-linear association persisted (p for non-linearity 0.04) after excluding the lowest and highest intake percentile of C4:0–C10:0 intake (**Supplemental Fig. 2**). Other individual SFAs that associated with a lower risk of MI incidence were C12:0 (Q5 0.80, 95%CI 0.66, 0.96), C14:0 (Q5 0.80, 95% CI 0.66, 0.96), and the sum of C12:0 and C14:0 (Table 3). No evidence for a non-linear relationship between intake of the sum of C12:0 to C18:0 and MI incidence was found (**Supplemental Fig. 3**). The interaction term for physical activity was borderline significant ($p = 0.05$) for the analysis of C12:0 to C18:0, but stratified analyses suggested similar associations across physical activity groups (**Supplemental Table 3**). We did not observe evidence for interaction by sex, age, smoking, or BMI for C12:0 to C18:0, nor for any interaction in the analysis of C4:0 to C10:0. Adjusting for possible intermediates in model 3 did not alter conclusions (Table 3), nor did restricting follow-up to the first eight years, excluding the first two years of follow-up (**Supplemental Table 2**), or adjusting for baseline diabetes (data not shown).

Isocaloric substitution modelling of the sum of C12:0 to C14:0 (median intake 1.8 en%/day), C16:0 (7.4 en%/day), C18:0 (3.2 en%/day)

Table 3
Hazard ratios (95%CI) for the associations between individual SFAs (in quintiles) and MI incidence risk.[a]

	Q1	Q2	Q3	Q4	Q5	P for trend	P for non-linearity
	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)		
Sum of C4:0–C10:0							
EPIC-Norfolk							
Median intake (IQR)	0.3 (0.2–0.4)	0.5 (0.5–0.6)	0.7 (0.7–0.8)	1.0 (0.9–1.1)	1.6 (1.4–2.0)		
Cases/subjects (n)	235/4410	247/4410	248/4410	221/4410	253/4410		
Model 1	Ref	1.00 (0.84, 1.20)	1.00 (0.84, 1.20)	0.85 (0.71, 1.03)	0.90 (0.75, 1.07)	0.08	0.21
Model 2	Ref	0.99 (0.82, 1.19)	0.99 (0.81, 1.20)	0.83 (0.67, 1.04)	0.85 (0.63, 1.14)	0.15	0.25
Model 3	Ref	1.00 (0.83, 1.20)	0.99 (0.82, 1.20)	0.84 (0.67, 1.05)	0.86 (0.64, 1.16)	0.18	0.26
EPIC-Denmark							
Median intake (IQR)	0.60 (0.47–0.71)	0.95 (0.88–1.02)	1.23 (1.16–1.30)	1.54 (1.45–1.64)	2.05 (1.87–2.33)		
Cases/subjects (n)	491/10675	438/10675	423/10675	417/10675	491/10675		
Model 1	Ref	0.94 (0.82, 1.06)	0.92 (0.81, 1.05)	0.88 (0.77, 1.01)	1.02 (0.90, 1.16)	0.56	0.06
Model 2	Ref	0.90 (0.79, 1.03)	0.87 (0.75, 1.00)**	0.81 (0.69, 0.94)**	0.90 (0.76, 1.06)	0.40	0.04**
Model 3	Ref	0.90 (0.79, 1.03)	0.87 (0.75, 1.00)**	0.81 (0.70, 0.94)**	0.90 (0.76, 1.06)	0.42	0.09
C12:0							
EPIC-Norfolk							
Median intake (IQR)	0.3 (0.2–0.3)	0.4 (0.4–0.4)	0.5 (0.4–0.5)	0.6 (0.6–0.6)	0.8 (0.7–1.0)		
Cases/subjects (n)	210/4410	210/4410	256/4410	268/4410	260/4410		
Model 1	Ref	0.96 (0.79, 1.16)	1.11 (0.92, 1.33)	1.04 (0.86, 1.25)	0.96 (0.80, 1.16)	0.79	0.17
Model 2	Ref	0.96 (0.79, 1.17)	1.11 (0.91, 1.36)	1.05 (0.85, 1.30)	1.01 (0.79, 1.29)	0.82	0.25
Model 3	Ref	0.96 (0.79, 1.17)	1.11 (0.91, 1.36)	1.05 (0.85, 1.30)	0.99 (0.77, 1.28)	0.88	0.23
EPIC-Denmark							
Median intake (IQR)	0.22 (0.18–0.25)	0.31 (0.29–0.33)	0.38 (0.36–0.40)	0.46 (0.44–0.48)	0.57 (0.53–0.63)		
Cases/subjects (n)	473/10675	427/10675	446/10675	479/10675	435/10675		
Model 1	Ref	0.94 (0.82, 1.07)	0.97 (0.85, 1.10)	1.03 (0.91, 1.17)	0.96 (0.84, 1.10)	0.97	0.51
Model 2	Ref	0.89 (0.78, 1.02)	0.89 (0.77, 1.03)	0.91 (0.78, 1.07)	0.80 (0.66, 0.96)**	0.05	0.53
Model 3	Ref	0.89 (0.78, 1.02)	0.89 (0.77, 1.03)	0.91 (0.78, 1.07)	0.79 (0.66, 0.96)**	0.05	0.61
C14:0							
EPIC-Norfolk							
Median intake (IQR)	0.8 (0.7–0.9)	1.1 (1.0–1.2)	1.3 (1.3–1.4)	1.6 (1.6–1.8)	2.2 (2.0–2.5)		
Cases/subjects (n)	228/4410	236/4410	238/4410	237/4410	265/4410		
Model 1	Ref	0.93 (0.77, 1.12)	0.92 (0.77, 1.11)	0.86 (0.71, 1.03)	0.86 (0.72, 1.04)	0.10	0.79
Model 2	Ref	0.90 (0.74, 1.09)	0.88 (0.71, 1.09)	0.80 (0.62, 1.03)	0.78 (0.55, 1.09)	0.16	0.75
Model 3	Ref	0.91 (0.75, 1.10)	0.88 (0.71, 1.10)	0.80 (0.62, 1.03)	0.78 (0.56, 1.11)	0.16	0.75
EPIC-Denmark							
Median intake (IQR)	0.93 (0.81–1.01)	1.20 (1.14–1.25)	1.40 (1.35–1.45)	1.62 (1.56–1.69)	1.95 (1.84–2.12)		
Cases/subjects (n)	436/10675	459/10675	430/10675	443/10675	492/10675		
Model 1	Ref	1.03 (0.91, 1.18)	0.95 (0.83, 1.09)	0.96 (0.84, 1.10)	1.05 (0.92, 1.20)	0.74	0.63
Model 2	Ref	0.89 (0.78, 1.02)	0.89 (0.77, 1.03)	0.91 (0.78, 1.07)	0.80 (0.66, 0.96)**	0.03**	0.53
Model 3	Ref	0.96 (0.83, 1.10)	0.84 (0.72, 0.99)**	0.81 (0.68, 0.96)**	0.81 (0.65, 1.01)	0.02**	0.63
Sum of C12:0 & C14:0							
EPIC-Norfolk							
Median intake (IQR)	1.1 (0.9–1.2)	1.5 (1.4–1.6)	1.8 (1.8–1.9)	2.2 (2.1–2.4)	3.0 (2.7–3.4)		
Cases/subjects (n)	215/4410	232/4410	257/4410	246/4410	254/4410		
Model 1	Ref	0.97 (0.80, 1.17)	1.01 (0.84, 1.21)	0.92 (0.76, 1.11)	0.87 (0.72, 1.05)	0.09	0.78
Model 2	Ref	0.94 (0.78, 1.15)	0.97 (0.79, 1.20)	0.87 (0.69, 1.10)	0.81 (0.59, 1.09)	0.14	0.77
Model 3	Ref	0.94 (0.78, 1.15)	0.97 (0.79, 1.19)	0.87 (0.69, 1.09)	0.80 (0.59, 1.09)	0.12	0.75
EPIC-Denmark							
Median intake (IQR)	1.2 (1.0–1.3)	1.4 (1.5–1.6)	1.8 (1.7–1.9)	2.1 (2.0–2.2)	2.5 (2.4–2.8)		
Cases/subjects (n)	447/10675	461/10675	420/10675	457/10675	477/10675		
Model 1	Ref	1.02 (0.90, 1.17)	0.92 (0.81, 1.06)	0.98 (0.86, 1.12)	1.03 (0.90, 1.17)	0.95	0.63
Model 2	Ref	0.95 (0.83, 1.09)	0.83 (0.71, 0.96)**	0.83 (0.70, 0.98)**	0.80 (0.66, 0.99)**	0.01**	0.48
Model 3	Ref	0.96 (0.83, 1.10)	0.84 (0.72, 0.99)**	0.81 (0.68, 0.96)**	0.81 (0.65, 1.01)	0.01**	0.62
Sum of C15:0 & C17:0							
EPIC-Norfolk							
Median intake (IQR)	0.2 (0.1–0.2)	0.2 (0.2–0.3)	0.3 (0.3–0.3)	0.4 (0.4–0.4)	0.5 (0.5–0.6)		
Cases/subjects (n)	228/4410	220/4410	245/4410	241/4410	270/4410		
Model 1	Ref	0.92 (0.76, 1.10)	0.91 (0.76, 1.09)	0.85 (0.71, 1.02)	0.85 (0.71, 1.02)	0.08	0.90
Model 2	Ref	0.89 (0.73, 1.08)	0.88 (0.71, 1.08)	0.80 (0.63, 1.02)	0.78 (0.58, 1.06)	0.19	0.87
Model 3	Ref	0.90 (0.74, 1.09)	0.88 (0.71, 1.08)	0.80 (0.63, 1.02)	0.78 (0.57, 1.07)	0.16	0.87
C15:0							
EPIC-Denmark							
Median intake (IQR)	0.06 (0.05–0.06)	0.08 (0.08–0.09)	0.10 (0.10–0.11)	0.12 (0.12–0.13)	0.16 (0.15–0.18)		
Cases/subjects (n)	485/10675	449/10675	437/10675	433/10675	456/10675		
Model 1	Ref	0.99 (0.87, 1.12)	0.97 (0.86, 1.11)	0.96 (0.85, 1.10)	1.02 (0.90, 1.16)	0.76	0.45
Model 2	Ref	0.94 (0.83, 1.08)	0.91 (0.78, 1.05)	0.86 (0.73, 1.01)	0.85 (0.70, 1.04)	0.11	0.41
Model 3	Ref	0.94 (0.82, 1.08)	0.91 (0.78, 1.05)	0.86 (0.73, 1.01)	0.85 (0.70, 1.04)	0.08	0.59
C16:0							

Table 3 (*continued*)

	Q1	Q2	Q3	Q4	Q5	P for trend	P for non-linearity
	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)		
EPIC-Norfolk							
Median intake (IQR)	5.0 (4.4–5.3)	6.1 (5.9–6.3)	7.0 (6.7–7.1)	7.7 (7.5–8.0)	9.1 (8.6–9.8)		
Cases/subjects (n)	211/4410	211/4410	241/4410	253/4410	258/4410		
Model 1	Ref	1.01 (0.84, 1.22)	1.01 (0.84, 1.22)	0.93 (0.77, 1.13)	0.94 (0.78, 1.14)	0.36	0.49
Model 2	Ref	0.99 (0.80, 1.21)	0.98 (0.77, 1.24)	0.90 (0.68, 1.18)	0.91 (0.63, 1.31)	0.53	0.67
Model 3	Ref	0.99 (0.80, 1.22)	0.98 (0.77, 1.24)	0.90 (0.68, 1.18)	0.91 (0.63, 1.31)	0.50	0.58
EPIC-Denmark							
Median intake (IQR)	5.6 (5.1–5.9)	6.7 (6.4–6.8)	7.4 (7.2–7.5)	8.0 (7.9–8.2)	9.0 (8.7–9.4)		
Cases/subjects (n)	347/10675	395/10675	419/10675	479/10675	620/10675		
Model 1	Ref	1.02 (0.88, 1.18)	0.98 (0.85, 1.14)	1.03 (0.89, 1.18)	1.13 (0.99, 1.30)	0.06	0.23
Model 2	Ref	1.03 (0.88, 1.20)	0.99 (0.83, 1.18)	1.04 (0.86, 1.26)	1.15 (0.91, 1.45)	0.23	0.25
Model 3	Ref	1.03 (0.88, 1.21)	0.99 (0.83, 1.19)	1.04 (0.86, 1.26)	1.15 (0.91, 1.46)	0.14	0.33
C18:0							
EPIC-Norfolk							
Median intake (IQR)	2.0 (1.7–2.1)	2.5 (2.4–2.6)	2.8 (2.7–2.9)	3.2 (3.1–3.3)	3.8 (3.6–4.2)		
Cases/subjects (n)	204/4410	251/4410	254/4410	250/4410	245/4410		
Model 1	Ref	1.08 (0.89, 1.30)	1.04 (0.87, 1.26)	0.99 (0.82, 1.19)	0.90 (0.74, 1.10)	0.14	0.31
Model 2	Ref	1.03 (0.84, 1.26)	0.97 (0.77, 1.22)	0.90 (0.69, 1.17)	0.79 (0.56, 1.13)	0.13	0.42
Model 3	Ref	1.03 (0.84, 1.27)	0.97 (0.77, 1.22)	0.89 (0.68, 1.17)	0.78 (0.55, 1.12)	0.13	0.35
EPIC-Denmark							
Median intake (IQR)	2.3 (2.1–2.5)	2.8 (2.7–2.9)	3.2 (3.1–3.3)	3.5 (3.4–3.6)	4.0 (3.9–4.3)		
Cases/subjects (n)	345/10675	394/10675	458/10675	476/10675	587/10675		
Model 1	Ref	1.01 (0.87, 1.17)	1.07 (0.93, 1.23)	1.02 (0.89, 1.18)	1.14 (0.99, 1.31)	0.06	0.56
Model 2	Ref	1.00 (0.86, 1.17)	1.05 (0.89, 1.25)	1.00 (0.83, 1.21)	1.11 (0.90, 1.37)	0.28	0.57
Model 3	Ref	1.00 (0.86, 1.18)	1.05 (0.89, 1.25)	1.00 (0.83, 1.21)	1.11 (0.90, 1.38)	0.19	0.65
Sum of C12:0–C18:0							
EPIC-Norfolk							
Median intake (IQR)	8.4 (7.4–9.1)	10.5 (10.1–10.8)	11.9 (11.6–12.3)	13.5 (13.1–14.0)	16.2 (15.2–17.6)		
Cases/subjects (n)	209/4410	250/4410	241/4410	247/4410	257/4410		
Model 1	Ref	1.05 (0.87, 1.26)	0.98 (0.81, 1.18)	0.94 (0.78, 1.14)	0.91 (0.75, 1.10)	0.16	0.22
Model 2	Ref	0.99 (0.81, 1.21)	0.90 (0.72, 1.13)	0.85 (0.66, 1.09)	0.78 (0.56, 1.09)	0.10	0.34
Model 3	Ref	0.99 (0.81, 1.21)	0.89 (0.71, 1.12)	0.83 (0.64, 1.08)	0.76 (0.54, 1.08)	0.08	0.27
EPIC-Denmark							
Median intake (IQR)	9.3 (8.4–9.9)	10.5 (11.2–11.6)	12.5 (12.2–12.8)	13.7 (13.4–14.0)	15.4 (14.9–16.2)		
Cases/subjects (n)	361/10675	414/10675	422/10675	491/10675	572/10675		
Model 1	Ref	1.03 (0.89, 1.19)	0.98 (0.85, 1.12)	1.05 (0.92, 1.21)	1.08 (0.94, 1.23)	0.26	0.27
Model 2	Ref	1.03 (0.89, 1.19)	0.98 (0.84, 1.14)	1.06 (0.91, 1.23)	1.08 (0.91, 1.28)	0.38	0.24
Model 3	Ref	1.03 (0.89, 1.20)	0.98 (0.84, 1.14)	1.06 (0.91, 1.24)	1.08 (0.91, 1.29)	0.17	0.32

[a] Model 1 adjusts for age, sex, total energy intake, BMI, education level, physical activity level, smoking status, hypertension, alcohol intake and use of post-menopausal hormones and in EPIC-Norfolk for aspirin use, multivitamin use, and family history of MI; Model 2 additionally adjusts for the sum of the other SFAs, intakes of protein, PUFA, and in EPIC-Norfolk for trans-fatty acids; Model 3 additionally adjusts for hypercholesterolemia and menopausal status. P for trend was calculated by linearly including quartile specific median FA intake in the model. P for non-linearity was calculated by performing a likelihood ratio test comparing the model with only the linear term to the model that included cubic splines.

** Statistically significant at $p < 0.05$ level.

and the sum of C12:0 to C18:0 (12.5 en%/day), by MUFA, PUFA, carbohydrates or plant protein, suggested that substituting any of these SFAs by plant protein was inversely associated with MI incidence, although this was not statistically significant for the sum of C12:0 and C14:0 (Table 4, **Supplemental Table 4**). Additional adjustment for hypercholesterolemia and menopausal status did not change the results of the substitution analyses (data now shown).

A higher intake of SFA from meat was associated with a higher risk of MI incidence (HR per 1 en% 1.08, 95%CI 1.04, 1.12; **Supplemental Table 5**).

3.2.3. Pooled results

We pooled results from the main analysis (model 2) between EPIC-Norfolk and EPIC-Denmark. An inverse association was observed for C14:0 (Q5 0.81, 95%CI 0.67, 0.97), the sum of C12:0 and C14:0, and the sum of C15:0 and C:17:0 (Q5 0.83, 95%CI 0.70–0.98) with MI incidence risk. For the intake of C4:0 to C10:0, pooled analysis yielded a HR of 0.82 (95%CI 0.72, 0.93) in quintile 4, and a HR of 0.88 (95%CI 0.76, 1.03) in quintile 5. Substantial heterogeneity (in terms of I^2) was observed when pooling results for C12:0, C18:0 and the sum of C12:0 to C18:0 (**Supplemental Table 6**).

4. Discussion

In the present study of two separate cohorts from the UK and Denmark, a higher consumption of C12:0 and C14:0 associated with a lower MI risk in Denmark. Intakes in the third and fourth quintile of C4:0–C10:0 also associated to lower MI risk in Denmark. Other individual SFAs were not associated with MI. In substitution analyses, substituting C16:0 and C18:0 with plant protein associated with lower risk of MI in Denmark. No associations were found in the UK cohort.

Differences in results between Denmark and the UK may have occurred due to differences in underlying food sources and dietary patterns (e.g. intake of SFA from total dairy and meat was higher in Denmark compared to the UK) or lifestyles (e.g. the Danish cohort smoked more often and was more physically active than the UK cohort), or differences in confounder definitions and availability (e.g. trans fat intake was only available for the UK cohort). Also, differences in samples size may explain why we only found statistically significant associations in EPIC-Denmark (n = 53,375), and not in EPIC-Norfolk (n = 22,050). By pooling results of the two studies we intended to increase our ability to find associations, and thereby further clarify which individual SFAs associate with MI risk. However, these analyses should be interpreted with caution because of the above described heterogeneity, which was

Table 4
Hazard ratios (95%CI) for the associations between the substitution of individual SFAs (in en%/day) for (starch) carbohydrates, PUFA, MUFA and plant protein, and MI incidence risk in EPIC-Norfolk and EPIC-Denmark.[a]

EPIC-Norfolk	HR (CI) per 1 en%	EPIC-Denmark	HR (CI) per 1 en%
Replacing sum C12:0 & 14:0 with		Replacing sum C12:0 & 14:0 with	
cisMUFA	0.95 (0.81, 1.11)	MUFA	1.08 (0.94, 1.23)
cisPUFA	0.99 (0.84, 1.16)	PUFA	1.08 (0.95, 1.24)
Starch carbohydrates	0.98 (0.83, 1.15)	Carbohydrates	1.08 (0.94, 1.24)
Plant protein	0.88 (0.73, 1.05)	Plant protein	0.94 (0.81, 1.09)
Replacing C16:0 with		Replacing C16:0 with	
cisMUFA	0.99 (0.87, 1.13)	MUFA	0.99 (0.90, 1.08)
cisPUFA	1.04 (0.91, 1.18)	PUFA	0.99 (0.89, 1.11)
Starch carbohydrates	1.03 (0.92, 1.15)	Carbohydrates	0.99 (0.91, 1.08)
Plant protein	0.93 (0.82, 1.04)	Plant protein	0.86 (0.78, 0.95)**
Replacing C18:0 with		Replacing C18:0 with	
cisMUFA	1.15 (0.93, 1.43)	MUFA	1.00 (0.91, 1.11)
cisPUFA	1.20 (0.98, 1.47)	PUFA	1.01 (0.90, 1.13)
Starch carbohydrates	1.19 (0.97, 1.45)	Carbohydrates	1.01 (0.92, 1.11)
Plant protein	1.07 (0.87, 1.31)	Plant protein	0.87 (0.79, 0.96)**
Replacing sum C12:0–C18:0 with		Replacing sum C12:0–C18:0 with	
cisMUFA	1.02 (0.94, 1.10)	MUFA	1.01 (0.96, 1.06)
cisPUFA	1.07 (0.99, 1.15)	PUFA	1.02 (0.95, 1.09)
Starch carbohydrates	1.05 (0.99, 1.12)	Carbohydrates	1.01 (0.97, 1.05)
Plant protein	0.94 (0.87, 1.02)	Plant protein	0.87 (0.82, 0.94)**

[a] Hazard ratios are adjusted for age, sex, total energy intake, BMI, education level, physical activity level, smoking status, hypertension, alcohol intake and use of post-menopausal hormones, the sum of the other SFAs, energy from MUFA, PUFA, protein (plant and other sources), and carbohydrates (UK; starch and other sources), and in EPIC-Norfolk for aspirin use, multivitamin use, family history of MI, and energy from trans-fatty acids.
** Statistically significant at $p < 0.05$ level.

also reflected by the high level of heterogeneity (I^2 values) for some of the pooled fatty acid analyses (e.g. C12:0, C18:0).

Four other observational cohort studies, two from the Netherlands and two from the US, investigated the association between individual SFAs and CHD risk [10–13], with divergent and sometimes conflicting results. When comparing our findings to those studies, our findings seem to be most in line with the Dutch EPIC-NL study, such as the inverse associations for C14:0 and C15:0 plus C17:0 (latter in pooled analyses only) [11]. In contrast, C15:0 and C17:0 were not associated with CHD risk [10,12,13] in the other studies, and C14:0 was either not associated [10,12] or adversely associated with CHD risk [13]. The finding that C4:0–10:0 associated with lower MI risk in quintiles 3 and 4 compared to 1 is to some extent also consistent with the EPIC-NL study that found a linear inverse association for C4:0–10:0 [11], whereas the other cohorts reported no associations [10,12,13]. The lack of associations between intakes of C16:0, and C18:0 and MI risk in our present study is in line with the EPIC-NL cohort as well, whereas C16:0 associated with higher CHD risk in the other three cohorts [10,12,13], as well as C18:0 in the US cohorts [10,13]. The inverse association in our present study for C12:0 intake is not consistent with results of all previous studies. The explanation for these divergent findings between the cohort studies is not straightforward, and we discuss possibilities below.

First, differences in food sources between European and US populations may (partly) explain differences in results. More specifically, the study populations differ with respect to the consumption of dairy products and meat, the two major sources of SFA. In the US, the major food sources of SFA are meat and mixed meals [43]. These food groups make an important contribution to the dietary intakes of C16:0 and C18:0, which were associated with an increased CHD risk in the US cohorts [10,13], but not in the European EPIC cohorts [11,12]. On the other hand, dairy products are a major SFA food source in the UK, Denmark, and the Netherlands [44,45]. C4:0–C10:0, C12:0, C14:0, C15:0, and C17:0, which in these European cohorts were often inversely or neutrally associated with CHD, all largely come from dairy food sources. In a previous cohort study, SFA from dairy foods and meat were associated with respectively a lower and a higher CHD risk [46]. In the present work we also showed that SFA from meat (in Denmark) associated with higher MI risk, whereas SFA from dairy did not associate with MI risk. These findings support that differences in underlying food sources could explain differences in results of SFAs on MI risk between European an US populations.

Second, we used baseline measures of SFA intake only, whereas the US cohorts used repeated measures of diet. It is conceivable that dietary intakes change over time [13], and that repeated dietary measures probably yield a more accurate measure of SFA intake during follow up, which might be another explanation for the divergent findings. However, sensitivity analysis with a shortened follow-up time in our study did not yield materially different results, compared to the original analyses.

Third, differences in adjustment of dietary factors could impact the interpretation of the results. For example in our main analyses, we adjusted for intakes of energy, remaining SFAs, PUFAs, proteins and trans fatty acids (latter UK only), whereas the most recent US study of Zong et al. adjusted for energy intake only [13]. In additional substitution analyses that did take these macronutrients into account, findings from the present study and of Zong et al. were more comparable, although some differences remain. In the present study, we found that substituting C16:0 and C18:0, and C12:0–C18:0 (which to a large extent are C16:0 and C18:0) with plant protein associated with lower risk of MI in Denmark, supporting previous reports that defining the substituting macronutrient is of importance in the relationship of SFAs with MI. In line with this, Zong et al. found inverse associations of replacing C16:0 and C12:0–C18:0 with plant proteins, but not for C18:0. [13]. Zong et al. [13] also found inverse associations for substituting C16:0 and C12:0–C18:0 with PUFA and whole grain carbohydrates, whereas we did not. This may be due to lack of our ability to disentangle between types of PUFAs and because we investigated total or starch carbohydrates instead of whole grain carbohydrates in our study.

Regarding the non-linear association of C4:0–C10:0 with MI we found, we should be careful with interpreting these results as non-linear because the intake range was very low, with average intakes around 1.5 energy% associating to lower MI risk and of around 2.0 energy% not. There is no (biological) explanation for why intakes of C4:0–C10:0 of slightly higher than 1.5 energy% are less protective for CHD, and these associations would have to be investigated in studies with higher intakes of those SFAs to further conclude about how higher intakes of C4:0–C10:0 associate with MI risk.

Taken together the evidence from our and the four previously performed observational cohort studies [10–13], in general, there appears

to be an inverse or neutral association between MI or CHD risk and the shorter chain and odd chain SFAs (C4:0–C10:0, C12:0, C14:0, C15:0, and C17:0) and a harmful or neutral association of the longer-chain SFAs (C16:0 and C18:0) as evident from substitution analyses on replacement of C16:0 and C18:0 with plant protein. These observations could reflect a difference in the underlying dietary pattern, e.g. the difference in consumption of dairy versus meat, but could also reflect actual differences of SFAs effects on CHD risk markers. Because of the high correlations between the SFAs, observational cohort studies alone will not suffice in answering the question whether individual SFAs have different associations with MI or CHD. Also in our study, high correlations between several SFA subtypes exist, what made it unclear whether the observed associations in our study pertain to all these SFAs, or represent the association of one of them. At present, controlled trials have been conducted for C12:0 and C14:0, but not for C4:0–C10:0 or C15:0 and C17:0. C12 and C14:0 were shown to increase serum LDL-cholesterol as compared to carbohydrates [5], but had little (C14:0) or beneficial (C12:0) effects on the ratio of total: HDL cholesterol, which is considered to be a stronger CHD risk predictor than LDL-cholesterol levels alone [47]. This could explain why in our study and previous studies [10–12], C12:0 and C14:0 were not harmfully associated with risk of MI or CHD.

Strengths of this study are the large sample sizes of the included cohorts, with a long follow-up time and a large number of MI endpoints. Also, the extensive assessment of population characteristics at baseline allowed us to adjust the observed associations for many potential confounders. Furthermore, because both cohorts are part of the international EPIC cohort, they have a similar recruitment period (between 1993 and 1997). Limitations of this study are that we had no or limited data on intake of C17:0 and trans fatty acids for the Danish cohort, and therefore did not include these in the analyses for the Danish cohort, and cannot exclude the possibility of residual confounding.

In conclusion, our study shows inverse associations of C12:0 and C14:0, the third and fourth quintiles of intake of C4:0–C10:0, and substituting C16:0 and C18:0 with plant proteins with risk of MI. Taking into account the results of the present and previous observational cohort studies, we conclude that the association between SFA and MI or CHD appears to differ for short- to medium-chain SFAs versus the long-chain SFAs. The short- to medium SFAs, as well as the odd-chain SFAs with 15 and 17 carbons, appear to be inversely associated or not associated to MI risk, whereas the longer-chain SFAs C16:0 and C18:0 may be adversely or not associated to MI risk. Whether this difference is caused by the SFAs as such, by the differences in underlying dietary pattern, or by residual confounding in observational studies is unclear, and cannot be solved using observational evidence alone. Therefore, for further examination of the effects of the short-to medium-chain SFAs on MI risk, evidence from intervention studies is needed.

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Conflicts of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.10.064.

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