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Dietary Intake of Saturated Fat Is Not Associated with Risk of Coronary Events or Mortality in Patients with Established Coronary Artery Disease[1–3]

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Abstract

Background: Data from recent meta-analyses question an association between dietary intake of saturated fatty acids (SFAs) and risk of cardiovascular disease (CVD). Moreover, the prognostic effect of dietary SFA in patients with established CVD treated with modern conventional medication has not been extensively studied.

Objective: We investigated the associations between self-reported dietary SFA intake and risk of subsequent coronary events and mortality in patients with coronary artery disease (CAD).

Methods: This study included patients who participated in the Western Norway B-Vitamin Intervention Trial and completed a 169-item semiquantitative food-frequency questionnaire after coronary angiography. Quartiles of estimated daily intakes of SFA were related to risk of a primary composite endpoint of coronary events (unstable angina pectoris, nonfatal acute myocardial infarction, and coronary death) and separate secondary endpoints (total acute myocardial infarction, fatal coronary events, and all-cause death) with use of Cox-regression analyses.

Results: This study included 2412 patients (81% men, mean age: 61.7 y). After a median follow-up of 4.8 y, a total of 292 (12%) patients experienced at least one major coronary event during follow-up. High intake of SFAs was associated with a number of risk factors at baseline. However, there were no significant associations between SFA intake and risk of coronary events [age- and sex-adjusted HR (95% CI) was 0.85 (0.61, 1.18) for the upper vs. lower SFA quartile] or any secondary endpoint. Estimates were not appreciably changed after multivariate adjustments.

Conclusions: There was no association between dietary intake of SFA and incident coronary events or mortality in patients with established CAD. *J Nutr* doi: 10.3945/jn.114.203505.

Keywords: established coronary artery disease, coronary events, dietary SFA, FFQ, mortality

Introduction

Cardiovascular disease (CVD)[12] is currently the number one cause of death globally (1), and the association between intake of SFAs, serum cholesterol, and risk of coronary artery disease (CAD) is well established (2). Thus, restriction of dietary SFA intake is included in current guidelines on CVD risk reduction (3). However, recent evidence from randomized controlled trials and observational studies does not endorse this diet-heart paradigm (4–6), and the causality of the association between dietary SFA and CAD outcomes is increasingly being questioned (2, 5, 7). Recent studies suggest that replacing SFAs with MUFAs and/or PUFAs may be beneficial, whereas replacing SFAs with carbohydrates having a high glycemic index might increase risk (4). Moreover, several recent analyses have questioned the deleterious effects of SFA from dairy products (8, 9).

Few studies have investigated the clinical impact of SFA intake in patients with established CAD who receive modern

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[3] Supplemental Table 1 is available from the ''Online Supporting Material'' link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
[12] Abbreviations used: ACS, acute coronary syndrome; AMI, acute myocardial infarction; CABG, coronary artery by-pass graft surgery; CAD, coronary artery disease; CVD, cardiovascular disease; PCI, percutaneous coronary intervention; WENBIT, Western Norway B-Vitamin Intervention Trial.
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conventional medication, including lipid-modifying therapy (10). The cholesterol-lowering drugs, statins, constitute the cornerstone of pharmacologic CVD prevention (3, 11). However, there are uncertainties as to whether the clinical effects are only due to the cholesterol lowering itself or also attributable to other pleiotropic mechanisms of statins (12).

The main objective of this study was to investigate whether dietary intake of SFA was associated with subsequent risk of coronary events in patients with CAD. Secondary aims were to investigate whether SFA intake was associated with total acute myocardial infarction (AMI), fatal coronary events, and all-cause death.

Methods

Study population. Between 1999 and 2004, 3090 adult patients undergoing coronary angiography because of CAD or aortic stenosis were recruited from Haukeland University Hospital (Bergen, Norway) and Stavanger University Hospital (Stavanger, Norway) and enrolled in the Western Norway B-Vitamin Intervention Trial (WENBIT). The main aim of this trial was to study clinical outcomes of homocysteine-lowering vitamin B therapy (13). The intervention did not reveal any benefits on cardiovascular outcomes or all-cause mortality (14). All eligible participants signed a consent form. The study protocol was in accordance with the principles of the Declaration of Helsinki and approved by the Regional Committee for Medical and Health Research Ethics, the Norwegian Medicines Agency, and the Data Inspectorate.

Dietary assessment. Information on dietary intake was obtained from participants who completed a semiquantitative FFQ handed out at the day of inclusion, filled in at home, and returned to the study center either by mail or at the follow-up appointment 1 mo later. The FFQ was developed at the Department of Nutrition, University of Oslo (Oslo, Norway) and has been validated for several nutrients (15–18). The 10-page questionnaire was designed to obtain information on habitual food intake during the past year and included 169 food items grouped according to Norwegian meal patterns. The frequency of consumption was given per day, week, or month, depending on the items in question. The portion sizes were given as household measures or units such as slices, pieces, spoons, and glasses. Questions on use of supplements were included in 3 intake categories: whole year or winter use only, times per week, and amount per time. Mean daily intake was used for the analyses. The nutrient intakes registered in the FFQ were estimated with use of a database and a software system developed at the Department of Nutrition, University of Oslo (Kostberegningssystem, version 3.2; University of Oslo). This food database is mainly based on the official Norwegian Food Table, which is continuously updated (17). Of the 3090 WENBIT patients, 2484 returned the FFQ. Patients handing in an FFQ with >1 blank page (n = 19) and participants who had very low (<3000 kJ for women and <3300 kJ for men) or very high (>15,000 kJ for women and >17,500 kJ for men) estimated daily energy intakes (n = 53) were excluded, leaving data from 2412 participants for final analyses.

Laboratory analyses and assessment of other covariates. Demographic, clinical, and routine laboratory data were obtained by study personnel at the respective 2 study centers as previously described (19). Standard blood laboratory markers were analyzed from fresh samples according to routine protocols at the hospital laboratories, whereas serum samples were collected before angiography and stored at −80°C until analysis. Reagent kits of type Tina-quant on Apo A-I, ver.2, Apo B, ver.2, and C-reactive protein (latex, high-sensitive assay) were obtained from Roche Diagnostics, and serum measurements were performed on the Hitachi 917 system (Roche Diagnostics). Plasma cotinine was analyzed by HPLC-MS/MS (20). LDL cholesterol was estimated with use of the Friedewald formula (14). Serum FA methyl esters were obtained and analyzed by GLC in a subset of 733 patients as previously described (21).

Diabetes mellitus was classified according to existing diagnosis (yes/no), or based on baseline serum fasting glucose concentrations ≥7.0 or nonfasting glucose concentrations ≥11.1 mmol/L (22). Smokers included self-reported current smokers, those reported having quit within the last 4 wk, and patients with plasma cotinine ≥85 nmol/L at baseline (23). Left ventricular ejection fraction (%) was determined by ventriculography or echocardiography, and values <50% were classified as impaired systolic function. Extent of CAD was graded as angiographically nonsignificant stenosis (luminal narrowing <50%) or as single-, double-, or triple-vessel disease (24).

Endpoints and follow-up. The primary endpoint was a composite of coronary events including unstable angina pectoris, nonfatal AMI, and coronary death. Secondary endpoints were total AMI (fatal and nonfatal), coronary death, and all-cause death.

Unstable angina pectoris was defined as an endpoint in patients who were urgently admitted to hospital because of acute attacks of ischemic symptoms accompanied by either electrocardiographic ST-T findings of myocardial ischemia at rest and/or a coronary angiography during the same hospital stay verifying substantial progression of CAD. Patients classified as having unstable angina did not have biomarkers equitable with myocardial necrosis (25). AMI was classified according to the revised definition of AMI published in 2000 (26). Procedure-related nonfatal AMIs occurring ≤24 h after coronary angiography, percutaneous coronary intervention (PCI), or coronary artery by-pass graft surgery (CABG) were excluded. Clinical data were obtained from hospitals and information on deaths from the Norwegian Cause of Death Registry. A coronary event was defined as fatal if death occurred ≤28 d after its onset.

Recording of endpoints during in-trial and post-trial follow-up continued until December 31, 2006, and all events were evaluated by members of the WENBIT endpoint committee.

Statistical analysis. Baseline and dietary variables are reported as means ± SDs, medians (25th, 75th percentiles), or proportions as appropriate. All participants were ranked according to quartiles of SFA consumption as a percentage of total energy intakes. Energy-adjusted data were used for analyses to reduce confounding by differences in energy intake. Baseline characteristics across quartiles of estimated daily intake of SFA were investigated with use of linear regression for continuous variables and logistic regression for binary variables. Spearman's rank correlation was used to assess the association between SFA intake and serum SFA.

The association between SFA intake and subsequent risk of main or secondary endpoints during follow up was evaluated by Cox proportional hazard models. We performed log (-log) plots and plotted Schoenfeld residuals to test the assumption of proportional hazards. HRs and 95% CIs were reported for each quartile increment, and P values were given for trends over quartiles. In the basic model we controlled for age and sex. The multivariate model also included the following additional clinical relevant covariates: hypertension (yes/no), current smoking (yes/no), diabetes mellitus (yes/no), left ventricular ejection fraction (continuous), acute coronary syndrome [(ACS) yes/no], and current use of statins (yes/no). Further adjustment for the following covariates did not appreciably alter the results and were not included in the final model: previous AMI, CABG, PCI, previous cerebrovascular disease or carotid artery stenosis, peripheral arterial disease (all yes/no), extent of CAD at coronary angiography (nonsignificant stenosis, single-, double-, or triple-vessel disease), LDL cholesterol (quartiles), ApoB-100:ApoA-1 ratio (quartiles), C-reactive protein (quartiles), current use of β-blockers (yes/no) or angiotensin-converting enzyme inhibitors (yes/no), B-6 and folate/B-12 study treatment, and SFA-rich food items (meat, cheese, butter, milk). Tests for trend were performed by assessing quartiles of SFA intakes as continuous variables in otherwise identical models. A competing risk regression analysis on fatal noncoronary events was also performed.

Subgroup analyses were performed with use of categorical variables or by stratifying continuous variables by the median value according to important CAD risk factors. BMI was categorized into 3 groups: ≤25, >25

TABLE 1 Baseline characteristics of patients with CAD by quartiles of dietary SFA intake (n = 2412)[1]

	Quartiles of SFA intake (E%)				
	1	2	3	4	P-trend[2]
SFA, range	3.94–9.79	9.80–11.47	11.48–13.18	13.19–26.73	
Age, y	62.4 ± 9.38	61.7 ± 9.69	60.9 ± 9.83	61.6 ± 9.96	0.88
Male sex, n (%)	480 (79.6)	491 (81.4)	484 (80.3)	486 (80.6)	0.80
BMI, kg/m^2	26.8 ± 3.8	26.7 ± 3.5	26.9 ± 3.6	27.0 ± 3.8	0.25
Cardiovascular history, n (%)					
Myocardial infarction	269 (44.6)	263 (43.6)	237 (39.3)	225 (37.3)	0.004
CABG	112 (18.6)	90 (14.9)	61 (10.1)	72 (11.9)	<0.001
PCI	141 (23.4)	141 (23.4)	116 (19.2)	123 (20.4)	0.08
Coronary risk factors, n (%)					
Hypertension[3]	305 (50.6)	275 (45.6)	276 (45.8)	262 (43.4)	0.02
Current smoker[4]	135 (22.4)	181 (30.0)	178 (29.5)	256 (42.5)	<0.001
Diabetes mellitus[5]	86 (14.3)	64 (10.6)	81 (13.4)	86 (14.3)	0.65
Clinical diagnosis before baseline coronary angiography, n (%)					
LVEF <50%	68 (11.3)	65 (10.8)	58 (9.6)	63 (10.4)	0.51
Stable angina pectoris	513 (85.1)	530 (87.9)	515 (85.4)	484 (80.3)	0.01
ACS	85 (14.1)	64 (10.6)	82 (13.6)	108 (17.9)	0.02
Extent of CAD at baseline coronary angiography, n (%)					
Nonsignificant CAD	54 (9.0)	68 (11.3)	73 (12.1)	73 (12.1)	0.07
One-vessel disease	172 (28.5)	169 (28.0)	201 (33.3)	181 (30.0)	0.24
Two-vessel disease	160 (26.5)	169 (28.0)	151 (25.0)	171 (28.4)	0.76
Triple-vessel disease	217 (36.0)	197 (32.7)	178 (29.5)	178 (29.5)	0.008
Serum lipids at baseline coronary angiography					
Total cholesterol, nmol/L	4.9 ± 1.2	5.0 ± 1.1	5.1 ± 1.1	5.2 ± 1.3	<0.001
LDL cholesterol, mmol/L	3.0 ± 1.0	3.1 ± 1.0	3.1 ± 1.0	3.2 ± 1.0	0.001
HDL cholesterol, mmol/L	1.3 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.3 ± 0.4	0.73
ApoB, g/L	0.86 ± 0.23	0.88 ± 0.23	0.88 ± 0.24	0.90 ± 0.25	0.004
ApoA1, g/L	1.26 ± 0.25	1.25 ± 0.24	1.25 ± 0.25	1.27 ± 0.27	0.50
TGs, mmol/L	1.7 ± 0.94	1.8 ± 1.2	1.8 ± 0.92	1.9 ± 1.5	0.005
SFAs,[6] wt%	33.1 ± 2.3	33.5 ± 3.3	33.3 ± 2.4	33.5 ± 2.2	0.18
Inflammation markers and renal function at baseline coronary angiography					
C-reactive protein,[7] mg/L	1.7 (0.8, 4.0)	1.7 (0.9, 3.9)	1.8 (0.9,3.5)	2.2 (1.1,4.9)	0.27
Hemoglobin, g/dL	14.3 ± 1.1	14.3 ± 1.2	14.4 ± 1.2	14.4 ± 1.2	0.18
eGFR, μmol/L	91.4 ± 14.3	92.3 ± 14.2	90.5 ± 15.5	91.7 ± 20.1	0.79
Medications before baseline coronary angiography, n (%)					
Acetylsalicylic acid	485 (80.4)	474 (78.6)	460 (76.3)	441 (73.1)	0.002
Statins	468 (77.6)	435 (72.1)	447 (74.1)	405 (67.2)	<0.001
β-Blockers	421 (69.8)	442 (73.3)	406 (67.3)	395 (65.5)	0.03
ACE inhibitors and/or ARBs	197 (32.7)	170 (28.2)	165 (27.4)	175 (29.0)	0.16
Calcium channel blockers	148 (24.5)	121 (20.1)	145 (24.0)	132 (21.9)	0.60
Loop diuretics	47 (7.8)	67 (11.1)	41 (6.8)	52 (8.6)	0.72
Medications after baseline coronary angiography, n (%)					
Acetylsalicylic acid	549 (91.0)	539 (89.4)	545 (90.4)	539 (89.4)	0.47
Statins	547 (90.7)	531 (88.1)	541 (89.7)	527 (87.4)	0.15
β-Blockers	466 (77.3)	485 (80.4)	459 (76.1)	469 (77.8)	0.71
ACE inhibitors and/or ARBs	211 (35.0)	186 (30.8)	175 (29.0)	189 (31.3)	0.13
Calcium channel blockers	144 (23.9)	136 (22.6)	143 (23.7)	125 (20.7)	0.28
Loop diuretics	53 (8.8)	68 (11.3)	48 (8.0)	54 (9.0)	0.59
WENBIT treatment, n (%)					
Folic acid	293 (48.6)	315 (52.2)	295 (48.9)	298 (49.4)	0.93
Vitamin B-6	290 (48.1)	308 (51.1)	314 (52.1)	299 (49.6)	0.55

[1] Values are means ± SDs unless otherwise indicated; n = 603 in each quartile. ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CABG, coronary artery by-pass graft surgery; CAD, coronary artery disease; E%, percentage of energy; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; WENBIT, Western Norway B-Vitamin Intervention Trial.
[2] Calculated with use of linear regression for continuous variables and logistic regression for binary variables.
[3] Receiving medical treatment for hypertension.
[4] Current smoker, based on self-report and cotinine concentrations >85 (includes ex-smokers <1 mo).
[5] Diabetes diagnosed or assessed according to baseline serum glucose concentrations ≥7.0 or nonfasting glucose ≥11.1 mmol/L.
[6] Serum SFAs were measured in 733 participants (n = 192, 189, 180, and 172 in quartiles 1–4, respectively).
[7] Values are medians (25th, 75th percentiles).

and ≤30, and >30 kg/m^2. All stratified analyses were adjusted for age and sex. Interactions between intake of SFA and subgroups were tested by adding interaction product terms in the Cox model.

Statistical analyses were performed with use of SPSS for Windows, version 20 (SPSS) and R, version 2.15.3 (R Development Core Team). Two-sided P values < 0.05 were considered statistically significant.

Results

Baseline characteristics. Baseline characteristics of 2412 participants (80.5% men) by quartiles of SFA intake (percentage of energy) are shown in **Table 1**. Most of the participants (84.7%) had stable angina pectoris. The age of subjects at inclusion ranged from 27 to 86 y, with a mean age of 62 ± 10 y. Mean dietary intakes of SFAs were 8.4 ± 1.1, 10.7 ± 0.5, 12.3 ± 0.5, and 15.0 ± 1.7 percentage of energy, for quartiles 1–4, respectively.

Participants with a higher SFA intake were less likely to have a history of AMI, CABG or hypertension, to be admitted for stable angina pectoris, or to have triple-vessel disease at baseline (P = 0.008). Furthermore, participants with high SFA intake were more likely to be current smokers and to have higher serum total and LDL cholesterol, apoB, and TGs (P = 0.005).

Drugs such as acetylsalicylic acid (77%), statins (73%), and β-blockers (69%) were used by a majority of the participants before baseline coronary angiography. Those having intakes corresponding to the lower quartile of SFA were more likely to already receive such conventional medication at baseline compared with those having the highest intake. After baseline coronary angiography there were no significant differences in drug usage across quartiles, and overall, 90% of participants used acetylsalicylic acid, 89% statins, and 78% β-blockers.

No significant associations between serum SFA and dietary SFA intake were demonstrated across quartiles (Table 1) nor by correlation analyses (Spearman's rho = 0.070, P = 0.06).

Baseline dietary intake. Increasing intake of SFAs corresponded to increasing intakes of both total energy (P < 0.001) and total fat (P < 0.001) across quartiles (**Table 2**). This seemed due to higher intakes of C12:0, C14:0, and C16:0 with increasing quartiles. Participants with the higher SFA intake also had higher consumption of mono- and polyunsaturated fat and of dietary cholesterol. Furthermore, a higher SFA intake was associated with lower consumption of total carbohydrates, dietary fiber, and alcohol. Patients with higher SFA intake also had higher intakes of meat, cheese, butter, milk, eggs, cakes, sugar, and sweets.

Dietary intake of SFAs and risk of coronary events. During a median follow-up of 4.8 y (2.9, 6.1), a total of 292 participants experienced a coronary event and a total of 137 patients died from any cause.

Table 3 shows both age- and sex-adjusted and multivariate-adjusted HRs for the endpoints by quartiles of SFA consumption as percentage of energy. There were no significant associations between SFA intake and coronary events [age- and sex-adjusted HR (95% CI) in the fourth vs. first quartile was 0.85 (0.61, 1.18)], or for the separate secondary endpoints AMI, fatal coronary events, or all-cause death. Estimates were not

TABLE 2 Baseline daily nutrient and food intake of patients with CAD by quartiles of dietary SFA intake (n = 2412)[1]

	Quartiles of SFA intake (E%)				
	1	2	3	4	P-trend[2]
SFA, range	3.94–9.79	9.80–11.47	11.48–13.18	13.19–26.73	
Energy, kJ	7875 ± 2310	8753 ± 2553	9016 ± 2559	9458 ± 2966	<0.001
Total fat, E%	25 ± 3.8	30.2 ± 3.2	33.0 ± 3.2	37.1 ± 3.9	<0.001
SFAs, g	18 ± 6.0	25 ± 8.0	30 ± 9.0	38 ± 13	<0.001
C12:0	1.0 ± 0.4	1.4 ± 0.6	1.7 ± 0.7	2.2 ± 1.0	<0.001
C14:0	1.8 ± 0.6	2.4 ± 0.8	3.0 ± 1.0	4.1 ± 1.5	<0.001
C16:0	9.0 ± 3.0	12.2 ± 3.7	14.2 ± 4.2	17.6 ± 5.9	<0.001
Monounsaturated fat, E%	8.3 ± 1.6	9.8 ± 1.4	10.6 ± 1.4	11.8 ± 1.5	<0.001
Polyunsaturated fat, E%	6.3 ± 1.7	7.1 ± 1.9	7.4 ± 2.0	7.5 ± 2.2	<0.001
Total n–3 FAs,[3] g	2.9 ± 1.5	3.3 ± 1.5	3.3 ± 1.4	3.4 ± 1.9	<0.001
Total n–6 FAs, g	10 ± 4.4	13.3 ± 5.9	14.5 ± 6.2	15.7 ± 7.9	<0.001
Cholesterol, mg	229 ± 93	280 ± 92	311 ± 103	357 ± 123	<0.001
Protein, E%	17.1 ± 2.8	16.8 ± 2.3	17.0 ± 2.5	16.7 ± 2.5	0.005
Carbohydrate, E%	55.0 ± 5.9	51.0 ± 4.7	48.1 ± 4.9	44.4 ± 5.3	<0.001
Dietary fiber, g	27 ± 9	26 ± 9	24 ± 8	22 ± 8	<0.001
Sugar, E%	6.2 ± 5.1	6.7 ± 4.3	6.5 ± 3.7	6.0 ± 4.0	0.26
Alcohol,[4] E%	1.2 (<0.0, 3.3)	1.1 (<0.0, 2.8)	1.0 (<0.0, 2.8)	0.9 (<0.0, 2.7)	0.001
Food items, g					
Meat	86 ± 47	114 ± 56	128 ± 61	137 ± 68	<0.001
Cheese	15 ± 15	24 ± 19	31 ± 25	44 ± 35	<0.001
Butter	20 ± 16	31 ± 19	37 ± 22	44 ± 25	<0.001
Milk	291 ± 238	319 ± 232	326 ± 239	347 ± 258	<0.001
Egg	13 ± 10	16 ± 11	18 ± 11	20 ± 13	<0.001
Cakes	19 ± 22	27 ± 27	33 ± 31	35 ± 35	<0.001
Sugar and sweets	6 ± 10	10 ± 13	11 ± 16	13 ± 16	<0.001

[1] Values are means ± SDs unless otherwise indicated; n = 603 in each quartile. CAD, coronary artery disease; E%, percentage of energy.
[2] Calculated with use of linear regression for trends across quartiles.
[3] α-Linolenic acid, DHA, docosapentaenoic acid, and EPA.
[4] Values are medians (25th, 75th percentiles); variable was log-transformed for regression analysis.

TABLE 3 HRs and 95% CIs for coronary events in patients with CAD by quartiles of dietary SFA intake[1]

	Quartiles of SFA intake (E%)				
	1	2	3	4	*P*-trend
SFA, range	3.94–9.79	9.80–11.47	11.48–13.18	13.19–26.73	
Total coronary events[2]					
Events, *n*	79	76	72	65	
Age- and sex-adjusted	1.00	0.97 (0.71, 1.33)	0.93 (0.68, 1.28)	0.85 (0.61, 1.18)	0.31
Multivariate[3]	1.00	1.02 (0.74, 1.39)	0.95 (0.69, 1.31)	0.83 (0.59, 1.16)	0.23
Total AMIs[4]					
Events, *n*	56	57	45	52	
Age- and sex-adjusted	1.00	1.04 (0.72, 1.50)	0.83 (0.56,1.23)	0.97 (0.66, 1.41)	0.60
Multivariate[3]	1.00	1.09 (0.75, 1.58)	0.85 (0.57, 1.26)	0.90 (0.61, 1.32)	0.37
Fatal coronary events					
Events, *n*	18	16	18	24	
Age- and sex-adjusted	1.00	0.92 (0.47, 1.81)	1.11 (0.58, 2.14)	1.41 (0.76, 2.59)	0.22
Multivariate[3]	1.00	0.98 (0.50, 1.94)	1.13 (0.59, 2.18)	1.29 (0.69, 2.42)	0.38
All-cause death					
Events, *n*	36	30	31	40	
Age- and sex-adjusted	1.00	0.87 (0.53, 1.41)	0.96 (0.59, 1.55)	1.18 (0.75, 1.85)	0.42
Multivariate[3]	1.00	0.85 (0.52, 1.38)	0.92 (0.57, 1.50)	1.02 (0.64, 1.62)	0.83

[1] Values are HRs (95% CIs) unless otherwise indicated. HRs and 95% CIs were calculated with use of Cox proportional hazards; $n = 603$ in each quartile. AMI, acute myocardial infarction; CAD, coronary artery disease; E%, percentage of energy.
[2] Composite of unstable angina pectoris (excluding procedure-related AMI), coronary death, and nonfatal AMI.
[3] Multivariate model adjusted for acute coronary syndrome (yes/no), age (continuous), diabetes mellitus (yes/no, diagnosed or assessed according to baseline serum glucose concentrations ≥7.0 or nonfasting glucose ≥11.1 mmol/L), hypertension (yes/no), left ventricular ejection fraction (continuous), sex, current smoker [based on self-report and cotinine concentrations >85 at baseline (includes ex-smokers <1 mo)], and current use of statins (yes/no).
[4] Fatal and nonfatal AMI.

appreciably changed after multivariate adjustments (Table 3). Results are also visualized with a Kaplan-Meier survival curve (**Figure 1**). Data on physical activity were missing in 549 (22.8%) patients. However, including this variable in the multivariate model among the rest of the study population did not affect the estimates (data not shown). Estimates from competing risk analysis are presented in **Supplemental Table 1**, showing no significant associations.

The relative strength of Cox regression for coronary events was estimated through stratification according to sex, age, BMI, diabetes, hypertension, smoking, Apo B:Apo AI ratio, and folic acid or vitamin B-6 intervention. **Figure 2** illustrates these subgroup analyses by comparing quartile 4 against quartile 1. There were no significant associations or interactions after stratification.

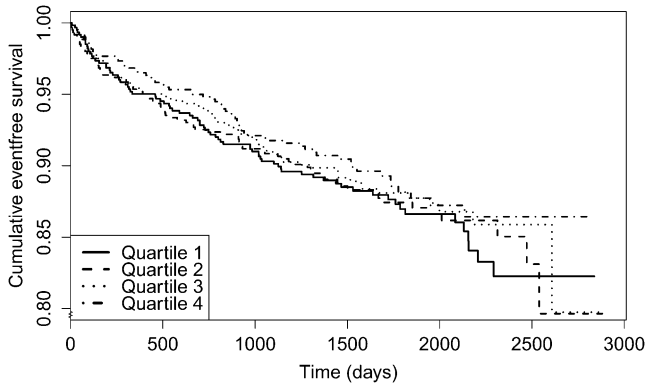

FIGURE 1 Kaplan-Meier plot illustrating coronary events in patients with coronary artery disease across quartiles of dietary SFA intake. Survival plot showing time to coronary events by each quartile of SFA intake among 2412 patients with coronary artery disease (log-rank, $P = 0.75$).

Discussion

In this prospective cohort study of 2412 patients with established CAD, treated with conventional medication, there were no significant associations between dietary intake of SFA and future coronary events or total mortality.

Strengths and limitations. The strengths of this study include the large and well-characterized population and close-to-complete follow-up for almost 5 y with respect to clinical endpoints. Although numerous potential confounders were adjusted for, residual confounding cannot be excluded in a prospective cohort study.

There are some additional limitations that should be addressed. The FFQs were not controlled for errors when handed in, and data from some participants had to be excluded. There were certain differences between participants who responded and those who did not respond to the FFQ. There was a higher frequency of women among nonrespondents than respondents. Furthermore, nonrespondents were less likely to have previously undergone a PCI and more likely to be smokers, have diabetes, have reduced ejection fraction, be admitted with acute coronary syndrome, be treated with loop diuretics, and have higher total cholesterol, Apo B, and C-reactive protein. Furthermore, the use of FFQs in estimating dietary intake of SFA is challenging because there are no good objective biomarkers enabling validation of SFA intakes (27–29). However, the estimated dietary intakes were comparable to previous surveys in the region that used the same questionnaire (27).

Participants with ACS at baseline were more likely to have a high intake of SFA than patients with stable angina. Dietary intake was estimated at baseline, whereas no such information was collected during follow-up. Thus, any change in dietary habits during follow-up could not be accounted for. However, the

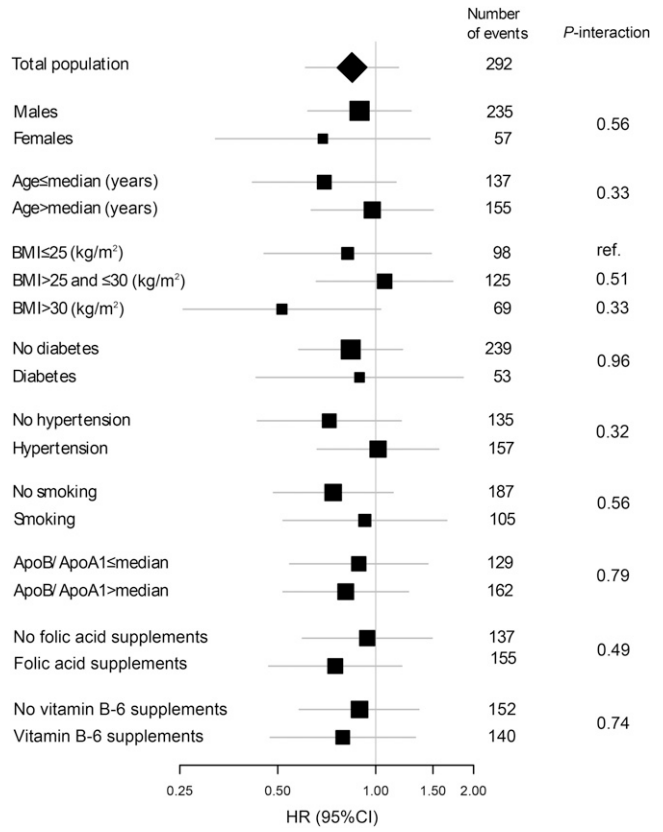

FIGURE 2 Forest plot illustrating HRs for coronary events in patients with coronary artery disease. Risk of coronary events was calculated with use of Cox proportional hazards modeling, comparing the fourth against the first quartile of dietary SFA (as percentage of total energy intake). The model was adjusted for age and sex.

majority of the patients in this selected cohort had stable angina and known disease at baseline. We may therefore assume that most patients willing to change their eating habits toward less intake of saturated fat had already done this before being included in the study because of already having established disease. Participants did not receive any dietary guidance before or at inclusion of this study, and we thus assume that dietary habits during follow-up did not change appreciably. However, because patients in the upper quartile of SFA intake were less frequently treated with conventional medication and had less-stable disease, one cannot exclude that some participants may have changed their habits during follow-up. We thus performed a sensitivity analysis excluding patients with ACS, which provided similar results (data not shown).

Baseline dietary intake of SFA. A 2–3% reduced risk of CVD in the general population has been suggested when 1% of energy from SFA is replaced with PUFA (30). Effects after replacement of SFA with carbohydrates and MUFA have not been clearly shown (3). However, according to the current dietary recommendations by many institutions (including the WHO, Nordic countries), intake of SFA should be restricted to <10% of energy (31). In our study, only 27% of the participants met these dietary recommendations. An overall lower intake is also recommended by the European Society of Cardiology's clinical guidelines on CVD prevention (3), and the AHA diet and lifestyle recommendations state that SFA intake should be <7% of energy (32).

The association between SFA intake and risk of coronary events and all-cause mortality. A recent meta-analysis showed no association between the consumption of SFAs and risk of cardiovascular outcomes among almost 350,000 healthy subjects. In this meta-analysis, 21 epidemiologic prospective cohort studies were evaluated, including generally healthy participants from several countries. The study concluded that there were no associations between dietary intake of SFA and outcome (5). Thus, our results extend recent findings, by suggesting no association between SFA intake and outcome also among patients with CAD who receive standard high-quality treatment. Similar to our study, the mentioned meta-analysis included studies that had used dietary assessments including FFQs (5). The proposed risk association between dietary SFA consumption and CAD development has also been questioned in a recent review (2).

In the current study, participants with the highest dietary SFA intake also had the highest consumption of milk and other dairy products. Dairy products, and especially full-fat milk, are typical sources of SFAs (33), and high consumption of dairy products has been associated with increased risk of CVD (34). However, a recent meta-analysis comprising 17 prospective studies revealed that consumption of milk was not associated with total mortality and may in fact be inversely associated with overall CVD risk (8). A potential protective association between SFA intake through milk consumption and the outcomes of AMI and incident CVD was further strengthened by findings in 2 recent meta-analyses based on prospective cohort studies (9, 35). Furthermore, a recent study concluded that high intake of cheese was associated with a reduced risk of AMI, whereas the use of butter on bread was associated with increased risk (36). In the current study, results were based on total estimated SFA intake, which was not classified according to food items. Despite the fact that the estimates did not change after adjustment for intake of SFA-rich foods, one cannot exclude an effect if the risk analysis had been based on specific SFA sources.

Because a high SFA intake was associated with several CVD risk factors at baseline but with no observed associations to clinical outcomes, this indicates that a high intake of SFA may have protective effects that may off-set potential adverse effects, at least in subgroups. When current prevention guidelines aim to limit the SFA intake to below 7–10% of energy, one can speculate whether this is appropriate in patients with CAD. Notably, most patients were treated with statin therapy, which, in addition to the major effect of lowering LDL cholesterol, also affects the FA composition of plasma phospholipids (37). Thus, we cannot exclude that statin treatment may have influenced the overall findings in this selected cohort of patients with CAD.

In conclusion, dietary intake of SFA was not associated with risk of future coronary outcomes among patients with established CAD. These findings may indicate that a high SFA intake may not be a substantial risk factor among patients with established CAD receiving modern secondary prevention, a hypothesis that needs further evaluation in similar cohorts.

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critically revised the manuscript. NGP had primary responsibility for the final content. All authors read and approved the final manuscript.

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