

The association between dietary saturated fatty acids and ischemic heart disease depends on the type and source of fatty acid in the European Prospective Investigation into Cancer and Nutrition–Netherlands cohort^{1,2}

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ABSTRACT

Background: The association between saturated fatty acid (SFA) intake and ischemic heart disease (IHD) risk is debated.

Objective: We sought to investigate whether dietary SFAs were associated with IHD risk and whether associations depended on 1) the substituting macronutrient, 2) the carbon chain length of SFAs, and 3) the SFA food source.

Design: Baseline (1993–1997) SFA intake was measured with a food-frequency questionnaire among 35,597 participants from the European Prospective Investigation into Cancer and Nutrition–Netherlands cohort. IHD risks were estimated with multivariable Cox regression for the substitution of SFAs with other macronutrients and for higher intakes of total SFAs, individual SFAs, and SFAs from different food sources.

Results: During 12 y of follow-up, 1807 IHD events occurred. Total SFA intake was associated with a lower IHD risk (HR per 5% of energy: 0.83; 95% CI: 0.74, 0.93). Substituting SFAs with animal protein, *cis* monounsaturated fatty acids, polyunsaturated fatty acids (PUFAs), or carbohydrates was significantly associated with higher IHD risks (HR per 5% of energy: 1.27–1.37). Slightly lower IHD risks were observed for higher intakes of the sum of butyric (4:0) through capric (10:0) acid (HR_{SD}: 0.93; 95% CI: 0.89, 0.99), myristic acid (14:0) (HR_{SD}: 0.90; 95% CI: 0.83, 0.97), the sum of pentadecylic (15:0) and margaric (17:0) acid (HR_{SD}: 0.91; 95% CI: 0.83, 0.99), and for SFAs from dairy sources, including butter (HR_{SD}: 0.94; 95% CI: 0.90, 0.99), cheese (HR_{SD}: 0.91; 95% CI: 0.86, 0.97), and milk and milk products (HR_{SD}: 0.92; 95% CI: 0.86, 0.97).

Conclusions: In this Dutch population, higher SFA intake was not associated with higher IHD risks. The lower IHD risk observed did not depend on the substituting macronutrient but appeared to be driven mainly by the sums of butyric through capric acid, the sum of pentadecylic and margaric acid, myristic acid, and SFAs from dairy sources. Residual confounding by cholesterol-lowering therapy and *trans* fat or limited variation in SFA and PUFA intake may explain our findings. Analyses need to be repeated in populations with larger differences in SFA intake and different SFA food sources. *Am J Clin Nutr* 2016;103:356–65.

Keywords: saturated fatty acids, ischemic heart disease, nutrition, epidemiology, follow-up studies

INTRODUCTION

Limiting the intake of dietary SFAs is an important component of recommendations for the prevention of ischemic heart disease (IHD).⁷ High SFA intake is associated with higher blood LDL-cholesterol levels (1), an established risk factor for IHD (2). However, the association between SFAs and IHD is now heavily debated (3–5), in part because evidence on this link appears to originate mainly from results of early ecologic studies (6), secondary prevention studies, and short-term biomarker studies (7–9), whereas a direct link between SFAs and IHD in prospective cohort studies is lacking. A meta-analysis that included 16 cohort studies showed no association between SFA intake and IHD risk, with an RR of 1.07 (95% CI: 0.96, 1.19) in the highest compared with the lowest quintile of intake (10). An update of this meta-analysis, including 4 additional prospective cohort studies (11) as well as a meta-analysis of a selection of 12 cohort studies (12), observed similar null associations with RRs of 1.03 (95% CI: 0.98, 1.07) (11) and 1.06 (95% CI: 0.95, 1.17)

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² Supplemental Figures 1–8 and Supplemental Tables 1–4 are 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://ajcn.nutrition.org>.

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⁷ Abbreviations used: EPIC-NL, European Prospective Investigation into Cancer and Nutrition–Netherlands; FFQ, food-frequency questionnaire; GI, glycemic index; IHD, ischemic heart disease; MESA, Multi-Ethnic Study of Atherosclerosis; MORGEN, Monitoring Project on Risk Factors for Chronic Diseases; NHS, Nurses’ Health Study.

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(12). However, the association between SFAs and IHD may depend on several factors that were not taken into account in all 3 meta-analyses.

First, the association may depend on the macronutrients that replace SFAs in the diet. A pooled analysis of 11 cohort studies showed that the association between SFAs and IHD differed when SFAs were replaced by PUFAs as opposed to carbohydrates or MUFAs (13).

Second, specific types of SFAs that differ in carbon chain length may also differ in their effects on blood lipids and thereby on IHD risk. SFAs consist predominantly of the long-chain fatty acids stearic acid (18:0), palmitic acid (16:0), myristic acid (14:0), and lauric acid (12:0). A meta-analysis of 60 controlled trials showed that compared with carbohydrates these different types of SFAs vary in their effect on blood lipid levels (1). The NHS (Nurses' Health Study) is the only prospective cohort study to our knowledge that has specifically addressed the relation between dietary SFAs differing in carbon chain length and IHD (14). This cohort study observed a moderately increased IHD risk for the sum of longer-chain SFAs (lauric acid through stearic acid), whereas for short- to medium-chain SFAs [butyric (4:0) through capric (10:0) acid] no associations with IHD were observed.

Finally, different food sources of SFAs may modulate the effect of SFAs on IHD risk. The major food sources of SFAs are of animal origin, including meat and dairy products. In addition to the difference in specific SFAs in these products, other nutrients in these foods (and the way they interact with SFAs) could affect the risk of IHD. Accordingly, in the MESA (Multi-Ethnic Study of Atherosclerosis) cohort, each 5-g/d intake of dairy SFAs was associated with a 16% lower risk of IHD, whereas each 5-g/d intake of meat SFAs was related to a 29% higher risk of IHD (15).

In this study we examined the association between SFA intake and incident IHD risk and whether associations differed based on 1) the type of macronutrient that replaces SFAs, 2) the type of SFA (differing in carbon chain length), and 3) the food source of SFAs.

METHODS

Study population

The EPIC-NL (European Prospective Investigation into Cancer and Nutrition–Netherlands) cohort consists of the Prospect-EPIC and MORGEN (Monitoring Project on Risk Factors for Chronic Diseases) cohorts. Both cohorts were set up simultaneously between 1993 and 1997 and recruited a total of 40,011 participants. The design and rationale of EPIC-NL are described in detail elsewhere (16). In brief, the Prospect-EPIC study included 17,357 women aged 49–70 y who lived in or near Utrecht and who participated in a nationwide breast cancer screening program. The MORGEN cohort consisted of 22,654 men and women aged 20–65 y selected from random samples of the Dutch population in 3 Dutch towns (Doetinchem, Amsterdam, and Maastricht). All participants signed informed consent before inclusion. Both studies complied with the Declaration of Helsinki. Prospect-EPIC was approved by the institutional review board of the University Medical Center Utrecht, and MORGEN was approved by the medical ethics committee of the Netherlands Organization for Applied Scientific Research (TNO). At baseline, a general and a food-frequency questionnaire (FFQ) were administered, and a physical

examination was performed that included blood pressure measurements, anthropometric data, and blood sampling (16).

For this study we excluded subjects who withheld permission for linkage with vital status and death registries ($n = 2717$); subjects with missing questionnaires ($n = 172$); subjects with an implausible energy intake based on the ratio of reported energy intake to estimated basal metabolic rate, i.e., the top or bottom 0.5% of the ratio ($n = 342$); and prevalent cases of cardiovascular disease at baseline ($n = 1183$), leaving a total of 35,597 subjects for analysis.

Intake of foods, saturated fat, and other nutrients

Food intake was assessed by a self-administered FFQ that measured the mean consumption frequency of 79 main food categories during the year before study enrollment (17). This FFQ allowed for the estimation of the habitual intake of 178 food items. Portion sizes were estimated with use of photographs of several food items. Based on frequencies and portion sizes, the mean daily intake (g/d) was calculated for each subject individually. The intakes of all macronutrients and micronutrients were then calculated based on an updated version of the computerized Dutch food composition table 1996 (18). Intakes of SFAs differing in chain length were calculated based on the Dutch food composition table 1998 (digital update; available on request from the National Institute for Public Health and the Environment). Before the start of the study, the FFQ was validated against twelve 24-h recalls among 121 men and women (19). Pearson correlation coefficients showed good relative validity for intakes of fat (men: 0.63; women: 0.61), carbohydrates (men: 0.76; women: 0.74), and protein (men: 0.76; women: 0.71) (19). Spearman rank correlation coefficients showed reasonable to good validity for intakes of total SFAs and the individual SFAs included in this study (butyric acid through stearic acid), ranging from 0.47 to 0.71 in men and from 0.30 to 0.66 in women (J Praagman et al., unpublished results, 2015). Furthermore, the FFQ showed good reproducibility for the measurement of both total and individual SFAs, with intraclass correlation coefficients ranging from 0.58 to 0.73 in men and from 0.66 to 0.83 in women.

Because of very low intakes of butyric, caproic (6:0), caprylic (8:0), and capric acids, these SFAs were summed and evaluated as short- to medium-chain SFAs in this study. For the same reason, intakes of pentadecylic (15:0) and margaric (17:0) acids were summed and evaluated as such. Based on the food groups that are predefined in the Dutch food composition table 1996 (18), we identified the following 7 mutually exclusive food groups that together contributed ~82% of the mean total SFA intake in the study population: cheese, meat, milk and milk products, fats, butter, cakes, and snacks. We separated the fats group into 2 subgroups based on SFA content: hard and solid fats (including margarines and fats in wrappers and solid frying fats, all of which contained ≥ 20 g SFAs/100 g of product) and soft and liquid fats (including soft margarines, vegetable oils, liquid fats, and frying oils, all of which contained < 20 g SFAs/100 g of product). The remaining food groups, which each contributed $< 2.5\%$ to the total SFA intake, were aggregated and labeled as other sources. Total SFAs was defined as the sum of individual fatty acids with only single bonds between the carbon atoms in the fatty acid chain. SFA intake from each food group was calculated by summing the amount of total SFAs present in all

foods included in that group. Total carbohydrates comprised all types of carbohydrates except dietary fiber. *cis* MUFAs included fatty acids with one double carbon bond with a *cis* configuration (**Supplemental Figure 1**). Total PUFAs included fatty acids with multiple double bonds and with *cis* and/or *trans* configurations (**Supplemental Figure 2**). *trans* Fat was the sum of all *trans* MUFAs and *trans* PUFAs. Protein intake was divided in animal- and vegetable-derived protein based on whether the food source was of animal or vegetable origin.

Alcohol consumption was categorized as follows: 0, 0.1–6.0, 6.1–12.0, 12.1–24.0, and >24 g/d for women and 0, 0.1–6.0, 6.1–12.0, 12.1–24.0, 24.1–60.0, and >60 g/d for men. The international table compiled by Foster-Powell et al. (20) was used to obtain the glycemic index (GI) of foods. Intake variables of total SFAs, SFAs differing in carbon chain lengths, SFAs from specific food groups, and other macronutrient intake variables were expressed as percentages of total energy intake. Other nutrients were adjusted for total energy intake through use of the residual method (21).

Other baseline assessments

Information on demographic characteristics, the presence of chronic diseases, and cardiovascular disease risk factors was obtained with the general questionnaire at baseline. Smoking status was categorized as never, former, or current. Education was defined in 3 categories: low (primary education up to completing intermediate vocational education), intermediate (up to higher secondary education), or high (higher vocational education and university). On the basis of information about the duration and types of physical activity, which were assessed through a validated questionnaire, the Cambridge physical activity index was calculated (22), and participants were divided into 4 categories for physical activity level (inactive, moderately inactive, moderately active, and active).

During the physical examination at baseline body weight, height and waist circumference were measured. BMI was calculated as weight divided by height squared (kg/m^2). Mean systolic and diastolic blood pressure were obtained by calculating the mean of 2 sequential measurements that were performed in the supine position with a cuff on the left arm through use of either a boso oscillomat (Bosch & Son) (Prospect-EPIC) or a random-zero sphygmomanometer (MORGEN). Hypertension was considered present when at least one of the following criteria were met: systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, self-reported use of antihypertensive medication, or self-reported physician-diagnosed hypertension. Total cholesterol concentrations were measured with use of enzymatic methods, and HDL and LDL cholesterol were measured with use of a standard homogeneous assay with an enzymatic endpoint.

Ascertainment of IHD

Morbidity data were obtained from the Dutch Center for Health Care Information, which holds a standardized computerized registry of hospital discharge diagnoses. Admission files from general and university hospitals in the Netherlands have been stored continuously since 1990. The records contain data on sex, date of birth, dates of admission and discharge, at least 1 principal diagnosis, and up to 9 optional additional diagnoses. All events were coded by qualified medical administrative personnel in the hospitals according to the International Classification of Diseases,

Ninth Revision, Clinical Modification. The National Medical Registry checked the data and collected them in the hospital discharge diagnosis database, which is linked to the cohort based on information of birthdate, sex, postal code, and general practitioner with a validated probabilistic method (23). Information on vital status was obtained through digital linkage with municipal registries, and causes of death were obtained through linkage with Statistics Netherlands. We identified all first-ever IHD events (International Classification of Diseases, Ninth Revision, Clinical Modification: 410–414, 427.5, 798.1, 798.2, and 798.9). Follow-up was complete until 1 January 2008.

Data analysis

Baseline characteristics of the study population were calculated across quintiles of total SFA intake in percentage of energy and presented as means with SDs for normally distributed variables, medians with IQRs for variables that were not normally distributed, or percentages for categorical variables. Pearson correlations between intakes of total SFAs, SFAs from food sources, and SFAs differing in carbon chain length were calculated.

Person-years were calculated as the time between the date of the study entry and the date of the first-ever IHD event, date of death, loss to follow-up, or end of follow-up (1 January 2008), whichever came first.

We used Cox proportional hazard regression models to calculate HRs with 95% CIs for the association between SFA intake and risk of IHD incidence (fatal and nonfatal). Total SFA intake was evaluated per 5% of energy and entered as a continuous variable into the Cox regression models. In addition to a crude model (model 1), 3 models were constructed to adjust for potential confounding. As potential confounders, we considered known risk factors for IHD and covariables that were associated with SFA intake and IHD risk in our population. Model 2 was adjusted for age. Model 3 was additionally adjusted for sex, total energy intake, BMI, waist circumference, educational level, physical activity index, smoking status, and alcohol intake (in categories). Model 4 was additionally adjusted for intakes of *trans* fat, animal protein, and vegetable protein (all in percentage of energy) and for energy-adjusted intakes of vitamin C, fiber, and dietary cholesterol. The HRs for SFA intakes after adjustment for models 1, 2, and 3 can be interpreted as the IHD risk for an increased intake of energy from total SFAs (or SFA type) at the expense of intakes of energy from all other types of fats, carbohydrates, and proteins. Because of additional adjustment for *trans* fat, animal protein, and vegetable protein (and the sum of other SFAs), the HRs after adjustment for model 4 can be interpreted as the IHD risk for an increased intake of energy from total SFAs (or SFA type) at the expense of intakes of energy from PUFAs, *cis* MUFAs, and carbohydrates.

To estimate the risk of IHD when energy intake from SFAs was substituted by an equal amount of energy from each of the other macronutrients, all 4 Cox models were converted into substitution models. These models included intakes of PUFAs, *cis* MUFAs, *trans* fat, total carbohydrates, animal protein, and vegetable protein (all expressed per 5% of energy), as well as total energy intake from all macronutrients except energy from alcohol consumption. By excluding SFA intake from the models, the HR for each macronutrient can be interpreted as the difference in IHD risk for each additional intake of 5% of energy from that particular macronutrient at the expense of 5% of energy from SFAs (21). To

distinguish between the quality of carbohydrates, subjects were ranked based on their GI intake. The analyses in which SFAs were substituted with total carbohydrates were then stratified for tertiles of this GI distribution (24). In this way, the substitution of SFAs with carbohydrates in GI tertiles 1, 2, and 3 represented the substitution of SFAs with carbohydrates in subjects with a low-, medium-, and high-GI diet, respectively. Intakes of SFAs differing in carbon chain length or SFAs from different food sources were separately evaluated by entering them into the Cox models as continuous variables per 1 SD of intake. The SDs for the sum of butyric through capric acid, lauric acid, myristic acid, palmitic acid, the sum of pentadecylic and margaric acid, and stearic acid were 0.27%, 0.24%, 0.44%, 1.19%, 0.11%, and 0.66% of energy, respectively. The SDs for SFAs from butter, cheese, milk and milk products, meat, cakes, snacks, hard and solid fats, soft and liquid fats, and other sources were 1.42%, 1.95%, 1.45%, 1.44%, 0.83%, 0.40%, 1.25%, 0.50%, and 1.06% of energy, respectively. The 4 previously mentioned Cox models were used, with additional adjustment in model 4 for the sum of all other consumed SFAs. To identify whether nonlinear associations existed, quadratic terms of the SFA intake variables were included in the fourth model. *P* values for quadratic terms were between 0.1 and 0.9 for all SFA intake variables except for SFAs from milk. However, the construction of restricted cubic splines showed no significant nonlinear association between SFAs from milk and IHD (*P* = 0.06) (**Supplemental Figure 3**). The proportional hazards assumption was tested by calculating Schoenfeld residuals and visual inspection of log-log plots, which showed no significant deviations. We performed a series of sensitivity analyses and checked for possible effect modification by sex by adding a product term of sex with SFAs to the final models. To check whether blood cholesterol or blood pressure were possible intermediates, we adjusted the fourth model for the baseline total cholesterol:HDL cholesterol ratio or systolic blood pressure. To minimize the possibility of reverse causation, we repeated the analyses in the population after excluding the first 2 y of follow-up. Because baseline dietary data could be unrelated to events occurring after a very long follow-up time, we repeated our analyses for the first 5 y of follow-up only by censoring everyone in the study population who in the first 5 y did not experience an event and was not lost to follow-up. Furthermore, we performed separate analyses for nonfatal IHD events (*n* = 1649) only because previously published studies have suggested that associations may differ for IHD mortality compared with nonfatal IHD (13). Because of the low number of IHD deaths in our population (*n* = 158), we did not perform a separate analysis for IHD mortality only. We repeated the analyses with age as the underlying time axis and additional stratification by birth year in 5-y intervals to adjust for calendar effects (25). Finally, we checked whether differences in associations were observed between the substitution of SFAs with *n*-3 PUFAs compared with *n*-6 PUFA, as suggested previously (26). All statistical analyses were executed in SAS 9.2 (SAS Institute), and *P* values <0.05 (2-sided) were considered statistically significant.

RESULTS

Baseline characteristics

The baseline characteristics of the total study population are presented in **Table 1**. Compared with subjects with the lowest

intake, subjects with a high intake of SFAs were more likely to be older women who smoked and who had a higher BMI and waist circumference, higher blood pressure, higher total cholesterol:HDL cholesterol ratio, and less education and physical activity. Subjects with high SFA intake also reported higher intakes of *cis* MUFAs, *trans* fat, cholesterol, animal protein, and calcium and lower intakes of carbohydrates, vegetable protein, fiber, vitamin C, and alcohol.

The mean baseline intake of total SFAs in the population was $15.0\% \pm 2.7\%$ of energy. More than 97% of the population exceeded the upper intake limit of 10% of energy/d as recommended by the Health Council of the Netherlands (27). Most SFA intake was represented by the long-chain SFAs palmitic acid (51.2%) and stearic acid (25.5%) (**Figure 1**). The main food sources of SFAs were cheese (17.4%), milk and milk products (16.6%), meat (17.5%), hard and solid fats (8.6%), and butter (7.3%) (**Figure 2**). Pearson correlation coefficients of intakes of all individual SFAs ranged between 0.30 and 0.63, except for palmitic and stearic acids, which were highly correlated (*r* = 0.92) because of shared food sources (**Table 2**). The main food sources of palmitic acid and stearic acid were meat and cheese. Milk and milk products and cheese were the top 2 contributors of the sum of butyric through capric acid, lauric acid, myristic acid, and the sum of pentadecylic and margaric acids (**Supplemental Figure 4**). The percentages of *cis* MUFAs and PUFAs provided by the predefined SFA food groups can be found in **Supplemental Figures 5 and 6**.

Total SFA intake and IHD risk

Over a median follow-up time of 12.2 y, 1807 incident IHD cases were documented; 158 (8.7%) of these were fatal. After multivariable adjustment for lifestyle and dietary factors (model 4), a higher intake of energy from SFAs was significantly associated with a 17% lower IHD risk (HR per 5% of energy: 0.83; 95% CI: 0.74, 0.93) (**Table 3**). **Table 4** presents the HRs for the association between a higher intake of energy from carbohydrates, *cis* MUFAs, PUFAs, or protein at the expense of an equal amount of energy from SFAs and incident IHD. After full adjustment (model 4), the substitution of SFAs with total carbohydrates (HR_{5en%}: 1.23; 95% CI: 1.09, 1.40), *cis* MUFAs (HR_{5en%}: 1.30; 95% CI: 1.02, 1.65), PUFAs (HR_{5en%}: 1.35; 95% CI: 1.14, 1.61), or animal protein (HR_{5en%}: 1.37; 95% CI: 1.14, 1.65) was significantly associated with higher IHD risks. We observed differences in IHD risk when SFAs were substituted with carbohydrates differing in GI values. The higher IHD risk for substitution of SFAs with high-GI carbohydrates was statistically significant (HR_{GI >56}: 1.27; 95% CI: 1.03, 1.56), whereas the IHD risk for substitution with low-GI carbohydrates was not statistically significant (HR_{GI <53}: 1.14; 95% CI: 0.91, 1.43). No significant association with IHD risk was observed for the substitution of SFAs with vegetable protein (HR_{5en%}: 0.81; 95% CI: 0.57, 1.17).

Intake of SFAs differing in carbon chain length and risk of IHD

Table 3 shows the HRs for the associations between intakes of SFAs differing in carbon chain length and risk of IHD. After

TABLE 1Baseline characteristics across quintiles of the saturated fat intake (en%) in 35,597 subjects from the EPIC-NL cohort¹

	Q1: 11.7 (2.3–12.8)	Q2: 13.6 (12.8–14.2)	Q3: 14.9 (14.2–15.5)	Q4: 16.2 (15.5–17.1)	Q5: 18.4 (17.1–28.7)
Subjects, <i>n</i>	7119	7120	7119	7120	7119
Age, y	48.1 ± 12.5 ²	47.8 ± 12.5	48.5 ± 12.0	49.7 ± 11.5	52.3 ± 10.2
Male, %	28	29	26	23	19
High educational level, %	24	23	21	18	15
BMI, kg/m ²	25.3 ± 3.8	25.5 ± 3.8	25.6 ± 4.0	25.8 ± 4.0	26.1 ± 4.3
Waist circumference, cm	84.5 ± 11.2	85.0 ± 11.3	85.1 ± 11.3	85.4 ± 11.4	85.7 ± 11.8
High physical activity, %	43	44	43	42	39
Current smokers, %	29	29	28	30	34
Hypertension, %	37	36	36	37	39
Blood pressure, mm Hg					
Systolic	126.4 ± 19.2	125.6 ± 18.4	125.7 ± 18.7	126.6 ± 19.0	127.5 ± 19.4
Diastolic	77.9 ± 10.8	77.7 ± 10.5	77.7 ± 10.7	78.2 ± 10.6	78.1 ± 10.6
Cholesterol, mmol/L	5.6 ± 1.2	5.6 ± 1.1	5.6 ± 1.1	5.7 ± 1.1	5.9 ± 1.1
HDL-C, mmol/L	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4
Total cholesterol:HDL-C	4.2 ± 1.5	4.3 ± 1.5	4.2 ± 1.5	4.3 ± 1.5	4.4 ± 1.5
Energy intake, kcal	1910 ± 596	2043 ± 602	2097 ± 602	2099 ± 597	2106 ± 606
Saturated fat, g/d	24.2 ± 8.3	30.8 ± 9.2	34.7 ± 10.0	37.9 ± 10.9	44.0 ± 13.2
Sum of butyric (4:0) through capric (10:0) acid, en%	0.4 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.7 ± 0.2	0.9 ± 0.3
Lauric acid (12:0), en%	0.4 ± 0.2	0.5 ± 0.2	0.6 ± 0.2	0.7 ± 0.2	0.8 ± 0.2
Myristic acid (14:0), en%	1.0 ± 0.2	1.2 ± 0.2	1.4 ± 0.2	1.6 ± 0.3	2.0 ± 0.4
Palmitic acid (16:0), en%	5.1 ± 0.6	6.0 ± 0.4	6.5 ± 0.4	7.1 ± 0.4	8.0 ± 0.7
Sum of pentadecylic (15:0) and margaric (17:0) acid, en%	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.4 ± 0.1	0.5 ± 0.1
Stearic acid (18:0), en%	2.5 ± 0.4	2.9 ± 0.3	3.2 ± 0.3	3.5 ± 0.3	4.0 ± 0.5
SFAs from source, %					
Butter	3.7 (2.0–6.1) ³	4.1 (2.5–6.7)	4.4 (2.7–7.6)	4.9 (3.1–9.7)	6.6 (3.5–17.2)
Cheese	13.5 (6.7–21.1)	14.6 (8.5–22.3)	15.6 (9.5–23.4)	16.5 (10.2–24.5)	18.6 (11.2–27.8)
Milk and milk products	15.7 (9.0–23.4)	15.8 (9.9–22.5)	15.9 (10.1–22.6)	15.7 (10.3–21.9)	14.1 (8.8–20.8)
Meat	16.9 (10.5–24.2)	17.3 (11.5–23.6)	17.3 (11.4–23.3)	16.9 (11.3–22.5)	15.7 (10.3–21.6)
Cakes	5.1 (2.3–9.3)	5.6 (2.9–9.6)	5.8 (3.0–9.6)	5.7 (3.0–9.5)	5.0 (2.4–8.5)
Snacks	2.3 (0.8–5.0)	2.4 (0.9–4.5)	2.2 (0.9–4.2)	1.9 (0.8–3.6)	1.3 (0.5–2.6)
Hard, solid fats	4.5 (1.4–8.8)	5.9 (2.5–10.6)	7.1 (3.2–11.9)	8.2 (3.9–14.0)	9.8 (4.6–16.7)
Soft, liquid fats	5.3 (2.8–8.5)	4.7 (2.4–7.4)	4.3 (2.2–6.9)	3.6 (1.6–6.0)	2.3 (0.7–4.5)
Other	21.8 (16.9–27.7)	19.3 (15.0–24.5)	17.2 (13.5–22.2)	15.5 (11.9–19.8)	12.6 (9.4–16.7)
PUFA, en%	6.7 ± 1.9	6.9 ± 1.8	7.0 ± 1.7	6.9 ± 1.7	6.7 ± 1.7
<i>cis</i> MUFA, en%	8.0 ± 1.7	9.0 ± 1.6	9.6 ± 1.6	10.2 ± 1.6	11.1 ± 1.8
<i>trans</i> Fat, en%	1.0 ± 0.4	1.2 ± 0.4	1.3 ± 0.4	1.4 ± 0.5	1.6 ± 0.5
Animal protein, en%	9.2 ± 2.8	9.6 ± 2.5	9.9 ± 2.4	10.2 ± 2.3	10.8 ± 2.4
Vegetable protein, en%	6.0 ± 1.2	5.8 ± 1.0	5.6 ± 0.9	5.4 ± 0.8	5.0 ± 0.8
Carbohydrates, en%	49.5 ± 7.0	47.0 ± 5.5	45.4 ± 5.0	43.6 ± 4.8	40.5 ± 5.0
Glycemic index ⁴	54.2 (51.4–56.9)	54.8 (52.4–57.2)	54.9 (52.6–57.2)	55.0 (52.7–57.2)	55.1 (52.7–57.3)
Alcohol, g/d	8.6 (1.1–24.0)	6.4 (1.0–18.5)	5.2 (0.9–14.9)	4.2 (0.7–12.2)	2.9 (0.3–10.3)
Cholesterol, ⁴ mg/d	182.1 ± 54.1	203.7 ± 52.2	216.3 ± 49	230.4 ± 52.4	255.9 ± 58.5
Fiber, ⁴ g/d	24.9 ± 5.7	24.1 ± 4.7	23.4 ± 4.4	22.8 ± 4.2	21.7 ± 4.2
Vitamin C, ⁴ mg/d	128.5 ± 56.0	114.8 ± 44.0	108.4 ± 40.8	102.8 ± 38.7	94.0 ± 36.1

¹*P* values for trends across quintiles were obtained from linear regression analysis (continuous variables) or the chi-square test (categorical variables) and were <0.0001 for all characteristics except for diastolic blood pressure (*P* = 0.01). en%, percentage of energy; EPIC-NL, European Prospective Investigation into Cancer and Nutrition–Netherlands; HDL-C, HDL cholesterol; Q, quintile.

²Mean ± SD (all such values).

³Median; IQR in parentheses (all such values).

⁴Adjusted for total energy intake.

adjustment for lifestyle and dietary factors (model 4), slightly but significantly lower IHD risks were observed for each additional SD of intake of energy from short- to medium-chain SFAs (HR: 0.93; 95% CI: 0.89, 0.99), myristic acid (HR: 0.90; 95% CI 0.83, 0.97), and the sum of pentadecylic and margaric acids (HR: 0.91; 95% CI: 0.83, 0.99). No significant associations were observed for intakes of lauric (HR: 0.97; 95% CI: 0.91, 1.02), palmitic (HR: 1.00; 95% CI: 0.91, 1.10), or stearic (HR: 1.05; 95% CI: 0.97, 1.14) acid.

Intake of SFAs from food sources and risk of IHD

After adjustment for lifestyle and dietary factors (model 4), slightly but significantly lower IHD risks were found for each additional SD of intake of SFAs from butter (HR: 0.94; 95% CI: 0.90, 0.99), SFAs from cheese (HR: 0.91; 95% CI: 0.86, 0.97), and SFAs from milk (HR: 0.92; 95% CI: 0.86, 0.97) (Table 5). No significant associations were observed for intakes of SFAs from other food sources.



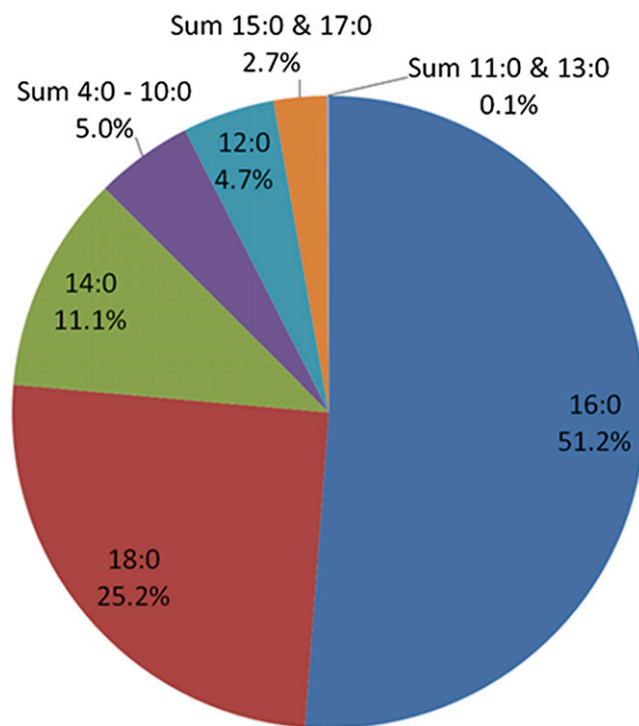


FIGURE 1 Contributions (in percentages) of SFA types to the baseline total SFA intake in 35,597 men and women of the European Prospective Investigation into Cancer and Nutrition–Netherlands cohort.

Sensitivity analyses

We observed no significant effect modification by sex (P values all between 0.2 and 0.9), except for SFAs from cheese ($P = 0.03$). Stratification for sex in the model for SFAs from cheese showed that the lowered risk was stronger in women (HR: 0.89; 95% CI: 0.83, 0.96) than in men (HR: 0.97; 95% CI: 0.88, 1.07). Our results did not materially change after including the baseline total cholesterol:HDL cholesterol ratio or systolic blood pressure in the models (**Supplemental Tables 1 and 2**), excluding the first 2 y of follow-up (**Supplemental Table 3**), analyzing the first 5 y of follow-up only (**Supplemental Table 4**), or analyzing nonfatal IHD events only (data not shown). The results for the analysis with age as the underlying time axis did not differ from the analysis with follow-up time as the time axis (e.g., HR per 5% energy of total SFA intake: 0.83; 95% CI: 0.74, 0.93). In addition, distinguishing between $n-3$ PUFAs (mean intake: 1.2 ± 0.5 g/d) and $n-6$ PUFAs (mean intake: 10.7 ± 4.9 g/d) as a replacement for SFAs did not yield different results (data not shown).

DISCUSSION

In this prospective cohort study in 35,597 Dutch men and women, a higher intake of total SFAs was associated with a lower risk of incident IHD. This association did not depend on the substituting macronutrient but rather on the chain length and food source of SFAs, with slightly lower IHD risks for higher intakes of the sum of butyric through capric acid, myristic acid, the sum of pentadecylic and margaric acids, and SFAs from dairy sources (milk and milk products, cheese, and butter).

Strengths of this study include the prospective study design, long follow-up period, large number of IHD events, and

robustness of findings in sensitivity analyses. Although we adjusted for a wide range of potential confounders, we cannot exclude that residual confounding partly explains our findings. For instance, our study lacks information on the initiation of cholesterol-lowering therapy during follow-up. It is conceivable that individuals with high SFA intake have high cholesterol (1) and will become eligible for cholesterol-lowering therapy during follow-up. In $\sim 15\%$ of the EPIC-NL cohort that is examined every 5 y, it was indeed observed that cholesterol-lowering therapy increased from $<2\%$ at baseline to $>10\%$ at 10 y of follow-up (28). Cholesterol-lowering therapy is a confounder and would reduce IHD risk substantially (29), which may at least partially explain the observed reduced IHD risk associated with SFA intake. Another limitation is that SFA intake was measured with use of an FFQ, a tool that relies on self-reporting. However, a validation study showed reasonable to good reproducibility and relative validity for SFA intake (J Praagman et al., unpublished results, 2015).

Three meta-analyses, including the study results of a total of 22 observational cohorts, observed no association between SFA intake and IHD incidence (10–12). We also did not observe an increased IHD risk with higher total SFA intake in this cohort study but found instead a reduced risk. Although this differs from the meta-analyses, it has been reported previously. In the MESA cohort, an even lower IHD risk was observed (HR per 5% of energy: 0.73; 95% CI: 0.56, 0.96) (15). Neither the MESA cohort study nor the meta-analyses (10–12) considered the macronutrients that substituted SFAs, which may affect the association between SFAs and IHD (30). Our results for the substitution of SFAs with *cis* MUFAs (13), total carbohydrates (13), and carbohydrates differing in GI (24) are essentially in line with most previous cohort studies (13, 24), although a recent

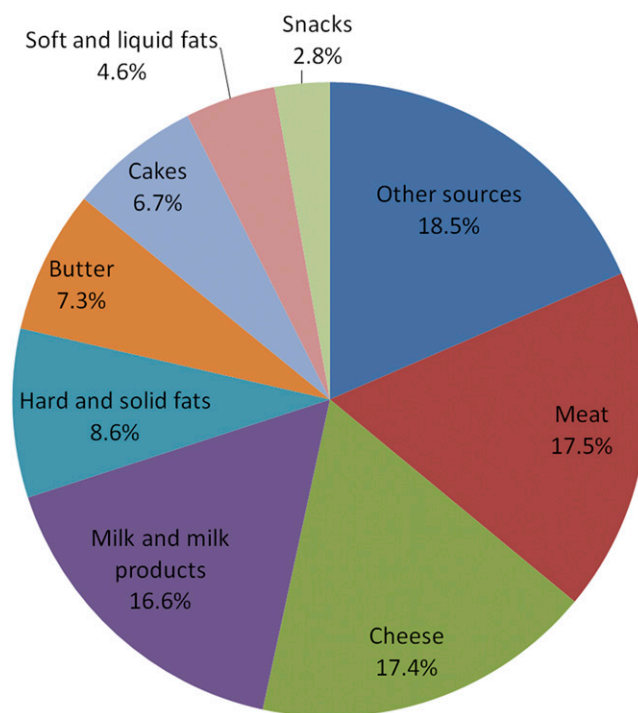


FIGURE 2 Contributions (in percentages) of food groups to the baseline total SFA intake in 35,597 men and women of the European Prospective Investigation into Cancer and Nutrition–Netherlands cohort.



TABLE 2

Pearson correlation coefficients between intakes of total SFAs, SFAs from its main food sources, and individual SFAs (all in en%) in 35,597 subjects from the EPIC-NL cohort¹

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)
(1) Total SFA	1														
(2) Sum of butyric (4:0) to capric (10:0) acid	0.59	1													
(3) Lauric acid (12:0)	0.55	0.73	1												
(4) Myristic acid (14:0)	0.82	0.84	0.72	1											
(5) Palmitic acid (16:0)	0.94	0.40	0.35	0.68	1										
(6) Sum pentadecylic (15:0) and margaric (17:0) acids	0.75	0.92	0.59	0.92	0.63	1									
(7) Stearic acid (18:0)	0.88	0.30	0.34	0.55	0.92	0.50	1								
(8) SFAs from butter	0.44	0.16	0.22	0.48	0.41	0.28	0.32	1							
(9) SFAs from cheese	0.42	0.74	0.37	0.57	0.29	0.76	0.23	0.01 ²	1						
(10) SFAs from milk	0.24	0.49	0.48	0.48	0.13	0.40	0.03	-0.04	-0.10	1					
(11) SFAs from meat	0.26	-0.27	-0.20	-0.08	0.45	-0.03	0.51	-0.03	-0.18	-0.16	1				
(12) SFAs from cakes	0.17	0.21	0.41	0.18	0.08	0.12	0.09	-0.03	0.01 ³	0.02 ²	-0.15	1			
(13) SFAs from snacks	-0.03	-0.25	-0.21	-0.23	0.08	-0.23	0.09	-0.10	-0.16	-0.18	0.04	-0.10	1		
(14) SFAs from hard, solid fats	0.41	-0.09	0.02	0.15	0.41	0.04	0.37	0.03	-0.10	0.00 ⁴	0.18	-0.04	-0.03	1	
(15) SFAs from soft, liquid fats	-0.11	-0.11	-0.08	-0.17	-0.15	-0.15	-0.13	-0.08	-0.03	-0.10	-0.04	-0.07	-0.08	-0.20	1
(16) SFAs from other sources	-0.01 ²	-0.29	-0.20	-0.28	0.04	-0.31	0.18	-0.07	-0.19	-0.23	-0.17	-0.03	0.32	-0.09	-0.06

¹All *P* values are <0.0001 unless stated otherwise. en%, percentage of energy; EPIC-NL, European Prospective Investigation into Cancer and Nutrition–Netherlands.

²*P* < 0.05

³*P* = 0.2

⁴*P* = 0.7

updated analysis in the NHS and Health Professionals Follow-Up Study showed lower IHD risks for the replacement of SFAs with MUFAs and with carbohydrates from whole grains (31). A meta-analysis of trials showed no significant association between replacing SFAs with MUFAs, carbohydrates, or protein and IHD events; however, these results were based on a limited number of studies and events with high heterogeneity (32). To our knowledge, no previous cohort studies have investigated the association between the substitution of SFAs with animal protein and IHD risk. The inverse association between the sub-

stitution of SFA with PUFAs and IHD risk in our study conflicts with a consistent body of evidence from previous trials that investigated the effects on blood lipids (1) or IHD outcomes (32, 33), as well as evidence from cohort studies (13, 31, 34). All these previous studies showed inverse associations between the substitution of SFAs with PUFAs and IHD risk, but one study did not show these associations (35). We are not certain what causes the discrepancy between our results and those from the other studies. Perhaps our analyses were limited by the small SFA intake range (IQR: 13.2–16.6% of energy) at a high mean

TABLE 3

Multivariable HRs with 95% CIs for the associations between the intake of total and individual SFAs with incidence of ischemic heart disease in 35,597 subjects from the EPIC-NL cohort¹

	Median intake, en%	HR expressed per en%	Model 1 ²	Model 2 ³	Model 3 ⁴	Model 4 ⁵
Total SFAs	14.9	5	1.14 (1.05, 1.24)	1.02 (0.94, 1.10)	0.94 (0.86, 1.02)	0.83 (0.74, 0.93)
Sum of butyric (4:0) to capric (10:0) acid	0.62	0.27	0.99 (0.94, 1.03)	0.85 (0.81, 0.90)	0.95 (0.90, 1.00)	0.93 (0.89, 0.99) ⁶
Lauric acid (12:0)	0.61	0.24	1.04 (1.00, 1.09)	0.88 (0.84, 0.93)	0.96 (0.91, 1.00)	0.97 (0.91, 1.02) ⁶
Myristic acid (14:0)	1.44	0.44	1.05 (1.01, 1.10)	0.92 (0.87, 0.96)	0.95 (0.90, 0.99)	0.90 (0.83, 0.97) ⁶
Palmitic acid (16:0)	6.5	1.19	1.06 (1.02, 1.11)	1.05 (1.01, 1.10)	0.98 (0.94, 1.03)	1.00 (0.91, 1.10) ⁶
Sum pentadecylic (15:0) and margaric (17:0) acids	0.35	0.11	1.03 (0.99, 1.08)	0.91 (0.87, 0.95)	0.96 (0.91, 1.01)	0.91 (0.83, 0.99) ⁶
Stearic acid (18:0)	3.2	0.66	1.08 (1.03, 1.13)	1.08 (1.03, 1.12)	1.00 (0.95, 1.04)	1.05 (0.97, 1.14) ⁶

¹Obtained from Cox proportional hazards regression models. en%, percentage of energy; EPIC-NL, European Prospective Investigation into Cancer and Nutrition–Netherlands.

²Crude model.

³Adjustment for age.

⁴Additional adjustment for sex, total energy, BMI, waist circumference, educational level, physical activity level, smoking status, and alcohol intake (categories).

⁵Additional adjustment for *trans* fat, vegetable protein, and animal protein (all in en%) and energy-adjusted intakes of cholesterol, fiber, and vitamin C.

⁶Additional adjustment for the sum of other SFAs.



TABLE 4

Multivariable HRs with 95% CIs for the association between the consumption of 5% of energy from different macronutrients at the expense of 5% of energy from total SFAs while keeping total energy intake constant and incident ischemic heart disease risk in 35,597 subjects from the EPIC-NL cohort¹

Macronutrient for SFAs	Model 1 ²	Model 2 ³	Model 3 ⁴	Model 4 ⁵
Carbohydrates	0.84 (0.75, 0.95)	1.31 (1.16, 1.48)	1.19 (1.05, 1.34)	1.23 (1.09, 1.40)
Carbohydrates with a low GI ⁶	0.90 (0.73, 1.11)	1.26 (1.02, 1.56)	1.14 (0.92, 1.41)	1.14 (0.91, 1.43)
Carbohydrates with a medium GI ⁶	0.89 (0.71, 1.11)	1.50 (1.18, 1.89)	1.31 (1.03, 1.67)	1.35 (1.05, 1.73)
Carbohydrates with a high GI ⁶	0.84 (0.70, 1.01)	1.43 (1.17, 1.75)	1.23 (1.01, 1.51)	1.27 (1.03, 1.56)
<i>cis</i> MUFAs	0.71 (0.56, 0.90)	1.57 (1.24, 1.99)	1.27 (1.00, 1.61)	1.30 (1.02, 1.65)
PUFAs	1.09 (0.91, 1.29)	1.52 (1.28, 1.81)	1.31 (1.10, 1.55)	1.35 (1.14, 1.61)
Protein	0.86 (0.73, 1.02)	1.41 (1.19, 1.67)	1.25 (1.05, 1.48)	1.29 (1.08, 1.54)
Animal protein	0.98 (0.82, 1.16)	1.57 (1.32, 1.87)	1.35 (1.13, 1.62)	1.37 (1.14, 1.65)
Vegetable protein	0.47 (0.35, 0.62)	0.83 (0.63, 1.11)	0.88 (0.67, 1.16)	0.81 (0.57, 1.17)

¹Obtained from Cox proportional hazards regression models. EPIC-NL, European Prospective Investigation into Cancer and Nutrition–Netherlands; GI, glycemic index

²Includes intakes of total carbohydrates, *cis* MUFAs, PUFAs, *trans* fat, animal protein, and vegetable protein (all expressed per 5% of energy), as well as total energy (excluding energy from alcohol intake).

³Additional adjustment for age.

⁴Additional adjustment for sex, BMI, waist circumference, educational level, physical activity level, smoking status, and alcohol intake (categories).

⁵Additional adjustment for energy-adjusted intakes of cholesterol, fiber, and vitamin C.

⁶Number of cases for low GI: 591; medium GI: 524; and high GI: 692.

intake level (15.0% of energy). In populations with SFA intakes covering a wider range, the association may be different from our study. To illustrate this point, the range of SFA intake in the pooled cohort study (13) was wider (with 80% central ranges between 6% and 26.9% of energy). Furthermore, because the range of PUFA intake was small (IQR: 5.6–7.9% of energy), this may have limited the possibility to model the substitution of these 2 macronutrients. Another explanation for our findings may be that certain PUFA food sources consumed in our study population also contained *trans* fat at that time. For instance, the most important PUFA source, margarines (17%) (**Supplemental Figure 7**), also provided 9% of the *trans* fat intake in our population (**Supplemental Figure 8**). Residual confounding caused by underestimating *trans* fat intakes may be present in the observed associations between the substitution of SFAs with

PUFAs or MUFAs because of the gradual but drastic reduction of the amount of *trans* fat in margarines and spread between 1994 and 1997 (36). Altogether, the lower IHD risk for higher SFAs at the expense of PUFA intake needs to be interpreted with caution.

When we distinguished between chain lengths of SFAs, we observed differences in associations with IHD risk. In our study, higher intakes of the short- to medium-chain SFAs (sum of butyric through capric acid), myristic acid, and the sum of pentadecylic and margaric acids, which are all mainly derived from dairy sources, were associated with a slightly reduced IHD risk. Intakes of lauric acid (which is largely derived not only from dairy but also from coconut oil), however, as well as the long-chain SFAs palmitic and stearic acids, were not associated with IHD risk. In contrast to our findings, a meta-analysis of 60

TABLE 5

Multivariable HRs with 95% CIs for the associations between SFA intake from its main food sources with the incidence of ischemic heart disease (fatal and nonfatal) in 35,597 subjects from the EPIC-NL cohort¹

SFAs from main food sources	Median intake, en%	HR expressed per en%	Model 1 ²	Model 2 ³	Model 3 ⁴	Model 4 ⁵
Butter	0.62	1.42	1.04 (1.00, 1.09)	0.99 (0.94, 1.03)	0.97 (0.92, 1.01)	0.94 (0.90, 0.99)
Cheese	2.15	1.95	0.96 (0.92, 1.01)	0.89 (0.85, 0.94)	0.96 (0.92, 1.01)	0.91 (0.86, 0.97)
Milk and milk products	2.14	1.45	1.04 (0.99, 1.09)	0.96 (0.92, 1.01)	0.99 (0.95, 1.04)	0.92 (0.86, 0.97)
Meat	2.33	1.44	1.19 (1.14, 1.24)	1.20 (1.15, 1.25)	1.07 (1.02, 1.12)	1.00 (0.95, 1.06)
Cakes	0.75	0.83	0.99 (0.95, 1.04)	0.86 (0.82, 0.91)	0.97 (0.93, 1.02)	0.96 (0.91, 1.02)
Snacks	0.28	0.40	0.80 (0.76, 0.84)	1.10 (1.05, 1.16)	1.03 (0.98, 1.09)	1.03 (0.97, 1.10)
Hard, solid fats	0.95	1.25	1.12 (1.07, 1.17)	1.08 (1.03, 1.12)	0.99 (0.95, 1.03)	0.97 (0.91, 1.02)
Soft, liquid fats	0.54	0.50	1.07 (1.02, 1.12)	1.04 (1.00, 1.09)	1.01 (0.97, 1.06)	0.99 (0.95, 1.04)
Other	2.35	1.06	0.79 (0.75, 0.84)	0.99 (0.94, 1.05)	0.96 (0.91, 1.01)	0.94 (0.88, 1.01)

¹Obtained from Cox proportional hazards regression models. en%, percentage of energy; EPIC-NL, European Prospective Investigation into Cancer and Nutrition–Netherlands.

²Crude model.

³Adjustment for age.

⁴Additional adjustment for sex, total energy, BMI, waist circumference, educational level, physical activity level, smoking status, and alcohol intake (categories).

⁵Additional adjustment for the sum of all other SFAs, *trans* fat, animal protein, vegetable protein, and energy-adjusted intakes of vitamin C, fiber, and cholesterol.



controlled trials showed that compared with carbohydrates the serum LDL-raising effects of the even-chained SFAs with 12–18 carbons decreased with increasing chain length (1). To our knowledge, the associations between SFAs differing in carbon chain length and IHD risk were previously investigated only in the NHS (14) that found no associations with short- to medium-chain SFAs (butyric through capric acid) and moderately increased IHD risk for long-chain SFAs (lauric through stearic acids). This suggests that short- to medium-chain SFAs appear to be more beneficial for cardiovascular disease risk than the long-chain SFAs, which is in line with our findings.

The results we observed for SFAs differing in carbon chain length and IHD risk correspond in part with our results for SFAs from food sources. Our results suggest that the inverse association between total SFAs and IHD was mainly driven by SFAs from dairy sources. To our knowledge, the associations between SFAs from food sources and IHD risk were previously investigated in the MESA study (15) only. Our findings for SFAs from dairy are in line with the results from MESA, which reported a 29% lower IHD risk per 5% of energy (HR per 5% of energy: 0.71; 95% CI: 0.52, 0.98). The null association between SFAs from other sources and IHD in our study is also in line with the results from MESA. On the other hand, MESA observed a nonsignificant increased IHD risk for higher intake of SFAs from meat (HR per 5% of energy: 1.57; 95% CI: 0.98, 2.51) (15), whereas in our study this association was essentially null. It is unclear whether the association between SFAs from dairy and IHD in our study is attributable to the type of SFA or to interactions of SFAs with other components in dairy such as calcium, magnesium, or potassium or whether it is caused by residual or unmeasured confounding from specific nutrients in dairy.

Whether the risk differences observed in our study are attributable to the SFA type or its food source or to unmeasured confounding remains unclear for now and warrants investigation.

To conclude, in this Dutch population with a relatively high SFA intake from dairy sources and modest range in SFA and PUFA intake, we observed a lower IHD risk with a higher intake of SFAs that did not depend on the type of substituting macronutrient. The association seems mainly driven by short- to medium-chain SFAs, myristic acid, the sum of pentadecylic and margaric acids, and SFAs from dairy sources including butter, cheese, and milk and milk products. We cannot exclude confounding by unmeasured initiation of cholesterol-lowering therapy during follow-up. The fact that we did not observe a lower IHD risk for the substitution of SFAs with PUFAs may have been caused by residual confounding by *trans* fat or by the small range in PUFA intake in this cohort. Further investigation is necessary in other populations with similar as well as different dietary patterns before definitive conclusions can be drawn.

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