Markers of dietary fat quality and fatty acid desaturation as predictors of total and cardiovascular mortality: a population-based prospective study

Eva Warensjö, Johan Sundström, Bengt Vessby, Tommy Cederholm, and Ulf Risérus

ABSTRACT

Background: Desaturase indexes, as markers of endogenous fatty acid desaturation, and a characteristic serum fatty acid (FA) composition are related to cardiovascular and metabolic diseases, but the relation to mortality is poorly investigated.

Objective: The objective was to evaluate the relation between dietary fat biomarkers, desaturase indexes, and mortality.

Design: In this community-based prospective sample, 50-y-old men were followed for a maximum of 33.7 y. Cox proportional hazard analysis was conducted to investigate desaturase indexes (stearoyl-CoA-desaturase and Δ6- and Δ5-desaturase) and the relation of individual serum esterified fatty acids (FAs) in relation to total and cardiovascular mortality in the total study sample (n = 2009) and in a healthy subsample (n = 1885). Desaturase indexes were estimated as product-to-precursor FA ratios.

Results: During follow-up, 1012 men in the total sample died and 931 men in the healthy subsample died. Desaturase indexes predicted both total and cardiovascular mortality. The relations were independent of smoking status, physical activity, BMI, total cholesterol, and hypertension. The adjusted and standardized (per SD) hazard ratios (HRs) and 95% CIs for cardiovascular mortality were 1.15 (1.04, 1.27) for stearoyl-CoA-desaturase, 1.12 (1.0, 1.24) for Δ6-desaturase, and 0.88 (0.80, 0.98) for Δ5-desaturase, respectively. The proportion of serum linoleic acid was inversely related, whereas serum FAs associated with saturated fat intake (palmitic, palmitoleic, and dihomo-γ-linoleic acids) were directly related to total and cardiovascular mortality.

Conclusions: Altered endogenous FA desaturation might contribute to mortality risk because we observed independent associations between desaturase activity indexes and mortality. The proportion of linoleic acid was inversely related, and FAs reflecting saturated fat intake were directly related to mortality. Am J Clin Nutr 2008; 88:203–9.

INTRODUCTION

There has been a continual interest in the diet-heart hypothesis, and the relation between dietary fat quality and the incidence of coronary heart disease (CHD) has been studied for decades. Ecologic studies, such as the Seven Countries Study (1); some prospective studies (2–5); some long-term intervention studies (6, 7); and secondary prevention studies (8, 9) suggest that saturated fatty acids (SFAs) increase, whereas unsaturated fat decrease the risk of CHD. However, some studies have not supported such a relation (10). The n−3 fatty acids (FAs) have received special attention because of their potential cardioprotective effects (11). The evidence for a relation between total fat intake and risk of CHD, however, is weak (10, 12, 13).

The effects of dietary fat quality on subsequent disease incidence are difficult to investigate in intervention studies, partly because of too short study durations. Also, such studies have generally been underpowered. Therefore, one must either rely on meta-analyses (14) or observational studies, which also have important shortcomings. The assessment of dietary fatty acid intake from different food sources with the use of food frequency questionnaires, for example, is associated with substantial measurement error. Therefore, serum esterified FAs as a measure of dietary fat quality probably is a more objective and accurate way to evaluate dietary FAs (15, 16). FA composition in serum lipids characterized by high proportions of palmitic (16:0), palmitoleic (16:1), and dihomo-γ-linoleic (DHLA, 20:3n−6) acids and a low proportion of linoleic acid (LA, 18:2n−6) predicts type 2 diabetes (17–19), myocardial infarction (20, 21), stroke (22), left ventricular hypertrophy (23), and the metabolic syndrome (24–26). Despite accumulating data on cardiovascular morbidity and risk factors, studies relating serum FA composition with mortality are sparse. In fact, only one study has been published on this topic. Laaksonen et al (27) reported that cardiovascular mortality in a cohort of Finnish middle-aged men was predicted by low dietary and low serum LA and polyunsaturated FAs (PUFAs).

Serum FA composition is influenced not only by dietary fat but also by the endogenous metabolism of FA, genetic variation, and intrauterine “imprinting” (24). Stearoyl-CoA desaturase (SCD), Δ6-desaturase (D6D), and Δ5-desaturase (D5D) catalyze the endogenous synthesis of long-chain unsaturated FAs, which mediate and modulate metabolic functions and physical properties of the cell (28, 29). FA indexes (ratios) used as surrogate measures of desaturase activities (30) might be at least as important

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203
for metabolic changes as are individual FAs per se and have been related to metabolic diseases and CHD (25). Recent data demonstrate that estimated SCD activity is independently associated with cardiovascular disease risk markers, including insulin resistance and low-grade inflammation (31, 32), but associations with mortality are unknown.

We hypothesized that FA indexes [SCD (16:1/16:0), D6D (18:3n−6/18:2n−6) and D5D (20:4n−6/20:3n−6)] and the FA composition of serum cholesteryl esters would predict cardiovascular and total mortality. We also examined whether high proportions of serum LA are associated with decreased mortality as reported in a Finnish population (27). Because current dietary recommendations mainly suggest limiting saturated fat while increasing unsaturated fat, it is clinically important to evaluate such recommendations, as mirrored in serum fatty acids, with regard to hard endpoints.

SUBJECTS AND METHODS

Study samples

The Uppsala Longitudinal Study of Adult Men (ULSAM) is a population-based cohort study that started in Uppsala, Sweden, in 1970 (Internet: http://www.pubcare.uu.se/ULSAM/). All men born between 1920 and 1924 living in Uppsala at that time were invited to participate. The participants were examined at baseline at age 50 y and reinvvestigated at ages 60, 70, 77, and 82 y. Only data from the baseline investigation were used for the present study. Eighty-two percent of the 2841 invited men (n = 2322) agreed to participate, and 2009 men had complete fatty acid data. We fitted all models to the entire sample with complete fatty acid data and to a healthy subsample from the same population, excluding persons with previous myocardial infarction (n = 7), stroke (n = 3), cancer (n = 7), and diabetes (n = 104) and those using lipid-lowering drugs (n = 21). In the healthy subsample, 1885 men had complete fatty acid data. The study was approved by the ethics committee at Uppsala University, and all participants provided informed consent.

Clinical examinations

All investigations were described in detail previously (33). The investigations included a medical questionnaire, an interview, blood sampling, anthropometric measurements and blood pressure measurement. BMI was calculated as weight (kg) divided by height (m) squared. Supine blood pressures were recorded after 10 min of rest in the right arm in a recumbent position with a mercury manometer (Kifa Ercamer, wall-model; Spiedel and Keller, Jungingen, Germany). Hypertension was defined in the presence of systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or regular use of antihypertensive medication.

Blood samples were taken from the antecubital vein after the subjects fasted overnight. Serum cholesterol concentrations were analyzed on a Technicon Auto Analyzer type II. A self-administered questionnaire was used to collect information on various factors, including physical activity, medical treatment, and previous and current disease. Smoking data were obtained from an interview by a physician.

Fatty acid measurements and estimation of desaturase activities

The serum cholesteryl ester fatty acid composition was analyzed as previously described (20, 34). Serum was extracted with a hexane-isopropanol solution, and cholesteryl esters were separated from the extract by thin-layer chromatography before interesterification with acidic methanol was performed. Free cholesterol that had been liberated in the reaction was removed by aluminum oxide to avoid contamination of the column. The percentage composition of methylated fatty acids from 14:0 to 22:6 was determined by gas chromatography (25-m NB-351 silica capillary column) with a flame ionization detector and helium as carrier gas. The CV varied between 0.2% and 5% in successive gas chromatography runs. The relative amount of fatty acids is expressed as the percentage of the total amount of fatty acids. The desaturase activities were estimated as product-to-precursor ratios of individual fatty acids in serum cholesteryl esters as follows; SCD = 16:1/16:0, D6D = 18:3n−6/18:2n−6, and D5D = 20:4n−6/20:3n−6. The cholesteryl ester fraction was used to measure FA composition because it was the only fraction available.

Follow-up and outcome measures

Follow-up was from the time of the baseline examination in 1970–1973 to 31 December 31 2003; the maximum duration of follow-up was 33.7 y (median: 30.7 y yielding 61 518 and 58 149 person-years at risk in the total sample and in the health subsample, respectively). The Swedish national register recording cause of death was used to define endpoints. The register includes all Swedish citizens, which minimizes loss to follow-up. The accuracy of the Swedish national cause-of-death registry is known to be high. The endpoints were defined a priori as cardiovascular mortality (ICD-9 codes 390–459 and ICD-10 codes I00-I99, to comply with current European guidelines) (35) and total mortality.

Statistical analysis

The statistical analyses were defined a priori and carried out by using the software package STATA (version 8.2; STATA Corporation, College Station, TX). Continuous variables are presented as means (±SD) or medians and interquartile ranges; categorical variables are presented as the number of individuals and the percentage. The normal distribution of continuous variables was examined with Shapiro-Wilk’s test, and nonnormally distributed variables (W < 0.95) were log transformed (16:1, 18:0, 18:3n−6, 20:5n−3, 22:6n−3, SCD and D6D). Independent variables—individual fatty acids (14:0–22:6) and estimated desaturase activities (SCD, D6D, and D5D)—were investigated in 2 ways: linear relations were investigated as the effect of 1-SD increments in continuous variables, and nonlinear relations were examined with the use of quartiles of the independent variables. We applied Cox proportional hazard models to examine the individual fatty acids and estimated desaturase activities to endpoints on the total study sample and on the healthy subsample. For each sample and endpoint, an unadjusted and a multivariable-adjusted (smoking status, physical activity, BMI, total cholesterol, and hypertension) model were examined. The proportional hazards assumption was checked by using Schoenfeld’s test. Hazard ratios (HRs) and 2-tailed 95% CIs are given.
DIETARY FAT QUALITY, DESATURASE INDEXES, AND MORTALITY

TABLE 1
Baseline characteristics in the total sample and in the healthy subsample

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total sample (n = 2009)</th>
<th>Healthy subsample (n = 1885)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking [n (%)]</td>
<td>1029 (51)</td>
<td>971 (51.5)</td>
</tr>
<tr>
<td>Diabetes [n (%)]</td>
<td>94 (5)</td>
<td></td>
</tr>
<tr>
<td>Hypertension [n (%)]</td>
<td>856 (43)</td>
<td>780 (41)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>6.9 ± 1.3 2</td>
<td>6.9 ± 1.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.0 ± 3.2</td>
<td>25.0 ± 3.2</td>
</tr>
</tbody>
</table>

1 Excludes persons with previous myocardial infarction, stroke, cancer, and diabetes and those using lipid-lowering drugs.
2 ± SD (all such values).

RESULTS

Baseline characteristics for both samples are presented in Table 1. During follow-up, 1012 men died (19.0/1000 person-years at risk) in the total sample (461 from cardiovascular causes); 931 died (rate 18.5/1000 person years at risk) in the total sample (461 from cardiovascular causes).

In the total sample, a 1-SD increase in the proportions of serum myristic (14:0), palmitic (16:0), palmitoleic (16:1), oleic (18:1), γ-linolenic (18:3n−6), and dihomo-γ-linolenic (DHLA, 20:3n−6) acids and estimated SCD and D5D activities were associated with an increased risk of both cardiovascular disease and all-cause mortality, whereas a high proportion of linoleic acid (LA) and estimated D5D activity was associated with decreased mortality (Table 2). When the SCD ratio was estimated as 18:1/18:0 (another way of estimating the SCD index), it was only associated with an increased risk of total mortality (data not shown).

The proportions of long-chain n−3 fatty acids—eicosapentaenoic acid (EPA, 20:5n−3) and docosahexaenoic acid (DHA, 22:6n−3)—and of stearic acid and arachidonic acid (AA, 20:4n−6) were not associated with any mortality risk. α-Linolenic acid (ALA, 18:3n−3) was nearly associated with cardiovascular disease mortality in the fully adjusted model (HR: 1.10; 95% CI: 1.0, 1.21), which was equivalent to a P value of 0.06.

For the majority of FAs and for SCD, D6D, and D5D, the associations followed the same pattern for both cardiovascular disease and total mortality and were most strongly associated with cardiovascular death. After adjustment for total cholesterol, BMI, smoking, physical activity, and hypertension, the HRs remained in the same ranges, but statistical significance was attenuated and sometimes lost. When quartiles of FAs were examined, no signs of threshold effects or nonlinear effects were observed; therefore, only models investigating standardized continuous FA variables are presented in Table 2.

Of the individual serum FAs, the greatest mortality risk was associated with palmitoleic acid, and the significance remained in the adjusted models. The proportion of serum LA was associated with a protective effect on both cardiovascular and total mortality. This effect remained in the adjusted model, associated with risk reduction of ≈15%. A plot of the cumulative hazard of cardiovascular disease mortality split by the median proportion of LA (54.5%) is presented in Figure 1.

In Table 3, the Cox proportional HRs in quartiles of estimated desaturase activities are presented. There was, in general, a dose-response trend in the hazard of the ascending quartiles compared with the referent level. The risk of cardiovascular disease death in the fourth quartile of SCD, compared with the referent level, was almost double in the crude model and 60% higher in the adjusted model. Plots of the cumulative hazard of cardiovascular disease mortality (total study sample) split by the median proportion of SCD, D6D, and D5D indexes are presented in Figure 2. For D6D, the 2 curves follow each other until ≈17 y after

TABLE 2
Standardized Cox proportional hazard ratios for fatty acids in serum cholesteryl esters and estimated desaturase activities (fatty acid ratios) in relation to cardiovascular disease and total mortality in the total study sample (n = 2009)4

<table>
<thead>
<tr>
<th>Fatty acid and estimated desaturase activities</th>
<th>Serum proportion 2</th>
<th>Cardiovascular disease mortality 4 (n = 461 events)</th>
<th>Total mortality 4 (n = 1012 events)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Crude</td>
<td>Adjusted 4</td>
</tr>
<tr>
<td>% of total FAs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myristic acid (14:0)</td>
<td>1.1 ± 0.3</td>
<td>1.16 (1.06, 1.27)</td>
<td>1.12 (1.02, 1.23)</td>
</tr>
<tr>
<td>Palmitic acid (16:0)</td>
<td>11.7 ± 0.99</td>
<td>1.25 (1.14, 1.37)</td>
<td>1.15 (1.04, 1.26)</td>
</tr>
<tr>
<td>Palmitoleic acid (16:1)</td>
<td>3.5 (3.0-4.4)</td>
<td>1.32 (1.21, 1.44)</td>
<td>1.18 (1.07, 1.30)</td>
</tr>
<tr>
<td>Stearic acid (18:0)</td>
<td>1.1 (0.97-1.3)</td>
<td>1.07 (0.97, 1.17)</td>
<td>1.04 (0.94, 1.15)</td>
</tr>
<tr>
<td>Oleic acid (18:1)</td>
<td>19.4 ± 2.7</td>
<td>1.29 (1.18, 1.41)</td>
<td>1.18 (1.07, 1.30)</td>
</tr>
<tr>
<td>Linoleic acid (18:2n−6)</td>
<td>53.9 ± 5.2</td>
<td>0.76 (0.70, 0.83)</td>
<td>0.85 (0.78, 0.94)</td>
</tr>
<tr>
<td>γ-Linolenic acid (18:3n−6)</td>
<td>0.71 ± 0.30</td>
<td>1.15 (1.05, 1.27)</td>
<td>1.09 (0.98, 1.21)</td>
</tr>
<tr>
<td>α-Linolenic acid (18:3n−3)</td>
<td>0.66 ± 0.16</td>
<td>1.08 (0.99, 1.18)</td>
<td>1.10 (1.01, 1.21)</td>
</tr>
<tr>
<td>Dihomo-γ-linolenic acid (20:3n−6)</td>
<td>0.57 ± 0.13</td>
<td>1.16 (1.07, 1.27)</td>
<td>1.06 (0.96, 1.18)</td>
</tr>
<tr>
<td>Arachidonic acid (20:4n−6)</td>
<td>4.8 ± 0.93</td>
<td>1.00 (0.92, 1.10)</td>
<td>0.95 (0.86, 1.05)</td>
</tr>
<tr>
<td>Eicosapentaenoic acid (20:5n−3)</td>
<td>1.3 (0.9-1.6)</td>
<td>1.07 (0.98, 1.17)</td>
<td>0.99 (0.90, 1.09)</td>
</tr>
<tr>
<td>Docosahexaenoic acid (22:6n−3)</td>
<td>0.68 (0.56-0.81)</td>
<td>0.97 (0.89, 1.07)</td>
<td>0.92 (0.84, 1.02)</td>
</tr>
<tr>
<td>SCD (16:1/16:0)</td>
<td>0.30 (0.26-0.37)</td>
<td>1.27 (1.16, 1.39)</td>
<td>1.15 (1.04, 1.27)</td>
</tr>
<tr>
<td>D6D (18:3n−6/18:2n−6)</td>
<td>0.012 (0.009-0.017)</td>
<td>1.20 (1.10, 1.32)</td>
<td>1.12 (1.10, 1.24)</td>
</tr>
<tr>
<td>D5D (20:4n−6/20:3n−6)</td>
<td>8.6 ± 2.0</td>
<td>0.84 (0.76, 0.93)</td>
<td>0.88 (0.80, 0.98)</td>
</tr>
</tbody>
</table>

1 FA, fatty acids; SCD, stearoyl-CoA-desaturase; D6D, Δ6-desaturase; D5D, Δ5-desaturase.
2 Values are ± SD or median (interquartile range).
3 Values are hazard ratios (95% CIs).
4 The adjusted model included total cholesterol, BMI, smoking, physical activity, and hypertension.
baseline and then a higher estimated D6D activity is associated with higher mortality. However, for both estimated SCD and D5D, the curves begin to separate already at baseline. When the associations between FAs, estimated desaturase activities, and mortality were examined in the healthy subsample, the associations did not substantially differ from those in the total study population (both in the crude and adjusted model) and are therefore not presented.

**DISCUSSION**

In the present study, a serum FA composition (including desaturase activities) previously associated with metabolic and cardiovascular diseases (17, 25, 36, 37), and saturated fat (24, 30) predicted mortality. The proportion of serum LA was inversely related to mortality and confirmed the finding of a previous Finnish prospective study that linked high dietary and serum LA to decreased cardiovascular disease mortality (27).

The role of estimated desaturase activities in cardiovascular disease and subsequent mortality is largely unknown. In a previous study we showed that high SCD and D6D indexes and a low D5D index were induced by a diet high in saturated fat, compared with a diet rich in unsaturated fat (rapeseed oil) (30). The present study showed independent associations between estimated desaturase activity indexes (high SCD and D6D and low D5D) and mortality. This might indicate that associations between estimated desaturase activities and mortality are influenced partly by the diet, but also by other metabolic mechanisms.

It is possible that desaturases may affect metabolic processes either via their product FAs or by their potential capacity to act as proteins that directly or indirectly interact with signal transducer proteins or transcription factors (38). The main mediating mechanism between dietary FAs and cardiovascular disease risk is thought to be blood cholesterol concentrations (39, 40); other mechanisms are related to insulin resistance, inflammation, and endothelial function (41, 42).

The increased risk of mortality associated with a high estimated D6D activity might be mediated by an increase in the proportion of DHLA, which has been shown to be associated with metabolic and cardiovascular diseases (17, 25, 36, 37), and saturated fat (24, 30).

**TABLE 3**

Cox proportional hazard ratios in quartiles of estimated desaturase activities (fatty acid ratios) in relation to cardiovascular disease and total mortality in the total study sample (n = 2009) 

<table>
<thead>
<tr>
<th>Quartiles of estimated desaturase activities</th>
<th>Serum proportions</th>
<th>Cardiovascular mortality (n = 461 events)</th>
<th>Total mortality (n = 1012 events)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of total FAs</td>
<td>Crude</td>
<td>Adjusted</td>
</tr>
<tr>
<td>SCD (16:1/16:0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (referent)</td>
<td>0.23 (0.22-0.25)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>0.28 (0.27-0.29)</td>
<td>1.30 (0.97, 1.70)</td>
<td>1.34 (0.99, 1.81)</td>
</tr>
<tr>
<td>3</td>
<td>0.33 (0.32-0.35)</td>
<td>1.58 (1.21, 2.08)</td>
<td>1.44 (1.08, 1.94)</td>
</tr>
<tr>
<td>4</td>
<td>0.44 (0.39-0.51)</td>
<td>1.94 (1.49, 2.54)</td>
<td>1.59 (1.18, 2.13)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td>0.000</td>
<td>0.002</td>
</tr>
<tr>
<td>D6D (18:3n−6/18:2n−6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (referent)</td>
<td>7.2 (5.9-8.0) × 10^−3</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>10.4 (9.7-11.3) × 10^−3</td>
<td>1.35 (1.02, 1.77)</td>
<td>1.33 (0.99, 1.79)</td>
</tr>
<tr>
<td>3</td>
<td>14.0 (13.0-15.1) × 10^−3</td>
<td>1.32 (1.0, 1.75)</td>
<td>1.24 (0.91, 1.68)</td>
</tr>
<tr>
<td>4</td>
<td>20.7 (18.2-24.1) × 10^−3</td>
<td>1.78 (1.34, 2.33)</td>
<td>1.50 (1.12, 2.0)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td>0.000</td>
<td>0.020</td>
</tr>
<tr>
<td>D5D (20:4n−6/20:3n−6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (referent)</td>
<td>6.4 (5.9-6.9)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>7.8 (7.6-8.1)</td>
<td>0.92 (0.72, 1.18)</td>
<td>1.0 (0.78, 1.31)</td>
</tr>
<tr>
<td>3</td>
<td>9.9 (8.7-9.3)</td>
<td>0.86 (0.67, 1.10)</td>
<td>0.88 (0.67, 1.15)</td>
</tr>
<tr>
<td>4</td>
<td>10.9 (10.3-11.9)</td>
<td>0.63 (0.48, 0.82)</td>
<td>0.76 (0.56, 1.02)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td>0.001</td>
<td>0.048</td>
</tr>
</tbody>
</table>

*FA, fatty acids; SCD, stearoyl-CoA-desaturase; D6D, Δ^6^-desaturase; D5D, Δ^5^-desaturase.
*Values are median (interquartile range).
*Values are hazard ratios (95% CIs).
*The adjusted model included total cholesterol, BMI, smoking, physical activity, and presence of hypertension.
with insulin resistance (43) and obesity (44). High estimated D5D activity was associated with decreased mortality (9% for each 1-SD increase) and may be related to improved insulin sensitivity (45). Estimated SCD activity, together with palmitoleic acid, predicted mortality most strongly (30% for each 1-SD increase) in the present cohort. High SCD activity may be associated with increased lipogenesis (46) and may influence ectopic fat deposition and thereby insulin resistance via lipotoxic mechanisms (47). Indeed, the estimated SCD ratio (16:1/16:0) was established as an independent predictor of directly measured insulin sensitivity over 20 y in the ULSAM cohort (32). The lipogenic enzyme SCD catalyzes the synthesis of monounsaturated FAs (MUFAs), eg, oleic and palmitoleic acids. Studies in mice lacking the SCD gene have suggested a key role of this enzyme in obesity-related metabolic diseases (48, 49), and it was recently shown that saturated fat induces an up-regulation of SCD activity (46). Thus, it might be possible that an elevated SCD activity is partly secondary to a high intake of saturated fats as reflected by increased serum proportions of palmitic acid and to some extent oleic acid.

Palmitoleic acid was associated with an increased risk of mortality. The content of palmitoleic acid in the diet is low, and most palmitoleic acid in serum is derived from the endogenous metabolism of palmitic acid catalyzed by SCD. Palmitoleic acid has been found to raise LDL cholesterol as much as palmitic acid (50), potentially linking high serum proportions of this FA to cardiovascular disease. The other main product of SCD desaturation, oleic acid, lowers cholesterol and is believed to be protective with regard to cardiovascular disease (51) and was not correlated with obesity in one of our studies (44). However, in the present study, high serum proportions of oleic acid predicted both cardiovascular disease and total mortality, associations that remained in the fully adjusted model. Notably, dietary oleic acid was mainly derived from meat and dairy products in Sweden when our data were collected in the 1970s (23). Plasma proportions of oleic acid reflected the dietary intake of SFAs in a previous study from the United States (52), and this might also have affected the relation between oleic acid and mortality in the present study population.

Serum proportions of LA are known to mirror the dietary intake well (15), although it should be remembered that endogenous metabolic processes may also, to some extent, influence serum LA concentrations. It was previously reported that a low serum proportion of LA predicted MI over 19 y in this cohort (20). Dietary LA potently lowers LDL cholesterol when replacing saturated fat and is known to reduce nonfatal coronary events (39, 40). High proportions of LA in serum cholesterol esters were inversely related to cardiovascular disease and total mortality in

![Nelson-Aalen plots of the cumulative hazard of cardiovascular mortality in the total study sample (n = 2009) by above compared with below the median of the estimated stearoyl-CoA desaturase (SCD) ratio (16:1/16:0) (A), Δ⁶-desaturase (D6D; 16:3n-6/18:2n-6) (B), and Δ⁵-desaturase (D5D; 20:4n-6/20:3n-6) (C) in serum cholesteryl esters.](image-url)
the present study. After adjustment for risk factors, each 1-SD increase in the proportion of LA was associated with a mortality risk reduction of \( \approx 15\% \). This is in agreement with clinical studies such as the Finnish Mental Hospital Study (7) and the Los Angeles Veteran Hospital Study (53) and prospective observational studies (10).

The essential n-6 FA LA is converted to DHLA and AA by the action of D6D, D5D, and elongases. DHLA and AA are in turn precursors of eicosanoids such as prostaglandins and leukotrienes, which are potent mediators. Some of these mediators are known to be involved in inflammation and hemostasis, providing a potential link between excessive n-6 FAs (with the exception of LA) and cardiovascular disease. On the other hand, lipoxins, which are antiinflammatory, can also be synthesized from AA (54); in the present study, a high proportion of AA was not associated with mortality. Serum proportions of long-chain n-3 FAs (ALA, EPA, and DHA), also known to partly reflect dietary intakes (55), were not associated with mortality in the present study. This might have been due to a relatively high n-3 FA content in the background diet in the present study population (between 1 and 2 g/d). Another possibility might be that we used the cholesteryl ester fraction rather than the phospholipid fraction, which contains a relatively higher amount of long chain n-3 FAs.

We showed that palmitic acid, but not stearic acid, was significantly associated with increased mortality, especially cardiovascular disease mortality. This may agree with experimental data suggesting that palmitic acid has unique effects on several cellular functions, such as apoptosis (56), endoplasmic reticulum stress (57), and up-regulation of SCD-1 (46) and may accumulate in lipid metabolites such as ceramide and diacylglycerol (28). In addition, palmitic acid is known to increase LDL cholesterol, whereas stearic acid is neutral with respect to cholesterol concentrations (40). It should be noted that saturated fat can be synthesized de novo from carbohydrates, although this process is limited during the consumption of Western high-fat diets (58).

The long follow-up time from baseline to event might have influenced our results. However, we know from a previous study in the ULSAM cohort that the proportion of serum FAs remained fairly stable from the 50-y to the 70-y investigation (59). In addition, 78% of those men with a SCD (16:1/16:0) index in the highest quartile at age 50 y remained in the 2 highest quartiles at the 70-y investigation.

This study had limitations. First, the cohort consisted of only men. Another limitation was the use of FA ratios as an indirect measure of enzyme activity. However, results from experimental studies suggest that increases in mRNA expression and protein levels are simultaneous to increases in tissue FA ratios (28, 46, 60). Also, the cellular activity of an SCD1-inhibitor was assessed by using the SCD index in human liver cells (61). The use of FA composition and estimated desaturase activities as markers of dietary fat quality and endogenous FA desaturation in such a large population are strengths, because most previous large studies have assessed fatty acid intake from subjective food records only.

In conclusion, the present study suggests that endogenous FA desaturation, partly independent of diet, is associated with, and might even contribute to, mortality. In addition, our results suggest a role of polyunsaturated fat, mainly LA, in the prevention of cardiovascular disease and subsequent mortality and support current dietary recommendations.

The authors’ responsibilities were as follows—EW, JS, and UR: planned and designed the study; EW and JS: planned and performed the analyses; and EW: drafted the manuscript. All authors contributed to the final version of the manuscript. The data were collected as part of an ongoing cohort study, ULSAM. None of the authors had any financial or personal conflicts of interest.

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