Dietary Fatty Acids and Risk of Coronary Heart Disease in Men
The Kuopio Ischemic Heart Disease Risk Factor Study
Jyrki K. Virtanen, Jaakko Mursu, Tomi-Pekka Tuomainen, Sari Voutilainen

Objective—The epidemiological evidence of the role of dietary saturated fatty acids (SFA) in the development of coronary heart disease (CHD) is inconsistent. We investigated the associations of dietary fatty acids with the risk of CHD and carotid atherosclerosis in men with high SFA intake and high rates of CHD.

Approach and Results—In total, 1981 men from the population-based Kuopio Ischemic Heart Disease Risk Factor Study (KIHD), aged 42 to 60 years and free of CHD at baseline in 1984 to 1989, were investigated. Food consumption was assessed with 4-day food recording. Multivariate nutrient-density models were used to analyze isocaloric replacement of nutrients. CHD events were ascertained from national registries. Carotid atherosclerosis was assessed by ultrasonography of the common carotid artery intima-media thickness in 1015 men. During the average follow-up of 21.4 years, 183 fatal and 382 nonfatal CHD events occurred. SFA or trans fat intakes were not associated with CHD risk. In contrast, monounsaturated fat intake was associated with increased risk and polyunsaturated fat intake with decreased risk of fatal CHD, whether replacing SFA, trans fat, or carbohydrates. The associations with carotid atherosclerosis were broadly similar, whereas the associations with nonfatal CHD were weaker.

Conclusions—Our results suggest that SFA intake is not an independent risk factor for CHD, even in a population with higher ranges of SFA intake. In contrast, polyunsaturated fat intake was associated with lower risk of fatal CHD, whether replacing SFA, trans fat, or carbohydrates. Further investigation on the effect of monounsaturated fat on the CHD risk is warranted. (Arterioscler Thromb Vasc Biol. 2014;34:2679-2687.)

Key Words: atherosclerosis ■ coronary disease ■ fatty acids

According to the classical lipid hypothesis, high low-density lipoprotein (LDL) cholesterol concentration leads to the development of atherosclerosis, which causes coronary heart disease (CHD). Several lines of research showed that high saturated fatty acid (SFA) intake increases and high polyunsaturated fatty acid (PUFA) intake decreases total and LDL cholesterol.1 This lead to the hypothesis that high SFA intake increases the risk of CHD, and reduction of SFA intake has received a high priority in dietary recommendations against CHD. However, recent reviews of prospective cohort studies challenged the role of SFA as a risk factor for CHD, when they found no significant association between SFA intake and CHD risk.2-5 Although these results did not necessarily challenge the classical lipid hypothesis, they at least suggested that LDL concentration is not the only risk factor for CHD and that the effects of dietary components cannot be predicted only based on their effects on LDL cholesterol. However, these analyses did not specify the role of the other macronutrients that SFA replaces in diet. This was evaluated in a pooled analysis of observational studies that concluded that the risk of CHD is reduced only when SFA are replaced with PUFA, not with monounsaturated fatty acids (MUFA) or carbohydrates.6 The beneficial effect of replacing SFA with PUFA was also found in a meta-analysis of dietary fat modification trials.7

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One potential limitation in the previous observational studies is that most of them assessed dietary intakes with a food frequency questionnaire or a 24-hour recall,2-6 not with 4- to 7-day food recording, which is regarded as the “gold standard” for dietary assessment.4 Thus, the lack of association between SFA intake and CHD risk may be because of random error in dietary estimations, which would bias the associations toward the null. Also, relatively few studies have been conducted in populations with a wider range of high SFA intakes,2-6 limiting the generalizability of the findings to populations with higher SFA intake. Therefore, we investigated the associations of dietary fatty acids, assessed with 4-day food recording, with the risk of CHD in middle-aged and older men free of previous CHD in the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD), a population with a high average SFA intake and high CHD rates. Because the associations may be stronger...
for fatal CHD, than for nonfatal CHD, we evaluated these outcomes separately. As secondary analyses, we also investigated the associations of the fatty acids with the generalized atherosclerotic disease process itself by examining the associations with carotid atherosclerosis in a subgroup for whom common carotid artery intima-media thickness measurements were available. Previous data on dietary fatty acids and atherosclerosis are scarce and conflicting.

Materials and Methods

Materials and Methods are available in the online-only Supplement.

Results

Baseline Characteristics
Baseline characteristics for the entire study population are presented in Table 1 and according to the fatty acid intakes in Tables I and II in the online-only Data Supplement. In general, higher SFA intake was associated with less favorable health and lifestyle characteristics and higher PUFA intake with more favorable characteristics, whereas the associations with trans fatty acid (TFA) and MUFA intakes were more mixed (Tables I and II in the online-only Data Supplement). Dairy intake was higher and margarine intake was lower in those with higher SFA intake, whereas opposite was observed with MUFA and PUFA intakes. Intake of fruits, berries, and vegetables was lower in those with higher SFA, TFA, and MUFA intakes and higher in those with higher PUFA intake. SFA was positively correlated with TFA and MUFA and negatively correlated with PUFA (Table 2). MUFA and PUFA had a strong positive correlation.

Dietary Fatty Acids and Risk of CHD
During the average follow-up of 21.4 years (min–max, 0.3–27.8 years), 183 fatal and 382 nonfatal CHD events occurred. Table 3 shows the associations between fatty acid intakes and risk of fatal CHD. Total fat, SFA, or TFA intakes were not associated with fatal CHD risk. MUFA intake showed a borderline statistically significant association with higher risk after adjusting for the other fatty acids (model 3). Higher PUFA intake was associated with borderline statistically significant decrease in the risk of fatal CHD after multivariable adjustments (model 2). Further adjustment for the other fatty acids strengthened the association (model 3). When the n-6 and n-3 PUFA were evaluated separately, both showed similar, borderline statistically significant associations with the risk. The hazard ratio (HR) in the highest versus lowest quartile was 0.52 (95% confidence interval [CI], 0.25–1.05; \( P \) trend=0.08; model 3) for n-6 PUFA and 0.64 (95% CI, 0.37–1.14; \( P \) trend=0.01) for n-3 PUFA.

### Table 1. Baseline Characteristics of the 1981 Men in the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) in 1984 to 1999

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>52.5±5.3</td>
</tr>
<tr>
<td>Education, y</td>
<td>9.0±3.6</td>
</tr>
<tr>
<td>Marital status, married, %</td>
<td>87</td>
</tr>
<tr>
<td>Living in rural area, %</td>
<td>27</td>
</tr>
<tr>
<td>Leisure-time physical activity, kcal/d</td>
<td>138±168</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.7±3.5</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>30</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>56</td>
</tr>
<tr>
<td>Family history of coronary heart disease, %</td>
<td>46</td>
</tr>
<tr>
<td>Statins during follow-up, %</td>
<td>37</td>
</tr>
<tr>
<td>Hypertension medication during follow-up, %</td>
<td>67</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mmol/L</td>
<td>1.31±0.29</td>
</tr>
<tr>
<td>Serum LDL cholesterol, mmol/L</td>
<td>4.00±0.99</td>
</tr>
<tr>
<td>Serum total/HDL cholesterol ratio</td>
<td>4.7±1.4</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>1.25±0.74</td>
</tr>
<tr>
<td>Serum C-reactive protein, mg/L</td>
<td>2.24±4.21</td>
</tr>
<tr>
<td>Alcohol intake, g/wk</td>
<td>73±115</td>
</tr>
</tbody>
</table>

### Table 2. Correlation Coefficients Between the Fatty Acid Intakes

<table>
<thead>
<tr>
<th></th>
<th>SFA</th>
<th>TFA</th>
<th>MUFA</th>
<th>Total PUFA</th>
<th>n-6 PUFA</th>
<th>n-3 PUFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFA</td>
<td>1</td>
<td>0.30</td>
<td>0.29</td>
<td>−0.39</td>
<td>−0.42</td>
<td>−0.38</td>
</tr>
<tr>
<td>TFA</td>
<td></td>
<td>1</td>
<td>0.23</td>
<td>0.10</td>
<td>0.11</td>
<td>−0.06</td>
</tr>
<tr>
<td>MUFA</td>
<td></td>
<td></td>
<td>1</td>
<td>0.62</td>
<td>0.59</td>
<td>0.37</td>
</tr>
<tr>
<td>Total PUFA</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>0.98</td>
<td>0.76</td>
</tr>
<tr>
<td>n-6 PUFA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>0.66</td>
</tr>
<tr>
<td>n-3 PUFA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

\( P<0.01 \) for all correlations. MUFA indicates monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; and TFA, trans fatty acids.

Materials and Methods
Materials and Methods are available in the online-only Supplement.
0.37–1.12; \( P \) trend=0.11) for n-3 PUFA. When we evaluated the joint association of the n-6 and n-3 PUFA, the risk of fatal CHD was the lowest when both classes of PUFA were above the median (HR, 0.52; 95% CI, 0.31–0.85 in those with both n-6 and n-3 PUFA intake above the median versus those with both intakes below the median; Figure 1).

After adjustment for age and examination year, total fat and MUFA intakes were associated with higher risk of nonfatal CHD (Table 4). However, after multivariable adjustments, only total fat intake remained statistically significantly associated with the risk. No associations were found with intakes of total PUFA (Table 4) and n-6 or n-3 PUFA (HR in the highest versus lowest quartile, 0.90; 95% CI, 0.55–1.45; \( P \) trend=0.86 for n-6 PUFA and HR, 1.15; 95% CI, 0.78–1.69; \( P \) trend=0.52 for n-3 PUFA; model 3), or in the joint analyses with n-6 and n-3 PUFA (HR, 0.90; 95% CI, 0.64–1.26), either.

### Isocaloric Models

Figure 2 shows the change in risk of CHD with multivariate-adjusted isocaloric substitution of 1 percentage of energy (E%) from one dietary component for another. Replacing energy from SFA, TFA, or carbohydrates with energy from MUFA was associated with higher risk and replacing with PUFA with lower risk of fatal CHD. The associations were similar but weaker with nonfatal CHD. In contrast, replacing energy from SFA or TFA with equivalent energy from carbohydrates was not associated with CHD risk.

We did not find evidence for the effect modification by carbohydrate quality, indicated by the glycemic index (GI), when assessing the effects of replacing SFA or TFA with carbohydrates. For fatal CHD, replacing 1 E% from SFA with 1 E% from lower-GI carbohydrates (GI<56, lower median) was associated with HR=1.02 (95% CI, 0.97–1.08). If SFA

### Table 3. Dietary Fatty Acid Intake and Risk of Fatal Coronary Heart Disease

<table>
<thead>
<tr>
<th>Intake Quartile</th>
<th>Median intake (E%)</th>
<th>No. of events</th>
<th>HR (95% CI)</th>
<th>( P ) Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n=495)</td>
<td>31.9</td>
<td>44</td>
<td>1.03 (0.66–1.60)</td>
<td>0.55</td>
</tr>
<tr>
<td>2 (n=495)</td>
<td>36.9</td>
<td>39</td>
<td>1.11 (0.73–1.68)</td>
<td>0.42</td>
</tr>
<tr>
<td>3 (n=496)</td>
<td>40.7</td>
<td>49</td>
<td>1.12 (0.74–1.69)</td>
<td></td>
</tr>
<tr>
<td>4 (n=495)</td>
<td>45.6</td>
<td>51</td>
<td>1.12 (0.71–1.75)</td>
<td></td>
</tr>
</tbody>
</table>

Values are hazard ratio (95% confidence interval). Model 1: adjusted for age, examination year and energy intake. Model 2: adjusted for model 1 and body mass index, diabetes mellitus, hypertension, family history of coronary heart disease, pack-years of smoking, education, leisure-time physical activity, intakes of alcohol and fiber, and percentage of energy from protein. Model 3: adjusted for model 2 and percentage of energy from remaining fatty acids (saturated fatty acids, trans fatty acids, monounsaturated fatty acids, and polyunsaturated fatty acids).
were replaced with higher-GI carbohydrates (GI≥56), the HR was 1.02 (95% CI, 0.97–1.09). For nonfatal CHD, HR=1.00 (95% CI, 0.96–1.04) when lower-GI carbohydrates replaced SFA and HR=1.03 (95% CI, 0.99–1.07) when higher-GI carbohydrates replaced SFA (P-interactions >0.2). Carbohydrate quality did not modify the replacement of TFA with carbohydrates, either (P-interactions >0.2).

**Sensitivity Analyses**

The associations with nonfatal CHD were generally similar if we excluded prolonged chest pain (n=120) from the outcome (data not shown). Dietary intakes were assessed only at baseline, so the large decrease in SFA intake during the follow-up in Finland could have attenuated the associations. However, no statistically significant associations were observed with SFA with shorter, 10-year follow-up (eg, HR for nonfatal CHD in the highest versus lowest SFA quartile, 1.04; 95% CI, 0.57–1.91; n of cases=164).

**Carotid Atherosclerosis**

Those who participated in the common carotid artery intima-media thickness measurements were younger and not only had lower systolic blood pressure and body mass index and higher education but also higher alcohol intake and they were more likely to smoke (P<0.05). They also had lower SFA and protein intakes and higher PUFA intake (P<0.05).

SFA, TFA, or MUFA intakes were not associated with common carotid artery intima-media thickness, whereas higher PUFA intake was associated with smaller mean and maximal common carotid artery intima-media thickness (Tables 5 and 6). The isocaloric substitution models (Figure 3) showed generally similar results than what were observed with CHD events (Figure 2).

**Discussion**

In this prospective, population-based cohort study of middle-aged and older men, SFA intake was not associated with risk of fatal CHD. In contrast, PUFA intake was associated with lower risk and MUFA intake with borderline higher risk. The findings for n-3 and n-6 PUFA were broadly similar and not significantly different from each other. The associations between the fatty acids and nonfatal CHD were weaker, non-significant, and consistent in direction. TFA intake, mainly from partially hydrogenated vegetable oils, was not independently associated with CHD risk. In isocaloric substitution models, PUFA intake was associated with lower risk of fatal CHD and MUFA intake with higher risk of both fatal and nonfatal CHD, whether replacing SFA, TFA, or carbohydrates. The associations between the fatty acids and carotid atherosclerosis in the substitution models were broadly similar to the findings with incident events.

Although SFA intake was associated with higher baseline LDL cholesterol concentrations and PUFA intake with lower concentrations in this study population, as is expected based on the experimental studies, there was no independent association with SFA intake and risk of CHD. This is in line with the results from the reviews of prospective cohort studies.

Reduction of SFA has been the main focus in dietary recommendations against CHD during the past decades. Fatty acids and the other macronutrients, carbohydrates and protein, differ from other nutrients because they provide energy. To distinguish the effect of SFA reduction from weight reduction on CHD risk, SFA must be isocalorically replaced with other macronutrients. Usually the comparison nutrients are carbohydrates or other fatty acids because they form the bulk of energy intake. The effect on CHD prevention of replacing SFA with PUFA has been investigated in dietary fat modification trials, mainly in the 1960s and 1970s. Although many of the trials had methodological limitations and most did not find statistically significant effects, a pooled analysis found a 10% lower CHD risk for each 5 E% higher PUFA intake in place of SFA. Only 1 trial, the Women’s Health Initiative, has investigated the effect of replacing SFA with carbohydrates, with no effect on CHD risk. The role of the replacement nutrient was also assessed in the pooled analysis of prospective cohort studies, which found that replacing SFA with PUFA rather than with MUFA or carbohydrates was associated with lower CHD risk. The association was stronger with fatal CHD than with fatal and nonfatal CHD combined, supporting our findings.

Based mainly on theoretical proinflammatory effects of n-6 PUFA, some concerns have been raised on the possible unfavorable effects of high n-6 PUFA intake or high n-6/n-3 PUFA ratio. In humans, high n-6 PUFA intake has not been shown to increase inflammatory markers, and metabolic feeding trials have demonstrated benefits on blood lipids. In population studies, higher dietary or circulating n-6 PUFA has generally been associated with lower CHD risk, and the recent meta-analysis of prospective cohort studies showed that dietary linoleic acid, the predominant n-6 PUFA in the diet, was inversely associated with CHD risk in a dose–response manner. In contrast, in the dietary fat modification trials, CHD risk was reduced only when SFA was replaced with both n-6 and n-3 PUFAs, not in trials with only n-6 PUFA. In our study, the associations with n-3 PUFA are likely underestimated because
4-day dietary recording may not accurately capture foods that are usually consumed 1 to 2 times per week, such as fish, a major source of n-3 PUFA. This is supported by our previous findings in KIHD, where serum long-chain n-3 PUFA concentration, a biomarker of intake, was associated with lower risk of cardiovascular diseases.22–24

PUFA has favorable effects on several CHD risk factors, including blood total/high-density lipoprotein cholesterol ratio, insulin resistance, blood pressure, and vascular function.16,25,26 In our study, PUFA intake was also inversely associated with carotid artery wall thickness, which was also observed in the Atherosclerosis Risk in Communities Study.10 However, the stronger associations of PUFA with fatal than with nonfatal CHD may also reflect the beneficial effect on ventricular arrhythmias,27 which often precede CHD death.28

The increased CHD risk with higher MUFA intake is a somewhat surprising finding, considering the cardiovascular benefits associated with a traditional Mediterranean-type diet, in which MUFA intake is high because of common use of olive oil.29 The beneficial effects of MUFA on serum lipids and lipoproteins, when consumed in place of SFA or carbohydrates, would predict a beneficial effect also on CHD risk.16,30 The recent reviews of prospective studies of MUFA intake and CHD risk have reached different conclusions, finding an inverse association,4 no association,2,5 or direct association6 with higher intake. Notably, in addition to olive oil and other vegetable oils and margarines, a major MUFA source in most cohort studies, also in our study, is animal products, such as meat and dairy.6 This may partly explain the lack of benefits, that is, MUFA may not be the main cardioprotective compound in olive oil or

### Table 4. Dietary Fatty Acid Intake and Risk of Nonfatal Coronary Heart Disease

<table>
<thead>
<tr>
<th>Intake Quartile</th>
<th>1 (n=495)</th>
<th>2 (n=495)</th>
<th>3 (n=496)</th>
<th>4 (n=495)</th>
<th>P Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total fat</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median intake (E%)</td>
<td>31.9</td>
<td>36.9</td>
<td>40.7</td>
<td>45.6</td>
<td>...</td>
</tr>
<tr>
<td>No. of events</td>
<td>86</td>
<td>81</td>
<td>92</td>
<td>123</td>
<td>...</td>
</tr>
<tr>
<td>Model 1</td>
<td>1</td>
<td>0.93 (0.69–1.26)</td>
<td>1.07 (0.79–1.44)</td>
<td>1.46 (1.10–1.94)</td>
<td>0.003</td>
</tr>
<tr>
<td>Model 2</td>
<td>1</td>
<td>0.99 (0.72–1.34)</td>
<td>1.06 (0.78–1.44)</td>
<td>1.38 (1.02–1.87)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Saturated fatty acids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median intake (E%)</td>
<td>13.4</td>
<td>16.5</td>
<td>19.1</td>
<td>22.8</td>
<td>...</td>
</tr>
<tr>
<td>No. of events</td>
<td>95</td>
<td>79</td>
<td>89</td>
<td>119</td>
<td>...</td>
</tr>
<tr>
<td>Model 1</td>
<td>1</td>
<td>0.76 (0.56–1.03)</td>
<td>0.87 (0.65–1.17)</td>
<td>1.21 (0.91–1.62)</td>
<td>0.07</td>
</tr>
<tr>
<td>Model 2</td>
<td>1</td>
<td>0.81 (0.60–1.11)</td>
<td>0.89 (0.65–1.22)</td>
<td>1.14 (0.83–1.57)</td>
<td>0.27</td>
</tr>
<tr>
<td>Model 3</td>
<td>1</td>
<td>0.78 (0.56–1.07)</td>
<td>0.83 (0.60–1.17)</td>
<td>1.05 (0.70–1.57)</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>Trans fatty acids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median intake (E%)</td>
<td>0.7</td>
<td>0.9</td>
<td>1.1</td>
<td>1.5</td>
<td>...</td>
</tr>
<tr>
<td>No. of events</td>
<td>103</td>
<td>69</td>
<td>103</td>
<td>107</td>
<td>...</td>
</tr>
<tr>
<td>Model 1</td>
<td>1</td>
<td>0.61 (0.45–0.83)</td>
<td>0.97 (0.73–1.27)</td>
<td>0.98 (0.74–1.28)</td>
<td>0.38</td>
</tr>
<tr>
<td>Model 2</td>
<td>1</td>
<td>0.63 (0.46–0.86)</td>
<td>1.01 (0.75–1.34)</td>
<td>0.99 (0.74–1.31)</td>
<td>0.38</td>
</tr>
<tr>
<td>Model 3</td>
<td>1</td>
<td>0.63 (0.45–0.86)</td>
<td>0.97 (0.71–1.32)</td>
<td>0.94 (0.70–1.26)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Monounsaturated fatty acids</strong></td>
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<td></td>
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<tr>
<td>Median intake (E%)</td>
<td>8.6</td>
<td>10.1</td>
<td>11.5</td>
<td>13.4</td>
<td>...</td>
</tr>
<tr>
<td>No. of events</td>
<td>79</td>
<td>101</td>
<td>93</td>
<td>109</td>
<td>...</td>
</tr>
<tr>
<td>Model 1</td>
<td>1</td>
<td>1.34 (0.99–1.80)</td>
<td>1.22 (0.91–1.65)</td>
<td>1.48 (0.91–1.65)</td>
<td>0.02</td>
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<tr>
<td>Model 2</td>
<td>1</td>
<td>1.29 (0.95–1.74)</td>
<td>1.20 (0.88–1.63)</td>
<td>1.40 (1.03–1.90)</td>
<td>0.06</td>
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<td>1.28 (0.93–1.76)</td>
<td>1.19 (0.82–1.73)</td>
<td>1.40 (0.90–2.20)</td>
<td>0.21</td>
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<td><strong>Polyunsaturated fatty acids</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median intake (E%)</td>
<td>2.9</td>
<td>3.9</td>
<td>4.8</td>
<td>6.3</td>
<td>...</td>
</tr>
<tr>
<td>No. of events</td>
<td>101</td>
<td>90</td>
<td>87</td>
<td>104</td>
<td>...</td>
</tr>
<tr>
<td>Model 1</td>
<td>1</td>
<td>0.90 (0.68–1.20)</td>
<td>0.88 (0.66–1.18)</td>
<td>1.13 (0.85–1.50)</td>
<td>0.35</td>
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<tr>
<td>Model 2</td>
<td>1</td>
<td>0.98 (0.74–1.31)</td>
<td>0.92 (0.68–1.24)</td>
<td>1.18 (0.88–1.59)</td>
<td>0.28</td>
</tr>
<tr>
<td>Model 3</td>
<td>1</td>
<td>0.95 (0.69–1.29)</td>
<td>0.83 (0.57–1.21)</td>
<td>1.00 (0.64–1.56)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Values are hazard ratio (95% confidence interval). Model 1: adjusted for age, examination year and energy intake. Model 2: adjusted for model 1 and body mass index, diabetes mellitus, hypertension, family history of coronary heart disease, pack-years of smoking, education, leisure-time physical activity, intakes of alcohol and fiber, and percentage of energy from protein. Model 3: adjusted for model 2 and percentage of energy from remaining fatty acids (saturated fatty acids, trans fatty acids, monounsaturated fatty acids, and polyunsaturated fatty acids).
in a Mediterranean diet, but other constituents in olive oil, such as the phenolic compounds in the virgin olive oil, or other aspects of the Mediterranean diet may explain the health benefits. Intake of red meat, especially processed red meat, has been associated with higher risk of cardiovascular disease. However, adjusting for red meat or processed red meat intake did not appreciably change the associations between MUFA intake and risk of CHD (data not shown), suggesting that the higher risk is not explained by the higher intake of red meat. We cannot completely exclude the possibility that the higher risk of fatal CHD is caused by the inclusion of 2 highly correlated variables (PUFA and MUFA) in the same model because the higher risk was only evident when they both were included (model 3 versus model 2 in Table 3). However, no such difference in the HR was observed between the models 2 and 3 with nonfatal CHD (Table 4), suggesting that collinearity may not explain the increase in risk.

Few studies have considered the type of carbohydrates that replaced SFA. Jakobsen et al reported that replacing SFA with lower-GI carbohydrates was associated with lower CHD risk and replacing with higher-GI carbohydrates was associated with higher risk. In our study, there was no difference whether SFA (or TFA) were replaced with lower-GI or higher-GI carbohydrates. However, the average GI values in our population were lower (median, 56) than in the previous study (median, 89), suggesting that the overall carbohydrate quality was relatively good.

Table 5. Mean Common Carotid Artery Intima-Media Thickness in Quartiles of Dietary Fatty Acid Intakes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intake Quartile</th>
<th>P Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (n=253)</td>
<td>2 (n=254)</td>
</tr>
<tr>
<td>Saturated fatty acids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median intake (E%)</td>
<td>12.9</td>
<td>15.7</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.751±0.007</td>
<td>0.729±0.007</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.756±0.007</td>
<td>0.731±0.007</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.761±0.008</td>
<td>0.734±0.007</td>
</tr>
<tr>
<td>Trans fatty acids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median intake (E%)</td>
<td>0.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.743±0.007</td>
<td>0.742±0.007</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.742±0.007</td>
<td>0.744±0.007</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.741±0.007</td>
<td>0.741±0.007</td>
</tr>
<tr>
<td>Monounsaturated fatty acids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median intake (E%)</td>
<td>8.6</td>
<td>10.2</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.753±0.007</td>
<td>0.745±0.007</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.757±0.007</td>
<td>0.743±0.007</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.747±0.009</td>
<td>0.740±0.007</td>
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<tr>
<td>Polyunsaturated fatty acids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median intake (E%)</td>
<td>3.1</td>
<td>4.2</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.754±0.007</td>
<td>0.749±0.007</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.751±0.007</td>
<td>0.749±0.007</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.754±0.009</td>
<td>0.750±0.007</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Model 1: adjusted for age, examination year, and energy intake. Model 2: adjusted for model 1 and body mass index, diabetes mellitus, hypertension, family history of coronary heart disease, pack-years of smoking, education, leisure-time physical activity, intakes of alcohol and fiber, and percentage of energy from protein. Model 3: adjusted for model 2 and percentage of energy from remaining fatty acids (saturated fatty acids, trans fatty acids, monounsaturated fatty acids, and polyunsaturated fatty acids). All models are also adjusted for the technical covariate focusing depth.

Figure 2. Change in risk of fatal and nonfatal coronary heart disease (CHD) with isocaloric substitution of 1 percentage of energy from one dietary component to the another. Models adjusted for age, examination year, body mass index, diabetes mellitus, hypertension, family history of coronary heart disease, pack-years of smoking, education, leisure-time physical activity, intakes of alcohol, fiber and energy, and percentage of energy from protein. In addition, when investigating the effects of substituting carbohydrates, monounsaturated fatty acids (MUFA) or polyunsaturated fatty acids (PUFA) for saturated fatty acids (SFA) or trans fatty acids (TRANS), all sources of energy, except SFA or TFA, were included. When the effects of substituting MUFA or PUFA for carbohydrates were investigated, the model included all sources of energy, except carbohydrates.
The limitation in the previous cohort studies is that most assessed dietary intakes with a single food frequency questionnaire or 24-hour dietary recall, not with 4- to 7-day dietary recording, which is regarded as the most accurate method for dietary assessment in population studies. Especially, a single 24-hour recall provides a poor estimate of the usual dietary habits and thus makes it difficult to rank people by their dietary intakes accurately. Such imprecision would attenuate the associations between dietary factors and disease, which might explain the lack of association between SFA intake and CHD risk. However, although dietary intakes were assessed with 4-day food recording, we did not find statistically significant associations between SFA intake and CHD risk. Also, few previous studies had high average SFA intakes, making it difficult to generalize the findings to populations with higher SFA intakes. However, our findings suggest that even with high average intake levels, SFA is not an independent risk factor for CHD.

The strength of the study is the use of 4-day food recording. Other strengths include the population-based recruitment and extensive examinations of potential confounders. Classification of CHD was detailed, which reduces the possibility that the weaker associations with nonfatal CHD would be because of misclassification of events. There was also virtually zero loss to follow-up.

There are also potential limitations. Intakes of most fatty acids have changed during the follow-up in Finland, with the largest change in the average SFA intake, from 18.3 E% in 1982 to 13.0 E% in 2007 among men. During the same...
time-period, TFA intake has decreased from 1.5 E% to 0.4 E%, MUFA intake has remained relatively stable and PUFA intake has increased from 4.3 E% to 5.9 E%.8 Because SFA intake was generally associated with eating behavior, so it may not accurately represent normal dietary habits.8 Because SFA intake was generally associated with unfavorable and PUFA with favorable lifestyle factors, impact of residual confounding cannot be excluded. However, in case of SFA, this would cause upward bias and thus would not explain the observed lack of association. Because our study population included only middle-aged and older men, the findings may not be generalizable to other age groups or to women.

In conclusion, our results suggest that SFA intake is not an independent risk factor for CHD, even in a population with higher ranges of SFA intake. In contrast, increasing PUFA intake is associated with lower risk of fatal CHD, whether replacing SFA, TFA, or carbohydrates. Further investigation of the effect of MUFA on CHD risk is warranted. Also, because there is evidence that CHD risk cannot be predicted simply on the basis of the fatty acid profile of a food, for example, the content of SFA,19 more research should be focused on the cardiovascular effect of different foods, food groups, and dietary patterns.

Sources of Funding

The work was supported by the University of Eastern Finland.

Disclosures

None.

References

The epidemiological evidence of the role of dietary saturated fat in the development of coronary heart disease (CHD) is inconsistent. However, few studies have investigated populations with high average saturated fat intake. In this study, among middle-aged and older Finnish men with high average saturated fat intake and high rates of CHD, saturated fat intake was not associated with CHD risk during the average 21-year follow-up. In contrast, monounsaturated fat intake was associated with increased risk and polyunsaturated fat intake with decreased risk of especially fatal CHD, whether replacing saturated fat, trans fat, or carbohydrates in the diet. The associations with carotid atherosclerosis were generally similar. Our results indicate that saturated fat intake is not an independent risk factor for CHD even in a population with high average saturated fat intake, whereas higher polyunsaturated fat intake is associated with lower risk.
Dietary Fatty Acids and Risk of Coronary Heart Disease in Men: The Kuopio Ischemic Heart Disease Risk Factor Study
Jyrki K. Virtanen, Jaakko Mursu, Tomi-Pekka Tuomainen and Sari Voutilainen

Arterioscler Thromb Vasc Biol. 2014;34:2679-2687; originally published online September 25, 2014;
doi: 10.1161/ATVBAHA.114.304082
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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Material & Methods

Study Population
KIHD was designed to investigate risk factors for CVD, atherosclerosis, and related outcomes in a population-based, randomly selected sample of men from eastern Finland.\textsuperscript{1} The baseline examinations were carried out in 1984-1989. A total of 2,682 men aged 42, 48, 54 or 60 years at baseline (82.9% of those eligible) were recruited. The baseline characteristics of the entire study population have been described.\textsuperscript{1} The KIHD study protocol was approved by the Research Ethics Committee of the University of Kuopio. All subjects gave written informed consent for participation. Subjects with history of CHD at baseline (n=680) or with missing dietary data (n=24) were excluded, leaving 1,981 men. Baseline CCA-IMT measurements were available for 1053 participants (53.2%). After excluding the outliers (n=38), there were 1015 participants in the analyses of carotid atherosclerosis.

Assessment of Dietary Intakes
Consumption of foods at baseline was assessed with an instructed food recording of four consecutive days, of which one was a weekend day, by household measures. A picture book of common foods and dishes was used to help in estimation of portion sizes. The picture book contains 126 most common foods and drinks consumed in Finland during the 1980’s, and for each food item the participant could choose from 3-5 commonly used portion sizes or describe the portion size in relation to those in the book. In order to further improve accuracy, instructions were given and completed food records were checked by a nutritionist together with a participant. Nutrient intakes were estimated using the NUTRICA® 2.5 software (Social Insurance Institution, Helsinki, Finland). The databank of the software is mainly based on Finnish values of nutrient composition of foods. We replicated the baseline food record data by 4-day food records (n=50) used in the 1-year follow-up visit of the KIHD study. The correlation coefficients were 0.84 for SFA, 0.63 for TFA, 0.46 for MUFA, 0.56 for total PUFA, 0.64 for n-6 PUFA, and 0.63 for n-3 PUFA. MUFA included 18:1n-9 and other cis-MUFAs. The n-6 PUFA included linoleic acid (18:2) and arachidonic acid (20:4); the n-3 PUFA included alpha-linolenic acid (18:3), eicosapentaenoic acid (EPA, 20:5) and docosahexaenoic acid (DHA, 22:6). TFA included 14:1t, 16:1t, 18:1t, 18:2t, 18:3t, 20:1t, 20:2t and 22:1t.\textsuperscript{2,3} Approximately 80% of TFA is comprised of 18:1t. Conjugated linoleic acid (CLA) is not included in the TFA.

Assessment of Carotid Atherosclerosis
The extent and severity of carotid atherosclerosis was assessed by high-resolution B-mode ultrasonographic examination of the right and left common carotid arteries (CCA) in a 1.0–1.5-cm section at the distal end of the CCA, proximal to the carotid bulb, as described earlier.\textsuperscript{4} Ultrasonographic examinations were conducted by one physician. All examinations were performed with the subject in a supine position. Intima-media thickness (IMT), calculated as the mean distance between the intima-lumen and media-adventitia interfaces, was estimated at approximately 100 points in both the right and left CCAs. For the present study, two measures of IMT were used: (1) the mean IMT, calculated as the mean of all IMT estimates from the right and left CCAs and considered an overall measure of the atherosclerotic process, and (2) the maximal IMT, the average of the points of maximal thickness from the right and left CCAs and indicative of the depth of intrusion of IMT into the lumen in this part of the CCA.
Other Measurements
Venous blood samples were collected between 8AM and 10AM at the baseline examinations. Subjects were instructed to abstain from ingesting alcohol for three days and from smoking and eating for 12 hours prior to giving the sample. Detailed descriptions of the determination of serum lipids and lipoproteins, serum fatty acids, assessment of medical history and medications at baseline, family history of diseases, smoking, alcohol intake, blood pressure, and physical activity, have been published. Information on the medication use during the follow-up was obtained from the national Drug Prescription Registry at the Social Insurance Institute. Serum C-reactive protein was measured with an immunometric assay (Immume High Sensitivity CRP Assay, DPC, Los Angeles, CA, USA). Education was assessed in years by using self-administered questionnaire. Annual income was obtained from a self-administered questionnaire.

Ascertainment of Follow-up Events
Deaths were ascertained by a computer link to the national death registry using the Finnish personal identification code (social security number). There were no losses to follow-up. All deaths that occurred from the study entry to December 31, 2011 were included. Deaths were ascertained by linkage to the national Causes of Death Register using the personal identification codes. Causes of deaths were coded according to the 9th and 10th International Classification of Disease (ICD) codes. Data on fatal and non-fatal coronary events from the beginning of study to the end of 2011 were obtained by computer linkage to the national hospital discharge and death certificate registers. Diagnostic information was collected from hospitals and classified using identical diagnostic criteria. Each suspected coronary event (ICD-9 codes 410–414 and ICD-10 codes I20–I25) was classified into 1) a definite acute myocardial infarction, 2) a probable acute myocardial infarction, 3) a typical acute chest pain episode of more than 20 min indicating CHD, 4) an ischemic cardiac arrest with successful resuscitation, or 5) no acute coronary event by a physician using the original patient records. Acute coronary events that did not lead to death during the following 24 hours were considered as a non-fatal event. If a subject had multiple non-fatal coronary events during the follow-up, the first was considered the end point.

Statistical Analysis
Cox proportional hazards regression models were used to estimate hazard ratios (HR) in quartiles of fatty acid intakes that were expressed as percent of energy (E%) (Tables 3&4). In the isocaloric substitution models (Figures 2&3) the HRs were estimated using the fatty acid intakes as continuous variables. The validity of the proportional hazards assumption was evaluated by using Schoenfeld residuals. Associations with carotid atherosclerosis were analyzed with linear regression and analysis of covariance. The multivariable nutrient-density model (Model 2) included relevant covariates (see below) and intakes of total energy (kcal/d), protein (E%), and the specific type of fat (SFA, TFA, MUFA or PUFA as E%). The coefficients from these models can be interpreted as substitution of the energy from the specific type of fat for energy from other types of fat and carbohydrates. For example, for SFA, the Model 2 included the relevant covariates (see below), and intakes of total energy and energy from protein (E%) and energy from SFA (E%). The coefficients for SFA from this model are interpreted as substitution of energy coming from SFA for equal amount of energy coming from TFA, MUFA, PUFA and carbohydrates. In further analyses (Model 3) we included in the Model 2 the specific types of fat simultaneously, which can be interpreted as substitution of energy from the specific type of fat for energy from carbohydrates. When we estimated the effects of substituting carbohydrates, MUFA or PUFA for SFA or TFA (Figures 2&3), all sources of energy, except SFA or TFA, were included. For example, when estimating the effects of substituting PUFA for SFA, the model included the relevant covariates (see below) and intakes of energy, protein (E%), carbohydrates (E%), TFA (E%), MUFA (E%) and PUFA (E%).
The multivariate models included age (years), examination year, body mass index (kg/m$^2$), diabetes (yes/no), hypertension (yes/no), family history of CHD (yes/no), pack-years of smoking, education years, leisure-time physical activity (kcal/day), and intakes of alcohol (g/day) and fiber (g/day). In the analyses of carotid atherosclerosis also the technical covariate focusing depth was included. Further adjustments for income; living in rural area; marital status; aspirin use; fruit, berry and vegetable consumption; or use of lipid-lowering or hypertension medication prior to CHD during the follow-up, did not change the associations (HR change <5%). Cohort mean was used to replace missing values in covariates (<1.7%).

Statistical significance of the interactions on a multiplicative scale was assessed by stratified analysis and likelihood ratio tests using a cross-product term. Tests of linear trend were conducted by assigning the median values for each category of exposure variable and treating those as a single continuous variable. Correlations were estimated by Spearman correlation coefficients. All $P$-values were 2-tailed ($\alpha=0.05$). Data were analyzed using SPSS 19.0 for Windows (SPSS Inc., Chicago, IL).

References
## Supplemental Table I. Baseline Characteristics According to Dietary Saturated and Trans Fatty Acid Intakes in Men in the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study in 1984-1989

<table>
<thead>
<tr>
<th>Quartile of Saturated Fat Intake</th>
<th>Q1 (n=495)</th>
<th>Q2 (n=495)</th>
<th>Q3 (n=496)</th>
<th>Q4 (n=495)</th>
<th>Quartile of Trans Fat Intake</th>
<th>Q1 (n=495)</th>
<th>Q2 (n=495)</th>
<th>Q3 (n=496)</th>
<th>Q4 (n=495)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median intake, E%</td>
<td>13.4</td>
<td>216.5</td>
<td>19.1</td>
<td>22.8</td>
<td>0.7</td>
<td>0.9</td>
<td>1.1</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Range, E%</td>
<td>&lt;15.2</td>
<td>15.2-17.7</td>
<td>17.8-20.6</td>
<td>&gt;20.6</td>
<td>&lt;0.8</td>
<td>0.8-1.0</td>
<td>1.0-1.3</td>
<td>&gt;1.3</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>52.5±5.6</td>
<td>51.7±5.6</td>
<td>52.2±5.2</td>
<td>53.4±4.6*</td>
<td>52.1±5.7</td>
<td>52.2±5.3</td>
<td>52.8±4.9</td>
<td>52.8±5.2*</td>
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<td>Education, y</td>
<td>9.6±3.8</td>
<td>9.6±3.9</td>
<td>9.1±3.8</td>
<td>7.6±2.5*</td>
<td>9.0±3.6</td>
<td>9.1±3.7</td>
<td>8.7±3.4</td>
<td>9.2±3.8</td>
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<td>Marital status, married, %</td>
<td>89</td>
<td>90</td>
<td>86</td>
<td>82*</td>
<td>89</td>
<td>87</td>
<td>85</td>
<td>87</td>
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<tr>
<td>Living in rural area, %</td>
<td>19</td>
<td>18</td>
<td>26</td>
<td>46*</td>
<td>23</td>
<td>28</td>
<td>36</td>
<td>23</td>
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<tr>
<td>Leisure-time physical activity, kcal/d</td>
<td>172±197</td>
<td>156±173</td>
<td>131±158</td>
<td>94±125*</td>
<td>152±163</td>
<td>133±179</td>
<td>133±174</td>
<td>135±154</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>27.2±3.8</td>
<td>26.5±3.3</td>
<td>26.5±3.3</td>
<td>26.6±3.5*</td>
<td>27.2±3.7</td>
<td>26.7±3.6</td>
<td>26.3±3.3</td>
<td>26.7±3.4*</td>
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<tr>
<td>Current smoker, %</td>
<td>21</td>
<td>28</td>
<td>29</td>
<td>41*</td>
<td>31</td>
<td>28</td>
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<td>30</td>
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<td>Diabetes, %</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>7</td>
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<tr>
<td>Hypertension, %</td>
<td>62</td>
<td>57</td>
<td>52</td>
<td>54*</td>
<td>59</td>
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<td>Family history of CHD, %</td>
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<td>47</td>
<td>42*</td>
<td>49</td>
<td>45</td>
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<tr>
<td>Statins during follow-up, %</td>
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<td>34</td>
<td>33</td>
<td>36</td>
<td>39</td>
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<td>Hypertension medication during follow-up, %</td>
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<td>71</td>
<td>64</td>
<td>66</td>
<td>68</td>
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<td>Serum HDL cholesterol, mmol/L</td>
<td>1.29±0.30</td>
<td>1.30±0.27</td>
<td>1.30±0.28</td>
<td>1.33±0.31*</td>
<td>1.31±0.31</td>
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<td>1.32±0.30</td>
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<tr>
<td>Serum LDL cholesterol, mmol/L</td>
<td>3.83±1.01</td>
<td>3.93±0.93</td>
<td>4.06±0.94</td>
<td>4.19±1.04*</td>
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<td>4.07±0.94</td>
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<tr>
<td>Serum total/HDL cholesterol ratio</td>
<td>4.7±1.5</td>
<td>4.7±1.3</td>
<td>4.8±1.4</td>
<td>4.8±1.4</td>
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<td>Serum triglycerides, mmol/L</td>
<td>1.40±0.82</td>
<td>1.30±0.86</td>
<td>1.15±0.60</td>
<td>1.16±0.61*</td>
<td>1.32±0.89</td>
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<td>1.17±0.70</td>
<td>1.31±0.71</td>
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</tr>
<tr>
<td></td>
<td>Serum C-reactive protein, mg/L</td>
<td>Alcohol intake, g/wk</td>
<td>Dietary intakes</td>
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<tr>
<td></td>
<td>2.39±5.32  2.00±3.70  2.22±3.64  2.37±3.94  2.37±3.53  2.06±3.80  2.44±5.50  2.10±3.70</td>
<td>99±159  74±107  68±95  51±78*  101±154  78±117  59±96  54±71*</td>
<td>Energy, kcal/d</td>
<td>2169±554  2315±553  2446±578  2636±718*  2250±588  2452±596  2481±692  2382±607*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total fat, E%</td>
<td>32.3±4.4  37.3±3.4  40.6±3.5  45.4±5.2*  35.7±6.8  37.8±5.2  40.6±5.1  41.4±6.4*</td>
<td></td>
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<td></td>
<td>Protein, E%</td>
<td>16.5±3.0  15.9±2.5  15.6±2.3  14.6±2.5*  16.2±2.9  15.8±2.7  15.2±2.3  15.3±2.6*</td>
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<td>Carbohydrates, E%</td>
<td>47.9±6.9  44.6±5.8  42.1±5.4  39.3±5.1*  44.7±7.5  44.2±5.61  42.8±5.8  42.2±6.7*</td>
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<td></td>
<td>Fiber, g/d</td>
<td>27±10  25±8  25±8  25±9*  26±9  26±9  25±9  25±8*</td>
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<td>Meat and meat products, g/d</td>
<td>147±78  164±80  172±85  162±81*  172±84  167±82  153±76  153±82*</td>
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<td>Fish, g/d</td>
<td>60±68  52±70  52±62  46±61*  55±66  56±72  50±64  49±58</td>
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<td></td>
<td>Dairy, g/d</td>
<td>588±323  607±331  681±332  828±406*  626±356  689±362  741±372  649±347</td>
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<td>Fruits, berries and vegetables, g/d</td>
<td>316±189  288±146  243±136  186±120†  286±176  259±146  243±148  245±155*</td>
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<td>Vegetable margarines, g/d</td>
<td>23±17  20±18  17±17  11±12*  8±6  12±8  15±11  35±21*</td>
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<td></td>
<td>Vegetable oils, g/d</td>
<td>3±4  3±4  2±3  2±3  3±4  2±3  2±4  2±3*</td>
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</tbody>
</table>

All values are mean±SD or percentages.

*P-trend across quartiles <0.05.
†Excluding potatoes.

CHD, coronary heart disease; E%, percent of energy; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Q, quartile.
Supplemental Table II. Baseline Characteristics According to Dietary Monounsaturated and Polyunsaturated Fatty Acid Intake in Men in the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study in 1984-1989

<table>
<thead>
<tr>
<th></th>
<th>Quartile of Monounsaturated Fat Intake</th>
<th></th>
<th>Quartile of Polyunsaturated Fat Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1 (n=495)</td>
<td>Q2 (n=495)</td>
<td>Q3 (n=496)</td>
</tr>
<tr>
<td>Median intake, E%</td>
<td>8.6</td>
<td>10.1</td>
<td>11.5</td>
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<tr>
<td>Range, E%</td>
<td>&lt;9.4</td>
<td>9.4-10.8</td>
<td>10.9-12.3</td>
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<tr>
<td>Age, y</td>
<td>53.2±4.9</td>
<td>52.9±5.1</td>
<td>52.4±5.4</td>
</tr>
<tr>
<td>Education, y</td>
<td>8.7±3.6</td>
<td>8.7±3.5</td>
<td>9.2±3.8</td>
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<tr>
<td>Marital status, married, %</td>
<td>88</td>
<td>87</td>
<td>88</td>
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<tr>
<td>Living in rural area, %</td>
<td>35</td>
<td>31</td>
<td>25</td>
</tr>
<tr>
<td>Leisure-time physical activity, kcal/d</td>
<td>151±207</td>
<td>137±158</td>
<td>133±149</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.7±3.4</td>
<td>26.6±3.7</td>
<td>26.7±3.5</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>23</td>
<td>30</td>
<td>31</td>
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<tr>
<td>Diabetes, %</td>
<td>4</td>
<td>5</td>
<td>4</td>
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<tr>
<td>Hypertension, %</td>
<td>59</td>
<td>56</td>
<td>55</td>
</tr>
<tr>
<td>Family history of CHD, %</td>
<td>46</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td>Statins during follow-up, %</td>
<td>38</td>
<td>32</td>
<td>38</td>
</tr>
<tr>
<td>Hypertension medication during follow-up, %</td>
<td>66</td>
<td>66</td>
<td>69</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mmol/L</td>
<td>1.28±0.27</td>
<td>1.31±0.29</td>
<td>1.32±0.28</td>
</tr>
<tr>
<td>Serum LDL cholesterol, mmol/L</td>
<td>3.98±1.02</td>
<td>4.03±0.99</td>
<td>4.03±1.01</td>
</tr>
<tr>
<td>Serum total/HDL cholesterol ratio</td>
<td>4.7±1.4</td>
<td>4.8±1.5</td>
<td>4.7±1.4</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>1.26±0.76</td>
<td>1.27±0.76</td>
<td>1.24±0.77</td>
</tr>
</tbody>
</table>

*Significant difference compared to Q1, p<0.05.
<table>
<thead>
<tr>
<th></th>
<th>Serum C-reactive protein, mg/L</th>
<th>Alcohol intake, g/wk</th>
<th>Dietary intakes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.99±3.77 2.10±3.83 2.29±3.26 2.59±5.58* 2.11±3.61 2.20±3.93 2.40±5.17 2.26±3.94</td>
<td>79±155 71±103 71±102 71±88 70±131 80±121 66±105 76±100</td>
<td>Energy, kcal/d Total fat, E% Protein, E% Carbohydrates, E% Fiber, g/d Meat and meat products, g/d Fish, g/d Dairy, g/d Fruits, berries and vegetables, g/d Vegetable margarines, g/d Vegetable oils, g/d</td>
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<td></td>
<td>2360±669 2422±616 2425±606 2358±619 2559±694 2450±667 2322±549 2235±541*</td>
<td>32.9±4.8 37.7±4.1 40.5±4.1 44.5±5.6* 38.6±6.4 37.7±6.1 38.3±5.7 40.9±6.7*</td>
<td>15.7±2.9 15.4±2.5 15.6±2.4 15.9±2.7 14.9±2.4 15.5±2.5 16.0±2.5 16.2±3.0*</td>
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<td>48.9±6.1 44.8±5.0 41.9±5.0 38.2±5.4* 44.4±6.3 44.4±6.9 44.0±6.2 41.2±6.5*</td>
<td>28±10 26±9 25±8 23±8*</td>
<td>26±9 26±9 26±9 24±8*</td>
</tr>
<tr>
<td></td>
<td>113±61 139±64 172±66 221±90* 130±64 157±77 171±79 187±93*</td>
<td>Fish, g/d Dairy, g/d Fruits, berries and vegetables, g/d Vegetable margarines, g/d Vegetable oils, g/d</td>
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<tr>
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<td>56±67 58±75 47±57 50±61* 45±52 53±66 52±70 62±71*</td>
<td>738±370 721±350 680±365 565±338* 850±370 731±373 614±318 510±288*</td>
<td>305±182 253±144 245±141 229±149* 221±142 259±158 280±162 272±161*</td>
</tr>
<tr>
<td></td>
<td>12±11 16±14 19±13 24±22* 8±7 13±10 20±15 30±22*</td>
<td>Vegetable margarines, g/d Vegetable oils, g/d</td>
<td></td>
</tr>
</tbody>
</table>
|                      | 2±3 2±3 3±3 4±5* 1±1 2±2 2±3 5±5* | All values are mean±SD or percentages. *P-trend across quartiles <0.05. †Excluding potatoes. CHD, coronary heart disease; E%, percent of energy; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Q, quartile.