

# Dietary Fat Predicts Coronary Heart Disease Events in Subjects With Type 2 Diabetes

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with type 2 diabetes who were free from CHD at baseline.

## RESEARCH DESIGN AND METHODS

### Baseline study

**Subjects.** A more detailed description of study subjects has been given elsewhere (12). Type 2 diabetic subjects aged 45–64 years who were born and living in the Turku University Central Hospital district (West Finland) and in the Kuopio University Hospital district (East Finland) were identified on the basis of a national drug reimbursement register. The final population consisted of 1,059 type 2 diabetic subjects. Of these, 328 men and 221 women were from West Finland (participation rate 79%) and 253 men and 257 women were from East Finland (participation rate 83%). Type 1 diabetes was excluded in all insulin-treated subjects by C-peptide measurements (12). Of the patients, 147 were treated with diet only, 762 with oral medication, and 150 with insulin.

**Methods.** The baseline examination between 1982 and 1984 included an interview concerning smoking, alcohol intake, physical activity, and the use of medication. The methods have been previously described in detail (12).

Patients with chest pain symptoms that were suggestive of CHD were interviewed by specially trained nurses using the Rose cardiovascular questionnaire (13). All medical records of subjects who reported that they had been admitted to the hospital for chest pain were reviewed. Review of the medical records was performed by two investigators (M.L. and T.R.) after a careful standardization of the methods between the reviewers. The World Health Organization criteria for verified definite or possible myocardial infarction (MI) based on chest pain symptoms, electrocardiogram changes, and enzyme determinations were used to define previous MI (14). Electrocardiogram abnormalities were classified according to the Minnesota code (13). Angina pectoris

**OBJECTIVE** — To investigate whether quantity or quality of dietary fat predicts coronary heart disease (CHD) events in middle-aged type 2 diabetic subjects.

**RESEARCH DESIGN AND METHODS** — The dietary habits of 366 type 2 diabetic men and 295 women, aged 45–64 years and free from CHD, were assessed with a 53-item food frequency questionnaire. They were followed up for 7 years.

**RESULTS** — Men in the highest tertile of the polyunsaturated/saturated fat (P/S) ratio ( $>0.28$ ) had a significantly lower risk for CHD death than men in the two lowest tertiles (5.0 vs. 14.2%,  $P = 0.009$ ). The risk for all CHD events was 14.2 vs. 23.2%, respectively ( $P = 0.044$ ). P/S ratio did not predict CHD events in women. In Cox multiple regression analyses taking into account other cardiovascular risk factors, the highest P/S ratio tertile was associated with the lowest rate of CHD death in men ( $P = 0.048$ ).

**CONCLUSIONS** — Low P/S ratio in men predicted future CHD events in type 2 diabetic subjects independently of conventional CHD risk factors.

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Coronary heart disease (CHD) is a major cause of death in type 2 diabetic patients. Recently, several prospective studies have shown that poor glycemic control is associated with increased CHD mortality in type 2 diabetes (1–4). Diet plays an important role in achieving and maintaining good glycemic control in diabetic patients. Several studies in nondiabetic subjects have indicated that a high intake of saturated fat (SAFA) is associated with increased risk of CHD, whereas high intakes of polyunsaturated fat (PUFA) and monounsaturated fat (MUFA) are associated with reduced risk (5–8). High intake of SAFA may induce

insulin resistance and thus worsen glycaemic control (9). Moreover, a decrease in dietary SAFA intake and an increase in PUFA and MUFA intake favorably influences plasma lipid and lipoprotein concentrations, which are important predictors of CHD events in nondiabetic and diabetic individuals (10,11). There are no prospective studies including a large representative cohort examining the effects of nutritional factors to predict CHD mortality and nonfatal CHD events in type 2 diabetes. In this long-term prospective study, we examined whether dietary factors predict future CHD events during a 7-year follow-up in 661 Finnish patients

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**Abbreviations:** CHD, coronary heart disease; DH, dietary history interview; FFQ, food frequency questionnaire; FR, food record; MI, myocardial infarction; MUFA, monounsaturated fat acid; P/S, polyunsaturated/saturated fat; PUFA, polyunsaturated fatty acid; SAFA, saturated fatty acid.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Validation of the FFQ against the DH and FR methods in 34 type 2 diabetic subjects

	FFQ (1 month)	DH (1 year)	FR (4 days)	Correlation between FFQ and DH	Correlation between FFQ and FR
Daily energy intake (kcal)	1,997 ± 481	2,223 ± 809	1,662 ± 511	0.46 (<0.01)	0.53 (<0.01)
Total fat (% energy)	42.5 ± 6.0	42.9 ± 10.2	36.8 ± 7.0	0.52 (<0.01)	0.47 (<0.01)
SAFA (% energy)	21.6 ± 4.9	21.1 ± 7.5	17.5 ± 4.6	0.75 (<0.001)	0.79 (<0.001)
MUFA (% energy)	14.1 ± 2.4	13.6 ± 3.0	12.1 ± 2.0	0.34 (<0.05)	0.21 (0.24)
PUFA (% energy)	4.7 ± 2.3	6.1 ± 2.3	5.5 ± 2.1	0.64 (<0.001)	0.51 (<0.01)
Protein (% energy)	18.4 ± 3.2	15.7 ± 3.3	18.1 ± 3.6	0.60 (<0.001)	0.37 (<0.05)
Carbohydrate (% energy)	40.4 ± 5.5	43.1 ± 9.0	47.1 ± 6.4	0.44 (<0.01)	0.54 (<0.01)
Alcohol (% energy)	1.0 ± 2.1	0.7 ± 1.6	0.8 ± 1.7	0.66 (<0.001)	0.65 (<0.001)
Dietary fiber (g/day)	19.5 ± 6.7	26.4 ± 8.0	22.3 ± 8.6	0.50 (<0.01)	0.40 (<0.05)
P/S ratio	0.25 ± 0.18	0.36 ± 0.27	0.37 ± 0.22	0.84 (<0.001)	0.68 (<0.001)

Data are means ± SD or correlations (*P*).

was defined as typical angina pectoris in Rose's cardiovascular questionnaire.

BMI was calculated from the formula  $BMI = \text{weight (kg)}/\text{height (m)}^2$ . All blood specimens were drawn at 8:00 A.M. after a 12-h fast. Fasting plasma glucose was determined by the glucose oxidase method (Boehringer Mannheim, Mannheim, Germany). HbA<sub>1c</sub> was determined by affinity chromatography (Isolab, Akron, OH). Serum lipids and lipoproteins were measured in fresh serum samples. Serum total cholesterol and triglycerides were determined enzymatically (Boehringer). Serum HDL cholesterol was determined enzymatically after precipitation of LDLs and VLDLs with dextran sulfate–MgCl<sub>2</sub>.

The food consumption data were collected by a food frequency questionnaire (FFQ), which was mailed to the participants. The questionnaire contained 53 food items and dishes, and the participants were asked to report the consumption of them during the past month. In addition, any other foods were recorded that were not listed in the questionnaire. Consumption of foods generally consumed daily were asked to be estimated per day and others per week. Amounts of food were estimated in household measures (glasses, slices, teaspoons, etc.). Alcohol consumption was calculated according to the subjects estimate of the average number of glasses or bottles of beer, wine, or other alcoholic drinks consumed per week. The questionnaire was carefully checked by a nurse in connection within the physical examination. Food and alcohol intake were transformed to grams.

The average daily intakes of energy, energy yielding nutrients, and dietary fi-

ber were calculated with the Nutrica dietary analysis program (version 1.0, 1986), developed at the Social Insurance Institution (15). The database of this program was validated by Hakala et al. (16). The correlation between the values calculated from the 3-day food records and those analyzed from chemical analyses of the same diets were as follows: for total energy intake ( $r = 0.70$ ), for fat ( $r = 0.61$ ), for different type of fats ( $r = 0.50–0.68$ ), and for dietary fiber ( $r = 0.60$ ).

**Validity of the FFQ.** After the baseline study, the validity of the FFQ was investigated in 34 randomly selected subjects from the original study population. Their food consumption was evaluated by a 1-h dietary history interview (DH), which dealt with the normal diet during the past year. A well-trained experienced nutritionist conducted all interviews. The subjects were asked how much and how often (per day, per week, per month, or per year) they had consumed each of the listed foods. At the end of the interview, the subjects received a food record (FR) and were asked to fill it out at home during the 4 subsequent days. The nutrient intake data calculated on the basis of the DH and the FR were compared with the data based on the FFQ (Table 1). With respect to total fat, the FFQ results were similar to those from the DH but higher than those from the FR method, and with respect to polyunsaturated/saturated fat (P/S) ratio, the FFQ values were lower than those from the other two methods. Except for MUFA, the correlation coefficients between dietary variables obtained by the FFQ and the other two methods were at least 0.37, but <0.50 in 5 coefficients and at least 0.50 in 13 of 18 coeffi-

cients. Regarding MUFA, the correlations between FFQ and the other two methods were poor. Therefore, we did not use MUFA data in the present study assessing the association between dietary intake and subsequent CHD events.

#### Follow-up study

In 1990, a questionnaire about hospitalization for acute chest pain was sent to every surviving participant of the original study cohort. Medical records of those subjects who died between the baseline examination and 31 December 1989 or who reported in the questionnaire that they had been admitted to the hospital because of chest pain between the baseline examination and 31 December 1989 were reviewed by one of the investigators (S.L.). The modified World Health Organization criteria for definite or possible MI were used similarly as in the baseline study. In the final classification of the causes of death, hospital records and autopsy records were used, if available. Copies of death certificates of those subjects who had died were obtained from the Central Statistical Office of Finland. To ensure that the data collection was complete, a computerized hospital discharge register was used to check for hospital admissions of all participants in the baseline study. In cases of diagnoses suggesting MI, medical records were also checked.

#### Relation between diet and CHD events.

In the present study, all subjects who had a history of previous definite or possible MI or angina pectoris (see RESEARCH DESIGN AND METHODS) at baseline were excluded from final statistical analyses (214 men, 183 women), because we assumed that

**Table 2—Baseline characteristics and daily intake of energy and nutrients of diabetic subjects with no MI or angina at baseline in relation to CHD mortality in the 7-year follow-up**

	CHD death in men			CHD death in women		
	No	Yes	P	No	Yes	P
n	325	41	—	271	24	—
Baseline characteristics						
Age (years)	57.0 ± 5.3	58.3 ± 4.7	NS	58.1 ± 5.1	61.3 ± 3.1	<0.001
BMI (kg/m <sup>2</sup> )	27.9 ± 4.4	27.6 ± 3.9	NS	30.7 ± 6.0	30.9 ± 6.5	NS
Duration of diabetes (years)	8.1 ± 4.2	9.4 ± 4.2	0.071	7.7 ± 3.8	9.8 ± 4.7	0.011
Fasting plasma glucose (mmol/l)	10.7 ± 3.6	12.1 ± 3.7	0.020	11.8 ± 3.8	14.1 ± 4.6	0.006
Total cholesterol (mmol/l)	6.2 ± 1.2	7.1 ± 1.5	0.001	6.8 ± 1.8	6.7 ± 1.3	NS
Triglycerides (mmol/l)	2.03 ± 1.80	2.53 ± 2.29	0.055	2.27 ± 2.35	2.99 ± 2.38	0.043
HDL cholesterol (mmol/l)	1.19 ± 0.32	1.23 ± 0.34	NS	1.33 ± 0.38	1.24 ± 0.38	NS
Current smokers (%)	24.6	29.3	NS	8.5	0	0.137
Hypertension (%)	52.0	51.2	NS	65.7	79.2	NS
Dietary intake						
Energy (kcal)	2,169 ± 580	2,469 ± 813	0.026	1,824 ± 480	1,846 ± 608	NS
Total fat (% of energy)	39.6 ± 6.2	38.9 ± 5.8	NS	39.3 ± 5.7	36.3 ± 5.9	0.016
Saturated fat (% of energy)	19.8 ± 4.4	19.7 ± 3.9	NS	20.1 ± 4.0	18.6 ± 4.5	0.088
Polyunsaturated fat (% of energy)	5.0 ± 2.4	4.3 ± 2.1	0.071	4.6 ± 2.1	4.3 ± 2.1	0.178
P/S ratio	0.27 ± 0.17	0.23 ± 0.15	NS	0.24 ± 0.15	0.25 ± 0.19	NS
Protein (% of energy)	18.6 ± 2.8	18.5 ± 2.5	NS	19.5 ± 2.9	20.1 ± 3.2	NS
Carbohydrate (% of energy)	41.1 ± 6.6	41.9 ± 6.4	NS	43.2 ± 5.9	45.8 ± 5.4	0.033
Dietary fiber (g)	19.7 ± 6.2	20.9 ± 7.3	NS	18.8 ± 5.6	19.8 ± 5.5	NS

Data are means ± SD or P.

they probably had changed their dietary habits because of CHD. One male diabetic subject from West Finland refused to fill out the dietary questionnaire and he was excluded. The final diabetic study population comprised 246 men and 163 women living in West Finland and 120 men and 132 women living in East Finland.

### Statistical methods

All statistical analyses were performed using the SPSS for Windows, version 10.0 (SPSS, Chicago). Data of continuous variables are given as means ± SD. Differences between the two groups were assessed by the Student's *t* test for independent samples. Triglycerides were analyzed after logarithmic transformation. The nonparametric Mann-Whitney *U* test was applied for other skewed variables. The  $\chi^2$  test was used for comparison of categorical variables and variables divided into tertiles. The Cox regression model was used in univariate and multivariate analyses to investigate the association between CHD risk factors and the time to CHD events.

**RESULTS**— At baseline, there were no significant differences between pa-

tients from West or East (men or women) Finland with respect to age, duration of diabetes, serum triglycerides, smoking habits, or blood pressure. Men and women from West Finland had higher BMI than men or women from East Finland ( $P = 0.034$  and  $0.001$ , respectively). Serum cholesterol was significantly higher in men and women from East Finland ( $P = 0.004$  and  $0.030$ , respectively). On the other hand, serum HDL cholesterol was also significantly higher in men from East Finland ( $P < 0.001$ ). Fasting plasma glucose was higher in men from East Finland ( $P = 0.045$ ).

The reported intakes of total fat and SAFA were substantially above the recommendations, and the reported intake of PUFA was below the recommendations (17). The reported intake of total energy was higher in East Finland in both sexes ( $P < 0.001$  and  $P = 0.002$ , respectively). In women but not in men, the reported intake of PUFA and the P/S ratio were higher in West Finland than in East Finland ( $P = 0.005$  and  $0.027$ , respectively). In the final analyses, patients from the two areas were combined, but the area of residence was included as a covariate.

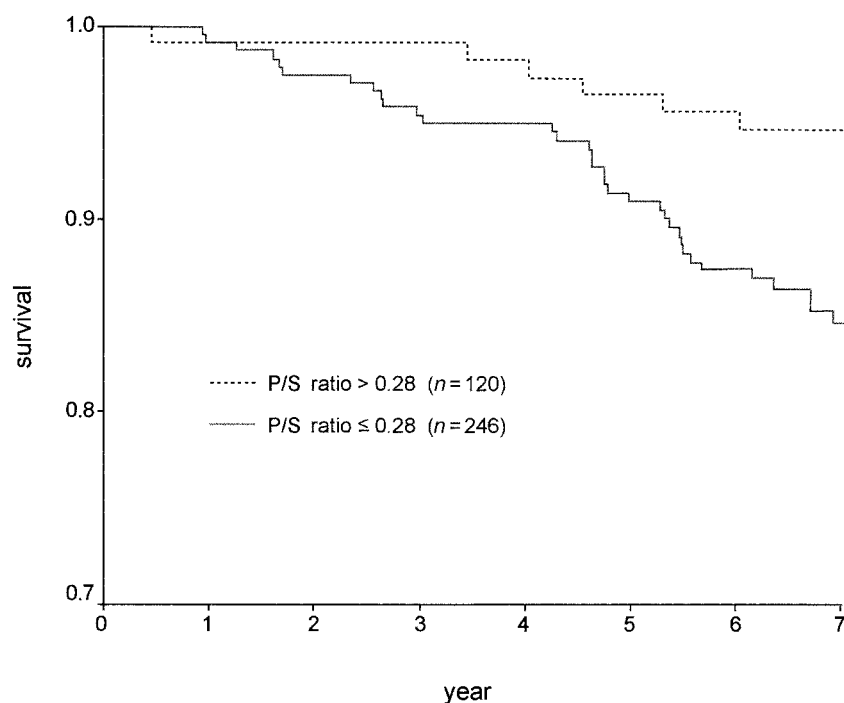
During the 7-year follow-up, 41 men and 24 women died from CHD. Also, 74

men and 43 women had a nonfatal MI or died from CHD.

Baseline characteristics of the study population in relation to CHD mortality in the 7-year follow-up are presented in Table 2. Women who died from CHD were significantly older ( $P < 0.001$ ) than surviving women. Duration of diabetes was longer in women who died from CHD compared with those who did not ( $P = 0.011$ ). There was a similar trend also in men ( $P = 0.071$ ). Fasting plasma glucose was higher in both men and women who had a fatal CHD event compared with those who did not ( $P = 0.020$  and  $0.006$ , respectively).

### Fat intake and CHD events

The mean reported intake of total fat and SAFA or the P/S ratio did not differ between men with or without a CHD event (Table 2). The reported intake of PUFA tended to be low in those men who died from CHD or had a nonfatal MI. Women who died from CHD or had a nonfatal or fatal MI had a lower reported intake of total fat ( $P = 0.016$  and  $P < 0.001$ ) and a higher reported intake of carbohydrates than women without these CHD events ( $P = 0.033$  and  $0.002$ , respectively). The mean reported intake of SAFA was lower



**Figure 1**—Kaplan-Meier estimates of the probability of death from CHD between type 2 diabetic men in the highest tertile in the P/S ratio and men in the lowest two tertiles ( $P = 0.008$ , log-rank test).

in women who died from CHD or had a nonfatal or fatal MI than in women who did not ( $P = 0.088$  and  $0.007$ , respectively).

Because of the skewed distribution of the P/S ratio, we analyzed the relation between it and CHD events in subjects also stratified by P/S ratio tertiles. Men in the highest P/S ratio tertile ( $>0.28$ ) had significantly lower risk for CHD death (5.0 vs. 14.2%,  $P = 0.009$ ,  $\chi^2$  test) than men in the lowest two tertiles (P/S ratio  $\leq 0.28$ ). The percentages for all CHD events were 14.2 vs. 23.2%, respectively ( $P = 0.044$ ,  $\chi^2$  test). Such an association was not observed among women.

Figure 1 shows the Kaplan-Meier estimates for the probability of death from CHD in men in the highest tertile of the P/S ratio and in men in the lowest two tertiles. Men in the highest tertile had a significantly better prognosis than men in the lowest two tertiles ( $P = 0.008$ , log-rank test). The difference was seen after 1 year from baseline and it substantially increased from 2 to 7 years of follow-up.

Men belonging to the highest tertile in the P/S ratio still had the lowest CHD death rate ( $P = 0.019$ ) when adjustment was made for age and diabetes duration. The association remained almost un-

changed ( $P = 0.027$ ) even after adjustment for total cholesterol, HDL cholesterol, and triglycerides. Further adjustment for smoking, hypertension, BMI, fasting plasma glucose, area of residence, and type of diabetes therapy weakened the association, but it still remained significant ( $P = 0.048$ ). If HbA<sub>1c</sub> was taken into the model instead of fasting plasma glucose, the association was similar ( $P = 0.044$ ). Regarding the relation between P/S ratio and all CHD events, adjustment for age, diabetes duration, and other risk factors weakened or even abolished the association (Table 3).

#### Fat on bread, fish intake, alcohol use, and CHD events

In unadjusted analyses, the risk for CHD death was 6.9% in men who used margarine as a spread and 14.6% in men who used butter ( $P = 0.036$ ). When adjusted for age and diabetes duration, the association between margarine and butter use and CHD death weakened ( $P = 0.043$ ). Among women this association was not found.

Women who ate at least one serving of fish per week ( $\geq 150$  g/week) had a significantly lower risk for CHD death (7.1%) than women who did not eat fish

at all (19.2%,  $P = 0.030$ ). With respect to all CHD events, the corresponding percentages were 13.4 and 26.9%, respectively ( $P = 0.062$ ). When adjusted for age and diabetes duration, these associations disappeared. Among men, there was no association between fish intake and CHD events.

In addition, the relation of reported alcohol intake to CHD events was studied. Analyses were not possible in women because 87.5% of women reported not using alcohol at all. Among men whose reported alcohol intake was  $<14$  g/day ( $n = 282$ ), the CHD death rate was 11.0%; in those whose consumption was between 14 and 42 g/day ( $n = 67$ ), 7.5%; and in those whose consumption was  $>42$  g/day ( $n = 17$ ), 29.4% (overall  $P = 0.036$ ). The percentages for all CHD events were 20.9, 14.9, and 29.4%, respectively (overall  $P = 0.343$ ). Adjustment for age, diabetes duration, and all other risk factors abolished the association between CHD death and alcohol intake.

**CONCLUSIONS**— To our knowledge, there are no previous prospective studies in type 2 diabetic subjects that examine the association between diet and CHD events. We found that in type 2 diabetic men, a low P/S ratio was associated with an increased rate of CHD death. In nondiabetic men, a similar strong inverse association between the P/S ratio and the risk of CHD has previously been reported (18).

The association between a higher P/S ratio and reduced CHD death risk in men remained significant, even after adjustment for total cholesterol, HDL cholesterol, and triglycerides. This result suggests that the impact of the P/S ratio on CHD death cannot be explained by its effects on serum lipids alone. Other mechanisms behind the beneficial effect of a high P/S ratio might involve the effects on endothelial function and thrombogenesis (19–22). Recently, Fard et al. (23) found that a high-fat diet in type 2 diabetic subjects elevates plasma asymmetric dimethylarginine, which also causes endothelial dysfunction. A low P/S ratio might also be associated with insulin resistance and thus increase the risk of CHD events (9).

At the time of the baseline study from 1982 to 1984, there were only few patients using hypolipidemic medication. In

Table 3—Relative risks and 95% CIs of CHD events in type 2 diabetic subjects divided in tertiles by P/S ratio in men (Cox regression model)

	CHD mortality		CHD mortality or nonfatal MI	
	Relative risk (95% CI)	P	Relative risk (95% CI)	P
Men in two lowest tertiles (P/S ratio $\leq$ 0.28) compared with those in the highest tertile (P/S ratio $>$ 0.28)				
Unadjusted	3.04 (1.28–7.23)	0.012	1.58 (0.91–2.73)	0.101
Model A	2.83 (1.19–6.73)	0.019	1.48 (0.86–2.57)	0.161
Model B	2.70 (1.12–6.48)	0.027	1.43 (0.82–2.49)	0.209
Model C	2.45 (1.01–5.93)	0.048	1.34 (0.76–2.35)	0.313

A, adjustment for age and diabetes duration; B, adjustment for age, diabetes duration, total cholesterol, HDL cholesterol, and triglycerides; C, adjustment for age, diabetes duration, total cholesterol, HDL cholesterol, triglycerides, smoking, hypertension, BMI, fasting plasma glucose, area of residence, and type of diabetes therapy.

our final study population, at the baseline study, only three subjects were receiving fibrates and only one subject was receiving other lipid-lowering medication. Thus statins, which are known to prevent CHD events also in diabetic patients (24,25), did not cause bias in statistical analysis of the data.

Among diabetic women, the reported intake of carbohydrates was significantly higher in those who died from CHD or had a nonfatal or fatal MI. The reported intake of dietary fiber was similar in both groups. Thus, it is possible that in women with high total carbohydrate intake, the relative intake of simple carbohydrates was increased. In accordance with our findings in diabetic women, in nondiabetic women, a high dietary glycemic load from carbohydrates has been reported to increase the risk of CHD (26).

### Limitations of the study

1) In the present study, the nutrient data were collected using the FFQ, a method that is considered not as accurate as the DH and FR methods. Therefore, the validation of the FFQ is highly recommended (27). However, several studies reveal that the FFQ is a simple method to estimate average nutrient intake in large epidemiologic studies (28–30). The correlation coefficients between dietary intake results by the FFQ and the two other methods in our validity study were fairly good for some critical variables such as the P/S ratio. The FFQ was planned 20 years ago, and during that time, the association between MUFA and CHD had not yet been reported. This means that when the FFQ was planned, the basic goal was to get information about the intake of total fat,

SAFA, and PUFA (P/S ratio), and the foods listed on the FFQ were selected to reach this goal. This may be one explanation for the finding that the correlation of MUFA intakes between the various methods was weaker than for other nutrients. Because of the poor correlation between the FFQ and the other two methods in assessing MUFA intake, we were unable to examine the possible predictive value of MUFA intake for CHD events in the present study.

2) We have only baseline data of dietary habits. The association between nutrient intake and CHD events would probably have been more reliable if we had also had follow-up data on dietary intake.

3) We have no follow-up data on subjects' weight before or after the baseline examination. Therefore, we were not able to test the possibility that higher energy intake at baseline would have led to higher destination weight, which might have had some effect on our results.

4) Diabetic patients may have silent ischemia more often than nondiabetic subjects. We determined CHD events as symptomatic MI or CHD death. Therefore, we may have slightly underestimated the incidence of CHD events. However, it is likely that silent MI occurs similarly in patients with various nutrient intakes, e.g., various P/S ratio values.

Our study demonstrates that a low P/S ratio is predictive of future fatal CHD events in men. Thus, our results support the idea that the dietary recommendations (17) given for the whole population aimed at the prevention of CHD are also valid for diabetic patients, at least for men.

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