

## Fish and Long-Chain $\omega$ -3 Fatty Acid Intake and Risk of Coronary Heart Disease and Total Mortality in Diabetic Women

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**Background**—Although several prospective cohort studies have found an inverse association between fish consumption and risk of coronary heart disease (CHD) or sudden cardiac death in the general population, limited data are available among diabetic patients.

**Methods and Results**—We examined prospectively the association between intake of fish and  $\omega$ -3 fatty acids and risk of CHD and total mortality among 5103 female nurses with diagnosed type 2 diabetes but free of cardiovascular disease or cancer at baseline. Between 1980 and 1996 (45 845 person-years of follow-up), we documented 362 incident cases of CHD (141 CHD deaths and 221 nonfatal myocardial infarctions) and 468 deaths from all causes. Compared with women who seldom consumed fish (<1 serving/mo), the relative risks (RRs) (95% CI) of CHD adjusted for age, smoking, and other established coronary risk factors were 0.70 (0.48 to 1.03) for fish consumption 1 to 3 times per month, 0.60 (0.42 to 0.85) for once per week, 0.64 (0.42 to 0.99) for 2 to 4 times per week, and 0.36 (0.20 to 0.66) for 5 or more times per week ( $P$  for trend=0.002). Higher consumption of fish was also associated with a significantly lower total mortality (multivariate RR=0.48 [0.29 to 0.80] for  $\geq 5$  times per week [ $P$  for trend=0.005]). Higher consumption of long-chain  $\omega$ -3 fatty acids was associated with a trend toward lower incidence of CHD (RR=0.69 [95% CI 0.47 to 1.03],  $P$  for trend=0.10) and total mortality (RR=0.63 [95% CI, 0.45 to 0.88],  $P$  for trend=0.02).

**Conclusions**—A higher consumption of fish and long-chain  $\omega$ -3 fatty acids was associated with a lower CHD incidence and total mortality among diabetic women. (*Circulation*. 2003;107:1852-1857.)

**Key Words:** coronary disease ■ nutrition ■ fish ■ fatty acids ■ women

The role of long-chain  $\omega$ -3 fatty acids in the management and treatment of diabetes has received much attention in the literature. Fish oil supplementation substantially lowers triglyceride levels in diabetic individuals.<sup>1</sup> Because hypertriglyceridemia is a hallmark of diabetic dyslipidemia and an important risk factor for cardiovascular disease among diabetic patients,<sup>2</sup> fish oil may have an important role in treating hypertriglyceridemia in diabetics. In addition, fish oil has been shown to decrease endothelial cell activation and improve endothelial dysfunction among diabetics.<sup>3</sup> Other potential benefits of long-chain  $\omega$ -3 fatty acids for diabetes include reduction of platelet aggregability<sup>4</sup> and antiarrhythmic effects.<sup>5</sup> Furthermore, higher fish intake has been associated with lower risk of microalbuminuria in type 1 diabetic patients.<sup>6</sup> A potential concern is that fish oil may worsen glycemic control among diabetic patients,<sup>7,8</sup> but this adverse effect was not substantiated in 2 recent meta-analyses of metabolic studies.<sup>9,10</sup>

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Although several prospective cohort studies have found an inverse association between fish consumption and risk of coronary heart disease (CHD) or sudden cardiac death in the general population,<sup>11–15</sup> limited data are available among diabetic patients. We therefore examined prospectively the association between fish and long-chain  $\omega$ -3 fatty acid intake and incidence of CHD and total mortality among diabetic women in the Nurses' Health Study cohort.

### Methods

#### Study Population

The Nurses' Health Study cohort was established in 1976 when 121 700 female registered nurses, 30 to 55 years old and residing in 11 large US states, completed a mailed questionnaire about their medical history and lifestyle. Every 2 years, follow-up questionnaires have been sent to update information on potential risk factors and to identify newly diagnosed cases of CHD and other illness. The

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present study included the 5103 women who reported physician-diagnosed type 2 diabetes mellitus on any questionnaire from 1976 to 1994 (1694 prevalent diabetic women in 1980 and 3409 incident diabetic women during the follow-up). Women with a history of CHD (including myocardial infarction, angina, and/or coronary revascularization), stroke, or cancer reported on the 1980 questionnaire (when diet was first assessed), or before, were excluded at baseline.

### Confirmation of Diabetes Mellitus

A supplementary questionnaire regarding symptoms, diagnostic tests, and hypoglycemic therapy was mailed to women who indicated on any biennial questionnaire that they had been diagnosed with diabetes. A case of diabetes was considered confirmed if at least 1 of the following was reported on the supplementary questionnaire: (1) classic symptoms plus fasting plasma glucose of  $\geq 140$  mg/dL (7.8 mmol/L) or random plasma glucose  $\geq 200$  mg/dL (11.1 mmol/L), (2)  $\geq 2$  elevated plasma glucose concentrations on different occasions (fasting plasma glucose  $\geq 140$  mg/dL [7.8 mmol/L] or random plasma glucose  $\geq 200$  mg/dL [11.1 mmol/L] and/or concentration  $\geq 200$  mg/dL after  $\geq 2$  hours on oral glucose tolerance testing) in the absence of symptoms, or (3) treatment with hypoglycemic medication (insulin or oral hypoglycemic agent). The validity of this questionnaire has been verified in a subsample of this study population.<sup>16</sup> Among a random sample of 84 women classified by the questionnaire as having type 2 diabetes mellitus, 71 gave permission for their medical records to be reviewed, and records were available for 62. An endocrinologist blinded to the information reported on the supplementary questionnaire reviewed the records according to National Diabetes Data Group criteria.<sup>17</sup> The diagnosis of type 2 diabetes mellitus was confirmed in 61 of 62 of the women (98%). We used the National Diabetes Data Group diagnostic criteria because the analytic cohort preceded the American Diabetes Association guideline published in 1997.<sup>18</sup> In our primary analyses, we used self-reported diabetes to define the analytic cohort. Secondary analyses including only diabetic women confirmed by the supplementary questionnaire yielded similar results (consisting of  $\approx 80\%$  of cases).

### Ascertainment of Diet

The semiquantitative food frequency questionnaire used in 1980 included 61 foods, including a single question assessing fish intake.<sup>19</sup> A common unit or portion size for each food (eg, 6 to 8 oz for fish) was specified, and each woman was asked how often on average during the previous year she had consumed that amount. Nine responses were possible for each food item, ranging from "almost never" to "6 or more times per day." In 1984, 1986, 1990, and 1994, the dietary questionnaire was expanded to include 4 fish and seafood items: (1) dark-meat fish such as mackerel, salmon, sardines, bluefish, or swordfish (3 to 5 oz); (2) canned tuna (3 to 4 oz); (3) other fish (3 to 5 oz); and (4) shrimp, lobster, or scallops as main dish (3 to 5 oz). The average daily intake of nutrients was calculated by multiplying the frequency of consumption of each item by its nutrient content per serving and totaling the nutrient intake for all food items. We first collected information on fish oil supplements in 1990. However, we were not able to study the effects of fish oil supplements because the use was very low in our cohort ( $\approx 1.6\%$  in 1990).

The calculation of long-chain  $\omega$ -3 fatty acid intake was described in detail elsewhere.<sup>14</sup> Briefly, to calculate intake of  $\omega$ -3 fatty acids (eicosapentaenoic acid and docosahexanoic acid), we assigned grams per serving as follows: 1.51 for dark-meat fish, 0.42 for canned tuna fish, 0.48 for other fish, and 0.32 for shrimp, lobster or scallops. These  $\omega$ -3 fatty acid values were derived by weighting the mean values of  $\omega$ -3 fatty acids for the most common types of fish on the basis of US landing data in 1984 (US Department of Commerce). For the 1980 questionnaire, we assigned 1.16 g of long-chain  $\omega$ -3 fatty acids per portion (6 to 8 oz) of fish. This number was calculated as a weighted average of the relative composition of  $\omega$ -3 fatty acid composition from dark-meat fish, canned tuna, and other fish on the 1984 dietary questionnaire. In a validation study, the energy-adjusted intake of eicosapentaenoic acid from fish estimated by the food frequency questionnaire was significantly correlated with percentage

of eicosapentaenoic acid in adipose tissue (Spearman correlation coefficient, 0.49;  $P < 0.001$ ).<sup>20</sup>

### End Point Ascertainment

The end point for this study was incidence of CHD (including CHD deaths and nonfatal myocardial infarction) and all-cause mortality occurring after return of the 1980 questionnaire but before June 1, 1996. We sought to review medical records for all self-reported myocardial infarctions. Records were reviewed by physicians with no knowledge of the self-reported risk factor status. Myocardial infarction was confirmed according to World Health Organization criteria: symptoms plus either diagnostic ECG changes or elevated cardiac enzymes.<sup>21</sup> Infarctions that required hospital admission and for which confirmatory information was obtained by interview or letter but for which no medical records were available were designated as probable (17%). Excluding probable cases from the analyses did not materially alter the results.

Deaths were identified from state vital records and the National Death Index or reported by next of kin and the postal system. Follow-up for the deaths was  $>98\%$  complete.<sup>22</sup> We obtained copies of death certificates and medical records and determined causes of death (classified according to the categories of the International Classification of Diseases, Ninth Revision [ICD-9]). Fatal coronary disease was defined as fatal myocardial infarction if this was confirmed by hospital records or autopsy or if coronary disease was listed as the cause of death on the certificate and this was the underlying and most plausible cause and evidence of previous coronary disease was available. We designated as presumed coronary disease (15% of fatal cases) those in which coronary disease was the underlying cause on the death certificate but no records were available.

### Statistical Analyses

For women who reported diabetes on the 1980 or earlier questionnaires, person-months of follow-up were calculated from the date of return of the 1980 questionnaire to the first end point, death, or June 1, 1996, whichever came first. For women who developed diabetes during the follow-up, person-months were calculated from the date of return of the questionnaire on which diabetes diagnosis was reported. Women who reported having cardiovascular disease on previous questionnaires were excluded from subsequent follow-up.

Because of the long follow-up period, dietary variables were updated to better represent long-term dietary patterns, using the information from 1980, 1984, 1986, 1990, and 1994 dietary questionnaires. We calculated intakes of fish and  $\omega$ -3 fatty acids as a cumulative average of intake from all available dietary questionnaires up to the start of each 2-year follow-up interval in which events were reported.<sup>23</sup> We stopped updating diet when a person developed hypertension or hypercholesterolemia during the follow-up, because development of these conditions may lead to changes in diet.<sup>24</sup> The other nutrient variables (fiber, trans fat, and the ratio of polyunsaturated to saturated fats) and intake of fruits and vegetables and red meat (beef, pork, or lamb as main dish or mixed dish) were also calculated as cumulative averages of intake.

We divided women into 5 categories according to frequency of fish consumption ( $<1$ /mo, 1 to 3/mo, 1/wk, 2 to 4/wk, and 5+/wk) or quintiles of  $\omega$ -3 fatty acids (as percentage of total energy) and calculated incidence rates by dividing the number of events by person-time of follow-up in each category. The relative risk (RR) was computed as the rate in a specific category of fish or  $\omega$ -3 fatty acid consumption divided by that in the lowest category, with adjustment for age in 5-year categories. In multivariate analyses using pooled logistic regression (asymptotically equivalent to Cox regression with time-varying covariate),<sup>25</sup> we simultaneously included total energy intake, cigarette smoking, body mass index, menopausal status and postmenopausal hormone use, alcohol use, history of hypertension and high cholesterol, multivitamin use, vitamin E supplement use, family history of myocardial infarction, physical activity (number of hours spent on moderate to vigorous exercise per week), and aspirin use. We also adjusted for duration of diabetes and use of insulin or other hypoglycemic therapy reported

**TABLE 1. Age-Adjusted Baseline Characteristics According to the Intake of Fish and  $\omega$ -3 Fatty Acids Among Diabetic Women in 1980**

	Fish Consumption, Servings			$\omega$ -3 Fat Intake		
	<1/mo (n=159)	1/wk (n=676)	5+ /wk (n=82)	Lowest (n=361)	Intermediate (n=405)	Highest (n=331)
Mean value						
Age, y	47.8	48.8	50.2	47.2	48.7	49.5
Body mass index, kg/m <sup>2</sup>	27.8	28.1	28.7	27.5	27.9	29.0
Physical activity, h/wk	3.1	3.2	4.0	3.1	3.1	4.0
Alcohol, g/d	2.7	3.9	1.9	4.2	3.9	3.0
Saturated fat, g/d	31.4	28.7	21.7	30.6	29.0	25.0
Polyunsaturated fat, g/d	9.5	9.6	8.3	9.5	9.7	8.8
<i>Trans</i> fat, g/d	4.2	4.1	2.7	4.3	4.2	3.3
Fiber, g/d	13.7	14.9	17.4	13.2	14.6	16.6
Glycemic index	53.9	53.2	50.9	53.7	53.5	51.5
Glycemic load	98.6	96.4	93.3	97.4	97.1	94.4
$\alpha$ -Linolenic acid, g/d	1.1	1.1	1.1	1.1	1.1	1.1
Fruits, servings/d	2.1	2.6	3.3	2.2	2.5	2.9
Vegetables, servings/d	2.0	2.1	2.9	1.7	2.0	2.7
Red and processed meats, servings/d	1.7	1.6	1.1	1.7	1.7	1.3
Duration of diabetes, y	7.0	8.1	8.0	8.4	8.0	7.9
Percent of women						
Parental history of MI before age 60 y	16.2	20.2	15.7	18.0	19.7	21.2
Current smoking	37.2	26.7	23.8	33.2	27.3	27.7
History of hypertension	44.6	46.4	63.7	40.1	44.8	51.1
History of hypercholesterolemia	15.9	15.0	20.2	13.7	17.8	22.4
Multivitamin use	39.6	34.7	52.2	36.2	30.5	42.5
Vitamin E supplement use	9.6	12.6	27.3	12.2	12.3	23.9
Current estrogen therapy among postmenopausal women	19.6	20.3	14.9	19.2	27.9	26.7
Aspirin use $\geq 1 \times$ /wk	40.9	37.9	40.6	42.6	42.1	38.4
Insulin use	37.5	45.3	41.7	43.7	47.3	44.9
Oral hypoglycemic medication only	25.6	27.0	24.0	25.9	27.4	29.7

on the supplementary diabetes questionnaire or the 1988 main questionnaire.

## Results

Between 1980 and 1996 (45 845 person-years of follow-up), we documented 362 incident cases of CHD (141 CHD deaths and 221 nonfatal myocardial infarctions) and 468 deaths from all causes (161 from CHD or stroke, 172 from cancer, and 135 from other causes). Compared with diabetic women who seldom ate fish, those with a higher fish consumption were older and slightly heavier, had a lower prevalence of current smoking, and had a higher prevalence of hypertension, high blood cholesterol, and multivitamin and vitamin E supplement use (Table 1). Fish consumption was positively associated with intake of fruits and vegetables and inversely associated with intake of red and processed meats.

Table 2 presents RRs of CHD and total mortality according to fish intake. We observed significant inverse associations between fish intake and incidence of CHD after adjustment for age ( $P$  for trend=0.003). After further adjustment for

other cardiovascular risk factors, RRs (95% CI) were 0.70 (0.48 to 1.02) for fish consumption 1 to 3 times per month, 0.60 (0.42 to 0.85) for once per week, 0.65 (0.43 to 0.99) for 2 to 4 times per week, and 0.38 (0.21 to 0.68) for  $\geq 5$  times per week ( $P$  for trend=0.002). Further adjustment for other dietary factors did not appreciably alter the results. A higher fish consumption was associated with a significantly lower risk of both fatal CHD (multivariate RR for 5+ /wk, 0.41; 95% CI, 0.18 to 0.94) and nonfatal myocardial infarction (multivariate RR for 5+ /wk, 0.28; 95% CI, 0.11 to 0.71). Additional adjustment for fruits, vegetables, and red meat did not materially affect the RRs. Among the 4 different types of fish on which we first collected information in 1984, only dark-meat fish and shrimp intakes were inversely associated with risk of CHD (multivariate RRs comparing  $\geq 2$  times/wk with <1/mo, 0.38 [0.05 to 2.75] for dark-meat fish and 0.43 [0.06 to 3.14] for shrimp). The wide 95% CIs reflect a small number of cases.

For total mortality, the age-adjusted RRs across categories of fish intake were 1.0, 0.64, 0.61, 0.56, and 0.54 ( $P$  for

**TABLE 2. RR (95% CI) of CHD in a Cohort of 5103 Diabetic Women Followed Up From 1980 to 1996 According to the Average Frequency of Fish Intake**

	Average Frequency of Fish Intake					P for Trend
	<1/mo	1-3/mo	1/wk	2-4/wk	5+/wk	
<b>CHD incidence</b>						
No. of cases	41	92	161	52	16	...
Person-years	3170	11 685	21 705	6495	2790	...
Age adjusted*	1.0	0.63 (0.43-0.91)	0.55 (0.39-0.78)	0.59 (0.39-0.99)	0.40 (0.22-0.71)	0.003
Multivariate I†	1.0	0.70 (0.48-1.02)	0.60 (0.42-0.85)	0.65 (0.43-0.99)	0.38 (0.21-0.68)	0.002
Multivariate II‡	1.0	0.70 (0.48-1.03)	0.60 (0.42-0.85)	0.64 (0.42-0.99)	0.36 (0.20-0.66)	0.002
<b>Total mortality</b>						
No. of deaths	48	114	219	60	27	...
Person-years	3209	11 784	21 837	6554	2808	...
Age adjusted*	1.0	0.64 (0.46-0.91)	0.61 (0.44-0.83)	0.56 (0.38-0.83)	0.54 (0.34-0.88)	0.01
Multivariate I†	1.0	0.75 (0.53-1.07)	0.67 (0.49-0.93)	0.69 (0.47-1.02)	0.49 (0.30-0.81)	0.006
Multivariate II‡	1.0	0.75 (0.53-1.07)	0.66 (0.48-0.92)	0.67 (0.45-1.01)	0.48 (0.29-0.80)	0.005

\*Adjusted for age (5-year categories) and time intervals.

†Adjusted for factors cited above and for smoking status (never, past, current 1-14.9, 15-24, ≥25 cigarettes/d), body mass index (<22, 22-22.9, 23-24.9, 25-28.9, ≥29 kg/m<sup>2</sup>), alcohol intake (0, 0.1-4.9, 5-14, ≥15 g/d), parental history of myocardial infarction, menopausal status and postmenopausal hormone use, moderate to vigorous activities (<1, 1-1.9, 2-3.9, 4-6.9, ≥7 h/wk), usual aspirin use (<1/wk, 1-2/wk, 3-6/wk, 7-14/wk, and 15+/wk), multivitamin supplement use (yes vs no), vitamin E supplement use (yes vs no), history of hypertension (yes vs no), hypercholesterolemia (yes vs no), duration of diabetes (<5, 5-10, 11-15, >15 y), and hypoglycemic medication (none, oral medicine only, insulin use).

‡Adjusted for factors cited above and *trans* fat, the ratio of polyunsaturated fat to saturated fat, and dietary fiber (all in quintiles).

trend=0.01). After adjustment for lifestyle and dietary factors, the RRs were 1.0, 0.75, 0.66, 0.67, and 0.48 (*P* for trend=0.005). The inverse association was observed for both cardiovascular disease mortality (multivariate RR comparing extreme categories of fish intake was 0.47; 95% CI, 0.21 to 1.03) and noncardiovascular mortality (corresponding RR, 0.50; 95% CI, 0.26 to 0.93).

Intake of long-chain ω-3 fatty acids was associated with a significantly lower risk of CHD in age-adjusted analysis (RR comparing extreme quintiles, 0.67; 95% CI, 0.46 to 0.98; *P*

for trend=0.03) (Table 3). The RRs were slightly attenuated in multivariate analyses (RR comparing extreme quintiles, 0.69; 95% CI, 0.47 to 1.03; *P* for trend=0.10). We considered the possibility that the weaker association with ω-3 fatty acids than with fish might be because of a more extreme contrast with the latter and perhaps greater measurement error in calculating ω-3 fatty acids. Also, the event rate for CHD in the reference group for ω-3 fatty acid analysis was somewhat lower than that in the reference group for fish analysis (7.5/1000 versus 12.9/1000).

**TABLE 3. RR\* (95% CI) of CHD in a Cohort of 5103 Diabetic Women Followed Up From 1980 to 1996 According to Quintiles of ω-3 Fatty Acid Intake**

	Quintiles of Average ω-3 Fatty Acids (Median Intake, g/d)					P for Trend
	1 (0.04)	2 (0.06)	3 (0.09)	4 (0.15)	5 (0.25)	
<b>CHD incidence</b>						
No. of cases	56	113	77	67	49	...
Person-years	7421	11 822	10 334	8462	7806	...
Age adjusted	1.0	1.04 (0.77-1.41)	0.88 (0.62-1.23)	0.92 (0.66-1.28)	0.67 (0.46-0.98)	0.03
Multivariate I	1.0	0.97 (0.71-1.32)	0.86 (0.61-1.21)	0.94 (0.67-1.32)	0.71 (0.48-1.04)	0.11
Multivariate II	1.0	0.96 (0.71-1.31)	0.85 (0.60-1.20)	0.92 (0.66-1.30)	0.69 (0.47-1.03)	0.10
<b>Total mortality</b>						
No. of deaths	77	131	101	87	72	...
Person-years	7475	11 924	10 420	8515	7857	...
Age adjusted	1.0	0.83 (0.64-1.08)	0.80 (0.60-1.07)	0.75 (0.56-1.01)	0.63 (0.46-0.86)	0.004
Multivariate I	1.0	0.78 (0.60-1.02)	0.77 (0.58-1.04)	0.79 (0.59-1.06)	0.65 (0.47-0.90)	0.02
Multivariate II	1.0	0.77 (0.58-1.00)	0.76 (0.56-1.02)	0.77 (0.57-1.05)	0.63 (0.45-0.88)	0.02

\*The covariates in the models are the same as those listed in Table 2.

Because aspirin also has antiplatelet activity, analyses were stratified by regular aspirin use. The inverse association between  $\omega$ -3 fatty acids and CHD appeared to be stronger for non-aspirin users (multivariate RR comparing extreme quintile, 0.56; 95% CI, 0.29 to 1.06) than for regular aspirin users (corresponding RR, 0.82; 95% CI, 0.49 to 1.36). However, the test for interaction between regular aspirin use and  $\omega$ -3 fatty acid intake was not statistically significant ( $P$  for interaction=0.30).

For total mortality, the age-adjusted RRs according to quintiles of  $\omega$ -3 fatty acid intake were 1.0, 0.83, 0.80, 0.75, and 0.63;  $P$  for trend=0.004. Adjustment for lifestyle and dietary factors did not appreciably change the RRs for total mortality (RR comparing extreme quintiles of  $\omega$ -3 fatty acids, 0.63; 95% CI, 0.45 to 0.88;  $P$  for trend=0.02).

The statistical test for interaction between diabetes status and fish consumption on CHD risk was not statistically significant ( $P$  for interaction=0.21), suggesting that the associations did not differ significantly between women with and without diabetes. The multivariate RRs of CHD for nondiabetic women (1257 CHD cases) across categories of fish consumption were 1.0, 0.88, 0.80, 0.75, and 0.78 ( $P$  for trend=0.028).

## Discussion

In this prospective cohort study of diabetic women, higher consumption of fish and  $\omega$ -3 fatty acids was associated with a lower incidence of both CHD and total mortality, even after adjustment for established cardiovascular risk factors. The inverse association was not explained by dietary predictors of CHD, including fiber, trans fatty acids, the ratio of polyunsaturated to saturated fats, and intake of fruits, vegetables, and red meat.

Type 2 diabetes is characterized by lipid and lipoprotein metabolism abnormalities, increased platelet aggregation and clotting, endothelial dysfunction, and increased cardiac arrhythmia risk, all of which are associated with accelerated cardiovascular incidence and mortality.<sup>26</sup>  $\omega$ -3 fatty acids may reduce CHD incidence and mortality among diabetics through multiple mechanisms, including reduction of blood triglycerides,<sup>27</sup> inhibition of platelet aggregability,<sup>4</sup> and antiarrhythmic effects.<sup>5</sup> In addition, fish oil may improve endothelial dysfunction, an early marker of atherosclerosis, especially among diabetic patients.<sup>28,29</sup> The antiarrhythmic effects of  $\omega$ -3 fatty acids are well established.<sup>5</sup> Because diabetics are more prone to ventricular arrhythmia and sudden cardiac death,<sup>30,31</sup> an adequate intake of long-chain  $\omega$ -3 fatty acids may be particularly important for diabetic patients. In the present study, we were not able to study sudden cardiac death as an end point because of a relatively small sample size.

In addition to cardiovascular benefits, higher fish consumption may reduce the risk of microvascular complications. In a nested case-control study of 1150 patients with type 1 diabetes,<sup>6</sup> higher fish intake was associated with a significantly lower risk of microalbuminuria, after adjustment for HbA1c, age, sex, and other potential confounding variables. Although we were not able to study the association between fish consumption and microvascular complications, our analyses suggest that a higher consumption of fish intake

was associated with a lower mortality from noncardiovascular causes.

Concerns have been raised that fish oil may worsen glycemic control by diverting substrates from lipogenesis to gluconeogenesis in the process of inhibiting hepatic triglyceride synthesis.<sup>7,8,32</sup> Two recent meta-analyses, however, found no significant adverse effects of fish oil supplementation on glycemic control, despite fish oil's lowering triglyceride levels by  $\approx$ 30%.<sup>9,10</sup> There is some evidence that fish oil supplements cause a slight increase in LDL cholesterol among diabetic patients.<sup>9,10</sup> Thus, the combined effects of fish oil and statins on diabetic dyslipidemia need to be investigated. In a recent study, fish oil supplementation was shown to potentiate the beneficial effects of statins on lipid profile for coronary patients with combined hyperlipemia by reducing postprandial hyperlipemia and small dense LDL.<sup>33</sup>

One limitation of our study is that we do not have direct measures of glycemic control and severity of diabetes. However, we adjusted for duration of diabetes and use of insulin and hypoglycemic medications and obtained similar results, suggesting that our findings are unlikely to be explained by confounding because of severity of the disease. Because diabetes is self-reported, there is a potential for misclassification. Nonetheless, self-report of this diagnosis has previously been shown to be valid in this cohort, and analyses restricted to confirmed cases yielded similar results.

Because of the observational nature of our study, we cannot completely exclude the possibility that the observed association is because of unmeasured or residual confounding, although we have carefully controlled for important dietary and lifestyle confounding variables. Previous clinical trials<sup>34-36</sup> have demonstrated protective effects of increased fish consumption or fish oil supplementation against coronary mortality and sudden cardiac death among patients with coronary disease, but controlled trials of the effects of fish oil supplementation on prevention of CHD and mortality among diabetic patients have not been conducted and would be useful. A recent study suggested that a higher mercury intake might attenuate the benefits of long-chain  $\omega$ -3 fatty acids.<sup>37</sup> We were not able to test this hypothesis because our study did not assess mercury exposure.

In conclusion, this prospective study provides evidence for an inverse association between fish and long-chain  $\omega$ -3 fatty acid consumption and risk of CHD and total mortality among diabetic women. These findings suggest that regular fish consumption should be considered as part of a healthy diet for diabetic management.

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