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Omega-3 fatty acids and incident type 2 diabetes: the Singapore Chinese Health Study[1–4]

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ABSTRACT

Background: The role of omega-3 (n–3) fatty acids (FAs) in the development of type 2 diabetes is uncertain, especially with regard to any differential influence of α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA).

Objective: The objective was to examine the association between total omega-3 FAs, marine omega-3 (EPA, DHA), nonmarine omega-3 (ALA), and omega-6 (n–6) FAs and omega-6:omega-3 ratio and risk of type 2 diabetes in a Chinese population in Singapore.

Design: The analysis included 43,176 Chinese men and women free of chronic disease, aged 45–74 y, in the Singapore Chinese Health Study. Baseline data collection occurred between 1993 and 1998, with follow-up interviews between 1999 and 2004. Cox regression models were used to examine the associations between FA intakes at baseline and risk of developing diabetes.

Results: Increased intakes of total omega-3 FAs were inversely associated with diabetes incidence [hazard ratio (HR) for the fifth compared with the first quintile: 0.78; 95% CI: 0.65, 0.94; *P* for trend = 0.02]. Omega-3 FAs from marine sources were not associated with diabetes risk, whereas nonmarine omega-3 FA intake was strongly associated (HR for the fifth compared with the first quintile: 0.79; 95% CI: 0.67, 0.93; *P* for trend = 0.004). Omega-6 and omega-6:omega-3 ratio were not associated with incidence of type 2 diabetes.

Conclusion: Consumption of nonmarine sources (ALA) of omega-3 FAs is associated with a decreased risk of type 2 diabetes in Chinese Singaporeans. *Am J Clin Nutr* 2011;94:520–6.

INTRODUCTION

High relative consumption of omega-3 (n–3) and omega-6 (n–6) polyunsaturated fatty acids is thought to be beneficial for a number of chronic diseases; however, the evidence is not conclusive for the association between omega-3 fatty acids (FAs) and type 2 diabetes risk. It is thought that omega-3 and omega-6 FAs may affect the development of diabetes by modulation of insulin sensitivity in phospholipid membranes (1). Evidence suggests omega-6 FAs are generally protective for diabetes risk (2–5), whereas the evidence for omega-3 FAs is mixed. Animal studies have provided a biological model of decreased insulin resistance with increased intake (6, 7), whereas there are mixed results in prospective population-based studies (8–14), and similar mixed or null findings in clinical trials (13, 15–17).

A further question is whether marine sources of omega-3 FA [docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)] have a differential association with diabetes risk compared with nonmarine sources of omega-3 FA [α-linolenic acid (ALA)], which are found in plant-based foods such as seed oils, certain grains, legumes, and soy. Both DHA and EPA are synthesized, albeit inefficiently, from ALA (18). Indeed, the various types of omega-3 FAs can have different effects on pathways at a molecular level (19, 20), and ALA in particular may be associated with improved insulin sensitivity/glucose tolerance in animal models (21).

The Singapore Chinese Health Study (SCHS) is a population-based prospective cohort investigation of >63,000 Chinese men and women in Singapore. The SCHS presents a unique opportunity to investigate the association between diabetes risk and omega-3 FAs because the majority of omega-3 intake in this population comes from nonmarine sources (ALA). We aimed to examine the associations between overall omega-3 FA intake, nonmarine sources of omega-3, and marine-derived omega-3, as well as omega-6 intake and the omega-6:omega-3 ratio, with incident type 2 diabetes.

SUBJECTS AND METHODS

Study population

The design of the SCHS has been described previously (22). Briefly, the cohort was drawn from men and women, aged 45–74 y, who belonged to one of the major dialect groups (Hokkien or Cantonese) of Chinese in Singapore. Between April 1993 and December 1998, 63,257 individuals completed an in-person interview that included questions on demographics, height, weight, use of tobacco, usual physical activity, menstrual and reproductive history (women only), medical history, and family history of cancer, and a 165-item food-frequency section that assessed usual dietary intake of the previous year. A follow-up telephone in-

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terview took place between 1999 and 2004 for 52,325 cohort members (83% of the recruited cohort), and questions were asked to update tobacco and alcohol use, medical history, and menopausal status of women. The institutional review boards at the National University of Singapore and the University of Minnesota approved this study.

Assessment of diet and covariates

A semiquantitative food-frequency questionnaire specifically developed for this population that assessed 165 commonly consumed food items was administered during the baseline interview. During the interview the respondent referred to photographs to select from 8 food-frequency categories (which ranged from ''never or hardly ever'' to ''2 or more times a day'') and 3 portion sizes. The food-frequency questionnaire has subsequently been validated against a series of 24-h dietary recall interviews in a random sample of >1000 participants that occurred on one weekday and one weekend day ≈2 mo apart (22), as well as against selected biomarker studies (23, 24). A range of 0.24–0.79 in correlation coefficients of energy/nutrients was obtained with the use of 2 methods, and the majority of macronutrients and food groups displayed correlation coefficients in the high end of this reported range (22).

In conjunction with this cohort, the Singapore Food Composition Table was developed, a food-nutrient database that lists the levels of 96 nutritive or nonnutritive components per 100 g of cooked food and beverages in the diet of the Singaporean Chinese. The combination of information obtained from the food-frequency questionnaire and the nutrient values provided in this food-nutrient database, which accounted for raw and cooked foods, and the use of food composition and nutrient data from the Cancer Research Center of Hawaii, as well as composition tables from China, Malaysia, and Taiwan, allowed us to compute the mean daily intakes of nutrients for each subject (22). Overall, marine-based omega-3 (EPA and DHA) accounted for ≈36% of population omega-3 intake. Nonmarine omega-3 (ALA) made up the majority of total omega-3 intake, and the main dietary sources as computed from the food-nutrient database were grains (≈21% of omega-3 intake), cooking oils (≈11%), and legumes and soy (≈9%). Other known or suspected risk factors for diabetes assessed with the baseline questionnaire included age (y); smoking habits/status (age started/quit, amount, frequency, type); highest educational level reached; body mass index (BMI; in kg/m^2) calculated with the use of self-reported height and weight; and amount (h) of moderate (eg, brisk walking) and strenuous (eg, jogging) physical activity on a weekly basis.

Assessment of diabetes

Self-reported diabetes, as diagnosed by a physician, was evaluated at baseline, and participants with a history of diagnosed diabetes were excluded from analysis. Diabetes status was assessed again by the following question asked during the follow-up telephone interview: "Have you been told by a doctor that you have diabetes (high blood sugar)?" If yes: "Please also tell me the age at which you were first diagnosed?" Participants were classified as having incident diabetes if they reported development of diabetes at any time between the initial enrollment interview and the follow-up telephone interview that occurred between July 1999 and October 2004.

A validation study of the incident diabetes mellitus cases used 2 different methods and was reported in detail by Odegaard et al (25, 26). We observed a positive predictive value of 99% on the basis of a hospital-based discharge summary database and a supplementary questionnaire about symptoms, diagnostic tests, and hypoglycemic therapy, which was competed during a telephone interview, (26). Alternatively, 2625 randomly selected participants who answered "no" to the question of diabetes diagnosis at baseline and follow-up and provided blood samples at their follow-up interview were analyzed for percentage of glycated hemoglobin (Hb A_{1c}). One hundred forty-eight subjects (5.6% of the sample) had an Hb A_{1c} ≥6.5%, which meets the most recent diagnostic guidelines for the presence of diabetes (27). Thus, 94.4% of persons who reported being free of diabetes at baseline and follow-up were below the Hb A_{1c} threshold for diabetes, which yielded a very high negative predictive value (25).

Data analysis

Participants were excluded who died before the follow-up interview (7722); reported baseline diabetes (5469), cancer, heart disease, or stroke (5975); or reported extreme sex-specific energy intakes (<600 or >3000 kcal for women and <700 or >3700 kcal for men). An additional 17 subjects (0.03%) from the initial cohort migrated out of Singapore, which suggests that emigration or loss-to-follow-up among the study participants is negligible. These, along with further exclusion of 20 participants whose diabetes status was not clear after the validation effort, left 43,176 participants in the present analysis.

Person-years for each participant were calculated from the year of recruitment to the year of reported type 2 diabetes diagnosis, or year of follow-up telephone interview for those who did not report diabetes diagnoses. FAs were divided into quintiles by grams of daily intake. Cox proportional hazards were used to examine associations between FA intake amounts and type 2 diabetes risk. There was no evidence that proportional hazards assumptions were violated, as indicated by the lack of significant interaction between the dietary FAs and a function of survival time in the models.

We created 2 models. Model 1 was adjusted for age (<50, 50–54, 55–59, 60–64, ≥65 y), sex, interview year (1993–95 or 1996–98), dialect (Hokkien or Cantonese), hypertensive status, smoking (no, former, current), alcohol frequency (never, monthly, weekly, daily), education (none, primary, secondary or more), BMI (continuous and quadratic), physical activity (any or none), and hypertension (yes or no). The second model was additionally adjusted for dietary factors. All individual nutrients and FAs were modeled with the use of the residual method (28). To examine the association of specific fat subtypes, we simultaneously adjusted for all fat subtypes (ie, omega-6 FAs, monounsaturated fat, and saturated fat for omega-3 FAs) and additionally for dietary fiber, protein, and total energy intake. Because we adjusted for dietary protein, the regression coefficients are an estimate of the association of substitution of a specific fat subtype for carbohydrates in the diet. We further analyzed intakes of fish and seafood with the use of the nutrient density approach and adjusted for the aforementioned demographic and lifestyle variables and a range of dietary factors that included intakes of fruit and vegetables, soy food, poultry, and red meat as well as starch, saturated fat, fiber, and total energy. Analyses that tested for interactions, as well as stratification of

sex, age, smoking, physical activity, and BMI with the FA and fish and seafood intake were completed. Statistical analyses were conducted with the use of SAS software, version 9.1 (SAS Institute Inc, Cary, NC). All *P* values quoted are 2-sided.

RESULTS

Of 43,176 men and women with 246,898 person-years of follow-up, 2252 developed type 2 diabetes. The average follow-up time was 5.7 y. Selected baseline characteristics by quintiles of overall omega-3 intake, marine omega-3 intake, and nonmarine omega-3 intake are presented in **Table 1**. Increased total omega-3 intake was associated with greater fiber, vegetable, fruit, meat, and seafood intake and overall energy intake. Increased levels of physical activity and education were also observed. Similar trends were observed across quintiles of marine and nonmarine omega-3 intake, except fiber and fruit intake decreased slightly when the population was grouped by marine omega-3 intake, and a decrease in fish intake and no trend in smoking across nonmarine omega-3 was observed.

Hazard ratios (HRs) and 95% CIs for omega-3, omega-6, and omega-6:omega-3 ratio are presented in **Table 2**. There was no association between omega-6 intake or the omega-6:omega-3 ratio with type 2 diabetes. In comparison with the lowest intake (first quintile), there was no association between increased quintiles of total omega-3 intake and incident diabetes when adjusted for demographic, lifestyle, and BMI variables. On adjustment for dietary confounders, a graded inverse association was observed, from the third quintile (HR: 0.88; 95% CI: 0.76, 1.02) to the fifth quintile (HR: 0.78; 95% CI: 0.65, 0.94).

HRs and 95% CIs for marine omega-3 and nonmarine omega-3 are presented in **Table 3**. An inverse association with diabetes was observed with increased intake of nonmarine-derived omega-3 FAs, with significant associations in the third, fourth, and fifth quintiles compared with the first. Comparatively, marine omega-3 FAs were not significantly associated with diabetes risk. In analyses that examined various fish and shellfish types (total, fresh only, preserved only) with type 2 diabetes, we observed no association regardless of how the data were analyzed (frequency of intake or quintile ranking; data not presented). There was no evidence of any effect modification by sex, age, hypertensive status, smoking, physical activity, or BMI with the FAs through tests for interaction and stratification. We also observed no association between monounsaturated FA intake and diabetes. Last, the exclusion of diabetes cases with <2 y of follow-up time did not materially alter the results, nor did consideration of case status from the validation study.

DISCUSSION

In this large prospective cohort of Chinese men and women in Singapore, we observed an inverse association between total omega-3 FA intake and risk of incident type 2 diabetes. On examination of the source of omega-3, the association between omega-3 FAs from marine sources (EPA and DHA) was null, whereas the inverse association was robust for increased omega-3 FA intake from nonmarine sources (ALA). No association was observed between diabetes incidence and omega-6 FA, or the omega-6:omega-3 ratio.

Previous prospective studies of omega-3 FA and their association with type 2 diabetes have yielded varied results. An analysis of polyunsaturated fatty acid intake among 36,000 women in the Iowa Women's Health Study (29) showed that plant-derived FAs showed a significant, protective association with incident diabetes, whereas omega-3 FAs were not associated. Analysis of the Health Professionals Follow-Up Study and the Nurses' Health Study, however, showed an increased risk of diabetes associated with increased total omega-3 intake, and ALA did not modify the association observed in omega-3 intake, although ALA intake was not directly reported (9, 11). Another recent study from the Women's Health Study population observed no association between ALA and type 2 diabetes risk but an increased risk with greater intake of marine omega-3 FAs. A cross-sectional study of middle-aged Japanese men and women showed an inverse association between insulin resistance and higher ALA intake, but no significant associations between EPA or DHA intake and insulin resistance (30).

Two prospective studies of biomarkers also yielded opposing results. A nested cohort in the Atherosclerosis Risk in Communities (ARIC) study (10) did not observe any significant associations between incident diabetes and cholesterol ester omega-3 concentrations but did find a significant inverse relation between diabetes incidence and phospholipid omega-3 concentrations. Conversely, a study of middle-aged Swedish men (5) observed a significant association between elevated cholesterol ester omega-3 concentrations and incident diabetes.

A randomized controlled trial of ALA, EPA, and DHA supplementation in healthy subjects showed no significant associations between each FA and glucose metabolism, although the EPA diet slightly raised fasting serum glucose concentrations (13). Similarly, controlled trials of fish-oil supplementation yielded null results (15–17).

Studies of fish consumption may help to determine the associations between types of omega-3 FAs and diabetes, but the evidence is similarly mixed. A study of Dutch adults (12) showed a significant, positive association between lean fish consumption and diabetes. A nested cohort in the European Prospective Investigation into Cancer and Nutrition (EPIC) (31) observed the opposite, and showed a significant association between increased fish consumption and decreased diabetes incidence. Greater fish intake has also been shown to be associated with better glucose tolerance prospectively (32) and cross-sectionally (33). Kaushik et al (9) and Djousse et al (14) observed that increased fish consumption was associated with a modest positive increase in diabetes risk, which agreed with their omega-3 findings. We, on the other hand, observed no association between fish consumption or marine omega-3 FAs and type 2 diabetes. One trial that examined codfish intake as a source of protein showed that it improved insulin sensitivity in insulin-resistant subjects relative to other sources of protein (34).

It has been posited that potential toxins commonly found in fish may play a role in the positive diabetes associations observed with greater intake amounts (9, 12). Yet, the body of literature on the topic is sparse (35, 36). Larger, predator fish inherently accumulate higher concentrations of environmental pollutants and contaminants, which provides a theoretically plausible role in diabetes etiology (37–39), but there is no clear understanding to date.

With regard to the results from the omega-6 FA portion of our analysis, the Nurses' Health Study (2) showed a significant

TABLE 1
Participant characteristics according to quintile (Q) of overall and partitioned omega-3 fatty acid intake[1]

	Total omega-3			Marine omega-3			Nonmarine omega-3		
Characteristic	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5
n	8635	8636	8635	8635	8636	8635	8635	8636	8635
Age (y)	57.1 ± 8.0[2]	55.0 ± 7.5	53.8 ± 7.1	56.5 ± 8.0	55.3 ± 7.5	53.9 ± 7.1	57.0 ± 8.0	55.0 ± 7.4	53.9 ± 7.2
BMI (kg/m^2)	23.0 ± 3.3	23.0 ± 3.2	23.1 ± 3.1	22.8 ± 3.2	23.0 ± 3.2	23.2 ± 3.2	23.1 ± 3.3	23.0 ± 3.2	23.0 ± 3.2
Sex, female (%)	68.3	57.2	47.2	64.2	58.9	46.8	67.3	56.9	48.5
Education (%)[3]	20.2	29.9	42.5	27.7	29.5	35.5	18.1	30.4	44.0
Hypertension (%)[4]	19.3	19.7	19.4	19.1	19.8	19.5	19.6	20.0	19.2
Physical activity (%)[5]	21.1	28.4	35.0	25.1	27.0	31.7	19.1	27.6	35.7
Smoking, ever (%)	26.2	27.1	29.1	25.2	26.2	32.5	27.9	26.8	27.6
Total energy (kcal)	1077 ± 272	1531 ± 325	2136 ± 540	1262 ± 399	1510 ± 434	2003 ± 549	1071 ± 266	1544 ± 322	2105 ± 562
Saturated fat (% kcal)	7.7 ± 2.4	9.0 ± 2.3	9.8 ± 2.5	8.1 ± 2.6	8.8 ± 2.4	9.8 ± 2.5	7.7 ± 2.4	9.0 ± 2.3	9.8 ± 2.6
MUFA (% kcal)	7.3 ± 1.9	8.5 ± 1.8	9.6 ± 1.9	7.6 ± 2.1	8.5 ± 1.8	9.5 ± 1.9	7.4 ± 1.9	8.5 ± 1.8	9.4 ± 2.0
Total omega-3 (g/d)	0.45 ± 0.09	0.82 ± 0.05	1.54 ± 0.40	0.56 ± 0.25	0.85 ± 0.28	1.36 ± 0.45	0.50 ± 0.15	0.82 ± 0.16	1.49 ± 0.44
Marine omega-3 (g/d)	0.16 ± 0.07	0.31 ± 0.10	0.52 ± 0.22	0.11 ± 0.05	0.30 ± 0.02	0.60 ± 0.16	0.23 ± 0.13	0.31 ± 0.15	0.43 ± 0.23
Nonmarine omega-3 (g/d)	0.29 ± 0.08	0.51 ± 0.10	1.02 ± 0.39	0.45 ± 0.24	0.55 ± 0.28	0.76 ± 0.39	0.27 ± 0.06	0.51 ± 0.03	1.06 ± 0.36
Omega-6 (g)	4.3 ± 1.77	7.5 ± 2.5	13.0 ± 4.63	5.7 ± 3.1	7.6 ± 3.36	11.2 ± 5.13	4.2 ± 1.8	7.5 ± 2.54	12.9 ± 4.6
Omega-6:omega-3 ratio	9.5 ± 3.49	9.1 ± 3.0	8.5 ± 2.7	10.1 ± 3.4	9.0 ± 2.9	8.2 ± 2.83	8.8 ± 3.4	9.3 ± 3.1	8.9 ± 2.7
Fiber (g/1000 kcal)	7.7 ± 2.9	8.3 ± 2.5	8.7 ± 2.4	8.4 ± 3.0	8.2 ± 2.5	8.2 ± 2.37	7.4 ± 2.7	8.3 ± 2.5	8.8 ± 2.5
Red meat (g/1000 kcal)	16.2 ± 10.9	18.8 ± 10.4	21.5 ± 11.5	14.3 ± 10.4	19.2 ± 10.3	22.5 ± 11.5	17.9 ± 11.3	18.6 ± 10.6	20.3 ± 11.4
Fish (g/1000 kcal)	27.5 ± 15.5	36.7 ± 16.3	42.8 ± 18.3	17.6 ± 8.8	36.7 ± 11.3	53.4 ± 17.6	38.3 ± 20.3	35.1 ± 16.4	35.1 ± 16.1
Vegetables (g/1000 kcal)	69.4 ± 37.1	72.2 ± 32.1	80.7 ± 36.8	71.4 ± 40.0	71.8 ± 31.5	79.1 ± 34.3	69.3 ± 34.3	72.5 ± 33.6	79.7 ± 36.8
Fruit/juices (g/1000 kcal)	121.6 ± 105.9	135.0 ± 95.1	144.0 ± 92.9	135.3 ± 109.1	133.5 ± 94.3	132.9 ± 90.7	114.8 ± 102.5	134.6 ± 92.9	146.7 ± 94.4
Alcohol (g/d)	1.5 ± 6.8	1.6 ± 7.1	2.1 ± 7.5	1.2 ± 5.8	1.7 ± 7.2	2.5 ± 8.8	1.8 ± 7.7	1.6 ± 6.9	1.7 ± 6.8

[1] MUFA, monounsaturated fatty acid. All *P* values for trend <0.0001, with the exception of BMI ($P = 0.09$) for total omega-3, fruit ($P = 0.05$) for marine omega-3, and BMI ($P = 0.02$), smoking ($P = 0.52$), omega-6:omega-3 ratio ($P = 0.96$), and alcohol ($P = 0.37$) for nonmarine omega-3. Levels of hypertension displayed no trend across any fatty acid.

[2] Mean ± SD (all such values).

[3] Secondary or greater.

[4] Self-reported, physician diagnosed.

[5] Report of any moderate or strenuous leisure physical activity.

TABLE 2
Relative risk of type 2 diabetes according to quintile (Q) of omega-3, omega-6, and omega-6:omega-3 ratio from the Singapore Chinese Health Study[1]

	Q1	Q2	Q3	Q4	Q5	*P* for trend
Total omega-3 intake						
Mean ± SD (g/d)	0.45 ± 0.09	0.66 ± 0.04	0.82 ± 0.05	1.02 ± 0.07	1.54 ± 0.40	
Cases/person-years	469/49,272	429/49,349	465/49,463	440/49,723	449/49,091	
Model 1						
HR	1.00	0.93	0.98	0.93	0.95	0.56
95% CI		0.81, 1.06	0.86, 1.11	0.81, 1.06	0.84, 1.09	
Model 2						
HR	1.00	0.87	0.88	0.80	0.78	0.02
95% CI		0.75, 1.00	0.76, 1.02	0.68, 0.94	0.65, 0.94	
Omega-6 intake						
Mean ± SD (g/d)	3.5 ± 0.8	5.4 ± 0.5	7.1 ± 0.5	9.3 ± 0.8	14.6 ± 3.8	
Cases/person-years	467/49,289	451/49,030	479/48,801	424/49,801	431/49,977	
Model 1						
HR	1.00	0.96	1.03	0.93	0.94	0.28
95% CI		0.84, 1.09	0.91, 1.17	0.82, 1.07	0.82, 1.07	
Model 2						
HR	1.00	0.94	1.00	0.91	0.93	0.47
95% CI		0.81, 1.08	0.87, 1.17	0.78, 1.07	0.87, 1.12	
Omega-6:omega-3 ratio						
Mean ratio ± SD	5.9 ± 0.7	7.2 ± 0.3	8.3 ± 0.4	10.0 ± 0.7	14.1 ± 2.5	
Cases/person-years	487/50,042	425/49,020	474/48,098	441/49,363	425/50,375	
Model 1						
HR	1.00	0.91	1.06	0.99	0.93	0.39
95% CI		0.80, 1.04	0.93, 1.20	0.87, 1.13	0.81, 1.06	
Model 2^{β}						
HR	1.00	0.93	1.08	1.03	0.98	0.99
95% CI		0.81, 1.06	0.94, 1.24	0.89, 1.20	0.85, 1.14	

[1] Model 1 adjusted for age, sex, dialect, year of interview, educational level, BMI, physical activity, smoking status, alcohol use, and hypertension. Model 2 further adjusted for intakes of omega-6 or omega-3, monounsaturated fat, saturated fat, dietary fiber, protein, and total energy. Model 2^{β} adjusted for intakes of monounsaturated fat and saturated fat, dietary fiber, protein, and total energy. HR, hazard ratio.

protective relation of omega-6 FAs with type 2 diabetes, as have a number of other epidemiologic studies (3–5). The ARIC study of cholesterol ester and phospholipid FA concentrations yielded a similar result (10).

Sparse evidence is available on omega-6:omega-3 ratio. Although there is evidence that omega-3 and omega-6 FAs compete for metabolic enzymes, and that a greater intake of one type may unbalance the protective effects of the other (40, 41), the connection between diabetes and the omega-6–to–omega-3 ratio remains unclear. As a result, to date, expert committees have deemed the ratio not likely pertinent to chronic disease etiology, and the American Heart Association maintains recommendations for regular consumption of both omega-6 (12–22 g/d) and omega-3 (1.5–3 g/d) as preventive measures (42, 43).

Overall, evidence of the association between omega-3 FAs and type 2 diabetes risk is not conclusive. Animal- and cell-based studies have provided potential biological mechanisms, but the prospective observational studies and minimal clinical trials on the subject have not provided consistent or clear evidence for a harmful or protective role in diabetes etiology. Thorough discussion of the clinical trials and their validity is beyond the scope of this article. Further context on the data from the prospective cohort studies may help move forward the understanding of the question. The data on omega-3 FAs from these prospective analyses are derived from food-frequency questionnaires, which are very useful for ranking within populations, but have provided narrow ranges of estimated intake that may be questionable as biologically relevant.

A further consideration is the single nutrient-disease.... This is a analytic approach. Omega-3 intake does not occur in isolation, but is a nutrient that is a part of a larger dietary pattern and lifestyle. Thus, the food medium for omega-3 FA intake (fish and seafood for marine derived), how that medium is cooked (eg, fried, broiled, canned, or raw), and the foods with which the fish is consumed are also important. Indeed, fish has been a prominent food in dietary patterns that show an inverse association with diabetes risk (11, 44, 45). However, fish was associated with an increased risk of diabetes in the same core studies when examined by itself (9). Thus, the results of our study and the previously published studies highlight the complex relations between FAs and the etiology of type 2 diabetes.

Strengths of the current study include the use of a food-frequency questionnaire that was specifically developed and validated in the population and has been shown to be internally consistent and reproducible. The prospective nature, high participant response rate, detailed collection of data through face-to-face interviews, very low level of participants lost to follow-up, and validated diabetes case status are other strengths to consider in interpretation of the results. The pattern of dietary FA intake in this population makes it a unique contributor to the literature base as well.

Limitations include the fact that, inevitably, diet was measured with some error, although this would most likely result in nondifferential misclassification and likely underestimation of risk. The self-report of other lifestyle-related data, such as

TABLE 3
Relative risk of type 2 diabetes according to quintile (Q) of marine and nonmarine omega-3 fatty acids from the Singapore Chinese Health Study[1]

	Q1	Q2	Q3	Q4	Q5	*P* for trend
Marine (EPA + DHA) omega-3 intake						
Mean ± SD (g/d)	0.11 ± 0.05	0.22 ± 0.02	0.30 ± 0.02	0.38 ± 0.02	0.60 ± 0.16	
Cases/person-years	402/48,255	445/49,061	451/49,597	464/50,371	490/49,614	
Model 1						
HR	1.00	1.05	1.05	1.03	1.09	0.30
95% CI		0.92, 1.20	0.92, 1.20	0.90, 1.18	0.95, 1.24	
Model 2						
HR	1.00	1.01	0.99	0.94	0.93	0.27
95% CI		0.88, 1.17	0.85, 1.14	0.80, 1.10	0.77, 1.11	
Nonmarine (ALA) omega-3 intake						
Mean ± SD (g/d)	0.27 ± 0.06	0.40 ± 0.03	0.51 ± 0.03	0.65 ± 0.05	1.06 ± 0.36	
Cases/person-years	514/49,980	485/49,853	428/49,299	409/49,196	416/48,570	
Model 1						
HR	1.00	0.97	0.87	0.85	0.88	0.03
95% CI		0.85, 1.09	0.77, 0.99	0.75, 0.97	0.77, 1.00	
Model 2						
HR	1.00	0.91	0.81	0.78	0.79	0.004
95% CI		0.80, 1.04	0.70, 0.93	0.67, 0.90	0.67, 0.93	

[1] Model 1 adjusted for age, sex, dialect, year of interview, educational level, BMI, physical activity, smoking status, alcohol use, and hypertension. Model 2 further adjusted for intakes of omega-6, alternate omega-3, monounsaturated fat, saturated fat, dietary fiber, protein, and total energy. EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; ALA, α-linolenic acid; HR, hazard ratio.

smoking, physical activity, and BMI, may also result in some misclassification and residual confounding in our models.

In conclusion, we observed a significant inverse association between increased total omega-3 intake and incident type 2 diabetes that appears to be driven by the nonmarine sources of omega-3 (ALA). Our study adds to the incongruous literature base on the topic. More research and different approaches such as randomized feeding or supplementation studies are warranted to investigate which, if any, specific types of omega-3 FAs are involved in type 2 diabetes etiology.

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The authors' responsibilities were as follows—DPB and AOO: analyzed the data and cowrote the manuscript; and all authors: contributed to the interpretation of the results, reviewed and edited the manuscript, and approved the final version of the article. None of the authors declared a conflict of interest.

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