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Original Contribution

Fish Intake and Risks of Total and Cause-specific Mortality in 2 Population-based Cohort Studies of 134,296 Men and Women

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Despite a proposed protective effect of fish intake on the risk of cardiovascular disease, epidemiologic evidence on fish intake and mortality is inconsistent. We investigated associations of fish intake, assessed through a validated food frequency questionnaire, with risks of total and cause-specific mortality in 2 prospective cohort studies of 134,296 Chinese men and women (1997–2009). Vital status and date and cause of death were ascertained through annual linkage to the Shanghai Vital Statistics Registry database and biennial home visits. Cox regression was used to calculate hazard ratios and corresponding 95% confidence intervals. After excluding the first year of observation, the analysis included 3,666 deaths among women and 2,170 deaths among men. Fish intake was inversely associated with risks of total, ischemic stroke, and diabetes mortality; the corresponding hazard ratios for the highest quintiles of intake compared with the lowest were 0.84 (95% confidence interval (CI): 0.76, 0.92), 0.63 (95% CI: 0.41, 0.94), and 0.61 (95% CI: 0.39, 0.95), respectively. No associations with cancer or ischemic heart disease mortality were observed. Further analyses suggested that the inverse associations with total, ischemic stroke, and diabetes mortality were primarily related to consumption of saltwater fish and intake of long-chain *n*-3 fatty acids. Overall, our findings support the postulated health benefits of fish consumption.

China; diet; fish intake; men; mortality; stroke; women

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FFQ, food frequency questionnaire; HR, hazard ratio; ICD-9, *International Classification of Diseases, Ninth Revision*; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study.

Fish is a major source of long-chain *n*-3 fatty acids, which have been suggested to have beneficial effects on cardiovascular disease (CVD) and diabetes in in vitro and experimental studies (1–5). However, a recent meta-analysis of clinical trials on the association between *n*-3 fatty acid supplementation and CVD risk did not support such an effect (6). Observational studies have found inconsistent associations of fish consumption with the risks of total and CVD-related mortality (7–10). These inconsistent findings may be partly explained by differences in fish intake and cooking methods; intake of deep-fried fish was not inversely associated with mortality (11, 12). Most cohort studies of fish consumption and mortality published to date have been conducted in North American and European countries, where deep-frying of fish is common; few studies have been carried out in non-Western populations with different preferred cooking methods. In addition, few previous studies in non-Western populations have comprehensively assessed associations with various causes of death (13). In this study, we conducted a comprehensive evaluation of the association of fish intake with risks of mortality from all causes and from specific causes, including CVD, cancer, and diabetes, using data from 2 large, ongoing, population-based prospective cohort studies that include 134,296 middle-aged and elderly Chinese men and women.

MATERIALS AND METHODS

Study population

Participants from the Shanghai Women's Health Study (SWHS) and the Shanghai Men's Health Study (SMHS) were included in the analysis. These 2 population-based, prospective cohort studies recruited residents of 8 communities in urban Shanghai, China, who were aged 40–70 years between 1997 and 2000 for the SWHS and aged 40–74 years between 2002 and 2006 for the SMHS (14, 15). For the SWHS, response rates were 92.7% at baseline, 99.8% for the first follow-up, and 92.0% for the most recent follow-up (through December 31, 2009). For the SMHS, response rates were 74.1% at baseline, 97.6% at the first follow-up, and 93.6% for the most recent follow-up. The study protocols were approved by the institutional review boards of all institutions involved in the study, and written informed consent was obtained from all participants prior to interview.

Dietary assessment

Intakes of fish, as well as red meat, poultry, fruits, and vegetables, were quantitatively assessed using food frequency questionnaires (FFQs), which were developed and validated separately for women (16) and men (17). Both FFQs used the same format and included the same questions for fish intake based on 5 items for fish and shellfish (i.e., saltwater fish, freshwater fish, shrimp, eel, and conch). The correlation coefficients for correlation between fish intakes derived from the FFQ and multiple 24-hour dietary recalls, which covered approximately the same period as the FFQ, were 0.49 for both women and men. Both FFQs assessed typical intake during the year before study enrollment by asking about the frequency of consumption (5 categories ranging from never to every day) and amount of consumption in liang (1 liang is equivalent to 50 g). The Chinese Food Composition Tables were used to calculate daily intakes of total calories and nutrients (18).

Cohort follow-up and death ascertainment

Participant files were linked to the Shanghai Vital Statistics Registry annually, and in-person visits to participants' homes were made biennially. All possible matches identified through the linkage were verified by home visits. The underlying cause of death reported on the death certificate was considered to be the cause of death in the analysis and was coded according to the *International Classification of Diseases, Ninth Revision* (ICD-9) (19). Causes of death were first grouped into 3 major diseases, including cancer (ICD-9 codes 140–208), CVD (ICD-9 codes 390–459), and diabetes mellitus (ICD-9 codes 250). Deaths due to CVD were further divided into the following categories: ischemic heart disease (ICD-9 codes 410–414), hemorrhagic stroke (ICD-9 codes 430–431), ischemic stroke (ICD-9 codes 433–435), acute myocardial infarction (ICD-9 codes 410), and other CVD (ICD-9 codes 390–409, 415–429, and 436–459).

Statistical analysis

All statistical analyses were conducted using SAS, version 9.3 (SAS Institute Inc., Cary, North Carolina). In the current analyses, we excluded participants with a reported total energy intake outside the range of 500–4,000 kcal/day (45 women, 91 men) and those with no follow-up (8 women, 14 men). We further excluded participants who died during the first year of follow-up (145 women, 248 men) to minimize the possibility of reverse causality. One male participant who did not answer all questions about smoking history was also excluded. The final analyses included 73,159 women and 61,137 men.

Quintiles of intakes of total fish, saltwater fish, freshwater fish, shrimp, and long-chain n-3 fatty acids (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)), which are found primarily in fatty fish, were created separately for women and men based on their distributions at baseline in each cohort. Tests for linear trend across quintiles were based on median values in each quintile and were conducted by modeling the median values as continuous variables. The risk of mortality was assessed as total (all causes) and cause-specific, as described above. Cox proportional hazards regression was used to calculate hazard ratios and corresponding 95% confidence intervals for each quintile of intake using the lowest quintile as the reference category. Hazard ratios and 95% confidence intervals were derived separately for men and women. Entry time was defined as age 1 year after study enrollment, and exit time was defined as age at death or censoring (December 31, 2009, which was the date of the latest record linkage available for analysis), whichever came first.

The final model was adjusted for age at baseline (years; continuous), total energy intake (kcal/day; continuous), smoking history (pack-years of smoking for men; ever/never smoking for women), income (sex-specific; 4 categories), occupation (3 categories), education (4 categories), comorbidity index (3 categories based on the number of existing chronic diseases) (20), physical activity (5 categories based on metabolic equivalent-hours per day), red meat intake (quintiles), poultry intake (quintiles), total vegetable intake (quintiles), total fruit intake (quintiles), and regular alcohol consumption for men (3 categories: none, moderate (<2 drinks per day), or high (≥2 drinks per day)). Regular tea consumption (ever having drunk tea ≥3 times per week continuously for ≥6 months) and use of vitamin supplements were assessed as potential confounders, but they did not affect the association between fish intake and total, all-cancer, or all-CVD mortality; hence, they were not included in the final model. We evaluated the proportional hazards assumption using plots of Schoenfeld residuals and found no evidence of violation of the assumption.

We combined results for men and women to obtain summary risk estimates using the meta-analysis approach and a random-effects model for risk estimates with significant heterogeneity and a fixed-effects model for risk estimates with nonsignificant heterogeneity (21, 22). Tests for heterogeneity (Cochran's Q statistic and its P value) (23) were used to assess gender differences for total and cause-specific mortality risk when comparing the highest quintile of total fish intake with the lowest quintile. We also evaluated nonlinear associations between total fish intake and mortality risks by

Table 1. Characteristics of the SMHS and SWHS Study Populations, by Quintile of Fish Intake, Shanghai, China, 1997–2009[a]

	Study Population and Quintile of Fish Intake											
	SMHS						SWHS					
	1 (*n* = 12,228)		3 (*n* = 12,228)		5 (*n* = 12,227)		1 (*n* = 14,632)		3 (*n* = 14,632)		5 (*n* = 14,631)	
	Mean (SE)	**%**	**Mean (SE)**	**%**	**Mean (SE)**	**%**	**Mean (SE)**	**%**	**Mean (SE)**	**%**	**Mean (SE)**	**%**
Age at baseline, years	57.5 (10.2)		55.1 (9.54)		53.4 (9.17)		55.9 (9.51)		51.8 (8.76)		50.4 (8.30)	
Education												
Elementary school or less		9.8		5.5		4.4		29.0		18.9		14.9
Middle school		39.0		32.6		28.9		41.5		37.7		35.8
High school		35.2		37.1		38.0		21.5		28.9		32.3
Professional education/ college or higher		16.0		24.8		28.7		8.1		14.5		17.1
Income[b]												
Low		18.6		11.1		10.5		22.0		14.5		14.3
Lower middle		46.6		42.5		38.1		42.1		37.9		36.0
Upper middle		29.1		36.3		38.4		24.5		29.0		28.6
High		5.7		10.2		13.1		11.4		18.6		21.1
Occupation												
Professional, administrator		20.3		27.3		31.2		19.8		30.4		33.8
Clerical or service worker		21.1		22.2		22.2		22.8		20.5		20.9
Manual laborer		58.6		50.5		46.6		57.4		49.1		45.3
Smoking												
Ever having smoked regularly[c]		72.3		68.9		68.1		3.8		2.3		2.2
Pack-years of smoking[d]	25.7 (0.17)		23.8 (0.17)		24.9 (0.17)		—[e]		—		—	
Alcohol consumption												
Ever having consumed alcohol regularly[f]		29.6		33.1		39.0		2.0		2.3		2.9
No. of drinks per day[d]	0.83 (0.02)		0.79 (0.02)		0.99 (0.02)		—[e]		—		—	
Regular tea consumption[g]		63.7		68.0		69.2		23.4		30.4		34.0
Body mass index[h]	23.5 (0.03)		23.7 (0.03)		23.9 (0.03)		24.1 (0.03)		23.9 (0.03)		24.0 (0.03)	
Use of vitamin supplements[i]		9.5		85.2		17.4		23.4		30.4		34.0
Physical activity, MET-hours/ day[d]	0.83 (0.02)		0.97 (0.02)		1.12 (0.02)		1.92 (0.03)		1.88 (0.03)		2.08 (0.03)	
Comorbidity		35.4		35.1		34.5		24.6		23.3		23.3
Hypertension		29.2		30.1		28.8		24.1		23.6		23.2
Diabetes		6.4		6.1		6.3		4.7		4.2		4.1
Ischemic heart disease		5.0		5.3		5.0		6.8		7.6		7.6
Total energy intake, kcal/day	1,740 (4.12)		1,886 (4.10)		2,131 (4.12)		1,500 (3.15)		1662 (3.11)		1,886 (3.13)	

Table continues

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Table 1. Continued

	Study Population and Quintile of Fish Intake											
	SMHS						SWHS					
	1 (*n* = 12,228)		3 (*n* = 12,228)		5 (*n* = 12,227)		1 (*n* = 14,632)		3 (*n* = 14,632)		5 (*n* = 14,631)	
	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%
Dietary intake, g/day												
Red meat	57.5 (0.35)		63.1 (0.34)		67.4 (0.35)		47.2 (0.27)		52.5 (0.26)		50.6 (0.27)	
Poultry	10.7 (0.17)		15.5 (0.16)		22.4 (0.17)		10.3 (0.14)		15.2 (0.14)		20.4 (0.14)	
Fish	11.1 (0.22)		39.6 (0.22)		121.9 (0.22)		11.5 (0.19)		38.9 (0.18)		119.0 (0.19)	
Vegetables	291.7 (1.59)		336.0 (1.57)		414.3 (1.61)		259.0 (1.30)		287.2 (1.25)		350.3 (1.30)	
Fruit	118.9 (1.10)		155.5 (1.08)		178.5 (1.11)		218.6 (1.41)		266.9 (1.36)		307.5 (1.41)	

Abbreviations: MET, metabolic equivalent; SE, standard error; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study.

[a] Data for all variables were adjusted for age at the baseline survey, except for age and food intakes. Food intakes were adjusted for age and total energy intake; age was not adjusted.

[b] Cutpoints for income were as follows: for the SMHS—low, <500 yuan/month per capita; lower middle, 500–999 yuan/month; upper middle, 1,000–1,999 yuan/month; and high, ≥2,000 yuan/month; for the SWHS—low, <10,000 yuan/year per household; lower middle, 10,000–19,999 yuan/year; upper middle, ≥20,000–29,999 yuan/year; and high, ≥30,000 yuan/year.

[c] ≥1 cigarette/day continuously for ≥6 months.

[d] Only smokers, alcohol drinkers, or persons who engaged in leisure-time physical activity were included.

[e] Because of the very small proportions of smokers and alcohol drinkers in the SWHS, these numbers were not provided.

[f] ≥3 times per week continuously for ≥6 months.

[g] Ever having drunk tea ≥3 times per week continuously for ≥6 months.

[h] Weight (kg)/height (m)^2.

[i] Use of any vitamin A, B, C, D, A/D, or E supplements or multivitamins.

Table 2. Risks of Total and Cause-specific Mortality According to Total Fish Intake, Shanghai, China, 1997–2009[a]

Cause of Death and Quintile	Men			Women			Men and Women		Heterogeneity	
	No. of Deaths	HR	95% CI	No. of Deaths	HR	95% CI	HR	95% CI	Q	P Value
Total										
1	682	Reference		1,247	Reference		Reference			
2	471	0.91	0.80, 1.02	797	0.92	0.84, 1.01	0.92	0.85, 0.99		
3	375	0.88	0.77, 1.00	619	0.88	0.79, 0.97	0.88	0.81, 0.95		
4	330	0.87	0.75, 1.00	539	0.86	0.77, 0.96	0.86	0.79, 0.94		
5	312	0.86	0.74, 1.00	464	0.82	0.73, 0.93	0.84	0.76, 0.92	0.29	0.59
P-trend		0.07			0.002		<0.0001			
All cancer										
1	263	Reference		432	Reference		Reference			
2	208	0.97	0.80, 1.16	340	1.02	0.88, 1.18	1.00	0.89, 1.12		
3	169	0.93	0.76, 1.14	303	1.04	0.89, 1.22	1.00	0.88, 1.13		
4	181	1.10	0.89, 1.35	267	0.99	0.84, 1.17	1.03	0.91, 1.17		
5	162	1.00	0.80, 1.25	234	0.92	0.77, 1.10	0.95	0.83, 1.09	0.84	0.36
P-trend		0.69			0.27		0.60			
All CVD										
1	237	Reference		423	Reference		Reference			
2	156	0.94	0.76, 1.16	240	0.89	0.75, 1.05	0.91	0.80, 1.03		
3	122	0.94	0.74, 1.18	158	0.76	0.62, 0.92	0.83	0.67, 1.03		
4	86	0.77	0.59, 1.00	149	0.84	0.69, 1.03	0.81	0.69, 0.96		
5	98	0.96	0.74, 1.26	120	0.78	0.62, 0.98	0.86	0.70, 1.05	1.23	0.27
P-trend		0.57			0.04		0.13			
Ischemic heart disease										
1	69	Reference		95	Reference		Reference			
2	53	1.03	0.71, 1.48	56	0.89	0.63, 1.25	0.96	0.74, 1.23		
3	37	0.89	0.58, 1.35	42	0.87	0.59, 1.29	0.88	0.66, 1.17		
4	27	0.73	0.45, 1.17	28	0.70	0.44, 1.10	0.72	0.52, 1.00		
5	39	1.10	0.70, 1.73	30	0.94	0.59, 1.49	1.02	0.74, 1.41	0.19	0.66
P-trend		0.87			0.61		0.90			
Ischemic stroke										
1	56	Reference		106	Reference		Reference			
2	37	1.01	0.66, 1.55	53	0.86	0.61, 1.21	0.92	0.70, 1.20		
3	26	0.95	0.58, 1.56	37	0.80	0.54, 1.20	0.86	0.63, 1.17		
4	13	0.58	0.30, 1.09	43	1.11	0.75, 1.64	0.84	0.44, 1.59		
5	11	0.56	0.28, 1.13	22	0.66	0.40, 1.10	0.63	0.41, 0.94	0.27	0.60
P-trend		0.04			0.27		0.04			
Hemorrhagic stroke										
1	50	Reference		108	Reference		Reference			
2	42	1.21	0.79, 1.85	62	0.80	0.58, 1.11	0.96	0.65, 1.43		
3	30	1.09	0.67, 1.75	42	0.66	0.46, 0.97	0.83	0.51, 1.34		
4	24	1.01	0.60, 1.71	40	0.70	0.47, 1.04	0.81	0.57, 1.15		
5	28	1.32	0.78, 2.24	34	0.62	0.40, 0.96	0.90	0.43, 1.87	3.59	0.06
P-trend		0.44			0.04		0.68			

Table continues

Table 2. Continued

Cause of Death and Quintile	Men			Women			Men and Women		Heterogeneity	
	No. of Deaths	HR	95% CI	No. of Deaths	HR	95% CI	HR	95% CI	*Q*	*P* Value
Other CVD										
1	45	Reference		87	Reference		Reference			
2	15	0.47	0.26, 0.85	56	0.97	0.69, 1.38	0.70	0.35, 1.43		
3	24	0.92	0.54, 1.55	28	0.62	0.40, 0.97	0.73	0.52, 1.03		
4	19	0.84	0.47, 1.50	34	0.91	0.59, 1.41	0.89	0.62, 1.26		
5	11	0.53	0.26, 1.09	27	0.88	0.54, 1.43	0.75	0.50, 1.12	1.28	0.26
P-trend		0.23			0.59		0.33			
Diabetes										
1	29	Reference		123	Reference		Reference			
2	17	0.83	0.45, 1.55	60	0.86	0.62, 1.18	0.86	0.65, 1.13		
3	12	0.78	0.38, 1.58	39	0.80	0.55, 1.18	0.80	0.57, 1.11		
4	4	0.33	0.11, 0.97	21	0.52	0.32, 0.84	0.48	0.31, 0.75		
5	7	0.57	0.23, 1.42	21	0.63	0.38, 1.04	0.61	0.39, 0.95	0.07	0.79
P-trend		0.12			0.02		0.005			

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

[a] Results were adjusted for age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only). The median fish intakes for the first to fifth quintiles were 10.8, 25.0, 39.1, 59.8, and 107.2 g/day, respectively, for men and 10.4, 24.3, 38.5, 58.7, and 105.2 g/day, respectively, for women.

using restricted cubic splines with 4 knots placed at the 5th, 35th, 65th, and 95th percentiles of total fish intake.

Subgroup analyses were conducted by income (for men, <1,000 yuan/month or ≥1,000 yuan/month per capita; for women, <20,000 yuan/year or ≥20,000 yuan/year per household); education (middle school or less and high school or more); the existence of comorbidity (20); prior history of hypertension, diabetes, or ischemic heart disease; regular leisure-time physical activity (exercise/sports at least once per week continuously for ≥3 months within the 5 years before interview); and body mass index (weight (kg)/height $(m)^2$; <25 or ≥25). Among men, subgroup analyses by smoking status (never or ever) and regular alcohol consumption were also conducted. An evaluation of differential associations (interaction effects) for subgroups was conducted by including the product terms in the model and assessing the *P* value. Sensitivity analyses were conducted by excluding the first 2 years of observation (273 deaths among women and 397 deaths among men during the second year of follow-up) and participants with a prior history of hypertension, diabetes, or ischemic heart disease. All *P* values were 2-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

A total of 3,666 deaths accrued after a median follow-up of 11.2 years in the SWHS, and 2,170 deaths accrued after a median follow-up of 5.6 years in the SMHS, after exclusion of deaths that occurred during the first year of follow-up. Median fish intakes were similar between men and women (39.1 g/day for men; 38.5 g/day for women). In both cohorts, persons with higher fish intake tended to have higher education and income and to have been office workers (Table 1). For men, smoking was more common among those who consumed less fish. Body mass indices by quintile of fish intake were generally similar in both cohorts. The existence of any comorbidity tended to be more common among persons in the lower quintiles of fish intake than among those in the higher quintiles, whereas prior histories of hypertension, diabetes, or ischemic heart disease tended to be similar. Higher fish intake tended to be associated with higher physical activity in both cohorts. Persons who consumed more fish tended to have higher intakes of total energy, red meat, poultry, vegetables, and fruits than those who consumed less fish. In both cohorts, the major food sources of EPA and DHA were saltwater fish and freshwater fish. Intake of these fish items combined contributed to 77% of EPA intake and 91% of DHA intake in the SMHS and to 80% of EPA intake and 90% of DHA intake in the SWHS.

Overall, fish intake was inversely associated with risks of total, ischemic stroke, and diabetes mortality (Table 2); the corresponding risk reductions were 16%, 37%, and 39% for the highest quintiles compared with the lowest (for total mortality, hazard ratio (HR) = 0.84, 95% confidence interval (CI): 0.76, 0.92 (*P*-trend < 0.0001); for ischemic stroke, HR = 0.63, 95% CI: 0.41, 0.94 (*P*-trend = 0.04); and for diabetes, HR = 0.61, 95% CI: 0.39, 0.95 (*P*-trend = 0.005)). The inverse association patterns were generally observed among both men and women. Associations were stronger in women than in men, except for the association with ischemic stroke risk. Differential associations were observed for

Table 3. Risks of Total and Cause-specific Mortality According to Intakes of Saltwater Fish, Freshwater Fish, and Shrimp, Shanghai, China, 1997–2009[a]

Cause of Death and Quintile	Saltwater Fish			Freshwater Fish			Shrimp		
	No. of Deaths	HR	95% CI	No. of Deaths	HR	95% CI	No. of Deaths	HR	95% CI
Total									
1	2,168	Reference		1,570	Reference		2,100	Reference	
2	1,110	0.86	0.80, 0.92	1,299	0.91	0.84, 0.98	1,368	0.85	0.79, 0.91
3	1,002	0.85	0.79, 0.92	978	0.91	0.84, 0.99	862	0.85	0.78, 0.92
4	894	0.88	0.81, 0.96	1,036	0.89	0.82, 0.96	754	0.88	0.80, 0.96
5	662	0.79	0.72, 0.86	953	0.89	0.82, 0.97	752	0.88	0.80, 0.96
P-trend		<0.0001			0.02			0.03	
All cancer									
1	796	Reference		634	Reference		774	Reference	
2	480	0.94	0.84, 1.06	543	0.89	0.79, 1.00	600	0.92	0.82, 1.02
3	488	1.03	0.91, 1.15	455	0.95	0.84, 1.08	415	0.98	0.86, 1.11
4	458	1.07	0.95, 1.21	487	0.90	0.80, 1.02	378	1.01	0.89, 1.16
5	337	0.93	0.81, 1.06	440	0.86	0.75, 0.98	392	1.03	0.90, 1.17
P-trend		0.59			0.07			0.58	
All CVD									
1	716	Reference		486	Reference		721	Reference	
2	357	0.90	0.79, 1.02	428	1.00	0.88, 1.15	433	0.84	0.74, 0.95
3	274	0.78	0.68, 0.90	277	0.90	0.77, 1.04	252	0.81	0.69, 0.94
4	261	0.90	0.78, 1.05	318	0.99	0.85, 1.14	191	0.77	0.65, 0.91
5	181	0.79	0.66, 0.94	280	0.97	0.83, 1.14	192	0.78	0.65, 0.92
P-trend		0.04			0.77			0.002	
Ischemic heart disease									
1	205	Reference		116	Reference		178	Reference	
2	88	0.76	0.59, 0.98	105	0.98	0.75, 1.28	126	0.93	0.73, 1.18
3	63	0.61	0.46, 0.81	83	1.04	0.78, 1.39	67	0.80	0.60, 1.07
4	64	0.73	0.54, 0.98	93	1.12	0.84, 1.49	48	0.75	0.53, 1.06
5	56	0.82	0.60, 1.13	79	1.07	0.79, 1.46	57	0.85	0.61, 1.18
P-trend		0.25			0.47			0.17	
Ischemic stroke									
1	172	Reference		119	Reference		177	Reference	
2	79	0.89	0.67, 1.16	107	1.05	0.80, 1.37	92	0.77	0.59, 1.00
3	71	0.95	0.71, 1.26	56	0.78	0.56, 1.08	55	0.81	0.59, 1.12
4	55	0.93	0.68, 1.28	62	0.83	0.60, 1.14	38	0.71	0.49, 1.02
5	27	0.58	0.38, 0.89	60	0.88	0.63, 1.24	42	0.85	0.60, 1.24
P-trend		0.02			0.29			0.45	
Hemorrhagic stroke									
1	152	Reference		114	Reference		185	Reference	
2	98	1.10	0.85, 1.42	112	1.10	0.84, 1.43	112	0.80	0.63, 1.02
3	75	0.95	0.71, 1.26	82	1.10	0.82, 1.47	60	0.69	0.51, 0.94
4	76	1.12	0.84, 1.50	78	0.98	0.72, 1.32	49	0.67	0.48, 0.94
5	59	1.12	0.58, 2.16	74	1.01	0.74, 1.38	54	0.72	0.51, 1.00
P-trend		0.58			0.69			0.02	

Table continues

Table 3. Continued

Cause of Death and Quintile	Saltwater Fish			Freshwater Fish			Shrimp		
	No. of Deaths	HR	95% CI	No. of Deaths	HR	95% CI	No. of Deaths	HR	95% CI
Other CVD									
1	147	Reference		101	Reference		133	Reference	
2	70	0.84	0.63, 1.12	78	0.90	0.67, 1.22	75	0.82	0.61, 1.10
3	50	0.65	0.47, 0.91	48	0.77	0.54, 1.10	59	1.01	0.73, 1.39
4	50	0.78	0.55, 1.09	66	1.02	0.73, 1.41	48	1.04	0.73, 1.48
5	29	0.56	0.37, 0.86	53	0.96	0.67, 1.37	31	0.64	0.25, 1.61
P-trend		0.008			0.82			0.28	
Diabetes									
1	170	Reference		93	Reference		167	Reference	
2	60	0.72	0.53, 0.97	95	1.30	0.97, 1.75	67	0.73	0.55, 0.98
3	55	0.78	0.57, 1.06	55	1.07	0.75, 1.51	37	0.71	0.49, 1.04
4	28	0.52	0.35, 0.78	50	1.01	0.71, 1.45	31	0.70	0.46, 1.05
5	20	0.46	0.29, 0.75	40	0.83	0.56, 1.23	31	0.91	0.60, 1.38
P-trend		<0.0001			0.10			0.53	

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

[a] Results were adjusted for age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only). Median saltwater fish, freshwater fish, and shrimp intakes for the first to fifth quintiles were 0.5, 6.0, 12.1, 26.2, and 52.4 g/day, respectively, for saltwater fish, 0, 4.8, 9.7, 21.1, and 42.1 g/day for freshwater fish, and 0.8, 4.8, 9.6, 12.5, and 20.9 g/day for shrimp among men and 0.5, 6.0, 12.1, 26.2, and 52.4 g/day, respectively, for saltwater fish, 1.0, 4.8, 12.6, 21.1, and 42.1 g/day for freshwater fish, and 0.4, 2.9, 4.8, 9.6, and 20.9 g/day for shrimp among women.

hemorrhagic stroke by gender: The association was positive but nonsignificant for men and inverse and significant for women, with suggestive evidence of heterogeneity (Q = 3.59; P = 0.06). Tests for nonlinear associations of total fish intake with total mortality were statistically significant among both men (P = 0.001) and women (P = 0.02). The nonlinearity test for CVD mortality for women (P = 0.02) was also significant, but it was suggestively significant only among men (P = 0.09).

When fish items were assessed individually, saltwater fish intake was inversely associated with total, ischemic stroke, other CVD, and diabetes mortality (Table 3). Compared with those in the lowest quintile, persons in the highest quintile had 21% lower risk of total mortality (HR = 0.79, 95% CI: 0.72, 0.86; P-trend < 0.0001), 42% lower risk of ischemic stroke mortality (HR = 0.58, 95% CI: 0.38, 0.89; P-trend = 0.02), 44% lower risk of other CVD mortality (HR = 0.56, 95% CI: 0.37, 0.86; P-trend = 0.008), and 54% lower risk of diabetes mortality (HR = 0.46, 95% CI: 0.29, 0.75; P-trend < 0.0001). Freshwater fish intake was significantly and inversely associated with total mortality (HR = 0.89, 95% CI: 0.82, 0.97; P-trend = 0.02) and all-cancer mortality (HR = 0.86, 95% CI: 0.75, 0.98; P-trend = 0.07), although the test for linear trend was not statistically significant for all-cancer mortality. Shrimp intake was inversely associated with mortality from all causes, all CVD, all stroke, and hemorrhagic stroke; the risk reduction for the highest quintiles of intake compared with the lowest quintiles ranged from 12% to 28%. Furthermore, intakes of long-chain n-3 fatty acids (EPA and DHA) were each significantly and inversely associated with total, all-CVD, all-stroke, ischemic stroke, other CVD, and diabetes mortality (Table 4). Similar association patterns were observed for combined intake of EPA and DHA. For acute myocardial infarction, another subcategory of CVD, no statistically significant associations with intake of any fish or long-chain n-3 fatty acids were noted in either cohort (data not shown).

The results from subgroup analyses were generally similar to those from the overall analyses (data not shown), including analyses of methods of cooking meat or fish, with no statistically significant interactions noted. The presence of any comorbidity at baseline (diabetes, hypertension, or ischemic heart disease) appeared to modify the associations of total fish intake with ischemic stroke mortality (P-interaction = 0.02) and all-cancer mortality (P-interaction = 0.05) among women, but not among men. For ischemic stroke mortality, fish intake was associated with nonsignificantly increased risk among persons with no comorbidity and with nonsignificantly decreased risk among persons with any of the 3 types of comorbidity. For all-cancer mortality, fish intake was associated with nonsignificantly lower risk among persons with no comorbidity and with nonsignificantly higher risk among persons with any of the 3 types of comorbidity. Adjustment for methods of cooking meat or fish did not materially alter the results (data not shown). Sensitivity analyses, in which we excluded the first 2 years of observation and participants with a prior history of hypertension, diabetes, or ischemic heart disease, did not materially change the results (data not shown). We

Table 4. Risks of Total and Cause-specific Mortality According to Intake of Long-Chain *n*-3 Fatty Acids, Shanghai, China, 1997–2009[a]

Cause of Death and Quintile	EPA			DHA			EPA + DHA		
	No. of Deaths	HR	95% CI	No. of Deaths	HR	95% CI	No. of Deaths	HR	95% CI
Total									
1	2,043	Reference		2,057	Reference		2,053	Reference	
2	1,220	0.88	0.81, 0.94	1,189	0.84	0.78, 0.91	1,197	0.86	0.80, 0.93
3	1,015	0.89	0.82, 0.96	991	0.86	0.79, 0.93	993	0.87	0.80, 0.94
4	855	0.89	0.81, 0.97	885	0.88	0.81, 0.96	881	0.90	0.83, 0.98
5	703	0.79	0.72, 0.87	714	0.78	0.71, 0.86	712	0.79	0.72, 0.87
P-trend		<0.0001			<0.0001			<0.0001	
All cancer									
1	707	Reference		731	Reference		721	Reference	
2	540	1.02	0.91, 1.14	518	0.94	0.84, 1.05	525	0.98	0.87, 1.10
3	494	1.10	0.97, 1.24	489	1.05	0.93, 1.18	496	1.09	0.97, 1.23
4	458	1.17	1.02, 1.32	459	1.10	0.97, 1.24	451	1.10	0.98, 1.26
5	360	0.97	0.84, 1.12	362	0.92	0.80, 1.06	366	0.96	0.83, 1.10
P-trend		0.84			0.55			0.73	
All CVD									
1	715	Reference		707	Reference		714	Reference	
2	362	0.81	0.71, 0.92	359	0.81	0.71, 0.92	356	0.82	0.63, 1.08
3	290	0.83	0.72, 0.96	272	0.78	0.67, 0.90	271	0.78	0.67, 0.90
4	232	0.83	0.70, 0.97	260	0.89	0.76, 1.03	258	0.90	0.77, 1.05
5	190	0.75	0.62, 0.89	193	0.76	0.63, 0.90	190	0.74	0.62, 0.88
P-trend		0.03			0.01			0.02	
Ischemic heart disease									
1	187	Reference		194	Reference		195	Reference	
2	102	0.83	0.64, 1.06	91	0.72	0.51, 1.00	91	0.72	0.55, 0.93
3	70	0.71	0.53, 0.95	67	0.65	0.47, 0.90	66	0.64	0.48, 0.86
4	57	0.71	0.52, 0.98	65	0.76	0.56, 1.02	65	0.76	0.57, 1.03
5	60	0.84	0.60, 1.16	59	0.79	0.57, 1.09	59	0.79	0.57, 1.09
P-trend		0.25			0.31			0.31	
Ischemic stroke									
1	170	Reference		172	Reference		169	Reference	
2	82	0.88	0.51, 1.52	80	0.79	0.60, 1.04	84	0.87	0.67, 1.14
3	74	1.04	0.78, 1.39	68	0.91	0.68, 1.23	67	0.94	0.70, 1.27
4	51	0.94	0.67, 1.31	56	0.93	0.68, 1.29	58	1.03	0.75, 1.41
5	27	0.56	0.36, 0.86	28	0.55	0.36, 0.83	26	0.53	0.34, 0.82
P-trend		0.004			0.02			0.02	
Hemorrhagic stroke									
1	174	Reference		162	Reference		165	Reference	
2	87	0.75	0.57, 0.97	94	0.87	0.67, 1.13	92	0.85	0.65, 1.10
3	71	0.75	0.56, 1.01	66	0.76	0.56, 1.02	69	0.78	0.58, 1.05
4	69	0.88	0.65, 1.20	76	1.01	0.76, 1.36	73	1.02	0.55, 1.90
5	59	0.81	0.58, 1.12	62	0.95	0.50, 1.82	61	0.88	0.64, 1.23
P-trend		0.39			0.93			0.99	

Table continues

Table 4. Continued

Cause of Death and Quintile	EPA			DHA			EPA + DHA		
	No. of Deaths	HR	95% CI	No. of Deaths	HR	95% CI	No. of Deaths	HR	95% CI
Other CVD									
1	137	Reference		137	Reference		139	Reference	
2	75	0.85	0.64, 1.14	73	0.85	0.63, 1.13	72	0.83	0.62, 1.11
3	59	0.85	0.62, 1.18	54	0.78	0.56, 1.08	52	0.74	0.53, 1.04
4	40	0.70	0.48, 1.02	49	0.83	0.58, 1.17	49	0.82	0.58, 1.17
5	35	0.70	0.46, 1.05	33	0.64	0.43, 0.97	34	0.66	0.44, 0.99
P-trend		0.07			0.04			0.06	
Diabetes									
1	167	Reference		162	Reference		164	Reference	
2	65	0.70	0.52, 0.94	70	0.79	0.59, 1.06	70	0.78	0.58, 1.04
3	53	0.77	0.55, 1.07	52	0.80	0.58, 1.10	49	0.73	0.52, 1.02
4	26	0.51	0.33, 0.79	27	0.53	0.35, 0.82	28	0.56	0.37, 0.85
5	22	0.49	0.30, 0.79	22	0.50	0.31, 0.81	22	0.49	0.30, 0.78
P-trend		<0.0001			0.002			<0.0001	

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HR, hazard ratio.

[a] Results were adjusted for age at baseline, total energy intake, income, occupation, education, comorbidity index, physical activity level, red meat intake, poultry intake, total vegetable intake, total fruit intake, smoking history (ever/never smoking for women; pack-years of smoking for men), and alcohol consumption (among men only). Median EPA and DHA intakes for the first to fifth quintiles were 0.006, 0.01, 0.02, 0.03, and 0.07 g/day, respectively, for EPA and 0.009, 0.02, 0.05, 0.08, and 0.15 g/day for DHA, respectively, among men and 0.005, 0.01, 0.02, 0.03 and 0.06 g/day for EPA and 0.008, 0.02, 0.04, 0.08, and 0.15 g/day for DHA among women.

also conducted analyses using energy density models (intake as g/1,000 kcal), and the results (see Web Tables 1–3, available at http://aje.oxfordjournals.org/) were materially similar to those of our energy-adjustment models.

DISCUSSION

In this analysis of data from 2 large, population-based cohort studies, including 134,296 men and women, total fish intake was inversely associated with total, ischemic stroke, and diabetes mortality. In general, similar patterns of association were observed for men and women, except for the association between fish intake and hemorrhagic stroke mortality. The inverse associations with fish intake were primarily related to intake of saltwater fish, not freshwater fish. Additionally, both long-chain *n*-3 fatty acids (EPA and DHA) were inversely associated with total, all-CVD, ischemic stroke, and diabetes mortality.

The inverse association of total fish intake with total mortality observed in our study is generally consistent with the findings of a previous case-control study conducted in Hong Kong (13) and a cohort study carried out in Japan (24). Our finding is also supported by reports of fish intake's having beneficial effects on CVD (e.g., antiarrhythmic and antiinflammatory effects), mainly through long-chain *n*-3 fatty acid content (2). This finding is also supported by the observation in our study of inverse associations between mortality risk and intakes of long-chain *n*-3 fatty acids and saltwater fish, which is higher in *n*-3 fatty acids than other types of fish assessed in our study population. In contrast to our finding, in a recent meta-analysis of clinical trials of *n*-3 fatty acid supplementation, Rizos et al. (6) reported no association with total mortality. The median level of fish intake (39 g/day) in our study was much lower than that reported in the Japanese study (87 g/day) (24) but was higher than that reported in the United States (intakes in the third quintile ranged from 12 g/day to 18 g/day) (25). It is noteworthy that a previous study in Britain with an intake level similar to ours did not find an inverse association (26). This discrepancy might be explained by differences in methods of cooking fish between these study populations; steaming and stir-frying are the predominant methods of cooking fish in Shanghai, while deep-frying may be more common in Europe and North America. This notion is supported by findings of stronger inverse associations between broiled or baked fish intake and coronary heart disease and stroke mortality reported in previous cohort studies in the United States (11) and Japan (12). In our study, the questions on cooking methods (i.e., roasting, stir-frying, or deep-frying) were asked for all types of meat and fish combined. In our study, the overall method of cooking meat did not modify the association between fish intake and mortality. In future studies of fish intake and mortality, cooking methods need to be considered.

The observed inverse association between total fish intake and diabetes mortality is generally consistent with the findings for Eastern countries (China and Japan, including our study populations) but not Western countries in a meta-analysis of 12 cohort studies (5), although the endpoint in that meta-analysis was incidence, not mortality. In another meta-analysis, Wallin et al. (4) reported a borderline-significant inverse association of fish and long-chain *n*-3 fatty acid intake with type 2 diabetes risk. Given that both meta-analyses found a weak association or no association for studies conducted in Western countries (4, 5), fish intake level, common methods of cooking fish, dietary patterns, or other factors associated with high fish intake may explain the discrepant findings. Taken together, our finding needs to be replicated in other populations, especially those with similar fish intake.

Our finding of no association of fish intake with ischemic heart disease mortality is in contrast to an overall inverse association reported in meta-analyses (8, 10), including a cohort study conducted in Shanghai (27) and a Hong Kong case-control study that was not included in these meta-analyses (13). The majority of the studies included in the meta-analyses found nonsignificant associations, despite the overall inverse association (8, 10). Differences in the distribution of risk factors and other characteristics of the study populations, length of follow-up, and endpoint definition may have contributed to some of the inconsistencies observed across studies. In addition, in previous studies that found an inverse association (10, 13), the reference category was no intake or was an intake level much lower than the reference category in our study. Hence, it is possible that in a population with moderate fish intake, like ours, there may be no additional benefit regarding ischemic heart disease mortality from increasing intake of fish. Our finding needs to be confirmed in populations with similar fish intakes.

The inverse association of total fish intake with ischemic stroke mortality observed in our study is generally consistent with a meta-analysis of prospective studies of stroke incidence or mortality (9) that included a case-control study of mortality in Hong Kong (13) and a previous cohort study of men in Shanghai (27). The meta-analysis also found an inverse association for total stroke (9). However, a null finding was reported in the recent meta-analysis of clinical trials of *n*-3 fatty acid supplementation (6) and in the previous cohort study of men in Shanghai (27). Our finding of an inverse association of fish and long-chain *n*-3 fatty acid intakes with ischemic stroke mortality also corroborates evidence that long-chain *n*-3 fatty acids may decrease platelet aggregation (7, 28). Altogether, few studies have investigated associations of fish intake with subtypes of stroke mortality, and more research is warranted.

A suggestive discrepancy by gender was observed in the association between total fish intake and hemorrhagic stroke mortality, with a significant inverse association among women and a nonsignificant positive association among men (heterogeneity: $Q = 3.59$; $P = 0.06$ (Table 2)). The inverse association observed among women is consistent with the finding of the recent meta-analysis of prospective studies (9), although it included only 2 studies conducted in Asian populations (4, 6). In our 2 cohorts, more than 95% of deaths from hemorrhagic stroke were further categorized as intracerebral hemorrhage; the rest were categorized as subarachnoid hemorrhage. The biological mechanisms underlying the inverse association between fish intake and hemorrhagic stroke are not well understood. Our finding among women may potentially be due to the postulated protective effects of long-chain *n*-3 fatty acids on endothelial function, inflammation, and lipid profiles (2, 28–30). Given the small number of deaths from hemorrhagic stroke among men in our study, our finding of a positive association needs to be reevaluated when more deaths have accrued. It also requires replication in other study populations.

Strengths of our study include the population-based, prospective study design and the high response rates for both initial recruitment and follow-up. Dietary intake was assessed quantitatively and prospectively by means of validated questionnaires. In contrast, some previous studies reported only the frequency of fish intake (12, 13), and in 1 study the relatives of deceased persons were retrospectively asked to obtain dietary information (13). Our study is one of the few to have assessed associations with fish intake by stroke subtype, which is known to vary in terms of etiology and risk factor profile (30, 31), and by several major causes of death.

There were some limitations of our study. The follow-up period for men was relatively short, which led to low statistical power for observing significant associations between fish intake and mortality. It is noteworthy that the SWHS had very few smokers (2.8%) or regular drinkers of alcohol (2.2%), reflecting the very low prevalence of these lifestyle factors among women in Shanghai, while the proportions of smokers (69.6%) and regular alcohol drinkers (33.7%) were high among men. Hence, some of the observed gender differences could have been driven by these differences between these 2 cohorts. Another concern is that dietary intake assessed at baseline may have been affected by preclinical conditions. Nevertheless, excluding the first 2 years of observation and participants with comorbidity at baseline did not alter the results of the overall analyses.

In summary, fish intake was inversely associated with total mortality and death from ischemic stroke, especially among men, and diabetes, especially among women. Our findings are consistent with the postulated beneficial effect of fish consumption, through increased intake of long-chain *n*-3 fatty acids, on risk of chronic diseases.

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