AJCN. First published ahead of print July 20, 2011 as doi: 10.3945/ajcn.111.012252.

Fish intake and type 2 diabetes in Japanese men and women: the Japan Public Health Center–based Prospective Study[1–3]

Akiko Nanri, Tetsuya Mizoue, Mitsuhiko Noda, Yoshihiko Takahashi, Yumi Matsushita, Kalpana Poudel-Tandukar, Masayuki Kato, Shino Oba, Manami Inoue, and Shoichiro Tsugane for the Japan Public Health Center–based Prospective Study Group

ABSTRACT

Background: Although fish intake can improve glucose metabolism, results of some prospective studies in Western populations suggest potential adverse effects of environmental contaminants in fish on type 2 diabetes risk. However, data from populations with high fish consumption are scarce.

Objective: We prospectively investigated the association between fish intake and type 2 diabetes risk in Japanese adults.

Design: The participants were 22,921 men and 29,759 women aged 45–75 y who completed a questionnaire of the second survey for the Japan Public Health Center–based Prospective Study and who had no history of diabetes. Diet was ascertained by using a 147-item food-frequency questionnaire. ORs of self-reported, physician-diagnosed type 2 diabetes over 5 y were estimated by using logistic regression.

Results: During the 5-y period, 971 new cases (572 men and 399 women) of type 2 diabetes were self-reported. In men, fish intake was significantly associated with a decreased risk of type 2 diabetes; multivariable-adjusted ORs of type 2 diabetes for the highest compared with the lowest quartile of intake were 0.73 (95% CI: 0.54, 1.00; *P*-trend = 0.04) for total fish and seafood and 0.68 (95% CI: 0.50, 0.92; *P*-trend = 0.016) for small and medium fish (horse mackerel and sardine, saury and mackerel, and eel). Additional analysis by fat content of fish did not detect any significant association for each category. In women, fish intake was not appreciably associated with type 2 diabetes risk.

Conclusion: In a population with high fish and seafood intake, fish consumption was associated with a lower risk of type 2 diabetes in men but not in women. *Am J Clin Nutr* doi: 10.3945/ajcn.111.012252.

INTRODUCTION

Fish and omega-3 (n−3) fatty acid intakes are thought to prevent cardiovascular disease (1, 2). Data from an ecologic study suggest that fish intake may also play a role in the prevention of type 2 diabetes (3), which is supported by an animal experiment showing a favorable effect of long-chain omega-3 fatty acids, which are abundant in fish, on insulin resistance (4). However, epidemiologic data are conflicting. Of 6 prospective studies in Western populations (5–10), 2 have shown a protective association of fish intake with type 2 diabetes (8) and glucose intolerance (6), whereas 3 recent studies have reported an increased risk of type 2 diabetes associated with fish intake (5, 7, 10), which the authors ascribed to potential adverse effects of selenium, mercury, or other environmental contaminants in fish. To our knowledge, no study has examined the association of fish intake with type 2 diabetes in Japanese, who consume large amounts of fish; fish and shellfish supply 61 and 20–25 kg/capita annually in Japan and Western countries, respectively (11). The aim of this study was to assess prospectively the association between fish intake and type 2 diabetes risk by using data from a large-scale, population-based cohort study in Japan.

SUBJECTS AND METHODS

Study population

The Japan Public Health Center–based Prospective (JPHC) Study was launched in 1990 for cohort I and in 1993 for cohort II (12). The participants of cohort I included residents aged 40–59 y in 5 Japanese public health center areas (Iwate, Akita, Nagano, Okinawa, and Tokyo); the participants of cohort II included residents aged 40–69 y in 6 public health center areas (Ibaraki, Niigata, Kochi, Nagasaki, Okinawa, and Osaka). Although we did not require written informed consent, the study participants were informed of the objectives of the study, and participants who responded to the questionnaire survey were considered to have consented to participate in the survey. A questionnaire survey was conducted at baseline (in 1990 for cohort I and in 1993 for cohort II), at the 5-y follow-up (in 1995 for cohort I and in 1998 for cohort II), and at the 10-y follow-up (in 2000 for cohort I and in

[1] From the Department of Epidemiology and Prevention, International Clinical Research Center, National Center for Global Health and Medicine, Tokyo, Japan (AN, TM, YM, and KP-T); the Department of Diabetes and Metabolic Medicine, National Center for Global Health and Medicine, Tokyo, Japan (MN and YT); the Japan Foundation for the Promotion of International Medical Research Cooperation, Tokyo, Japan (MK); the Department of Health Promotion, National Institute of Public Health, Wako, Japan (SO); and the Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan (MI and ST).

[2] Supported by Grants-in-Aid for Cancer Research (19shi-2) and a Health Sciences Research Grant (Research on Comprehensive Research on Cardiovascular Diseases H19-016) from the Ministry of Health, Labour and Welfare of Japan.

[3] Address correspondence to A Nanri, Department of Epidemiology and Prevention, International Clinical Research Center, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan. E-mail: nanri@ri.ncgm.go.jp.

Received January 16, 2011. Accepted for publication June 8, 2011.
doi: 10.3945/ajcn.111.012252.

2003 for cohort II). Information on medical histories and health-related lifestyle, smoking, drinking, and dietary habits was obtained at each survey. This study was approved by the Institutional Review Board of the National Cancer Center of Japan.

From the study population at baseline (n = 140,420), 113,403 participants responded to the questionnaire survey at baseline. Of these, 89,947 participants responded to the 5-y follow-up survey (second survey), including the diet-related portion. We excluded 14,359 participants who reported a history of type 2 diabetes (n = 6816) or severe disease (n = 8680), including cancer, cerebrovascular disease, myocardial infarction, chronic liver disease, and renal disease at the second survey. Then, we excluded 14,166 participants who had missing information on fish consumption of ≥1 out of 19 fish/seafood items and 511 participants who reported extreme total energy intakes (ie, outside the mean ± 3 SD according to sex). Finally, we excluded 8231 participants, including 1364 participants who died before the 10-y follow-up survey, who did not respond to the subsequent 10-y follow-up survey (third survey), which left a total of 52,680 participants (22,921 men and 29,759 women) in our analysis.

Food-frequency questionnaire

At the baseline, second, and third surveys, participants completed a self-administered questionnaire. In the current analysis, data from the second survey were used as baseline survey data, because the questionnaire used for the second survey more comprehensively inquired about food intakes than did that used for the baseline survey. At the second survey, a food-frequency questionnaire (FFQ) was used to assess the average intake of 147 food and beverage items, including 19 items of fish/seafood [7 fresh fish: salmon, skipjack/tuna, cod/flatfish, sea bream, horse mackerel/sardine, saury/mackerel, and eel; 5 seafood other than fish: squid, octopus, shrimp, clam, and pond snail; 4 salted and dried fish products: salted fish, dried fish, dried whitebait, and salted fish roe; 3 other fish products: canned tuna; and 2 items of fish-paste products (*chikuwa* and *kamaboko*)] over the previous year (13). For most food items, 9 response options were available to describe consumption frequency, ranging from rarely (<1 time/mo) to ≥7 times/d. A standard portion size was specified for each food, and respondents were asked to denote their usual portion size from 3 options (≤0.5 times, standard, or ≥1.5 times). The daily intake of fish/seafood was calculated by multiplying daily consumption frequency by the typical portion size.

We examined the validity and reproducibility of the FFQ in a subsample of the participants in the JPHC Study cohort I and cohort II (215 men and women in cohort I and 350 men and women in cohort II for validity; 209 men and women in cohort I and 289 men and women in cohort II for reproducibility). Details of the validation study were described elsewhere (14–17). The participants completed both FFQs at a 1-y interval and a total of 28- or 14-d dietary records. For validity of the FFQ, Spearman's correlation coefficients between intake values for fish/seafood derived from the FFQ and those derived from dietary records were 0.29–0.46 for cohorts I and II (14, 16). With regard to the reproducibility of the FFQ, Spearman's correlation coefficients for intake of fish/seafood derived from the 2 FFQs administered 1 y apart were 0.58–0.65 for cohorts I and II (14, 15).

Ascertainment of type 2 diabetes

Type 2 diabetes newly diagnosed during the 5-y period after the second survey was determined by a self-administered questionnaire at the third survey. At the third survey, study participants were asked if they had ever been diagnosed with diabetes, and, if so, when the initial diagnosis had been made. Because the second survey was used as the starting point of observation for the incidence of type 2 diabetes, only those participants with diabetes diagnosed after 1995 for cohort I and after 1998 for cohort II were regarded as incident cases during follow-up. Details regarding assessment of the validity of self-reported diabetes are described elsewhere (18). In a previous study that we conducted, 94% of self-reported diabetes cases were confirmed as such by medical records. We also conducted a cross-sectional survey in 1990 to examine the sensitivity of diagnosed diabetes according to the criteria at that time for a JPHC subpopulation (health check-up participants) whose plasma glucose data were available (18). Of 6118 participants with plasma glucose data, 248 participants had diagnosed diabetes. Of 5870 participants who did not have diagnosed diabetes, 49 participants (0.83%) had diabetes based on the commonly used diagnostic standards in Japan in 1990 [fasting plasma glucose ≥7.8 mmol/L; casual plasma glucose ≥11 mmol/L (19)] based on a single measurement. Taking into account the abovementioned positive predictive value, the sensitivity and specificity of diagnosed diabetes were 85.5% and 99.7, respectively, in men and 79.3% and 99.7%, respectively, in women.

Statistical analysis

Participants were classified into quartiles of fish/seafood intake by sex. The confounding variables considered were as follows: age (y, continuous), study area (11 areas), BMI (<21, 21–22.9, 23–24.9, 25–26.9, or ≥27; in kg/m^2), smoking status (lifetime nonsmoker, former smoker, or current smoker with a consumption of either <20 or ≥20 cigarettes/d), alcohol consumption (nondrinker, occasional drinker, or drinker with a consumption of <150, 150–299, 300–449, or ≥450 g ethanol/wk for men and <150 or ≥150 g ethanol/wk for women), family history of diabetes mellitus (yes or no), total physical activity (metabolic equivalent task hours/d, quartiles), history of hypertension (yes or no), total energy intake (kcal/d, continuous), coffee consumption (almost never or <1, 1, or ≥2 cups/d; 1 cup = 120 mL), and intakes of calcium (mg/d, continuous), magnesium (mg/d, continuous), dietary fiber (g/d, continuous), vegetables (g/d, continuous), fruit (g/d, continuous), meat (g/d, continuous), and rice (g/d, continuous). An indicator variable for missing data were created for each covariate. Trend associations between confounding factors and fish/seafood intake were tested by using a Mantel-Haenszel chi-square test for categorical variables and linear regression analysis for continuous variables.

Multiple logistic regression analysis was performed to estimate odds ratios of type 2 diabetes for the quartiles of intakes of total fish/seafood, fresh fish, seafood other than fish, salted and dried fish products, and other fish products, with the lowest category as the reference. The first model was adjusted for age and study area, and the second model was additionally adjusted for BMI, smoking status, alcohol consumption, family history of diabetes mellitus, total physical activity, history of hypertension, total energy intake, coffee consumption, and intakes of calcium, magnesium, dietary fiber, vegetable, fruit, meat, and rice. Trend association was assessed by assigning the ordinal numbers 0–3 to the 4 categories of each fish/seafood consumption. Because big fish, which are in a higher rank of the food chain, are likely have higher concentrations of environmental contaminants (2) and oily fish also might have higher fat-soluble environmental contaminants, fresh fish was also analyzed separately by size (big fish: salmon, skipjack/tuna, cod/flatfish, and sea bream; small and medium fish: horse mackerel/sardine, saury/mackerel, and eel) and fat content (oily fish: salmon, horse mackerel/sardine, saury/mackerel, eel, and sea bream; lean fish: skipjack/tuna and cod/flatfish). An interaction term was created by multiplying each fish/seafood intake (g/d, continuous) and sex and added to the model to assess statistical interactions. Two-sided P values <0.05 were regarded as significant. All analyses were performed by using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

During the 5-y period, 971 participants had newly diagnosed diabetes (572 men and 399 women). Total fish/seafood intake was positively associated with age in men and with BMI in women (**Table 1**). Both men and women with a higher total fish/seafood intake were more likely to be physically active, to be an alcohol drinker, and to consume more magnesium, vitamin D, and polyunsaturated fatty acids but less coffee. Of the 19 fish/seafood items, the major sources of total fish/seafood intake were skipjack/tuna (12.7%), horse mackerel/sardine (11.8%), salted fish (11.5%), saury/mackerel (11.4%), and salmon (9.3%) in men and horse mackerel/sardine (12.8%), saury/mackerel (11.8%), salted fish (11.4%), skipjack/tuna (10.1%), and salmon (9.6%) in women.

In men, total fish/seafood intake was significantly associated with a decreased risk of type 2 diabetes; the multivariate-adjusted odds ratio for type 2 diabetes for the highest compared with the lowest quartile of intake was 0.73 (95% CI: 0.54, 1.00; P-trend = 0.04) (**Table 2**). Additional adjustment of vitamin D or polyunsaturated fatty acids intake attenuated the association; the multivariate-adjusted odds ratios for type 2 diabetes for the highest compared with lowest quartile of intake were 0.81 (95% CI: 0.55, 1.20; P-trend = 0.26) after additional adjustment of vitamin D and 0.78 (95% CI: 0.56, 1.09; P-trend = 0.13) after additional adjustment of polyunsaturated fatty acids. Intake of each of the 4 categories of fish/seafood (fresh fish, seafood other than fish, salted and dried fish products, and other fish products) was not statistically significantly associated with type 2 diabetes risk. Moreover, when we examined the association between shellfish (including shrimp, clam, and pond snail) and type 2 diabetes, no significant association was observed; the multivariate-adjusted odds ratios (95% CI) of type 2 diabetes for the lowest through the highest quartile category of intake were 1.00 (reference), 1.10 (0.88, 1.38), 0.94 (0.71, 1.26), and 0.97 (0.75, 1.27) (P-trend = 0.57) in men. In women, any kind of fish/seafood intake was not associated with type 2 diabetes risk.

In the analysis by fish size, small and medium fish intake was significantly associated with a decreased risk of type 2 diabetes in men (P-trend = 0.02) (**Table 3**), whereas big fish was not associated with type 2 diabetes. The association of small and medium fish intake with type 2 diabetes was marginally significant after further adjustment for vitamin D or polyunsaturated fatty acids; the multivariate-adjusted odds ratios for the highest compared with the lowest quartile of intake were 0.72 (95% CI: 0.52, 1.00; P-trend = 0.065) after additional adjustment of vitamin D and 0.72 (95% CI: 0.52, 0.98; P-trend = 0.050) after additional adjustment of polyunsaturated fatty acids. In men, type 2 diabetes risk tended to decrease with oily fish intake (P-trend = 0.10), but not with lean fish intake. In women, no significant association was observed between fish intake and type 2 diabetes in analyses by the size or fat content of fresh fish. Moreover, when we assessed the association between small and medium fish or oily fish intake and type 2 diabetes risk in women using a linear spline regression with 3 knots (which corresponds to the quartiles) to detect nonlinearity or U-shaped association, the associations between their intake and type 2 diabetes risk were not U-shaped.

DISCUSSION

In this large-scale population-based prospective study in Japanese adults, total fish/seafood and small and medium fish (horse mackerel/sardine, saury/mackerel, and eel) intakes were significantly associated with a decreased risk of type 2 diabetes in Japanese men. An unfavorable effect of fish intake on type 2 diabetes was not observed. To our knowledge, this was the first study to examine the association of fish intake with type 2 diabetes in an Asian population.

An inverse association of fish intake with risk of type 2 diabetes (8) or glucose intolerance (6) has also been reported in 2, but not in all, prospective studies (5, 7, 9, 10). Fish, especially oily fish, is a major dietary source of n−3 fatty acids and vitamin D, and these nutrients have been reported to decrease the risk of type 2 diabetes (20, 21). In a study in the United Kingdom (8), an inverse association was observed not only for oily fish intake but also for white (likely nonoily) fish intake. In the current study, although the inverse association between total fish/seafood intake and type 2 diabetes was attenuated after adjustment for vitamin D and polyunsaturated fatty acids, oily fish was not significantly associated with a lower risk of type 2 diabetes. The decreased risk of type 2 diabetes associated with fish intake might be ascribed not only to vitamin D and polyunsaturated fatty acids but also to other components such as fish protein or the synergistic effect of several nutrients contained.

Three studies in the Netherlands (10) and in the United States (5, 7) recently reported an increased risk of type 2 diabetes associated with fish intake. Environmental contaminants such as dioxins in fish have been suggested to increase the risk of type 2 diabetes (22) through the inhibition of glucose uptake (23) and alterations in the insulin signaling pathway (24). In a Japanese population with much higher fish intakes than Western populations (25, 26), however, we observed no increase in the risk of type 2 diabetes with intake of not only total fish/seafood but also big fish, which are in a higher rank of the food chain and are thus likely to have higher concentrations of environmental contaminants. This result suggests that overall fish intake does not confer type 2 diabetes risk of Japanese population; conversely, it was associated with decreased risk, as discussed above. However, a possibility remains that the null association for big fish intake was a result of relatively high levels of environmental contaminants, such as mercury and organochlorine pollutants, which have been

TABLE 1
Baseline characteristics of participants according to quartile (Q) categories of total fish/seafood intake[1]

	Total fish/seafood intake				
	Q1 (low)	Q2	Q3	Q4 (high)	*P*-trend[2]
Men					
n	5730	5731	5729	5731	
Median intake (g)	36.6	65.0	100.8	171.7	
Age (y)	55.8 ± 8.0[3]	55.3 ± 7.6	56.0 ± 7.5	56.7 ± 7.4	<0.01
BMI (kg/m^2)	23.6 ± 2.9	23.5 ± 2.8	23.6 ± 2.8	23.6 ± 2.8	0.73
Total physical activity (MET-h/wk)	33.0 ± 6.6	33.5 ± 6.7	34.0 ± 6.7	35.0 ± 6.8	<0.01
Current smoker (%)	44.8	46.5	45.9	48.2	<0.01
Current drinker (%)	60.3	68.8	72.9	74.8	<0.01
Family history of diabetes (%)	7.8	8.6	8.6	8.6	0.14
History of hypertension (%)	15.5	15.9	17.4	16.9	<0.01
Daily food and nutrient intake					
Total energy intake (kcal)	1807 ± 551	2090 ± 542	2320 ± 590	2820 ± 745	<0.01
Carbohydrate (% of energy)	56.3 ± 10.4	54.1 ± 9.0	51.9 ± 8.5	48.0 ± 8.2	<0.01
Fat (% of energy)	21.2 ± 7.4	22.7 ± 6.6	23.7 ± 6.3	26.4 ± 6.2	<0.01
Protein (% of energy)	11.8 ± 2.0	12.9 ± 1.8	13.9 ± 1.8	15.9 ± 2.4	<0.01
Calcium (mg)	496 ± 254	510 ± 224	508 ± 212	504 ± 186	0.11
Magnesium (mg)	264 ± 55	277 ± 53	286 ± 50	301 ± 51	<0.01
Dietary fiber (g)	10.9 ± 4.5	11.6 ± 4.3	11.9 ± 4.1	12.3 ± 4.3	<0.01
Vitamin D (μg)	5.7 ± 2.8	8.3 ± 3.6	11.0 ± 4.8	15.5 ± 8.0	<0.01
Polyunsaturated fatty acids (g)	11.6 ± 3.8	12.3 ± 3.4	12.9 ± 3.2	14.2 ± 3.1	<0.01
Fruit (g)	128 ± 138	173 ± 173	203 ± 173	266 ± 219	<0.01
Vegetables (g)	148 ± 130	186 ± 133	218 ± 141	291 ± 200	<0.01
Meat (g)	50 ± 46	62 ± 48	72 ± 54	97 ± 73	<0.01
Rice (g)	403 ± 177	433 ± 185	447 ± 189	464 ± 196	<0.01
Big fish (g)	9.7 ± 6.3	18.5 ± 10.1	29.7 ± 17.0	57.4 ± 50.9	<0.01
Small and medium fish (g)	8.9 ± 5.5	16.1 ± 9.1	25.8 ± 14.6	51.2 ± 40.3	<0.01
Coffee consumption, ≥1 cup (%)	36.4	36.0	33.0	32.1	<0.01
Women					
n	7438	7440	7441	7440	
Median intake (g)	35.3	63.0	97.7	163.1	
Age (y)	56.6 ± 8.3	55.7 ± 7.8	56.1 ± 7.5	56.6 ± 7.2	0.38
BMI (kg/m^2)	23.4 ± 3.2	23.3 ± 3.1	23.4 ± 3.1	23.5 ± 3.0	<0.01
Total physical activity (MET-h/wk)	32.4 ± 5.7	32.8 ± 5.6	32.9 ± 5.6	33.3 ± 5.9	<0.01
Current smoker (%)	5.0	4.8	4.5	4.4	0.09
Current drinker (%)	10.8	14.0	14.4	13.9	<0.01
Family history of diabetes (%)	7.8	8.9	9.4	9.9	<0.01
History of hypertension (%)	18.2	17.1	18.1	17.0	0.24
Daily food and nutrient intake					
Total energy intake (kcal)	1526 ± 479	1769 ± 473	1999 ± 507	2459 ± 667	<0.01
Carbohydrate (% of energy)	59.5 ± 8.7	57.0 ± 7.5	54.7 ± 7.1	51.0 ± 7.1	<0.01
Fat (% of energy)	25.4 ± 7.6	26.9 ± 6.4	28.2 ± 6.0	30.3 ± 5.7	<0.01
Protein (% of energy)	13.1 ± 1.7	14.4 ± 1.5	15.5 ± 1.6	17.3 ± 2.1	<0.01
Calcium (mg)	560 ± 248	564 ± 216	559 ± 197	531 ± 177	<0.01
Magnesium (mg)	260 ± 53	270 ± 47	279 ± 47	287 ± 44	<0.01
Dietary fiber (g)	12.9 ± 4.7	13.4 ± 4.2	13.7 ± 4.2	13.6 ± 3.9	<0.01
Vitamin D (μg)	5.8 ± 2.8	8.6 ± 3.6	11.0 ± 4.7	14.4 ± 6.8	<0.01
Polyunsaturated fatty acids (g)	12.2 ± 3.4	12.6 ± 2.9	13.1 ± 2.8	13.7 ± 2.6	<0.01
Fruit (g)	176 ± 171	242 ± 192	284 ± 212	367 ± 265	<0.01
Vegetables (g)	183 ± 151	217 ± 145	258 ± 166	332 ± 207	<0.01
Meat (g)	45 ± 48	54 ± 46	64 ± 50	85 ± 66	<0.01
Rice (g)	322 ± 136	339 ± 137	353 ± 141	364 ± 144	<0.01
Big fish (g)	8.7 ± 6.1	17.0 ± 9.6	26.5 ± 15.2	49.3 ± 38.3	<0.01
Small and medium fish (g)	8.3 ± 5.4	15.6 ± 9.1	25.6 ± 14.3	50.6 ± 42.9	<0.01
Coffee consumption, ≥1 cup (%)	39.0	40.4	36.2	34.4	<0.01

[1] MET-h, metabolic equivalent hours.

[2] Based on the Mantel-Haenszel chi-square test for categorical variables and linear regression analysis for continuous variables, with ordinal numbers of 0 to 3 assigned to the categories of total fish/seafood intake.

[3] Mean ± SD (all such values).

TABLE 2
ORs and 95% CIs of type 2 diabetes according to quartile (Q) categories of fish intake[1]

	Men					Women				
	Q1 (low)	Q2	Q3	Q4 (high)	*P*-trend[2]	Q1 (low)	Q2	Q3	Q4 (high)	*P*-trend[2]
Total fish/seafood										
Median intake (g/d)	36.6	65.0	100.8	171.7		35.3	63.0	97.7	163.1	
No. of cases/participants	164/5730	143/5731	137/5729	128/5731		99/7438	98/7440	101/7441	101/7440	
Age- and area-adjusted[3] OR (95% CI)	1.00 (ref)	0.87 (0.69, 1.10)	0.84 (0.66, 1.06)	0.78 (0.61, 0.99)	0.04	1.00 (ref)	1.04 (0.78, 1.39)	1.05 (0.78, 1.40)	1.01 (0.75, 1.36)	0.95
Multivariate-adjusted[4] OR (95% CI)	1.00 (ref)	0.84 (0.67, 1.07)	0.80 (0.62, 1.03)	0.73 (0.54, 1.00)	0.04	1.00 (ref)	1.06 (0.79, 1.42)	1.04 (0.75, 1.43)	1.01 (0.69, 1.49)	0.96
Fresh fish										
Median intake (g/d)	17.3	32.3	53.6	96.4		15.7	30.0	50.8	89.3	
No. of cases/participants	156/5723	147/5736	135/5732	134/5730		108/7439	91/7444	98/7437	102/7439	
Age- and area-adjusted[3] OR (95% CI)	1.00 (ref)	0.95 (0.76, 1.20)	0.88 (0.69, 1.11)	0.87 (0.68, 1.10)	0.19	1.00 (ref)	0.88 (0.66, 1.17)	0.92 (0.69, 1.22)	0.92 (0.69, 1.21)	0.62
Multivariate-adjusted[4] OR (95% CI)	1.00 (ref)	0.93 (0.74, 1.18)	0.87 (0.68, 1.12)	0.89 (0.66, 1.18)	0.33	1.00 (ref)	0.92 (0.69, 1.23)	0.95 (0.70, 1.28)	0.93 (0.66, 1.31)	0.72
Seafood other than fish										
Median intake (g/d)	4.7	9.7	14.3	31.3		4.0	9.0	13.6	28.2	
No. of cases/participants	156/5602	150/5858	124/5731	142/5730		105/7490	107/8188	94/6702	93/7379	
Age- and area-adjusted[3] OR (95% CI)	1.00 (ref)	0.93 (0.74, 1.17)	0.79 (0.62, 1.01)	0.91 (0.72, 1.15)	0.23	1.00 (ref)	0.99 (0.75, 1.30)	1.08 (0.81, 1.44)	0.95 (0.71, 1.27)	0.86
Multivariate-adjusted[4] OR (95% CI)	1.00 (ref)	0.92 (0.73, 1.16)	0.77 (0.59, 0.99)	0.89 (0.67, 1.16)	0.20	1.00 (ref)	0.99 (0.75, 1.31)	1.07 (0.79, 1.44)	0.93 (0.67, 1.31)	0.84
Salted and dried fish products										
Median intake (g/d)	0.7	9.7	20.7	45.3		1.3	10.0	21.3	44.8	
No. of cases/participants	155/5732	139/5740	141/5783	137/5666		118/7499	72/7386	117/7536	92/7338	
Age- and area-adjusted[3] OR (95% CI)	1.00 (ref)	0.89 (0.67, 1.17)	0.90 (0.68, 1.19)	0.89 (0.67, 1.19)	0.57	1.00 (ref)	0.65 (0.46, 0.91)	0.99 (0.71, 1.38)	0.77 (0.54, 1.08)	0.71
Multivariate-adjusted[4] OR (95% CI)	1.00 (ref)	0.86 (0.65, 1.14)	0.90 (0.67, 1.21)	0.91 (0.66, 1.25)	0.78	1.00 (ref)	0.65 (0.46, 0.93)	1.01 (0.71, 1.42)	0.74 (0.51, 1.09)	0.64
Other fish products										
Median intake (g/d)	1.3	3.3	6.3	14.2		2.0	4.0	7.7	15.6	
No. of cases/participants	154/5678	136/5709	143/5883	139/5651		96/7600	98/7278	97/7466	108/7415	
Age- and area-adjusted[3] OR (95% CI)	1.00 (ref)	0.87 (0.69, 1.10)	0.88 (0.69, 1.11)	0.88 (0.69, 1.11)	0.29	1.00 (ref)	1.11 (0.83, 1.47)	1.02 (0.77, 1.36)	1.12 (0.84, 1.49)	0.56
Multivariate-adjusted[4] OR (95% CI)	1.00 (ref)	0.88 (0.69, 1.11)	0.89 (0.69, 1.13)	0.91 (0.70, 1.18)	0.47	1.00 (ref)	1.15 (0.86, 1.53)	1.05 (0.78, 1.41)	1.15 (0.84, 1.57)	0.52

[1] There were a total of 19 fish/seafood items (7 fresh fish: salmon, skipjack/tuna, cod/flatfish, sea bream, horse mackerel/sardine, saury/mackerel, and eel; 5 seafood other than fish: squid, octopus, shrimp, clam, and pond snail; 4 salted and dried fish products: salted fish, dried fish, dried whitebait, and salted fish roe; 3 other fish products: canned tuna; and 2 fish-paste products). ref, reference.

[2] Based on multiple logistic regression analysis, with ordinal numbers of 0 to 3 assigned to the quartile categories of fish intake.

[3] Adjusted for age (y) and study area (11 areas).

[4] Adjusted for age (y), study area (11 areas), BMI (in kg/m^2; <21, 21–22.9, 23–24.9, 25–26.9, or ≥27), smoking status (never; past; current: <20 or ≥20 cigarettes/d), alcohol consumption (nondrinker, occasional drinker, or drinker with a consumption of <150, 150–299, 300–449, or ≥450 g ethanol/wk for men; nondrinker, occasional drinker, or drinker with a consumption of <150 or ≥150 g ethanol/wk for women), family history of diabetes mellitus (yes or no), total physical activity (quartile, metabolic equivalent-h/d), history of hypertension (yes or no), total energy intake (kcal/d), coffee consumption (almost never or <1, 1, or ≥2 cups/d), and intakes of calcium (mg/d), magnesium (mg/d), dietary fiber (g/d), vegetables (g/d), fruit (g/d), meat (g/d), and rice (g/d).

TABLE 3

ORs and 95% CIs of type 2 diabetes according to quartile (Q) categories of fish intake by size and fat content[1]

	Men					Women				
	Q1 (low)	Q2	Q3	Q4 (high)	*P*-trend[2]	Q1 (low)	Q2	Q3	Q4 (high)	*P*-trend[2]
Size										
Big fish										
Median intake (g/d)	6.7	15.2	26.6	54.3		5.7	13.3	24.3	47.9	
No. of cases/participants	146/5634	145/5917	139/5661	142/5709		106/7446	102/7439	86/7434	105/7440	
Age- and area-adjusted[3] OR (95% CI)	1.00 (ref)	0.98 (0.77, 1.24)	1.00 (0.78, 1.28)	1.01 (0.79, 1.30)	0.88	1.00 (ref)	1.02 (0.77, 1.36)	0.83 (0.61, 1.12)	0.97 (0.72, 1.29)	0.53
Multivariate-adjusted[4] OR (95% CI)	1.00 (ref)	0.97 (0.76, 1.24)	1.02 (0.79, 1.32)	1.06 (0.80, 1.41)	0.63	1.00 (ref)	1.07 (0.80, 1.43)	0.85 (0.62, 1.17)	1.00 (0.71, 1.40)	0.66
Small and medium fish[5]										
Median intake (g/d)	5.3	12.3	25.7	47.9		5.3	11.2	25.7	48.6	
No. of cases/participants	141/4910	171/6709	149/5968	111/5334		110/7043	90/7919	100/8220	99/6577	
Age- and area-adjusted[3] OR (95% CI)	1.00 (ref)	0.87 (0.69, 1.11)	0.85 (0.66, 1.08)	0.69 (0.53, 0.90)	0.009	1.00 (ref)	0.77 (0.58, 1.04)	0.78 (0.59, 1.05)	0.96 (0.71, 1.29)	0.84
Multivariate-adjusted[4] OR (95% CI)	1.00 (ref)	0.86 (0.67, 1.09)	0.82 (0.63, 1.06)	0.68 (0.50, 0.92)	0.02	1.00 (ref)	0.80 (0.59, 1.08)	0.80 (0.59, 1.09)	1.02 (0.73, 1.44)	0.998
Fat content										
Oily fish[5]										
Median intake (g/d)	10.7	21.6	37.7	71.2		10.7	21.5	37.5	68.1	
No. of cases/participants	156/5739	151/5711	142/5861	123/5610		113/7919	95/6975	89/7338	102/7527	
Age- and area-adjusted[3] OR (95% CI)	1.00 (ref)	0.98 (0.78, 1.23)	0.89 (0.71, 1.13)	0.80 (0.63, 1.02)	0.056	1.00 (ref)	1.00 (0.76, 1.33)	0.86 (0.65, 1.15)	0.93 (0.70, 1.23)	0.42
Multivariate-adjusted[4] OR (95% CI)	1.00 (ref)	0.94 (0.75, 1.19)	0.88 (0.69, 1.12)	0.79 (0.59, 1.05)	0.098	1.00 (ref)	1.04 (0.78, 1.38)	0.87 (0.64, 1.17)	0.93 (0.67, 1.29)	0.46
Lean fish										
Median intake (g/d)	3.3	6.7	15.5	30.0		2.7	6.7	12.9	23.3	
No. of cases/participants	145/5560	158/6305	125/5321	144/5735		120/8640	84/6259	94/7448	101/7412	
Age- and area-adjusted[3] OR (95% CI)	1.00 (ref)	1.00 (0.79, 1.26)	0.95 (0.74, 1.22)	1.02 (0.80, 1.31)	0.98	1.00 (ref)	1.04 (0.78, 1.39)	0.94 (0.71, 1.26)	0.98 (0.74, 1.31)	0.77
Multivariate-adjusted[4] OR (95% CI)	1.00 (ref)	0.99 (0.78, 1.26)	0.95 (0.73, 1.23)	1.05 (0.80, 1.38)	0.83	1.00 (ref)	1.09 (0.81, 1.46)	0.98 (0.73, 1.32)	1.02 (0.75, 1.40)	0.98

[1] By size (big fish: salmon, skipjack/tuna, cod/flatfish, and sea bream; small and medium fish: horse mackerel/sardine, saury/mackerel, and eel); by fat content (oily fish: salmon, horse mackerel/sardine, saury/mackerel, eel, and sea bream; lean fish: skipjack/tuna and cod/flatfish). ref, reference.

[2] Based on multiple logistic regression analysis, with ordinal numbers of 0 to 3 assigned to the quartile categories of fish intake.

[3] Adjusted for age (y) and study area (11 areas).

[4] Adjusted for age (y), study area (11 areas), BMI (in kg/m^2; <21, 21–22.9, 23–24.9, 25–26.9, or ≥27), smoking status (never; past; current: <20 or ≥20 cigarettes/d), alcohol consumption (nondrinker, occasional drinker, or drinker with a consumption of <150, 150–299, 300–449, or ≥450 g ethanol/wk for men; and nondrinker, occasional drinker, or drinker with a consumption of <150 or ≥150 g ethanol/wk for women), family history of diabetes mellitus (yes or no), total physical activity (quartile, metabolic equivalent-h/d), history of hypertension (yes or no), total energy intake (kcal/d), coffee consumption (almost never or <1, 1, or ≥2 cups/d), and intakes of calcium (mg/d), magnesium (mg/d), dietary fiber (g/d), vegetable (g/d), fruit (g/d), meat (g/d), and rice (g/d).

[5] *P*-interaction between fish intake and sex = 0.01 for small and medium fish and 0.03 for oily fish.

associated with insulin resistance and type 2 diabetes (22, 27) and thus may have diminished the antidiabetic effects of fish. Similarly, we speculated that the null finding in women in the current study may have been due to their relatively high proportion of body fat mass, which may have been responsible for higher levels of accumulation of fat-soluble chemicals, which negated the benefit of fish intake on glucose metabolism.

The effect of fish intake on glucose metabolism may differ according to cooking method. Compared with raw fish, deep-fried fish intake is associated with higher concentrations of contaminants (28) and, because of a reduction in eicosapentaenoic and docosahexaenoic acids, has a lower potential for favorable health effects (29). Patel et al (8) observed an inverse association of type 2 diabetes with nonfried (fresh, frozen, or canned) fish intake, but not with fried fish. Although we did not have dietary intake data by cooking method, we confirmed that the current participants used grilling (58.9%) and stewing (26.4%) much more commonly than frying (3.9%) as methods for cooking seafood. The high consumption of nonfried fish in Japanese might partly account for the inverse association between fish intake and type 2 diabetes in the current study. Salting and drying, which are used to preserve fish, can also modify the association between fish intake and risk of type 2 diabetes. A salty diet could deteriorate insulin metabolism (30), and the drying of fish may accelerate the oxidation of polyunsaturated fatty acids, which in turn induce inflammation (31)—a known predictor of type 2 diabetes (32). In the current study, however, a high intake of salted and dried fish was associated with neither an increased nor a decreased risk of type 2 diabetes. These results may imply that the salting and drying of fish diminishes, or even surpasses, favorable effects that fresh fish have on glucose metabolism.

The strengths of the current study include our large sample size, the population-based prospective design, and the use of a validated FFQ. Furthermore, the dietary data of the Japanese population allowed us to assess any potential association at relatively high fish/seafood intakes, and we examined the association by size and fat content of fish. Our study also had some limitations. First, we had no source of information other than the questionnaire for type 2 diabetes. However, a validation study conducted in our study population showed fairly good agreement between self-reported diabetes and diabetes, as documented in medical records (94%), and the sensitivity of self-reported diabetes was reasonably high (83%). Nevertheless, the 5-y incidence of type 2 diabetes in the current study (1.8%) was lower than that in another Japanese study (33), which ascertained type 2 diabetes by the same method during the same period as in the current study. If we could have confirmed new cases of type 2 diabetes by using another method, such as the measurement of plasma glucose concentrations, the incidence of type 2 diabetes might have been higher. However, it may not be feasible to measure plasma glucose in a large sample. Although case ascertainment based on self-reporting might underestimate the incidence of type 2 diabetes, this misclassification would occur virtually independent of fish intake and thus might not cause serious bias in our estimate. However, we cannot rule out the possibility that participants with higher fish intakes are more health conscious than are those with lower intakes. Second, in the current study, a large number of participants were excluded because of a lack of response to the third survey, history of type 2 diabetes and severe disease, and missing information on fish/seafood intake. For the current analysis, although these exclusions were necessary, we could not rule out the possibility of selection bias as a result of these exclusions. Third, because we excluded participants who had missing values for $\geq$1 of 19 fish/seafood items, a large number of participants were excluded. However, the findings were similar to those obtained in participants with dietary information necessary for the analysis of each subcategory of fish intake. Fourth, dietary intakes assessed at only one time point may not reflect long-term intake. Repeated assessment of diet over a long period of time before disease onset will likely provide a better estimate of exposure status. Fifth, because we had no information about potential toxins from fish, we could not directly examine the association between environmental contaminants from fish and type 2 diabetes risk. Finally, we cannot rule out the possibility of unmeasured and residual confounding.

In conclusion, total fish/seafood and small and medium fish intakes were associated with a decreased risk of type 2 diabetes in men. Fish intake was not associated with an increased risk of type 2 diabetes in either men or women. The current study provides evidence to support a protective role of fish intake against type 2 diabetes in Japanese men. Biological mechanisms underlying the inverse association between fish intake and type 2 diabetes need to be clarified.

Members of the JPHC Study Group (Principal Investigator: S Tsugane) are as follows: S Tsugane, M Inoue, T Sobue, and T Hanaoka (National Cancer Center, Tokyo, Japan); J Ogata, S Baba, T Mannami, A Okayama, and Y Kokubo (National Cardiovascular Center, Osaka, Japan); K Miyakawa, F Saito, A Koizumi, Y Sano, I Hashimoto, T Ikuta, and Y Tanaba (Iwate Prefectural Ninohe Public Health Center, Iwate, Japan); Y Miyajima, N Suzuki, S Nagasawa, Y Furusugi, and N Nagai (Akita Prefectural Yokote Public Health Center, Akita, Japan); H Sanada, Y Hatayama, F Kobayashi, H Uchino, Y Shirai, T Kondo, R Sasaki, Y Watanabe, Y Miyagawa, and Y Kobayashi (Nagano Prefectural Saku Public Health Center, Nagano, Japan); Y Kishimoto, E Takara, T Fukuyama, M Kinjo, M Irei, and H Sakiyama (Okinawa Prefectural Chubu Public Health Center, Okinawa, Japan); K Imoto, H Yazawa, T Seo, A Seiko, F Ito, F Shoji, and R Saito (Katsushika Public Health Center, Tokyo, Japan); A Murata, K Minato, K Motegi, and T Fujieda (Ibaraki Prefectural Mito Public Health Center, Ibaraki, Japan); K Matsui, T Abe, M Katagiri, and M Suzuki (Niigata Prefectural Kashiwazaki and Nagaoka Public Health Center, Niigata, Japan); M Doi, A Terao, Y Ishikawa, and T Tagami (Kochi Prefectural Chuo-Higashi Public Health Center, Kochi, Japan); H Sueta, H Doi, M Urata, N Okamoto, and F Ide (Nagasaki Prefectural Kamigoto Public Health Center, Nagasaki, Japan); H Sakiyama, N Onga, H Takaesu, and M Uehara (Okinawa Prefectural Miyako Public Health Center, Okinawa, Japan); F Horii, I Asano, H Yamaguchi, K Aoki, S Maruyama, M Ichii, and M Takano (Osaka Prefectural Suita Public Health Center, Osaka, Japan); Y Tsubono, Tohoku University, Miyagi, Japan); K Suzuki (Research Institute for Brain and Blood Vessels Akita, Akita, Japan); Y Honda, K Yamagishi, S Sakurai, and N Tsuchiya (Tsukuba University, Ibaraki, Japan); M Kabuto (National Institute for Environmental Studies, Ibaraki, Japan); M Yamaguchi, Y Matsumura, S Sasaki, and S Watanabe (National Institutes of Health and Nutrition, Tokyo, Japan); M Akabane (Tokyo University of Agriculture, Tokyo, Japan); T Kadowaki (Tokyo University, Tokyo, Japan); M Noda and T Mizoue (National Center for Global Health and Medicine, Tokyo, Japan); Y Kawaguchi (Tokyo Medical and Dental University, Tokyo, Japan); Y Takashima and M Yoshida (Kyorin University, Tokyo, Japan); K Nakamura (Niigata University, Niigata, Japan); S Matsushima and S Natsukawa (Saku General Hospital, Nagano, Japan); H Shimizu (Sakihae Institute, Gifu, Japan); H Sugimura (Hamamatsu University, Shizuoka, Japan); S Tominaga (Aichi Cancer Center Research Institute, Aichi, Japan); H Iso (Osaka University, Osaka, Japan); M Iida, W Ajiki, and A Ioka (Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka, Japan); S Sato (Chiba Prefectural

Institute of Public Health, Chiba, Japan); E Maruyama (Kobe University, Hyogo, Japan); M Konishi, K Okada, and I Saito (Ehime University, Ehime, Japan); N Yasuda (Kochi University, Kochi, Japan); and S Kono (Kyushu University, Fukuoka, Japan).

We thank Atsushi Goto (National Center for Global Health and Medicine) for helpful discussions.

The authors' responsibilities were as follows—ST (Principal Investigator): involved in the design of study; ST and MI: conducted the survey; AN, TM, MN, YT, YM, KP-T, MK, and SO: drafted the plan for the data analyses; AN: conducted the data analysis; TM: provided statistical expertise; AN: drafted the manuscript; and AN and TM: had primary responsibility for the final content. All authors were involved in the interpretation of the results and the revision of the manuscript and approved the final version of the manuscripts. None of the authors had a conflict of interest.

REFERENCES

1. Breslow JL. n−3 Fatty acids and cardiovascular disease. Am J Clin Nutr 2006;83:1477S–82S.
2. Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. JAMA 2006;296:1885–99.
3. Nkondjock A, Receveur O. Fish-seafood consumption, obesity, and risk of type 2 diabetes: an ecological study. Diabetes Metab 2003;29:635–42.
4. Fedor D, Kelley DS. Prevention of insulin resistance by n−3 polyunsaturated fatty acids. Curr Opin Clin Nutr Metab Care 2009;12:138–46.
5. Djoussé L, Gaziano JM, Buring JE, Lee IM. Dietary omega-3 fatty acids and fish consumption and risk of type 2 diabetes. Am J Clin Nutr 2011;93:143–50.
6. Feskens EJ, Bowles CH, Kromhout D. Inverse association between fish intake and risk of glucose intolerance in normoglycemic elderly men and women. Diabetes Care 1991;14:935–41.
7. Kaushik M, Mozaffarian D, Spiegelman D, Manson JE, Willett WC, Hu FB. Long-chain omega-3 fatty acids, fish intake, and the risk of type 2 diabetes mellitus. Am J Clin Nutr 2009;90:613–20.
8. Patel PS, Sharp SJ, Luben RN, Khaw KT, Bingham SA, Wareham NJ, Forouhi NG. Association between type of dietary fish and seafood intake and the risk of incident type 2 diabetes: the European prospective investigation of cancer (EPIC)-Norfolk cohort study. Diabetes Care 2009;32:1857–63.
9. Schulze MB, Manson JE, Willett WC, Hu FB. Processed meat intake and incidence of Type 2 diabetes in younger and middle-aged women. Diabetologia 2003;46:1465–73.
10. van Woudenbergh GJ, van Ballegooijen AJ, Kuijsten A, Sijbrands EJ, van Rooij FJ, Geleijnse JM, Hofman A, Witteman JC, Feskens EJ. Eating fish and risk of type 2 diabetes: a population-based, prospective follow-up study. Diabetes Care 2009;32:2021–6.
11. FAO Statistics Division 2010. Available from: http://faostat.fao.org/ (cited 13 October 2010).
12. Tsugane S, Sobue T. Baseline survey of JPHC study–design and participation rate. Japan Public Health Center-based Prospective Study on Cancer and Cardiovascular Diseases. J Epidemiol 2001;11:S24–9.
13. Sasaki S, Kobayashi M, Ishihara J, Tsugane S. Self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC Study: questionnaire structure, computation algorithms, and area-based mean intake. J Epidemiol 2003;13:S13–22.
14. Ishihara J, Sobue T, Yamamoto S, Yoshimi I, Sasaki S, Kobayashi M, Takahashi T, Iitoi Y, Akabane M, Tsugane S. Validity and reproducibility of a self-administered food frequency questionnaire in the JPHC Study Cohort II: study design, participant profile and results in comparison with Cohort I. J Epidemiol 2003;13:S134–47.
15. Sasaki S, Ishihara J, Tsugane S. Reproducibility of a self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC Study Cohort I to assess food and nutrient intake. J Epidemiol 2003;13:S115–24.
16. Sasaki S, Kobayashi M, Tsugane S. Validity of a self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC Study Cohort I: comparison with dietary records for food groups. J Epidemiol 2003;13:S57–63.
17. Tsugane S, Sasaki S, Kobayashi M, Tsubono Y, Akabane M. Validity and reproducibility of the self-administered food frequency questionnaire in the JPHC Study Cohort I: study design, conduct and participant profiles. J Epidemiol 2003;13:S2–12.
18. Kato M, Noda M, Inoue M, Kadowaki T, Tsugane S. Psychological factors, coffee and risk of diabetes mellitus among middle-aged Japanese: a population-based prospective study in the JPHC study cohort. Endocr J 2009;56:459–68.
19. Kosaka K. Diagnostic criteria for diabetes mellitus in Japan–from a report of the Japan Diabetes Society (JDS) Committee on the Diagnosis of Diabetes Mellitus, 1982. Diabetes Res Clin Pract 1994;24 (suppl):S59–62.
20. Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. J Clin Endocrinol Metab 2007;92:2017–29.
21. Salmeron J, Hu FB, Manson JE, Stampfer MJ, Colditz GA, Rimm EB, Willett WC. Dietary fat intake and risk of type 2 diabetes in women. Am J Clin Nutr 2001;73:1019–26.
22. Rignell-Hydbom A, Lidfeldt J, Kiviranta H, Rantakokko P, Samsioe G, Agardh CD, Rylander L. Exposure to p,p'-DDE: a risk factor for type 2 diabetes. PLoS ONE 2009;4:e7503.
23. Olsen H, Enan E, Matsumura F. Regulation of glucose transport in the NIH 3T3 L1 preadipocyte cell line by TCDD. Environ Health Perspect 1994;102:454–8.
24. Liu H, Biegel L, Narasimhan TR, Rowlands C, Safe S. Inhibition of insulin-like growth factor-I responses in MCF-7 cells by 2,3,7,8-tetrachlorodibenzo-p-dioxin and related compounds. Mol Cell Endocrinol 1992;87:19–28.
25. Kenko Eiyo Joho Kenkyukai. The National Health and Nutrition Survey in Japan, 2006. Tokyo, Japan: Daiichi-shuppan, 2009 (in Japanese).
26. Wang Y, Beydoun MA, Caballero B, Gary TL, Lawrence R. Trends and correlates in meat consumption patterns in the US adult population. Public Health Nutr 2010;13:1333–45.
27. Chang JW, Chen HL, Su HJ, Liao PC, Guo HR, Lee CC. Simultaneous exposure of non-diabetics to high levels of dioxins and mercury increases their risk of insulin resistance. J Hazard Mater 2011;185: 749–55.
28. Burger J, Dixon C, Boring CS, Gochfeld M. Effect of deep-frying fish on risk from mercury. J Toxicol Environ Health A 2003;66:817–28.
29. Candela M, Astiasarán I, Bello J. Deep-fat frying modifies high-fat fish lipid fraction. J Agric Food Chem 1998;46:2793–6.
30. Thorburn AW, Brand JC, Truswell AS. Salt and the glycaemic response. Br Med J (Clin Res Ed) 1986;292:1697–9.
31. Zimmerman GA, Prescott SM, McIntyre TM. Oxidatively fragmented phospholipids as inflammatory mediators: the dark side of polyunsaturated lipids. J Nutr 1995;125:1661S–5S.
32. Schmidt MI, Duncan BB, Sharrett AR, Lindberg G, Savage PJ, Offenbacher S, Azambuja MI, Tracy RP, Heiss G. Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities study): a cohort study. Lancet 1999;353:1649–52.
33. Kirii K, Iso H, Date C, Fukui M, Tamakoshi A. Magnesium intake and risk of self-reported type 2 diabetes among Japanese. J Am Coll Nutr 2010;29:99–106.