Association between fish consumption and risk of chronic obstructive pulmonary disease among Chinese men and women: an 11-year population-based cohort study

Short Title: Fish consumption and risk of COPD among Chinese

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Abbreviations used: CKB, China Kadoorie Biobank; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second; FFQ, food frequency questionnaire; FVC, forced vital capacity; HI, health insurance; ICD, International Classification of Diseases; MET, metabolic equivalent task; PUFA, polyunsaturated fatty acid

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Abstract

Background: Epidemiological evidence on the relationship between fish consumption and chronic obstructive pulmonary disease (COPD) is limited, especially among Chinese.

Objectives: To explore the prospective association between fish consumption and COPD among a large population-based Chinese cohort.

Methods: The China Kadoorie Biobank (CKB) recruited over 0.5 million participants from ten geographically diverse regions across China from 2004 to 2008. Consumption frequency of fish at baseline was assessed by a validated food frequency questionnaire. 169,188 men and 252,238 women who had no prior COPD and other major chronic diseases at baseline were included in our analyses. Cox proportional hazard models were employed to estimate the hazard ratio (HR) and 95% confidence interval (CI) for fish consumption categories in relation to incident COPD.

Results: During a median follow-up of 11.1 years, 5542 incident COPD cases were documented. Fish consumption was inversely associated with COPD risk among women, with a 17% reduction in risk for participants who consumed fish ≥4 days/week compared with non-consumption (HR: 0.83 ; 95% CI: 0.70, 0.99; *p* for trend = 0.017), whereas we did not observe such a dose-response relationship among men (HR: 0.89; 95% CI: 0.76, 1.05; *p* for trend = 0.373). The joint analysis showed that COPD risk was

38% and 48% lower in men and women who consumed fish ≥4 days/week and had a healthy lifestyle (having ≥4 of the following healthy lifestyle factors: not smoking currently, never or rarely drinking alcohol, adequate physical activity, BMI 18.5-23.9 kg/m^2, normal waist circumference, reasonable diet), compared with participants with fish consumption <4 days/week and unhealthy lifestyle (≤1 factors).

Conclusion: Higher fish consumption was associated with lower COPD risk among Chinese women but not men. Such association was independent of lifestyle factors. Eating adequate fish with an overall healthy lifestyle might help to lower the risk of COPD.

Keywords: fish, diet, COPD, obstructive lung disease, lifestyle

1 Introduction

Chronic obstructive pulmonary disease (COPD), as one of major public health issues, was the third leading cause of death worldwide, killing over 3 million people every year (1). The disease burden was particularly severe in low- and middle-income countries (1). A recent national representative survey in Chinese adults aged 20 years or older reported that 8.6% were suffering from COPD, and the prevalence was higher in individuals aged 40 years or older (13.7%) (2).

Modifiable risk factors, such as dietary habits, played an essential role in COPD prevention. Fish is an excellent source of long-chain n-3 polyunsaturated fatty acid (PUFA) and may inhibit inflammation to protect against COPD (3). However, epidemiological evidence on the relationship between fish intake and COPD was scarce, especially in women. For men, several prospective studies showed no significant association between fish intake and COPD mortality or incidence (4-6). For women, one prospective study based on the Nurses' Health Study initially reported a 29% reduction in COPD risk for women who consumed fish ≥4 servings/week compared with <1 servings/week (hazard ratio [HR]: 0.71; 95% confidence interval [CI]: 0.52, 0.98). However, after further adjustment for dietary patterns, the significant association diminished (6). These results should be interpreted with great caution due to the limited sample size and population specificity, as most previous studies were conducted in western populations. The relationship between fish intake and COPD risk might be different in the Asia population due to genetic background, lifestyle behaviors, and environmental factors.

Therefore, we examined the prospective association between fish consumption and COPD among a large population-based Chinese cohort.

2 Method

2.1 Study Population

The present study was based on the China Kadoorie Biobank (CKB), a large-scale cohort recruiting over 0.5 million participants from ten geographically diverse regions across China. Details about the CKB have been documented elsewhere (7, 8). Briefly, 512,726 participants aged 30-79 provided valid baseline data between June 2004 and July 2008. Since recruitment, about 5% of the participants were randomly selected for resurveys every 4 to 5 years. The procedure of resurveys was generally consistent with the baseline survey, and the contents became broader and more detailed. Up to now, three resurveys have been completed.

In the present study, we excluded 37,057 participants with prevalent COPD defined by self-report or spirometry (FEV1/FVC <0.7), 1566 with asthma, 6383 with tuberculosis, 13,275 with coronary heart disease, 6785 with stroke, 2132 with cancer, and 23,757 with diabetes at baseline, in order to minimize the reverse causality. Additionally, we also excluded 343 participants with an abnormal value of FEV1/FVC (>1) and 2 missing body mass index (BMI). The final analysis included 169,188 men and 252,238 women (**Supplemental Figure S1**).

All participants provided written informed consent. The Ethical Review Committee of the Chinese Center for Disease Control and Prevention (Beijing, China, 005/2004)

and the Oxford Tropical Research Ethics Committee, University of Oxford (UK, 025-04) approved the study.

2.2 Dietary Assessment

A self-designed food frequency questionnaire (FFQ) was employed to collect information on dietary habits. At baseline, we asked participants about the consumption frequency of 12 common food groups in China during the past 12 months (qualitative FFQ), including rice, wheat, other staple foods, meat, poultry, fish (fish or seafood), fresh eggs, fresh vegetables, preserved vegetables, soybean, fresh fruit, and dairy products. The frequency categories included never or rarely, monthly, 1-3 days/week, 4-6 days/week, and daily. At the second resurvey during 2013-2014, we further asked about the intake amount (quantitative FFQ), allowing us to estimate the usual consumption amount for each baseline frequency level during the follow-up period.

We confirmed the good reproducibility and relative validity against twelve 24-h dietary recalls of the two FFQs by conducting a study among 432 CKB participants from 2015 to 2016. The weighted kappa coefficients for fish were above 0.70 (9).

2.3 Assessment of Covariates

An interviewer-administered laptop-based questionnaire was used to collect information on socio-demographic variables (sex, age, education, marital status, and

annual household income), lifestyle behaviors (tobacco smoking, alcohol drinking, physical activity, dietary habits, nutritional supplements, passive smoking, cook fuel pollution, and heat fuel pollution). In detail, for smoking history, we asked about the frequency, usual type, and daily amount of tobacco for smokers, and the duration and reason for stopping smoking for former smokers. For alcohol drinking, we assessed the frequency, usual type, and daily amount. The daily intensity of physical activity was estimated as the total metabolic equivalent task-hours (MET-h) of all products of the MET of each type and the corresponding time spent on physical activity (occupation, commuting, housework, or leisure-time exercise).

Additionally, trained staff measured body weight, height, and waist circumference by following standard protocol and using calibrated instruments. BMI was calculated as weight (kg) divided by height square (m^2).

2.4 Ascertainment of Incident COPD

Several national systems laid the foundations for long-term follow-up of the CKB cohort. The local disease surveillance points system, death registries, and residential records were used to ascertain vital status. Since 2011, the CKB started to establish electronic linkage with national health insurance (HI) databases and has covered about 98% of participants till now, which could provide hospitalization records accurately.

Training staff carried out active follow-up annually for participants who moved out of the study areas or failed to link with the HI system.

Professional staff “blinded” to baseline information coded the cause of death or hospitalization using the 10th version of the International Classification of Diseases (ICD-10). In the present study, the outcome was COPD (J41-J44). We followed up until the date of COPD incidence, death, loss to follow-up, or 31 December 2017, whichever came first.

Five professional physicians adjudicated 1069 COPD events by multiple evidence, including exposure history of risk factors (tobacco smoking, occupational exposure, and household air pollution), respiratory symptoms, and radiological examinations. And 85% COPD cases were confirmed, meaning the positive predictive value of COPD diagnosis in CKB was 85% (10).

2.5. Statistical Analysis

We regrouped participants into 4 groups for fish intake: never or rarely, monthly, 1-3 days/week, and ≥4 days/week, due to the small number of participants eating fish daily (<5%). Age- and region-standardized means or percentages were calculated using linear or logistic regression models to describe baseline characteristics across fish consumption categories (11, 12).

All analyses were conducted by sex to estimate the association between fish consumption and COPD risk in men and women. Cox proportional hazard models were employed to obtain the HR and 95% CI for COPD incidence across exposure categories, using age as the underlying timescale and stratified by age at baseline (in 5-year intervals) and ten study areas. Multivariate model was adjusted education level (no formal school, primary school, middle school, high school, or college/university), marital status (married or other), household income (<10,000, 10,000-19,999, or ≥20,000 Chinese yuan/year), tobacco smoking (never/occasional, former and having quit ≥5 years or <5 years, current and 1 to 14 cigarettes/day, 15 to 24 cigarettes/day, or ≥25 cigarettes/day), alcohol consumption (ex-regular drinkers, not weekly drinking, weekly but not daily, daily and <15 g/day, 15-29 g/day, 30-59 g/day, or ≥60 g/day), BMI (<18.5, 18.5-23.9, 24.0-27.9, or ≥28.0 kg/m^2), waist circumference (men: <70.0, 70.0-84.9, 85.0-89.9, 90.0-94.9, or ≥95.0 cm; women: <65.0, 65.0-79.9, 80.0-84.9, 85.0-89.9, or ≥90.0 cm), physical activity (continuous, MET-h), daily energy intake (continuous in log-transformed formal, kJ/day), passive smoking (never lived with smoker, lived with smoker for <20 years, lived with smoker for ≥20 years and exposure <20 h/week, or lived with smoker for ≥20 years and exposure ≥20 h/week), cook fuel pollution (never or occasionally cook, daily cook with clean fuel, daily cook with solid fuel, or daily cook with other fuel), heat fuel pollution (never or occasionally heat, heat with clean fuel, heat with solid fuel, or heat with other fuel), consumption frequency of other food groups (fresh

fruit, fresh vegetable, red meat) (never or rarely, monthly, 1-3 days/week, 4-6 days/week, and daily), and take situation of dietary supplements (regularly taking fish oil/cod liver oil, regularly taking vitamins/calcium/iron/zinc/ginseng/other herbal products, or not regularly taking supplements). The adjusted variables were carefully selected to control established and potential confounders according to previous studies (6, 13-15). In addition, we assigned 0, 0.5, 2.0, and 5.6 times/week to the four fish intake groups, respectively, and then examined the linear trend of the association. Both Kaplan–Meier survival curve and the interaction term between fish consumption frequency and time found no violation of the proportional hazard assumption for fish consumption frequency.

To correct regression dilution bias, we used data from 21,118 participants selected for the second resurvey from 2013 to 2014, and estimated the usual amount of fish consumption (**Supplemental Method, Supplemental Table S1**). Dose-response relationship and adjusted HRs per daily portion (50 g) of fish were estimated accordingly. The interaction between sex and fish consumption frequency (categorical variable) as well as the usual fish intake (continuous variable) on COPD risk were examined by likelihood ratio tests, comparing models with and without the cross-product term.

The following sensitivity analyses were performed to examine the robustness of the main findings: a) excluding the incident COPD cases in the first two years of follow-up to

minimize reverse causality; b) adjusting major dietary patterns rather than other food groups (fresh fruit, fresh vegetable, red meat); c) additionally adjusting menopause status among women; d) using the original fish consumption frequency groups (5 categories: never or rarely, monthly, 1-3 days/week, 4-6 days/week, and daily).

Additionally, we hypothesized that lifestyle behaviors would modify the association between fish intake and COPD risk, and constructed a healthy lifestyle score using 6 variables (namely tobacco smoking, alcohol consumption, physical activity, BMI, and waist circumference, dietary habits). For each lifestyle factor, we respectively defined the healthy group as those who not smoked currently, never or rarely drank alcohol, engaged in a sex-specific upper quarter of total physical activity, had a BMI of 18.5-23.9 kg/m^2, had a normal waist circumference (men: 70.0-84.9 cm; women: 65.0-79.9 cm), and ate properly (eating fresh vegetables and fresh fruits every day, and red meat less than daily) (**Supplemental Table S2**). Each variable scored 1 point if it was healthy, and participants were categorized into 3 groups (i.e., unhealthy, intermediate, and healthy lifestyle with a total score of ≤1, 2 or 3, ≥4 respectively). To increase the power of the analysis, we dichotomized the frequency of fish intake into healthy (≥4 days/week) or unhealthy (<4 days/week). Therefore, a joint analysis based on the combinations of fish intake (2 groups) and lifestyle scores (3 groups) was performed using individuals who ate fish <4 days/week and had an unhealthy lifestyle as the reference group. Additionally, we also conducted subgroup analyses to explore the

modification effect of individual lifestyle factors (i.e., smoke status, alcohol drinking, BMI, physical activity, waist circumference, diet). The interaction effects were also checked by likelihood ratio tests.

The statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and all statistical tests were two-sided. $P < 0.05$ was used as the significance level.

3 Results

Of the 169,188 men with a mean age at baseline of 51.3 years, 9.7% reported consuming fish ≥4 days/week, and 30.0% never or rarely consumed fish. Participants who ate fish more frequently were younger, from urban and southern areas, married, and had a higher education level and annual household income. They also tended to consume alcohol weekly, had a lower intensity of physical activity, had a higher BMI and waist circumference, and regularly took fish oil, meat, and fresh fruit. However, they were less likely to use solid fuel to cook and heat. For women, similar characteristics were observed across fish consumption categories, except for far lower percentages of current smoker (women: 2.3%; men: 67.8%) and alcohol drinker (women: 2.1%; men: 34.4%), and higher exposure to second smoke (women: 83.6%; men: 63.4%) and cooking pollution (women: 50.1%; men: 17.6%) (**Table 1**).

Among 421,426 participants, during a median follow-up of 11.1 years (interquartile range 1.9 years; total person-year 4.6 million), 5542 incident COPD cases among men and 5750 cases among women were recorded. In the whole cohort, the frequency of fish consumption was inversely associated with the risk of COPD in a dose-response manner (*p* for trend = 0.037). Participants who consumed fish ≥4 days/week had the lowest risk of COPD (HR: 0.85; 95% CI: 0.76, 0.95) as compared with those who never or rarely ate fish. The association was modified by sex (*p* value for interaction <0.001, **Table 2**). In women, the adjusted HRs (95% CIs) for incident COPD were 0.98 (0.90, 1.08), 0.92 (0.83, 1.03), and 0.83 (0.70, 0.99) for those ate fish monthly, 1-3 days/week, and ≥4 days/week, respectively (*p* for trend = 0.017). However, such a dose-response relationship was not observed in men (*p* for trend = 0.373). After correcting for regression dilution bias, a similar sex difference was observed in the associations between usual fish intake and risk of COPD (*p* value for interaction <0.001), i.e., usual fish intake was inversely associated with risk of COPD in women, but in men, the interaction was insignificant. The multivariate-adjusted HRs per daily portion of fish were 0.86 (95% CI: 0.75, 0.98) and 0.92 (95% CI: 0.82, 1.04) for women and men, respectively (**Figure 1**). The associations did not change substantially in the sensitivity analyses (**Supplemental Table S3**) as well as in the analysis of the 5-category fish consumption frequency (**Supplemental Table S4**).

In the joint analysis of fish consumption and lifestyle behaviors, we used participants who lived an unhealthy lifestyle and had fish intake <4 days/week as reference (**Figure 2**). For the men with a healthy lifestyle, a reduced risk of COPD was observed for those who consumed fish ≥4 days/week (HR: 0.62; 95% CI: 0.45, 0.83). In women, the corresponding HR was 0.52 (95% CI: 0.41, 0.66). However, no significant interactions were observed in both sexes (*p* for interaction were 0.691 and 0.758, respectively). As for each individual lifestyle factor (i.e., smoke status, alcohol drinking, BMI, physical activity, waist circumference, diet), we did not find any significant interactions with fish consumption, either (all *p* values for interaction were >0.05, **Supplemental Table S5**).

4 Discussion

Based on a large cohort study in China, the present study found fish consumption was inversely associated with COPD risk among women, with an 17% reduction in risk for participants who consumed fish ≥4 days/week compared with non-consumption, whereas we did not observe the association among men. Compared with participants who lived an overall unhealthy lifestyle and had fish intake <4 days/week, the COPD risk was 38% and 48% lower in men and women with a healthy lifestyle and consuming fish ≥4 days/week, respectively.

According to Scientific Research Report on Dietary Guidelines for Chinese Residents in 2021, the average daily fish consumption was only 24.3 g, and less than one-third of Chinese adults met the recommended level (40-75 g/day) (16). In the present study, only participants who had fish intake ≥4 days/week consumed more than 40 g/day of fish (Supplemental Table S1), accounting for less than 10% of the total population (Table 1). Our findings provided further scientific evidence for encouraging Chinese adults to consume adequate fish.

In the present study, we observed a protective effect of fish on COPD in women but not men. We also found the relationship between fish consumption and COPD risk was independent of lifestyle factors, and eating adequate fish with an overall healthy lifestyle could lower COPD risk significantly. In China, the gender difference in lifestyle factors is huge. For example, in the CKB population, men smoked and drank far more than women. Tobacco smoking, a well-documented risk factor for COPD, could lead to intense oxidative stress and associated inflammation, which could persist long even after quitting smoking (17, 18). Therefore, smoking cessation is the primary action to prevent COPD. Alcohol drinking may affect COPD in an indirect manner. For one thing, heavy drinkers tended to have other unhealthy lifestyle factors (e.g., current smoking, physical inactivity, and low fruit intake) (19). For another, one study found heavy drinking was associated with lower lung function in smokers (20). Our findings confirmed the importance of a healthy lifestyle in the prevention of COPD, suggesting

the combination of fish consumption and other healthy lifestyle behaviors could significantly reduce COPD risk.

Many nutrients in fish may be involved in the mechanistic pathways related to the pathogenesis of COPD. For example, n-3 PUFAs compete with n-6 PUFA for metabolic enzymes, thus inhibiting the synthesis of active eicosanoids with properties of pro-inflammation, thrombosis, and vaso- and bronco-constriction (21). Besides, n-3 PUFA involves the production of pro-resolving mediators such as resolvins and protectins, which could remove inflammatory mediators and promote healing (22). Other bioactive compounds, like vitamin D, riboflavin, iodine, and calcium, may also contribute to the beneficial effect of fish on health (13).

To the best of our knowledge, the present study is the first large prospective study to examine the association between fish consumption and COPD risk in Chinese adults, which enables us to minimize the reverse causality by excluding COPD and other major diseases at baseline. The design of periodic resurvey of the CKB project enabled us to estimate the usual amount of fish intake, therefore controlling regression dilution bias in our analysis. However, several limitations should be addressed. First, the CKB study did not collect the type and amount of fish consumption, as well as the cooking method. Second, the incident cases of COPD were collected through linkage with databases. We can hardly avoid the misclassification bias for incident COPD, since only 2.6% of Chinese adults with spirometry-defined COPD was diagnosed by a doctor according to

a recent nationally representative survey (2). Third, we cannot exclude the influence of residual confounding due to the nature of observational studies.

5 Conclusion

Higher fish consumption was associated with lower COPD risk among Chinese women but not men. The relationship between fish consumption and COPD risk was independent of lifestyle factors. Eating adequate fish with an overall healthy lifestyle might help to lower the risk of COPD. Given the insufficient fish intake in China, we recommend that Chinese adults consume an adequate daily fish intake while maintaining a comprehensively healthy lifestyle. More high-quality studies are needed to confirm our findings.

Data sharing plan: The access policy and procedures are available at www.ckbiobank.org. All researchers can apply to use the CKB data by registering and applying at the website: http://www.ckbiobank.org/site/Data+Access.

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Statement of authors' contributions to manuscript: CY, WY, JL, CJ, HD, YC and LY conceived and designed the study; LL and ZC, as the members of CKB Steering Committee, designed and supervised the conduct of the whole study; YG, PP, QX, XS,

ZC and LL acquired the data; WY and KS analyzed the data; WY drafted the manuscript; WC, JL, HD, YC, LY, JC and CY contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content; RS and SS developed the software and provided technical support. CY had primary responsibility for final content. All authors have read and approved the final manuscript. The authors report no conflicts of interest.

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Table 1 Baseline characteristics of participants according to the frequency of fish consumption[1]

Baseline characteristic	Frequency of fish consumption							
	Men				Women			
	Never/rarely	Monthly	1-3 days/ week	≥4 days/ week	Never/rarely	Monthly	1-3 days/ week	≥4 days/ week
Participants, n	50,667	34,994	67,097	16,430	85,219	52,872	92,126	22,021
Age, y [mean (SD)]	54.1 (10.7)	51.3 (10.6)	49.8 (10.3)	48.8 (10.2)	52.5 (10.2)	50.2 (10.2)	48.6 (9.9)	47.7 (10.2)
Urban area, %	4.9	34.6	64.2	82.0	6.3	38.0	69.0	85.6
Southern area, %	24.1	70.8	75.2	76.4	30.4	72.7	76.3	83.7
Married, %	89.1	92.9	95.4	96.1	87.7	89.5	91.6	92.7
High school and above, %	16.4	24.9	32.0	34.9	10.6	17.3	22.9	26.6
Household income ≥20,000 CNY/year, %	28.0	43.1	53.4	60.1	25.3	37.9	47.3	54.1
Current smoker, %	68.3	67.3	66.9	71.0	2.7	2.1	1.7	2.4
Current drinker, %	25.1	33.2	38.7	46.3	1.5	1.9	2.7	4.8
Passive smoker, %	63.6	61.8	63.3	66.2	84.5	83.6	82.7	84.5
Cooking with solid fuel, %[2]	19.4	18.8	15.7	14.0	56.7	51.6	45.4	39.8
Heating with solid fuel, %[2]	46.3	45.0	41.5	37.8	39.2	37.5	34.7	30.6
Physical activity, MET-h/d [mean (SD)]	25.5 (16.8)	23.2 (15.1)	22.2 (14.4)	21.4 (13.4)	21.9 (12.6)	21.2 (13.7)	20.9 (12.8)	20.4 (11.2)
BMI, kg/m^2 [mean (SD)]	22.9 (3.0)	23.3 (3.2)	23.8 (3.2)	24.1 (3.2)	23.6 (3.4)	23.7 (3.4)	23.8 (3.3)	24.0 (3.4)
Waist circumference, cm [mean (SD)]	79.7 (9.0)	81.7 (9.8)	83.0 (9.6)	84.2 (9.3)	78.1 (9.5)	78.6 (9.2)	78.7 (9.1)	79.3 (8.9)
Regularly taking fish oil, %	1.4	1.8	2.4	3.6	1.8	2.7	3.6	5.7
Daily consumption of foods, %								
Meat	18.3	30.7	38.6	43.2	14.7	25.2	31.4	34.8
Fresh vegetables	93.2	95.3	95.3	97.0	93.1	94.7	94.7	97.5
Fresh fruit	6.5	11.7	17.2	22.5	11.3	18.3	26.7	36.0

[1]The results were shown as means or percentages adjusted for age and region, as appropriate. CNY = unit of Chinese money Yuan; MET = metabolic equivalent task.
[2]Solid fuel included coal and wood.

Table 2 Prospective association between the frequency of fish consumption and risk of COPD in Chinese men and women[1]

	Frequency of fish consumption				*p* for trend
	Never/rarely	Monthly	1-3 days/week	≥ 4 days/week	
Total (n = 421,426)					
Case	3987	3105	3472	728	
Cases/1000 PYs	2.70	3.26	2.01	1.74	
Model 1[2]	1.00	0.89 (0.83, 0.95)	0.85 (0.79, 0.91)	0.81 (0.72, 0.90)	0.002
Model 2[3]	1.00	0.90 (0.85, 0.96)	0.87 (0.80, 0.94)	0.84 (0.74, 0.94)	0.018
Model 3[4]	1.00	0.91 (0.85, 0.97)	0.88 (0.82, 0.95)	0.85 (0.76, 0.95)	0.037
Men (n = 169,188)					
Case	1574	1556	1996	416	
Cases/1000 PYs	2.91	4.20	2.78	2.33	
Model 1[2]	1.00	0.91 (0.83, 1.00)	0.88 (0.79, 0.98)	0.89 (0.76, 1.03)	0.264
Model 2[3]	1.00	0.91 (0.83, 1.01)	0.88 (0.79, 0.98)	0.87 (0.74, 1.02)	0.207
Model 3[4]	1.00	0.92 (0.83, 1.02)	0.90 (0.80, 1.01)	0.89 (0.76, 1.05)	0.373
Women (n = 252,238)					
Case	2413	1549	1476	312	
Cases/1000 PYs	2.58	2.67	1.46	1.30	
Model 1[2]	1.00	0.95 (0.87, 1.04)	0.88 (0.79, 0.97)	0.76 (0.64, 0.90)	<0.001
Model 2[3]	1.00	0.98 (0.89, 1.07)	0.92 (0.82, 1.02)	0.82 (0.69, 0.98)	0.017
Model 3[4]	1.00	0.98 (0.90, 1.08)	0.92 (0.83, 1.03)	0.83 (0.70, 0.99)	0.017

[1]Results were presented as HR (95% CI), unless otherwise stated.
[2]Model 1 was adjusted for sex (only in total population), education level, marital status, and household income.
[3]Model 2 was further adjusted for tobacco smoking, alcohol consumption, BMI, waist circumference, physical activity, daily energy intake, passive smoking, cook fuel pollution, and heat fuel pollution.
[4]Model 3 additionally included consumption of fresh fruit, fresh vegetable, red meat, and dietary supplements. *P*-value for interaction between sex and frequency of fish consumption was <0.001. PY, person-year.

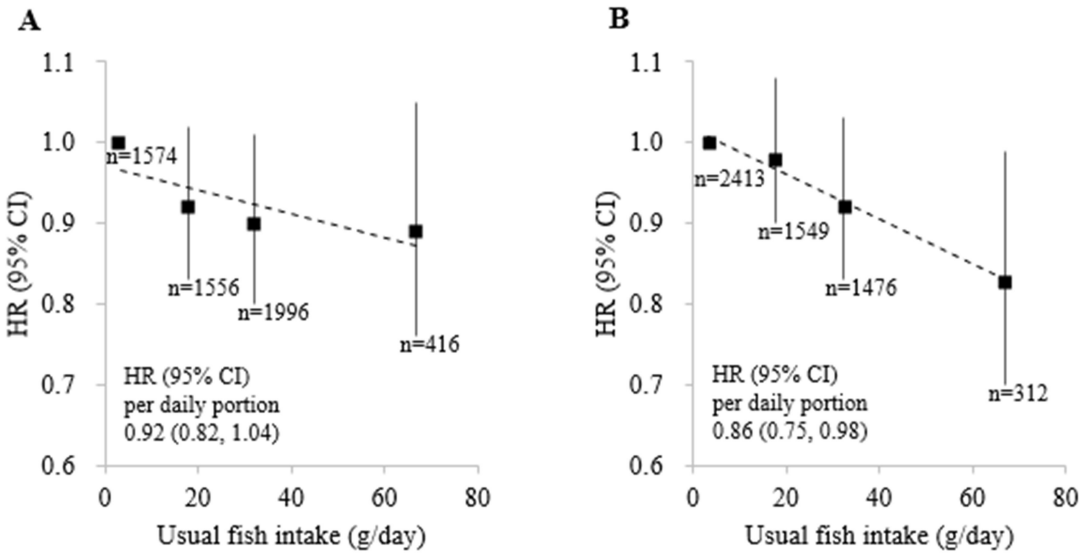

Figure 1 Adjusted HRs for COPD events based on the usual amount of fish consumption in Chinese men (A) and women (B).

Results were based on model 3, adjusting education level, marital status, household income, tobacco smoking, alcohol consumption, BMI, waist circumference, physical activity, passive smoking, cook fuel pollution, heat fuel pollution, consumption of fresh fruit, fresh vegetable, red meat, and dietary supplements.

Black squares, HRs; vertical lines, 95% CIs; dashed line, linear trend of the association between fish intake and COPD risk; 1 portion = 50 g. Values below represented the number of COPD events.

P-value for interaction between sex and usual fish intake was <0.001.

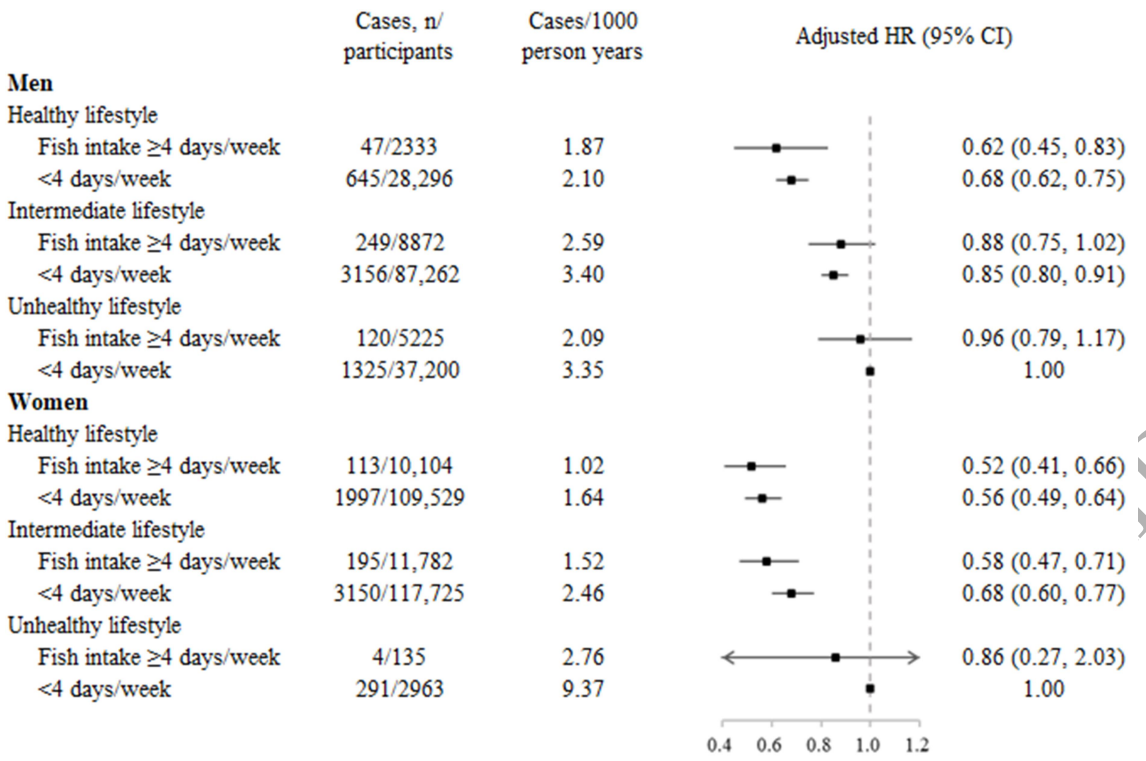

Figure 2 Adjusted HRs for COPD according to the joint classification of fish intake frequency and lifestyle behaviors in Chinese men and women.
Participants with ≤1, 2 or 3, ≥4 healthy lifestyle components were considered to have unhealthy, intermediate, and healthy lifestyles, respectively. The model was adjusted for education level, marital status, household income, daily energy intake, passive smoking, cook fuel pollution, heat fuel pollution, consumption of dietary supplements. No significant interaction was found between fish intake frequency and lifestyle score (*p* values for men and women were 0.691 and 0.758, respectively).