RESEARCH ARTICLE

Dietary intake of isoflavones and polyunsaturated fatty acids associated with lung function, breathlessness and the prevalence of chronic obstructive pulmonary disease: Possible protective effect of traditional Japanese diet

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The Japanese diet is high in soy products and fish. A case–control study was conducted in Japan to investigate the relationship between dietary intake of isoflavones and fatty acids and lung function, breathlessness and chronic obstructive pulmonary disease (COPD). A total of 278 referred patients aged 50–75 years with COPD diagnosed within the past 4 years, and 340 community-based controls were assessed for respiratory symptoms and undertook spirometric measurements of lung function. A validated food frequency questionnaire was administered face-to-face to obtain information on habitual food consumption. Dietary intakes of isoflavones and fatty acids were derived from the Japanese food composition tables. The COPD patients had significantly lower habitual intakes of isoflavones (genistein and daidzein) and polyunsaturated fatty acids (PUFA; both omega-3 and omega-6) than control subjects. Lung function measures were found to be positively associated with isoflavones and PUFA intake. Substantial reductions in prevalence of COPD and breathlessness were observed for isoflavones, the respective adjusted odds ratio being 0.36 (95% confidence interval 0.19–0.68) and 0.60 (95% confidence interval 0.33–1.10) for the highest *versus* lowest levels of total isoflavone intake. The corresponding tests for linear trend were significant. High intakes of PUFA and omega-6 fatty acids (derived from foods excluding oils and fats as seasonings) also appeared to reduce the risks of COPD and breathlessness symptom, but no evidence of association was found for other types of fatty acids. The study provided evidence of possible protective effect of traditional Japanese diet against tobacco carcinogens.

Keywords:
Chronic obstructive pulmonary disease / Fatty acids / Isoflavone / Lung function / Soy products

1 Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of death and disability worldwide (http://www.who.int/respiratory/copd/burden/en/index.html). It is characterized by a progressive irreversible airflow limitation with cigarette smoking being the principal risk factor (http://www.goldcopd.dk/index_uk.htm). Although 95% of

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Abbreviations: BMI, body mass index; **COPD,** chronic obstructive pulmonary disease; **EPA,** eicosapentaenoic acid; **FEV1,** forced expiratory volume in 1 s; **FVC,** forced vital capacity; **MUFA,** monounsaturated fatty acids; **OR,** odds ratio; **PUFA,** polyunsaturated fatty acids; **SFA,** saturated fatty acids.

COPD patients are or have been cigarette smokers, only about 20% of smokers develop COPD [1]. Therefore, environmental factors such as dietary habits may play an important role in the etiology of this disease. Apart from tobacco abstinence, a good diet may offer protection and consequently, reduce the disease burden and health care costs associated with COPD. Our literature review of dietary factors suggested that fruit intake is positively associated with lung function and inversely related to COPD mortality and respiratory symptoms [2]. Increased vegetable consumption can reduce the risk of COPD and a high fish intake is also beneficial to lung function [2].

The Japanese diet is high in soy products and fish [3]. Soy foods, especially tofu (soybean curd) and natto (fermented soybeans), are rich in isoflavones (509 and 1273 μg *per* gram, respectively) [4]. We recently reported an inverse association between soy consumption and the risk of COPD and respiratory symptoms for Japanese adults [5]. A cohort study of 63 257 adults in Singapore similarly found a high isoflavone intake was negatively associated with cough plus phlegm, while individual aglycones (genistein, daidzein and glycitein) were also negatively associated with these symptoms [6].

Polyunsaturated fatty acids (PUFA) are primarily derived from fish, seafood and vegetable oils in Japan. Omega-3 (n-3) and omega-6 (n-6) fatty acids are classified into PUFA. According to a cross-sectional study of 13 820 adults in the Netherlands, increased dietary intake of C22:5(n-6) docosapentaenoic acid, an (n-6) fatty acid, was associated with improved lung function, but all other (n-6) and (n-3) fatty acids had little effects [7]. Among the (n-3) fatty acids, a high intake of eicosapentaenoic acid (EPA) and docosahexaenoic acid appeared to lower the risk of COPD among smokers in the USA [8]. However, the recent study in the Netherlands did not observe any significant reduction in COPD risk by EPA [6]. Meanwhile, a population-based cohort study undertaken in seven countries reported an inverse relationship between COPD mortality and EPA and docosahexaenoic acid, but not total (n-6) and total (n-3) fatty acids [9].

In summary, findings concerning isoflavones and fatty acids from other countries are limited and inconsistent. Therefore, the present study aimed to evaluate the effects of these two types of dietary nutrients on lung function, breathlessness and the prevalence of COPD. We did not investigate antioxidants and other micronutrients such as vitamin C, vitamin D and carotenes, because they have been extensively assessed in the literature. The study formed part of a research project assessing the role of nutritional factors for the prevention of this major disease.

2 Materials and methods

2.1 Subjects

A case–control study was conducted in Kyoto, and Aichi and Gifu prefectures of central Japan in 2006. Details of the methodology have been described elsewhere [5]. A total of 278 COPD patients (244 men and 34 women) were referred by respiratory physicians from the outpatient departments of six hospitals. Diagnosis of COPD was confirmed by spirometry based on the standard protocol (http://www.goldcopd.dk/index_uk.htm) with forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) <0.7. Inclusion criteria were 50–75 years of age and COPD being diagnosed as the primary functionally limiting illness within the past 4 years. Patients were excluded if they had a recent stroke, dementia or other health conditions that prohibited them from being interviewed.

During the same period, 340 community-dwelling adults (272 men and 68 women) were recruited from the same catchment areas as the cases. These controls were frequency matched to the cases by age (within 5 years) based on the same exclusion criteria. Recruitment was spread evenly between the locations at shopping malls, community centers and hospital outpatient clinics. All participants underwent spirometric measurements of respiratory function to ensure correct classification of their case–control status. Ethics approval was obtained from the Human Research Ethics Committee of the researchers' institution (approval number HR 90/2005) and all participating hospitals.

2.2 Questionnaire and interview

The first author interviewed all participants face-to-face using a structured questionnaire. Confidentiality of the information provided and the right to withdraw without prejudice were ensured before obtaining their written consent. Interviews of the cases were conducted in the presence of the next-of-kin to reduce recall error. On average, the interview process took about 30–45 min and was held in the outpatient department for cases or the place of recruitment for controls.

The first part of the questionnaire sought information on demographic and lifestyle characteristics including age, gender, current height (m) and weight (kg), weight (kg) 5 years ago, education level (high school or below; college or university), cigarette smoking (never or ex-smoker; current smoker), smoking pack-years and alcohol drinking status (non-drinker; drinker). The second part consisted of a 138-item food frequency questionnaire taken from the Japan Public Health Center-based prospective study on cancer and cardiovascular disease [10], with validity and reproducibility established for the Japanese adult population [11, 12]. The reference recall for habitual diet was set at 5 years before interview so that dietary exposure of the prevalent cases was captured before the onset of the disease. The frequency of food intake was classified by nine categories ranging from "almost never" to "seven or more times *per* day". Standard portion size consumed *per* meal was specified for each item, with amount expressed as small (50% smaller), medium

and large (50% larger) and quantified in terms of grams *per* day. Photographs of foods and utensils were shown to clarify the size and amount consumed by participants. The soy products included in the questionnaire were tofu, natto, miso soup, aburaage (fried bean curd), bean sprouts and soy milk.

The third part of the structured questionnaire contained two screening instruments to assess the breathlessness symptom of each individual: ''dyspnoea'' scale of the Medical Research Council [13] and the ''Feeling Short of Breath'' scale of the Australian Lung Foundation (http://www.copdx.org.au/checklist/index.asp). The Japanese version of the dyspnoea scale was readily available from the literature, whereas the latter scale was translated into Japanese by two Japanese translators.

2.3 Statistical analysis

The quantity of nutrients contained in each food item was obtained from the Japanese food composition tables [10]. The nutrients investigated in this study were isoflavones (genistein and daidzein), fatty acids (total fatty acids, saturated fatty acids (SFA), monounsaturated fatty acids (MUFA) and PUFA) as well as the ratio of (n-6) to (n-3) fatty acids. For each participant, dietary intake of each nutrient was derived by adding the corresponding food items and multiplying the portion size (in grams) by frequency of consumption*per* day. Daily total energy intake (kcal) was similarly estimated by summing the energy intake across individual food items. Genistein and daidzein intakes were expressed in milligram *per* day, while fatty acids intakes were quantified in terms of grams *per* day.

Descriptive statistics were first applied to summarize participant characteristics and lung function measures. After comparing the isoflavones and fatty acids intake pattern between case and control groups, unconditional logistic regression analyses were conducted to assess the effects of specific nutrient on the COPD risk and the prevalence of breathlessness with adjustment for total energy intake. Each quantitative nutrient variable was tested for linear trend and further categorized into quartiles based on the empirical distribution of controls or participants without symptoms of breathlessness. The lowest intake level was adopted as the reference category in each model. Other independent variables included in the multivariable models were age, gender, body mass index (BMI = weight/height^2) of 5 years ago, education level, cigarette smoking, smoking pack-years and alcohol drinking status. These variables were either established risk factors or plausible confounding variables from the literature [2]. Statistical analyses were performed using the SPSS package version 13 (SPSS, Chicago, IL, USA).

3 Results

Table 1 presents the characteristics of the participants by gender and case–control status. The mean age was about 66 years and most participants had high school or below education, but the mean BMI (5 years ago) of COPD patients was lower than that of controls. For the case group, 220 patients (80%) had their COPD diagnosed within the past 2 years. It is alarming that some patients (21.8% of males and 27.3% of females) continued to smoke after their diagnosis of COPD and as expected, they had lower lung function measures especially FEV1 ($p<0.001$) than their counterparts without the disease. The COPD patients also had significantly lower total energy intake for males ($p=0.024$) but similar to control subjects for females

Table 1. Participant characteristics by case–control status and gender

Variable	COPD patients		Controls		*p*-value[a)]
Gender	Male ($n=244$)	Female ($n=34$)	Male ($n=272$)	Female ($n=68$)	
Mean age (years)	66.51 (SD 6.82)	66.10 (SD 6.13)	65.15 (SD 5.41)	66.12 (SD 5.76)	0.028
Mean BMI 5 years ago (kg/m^2)	22.09 (SD 2.94)	20.67 (SD 3.89)	23.61 (SD 2.85)	23.30 (SD 3.25)	<0.001
Education: high school or below	195 (80.2%)	26 (78.8%)	166 (61.9%)	47 (70.1%)	<0.001
Alcohol drinkers	150 (61.5%)	8 (23.5%)	202 (74.5%)	21 (30.9%)	0.023
Current smokers	53 (21.8%)	9 (27.3%)	63 (23.2%)	2 (2.9%)	0.316
Mean smoking (pack-years)	65.03 (SD 24.91)	43.25 (SD 31.67)	30.90 (SD 28.81)	2.04 (SD 9.68)	<0.001
FEV1	1.64 (0.69)	1.15 (0.47)	2.56 (0.51)	1.76 (0.35)	<0.001
FVC	3.08 (0.83)	2.07 (0.52)	3.31 (0.60)	2.17 (0.41)	0.104
Breathlessness	157 (66%)	20 (65.5%)	33 (12.4%)	7 (10.3%)	<0.001
Mean total energy intake (kcal)	1166.13 (SD 441.81)	1145.33 (SD 460.10)	1260.27 (SD 491.83)	1117.33 (SD 374.96)	0.069

a) Comparison between cases and controls.

($p = 0.743$). Moreover, the prevalence of breathlessness was significantly higher among cases (66%) than controls (12%) and their median dyspnea scores were also different ($p < 0.001$). The observed Spearman rank correlation of 0.7 confirmed a good agreement between the two scales.

Table 2 shows the dietary intake of isoflavones and fatty acids by participants from 5 years ago. The COPD patients had significantly lower daily intake of total isoflavone, genistein, daidzein and PUFA especially (n-6) fatty acids than controls according to independent samples *t*-tests. Habitual intakes of total fatty acids, SFA, MUFA and the ratio (n-6):(n-3) were similar between the two groups.

The relationship with lung function was next investigated. Both observed lung function measures (FEV1 and FVC) were positively correlated with these nutrients ($r = 0.11$–0.17). Multiple regression analyses (results omitted for brevity) further confirmed the significant positive association between lung function and dietary intakes of total isoflavone, genistein, daidzein, PUFA and (n-6) fatty acids after adjustment for total energy intake and other confounding factors listed at the end of Section 2.3.

Table 3 summarizes logistic regression results in relation to COPD prevalence. Significant reductions in risk were evident for isoflavones, the adjusted odds ratio (OR) being 0.36 (95% confidence interval (CI) 0.19–0.68) for the highest *versus* lowest quartiles of total isoflavone intake. The corresponding tests for linear trend were significant ($p = 0.001$). Decreases in COPD risk were also associated with higher levels of PUFA and (n-6) fatty acids, but no evidence of association was found for other types of fatty acids.

Logistic regression results in Table 4 further suggested an inverse relationship between daily isoflavone intake and the prevalence of breathlessness. The adjusted OR was 0.60 (95% CI 0.33–1.10) for the highest *versus* lowest quartiles of total isoflavone intake, and p for trend = 0.034. High intakes of PUFA and (n-6) fatty acids also appeared to reduce the prevalence of breathlessness by about 50%, with significant dose–response relationships. In contrast, increasing the consumption levels of other fatty acids had relatively little impact on breathlessness.

4 Discussion

This is the first study to report the effects of dietary isoflavone and fatty acids intake on lung function, breathlessness and the prevalence of COPD in a Japanese population. The sample size of 618 subjects provided sufficient statistical power for our evaluation. Spirometry was performed for each participant to ensure correct classification of case–control status. The majority (80%) of the patients had COPD diagnosed within the past 2 years, and all cases were interviewed within 4 years of confirmed COPD diagnosis, which enabled accurate capture of their habitual dietary exposure. In this study, COPD patients had significantly lower dietary intake of isoflavone than participants without the disease. Nevertheless, their consumption level (mean 28 mg/day) was still higher than those in many western countries [3, 14], but well below the upper limit of 70–75 mg/day recommended by the Food Safety Commission of Japan (http://www.fsc.go.jp). The COPD patients also had lower intakes of PUFA (both (n-6) and (n-3) fatty acids) than control subjects. PUFA are present in soy products and fish which comprise the daily staples of most Japanese older adults. The observed (n-6):(n-3) ratios of fatty acids (3.71 for cases and 3.89 for controls) were not high and comparable to the estimated ratio of 4.2 from a previous survey of the Japanese population [15].

A new finding was the significant positive association between lung function and the intake of isoflavone including genistein and daidzein. The apparent positive correlations with PUFA and (n-6) fatty acids provided additional evidence to a recent study in the Netherlands which reported that increasing dietary intake of docosapentaenoic acid could improve FEV1 [7].

Table 2. Comparison of habitual dietary isoflavone and fatty acids intake between case and control groups

Nutrient intake from food sources per day[a)]	COPD patients ($n = 278$)		Controls ($n = 340$)		*t*-test[b)]
	Mean	SD	Mean	SD	*p*-value
Total isoflavone (mg)	27.82	20.66	39.57	39.21	<0.001
Genistein (mg)	17.25	12.96	24.65	24.63	<0.001
Daidzein (mg)	10.57	7.72	14.92	14.60	<0.001
Total fatty acids (g)	2.99	1.36	3.10	1.30	0.323
SFA (g)	1.27	0.65	1.27	0.59	0.969
MUFA (g)	1.16	0.56	1.17	0.50	0.678
PUFA (g)	0.56	0.23	0.65	0.32	<0.001
(n-6) fatty acids (g)	0.45	0.19	0.52	0.26	<0.001
(n-3) fatty acids (g)	0.13	0.06	0.14	0.07	0.028
(n-6):(n-3) ratio	3.71	1.23	3.89	1.17	0.07

a) Excluding cooking oils, margarine, butter, mayonnaise and salad dressings.
b) Mean difference between cases and controls.

Table 3. Dietary intake of isoflavone and fatty acids and prevalence of COPD for Japanese adults

Nutrient intake *per* day[a)]	Cases, *n* (%)	Controls, *n* (%)	Crude		Adjusted[b)]		Test for trend
			OR	95% CI	OR	95% CI	
Isoflavone (mg)							$p = 0.001$
≤17.68	112 (40.3)	84 (24.9)	1	–	1	–	
17.69–29.63	71 (25.5)	84 (24.9)	0.63	0.42, 0.97	0.43	0.25, 0.76	
29.64–55.40	58 (20.9)	85 (25.2)	0.51	0.33, 0.79	0.43	0.24, 0.79	
≥55.41	37 (13.3)	84 (24.9)	0.33	0.21, 0.53	0.36	0.19, 0.68	
Genistein (mg)							$p = 0.001$
≤10.85	111 (39.9)	84 (24.9)	1	–	1	–	
10.86–18.33	72 (25.9)	84 (24.9)	0.65	0.43, 0.99	0.45	0.26, 0.80	
18.34–34.33	58 (20.9)	84 (24.9)	0.52	0.34, 0.81	0.47	0.26, 0.84	
≥34.34	37 (13.3)	84 (24.9)	0.33	0.21, 0.54	0.37	0.19, 0.71	
Daidzein (mg)							$p = 0.001$
≤6.78	112 (40.3)	84 (24.9)	1	–	1	–	
6.79–11.40	72 (25.9)	84 (24.9)	0.64	0.42, 0.98	0.45	0.26, 0.78	
11.41–20.67	57 (20.5)	85 (25.2)	0.50	0.32, 0.78	0.43	0.23, 0.78	
≥20.68	37 (13.3)	84 (24.9)	0.33	0.21, 0.53	0.35	0.18, 0.67	
Total fatty acids (g)							$p = 0.929$
≤2.16	79 (28.4)	84 (24.9)	1	–	1	–	
2.17–2.90	68 (24.5)	84 (24.9)	0.86	0.55, 1.34	0.88	0.48, 1.62	
2.91–3.83	67 (24.1)	84 (24.9)	0.85	0.54, 1.32	1.27	0.67, 2.41	
≥3.84	64 (23.0)	84 (24.9)	0.81	0.52, 1.27	1.15	0.53, 2.52	
SFA (g)							$p = 0.242$
≤0.83	78 (28.1)	84 (24.9)	1	–	1	–	
0.84–1.19	62 (22.3)	84 (24.9)	0.80	0.51, 1.25	0.99	0.53, 1.84	
1.20–1.62	70 (25.2)	85 (25.2)	0.89	0.57, 1.38	1.45	0.77, 2.74	
≥1.63	68 (24.5)	84 (24.9)	0.87	0.56, 1.36	1.41	0.68, 2.94	
MUFA (g)							$p = 0.702$
≤0.81	82 (29.5)	84 (24.9)	1	–	1	–	
0.82–1.08	62 (22.3)	84 (24.9)	0.76	0.48, 1.18	0.78	0.42, 1.44	
1.09–1.42	68 (24.5)	85 (25.2)	0.82	0.53, 1.27	1.08	0.58, 2.02	
≥1.43	66 (23.7)	84 (24.9)	0.81	0.52, 1.25	1.01	0.48, 2.13	
PUFA (g)							$p = 0.002$
≤0.44	101 (36.3)	84 (24.9)	1	–	1	–	
0.45–0.57	70 (25.2)	84 (24.9)	0.69	0.45, 1.07	0.83	0.47, 1.48	
0.58–0.75	60 (21.6)	84 (24.9)	0.59	0.38, 0.92	0.70	0.37, 1.31	
≥0.76	47 (16.9)	84 (24.9)	0.47	0.29, 0.74	0.48	0.23, 1.01	
(n-6) fatty acids (g)							$p = 0.002$
≤0.34	97 (34.9)	83 (24.6)	1	–	1	–	
0.35–0.45	71 (25.5)	84 (24.9)	0.72	0.47, 1.11	0.71	0.39, 1.27	
0.46–0.62	61 (21.9)	84 (24.9)	0.62	0.40, 0.97	0.74	0.40, 1.38	

Table 3. Continued

Nutrient intake *per* day[a)]	Cases, *n* (%)	Controls, *n* (%)	Crude		Adjusted[b)]		Test for trend
			OR	95% CI	OR	95% CI	
≥ 0.63	49 (17.6)	86 (25.5)	0.49	0.31, 0.77	0.55	0.26, 1.14	
(n-3) fatty acids (g)							$p = 0.170$
≤ 0.08	86 (30.9)	84 (24.9)	1	–	1	–	
0.09–0.11	70 (25.2)	84 (24.9)	0.81	0.53, 1.26	0.79	0.43, 1.43	
0.12–0.15	60 (21.6)	85 (25.2)	0.69	0.44, 1.08	0.78	0.42, 1.46	
≥ 0.16	62 (22.3)	84 (24.9)	0.72	0.46, 1.13	0.95	0.46, 1.13	
(n-6):(n-3) ratio							$p = 0.108$
≤ 3.08	82 (29.5)	84 (24.9)	1	–	1	–	
3.09–3.80	78 (28.1)	84 (24.9)	0.95	0.62, 1.47	1.07	0.60, 1.89	
3.81–4.53	58 (20.9)	84 (24.9)	0.71	0.45, 1.11	0.76	0.42, 1.40	
≥ 4.54	60 (21.6)	84 (24.9)	0.73	0.47, 1.15	0.69	0.38, 1.24	

a) Excluding cooking oils, margarine, butter, mayonnaise and salad dressings.
b) Adjusted odds ratios from logistic regression models including age, gender, BMI (5 years ago), education level (high school or below; college or university), alcohol drinking (non-drinker; drinker), cigarette smoking (never/ex-smoker; current smoker), smoking pack-years and daily total energy intake.

The traditional Japanese diet includes many soy products which are high in isoflavones [3]. In this study, total isoflavone, genistein and daidzein were significantly associated with decreased risks of COPD and the breathlessness symptom. The findings were consistent with our previously reported results that habitual soy consumption can lead to significant reductions in the prevalence of COPD and respiratory symptoms among Japanese adults [5]. Epidemiological evidence from a cohort study in Singapore also suggested inverse associations between dietary isoflavone intakes and cough plus phlegm symptoms [6]. The beneficial effects of soy and dietary isoflavone on other chronic diseases have been well documented [3, 14, 16–18], whereas adverse effects of high intake on lung health have not been reported in the literature. It is likely that isoflavones and their aglycones act as anti-inflammatory agents in the lung and protect against tobacco carcinogens for smokers [6]. However, more research is needed to understand the underlying biological mechanism in order to confirm their protective effect against COPD.

Another new finding was the beneficial effects of increasing dietary intakes of total PUFA and (n-6) fatty acids, which could potentially lead to 50% reductions in prevalence of COPD and breathlessness, with significant dose–response relationships. Reports of the effects of PUFA on lung health have been mixed [7, 8]. It is interesting to note that recent pooled data of 340 000 people from the USA, Scandinavia and Israel showed a low intake of SFA (mainly from dairy and meat) and a proportionally higher intake of omega-6 PUFA was associated with a significant reduction of coronary heart disease [19]. It has been suggested that ''the adverse effects of (n-6) fatty acids may occur in cell culture and laboratory animals, but they apparently do not determine heart disease risk in humans'' [20]. Further research is required to ascertain the role of PUFA in relation to COPD and respiratory symptoms.

There are several limitations which should be taken into consideration when interpreting the findings. First, glycitein was not available in the nutrient database [10], so that its effect could not be evaluated. Secondly, the intakes of fatty acids were derived only from foods eaten by the participants, which did not include indirect sources such as cooking oils, margarine, butter, mayonnaise and salad dressings. In Japan, men were seldom involved in cooking and therefore unaware of the amount and quantity of their consumption. Questions on oily products were thus omitted from the questionnaire. Therefore, both (n-6) and (n-3) PUFA intakes were underestimated in Table 2. Nevertheless, the observed differences in PUFA intakes between COPD patients and control subjects were statistically significant.

The present case–control study was retrospective in design so that the possibility of recall bias could not be denied. Although habitual diet was assessed using a validated and reliable food frequency questionnaire for the Japanese population, the self-reported information was subjected to measurement errors. Face-to-face interviews were thus

Table 4. Dietary intake of isoflavone and fatty acids and prevalence of breathlessness for Japanese adults

Nutrient intake *per* day[a)]	Breathlessness		Crude		Adjusted[b)]		Test for trend
	Yes, *n* (%)	No, *n* (%)	OR	95% CI	OR	95% CI	
Isoflavone (mg)							$p = 0.034$
≤17.09	77 (35.6)	96 (24.8)	1	–	1	–	
17.10–29.02	64 (29.6)	97 (25.1)	0.82	0.53, 1.27	0.85	0.51, 1.40	
29.03–52.54	45 (20.8)	97 (25.1)	0.58	0.36, 0.92	0.65	0.38, 1.11	
≥52.55	30 (13.9)	97 (25.1)	0.39	0.23, 0.64	0.60	0.33, 1.10	
Genistein (mg)							$p = 0.039$
≤10.45	77 (35.6)	96 (24.8)	1	–	1	–	
10.46–17.88	64 (29.6)	97 (25.1)	0.82	0.53, 1.27	0.86	0.52, 1.42	
17.89–32.55	45 (20.8)	98 (25.3)	0.57	0.36, 0.91	0.65	0.38, 1.11	
≥32.56	30 (13.9)	96 (24.8)	0.39	0.23, 0.65	0.61	0.33, 1.12	
Daidzein (mg)							$p = 0.027$
≤6.54	77 (35.6)	96 (24.8)	1	–	1	–	
6.55–11.12	64 (29.6)	97 (25.1)	0.82	0.53, 1.27	0.85	0.51, 1.40	
11.13–20.00	45 (20.8)	98 (25.3)	0.58	0.36, 0.92	0.65	0.38, 1.11	
≥20.01	30 (13.9)	96 (24.8)	0.39	0.23, 0.64	0.59	0.32, 1.08	
Total fatty acids (g)							$p = 0.417$
≤2.20	67 (31.0)	96 (24.8)	1	–	1	–	
2.21–2.96	58 (26.9)	97 (25.1)	0.86	0.55, 1.35	0.85	0.50, 1.47	
2.97–3.95	55 (25.5)	97 (25.1)	0.81	0.52, 1.28	1.09	0.61, 1.95	
≥3.96	36 (16.7)	97 (25.1)	0.53	0.33, 0.87	0.83	0.39, 1.77	
SFA (g)							$p = 0.730$
≤0.87	70 (32.4)	96 (24.8)	1	–	1	–	
0.88–1.24	58 (26.9)	98 (25.3)	0.81	0.52, 1.27	0.95	0.56, 1.64	
1.25–1.66	47 (21.8)	97 (25.1)	0.67	0.42, 1.06	0.93	0.53, 1.65	
≥1.67	41 (19.0)	96 (24.8)	0.59	0.36, 0.95	0.92	0.47, 1.82	
MUFA (g)							$p = 0.728$
≤0.82	68 (31.5)	96 (24.8)	1	–	1	–	
0.83–1.11	53 (24.5)	97 (25.1)	0.77	0.49, 1.22	0.84	0.48, 1.45	
1.12–1.47	57 (26.4)	97 (25.1)	0.83	0.53, 1.30	0.97	0.55, 1.69	
≥1.48	38 (17.6)	97 (25.1)	0.55	0.34, 0.90	0.75	0.36, 1.56	
PUFA (g)							$p = 0.025$
≤0.43	77 (35.6)	96 (24.8)	1	–	1	–	
0.44–0.58	62 (28.7)	96 (24.8)	0.81	0.52, 1.25	1.12	0.67, 1.88	
0.59–0.77	48 (22.2)	96 (24.8)	0.62	0.39, 0.99	0.74	0.42, 1.33	
≥0.78	29 (13.4)	97 (25.1)	0.37	0.22, 0.62	0.53	0.26, 1.09	
(n-6) fatty acids (g)							$p = 0.021$
≤0.33	75 (34.7)	96 (24.8)	1	–	1	–	
0.34–0.46	72 (33.3)	97 (25.1)	0.95	0.62, 1.46	1.13	0.68, 1.88	
0.47–0.63	39 (18.1)	97 (25.1)	0.52	0.32, 0.83	0.58	0.32, 1.06	
≥0.64	30 (13.9)	97 (25.1)	0.40	0.24, 0.66	0.51	0.25, 1.05	

Table 4. Continued

Nutrient intake *per* day[a)]	Breathlessness		Crude		Adjusted[b)]		Test for trend
	Yes, *n* (%)	No, *n* (%)	OR	95% CI	OR	95% CI	
(n-3) fatty acids (g)							$p = 0.278$
≤ 0.08	76 (35.2)	97 (25.1)	1	–	1	–	
0.09–0.11	56 (25.9)	97 (25.1)	0.74	0.47, 1.15	0.86	0.50, 1.46	
0.12–0.15	36 (16.7)	97 (25.1)	0.47	0.29, 0.77	0.65	0.36, 1.18	
≥ 0.16	48 (22.2)	96 (24.8)	0.64	0.40, 1.01	1.05	0.54, 2.03	
(n-6):(n-3) ratio							$p = 0$ .357
≤ 3.09	64 (29.6)	96 (24.8)	1	–	1	–	
3.10–3.76	53 (24.5)	97 (25.1)	0.82	0.52, 1.30	0.84	0.49, 1.42	
3.77–4.57	58 (26.9)	97 (25.1)	0.90	0.57, 1.41	1.06	0.62, 1.79	
≥ 4.58	41 (19.0)	97 (25.1)	0.63	0.39, 1.03	0.63	0.36, 1.09	

a) Excluding cooking oils, margarine, butter, mayonnaise and salad dressings.
b) Adjusted odds ratios from logistic regression models including age, gender, BMI (5 years ago), education level (high school or below; college or university), alcohol drinking (non-drinker; drinker), cigarette smoking (never/ex-smoker; current smoker), smoking pack-years and daily total energy intake.

conducted to help interpretation and to improve the accuracy of their answers. Moreover, the same investigator (first author) conducted all interviews to eliminate inter-interviewer bias. The control subjects were recruited during the same period and from the same catchment area as the cases. They should therefore provide valid estimates of nutrients intake. But the inherent selection bias was unavoidable because of their voluntary participation in the study. Information bias was unlikely, because the effects of dietary isoflavone and fatty acids were not established for COPD and all participants were blinded to the study hypothesis. Nevertheless, residual confounding might still present although plausible confounding factors were controlled for in the multivariable analyses. Finally, although a small number of female patients were recruited, the gender ratio was typical of the elderly COPD population in Japan due to the higher prevalence of smoking among males [21].

In conclusion, inverse associations were found between dietary isoflavone and PUFA intake and the prevalence of COPD for Japanese adults, together with significant dose–response relationships for the breathlessness symptom. The findings suggested that the traditional Japanese diet, with a high intake of soy foods and fish, but a relatively low consumption of red meat, may be beneficial to lung health and offer some protection against the effects of tobacco. Further replications and prospective cohort studies are recommended to confirm the observed protective effects in other populations, and to determine whether increased intakes of these nutrients can improve the mortality rate due to COPD. Experimental research is also needed to investigate the underlying biological mechanisms.

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