ORIGINAL

Associations between intake of dietary fermented soy food and concentrations of inflammatory markers : a cross-sectional study in Japanese workers

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Abstract : Epidemiological investigations have shown that consumption of soybeans or soy foods reduces the risk of the development of cardiovascular disease, cancer and osteoporosis. The aim of this study was to determine the associations between different soy foods and inflammatory markers, including high-sensitivity C-reactive protein (hs-CRP), interleukin (IL)-6, and IL-18, in Japanese workers. The cross-sectional study included 1,426 Japanese workers (1,053 men and 373 women) aged 20 to 64 years. Intake of 12 soy foods was estimated by a validated food frequency questionnaire. Associations of total soy foods, fermented soy food, non-fermented soy food, soy isoflavone with hs-CRP, IL-6, and IL-18 levels were examined by general linear model regression analysis. We found that total fermented soy food intake was inversely associated with multivariable-adjusted geometric concentration of IL-6 in men (Q1 : 1.03 pg/mL, Q5 : 0.94 pg/mL ; P for trend = 0.031). Furthermore, it was shown that IL-6 concentrations were inversely associated with miso intake (β = -0.068 ; p = 0.034) and soy sauce intake in men (β = -0.074 ; p = 0.018). This study suggests that intake of total fermented soy food, miso and soy sauce be associated with IL-6 concentrations in Japanese men. J. Med. Invest. 65 : 74-80, February, 2018

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INTRODUCTION

Some inflammatory biomarkers including Interleukin (IL)-6, IL-18 and C-reactive protein (CRP) have been shown to be associated with increased risk of type 2 diabetes (1, 2), cardiovascular disease (3-5), and many types of cancer (6-9). Dietary factors can modulate inflammatory status by suppressing immune responses (10).

Consumption of soy foods has been shown to have beneficial effects on various aspects of human health including reduced risk of inflammation-related diseases, such as cardiovascular disease (11, 12), diabetes (13), and certain types of cancers (14, 15). Soy and soy isoflavone have been shown to inhibit cell adhesion molecule expression in cultured endothelial cells (16, 17), reduce production of proinflammatory cytokines, and decrease oxidative stress in animal models (18-22). Several recent clinical trials have shown that a soy-rich diet substantially lowers the levels of interleukin IL-6, CRP, and IL-18 (12, 23), although results are somewhat inconsistent (24, 25).

Soy foods are divided into fermented products (miso and natto) and non-fermented products based on their manufacturing process. Some studies have shown that components of fermented soy products maintain the functions of various organs and prevent coronary heart disease (26, 27). Fermented soy foods have been shown to contain greater amounts of polyamines including spermidine than the amounts in non-fermented soy products, and polyamines have been shown to be associated with cardioprotection and lifespan extension (28, 29). Recently, two cross-sectional studies were conducted in Japanese, and it was shown that natto intake had a significant inverse association with the risk of mortality from cardiovascular disease (30) and that intake of fermented soy foods (miso and natto) had an inverse association the development of high blood pressure in a population with normal blood pressure (31).

In this study, we examined the associations of soy foods (total, fermented soy foods, non-fermented soy foods, soy isoflavone) with high-sensitivity (hs)-CRP, IL-6, and IL-18 levels in workers in Tokushima Prefecture of Japan. We also examined associations between each soy food levels of and hs-CRP, IL-6 and IL-18.

MATERIALS AND METHODS

Study population

The study population consisted of participants in epidemiological research, including 1,460 men and women, who were recruited from Japanese workers in Tokushima Prefecture in 2010. We excluded participants who had missing data for potential confounders including history of stroke (n = 1), smoking habit (n = 1), drinking habit (n = 3), regular exercise (n = 4) and past or current history of allergic disease (n = 3). We also excluded participants who had missing data for inflammatory markers including hs-CRP (n = 1), IL-6 (n = 2) and IL-18 (n = 2). Two participants with missing data for

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HbA1c (n = 1) and glucose (n = 1) were also excluded. Fifteen participants with a total energy intake exceeding mean ± 3 standard deviations, ≧ 3,513 kcal/day for men (n = 13) and ≧ 2,947 kcal/day for women (n = 2), were also excluded. Finally, data for a total of 1,426 adults (1,053 men and 373 women) aged 20-64 years were used for analysis.

All participants had valid data with a completed questionnaire, physical measurements and a written informed consent form. The study protocol was approved by institutional review board of the Tokushima University Hospital.

Measurement of biomarkers

A fasting blood sample was obtained from each participant by trained staff. Glucose level was determined by using the glucose oxidase-peroxidase method (ADAMS glucose GA-1170, ARKRAY Inc. Kyoto, Japan). High-sensitivity hs-CRP concentration was determined by using a commercially available latex turbidimetric immunoassay (LT CRP-HS II, Wako Pure Chemical Ltd., Osaka, Japan). HbA1c was determined by using the high-performance liquid chromatography method (HLC-723G11, Tosoh Corp. Inc. Tokyo, Japan). IL-6 concentration was determined using the chemiluminescent enzyme immunoassay (Human IL-6 CLEIA, Fujirebio, Inc., Tokyo, Japan). IL-18 concentration was determined by using the enzyme-linked immunosorbent assay (Human IL-18 ELISA Kit, Medical & Biological Laboratories Co., Ltd., Nagoya, Japan).

Food intake

Habitual soy food intake was estimated using a validated quantitative food-frequency questionnaire (32). The questionnaire included 12 common soy food items : miso (soybean paste), soy sauce, natto (fermented soybean), tofu, soy milk, fried tofu, yuba (dried bean cured), okara (soybean cured refuse) and green soy bean, bean sprouts and kinako (soy flour), ganmodoki (fried bean cured with vegetable). We defined miso, soy sauce and natto as fermented soy foods. Other soy foods were defined as non-fermented soy foods. Nutritional calculation was performed according to the Standard Tables of Food Composition in Japan. The amount of total isoflavone intake was determined by using a database with isoflavone contents in soy foods (33). Food and energy intake was estimated by the validated FFQ method (34). The questionnaire included questions on 29 food items and 10 cooked meals. We estimated food intake for each of 18 food groups.

Other variables

We obtained covariates from the standardized questionnaires, including sociodemographic characteristics (age, sex), lifestyle behaviors (alcohol consumption, smoking, exercise habits, and intake of vegetables, fresh fruits, and fish), personal health and medical history (hypertension, diabetes, allergy, and stroke).

Trained staff measured body weight, height, and blood pressure using calibrated instruments. Hypertension was defined as systolic blood pressure of more than 140 mm Hg, diastolic blood pressure of more than 90 mm Hg, or self-reports of hypertension medicine usage. Allergy was self-reported diagnosis of an allergy. Prevalent diabetes was defined as a measured fasting blood glucose concentration of 126 mg/dL, HbA1c level of 6.5% or more, or self-reports of diabetes medicine usage.

Statistical analysis

We performed analysis on the basis of energy-adjusted intake using the density method (amount of food intake per 1,000 kcal of energy) for all soy food items, vegetables, fruits, and fish. The subjects were divided into quintiles with almost the same number of subjects in each category. The values of inflammatory markers were log-transformed to be a normal distribution. Continuous variables are expressed as means and standard deviations, and categorical variables are expressed as proportion (%). ANOVA and the chi-square test were used to compare characteristics among the quintiles of dietary soy fermented intake.

General linear models were used to evaluate the associations of dietary total soy food, fermented soy food, non-fermented soy food and total soy isoflavone intake with inflammatory markers after adjusting for the following probable covariates in three different models. Model 1 was adjusted for age. Model 2 was model 1 plus adjustments for BMI (logarithm), current smoker (yes or no), current drinker (yes or no), regular exerciser (yes or no), diabetes (yes or no), hypertension (yes or no), allergic disease (yes or no), and total energy intake. Model 3 was model 2 plus adjustments for vegetable intake, fruit intake and fish intake. Multiple regression analyses were used to evaluate the association between intake of each of the 12 soy food items and inflammatory makers. P values < 0.05 were considered statistically significant using two-tailed tests. All analyses were conducted using IBM SPSS Statistics (version 24.0).

RESULTS

Characteristics of men and women according to quintiles of total fermented soy food intake

The mean ages of the participants were 40.2 ± 9.7 years for men and 38.7 ± 9.8 years for women, and mean BMIs were 23.8 ± 3.3 kg/m^2 for men and 21.4 ± 3.1 kg/m^2 for women. The estimated daily energy levels were 1,848 ± 443 kcal/day for men and 1,711 ± 375 kcal/day for women. The characteristics of the 1,426 participants (1,053 men and 373 women) according to quintiles of energy-adjusted soy fermented food intake are shown in Table 1. Regarding nutrient intake, men in the highest quintile of the fermented soy food group had less energy intake and higher intake levels of non-fermented soy food, vegetables, fruits and fish than did men in the lowest quintile. In addition, men in the highest quintile of the fermented soy food group were olderer than men in the lowest quintile. Women in the highest quintile of the fermented soy food group had lower percentage of current drinkers and higher intake levels of non-fermented soy food, vegetables, fruits and fish than did women in the lowest quintile (Table 1). In the study population including men and women, there was a 7.9-fold difference in total soy fermented food intake between the highest and lowest quintiles (median : 24.5g/d in the highest quintile vs. 3.1 g/d in the lowest quintile).

Multivariate-adjusted mean (and 95% CI) of inflammatory markers by quintiles of soy food intake

We investigated associations between levels of inflammatory markers and soy food intake using the general linear models in men and women. A higher level of fermented soy food intake was associated with 10% lower IL-6 concentration between the highest and lowest quintiles (Q1 : 1.04 pg/mL, Q5 : 0.94 pg /mL ; P for trend = 0.019) in men. Further adjustment for smoking, alcohol consumption, exercise, diabetes, allergy and energy intake plus intake of vegetable, fruits and fish did not alter the results (Q1 : 1.03 pg/mL, Q5 : 0.94 pg /mL ; P for trend = 0.031). An inverse association was found between serum IL-6 concentration and fermented soy food intake, but this inverse association was not found for total soy food or non-fermented soy food in men. In addition, soy intake including total soy food, non-fermented soy food and soy isoflavone did not affect serum concentrations of hs-CRP, IL-6 and IL-18. In contrast to the results found for men, no difference was found for women (Table 2).

Table 1 Characteristics of men and women according to quintiles of total fermented soy food intake

	Energy adjusted total fermented soy food (quintiles)							
	Men			*P*	Women			*P*
	Q1 (n = 195)	Q3 (n = 211)	Q5 (n = 221)		Q1 (n = 90)	Q3 (n = 75)	Q5 (n = 64)	
Age, years[a]	37.5± 9.9	39.3± 9.0	42.7± 9.7	<.001	37.0± 9.1	39.2± 9.5	39.6± 9.7	0.059
BMI, kg/m^2 [a]	23.9± 3.3	23.7± 3.4	23.9± 3.5	0.713	21.5± 3.4	21.4± 2.6	21.3± 3.4	0.996
Past history or current treatment[b]								
Diabetes, n (%)	8(4.1)	6(2.8)	10(4.5)	0.898	2(2.2)	0(0.0)	0(0.0)	0.597
Hypertension, n (%)	31(15.9)	48(22.7)	46(20.8)	0.287	8(8.9)	5(6.7)	4(6.3)	0.752
Allergic, n (%)	72(36.9)	92(43.6)	100(45.2)	0.459	50(55.6)	39(52.0)	37(57.8)	0.959
Current Smoker, n yes (%)[b]	72(36.9)	66(31.3)	80(36.2)	0.782	10(11.1)	2(2.7)	5(7.8)	0.136
Current Drinker, n yes (%)[b]	103(52.8)	128(60.7)	139(62.9)	0.098	27(30.0)	20(26.7)	24(37.5)	0.015
Regular exerciser, n yes (%)[b]	101(51.8)	101(47.9)	105(47.5)	0.517	55(61.1)	40(53.3)	26(40.6)	0.170
Dietary intake[a,c]								
Total energy, kcal/day	1929± 482	1898± 413	1732± 427	<.001	1726± 384	1750± 413	1675± 361	0.751
Total soyfood, g/1000 kcal/day	36.7± 29.4	56.3± 32.2	85.7± 48.3	<.001	43.4± 47.2	51.7± 24.3	92.7± 47.0	<.001
Fermented soy food, g/1000 kcal/day	3.2± 1.4	9.9± 0.9	24.7± 8.9	<.001	2.9± 1.3	9.9± 0.9	23.8± 8.5	<.001
Non-fermented soy food, g/1000 kcal/day	33.5± 29.4	46.4± 32.2	61.0± 45.6	<.001	40.5± 47.0	41.8± 24.2	67.6± 43.1	0.001
Total soy isoflavone, mg/1000 kcal/day	7.6± 6.4	13.5± 7.6	24.2± 12.6	<.001	9.1± 10.9	12.8± 4.7	25.3± 11.5	<.001
Miso, g/1000 kcal/day	2.0± 1.4	7.0± 2.4	13.3± 6.9	<.001	1.8± 1.2	6.6± 2.8	13.2± 8.2	<.001
Soy sauce, g/1000 kcal/day	0.9± 0.9	1.5± 1.3	2.7± 2.7	<.001	0.7± 0.6	1.3± 1.1	2.4± 3.4	<.001
Natto, g/1000 kcal/day	0.3± 0.6	1.4± 1.9	8.8± 9.6	<.001	0.4± 0.8	2.0± 2.5	8.3± 8.0	<.001
Vegetables,g/1000 kcal/day	56.5± 37.0	73.3± 39.0	85.9± 43.3	<.001	85.4± 44.7	89.0± 37.5	109.0± 63.8	0.015
Fruits, g/1000 kcal/day	15.1± 20.3	21.0± 29.9	20.7± 22.6	<.001	27.6± 33.1	30.7± 28.2	32.4± 29.3	<.001
Fish, g/1000 kcal/day	22.5± 16.7	28.5± 16.0	33.5± 19.4	0.001	24.6± 16.0	29.7± 17.5	31.5± 17.1	0.053
Inflammatory biomarker[a]								
hs-CRP, mg/dL	0.08± 0.14	0.12± 0.30	0.10± 0.36	0.608	0.03± 0.05	0.04± 0.04	0.05± 0.17	0.244
IL-6, pg/mL	1.20± 0.90	1.11± 1.06	1.11± 0.87	0.027	1.05± 0.66	1.26± 2.01	1.01± 0.94	0.693
IL-18, ng/L	221.5± 77.6	202.9± 61.7	215.8± 62.5	0.052	170.5± 55.5	164.4± 61.9	171.0± 47.7	0.870

Values are means ± SD[a] or number and percentages[b]. men (n = 1,053), women (n = 373).
Q, quintiles ; BMI, Body mass index ; hs-CRP, high-sensitivity C-reactive protein ; IL-6, Interleukin-6 ; IL-18, Interleukin-18.
Dietary intakes were adjusted for total energy using the density method[c].

Multiple regression analysis for inflammatory markers by intake of each soy food

We examined associations between 12 items of soy food and inflammatory markers using multiple regression analyses (Table 3). In men, after multivariable adjustment, IL-6 showed significant negative associations with miso (β = -0.068, p = 0.034) and soy sauce (β = -0.074, p = 0.018) intake, but hs-CRP and IL-18 showed no associations. For women, significant positive associations were found between tofu intake and IL-6 concentration (β = 0.107, p = 0.049) and between soy milk intake and serum hs-CRP concentration (β = 0.104, p = 0.049).

DISCUSSION

We found that intake of fermented soy foods including miso and soy sauce was associated with reduction of serum IL-6 level (Tables 2 and 3). The mechanisms by which fermented soy foods and their constituents affect inflammatory biomarkers in men remain to be clarified. Although human studies on anti-inflammatory effects of fermented soy products are limited, animal studies have shown anti-inflammatory properties of fermented soy products. *Meju* is a naturally fermented soy block used to produce soy paste and soy sauce in Korea. Feeding mice fermented soybean fibers from *meju* reduced plasma cholesterol and triglyceride levels, adipocyte size and hepatic lipid accumulation. Levels of plasma C-reactive protein, TNF-α and IL-6 were also significantly reduced in mice treated with *meju* components (35). Furthermore, two studies have shown that fermented soy products suppress inflammation in a gut inflammatory bowel disease model. Kawahara *et al.* examined the effect of fermented soy milk with *Lactococcus lactis subsp. Lactis* S-SU2 on dextran sodium sulfate-induced colitis and found that treatment with fermented soy milk reduced the clinical severity score in a colitis model (36). In another study, treatment with fermented soy germ extract improved the severity of colitis, enhanced gut permeability and suppressed IL-1β production in 2, 4, 6-trinitrobenzen sulphonic acid-induced colitis (37).

In the present study, intake of fermented soy products was evaluated as the sum intake of miso, soy sauce and natto. Functional effects of fermented soy products have been studied. Soy sauce has anti-microbial activity, an anti-hypertensive effect, an anti-carcinogenic effect and anti-platelet activity (38). Natto contains inhibitors against the angiotensin-converting enzyme and thereby might have an anti-hypertensive effect (39). In an obese *db/db* mouse model, fermented soybean extracts reduced serum total cholesterol and LDL cholesterol levels (40). In a human study by Sapbamrer *et al.* on the effects of dietary traditional fermented soybean intake on BMI, reproductive hormones, lipids and glucose in postmenopausal women, it was found that treatment with fermented soybeans for 6 months had favorable effects on progesterone and cholesterol (42). In two prospective cohort studies targeting Japanese, it

Table 2 Multivariate-adjusted mean (and 95% CI) of inflammatory markers by quintiles of soy food intake

	Energy adjusted soy food intake (quintiles)							
	Men				Women			
	Q1	Q3	Q5	*P*-trend	Q1	Q3	Q5	*P*-trend
	Adjusted Means (95% CI)	Adjusted Means (95%CI)	Adjusted Means (95%CI)		Adjusted Means (95%CI)	Adjusted Means (95%CI)	Adjusted Means (95%CI)	
Total soy food	n = 211	n = 223	n = 207		n = 74	n = 63	n = 78	
hs-CRP, mg/dL								
Medle 1	0.05 (0.04-0.05)	0.05 (0.04-0.05)	0.04 (0.03-0.05)	0.611	0.03 (0.02-0.03)	0.02 (0.02-0.03)	0.02 (0.02-0.03)	0.924
Medle 2	0.04 (0.04-0.05)	0.05 (0.04-0.05)	0.04 (0.04-0.05)	0.530	0.03 (0.02-0.03)	0.02 (0.02-0.03)	0.02 (0.02-0.03)	0.969
Medle 3	0.05 (0.04-0.05)	0.05 (0.04-0.05)	0.04 (0.03-0.05)	0.468	0.03 (0.02-0.03)	0.02 (0.02-0.03)	0.02 (0.02-0.03)	0.970
IL-6, pg/mL								
Medle 1	1.05 (0.97-1.13)	1.00 (0.93-1.07)	0.96 (0.89-1.03)	0.394	0.95 (0.84-1.08)	0.85 (0.74-0.98)	0.87 (0.77-0.99)	0.742
Medle 2	1.04 (0.96-1.11)	1.01 (0.94-1.09)	0.96 (0.89-1.03)	0.635	0.94 (0.83-1.06)	0.87 (0.76-1.00)	0.88 (0.78-1.00)	0.929
Medle 3	1.04 (0.97-1.12)	1.02 (0.95-1.09)	0.96 (0.89-1.03)	0.554	0.94 (0.83-1.06)	0.86 (0.76-0.99)	0.89 (0.78-1.00)	0.929
IL-18, ng/L								
Medle 1	210.4 (202.4-219.0)	205.6 (197.8-213.5)	203.2 (195.2-211.5)	0.794	164.1 (154.8-174.0)	160.7 (152.2-169.9)	167.9 (158.7-177.8)	0.611
Medle 2	208.4 (200.8-216.6)	206.5 (199.2-214.3)	204.2 (196.6-212.4)	0.898	163.3 (154.3-172.9)	157.4 (148.0-167.6)	166.7 (157.8-176.5)	0.605
Medle 3	207.5 (199.6-215.6)	206.5 (199.2-214.4)	205.1 (197.4-213.5)	0.929	163.3 (154.3-173.0)	156.7 (147.2-166.7)	167.1 (157.9-176.9)	0.596
Fermented soy food	n = 195	n = 211	n = 221		n = 90	n = 75	n = 64	
hs-CRP, mg/dL								
Medle 1	0.04 (0.04-0.05)	0.05 (0.04-0.05)	0.04 (0.04-0.05)	0.885	0.02 (0.02-0.03)	0.02 (0.02-0.03)	0.02 (0.02-0.03)	0.444
Medle 2	0.04 (0.04-0.05)	0.05 (0.04-0.05)	0.04 (0.04-0.05)	0.824	0.02 (0.02-0.03)	0.02 (0.02-0.03)	0.02 (0.02-0.03)	0.296
Medle 3	0.04 (0.04-0.05)	0.05 (0.04-0.05)	0.04 (0.04-0.05)	0.721	0.02 (0.02-0.03)	0.02 (0.02-0.03)	0.02 (0.02-0.03)	0.313
IL-6, pg/mL								
Medle 1	1.04 (0.96-1.13)	0.94 (0.87-1.01)	0.94 (0.87-1.01)	0.019	0.92 (0.82-1.03)	0.91 (0.80-1.03)	0.81 (0.71-0.94)	0.524
Medle 2	1.03 (0.95-1.11)	0.95 (0.88-1.02)	0.94 (0.88-1.01)	0.039	0.89 (0.80-1.00)	0.91 (0.81-1.03)	0.82 (0.72-0.94)	0.637
Medle 3	1.03 (0.95-1.11)	0.95 (0.88-1.02)	0.94 (0.87-1.01)	0.031	0.89 (0.79-0.99)	0.92 (0.81-1.03)	0.81 (0.71-0.93)	0.566
IL-18, ng/L								
Medle 1	213.3 (204.9-222.4)	195.9 (188.4-203.7)	205.1 (197.3-213.0)	0.036	164.8 (156.1-173.7)	157.8 (148.8-167.1)	165.2 (155.3-176.1)	0.662
Medle 2	212.8 (204.4-221.1)	197.2 (190.0-204.8)	204.6 (197.0-212.2)	0.075	162.9 (154.6-171.7)	157.8 (149.1-167.0)	167.1 (157.0-177.5)	0.693
Medle 3	211.8 (203.3-220.3)	197.2 (190.0-204.8)	205.1 (197.5-212.9)	0.105	162.6 (154.2-171.2)	158.1 (149.6-167.5)	167.5 (157.6-178.3)	0.688
Non-fermented soy food	n = 209	n = 220	n = 203		n = 76	n = 66	n = 82	
hs-CRP, mg/dL								
Medle 1	0.04 (0.04-0.05)	0.05 (0.04-0.06)	0.04 (0.04-0.05)	0.382	0.02 (0.02-0.03)	0.03 (0.02-0.03)	0.02 (0.02-0.03)	0.842
Medle 2	0.04 (0.04-0.05)	0.05 (0.04-0.06)	0.04 (0.04-0.05)	0.515	0.02 (0.02-0.03)	0.03 (0.02-0.03)	0.02 (0.02-0.03)	0.977
Medle 3	0.04 (0.04-0.05)	0.05 (0.04-0.06)	0.04 (0.04-0.05)	0.454	0.02 (0.02-0.03)	0.03 (0.02-0.03)	0.02 (0.02-0.03)	0.967
IL-6, pg/mL								
Medle 1	1.00 (0.93-1.08)	0.98 (0.91-1.05)	0.97 (0.90-1.05)	0.180	0.92 (0.81-1.04)	0.90 (0.78-1.03)	0.87 (0.78-0.99)	0.829
Medle 2	1.00 (0.93-1.07)	0.99 (0.92-1.06)	0.98 (0.91-1.06)	0.415	0.91 (0.80-1.03)	0.90 (0.79-1.02)	0.87 (0.78-0.98)	0.935
Medle 3	1.00 (0.93-1.08)	0.99 (0.92-1.06)	0.98 (0.91-1.05)	0.357	0.91 (0.80-1.03)	0.89 (0.78-1.01)	0.88 (0.78-0.99)	0.945
IL-18, ng/L								
Medle 1	208.0 (200.0-216.5)	203.2 (195.7-211.3)	204.6 (196.6-213.1)	0.807	163.7 (154.4-173.3)	162.6 (152.8-172.8)	171.0 (161.9-180.9)	0.295
Medle 2	207.5 (199.6-215.4)	204.2 (196.7-211.7)	206.5 (198.6-214.6)	0.984	163.3 (154.2-172.6)	162.6 (153.1-172.8)	169.8 (160.8-179.2)	0.442
Medle 3	206.5 (198.6-214.5)	204.2 (196.6-211.7)	207.5 (199.5-215.8)	0.981	162.9 (154.1-172.6)	162.6 (153.0-172.7)	169.8 (160.8-179.5)	0.464
Soy isoflavone	n = 209	n = 213	n = 209		n = 76	n = 73	n = 76	
hs-CRP, mg/dL								
Medle 1	0.05 (0.04-0.05)	0.05 (0.04-0.05)	0.04 (0.04-0.05)	0.736	0.03 (0.02-0.03)	0.02 (0.02-0.03)	0.03 (0.02-0.03)	0.659
Medle 2	0.04 (0.04-0.05)	0.05 (0.04-0.06)	0.04 (0.04-0.05)	0.604	0.02 (0.02-0.03)	0.02 (0.02-0.03)	0.03 (0.02-0.03)	0.605
Medle 3	0.05 (0.04-0.05)	0.05 (0.04-0.06)	0.04 (0.04-0.05)	0.572	0.02 (0.02-0.03)	0.02 (0.02-0.03)	0.03 (0.02-0.03)	0.593
IL-6, pg/mL								
Medle 1	1.06 (0.98-1.14)	1.01 (0.94-1.09)	0.95 (0.88-1.03)	0.324	0.93 (0.82-1.05)	0.89 (0.78-1.01)	0.84 (0.74-0.95)	0.787
Medle 2	1.04 (0.97-1.12)	1.03 (0.95-1.10)	0.96 (0.89-1.03)	0.598	0.92 (0.82-1.05)	0.91 (0.80-1.03)	0.86 (0.76-0.98)	0.863
Medle 3	1.05 (0.97-1.13)	1.03 (0.95-1.10)	0.95 (0.88-1.03)	0.521	0.92 (0.81-1.04)	0.91 (0.80-1.03)	0.86 (0.76-0.98)	0.911
IL-18, ng/L								
Medle 1	212.8 (204.4-221.2)	202.3 (194.7-210.6)	205.1 (197.0-213.2)	0.480	161.1 (152.2-170.8)	154.2 (145.5-163.6)	168.3 (158.8-178.2)	0.266
Medle 2	209.9 (202.0-218.1)	203.7 (196.1-211.3)	206.1 (198.3-214.0)	0.639	160.7 (152.0-170.2)	154.9 (146.2-164.0)	169.0 (159.7-178.9)	0.263
Medle 3	208.4 (200.6-216.9)	203.2 (196.0-211.2)	207.0 (199.2-215.3)	0.650	160.3 (151.3-169.6)	153.8 (145.4-163.1)	169.8 (160.3-179.6)	0.168

Men (n = 1,053), women (n = 373).
All values are adjusted mean inflammatory markers ; 95% confidence interval in parentheses.
Model 1 : adjusted for age (continuous).
Model 2 : model 1 plus adjusted for BMI ((logarithm), current smoker (y/n), current drinker (y/n), regular exerciser (y/n), diabetes (y/n), hypertension (y/n), allergic (y/n), and energy intake (continuous).
Model 3 : model 2 plus adjusted for vegetables, friuts and fish intake (continuous).

Table 3 Multiple regression analysis for inflamatory markers by intake of each soy food

		Log hs-CRP, mg/dL				Log IL-6, pg/mL				Log IL-18, ng/L			
		Unstandardised coefficients		Standardised coefficients	*P*	Unstandardised coefficients		Standardised coefficients	*P*	Unstandardised coefficients		Standardised coefficients	*P*
		B	SE	β		B	SE	β		B	SE	β	
Men	Miso, g/1000 kcal/day	0.000	0.003	-0.001	0.965	-0.003	0.001	-0.068	0.034	-0.001	0.001	-0.023	0.467
	Soy sauce, g/1000 kcal/day	0.001	0.008	0.003	0.922	-0.010	0.004	-0.074	0.018	0.001	0.002	0.015	0.628
	Natto, g/1000 kcal/day	-0.005	0.002	-0.057	0.057	-0.002	0.001	-0.039	0.210	0.000	0.001	-0.002	0.954
	Tofu, g/1000 kcal/day	0.000	0.001	0.006	0.832	0.000	0.000	-0.027	0.392	0.000	0.000	0.018	0.558
	Soy milk, g/1000 kcal/day	-0.001	0.001	-0.028	0.345	0.000	0.000	0.027	0.377	0.000	0.000	-0.006	0.851
	Fried tofu, g/1000 kcal/day	-0.002	0.012	-0.006	0.849	-0.003	0.006	-0.015	0.630	-0.004	0.003	-0.034	0.261
	Dried bean cured, g/1000 kcal/day	-0.302	0.237	-0.038	0.204	-0.151	0.128	-0.036	0.241	-0.007	0.067	-0.003	0.917
	Soybean cured refuse, g/1000 kcal/day	-0.012	0.010	-0.038	0.201	-0.002	0.005	-0.013	0.664	-0.002	0.003	-0.023	0.446
	Green soy bean, g/1000 kcal/day	0.001	0.003	0.005	0.858	-0.002	0.002	-0.033	0.282	0.000	0.001	0.008	0.792
	Bean sprouts, g/1000 kcal/day	-0.001	0.001	-0.026	0.382	0.000	0.001	0.004	0.901	0.000	0.000	-0.020	0.510
	Soy flour, g/1000 kcal/day	0.003	0.055	0.002	0.959	0.022	0.029	0.023	0.463	0.000	0.015	0.001	0.984
	Fried bean cured with vegetable, g/1000 kcal/day	-0.004	0.006	-0.019	0.529	-0.002	0.003	-0.024	0.432	-0.003	0.002	-0.049	0.107
Women	Miso, g/1000 kcal/day	0.002	0.004	0.023	0.680	-0.001	0.002	-0.018	0.741	0.002	0.001	0.103	0.068
	Soy sauce, g/1000 kcal/day	0.003	0.013	0.012	0.820	-0.011	0.007	-0.081	0.136	-0.002	0.003	-0.025	0.653
	Natto, g/1000 kcal/day	-0.001	0.005	-0.013	0.812	-0.004	0.003	-0.071	0.186	0.000	0.001	-0.014	0.794
	Tofu, g/1000 kcal/day	0.001	0.001	0.035	0.521	0.001	0.001	0.107	0.049	0.001	0.000	0.090	0.106
	Soy milk, g/1000 kcal/day	0.002	0.001	0.104	0.049	0.000	0.000	0.048	0.364	0.000	0.000	0.021	0.691
	Fried tofu, g/1000 kcal/day	0.004	0.014	0.018	0.749	0.012	0.008	0.088	0.114	0.001	0.004	0.009	0.877
	Dried bean cured, g/1000 kcal/day	0.959	0.768	0.067	0.213	0.371	0.443	0.045	0.402	-0.021	0.207	-0.006	0.918
	Soybean cured refuse, g/1000 kcal/day	0.014	0.016	0.045	0.407	-0.003	0.009	-0.019	0.723	-0.004	0.004	-0.056	0.306
	Green soy bean, g/1000 kcal/day	0.000	0.008	0.000	0.996	0.000	0.005	-0.001	0.980	-0.002	0.002	-0.059	0.313
	Bean sprouts, g/1000 kcal/day	-0.002	0.001	-0.088	0.105	0.000	0.001	-0.014	0.791	-0.001	0.000	-0.106	0.055
	Soy flour, g/1000 kcal/day	0.005	0.056	0.005	0.930	-0.032	0.032	-0.052	0.329	0.018	0.015	0.065	0.238
	Fried bean cured with vegetable, g/1000 kcal/day	0.012	0.011	0.059	0.280	-0.006	0.006	-0.051	0.352	-0.001	0.003	-0.027	0.627

Men (n = 1,053), women (n = 373). Each soy food intake was adjusted for total energy using the density method.
Adjusted for age (continuous), BMI (logarithm), current smoker (y/n), current drinker (y/n), regular exerciser (y/n), hypertension (y/n), allergic (y/n), and energy intake (continuous), vegetables, friuts and fish intake (continuous).

was shown that intake of fermented soy foods including miso and natto was inversely associated with the development of high blood pressure in both men and women with normal blood pressure and that natto intake reduced the risk of cardiovascular disease mortality (30, 31).

Although intervention studies have been carried out to determine the relationships between soy, soy isoflavone and inflammation status, the results are not consistent. Reverri *et al*. conducted a randomized, controlled, cross-over study to evaluate the effects of soy nut consumption on inflammatory biomarkers and endothelial function. In that study, they measured CRP, TNF-α, IL-6, IL-18, IL-10 and oxide LDL levels after 4 weeks of intervention, but they did not found a significant difference in any biomarker (42). Jenkins *et al*. examined the effects of high (73 mg/day) and low (10 mg/day)-isoflavone soy protein foods on acute-phase proteins and proinflammatory cytokines in men and women. A high level of isoflavone intake increased the serum concentration of IL-6 but not that of CRP or TNF-α in women. In men, a difference in serum cytokine concentrations was not found (43). Mangano *et al*. evaluated the long-term effects of soy protein and/or soy isoflavone supplementation on serum lipids and inflammatory markers in women over 60 years of age in a 1-year randomized, double-blind placebo-control, clinical trial. Interestingly, it was found that soy protein significantly decreased the level of the inflammatory maker IL-6 and that soy isoflavones tended to decrease IL-6 level. No difference was found in the inflammatory maker CRP (44). In our study, an inverse association was not found between intake of soy foods and/or soy isoflavone and inflammatory markers (Table 2). Considering previous studies and our study, soy foods and/or soy-derived constituents might influence each inflammatory makers differently.

The reason why the effects of fermented and non-fermented soy products on inflammatory makers are different is not clear. At least, soy isoflavones cannot explain the discrepancy because intake of soy isoflavone derived from non-fermented soy products is higher than that derived from fermented soy products. Kim *et al*. examined the relationships of fermented soy food consumption and non-fermented soy food consumption with gastric cancer by a meta-analysis. It was shown that a high intake of fermented soy foods was significantly associated with an increased risk of gastric cancer, whereas an increased intake of non-fermented soy foods was significantly associated with a decreased risk of gastric cancer (45). The results of that study indicate the possibility that the effects of fermented soy food are different from those of non-fermented soy food in some aspects.

Our study shows the associations between intake of fermented soy food and inflammatory markers, but our study has some limitations. First, because of the cross-sectional design, we cannot infer causality from our results. Second, despite extensive adjustments for potential confounding factors, we cannot rule out the possibility that part of the observed associations might be related to a healthy lifestyle and/or other bioactive compounds not examined in this study. In this study, high level of tofu intake and soymilk intake were associated with increased IL-6 and hs-CRP concentrations, respectively (Table 3). These findings are unexpected. Third, we used a food-frequency questionnaire to estimate participants' dietary intake. The questionnaire is not a measure of absolute intake but is suited for classifying individuals into intake categories and is the most commonly used approach for assessing intake in epidemiological studies. Measurement error in reporting might lead to random errors that could dilute the real associations between soy foods and inflammatory markers. Fourth, as with any observational study, observed associations might be in part due to residual confounding despite extensive adjustment for known confounding factors. Lastly, the sample size was small and all of the subjects were Japanese, so applicability to other populations is unclear.

In conclusion, we found that high intake levels of fermented soy foods including miso and soy sauce in men were associated with a reduction in serum IL-6 level, which has been shown to be associated with many chronic diseases. We did not observe any effect of soy foods on IL-18 in level in men or women. Further study is needed to confirm the effects of fermented soy foods on inflammatory markers.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

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