Soy product and isoflavone intake associations with allergic diseases in Japanese workers: rhinitis, dermatitis and asthma

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ABSTRACT

Background and Objectives: The aim of this study was to determine the associations of intake of soy products and isoflavones with allergic diseases. **Methods and Study Design:** We conducted a cross-sectional study in 1437 participants (aged 20-64 years) who were living in Tokushima Prefecture, Japan during the period 2010–2011. We obtained anthropometric data and information on life style characteristics including dietary intake and current medical histories of allergic diseases using a structural self-administered questionnaire. Multiple logistic regression models were used to assess the associations of soy products and isoflavones with allergic diseases after controlling for age, family history of allergic diseases, smoking, drinking, physical activity, energy intake, BMI and dietary factors. **Results:** Intake of soy products showed significant inverse dose-response relationships with allergic rhinitis and asthma. The third quartile for soy products had an adjusted OR of 0.56 (95% CI: 0.35-0.91) compared to the reference group (first quartile), though intake of soy products showed no dose-response relationship with atopic dermatitis. Intake of soy isoflavones showed a significant inverse dose-response relationship with atopic dermatitis, though the association between intake of soy isoflavones and atopic dermatitis was U-shaped after adjustments for potential confounders. On the other hand, the associations between intake of soy isoflavones and other allergic diseases were not significant. **Conclusions:** The results indicate that higher intake of soy products is associated with reduced risk of allergic rhinitis and/or asthma in Japanese workers. Furthermore, moderate intake amounts of soy products and soy isoflavones are associated with inverse risk of atopic dermatitis.

Key Words: allergic diseases, soy products, soy isoflavones, Japanese workers, cross-sectional study

INTRODUCTION

In the past several decades, the rate of morbidity from allergic diseases has been increasing, mainly in developed countries.[1-3] In a previous report about the recent trend of allergic diseases in Asia, it was shown that the incidence of allergic diseases was increasing due to the changing lifestyle.[4] A survey on the prevalence of allergies and arthritis was carried out in Japan, and it was shown that the prevalence of asthma among adults had consistently increased from 1985 to 2006.[5]

Soybean is a member of the legume family and is a part of the traditional Asian diet. Soybeans and soy products are rich sources of various nutrients such as plant protein, fibers,

vitamins, minerals, and phytoestrogens (isoflavones).[6] Soy isoflavones are agonists of estrogen receptors, especially the β form, and may thus mimic the effects of estrogen.[7] Estrogen has been shown to stimulate the immune system.[8,9] Therefore, isoflavones may exert beneficial effects on the immune system because they structurally resemble estradiol. In previous studies, it was shown that isoflavones such as genistein may modulate the immune response through increases in the activities of cytotoxic T cells and natural killer cells.[10,11] Previous experimental studies showed that genistein blocks proliferation of lymphocytes and the cell-mediated immune response[12] and that genistein decreased the interferon-gamma production level in NC mice, atopic model mice.[13] Thus, isoflavones have biphasic effects and may modulate the immune system by functioning as an estrogen agonist or antagonist.[14]

Incoherent associations between the intake of soy products and/or isoflavones and some allergic diseases have been shown in several epidemiological studies. In a cross-sectional study, a positive association of soy drink intake and prevalence of asthma was shown in Australian adults.[15] On the other hand, it was reported that a high intake of soy products, soy protein and isoflavones reduced the prevalence of allergic rhinitis in Japanese pregnant woman.[16] In two prospective studies, it was shown that consumption of some soy foods and/or isofavones was not associated with the risk of allergic symptoms among Asians.[17,18]

Thus, the associations of intake of soy products and isoflavones with allergic diseases including allergic rhinitis, atopic dermatitis and asthma, have not been elucidated. Therefore, we analyzed the associations of intake of soy products and isoflavones with some allergic diseases in Japanese.

MATERIALS AND METHODS

Study population

The study participants included 821 workers (550 men and 271 women) in Tokushima Prefecture, which is located in Shikoku Island of Japan, who were aged 20-60 years at the first study wave of the study (June 2008-February 2009). Workers in Tokushima Prefecture aged 20 years or older were also newly recruited every year. The participants were followed up every year from the first-wave survey to the fifth-wave survey (June 2012-February 2013). The participants were then followed up every 5 years from the sixth-wave survey (June 2013-February 2014). The follow-up survey in the 10th year was implemented during the period from June 2017 to February 2018. The survey is still ongoing. In this cross-sectional occupation-based study, data from the third-wave survey (June 2010-February 2011) were used. The participants were essentially voluntary participants.

The present study population consisted of 1460 men and women aged 20-64 years. Of the 1460 participants who were asked to take part in our study, participants whose data for current medical history of allergic rhinitis (n=2), atopic dermatitis (n=1) or asthma (n=1), smoking habits (n=1), physical activity (n=4) or family history of allergic diseases (n=1) were missing were excluded. We also excluded 15 participants whose daily total energy intake was extremely high (mean + 3 standard deviation (SD): 3512.7 kcal/day in men and 2947.1 kcal/day in women) or low (mean – 3SD: 242.4 kcal/day in men and 498.6 kcal/day in women). Finally, data from the remaining 1437 participants (1058 men and 379 women) were analyzed in this study. The study protocol was approved by the institutional review boards of Tokushima University Hospital (Ethical approval number: 2868).

Assessment of allergic diseases

Allergic diseases were assessed by the simple question "Have you ever been diagnosed with any allergic diseases by a doctor?" Similar questions were asked for allergic rhinitis, atopic dermatitis, and asthma. We defined participants who answered 'Yes' for this question as cases of each allergic disease. Questions were also given about the age at first diagnosis of each allergic disease and family history of allergic diseases.

Dietary assessment

The participants were requested to complete a questionnaire to obtain data on dietary intake. Questions were given regarding the frequency and amount of soy foods consumed at each meal (how many times and how much is consumed per day, week, month, or year) in order to calculate intake of total soy products and soy isoflavones. We assessed soy food consumption using a semiquantitative FFQ[19] proposed by Nagata et al., which was a modification of the questionnaire used in the Takayama study[20] in Gifu Prefecture. The following 12 food items were included in the questionnaire: soybean curd, fermented soybeans, soybean paste, bean curd refuse, fried bean curd, fried bean curd with vegetables, soy flour, dried bean curd, soy milk, soy sauce, green soybeans, and bean sprouts. The validity of the Takayama study questionnaire was confirmed in a previous study by comparing food intake using the weighing method for three consecutive days.[20] The total soy product intake was calculated as the sum of all 12 soy products. Total soy isoflavones intake was estimated by summing the contents of isoflavones in the above 12 soy products according to estimates on the basis of previously published data for isoflavone concentrations in those soy products summarized by Toda.[21]

Regarding the amount of energy intake, participants were asked about meals taken in the past month using "The FFQg ver.2.0" (Kenpakusha Inc.) as a food frequency questionnaire method for determining frequency and amount of food intake. Food intake was estimated using questionnaires about both the amounts and frequencies of 29 food items and 10 cooked meals. Amounts of food intake were finally calculated for 18 food groups (cereals, potatoes, deep yellow vegetables, other vegetables and mushrooms, seaweeds, legumes, fish and shellfish, meats, eggs, fruits, sweets, beverages, sugar, nuts, oil and fats, and spices and condiments). The validity of FFQg was verified by Takahashi et al. by comparing food intake amounts using the weighting method for seven consecutive days.[22] The frequency and amount of all foods consumed at each meal were asked (how many times and how much is consumed per week). The amount of each food consumed per week was calculated by summing the product of the frequency of intake and the amount consumed at each meal.

Other measurements

The participants were requested not to eat overnight and they underwent a medical health check-ups the following day in each worksite. Body height was measured to the nearest 0.1 cm with participants standing without shoes, and body weight was measured to the nearest 0.1 kg with participants wearing lightweight clothing. BMI was calculated by weight (kg) / height $(m)^2$. Data for medical history (binary; yes or no), current physical activity (binary; yes or no), and daily alcohol intake (g/day) and smoking habits (binary; current/past or never) were obtained by a self-administered questionnaire.

Statistical analysis

At first, comparisons of the basic and dietary characteristics of participants according to total intake of soy isoflavones were performed. Continuous variables were expressed as means ± SD, and simple comparisons of the means of data were performed using analysis of variance. Categorical variables were expressed as numbers (percentages), and comparisons of proportions were performed using the chi-square test. The Jonckheere-Terpstra test was used for continuous variables and the Mantel-Haenszel test was used for categorical variables to calculate *p* for trend.

Next, multiple logistic regression analysis was used to estimate the ORs and 95% CIs for medical history of allergic diseases according to intake of soy isoflavones after controlling for the following variables. The confounding variables were 1) sex and age adjusted model, sex (binary: men and women) and age (continuous); 2) Model 1, sex and age adjusted model +

family history of allergic diseases (binary: yes or no), smoking habit (binary: current/past or never), daily alcohol intake (continuous), current physical activity (binary: yes or no) and energy intake (categorized value as quartiles); 3) Model 2, Model 1 + BMI (continuous); 4) Model 3, Model 2 + total vegetable intake (continuous); 5) Model 4, Model 2 + fruit intake (continuous); 6) Model 5, Model 2 + fish and shellfish intake (continuous); 7) Model 6, Model 2 + meat intake (continuous). We controlled for the total intake of soy products in addition to confounding variables in each model for the associations between soy isoflavones and allergic diseases. Total intake of soy products and total intake of soy isoflavones were divided into quartiles, and the first quartile was defined as the reference.

All statistical tests were based on two-sided probabilities and were performed using SPSS version 18.0J for Windows (SPSS Inc., Japan, Tokyo Japan). All p values<0.05 were considered statistically significant.

RESULTS

Characteristics of the participants

Table 1 shows the characteristics of participants according to total intake of soy isoflavones. Age, alcohol intake, and intake of all soy products and soy isoflavones were increasing with an increase in intake of soy isoflavones. On the other hand, the proportion of participants with a current physical activity, proportion of current smokers and total energy intake were decreasing with an increase in intake of soy isoflavones.

Intake of each food group according to total intake of soy isoflavones is shown in Table 2. The amounts of intake of potatoes, deep yellow vegetables, other vegetables and mushrooms, seaweeds, legumes, fish and shellfish, fruits, sugar and spices and condiments were increasing with an increase in intake of soy isoflavones. On the other hand, the amount of intake of meats, sweets, beverage, nuts, and oil and fats were decreasing with an increase in intake of soy isoflavones. There was no association between intake of soy isoflavones and intake of eggs or dairy products.

The results (Tables 1, 2) are similar to the characteristics of participants according to total intake of soy products.

Associations of intake of soy products and soy isoflavones with allergic diseases

Table 3 shows multivariate-adjusted associations of total intake of soy products or soy isoflavones with each allergic diseases.

Intake of soy products showed significant inverse dose-response relationships with allergic rhinitis and a U-shape association with atopic dermatitis. The highest quartile for soy products had an adjusted OR of 0.66 (95% CI: 0.46-0.94) compared to the reference group (first quartile), and intake of soy products showed significant inverse dose-response relationships with allergic rhinitis (*p* for trend=0.043). Although intake of soy products showed no dose-response relationship with atopic dermatitis, the third quartile for soy products had an adjusted odds ratio of 0.56 (95% CI: 0.35-0.91) compared to the reference group. The highest quartile for soy products had an adjusted OR of 0.33 (95% CI: 0.12-0.94) compared to the reference group, though intake of soy products showed no dose-response relationship with asthma.

Intake of soy isoflavones showed a significant inverse dose-response relationship with atopic dermatitis, though the association between intake of soy isoflavones and atopic dermatitis was U-shaped. On the other hand, the associations between intake of soy isoflavones and other allergic diseases such as allergic rhinitis and asthma were not significant.

To determine whether the associations between intake of soy products and soy isoflavones and each allergic diseases were confounded by other dietary factors including total vegetable, fruits, fish and shellfish or meats intake was further adjusted (Table 4). After adjustment for other dietary factors, the results were essentially similar.

DISCUSSION

In our study, higher intake of soy products was associated with reduced risk of allergic rhinitis and/or asthma. On the other hand, no significant association was found between intake of soy isoflavones and allergic rhinitis or asthma. Furthermore, the associations between intake of soy products and soy isoflavones and atopic dermatitis were U-shaped. After adjustment for other dietary factors including total intake of vegetables, fruits, fish and shellfish or meat, the results were essentially similar.

Our results showed that there is an inverse association between intake of soy products and allergic rhinitis or asthma. These results concur with results of some previous studies in Asian populations.[16,17] In a previous cross-sectional study including 1002 Japanese pregnant woman, the highest quartile for total soy products had the lowest adjusted OR compared to the reference group (first quartile).[16] In a prospective study in Singapore Chinese aged 45-74 years, dietary patterns including soy foods were inverse associated with asthma, though there was no significant association (*p* for trend=0.08).[17] On the other hand, in a prospective study,

Nagata et al. found that there was no effect of total amount of soy products on cedar pollinosis among 11229 Japanese adults aged ≥35 years.[18] Furthermore, another cross-sectional study showed that higher soy drink intake was significantly associated with an increased risk of asthma in Australian young adults aged 20-44 years.[15] The differences in these results might be caused by differences in study populations, dietary habits of the participants, dietary assessment methods, and study design.

In our study, although it was shown that higher intake of soy products was associated with reduced risk of allergic rhinitis or asthma, no significant association between intake of soy isoflavones and allergic rhinitis or asthma was found. One reason for this result may be that in vivo metabolism of isoflavones was not considered in this study. Daidzein is a phytoestrogen that is metabolized extensively by the intestinal microflora.[23] Some previous reports suggested that 30-50% of Japanese have equol-producing ability depending on the intestinal bacteria,[24] and this ability is increased by dietary habits such as greater consumption of dietary fiber and plant protein.[25] Furthermore, it has been reported that prevention of bone mineral density loss in response to soymilk intervention was more obvious in equol producers than in equol non-producers.[26] Therefore, there may be a discrepancy between the estimated intake of isoflavones and the actual metabolized amount of isoflavones. In addition, according to a recent meta-analysis, purified or isolated components of soy (isoflavones or soy protein) were not as effective as whole soy foods for improving glycemic control.[27,28] The reasons for this may include the presence of other components of soy, such as dietary fiber, saponin, polysaccharides, phytosterol, and unsaturated fatty acids, or their interactions. However, the effects and mechanisms of the effects of isoflavones on allergic diseases have not been fully clarified and warrant further study.

Our results showed that the third quartile for soy products and soy isoflavones had the lowest ORs for atopic dermatitis compared to the reference group. To our knowledge, this is the first study showing an association of moderate intake amounts of soy products and soy isoflavones with atopic dermatitis in Japanese. However, our results do not agree with the results of a previous study about the relationship between intake of soy foods and atopic dermatitis. It was shown that soy milk intake was not associated with atopic dermatitis in a cross-sectional study including 1601 Australian young adults aged 20-44 years.[15] The differences in these results might be caused by differences in study populations and dietary habits of the participants, and further human study is needed. One explanation for the decreased risk of atopic dermatitis is that exposure to isoflavones changes the immune balance, for example, enhancing Th1-type and suppressing Th2-type immune responses. In

experimental studies, genistein suppressed the production of interleukin (IL)-4 and IL-5.[29-31] In addition, Sakai et al. showed that genistein, which is one of the isoflavones, suppresses the development of spontaneous atopic-like dermatitis in NC/Nga mice (an atopic model).[13] Soybean extract suppresses peanut-allergy symptoms, including skin symptoms,[32] in peanut-allergic mice.[33] Masilamani et al showed that isoflavones suppress peanut-allergy symptoms though regulation of dendritic cell function.[34] Based on these reports, intake of isoflavones might decrease the risk of atopic dermatitis through decreasing the production of IL-4 and/or IL-5. Another mechanism of the preventive effect of intake of isoflavones on atopic dermatitis might be related to the antioxidant actions of isoflavones.[6]

In this study, the relationship between intake of soy products and soy isoflavones and atopic dermatitis was U-shaped. The first reason for this result may be that the participants with the third quartile for soy products and soy isoflavones had a healthier lifestyle (including physical activity, no physical or mental stress and/or taking rest) other than dietary intake compared to other groups. The second reason is that the number of participants with a family history of allergic diseases was smaller in the third quartile for soy products and soy isoflavones than in the second and highest quartiles (percentage of participants with a family history of allergic diseases: 32.7% in Q2, 27.4% in Q3 and 31.5% in Q4). It has been reported that a positive family history of allergic diseases is a risk factor for presentation of atopic dermatitis.[35] Therefore, although we examined the relationship between intake of soy products and soy isoflavones and atopic dermatitis by further adding family history of allergic diseases into the logistic regression model, the U-shaped relationship was maintained (Tables 3, 4). Another reason is that isoflavones have biphasic effects and may modulate the immune system by functioning as an estrogen agonist or antagonist.[14] Thus, only a moderate intake of soy products and isoflavones might be sufficient for prevention of atopic dermatitis in Japanese.

Our study has some limitations. First, because of the cross-sectional approach, the temporal relationship between intake of soy products and isoflavones and each of the allergic diseases remains obscure. Second, the sample size of this study was small. Third, the findings might not be generalizable to other populations because the study participants were only Japanese workers. We could not obtain information on the kind of occupation for each of the participants, though the kind of occupation is important information for the workers. Fourth, dietary intake including energy and/or soy products was estimated from two different FFQs, though the validity of both FFQs has been confirmed.[19,22] Fifth, participants in this study had a lower intake of isoflavones (the median of the highest quartile being 19.0 mg/1000 kcal/day)

than that of participants in a previous study.[36] Messina et al reported that more moderate doses of isoflavones (50-100 mg/day) may prove to be more efficacious for promoting bone health.[36] Therefore, the true association between soy isoflavones and each of the allergic diseases may have been masked because the amount of isoflavones from soy foods consumed by participants in this study was less than that in previous studies. Sixth, although it is known that allergic diseases, especially atopic dermatitis, develop mostly in infancy, soy isoflavone intake was assessed during adulthood. This time lag may have resulted in a random measurement error in exposure variables. However, the effect may be toward an attenuation of the relation. Seventh, information on current medical history of allergic diseases was based on self-reporting, and occult and undiagnosed patients may have been missed. In the case of misclassifications of self-reported information, the effect may also be to mask the true effects. In addition, because there are few cases of asthma (prevalence rate=2.7%) in our study, our results about asthma may have been accidentally obtained. Therefore, interpretation of our results about asthma needs to be done carefully. Finally, there may be confounding factors that were not removed completely, though various potentially-important confounders were adjusted in analysis.

In conclusion, our results indicate the possibility that intake of soy products and/or soy isoflavones is a protective factor against allergic diseases. A further large-scale prospective study on the effects of intake of soy products and isoflavones on allergic diseases is needed.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

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Table 1. Characteristics of participants according on total intake of soy isoflavones[†]

	Total intake of soy isoflavones[‡]				*p* value[§]	*p* for trend[¶]
	Q1	Q2	Q3	Q4		
n	356	361	358	362		
Age (years)	37.8±9.2	39.7±9.3	40.1±10.0	41.8±10.1	<0.001	<0.001
Male	267 (75.0)	262 (72.6)	267 (74.6)	262 (72.4)	0.799	0.573
Body mass index (kg/m^2)	23.3±3.4	23.1±3.4	23.2±3.5	23.1±3.4	0.866	0.572
Current physical activity	194 (54.5)	184 (51.0)	166 (46.4)	161 (44.5)	0.032	0.003
Smoking habit						
Current	124 (34.8)	101 (28.0)	86 (24.0)	82 (22.7)	0.001	<0.001
Never / Past	232 (65.2)	260 (72.0)	272 (76.0)	280 (77.3)		
Medical history						
Allergic rhinitis	118 (33.1)	132 (36.6)	124 (34.6)	132 (36.5)	0.740	0.478
Atopic dermatitis	54 (15.2)	34 (9.4)	31 (8.7)	40 (11.0)	0.027	0.079
Asthma	11 (3.1)	16 (4.4)	6 (1.7)	6 (1.7)	0.065	0.065
Family history of allergic diseases	93 (26.1)	118 (32.7)	98 (27.4)	114 (31.5)	0.159	0.318
Daily alcohol intake (g/day)	9.8±19.4	10.8±19.9	12.3±20.0	13.5±20.6	0.068	<0.001
Total energy intake (kcal/day)	1856.0±466.9	1837.3±415.4	1821.1±425.5	1729.6±400.9	<0.001	<0.001
Total soy products (g/day)	43.7±21.8	78.6±24.8	112.1±35.5	189.6±79.5	<0.001	<0.001
Soybean curd (g/day)	16.1±12.0	34.2±16.9	54.4±26.8	87.4±55.6	<0.001	<0.001
Fried bean curd (g/day)	0.7±1.3	1.4±1.9	1.7±2.0	3.0±11.3	<0.001	<0.001
Fried bean curd with vegetables (g/day)	0.5±1.4	1.0±1.9	2.2±4.6	2.9±7.0	<0.001	<0.001
Fermented soybeans (g/day)	1.1±2.3	2.7±4.3	5.2±7.4	11.5±15.5	<0.001	<0.001
Bean curd refuse (g/day)	0.3±0.9	0.5±1.5	0.7±1.7	1.4±3.8	<0.001	<0.001
Dried bean curd (g/day)	0.0±0.0	0.0±0.1	0.0±0.1	0.0±0.1	<0.001	<0.001
Soy milk (g/day)	0.6 ±3.1	2.4 ±8.6	4.4 ±13.2	26.2 ±58.7	<0.001	<0.001
Soy flour (g/day)	0.0 ±0.3	0.1 ±0.5	0.1 ±0.5	0.2 ±0.6	0.014	0.002
Bean sprouts (g/day)	13.4 ±14.7	19.7 ±18.2	23.0 ±25.7	31.5 ±36.4	<0.001	<0.001
Green soybeans (g/day)	1.7 ±3.3	2.6 ±5.8	2.8 ±5.3	5.3 ±11.1	<0.001	<0.001
Soybean paste (g/day)	6.7 ±5.5	11.1 ±6.8	14.6 ±8.4	17.3 ±10.3	<0.001	<0.001
Soy sauce (g/day)	2.6 ±3.3	2.8 ±2.8	3.1 ±3.0	3.3 ±3.3	0.013	<0.001
Total soy isoflavones (mg/day)	9.5 ±4.3	18.6 ±4.9	28.2 ±7.2	48.8 ±19.3	<0.001	<0.001
Daidzein (mg/day)	3.9 ±1.7	7.6 ±2.0	11.4 ±2.9	19.8 ±7.9	<0.001	<0.001
Genistein (mg/day)	5.6 ±2.6	11.1 ±2.9	16.8 ±4.3	29.0 ±11.5	<0.001	<0.001

[†]Values are mean±SD, or number (%).
[‡]Total soy isoflavones (mg/1000 kcal/day): Q1:0-7.831, Q2:7.831-12.588, Q3:12.588-19.015, Q4:19.015-.
[§]The analysis of variance was used for continuous variables and the chi-square test was used for categorical variables to determine the significant differences.
[¶]The Jonckheere-Terpstra test was used for continuous variables and the Mantel-Haenszel test was used for categorical variables to calculate *p* for trend.

Table 2. Food groups intake of the participants according on total intake of soy isoflavones[†]

	Total intake of soy isoflavones[‡]				*p* value[§]	*p* for trend[¶]
	Q1 n=356	Q2 n=361	Q3 n=358	Q4 n=362		
Cereals (g/day)	350.9±105.8	355.0±107.3	361.4±100.5	340.5±106.1	0.056	0.719
Potatoes (g/day)	19.4±19.1	23.2±20.0	24.3±20.9	23.4±20.7	0.005	0.001
Deep yellow vegetables (g/day)	42.1±29.7	48.7±29.5	57.0±34.7	59.8±35.5	<0.001	<0.001
Other vegetables and mushrooms (g/day)	69.8±45.5	83.2±48.8	93.1±53.8	99.5±57.4	<0.001	<0.001
Seaweeds (g/day)	2.0±1.9	3.1±2.7	3.4±2.9	3.8±3.0	<0.001	<0.001
Legumes (g/day)	24.0±24.8	36.2±23.8	46.3±28.0	62.2±40.1	<0.001	<0.001
Fish and shellfish (g/day)	45.0±37.4	52.0±34.6	53.3±34.0	56.2±34.0	<0.001	<0.001
Meats (g/day)	96.1±52.3	88.3±43.6	82.7±42.0	74.6±43.6	<0.001	<0.001
Eggs (g/day)	29.1±18.6	29.4±17.6	28.6±15.3	28.1±16.5	0.730	0.695
Daily products (g/day)	103.5±110.5	113.1±99.8	103.3±98.5	103.9±101.0	0.504	0.940
Fruits (g/day)	35.0±45.9	40.9±48.7	46.7±50.2	51.7±60.3	<0.001	<0.001
Sweets (g/day)	82.0±60.2	72.8±52.3	70.0±53.1	56.9±43.8	<0.001	<0.001
Beverage (g/day)	291.6±281.9	261.4±257.1	242.5±211.4	233.4±243.2	0.010	0.007
Sugar (g/day)	5.1±4.6	5.3±4.2	5.7±4.9	5.7±4.4	0.300	0.018
Nuts (g/day)	1.7±3.2	1.8±3.4	2.0±3.5	1.8±2.5	0.454	<0.001
Oil and fats (g/day)	12.9±6.3	13.4±6.9	12.7±6.5	12.0±6.7	0.028	0.003
Spices and condiments (g/day)	20.5±12.7	22.6±11.5	26.4±14.7	25.6±12.1	<0.001	<0.001

[†]Values are mean±SD, or number (%).

[‡]Total soy isoflavones (mg/1000 kcal/day): Q1:0-7.831, Q2:7.831-12.588, Q3:12.588-19.015, Q4:19.015-.

[§]Differences in the mean ± standard deviation between each food group according to total intake of soy isoflavones were evaluated by analysis of variance.

[¶]*p* for trend as regards the 17 food groups according to total intake of soy isoflavones were evaluated by Jonckheere-Terpstra trend test.

Table 3. Odds ratios (95% confidence intervals) for each allergic diseases according to total intake of soy products or soy isoflavones[†]

	Total intake of soy products or soy isoflavones							*p* for trend
	Referent (lowest)	Q2	95% CI	Q3	95% CI	Q4 (highest)	95% CI	
Allergic rhinitis								
Total soy products[‡]								
No. of cases/subjects	124/358	128/360		140/360		114/359		
Sex and age adjusted model[§]	1	1.04	(0.76-1.42)	1.20	(0.89-1.64)	0.86	(0.63-1.18)	0.208
Model 1[¶]	1	0.91	(0.64-1.29)	1.06	(0.75-1.49)	0.66	(0.46-0.94)	0.043
Model 2[††]	1	0.91	(0.64-1.29)	1.06	(0.75-1.49)	0.66	(0.46-0.94)	0.043
Total soy isoflavones[‡‡]								
No. of cases/participants	118/356	132/361		124/358		132/362		
Sex and age adjusted model[§]	1	1.14	(0.84-1.56)	1.06	(0.77-1.44)	1.12	(0.82-1.54)	0.829
Model 1[¶]	1	0.97	(0.68-1.40)	1.01	(0.68-1.50)	1.05	(0.61-1.80)	0.99
Model 2[††]	1	0.97	(0.68-1.40)	1.01	(0.68-1.50)	1.05	(0.61-1.80)	0.99
Atopic dermatitis								
Total soy products[‡]								
No. of cases/participants	53/358	41/360		32/360		33/359		
Sex and age adjusted model[§]	1	0.77	(0.50-1.20)	0.58	(0.36-0.93)	0.64	(0.40-1.02)	0.094
Model 1[¶]	1	0.73	(0.47-1.15)	0.56	(0.35-0.90)	0.63	(0.39-1.02)	0.081
Model 2[††]	1	0.73	(0.47-1.14)	0.56	(0.35-0.91)	0.63	(0.39-1.02)	0.084

[†]Wald confidence intervals for adjusted ORs (95% CIs).
[‡]Sex and age adjusted model: adjusted for sex (binary) and age (continuous).
[§]Model 1 for total soy products: adjusted for sex, age, family history of allergic diseases (binary; yes or no), smoking habit (binary; current/past or never), dairy alcohol intake (continuous), current physical activity (binary; yea or no) and energy intake (continuous).
[¶]Model 2 for total soy products: adjusted for Model 1 + BMI (continuous).
[††]Model 1 for total soy isoflavones: adjusted for sex, age, family history of allergic diseases (binary; yes or no), smoking habit (binary; current/past or never), dairy alcohol intake (continuous), current physical activity (binary; yea or no), energy intake (continuous) and total soy products intake (continuous).
[‡‡]Model 2 for total soy isoflavones: adjusted for Model 1 + BMI (continuous).
[§§]Total soy products (g/1000 kcal/day): Q1:0-33.152, Q2:33.152-50.743, Q3:50.743-75.676, Q4:75.676-
[¶¶]Total soy isoflavones (mg/1000 kcal/day): Q1:0-7.831, Q2:7.831-12.588, Q3:12.588-19.015, Q4:19.015- (Please list the correct footnotes to the correct symbols,: Footnote symbols: †, ‡, §, ¶, ††, should be used (in that order).

Table 3. Odds ratios (95% confidence intervals) for each allergic diseases according to total intake of soy products or soy isoflavones[†] (cont.)

	Total intake of soy products or soy isoflavones							*p* for trend
	Referent (lowest)	Q2	95% CI	Q3	95% CI	Q4 (highest)	95% CI	
Total soy isoflavones[‡‡]								
No. of cases/participants	54/356	34/361		31/358		40/362		
Sex and age adjusted model[§]	1	0.60	(0.38-0.96)	0.56	(0.35-0.89)	0.76	(0.49-1.19)	0.055
Model 1[¶]	1	0.56	(0.34-0.91)	0.54	(0.32-0.93)	0.75	(0.36-1.53)	0.041
Model 2[††]	1	0.56	(0.35-0.91)	0.54	(0.32-0.94)	0.76	(0.37-1.56)	0.042
Asthma								
Total soy products[‡]								
No. of cases/participants	14/358	12/360		8/360		5/359		
Sex and age adjusted model[§]	1	0.87	(0.40-1.92)	0.57	(0.24-1.39)	0.36	(0.13-1.03)	0.213
Model 1[¶]	1	0.82	(0.37-1.83)	0.52	(0.21-1.27)	0.33	(0.11-0.94)	0.150
Model 2[††]	1	0.81	(0.36-1.81)	0.53	(0.22-1.30)	0.33	(0.12-0.94)	0.159
Total soy isoflavones[‡‡]								
No. of cases/participants	11/356	16/361		6/358		6/362		
Sex and age adjusted model[§]	1	1.48	(0.67-3.25)	0.55	(0.20-1.51)	0.55	(0.20-1.52)	0.090
Model 1[¶]	1	1.14	(0.50-2.60)	0.40	(0.13-1.18)	0.26	(0.06-1.16)	0.071
Model 2[††]	1	1.16	(0.51-2.64)	0.40	(0.14-1.20)	0.26	(0.06-1.21)	0.084

[†]Wald confidence intervals for adjusted ORs (95% CIs).
[‡]Sex and age adjusted model: adjusted for sex (binary) and age (continuous).
[§]Model 1 for total soy products: adjusted for sex, age, family history of allergic diseases (binary; yes or no), smoking habit (binary; current/past or never), dairy alcohol intake (continuous), current physical activity (binary; yea or no) and energy intake (continuous).
[¶]Model 2 for total soy products: adjusted for Model 1 + BMI (continuous).
[††]Model 1 for total soy isoflavones: adjusted for sex, age, family history of allergic diseases (binary; yes or no), smoking habit (binary; current/past or never), dairy alcohol intake (continuous), current physical activity (binary; yea or no), energy intake (continuous) and total soy products intake (continuous).
[‡‡]Model 2 for total soy isoflavones: adjusted for Model 1 + BMI (continuous).
[§§]Total soy products (g/1000 kcal/day): Q1:0-33.152, Q2:33.152-50.743, Q3:50.743-75.676, Q4:75.676-.
[¶¶]Total soy isoflavones (mg/1000 kcal/day): Q1:0-7.831, Q2:7.831-12.588, Q3:12.588-19.015, Q4:19.015- (Please list the correct footnotes to the correct symbols,: Footnote symbols: †, ‡, §, ¶, ††, should be used (in that order).

Table 4. Odds ratios (95% confidence intervals) for each allergic diseases according to total intake of soy products or soy isoflavones after adjustment for dietary factors[†]

	Total intake of soy products or soy isoflavones							*p* for trend
	Referent (lowest)	Q2	95% CI	Q3	95% CI	Q4	95% CI	
Allergic rhinitis								
Total soy products[‡]								
No. of cases/participants	124/358	128/360		140/360		114/359		
Model 3[§]	1	0.89	(0.63-1.27)	1.01	(0.71-1.44)	0.63	(0.43-0.91)	0.030
Model 4[¶]	1	0.91	(0.64-1.29)	1.04	(0.74-1.48)	0.65	(0.45-0.93)	0.039
Model 5[††]	1	0.91	(0.64-1.30)	1.06	(0.75-1.50)	0.66	(0.46-0.95)	0.046
Model 6[‡‡]	1	0.92	(0.64-1.31)	1.07	(0.75-1.51)	0.67	(0.46-0.96)	0.049
Total soy isoflavones[§§]								
No. of cases/participants	118/356	132/361		124/358		132/362		
Model 3[§]	1	0.96	(0.67-1.38)	0.98	(0.66-1.46)	1.00	(0.58 1.73)	0.994
Model 4[¶]	1	0.97	(0.67-1.40)	1.00	(0.68-1.49)	1.03	(0.60-1.78)	0.994
Model 5[††]	1	0.98	(0.68-1.41)	1.02	(0.68-1.51)	1.06	(0.61-1.82)	0.991
Model 6[‡‡]	1	0.98	(0.68-1.41)	1.03	(0.69-1.52)	1.06	(0.62-1.83)	0.990
Atopic dermatitis								
Total soy products[‡]								
No. of cases/participants	53/358	41/360		32/360		33/359		
Model 3[§]	1	0.74	(0.47-1.17)	0.59	(0.36-0.96)	0.67	(0.41-1.09)	0.163
Model 4[¶]	1	0.73	(0.47-1.15)	0.58	(0.36-0.94)	0.66	(0.41-1.07)	0.129
Model 5[††]	1	0.75	(0.47-1.17)	0.58	(0.36-0.93)	0.65	(0.40-1.06)	0.118
Model 6[‡‡]	1	0.76	(0.48-1.20)	0.59	(0.37-0.96)	0.68	(0.42-1.10)	0.163

[†]Wald confidence intervals for adjusted ORs (95% CIs).
[‡]Total soy products (g/1000 kcal/day): Q1:0-33.152, Q2:33.152-50.743, Q3:50.743-75.676, Q4:75.676-.
[§]Model 3: adjusted for Model 2 for total soy products or soy isoflavones + total vegetables intake (continuous).
[¶]Model 4: adjusted for Model 2 for total soy products or soy isoflavones + fruits intake (continuous).
[††]Model 5: adjusted for Model 2 for total soy products or soy isoflavones + fish and shellfish intake (continuous).
[‡‡]Model 6: adjusted for Model 2 for total soy products or soy isoflavones + meats intake (continuous).
[§§]Total soy isoflavones (mg/1000 kcal/day): Q1:0-7.831, Q2:7.831-12.588, Q3:12.588-19.015, Q4:19.015- .

Table 4. Odds ratios (95% confidence intervals) for each allergic diseases according to total intake of soy products or soy isoflavones after adjustment for dietary factors[†] (cont.)

	Total intake of soy products or soy isoflavones							*p* for trend
	Referent (lowest)	Q2	95% CI	Q3	95% CI	Q4	95% CI	
Total soy isoflavones[§§]								
No. of cases/participants	54/356	34/361		31/358		40/362		
Model 3[§]	1	0.58	(0.35-0.94)	0.58	(0.33-0.99)	0.82	(0.40-1.70)	0.058
Model 4[¶]	1	0.57	(0.35-0.92)	0.56	(0.33-0.97)	0.80	(0.39-1.65)	0.048
Model 5[††]	1	0.58	(0.35-0.94)	0.56	(0.33-0.96)	0.80	(0.39-1.64)	0.052
Model 6[‡‡]	1	0.58	(0.36-0.95)	0.58	(0.34-1.00)	0.81	(0.39-1.68)	0.066
Asthma								
Total soy products[‡]								
No. of cases/participants	14/358	12/360		8/360		5/359		
Model 3[§]	1	0.81	(0.36-1.81)	0.53	(0.21-1.31)	0.33	(0.11-0.95)	0.171
Model 4[¶]	1	0.80	(0.36-1.79)	0.51	(0.21-1.25)	0.31	(0.11-0.90)	0.131
Model 5[††]	1	0.80	(0.36-1.80)	0.53	(0.22-1.29)	0.33	(0.11-0.94)	0.158
Model 6[‡‡]	1	0.84	(0.37-1.87)	0.55	(0.23-1.36)	0.35	(0.12-1.02)	0.211
Total soy isoflavones[§§]								
No. of cases/participants	11/356	16/361		6/358		6/362		
Model 3[§]	1	1.16	(0.50-2.65)	0.40	(0.13-1.22)	0.26	(0.06-1.23)	0.080
Model 4[¶]	1	1.15	(0.50-2.62)	0.38	(0.13-1.15)	0.25	(0.05-1.14)	0.060
Model 5[††]	1	1.15	(0.50-2.64)	0.40	(0.13-1.20)	0.26	(0.06-1.21)	0.075
Model 6[‡‡]	1	1.20	(0.52-2.76)	0.43	(0.14-1.29)	0.29	(0.06-1.32)	0.089

[†]Wald confidence intervals for adjusted ORs (95% CIs).
[‡]Total soy products (g/1000 kcal/day): Q1:0-33.152, Q2:33.152-50.743, Q3:50.743-75.676, Q4:75.676-.
[§]Model 3: adjusted for Model 2 for total soy products or soy isoflavones + total vegetables intake (continuous).
[¶]Model 4: adjusted for Model 2 for total soy products or soy isoflavones + fruits intake (continuous).
[††]Model 5: adjusted for Model 2 for total soy products or soy isoflavones + fish and shellfish intake (continuous).
[‡‡]Model 6: adjusted for Model 2 for total soy products or soy isoflavones + meats intake (continuous).
[§§]Total soy isoflavones (mg/1000 kcal/day): Q1:0-7.831, Q2:7.831-12.588, Q3:12.588-19.015, Q4:19.015.

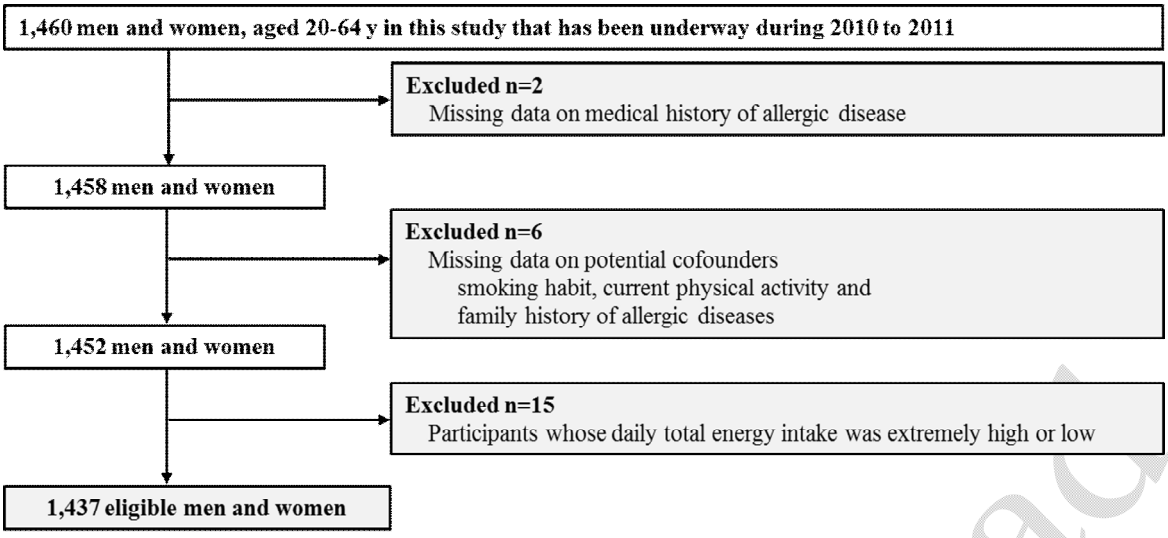

Figure1 *Nakamoto et al.*

Figure 1. Overview of the participants. Of 1460 participants aged 20-64 years, we excluded participants whose data were not available. We also excluded 15 participants whose daily total energy intake was extremely high or low. Data for the remaining 1437 participants (1058 men and 379 women) were used for analysis in this study.