ORIGINAL

Association between total soy product intake and metabolic syndrome in middle-aged Japanese workers : Cross-sectional and longitudinal study findings

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Abstract : The aim of this study was to determine the association between total soy product intake and metabolic syndrome (MetS) in Japanese workers. The cross-sectional study included 698 participants aged over 40 years, and the longitudinal study included 527 participants aged over 40 years in 2012 who participated at least once from 2013 to 2018. Dietary intake of total soy products was summed based on the total amount of 12 kinds of soy products assessed using a food frequency questionnaire. Participants were diagnosed as having MetS if they had abdominal obesity and at least one of the following conditions : hypertriglyceridemia, high blood pressure, and hyperglycemia. To calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for MetS according to tertile of total soy product intake, multivariable logistic regression was performed for the cross-sectional analysis, and generalized estimating equations were used for the longitudinal analysis. Cross-sectional analysis showed that there was an inverse association between total soy product intake and MetS, and the OR of tertile 3 was significantly higher than that of tertile 1. However, the inverse association disappeared in the longitudinal analysis. Further long-term studies are needed to determine the association between total soy product intake and MetS. J. Med. Invest. 72 : 343-353, August, 2025

Keywords **:** *total soy product intake, metabolic syndrome, Japanese worker, cross-sectional study, longitudinal study*

INTRODUCTION

Metabolic syndrome (MetS) was proposed by the World Health Organization (WHO) in 1999 (1) as a condition based on visceral obesity, in which impaired glucose tolerance, lipid metabolism disorders, and high blood pressure are stacked (2). The prevalence of MetS is increasing worldwide (3), and it has become a public health problem. In Japan, the National Health and Nutrition Survey 2019 reported that the percentage of people strongly suspected of having MetS was 28.2% for men and 10.3% for women (4), and the number of cases aged over 40 years was particularly higher in both sexes. In addition, since MetS has been reported to be a risk factor for cardiovascular disease (CVD), type 2 diabetes mellitus, and death (5), early prevention of MetS is important. Associations between MetS and multiple factors including lifestyle (smoking habits, dietary habits, and physical activity) and genetic factors have been reported (6).

Soybean, a member of the legume family, is a familiar food of the traditional Asian diet (7). Asian people, including Japanese, consume large quantities of soy products (8). Soybean/soy products are rich sources of various nutrients, such as plant proteins, fiber, vitamins, minerals, and phytoestrogens (isoflavones) (9). Isoflavones are estrogen-like compounds found in several plants and/or plant foods, such as beans, soy, and sprouts (10, 11). Several observational studies have shown that the consumption of soy products is related to the prevention of hyperglycemia, including diabetes mellitus (12), obesity (13, 14), and high blood pressure (15-18). Each of the 12 soy products contains various functional components, such as soy isoflavone (19-21) and soy protein (22). Therefore, the association of total intake of soy products with MetS was examined in this study.

Although it has been reported that the intake of soy products reduces the risk of impaired glucose tolerance, high blood pressure, and abdominal obesity, which are components of MetS, few papers have examined the association between total soy product intake and the onset of the components of MetS (23, 24). It was previously shown that there were no associations between soy protein intake and MetS and MetS components in 2,811 middle-aged and elderly Chinese men and women in a cross-sectional study (23). However, there was an inverse association between soy protein intake and MetS in women, but not in men, in a longitudinal study involving 5,509 Korean men and women aged 40 years or older (24). Therefore, the results for the association between the intake of soy products and soy-containing ingredients and MetS are inconsistent. In addition, although two studies (23, 24) examined the relationship between soy-containing ingredients and MetS in an Asian population, the observed population was not Japanese, and it is necessary to evaluate the effect of the intake of soy products on the onset of MetS in the

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Japanese population.

Therefore, in this study, the relationships between total soy product intake and the prevalence and incidence of MetS in Japanese workers aged over 40 years were examined.

PARTICIPANTS AND METHODS

Study participants

The cross-sectional analysis in the present study was based on data from the fifth wave (June 2012 to February 2013) of an occupation-based dynamic cohort established in Tokushima Prefecture in Japan. Details of the occupation-based annual examinations in Tokushima Prefecture have been reported elsewhere (25). In brief, participants in the occupation-based annual examinations were all volunteers from Tokushima Prefecture in Japan. The first wave of the occupation-based annual examinations was carried out from June 2008 to February 2009 and included 821 participants (550 men and 271 women ; age range, 20–60 years). The participants were followed up every year. Male and female workers aged 20 years or older were also newly recruited annually. For dietary intake and physical activity assessment, the participants were followed up at an interval of 5 years from the fifth wave.

The study population in the fifth wave survey (2012 to 2013) included 1,398 men and women aged 20 to 63 years who were living in Tokushima Prefecture, Japan. Those who participated in the fifth-wave survey for whom there were incomplete data for soy food intake (n = 12), lipid markers (n = 1), blood pressure (n = 1), drinking habits and/or physical activity (n = 4), and non-fasting blood tests (n=84) were excluded. From the total of 1,299 men and women, 601 participants whose age was under 40 years were excluded because there were only 28 cases of MetS (prevalence rate = 4.7%) in younger participants aged under 40 years in this study. Data of 698 participants were used for the cross-sectional analysis.

For the longitudinal analysis in the present study, those who participated in the fifth-wave survey (baseline) and at least once in the sixth to eleventh-wave surveys (follow-up surveys) were selected : fifth study survey (2012–2013, n = 1,394), sixth study survey (2013–2014, n = 1,432), seventh study survey (2014–2015, n = 1,414), eighth study survey (2015–2016, n = 1,430), ninth study survey (2016–2017, n = 1,455), tenth study survey (2017–2018, n = 1,394), and eleventh study survey (2018–2019, n = 1,373). Of the 698 participants in the cross-sectional analysis, those with MetS at baseline (n=87) were excluded. Those who only participated in the baseline survey (n=84) were also excluded. The remaining 527 participants aged over 40 years of age were included in the analysis (Figure 1).

Dietary assessment

The participants were requested to complete a questionnaire to obtain data on dietary intake. Questions asked about the frequency and amount of soy foods consumed at each meal (how

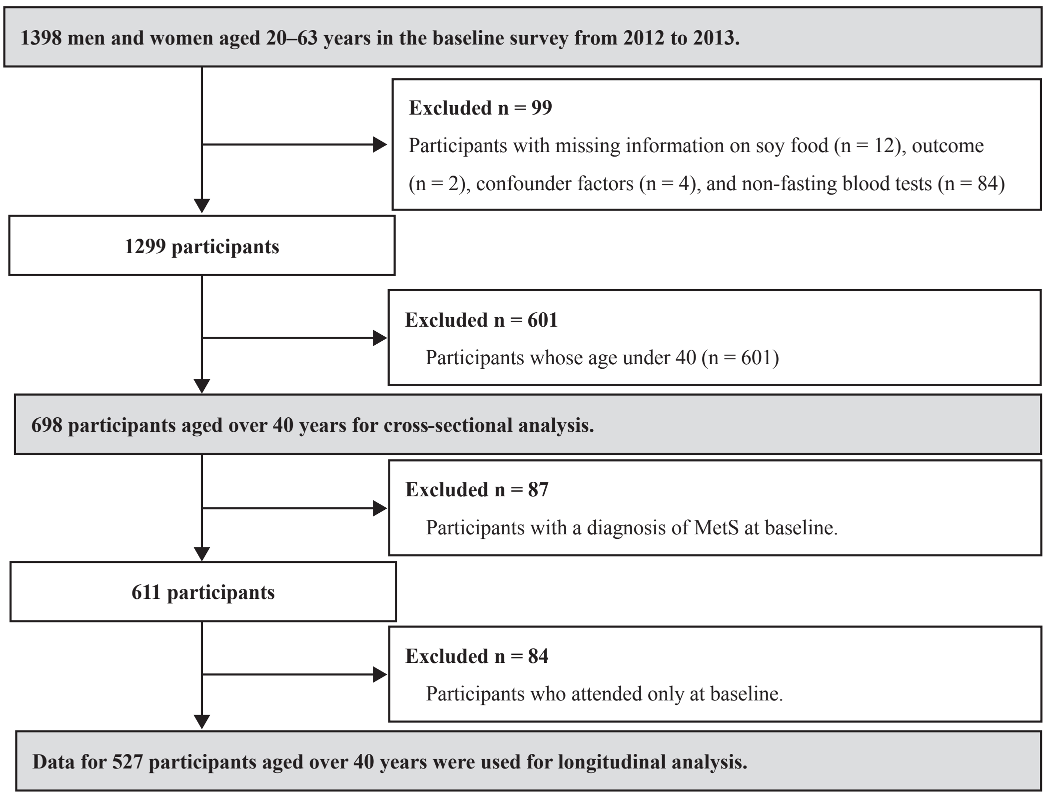

Figure 1. Overview of the participants included in the analysis
Of the 1,398 men and women aged 20-63 years at baseline (2012 to 2013), 99 participants with missing information on lipid markers, blood pressure, drinking habits, physical activity, and non-fasting blood tests were excluded. From the total of 1,299 men and women, 601 participants whose age was under 40 years were excluded because there were few cases of metabolic syndrome in younger participants aged under 40 years in this study. Data for 698 participants were used for the cross-sectional analysis.
In the longitudinal analysis, 87 participants with a diagnosis of metabolic syndrome at baseline were also excluded. Next, 84 participants who attended only at baseline were excluded. The remaining 527 participants aged over 40 years were included in the analysis.

many times and how much is consumed per day, week, month, or year) to calculate the total intake of soy products and soy isoflavones. Soy food consumption was assessed using a semi-quantitative food frequency questionnaire (FFQ) (26) proposed by Nagata *et al*., which was a modification of the questionnaire used in the Takayama study (27) 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 (27). The total soy product intake was calculated as the sum of all 12 soy products.

Regarding the amount of energy intake, participants were asked about meals taken in the past month using "The FFQg ver.3.5" (Kenpakusha Inc., Tokyo, Japan) as an FFQ method for determining the 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 17 food groups (cereals, potatoes, deep yellow vegetables, other vegetables and mushrooms, seaweeds, legumes, fish and shellfish, meats, eggs, dairy products, 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 (28). The frequency and amount of all foods consumed at each meal were asked (how many times and how much are consumed per week). The amount of each food consumed per week was calculated by summing the product of intake frequency and the amount consumed at each meal.

Dietary patterns that consist of a correlation matrix for 17 food groups were assessed using principal component factor analysis. The first principal component was selected on the basis of eigenvalues >1.3, with factor loading of each food group of over 0.40 and interpretability (Supplemental Table 1). Principal component scores were saved for each individual and used as continuous variables. The first principal component was named the healthy pattern because it contained higher factor loading of ten food groups : potatoes and starches, sugars and sweeteners, pulses, other vegetables and mushrooms, deep yellow vegetables, fruits, algae, fish, mollusks and crustaceans, fats and oils, and seasonings and spices. This pattern explained 22.9% of the variance. Scores of the first principal components were saved for each participant and used for analysis.

Anthropometric measurements and diagnosis of metabolic syndrome

Participants were requested to fast overnight for at least 10 hours before blood collection at baseline and follow-up. Data for serum levels of triglycerides (TG) and HDL-cholesterol and for plasma blood glucose levels were obtained during the medical health check-ups in the morning. Waist circumference and systolic and diastolic blood pressure were measured at the same time. The plasma glucose level was determined by a glucose-oxidase method. HDL-C was determined by a direct method. Total cholesterol and triglyceride levels were determined enzymatically. Blood pressure measurements were performed using an appropriately sized cuff. Waist circumference was obtained during medical health check-ups. Each subject completed a self-administered questionnaire covering medical history and use of antidiabetic, antidyslipidemic, and antihypertensive medications, which were confirmed by interviews with the participants.

The diagnosis of MetS was based on the Japanese MetS criteria (29). MetS was defined as central obesity (waist circumferences ≥ 85 cm in men and ≥ 90 cm in women) plus at least two of the following three components : (1) high blood pressure (blood pressure ≥ 130/85 mmHg or taking antihypertensive medication) ; (2) high fasting plasma glucose (fasting plasma glucose ≥ 110 mg/dl or medication for diabetes mellitus or hemoglobin A1c (HbA1c) ≥ 6.0%) ; and (3) abnormal lipid metabolism including HDL-C <40 mg/dl with or without hypertriglyceridemia (serum triglycerides ≥ 150 mg/dl or medication for hyperlipidemia).

Other measurements

Other measurements were obtained at baseline. Body height was measured to the nearest 0.1 cm with participants standing without shoes or sandals, and body weight was measured to the nearest 0.1 kg with subjects wearing lightweight clothing. Body mass index (BMI) was calculated using the following formula : BMI = weight (kg)/[height(m)]^2. Daily values of physical activity (MET-hours/week) were calculated using the International Physical Activity Questionnaire (30). Information on medical history (binary : yes or no), education level (categorical : elementary, junior high and high school, tertiary college, career college and junior college, college, and graduate school or other), drinking habit (categorical : current, former, never), and smoking habit (categorical : current, former, never) was obtained by a self-administered questionnaire. Subjects completed the questionnaire before the physical examination day, and it was checked and collected. Follow-up duration (years) was calculated from the number of years that had elapsed since baseline study participation for each subject.

Statistical analysis

The basic characteristics of the participants by tertile of total soy product intake are shown. Continuous variables are presented as means ± standard deviation (SD) or medians (25th percentile, 75th percentile), and comparisons of mean values were made using one-way ANOVA or the Kruskal-Wallis test. Categorical variables are expressed as numbers (%), and comparisons of proportions were made using the chi-squared test. In post hoc analyses, trend tests of proportions and continuous variables by tertile of total soy product intake were assessed using the Mantel-Haenszel test or the Jonckheere-Terpstra test, respectively.

Multivariable logistic regression analysis was used to calculate the odds ratios (ORs) and 95% confidence intervals (95% CIs) for MetS by tertile of total soy product intake after controlling for the following variables : age and sex-adjusted model, age (continuous, years), and sex (binary : male, female) ; Model 1, age and sex-adjusted model + energy intake (continuous, kcal/day), body mass index (continuous, kg/m^2), physical activity (continuous, MET-hours/week), smoking habit (binary : current, former/never), drinking habit (binary : current, former/never), and education (categorical : elementary, junior high and high school, tertiary college, career college and junior college, college, and graduate school or other). Moreover, to assess the compounding effects of a healthy dietary pattern including total vegetables and fish, mollusks, and crustaceans, the association between total soy product intake and MetS was also calculated after adjustment for the healthy dietary pattern : Model 2 consisting of Model 1 and the healthy dietary pattern (continuous, score).

In the longitudinal analysis, cumulative data obtained during follow-up surveys were analyzed using generalized estimating equations (GEEs). A GEE takes into account the dependency of repeated observations within participants. An additional advantage of a GEE is that missing values can also be used during analysis. Thus, subjects who were lost to follow-up surveys after the early wave examination were also included in the analyses. GEE models were fitted by the GENLIN syntax in SPSS. This procedure corresponds to generalized linear models. In the present analyses, compound symmetry was specified for the correlation structure. GEE analyses were used to estimate the ORs and 95% CIs for MetS in follow-up surveys by tertile of total soy product intake at baseline after controlling for the following variables. The confounding variables that were adjusted in the age and sex-adjusted model were age, sex, and follow-up time (continuous, years). Model 1 consisted of age, energy intake, body mass index, physical activity, smoking habit, drinking habit, and education. Model 2 consisted of the adjustments in Model 1 and adjustment for the healthy dietary pattern.

All statistical analyses were performed using SPSS (IBM Corporation, Tokyo, Japan) version 28.0 for Windows. All statistical tests were based on two-sided probabilities, and all *p*-values <0.05 were considered significant.

RESULTS

Characteristics of the participants

Table 1 lists the characteristics of the participants by tertile of total soy product intake in the cross-sectional analysis. Total soy product intake, age, physical activity, and HDL-cholesterol increased with increasing total soy product intake. In contrast, BMI and waist circumference decreased with increasing total soy product intake. Total energy intake, cereals, meat, confectioneries, beverages, and fat and oil intake decreased, but intakes of potatoes and starches, deep yellow vegetables, other vegetables and mushrooms, algae, pulses, fish and crustaceans, mollusks, fruits, sugars and sweeteners, nuts and seeds, and seasonings and spices were increased (Supplemental Table 2).

In the longitudinal analysis, the cumulative incidence of MetS was 6.2% (180 participants) (Table 2). The mean cumulative follow-up term and cumulative participation were 2.7 ± 2.0 years and 5.5 ± 1.8 times, respectively (Table 2). The characteristics of participants by tertile of total soy product intake in the longitudinal analysis were almost similar to those in the cross-sectional analysis (Table 3 and Supplemental Table 3).

Table 1. Participants characteristics according to total soy products in the cross-sectional analysis (n = 698)[§§]

	Lowest group (n=232)	Moderate group (n=233)	Highest group (n=233)	*p*-value	*p* for trend
Total soy products/1000kcal (g)[†,¶]	25.7 ± 8.5	53.0 ± 8.8	108.1 ± 42.9	<0.001	<0.001
Age (y)[†,¶]	47.6 ± 5.6	48.2 ± 6.0	49.9 ± 6.7	<0.001	<0.001
Gender[‡,‡‡]				0.200	0.407
Men	182 (78.4)	166 (71.2)	175 (75.1)		
Women	50 (21.6)	67 (28.8)	58 (24.9)		
Body mass index (kg/m^2)[†,¶]	23.9 ± 3.3	23.1 ± 2.9	23.3 ± 3.1	0.026	0.037
Physical activity (MET-hours/week)[§,††]	8.0 [1.0 - 18.8]	11.0 [3.3 - 28.3]	12.0 [3.6 - 27.4]	0.003	0.002
Education level[‡,‡‡]				0.240	0.431
Elementary, junior high school, and high school	85 (36.6)	80 (34.3)	66 (28.3)		
Tertiary college, career college, and junior college	37 (15.9)	43 (18.5)	58 (24.9)		
College and graduate school	102 (44.0)	102 (43.8)	103 (44.2)		
Other	8 (3.4)	8 (3.4)	6 (2.6)		
Smoking habit[‡,‡‡]				0.272	0.148
Current	63 (27.2)	51 (21.9)	50 (21.5)		
Former/Never	169 (72.8)	182 (78.1)	183 (78.5)		
Drinking habit[‡,‡‡]				0.435	0.378
Current	122 (52.6)	136 (58.4)	132 (56.7)		
Former/Never	110 (47.4)	97 (41.6)	101 (43.3)		
Medical history[‡,‡‡]					
Hypertension (+)	19 (8.2)	9 (3.9)	15 (6.4)	0.149	0.434
Dyslipidemia (+)	4 (1.7)	5 (2.1)	5 (2.1)	0.932	0.746
T2D (+)	8 (3.4)	5 (2.1)	1 (0.4)	0.066	0.020
Waist circumference (cm)[†,¶]	83.2 ± 9.5	81.1 ± 8.7	81.4 ± 9.0	0.023	0.032
Triglycerides (mg/dL)[†,¶]	113.8 ± 73.4	118.3 ± 112.6	103.4 ± 70.8	0.173	0.127
HDL-cholesterol (mg/dL)[†,¶]	55.3 ± 14.0	56.9 ± 14.4	59.5 ± 15.1	0.006	0.002
LDL-cholesterol (mg/dL)[†,¶]	121.2 ± 28.7	121.8 ± 29.1	119.3 ± 29.1	0.609	0.574
Non-HDL cholesterol (mg/dL)[†,¶]	144.9 ± 32.63	145.6 ± 31.7	141.4 ± 32.1	0.322	0.349
Total cholesterol (mg/dL)[†,¶]	200.2 ± 31.2	202.4 ± 30.2	200.9 ± 31.6	0.722	0.687
Systolic blood pressure (mmHg)[†,¶]	128.7 ± 18.0	126.4 ± 17.0	128.3 ± 21.6	0.352	0.400
Diastolic blood pressure (mmHg)[†,¶]	80.7 ± 12.0	79.0 ± 11.6	78.7 ± 14.3	0.183	0.056
Fasting blood glucose (mg/dL)[†,¶]	92.8 ± 13.4	92.8 ± 11.6	92.2 ± 8.7	0.803	0.932

[†] Mean ± standard deviation [‡] Number (%) [§] Median (25th, 75th percentile)
[¶] The ANOVA test was used to calculate the *p* value and the Jonckheere-Terpstra test was used to calculate the *p* for trend.
[††] The Kruskal-Wallis test was used to calculate the *p* value and the Jonckheere-Terpstra test was used to calculate the *p* for trend.
[‡‡] The chi-square test was used to calculate the *p* value and the Mantel-Haenszel test was used to calculate the *p* for trend.
[§§] Total soy products (g/1000kcal) : Lowest group (tertile 1) : 0 - 39.1680451364088, Moderate group (tertile 2) : 39.1680451364089 - 69.4945352888106, Highest group (tertile 3) : 69.4945352888107 - highest

Table 2. Participation during the follow-up period and the incidences of metabolic syndrome

Follow-up year	Number of participants	Follow-up ratio (%)	Cases of MetS	Incidences of MetS (%)
2012	527	–	–	–
2013	480	(91.1)	32	(6.7)
2014	422	(80.1)	26	(6.2)
2015	409	(77.6)	30	(7.3)
2016	370	(70.2)	20	(5.4)
2017	362	(68.7)	36	(9.9)
2018	333	(63.2)	36	(10.8)
Cumulative number	2,903		180	(6.2)
Mean cumulative follow-up (y) ‡		2.7 ± 2.0		
Mean cumulative participation (times) ‡		5.5 ± 1.8		

‡ Mean ± standard deviation

Table 3. Participants' characteristics according to total soy products at baseline in the longitudinal analysis (baseline n = 527)§§

	Lowest group (n=176)	Moderate group (n=176)	Highest group (n=175)	*p*-value	*p* for trend
Total soy products (g/1000kcal)†, ¶	25.8 ± 8.3	52.5 ± 9.1	108.8 ± 45.4	<0.001	<0.001
Age (y) †, ¶	47.7 ± 5.6	47.7 ± 5.7	49.0 ± 6.6	0.057	0.093
Gender ‡, ‡‡				0.480	0.607
Men	134 (76.1)	124 (70.5)	129 (73.7)		
Women	42 (23.9)	52 (29.5)	46 (26.3)		
Body mass index (kg/m^2) †, ¶	23.2 ± 3.0	22.7 ± 2.6	22.7 ± 2.9	0.201	0.158
Physical activity (METs-min/day?) §, ††	8.0 [1.7 - 18.5]	11.5 [3.7 - 28.3]	11.8 [3.4 - 25.3]	0.038	0.031
Education level ‡, ‡‡				0.110	0.328
Elementary, junior high school, and high school	69 (39.2)	64 (36.4)	49 (28.0)		
Tertiary college, career college, and junior college	28 (15.9)	34 (19.3)	45 (25.7)		
College and graduate school	71 (40.3)	72 (40.9)	78 (44.6)		
Other	8 (4.5)	6 (3.4)	3 (1.7)		
Smoking habit ‡, ‡‡				0.162	0.221
Current	50 (28.4)	35 (19.9)	40 (22.9)		
Former/Never	126 (71.6)	141 (80.1)	135 (77.1)		
Drinking habit ‡, ‡‡				0.179	0.217
Current	85 (48.3)	102 (58.0)	96 (54.9)		
Former/Never	91 (51.7)	74 (42.0)	79 (45.1)		
Medical history ‡, ‡‡					
Hypertension (+)	13 (7.4)	6 (3.4)	10 (5.7)	0.259	0.491
Dyslipidemia (+)	4 (2.3)	4 (2.3)	2 (1.1)	0.670	0.439
Waist circumference (cm)†, ¶	81.3 ± 9.1	79.7 ± 7.8	79.9 ± 8.4	0.161	0.162
Triglycerides (mg/dL)†, ¶	100.1 ± 59.9	105.8 ± 108.1	92.2 ± 54.5	0.262	0.245
HDL-cholesterol (mg/dL)†, ¶	57.7 ± 14.2	58.3 ± 14.1	60.4 ± 15.0	0.198	0.108
LDL-cholesterol (mg/dL)†, ¶	119.8 ± 28.5	122.2 ± 29.5	117.7 ± 29.1	0.345	0.568
Non-HDL cholesterol (mg/dL)†, ¶	79.0 ± 16.4	79.9 ± 16.7	80.8 ± 16.0	0.582	0.217
Total cholesterol (mg/dL)†, ¶	198.8 ± 30.6	202.1 ± 31.6	198.5 ± 31.6	0.484	0.864
Systolic blood pressure (mmHg)†, ¶	126.0 ± 17.3	124.8 ± 17.4	125.2 ± 21.2	0.819	0.272
Diastolic blood pressure (mmHg)†, ¶	79.1 ± 12.1	77.5 ± 11.3	77.0 ± 14.1	0.252	0.034
Fasting blood glucose (mg/dL)†, ¶	90.8 ± 7.8	91.8 ± 7.7	91.5 ± 8.2	0.453	0.605

† Mean ± standard deviation ‡ Number (%) § Median (25th, 75th percentile)
¶ The ANOVA test was used to calculate the *p* value and the Jonckheere-Terpstra test was used to calculate the *p* for trend.
†† The Kruskal-Wallis test was used to calculate the *p* value and the Jonckheere-Terpstra test was used to calculate the *p* for trend.
‡‡ The chi-square test was used to calculate the *p* value and the Mantel-Haenszel test was used to calculate the *p* for trend.
§§ Total soy products (g/1000kcal) : Lowest group (tertile 1) : 0 - 39.0391936895181359, Moderate group (tertile 2) : 39.039193689518136 - 69.770436910396359, Highest group (tertile 3) : 69.77043691039636 - highest

Association between total soy product intake and metabolic syndrome

The ORs for MetS for the highest group (tertile 3) were 0.416 (95% CI : 0.230 - 0.752) and 0.401 (95% CI : 0.199 - 0.809) in the age and sex-adjusted model (p for trend = 0.009) and Model 1 (p for trend = 0.048), respectively. In the analysis with adjustment for the healthy dietary pattern, a similar attenuated association between total soy product intake and MetS was found. In addition, the association between total soy product intake and each MetS component was assessed. It was found that the highest total soy product intake had a significantly lower OR for each MetS component, including high waist circumference and high lipid markers, compared with the lowest group in the age and sex-adjusted model (Table 4).

Table 5 shows the longitudinal associations between total soy product intake and cumulative ORs for MetS and MetS components. However, those inverse associations between total soy product intake and MetS disappeared in the longitudinal analysis.

DISCUSSION

The present cross-sectional study showed that total soy product intake had an inverse association with the risk of MetS, and the association was essentially similar after adjusting for a healthy dietary pattern (Table 4). However, there was no significant association between total soy product intake and MetS in the longitudinal analysis (Table 5).

Although a few previous reports have shown an association between soy products or their nutrients such as soy protein and the incidence of MetS, consistent associations have not been obtained (23, 24). It has been reported that there were no associations between soy protein intake and MetS and/or MetS components in 2,811 middle-aged and elderly Chinese men and women in a cross-sectional study (23). In contrast, an inverse association between soy protein intake and MetS was shown in women, but not in men, in a longitudinal study of 5,509 Korean men and women aged 40 years or older (24). In the present study, a significant inverse association between total soy product intake and the prevalence of MetS and/or MetS components was observed (Table 4). However, no significant association was

Table 4. Adjusted odds ratios of Metabolic syndrome according to total soy products in the cross-sectional analysis (n = 698)[†,‡,§§]

	Lowest group (tertile 1)	Moderate group (tertile 2)	Highest group (tertile 3)	p for trend
MetS				
cases / total subjects	40/232	27/233	20/233	
Age and sex-adjusted model[§]	referent	0.667 (0.389 - 1.144)	0.416** (0.230 - 0.752)	0.009
Model 1[¶]	referent	0.760 (0.407 - 1.419)	0.401* (0.199 - 0.809)	0.048
Model 2[††]	referent	0.774 (0.406 - 1.475)	0.413* (0.196 - 0.871)	0.090
High waist circumference				
cases / total subjects	96/232	71/233	75/233	
Age and sex-adjusted model[§]	referent	0.600** (0.408 - 0.883)	0.608* (0.413 - 0.897)	0.012
Model 1[¶]	referent	0.848 (0.447 - 1.608)	0.796 (0.417 - 1.519)	0.492
Model 2[††]	referent	0.871 (0.450 - 1.688)	0.830 (0.413 - 1.669)	0.602
High lipid markers				
cases / total subjects	67/232	63/233	50/233	
Age and sex-adjusted model[§]	referent	0.895 (0.596 - 1.345)	0.630* (0.410 - 0.968)	0.279
Model 1[¶]	referent	1.183 (0.754 - 1.856)	0.722 (0.449 - 1.163)	0.761
Model 2[††]	referent	1.169 (0.735 - 1.860)	0.708 (0.424 - 1.183)	0.812
High Blood pressure				
cases / total subjects	126/232	117/233	112/233	
Age and sex-adjusted model[§]	referent	0.809 (0.558 - 1.172)	0.666 (0.457 - 0.971)	0.151
Model 1[¶]	referent	0.992 (0.649 - 1.515)	0.757 (0.491 - 1.166)	0.467
Model 2[††]	referent	0.972 (0.631 - 1.499)	0.729 (0.457 - 1.162)	0.456
High fasting plasma glucose				
cases / total subjects	14/232	11/233	11/233	
Age and sex-adjusted model[§]	referent	0.731 (0.323 - 1.653)	0.648 (0.282 - 1.489)	0.363
Model 1[¶]	referent	0.847 (0.367 - 1.956)	0.696 (0.294 - 1.652)	0.478
Model 2[††]	referent	0.778 (0.328 - 1.848)	0.616 (0.246 - 1.540)	0.361

[†] Adjusted odd ratio (95% confidence interval)
[‡] Logistic regressions were used to calculate the p-value.
[§] Age and sex-adjusted model : age (continuous, years) and sex (binary ; men, women)
[¶] Model 1 : Age and sex adjusted model + energy intake (continuous, kcal/day), body mass index (continuous, kg/m^2), physical activity (continuous, MET-hours/week), smoking habit (binary ; current, former/never), drinking habit (binary ; current, former/never) and education (categorical ; elementary, junior high and high school, tertiary college, career college and junior college, college, and graduate school or other).
[††] Model 2 : Model 1 + healthy dietary pattern (continuous, score)
[‡‡] Total soy products (g/1000kcal) : Lowest group (tertile 1) : 0 - 39.1680451364088, Moderate group (tertile 2) : 39.1680451364089 - 69.4945352888106, Highest group (tertile 3) : 69.4945352888107 – highest
* p <0.05 vs T1, ** p < 0.01 vs Tertile 1

Table 5. Adjusted odds ratios of Metabolic syndrome according to total soy products in the longitudinal analysis (baseline n = 527, cumurative n = 2903)†,‡,§§

	Lowest group (tertile 1)	Moderate group (tertile 2)	Highest group (tertile 3)	*p* for trend
MetS				
cases / total subjects	73/988	45/962	62/953	
Age and sex-adjusted model§	referent	0.636 (0.333 - 1.212)	0.812 (0.458 - 1.439)	0.579
Model 1¶	referent	1.052 (0.563 - 1.969)	0.828 (0.410 - 1.673)	0.818
Model 2††	referent	1.030 (0.528 - 2.010)	0.817 (0.398 - 1.677)	0.847
High waist circumference				
cases / total subjects	354/988	262/962	303/953	
Age and sex-adjusted model§	referent	0.653* (0.429 - 0.995)	0.836 (0.561 - 1.247)	0.538
Model 1¶	referent	0.939 (0.555 - 1.587)	1.104 (0.662 - 1.839)	0.644
Model 2††	referent	1.026 (0.588 - 1.791)	1.272 (0.726 - 2.228)	0.352
High lipid markers				
cases / total subjects	179/988	140/962	151/953	
Age and sex-adjusted model§	referent	0.837 (0.538 - 1.301)	0.833 (0.533 - 1.302)	0.244
Model 1¶	referent	0.989 (0.623 - 1.569)	0.906 (0.574 - 1.431)	0.657
Model 2††	referent	0.974 (0.615 - 1.545)	0.883 (0.560 - 1.395)	0.578
High Blood pressure				
cases / total subjects	518/988	446/962	459/953	
Age and sex-adjusted model§	referent	0.849 (0.600 - 1.201)	0.803 (0.572 - 1.126)	0.227
Model 1¶	referent	0.930 (0.649 - 1.331)	0.857 (0.604 - 1.215)	0.388
Model 2††	referent	0.884 (0.606 - 1.288)	0.945 (0.653 - 1.367)	0.520
High fasting plasma glucose				
cases / total subjects	36/988	47/962	42/953	
Age and sex-adjusted model§	referent	1.212 (0.491 - 2.990)	1.102 (0.442 - 2.748)	0.881
Model 1¶	referent	1.119 (0.450 - 2.781)	1.284 (0.521 - 3.167)	0.582
Model 2††	referent	1.027 (0.403 - 2.615)	0.899 (0.324 - 2.495)	0.809

† Cumulative adjusted odd ratio (95% confidence interval)
‡ Cumulative data during follow-up surveys were analyzed using generalized estimating equations. Generalized estimating equations were used to calculate the *p*-value.
§ Age and sex-adjusted model : age (continuous, years), sex (binary ; men, women) and follow-up year (continuous, years)
¶ Model 1 : Age and sex adjusted model + energy intake (continuous, kcal/day), body mass index (continuous, kg/m^2), physical activity (continuous, MET-hours/week), smoking habit (binary ; current, former/never), drinking habit (binary ; current, former/never) and education (categorical ; elementary, junior high and high school, tertiary college, career college and junior college, college, and graduate school or other).
†† Model 2 : Model 1 + healthy dietary pattern (continuous, score)
‡‡ Total soy products (g/1000kcal) : Lowest group (tertile 1) : 0 - 39.0391936895181359, Moderate group (tertile 2) : 39.039193689518136 - 69.770436910396359, Highest group (tertile 3) : 69.77043691039636 – highest
* *p* <0.05 vs Tertile 1

observed between total soy product intake and the incidence of MetS and/or MetS components in the longitudinal analysis (Table 5). The difference in the results between the present and previous studies means that, even in Asians who consume large amounts of soy products, the effect of soy product intake on MetS might differ depending on factors such as age, sex, and food culture. However, since these results alone cannot establish an association between soy product intake and MetS, further long-term and large-scale observational studies are needed.

This cross-sectional analysis showed a significant negative association between high intake of total soy products and the prevalence of MetS. In contrast, although no significant differences in the components of MetS were observed in the highest group, the risk tended to be lower (Table 4). This suggests that the various nutrients and functional components contained in soy products may affect abdominal obesity, lipid metabolism disorders, and high blood pressure, thus reducing the risk of MetS. However, it should be noted that this effect was only observed in a cross-sectional analysis and disappeared in a six-year longitudinal analysis. To evaluate the long-term effects of soy product intake on MetS, further research is needed to verify the impact of high soy product intake on MetS and its component factors over a longer period.

Although total soy product intake might have had a favorable effect on MetS only in the cross-sectional analysis (Table 4), there was a U-shaped association in the longitudinal analysis (Table 5). The beneficial effects of soy intake on outcomes related to MetS such as obesity, lipid metabolism, and blood glucose levels have been shown previously (12-18). While the mechanism of the U-shaped association is unclear, the relationship between soy product intake and various diseases (e.g. MetS (24), insulin resistance (31), type 2 diabetes mellitus (32), and/or CVD (33)) shows a U-shape. The inconsistency in the results between the cross-sectional and longitudinal analyses in the present study might be due to differences in the number of participants between the cross-sectional (n = 698) and longitudinal (n = 527) analyses and the low cumulative incidence of MetS (cumulative case number = 180, 6.2%) during the follow-up period of 6 years. Therefore, longer-term and larger numbers of observational studies would enable us to understand the associations between the intakes of various soy products and the incidence of MetS.

The present study has several limitations. First, the results seen in the present cross-sectional analyses are insufficient to demonstrate a cause-and-effect relationship between total soy product intake and the prevalence of MetS. The present cross-sectional analysis is only useful for establishing preliminary evidence suggesting such an association, but interpretation requires caution. Second, the participants in the present study lived in a small residential area and included only Japanese workers, so the findings might not be generalizable to other populations. Third, the number of MetS cases in the longitudinal study was small, with a cumulative incident case number of 166 (5.9%). Fourth, the occupations of the participants were not assessed, and therefore, the effects of specific occupations on MetS could not be examined.

In conclusion, the results of the present study suggest that the effect of soy product intake on decreasing MetS risk might be limited. Longer-term, larger-scale studies are needed to clarify the effect of soy product intake on MetS.

CONFLICT OF INTEREST

All authors state that they have no conflicts of interest.

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AUTHOR CONTRIBUTIONS

All authors (M. N., K. Y., B. T. T., A. N., A. H., N. A., Y. S., Y. B., T. I., T. M., A. T., Y. K., M. F., and T. S.) conceptualized the study and collected the data. Measurements and data analysis were performed by M. N., K. Y., and B. T. T., T. S. and A. N. provided nutritional advice regarding the interpretation of the data. M. N. drafted the manuscript with the assistance of S. T. All authors read and approved the final version of the manuscript.

ETHICAL STANDARDS OF DISCLOSURE

The study was conducted according to the ethical standards of the Declaration of Helsinki, and the protocol was approved by the institutional review board of Tokushima University Hospital (Ethical approval number : 662). Written consent was obtained from all participants.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Supplemental Table 1. Factor loading matrix for healthy dietary patterns

Food groups	Value of factor loading
Cereals	0.234
Potatoes and strarches	**0.577**
Sugars and sweeteners	**0.545**
Pulses	**0.613**
Nuts and seeds	0.192
Other vegetables and mushrooms	**0.737**
Deep yellow vegetables	**0.703**
Fruits	**0.480**
Algae	**0.619**
Fish, mullusks and crustaceans	**0.607**
Meat	0.383
Eggs	0.347
Milk and milk products	0.274
Fats and oils	**0.412**
Confectioneries	0.087
Beverages	-0.079
Seasonings and spices	**0.508**
Eigen value	3.9
Contribution rate, %	22.9

The healthy dietary pattern was first principal components among present population, and was selected on the basis of eigenvalues >1.3 and interpretability. The cut-off value of factor loading for food groups was greater than 0.4. Principal components scores were saved for each individual.

Supplemental Table 2. Dietary characteristics according to total soy products in cross-sectional analysis (n = 698) [†,¶,§]

	Lowest group (n=232)			Moderate group (n=233)			Highest group (n=233)			*p*-value	*p* for trend
Energy (kcal/day)	1829.7	±	428.8	1817.2	±	401.3	1740.2	±	417.1	0.043	0.019
Healthy dietary pattern (score)	-0.216	±	0.920	0.174	±	0.909	0.387	±	1.102	<0.001	<0.001
Cereals (g/day)	399.8	±	124.4	382.6	±	97.9	367.3	±	114.0	0.008	0.009
Potatoes and starches (g/day)	18.5	±	19.0	23.6	±	20.3	23.6	±	22.2	0.009	0.005
Deep yellow vegetables (g/day)	45.1	±	32.1	54.3	±	34.5	59.2	±	36.7	<0.001	<0.001
Other vegetables and mushrooms (g/day)	77.4	±	55.4	91.7	±	48.7	101.4	±	60.3	<0.001	<0.001
Algae (g/day)	2.3	±	2.2	3.1	±	2.4	3.9	±	2.9	<0.001	<0.001
Pulses (g/day)	26.2	±	20.0	40.9	±	23.0	60.8	±	39.6	<0.001	<0.001
Fish, mollusks, and crustaceans (g/day)	48.1	±	32.8	56.1	±	35.0	60.5	±	40.1	0.001	<0.001
Meat (g/day)	84.0	±	45.5	78.3	±	40.6	70.5	±	42.1	0.003	0.001
Eggs (g/day)	26.3	±	16.6	27.5	±	16.6	28.0	±	18.3	0.539	0.328
Milk and milk products (g/day)	100.9	±	100.1	101.5	±	95.8	105.6	±	92.1	0.850	0.341
Fruits (g/day)	42.3	±	50.7	53.0	±	50.0	63.6	±	62.7	<0.001	<0.001
Confectioneries (g/day)	68.3	±	51.2	62.7	±	44.9	52.0	±	39.6	<0.001	<0.001
Beverages (g/day)	255.3	±	230.1	228.5	±	209.0	198.7	±	183.7	0.014	0.007
Sugars and sweeteners (g/day)	5.2	±	5.3	5.8	±	4.5	5.6	±	4.2	0.385	0.011
Nuts and seeds (g/day)	1.9	±	3.3	2.1	±	3.1	3.0	±	4.0	0.002	<0.001
Fats and oils (g/day)	13.0	±	6.7	13.8	±	7.0	12.1	±	7.3	0.037	0.037
Seasonings and spices (g/day)	20.1	±	9.8	24.4	±	10.6	24.8	±	10.6	<0.001	<0.001

† Mean ± standard deviation

¶ The ANOVA test was used to calculate the *p* value and the Jonckheere-Terpstra test was used to calculate the *p* for trend.

§§ Total soy products (g/1000kcal) : Lowest group (tertile 1) : 0 - 39.1680451364088, Moderate group (tertile 2) : 39.1680451364089 - 69.4945352888106, Highest group (tertile 3) : 69.4945352888107 - highest

Supplemental Table 3. Baseline dietary characteristics according to total soy products in longitudinal analysis (n = 527) †,¶,§

	Lowest group (n=176)			Moderate group (n=176)			Highest group (n=175)			*p*-value	*p* for trend
Energy (kcal/day)	1816.1	±	420.7	1798.8	±	388.4	1751.5	±	429.9	0.318	0.118
Healthy dietary pattern (score)	-0.226	±	0.895	0.120	±	0.902	0.394	±	1.106	<0.001	<0.001
Cereals (g/day)	393.0	±	123.6	378.5	±	96.5	368.0	±	115.2	0.113	0.090
Potatoes and starches (g/day)	18.3	±	18.8	23.6	±	20.1	24.4	±	23.0	0.011	0.005
Deep yellow vegetables (g/day)	45.9	±	31.6	53.7	±	34.6	60.0	±	37.8	0.001	<0.001
Other vegetables and mushrooms (g/day)	78.3	±	55.6	90.3	±	47.2	102.4	±	60.6	<0.001	<0.001
Algae (g/day)	2.1	±	2.0	3.0	±	2.3	4.0	±	3.1	<0.001	<0.001
Pulses (g/day)	26.0	±	20.6	40.2	±	23.0	58.2	±	34.8	<0.001	<0.001
Fish, mollusks, and crustaceans (g/day)	47.6	±	32.7	53.3	±	32.9	58.5	±	38.9	0.014	0.004
Meat (g/day)	79.4	±	41.1	77.3	±	41.8	72.5	±	43.2	0.289	0.086
Eggs (g/day)	27.4	±	16.9	28.1	±	17.0	27.1	±	16.7	0.841	0.979
Milk and milk products (g/day)	103.8	±	101.3	102.8	±	93.1	103.7	±	94.8	0.994	0.955
Fruits (g/day)	40.7	±	47.3	51.8	±	50.0	62.1	±	62.2	0.001	<0.001
Confectioneries (g/day)	70.2	±	53.7	62.9	±	45.3	54.8	±	41.2	0.009	0.007
Beverages (g/day)	247.9	±	232.3	226.0	±	212.3	198.5	±	189.3	0.093	0.038
Sugars and sweeteners (g/day)	5.5	±	5.6	5.5	±	4.1	5.6	±	4.1	0.946	0.078
Nuts and seeds (g/day)	2.1	±	3.6	2.2	±	3.3	3.1	±	4.3	0.013	0.003
Fats and oils (g/day)	13.2	±	6.5	13.6	±	7.0	12.8	±	7.1	0.567	0.278
Seasonings and spices (g/day)	19.3	±	9.1	23.6	±	10.0	25.0	±	10.4	<0.001	<0.001

† Mean ± standard deviation
¶ The ANOVA test was used to calculate the *p* value and the Jonckheere-Terpstra test was used to calculate the *p* for trend.
§§ Total soy products (g/1000kcal) : Lowest group (tertile 1) : 0 - 39.0391936895181359, Moderate group (tertile 2) : 39.039193689518136 - 69.770436910396359, Highest group (tertile 3) : 69.77043691039636 - highest