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Inverse association between soya food consumption and insulin resistance in Japanese adults

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Abstract
Objective: The purpose of the present study was to examine the association between soya food consumption and insulin resistance using baseline data of the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study in Tokushima, Japan.
Design: This cross-sectional study included 1274 subjects, aged 34–70 years at baseline, living in Tokushima Prefecture between 2008 and 2013. Fasting blood samples were collected and information on lifestyle characteristics including soya food intake and medical history were obtained using a structured self-administered questionnaire. The homeostasis model assessment of insulin resistance (HOMA-IR) was measured and those with HOMA-IR $\geq 2{\cdot}5$ were defined as having insulin resistance. Multiple logistic regression models were used to analyse the association between soya product intake and the prevalence of insulin resistance.
Setting: Rural communities located in Tokushima Prefecture, Japan, between 2008 and 2013.
Subjects: A total of 1148 adults (565 men and 583 women), aged 34–70 years.
Results: The frequency of intake of miso soup, total non-fried soya products and total soya products showed significant inverse dose–response relationships with insulin resistance, after adjustments for potential confounders. When soya product intake was calculated as soya protein and isoflavone, the odds ratios of insulin resistance decreased significantly as the estimated intake of soya protein increased. Furthermore, significant inverse dose–response relationships were observed for total non-fried soya products and total soya products, after adjustment for total vegetable or total fibre consumption.
Conclusions: The present results indicate that the intake of soya products and non-fried soya products is associated with reduced insulin resistance in the Japanese population.

Keywords
HOMA-IR
Soya product intake
Soya isoflavone
Cross-sectional study

Type 2 diabetes is associated with severe complications including retinopathy, nephropathy, neuropathy, stroke and CVD, and has become a worldwide concern for public health. The number of patients with diabetes worldwide has been estimated to increase from 171 million in 2000 to 366 million by the year 2030[1]. An increased incidence rate of type 2 diabetes has also been reported in both adults and children during the past several decades[2,3].

Diabetes is characterized by a hyperglycaemic condition due to insulin hyposecretion or insulin resistance at target organs, including adipose tissue, liver and muscle. Insulin resistance has been aetiologically linked to a pro-inflammatory state[4]. Inflammatory pathways in insulin resistance can be initiated by extracellular mediators such as cytokines and NEFA, or by intracellular stresses such as the excessive production of reactive oxygen species[5,6].

Soyabean is a member of the legume family and is a part of the traditional Asian diet. Soyabean and soya products are rich sources of various nutrients such as plant protein, fibre, vitamins, minerals and phyto-oestrogens (isoflavones)[7].

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Isoflavones may exert beneficial effects on glucose homeostasis because they structurally resemble oestradiol. Previous experimental studies have reported that soyabean phytochemical extracts inhibit glucose uptake in the intestine[8] and isoflavones have been shown to directly stimulate insulin production in pancreatic islet β cells through the cyclic adenosine monophosphate pathway[9]. Furthermore, the administration of soya protein and isoflavones led to increased insulin production, improved glucose metabolism[10] and lower insulin requirements[11] in animals.

An inverse association between soya food intake and type 2 diabetes has been reported in several, but not all human studies. A diet with soyanuts[12] and supplements with soya protein, fibre, isoflavone and other soya products improved glucose homeostasis in patients with type 2 diabetes[13,14]. An inverse association between soya food intake and the prevalence of glycosuria was also reported in postmenopausal non-obese Chinese women[15]. Furthermore, a recent prospective study in Japan showed that higher intake of soya products and isoflavones was associated with a decreased odds ratio of diabetes among overweight or postmenopausal women[16]. The consumption of some soya foods was inversely associated with the risk of type 2 diabetes among Asians in two prospective studies[17,18]. On the other hand, soya intake was positively associated with the risk of diabetes in another cohort study in Hawaii[19].

To date, no studies have examined the association between soya intake and insulin resistance in Japan. Therefore, we investigated the association between soya product intake and insulin resistance levels in the Japanese population.

Methods

Study population

The present study population included participants in the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study, which intends to examine associations between lifestyle and genetic factors and their interactions with lifestyle-related diseases. Details of the survey method have been reported elsewhere[20]. The study population consisted of two groups. The first group (group 1) comprised 577 men and women who had attended the Tokushima Prefectural General Health Check-up Center between 23 January 2008 and 24 November 2011 and agreed to participate in the J-MICC Study (response rate = 14·8 %). The second group (group 2) consisted of 697 men and women living in Tokushima city. We distributed approximately 98 700 leaflets explaining the objective and the method of the J-MICC Study all over Tokushima city (total population = 264 500) from July 2012 to February 2013. These 697 individuals read the leaflet and attended the health check-ups performed by our research team between 25 July 2012 and 27 February 2013. From the total of 1274 men and women (groups 1 + 2) aged 34–70 years, we excluded individuals with a previous history of stroke (n 14), IHD (n 29), medical history of or medical treatment for diabetes (n 68), those whose data on the health check-up (n 10) or soya products (n 2) were not available and those whose daily total energy intake was low (<4189 kJ/d) or high (>16 756 kJ/d; n 10)[21]. The remaining 1148 individuals (565 men and 583 women) were used for analysis in the present study (Fig. 1). Participation was essentially voluntary and after explaining the details of the study, we obtained written informed consent from each participant. The study protocol was reviewed and approved by the Ethics Committees of the authors' institutions.

Questionnaires and calculation of the intake of soya protein and soya isoflavone

Study participants were requested to complete a structured self-administered questionnaire, including questions on physical activity during leisure time, frequency of intake of foods and beverages, smoking and drinking habits, and current and previous history of diseases.

Participants answered a validated, short FFQ on their dietary habits, which asked how often they had consumed forty-seven items of food/recipes and beverages over the past year[22–25]. The questionnaire included four items on soya product consumption: miso soup (= 1); tofu (= 2); fermented soyabeans and soyabeans (= 3); and fried tofu mixed with vegetables, fried bean curd and thick deep-fried tofu (hereafter 'deep-fried tofu'; = 4). The frequency of soya product intake was classified into the following eight categories: '3 times/day' (21/week), 'twice/day' (14/week), 'once/day' (7/week), '5–6 times/week' (5·6/week), '3–4 times/week' (3·5/week), '1–2 times/week' (1·4/week), '1–3 times/month' (0·7/week) and 'almost never' (0/week). The total frequency of non-fried soya product intake was calculated as the sum of miso soup, tofu and boiled or fermented soyabeans (1 + 2 + 3). The total frequency of soya product intake was calculated as the sum of miso soup, tofu, boiled or fermented soyabeans and deep-fried tofu (1 + 2 + 3 + 4).

Since the portion size of each soya product was not queried, the intake per meal from four 3 d diet records, which were collected within an interval of 4 months or shorter in a group of twenty-eight participants, was used to calculate the weekly intake of soya products. The portion sizes of miso soup (1), tofu (2), boiled or fermented soyabeans (3) and deep-fried tofu (4) were 9·9 (the amount used as miso), 53·8, 31·7 and 19·5 g/meal, respectively. Total soya protein intake was estimated by summing the soya protein contained in each specific soya food on the basis of the Standard Tables of Food Composition in Japan (Ministry of Education, Culture, Sports, Science and Technology, 2010). Total soya isoflavone intake was estimated by summing the soya isoflavone contained in each soya food according to estimates by the Ministry of Agriculture, Forestry and Fisheries of Japan.

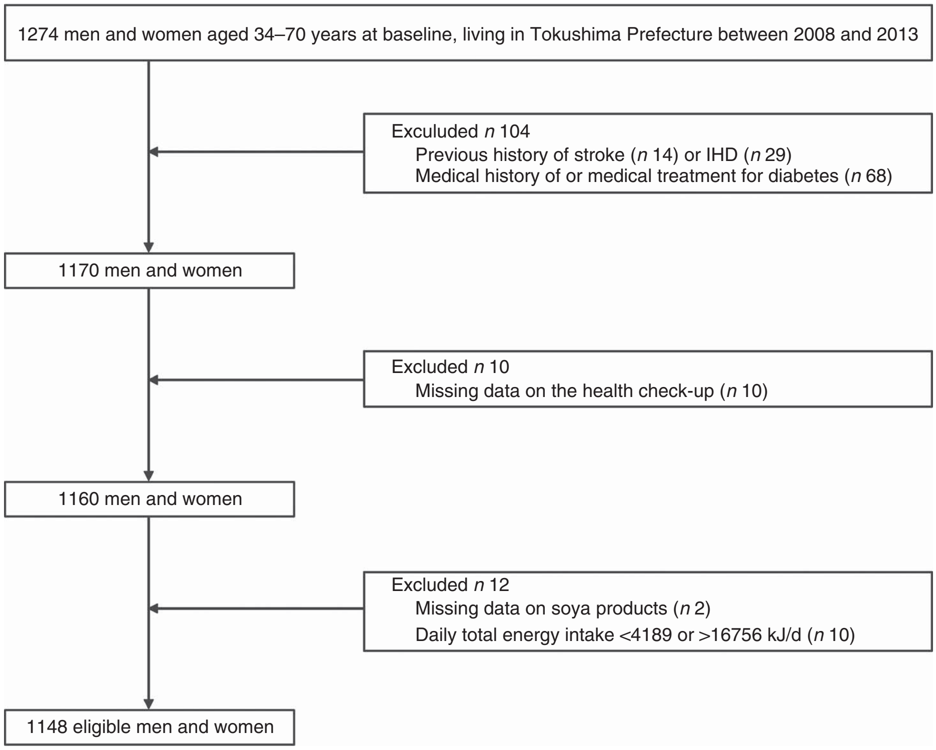

Fig. 1 An overview of the analysed individuals. Among 1274 men and women aged 34–70 years at baseline, living in Tokushima Prefecture between 2008 and 2013, who participated, 1148 eligible individuals (565 men and 583 women) were finally analysed

The total energy intake of each participant was estimated using a program developed at the Department of Public Health, Nagoya City University School of Medicine[22,23]. Physical activity during leisure time was evaluated by multiplying the frequency and level of exercise-related metabolism, which consisted of three steps, summed and expressed as MET-h/week (where MET is metabolic equivalent of task). The three steps of exercise-related metabolism level were light (including walking and golf, 3·4 MET), moderate (including jogging and swimming, 7·0 MET) and heavy exercise (including marathon running and fighting sports, 10·0 MET).

Anthropometric and biochemical measurements

Body height, weight, waist circumference, blood pressure, fasting plasma glucose and serum levels of TAG and HDL cholesterol were obtained at the time of health check-ups. Participants were requested not to eat after 20.00 hours, and received a medical check-up from 08.00 to 11.30 hours the following day. Serum insulin was measured using a chemiluminescence immunoassay at BML Inc. (Tokyo, Japan). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following equation: fasting insulin (mU/l) × fasting plasma glucose (g/dl)/405. Insulin resistance was defined as HOMA-IR $\geq$ 2·5.

Statistical analysis

Continuous variables were expressed as mean and standard deviation, whereas those with skewed distribution were expressed as median and 25th–75th percentile. The one-way ANOVA, Kruskal–Wallis test or χ^2 test was used to determine significant differences between the characteristics of participants according to total soya products consumption. The associations of soya food consumption with the prevalence of insulin resistance were examined using multiple logistic regression analysis, after adjustment for gender, age (continuous), recruitment (binary), family history of type 2 diabetes mellitus (without a family history, unclear and with a family history) in father and mother, total energy intake (quartiles), physical activity (quartiles), smoking (current, no and ex-smokers) and drinking habits (current drinkers and others) in model 1, and additionally for BMI (continuous) in model 2. All multivariate models were further adjusted for total vegetable intake (quartiles) or total fibre intake (quartiles). Furthermore, in multiple logistic regression analysis, we adjusted for menopause status (men, premenopausal women, perimenopausal women and postmenopausal woman) in place of gender. The consumption of miso soup, tofu, total non-fried soya products and total soya products was divided into quartiles, with the first quartile being defined as the reference. Dummy variables were created for categorical variables and those except for reference categories were included in the models. Odds ratios and 95 % profile likelihood confidence intervals were calculated. We conducted tests for trend using the median value of each quartile for the consumption of each soya food and the likelihood ratio test in logistic models.

All statistical tests were based on two-sided probabilities and performed using the SAS statistical software package version 8·2. All P values $< 0·05$ were considered significant[26].

Results

Characteristics of the participants

The total number of participants was 1148 (565 men and 583 women). The mean age was 52·6 (SD 9·9) years in men and 52·0 (SD 9·8) years in women. Table 1 shows the characteristics of the participants according to the frequency of total soya product intake. Age, physical activity, serum levels of HDL cholesterol and total energy intake increased as the consumption of total soya products (1 + 2 + 3 + 4) increased. On the other hand, fasting insulin, HOMA-IR and the proportion of current smokers decreased with increasing total soya product intake. Table 1 also shows the estimated intake of soya protein and isoflavone, presented for two types of soya products (1 + 2 + 3 and 1 + 2 + 3 + 4), according to frequency of total soya product intake.

Associations of the intake of each soya product with insulin resistance

Gender-, age- and multivariate-adjusted associations between the consumption of each soya product and insulin resistance are presented in Table 2. After adjustments for age, gender, recruitment, family history of type 2 diabetes mellitus, total energy intake, physical activity, and smoking and drinking habits (model 1), the OR of insulin resistance decreased significantly as the consumption of miso soup, total non-fried soya products (1 + 2 + 3) and total soya products (1 + 2 + 3 + 4) increased (P for trend <0·05). On the other hand, the association between the intake of tofu and insulin resistance was rather U-shaped, although the P for trend was <0·05. To assess whether the association between soya product intake and insulin resistance was confounded or mediated by obesity, an analysis was performed with an additional adjustment for BMI (model 2). The relationships of miso soup, total non-fried soya products (1 + 2 + 3) and total soya products (1 + 2 + 3 + 4) with insulin resistance remained significant (Table 2, Fig. 2(a)).

Associations of the estimated intake of soya protein and soya isoflavone with insulin resistance

Table 3 shows the gender-, age-, and multivariate-adjusted associations between the estimated intake of soya protein and soya isoflavone from non-fried soya products (1 + 2 + 3) and total soya products (1 + 2 + 3 + 4) with insulin resistance. After adjustments for age, gender, recruitment, family history of type 2 diabetes mellitus, total energy intake, physical activity, and smoking and drinking habits (model 1), the OR of insulin resistance decreased significantly as the estimated intake of soya protein from non-fried soya products (1 + 2 + 3) and total soya products (1 + 2 + 3 + 4), and isoflavone from total soya products (1 + 2 + 3 + 4), increased (P for trend <0·05). On the other hand, the OR was lowest in the third quartile and the association between the intake of isoflavone contained in non-fried soya products (1 + 2 + 3) and insulin resistance was U-shaped, although the P for trend was <0·05. After an additional adjustment for BMI (model 2), the associations between the intake of soya protein from non-fried soya products (1 + 2 + 3) and total soya products (1 + 2 + 3 + 4) with insulin resistance were significant (Fig. 2(b)).

To assess whether the associations between the intake of soya products and insulin resistance were confounded by other factors, menopausal status, total vegetable intake or total fibre intake was further adjusted (data not shown). After adjustment for menopausal status, the results were essentially similar. When total vegetable intake was adjusted, the inverse association remained significant for miso soup, total non-fried soya products and total soya products. On the other hand, after adjustment for total fibre intake, the associations were significant for total non-fried soya product and total soya product intake, regardless of adjustment for BMI.

Discussion

In the present study we showed that a higher frequency of consumption of total non-fried soya products and total soya products was associated with reduced OR of insulin resistance among a Japanese population. When soya product intake was calculated as soya protein and soya isoflavone, the associations were slightly attenuated.

The association between the high intake of soya products and decreased OR of insulin resistance observed in the present study was not unexpected. The consumption of soya foods (tofu and other soya products) was previously associated with a significantly reduced prevalence of glycosuria in 39 385 Chinese women aged 40–70 years without diabetes, especially postmenopausal women with BMI < 25 kg/m^2[15]. Nanri *et al.* reported a significant correlation between soya products and daidzein intake and a reduced cumulative incidence of type 2 diabetes among women with BMI > 25 kg/m^2 and postmenopausal women[16]. In a prospective study in China, Villegas *et al.* reported that the consumption of legumes and soya foods was associated with a decreased risk of type 2 diabetes in 64 227 women aged 40–70 years[17]. Mueller *et al.* also observed that while unsweetened soya product intake was protective against diabetes, no significant correlation between the intake of soya-derived components and insulin resistance was observed in 43 176 Chinese Singaporeans[18]. On the other hand, higher soya food intake was associated with a slightly elevated diabetes risk in three ethnic groups in a recent cohort study performed in the USA, and this increased risk was limited to overweight and obese subjects[19]. Some

Table 1 Characteristics of the participants according to intake frequency of total soya products; 565 men and 583 women aged 34–70 years baseline, living in Tokushima Prefecture between 2008 and 2013, Japan Multi-Institutional Collaborative Cohort (J-MICC) Study

	Q1 (*n* 312)		Q2 (*n* 282)		Q3 (*n* 280)		Q4 (*n* 274)		
	n, mean or median	%, SD or P25–P75	*n*, mean or median	%, SD or P25–P75	*n*, mean or median	%, SD or P25–P75	*n*, mean or median	%, SD or P25–P75	*P*
Sex*									
Men	152	48·7	148	52·5	146	52·1	119	43·4	0·12
Women	160	51·3	134	47·5	134	47·9	155	56·6	
Age (years)†	50·5	9·6	50·6	9·9	52·9	9·4	55·7	9·6	<0·001
BMI (kg/m^2)†	23·5	3·6	23·1	3·3	23·1	3·4	23·0	3·3	0·22
Physical activity (MET-h/week)‡	3·8	0·40–17·9	4·0	0·40–16·4	7·7	1·2–18·4	12·6	3·0–30·6	<0·001
Waist circumference (cm)†	82·8	10·4	82·0	9·6	82·1	10·6	81·4	9·2	0·42
Systolic blood pressure (mmHg)†	124·1	18·7	122·8	18·6	123·4	18·4	124·7	17·8	0·63
Diastolic blood pressure (mmHg)†	75·6	12·6	74·8	12·5	74·2	12·2	75·0	11·2	0·57
TAG (mg/dl)‡	91	64·5–130	87	60·0–123	87	63·0–122	80·5	57·0–126	0·30
HDL cholesterol (mg/dl)†	58·4	15·7	60·2	14·9	58·8	14·7	62·8	17·4	0·003
Fasting plasma glucose (mg/dl)†	92·9	12·7	94·5	15·1	94·6	10·7	93·4	9·7	0·25
Fasting insulin (mU/l)‡	5·2	3·8–7·9	5·0	3·5–7·2	5·0	3·5–7·6	4·3	3·1–5·9	<0·001
HOMA-IR‡	1·2	0·84–1·8	1·1	0·76–1·8	1·2	0·78–1·9	0·96	0·69–1·4	<0·001
Place of recruitment*									
Tokushima Prefectural General Health Check-up Center	122	39·1	133	47·2	139	49·6	123	44·9	0·06
Western area in Tokushima Prefecture	190	60·9	149	52·8	141	50·4	151	55·1	
Father's history of type 2 diabetes mellitus*									
Without a family history	210	67·3	186	66·0	197	70·4	202	73·7	0·11
Unclear	60	19·2	52	18·4	35	12·5	41	15·0	
With a family history	42	13·5	44	15·6	48	17·1	31	11·3	
Mother's history of type 2 diabetes mellitus*									
Without a family history	239	76·6	212	75·2	223	79·6	209	76·3	0·84
Unclear	41	13·1	38	13·5	27	9·6	34	12·4	
With a family history	32	10·3	32	11·4	30	10·7	31	11·3	
Smoking habit*									
Current	70	22·4	49	17·4	44	15·7	27	9·9	0·002
Past	67	21·5	76	27·0	81	28·9	67	24·5	
Never	175	56·1	157	55·7	155	55·4	180	65·7	
Drinking habit*									
Current	160	51·3	162	57·4	167	59·6	139	50·7	0·16
Past	8	2·6	5	1·8	2	0·7	4	1·5	
Never	144	46·2	115	40·8	111	39·6	131	47·8	
Total energy intake (kJ/d)†	6833	1497	6998	1317	7359	1497	7304	1443	<0·001
Frequency of each soya product intake (times/week)									
(1) Miso soup (times/week)‡	1·4	0·7–1·4	3·5	1·4–3·5	5·6	3·5–7·0	7·0	5·6–7·0	<0·001
(2) Tofu (times/week)‡	0·7	0·7–1·4	1·4	0·7–1·4	1·4	1·4–3·5	3·5	1·4–5·6	<0·001
(3) Boiled or fermented soyabeans (times/week)‡	0·7	0·35–1·1	0·7	0·7–1·4	1·4	0·7–1·4	3·5	1·4–7·0	<0·001
(4) Deep-fried tofu (times/week)‡	0·7	0·0–0·7	0·7	0·7–1·4	0·7	0·7–1·4	1·4	0·7–3·5	<0·001
(1 + 2 + 3) Total non-fried soya products (times/week)‡,§	2·8	2·1–3·5	5·6	4·9–6·3	8·4	7·7–9·1	14·0	11·9–16·8	<0·001
(1 + 2 + 3 + 4) Total soya products (times/week)‡,‖	3·5	2·8–4·2	7·0	6·3–7·0	9·8	9·1–10·5	15·4	13·3–18·2	<0·001
Soya protein consumption (g/week)									
(1 + 2 + 3) Total non-fried soya products calculated on soya protein (g/week)‡,§,¶	7·3	6·1–9·7	13·0	10·4–15·4	18·6	15·6–23·5	36·3	27·6–46·8	<0·001
(1 + 2 + 3 + 4) Total soya products calculated on soya protein (g/week)‡,‖,¶	9·3	7·3–12·8	15·4	12·2–18·2	21·8	18·8–26·1	40·1	32·2–51·1	<0·001
Soya isoflavone consumption (mg/week)									
(1 + 2 + 3) Total non-fried soya products calculated on soya isoflavone (mg/week)‡,§,**	29·6	23·1–39·9	52·2	40·6–62·6	73·3	63·6–84·9	140·9	108·6–201·0	<0·001
(1 + 2 + 3 + 4) Total soya products calculated on soya isoflavone (mg/week)‡,‖,**	34·9	26·1–46·8	58·9	46·4–67·9	83·1	71·2–92·7	154·2	119·2–211·7	<0·001

Q, quartile; MET, metabolic equivalent of task; HOMA-IR, homeostasis model assessment of insulin resistance.
*Values are presented as *n* and %
†Values are presented as mean and SD.
‡Values are presented as median and 25th–75th percentile (P25–P75).
§Total non-fried soya product intake included miso soup, tofu and boiled or fermented soyabeans.
‖Total soya intake included miso soup, tofu, boiled or fermented soyabeans and deep-fried tofu.
¶Total soya product intake was estimated by summing the soya protein of each specific soya food on the basis of the Standard Tables of Food Composition in Japan (Ministry of Education, Culture, Sports, Science and Technology, 2010).
**Total soya product intake was estimated by summing the soya isoflavone of each specific soya food according to estimates of the Ministry of Agriculture, Forestry and Fisheries of Japan.

Table 2 Association between the intake frequency of each soya product and insulin resistance* among 565 men and 583 women aged 34–70 years baseline, living in Tokushima Prefecture between 2008 and 2013, Japan Multi-Institutional Collaborative Cohort (J-MICC) Study

	Intake frequency (times/week)							
	Q1	Q2		Q3		Q4		
	OR	OR	95 % CI	OR	95 % CI	OR	95 % CI	P for trend
Miso soup (times/week)†								
No. of cases/participants	59/394	25/292		41/414		5/48		
Age- and gender-adjusted model‡	1·00	0·45	0·27, 0·74	0·50	0·32, 0·77	0·54	0·18, 1·34	0·014
Model 1§	1·00	0·42	0·25, 0·71	0·44	0·27, 0·69	0·47	0·15, 1·20	0·004
Model 2‖	1·00	0·50	0·27, 0·90	0·46	0·27, 0·79	0·31	0·09, 0·91	0·004
Tofu (times/week)¶								
No. of cases/participants	58/420	50/421		14/220		8/87		
Age- and gender-adjusted model‡	1·00	0·83	0·55, 1·26	0·46	0·24, 0·83	0·63	0·26, 1·33	0·041
Model 1§	1·00	0·91	0·59, 1·40	0·47	0·24, 0·86	0·64	0·26, 1·39	0·046
Model 2‖	1·00	0·88	0·54, 1·45	0·52	0·24, 1·04	0·56	0·21, 1·36	0·071
Total non-fried soya products (times/week)**								
No. of cases/participants	51/321	31/279		28/273		20/275		
Age- and gender-adjusted model‡	1·00	0·57	0·35, 0·93	0·54	0·32, 0·89	0·38	0·22, 0·66	<0·001
Model 1§	1·00	0·54	0·32, 0·89	0·47	0·27, 0·79	0·35	0·19, 0·63	<0·001
Model 2‖	1·00	0·71	0·39, 1·26	0·53	0·28, 0·99	0·37	0·19, 0·72	0·002
Total soya products (times/week)††								
No. of cases/participants	48/312	34/282		28/280		20/274		
Age- and gender-adjusted model‡	1·00	0·68	0·42, 1·10	0·55	0·33, 0·91	0·43	0·24, 0·75	<0·001
Model 1§	1·00	0·63	0·38, 1·04	0·49	0·29, 0·83	0·38	0·21, 0·68	<0·001
Model 2‖	1·00	0·81	0·45, 1·43	0·55	0·29, 1·02	0·37	0·19, 0·73	0·002

Q, quartile.
*Adjusted odds ratios and 95 % profile likelihood confidence intervals.
†Miso soup (times/week): Q1, 0–1·4; Q2, 1·4–3·5; Q3, 3·5–7·0; Q4, > 7·0.
‡Age- and gender-adjusted model: adjusted for age (continuous), gender and recruitment (binary).
§Model 1: adjusted for age (continuous), gender, recruitment (binary), family history of type 2 diabetes mellitus (categorical), total energy intake (categorical), physical activity (categorical), smoking (categorical) and drinking habits (binary).
‖Model 2: adjusted for age (continuous), gender, recruitment (binary), family history of type 2 diabetes mellitus (categorical), total energy intake (categorical), physical activity (categorical), smoking (categorical), drinking habits (binary) and BMI (continuous).
¶Tofu (times/week): Q1, 0–0·70; Q2, 0·70–1·4; Q3, 1·4–3·5; Q4, > 3·5.
**Total unsweetened and non-fried soya products (times/week): Q1, 0–4·2; Q2, 4·2–7·0; Q3, 7·0–9·8; Q4, > 9·8.
††Total soya products (times/week): Q1, 0–4·9; Q2, 4·9–7·7; Q3, 7·7–11·2; Q4, > 11·2.

randomized controlled trials have reported that soya products[12], soya protein[12–14] and soya isoflavone[14] improve glycaemic control and insulin sensitivity. However, others showed no significant effect of soya protein[27–29] and soya isoflavone[27,30,31].

The results of an experimental study suggested that soyabean protein has the potential to improve insulin resistance or ameliorate obesity by inhibiting lipogenesis and promoting lipolysis in the liver and adipose cells[32]. Furthermore, isoflavone is similar to endogenous oestrogen in structure and exhibits a weak oestrogen-like action by combining with the oestrogen receptor in various organs[32]. By adjusting the function of adipose cells and inhibiting lipoprotein lipase, oestrogen has been shown to adjust the number of adipose cells, adipose deposition and lipid production[33–35].

Therefore, we assessed the association between the intake of soya protein and isoflavone and insulin resistance. However, the frequency of the consumption of total soya products showed a clearer linear association with insulin resistance than the estimated intake of soya protein or isoflavones. One reason for this result may be that an *in vivo* metabolism of isoflavones was not considered in the present study. The soya isoflavones, such as daidzein and genistein, are phyto-oestrogens metabolized extensively by the intestinal microflora[36]. Some previous reports have suggested that 30–50 % of Japanese have isoflavone-producing ability depending on the intestinal bacteria[37] and this ability is increased by dietary habits such as higher consumption of fibre, green tea and fish oil[38]. Therefore, there may be a discrepancy between the estimated intake of soya isoflavone and the actually metabolized amount of soya isoflavone. In addition, according to a recent meta-analysis, the purified or isolated components of soya (isoflavones or soya protein) were not as effective as whole soya foods in improving glycaemic control[39,40]. The reasons for this may include the presence of other components of soya, such as fibre, saponin, polysaccharides, phytosterol and unsaturated fatty acids, or their interactions. Thus, various experimental and human studies have reported the beneficial effects of soya or nutrient components of soya on glucose metabolism. However, the effects and mechanisms of soya and soya foods on insulin resistance have not been fully clarified and warrant further study.

After adjustment for BMI, the OR and *P* for trend for the association between the intake of soya products, soya protein or soya isoflavone were not greatly altered (model 1 *v.* model 2 in Tables 2 and 3). These results

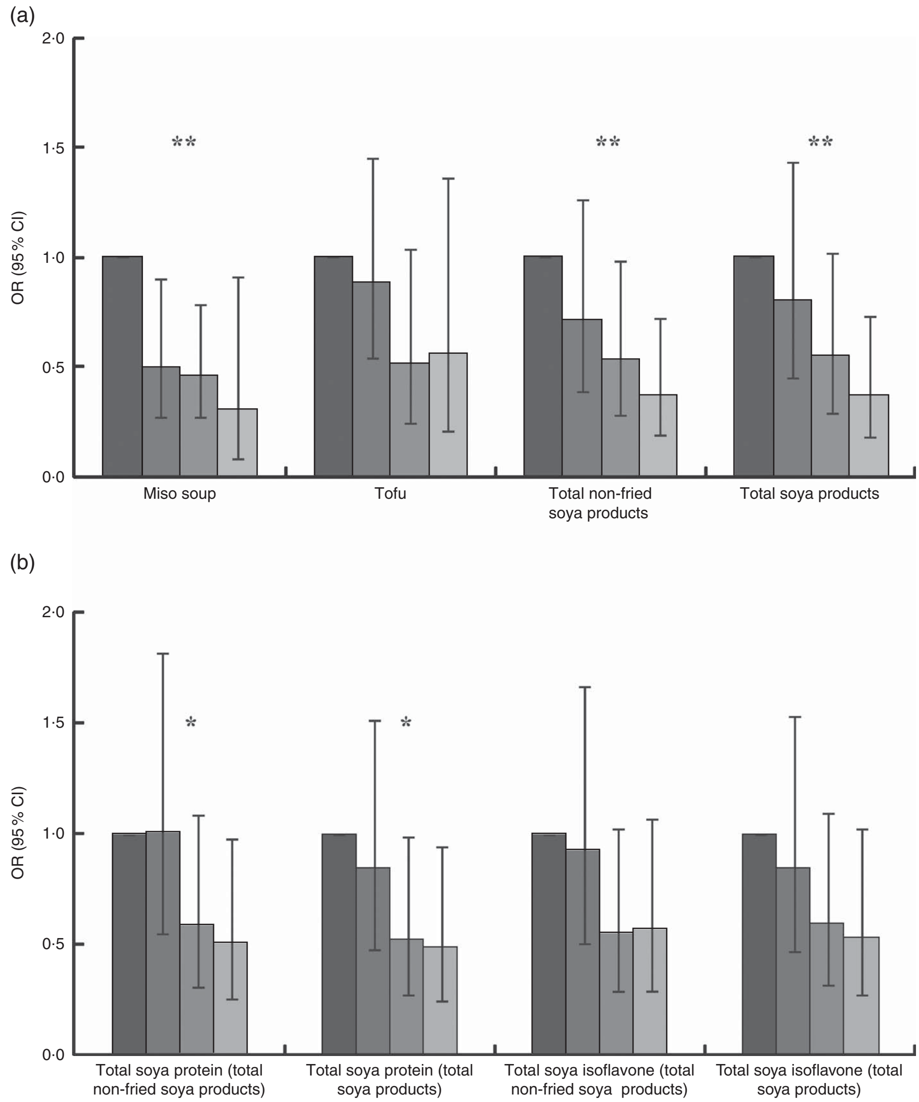

Fig. 2 Association between the intake of each soya product (1 = miso soup; 2 = tofu; 3 = fermented soybeans and soybeans; 4 = fried tofu mixed with vegetables, fried bean curd and thick deep-fried tofu) and insulin resistance among 565 men and 583 women aged 34–70 years baseline, living in Tokushima Prefecture between 2008 and 2013, Japan Multi-Institutional Collaborative Cohort (J-MICC) Study. Consumption was divided into quartiles (■, Q1; ■, Q2; ■, Q3; □, Q4), with Q1 being defined as the reference. Results are presented as odds ratios with their 95 % profile likelihood confidence intervals represented by vertical bars, and are adjusted for gender, age, recruitment, family history of type 2 diabetes mellitus, total energy intake, physical activity, smoking and drinking habits, and BMI. (a) No significant linear trend was observed for the association between the frequency of intake of tofu and log (OR) of insulin resistance. However, the relationships of intake of miso soup, total non-fried soya products (1 + 2 + 3) and total soya products (1 + 2 + 3 + 4) with insulin resistance were significant. (b) The OR of insulin resistance decreased significantly as the estimated intake of soya protein from total non-fried soya products (1 + 2 + 3) and total soya products (1 + 2 + 3 + 4) increased (*P* for trend <0·05). However, the associations between the estimated intake of soya isoflavone from total non-fried soya products (1 + 2 + 3) and total soya products (1 + 2 + 3 + 4) and insulin resistance were slightly attenuated. **P* for trend <0·05, ***P* for trend <0·01

suggest that the inverse association between soya product intake and insulin resistance was not strongly confounded or intermediated by obesity.

Our study has some limitations. First, the temporal relationship between soya product intake and insulin resistance remains obscure because our study was a cross-sectional design. Second, the sample size of the study was small. Third, information on soya product consumption was self-reported and our FFQ did not include information on portion size. However, we used information on soya product intake per meal, which was calculated from the four 3 d diet records of twenty-eight participants, in order to estimate the intake of soya protein and isoflavone. In consequence, Spearman's rank-correlation coefficient of the estimated intake of soya protein from total non-fried soya products (1 + 2 + 3) and total soya products (1 + 2 + 3 + 4), and the estimated intake of soya isoflavone from total non-fried soya products (1 + 2 + 3) and total soya

Table 3 Associations of the estimated intake of soya protein and soya isoflavone with insulin resistance* among 565 men and 583 women aged 34–70 years baseline, living in Tokushima Prefecture between 2008 and 2013, Japan Multi-Institutional Collaborative Cohort (J-MICC) Study

	Intake amount (g/week)							
	Q1	Q2		Q3		Q4		
	OR	OR	95 % CI	OR	95 % CI	OR	95 % CI	*P* for trend
Total unsweetened and non-fried soya products calculated on soya protein (g/week)†								
No. of cases/participants	46/303	34/253		27/306		23/286		
Age- and gender-adjusted model‡	1·00	0·84	0·51, 1·36	0·50	0·30, 0·84	0·52	0·29, 0·88	0·011
Model 1§	1·00	0·78	0·47, 1·30	0·48	0·28, 0·82	0·50	0·28, 0·88	0·013
Model 2‖	1·00	1·00	0·55, 1·82	0·59	0·31, 1·09	0·51	0·26, 0·97	0·022
Total soya products calculated on soya protein (g/week)¶								
No. of cases/participants	45/287	37/286		24/286		24/289		
Age- and gender-adjusted model‡	1·00	0·77	0·47, 1·24	0·46	0·26, 0·77	0·53	0·30, 0·91	0·016
Model 1§	1·00	0·74	0·45, 1·21	0·45	0·26, 0·79	0·51	0·28, 0·90	0·019
Model 2‖	1·00	0·85	0·47, 1·51	0·52	0·27, 0·98	0·49	0·25, 0·95	0·023
Total unsweetened and non-fried soya products calculated on soya isoflavone (mg/week)**								
No. of cases/participants	47/308	34/254		24/296		25/290		
Age- and gender-adjusted model‡	1·00	0·80	0·49, 1·31	0·45	0·26, 0·77	0·56	0·32, 0·94	0·027
Model 1§	1·00	0·75	0·45, 1·25	0·44	0·25, 0·76	0·54	0·31, 0·94	0·037
Model 2‖	1·00	0·92	0·51, 1·66	0·55	0·29, 1·02	0·56	0·29, 1·07	0·061
Total soya products calculated on soya isoflavone (mg/week)††								
No. of cases/participants	44/288	35/268		28/306		23/286		
Age- and gender-adjusted model‡	1·00	0·81	0·49, 1·32	0·54	0·32, 0·90	0·53	0·30, 0·92	0·020
Model 1§	1·00	0·76	0·45, 1·26	0·54	0·31, 0·91	0·51	0·28, 0·91	0·024
Model 2‖	1·00	0·85	0·47, 1·54	0·60	0·32, 1·10	0·53	0·27, 1·03	0·050

*Adjusted odds ratios and 95 % profile likelihood confidence intervals.
†Total unsweetened and non-fried soya products calculated on soya protein (g/week): Q1, 0–9·73448; Q2, 9·73448–15·39853; Q3, 15·39853–25·38757; Q4, >25·38757.
‡Age- and gender-adjusted model: adjusted for age (continuous), gender and recruitment (binary).
§Model 1: adjusted for age (continuous), gender, recruitment (binary), family history of type 2 diabetes mellitus (categorical), total energy intake (categorical), physical activity (categorical), smoking (categorical) and drinking habits (binary).
‖Model 2: adjusted for age (continuous), gender, recruitment (binary), family history of type 2 diabetes mellitus (categorical), total energy intake (categorical), physical activity (categorical), smoking (categorical), drinking habits (binary) and BMI (continuous).
¶Total soya products calculated on soya protein (g/week): Q1, 0–11·93971; Q2, 11·93971–18·06136; Q3, 18·06136–28·57594; Q4, >28·57594.
**Total unsweetened and non-fried soya products calculated on soya isoflavone (mg/week): Q1, 0–39·89579; Q2, 39·89579–62·55006; Q3, 62·55006–99·25788; Q4, >99·25788.
††Total soya products calculated on soya isoflavone (mg/week): Q1, 0–45·25961; Q2, 45·25961–67·91388; Q3, 67·91388–107·98101; Q4, > 107·98101.

products (1 + 2 + 3 + 4), was 0·55 ($P = 0·002$), 0·47 ($P = 0·011$), 0·64 ($P < 0·001$) and 0·59 ($P = 0·001$), respectively (see online supplementary material, Supplemental Table 1). On the other hand, the intake of soya products, soya protein or isoflavone may have been underestimated. The median estimated soya isoflavone intake from soya foods based on the National Nutrition Survey of 2002 was 16–22 mg/d, which is equivalent to Q4 in the present study. Fourth, some potential confounders which have a great effect on insulin resistance may have not been completely adjusted for. However, the relationship between insulin resistance and soya products was robust after adjustments for menopause status, vegetable intake or total fibre intake. Finally, because all participants in the study were Japanese, our results may not be applicable to other ethnic groups.

Conclusion

In conclusion, our results showed that habitual high intake of soyabeans and soya products may be associated with a lower level of insulin resistance. The frequency of the intake of soya products, rather than the estimated intake of soya protein or isoflavone, showed a clearer relationship with insulin resistance. In the future, further studies are needed to clarify the relationship between insulin resistance and metabolites of soya products, using urine and blood samples.

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Supplementary material

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