ORIGINAL ARTICLE

Effects of soybean product intake on fasting and postload hyperglycemia and type 2 diabetes in Japanese men with high body mass index: The Saku Study

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ABSTRACT

Aims/Introduction: The inverse association between soybean intake and type 2 diabetes mellitus has been reported. We investigated the effects of soybean product intake on the incidence of type 2 diabetes mellitus considering fasting and postload hyperglycemia.

Materials and Methods: The present 4-year, cohort study included 1,738 men and 1,301 women, aged 30–69 years, without diabetes mellitus at baseline who underwent comprehensive medical check-ups between April 2006 and March 2007 at Saku Central Hospital. Participants were stratified by sex and body mass index (BMI), and further classified into three groups based on soybean product intake: group 1 (0–1 time/week), group 2 (2–3 times/week) and group 3 (four or more times per week). Participants underwent annual standard 75-g oral glucose tolerance testing during follow-up periods until March 2011. Main outcomes were incidence of fasting hyperglycemia, postload hyperglycemia and type 2 diabetes mellitus.

Results: During 10,503 person-years of follow up, 204 participants developed type 2 diabetes mellitus, including 61 who developed fasting hyperglycemia and 147 who developed postload hyperglycemia. Among men with a high BMI, group 3 had significantly lower risk for the incidence of type 2 diabetes mellitus, fasting hyperglycemia and postload hyperglycemia than group 1, and multivariable-adjusted hazard ratios and 95% confidence intervals were 0.44 (0.22–0.89), 0.36 (0.15–0.96) and 0.40 (0.18–0.92), respectively. Similar results were not observed among men with low BMI or women.

Conclusions: Soybean product intake prevented fasting and postload hyperglycemia and type 2 diabetes mellitus in men with a high BMI. Further long-term observation is necessary. (J Diabetes Invest, doi: 10.1111/jdi.12100, 2013)

KEY WORDS: Postload hyperglycemia, Soybean, Type 2 diabetes mellitus

INTRODUCTION

The prevalence of type 2 diabetes mellitus is increasing worldwide. Type 2 diabetes mellitus is a major risk factor for cardiovascular morbidity and mortality. It has been reported that among patients with coronary artery disease, approximately 35 and 15% have had diabetes or prediabetes, respectively[1]. In addition, individuals with high postload plasma glucose (PG) levels have a higher risk of cardiovascular and all-cause mortality than individuals with high fasting plasma glucose (FPG) levels[2–5]. Therefore, it is important to prevent postload PG levels, as well as FPG levels, from rising.

Type 2 diabetes mellitus is strongly associated with lifestyle, and many modifiable risk factors have been reported. Dietary soy is beneficial to health because of a high polyunsaturated fat, fiber, vitamin and mineral content combined with a low saturated fat content[6]. A meta-analysis showed that the substitution of soy protein for animal protein in the diet significantly lowered total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides without affecting high-density lipoprotein (HDL) cholesterol[7]. Dietary soy also has the potential to decrease the incidence of type 2 diabetes mellitus. It has been reported that legume intake is associated with the modification of risk factors related to glucose intolerance[8]. Furthermore, the inverse association between soybean product intake and type 2 diabetes mellitus has been reported among women in two prospective studies[9,10]. However, the definition of type 2 diabetes mellitus in the two studies was based on self-report. In addition, there has been no study investigating the effects of soybean product intake on the incidence of type

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2 diabetes mellitus, and considering postload PG levels and FPG levels.

Therefore, we investigated the effects of soybean intake on postload PG levels, FPG levels and the incidence of type 2 diabetes mellitus. Specifically, the annual PG levels were determined in a Japanese population using a standard 75-g oral glucose tolerance test (OGTT).

MATERIALS AND METHODS

Participants

The Saku Study included community residents in the neighborhood around Saku Central Hospital (Nagano, Japan) who underwent annual comprehensive medical check-ups for the prevention and early detection of various diseases, including type 2 diabetes mellitus, cardiovascular disease and cancer. The Saku Study attempted to elucidate the incidence of and risk factors for type 2 diabetes mellitus among the Japanese population[11]. The cohort consisted of 4,318 individuals, aged 30–69 years, who underwent a baseline comprehensive medical check-up over 2 days and 1 night between April 2006 and March 2007 at Saku Central Hospital. Of these individuals, 3,726 did not have diabetes mellitus at baseline, based on four criteria: (i) no history of diabetes mellitus, as determined by interviews carried out by the physicians; (ii) FPG concentrations <7.0 mmol/L; (iii) 2-h postload PG (2-h PG) concentrations <11.1 mmol/L; and (iv) glycated hemoglobin (HbA_{1c}) concentrations (National Glycohemoglobin Standardization Program [NGSP]) <6.5%. Of these individuals, 3,069 underwent at least one follow-up examination by the end of March 2011; we excluded 30 participants with missing data at baseline and/or annual follow-up examinations. Thus, a total of 3,039 participants (1,738 men and 1,301 women), aged 30–69 years, were eligible for our analysis. Of these 3,039 participants, 2,157 (71.0%) underwent comprehensive annual medical check-ups for 4 years after the baseline examination.

The study protocol was in accordance with the Helsinki Declaration, and approved by the Ethical Committee of Saku Central Hospital.

Soybean Product Intake

Food intakes were assessed by a self-administered questionnaire (see Appendix S1). Soybean products included soybean, tofu, koyadofu (freeze-dried tofu), aburaage (deep-fried tofu) and natto (fermented soybeans). Participants were asked about the frequency of soybean product intake. Participants described the frequency of intake by choosing from the following options: zero to one time/week, two to three times/week and four or more times/week. The standard portion size of soybean products per time was 100 g. Milk, egg, fish, meat, fruits, vegetables and grain intakes at baseline also were assessed by a self-administered questionnaire. For grain intake only, participants were asked about the frequency of intake per day. A standard portion size was specified for each food.

Study Procedure

In the morning after an overnight fast (12 h), all participants underwent a standard 75-g OGTT. Blood samples were obtained at 0 (fasting), 30, 60 and 120 min, with PG measured at all four times in the clinical laboratory of Saku Central Hospital. Blood glucose, HDL cholesterol and LDL cholesterol concentrations were measured by enzymatic methods. HbA_{1c} concentrations were measured by high-performance liquid chromatography. HbA_{1c} (%) was estimated as a NGSP equivalent value (%) and calculated using the formula HbA_{1c} (%) = HbA_{1c} (Japan Diabetes Society; %) + 0.4%[12,13].

Weight and height were measured in the morning during the fasting state. Body mass index (BMI) was calculated as the weight (kg) divided by the height squared (m^2). Blood pressure was measured by trained nurses using an automatic sphygmomanometer, with the participant in a seated position after at least a 5-min rest. Additionally, the examination included standard questionnaires regarding demographic characteristics, medical history, family history and health-related habits. Smoking status was categorized as never-smoker, ex-smoker and current smoker. Alcohol consumption (ethanol) was categorized as 0, 1–139 or ≥140 g/week, and exercise was categorized into 0, 1–119 or ≥120 min/week.

Definition of Main Outcomes and Follow Up

We used the 1999 World Health Organization criteria to define type 2 diabetes mellitus[14]. Fasting hyperglycemia (FPG levels ≥7.0 mmol/L) and/or postload hyperglycemia (2-h PG levels ≥11.1 mmol/L) were indicative of type 2 diabetes mellitus. In addition, receiving medical treatment for type 2 diabetes mellitus was included in the definition of type 2 diabetes mellitus. All 3,039 participants were followed up annually at Saku Central Hospital by comprehensive medical check-ups over 2 days and 1 night, including the 75-g OGTT, until they developed type 2 diabetes mellitus or until March 2011. Individuals not examined during follow up were censored on the date of their last examination.

Statistical Analysis

We stratified participants by sex and medians of BMI (23.6 kg/m^2 in men and 22.0 kg/m^2 in women) as follows: men with a low BMI, men with a high BMI, women with a low BMI and women with a high BMI. Additionally, based on their soybean product intake, participants were classified into three groups in each category of sex and BMI status: group 1 (0–1 time/week), group 2 (2–3 times/week) and group 3 (four or more times per week). Differences in baseline characteristics among these three groups were determined by using an analysis of variance for continuous data with a normal distribution, a Kruskal–Wallis *H*-test for continuous data with a non-normal distribution, and a chi-squared-test and Fisher's exact test for dichotomous data and categorical data.

Cox proportional hazards regression was used to estimate adjusted type 2 diabetes mellitus incidence hazard ratios (HRs) and 95% confidence intervals (CIs) for group 2 and group 3 compared with group 1. Furthermore, HRs and 95% CIs for fasting hyperglycemia (FPG levels ≥7.0 mmol/L) and postload hyperglycemia (2-h PG levels ≥11.0 mmol/L) were estimated. Model 1 was adjusted by age, and model 2 was adjusted by age, BMI, smoking status, alcohol consumption, physical activity, a family history of diabetes mellitus, green vegetable intake and fruit intake. The assumptions required for proportional hazards were met, and these were assessed with graphs of log–log plots. In addition, incident rates of impaired glucose tolerance (2-h PG ≥7.8 mmol/L) and impaired fasting glucose (FPG ≥6.1 mmol/L) among participants with normoglycaemia (2-h PG <7.8 mmol/L and FPG <6.1 mmol/L) at baseline were calculated. All data were analyzed using SPSS statistical software (Version 19.0J; SPSS Japan Inc., Tokyo, Japan). All reported *P*-values are two-tailed; those <0.05 were considered statistically significant.

Table 1 | Baseline characteristics according to groups categorized by intake of soybean products in men

	Group 1 0–1 time/week	Group 2 2–3 times/week	Group 3 ≥4 times/week	*P*
Men with low BMI, *n* (<23.6 kg/m^2)	71	304	487	
Age (years)	53.6 ± 9.3	55.2 ± 7.3	55.9 ± 8.1	0.042
BMI (kg/m^2)	21.3 ± 1.7	21.7 ± 1.3	21.6 ± 1.5	0.080
Systolic blood pressure (mmHg)	116.8 ± 14.1	116.6 ± 16.1	117.6 ± 14.0	0.661
HDL-cholesterol (mmol/L)	1.40 ± 0.33	1.46 ± 0.35	1.49 ± 0.37	0.100
LDL-cholesterol (mmol/L)	3.11 ± 0.66	3.05 ± 0.76	3.08 ± 0.75	0.814
Fasting PG (mmol/L)	5.45 ± 0.4	5.48 ± 0.45	5.47 ± 0.48	0.860
2-h PG (mmol/L)	6.22 ± 1.26	6.55 ± 1.41	6.58 ± 1.40	0.126
HbA_{1c} (%)	5.42 ± 0.41	5.49 ± 0.34	5.45 ± 0.32	0.156
Smoking status, % (never, current, ex-)	26.8, 42.3, 31.0	26.3, 35.2, 38.5	29.2, 24.2, 46.6	0.001
Alcohol consumption, % (0, 1–139, ≥140 g/week)	16.9, 49.3, 33.8	15.5, 43.1, 41.4	15.8, 44.8, 39.4	0.835
Physical activity, % (0, 1–119, ≥120 min/week)	59.2, 22.5, 18.3	49.3, 31.9, 18.8	47.2, 32.2, 20.5	0.391
Green vegetable intake, % (0–1, 2–3, ≥4 times/week)	21.1, 46.5, 32.4	8.9, 41.4, 49.7	3.1, 20.3, 76.6	<0.001
Other vegetable intake, % (0–1, 2–3, ≥4 times/week)	21.1, 36.6, 42.3	4.3, 37.2, 58.6	0.8, 15.6, 83.6	<0.001
Fruit intake, % (0–1, 2–3, ≥4 times/week)	54.9, 25.4, 19.7	31.6, 36.8, 31.6	17.0, 32.0, 50.9	<0.001
Egg intake, % (0–1, 2–3, ≥4 times/week)	28.2, 50.7, 21.1	12.8, 44.7, 42.4	10.1, 35.7, 54.2	<0.001
Milk intake, % (0–1, 2–3, ≥4 times/week)	42.3, 19.7, 38.0	31.3, 22.7, 46.1	19.1, 16.8, 64.1	<0.001
Meat intake, % (0–1, 2–3, ≥4 times/week)	26.8, 60.6, 12.7	16.4, 56.9, 26.6	13.1, 42.7, 44.1	<0.001
Fish intake, % (0–1, 2–3, ≥4 times/week)	23.9, 53.5, 22.5	7.9, 53.0, 39.1	2.7, 24.2, 73.1	<0.001
Grain intake (times/day)	3.5 ± 1.2	3.4 ± 1.0	3.6 ± 1.0	0.212
Men with high BMI, *n* (≥23.6 kg/m^2)	62	317	497	
Age (years)	55.4 ± 6.8	55.1 ± 7.7	56.3 ± 8.2	0.098
BMI (kg/m^2)	25.9 ± 1.7	25.9 ± 2.1	25.8 ± 2.0	0.814
Systolic blood pressure (mmHg)	124.5 ± 18.6	121.5 ± 14.4	122.8 ± 15.1	0.274
HDL-cholesterol (mmol/L)	1.34 ± 0.38	1.28 ± 0.27	1.32 ± 0.29	0.122
LDL-cholesterol (mmol/L)	3.20 ± 0.81	3.31 ± 0.77	3.24 ± 0.79	0.332
Fasting PG (mmol/L)	5.73 ± 0.46	5.66 ± 0.47	5.62 ± 0.45	0.127
2-h PG (mmol/L)	6.88 ± 1.61	6.83 ± 1.32	7.04 ± 1.36	0.098
HbA_{1c} (%)	5.56 ± 0.34	5.56 ± 0.31	5.54 ± 0.34	0.707
Smoking status (never, current, ex-)	16.1, 30.6, 53.2	24.0, 28.7, 47.3	26.6, 24.7, 48.7	0.342
Alcohol consumption, % (0, 1–139, ≥140 g/week)	22.6, 30.6, 46.8	15.8, 45.1, 39.1	10.9, 48.7, 40.4	0.015
Physical activity, % (0, 1–119, ≥120 min/week)	53.2, 33.9, 12.9	52.1, 28.1, 19.9	44.3, 31.6, 24.1	0.093
Green vegetable intake, % (0–1, 2–3, ≥4 times/week)	33.9, 27.4, 38.7	6.6, 43.2, 50.2	2.2, 21.3, 76.5	<0.001
Other vegetable intake,% (0–1, 2–3, ≥4 times/week)	12.9, 37.1, 50.0	2.8, 32.8, 64.4	0.4, 13.1, 86.5	<0.001
Fruit intake, % (0–1, 2–3, ≥4 times/week)	54.8, 14.5, 30.6	33.8, 33.4, 32.8	18.1, 31.4, 50.5	<0.001
Egg intake, % (0–1, 2–3, ≥4 times/week)	35.5, 32.3, 32.3	13.2, 45.7, 41.0	8.5, 30.8, 60.8	<0.001
Milk intake, % (0–1, 2–3, ≥4 times/week)	32.2, 25.8, 41.9	27.1, 22.7, 50.2	15.3, 20.5, 64.2	<0.001
Meat intake, % (0–1, 2–3, ≥4 times/week)	45.2, 46.8, 8.1	17.0, 54.6, 28.4	14.5, 41.2, 44.3	<0.001
Fish intake, % (0–1, 2–3, ≥4 times/week)	30.6, 48.4, 21.0	4.7, 49.2, 46.1	2.6, 26.0, 71.4	<0.001
Grain intake (times/day)	3.4 ± 1.3	3.4 ± 1.0	3.5 ± 1.1	0.551

BMI, body mass index; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PG, plasma glucose. Continuous data with a normal distribution were analyzed with the analysis of variance: mean ± standard deviation. Dichotomous and categorical data were analyzed with the chi-squared-test and Fisher's exact test: %.

RESULTS

Table 1 summarizes the baseline characteristics according to categories of soy product intake in men. In men with a low BMI, age and smoking status were significantly different among groups of different soy product intake. In men with a high BMI, alcohol consumption was significantly different among groups of different soy product intake. Table 2 summarizes the baseline characteristics according to categories of soy product intake in women. In women with a low BMI, age, HbA_{1c}, smoking status and physical activity were significantly different among groups of different soy product intake. In women with a high BMI, age, alcohol consumption and physical activity were significantly different among groups of different soy product intake. Dietary intakes except for grain intake were significantly different among both sex and BMI groups.

Table 2 | Baseline characteristics according to groups categorized by intake of soybean products in women

	Group 1 0–1 time/week	Group 2 2–3 times/week	Group 3 ≥4 times/week	*P*
Women with low BMI, *n* (<22.0 kg/m^2)	21	190	433	
Age (years)	51.3 ± 9.4	53.6 ± 7.8	56.1 ± 7.8	<0.001
BMI (kg/m^2)	20.1 ± 1.3	19.9 ± 1.4	20.0 ± 1.4	0.743
Systolic blood pressure (mmHg)	114.4 ± 19.9	114.8 ± 15.3	115.7 ± 15.8	0.775
HDL-cholesterol (mmol/L)	1.62 ± 0.26	1.73 ± 0.36	1.74 ± 0.38	0.410
LDL-cholesterol (mmol/L)	3.20 ± 0.84	3.09 ± 0.71	3.22 ± 0.69	0.091
Fasting PG (mmol/L)	5.21 ± 0.22	5.28 ± 0.42	5.29 ± 0.45	0.704
2-h PG (mmol/L)	6.30 ± 1.14	5.99 ± 1.31	6.00 ± 1.28	0.553
HbA_{1c} (%)	5.40 ± 0.33	5.43 ± 0.38	5.51 ± 0.32	0.016
Smoking status, % (never, current, ex-)	71.4, 19.0, 9.5	85.8, 9.5, 4.7	90.8, 4.4, 4.8	0.012
Alcohol consumption, % (0, 1–139, ≥140 g/week)	57.1, 33.3, 9.5	56.3, 36.8, 6.8	56.1, 40.2, 3.7	0.370
Physical activity, % (0, 1–119, ≥120 min/week)	57.1, 38.1, 4.8	57.9, 26.3, 15.8	41.1, 33.7, 25.2	0.001
Green vegetable intake, % (0–1, 2–3, ≥4 times/week)	14.3, 47.6, 38.1	3.7, 33.7, 62.6	2.3, 12.2, 85.5	<0.001
Other vegetable intake, % (0–1, 2–3, ≥4 times/week)	14.3, 42.9, 42.9	2.1, 26.3, 71.6	0.9, 6.7, 92.4	<0.001
Fruit intake, % (0–1, 2–3, ≥4 times/week)	14.3, 38.1, 47.6	15.3, 27.9, 56.8	4.2, 20.1, 75.8	<0.001
Egg intake, % (0–1, 2–3, ≥4 times/week)	19.0, 52.4, 28.6	14.2, 45.3, 40.5	9.5, 39.3, 51.3	0.033
Milk intake, % (0–1, 2–3, ≥4 times/week)	28.6, 19.0, 52.4	11.1, 26.8, 62.1	7.4, 16.4, 76.2	<0.001
Meat intake,% (0–1, 2–3, ≥4 times/week)	42.9, 38.1, 19.0	15.3, 52.6, 32.1	13.4, 39.5, 47.1	<0.001
Fish intake,% (0–1, 2–3, ≥4 times/week)	38.1, 28.6, 33.3	6.3, 45.8, 47.9	1.4, 25.2, 73.4	<0.001
Grain intake (times/day)	3.0 ± 0.9	2.9 ± 0.7	2.9 ± 0.7	0.940
Women with high BMI, *n* (≥22.0 kg/m^2)	19	182	456	
Age (years)	53.6 ± 8.5	54.5 ± 7.9	56.7 ± 7.2	0.001
BMI (kg/m^2)	24.2 ± 2.3	24.8 ± 2.5	24.7 ± 2.5	0.618
Systolic blood pressure (mmHg)	117.0 ± 21.5	123.3 ± 17.0	123.3 ± 16.6	0.272
HDL-cholesterol (mmol/L)	1.51 ± 0.41	1.55 ± 0.35	1.57 ± 0.34	0.675
LDL-cholesterol (mmol/L)	3.36 ± 0.58	3.45 ± 0.71	3.46 ± 0.74	0.862
Fasting PG (mmol/L)	5.39 ± 0.35	5.49 ± 0.45	5.41 ± 0.43	0.122
2-h PG (mmol/L)	6.28 ± 1.32	6.65 ± 1.34	6.64 ± 1.35	0.504
HbA_{1c} (%)	5.60 ± 0.29	5.60 ± 0.34	5.57 ± 0.31	0.605
Smoking status,% (never, current, ex-)	94.7, 5.3, 0.0	89.0, 7.1, 3.8	93.9, 3.5, 2.6	0.253
Alcohol consumption, % (0, 1–139, ≥140 g/week)	47.4, 52.6, 0.0	68.1, 26.4, 5.5	58.6, 36.8, 4.6	0.045
Physical activity, % (0, 1–119, ≥120 min/week)	73.7, 21.1, 5.3	58.8, 26.9, 14.3	42.5, 35.5, 21.9	0.001
Green vegetable intake, % (0–1, 2–3, ≥4 times/week)	15.8, 47.4, 36.8	2.2, 33.0, 64.8	0.7, 11.8, 87.5	<0.001
Other vegetable intake, % (0–1, 2–3, ≥4 times/week)	5.3, 36.8, 57.9	0.5, 22.0, 77.5	0.0, 6.4, 93.6	<0.001
Fruit intake, % (0–1, 2–3, ≥4 times/week)	21.1, 26.3, 52.6	14.8, 36.3, 48.9	8.1, 19.7, 72.1	<0.001
Egg intake,% (0–1, 2–3, ≥4 times/week)	31.6, 47.4, 21.1	12.6, 49.5, 37.9	10.5, 33.8, 55.7	<0.001
Milk intake, % (0–1, 2–3, ≥4 times/week)	31.6, 26.3, 42.1	15.9, 25.8, 58.2	10.7, 20.0, 69.3	0.005
Meat intake, % (0–1, 2–3, ≥4 times/week)	21.1, 68.4, 10.5	18.1, 50.5, 31.3	13.6, 39.5, 46.9	<0.001
Fish intake, % (0–1, 2–3, ≥4 times/week)	21.1, 52.6, 26.3	8.8, 41.8, 49.5	2.9, 17.3, 79.8	<0.001
Grain intake (times/day)	2.9 ± 0.5	2.9 ± 0.8	2.9 ± 0.7	0.973

BMI, body mass index; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PG, plasma glucose. Continuous data with a normal distribution were analyzed with the analysis of variance: mean ± standard deviation. Dichotomous and categorical data were analyzed with the chi-squared-test and Fisher's exact test: %.

Table 3 | Multivariable adjusted hazard ratios for incidence of diabetes according to groups categorized by intake of soybean products

	Group 1 0–1 time/week	Group 2 2–3 times/week	Group 3 ≥4 times/week	*P* for trend
Men with low BMI, *n* (<23.6 kg/m^2)	71	304	487	
Incidence of type 2 diabetes mellitus				
Case	2	23	28	
Incidence rate/1000 person-years	8.3	21.8	16.9	
HRs (95% CIs)				
Model 1	1.00	2.55 (0.60–10.81)	1.79 (0.43–7.52)	0.816
Model 2	1.00	2.49 (0.58–10.67)	1.84 (0.42–8.02)	0.952
Incidence of fasting hyperglycemia				
Case	1	3	8	
Incidence rate/1000 person-years	4.1	2.8	4.7	
HRs (95% CIs)				
Model 1	1.00	0.67 (0.07–6.48)	1.01 (0.13–8.09)	0.721
Model 2	1.00	0.74 (0.08–7.29)	1.17 (0.13–10.52)	0.656
Incidence of postload hyperglycemia				
Case	2	20	22	
Incidence rate/1000 person-years	8.3	18.9	13.0	
HRs (95% CIs)				
Model 1	1.00	2.21 (0.52–9.44)	1.39 (0.33–5.93)	0.543
Model 2	1.00	2.17 (0.50–9.39)	1.48 (0.33–6.54)	0.729
Men with high BMI, *n* (≥23.6 kg/m^2)	62	317	497	
Incidence of type 2 diabetes mellitus				
Case	11	38	44	
Incidence rate/1000 person-years	53.9	35.2	25.5	
HRs (95% CIs)				
Model 1	1.00	0.66 (0.34–1.29)	0.45 (0.23–0.88)	0.011
Model 2	1.00	0.65 (0.33–1.29)	0.44 (0.22–0.89)	0.014
Incidence of fasting hyperglycemia				
Case	6	14	18	
Incidence rate/1000 person-years	28.6	12.6	10.3	
HRs (95% CIs)				
Model 1	1.00	0.44 (0.17–1.15)	0.35 (0.14–0.89)	0.060
Model 2	1.00	0.46 (0.17–1.21)	0.36 (0.15–0.96)	0.075
Incidence of postload hyperglycemia				
Case	8	24	29	
Incidence rate/1000 person-years	38.3	21.8	16.6	
HRs (95% CIs)				
Model 1	1.00	0.57 (0.26–1.28)	0.41 (0.19–0.90)	0.030
Model 2	1.00	0.57 (0.25–1.28)	0.40 (0.18–0.92)	0.032

HR, hazard ratio; CI, confidence interval; FPG, fasting plasma glucose; PG, plasma glucose. Model 1 adjusted by age. Model 2 adjusted by age, body mass index (BMI), alcohol consumption, smoking status, physical activity, family history of diabetes, green vegetable intake and fruit intake.

The median follow up was 4.0 years (total person-years: 10,503), during which 204 individuals developed type 2 diabetes mellitus, including 26 defined as having type 2 diabetes mellitus by receiving medical treatment for this disease. Of those, 61 participants developed fasting hyperglycemia and 147 participants developed postload hyperglycemia. Because the youngest of these individuals was 40-years-old at baseline, all incident cases were assumed to be type 2 diabetes mellitus. Table 3 shows the multivariable-adjusted HRs and 95% CIs for the incidence of type 2 diabetes mellitus, fasting hyperglycemia and postload hyperglycemia according to groups categorized by soybean product intake in men. Among men with a high BMI, men of group 3 had a significantly lower risk for incidences of type 2 diabetes mellitus, fasting hyperglycemia and postload hyperglycemia than men of group 1, and the multivariable-adjusted HRs and 95% CIs were 0.44 (0.22–0.89), 0.36 (0.15–0.96) and 0.40 (0.18–0.92), respectively. In addition, there were significant linear decreases in the multivariable-adjusted HRs for the incidence of type 2 diabetes mellitus and postload hyperglycemia (*P* for trend = 0.014 and 0.032, respectively). Figure 1 shows FPG and 2-h PG levels at the follow-up end among men who were diagnosed type 2 diabetes mellitus by

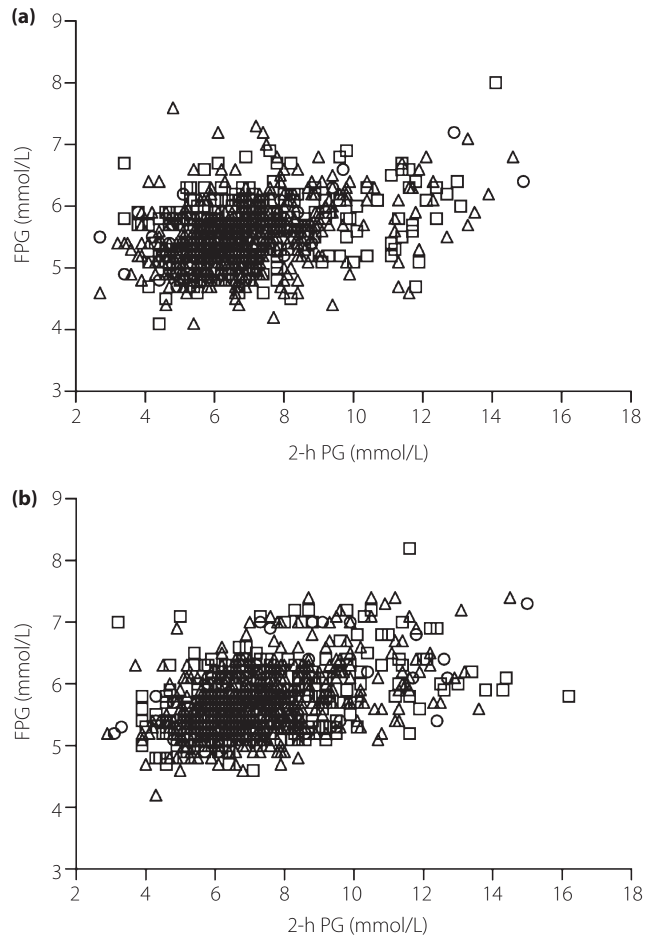

Figure 1 | Fasting plasma glucose (FPG) levels and 2-h plasma glucose (PG) levels at the end of follow up among men. (a) Men with low body mass index (BMI). (b) Men with high BMI. The circles show group 1, the squares show group 2 and the triangles show group 3.

75-g OGTT. Of the men who developed type 2 diabetes mellitus among the men with high BMI, the number of men whose HbA_{1c} increased to more than 6.5% was eight (group 1: 0, group 2: 4, group 3: 4). When high BMI was defined as BMI ≥25.0 kg/m^2, the number of men with high BMI were 514 (group 1: 37, group 2: 189, group 3: 288) and the multivariable-adjusted HRs and 95% CIs for type 2 diabetes mellitus, fasting hyperglycemia and postload hyperglycemia among group 3 in men with high BMI were 0.35 (0.15–0.81), 0.32 (0.09–1.11) and 0.31 (0.12–0.83), respectively. These significant associations between soybean product intake and incidence of type 2 diabetes mellitus were observed after further adjustment for fish intakes.

In addition, incident rates of impaired glucose tolerance and impaired fasting glucose among a subcohort of men with normoglycaemia at baseline are shown in Table 4. Incident rates in group 3 were lower than that in group 1 among men with high BMI. The number of incident cases in women was too small to calculate the adjusted HRs, especially in group 1: 26 cases (group 1: 0, group 2: 11, group 3: 15) among women with a low BMI and 32 cases (group 1: 1, group 2: 7, group 3: 24) among women with a high BMI.

DISCUSSION

This is the first report of a prospective cohort study investigating the association between soybean product intake and incidence of type 2 diabetes mellitus considering fasting and postload hyperglycemia. The main findings showed that soybean product intake prevented the increase of 2-h PG, as well as FPG, in men with a high BMI. The findings are very important with regard to the prevention of cardiovascular disease, as well as type 2 diabetes mellitus.

The effect of soybean product intake on type 2 diabetes mellitus might be accounted for by the dietary fiber content and the glycemic index (GI) of soybean products. A previous study involving rats reported that long-term dietary fiber intake significantly improved the area under the curve of plasma glucose concentration over time, and lowered FPG and HbA_{1c} levels[15]. In addition, it has been reported that ingesting a low-glycemic load meal containing dietary fiber at breakfast significantly improves the breakfast postload glycemic response in adults with type 2 diabetes mellitus[16]. Soybean products include substantial concentrations of dietary fiber. Although rice, which is

Table 4 | Incident rates of impaired glucose tolerance and impaired fasting glucose according to groups categorized by intake of soybean products among a subcohort of men with normoglycemia at baseline

	Group 1 0 –1 time/week	Group 2 2 –3 times/week	Group 3 ≥4 times/week
	Case (incident rates/1000 person-years)		
Men with low BMI, *n* (<23.6 kg/m^2)	57	213	341
Impaired glucose tolerance	12 (67.4)	53 (77.5)	86 (78.2)
Impaired fasting glucose	6 (32.6)	34 (47.8)	33 (28.4)
Men with high BMI, *n* (≥23.6 kg/m^2)	46	219	346
Impaired glucose tolerance	19 (159.7)	75 (113.6)	129 (125.4)
Impaired fasting glucose	9 (63.4)	38 (53.4)	63 (55.3)

BMI, body mass index. Impaired glucose tolerance was defined as 2 h plasma glucose ≥7.8 mmol/L. Impaired fasting glucose was defined as fasting plasma glucose ≥6.1 mmol/L.

a major grain in Japan, has a high GI, the reduction of the GI occurred whether soybean products were taken together, before or after rice intake[17]. These effects of soybean products might play an important role in the prevention of increasing 2-h PG levels. In contrast, a previous cross-sectional study reported that dietary fiber intake was not associated with impaired glucose tolerance or fasting glucose[18]. The FPG, 2-h PG and HbA_{1c} levels at baseline were not associated with soybean product intake in the present study (Table 1). Therefore, the effects of soybean product intake might appear in the long term.

The effects of soybean product intake on type 2 diabetes mellitus were not observed in men with a low BMI. Obesity is a major risk factor for the incidence of type 2 diabetes mellitus. FPG, 2-h PG and HbA_{1c} levels were better at baseline in men with a low BMI than in men with a high BMI. Therefore, men with a low BMI were at a lower risk for incidence of type 2 diabetes mellitus than men with a high BMI. To confirm the effects of soybean product intake on type 2 diabetes mellitus in men with a low BMI, long-term observation might be necessary.

Participants with a high intake of soybean products also consumed other healthy foods, such as vegetables or fruits. It has been reported that dietary patterns including higher intake of vegetables, fruits and soybean products were inversely associated with the risk of incidence of type 2 diabetes mellitus[19,20]. Because we adjusted for vegetable and fruit intake in estimating the risk of type 2 diabetes mellitus, soybean product intake could be effective for type 2 diabetes mellitus alone. However, we cannot completely eliminate the effects of the intake of other healthy foods.

The strengths of the present study include the large, community-based cohort and extensive data on the diagnosis of type 2 diabetes mellitus based on OGTT using the current definition of the disease[14]. Furthermore, the 12-h overnight fast before OGTT was managed by being hospitalized from the day before, and the type 2 diabetes mellitus patients were screened every year. However, the study had several limitations. First, a non-validated questionnaire for food intake was used in the present study so that elderly participants could answer easily. Some misclassification of exposure to soybean product intake was inevitable. Second, an issue regarding dietary assessment is that total energy and nutrient intake determined from the questionnaire were not calculated and validated. Participants with a high intake of soybean products probably consumed more energy than those with a low intake of soybean products; high-energy intake usually increases the risk of type 2 diabetes mellitus, and the lack of adjustment for energy intake might cause an erroneous positive association. However, energy adjustment only strengthens, rather than diminishes, the inverse association between soybean product intake and the incidence of type 2 diabetes mellitus, which is the major finding of the present study. Third, the number of cases in some groups was small. The statistical power of group 3 in men with high BMI for the incidence of type 2 diabetes mellitus was approximately 75%. Further studies with large sample size are required. Finally, the estimated risks might be underestimated because of the regression dilution bias given that the question about soybean product intake was asked only once[21].

In conclusion, the present findings suggest that soybean product intake prevented fasting and postload hyperglycemia in men with a high BMI. There was a dose–response relationship between soybean product intake and these outcomes. Although obesity is a major risk factor of type 2 diabetes mellitus, dietary habits could lower the risk of postload hyperglycemia, as well as fasting hyperglycemia. Furthermore, long-term observation is necessary to confirm the effects of soybean product intake on fasting and postload hyperglycemia in men with a low BMI.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1| Food frequency questionnaire in the present study.