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Appendix

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Soy Product and Isoflavone Intakes Are Associated with a Lower Risk of Type 2 Diabetes in Overweight Japanese Women^{1,2}

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Abstract

Isoflavones have been shown to improve glucose metabolism, but epidemiologic data are limited. We prospectively investigated the relationship between soy product and isoflavone intake and the risk of developing type 2 diabetes among Japanese adults. Participants were 25,872 men and 33,919 women aged 45–75 y, who participated in the second survey of the Japan Public Health Center-Based Prospective Study and had no history of diabetes. Soy product and isoflavone intakes were ascertained using a 147-item FFQ. Odds ratios of self-reported, physician-diagnosed type 2 diabetes over 5 y were estimated using logistic regression analysis. A total of 1114 new cases of type 2 diabetes were self-reported. Intakes of soy products and isoflavones were not significantly associated with type 2 diabetes in either men or all women. However, among overweight women (BMI ≥ 25 kg/m²), a higher intake of soy products was associated with a lower risk of type 2 diabetes; multivariable-adjusted odds ratios (95% CI) for the lowest through highest quintiles of soy product intake were 1.00 (reference), 0.78 (0.52–1.18), 0.79 (0.52–1.20), 0.62 (0.39–0.99), and 0.89 (0.55–1.44), respectively, and we found a similar risk pattern for daidzein and genistein intakes. Overall, our results suggest that there are no benefits of soy product or isoflavone intake with respect to risk of type 2 diabetes in either men or women. The possible protective associations of soy and isoflavone intakes among overweight women deserves further investigation. *J. Nutr.* 140: 580–586, 2010.

Introduction

The prevalence of type 2 diabetes is increasing worldwide (1) and is now relatively high among the Japanese, who have experienced rapid economic growth over the past several decades (2). Reports have suggested that soybeans and soy products such as tofu and *natto* (fermented soybeans), foods commonly consumed by the Japanese, may have beneficial effects on health (3). Animal studies have found that isoflavones, a major phytoestrogen found in these foods, improve glucose tolerance and exert an antidiabetic effect (4), suggesting that soy product and isoflavone intake may decrease risk of type 2 diabetes. However, human data on this issue are limited.

Of 2 cross-sectional studies that examined the association between isoflavone intake and glucose tolerance, 1 reported lower levels of fasting and postchallenge insulin concentrations

among persons with high isoflavone intake than among those with low intake (5), whereas another found no link between isoflavone intake and glycated hemoglobin or fasting insulin (6). In prospective studies, elevated intake of soybeans and other legumes has been linked to a decreased risk of glucose intolerance (7,8) and type 2 diabetes (9); however, the association with isoflavone intake was not assessed in these reports. Some (10,11), but not all (12–14), intervention studies of patients with type 2 diabetes have reported favorable effects of isoflavones and soy-based meal on glycated hemoglobin or insulin resistance.

Here, to assess the association of soy products and isoflavones with the development of type 2 diabetes, we prospectively investigated the relationship of dietary intake of soy products and isoflavones (genistein and daidzein) with the risk of developing type 2 diabetes using data from a large-scale, population-based cohort study in Japan.

Participants and methods

Study population. The Japan Public Health Center-Based Prospective (JPHC) Study was launched in 1990 for cohort I and in 1993 for cohort II

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(15). Participants were residents of 11 public health centers aged 40–69 y (assessed at each baseline survey). Our study was approved by the Institutional Review Board of the National Cancer Center of Japan.

Among the study population at baseline ($n = 140,420$), we excluded those who resided in 2 public center areas because of the differences in recruitment criteria. Of the remaining 116,672 eligible participants, 95,373 (81.7%) responded to the questionnaire survey at the baseline. Of these, 80,128 (84.0%) also responded to the 5-y survey (second survey), which is the baseline of the present analysis. Of these, 71,075 (88.7%) responded to the 10-y survey (third survey). We excluded participants who reported a history of type 2 diabetes ($n = 5183$) or severe diseases ($n = 6284$), including cancer, cerebrovascular disease, myocardial infarction, chronic liver disease, and renal disease, at baseline or second surveys. An additional 590 participants who reported extreme total energy intake (outside of mean ± 3 SD, according to sex) were excluded, leaving a total of 59,791 participants (25,872 men and 33,919 women) ultimately enrolled in our analysis.

Soy product and isoflavone intake. At baseline, second, and third surveys, participants completed a self-administered questionnaire that included queries regarding height, body weight, medical history, smoking habit, alcohol consumption, physical activity, diet, and other lifestyle factors. In the present analysis, we used data from the second survey, which was conducted in 1995 for cohort I and in 1998 for cohort II, as baseline. We did this because the questionnaire used for that survey contained more comprehensive information on food intake than that used for the baseline survey. At the second survey, a FFQ was used to assess intakes of 147 food and beverage items over the past year (16). *Miso* (fermented soybean paste) soup, *tofu*, *yushidofu* (predrained tofu), *koyadofu* (freeze-dried tofu), *aburaage* (deep-fried tofu), *natto* (fermented soybeans), and soy milk were included in the FFQ as soy products. For *miso* soup, potential responses regarding intake frequency were: almost never, 1–3 d/mo, 1–2 d/wk, 3–4 d/wk, 5–6 d/wk, or daily. Potential responses to the number of bowls consumed were: <1, 1, 2, 3, 4, 5, 6, 7–9, or ≥ 10 /d. For items other than *miso* soup and soy milk, participants described consumption frequency by choosing 1 of 9 options (almost none, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, 5–6 times/wk, once/d, 2–3 times/d, 4–6 times/d, or ≥ 7 times/d). A standard portion size was specified for each food and respondents were asked to choose their usual portion size among 3 options (less than one-half of the standard portion size, standard portion size, or >1.5 times of the standard portion size). Nine frequency options were given for soy milk: almost none, 1–2 times/wk, 3–4 times/wk, 5–6 times/wk, 1 cup (1 cup = 200 mL)/d, 2–3 cups/d, 4–6 cups/d, 7–9 cups/d, or ≥ 10 cups/d. Total soy product consumption was calculated from these responses, and total isoflavones (daidzein and genistein) intake was calculated based on a food composition table specifically developed to assess isoflavone content in Japanese foods (17,18). Validity was assessed among subsamples using either 14- or 28-d dietary records. Spearman correlation coefficients between energy-adjusted intake for soy products, daidzein, and genistein derived from the FFQ and that derived from the dietary records were 0.44–0.60 for cohorts I and II (19–21). The corresponding values for daidzein and genistein between energy-adjusted intake derived from the FFQ and serum concentration was 0.26 and 0.22, respectively, whereas that between energy-adjusted intake derived from the FFQ and creatinine-adjusted urinary excretion was 0.40 and 0.30, respectively (21). With regard to the reproducibility of estimations between the 2 FFQ administered 1 y apart, Spearman correlation coefficients for energy-adjusted intake of soy products, daidzein, and genistein were 0.41–0.67 for cohorts I and II (19,21,22).

Ascertainment of type 2 diabetes. Type 2 diabetes newly diagnosed during the 5-y period after the second survey was determined by a self-administered questionnaire at the third survey. At the third survey, study participants were asked if they had ever been diagnosed with diabetes and, if so, when the initial diagnosis had been made. Because we used the second survey as the starting point of observation for the incidence of type 2 diabetes, only patients who were diagnosed after 1995 for cohort I and 1998 for cohort II were regarded as incident cases during follow-up. Details regarding assessment of the validity of self-reported diabetes

have been described elsewhere (23). In a previous study we conducted, 94% of self-reported diabetes cases were confirmed as such by medical records. On application of these data to the survey results obtained from a JPHC subpopulation (health checkup participants) whose plasma glucose data were available, the sensitivity and specificity of self-reported diabetes were estimated to be 82.6 and 99.7%, respectively.

Statistical analysis. Soy product, daidzein, and genistein intakes were adjusted for total energy intake using a residual method. Participants were divided by gender into intake quintiles. Confounding variables considered were as follows: age (year, continuous), study area (9 areas), BMI (<21 , 21–22.9, 23–24.9, 25–26.9, or ≥ 27 kg/m²), smoking habit (lifetime nonsmoker, former smoker, or current smoker with a consumption of either <20 or ≥ 20 cigarettes/d), alcohol consumption (nondrinker, occasional drinker, or drinker with a consumption of <150 , 150–299, 300–449, or ≥ 450 g ethanol/d for men and nondrinker, occasional drinker, or drinker with a consumption of <150 or ≥ 150 g ethanol/d for women), leisure-time physical activity (<1 once/mo, 1–3 times/mo, or ≥ 1 once/wk), history of hypertension (yes or no), family history of diabetes mellitus (yes or no), coffee consumption (almost never, <1 cup/d, 1 cup/d, 2–3 cups/d, or ≥ 4 cups/d), energy-adjusted magnesium intake (mg/d, continuous), energy-adjusted calcium intake (mg/d, continuous), energy-adjusted fiber intake (g/d, continuous), energy-adjusted vegetable intake (g/d, continuous), energy-adjusted fish intake (g/d, continuous), and total energy intake (kJ/d, continuous). An indicator variable for missing data was created for each covariate. We confirmed that the results were unchanged when analyses were conducted among participants with no missing information of all covariates. Trends of differences in proportions and means of confounding factors according to quintile categories of soy product intake were statistically tested using the Mantel-Haenszel chi-squared test for categorical variables and linear regression analysis for continuous variables, with ordinal numbers 0–4 assigned to the quintile categories of soy product intake.

Odds ratios and 95% CI of type 2 diabetes for the quintiles of soy product, daidzein, and genistein intakes were estimated using multiple logistic regression analysis, taking the lowest quintile category as reference. The first model was adjusted for age and study area, and the multivariable model was further adjusted for BMI, smoking habit, alcohol consumption, leisure-time physical activity, history of hypertension, family history of diabetes, coffee consumption, green tea consumption, magnesium intake, calcium intake, fiber intake, vegetable intake, fish intake, and total energy intake. We also analyzed data by BMI (<25 kg/m² or ≥ 25 kg/m²), smoking status (nonsmoker or current smoker) in men only, and menopausal status (premenopausal or postmenopausal) in women only. The cutoff for BMI used in this study was the lower limit of obesity for Japanese populations, which was determined by the Japan Society for the Study of Obesity (24). Because most women (95.8%) were nonsmokers, we did not perform analysis stratified by smoking status among women. The significance of the interactions between soy product, daidzein, and genistein intakes and stratifying variables was assessed by the Wald chi-squared statistic. Two-sided P -values <0.05 were considered significant. All analyses were performed using SAS version 9.1 (SAS Institute).

Results

We identified 1114 new cases (634 men and 480 women) of self-reported type 2 diabetes over the 5-y period between the second and third surveys. At the time of the second survey (the baseline of the present analysis), both men and women with incident type 2 diabetes had a higher BMI and were more likely to report a family history of diabetes mellitus and own history of hypertension than those without (Table 1). Women with incident type 2 diabetes were also more likely to be older and physically inactive during leisure time and consumed less coffee than those without type 2 diabetes.

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TABLE 1 Baseline characteristics according to participants with and without incident type 2 diabetes during follow-up in the JPHC Study^{1,2}

	Men			Women		
	Nondiabetics	Diabetics	<i>P</i> -value ³	Nondiabetics	Diabetics	<i>P</i> -value ³
Participants, <i>n</i>	25,238	634		33,439	480	
Age, <i>y</i>	56.6 ± 7.7	58.9 ± 7.3	0.29	57.1 ± 7.8	58.3 ± 7.7	0.001
BMI, <i>kg/m</i> ²	23.5 ± 2.8	25.2 ± 3.3	<0.001	23.5 ± 3.1	25.7 ± 3.7	<0.001
Current smoker, %	46.5	48.8	0.26	4.2	5.9	0.08
Alcohol consumption ≥1 d/wk, %	68.3	67.3	0.59	11.1	7.5	0.02
Leisure-time physical activity ≥1 d/wk, %	21.0	22.5	0.37	20.3	16.6	0.052
Family history of diabetes mellitus, %	7.7	14.7	<0.001	8.1	14.6	<0.001
History of hypertension, %	17.1	24.8	<0.001	19.0	35.0	<0.001
Coffee consumption ≥1 cup/d, ⁴ %	32.0	30.8	0.51	35.0	29.3	0.01
Green tea consumption ≥1 cup/d, ⁴ %	60.3	59.8	0.83	62.1	59.3	0.22
Total energy intake, <i>KJ/d</i>	9408 ± 3147	9218 ± 3111	0.13	8019 ± 2787	7959 ± 3023	0.64
Soy products, ⁵ <i>g/d</i>	88 ± 76	90 ± 71	0.43	88 ± 76	94 ± 82	0.09
Miso soup, <i>mL/d</i>	261 ± 175	271 ± 175	0.16	215 ± 151	212 ± 157	0.64
Daidzein, <i>mg/d</i>	16.0 ± 11.2	16.1 ± 11.3	0.76	15.8 ± 11.0	16.4 ± 12.5	0.21
Genistein, <i>mg/d</i>	25.6 ± 18.9	25.9 ± 18.9	0.73	25.5 ± 18.6	26.7 ± 20.9	0.18
Magnesium, <i>mg/d</i>	279 ± 56	278 ± 56	0.54	271 ± 50	273 ± 53	0.50
Calcium, <i>mg/d</i>	498 ± 223	497 ± 228	0.88	540 ± 211	524 ± 203	0.09
Vegetables, <i>g/d</i>	198 ± 120	193 ± 122	0.38	230 ± 134	236 ± 155	0.32
Fiber, <i>g/d</i>	11.6 ± 4.5	11.4 ± 4.4	0.33	13.2 ± 4.4	13.5 ± 4.6	0.22
Fish, <i>g/d</i>	91 ± 58	89 ± 52	0.46	86 ± 50	87 ± 52	0.61

¹ Values are mean ± SD or percent.

² Diagnosis of type 2 diabetes was based on self-report.

³ Based on *t* test for continuous variables and chi-square test for categorical variables.

⁴ 1 cup = 120 mL.

⁵ Soy products include miso soup, tofu, yushidofu, koyadofu, aburage, natto, and soy milk.

Among both men and women, participants with a relatively higher intake of soy products were older and physically more active in their leisure time and were less likely to be smokers (Table 2). These individuals also had a higher BMI and consumed more magnesium and calcium but less alcohol and coffee and were more likely to report a history of hypertension than participants with lower soy intakes. Women with higher intakes of soy products were less likely to have a family history of diabetes mellitus. Both men and women with high intakes of soy products reported lower total energy intake than those with low soy product intake.

Overall, there were no measurable associations between soy product, daidzein, and genistein intakes and type 2 diabetes in either men or women, although we found somewhat lower odds ratios among women in the higher intake categories (Table 3). In an analysis stratified by BMI, elevated intakes of soy products, daidzein, and genistein were associated with decreased incidence of type 2 diabetes in overweight women (BMI ≥25 kg/m²) (Table 4). Further, risk was significantly decreased in the 4th, but not the highest, quintile of energy-adjusted intakes of soy products, daidzein, and genistein compared with the lowest quintile. The multivariable-adjusted odds ratios (95% CI) of type 2 diabetes for the second through highest quintiles of energy-adjusted intake of soy product versus the lowest quintile were 0.78 (0.52–1.18), 0.79 (0.52–1.20), 0.62 (0.39–0.99), and 0.89 (0.55–1.44), respectively. Similarly, overweight women in the 4th quintile of energy-adjusted intakes of genistein and daidzein had an ~40% lower risk of developing type 2 diabetes than those in the lowest quintile. In the analysis by menopausal status, postmenopausal women in the 4th quintile of energy-adjusted intakes of genistein and daidzein had an ~30% lower risk of type 2 diabetes compared with those in the lowest quintile

(genistein: OR 0.73, 95% CI, 0.51–1.05; daidzein: OR 0.69, 95% CI, 0.48–1.00), although the trend association was not clear (genistein: *P*-trend = 0.67; daidzein: *P*-trend = 0.49) (data not shown). Such decreases in odds ratios were not observed in women with a BMI <25 kg/m² or in premenopausal women. The *P*-values for the interactions between soy products, daidzein, and genistein and BMI were 0.33, 0.03, and 0.02, respectively, and those between soy products, daidzein, and genistein and menopausal status were 0.36, 0.08, and 0.17, respectively.

To confirm the results suggestive of a protective association in subgroups of women, we repeated the analysis by creating quintiles based on crude dietary intakes instead of energy-adjusted ones (Table 4). In women with a BMI ≥ 25 kg/m², we observed inverse associations for crude intakes of soy products (*P*-trend = 0.027), daidzein (*P*-trend = 0.042), and genistein (*P*-trend = 0.052). The multivariable-adjusted odds ratio of type 2 diabetes was ~40–50% lower in the highest quintile of crude intakes of soy product, daidzein, and genistein than in the lowest. Such a monotonic decreasing trend was also observed among postmenopausal women, with the odds ratio of type 2 diabetes being 30–40% lower in the highest versus lowest quintiles (data not shown).

In men, there was no measurable association between soy product and isoflavone intakes and risk of type 2 diabetes in any subgroup stratified by BMI or smoking status; the multivariable-adjusted odds ratios of type 2 diabetes for the highest versus the lowest quintile of energy-adjusted intake of soy products were 1.19 (95% CI, 0.77–1.83; *P*-trend = 0.42) in nonoverweight persons, 0.83 (95% CI, 0.53–1.29; *P*-trend = 0.28) in overweight persons, 1.15 (95% CI, 0.76–1.76; *P*-trend = 0.62) in nonsmokers, and 0.87 (95% CI, 0.55–1.39; *P*-trend = 0.62) in smokers (data not shown).

TABLE 2 Baseline characteristics according to quintile categories of soy product intake in the JPHC Study¹⁻³

	Q1 (low)	Q2	Q3	Q4	Q5 (high)	P-trend ⁴
Men, n = 25,872						
Participants, n	5,174	5,175	5,174	5,175	5,174	
Age, y	55.6 ± 7.9	56.1 ± 7.8	56.5 ± 7.7	57.0 ± 7.5	57.8 ± 7.6	<0.001
BMI, kg/m ²	23.5 ± 2.9	23.4 ± 2.8	23.5 ± 2.8	23.6 ± 2.8	23.8 ± 2.8	<0.001
Current smoker, %	51.6	50.1	46.9	44.4	39.8	<0.001
Alcohol consumption ≥1 d/wk, %	68.3	70.8	69.4	68.7	63.8	<0.001
Leisure-time physical activity ≥1 d/wk, %	18.6	19.8	21.0	21.4	24.6	<0.001
Family history of diabetes mellitus, %	7.5	7.7	8.5	8.0	7.7	0.56
History of hypertension, %	14.1	16.5	16.9	19.1	20.0	<0.001
Coffee consumption ≥1 cup/d, ⁵ %	41.0	33.8	30.3	28.3	26.8	<0.001
Green tea consumption ≥1 cup/d, ⁵ %	53.2	61.0	64.2	61.8	60.7	<0.001
Total energy intake, kJ/d	9446 ± 3379	9482 ± 3038	9506 ± 3035	9425 ± 2975	9159 ± 3272	<0.001
Soy products, g/d	29 ± 10	53 ± 6	73 ± 6	99 ± 10	186 ± 117	<0.001
Miso soup, mL/d	130 ± 102	238 ± 134	292 ± 159	315 ± 179	331 ± 204	<0.001
Daidzein, mg/d	5.7 ± 2.4	10.5 ± 2.5	14.6 ± 3.6	19.4 ± 5.3	29.9 ± 15.4	<0.001
Genistein, mg/d	8.8 ± 3.7	16.4 ± 4.0	22.9 ± 5.7	30.8 ± 8.3	49.4 ± 26.2	<0.001
Magnesium, mg/d	242 ± 49	262 ± 44	278 ± 46	292 ± 46	321 ± 60	<0.001
Calcium, mg/d	434 ± 253	460 ± 208	488 ± 204	517 ± 194	592 ± 216	<0.001
Vegetables, g/d	163 ± 133	188 ± 120	200 ± 122	208 ± 120	228 ± 141	<0.001
Fiber, g/d	9.2 ± 4.2	10.7 ± 3.8	11.7 ± 3.9	12.6 ± 4.0	13.8 ± 4.9	<0.001
Fish, g/d	84 ± 59	89 ± 51	93 ± 53	95 ± 56	93 ± 60	<0.001
Women, n = 33,919						
Participants, n	6,783	6,784	6,784	6,784	6,784	
Age, y	56.5 ± 8.4	56.8 ± 7.9	56.9 ± 7.7	57.3 ± 7.5	58.1 ± 7.3	<0.001
BMI, kg/m ²	23.4 ± 3.1	23.4 ± 3.0	23.5 ± 3.1	23.6 ± 3.1	23.9 ± 3.2	<0.001
Current smoker, %	6.5	4.2	3.8	3.4	3.5	<0.001
Alcohol consumption ≥1 d/wk, %	12.9	12.1	12.0	9.7	8.6	<0.001
Leisure-time physical activity ≥1 d/wk, %	18.7	19.5	20.0	20.8	22.1	<0.001
Family history of diabetes mellitus, %	8.9	8.5	8.4	7.5	7.7	0.002
History of hypertension, %	16.3	18.8	18.4	19.4	23.3	<0.001
Coffee consumption ≥1 cup/d, ⁵ %	46.3	37.2	33.5	30.0	28.0	<0.001
Green tea consumption ≥1 cup/d, ⁵ %	58.4	64.4	65.3	63.5	58.3	0.45
Total energy intake, kJ/d	7989 ± 3058	8164 ± 2803	8139 ± 2664	8000 ± 2565	7800 ± 2823	<0.001
Soy products, g/d	29 ± 10	52 ± 5	72 ± 6	97 ± 9	190 ± 117	<0.001
Miso soup, mL/d	113 ± 91	192 ± 120	234 ± 140	282 ± 155	276 ± 175	<0.001
Daidzein, mg/d	5.6 ± 2.3	10.4 ± 2.6	14.4 ± 3.6	18.9 ± 5.2	29.6 ± 14.8	<0.001
Genistein, mg/d	8.8 ± 3.7	16.3 ± 4.1	22.9 ± 5.8	30.4 ± 8.1	49.4 ± 25.3	<0.001
Magnesium, mg/d	237 ± 43	258 ± 41	270 ± 39	282 ± 41	309 ± 56	<0.001
Calcium, mg/d	486 ± 245	517 ± 207	530 ± 190	552 ± 183	615 ± 203	<0.001
Vegetables, g/d	199 ± 133	222 ± 127	233 ± 126	239 ± 126	258 ± 152	<0.001
Fiber, g/d	11.1 ± 4.1	12.6 ± 3.9	13.3 ± 3.9	14.0 ± 4.0	15.1 ± 5.0	<0.001
Fish, g/d	82 ± 56	86 ± 47	88 ± 46	89 ± 47	86 ± 53	<0.001

¹ Values are mean ± SD or percent.² Soy products include miso soup, tofu, yushidofu, koyadofu, aburaage, natto, and soy milk.³ Quintiles of soy product intake: men, Q1: <43.1 g, Q2: 43.1 to <62.5 g, Q3: 62.5 to <83.7 g, Q4: 83.7 to <117.3 g, Q5: ≥117.3 g; women, Q1: <42.8 g, Q2: 42.8 to <61.7 g, Q3: 61.7 to <82.8 g, Q4: 82.8 to <116.0 g, Q5: ≥116.0 g.⁴ Based on the Mantel-Haenszel chi-squared test for categorical variables and linear regression analysis for continuous variables, assigning ordinal numbers 0-4 to quintile categories of soy product intake.⁵ 1 cup = 120 mL.

Discussion

In this large-scale, population-based prospective study among Japanese adults, soy product and isoflavone intakes overall were not found to be significantly associated with risk of developing type 2 diabetes in either men or women. In stratified analyses by BMI or menopausal status (women only), however, we found a decrease in risk of type 2 diabetes associated with higher levels of soy product, daidzein, and genistein intakes in overweight women and, to a lesser extent, in postmenopausal women. To

our knowledge, ours is the first prospective study to examine the association of isoflavone intakes with type 2 diabetes in an apparently healthy population.

With regard to findings in women, although intake of soy products or isoflavones was not associated with risk of type 2 diabetes for all women in the present study, a suggestive protective association was noted among overweight women. No previous study to our knowledge has assessed the association between intake of these food factors and type 2 diabetes or glucose intolerance stratified by BMI. Among studies

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TABLE 3 Odds ratios and 95% CI of type 2 diabetes according to quintile categories of soy product, daidzein, and genistein intakes in the JPHC Study¹

	Men, n = 25,872					Women, n = 33,919				
	Range of intake	Participants, n	Cases, n	Age- and area-adjusted OR (95% CI)	Multivariable-adjusted ² OR (95% CI)	Range of intake	Participants, n	Cases, n	Age- and area-adjusted OR (95% CI)	Multivariable-adjusted ² OR (95% CI)
Soy products										
Q1 (low)	<43.1 g	5174	124	1.00 (reference)	1.00 (reference)	<42.8 g	6783	103	1.00 (reference)	1.00 (reference)
Q2	43.1–62.5	5175	129	1.05 (0.81, 1.35)	1.05 (0.82, 1.36)	42.8–61.7	6784	85	0.82 (0.62, 1.10)	0.84 (0.62, 1.13)
Q3	62.5–83.7	5174	123	1.00 (0.77, 1.29)	1.00 (0.76, 1.30)	61.7–82.8	6784	97	0.94 (0.70, 1.25)	0.93 (0.69, 1.25)
Q4	83.7–117.3	5175	125	1.01 (0.78, 1.31)	1.00 (0.76, 1.32)	82.8–116.0	6784	82	0.78 (0.57, 1.05)	0.77 (0.55, 1.06)
Q5 (high)	≥117.3	5174	133	1.06 (0.82, 1.38)	1.02 (0.75, 1.38)	≥116.0	6784	113	1.05 (0.79, 1.40)	0.98 (0.70, 1.39)
P-trend ³				0.78	0.95				0.88	0.73
Daidzein										
Q1 (low)	<7.9 mg	5174	119	1.00 (reference)	1.00 (reference)	<7.7 mg	6783	107	1.00 (reference)	1.00 (reference)
Q2	7.9–11.8	5175	132	1.13 (0.88, 1.46)	1.12 (0.86, 1.45)	7.7–11.5	6784	83	0.78 (0.58, 1.05)	0.78 (0.58, 1.05)
Q3	11.8–16.0	5174	140	1.21 (0.94, 1.59)	1.20 (0.92, 1.56)	11.5–15.8	6784	95	0.90 (0.67, 1.20)	0.92 (0.68, 1.24)
Q4	16.0–22.4	5175	119	1.03 (0.78, 1.35)	1.00 (0.75, 1.34)	15.8–22.0	6784	87	0.81 (0.60, 1.10)	0.79 (0.57, 1.09)
Q5 (high)	≥22.4	5174	124	1.08 (0.82, 1.42)	1.01 (0.72, 1.40)	≥22.0	6784	108	1.00 (0.75, 1.34)	0.92 (0.64, 1.32)
P-trend ³				0.88	0.81				0.88	0.66
Genistein										
Q1 (low)	<12.3 mg	5174	122	1.00 (reference)	1.00 (reference)	<12.2 mg	6783	110	1.00 (reference)	1.00 (reference)
Q2	12.3–18.4	5175	128	1.05 (0.82, 1.37)	1.05 (0.82, 1.36)	12.2–18.4	6784	77	0.70 (0.52, 0.95)	0.71 (0.52–0.96)
Q3	18.4–25.3	5174	140	1.18 (0.91, 1.52)	1.16 (0.91, 1.51)	18.4–25.3	6784	94	0.86 (0.65, 1.15)	0.86 (0.65, 1.19)
Q4	25.3–35.0	5175	122	1.03 (0.78, 1.34)	1.00 (0.78, 1.33)	25.3–35.8	6784	91	0.83 (0.62, 1.11)	0.81 (0.59, 1.11)
Q5 (high)	≥35.0	5174	122	1.03 (0.79, 1.35)	0.95 (0.71, 1.32)	≥35.8	6784	108	0.97 (0.73, 1.29)	0.90 (0.63, 1.29)
P-trend ³				0.98	0.71				0.79	0.77

¹ Diagnosis of type 2 diabetes were based on self-report.

² Adjusted for age (y, continuous), study area (9 areas), BMI (<21, 21–22.9, 23–24.9, 25–26.9, or ≥27 kg/m²), smoking habit (never, past, current with a consumption of <20 or ≥20 cigarettes/d), alcohol consumption (nondrinker, occasional drinker, or drinker with a consumption of <150, 150–299, 300–449, or ≥450 g ethanol/wk for men; and nondrinker, occasional drinker, or drinker with a consumption of <150 or ≥150 g ethanol/wk for women), family history of diabetes mellitus (yes or no), leisure time physical activity (<once/ mo, 1–3 times/mo, or ≥once/wk), history of hypertension (yes or no), coffee consumption (almost never, <1 cup/d, 1 cup/d, or ≥2 cups/d), green tea consumption (almost never, <1 cup/d, 1 cup/d, 2–3 cups/d, or ≥4 cups/d), magnesium intake (mg/d, continuous), calcium intake (mg/d, continuous), vegetable intake (g/d, continuous), fiber intake (g/d, continuous), fish intake (g/d, continuous), and total energy intake (kJ/d, continuous).

³ Based on multiple logistic regression analysis, assigning ordinal numbers 0–4 to the quintile categories of soy product, daidzein, or genistein intakes.

demonstrating a protective association, most have been conducted among Western populations (5,7,8), whose obesity level is much higher than that among the Japanese. Given that obesity induces insulin resistance (25), soy products and isoflavones may reduce risk of type 2 diabetes by improving insulin sensitivity. Further, a decreased risk of type 2 diabetes associated with high isoflavone intake may be due to the potential favorable effects that isoflavones have on weight control (26,27). In the present study, however, women with an elevated intake of soy products tended to weigh more than those with a decreased intake at baseline (Table 2), and thus the weight reduction pathway does not explain the observed association.

We obtained data suggesting an inverse association between isoflavone intake, especially its crude intake, and risk of type 2 diabetes among postmenopausal but not premenopausal women. Such a differential association by menopausal status has not been documented before. In several previous studies showing a protective association between legume or isoflavone intakes and type 2 diabetes or glucose intolerance, the participants were all postmenopausal women (5,7) or relatively older women [age range: 40–70 y (9)]. Data on premenopausal women, however, are sparse (28). Risk of type 2 diabetes increases after menopause and hormone replacement therapy is known to be related to a decreased risk of type 2 diabetes (29), suggesting a protective role of estrogen in glucose metabolism. In addition, phytoestrogens have been hypothesized to act as

estrogen agonists in the low-estrogen milieu after menopause (30). The inverse association among postmenopausal women in the present study may thus be ascribed at least in part to weak estrogenic effects of isoflavones.

The inverse associations we observed among overweight or postmenopausal women became more pronounced when crude intake, rather than an energy-adjusted value using the residual method, was used to create quintiles of dietary exposure. This may suggest that absolute intake of soy food is etiologically more relevant than energy-adjusted intake. However, other explanations are also possible; for instance, energy adjustment may have attenuated the association if those at an elevated risk of developing diabetes tended to decrease energy intake while maintaining soy food intake. Alternatively, the difference may simply be due to a random variation, given that the CI overlapped with each other considerably. The reason behind this discrepancy between the 2 analytical procedures should be identified before any inference regarding a dose-response relationship is made.

We observed no association between intake of soy products and isoflavones and risk of developing type 2 diabetes in overall men or in any subgroup of men. Previously, 2 studies explored the association between these intakes and glucose intolerance in men, but the results were inconsistent (6,8). The etiology of type 2 diabetes may be sex specific, as endogenous sex hormones differentially modulate glycemic status and risk of type 2 diabetes in men and women (31). Our finding indicates that

TABLE 4 Multivariable-adjusted odds ratios and 95% CI of type 2 diabetes according to quintile categories of soy product, daidzein, and genistein intakes by BMI in women of the JPHC Study^{1,2}

	BMI <25 kg/m ² , n = 23,586			BMI ≥25 kg/m ² , n = 9459					
	Quintile of energy-adjusted intake			Quintile of crude intake			Quintile of energy-adjusted intake		
	Participants, n	Cases, n	OR (95% CI)	Participants, n	Cases, n	OR (95% CI)	Participants, n	Cases, n	OR (95% CI)
Soy products									
Q1 (low)	4756	46	1.00 (reference)	1797	60	1.00 (reference)	1784	55	1.00 (reference)
Q2	4900	39	0.82 (0.53, 1.28)	1772	42	0.65 (0.43, 0.99)	1730	44	0.78 (0.52, 1.18)
Q3	4736	50	1.05 (0.69, 1.61)	1885	42	0.55 (0.36, 0.87)	1854	47	0.79 (0.52, 1.20)
Q4	4666	38	0.82 (0.51, 1.32)	1908	54	0.67 (0.43, 1.05)	1957	40	0.62 (0.39, 0.99)
Q5 (high)	4468	46	0.93 (0.55, 1.56)	2097	51	0.49 (0.29, 0.83)	2134	63	0.89 (0.56, 1.44)
P-trend ³			0.80			0.027			0.41
Daidzein									
Q1 (low)	4698	47	1.00 (reference)	1881	56	1.00 (reference)	1849	58	1.00 (reference)
Q2	4767	37	0.77 (0.50, 1.21)	1864	50	0.86 (0.58, 1.29)	1856	44	0.73 (0.48, 1.10)
Q3	4795	47	0.99 (0.64, 1.54)	1839	43	0.67 (0.43, 1.05)	1847	47	0.80 (0.53, 1.22)
Q4	4719	48	0.97 (0.61, 1.54)	1921	49	0.69 (0.43, 1.10)	1912	37	0.58 (0.36, 0.92)
Q5 (high)	4607	40	0.77 (0.45, 1.33)	1954	51	0.58 (0.33, 1.01)	1995	63	0.92 (0.56, 1.52)
P-trend ³			0.70			0.042			0.47
Genistein									
Q1 (low)	4698	49	1.00 (reference)	1866	56	1.00 (reference)	1846	60	1.00 (reference)
Q2	4775	34	0.89 (0.44, 1.09)	1869	50	0.86 (0.57, 1.29)	1853	41	0.65 (0.43, 0.99)
Q3	4795	48	0.99 (0.64, 1.54)	1822	42	0.66 (0.42, 1.03)	1846	45	0.74 (0.49, 1.14)
Q4	4717	50	0.89 (0.63, 1.57)	1938	48	0.67 (0.42, 1.07)	1915	39	0.59 (0.37, 0.94)
Q5 (high)	4601	39	0.73 (0.43, 1.27)	1964	53	0.61 (0.35, 1.05)	1999	64	0.91 (0.56, 1.50)
P-trend ³			0.76			0.052			0.57

¹ Diagnosis of type 2 diabetes were based on self-report.

² Adjusted for age (y, continuous), study area (9 areas), BMI (<21, 21–22.9, 23–24.9, 25–26.9, or ≥27 kg/m²), smoking habit (never, past, current with a consumption of <20 or ≥20 cigarettes/d), alcohol consumption (nondrinker, occasional drinker, or drinker with a consumption of <150, 150–299, 300–449, or ≥450 g ethanol/wk for men; and nondrinker, occasional drinker, or drinker with a consumption of <150 or ≥150 g ethanol/wk for women), family history of diabetes mellitus (yes or no), leisure time physical activity (<once/mo, 1–3 times/mo, or ≥once/wk), history of hypertension (yes or no), coffee consumption (almost never, <1 cup/d, 1 cup/d, or ≥2 cups/d), green tea consumption (almost never, <1 cup/d, 1 cup/d, 2–3 cups/d, or ≥4 cups/d), magnesium intake (mg/d, continuous), calcium intake (mg/d, continuous), vegetable intake (g/d, continuous), fiber intake (g/d, continuous), fish intake (g/d, continuous), and total energy intake (kJ/d, continuous).

³ Based on multiple logistic regression analysis, assigning ordinal numbers 0–4 to the quintile categories of soy product, daidzein, or genistein intakes.

isoflavones may not play an important role in the pathogenesis of type 2 diabetes in men.

The mechanism by which isoflavones exert their antidiabetic effect is unclear. Isoflavones are structurally similar to endogenous estrogens and thus have a weak estrogenic effect by binding to the intranuclear estrogen receptors in various tissues (26,27). Estrogen has been suggested to participate in glucose homeostasis by modulating the expression of genes that are involved in insulin sensitivity and glucose uptake (32). Further, estrogen is a major regulator of adipocyte development and adipocyte number and inhibits lipogenesis by reducing the activity of lipoprotein lipase, an enzyme that regulates lipid uptake by adipocytes (27). Isoflavones may also affect glucose metabolism by nonestrogen receptor-mediated mechanisms (26). For example, isoflavones have been reported to have an antidiabetic effect through activation of PPAR, nuclear receptors that participate in cellular lipid homeostasis and insulin action (4). In addition to their estrogenic activity, isoflavones may inhibit intestinal glucose uptake, prevent glucose-induced lipid peroxidation, and improve basal metabolic rate and energy metabolism (26). Further, soy protein may improve insulin resistance and reduce adiposity by inhibiting insulin secretion from pancreatic β cells or by inhibiting lipogenesis and increasing lipolysis in the liver and adipocytes (26).

Strengths of the present study include our large sample size, the population-based prospective design, the use of a validated

FFQ, and extensive adjustment of potentially important confounding factors, including obesity, smoking habit, family history of diabetes, and total energy. However, several limitations to the present study warrant mention. First, the diagnosis of type 2 diabetes was ascertained by self-report. However, a validation study conducted among our study population showed fairly good agreement between self-reported diabetes and diabetes documented in medical records (94%) and sensitivity of self-reported diabetes was reasonably high (83%). Second, dietary intakes of soy products and isoflavones were measured at only 1 time point (the second survey, which is the baseline of the present analysis) and thus may not reflect long-term intake levels. Repeated assessment of diet over a long period of time prior to the onset of a disease will provide a better estimate of exposure status. Third, because soy foods are the sole source of isoflavones, our study could not differentiate the effect of isoflavones from other substances in soy foods. To address this issue, measurements of isoflavone concentrations in blood or urine are required.

In conclusion, the present study found no evidence to support the hypothesis that higher intakes of soy product and isoflavones prevent type 2 diabetes in either men or all women. However, we did observe associations suggestive of a protective role of these food factors in overweight women or, to a lesser extent, postmenopausal women. Our findings warrant further investigation.

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