Eur J Nutr (2012) 51:1033–1040
DOI 10.1007/s00394-011-0276-2

ORIGINAL CONTRIBUTION

Soy intake and risk of type 2 diabetes mellitus in Chinese Singaporeans

Soy intake and risk of type 2 diabetes

Noel T. Mueller · Andrew O. Odegaard · Myron D. Gross · Woon-Puay Koh · Mimi C. Yu · Jian-Min Yuan · Mark A. Pereira

Received: 15 August 2011 / Accepted: 3 November 2011 / Published online: 18 November 2011

Abstract
Purpose To examine the association between soy products and their components, isoflavones and protein, and incident type 2 diabetes in a population with varied soy intake and high rates of diabetes.
Methods We used data from the Singapore Chinese Health Study, including 43,176 Chinese men and women aged 45–74 years, free of chronic disease at baseline (1993–1998) and followed through 2004. Intake of individual soy items, total unsweetened soy, and soy components was assessed by food-frequency questionnaire and examined with type 2 diabetes risk using Cox regression.
Results During an average follow-up of 5.7 years, 2,252 of the 43,176 participants included in the current analyses developed diabetes. After adjustment for potential confounders and BMI, consumption of unsweetened soy was inversely associated with diabetes risk. Hazard ratios (HRs) and 95% CI for diabetes across unsweetened soy intake categories (none, 1–4/month, 1–2/week, 3–4/week, ≥5/week) were: 1 (referent), 0.81 (0.67–0.97), 0.76 (0.63–0.91), 0.76 (0.63–0.92), and 0.72 (0.59–0.89), respectively ($P_{trend} = 0.015$). Conversely, in multivariate models, consuming sweetened soybean drink was positively associated with diabetes risk. HRs for diabetes across soybean drink intake categories (none, 1–3/month, 1/week, ≥2/week) were: 1 (referent), 1.07 (0.95–1.20), 1.12 (1.00–1.26), and 1.13 (1.00–1.28), respectively ($P_{trend} = 0.03$). Furthermore, after full adjustment, including adjustment for sweetened soy items, we observed a marginally significant inverse association between isoflavone intake and diabetes (HR for the fifth compared to the first quintile: 0.76; 95% CI: 0.58–1.00; $P_{trend} = 0.08$).
Conclusions The current findings support a protective role for unsweetened soy foods and isoflavones on risk of type 2 diabetes.

Keywords Soy · Isoflavones · Type 2 diabetes · Chinese · Cohort study

N. T. Mueller (✉) · A. O. Odegaard · M. D. Gross · J.-M. Yuan · M. A. Pereira
Division of Epidemiology and Community Health, University of Minnesota, 1300 South 2nd St., Suite 300, Minneapolis, MN 55454, USA
e-mail: muel0266@umn.edu

W.-P. Koh
Department of Epidemiology and Public Health, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

M. C. Yu · J.-M. Yuan
The Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA

Introduction

Type 2 diabetes has become a global public health challenge. In Southeast Asia, the prevalence has increased three- to fivefold over 30 years and is projected to rise higher [1, 2]. In Singapore, diabetes prevalence in adults aged 18–69 years has risen from 2% when first measured in 1975, to 4.7% in 1984, 8.6% in 1992, and 9% in 1998 [3]. Insight into the role of dietary factors in the development of type 2 diabetes may contribute to its prevention.

It has been postulated that whole soy foods as well as components of soy—isoflavones and protein—may help prevent the progression of type 2 diabetes [4–6]. Two cross-sectional studies have assessed the association between isoflavone intake and glucose tolerance [7, 8]. One study found lower levels of post-challenge insulin

concentrations among persons with high isoflavone intake than among those with low intake [7], while the other found no association between isoflavones and glycated hemoglobin and fasting insulin [8]. In prospective studies, soy product and isoflavone intake has been linked to decreased risk of glucose intolerance [9, 10] and type 2 diabetes [11, 12]. However, another cohort study found that soy consumption had no significant association with diabetes incidence [13]. A meta-analysis of intervention studies on soy intake and glycemic control found no effect of isoflavone or soy protein extracts on fasting insulin or glucose; however, a favorable change in fasting glucose concentrations was observed in studies that used whole soy foods or a soy diet [14]. Thus, the role of soy food intake and its components with the development of type 2 diabetes is inconclusive.

No studies to date have examined the association between intake of individual soy items and incident type 2 diabetes in a population with high rates of diabetes and varied soy food consumption. Previously, our group observed an inverse association between consuming a vegetable, fruit, and soy-rich dietary pattern and risk of type 2 diabetes [15]. Here, we prospectively evaluated individual soy foods and drink, as well as isoflavones and soy protein, in a large cohort of Singaporean Chinese adults. We hypothesized that intake of soy foods and their components, isoflavones and protein, would be inversely associated with risk of type 2 diabetes.

Subjects and methods

Subjects

The Singapore Chinese Health Study (SCHS) is a population-based, prospective investigation into diet and cancer risk [16]. The study was approved by the Institutional Review Boards of the National University of Singapore and the University of Minnesota, and all subjects who were enrolled gave informed consent. The cohort was drawn from permanent residents of government-built housing estates, where 86% of the Singapore population resided during the enrollment period. Study subjects were restricted to the two major dialect groups of Chinese in Singapore, the Hokkiens and Cantonese, who originated from the contiguous provinces of Fujian and Guangdong, respectively, in the southern part of China. Recruitment was initiated with a letter informing potential participants of the study and inviting them to take part. Five to seven days later, study staff went door-to-door to invite subjects to participate. Approximately 85% of eligible subjects who were invited agreed to participate [16]. At recruitment, each subject was interviewed face-to-face in their home by a trained interviewer using a structured, scanner-readable questionnaire which requested information on demographics, height, weight, use of tobacco, usual physical activity, menstrual and reproductive history (women only), medical history, familial history of cancer, and dietary intake. Between April 1993 and December 1998, 63,257 Chinese women and men aged 45–74 years (mean age 56.5) were enrolled in the study [16].

Dietary assessment

A semiquantitative food-frequency questionnaire (FFQ), specifically developed for this population and assessing 165 commonly consumed food items, was administered during the baseline interview. During the interview, the respondents were shown accompanying photographs that listed eight food-frequency categories (ranging from "never or hardly ever" to "two or more times a day") and depicted three portion sizes. The FFQ has been validated against a series of 24-h dietary recall interviews in a random sample of 1,022 participants that occurred on one weekday and one weekend day approximately 2 months apart [16], and against selected biomarkers [17].

Soy product and component intake

Seven soy items are common in the Singapore Chinese diet, and all are non-fermented: plain tofu, tau pok, tau kwa, foo pei, foojook, tofu far, and soybean drink [18, 19]. We expressed soy product intake in terms of reported frequency for each soy item, except for foo pei as it was not assessed individually on the FFQ. Unsweetened soy product consumption was calculated by adding the frequency of individual unsweetened, non-fried soy items, which included plain tofu, tau kwa, and foo jook. Tofu far and soybean drink are sweetened soy items, and tau pok is deep-fried. We additionally assessed soy components by deriving grams of soy protein and milligrams of soy isoflavones [18]. For a given subject, total soy protein intake was the summation of the protein contents of soy foods listed in the Singapore Food Composition Database. In addition, we previously measured concentrations of genistein, daidzein, and glycitein in market samples of common soy foods in Singapore [18]. Total soy isoflavone intake for a given subject was computed based on the FFQ and the summation of the genistein, daidzein, and glycitein content of the soy foods in the Singapore Food Composition Database. In a dietary validation study of SCHS subjects, we found correlation coefficients of 0.63, 0.39, and 0.32 between the FFQ and a series of 24-h recalls for soy products, isoflavone, and soy protein, respectively [16]. Furthermore, dietary intake of individual soy items was statistically associated, in a dose-dependent manner, with the sum of

urinary soy daidzein, genistein, and glycitein (P for linear trend = 0.04), and there was a 4.9-fold difference between the 25th and 75th percentile values for the sum of the urinary isoflavonoids ($P = 0.04$) [17].

Ascertainment of type 2 diabetes

Self-reported diabetes as diagnosed by a physician was evaluated at baseline, and participants with a history of diagnosed diabetes were excluded from analysis. Diabetes status was assessed again by the following question asked during the follow-up telephone interview: "Have you been told by a doctor that you have diabetes (high blood sugar)?" If yes: "Please also tell me the age at which you were first diagnosed?" Participants were classified as having incident diabetes if they reported developing diabetes anytime between the initial enrollment interview and the follow-up telephone interview that occurred between July 1999 and October 2004.

A validation study of the incident diabetes mellitus cases used two different methods and is reported in detail in Odegaard et al. [20]. Based on a hospital-based discharge summary database and a supplementary questionnaire regarding symptoms, diagnostic tests, and hypoglycemic therapy during a telephone interview, we observed a positive predictive value of 99% [20]. Alternatively, 2,625 randomly selected participants who answered "no" to the question of diabetes diagnosis at baseline and follow-up, and provided blood samples at their follow-up interview, were analyzed for HbA1c % (glycated hemoglobin). One hundred and forty-eight subjects (5.6% of the sample) had an HbA1c $\geq$ 6.5%, meeting the most recent diagnostic guidelines for the presence of diabetes [21, 22]. Thus, 94.4% of persons who reported being free of diabetes at baseline and follow-up were below the HbA1c threshold for diabetes [20].

Statistical analysis

Participants who died before the follow-up interview ($n = 7{,}722$), reported baseline diabetes ($n = 5{,}469$), cancer, heart disease, or stroke ($n = 5{,}975$), reported extreme sex-specific energy intakes (<600 or >3,000 kcal for women) (<700 or >3,700 kcal for men), or subjects from the initial cohort that migrated out of Singapore ($n = 17$) were not included in these analyses. These, along with further exclusion of 20 participants whose diabetes status was not clear after the validation effort, left 43,176 participants in the present analysis.

Age-, sex-, and energy-adjusted baseline participant characteristics were compared across categories of unsweetened soy intake. Person-years for each participant were calculated from the year of recruitment to the year of reported type 2 diabetes diagnosis, or year of follow-up telephone interview for those who did not report diabetes diagnoses. Cox regression was applied to calculate hazard ratios and 95% confidence intervals. Total unsweetened soy intake was grouped into five categories (none, 1–4 times/month, 1–2 times/week, 3–4 times/week, and $\geq$5 times/week). Energy-adjusted intakes of soy isoflavones (mg/1,000 kcal) and soy protein (% kcal) were categorized by quintile distribution with the lowest quintile as the reference.

The selection of potential confounders was based primarily on prior consideration of their associations with both soy intake, in this population, and type 2 diabetes. All models included age (five categories), year of baseline interview, sex and dialect (Hokkiens/Cantonese), education level (none, primary, secondary, secondary +), any moderate or strenuous physical activity (y/n), smoking status (never, former, current), alcohol consumption (none, weekly, daily), and baseline hypertensive status (y/n). Additionally, soy food models were adjusted for intake of noodles (g/1,000 kcal), rice (g/1,000 kcal), other grains (i.e., bread and cereal grains) (g/1,000 kcal), green vegetables (g/1,000 kcal), red meat (g/1,000 kcal), soybean drink (four categories), and total energy (kcal/day). The soybean drink model was additionally adjusted for soft drinks (never, 1–4 times/month, $\geq$2 times/week), juice drinks (never, 1–4 times/month, $\geq$2 times/week), green tea (none/monthly, weekly, daily), coffee (none/monthly, 1–3 times/week, $\geq$4 times/week), unsweetened soy (five categories), and total energy (kcal/day).

Soy protein and isoflavone models were adjusted for consumption of carbohydrate (% kcal), polyunsaturated fatty acid (% kcal), non-soy protein (% kcal), calcium (g/1,000 kcal), and total energy (kcal/day). In a separate model, we additionally adjusted for sweetened soy items—soybean drink (four categories) and tofu far (five categories). All multivariate models were then further adjusted for BMI (five categories). Other variables were evaluated but not included in the analysis because they were unrelated either to soy food intake or to risk of diabetes. These included intake of fruits and dairy for soy food models, and saturated fat and dietary fiber for soy-component models. Soy isoflavones were highly correlated with total soy products ($r = 0.98$) and soy protein ($r = 0.94$) and thus were not included in the same model. Tests for trend were performed by entering ordinal categorical variables as continuous variables in the Cox regression models.

We assessed pre-specified interaction by sex, menopausal status, smoking status, and BMI. Ethnic-specific cutoffs for overweight and obesity by BMI (kg/m^2) were applied: 23 and 27.5 kg/m^2 for Singaporean Chinese [23]. The log-likelihood ratio test was used to evaluate the interaction terms. All analyses were performed using SAS

(version 9.2; SAS Institute Inc, Chicago, IL), and all tests of statistical significance were based on two-sided probability.

Results

The 43,176 participants had a mean age of 55.2 years at enrollment, and 57.6% were women. Baseline characteristics according to frequency of unsweetened, non-fried soy intake are shown in Table 1. Participants consuming greater amounts of unsweetened soy products were more likely to be women, educated, and were more likely to engage in some level of physical activity. They also had a lower prevalence of smoking and hypertension. Unsweetened soy consumption was positively associated with green vegetable, calcium, and total energy intake. It was inversely associated with consuming noodles, rice, red meat, and carbohydrate.

During an average follow-up of 5.7 years, 2,252 participants developed type 2 diabetes (approximately 5.2%). Hazard ratios (HRs) and 95% confidence intervals (CI) for incident type 2 diabetes across intakes of individual soy items are presented in Table 2. After multivariate adjustment, plain tofu was inversely associated with risk of diabetes (P for trend = 0.01). This association was slightly attenuated after adjustment for BMI (HR for ≥2/week compared to none: 0.89; 95% CI: 0.77, 1.03; P for trend = 0.05) (Table 2). After full covariate adjustment, consumption of tau kwa (e.g., firm tofu) 2–3 times per month (HR: 0.86; 95% CI: 0.75, 0.98) and 1 time per week (HR: 0.88; 95% CI: 0.77, 1.00) was associated with a decreased risk of diabetes. However, there was no evidence of reduced diabetes risk in the higher intake categories (P for trend = 0.24). Likewise, intake of foojook was associated with a decreased risk of diabetes at the 2–3 times per month level (HR: 0.87; 95% CI: 0.78, 0.97; P for trend = 0.07), but there was no evidence of association in the higher intake categories. When examining the overall frequency of unsweetened soy items with adjustment for demographic, lifestyle, and dietary factors, as well as BMI, we found that consumption of unsweetened soy was inversely associated with risk of diabetes in a graded fashion. HRs and 95% CI for diabetes across unsweetened

Table 1 Baseline characteristics according to categories of unsweetened, non-fried soy intake

	None	1–4/month	1–2/week	3–4/week	≥5/week
Participants (*n*)	2,155	8,820	14,235	11,548	6,418
Female (%)	51.1	55.1	57.7	59.8	58.7
Age at baseline (year)	55.7 ± 0.16	55.4 ± 0.08	55.1 ± 0.06	55.4 ± 0.07	54.9 ± 0.09
BMI[a] (kg/m^2)	23.0 ± 0.07	23.0 ± 0.03	23.1 ± 0.03	23.1 ± 0.03	22.9 ± 0.04
Current smokers[a] (%)	20.9	19.7	18.2	17.4	15.6
Alcohol[a] (% ≥1 drink/week)	18.7	20.4	19.7	20.2	20.2
Physical activity[a] (% ever)	20.4	24.4	27.3	29.7	32.2
Hypertension[a] (%)	22.1	19.0	19.5	19.2	19.5
Secondary education[a] (%)	29.1	31.4	29.5	30.8	33.0
Energy intake[a] (kcal/day)	1,398.8 ± 9.9	1,421.3 ± 4.9	1,490.6 ± 3.9	1,643.7 ± 4.3	1,851.5 ± 5.7
Total soy[b,c] (g/day)	58.1 ± 1.51	75.4 ± 0.75	93.9 ± 0.59	126.0 ± 0.65	200.1 ± 0.90
Soy protein[c] (g/day)	2.9 ± 0.07	3.8 ± 0.04	4.9 ± 0.03	6.7 ± 0.03	10.9 ± 0.04
Isoflavones[c] (mg/day)	10.0 ± 0.28	13.0 ± 0.14	15.9 ± 0.11	21.0 ± 0.12	32.8 ± 0.17
Noodles[c] (g/day)	59.5 ± 0.86	55.5 ± 0.43	54.5 ± 0.33	54.5 ± 0.37	52.5 ± 0.51
Rice[c] (g/day)	452.6 ± 3.23	448.2 ± 1.61	439.2 ± 1.26	405.1 ± 1.40	348.36 ± 1.92
Green vegetables[c] (g/day)	60.0 ± 0.73	60.8 ± 0.36	63.2 ± 0.28	70.4 ± 0.32	88.2 ± 0.43
Red meat[c] (g/day)	32.2 ± 0.39	30.9 ± 0.19	31.1 ± 0.15	31.1 ± 0.17	27.5 ± 0.23
Calcium[c] (mg/day)	369.5 ± 3.73	382.2 ± 1.85	395.4 ± 1.45	430.2 ± 1.61	500.6 ± 2.22
Polyunsaturated fat[c] (g/day)	7.6 ± 0.07	8.0 ± 0.03	8.5 ± 0.03	9.3 ± 0.03	11.1 ± 0.04
Carbohydrate[c] (g/day)	238.0 ± 0.62	237.2 ± 0.31	233.9 ± 0.24	226.4 ± 0.27	214.0 ± 0.37

Unsweetened, non-fried soy items include plain tofu, tau kwa, and foojook. Values are means ± SE unless otherwise noted and were derived by chi-square tests for categorical variables and ANOVA tests for continuous variables. All trends were significant by the Wald test ($P < 0.05$)

[a] Values adjusted for age and sex

[b] Tofu equivalents derived from plain tofu, tau pok, tau kwa, foo pei, foojook, tofu far, and soybean drink

[c] Values additionally adjusted for total energy intake (kcal/day)

Table 2 Hazard ratios (HRs) and 95% confidence intervals (CI) for the association between soy products and incident type 2 diabetes

	None	1/month	2–3/month	1/week	≥2/week	*P* for trend[e]
Unsweetened soy						
Plain tofu						
Cases (*n*)/person-years	381/38,617	251/25,736	579/60,163	650/74,870	391/47,512	
Multivariable-adjusted[a]	1.0 (reference)	1.02 (0.87, 1.20)	0.98 (0.86, 1.12)	0.90 (0.79, 1.02)	0.86 (0.74, 1.00)	0.014
Multivariable-adjusted + BMI[b]	1.0 (reference)	1.01 (0.86, 1.19)	0.97 (0.85, 1.11)	0.91 (0.80, 1.04)	0.89 (0.77, 1.03)	0.046
Tau kwa						
Cases (*n*)/person-years	451/45,417	278/30,851	521/58,990	579/66,860	423/44,780	
Multivariable-adjusted[a]	1.0 (reference)	0.91 (0.78, 1.06)	0.87 (0.76, 0.99)	0.87 (0.76, 0.98)	0.94 (0.81, 1.08)	0.183
Multivariable-adjusted + BMI[b]	1.0 (reference)	0.91 (0.78, 1.06)	0.86 (0.75, 0.98)	0.88 (0.77, 1.00)	0.94 (0.82, 1.08)	0.239
Foojook						
Cases (*n*)/person-years	1,115/116,583	447/50,009	427/50,445	178/20,516	85/9,345	
Multivariable-adjusted[a]	1.0 (reference)	0.94 (0.84, 1.05)	0.88 (0.78, 0.98)	0.89 (0.76, 1.05)	0.96 (0.77, 1.21)	0.055
Multivariable-adjusted + BMI[b]	1.0 (reference)	0.94 (0.84, 1.05)	0.87 (0.78, 0.97)	0.91 (0.77, 1.06)	0.99 (0.79, 1.24)	0.069
	None	1–4/month	1–2/week	3–4/week	≥5/week	*P* for trend[e]
Total unsweetened soy[c]						
Cases (*n*)/person-years	141/117,74	457/49,154	747/82,791	603/66,525	304/36,654	
Multivariable-adjusted[a]	1.0 (reference)	0.80 (0.66, 0.97)	0.76 (0.63, 0.91)	0.76 (0.63, 0.92)	0.70 (0.57, 0.86)	0.003
Multivariable-adjusted + BMI[b]	1.0 (reference)	0.81 (0.67, 0.97)	0.76 (0.63, 0.91)	0.76 (0.63, 0.92)	0.72 (0.59, 0.89)	0.015
	None	1/month	2–3/month	1/week	≥2/week	*P* for trend[e]
Deep-fried soy						
Tau pok						
Cases (*n*)/person-years	1,131/124,895	401/42,215	380/40,591	238/27,751	102/11,446	
Multivariable-adjusted[a]	1.0 (reference)	1.04 (0.92, 1.16)	1.02 (0.91, 1.15)	0.96 (0.83, 1.11)	1.00 (0.81, 1.23)	0.857
Multivariable-adjusted + BMI[b]	1.0 (reference)	1.02 (0.91, 1.14)	1.04 (0.93, 1.17)	0.98 (0.85, 1.13)	1.00 (0.82, 1.24)	0.917
	None	1/month	2–3/month	1/week	≥2/week	*P* for trend[e]
Sweetened soy						
Tofu far						
Cases (*n*)/person-years	1,024/112,804	351/39,138	402/43,096	333/36,513	142/15,347	
Multivariable-adjusted[a]	1.0 (reference)	1.00 (0.88, 1.13)	1.04 (0.92, 1.18)	0.99 (0.87, 1.14)	1.01 (0.83, 1.23)	0.869
Multivariable-adjusted + BMI[b]	1.0 (reference)	1.01 (0.89, 1.15)	1.05 (0.93, 1.19)	1.01 (0.88, 1.15)	1.04 (0.86, 1.26)	0.651

	None	1–3/month	1/week	≥2/week	*P* for trend[e]
Soybean drink[d]					
Cases (*n*)/person-years	679/77,355	517/57,103	578/62,941	478/49,499	
Multivariable-adjusted[a]	1.0 (reference)	1.07 (0.95, 1.20)	1.13 (1.01, 1.27)	1.15 (1.01, 1.30)	0.018
Multivariable-adjusted + BMI[b]	1.0 (reference)	1.07 (0.95, 1.20)	1.12 (1.00, 1.26)	1.13 (1.00, 1.28)	0.031

[a] Adjusted for age (<50, 50–54, 55–59, 60–64, ≥65), sex, dialect (Hokkiens/Cantonese), year of interview, educational level (none, primary, secondary plus), smoking status (never, former, current), alcohol use (none, occasional, weekly, daily), any physical activity (y/n), baseline hypertensive status (y/n), rice (g/1,000 kcal), noodles (g/1,000 kcal), other grains (g/1,000 kcal), red meat (g/1,000 kcal), green vegetable (g/1,000 kcal), soybean drink (four categories), and total energy (kcal/day)

[b] Additional adjustment for body mass index (five categories)

[c] Represents aggregate of all unsweetened, non-fried soy products

[d] Soybean drink models additionally adjusted for soft drinks (never, 1–4/month, ≥2/week), fruit drinks (never, 1–4/month, ≥2×/week), green tea (none/monthly, weekly, daily), coffee (none/monthly, 1–3/week, ≥4/week), and unsweetened soy (never, 1–4/month, 1–2/week, 3–4/week, ≥5/week)

[e] Tests for trend were performed by treating the ordinal categories as continuous variables in the models

soy intake categories (none, 1–4/month, 1–2/week, 3–4/week, ≥5/week) were 1 (referent), 0.81 (0.67, 0.97), 0.76 (0.63, 0.91), 0.76 (0.63, 0.92), and 0.72 (0.59, 0.89), respectively (P for trend = 0.02). Conversely, in multivariate models, consuming sweetened soybean drink was positively associated with risk of diabetes. HRs for diabetes across soybean drink intake categories (none, 1–3/month, 1/week, ≥2/week) were 1 (referent), 1.07 (0.95, 1.20), 1.12 (1.00, 1.26), and 1.13 (1.00, 1.28), respectively (P for trend = 0.03). Deep-fried (tau pok) or sweetened (tofu far) soy food dishes were not statistically associated with risk of diabetes.

We also investigated soy isoflavones and soy protein in relation to type 2 diabetes. After full covariate adjustment—including adjustment for sweetened soy and BMI—we observed a marginally significant inverse association between soy isoflavone intake and diabetes in a comparison of the top with the bottom quintile (HR: 0.76; 95% CI: 0.58, 1.00; P for trend = 0.08) (Table 3). A weak non-significant inverse association between soy protein intake and diabetes risk was observed (HR for fifth compared to the first quintile: 0.86; 95% CI: 0.67, 1.10; P for trend = 0.34).

We tested for the potential interaction between soy intakes and sex, menopausal status, smoking status, and BMI on type 2 diabetes risk. There was no statistical evidence supporting any interaction effect. Analyses excluding diabetes cases that occurred within 2 years post-enrollment did not materially alter the results.

Conclusions

In this large, population-based, prospective study of 43,176 Singaporean Chinese men and women, we observed an inverse association between greater frequency of consumption of unsweetened, non-fried soy items and risk of type 2 diabetes. Consistent with the analysis focused on whole soy foods, we observed a marginally significant inverse association between intake of soy isoflavones and diabetes. Our results are in accordance with some of the previous cohort studies. Villegas et al. [11] reported that soy intake was inversely associated with incidence of diabetes in Chinese women aged 40–70 years. Nanri et al. [12] observed an inverse association in overweight postmenopausal Japanese women, although a null association between soy intake and diabetes in the entire population of men and women aged 40–69 years. Our results deviate from those of Morimoto and colleagues [13], who observed a null to marginally positive association between reported soy intake and diabetes in multiethnic population of men and women in Hawaii aged 45–65 years who had low levels of soy intake (median intakes ranged from 0 g/day for Caucasians to 14.5 g/day for Japanese Americans).

There are multiple considerations when reviewing the inconsistent findings between studies. The prospective studies on this topic, including ours, were conducted in culturally and geographically unique regions of the world among populations with very different dietary patterns and sources of soy. One way to enhance the interpretation of

Table 3 Hazard ratios (HRs) and 95% confidence intervals (CI) for the association between soy nutrients and type 2 diabetes

	Q1	Q2	Q3	Q4	Q5	P for trend[d]
Soy isoflavones						
Mean (mg/1,000 kcal)	3.05	6.73	10.02	14.28	25.67	
Cases (n)/person-years	444/48,806	445/49,635	458/49,550	455/49,644	450/49,263	
Multivariable-adjusted[a]	1.0	1.00 (0.87, 1.15)	1.03 (0.89, 1.19)	1.02 (0.87, 1.20)	1.02 (0.83, 1.25)	0.789
Multivariable-adjusted + sweetened soy[b]	1.0	0.93 (0.81, 1.08)	0.90 (0.76, 1.07)	0.84 (0.69, 1.03)	0.76 (0.58, 1.01)	0.065
Multivariable-adjusted + BMI[c]	1.0	0.93 (0.81, 1.08)	0.91 (0.77, 1.08)	0.85 (0.70, 1.05)	0.76 (0.58, 1.00)	0.080
Soy protein						
Mean (% kcal)	0.44	0.91	1.30	1.80	3.03	
Cases (n)/Person-years	432/48,882	454/49,737	463/49,718	465/49,565	438/48,996	
Multivariable-adjusted[a]	1.0	1.03 (0.90, 1.19)	1.02 (0.88, 1.19)	1.02 (0.86, 1.21)	0.93 (0.74, 1.18)	0.800
Multivariable-adjusted + sweetened soy[b]	1.0	1.00 (0.87, 1.15)	0.97 (0.83, 1.13)	0.95 (0.79, 1.14)	0.85 (0.66, 1.08)	0.276
Multivariable-adjusted + BMI[c]	1.0	1.00 (0.87, 1.15)	0.99 (0.84, 1.16)	0.96 (0.80, 1.15)	0.86 (0.67, 1.10)	0.337

[a] Adjusted for age (<50, 50–54, 55–59, 60–64, ≥65), sex, dialect (Hokkiens/Cantonese), year of interview, and soybean drink (never, 1–3/month, 1/week, ≥2–3/week), educational level (none, primary, secondary plus), smoking status (never, former, current), alcohol use (none, occasional, weekly, daily), any physical activity (y/n), baseline hypertensive (y/n), calcium (g/1,000 kcal), carbohydrate (% kcal), polyunsaturated fatty acid (% kcal), non-soy protein (% kcal), and total energy (kcal/day)

[b] Additional adjustment for sweetened soybean drink and tofu far

[c] Additional adjustment for body mass index (five categories)

[d] Tests for trend were performed by treating the ordinal categorical values as continuous variables in the models

findings is to consider them in context of an overall dietary pattern. For example, previously we found that a vegetable, fruit, and soy-rich dietary pattern was inversely associated with risk of type 2 diabetes [15]. In our study, overall soy intake comprised a heterogeneous variety of soy items with differing associations with risk of incident diabetes. Intake of unsweetened soy items was associated with a decreased risk of diabetes, whereas sweetened soybean drink was marginally associated with an increased risk. Furthermore, the inverse association between soy isoflavones and diabetes became significant after adjustment for sweetened soy items. Hence, heterogeneity of soy products and residual bias from dietary content and preparation of soy items may have influenced the results of previous studies.

A systematic review of the intervention studies found that while soy isoflavone extracts did not have antidiabetic effects, soy foods and diets did reduce fasting glucose concentrations [14]. This review is largely consistent with our findings, and those from other prospective studies [11, 12], in that consumption of unsweetened soy items was associated with a decreased risk of diabetes. The association between combined frequency of unsweetened soy and diabetes in our study was much stronger than, and robust to adjustment for, soy isoflavones and protein. This suggests that other components in soy (e.g., soy fiber, polysaccharides, phytoesterol, and unsaturated fatty acid) and their interactions might play a role in the favorable association. Additionally, whole soy foods, the foods they are eaten with, and overall dietary pattern may be more important than individual components of soy, which an observational study such as this is not able to delineate.

We also observed a marginally significant inverse association between soy isoflavones and risk of type 2 diabetes. The weak associations observed for nutrient components of soy may be a function of their lack of reliability. The measures for soy isoflavones and soy protein obtained from the FFQ did not correlate as well with multiple 24-h dietary recalls as did the measures for soy products (0.39 and 0.32 vs. 0.63, respectively) and, thus, are not as good at estimating the underlying variables [16]. As such, the marginal association of these variables may be due to a true weak effect or due to the poor reliability of the diet assessment tool being used.

The observed association between soy isoflavones and diabetes is biologically plausible. Soy isoflavones have been shown to increase serum insulin and pancreatic insulin contents via enhanced insulin signaling and PPAR-gamma activity [6]. It has also been posited that soy isoflavones inhibit insulin release from the pancreas and glucose uptake into the intestinal brush border by restraining protein tyrosine kinase activity [24] or decreasing sodium-dependent glucose transporters [25]. An alternative hypothesis is that soy isoflavones are a marker of a healthy soy-based diet. The effect and mechanism of soy components on glucose metabolism remains inconclusive and warrants further research.

The suggestive positive association between soybean drink and type 2 diabetes observed in our study may be due to the 17 g of sugar per 8.45 fl. oz. drink [17], as other sugar-sweetened beverages have been shown to increase the risk of diabetes in this population [20]. On the other hand, it may be that individuals who consume higher levels of soybean drink have other components of their overall diet that account for the observation. However, in our study, soybean drink was marginally positively associated with diabetes after control for total calories and inclusion of other food groups.

The strengths of our study include the large sample size, prospective nature, high participant response rate, detailed collection of data through face-to-face interview, few participants lost to follow-up, validated diabetes case status, the inclusion of many potential confounding demographic and lifestyle factors, and the use of a validated FFQ that was particularly extensive and designed for this study population. Nevertheless, we acknowledge some limitations. Measurement error in dietary intake and other self-reported variables may result in non-differential misclassification and residual confounding; thus, the observed results are more likely an underestimate than an overestimate. Finally, these results may only apply to physician-diagnosed diabetes. Even with high levels of validity, there is potential for numerous individuals with undiagnosed type 2 diabetes due to the nature of the disease. If the soy intake led to increased or decreased physician diagnosis, the associations could be overestimated.

In conclusion, we observed an inverse association between greater intake frequency of unsweetened, non-fried soy items and incidence of type 2 diabetes in a Chinese population with relatively high and varied soy food consumption. Our findings may be due to a true protective role of soy in the etiology of diabetes or, alternatively, reflect an overall healthy dietary pattern. Moreover, while intake of unsweetened soy items may be protective for diabetes risk, consumption of sweetened soybean drink may increase risk of diabetes. The suggestive positive association between the soybean drink, which is high in added sugar, and diabetes aligns with previous studies examining sugar-sweetened beverages. Overall, our study suggests the context in which soy is consumed (i.e., unsweetened vs. sweetened) is likely important. Yet, the relation of soy foods with type 2 diabetes risk is inconclusive, so further investigation into the topic will continue to inform on this staple food for many cultures.

Acknowledgments We thank Siew-Hong Low of the National University of Singapore for supervising the fieldwork of the

Singapore Chinese Health Study and Renwei Wang of the University of Minnesota for the development and maintenance of the cohort study database. This study was supported by National Institutes of Health, USA (NHLBI T32 NCI RO1 CA055069, R35 CA053890, R01 CA080205, R01 CA098497, and R01 CA144034).

Conflict of interest All authors have no financial or non-financial interests that may be relevant to the submitted work.

References

1. Shaw JE, Sicree RA, Zimmet PZ (2010) Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 87:4–14
2. Yoon KH, Lee JH, Kim JW et al (2006) Epidemic obesity and type 2 diabetes in Asia. Lancet 368:1681–1688
3. Lee WR (2000) The changing demography of diabetes mellitus in Singapore. Diabetes Res Clin Pract 50:S35–S39
4. Bhathena SJ, Velasquez MT (2002) Beneficial role of dietary phytoestrogens in obesity and diabetes. Am J Clin Nutr 76:1191–1201
5. Jayagopal V, Albertazzi P, Kilpatrick ES et al (2002) Beneficial effects of soy phytoestrogen intake in postmenopausal women with type 2 diabetes. Diabetes Care 25:1709–1714
6. Kwon DY, Daily JW III, Kim HJ et al (2010) Antidiabetic effects of fermented soybean products on type 2 diabetes. Nutr Res 30:1–13
7. Goodman-Gruen D, Kritz-Silverstein D (2001) Usual dietary isoflavone intake is associated with cardiovascular disease risk factors in postmenopausal women. J Nutr 131:1202–1206
8. van der Schouw YT, Sampson L, Willett WC et al (2005) The usual intake of lignans but not that of isoflavones may be related to cardiovascular risk factors in U.S. men. J Nutr 135:260–266
9. Feskens EJ, Bowles CH, Kromhout D (1991) Carbohydrate intake and body mass index in relation to the risk of glucose intolerance in an elderly population. Am J Clin Nutr 54:136–140
10. Feskens EJ, Virtanen SM, Rasanen L et al (1995) Dietary factors determining diabetes and impaired glucose tolerance. A 20-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study. Diabetes Care 18:1104–1112
11. Villegas R, Gao YT, Yang G et al (2008) Legume and soy food intake and the incidence of type 2 diabetes in the Shanghai Women's Health Study. Am J Clin Nutr 87:162–167
12. Nanri A, Mizoue T, Takahashi Y et al (2010) Soy product and isoflavone intakes are associated with a lower risk of type 2 diabetes in overweight Japanese women. J Nutr 140:580–586
13. Morimoto Y, Steinbrecher A, Kolonel LN et al (2010) Soy consumption is not protective against diabetes in Hawaii: the multiethnic cohort. Eur J Clin Nutr 65:279–282
14. Zhao-min L, Yu-ming C, Suzanne CH (2011) Effects of soy intake on glycemic control: a meta-analysis of randomized controlled trials. Am J Clin Nutr 93:1092–1101
15. Odegaard AO, Koh WP, Butler LM et al (2011) Dietary patterns and incident type 2 diabetes in Chinese men and women: the Singapore Chinese Health Study. Diabetes Care 34:880–885
16. Hankin JH, Stram DO, Arakawa K et al (2001) Singapore Chinese Health Study: development, validation, and calibration of the quantitative food frequency questionnaire. Nutr Cancer 39:187–195
17. Seow A, Shi CY, Franke AA et al (1998) Isoflavonoid levels in spot urine are associated with frequency of dietary soy intake in a population-based sample of middle-aged and older Chinese in Singapore. Cancer Epidemiol Biomarkers Prev 7:135–140
18. Wu AH, Stanczyk FZ, Seow A et al (2002) Soy intake and other lifestyle determinants of serum estrogen levels among postmenopausal Chinese women in Singapore. Cancer Epidemiol Biomarkers Prev 11:844–851
19. Franke AA, Hankin JH, Yu MC et al (1999) Isoflavone levels in soy foods consumed by multiethnic populations in Singapore and Hawaii. J Agric Food Chem 47:977–986
20. Odegaard AO, Koh WP, Arakawa K, Yu MC, Pereira MA (2010) Soft drink and juice consumption and risk of physician-diagnosed incident type 2 diabetes: the Singapore Chinese Health Study. Am J Epidemiol 171:701–708
21. Steffes MW, Cleary P, Goldstein D et al (2005) Hemoglobin A1c measurements over nearly two decades: sustaining comparable values throughout the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications Study. Clin Chem 51:753–758
22. International Expert Committee (2009) International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 32:1327–1334
23. WHO Expert Consultation (2004) Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 363:157–163
24. Akiyama T, Ishida J, Nakagawa S et al (1987) Genistein, a specific inhibitor of tyrosine-specific protein kinases. J Biol Chem 262:5592–5595
25. Vedavanam K, Srijayanta S, O'Reilly J et al (1999) Antioxidant action and potential antidiabetic properties of an isoflavonoid-containing soyabean phytochemical extract (SPE). Phytother Res 13:601–608