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Consumption of soy foods and isoflavones and risk of type 2 diabetes: a pooled analysis of three US cohorts

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Abstract

Background—Evidence regarding the consumption of soy foods and isoflavones in relation to risk of type 2 diabetes (T2D) is scarce.

Objective—Our study was to evaluate the association between soy food and isoflavone consumption and risk of T2D in US men and women.

Methods—We followed 63,115 women in the Nurses' Health Study (1998-2012), 79,061 women in the Nurses' Health Study II (1999-2013), and 21,281 men in the Health Professionals Follow-Up Study (2002-2010). Diet was assessed by a validated food-frequency questionnaire, and was updated every 4 y. Self-reports of incident T2D was confirmed by a validated supplementary questionnaire.

Results—During 1,966,321 person-years of follow-up, 9,185 incident T2D cases were documented. After multivariate adjustment for covariates, consumption of soy foods (tofu and soy

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Contributors

QS and FBH obtained funding from the National Institutes of Health. MD analyzed the data and wrote the first draft of the manuscript. AP, JEM, WCW, VM, BR, and EG contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. QS is the guarantor of this investigation.

Competing Interests

None of the authors had any financial or personal conflict of interest to disclose.

milk) was not associated with a lower T2D risk. Compared to non-consumers of soy foods, the hazard ratio (HR) was 1.00 (95% CI: 0.93, 1.07) for <1 serving/week, and 0.93 (95% CI: 0.83, 1.03) for 1 serving/week of soy foods (P for trend = 0.14). In contrast, intake of total isoflavones was inversely associated with T2D risk. Comparing extreme quintiles of isoflavones, the HR was 0.89 (95% CI: 0.83, 0.96; P for trend = 0.009). Inverse associations were also found for consumption of major individual isoflavones, including daidzein and genistein, with risk of T2D.

Conclusions—Intake of isoflavones was associated with a modestly lower T2D risk in US men and women who typically consumed low to moderate amounts of soy foods. These findings warrant replications in other populations with similar soy intake levels.

Keywords

isoflavones; soy food; type 2 diabetes

INTRODUCTION

Type 2 diabetes (T2D) is a chronic disease with increasing prevalence worldwide. The total number of people with diabetes, globally, is 382 million in 2013 and is estimated to reach 592 million by the year 2035.¹ Identification of modifiable lifestyle and dietary risk factors for T2D prevention is of high priority. Specific components of plant-based foods have been shown to exert significant health benefits.² For example, consumption of coffee and blueberries has been associated with a lower risk of T2D in Western populations, and certain flavonoid subclasses, such as phenolic acids and anthocyanins, may contribute to the health benefits of these foods.³⁻⁵ In contrast, evidence regarding other plant-based foods, such as soy foods, that are regarded as healthful but not intrinsic to the traditional Western diet is sparse.

Soy foods are uniquely rich in isoflavones compared to other foods.⁶ Isoflavones are in the family of flavonoids that share a common chemical structure of 2 aromatic rings bound together by 3 carbon atoms that form an oxygenated heterocycle.⁷ Depending on the position of hydroxyl groups in replacement of hydrogen atoms, isoflavones can be categorized into three subtypes: daidzein, genistein, and glycitein. The contents of these isoflavones are much higher in soy foods, such as tofu and soy milk, than other foods that do not contain soy ingredients, with daidzein and genistein contents higher than glycitein in soy foods. Isoflavones have a structure analogous to 17- β -estradiol and have weak estrogen-like effects by binding to estrogen receptors.⁸ Because the structural conformation of genistein resembles estradiol the most, genistein has the strongest binding capacity to estrogen receptor.⁹ Daidzein and genistein could be converted by gut bacteria into metabolites such as equol, desmethylangolensin (DMA), dihydrogenistein (DHGE), and dihydrodaidzein (DHDE). Several clinical trials have been conducted to examine the effects of soy foods and isoflavones on glucose homeostasis, and results have suggested that soy foods and soy-rich diets may lower blood glucose.¹⁰⁻¹³ However, these clinical trials are limited by small sample sizes and short durations of follow-up. Few prospective studies have been conducted to evaluate the associations between intakes of soy foods and isoflavones and T2D risk in Western populations who consume low to moderate amounts of soy foods¹⁴.

We conducted a prospective analysis of data collected in 3 large US cohorts, the Nurses' Health Study (NHS), the NHSII, and the Health Professionals Follow-Up Study (HPFS) to examine the associations between consumption of soy food and isoflavones and risk of T2D.

METHODS

Study population

The NHS began in 1976, when 121,700 female registered nurses aged 30-55 y residing in 11 states were enrolled and completed a baseline questionnaire about their lifestyle and medical history. The NHSII was established in 1989 and consisted of 116,671 younger female registered nurses aged 25-42 y at baseline. These women responded to a baseline questionnaire similar to the one used in NHS. The HPFS was initiated in 1986, and was composed of 51,529 male dentists, pharmacists, veterinarians, optometrists, osteopathic physicians, and podiatrists aged 40-75 y at baseline. The male participants returned a baseline questionnaire about their medical history, lifestyle, and usual diet. In all three cohorts, questionnaires were administered at baseline and biennially thereafter to update information on lifestyle factors and the occurrence of chronic diseases.

For the current analysis, we excluded participants who reported diagnosed diabetes (including type 1 and type 2 diabetes, and gestational diabetes), cardiovascular disease (CVD), or cancer at baseline (1998 for the NHS, 1999 for the NHSII, and 2002 for the HPFS). We further excluded participants with missing soy or isoflavone consumption at baseline (when soy milk was first included) and those who left more than 70 food items blank or had daily energy intakes <600 or > 3500 kcal for women and <800 or >4200 kcal for men. Overall, 21,665 NHS participants, 8,537 NHSII participants, and 16,120 HPFS participants were excluded from the analysis. After these exclusions, data from 63,115 NHS participants, 79,061 NHSII participants, and 21,281 HPFS participants were available for the analysis. The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and Harvard School of Public Health. The completion of the self-administered questionnaire was considered to imply informed consent.

Assessment of isoflavone and soy food consumption

In 1984, a 116-item food frequency questionnaire (FFQ) was administered to the NHS participants to obtain information on usual intake of food and beverages. Since 1986, an expanded FFQ has been administered every 4 years to update diet. Using a similar FFQ, dietary data were collected every four years from the NHSII participants since 1991 and from the HPFS participants since 1986. In all FFQs, participants were asked how often (from "never or less than once per month" to "6 or more times per day") on average they consumed each food item of a standard portion size during the previous year. Major soy foods, i.e., tofu and soy milk, have been simultaneously included on the FFQs since 1998 in the NHS, 1999 in the NHSII, and 2002 in the HPFS. We therefore used these years as study baselines. Intake of isoflavones and other nutrients was calculated by multiplying the consumption frequency of each food item by the nutrient content of the specified portion and summing the contributions from all food items. We calculated consumption of genistein, daidzein, and glycitein from foods. Isoflavones from supplements were not included in these

calculations. The food composition of isoflavones was created primarily from the USDA Database for the Isoflavone Content of Selected Foods, Release 2.0⁶. Consumption of total soy food was calculated as the sum of the consumption of tofu and soy milk in servings/day. The validity and reproducibility of the FFQ has been described in detail elsewhere.¹⁵⁻¹⁸ The correlation coefficient for tofu consumption assessed by FFQs and diet records was 0.56.¹⁵

Assessment of covariates

In the biennial follow-up questionnaires, we collected and updated information on age, body weight and height, smoking status, physical activity, medication use, family history of diabetes, and disease status, including hypertension, hypercholesterolemia, CVD, and cancer. We also ascertained data on menopausal status and postmenopausal hormone use in both NHS and NHSII, as well as oral contraceptive use in NHSII. An overall measurement of diet quality was derived using the alternate Healthy Eating Index (aHEI) score excluding tofu and soy milk.

Assessment of type 2 diabetes (T2D)

Participants with self-reported incident T2D were mailed a validated supplementary questionnaire regarding symptoms, diagnostic tests, and hypoglycemic therapy to confirm the diagnosis of diabetes. Cases were ascertained using the American Diabetes Association criteria:¹⁹ 1) one or more classic symptoms (excessive thirst, polyuria, weight loss, hunger) and fasting plasma glucose concentrations ≥ 7.0 mmol/L or random plasma glucose concentrations ≥ 11.1 mmol/L; 2) 2 elevated plasma glucose concentrations on different occasions (fasting concentrations ≥ 7.0 mmol/L, random plasma glucose concentrations ≥ 11.1 mmol/L, and/or concentrations of ≥ 11.1 mmol/L after 2 h shown by oral-glucose-tolerance testing) in the absence of symptoms; or 3) treatment with hypoglycemic medication (insulin or oral hypoglycemic agent). In addition, hemoglobin A1c $\geq 6.5\%$ was added to the diagnosis criteria since 2010. Only cases confirmed by the supplemental questionnaires were included in our analysis.

The validity of the supplementary questionnaire for the diagnosis of diabetes has been documented previously. In a validation study, of the 62 cases in the NHS and 59 cases in HPFS who were confirmed by the supplemental questionnaire, 61 (98%) and 57 (97%) were reconfirmed by reviewing medical records.^{20,21}

Statistical analysis

We calculated person-time for each individual from the date of the return of the baseline questionnaire to the date of diagnosis of T2D, death, or the end of follow-up (30 June 2012 for the NHS, 30 June 2013 for the NHSII, and 31 January 2010 for the HPFS), whichever came first. We used cumulative averages of soy food or isoflavone consumption to reflect long-term dietary habits. We stopped updating diet after incident cancer or CVD as these diseases may result in changes of diet that might confound the association between soy foods and risk of T2D. In addition, to minimize missing values during follow-up, we replaced missing soy food/isoflavone intakes during follow-up with valid values in the previous cycle. We used Cox proportional hazards regression models to examine the associations between soy foods and isoflavone consumption (quintiles) and risk of T2D. The

regression models included calendar time in 2-y intervals as the time scale, and were stratified by age in years. In multivariable analysis, we further adjusted for race (Caucasian, African American, Asian, and others), family history of T2D (yes, no), baseline disease status (hypertension and hypercholesterolemia), BMI (<20.9, 21-22.9, 23-24.9, 25-29.9, 30-34.9, ≥ 35 kg/m²), physical activity (quintiles, met-hr/week), aHEI score (in quintiles), total energy intake (quintiles), and smoking status (never smoked, past smoker, currently smoked 1-14 cigarettes/d, and currently smoked >14 cigarettes/d). We additionally adjusted for menopausal status (yes, no), and postmenopausal hormone use (yes, no) in women. Test for linear trend was conducted by assigning the median value of exposure in each category to that category and treating the median value as a continuous variable in the regression model, with $P < 0.05$ denoting a significant association.

Analyses were performed separately in each cohort first. The pooled hazard ratios (HRs) were estimated by a stratified Cox model, which allowed baseline hazard to be different across the three cohorts while gave common effect estimates of the covariates. We examined potential effect modifications by BMI, age, and aHEI score for both men and women, and menopausal status and postmenopausal hormone use for women. Meta-regressions were used to test for potential interactions, with P value <0.05 denoting effect modification. The tests for interaction were conducted in analyses within individual cohorts as well as in analyses based on pooled data from all three cohorts. Previous studies showed that coffee intake also contributes to total isoflavone intake²² and was associated with a lower T2D risk in these cohorts.⁵ To examine whether the association of isoflavones with diabetes risk may be due to coffee intake, we further calculated coffee-adjusted residuals of isoflavones using generalized equation estimation (GEE), and conducted a sensitivity analysis by using these residuals as the main exposure. All statistical tests were 2-sided and performed using SAS version 9.3 (SAS Institute Inc.). The meta-analysis was performed using STATA, version 9.2 (StataCorp).

RESULTS

Baseline characteristics according to soy food consumption

Baseline characteristics of the participants in each cohort according to soy food consumption are shown in Table 1. Most of the participants were non-consumers of soy foods at baseline in the three cohorts. Soy food consumers had a higher aHEI score, higher consumption of fruit, vegetables, and fish, lower consumption of meat and soda (including sugar-sweetened beverages), and were more physically active than non-consumers.

The association of soy foods with risk of T2D

In the age-adjusted model, soy food consumption was inversely associated with risk of T2D. After multivariate adjustment, the association was attenuated and soy food consumption was non-significantly associated with a lower risk of T2D (Table 2). Compared with those who did not consume soy foods, the HR (95% CI) was 1.00 (0.93, 1.07) for those consuming < 1 serving/week of soy foods, and 0.93 (0.83, 1.03; $P = 0.14$) for those consuming 1 serving/week of soy foods in the pooled analysis. We further examined the association separately with tofu and soy milk intake. Compared with non-consumers, the HR was 1.00 (95% CI:

0.93, 1.08) for those consuming < 1 serving/week of tofu, and 0.93 (95% CI: 0.84, 1.04) for those consuming ≥ 1 serving/week of tofu. For soy milk, compared with non-consumers, the HR was 0.92 (95% CI: 0.83, 1.02) for soy milk consumers. No significant associations of total soy foods, tofu, and soy milk with risk of T2D were found in the NHS, NHSII, and HPFS cohorts, and the associations did not vary significantly across the three cohorts (all P values for heterogeneity >0.30).

The association of isoflavone consumption with risk of T2D

Total isoflavone consumption was significantly, inversely associated with risk of T2D (Table 3). As compared with the lowest quintile of isoflavones consumption, the HRs (95% CIs) were 0.89 (0.83, 0.96) for highest quintiles in the pooled analysis (P for trend = 0.009). We further evaluated individual isoflavones with meaningful intake levels in our cohorts (Table 4). For daidzein, the HR (95% CI) was 0.87 (0.81, 0.94) comparing extreme quintiles (P for trend = 0.0003). For genistein, the HR (95% CI) was 0.91 (0.85, 0.98) for the same comparison (P for trend = 0.02).

Of note, on average, regular soy food consumers (≥ 1 serving/week) had higher isoflavone intake levels than participants in the highest quintile of total isoflavones, but the associations for soy food intake were not significant, suggesting that the association for isoflavones may not be linear at relatively high intake level. However, when we further examined the dose-response relationship between isoflavone intake and risk of T2D using spline regression, we did not observe a clear non-linear association (P for non-linearity: 0.76; P for trend = 0.02; Supplemental figure 1).

Stratified analysis

We conducted analyses stratified by menopausal status (premenopausal vs postmenopausal; women only), BMI (<30 kg/m² vs ≥ 30 kg/m²), age (<60 y vs ≥ 60 y), and aHEI score (< median vs ≥ median), and no significant interactions were found between soy food and risk of T2D: P values for interaction were 0.20 for menopausal status, 0.78 for BMI, 0.34 for age, and 0.52 for aHEI score (Supplemental Table 1). No significant interactions were found between isoflavones consumption and these factors in relation to T2D risk (Supplemental Table 2). We further tested effect modification by postmenopausal hormone use on the associations between consumptions of soy food and isoflavones and risk of T2D among postmenopausal women, but no significant effect modification was found. We performed further analyses restricted within postmenopausal women who were never users of hormone therapy and within women who were never users of soy supplements. The associations between intakes of soy foods and isoflavones and risk of T2D did not change substantially.

Sensitivity analysis

As coffee was one of the food sources of isoflavones consumption,²² we conducted sensitivity analysis using coffee-adjusted residuals of isoflavones consumption. Similar to the results of isoflavones, inverse associations of residual consumption of isoflavones, daidzein, and genistein with risk of T2D were found (Supplemental table 3). As soy food consumption was associated with a healthy lifestyle, we further repeated our analysis on the association of soy food and isoflavones with risk of T2D using propensity score analysis.

The results did not change significantly comparing with the main analysis (Supplemental table 4, 5). We repeated our analysis using stratified Cox model, and the associations of soy food and isoflavones with risk of T2D did not change significantly.

DISCUSSION

In three large US cohorts of men and women, we found that isoflavone consumption was modestly associated with a lower risk of T2D, whereas the two major soy foods, i.e., tofu and soy milk, were not associated with T2D risk. These associations were independent of established and potential lifestyle and dietary risk factors of T2D.

The association of soy foods and isoflavones with risk of T2D has been investigated primarily among Asian populations who have much higher intake levels compared with Western populations, and the results have been largely mixed. Villegas et al. found that higher intakes of soybean and soy milk were significantly associated with a lower T2D incidence in the Shanghai Women's Health Study.²³ In the Singapore Chinese Health Study, Mueller et al. further documented that intakes of unsweetened soy products (servings/week), but not sugar-sweetened soy foods, were associated with a lower T2D risk.²⁴ However, a Japanese study found that intake of total soy foods (gram/day) with various soy protein densities was not associated with T2D risk,²⁵ whereas intake of total soy foods (gram/day) was associated with a higher T2D risk in a multi-ethnic population living in Hawaii.²⁶ Lastly, no association between total isoflavone intake and risk of T2D was found in the EPIC-InterAct Study.¹⁴ The sources of heterogeneity in these findings are unclear, although study participant characteristics, including genetics, total energy intake, different exclusion criteria, various cooking methods, types of soy products, and measurement error in soy food or isoflavone assessment may partially explain the mixed results. In the current analysis, we evaluated both major soy foods and isoflavones in relation to T2D risk and found the associations did not vary significantly across three cohorts of men and women. We found that isoflavones rather than soy foods were associated with a lower risk of T2D and the reason might be that the isoflavones contents and other dietary constitutions of soy food differed across regions.

In contrast to the paucity of evidence from long-term prospective observational studies, data from short-term clinical trials that examined the effects of soy foods or isoflavones on diabetes risk factors were abundant, and results were mixed. In a comprehensive meta-analysis of randomized controlled trials, supplementation of soy foods or isoflavones did not significantly lower fasting glucose or insulin levels, although a subgroup analysis showed that whole soy foods might reduce fasting glucose.¹¹ In another meta-analysis that focused on premenopausal and postmenopausal non-Asian women who did not take hormone replacement therapy, isoflavone supplementation significantly lowered fasting insulin and HOMA-IR levels, although no effects were observed on fasting glucose levels.¹⁰ In addition, soy products improved blood lipid profiles among diabetes patients, although the effects on glucose metabolism parameters were not substantiated.¹²

Isoflavones have a structure analogous to 17- β -estradiol, which enables isoflavones bind to estrogen receptors β with 10^3 - 10^4 less potency than estradiol.⁸ Isoflavones exert either

estrogenic or anti-estrogenic effect depending on the concentration of serum estradiol. Isoflavones exert estrogen-like effects when the concentration of endogenous estrogen is low, otherwise, isoflavones might have anti-estrogenic effect.²⁷ Isoflavones also activate nuclear receptors including peroxisome-proliferator activated receptors (PPAR) α , PPAR γ , sterol regulated element binding protein, and liver X binding receptor to regulate lipid and glucose metabolism.²⁸⁻³⁰ Isoflavones have been shown to improve hyperglycemia, glucose tolerance, and circulating insulin concentrations.³¹ Isoflavones also stimulate the phosphorylation of AMP-activated protein kinase and acetyl-CoA carboxylase to increase glucose uptake and fatty acid oxidation.³² Estrogen increases insulin sensitivity in the liver, promotes pancreas β cell proliferation and differentiation, modulates appetite and energy expenditure by regulating the expression of leptin and ghrelin, effects glucose disposal in muscle by upregulating expression of glucose transporter 4 and proteins involving the insulin signaling pathway,³³ and inhibits lipogenesis in adipose tissue by inhibiting the activity of lipoprotein lipase.³⁴ Whether isoflavones have those effects analogous to estrogen is speculated and needs further investigation.

Our study has several strengths. First, the analysis was based on three well-characterized large cohorts with detailed measurements of diet and lifestyle. Second, consumption of isoflavones and soy products was assessed every 4 years during the follow-up. The repeated measurements not only reduce measurement error but also represent long-term dietary habits. Third, the aHEI score was used to adjust for confounding of the overall diet quality. We also controlled for a wide range of lifestyle factors in the analysis. Our study also has several limitations. First, although we used the comprehensive USDA food composition database of isoflavones to derive isoflavone intake and included major soy foods in the current analysis, measurement error may still exist and may attenuate the true associations towards the null due to the longitudinal study design. Second, the low consumption levels of soy products in our cohorts (90% of participants were non-consumers), typically seen among Western populations, limited the statistical power for the analysis of soy food. Third, residual confounding by lifestyle factors (e.g., dietary factors, physical activity, and smoking) may still exist due to model-misspecification and measurement error of potential confounders. Last, our study was conducted primarily among white health professionals, and thus the results may not be generalizable to other populations.

In conclusion, our analysis showed that consumption of isoflavones, but not tofu or soy milk, was associated with a modest reduction in risk of T2D in three large cohorts of U.S. men and women. Further studies are needed to replicate these observations in other populations, especially those with similar isoflavone intake levels.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Baseline characteristics of participants by consumption of soy foods in the NHS, NHS II, and HPFS

	NHS (1998)			NHS II (1999)			HPFS (2002)		
	Non-consumer	<1 serving/week	1 serving/week	Non-consumer	<1 serving/week	1 serving/week	Non-consumer	<1 serving/week	1 serving/week
N	56,858	4,259	1,998	66,608	7,930	4,523	16,517	2,785	1,979
Age (year)	64	62	62	44	45	45	67	66	66
Total soy food (serving/d)	0	0.09	0.83	0	0.09	0.85	0	0.09	0.88
Soy milk (serving/d)	0	0	0.46	0	0.01	0.49	0	0.01	0.47
Tofu (serving/d)	0	0.08	0.37	0	0.08	0.36	0	0.08	0.41
Isoflavones (mg/d)	0.62	2.00	10.58	0.70	2.55	12.20	0.63	2.62	13.13
Daidzein (mg/d)	0.27	0.74	3.89	0.30	0.92	4.46	0.29	1.04	5.08
Genistein (mg/d)	0.31	1.10	5.05	0.37	1.41	5.87	0.31	1.25	5.70
Glycecin (mg/d)	0.04	0.17	1.72	0.04	0.21	1.88	0.03	0.33	2.34
Physical activity (MET-h/wk)	18	24	26	18	23	27	35	40	44
aHEI	53	61	64	50	59	63	56	63	68
Total energy intake (kcal/d)	1719	1816	1865	1809	1879	1928	1983	2009	2050
Fruits (serving/d)	2.36	2.93	3.12	1.76	2.26	2.57	2.57	3.09	3.52
Vegetables (serving/d)	3.07	3.92	4.25	3.19	4.10	4.60	3.36	4.04	4.48
Meat (serving/d)	1.24	1.01	0.85	1.42	1.17	0.92	1.58	1.33	1.12
Fish (serving/d)	0.22	0.29	0.30	0.19	0.27	0.28	0.28	0.38	0.38
Total soda (serving/d)	0.58	0.43	0.31	1.17	0.77	0.55	0.65	0.57	0.43
Coffee (cups/d)	1.82	1.62	1.30	1.51	1.56	1.31	1.64	1.45	1.22
Total alcoholic beverages (serving/d)	0.47	0.48	0.37	0.32	0.42	0.34	0.96	0.91	0.74
Dairy products (serving/d)	2.22	2.37	2.07	2.25	2.36	2.54	2.81	2.53	2.16
BMI (kg/m ²)	26	25	25	24	23	22	26	26	25
Hypertension, %	41	37	35	13	11	8	44	43	39
Hypercholesterolemia, %	56	54	54	24	22	21	55	60	55
Family history of diabetes, %	27	27	25	35	34	32	21	22	21

	NHS (1998)		NHS II (1999)		HPFS (2002)	
	Non-consumer	<1 serving/week	Non-consumer	<1 serving/week	Non-consumer	<1 serving/week
Postmenopausal women, %	94	93	15	13	NA	NA
Current menopausal hormone use, (% among total women)	53	54	14	11	NA	NA
Current smokers, %	17	13	9	6	4	2
Race, Caucasian, %	98	92	97	93	92	91
Race, Asian, %	0	6	1	5	6	6
					0	5

aHEI, Alternative Healthy Eating Index, with a higher score indicating healthier dietary pattern; BMI, body mass index; HPFS, Health Professionals Follow-up Study; MET, metabolic-equivalent task; NHS, Nurses' Health Study.

Table 2

Hazard ratios (HRs) for the associations between soy containing foods and risk of type 2 diabetes in the three cohorts

Total soy food	Non-consumer	< 1 serving/week	1 serving/week	P for trend
<i>NHS (1998-2012)</i>				
Cases/Person-years	3,886/645,060	399/81,561	234/54,968	
Median intake (g/d) (range)	0 0	0.05 (0.02, 0.14)	0.43 (0.14, 6.00)	
Age-adjusted Model	1.00	0.86 (0.77, 0.95)	0.75 (0.66, 0.86)	0.004
Multivariate-adjusted Model	1.00	0.98 (0.88, 1.09)	0.97 (0.84, 1.11)	0.83
<i>NHS II (1999-2013)</i>				
Cases/Person-years	3,147/771,898	502/156,467	271/108,577	
Median intake (g/d) (range)	0 0	0.07 (0.02, 0.14)	0.43 (0.14, 8.50)	
Age-adjusted Model	1.00	0.79 (0.72, 0.87)	0.59 (0.52, 0.67)	< 0.001
Multivariate-adjusted Model	1.00	1.03 (0.93, 1.14)	0.92 (0.80, 1.05)	0.20
<i>HPFS (2002-2010)</i>				
Cases/Person-years	589/109,009	96/22,026	57/16,238	
Median intake (g/d) (range)	0 0	0.07 (0.04, 0.14)	0.50 (0.18, 10.50)	
Age-adjusted Model	1.00	0.83 (0.66, 1.02)	0.67 (0.51, 0.87)	0.003
Multivariate-adjusted Model	1.00	0.89 (0.71, 1.11)	0.88 (0.66, 1.17)	0.37
<i>Overall pooled</i>				
Multivariate-adjusted Model	1.00	1.00 (0.93, 1.07)	0.93 (0.83, 1.03)	0.14
Tofu				
<i>NHS (1998-2012)</i>				
Cases/Person-years	3,999/668,830	334/69,805	186/42,955	
Median intake (g/d) (range)	0 0	0.05 (0.02, 0.07)	0.22 (0.09, 6.00)	
Age-adjusted Model	1.00	0.84 (0.75, 0.94)	0.75 (0.65, 0.87)	0.001
Multivariate-adjusted Model	1.00	0.98 (0.88, 1.10)	0.98 (0.84, 1.14)	0.97
<i>NHS II (1999-2013)</i>				
Cases/Person-years	3,282/812,630	416/130,915	222/93,398	

Tofu	Non-consumer	< 1 serving/week	1 serving/week
Median intake (g/d) (range)	0 0	0.05 (0.02, 0.07)	0.22 (0.09, 6.00)
Age-adjusted Model	1.00	0.79 (0.71, 0.87)	0.58 (0.50, 0.66) <0.001
Multivariate-adjusted Model	1.00	1.02 (0.92, 1.14)	0.91 (0.78, 1.05) 0.25
<i>HPFS (2002-2010)</i>			
Cases/Person-years	614/114,355	77/17,834	51/15,083
Median intake (g/d) (range)	0 0	0.07 (0.04, 0.07)	0.29 (0.11, 6.00)
Age-adjusted Model	1.00	0.83 (0.65, 1.05)	0.64 (0.48, 0.85) 0.002
Multivariate-adjusted Model	1.00	0.90 (0.71, 1.15)	0.81 (0.60, 1.10) 0.23
<i>Overall pooled</i>			
Multivariate-adjusted Model	1.00	1.00 (0.93, 1.08)	0.93 (0.84, 1.04) 0.19
Soy milk			
Non-consumer			
Consumer			
<i>NHS (1998-2012)</i>			
Cases/Person-years	4,287/726,315	232/55,274	
Median intake (g/d) (range)	0 0	0.22 (0.02, 6.00)	
Age-adjusted Model	1.00	0.79 (0.69, 0.90)	0.24
Multivariate-adjusted Model	1.00	0.96 (0.84, 1.10)	0.84
<i>NHS II (1999-2013)</i>			
Cases/Person-years	3,621/920,118	299/116,823	
Median intake (g/d) (range)	0 0	0.17 (0.02, 6.00)	
Age-adjusted Model	1.00	0.65 (0.58, 0.73)	<0.001
Multivariate-adjusted Model	1.00	0.90 (0.80, 1.02)	0.11
<i>HPFS (2002-2010)</i>			
Cases/Person-years	691/133,130	51/14,143	
Median intake (g/d) (range)	0 0	0.43 (0.04, 6.00)	
Age-adjusted Model	1.00	0.72 (0.54, 0.95)	0.02
Multivariate-adjusted Model	1.00	0.93 (0.69, 1.24)	0.58
<i>Overall pooled</i>			
Multivariate-adjusted Model	1.00	0.92 (0.83, 1.02)	0.11

Abbreviations: NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study;

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Multivariate-adjusted model: adjusted for race (Caucasians, African Americans, Asian Americans, and others), family history of T2D (yes vs. no), baseline disease status (hypertension, hypercholesterolemia), body mass index (<21, 21-22.9, 23-24.9, 25-29.9, 30-34.9, 35 kg/m²), physical activity (quintiles), overall dietary pattern (Alternative Healthy Eating Index score, in quintiles), total energy intake (quintiles), coffee consumption (quintiles), smoking status (never, former, current 1-14 cigarettes/d, current >14 cigarettes/d), Menopausal status (yes vs. no) and postmenopausal hormone use (yes vs. no) were further adjusted for in women.

Table 3
Associations between isoflavone consumption and risk of type 2 diabetes in the three cohorts

	Q1	Q2	Q3	Q4	Q5	P for trend
NHS (1998-2012)						
Cases/Person-years	894/151,060	1042/160,232	934/157,173	848/155,786	801/157,339	
Median intake (range #) (mg/d)	0.17 (0.01, 0.44)	0.29 (0.17, 0.59)	0.40 (0.26, 0.80)	0.62 (0.37, 1.78)	2.78 (0.57, 76.57)	
Age-adjusted Model	1.00	1.09 (1.00, 1.19)	1.00 (0.91, 1.10)	0.92 (0.83, 1.01)	0.85 (0.77, 0.93)	< 0.001
Multivariate-adjusted Model	1.00	1.08 (0.99, 1.18)	1.02 (0.93, 1.12)	0.96 (0.87, 1.05)	0.97 (0.88, 1.07)	0.13
NHS II (1999-2013)						
Cases/Person-years	913/199,825	905/210,571	753/209,716	724/208,238	625/208,591	
Median intake (range) (mg/d)	0.17 (0.01, 0.46)	0.31 (0.17, 0.75)	0.48 (0.27, 1.50)	1.10 (0.42, 3.97)	5.73 (1.14, 130.50)	
Age-adjusted Model	1.00	0.94 (0.86, 1.03)	0.77 (0.70, 0.85)	0.74 (0.67, 0.81)	0.63 (0.57, 0.70)	< 0.001
Multivariate-adjusted Model	1.00	0.95 (0.86, 1.04)	0.82 (0.74, 0.90)	0.85 (0.77, 0.94)	0.85 (0.76, 0.95)	0.11
HPFS (2002-2010)						
Cases/Person-years	170/29,598	144/29,356	151/29,252	160/29,530	117/29,537	
Median intake (range) (mg/d)	0.31 (0.01, 0.49)	0.47 (0.35, 0.66)	0.64 (0.48, 0.93)	1.10 (0.66, 2.27)	5.09 (1.87, 238.02)	
Age-adjusted Model	1.00	0.86 (0.68, 1.07)	0.90 (0.73, 1.13)	0.95 (0.76, 1.18)	0.69 (0.54, 0.87)	0.004
Multivariate-adjusted Model	1.00	0.83 (0.67, 1.04)	0.87 (0.70, 1.09)	0.93 (0.74, 1.15)	0.80 (0.62, 1.02)	0.24
Pooled						
Multivariate-adjusted Model	1.00	0.99 (0.93, 1.06)	0.91 (0.86, 0.97)	0.91 (0.85, 0.97)	0.89 (0.83, 0.96)	0.009

NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study

Multivariate-adjusted for race (Caucasians, African Americans, Asian Americans, and others), family history of T2D (yes vs. no), baseline disease status (hypertension, hypercholesterolemia), BMI (<21, 21-22.9, 23-24.9, 25-29.9, 30-34.9, 35 kg/m²), physical activity (quintiles), overall dietary pattern (AHEI score, in quintiles), total energy intake (quintiles), smoking status (never, former, current (1-14 cigarettes/d), current (>14 cigarettes/d)). Menopausal status (yes vs. no) and postmenopausal hormone use (yes vs. no) were further adjusted for in women.

: Overlap of range was due to that the quintile was divided within each time interval of the Cox model.

Table 4

Hazard ratio (HR) for the association between subtypes of isoflavone consumption and risk of type 2 diabetes in the three cohorts.

	Q1	Q2	Q3	Q4	Q5	P for trend
Daidzein						
<i>NHS (1998-2012)</i>	904/148,554	1069/163,641	947/155,285	811/156,098	788/158,012	
Median intake (range #) (mg/d)	0.08 (0.01, 0.20)	0.15 (0.08, 0.28)	0.23 (0.14, 0.39)	0.33 (0.22, 0.72)	1.05 (0.35, 25.46)	
Age-adjusted Model	1.00	1.06 (0.97, 1.15)	1.00 (0.91, 1.09)	0.85 (0.77, 0.93)	0.80 (0.73, 0.88)	< 0.001
Multivariate-adjusted Model	1.00	1.05 (0.96, 1.15)	1.02 (0.93, 1.12)	0.90 (0.81, 0.99)	0.92 (0.84, 1.02)	0.01
<i>NHS II (1999-2013)</i>	908/198,618	966/209,843	727/210,988	699/208,319	620/209,174	
Median intake (range) (mg/d)	0.07 (0.01, 0.22)	0.16 (0.08, 0.36)	0.27 (0.14, 0.63)	0.49 (0.25, 1.50)	2.09 (0.50, 41.70)	
Age-adjusted Model	1.00	1.00 (0.92, 1.10)	0.74 (0.67, 0.82)	0.71 (0.64, 0.78)	0.62 (0.56, 0.69)	< 0.001
Multivariate-adjusted Model	1.00	0.99 (0.91, 1.09)	0.80 (0.73, 0.89)	0.84 (0.75, 0.93)	0.85 (0.76, 0.94)	0.03
<i>HPFS (2002-2010)</i>	166/29,178	158/30,164	153/28,814	146/29,621	119/29,496	
Median intake (range) (mg/d)	0.14 (0.01, 0.22)	0.22 (0.16, 0.31)	0.32 (0.24, 0.45)	0.53 (0.35, 0.92)	1.98 (0.77, 75.11)	
Age-adjusted Model	1.00	0.91 (0.74, 1.14)	0.94 (0.76, 1.17)	0.87 (0.69, 1.08)	0.71 (0.56, 0.89)	0.005
Multivariate-adjusted Model	1.00	0.90 (0.72, 1.12)	0.91 (0.73, 1.14)	0.83 (0.67, 1.04)	0.81 (0.64, 1.04)	0.23
<i>Pooled</i>						
Multivariate-adjusted Model	1.00	1.01 (0.95, 1.07)	0.91 (0.85, 0.97)	0.86 (0.81, 0.92)	0.87 (0.81, 0.94)	0.0003
Genistein						
<i>NHS (1998-2012)</i>	910/156,013	965/158,628	913/153,330	927/156,833	804/156,785	
Median intake (range) (mg/d)	0.08 (0.01, 0.21)	0.13 (0.09, 0.27)	0.17 (0.12, 0.37)	0.26 (0.15, 0.87)	1.38 (0.22, 44.72)	
Age-adjusted Model	1.00	1.04 (0.95, 1.14)	1.03 (0.94, 1.13)	1.01 (0.92, 1.11)	0.87 (0.79, 0.96)	0.003
Multivariate-adjusted Model	1.00	1.04 (0.95, 1.14)	1.03 (0.94, 1.13)	1.02 (0.93, 1.12)	0.98 (0.89, 1.08)	0.27
<i>NHS II (1999-2013)</i>	903/205,677	820/196,157	816/220,327	759/206,270	622/208,510	
Median intake (range) (mg/d)	0.09 (0.01, 0.22)	0.15 (0.09, 0.34)	0.19 (0.12, 0.74)	0.54 (0.17, 1.99)	2.87 (0.58, 78.62)	
Age-adjusted Model	1.00	0.95 (0.87, 1.05)	0.84 (0.76, 0.92)	0.82 (0.74, 0.90)	0.66 (0.59, 0.73)	< 0.001
Multivariate-adjusted Model	1.00	0.97 (0.88, 1.07)	0.86 (0.78, 0.95)	0.91 (0.82, 1.00)	0.87 (0.78, 0.97)	0.11
<i>HPFS (2002-2010)</i>	158/28,674	148/29,339	161/29,819	158/29,945	117/29,496	

	Q1	Q2	Q3	Q4	Q5	P for trend
Median intake (range) (mg/d)	0.15 (0.01, 0.24)	0.21 (0.17, 0.32)	0.28 (0.22, 0.43)	0.51 (0.29, 1.08)	2.29 (0.88, 142.09)	
Age-adjusted Model	1.00	0.91 (0.73, 1.14)	0.97 (0.78, 1.22)	0.96 (0.77, 1.20)	0.71 (0.56, 0.91)	0.005
Multivariate-adjusted Model	1.00	0.90 (0.72, 1.13)	0.94 (0.75, 1.17)	0.96 (0.77, 1.21)	0.84 (0.65, 1.07)	0.28
<i>Pooled</i>						
Multivariate-adjusted Model	1.00	0.99 (0.93, 1.06)	0.95 (0.89, 1.01)	0.97 (0.91, 1.03)	0.91 (0.85, 0.98)	0.02

Age-adjusted Model: age-adjusted model.

Multivariate-adjusted model: multivariate model adjusted for race (Caucasians, African Americans, and others), family history of T2D (yes vs. no), baseline disease status (hypertension, hypercholesterolemia), BMI (<21, 21-22.9, 23-24.9, 25-29.9, 30-34.9, 35 kg/m²), physical activity (quintiles), overall dietary pattern (AHEI score, in quintiles), total energy intake (quintiles), smoking status (never, former, current (1-14 cigarettes/d), current (>14 cigarettes/d)), Menopausal status (yes vs. no) and postmenopausal hormone use (yes vs. no) were further adjusted for in women.

: Overlap of range was due to that the quintile was divided within each time interval of the Cox model.