Legume and soy intake and risk of type 2 diabetes: a systematic review and meta-analysis of prospective cohort studies

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ABSTRACT

Background: Previous findings on the associations of legume and soy intake with the risk of type 2 diabetes are conflicting.

Objective: We aimed to summarize the longitudinal associations between legume and soy intake and risk of type 2 diabetes.

Methods: We searched for relevant prospective cohort studies in PubMed, EMBASE, and Ovid up to August 2019. Study-specific, multivariable-adjusted RRs and 95% CIs were pooled by random-effects models.

Results: We identified 15 unique cohorts including 565,810 individuals and 32,093 incident cases. The summary RRs (95% CIs) of incident type 2 diabetes were 0.95 (0.79, 1.14; NS) for total legumes, 0.83 (0.68, 1.01; NS) for total soy, 0.89 (0.71, 1.11; NS) for soy milk, 0.92 (0.84, 0.99) for tofu, 0.84 (0.75, 0.95) for soy protein, and 0.88 (0.81, 0.96) for soy isoflavones, respectively. High heterogeneity was found for total legumes (I^2 = 84.8%), total soy (I^2 = 90.8%), and soy milk (I^2 = 91.7%). Potential sources of heterogeneity were not evident for total legumes or soy milk, whereas for total soy, geographic location (Asia, United States; $P = 0.04$) and study quality (high, moderate, or low; $P = 0.02$) significantly predicted heterogeneity. In dose–response analysis, significant linear inverse associations were observed for tofu, soy protein, and soy isoflavones (all $P < 0.05$). Overall quality of evidence was rated as moderate for total legumes and low for total soy and soy subtypes.

Conclusions: Dietary intakes of tofu, soy protein, and soy isoflavones, but not total legumes or total soy, are inversely associated with incident type 2 diabetes. Our findings support recommendations to increase intakes of certain soy products for the prevention of type 2 diabetes. However, the overall quality of evidence was low and more high-quality evidence from prospective studies is needed. This trial was registered as PROSPERO CRD42019126403 (https://www.crd.york.ac.uk/PROSPERO). *Am J Clin Nutr* 2020;111:677–688.

Keywords: legume, soy, type 2 diabetes, cohort, meta-analysis

Introduction

Legumes, including soybeans, peanuts, green/dry beans, peas, chickpeas, lentils, broad beans, alfalfa, clover, and lupine, are consumed worldwide and are rich in dietary fiber, plant protein, vitamins, and minerals combined with a low glycemic index (1, 2). Accumulating evidence supports various health benefits of the dietary intake of legumes (3). Legumes have long been considered as an important part of plant-based diets, which was reported to be beneficial for the primary prevention of type 2 diabetes (4). As one main species of legumes native to east Asia, soybeans are rich in soy isoflavones and protein (5), which were found to alleviate some of the symptoms associated with type 2 diabetes such as glucose intolerance and insulin resistance (6–8). Due to the low glycemic index, unique nutritional profile, and considerable antidiabetic potential, several nutritional recommendations have been proposed to promote the dietary intake of legumes and soy products for the prevention and management of type 2 diabetes (9, 10). However, the evidence from prospective observational studies is not consistent, with some studies reporting an inverse association between legumes and soy food intake and the risk of type 2 diabetes (11–14), whereas others reported a null (15–21) or a positive (22, 23) association.

To date, a few reviews have quantitatively investigated the association between legume and soy intake and incident type 2 diabetes. One meta-analysis reported that legume intake was not associated with type 2 diabetes (24). However, the authors

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Supplemental Text, Supplemental Tables 1–3, and Supplemental Figures 1–5 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Data described in the manuscript, code book, and analytic code will be made available upon request.

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only included 2 prospective studies (11, 15), with ≥4 eligible publications (16, 17, 19, 22) that were missed based on the authors' search strategies. Thereafter, one more study on the same topic was published, which suggested that total legume intake was inversely associated with the risk of type 2 diabetes (13). Recently, 2 meta-analyses reported that soy intake was associated with a lower risk of type 2 diabetes (25, 26), but they had several apparent limitations including lack of a dose–response analysis, insufficient investigation on subtypes of soy foods, and inadequate quality assessment of evidence. Thus, uncertainty remains with regard to the role of legumes and soy foods in the prevention of type 2 diabetes. To address these knowledge gaps, we conducted a systematic review and meta-analysis of prospective cohort studies to summarize the longitudinal associations of legume and soy intake with the risk of type 2 diabetes, and specifically aimed to explore the potential linear or curvilinear associations by dose–response analysis.

Methods

The systematic review and meta-analysis was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines (27). The protocol was published in the PROSPERO database (www.crd.york.ac.uk/PROSPERO; registration number: CRD42019126403).

Search strategy and inclusion criteria

A systematic literature research was performed in PubMed, Embase, and Ovid up to August 2019. The search items included those related to types of legumes, soy food, diabetes, and prospective study design (details are presented in the **Supplemental Text**). The search was restricted to human studies, without restriction on language. After removing duplicates, 2 of the authors (JT and YW) screened the articles independently, and discrepancies were resolved by group discussion with a third investigator (FF). We considered studies to be eligible if they met the following criteria: *1*) studies used a prospective study design (cohort, case-cohort, or nested case-control study), *2*) the exposures of interest were total or subtypes of legumes and soy foods, *3*) the outcome was incident type 2 diabetes, and *4*) the risk estimates with corresponding 95% CIs of type 2 diabetes for legume or soy intake were available or the study provided other statistics which could be converted to the required format. We excluded studies that used a retrospective study design (cross-sectional or case-control study) or studies reported from a conference abstract.

Data extraction and quality assessment

Two investigators (JT and YW) extracted information in a standardized manner, including basic information on participants such as the following: age, sex, and BMI; first author and publication year of the article; cohort name; region; number of cases; duration of follow-up; method of dietary assessment and case ascertainment; types of legumes and soy foods consumed and their RRs with 95% CIs of type 2 diabetes; and covariates. We extracted study-specific effect estimates that were adjusted for adiposity and sociodemographic and lifestyle factors. We also extracted risk estimates stratified by age, sex, and ethnicity, if reported, to assess potential sources of heterogeneity in meta-regression. Additional information on the study design and quality was obtained from identified articles as well as relevant articles of identified cohorts published elsewhere if needed.

Risk of bias for the included studies was examined based on a Cochrane risk-of-bias assessment tool (28) and a tool for nonrandomized studies of interventions (29). Seven domains of bias were assessed: confounding, selection, exposure measurement, misclassification, missing data, outcome measurement, and selective reporting. A "high," "low," or "unknown" risk of bias was assigned to each domain, followed by a consideration of overall risk of bias for each study (see Supplemental Text for details). In addition, quality assessment for individual study was conducted in accordance with the Newcastle–Ottawa criteria for nonrandomized studies (30). In this scale, a maximum of 9 points was assigned to each study, including 4 points for selection, 2 points for comparability, and 3 points for assessment of outcomes. Scores of 0–3, 4–6, and 7–9 were regarded as low, moderate, and high quality, respectively. Overall quality of evidence from the present meta-analysis was graded based on risk-of-bias assessment and results from sensitivity analysis, in accordance with the principles of the GRADE (Grading of Recommendation, Assessment, Development, and Evaluation) approach (31).

Data synthesis and analysis

We used Stata 14.0 (StataCorp) for all analyses; a 2-tailed P value <0.05 was regarded as statistically significant. The RR was used as the common risk estimate, the HR was treated as the RR directly. Each of total legumes, soy, and their subtypes was considered as the main exposure. RRs across exposure categories from each study were adopted. If a study reported stratified risk estimates, we pooled the risk estimates by a fixed-effects model to obtain a cohort-specific risk estimate, assuming an internal consistency within a single study.

We performed random-effects meta-analyses, assuming that that biological effects of legume and soy intake in different populations would vary randomly, to pool RRs and 95% CIs for the highest versus lowest categories of exposures (32). Heterogeneity between studies was evaluated by I^2 statistics. I^2 values of 25%, 50%, and 75% corresponded to cutoff points for low, moderate, and high degrees of heterogeneity, respectively. We did not conduct a meta-analysis for exposures that were reported by <2 studies.

Dose–response analysis, meta-regression, and sensitivity analysis were carried out using study-specific multivariable-adjusted RRs and 95% CIs. Original studies that reported ≥3 exposure categories were eligible for the dose–response analysis. The median dose of each exposure category and related RR and 95% CI were used. If the median dose was not reported, the midpoint of the upper and lower boundaries was regarded as the dose of each category. If the highest category was open-ended, the dose was regarded as 1.2-fold of the highest boundary (33). If the lowest category was open, the dose of lowest quartile was defined as the midpoint of the lowest boundary and zero. For consistency, we defined 1 serving equal to 1 standardized portion (100 g for legumes and soy, 242 g for soy milk, and 124 g for tofu) based on previous studies (24) and dietary guidelines (34). To estimate a potential curvilinear association, a 2-step random-effects meta-analysis was performed by modeling the dose using a restricted cubic spline model with 3 knots at 25%, 50%, and 75% of the distribution (35). A *P* value for curvilinearity was calculated by testing the null hypothesis that the second spline is equal to zero (36). A linear dose–response analysis was performed to estimate RRs for a 1-serving/d increment of legume and soy intake with type 2 diabetes risk, by using a generalized least-squares regression (37).

Meta-regression was performed to investigate whether potential heterogeneity of associations across studies was induced by sociodemographic characteristics, study design and quality, or indicators of bias. Stratified analysis was performed by factors that indicated significant heterogeneity ($P < 0.05$) and by preset factors including geographic location, sex, duration of follow-up, methods of dietary measurement and case ascertainment, overall risk of bias, and study quality. I^2 was calculated as an indicator of heterogeneity within each subgroup.

Sensitivity analyses were carried out with the deletion of 1 study at a time to examine whether the pooled associations could be dramatically affected by a single study. Sensitivity analyses were also conducted by pooling study-specific risk estimates using random-effects and fixed-effects models, respectively. Publication bias was evaluated by Begg's funnel plot and Egger's regression test (38, 39). If the Begg's test was significant, the trim-and-fill method was adopted to correct the potential publication bias (40).

Results

Literature search and study characteristics

We retrieved 5790 articles from the searched databases after removing the duplicates. We excluded 5764 articles by screening titles and abstracts and reviewed the full texts of 26 articles (**Supplemental Figure 1**). Thereafter, 13 articles were further excluded based on the inclusion and exclusion criteria (see the detailed reasons in **Supplemental Table 1**). Finally, we identified 15 unique cohort studies from 13 published articles (11–23).

The basic characteristics of the 15 included studies are listed in **Table 1**. Among them, 7 studies were from the United States (15, 17, 21–23), 5 were from Asia (11, 12, 14, 18, 20), 2 were from Europe (13, 19), and 1 was from Australia (16). Seven studies involving 11,232 cases among 271,709 individuals reported the associations between total legume intake and type 2 diabetes (11, 13, 15–17, 19, 22), among which 1 study reported the intake of peanuts (11) and another reported intakes of lentils, chickpeas, dry beans, and fresh peas (13). Nine studies involving 21,757 cases among 358,328 individuals described the associations between total soy intake and type 2 diabetes (11, 12, 14, 18, 20, 21, 23), in which 5 studies futher reported the intake of soy milk (11, 12, 21), 4 reported tofu intake (12, 21), 3 reported soy protein intake (11, 12, 14), and 6 reported the intake of soy isoflavones (12, 14, 18, 21). Publication date, duration of follow-up, and incidence rate varied across the included studies, ranging from 1999 to 2019, from an average of 4–18 y, and from 0.48% to 11.37%, respectively.

Risk-of-bias assessment and study quality

Domain-specific and overall risk of bias were examined for each study (**Table 2**, **Supplemental Table 2**, Supplemental Text for risk-of-bias assessment). Due to the observational study design, no study was assigned with a low risk of overall bias. Confounding is likely to exist in all of the included studies, although they had measured and adjusted for various potential confounders, such as demographic and socioeconomic variables and lifestyle and clinical factors (Supplemental Table 2). Exposure measurement was considered to be with a high risk of bias in several studies (11, 16, 17, 20, 23), due to a lack of validity of dietary measurement within a study population (Supplemental Table 2). Misclassification might exist in some studies (12, 14–20, 23) that only used the baseline dietary information, but it is not likely that this domain of bias could influence the overall bias. A high risk of overall bias was assigned to each of 2 studies (14, 20), due to a substantial loss to follow-up (14) and selective reporting of results (20), respectively. In addition, based on the Newcastle–Ottawa scale, all of the included studies scored ≥4 (**Supplemental Table 3**), indicating a moderate or high study quality.

Legume and soy intake and type 2 diabetes

Figure 1 summarizes the findings from our meta-analysis. Total legume intake was not associated with type 2 diabetes (RR: 0.95; 95% CI: 0.79, 1.14; $I^2 = 84.8\%$). We did not conduct a meta-analysis for legume subtypes because there was only 1 study for each subtype; instead, we presented risk estimates for peanuts, lentils, chickpeas, dry beans, and fresh peas in **Supplemental Figure 2**. Total soy intake was not associated with type 2 diabetes (RR: 0.83; 95% CI: 0.68, 1.01; $I^2 = 90.8\%$). In the analysis of soy subtypes, soy milk was not associated with type 2 diabetes (RR: 0.89; 95% CI: 0.71, 1.11; $I^2 = 91.7\%$), whereas tofu (RR: 0.92; 95% CI: 0.84, 0.99; $I^2 = 0.0\%$), soy protein (RR: 0.84; 95% CI: 0.75, 0.95; $I^2 = 0.0\%$), and soy isoflavones (RR: 0.88; 95% CI: 0.81, 0.96; $I^2 = 37.2\%$) were all inversely associated with type 2 diabetes.

No significant curvilinear or linear association with type 2 diabetes was found for total legume (*P*-curvilinearity = 0.56; *P*-linearity = 0.62) (**Figure 2**A), total soy (*P*-curvilinearity = 0.24; *P*-linearity = 0.59) (Figure 2B), or soy-milk (*P*-curvilinearity = 0.51; *P*-linearity = 0.98) intakes (Figure 2C). The RRs (95% CIs) for a daily increment of 100 g legumes, 100 g soy, and 242 g soy milk were 0.91 (0.64, 1.31), 1.10 (0.77, 1.58), and 0.91 (0.40, 2.05), respectively. Tofu (*P*-linearity = 0.02) (Figure 2D), soy protein (*P*-linearity = 0.02) (Figure 2E), and soy isoflavones (*P*-linearity = 0.04) (Figure 2F) showed significant linear associations with incident type 2 diabetes. A daily increment of 1 serving (124 g) of tofu, 10 g soy protein, and 10 mg soy isoflavones was associated with 32% (RR: 0.68; 95% CI: 0.50, 0.93), 9% (RR: 0.91; 95% CI: 0.84, 0.99), and 4% (RR: 0.96; 95% CI: 0.92, 0.99) lower risks of type 2 diabetes, respectively.

TABLE 1 Basic characteristics of the included prospective cohort studies by exposures reported[1]

First author, cohort, country (ref)[2]	Baseline years[3]	Follow-up, y	Age (range or mean), y	Men, %	Exposure assessment	Case ascertainment[4]	No. of cases (rate/1000)
Studies reporting total legumes ($n = 7$)							
Meyer, IWHS, USA (15)	1986	6	55–69	0	FFQ	Self-report	1141 (31.7)
Hodge, MCCS, Australia (16)	1990–1994	4	54.3	/	FFQ	Self-report	303 (9.6)
Liu, WHS, USA (17)	1993	8.8	≥ 45	0	FFQ	Self-report	1614 (4.8)
Bazzano, NHS, USA (22)	1980	18	50.1	0	FFQ	Self-report, biomarkers	4529 (63.4)
Villegas, SWHS, China (11)	1997–2000	4.6	40–70	0	FFQ	Self-report, biomarkers	896 (12.0)
Ericson, MDC, Sweden (19)	1991–1996	12	45–74	38.9	Diet record	Self-report, records	1709 (63.0)
Becerra-Tomás, PREDIMED, Spain (13)	2003	4.3	66.7	37.8	FFQ	Records, biomarkers	266 (79.4)
Studies reporting peanuts ($n = 1$)							
Villegas, SWHS, China (11)	1997–2000	4.6	40–70	0	FFQ	Self-report, biomarkers	896 (12.0)
Studies reporting lentils, chickpeas, dry beans, and fresh peas ($n = 1$)							
Becerra-Tomás, PREDIMED, Spain (13)	2003	4.3	66.7	37.8	FFQ	Records, biomarkers	266 (79.4)
Studies reporting total soy ($n = 9$)							
Villegas, SWHS, China (11)	1997–2000	4.6	40–70	0	FFQ	Self-report, biomarkers	896 (12.0)
Nanri, JPHC, Japan (18)	1990, 1993	10	45–75	43.3	FFQ	Self-report	1114 (18.6)
Morimoto, MEC, USA (23)	1993–1996	14	45–75	48.1	FFQ	Self-report, biomarkers	8564 (113.7)
Mueller, SCHS, Singapore (12)	1993–1998	5.7	55.2	42.4	FFQ	Self-report, biomarkers	2252 (52.2)
Tatsumi, Saku, Japan (20)	2006–2007	4	30–69	100	FFQ	Records, biomarkers	204 (67.1)
Ding, NHS, USA (21)	1998	12.4	63.8	0	FFQ	Self-report, biomarkers	4519 (71.6)
Ding, NHS II, USA (21)	1999	13.1	44.2	0	FFQ	Self-report, biomarkers	3920 (49.6)
Ding, HPFS, USA (21)	2002	6.9	66.8	100	FFQ	Self-report, biomarkers	742 (34.9)
Konishi, Takayama, Japan (14)	1992	9.7	51.6	43.5	FFQ	Self-report	438 (32.4)
Studies reporting soy milk ($n = 5$)							
Villegas, SWHS, China (11)	1997–2000	4.6	40–70	0	FFQ	Self-report, biomarkers	896 (12.0)
Mueller, SCHS, Singapore (12)	1993–1998	5.7	55.2	42.4	FFQ	Self-report, biomarkers	2252 (52.2)
Ding, NHS, USA (21)	1998	12.4	63.8	0	FFQ	Self-report, biomarkers	4519 (71.6)
Ding, NHS II, USA (21)	1999	13.1	44.2	0	FFQ	Self-report, biomarkers	3920 (49.6)
Ding, HPFS, USA (21)	2002	6.9	66.8	100	FFQ	Self-report, biomarkers	742 (34.9)
Studies reporting tofu ($n = 4$)							
Mueller, SCHS, Singapore (12)	1993–1998	5.7	55.2	42.4	FFQ	Self-report, biomarkers	2252 (52.2)
Ding, NHS, USA (21)	1998	12.4	63.8	0	FFQ	Self-report, biomarkers	4519 (71.6)
Ding, NHS II, USA (21)	1999	13.1	44.2	0	FFQ	Self-report, biomarkers	3920 (49.6)
Ding, HPFS, USA (21)	2002	6.9	66.8	100	FFQ	Self-report, biomarkers	742 (34.9)

(*Continued*)

TABLE 1 (*Continued*)

First author, cohort, country (ref)[2]	Baseline years[3]	Follow-up, y	Age (range or mean), y	Men, %	Exposure assessment	Case ascertainment[4]	No. of cases (rate/1000)
Studies reporting soy protein ($n = 3$)							
Villegas, SWHS, China (11)	1997–2000	4.6	40–70	0	FFQ	Self-report, biomarkers	896 (12.0)
Mueller, SCHS, Singapore (12)	1993–1998	5.7	55.2	42.4	FFQ	Self-report, biomarkers	2252 (52.2)
Konishi, Takayama, Japan (14)	1992	9.7	51.6	43.5	FFQ	Self-report	438 (32.4)
Studies reporting soy isoflavones ($n = 6$)							
Nanri, JPHC, Japan (18)	1990, 1993	10	45–75	43.3	FFQ	Self-report	1114 (18.6)
Mueller, SCHS, Singapore (12)	1993–1998	5.7	55.2	42.4	FFQ	Self-report, biomarkers	2252 (52.2)
Ding, NHS, USA (21)	1998	12.4	63.8	0	FFQ	Self-report, biomarkers	4519 (71.6)
Ding, NHS II, USA (21)	1999	13.1	44.2	0	FFQ	Self-report, biomarkers	3920 (49.6)
Ding, HPFS, USA (21)	2002	6.9	66.8	100	FFQ	Self-report, biomarkers	742 (34.9)
Konishi, Takayama, Japan (14)	1992	9.7	51.6	43.5	FFQ	Self-report	438 (32.4)

[1]HPFS, Health Professionals Follow-Up Study; IWHS, Iowa Women's Health Study; JPHC, Japan Public Health Center–Based Prospective Study; MCCS, Melbourne Collaborative Cohort Study; MDC, Malmö Diet and Cancer Study; MEC, Multiethnic Cohort; NHS, Nurses' Health Study; NHS II, Nurses' Health Study II; PREDIMED, Prevención con Dieta Mediterránea; ref, reference; SCHS, Singapore Chinese Health Study; SWHS, Shanghai Women's Health Study; WHS, Women's Health Study.

[2]Ordered by exposures reported and publication year. Numbers represent citations. JPHC and MEC reported results stratified by sex; Saku reported results stratified by adiposity status; stratified estimates were aggregated in advance before overall meta-analysis.

[3]Baseline years were defined as included in the study analyzed.

[4]Records included medical records or other registered records. Biomarkers included fasting glucose, glycated hemoglobin, or oral-glucose-tolerance test.

Sensitivity analysis and quality of evidence

We found high heterogeneity for total legume ($I^2 = 84.8\%$), total soy ($I^2 = 90.8\%$), and soy-milk ($I^2 = 91.7\%$) intakes. Meta-regression was performed to investigate potential sources of heterogeneity for these 3 exposures (**Table 3**), but not for tofu, soy protein, and soy isoflavones due to the low heterogeneity indicated. None of the factors examined could explain the heterogeneity found in total legumes and soy milk. Results for total legumes remained unchanged (null) in most subgroups, except that 1 study conducted in Asia showed an inverse association (RR: 0.62; 95% CI: 0.51, 0.75). For soy milk, the inverse association turned out to be null or marginally significant in all subgroups, which could be partly explained by limited numbers of studies included. For total soy, geographic location (P-heterogeneity $= 0.04$) and study quality ($P = 0.02$) significantly predicted heterogeneity. The association was not significant in studies conducted in the United States (RR: 1.00; 95% CI: 0.86, 1.16), but was significantly inverse in studies conducted in Asian countries (RR: 0.71; 95% CI: 0.55, 0.91). Likewise, studies with moderate or low quality supported a null finding (RR: 0.94; 95% CI: 0.82, 1.08), whereas studies with high quality showed an inverse association (RR: 0.61; 95% CI: 0.45, 0.83).

Publication bias was not evident for any of the investigated exposures (all $P > 0.05$; **Supplemental Figure 3**). Sensitivity analysis indicated that excluding any individual study did not change the overall findings substantially for total legumes, soy milk, or soy isoflavones. For total soy, excluding the Multiethnic Cohort (23) altered the association from marginally to significantly inverse. For tofu, the overall estimates were slightly weakened when excluding the Singapore Chinese Health Study (12) or the Nurses' Health Study II (21) cohort (**Supplemental Figure 4**). Compared with a random-effects model, a fixed-effects model slightly changed the results for total soy and soy milk, but not for total legumes, tofu, soy protein, or soy isoflavones (**Supplemental Figure 5**). Nevertheless, as there was high between-study heterogeneity for total legumes, total soy, and soy milk, we used pooled estimates by a random-effects model as our main findings.

We rated the quality of evidence in the present meta-analysis. The evidence for legume was rated as being of moderate quality, because the overall null finding remained robust against potential bias or publication bias and remained stable in stratified analysis despite the high degree of unexplained heterogeneity. We rated the evidence for total soy to be of low quality, because the association was influenced by adiposity, was not stable in sensitivity analysis, and varied by geographic location and study quality. The evidence of soy subtypes including soy milk, tofu, soy protein, and soy isoflavones was also rated as being of low quality, due to the limited numbers of studies included and instability or insufficiency in sensitivity analysis.

Discussion

The present systematic review and meta-analysis reported the most updated evidence regarding the associations of legume and soy intake with incident type 2 diabetes. We found that total legume intake was not associated with the risk of type 2 diabetes.

TABLE 2 Risk-of-bias assessment for cohort studies included in the present meta-analysis[1]

First author, cohort (ref)[2]	Domains of bias: Confounding	Selection	Exposure measurement	Misclassification	Missing data	Outcome measurement	Selective reporting	Overall	Additional consideration on potential sources of bias
Meyer, IWHS (15)	U	L	U	H	L	H	L	U	Potential misclassification of exposures and outcomes might have caused bias
Hodge, MCCS (16)	U	L	H	H	L	L	L	U	Habitual diet was not measured well
Liu, WHS (17)	U	L	H	H	U	U	L	U	Habitual diet was not measured well
Bazzano, NHS (22)	U	L	U	L	L	L	U	U	A risk of bias was unlikely to be high
Villegas, SWHS (11)	U	L	H	L	L	L	L	U	A risk of bias was unlikely to be high
Nanri, JPHC (18)	U	L	U	H	U	U	L	U	A risk of bias was unlikely to be high
Morimoto, MEC (23)	U	L	H	H	L	L	L	U	Habitual diet was not measured well
Mueller, SCHS (12)	U	L	U	H	L	L	U	U	A risk of bias was unlikely to be high
Ericson, MDC (19)	U	L	U	H	L	L	L	U	A risk of bias was unlikely to be high
Tatsumi, Saku (20)	U	L	H	H	L	L	H	H	Results were reported selectively
Ding, NHS (21)	U	L	U	L	U	L	U	U	A risk of bias was unlikely to be high
Ding, NHS II (21)	U	L	U	L	U	L	L	U	A risk of bias was unlikely to be high
Ding, HPFS (21)	U	L	U	L	U	L	L	U	A risk of bias was unlikely to be high
Becerra-Tomás, PREDIMED (13)	U	L	U	L	L	L	L	U	A risk of bias was unlikely to be high
Konishi, Takayama (14)	U	L	U	H	H	U	L	H	Exclusion of 44% participants during follow-up might have caused bias

[1]H, high risk of bias; HPFS, Health Professionals Follow-Up Study; IWHS, Iowa Women's Health Study; JPHC, Japan Public Health Center–Based Prospective Study; L, low risk of bias; MCCS, Melbourne Collaborative Cohort Study; MDC, Malmö Diet and Cancer Study; MEC, Multiethnic Cohort; NHS, Nurses' Health Study; NHS II, Nurses' Health Study II; PREDIMED, Prevención con Dieta Mediterránea; ref, reference; SCHS, Singapore Chinese Health Study; SWHS, Shanghai Women's Health Study; U, unknown risk of bias; WHS, Women's Health Study.

[2]Ordered by publication year. Overall risk of bias was assessed by considering whether multiple potential sources of bias would affect overall estimates with certainty and plausibility. See details for bias assessment in Supplemental Text; also see Supplemental Table 2 for potential confounders adjusted and validity assessment of dietary measurement in included studies. Influences of overall risk of bias have been examined in sensitivity analysis (Table 3).

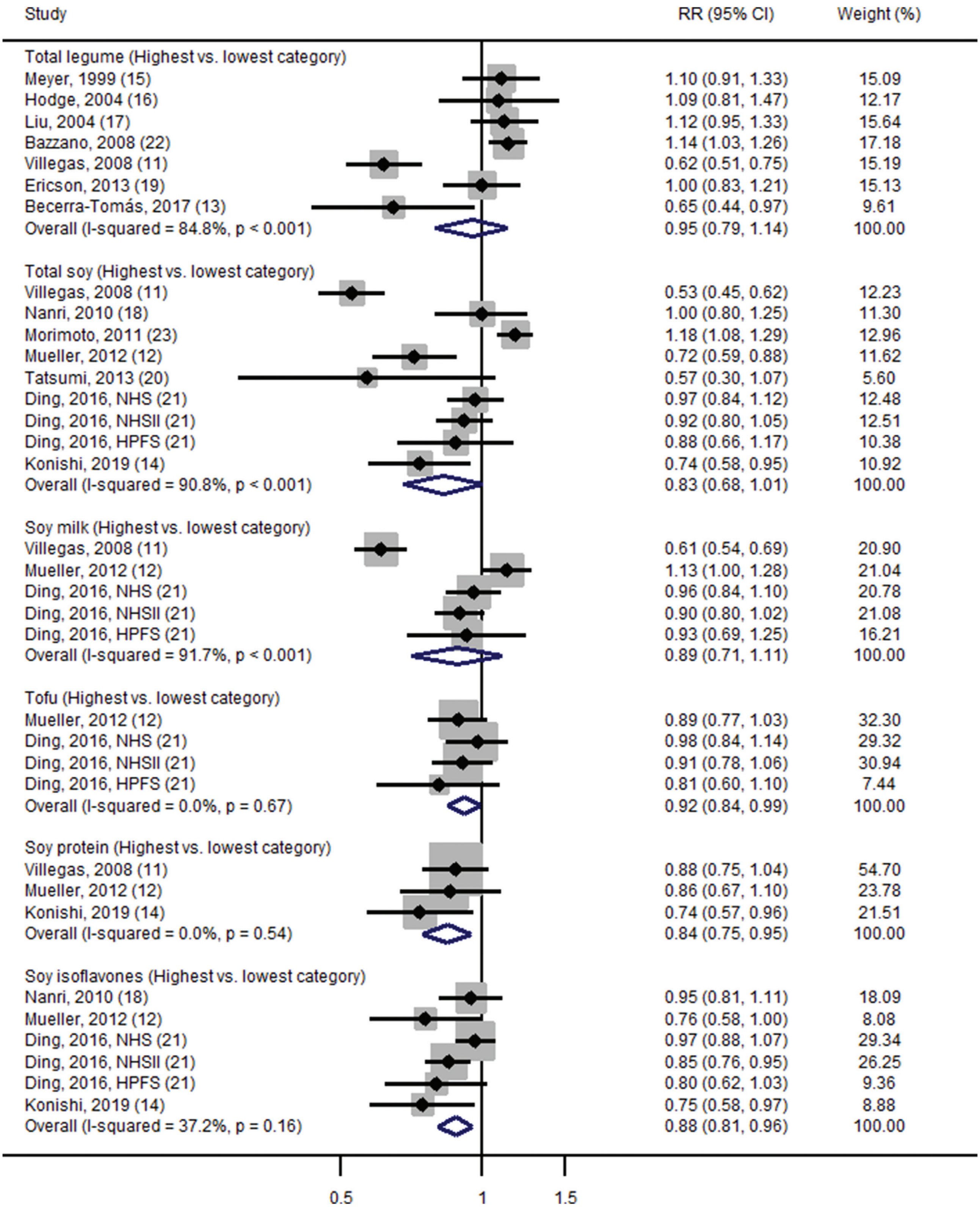

FIGURE 1 Forest plot to quantify the association of legume and soy intake with incident type 2 diabetes. The summary RRs were pooled by using a random-effects model for the highest versus the lowest category. HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; NHS II, Nurses' Health Study II.

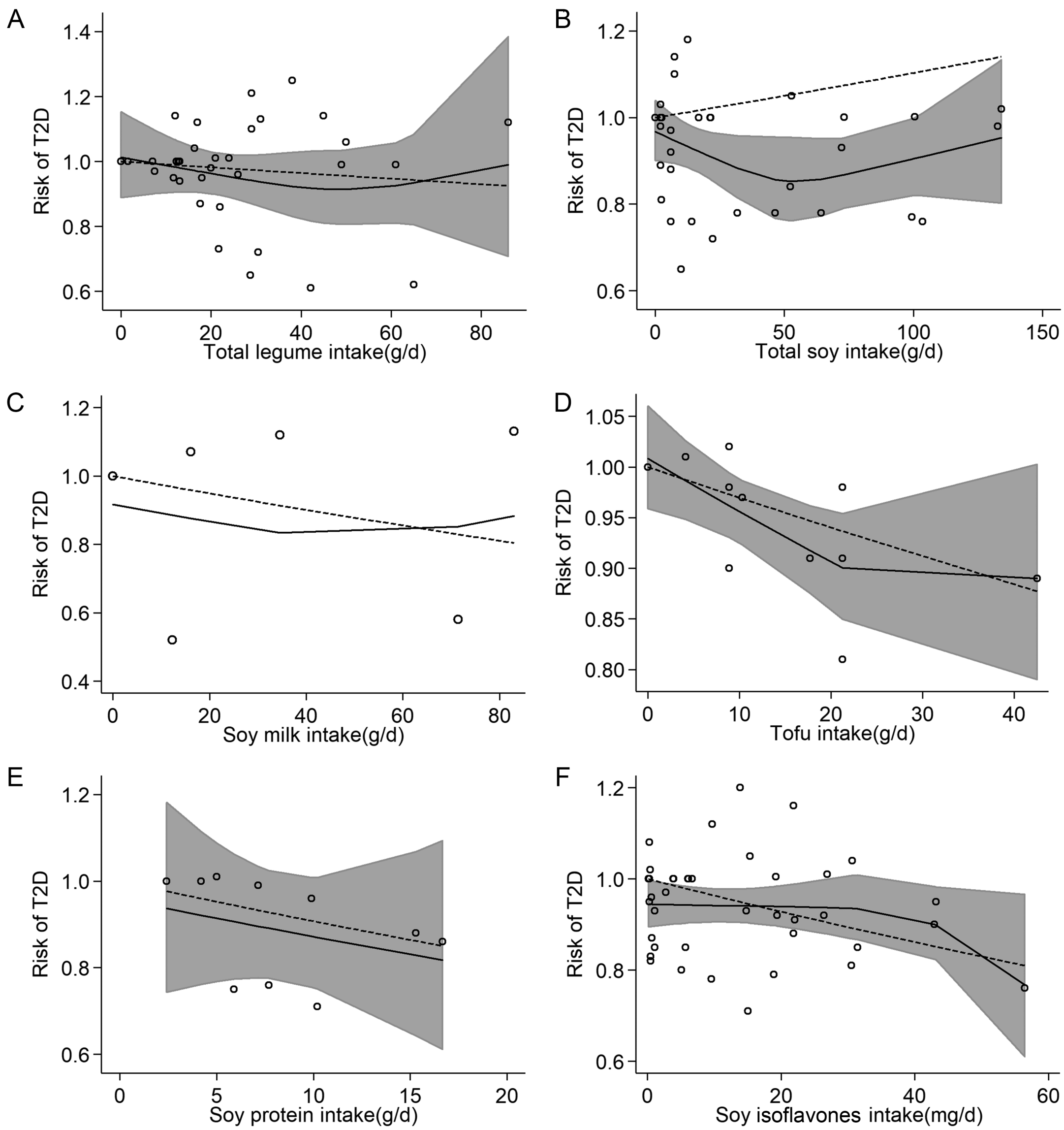

FIGURE 2 Dose–response analysis for the potential curvilinear or linear associations of legume and soy intake with incident T2D. Dose–response analysis was conducted for total legumes (A), total soy (B), soy milk (C), tofu (D), soy protein (E), and soy isoflavones (F), respectively. The circles represent dose-specific RRs from eligible studies. The gray areas represent the 95% CIs for the fitted curvilinear trend (solid lines). The dashed lines represent the linear trend. For soy milk (C), the gray area is not presented because it is too large. The *P* values for curvilinearity and linearity were 0.56 and 0.62 for total legumes, 0.24 and 0.59 for total soy, 0.51 and 0.98 for soy milk, 0.10 and 0.02 for tofu, 0.36 and 0.02 for soy protein, and 0.62 and 0.04 for soy isoflavones, respectively. T2D, type 2 diabetes.

Likewise, total soy intake was not associated with incident type 2 diabetes. For soy subtypes, intakes of tofu, soy protein, and soy isoflavones were associated with a lower risk of type 2 diabetes, whereas the quality of evidence for each of the 3 subtypes was rated as low due to insufficient sensitivity analysis and limited study numbers.

Interpretation in relation to other studies

Our findings agree with 1 previous meta-analysis, which found no significant association of legume intake with type 2 diabetes, although it only included 2 individual studies (24). However, the observed null association seemed to conflict with 1 recent meta-analysis that demonstrated a strengthened inverse association between a plant-based dietary pattern and type 2 diabetes risk, where legumes, nuts, vegetables, and fruits were included in the definition of plant-based patterns (4). One explanation could be that specific plant foods might not confer benefits equally (41)—that is, the effect of plant-based diets on the incidence of type 2 diabetes may not be driven by legumes. Likewise, different legumes may also exert discrepant effects on type 2 diabetes. One cohort study investigated the associations of total and subtypes of legumes with incident type 2 diabetes and found that the consumption of lentils and chickpeas, but not dry beans or fresh peas, was associated with a lower risk of type 2 diabetes (13), indicating that the intake of specific subtypes, but not total legumes, would play a beneficial role for the prevention of type 2 diabetes. However, the present meta-analysis did not summarize

TABLE 3 Potential sources of heterogeneity for the associations of legume and soy intake with incident type 2 diabetes[1]

	Total legumes				Total soy				Soy milk			
Factors	*n*	RR (95% CI)	I^2, %	*P*	*n*	RR (95% CI)	I^2, %	*P*	*n*	RR (95% CI)	I^2, %	*P*
Geographic location												
Asia	1	0.62 (0.51, 0.75)	—		5	0.71 (0.55, 0.91)	81.3		2	0.83 (0.45, 1.52)	97.8	
Australia	1	1.09 (0.81, 1.47)	—		—	—	—		—	—	—	
Europe	2	0.84 (0.55, 1.27)	72.4		—	—	—		—	—	—	
United States	3	1.13 (1.05, 1.22)	0.0	0.32	4	1.00 (0.86, 1.16)	76.8	0.04	3	0.93 (0.85, 1.01)	0.0	0.67
Sex												
Men	1	1.00 (0.77, 1.29)	—		5	1.00 (0.83, 1.20)	56.8		1	0.93 (0.69, 1.25)	—	
Women	5	0.98 (0.78, 1.22)	88.3		6	0.88 (0.73, 1.07)	87.6		3	0.81 (0.61, 1.06)	92.7	
Both	2	0.86 (0.52, 1.42)	75.6	0.64	1	0.72 (0.59, 0.88)	—	0.28	1	1.13 (1.00, 1.28)	—	0.57
Duration of follow-up												
≥8 y	3	1.11 (1.03, 1.20)	0.0		5	0.95 (0.81, 1.11)	80.1		3	0.93 (0.85, 1.01)	0.0	
<8 y	4	0.84 (0.60, 1.18)	86.7	0.22	4	0.70 (0.50, 0.96)	85.6	0.10	2	0.83 (0.45, 1.52)	97.8	0.67
No. of dietary measurements												
Only at baseline	4	1.08 (0.98, 1.19)	0.0		5	0.86 (0.66, 1.12)	87.0		1	1.13 (1.00, 1.28)	—	
Repeated	3	0.78 (0.49, 1.27)	94.5	0.18	4	0.80 (0.60, 1.07)	91.9	0.72	4	0.83 (0.66, 1.05)	89.3	0.29
Ascertainment of type 2 diabetes												
Self-report only	3	1.11 (0.99, 1.24)	0.0		2	0.86 (0.64, 1.16)	67.0		—	—	—	
Objective measures	4	0.84 (0.61, 1.16)	91.8	0.23	7	0.82 (0.65, 1.04)	92.8	0.61	5	0.89 (0.71, 1.11)	91.7	
Overall risk of bias												
High	—	—	—		2	0.71 (0.56, 0.90)	0.0		—	—	—	
Unknown	7	0.95 (0.79, 1.14)	84.8		7	0.86 (0.69, 1.07)	92.6	0.37	5	0.89 (0.71, 1.11)	91.7	
Study quality												
High	5	0.87 (0.67, 1.13)	83.9		2	0.61 (0.45, 0.83)	82.1		2	0.83 (0.45, 1.52)	97.8	
Moderate or low	2	1.14 (1.04, 1.23)	0.0	0.26	7	0.94 (0.82, 1.08)	74.5	0.02	3	0.93 (0.85, 1.01)	0.0	0.67

[1]Stratified analysis was conducted by prespecified factors and factors that significantly predicted heterogeneity ($P < 0.01$). Random-effects meta-analysis was performed in each stratum to pool RRs and 95% CIs.

the associations of different legume subtypes (except for soy) with incident type 2 diabetes due to the limited available data so far.

We found a marginally inverse association between total soy intake and risk of type 2 diabetes. Two previous quantitative reviews on the same topic were published, but they did not examine the potential curvilinear and linear associations and evaluate the quality of evidence (25, 26). In accordance with our finding, one of the studies found that total soy intake was marginally inversely associated with type 2 diabetes (25). However, the other suggested that the highest intake of total soy products was associated with a 23% lower risk of type 2 diabetes, compared with the lowest category (26). This inconsistency could be largely attributed to the inclusion criteria adopted: these studies included observational studies that used a cohort or cross-sectional study design, whereas the present meta-analysis only included prospective cohort studies. Consistently, the overall inverse association in the previous study turned out to be marginally significant when only focusing on cohort studies (26).

Plausibility and potential mechanisms

The plausibility of our findings deserves discussion. Legumes, a low-energy, nutrient-dense, high-fiber and low–glycemic-index food, have been long speculated to have antidiabetic effects. Legumes contain high amounts of flavonoids, which were suggested to have antioxidative and anti-inflammatory properties and consequently play beneficial roles in glycemic control (42, 43). They also contain considerable amounts of minerals such as calcium, potassium, and magnesium (42). As enzyme cofactors, these minerals contribute to various physiological processes, including glucose homeostasis (44), and are reported to be inversely correlated with incident type 2 diabetes (45–47). However, based on the present evidence, total legume intake was not associated with incident type 2 diabetes. As discussed earlier, 1 explanation could be that different subtypes of legumes might exert discrepant effects on type 2 diabetes. A clearer understanding of which subtype of legumes plays a beneficial role is of further research interest.

Similarly, the present meta-analysis suggests that total legume intake was not associated with the risk of type 2 diabetes, and specific types of soy foods or soy components showed discrepant associations with incident type 2 diabetes. In brief, tofu, soy protein, and isoflavones, but not milk, were inversely associated with type 2 diabetes. Soy protein and isoflavones, generally believed to be the 2 major functional components in soy foods, were found in animal models to decrease the concentrations of proinflammatory cytokines such as TNF-α and IL-1 (48, 49), which are able to suppress the cascade of insulin signaling. Soy isoflavones have also been shown to increase serum insulin via enhanced insulin signaling (50); similarly, soy protein was shown to be associated with increased gene expression of peroxisome proliferator-activated receptors and related fatty acid oxidation in liver (51) and adipose tissue (52). In addition, soy isoflavones such as genistein could directly act on pancreatic β cells and eventually increase insulin secretion, and soy β-conglycinin could improve the glucose uptake in skeletal muscle by the activation of cAMP/protein kinase A signaling pathway (53, 54). In line with these mechanisms, the present meta-analysis suggested that a daily increment of 10 g soy protein and 10 mg soy isoflavone intake was associated with a 9% and 4% lower risk of type 2 diabetes, respectively, despite the low quality of evidence.

We found that tofu was inversely associated, while soy milk was not associated, with incident type 2 diabetes. Soy milk is a plant-based drink produced by soybeans, and tofu is a food made by coagulating soy milk. Both contain considerable amounts of soy protein and isoflavones (55). If both soy protein and isoflavones are protective against type 2 diabetes, the present findings on soy milk and tofu would appear to be contradictory. One possible explanation could be that soy milk is often sweetened and its antidiabetic effects may be counteracted by the contained sugar, given that sweetened beverages have been shown to be associated with a greater risk of type 2 diabetes (56). Consistent with this hypothesis, 1 cohort study reported that unsweetened soy was inversely associated, whereas sweetened soy milk was positively associated, with incident type 2 diabetes (12).

Strengths and limitations

Our systematic review and meta-analysis has several strengths. First, we conducted a comprehensive literature search for all available evidence from existing cohort studies and performed a reproducible statistical analysis to investigate the associations of legume and soy intake with incident type 2 diabetes. Second, an extensive meta-regression and sensitivity analysis was conducted to explore potential sources of heterogeneity and their influence on pooled risk estimates. Third, we assessed the risk of bias for the included studies and rated the quality of evidence of the present review.

Several limitations should also be considered. First, although demographic, socioeconomic, and dietary factors were considered both in the included studies and the present meta-analysis, measures of these variables might involve errors and residual confounding might exist. For example, the time-varying confounding caused by the possibility that dietary habits might change over time could also exist and bias the results in an unknown direction. Second, despite a comprehensive literature research and inclusion of a considerable number of studies, limited data were available for subtypes of legume and soy foods. Only 3 studies were available in the analysis of soy protein, and only 1 study was available for each legume category including peanuts, lentils, chickpeas, dry beans, and fresh peas. Third, our analysis might introduce error by statistical approximation. In dose–response analysis, dose was set as the midpoint of a category, and 1 serving of exposures across studies were regarded as 1 standard portion. Fourth, we did not account for multiple comparisons for different legume or soy types, which may potentially lead to false-positive results. Fifth, the energy-adjusted models used by the individual studies did not explicitly model what legume or soy intake was replaced and there is likely to be heterogeneity in background diets. Thus, it is difficult to know ultimately what legumes and soy are being compared to in interpreting their relation with type 2 diabetes risk. Finally, assessing the risk of bias and evaluating the quality of evidence might involve subjectivity, although they were examined in accordance with standard procedures.

In conclusion, the present meta-analysis suggested that total legume or total soy intake was not associated with incident type 2 diabetes. In contrast, some certain types or components of soy foods including tofu, soy protein, and soy isoflavones were found to be inversely associated with incident type 2 diabetes, although the quality of evidence was rated as low. Our findings suggest that some certain types of soy foods may be beneficial for the prevention of type 2 diabetes. More high-quality, prospective, observational studies are needed to interpret the unexplained heterogeneity, and to verify which subtypes or components of legumes and soy foods might play a beneficial role.

The authors' responsibilities were as follows—FF and J-SZ: designed the study; JT and YW: extracted the data; JT, YW, MZ, and HZ: analyzed the data; JT and J-SZ: drafted the manuscript; and all authors: were involved in revising the manuscript and authors read and approved the final manuscript. The authors report no conflicts of interest.

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