Original scientific paper

European Journal of Preventive Cardiology

European Journal of Preventive Cardiology
2017, Vol. 24(7) 735–747

DOI: 10.1177/2047487316686441
journals.sagepub.com/home/ejpc

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Association between consumption of soy and risk of cardiovascular disease: A meta-analysis of observational studies

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Abstract

Background: The relationships between dietary intake of soy foods and risk of cardiovascular disease are uncertain. The aims of this study were to evaluate and summarize the evidence on the association between consumption of soy and risk of cardiovascular disease (including stroke and coronary heart disease).

Methods: We systematically searched the MEDLINE and EMBASE databases from their inception up to 22 February 2016. We included only observational studies, and used random-effects models to calculate summary relative risks (SRRs) and 95% confidence intervals (CIs).

Results: A total of 10 prospective cohort and seven case-control studies met the inclusion criteria. There were a total of 17,269 cardiovascular disease events, including 6265 stroke events, 10,806 coronary heart disease events, and 198 other cardiovascular disease events. A significant negative association was shown between soy intake and risk of cardiovascular disease (SRR = 0.84 95% CI: 0.75–0.94; $p_{heterogeneity}<0.001$, $I^2 = 71.4\%$). Subgroup meta-analyses indicated that a statistically significant protective effect was primarily observed in case-control studies and in Asian populations. There was a borderline significant association between intake of tofu and the risk of cardiovascular disease (SRR = 0.80, 95% CI: 0.64–1.00). A significant negative association was shown for the association between soy intake and risk of stroke (SRR = 0.82, 95% CI: 0.68–0.99) and coronary heart disease (SRR = 0.83, 95% CI: 0.72–0.95). There were no associations between soy isoflavones consumption and risk of cardiovascular disease, stroke, and coronary heart disease.

Conclusion: Overall evidence indicated that consumption of soy was negatively associated with the risk of cardiovascular disease, stroke, and coronary heart disease risk.

Keywords
Cardiovascular disease, coronary heart disease, soy consumption, stroke, soy isoflavones

Received 3 August 2016; accepted 26 November 2016

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, which is affecting millions of people in both developing and developed countries. Actually, the prevalence of CVD has evidently increased in low and middle income countries, especially in Asian countries which will account for more than 80% of global CVD by 2020.[1] The association between dietary consumption and CVD risk has been widely investigated, although specific food groups beneficial for this disease remain to be clarified. In recent decades, concern has mounted regarding the association between consumption of soy and soy products, and the risk of CVD. Soy foods are a major source of vegetable protein, soluble

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fibers, polyunsaturated fat, and isoflavones. In several clinical intervention studies, investigators have found that consumption of soy protein or isoflavones was negatively associated with risk factors for CVD such as hypertension,[2] blood lipid profile,[3] glycemic control,[4] arterial stiffness,[5] and endothelial function.[6]

In a recent systematic review and meta-analysis,[7] Afshin and his coauthors reported that consumption of legumes (including soy and non-soy) was negatively associated with risk of total ischemic heart disease (five studies; relative risk (RR)=0.86; 95% confidence interval (CI): 0.78–0.94) but not significantly associated with stroke (six studies; RR=0.98; 95% CI: 0.84–1.14). However, the majority of studies have evaluated the effects of whole legume consumption rather than soy legumes which are more commonly consumed in the East Asia than in Western countries.[8] Recently, lots of observational studies have examined the association between consumption of soy and soy products and risk of CVD (including stroke and coronary heart disease (CHD)), and have generated mixed findings.[8–24] Therefore, we conducted a meta-analysis of observational studies to quantify the association between consumption of soy and risk of CVD.

Methods

Literature search

A systemic search of MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed) and EMBASE (http://www.embase.com) from their inception up to 22 February 2016 was conducted by two investigators (ZY and XZ). We used the following medical subject headings or key words: (a) soy OR tofu OR soybeans OR soymilk OR miso OR natto OR sufu OR douche OR genistein OR daidzein OR isoflavone OR phytoestrogens; and (b) cardiovascular disease OR cerebrovascular accident OR brain ischemia OR hemorrhage OR stroke OR acute coronary syndromes OR myocardial infarction OR coronary heart disease. Both miso and natto are common menu items in Japanese cuisine, and sufu and douche are common menu items in Chinese cuisine. Both genistein and daidzein, primarily present in soy, are two major forms of soy isoflavones. Broadly defined, isoflavones are the major forms of phytoestrogens.[25] Only English articles were included. Reference lists in articles retrieved from all of the obtained literature were also scanned.

Study selection

Two investigators (ZY and XZ) independently reviewed all potentially relevant articles, and disagreement was resolved by a third reviewer (CL). Studies were included in this meta-analysis if they satisfied the following criteria: the study design was a case-control or cohort; the exposure of interest was consumption of soy foods or soy products; the outcome of interest was CVD, including stroke (fatal and nonfatal) and CHD (fatal and nonfatal); and the odds ratio (OR)/RR/hazard ratio (HR) and associated 95% CI were presented. We included studies using dietary intake of isoflavones, but excluded studies using isoflavone level in urine/plasma as the exposure measurement. Animal studies, in vitro research, case reports, ecological studies, and reviews were not considered. If study populations were reported more than once, we used the result with longer follow-up time.

Data extraction

Data extraction from each included study was carried out independently by two authors (ZY and XZ) using a standard extraction form. We extracted the relevant data, including: authors, publication year, study locations, study design, duration of follow-up in cohort studies, the sample size (number of participants and cases), methods of data available, type of Food Frequency Questionnaire (FFQ), endpoints (CHD, stroke, or both), and covariates adjusted for. For studies which examined more than one types of soy foods, we selected the most representative risk estimate for overall soy consumption or a soy food item that was the most commonly consumed in a descending order: total soy foods or soy products, tofu (bean curd) or miso soup, soy isoflavone or soy protein. For studies which had several adjustment models, we extracted those that reflected the maximum extent of adjustment for potentially confounding variables. Any results stratified by sex were treated as two separate reports. Those articles reporting both CHD and stroke were also treated as two separate reports.

Assessment of study quality

Two investigators (ZY and XZ) evaluated the quality of each selected study using the Newcastle-Ottawa Scale (NOS).[26] This scale consists of three parameters of quality: four stars for selection of participants, two stars for comparability, and three stars for assessment of exposure (for case-control studies)/outcomes (for cohort studies). Thus, a maximum of nine stars reflected the highest quality. We assigned scores of 0–6 and 7–9 for low and high quality studies, respectively.

Statistical methods

We used the statistical program STATA, version 11.0 (STATA, College Station, Texas, USA) for the

analysis. A two-tailed $p < 0.05$ was considered statistically significant unless where explicitly stated. Because a random-effects model could account for heterogeneity among studies, we used this method to calculate summary relative risk (SRR) and 95% CI for the highest vs lowest analysis. Heterogeneity among studies was quantified by using the Q statistic and I^2 statistics. Results were defined as heterogeneous for p-values < 0.10. I^2 values represent the amount of total variation explained by variation among studies, with a value of >50% indicating severe heterogeneity and a value of <25% indicating the absence of significant heterogeneity.[27]

We conducted analyses stratified by sex, study quality, study locations, study design (case-control vs prospective studies), methods of data available (interview vs self-administered), type of FFQ (validated vs non-validated), outcome (incidence vs mortality), and adjustments. Differences in results across strata were tested using meta-regression models.

For sensitivity analysis, we performed analysis by excluding one study in the meta-analysis and calculating a pooled estimate for the remainder of the studies to evaluate whether the results were significantly affected by a single study.

Publication bias was explored with funnel plots: Begg's adjusted rank correlation[28] and Egger's regression asymmetry test.[29] A value of $p < 0.10$ was considered to be representative of a significant statistical publication bias. To reduce the potential influence of publication bias, we used the trim-and-fill method.[30]

Results

Literature search

The flow of articles from the initial search to final inclusion in this meta-analysis is shown in Figure 1. The search of MEDLINE, EMBASE and reference lists identified a total of 3667 articles, 3590 of which were excluded because they were duplicates ($n = 1126$) or their title/abstract was not related to the examined associations ($n = 2464$). Of the 77 articles retrieved for critical review, a total of 17 articles,[8–24] published between 2001–2015, were included in the meta-analysis (Table 1).

Study characteristics

Seven case-control[9–15] and 10 cohort studies[8,16–24] recruited a total of 17,269 CVD cases (including 6265 stroke events, 10,806 CHD events, and 198 other CVD events). The countries where the studies were conducted were: China ($n = 6$), Japan ($n = 5$), the USA ($n = 2$), the Netherland ($n = 1$), Norway ($n = 1$), Italy ($n = 1$) and Singapore ($n = 1$). All studies used a semiquantitative FFQ as a tool to collect dietary information.

According to the NOS, the quality scores ranged from 4–9. The majority of included studies (14/17) were of high quality (NOS score ≥ 7; Supplementary Material, Table 1).

Association between soy consumption and risk of CVD

When pooling the studies that reported results on consumption of soy and CVD risk, the SRR was 0.83 (95%

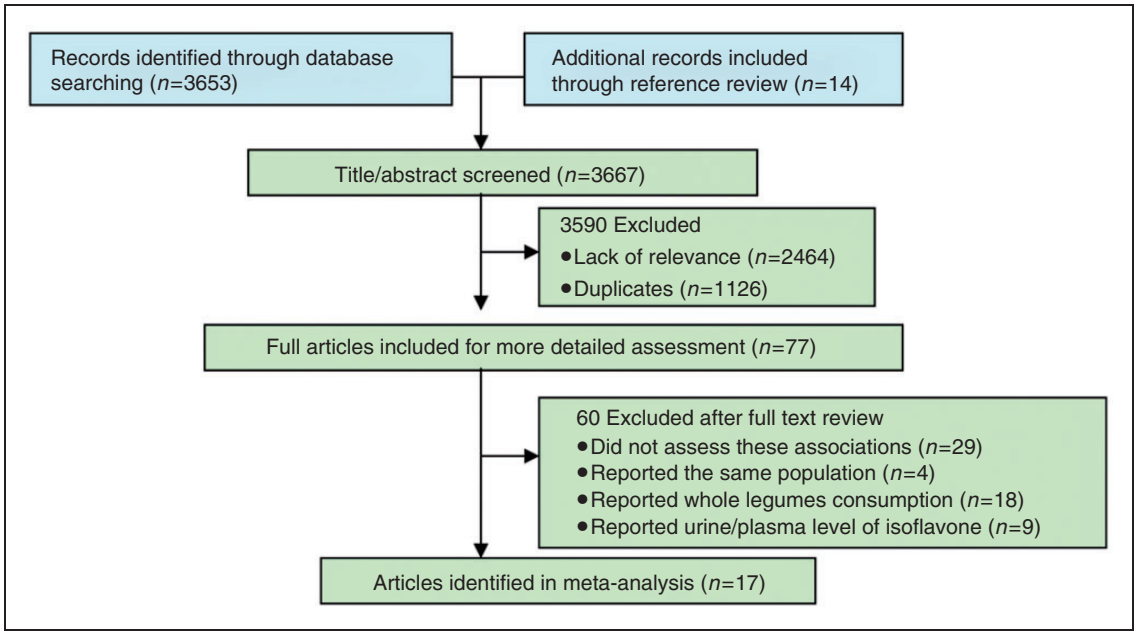

Figure 1. Flow diagram of systematic literature search on soy foods and the risk of cardiovascular disease.

Table 1. Characteristics of studies on the association between soy consumption and risk of cardiovascular disease (CVD).

First author, year	Country	Study characteristics	Dietary assessment	Exposure details	Endpoint determined	Endpoint (*n*)	Adjustments	NOS score
Case-control								
Sasazuki, 2001[9]	Japan	1277 Controls	Interview FFQ-23, NA	Tofu: T3 vs T1	Symptoms plus electrocardiogram, enzyme changes	Incident CHD (632)	++	8
Fang, 2006[10]	USA	204 Controls	Interview FFQ-49, validated	Soybean: ≥ 3 vs < 3 times/ week	Symptoms plus imaging	Incident stroke (187)	+	4
Ho, 2006[11]	China	10,968 Controls	Proxy report FFQ, NA	Soy:4+/week vs <1/mon	Death registry	Fatal stroke (2160) Fatal CHD (2016)	+++	6
Okamoto, 2006[12]	Japan	201 Controls	Interview FFQ, NA	Soy products: Q4 vs Q1	Surgical inspection, computed tomography or angiography	Incident SAH (201)	++	8
Tavani, 2006[15]	Italy	682 Controls	Interview FFQ-78, validated	Isoflavones: >32.91 vs <14.59 ug/day	World Health Organization criteria	Non-fatal CHD (760)	++	7
Liang, 2009[13]	China	464 Controls	Interview FFQ-125 validated	Total soy foods, ≥300 vs<50 g/ week	Symptoms plus imaging	Incident IS (374)	+++	7
Guo, 2013[14]	China	2235 Controls	Self-report FFQ-19, NA	Tofu: >3 vs<0.75 times/week	Symptoms plus electrocardiogram	Incident CHD (1312)	++	6
Prospective cohort								
Nagata, 2002[20]	Japan	Takayama study *n* = 31,552 Follow-up: 7 y	Self-administered FFQ-169, validated	Total soy products: 166.4 vs 40.6 g/day	Death registry and ICD-10	Fatal stroke (269) Fatal CHD (115)	++	8
Zhang, 2003[16]	China	SWHS *n* = 75,044 Follow-up: 2.5 y	Interview FFQ-125, validated	Total soy protein: 1.99 vs 0.47 g/ 1000 kJ/day	Medical records and/or death certificates and ICD-9	Incident CHD (62)	+++	8
Van der Schouw, 2005[17]	Netherland	EPIC *n* = 16,165, Follow-up: 6.3 y	Self-administered FFQ-79, validated	Isoflavones: Q4 vs Q1	Medical records and/or death certificates and ICD-9	Incident stroke (147) Incident CHD (72)	++	9
Mink, 2007[23]	Norway	IWHS *n* = 34,489 Follow-up: 16 y	Self-administered FFQ-127, validated	Isoflavones: 0.8 vs 0.1 mg/day	Death registry and ICD-9	Fatal CVD (2316) Fatal stroke (469) Fatal CHD (1329)	++	9
Kokubo, 2007[18]	Japan	JPHC *n* = 40,462 Follow-up: 12.5 y	Self-administered FFQ-147, validated	Soy: ≥ 5 vs 0–2 d/week	Medical records and death records	Incident IS (587) Incident CHD (308)	+++	9
McCullough, 2012[21]	USA						++	9

(continued)

Table 1. Continued

First author, year	Country	Study characteristics	Dietary assessment	Exposure details	Endpoint determined	Endpoint (*n*)	Adjustments	NOS score
		CPS II *n* = 98,469 Follow-up: 7 y	Self-administered FFQ-152, validated	Isoflavones: >0.567 vs <0.025 mg/day	Death registry and ICD-9,10	Fatal stroke (573) Fatal CHD (1286)		
Yu, 2014[8]	China	SMHS *n* = 55,474 Follow-up: 5.4 y	Interview FFQ-125 validated	Soy: 41.1 vs 11.3 g/day	Medical records and/or death certificates	Incident CHD (217)	+++	8
Talaei, 2014[19]	Singapore	SCHS *n* = 63,257 Follow-up: 14.7 y	Interview FFQ-165, validated	Tofu equivalents: 197 vs 42.8 g/day	Death registry and ICD-9	Fatal stroke (1298) Fatal CHD (2697)	+++	8
Yu, 2015[22]	China	SWHS *n* = 66,832 Follow-up: 10 y	Interview FFQ-77, validated	Isoflavones: 53.6 vs 9.0 mg/day	Medical records	Incident IS (3110)	+++	9
Yamasaki, 2015[24]	Japan	Jichi Medical School Cohort Study *n* = 11,066 Follow-up: 11.8 y	Self-administered FFQ-30, validated	Soy: daily vs rarely	Death registry and ICD-10	Fatal stroke (108) Fatal CHD (90)	++	8

CHD: coronary heart disease; CPS II: Cancer Prevention Study II; EPIC: European Prospective study Into Cancer; FFQ: Food Frequency Questionnaire; ICD: international classification of disease; IS: ischemic stroke; IWHS: the IowaWomen's Health Study; JPHC: Japan Public Health Center–Based Study; mon: month; Na: not available; NOS: the Newcastle-Ottawa Scale; Q: quartile; SAH: subarachnoid hemorrhage; SCHS: Singapore Chinese Health Study; SMHS: Shanghai Men's Health Study; SWHS: Shanghai Women's Health Study; T: tertile; y: years.
Degrees of adjustment for confounders were as follows: model 1: sociodemographics (+), model 2: sociodemographics plus risk factors for CVD (++), and Model 3: sociodemographics plus other risk factors and dietary variables (+++).

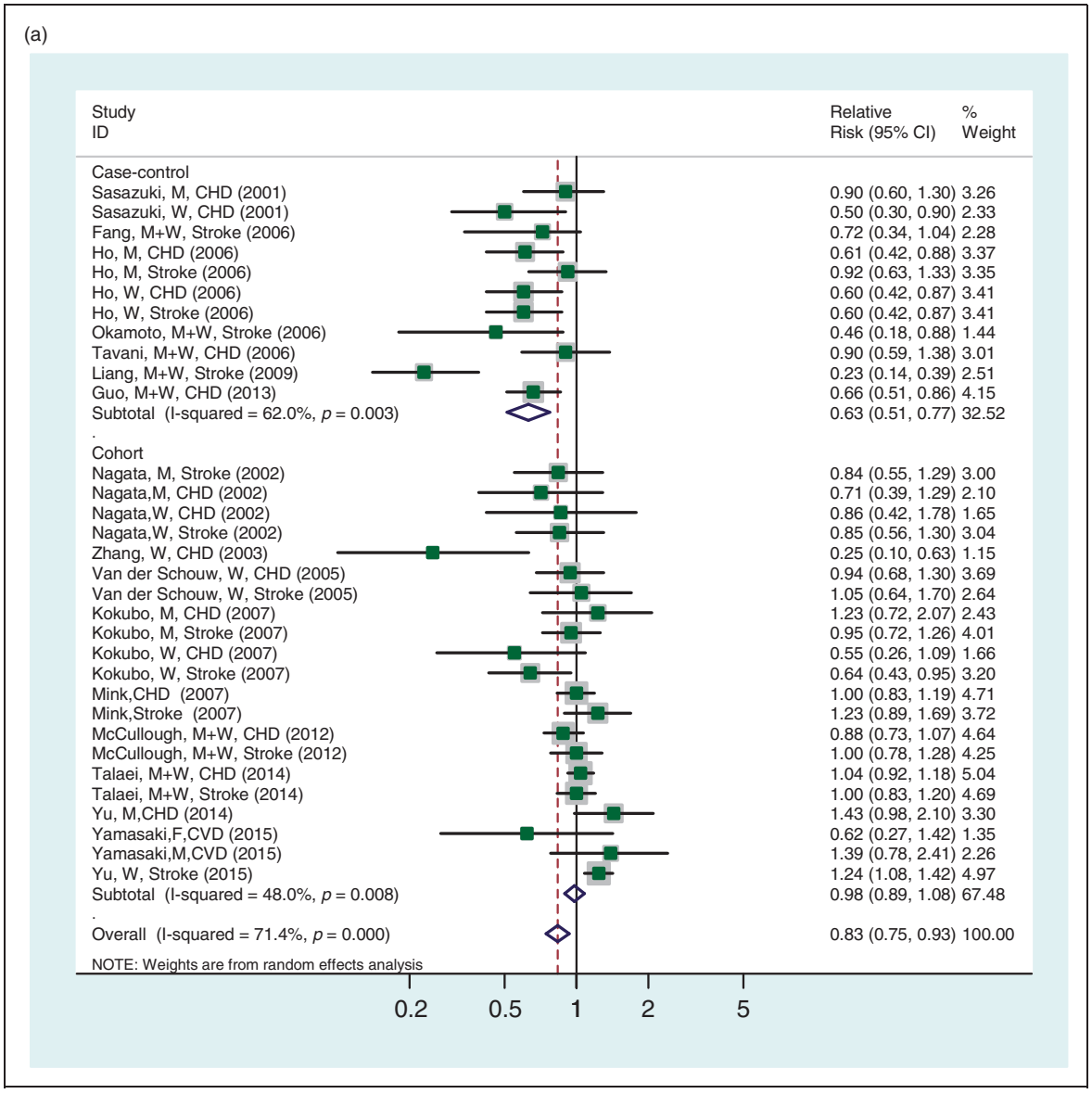

Figure 2. The summary risk association of (a) cardiovascular disease (CVD), (b) stroke, and (c) coronary heart disease (CHD) with consumption of soy foods according to the highest vs lowest analysis.
CI: confidence interval.

CI: 0.75–0.93) for subjects in the highest vs. lowest category, with significant heterogeneity among studies ($p_{\text{heterogeneity}}<0.001$, $I^2=71.4\%$; Figure 2(a)).

Table 2 was shown for subgroup analyses. Summarizing cohort studies yielded a SRR of 0.98 (95% CI: 0.89–1.08), whereas summarizing case-control studies led to a SRR of 0.63 (95% CI: 0.51–0.77). Pooling four studies[15,17,21,23] from the Westerns led to a non-significant SRR (0.98, 95% CI: 0.89–1.08), whereas pooling 13 studies in Asians led to a significant risk estimation (SRR = 0.77, 95% CI: 0.67–0.90). In stratified analysis by genders, a significant risk association was observed in females (SRR = 0.83, 95% CI: 0.69–0.99), but not in males (SRR = 0.91, 95% CI: 0.79–1.05). Restricting studies using adjustment variables as sociodemographics plus other risk factors for CVD (such as smoking history, alcohol use, physical activity, and BMI) led to a significant association of soy consumption with risk of CVD (SRR = 0.84, 95% CI: 0.75–0.94). In addition, restricting studies using the above adjustment variables plus dietary variables in the model also led to a significant association of soy consumption with risk of CVD (SRR = 0.74, 95% CI: 0.58–0.95).

Meta-regression analysis showed that both study design ($p=0.003$) and whether usage of a validated

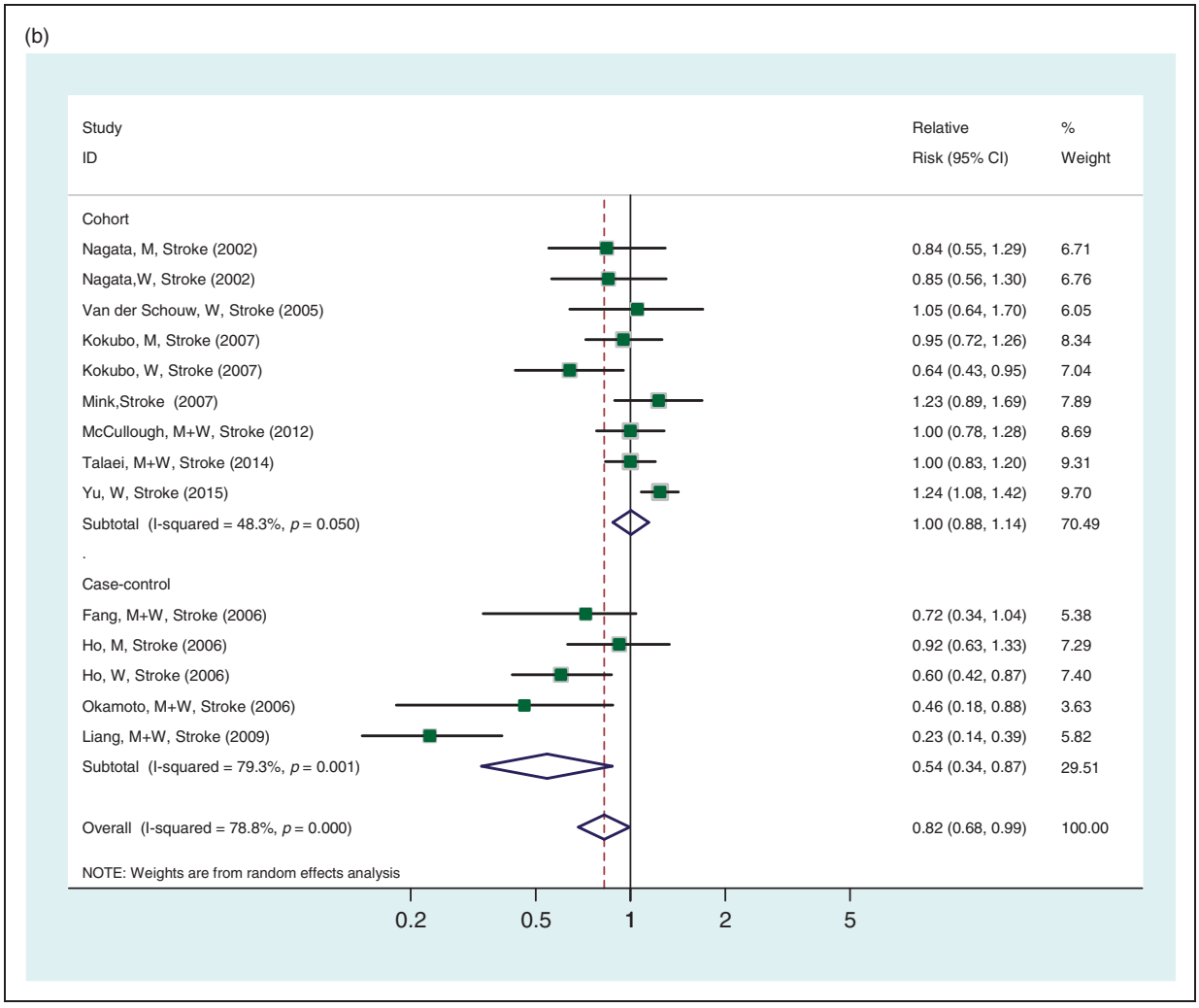

Figure 2. Continued.

FFQ ($p = 0.08$) were significant factors for the association between dietary soy intake and CVD risk. The calculation of overall homogeneity and effect size by removing one study at a time from the analysis confirmed the stability of this negative association (Supplementary Material, Figure 1). For example, when removing the study [10] that reported the association between soy consumption and subarachnoid hemorrhage risk, increased soy intake was still negatively associated with risk of CVD (SRR = 0.81, 95% CI: 0.72–0.92; $p_{\text{heterogeneity}} < 0.001$, $I^2 = 73.8\%$).

Association between soy consumption and risk of stroke

Four case-control[10–13] and seven cohort studies[17–23] reported results on consumption of soy and stroke risk. When these studies were pooled, the SRR was 0.82 (95% CI: 0.68–0.99) for the highest vs the lowest category of soy consumption, with significant heterogeneity among studies ($p_{\text{heterogeneity}} < 0.001$, $I^2 = 78.8\%$; Figure 2(b)). Subgroup analyses revealed an overall significant negative association in case-control studies, Asian countries, and studies with low-quality score (Supplementary Material, Table 2).

Association between soy consumption and risk of CHD

Four case-control[9,11,14,15] and eight cohort studies[8,16–21,23] reported results on consumption of soy and CHD risk. When these studies were pooled, the SRR was 0.83 (95% CI: 0.72–0.95) for the highest vs the lowest category of soy consumption, with significant heterogeneity among studies ($p_{\text{heterogeneity}} < 0.001$, $I^2 = 64.6\%$; Figure 2(c)). Subgroup analyses revealed an overall significant negative association in case-control studies, Asian countries, females and

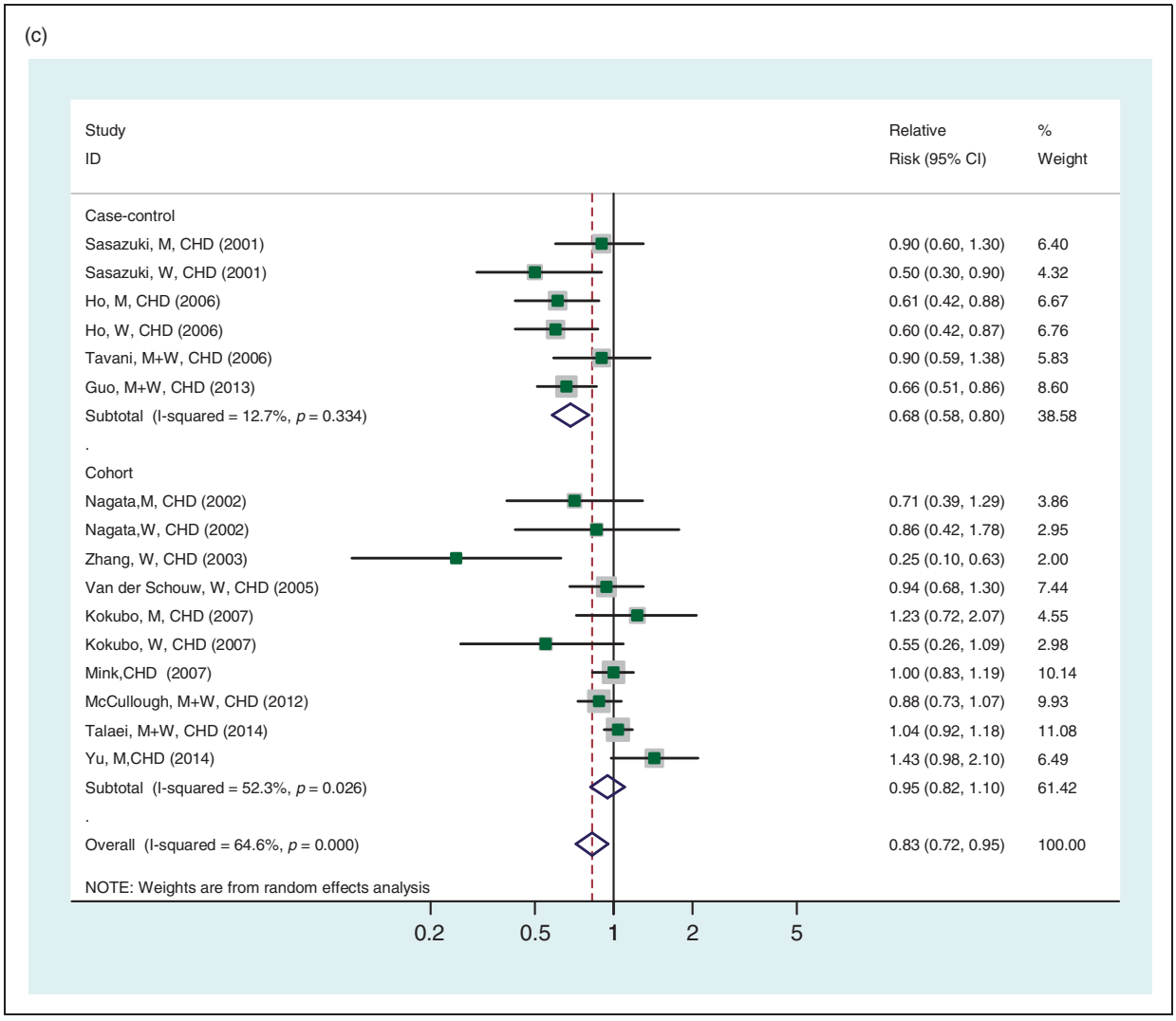

Figure 2. Continued.

studies with low quality score (Supplementary Material, Table 2).

Association between soy isoflavones consumption and risk of CVD, stroke and CHD

Eight studies[8,15,17–19,21–23] presented results on dietary soy isoflavones intake and CVD risk. The SRR was 0.98 (95% CI: 0.88–1.10; $p_{\text{heterogeneity}}<0.001$, $I^2=63.3\%$) for the highest vs the lowest analysis (Supplementary Material, Figure 2A). Six studies[17–19,21–23] presented results on stroke risk. The SRR was 1.00(95% CI: 0.81–1.23; $p_{\text{heterogeneity}}<0.001$, $I^2=76.0\%$) for the highest vs the lowest analysis (Supplementary Material, Figure 2B). Seven studies[8,15,17–19,21,23] presented results on CHD risk. The SRR was 0.96 (95% CI: 0.86–1.07; $p_{\text{heterogeneity}}=0.212$, $I^2=27.1\%$) for the highest vs the lowest analysis (Supplementary Material, Figure 2C).

Association between miso, tofu and soy protein consumption and risk of CVD

Two studies[9,18] presented results on miso intake and CVD risk, and the SRR was 0.82 (95% CI: 0.64–1.06; $p_{\text{heterogeneity}}=0.212$, $I^2=29.8\%$) for the highest vs the lowest category of consumption (Supplementary Material, Figure 3). Likewise, combining four studies[9,13,14,19] resulted in a SRR of 0.80 (95% CI: 0.64–1.00) for tofu consumption and the risk of CVD. Four studies[8,16,19,22] presented results on soy protein intake and the risk of CVD, and the SRR was 1.08 (95% CI: 0.89–1.30) for the highest vs the lowest category of consumption (Supplementary Material, Figure 3).

Table 2. Stratified analyses for the association between intake of soy and risk of cardiovascular disease.

Characteristic	Subgroup	No.	SRR (95% CI)	p_h	I^2(%)	p_d
All		17	0.83 (0.75–0.93)	<0.001	71.4	
Study design	Cohort	10	0.98 (0.89–1.08)	0.008	48.0	0.003
	Case control	7	0.63 (0.51–0.77)	0.003	62.0	
Study locations	Asian	13	0.77 (0.67–0.90)	<0.001	77.3	0.232
	Western	4	0.98 (0.89–1.08)	0.922	0	
Sex	Men	7	0.91 (0.79–1.05)	0.076	39.7	0.393
	Women	9	0.83 (0.69–0.99)	<0.001	73.5	
Study quality	High	14	0.89 (0.79–0.99)	<0.001	69.0	0.189
	Low	3	0.67 (0.58–0.77)	0.579	0	
Validated FFQ	Yes	13	0.87 (0.76–1.00)	<0.001	72.0	0.080
	No	4	0.67 (0.58–0.78)	0.339	11.7	
Outcome[a]	Mortality	7	0.90 (0.84–1.00)	0.031	43.0	0.704
	Incidence	11	0.76 (0.61–0.95)	<0.001	81.0	
Adjustments	Model 2	16	0.84 (0.75–0.94)	<0.001	72.1	-
	Model 3	7	0.74 (0.58–0.95)	<0.001	85.3	-

CI: confidence interval; FFQ: Food Frequency Questionnaire; SRR: summary relative risk.
[a]One study[16] reported outcome as both incidence and mortality of coronary heart disease. Degrees of adjustment for confounders were as follows: model 2: sociodemographics plus risk factors for CVD (++); Model 3: sociodemographics plus other risk factors and dietary variables (+++).

Publication bias

We observed evidence of publication bias for the association between consumption of soy and CVD risk ($p_{\text{Egger' test}}$=0.016 and $p_{\text{Begg's test}}$ = 0.019; Figure 3(a)) and for the association between consumption of soy and stroke risk ($p_{\text{Egger' test}}$=0.011 and $p_{\text{Begg's test}}$=0.016; Figure 3(b)). The trim-and-fill method indicated that no additional risk estimates were needed to balance the funnel plot, and the summary risk estimates were not changed. Whereas, for studies on the association between consumption of soy and CHD risk, there was no indication of publication bias ($p_{\text{Egger' test}}$=0.299 and $p_{\text{Begg's test}}$=0.163; Figure 3(c)).

Discussion

According to the meta-analysis of 17 observational studies, we found that consumption of soy foods was associated with a reduced risk of CVD (including CHD and stroke). These negative associations were primarily observed in studies based on a case-control design and from Asian populations. There was evidence of high heterogeneity among studies. We found no association of dietary isoflavone intake with the risk of CVD, stroke, and CHD.

It is biologically plausible that higher consumption of soy foods is associated with a lower risk of CVD. Soy foods and products are good sources of unsaturated fatty acids, fiber, iron, calcium, zinc, and B vitamins.[31] Mechanistic studies have indicated a protective effect of soy components on atherosclerosis progression through various routes, such as inhibition of proliferation and migration of vascular smooth muscle cells,[32] anti–platelet aggregation,[33] antioxidant effects,[34] and reduction in adhesion molecules.[35,36] Importantly, soybeans are the most widely consumed food that contains isoflavones. A meta-analysis of 11 randomized trials observed significant reductions in body weight, glucose level, and fasting insulin level with soy isoflavone supplementation compared with a placebo control group in non-Asian postmenopausal women.[37]

Results from our study suggested that consumption of soy foods, but not isoflavones, was associated with a lower risk of total CVD (including CHD and stroke), suggesting that other components, such as fiber, in the soy foods might account for these negative associations. For example, prospective epidemiologic studies have identified that high intake of dietary fiber was associated with a lower incidence of CHD[38,39] and stroke.[40,41] Mechanically, dietary fiber might bind to bile acids in the intestines and prevent re-absorption into the body, leading to a decrease in the circulating cholesterol levels in the blood.[42] In addition, research studies have reported that intake of fiber was likely to decrease insulin resistance and insulin levels in humans. On the other hand, larger measurement errors in the assessment of isoflavone intake than those related to soy food intake may also contribute to these null associations.

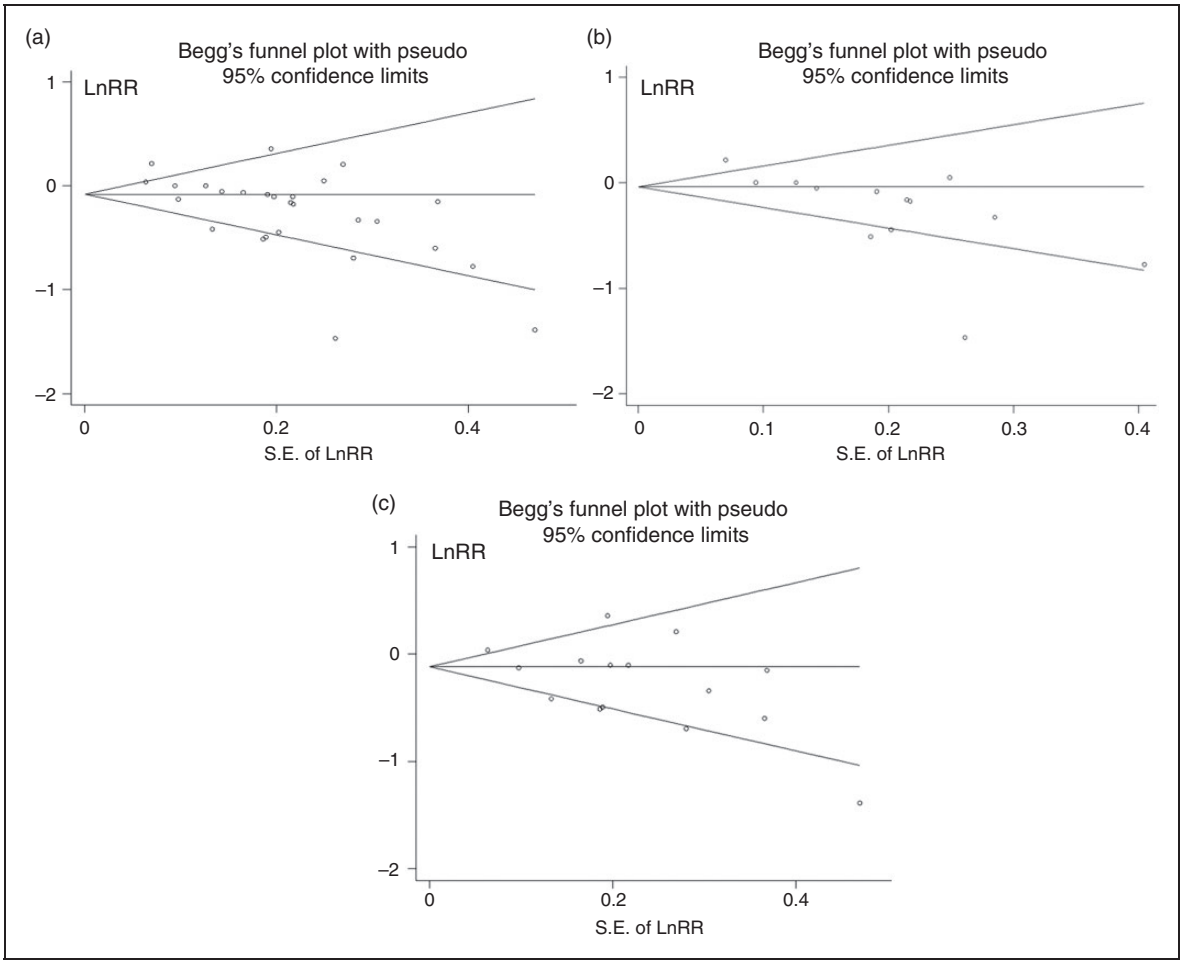

Figure 3. Begg's funnel plot of risk association of (a) cardiovascular disease, (b) stroke, and (c) coronary heart disease with consumption of soy foods.
LnRR: log of relative risk; S.E.: standard error.

Results from our subgroup analysis according to study locations showed a significant negative relationship of soy intake in Asians but not in Westerners. Such a difference could be attributed to the much higher intake of soy in Asians than that in Westerners. Soy consumption is traditionally common in Asians. For instance, two studies estimated isoflavone intakes to be 9–48 mg genistein/d and about 6–30 mg daidzein/d among the Japanese,[43] and an interquartile intake range of 4–22 mg isoflavones/d in Singapore women,[44] respectively. On the contrary, Schabath et al.[45] reported a median intake of less than 0.6 mg soy isoflavones/d in elderly adults in Houston, USA. In addition, these findings may be partly explained by differences in population characteristics, type of soy products consumed, and variations in isoflavone metabolism.[22]

Results from summarizing cohort studies showed no significant protective effects of soy foods consumption on the risk of CVD, CHD, and stroke, although significant protective effects were indicated in the meta-analysis of case-control studies. Case-control studies may be subjected to greater recall and selection biases, because cases reported exposure information on dietary intake after a CVD diagnosis. Thus, the overall findings of a reduction in risk of CVD, stroke, and CHD should not be overemphasized.

Our study has several strengths. To our knowledge, it is the first meta-analysis focusing on the association between soy foods consumption and risk of CVD, stroke, and CHD. We included studies based on a comprehensive, systematic search of the literature to capture all relevant information. In addition, we used models adjusting for most established risk factors (including diet factors, alcohol use, physical activity, smoking, and CVD intermediate biomarkers) and performed stratified analyses to explore whether some factors could explain the results.

Several limitations of our study should be taken into account. First, errors in measurement of soy intake and other dietary habits could have attenuated individual

study results.[46,47] It is very difficult for persons to accurately report their intake of soy foods due to the following: dietary data based on recall or questionnaire has fallen into disrepute, because research studies[48] have indicated that more than 50% of these data are not physiologically plausible. Some studies have assessed soy foods intake by questionnaire not to be validated and reproducible, and subgroup analyses indicated that the use of a validated vs non-validated FFQ did significantly change the association between dietary soy intake and CVD risk ($p = 0.08$). Some studies used the self-administered questionnaires, but not the interviewer-administered ones. Additionally, persons with non-evident CVD could be defined as controls/non-cases, especially in case-control studies, which might attenuate the results.

Second, high between-study heterogeneity was present. This inconsistency could be due to a number of possible reasons, including a wide variety of soy products (e.g. traditional soy foods, isolated soy protein, soy extracts, and purified isoflavones), different intake levels of soy foods and the degree to which dietary intake is controlled. The evident heterogeneity still presented in some subgroups, although we carried out stratified analyses using the random effects model, suggesting that other factors could be involved in the high heterogeneity.

Third, residual confounding cannot be completely ruled out because of the inability to fully control for various confounding factors. Soy foods may be markers of other dietary factors and lifestyles, such as lower rates of smoking, a lower intake of saturated fat, higher levels of fruit and vegetable consumption compared to those who do not eat many soy foods. Such healthy diets and lifestyles have been shown to reduce the risk of CVD.[49–51] However, all studies except one[10] have adjusted for risk factors (such as smoking, body mass index (BMI), alcohol drinking, physical activity) and intermediate biomarkers for CVD (e.g. blood cholesterol, blood pressure, hyperglycemia). Additionally, the cooking methods of soy and the amount of salt added to soy, an established risk factor for CVD,[52,53] were not available in all of the included studies.

Fourth, we were not able to investigate a dose-response relationship due to different methods used to assess and categorize dietary intake of soy across studies. In fact, studies provided results according to g/day, servings/week, g/1000 kJ/d, d/week, and servings per month. In addition, while the number of total stroke events is large, the number of stroke subtypes, especially hemorrhagic stroke, is relatively small. Thus, results for stroke subtypes should be interpreted with caution. Furthermore, our analysis is limited to data mostly from Asian populations, and only three studies were from Western areas (the Netherlands, Italy, and the USA); thus, additional research in other populations, especially in Western areas, is warranted to generalize these findings.

Finally, only English articles were included in the current meta-analysis, which could lead to language bias. Indeed, Begg's and Egger's test provided evidence for publication bias in the association between soy intake and risk of stroke and CVD. However, further examination using the trim-and-fill method showed no need to include additional risk estimates to balance the funnel plot, and the summary risk estimates remained unchanged.

In summary, results from our meta-analysis indicated that consumption of soy was negatively associated with the risk of CVD, stroke, and CHD risk. Further well-designed investigations are needed to examine these associations.

Author contribution

YZL, ZXY, LCL contributed to the conception or design of the work. YZL, ZXY contributed to the data acquisition, analysis, or interpretation of data. YZL, JSC, DWY drafted the manuscript. YZL, ZXY, JSC critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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