RESEARCH
Review

Soy, Soy Isoflavones, and Protein Intake in Relation to Mortality from All Causes, Cancers, and Cardiovascular Diseases: A Systematic Review and Dose–Response Meta-Analysis of Prospective Cohort Studies

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ABSTRACT

Objective We conducted a systematic review and dose–response meta-analysis of prospective studies to summarize findings on the associations between intakes of soy, soy isoflavones, and soy protein and risk of mortality from all causes, cancers, and cardiovascular diseases.

Methods Online databases were systematically searched to identify relevant articles published earlier than May 2018. We applied restricted cubic splines using random-effects analysis to assess dose–response associations. Between-study heterogeneity was assessed by I^2 value and Cochrane Q test. Potential publication bias was assessed by visual inspection of funnel plots and Begg regression test.

Results In total, 23 prospective studies with an overall sample size of 330,826 participants were included in the current systematic review and the meta-analysis. Soy/soy products consumption was inversely associated with deaths from cancers (pooled relative risk 0.88, 95% CI 0.79 to 0.99; P=0.03; I^2=47.1%, 95% CI 0.0% to 75.4%) and cardiovascular diseases (pooled effect size: 0.85, 95% CI 0.72 to 0.99; P=0.04; I^2=50.0%, 95% CI 0.0% to 77.6%). Such significant associations were also observed for all-cause mortality in some subgroups of the included studies, particularly those with higher quality. In addition, higher intake of soy was associated with decreased risk of mortality from gastric, colorectal, and lung cancers as well as ischemic cardiovascular diseases. Participants in the highest category of dietary soy isoflavones intake had a 10% lower risk of all-cause mortality compared with those in the lowest category. We also found that a 10-mg/day increase in intake of soy isoflavones was associated with 7% and 9% decreased risk of mortality from all cancers and also breast cancer respectively. Furthermore, a 12% reduction in breast cancer death was indicated for each 5-g/day increase in consumption of soy protein. However, intake of soy protein was not significantly associated with all-cause and cardiovascular diseases mortality.

Conclusions Soy and its isoflavones may favorably influence risk of mortality. In addition, soy protein intake was associated with a decreased risk in the mortality of breast cancer. Our findings may support the current recommendations to increase intake of soy for greater longevity.
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IT HAS BEEN HYPOTHESIZED THAT A HIGH CONSUMPTION of soy products have protective effect against various chronic conditions such as obesity, cardiovascular diseases (CVDs) and some of the cancers.[1] Soy is the major source of isoflavones, and previous studies have revealed potential antiatherosclerotic and anticarcinogenic properties of soy.[2-4] Furthermore, some studies indicated that a higher intake of soy proteins was associated with a lower incidence of cardiovascular events and some types of cancers.[5,6]

However, the relationship between intake of soy products and prognosis of various types of cancers remains unknown.

In vivo and in vitro studies have indicated that daidzein, genistein, and glycitein, which comprise 40%, 50%, and 10% of the soybean isoflavones, respectively, may compete with endogenous estrogens to bind to estrogen receptors and possess both estrogen-like and antiestrogenic activities.[7,8] Based on these studies, soy isoflavones may inhibit cells' transformation, angiogenesis, metastasis, and induce apoptosis.[9] Whereas other studies have reported that isoflavones enhance the proliferation of cells, and possibly promote tumor growth.[10] In addition, findings from epidemiologic studies on the association between intake of soy products and prognosis of chronic diseases are conflicting.[11-33] For instance, in an observational study in Japan, higher intake of traditional soy products was associated with lower risks of cerebral infarction and deaths from CVDs,[34] whereas such findings were not supported among Western populations that consumed soy products much lower than Asians.[35] Such conflicting results were also observed for the association between intake of soy products and all-cause mortality.[12,19]

Although several studies have assessed dietary intake of soy, soy isoflavones, and protein in relation to risk of mortality, no study summarized and reviewed those findings. Moreover, no information is available for the dose–response relationship between soy intake and mortality. Investigating the link between soy consumption and mortality is important for guiding consumer choices and prioritizing dietary guidelines to reduce the risk. In the current study, we performed a systematic review and meta-analysis of prospective cohort studies to summarize the association of dietary soy, soy isoflavones, and protein consumption with risk of mortality from all causes, total cancer, specific types of cancers, and CVDs.

RESEARCH SNAPSHOT

Research Question: What are the associations between the consumption of soy, soy isoflavones, and protein and the risk of mortality from all causes, cancers, and cardiovascular diseases (CVDs)?

Key Findings: This meta-analysis found that consuming soy/soy products was inversely associated with deaths from all causes, cancers, and CVDs. In addition, a higher intake of soy was associated with a decreased risk of mortality from gastric, colorectal, and lung cancers as well as ischemic CVDs. Participants in the highest category of dietary soy isoflavones intake had a 10% lower risk of all-cause mortality compared with those in the lowest category. We also found that a 10-mg/day increase in dietary intake of soy isoflavones was associated with 7% and 9% lower risk of mortality from all cancers and breast cancer alone, respectively. Furthermore, each 5-g/day increase in intake of soy protein was related to a 12% reduction in risk of breast cancer death.

METHODS

This study was designed, implemented and analyzed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol.[36]

Search Strategy

A literature search was performed independently by two researchers (S. M. and J. A. S.) on the PubMed, Web of Science, Scopus, ProQuest, Science Direct, and Embase databases for relevant publications up to May 2018, using the appropriate key words (Figure 1, available at www.jandonline.org). In addition, reference lists of relevant articles and published systematic reviews and meta-analyses were hand searched to identify studies that might have been missed. Furthermore, no restrictions were applied on the time of publication and language. In the search strategy, unpublished studies and duplicate citations were excluded.

Inclusion Criteria

Studies with the following criteria were eligible for inclusion to our meta-analysis: studies that were of prospective design; the ones that considered dietary intake of soy and its constituents, including isoflavones or protein as an exposure and mortality from all causes, total cancer, specific types of cancers, and CVDs as the outcomes of interest; studies that were conducted on adults (aged >18 years); those who reported odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) along with 95% CI for the association between consumption of dietary soy, soy isoflavones, or protein and mortality risk. In case of multiple published reports on the same dataset, we chose the most recent; otherwise, the one with the greatest number of cases was selected.

Excluded Studies

We excluded letters, comments, short communications, reviews, meta-analyses, ecologic studies, and animal studies from the analysis. In our initial search, we found 972 articles in total. After removing duplicates, 925 articles were selected for a more detailed review. We excluded 876 articles after screening for titles and abstracts that left 49 articles. In addition, another 26 studies were excluded for the following reasons: studies that assessed the association between other dietary factors except soy or its constituents and mortality (n=15); those that evaluated consumption of soy in relation to risk of cancers or CVDs, but not mortality risk (n=2)[37,38]; studies that assessed cancer recurrence in relation to dietary soy intake (n=1)[39]; studies that examined the association between a soy-rich dietary pattern and mortality (n=5)[34,40-43]; studies on the association between urinary or dietary phytoestrogens and mortality (n=2).[44,45] In addition, from the Women's Healthy Eating and Living study, two different articles were published about the association between the intake of soy isoflavones and risks of all-cause and breast cancer mortality.[27,46] To avoid double-counting data, we included the last report from the Women's Healthy Eating and Living study because it had a larger duration of follow-up and the greater number of deaths.[27] Although Leo and colleagues[12] and Conroy and colleagues[15] performed their analysis on a same dataset, the participants included in their statistical analyses were different from each other. Therefore, both studies were included. Finally, 23 prospective studies were included in the current systematic review and meta-analysis.[11-33] A flowchart of the study selection is presented in Figure 2 (available at www.jandonline.org).

Data Extraction

Data extraction was conducted independently by two investigators (S. M. and J. A. S.) using a standardized data collection form. Any disagreement has been discussed and resolved accordingly. Intakes of dietary soy, soy products, specific soy foods, soy protein, or isoflavones were considered as the primary exposure variables. Based on published studies, soy or soy product intake was obtained by summing the intakes of various soy foods, including tofu, miso, tempeh, miso, soybeans, soybean sprouts, fermented soy beans, alfalfa sprouts, soy yogurt, soy ice cream, soy flour, soy cheese, soy hot dogs and cold cuts, soy nuts, bean curd, fried soy, soy sauce, natto, soymilk, soybean drink, okara, dried tofu, deep-fried tofu, fried tofu, fried tofu, and minced vegetables/seaweed. Moreover, specific soy foods intake included the consumption of natto, tofu, and miso. The analyses were stratified based on the exposures (soy/soy products vs specific soy foods) to indicate separate associations of the exposures with mortality as the outcome. The key outcome variable was the incidence of death from all causes, total and specific types of cancers, and CVDs.

To facilitate the comparisons between studies, the following information was extracted: first author; year of publication; cohort name; country of origin; age range at study baseline; sex; sample size; number of cases; duration of follow-up; methods used to assess consumption of soy or its constituents, including isoflavones and protein; ascertainment of outcomes; and statistical adjustment for confounding variables (Tables 1, 2, 3, available at www.jandonline.org). If some studies did not provide required estimates, then we calculated these estimates using standard methods. If a study provided sex-stratified data, then we considered the study as two separate studies.

Assessment of the Quality of Studies

Quality assessment was performed using the Newcastle-Ottawa scale, designed for observational studies.[47] Any discrepancy was figured out by discussing. This scale assigns a maximum of 9 points to each prospective study as follow: 4 points for the selection of participants and measurement of exposure, 2 points for comparability, and 3 points for assessment of outcomes and adequate duration of follow-up. In the present study, those that achieved a score of 5 or more were considered high-quality publications.

Statistical Analysis

Log RRs and their standard errors were calculated using ORs, RRs, or HRs and their 95% CIs reported for the highest vs lowest categories of intakes of soy or its constituents, including isoflavones and protein. Then, the pooled effect sizes were calculated using random-effects model (DerSimonian–Laird method), which takes between-study variations into account.[48] Because heterogeneity modeling was deemed important, the random-effects model was used. This model was performed by *metan* command in STATA.[48] To evaluate the weight of each study, the standard error for the log RR of each study was regarded as the estimated variance of the log RR, using an inverse variance method.[49] The heterogeneity was assessed by using I^2 value (with 95% CI) and Cochrane Q test (by *metaan* command in STATA).[50,51] Furthermore, we conducted subgroup analyses according to the predefined criteria to find probable sources of heterogeneity (*metan* command).[48] In addition to the main analyses, we carried out sensitivity analysis by *metaninf* command in STATA to determine whether the overall estimates were dependent on the effect size from a single study.[52] Potential publication bias was assessed by visual inspection of funnel plots (obtained from *metafunnel* command) and also using Begg regression test (using *metabias* command) for each association with >10 studies.[53,54] Publication bias tests are unpowered to detect such bias for a meta-analysis on <10 studies.[55]

A method suggested by Greenland and Longnecker[56] and Orsini and colleagues[57] was used to assess the dose–response associations between dietary intake of soy isoflavones or protein and mortality. Due to the lack of necessary data, we were not able to examine the same associations for intake of soy/soy products. In the mentioned method, the distribution of cases and the OR/RR/HR with the variance estimates for ≥3 quantitative categories of exposure were required. We considered the midpoint of soy isoflavones and protein intakes in each category as the corresponding OR/RR/HR estimate. For studies that reported a range for soy isoflavones and protein intake, we estimated the midpoint in each category by calculating the mean of the lower and upper bound. When the highest and lowest categories were open-ended, the length of these open-ended intervals was assumed to be the same as that of the adjacent intervals. A two-stage random-effects dose–response meta-analysis was applied to examine a probable nonlinear associations between intakes of soy isoflavones and protein with mortality.[57] This was done through modeling for intakes of soy isoflavones and protein and restricted cubic splines with three knots at fixed percentiles (10%, 50%, and 90%) of distribution.[58] Based on the Orsini method, we calculated restricted cubic spline model using generalized least-squares trend estimation method (by *glst* command in STATA), which takes the correlation within each set of reported OR/RR/HR into account.[57] Then, all the study-specific estimates were combined by the use of the restricted maximum likelihood method in a multivariate random-effects meta-analysis.[59] A probability value for nonlinearity was estimated using null hypothesis testing in which the coefficient of the second spline was considered equal to 0. A linear dose–response association of a 10-mg/day increment in intake of soy isoflavones or a 5-g/day increase in intake of soy protein with mortality was investigated using the two-stage generalized least-squares trend estimation method (by use of *glst* and *metan* commands in STATA).[56,57,60] First, study-specific slope lines were estimated (using *glst* command) and then, these lines were combined to obtain an overall average slope.[57] Study-specific slope lines were combined using a random-effects model (*metan* command).[48] Statistical analyses were done using STATA version 11.2 (Stata Corp).[61] P values were considered significant at the level <0.05.

RESULTS

Findings from the Systematic Review

Characteristics of 23 prospective studies[11-33] that were included in our systematic review are shown in Tables 1, 2, and 3 (available at www.jandonline.org). All of the included studies were published between 2002 and 2018. Of the 23 included studies, 2 were done in the United States[12,15]; 19 in Asian counties[11,13,14,16-20,22,23,25,26-33]; one in the United States, Canada, and Australia[24]; and another one on a dataset from

the United States and China.[27] The sample size of included studies varied from 127 to 64,915 participants (total=330,826) aged 18 years and older. During the follow-up, periods ranged from 2.5 to 24 years, the total number of all-cause mortalities was 26,900, and total numbers for deaths from cancers and CVDs were 11,005 and 13,418, respectively. From 23 included studies, 12 were done on both sexes[11-14,17,19-23,25,28] and the rest of the studies were conducted only on women.[15,16,18,20,24,26,27,29-33] However, nine studies presented sex-stratified analyses.[11,13,14,17,19-23] Based on the Newcastle-Ottawa scale, all of the included studies were of high quality (Table 4, available at www.jandonline.org).

Among five studies considering the association of intake of soy/soy-specific foods with all-cause mortality,[12,13,15,19,22] one found an inverse association,[19] one reported a marginally significant inverse association,[22] and others failed to find any significant associations. Out of nine studies that investigated the associations between soy or soy-specific foods intake and cancer mortality,[12,13,15,16,18,19-22] only one study showed an inverse association and the rest did not report any significant relationship.[19] Only one study out of six showed a significant inverse association between intake of soy or soy-specific foods and mortality from CVDs.[19] One study showed a protective effect for soy isoflavones intake against all-cause mortality,[24] whereas two publications confirmed that intake of soy isoflavones prevents mortality from cancer.[26,33] None of the included studies indicated any significant relationship between soy isoflavones intake and CVD mortality. Inverse associations were reported between soy protein intake, and all-cause mortality (one study),[31] and cancer mortality (three studies).[26,31,33] No studies revealed any significant association between soy protein intake and CVD mortality.

Findings from the Meta-Analysis

All 23 studies included in the systematic review were included in the meta-analysis as well. Three types of exposures, including intake of soy (soy, soy products, and soy-specific foods), soy isoflavones, and protein were assessed in relation to three types of outcomes (mortality from all causes, cancers, and CVDs). We considered soy, soy products, and soy-specific foods as the same. However, a subgroup analysis was also done for soy/soy products compared with soy-specific foods. Coronary heart disease included in our analyses as a part of ischemic CVDs. All included studies presented effect sizes for the highest vs the lowest categories of exposure except two studies (Yang and colleagues[16] and Yamasaki and colleagues[13]). In those two studies, participants with moderate intake but not the lowest intake of soy or soy isoflavones were considered as the reference group.[13,16] To include those two studies in our meta-analysis, we used their published data to calculate RR of mortality for the highest vs the lowest intake of soy or isoflavones. The same calculation was also done for two other studies that presented the required data.[28,30] Kokubo and colleagues[17] reported the risk estimates separately for dietary intake of soy, miso soup, and soy beans. To obtain one risk estimate for total soy intake, we pooled those estimates and then included them in the meta-analysis. The same combining method was also used for effect sizes that were reported for tofu and miso soup in Khan and colleagues[20] and Kurozawa and colleagues.[21] In the study by Shu and colleagues,[31] although 80% of patients with breast cancer relapse died due to breast cancer, the statistical analyses were not performed separately for those patients. Therefore, we considered risk estimates on relapse/breast cancer-specific mortality as breast cancer mortality in this study.[31] The results of our meta-analysis are reported separately for the relation of each exposure to each outcome.

Soy Consumption and All-Cause Mortality

Overall, no significant association between soy consumption and all-cause mortality was found after combining eight effect sizes from five studies[12,13,15,19,22] that included 78,381 participants and 24,497 deaths (pooled effect size 0.90, 95% CI 0.77 to 1.04; P=0.16) (Table 5). We found a significant heterogeneity between the studies (I^2=75.1%, 95% CI 49.9% to 87.6%; P-Q test <0.001). No study showed any relationship between soy-specific foods and all-cause mortality. To find the source of heterogeneity, we performed a subgroup analysis according to sex, geographic region (Asian vs non-Asian countries), sample size (≥10,000 vs <10,000 participants), duration of follow-up (<10 years vs ≥10 years), year of publication (up to 2010 vs 2010 and later), and adjustment for energy intake or body mass index (BMI) (Table 5). Subgroup analysis was based on sample size and year of publication that could explain the between-study heterogeneity. Findings from subgroup analyses revealed a significant inverse association between soy intake and all-cause mortality in those studies with a sample size ≥10,000 participants, those with follow-up duration <10 years, studies published up to the year 2010, publications that considered energy intake as a covariate, and those publications that did not adjust their association models for BMI. We were unable to examine the dose–response association between soy intake and all-cause mortality due to the lack of necessary data.

Soy Consumption and Cancer Mortality

Overall, nine publications that investigated the association between soy consumption and cancer mortality were included in the meta-analysis.[12,13,15,16,18,19,20,21,22] Those nine studies included 165,288 participants and 9,804 deaths from cancers. Combining 14 effect sizes that were captured from those nine studies indicated that the intake of different types of soy (a combination of soy or soy products and soy-specific foods) was inversely associated with cancer mortality (pooled RR 0.90, 95% CI 0.81 to 1.00; P=0.05) (Table 5); however, such association was marginally significant. There was a moderate evidence of between-study heterogeneity (I^2=41.8%, 95% CI 0.0% to 69.0%; P for Q test=0.06).

In a subgroup analysis based on exposure (soy or soy products intake compared with soy-specific foods intake), a significant inverse association was observed between intake of soy/soy products and cancer mortality (pooled RR 0.88, 95% CI 0.79 to 0.99; P=0.03), but such association was not observed for soy-specific foods (pooled effect size 0.99, 95% CI 0.78 to 1.25; P=0.90). Further subgroup analyses showed a significant inverse associations between soy/soy products intake and cancer mortality in women, those studies that were conducted in Asian countries, those with a sample size ≥10,000, studies with <10 years' duration of follow-up, studies that published up to the year 2010, publications that considered energy intake as a covariate, and those that did not adjust for BMI (Table 5). Subgroup analysis was not

Table 5. Pooled effect sizes for the association between soy intake and mortality

	References	Effect size[a] (n)	I^2 (%) (95% CI)[b]	*P* value for *Q* test	Pooled relative risk (95% CI)[c]
All-cause mortality					
Soy/soy product intake					
Overall	12, 13, 15, 19, 22	8	75.1 (49.9-87.6)	<0.001	0.90 (0.77-1.04)
Subgroup analysis					
Sex					
Both	12	1	N/A[d]	N/A	0.93 (0.76-1.14)
Male	13, 19, 22	3	86.9 (62.7-95.4)	<0.001	0.93 (0.68-1.26)
Female	13, 15, 19, 22	4	72.8 (23.2-90.3)	0.01	0.86 (0.70-1.06)
Country					
Asian	13, 19, 22	6	81.4 (60.2-91.3)	<0.001	0.88 (0.72-1.06)
Non-Asian	12, 15	2	0.0 (0.0-100)	0.53	0.97 (0.83-1.13)
Sample size, n					
<10,000	12, 13, 15	4	47.7 (0.0-82.6)	0.12	1.06 (0.93-1.21)
≥10,000	19, 22	4	11.3 (0.0-86.4)	0.34	0.77 (0.69-0.86)
Follow-up, y					
<10	12, 22	3	0.0 (0.0-89.6)	0.66	0.86 (0.77-0.97)
≥10	13, 15, 19	5	84.3 (64.8-93.0)	<0.001	0.92 (0.73-1.17)
Adjustment for energy intake					
Adjusted effect size	12, 15, 22	4	0.0 (0.0-84.6)	0.47	0.89 (0.80-0.99)
Nonadjusted effect size	13, 19	4	88.3 (72.5-95.0)	<0.001	0.90 (0.67-1.20)
Adjustment for body mass index					
Adjusted effect size	12, 13, 15, 22	6	63.6 (12.0-84.9)	0.01	0.97 (0.85-1.12)
Nonadjusted effect size	19	2	5.1 (0.0-10)	0.30	0.71 (0.61-0.83)
Year of publication					
Up to 2010	19, 22	4	11.3 (0.0-86.4)	0.34	0.77 (0.69-0.86)
2010 and later	12, 13, 15	4	47.7 (0.0-82.6)	0.12	1.06 (0.93-1.21)
Cancer mortality					
Total soy[e]					
Overall	12, 13, 15, 16, 18, 19, 20, 21, 22	14	41.8 (0.0-69.0)	0.06	0.90 (0.81-1.00)
Soy/soy products intake					
Overall	12, 13, 15, 16, 19, 22	9	47.1 (0.0-75.4)	0.07	0.88 (0.79-0.99)
Subgroup analysis					
Sex					
Both	12	1	N/A	N/A	0.92 (0.72-1.18)
Male	13, 19, 22	3	70.3 (0.0-91.3)	0.02	0.93 (0.69-1.26)
Female	13, 15, 16, 19, 22	5	0 (0.0-79.2)	0.33	0.83 (0.74-0.92)
Country					
Asian	13, 16, 19, 22	7	56.6 (0.0-81.3)	0.04	0.87 (0.75-0.99)
Non-Asian	12, 15	2	0.0 (0.0-100)	0.62	0.95 (0.77-1.17)

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Table 5. Pooled effect sizes for the association between soy intake and mortality (*continued*)

	References	Effect size[a] (n)	I^2 (%) (95% CI)[b]	*P* value for *Q* test	Pooled relative risk (95% CI)[c]
Sample size, n					
<10,000	12, 13, 15, 16	5	59.9 (0.0-85.0)	0.02	0.97 (0.81-1.15)
≥10,000	19, 22	4	0.0 (0.0-84.6)	0.78	0.77 (0.67-0.90)
Follow-up, y					
<10	12, 16, 22	4	0.0 (0.0-84.6)	0.72	0.82 (0.75-0.90)
≥10	13, 15, 19	5	62.7 (1.5-85.9)	0.02	0.92 (0.74-1.15)
Adjustment for energy intake					
Adjusted effect size	12, 15, 16, 22	5	2.9 (0.0-79.8)	0.61	0.83 (0.76-0.91)
Nonadjusted effect size	13, 19	4	71.1 (17.7-89.8)	0.01	0.91 (0.70-1.17)
Adjustment for body mass index					
Adjusted effect size	12, 13, 15, 16, 22	7	46.6 (0.0-77.4)	0.07	0.93 (0.81-1.07)
Nonadjusted effect size	19	2	0.0 (0.0-100)	0.82	0.74(0.61-0.88)
Year of publication					
Up to 2010	19, 22	4	0.0 (0.0-84.6)	0.78	0.77 (0.67-0.90)
2010 and later	12, 13, 15, 16	5	59.9 (0.0-85.0)	0.02	0.97 (0.81-1.15)
Specific soy foods intake[f]					
Overall	18, 20, 21	5	22.2 (0.0-67.6)	0.28	0.99 (0.78-1.25)
Gastric cancer					
Total soy	18, 20, 21	6	0.0 (0.0-74.6)	0.64	0.49 (0.35-0.68)
Lung cancer					
Total soy	16, 19, 20	4	0.0 (0.0-84.6)	0.83	0.79 (0.71-0.87)
Colorectal cancer					
Total soy	19, 20	4	0.0 (0.0-84.6)	0.59	0.59 (0.41-0.84)
Hepatic cancer					
Total soy	19, 21	4	0.0 (0.0-84.6)	0.91	0.89 (0.71-1.12)
Cardiovascular disease mortality					
Total soy[e]					
Overall	11, 13, 14, 17, 19, 22	12	60.6 (26.0-79.0)	0.004	0.91 (0.81-1.03)
Soy/soy products intake					
Overall	13, 17, 19, 22	8	50.0 (0.0-77.6)	0.05	0.85 (0.72-0.99)
Subgroup analysis					
Sex					
Male	13, 17, 19, 22	4	62.3 (0.0-87.3)	0.04	0.92 (0.72-1.17)
Female	13, 17, 19, 22	4	22.5 (0.0-88.1)	0.34	0.76 (0.63-0.91)
Sample size, n					
<10,000	13	2	26.9 (0.0-100)	0.24	1.10 (0.82-1.46)
≥10,000	17, 19, 22	6	29.5 (0.0-71.2)	0.27	0.78 (0.68-0.91)
Follow-up, y					
<10	22	2	0.0 (0.0-100)	0.57	0.84 (0.65-1.08)
≥10	13, 17, 19	6	62.4 (8.7-84.5)	0.01	0.85 (0.69-1.06)

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Table 5. Pooled effect sizes for the association between soy intake and mortality (*continued*)

	References	Effect size[a] (n)	I^2 (%) (95% CI)[b]	*P* value for *Q* test	Pooled relative risk (95% CI)[c]
Adjustment for energy intake					
Adjusted effect size	17, 22	4	0.0 (0.0-84.6)	0.54	0.88 (0.74-1.05)
Nonadjusted effect size	13, 19	4	73.2 (24.6-90.4)	0.01	0.84 (0.63-1.13)
Adjustment for body mass index					
Adjusted effect size	13, 17, 22	6	13.6 (0.0-78.0)	0.34	0.95 (0.81-1.10)
Nonadjusted effect size	19	2	0.0 (0.0-100)	0.58	0.68 (0.57-0.82)
Year of publication					
Up to 2010	17, 19, 22	6	29.5 (0.0-71.2)	0.27	0.78 (0.68-0.91)
2010 and later	13	2	26.9 (0.0-100)	0.24	1.10 (0.82-1.46)
Specific soy foods intake[f]					
Overall	11, 14	4	34.6 (0.0-77.1)	0.16	1.03 (0.90-1.18)
Ischemic cardiovascular disease					
Total soy[e]	14, 17, 19, 25	6	68.3 (25.1-86.6)	0.004	0.79 (0.63-0.99)
Stroke					
Total soy[e]	11, 14, 19, 25	6	51.4 (0.0-80.6)	0.06	0.87 (0.73-1.04)

[a]Effect sizes were presented for the highest vs lowest categories of soy/soy products or soy specific foods intakes.
[b]Inconsistency, percentage of variation across studies due to heterogeneity; we calculated 95% CI for each association with ≥2 effect sizes.
[c]Obtained from random-effects analysis.
[d]N/A=not applicable.
[e]Total soy was considered as soy, soy products, and soy-specific foods.
[f]Miso and tofu.

performed for soy-specific foods due to the limited number of studies. Out of nine studies that investigated the association between intake of different type of soy and cancer mortality, only three had required data for conducting dose–response analysis.[15,16,22] Therefore, we did not perform such an analysis for the association.

Soy Consumption and Cancer-Specific Mortality

We found that soy intake was inversely associated with deaths from gastric (pooled effect size 0.49, 95% CI 0.35 to 0.68; $P<0.001$), lung (pooled effect size 0.79, 95% CI 0.71 to 0.87; $P<0.001$), and colorectal cancers (pooled effect size 0.59, 95% CI 0.41 to 0.84; $P=0.003$), but not with hepatic cancer (pooled effect size 0.89, 95% CI 0.71 to 1.12; $P=0.30$) after combining six effect sizes (from three studies[19,20,23]) for gastric cancer, four effect sizes (from three studies[16,19,20]) for lung cancer, four effect sizes (from two studies[19,20]) for colorectal cancer, and four effect sizes (from two studies[19,21]) for hepatic cancer. There was low between-study heterogeneity for all of the associations (Table 5). Further analysis based on exposure (soy/soy products intake compared with soy-specific foods) was not possible because of the limited numbers of the studies.

Soy Intake and CVD Mortality

Overall, combining 12 effect sizes from six studies that included 11,628 deaths among 178,394 participants demonstrated no significant association between soy intake (a combination of soy/soy products and soy-specific foods) and CVDs mortality (pooled effect size 0.91, 95% CI 0.81 to 1.03; $P=0.15$), with a significant between-study heterogeneity ($I^2=60.6\%$, 95% CI 26.0% to 79.0%; *P* for *Q* test=0.004) (Table 5). Stratified analysis based on exposure (soy/soy products intake compared with soy-specific foods) indicated a significant inverse association between soy/soy products intake and CVD mortality (pooled effect size 0.85, 95% CI 0.72-0.99; $P=0.04$), but not for soy-specific foods (pooled effect size 1.03, 95% CI 0.90-1.18; $P=0.68$). Moderate between-study heterogeneity has been observed for both soy/soy products and soy-specific foods. Further subgroup analyses were done for studies investigated the consumption of dietary soy/soy products. However, it was impossible to do for those studies looked at the intake of soy-specific foods due to the limited number of studies in that area. Based on this analysis, soy intake was inversely associated with CVD mortality in women, in studies with a sample size ≥10,000 participants, those that published up to the year 2010, and studies that did not adjust for BMI in their statistical analyses. We could not perform dose–response meta-analysis due to the lack of necessary information for studies included in this part.

Soy Consumption and Mortality from Specific CVDs

After considering six effect sizes from four studies for ischemic CVDs[14,17,19,25] and six effect sizes from four studies for stroke,[11,14,19,25] we observed an overall pooled effect size of 0.79 (95% CI 0.63 to 0.99; $P=0.04$) for mortality from ischemic CVDs and 0.87 (95% CI 0.73 to 1.04; $P=0.13$) for death from stroke in relation to intake of total soy (Table 5).

Table 6. Pooled effect sizes for the association between soy isoflavones intake and mortality

	References	Effect size[a] (n)	I^2 (%) (95% CI)[b]	*P* value for *Q* test	Pooled relative risk (95% CI)[c]
All-cause mortality					
Overall	15, 22, 24, 27, 28	7	0.0 (0.0-70.8)	0.62	0.90 (0.82-0.98)
Subgroup analysis					
Sex					
Both	28	1	N/A[d]	N/A	0.30 (0.05-1.69)
Male	22	1	N/A	N/A	0.88 (0.73-1.07)
Female	15, 22, 24, 27	5	0.0 (0.0-79.2)	0.59	0.91 (0.82-1.01)
Country					
Asian	22, 27, 28	4	0.0 (0.0-84.6)	0.60	0.90 (0.78-1.02)
Non-Asian	15, 27, 28	3	20.7 (0.0-92.5)	0.28	0.90 (0.78-1.04)
Sample size, n					
<10,000	15, 24, 27, 28	5	3.3 (0.0-81.8)	0.38	0.89 (0.78-1.01)
≥10,000	22	2	0.0 (0.0-100)	0.64	0.91 (0.79-1.05)
Follow-up, y					
<10	15, 22, 24, 28	5	5.8 (0.0-79.2)	0.37	0.90 (0.81-0.99)
≥10	27	2	0.0 (0.0-100)	0.71	0.90 (0.71-1.15)
Adjustment for energy intake					
Adjusted effect size	15, 22, 24	4	0.0 (0.0-84.6)	0.44	0.90 (0.81-0.99)
Nonadjusted effect size	27, 28	3	0.0 (0.0-89.6)	0.43	0.88 (0.69-1.13)
Adjustment for body mass index					
Adjusted effect size	15, 22, 24, 27	6	0.0 (0.0-74.6)	0.72	0.90 (0.82-0.99)
Nonadjusted effect size	28	1	N/A	N/A	0.30 (0.05-1.69)
Year of publication					
Up to 2010	22	2	0.0 (0.0-100)	0.64	0.91 (0.79-1.05)
2010 and later	15, 24, 27, 28	5	12.8 (0.0-81.8)	0.38	0.89 (0.78-1.01)
Cancer mortality					
Overall	15, 16, 26, 27, 29, 30	9	53.6 (1.5-78.1)	0.004	0.80 (0.67-0.94)
Subgroup analysis					
Country					
Asian	16, 26, 29, 30	7	61.3 (11.7-83.0)	0.006	0.77 (0.63-0.94)
Non-Asian	15, 27	2	0.0 (0.0-100)	0.59	0.90 (0.72-1.13)
Follow-up, y					
<10	15, 16, 26, 29, 30	7	66.9 (26.4-85.1)	0.001	0.79 (0.65-0.97)
≥10	27	2	0.0 (0.0-100)	0.70	0.81 (0.61-1.07)
Adjustment for energy intake					
Adjusted effect size	15, 16, 30	3	77. (28.8-93.1)	0.004	0.84 (0.64-1.10)
Nonadjusted effect size	26, 27, 29	6	32.4 (0.0-72.7)	0.06	0.76 (0.58-0.98)
Adjustment for body mass index					
Adjusted effect size	15, 16, 27	4	47.2 (0.0-82.5)	0.14	0.77 (0.65-0.91)
Nonadjusted effect size	26, 29, 30	5	70.8 (25.9-88.5)	0.01	0.78 (0.57-1.07)

(*continued on next page*)

Table 6. Pooled effect sizes for the association between soy isoflavones intake and mortality (*continued*)

	References	Effect size[a] (n)	I^2 (%) (95% CI)[b]	*P* value for *Q* test	Pooled relative risk (95% CI)[c]
Year of publication					
Up to 2010	30	1	N/A	N/A	0.98 (0.76-1.26)
2010 and later	15, 16, 26, 27, 29	8	44.4 (0.0-75.4)	0.02	0.77 (0.65-0.91)
Breast cancer					
Overall	15, 26, 27, 29, 30	8	15.5 (0.0-58.4)	0.07	0.83 (0.69-0.99)
Subgroup analysis					
Country					
Asian	26, 29, 30	6	53.7 (0.0-81.4)	0.02	0.78 (0.60-1.02)
Non-Asian	15, 27	2	0.0 (0.0-100)	0.59	0.90 (0.72-1.13)
Follow-up, y					
<10	15, 26, 29, 30	6	49.7 (0.0-80.0)	0.02	0.82 (0.65-1.05)
≥10	27	2	0.0 (0.0-100)	0.70	0.81 (0.61-1.07)
Adjustment for energy intake					
Adjusted effect size	15, 30	2	0.0 (0.0-100)	0.87	0.97 (0.80-1.17)
Nonadjusted effect size	26, 27, 29	6	32.4 (0.0-72.7)	0.06	0.76 (0.58-0.98)
Adjustment for body mass index					
Adjusted effect size	15, 27	3	0.0 (0.00-89.60)	0.68	0.87 (0.71-1.07)
Nonadjusted effect size	26, 29, 30	5	70.8 (25.9-88.5)	0.01	0.78 (0.57-1.07)
Year of publication					
Up to 2010	30	1	N/A	N/A	0.98 (0.76-1.26)
2010 and later	15, 26, 27, 29	7	21.7 (0.0-64.9)	0.07	0.79 (0.64-0.99)
Estrogen receptor status					
+	15, 26, 27	3	42.7 (0.0-82.7)	0.17	0.82 (0.59-1.12)
−	15, 26, 27	3	0.0 (0.0-89.6)	0.62	0.77 (0.60-0.99)
Cardiovascular disease mortality					
Overall	14, 17, 25, 28	6	11.2 (0.0-77.4)	0.62	0.98 (0.90-1.06)
Subgroup analysis					
Sex					
Both	25, 28	2	0.0 (0.0-100)	0.61	0.91 (0.75-1.09)
Male	14, 17	2	0.0 (0.0-100)	0.57	1.06 (0.94-1.19)
Female	14, 17	2	0.0 (0.0-100)	0.92	0.92 (0.80-1.06)
Sample size, n					
<10,000	28	1	N/A	N/A	0.48 (0.04-5.61)
≥10,000	14 17 25	5	13.5 (0.0-82.0)	0.52	0.98 (0.90-1.06)
Follow-up, y					
<10	28	1	N/A	N/A	0.48 (0.04-5.61)
≥10	14, 17, 25	5	13.5 (0.0-82.0)	0.52	0.98 (0.90-1.06)
Adjustment for energy intake					
Adjusted effect size	14, 17, 25	5	13.5 (0.0-82.0)	0.52	0.98 (0.90-1.06)
Nonadjusted effect size	28	1	N/A	N/A	0.48 (0.04-5.61)

(*continued on next page*)

Table 6. Pooled effect sizes for the association between soy isoflavones intake and mortality (*continued*)

	References	Effect size[a] (n)	I^2 (%) (95% CI)[b]	*P* value for *Q* test	Pooled relative risk (95% CI)[c]
Adjustment for body mass index					
Adjusted effect size	14, 17, 25	5	13.5 (0.0-82.0)	0.52	0.98 (0.90-1.06)
Nonadjusted effect size	28	1	N/A	N/A	0.48 (0.04-5.61)
Year of publication					
Up to 2010	17	2	0.0 (0.0-100)	0.55	1.15 (0.66-2.01)
2010 and later	14, 25, 28	4	19.8 (0.0-87.7)		0.98 (0.90-1.06)
Ischemic cardiovascular disease					
Overall	14, 17	3	0.0 (0.0-89.6)	0.73	1.00 (0.89-1.12)

[a]Effect sizes were presented for the highest vs lowest categories of soy isoflavones intakes.
[b]Inconsistency, percentage of variation across studies due to heterogeneity; we calculated 95% CI for each association with ≥2 effect sizes.
[c]Obtained from random-effects analysis.
[d]N/A=not applicable.

There was evidence of between-study heterogeneity in the case of ischemic CVDs (I^2=68.3%, 95% CI 25.1% to 86.6%; *P* for *Q* test=0.004) and stroke (I^2=51.4%, 95% CI 0.0% to 80.6%; *P* for *Q* test=0.06). It was not possible to perform a subanalysis based on exposures (eg, soy/soy products intake compared with soy-specific foods) due to the limited number of studies.

Soy Isoflavones Intake and All-Cause Mortality

Of 23 included studies, five studies with a total sample size of 51,270 and 5,269 cases of death had evaluated the relationship between soy isoflavones intake and all-cause mortality.[15,22,24,27,28] Combining seven effect sizes from five mentioned studies revealed that a higher consumption of soy isoflavones was associated with a 10% lower risk of all-cause mortality (pooled effect size 0.90; 95% CI 0.82 to 0.98; *P*=0.02) and no significant between-study heterogeneity (I^2=0.0%, 95% CI 0.0% to 70.8%; *P* for *Q* test=0.62) (Table 6). In addition, a subgroup analysis indicated the same significant inverse association in the studies with <10 years' follow-up and those studies that considered energy intake or BMI as a covariate in their analyses.

Four of five studies on the association between intake of soy isoflavones and all-cause mortality were included in the dose–response analysis,[15,22,24,27] with 5,261 cases of death among 51,143 participants. We did not include a study in which risk estimates were reported across two categories of isoflavones intake.[28] A nonlinear significant inverse relationship was found between soy isoflavones intake and all-cause mortality (*P* for nonlinearity=0.04) (Figure 3A, available at www.jandonline.org). Furthermore, based on findings from linear dose–response meta-analysis, no significant association was observed between soy isoflavones intake and all-cause mortality by a 10-mg/day increase in soy isoflavones intake (pooled effect size 0.98, 95% CI 0.94 to 1.01; *P*=0.17) (Figure 4). Between-study heterogeneity was not significant in these studies (I^2=0.0%, 95% CI 0.0% to 74.6%; *P* for *Q* test=0.17).

Soy Isoflavones Intake and Cancer Mortality

Overall, seven studies with a total sample size of 16,683 participants and 2,228 cases of cancer mortality were included regarding the association between soy isoflavones intake and cancer mortality.[15,16,26,27,29,30,33] After combining nine effect sizes from aforementioned studies, participants in the top category of soy isoflavones intake had 20% lower risk of cancer mortality compared with those in the bottom category (pooled effect size 0.80, 95% CI 0.67 to 0.94; *P*=0.008) (Table 6). Between-study heterogeneity was significant for those studies (I^2=53.6%, 95% CI 1.5% to 78.1%; *P* for *Q* test=0.004). A subgroup analysis based on geographical region and follow-up period explained between-study heterogeneity. In addition, soy isoflavones intake was inversely associated with cancer mortality in studies conducted in Asian countries, those with <10 years' follow-up, publications that considered BMI as a confounder in the analyses and those that created the models without any adjustment for the energy intake.

In dose–response analysis, six studies were included with 1,932 deaths among 15,228 participants[15,16,26,27,29,33] and one was excluded because of missing information.[30] We found a nonlinear relationship between soy isoflavones intake and cancer mortality (*P* for nonlinearity <0.001) (Figure 3B, available at www.jandonline.org). Based on linear dose–response meta-analysis, an increase of 10 mg/day in soy isoflavones intake was associated with a 7% lower risk of cancer mortality (pooled effect size 0.93, 95% CI 0.89 to 0.98; *P*=0.003) (Figure 4). However, between-study heterogeneity was significant (I^2=50.8%, 95% CI 0.0% to 78.0%; *P* for *Q* test=0.04).

Soy Isoflavones Intake and Breast Cancer Mortality

Considering eight effect sizes from six studies[15,26,27,29,30,33] that included 16,239 participants and 1,910 deaths, a significant inverse association was found between soy isoflavones intake and mortality caused by breast cancer (pooled effect size 0.83, 95% CI 0.69 to 0.99; *P*=0.04) with moderate evidence of between-study heterogeneity (I^2=15.5%, 95% CI 0.0% to 81.4%; *P* for *Q* test=0.07) (Table 6). In a subgroup analysis, such a significant inverse association was also observed in the studies published during the year 2010 and later, and those that did not adjust for energy intake in the analyses. Out of six studies in this section, five were included in the

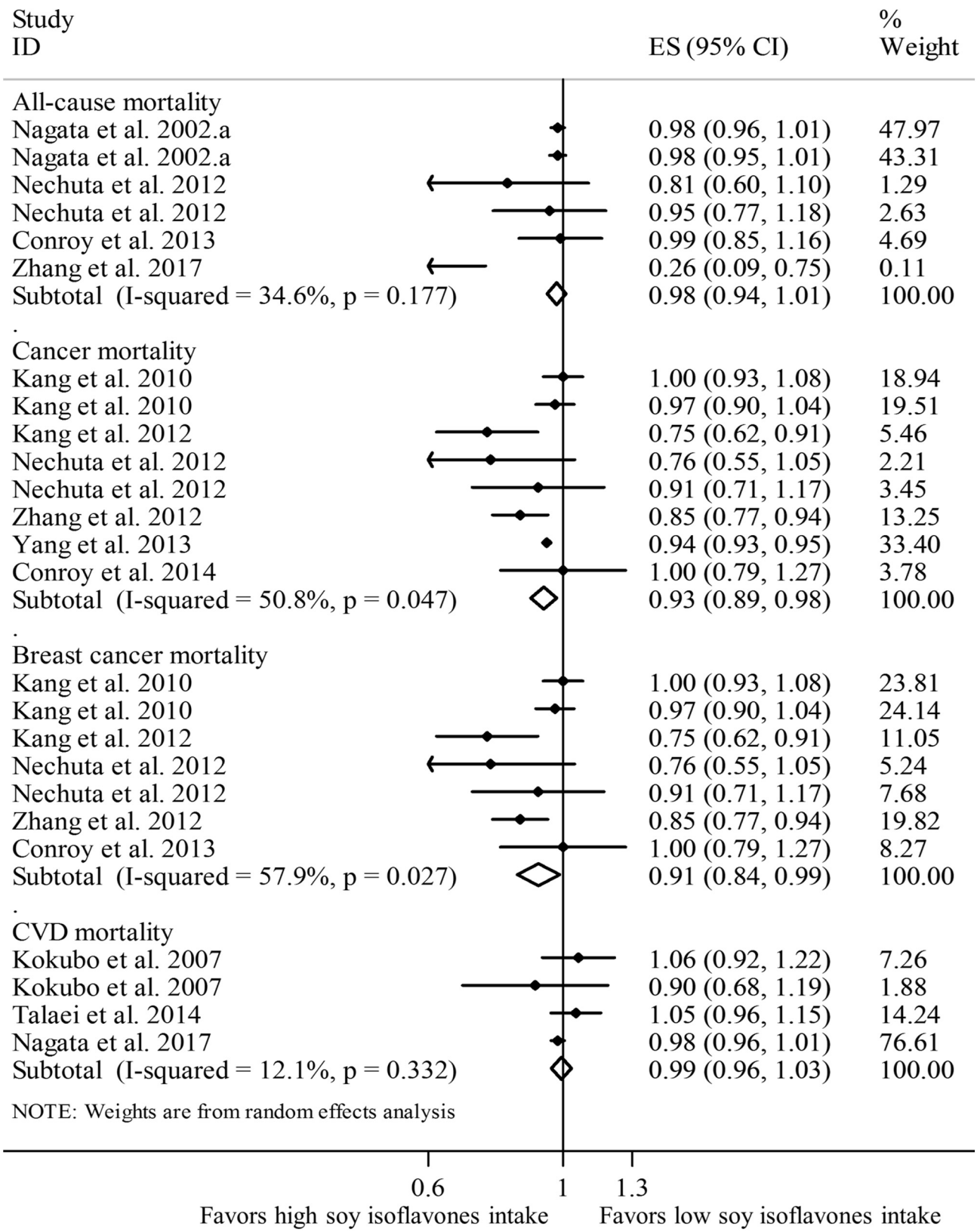


Figure 4. Forest plot for the linear association between soy isoflavones intake and death from all causes, total cancer, breast cancer, and cardiovascular diseases. Horizontal lines represent 95% CI. Diamonds represent pooled estimates from random-effects analysis. CVD=cardiovascular disease; ES=effect size.

Table 7. Pooled effect sizes for the association between soy protein intake and mortality

	References	Effect size[a] (n)	I^2 (%) (95% CI)[b]	*P* value for *Q* test	Pooled relative risk (95% CI)[c]
Breast cancer					
Overall	26, 30, 31, 33	4	63.5 (0.0-87.7)	0.03	0.73 (0.55-0.96)
Subgroup analysis					
Adjustment for energy intake					
Adjusted effect size	30	1	N/A[d]	N/A	0.99 (0.77-1.27)
Nonadjusted effect size	26, 31, 33	3	0.0 (0.0-89.6)	0.37	0.66 (0.55-0.79)
Adjustment for body mass index					
Adjusted effect size	31	1	N/A	N/A	0.66 (0.52-0.84)
Nonadjusted effect size	26, 30, 33	3	73.3 (10.7-92.0)	0.04	0.74 (0.50-1.10)
Year of publication					
Up to 2010	30, 31	2	80.9 (18.9-95.5)	0.02	0.81 (0.54-1.20)
2010 and later	26, 33	2	49.5 (0.0-100)	0.15	0.58 (0.33-1.03)
Estrogen receptor status					
+	30, 31, 33	3	38.6 (0.0-80.8)	0.18	0.75 (0.57-0.99)
−	30, 31, 33	3	0.0 (0.0-89.6)	0.99	0.77 (0.62-0.96)
Cardiovascular disease mortality					
Overall	14, 25, 32	4	66.0 (0.5-88.4)	0.03	0.99 (0.84-1.17)
Ischemic cardiovascular disease					
Overall	14, 25, 32	3	18.0 (0.0-91.4)	0.45	1.03 (0.92-1.17)

[a]Effect sizes were presented for the highest vs lowest categories of soy protein intake.
[b]Inconsistency, percentage of variation across studies due to heterogeneity; we calculated 95% CI for each association with ≥2 effect sizes.
[c]Obtained from random-effects analysis.
[d]N/A=not applicable.

dose–response analysis with 1,614 deaths among 14,784 participants and one was excluded due to lack of required information. We found a nonlinear significant association between soy isoflavones intake and breast cancer mortality (*P* for nonlinearity=0.008) (Figure 3C, available at www.jandonline.org). In addition, based on linear dose–response analysis, a 10-mg/day increase in soy isoflavones intake was associated with a 9% lower risk of death from breast cancer (pooled effect size 0.91, 95% CI 0.84 to 0.99; *P*=0.02) (Figure 4). However, a significant heterogeneity was observed between the studies (I^2=57.9%, 95% CI 2.5% to 81.7%; *P* for *Q* test=0.02).

Out of six studies, three studies[15,27,33] examined the association between soy isoflavones intake and breast cancer mortality based on estrogen receptor (ER) status (positive or negative) in patients with breast cancer patients (Table 6). We found that soy isoflavones intake was inversely related to death from breast cancer among women with ER-negative breast cancer (pooled effect size 0.77, 95% CI 0.60 to 0.99; *P*=0.04), but not in those with ER-positive (pooled effect size 0.82, 95% CI 0.59 to 1.12; *P*=0.10).

Soy Isoflavones Intake and CVD Mortality

Overall, four studies with a sample size of 132,913 participants and 6,693 deaths from CVDs were included to examine the association between soy isoflavones intake and CVD mortality.[14,17,25,28] After combining six effect sizes from mentioned studies, we found no significant association between soy isoflavones intake and CVDs mortality (pooled effect size 0.98, 95% CI 0.90 to 1.06; *P*=0.61) (Table 6). The between-study heterogeneity was not significant for those studies (I^2=11.2%, 95% CI 0.0% to 77.4%; *P* for *Q* test=0.62). In addition, no association was observed in a subgroup analysis based on sex, geographic region, sample size, duration of follow-up, year of publication, and adjustment for energy intake and BMI. Three of the four studies included in this part were subjected to dose–response analysis[14,17,25] and one study was excluded because it categorized participants based on two different categories of soy isoflavones intake.[28] No significant nonlinear association was found between soy isoflavones intake and risk of death from CVDs (*P* for nonlinearity=0.99) (Figure 3D, available at www.jandonline.org). Furthermore, linear dose–response analysis revealed no significant association between an increase of 10 mg/day in soy isoflavones intake and CVDs mortality (pooled effect size 0.99, 95% CI 0.96 to 1.03; *P*=0.74 and I^2=12.1%, 95% CI 0.0% to 86.5%, *P* for *Q* test=0.33) (Figure 4).

Combining three effect sizes that captured from two studies[14,17] examined the association between soy isoflavones intake and deaths from ischemic CVDs revealed no

significant association between the predictor and outcome. There was also no significant heterogeneity between those studies (Table 6).

Soy Protein Intake and All-Cause Mortality

Only one study investigated the relationship between soy protein intake and all-cause mortality and showed a significant inverse association between the predictor and oucome.[31] Therefore, we could not conduct a meta-analysis on this topic.

Soy Protein Intake and Breast Cancer Mortality

All included studies that considered soy protein intake as their main exposure and cancer mortality as their main outcome assessed deaths only from breast cancer. Hence, we had no study regarding deaths from other cancers. Combining four effect sizes from four studies[26,30,31,33] that included 7,395 participants and 1,034 deaths indicated that a higher intake of soy protein was associated with a lower risk of breast cancer mortality (pooled effect size 0.73, 95% CI 0.55 to 0.96; P=0.02), with a significant between-study heterogeneity (I^2=63.5%, 95% CI 0.0% to 87.7%; P for Q test=0.03) (Table 7). Because of the limited number of studies, we could not do a subgroup analysis based on sex, geographic region, sample size, and duration of follow-up. However, the subgroup analysis was done according to the year of publication and adjustment for energy intake and BMI. Subgroup analysis according to adjustment for energy intake may explain between-study heterogeneity and showed a significant inverse association between soy protein intake and cancer mortality in the studies that did not consider energy intake as a confounder.

Out of four studies on the association between soy protein intake and breast cancer mortality, three were included in dose–response analysis[26,31,33] and one was excluded due to missing data.[30] A significant nonlinear association was found between soy protein intake and deaths from breast cancer (P for nonlinearity<0.001) (Figure 3E, available at www.jandonline.org). Findings from linear dose–response meta-analysis revealed a summary RR of 0.88 for breast cancer mortality with an increase of 5 g/day soy protein intake: it means that a 5-g/day increase in soy protein intake was associated with a 12% lower risk of death from breast cancer (pooled effect size 0.88, 95% CI 0.83 to 0.93; P<0.001) with no between-study heterogeneity (I^2=7.4%, 95% CI 0.0% to 90.3%; P for Q test=0.34) (Figure 5).

Among four studies that examined the association between soy protein intake and breast cancer mortality, only three assessed ER status.[30,31,33] Combining effect sizes from these studies showed a significant inverse association between soy protein intake and deaths from breast cancer in women with either ER-positive (pooled effect size 0.75, 95% CI 0.57 to 0.99; P=0.04) or ER-negative (pooled effect size 0.77, 95% CI 0.62 to 0.96; P=0.02) breast cancer (Table 7). It is worth noting that the between-study heterogeneity was not significant for those aforementioned studies.

Soy Protein Intake and CVD Mortality

Regarding the association between soy protein intake and CVD mortality, we included three studies that recruited 157,250 participants and 6,477 deaths.[14,25,32] Combining four effect sizes from those studies showed no significant association between soy protein intake and deaths from CVDs (pooled effect size 0.99, 95% CI 0.84 to 1.17; P=0.56) (Table 7). However, between-study heterogeneity was significant (I^2=66.0%, 95% CI 0.5% to 88.4%; P for Q test=0.03). It was not possible to perform a subgroup analysis due to limited number of studies. All studies in this part were included in the dose–response analysis. No linear (Figure 5) and nonlinear (Figure 3F, available at www.jandonline.org) associations were observed between soy protein intake and CVDs mortality (P for nonlinearity=0.99).

In terms of specific CVDs, we combined three effect sizes from three studies[14,25,32] for ischemic heart disease and found no significant association between soy protein intake and ischemic heart disease mortality and no significant between-study heterogeneity.

Sensitivity Analysis and Publication Bias

We assessed publication bias for those associations with ≥10 effect sizes and found no evidence of such a bias based on visual inspection of funnel plots as well as findings from Begg test (P>0.4). Although publication bias was not captured for those associations with <10 effect sizes, inconsistent results that were observed for these relationships might reject any potential evidences for this bias. In terms of sensitivity analysis, we found that pooled effect sizes obtained for the reported associations were unlikely to depend on a particular study.

DISCUSSION

This study is the first to summarize the findings of the associations between intakes of soy and its constituents (including soy isoflavones and protein) and deaths from all causes, cancers, and CVDs. Based on our findings, soy intake was inversely associated with all-cause and CVD mortality. However, this significant association for all-cause mortality was observed only in the high-quality studies (studies with sample size ≥10,000 participants and those that presented energy-adjusted effect sizes). Furthermore, higher intake of soy isoflavones was related to a decrease in risk of deaths from all causes, but not CVDs. No significant association was observed between dietary intake of soy protein and risk of CVD mortality. In line with our findings, in a meta-analysis, Akhlaghi and colleagues[62] reported that soy isoflavones intake significantly decreased BMI that was positively associated with death. Available evidence suggests that intake of nonprotein soy constituents favorably affect the markers of cardiovascular health.[63] In a clinical trial, soy consumption decreased plasma coagulation factor IX activity, which is a risk factor for thrombosis in patients with CVD.[64] Conversely, findings from a meta-analysis revealed no significant association between soy products intake and deaths from all causes and CVDs.[65] Nevertheless, it must be kept in mind that mentioned meta-analysis included three studies on all-cause mortality and four studies for CVDs mortality, whereas we included five studies for all-cause and six for CVD mortality.

In the current study, we observed that dietary intake of soy/soy products, soy specific foods, soy isoflavones, and protein were inversely associated with deaths from cancers. However, all effect sizes on the association between soy protein intake and cancer mortality were for breast cancer

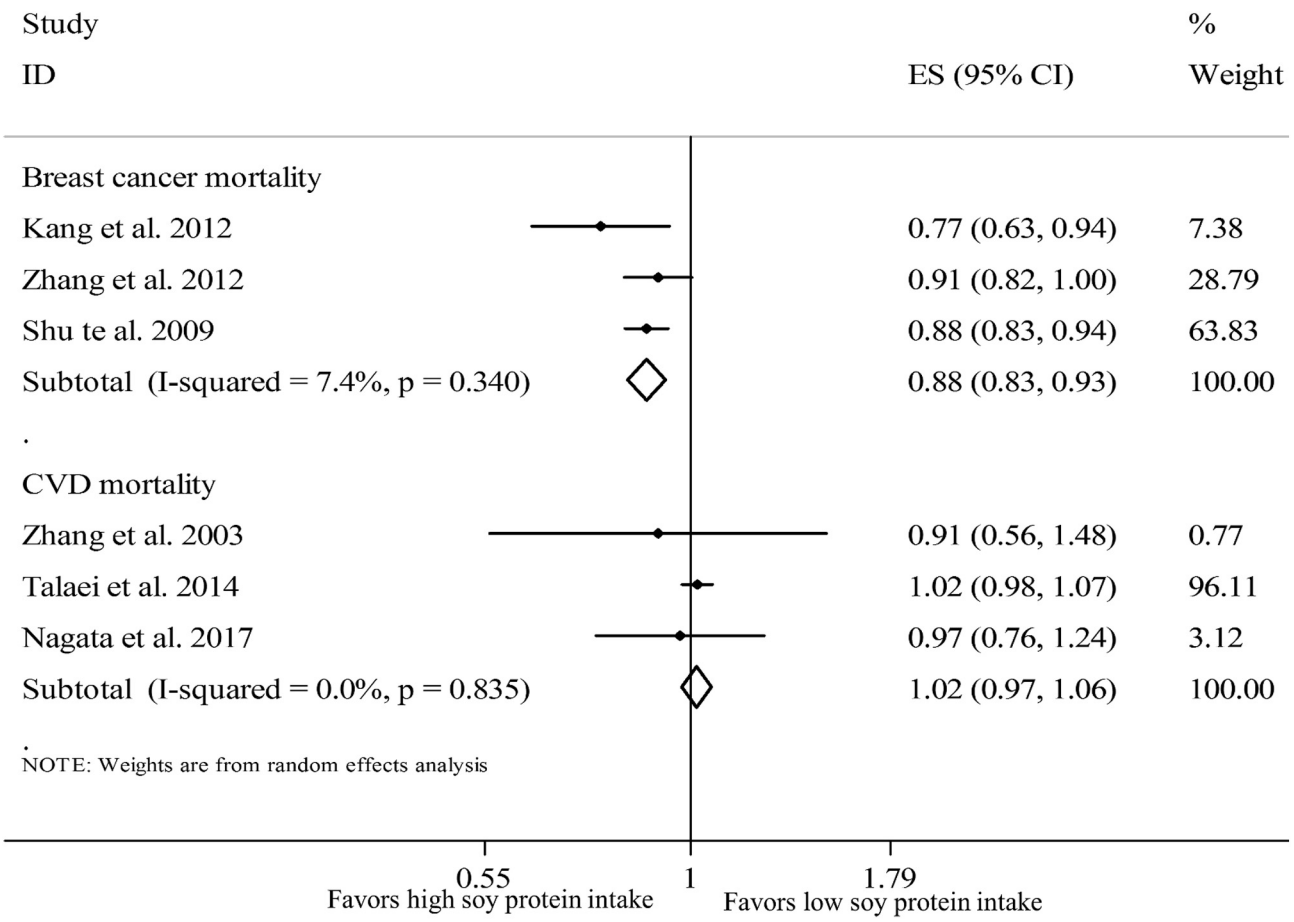


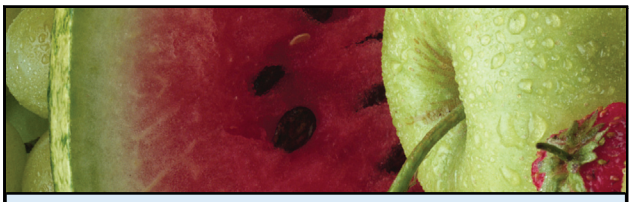
Figure 5. Forest plot for the linear association between soy protein intake and death from breast cancer and cardiovascular disease. Horizontal lines represent 95% CI. Diamonds represent pooled estimates from random-effects analysis. CVD=cardiovascular disease; ES=effect size.

mortality. In line with our findings, Messina and colleagues[66] reported that postdiagnosis intakes of soy and isoflavones beneficially affected markers of breast cancer, so that they reduced the recurrence and improved survival of patients. In a systematic review of clinical trials, intake of soy isoflavones favorably influenced prostate-specific antigen levels.[67] In an experimental study, replacing casein with a soy protein isolate led to a considerable reduction in hepatic tumor progression that was associated with hepatic injury and inflammation.[68] The antimetastatic properties of genistein as a component of soy products were reported in a study on prostate cancer.[69] Among studies included in our meta-analysis, we observed conflicting results on the association between soy and its constituents intake and deaths from cancers; however, most of the studies with high quality showed an inverse association in this regard. As seen in the subgroup analysis, studies that considered energy intake and BMI as covariates revealed that soy and soy isoflavones intakes were inversely associated with cancer mortality.

Among the interesting findings in the current study was the inverse association between soy isoflavones intake and breast cancer mortality. This was in line with findings from a meta-analysis reported protective effects for soy consumption against incidence of breast cancer.[70] Based on our findings, the beneficial effects of isoflavones intake on breast cancer mortality was observed in women with ER-negative breast cancer, but not in those with ER-positive breast cancer. Women with ER-negative breast cancer have a poorer prognosis than those with ER-positive breast cancer. Therefore, the protective effects of soy isoflavones intake are more obvious among women with ER-negative breast cancer compared with those with ER-positive breast cancer.[71]

Inflammation has a key role in the inverse associations between intake of soy and its constituents, and mortality from cancers and CVDs. Inflammation is associated with diseases recurrence and poor prognosis among patients with cancers and CVDs.[72-74] The anti-inflammatory properties of soy and its constituents have been reported in earlier studies.[75,76] In addition, antioxidant properties of soy's constituents provide additional reasons for the inverse association between soy intake and mortality.[77,78]

Soy or soy products intake among the participants in the included studies have been defined in different ways. Some studies considered all types of soy or soy products, including tofu, natto, soy milk, soybeans, miso, soy nuts, and soy sauce as total soy,[11,22,25,26] whereas others, such as a study that was performed by Sakauchi and colleagues[18] measured soy intake by summing the intakes of tofu and soy sauce. Although soy intake was considered to be the



PRACTICE IMPLICATIONS

What Is the Current Knowledge on this Topic?

Data on the association of soy, soy protein, and isoflavones consumption with risk of mortality from all causes, cancer, and cardiovascular diseases are conflicting and no study, until now, has summarized findings in this regard.

How Does this Research Add to Knowledge on this Topic?

Consumption of soy/soy products can be inversely associated with mortality from all causes, cancer, and cardiovascular diseases. This beneficial effect of soy may be due to isoflavones and protein content.

How Might this Knowledge Influence Current Dietetics Practice?

Our findings can help future clinical studies to examine effects of soy, soy protein, and isoflavones on outcomes of cancers and cardiovascular diseases.

main exposure factor in the present study, we did not limit the included studies to those with a specific definition of soy intake due to limited numbers of studies. In addition, the cutoffs used to categorize participants based on intake of soy or its constituents were not the same through the different studies. Some studies considered intake of the specific soy foods, but not total soy, as their main exposure factor. However, subgroup analyses in those studies were performed based on the exposures (total soy intake compared with specific soy foods). These points should be considered carefully when interpreting our results.

In the current study, we were unable to assess publication bias in some of those associations due to the limited number of studies. However, in such associations, there were "positive" and "negative" studies that might decline any evidence of publication bias. An important variable that can make a bias in our meta-analysis is publication year of included studies. Based on the study that performed by Kicinski and colleagues,[79] the amount of overrepresentation of findings that are favorable to treatment is larger in older studies compared with the recent ones. Because of this issue, we performed a subgroup analysis based on year of publication (up to 2010 vs 2010 and later) and found protective effects for soy intake in studies published up to 2010, but not for those studies that were published during the year 2010 and later. In contrast, for isoflavones intake in relation to mortality, most protective effects were obtained in those studies that were published during 2010 and later. Overall, it seems that publication year has a low effect on the overall estimates in the current meta-analysis.

Strengths and Limitations

Our meta-analysis has some strengths. To the best of our knowledge, this is the first comprehensive meta-analysis to explore the association between the intake of soy and its constituents and mortality. Prospective studies were included in this meta-analysis. Prospective design can decrease the possibility of recall and selection biases that could be of concern in the case-control studies. In addition, we assessed the associations separately for predictors (soy/soy products, soy isoflavones, and protein) and outcome measures (mortality from all causes, total and specific cancers, and CVDs). The quality assessment indicated that all the studies included in this meta-analysis were of high quality, and most of the association models in those studies had been adjusted for important confounders.

Despite the strengths, several limitations need to be noted. First, some nondifferential misclassification of participants in terms of intake of soy or its constituents might have occurred in the included studies and also in the meta-analysis, which may have attenuated the true associations between soy intake and mortality. Although it would be better to separately analyze each food item in a specific soy foods category, we had to pool all specific soy foods together due to the limited numbers of studies examined the effect of each specific food. Because our meta-analysis was conducted on the observational studies, we cannot rule out the possible effect of residual confounding on the results of both each single study and also the pooled estimates in the meta-analyses. The meta-analysis of dose–response relations for soy isoflavones or protein intake included a limited number of studies: four examined the intake of soy isoflavones in relation to all-cause mortality, six investigated the intake of soy isoflavones in relation to cancer mortality, and three studied the association between soy isoflavones or protein intake and CVD mortality. Dose-response meta-analysis may not have captured the true dose–response relationship between soy isoflavones and protein intake and risk of mortality, particularly due to the limited number of studies. However, a large number of studies enables dose–response models to be only empowered to detect massive associations.[80,81] It means that this analysis has a potential to present a general view of diet–disease relationships. Overall, caution in the interpretation of findings from the dose–response analysis is required.

CONCLUSIONS

In this meta-analysis of prospective studies, we found that soy intake was inversely associated with deaths from all causes, cancers, and CVDs. In addition, a higher intake of soy was associated with a decreased risk of mortality from gastric, colorectal, and lung cancers as well as ischemic CVDs. In terms of soy isoflavones intake, participants in the highest category of dietary intake had a 10% lower risk of all-cause mortality compared with those in the lowest category. We also found that a 10-mg/day increase in soy isoflavones intake was associated with 7% and 9% lower risk of total and breast cancer mortality, respectively. Furthermore, a 12% reduction in breast cancer death was observed for each 5-g/day increase in soy protein intake. However, soy protein was not significantly associated with all-cause and CVDs mortality. Our findings may support the current recommendations to increase intake of soy for greater longevity.

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STATEMENT OF POTENTIAL CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

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AUTHOR CONTRIBUTIONS

S. M. Nachvak, S. Moradi, M. Nasiri, and O. Sadeghi contributed to the conception, design, data interpretation, and drafted the manuscript. S. Moradi, J. Anjom-shoae and J. Rahmani conducted the literature search and data extraction. O. Sadeghi, V. Maleki, and M. Nasiri conducted the statistical analyses and drafted the manuscript. All authors approved the final version of the manuscript.

Concept 1	"Soy foods" OR "soy milk" OR "soybean" OR "soybean protein" OR "soybean oil" OR "isoflavones" OR "genistein" OR "Soy" OR "tofu" OR "miso" OR "natto" OR "soybean" OR "daidzein" OR "soybean oil" OR "soybean protein" OR "Bean crud" OR "isoflavone*" OR "genistein"
Concept 2	"Mortality" OR "Death" OR "Fatal Outcome" OR "Survival" OR "Mortality" OR "Death" OR "Fatal Outcome" OR "Survival" OR "Fatal Outcome"
Concept 3	"Cohort Studies" OR "Prospective Studies" OR "Retrospective Studies" OR "Cross-Sectional" OR "Cohort" OR "Prospective" OR "Retrospective"

Figure 1. Medical subject headings (MeSH) and non-MeSH keywords used to search relevant publications. This combination of keywords was used to search online databases: "concept 1" AND "concept 2" AND "concept 3".

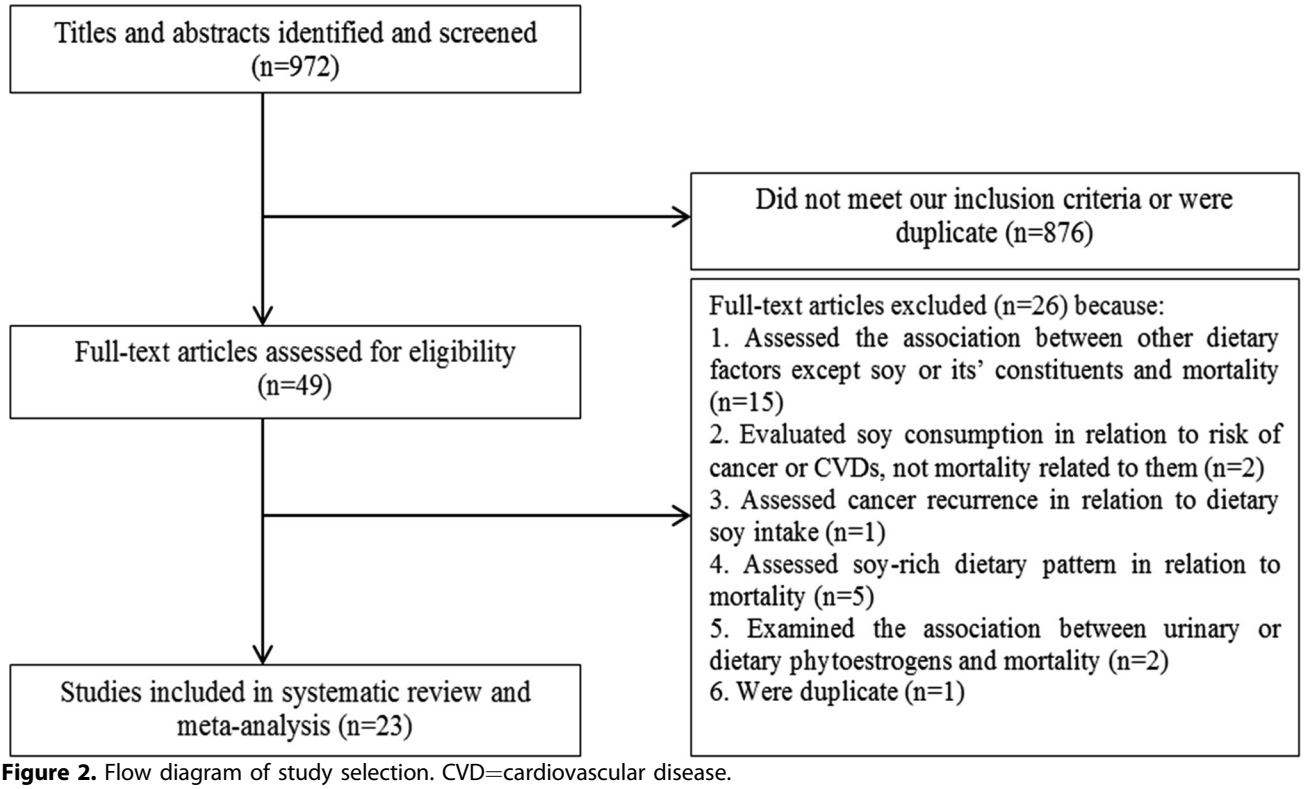

Figure 2. Flow diagram of study selection. CVD=cardiovascular disease.

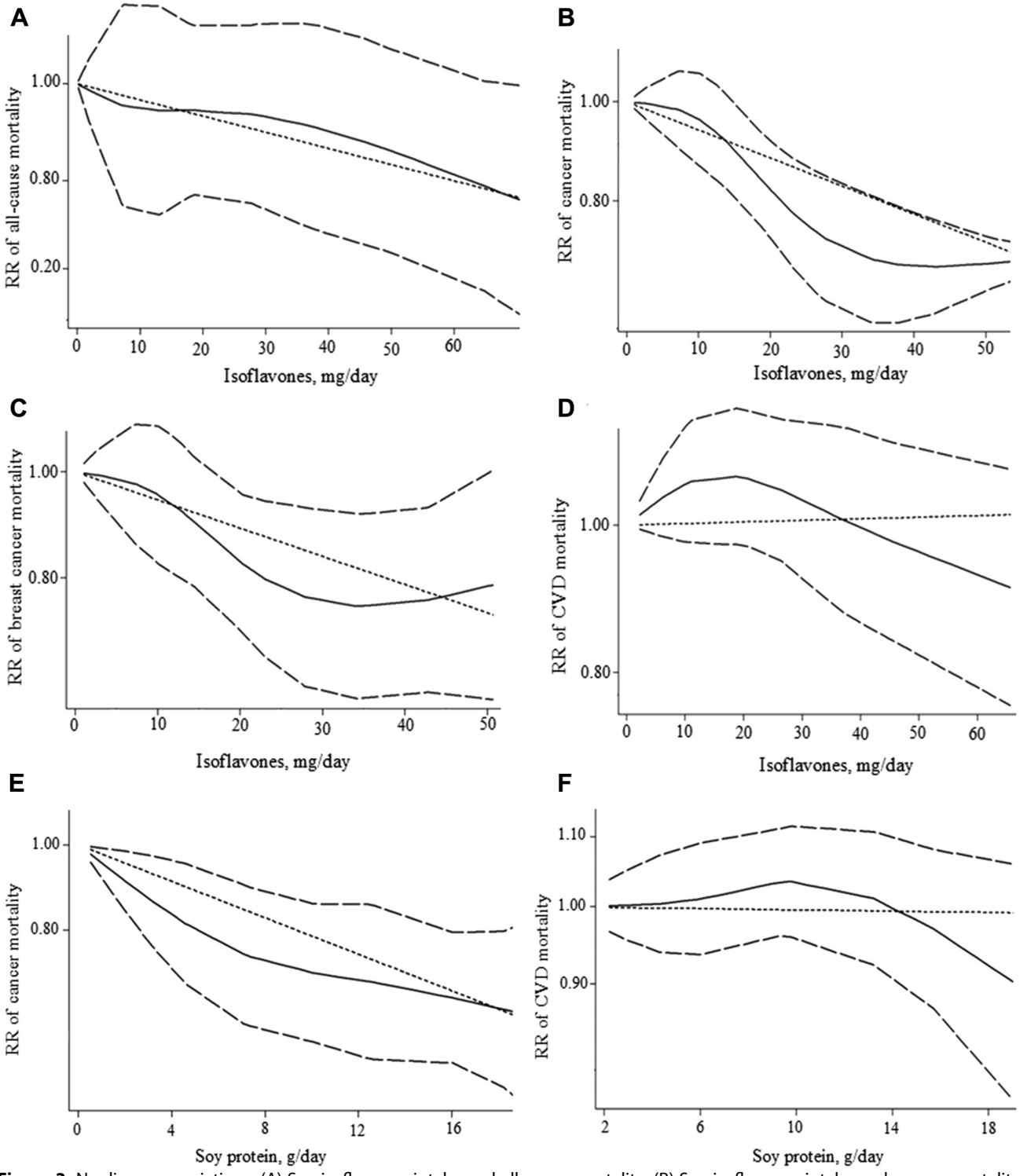

Figure 3. Nonlinear associations. (A) Soy isoflavones intake and all-cause mortality. (B) Soy isoflavones intake and cancer mortality. (C) Soy isoflavones intake and breast cancer mortality. (D) Soy isoflavones intake and cardiovascular disease (CVD) mortality. (E) Soy protein intake and breast cancer mortality. (F) Soy protein intake and CVD mortality. Dietary intakes of soy isoflavones and protein were modeled with restricted cubic splines in a multivariate random-effects dose−response model. Dashed line indicates the linear model. Solid line indicates the spline model. The 95% CI on the vertical axis is on a log scale. RR=relative risk.

Table 1. Studies on the association of soy/soy products and soy-specific foods intakes with mortality from all-cause, total, and specific cancers and cardiovascular diseases (CVDs)

Author(s), reference, y	Study name	Country	Age range, y	Sex	Sample size	Cases	Follow-up, y	Exposure assessment	Outcome	Comparison	OR[a], RR[b], or HR[c] (95% CI)[d]	Adjustment[e]
Nguyen and colleagues,[11] 2018	National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged	Japan	≥30	M[f]	4,046	217	24	Food records	Stroke mortality	Tofu: Q[g]4 vs Q1 ≥25 vs ≤3.1 g/1,000 kcal	HR 1.23 (0.86-1.77)	1, 9, 21, 23, 24, 27-31, 38, 45
				F[h]	5,198	200			Stroke mortality	≥26 vs ≤3.4 g/1,000 kcal	HR 0.79 (0.54-1.15)	
Leo and colleagues,[12] 2016	Multiethnic Cohort	United States	45-75	M/F	2,339	1,343 903	4.5	Self-reported FFQ[i]	All-cause mortality NHL[j] mortality	Soy: T[k]3 vs T1 >4.3 vs <0.5 g/1,000 kcal	HR 0.93 (0.76-1.14) HR 0.92 (0.72-1.18)	1, 2, 5, 11-13, 17, 21, 38, 45
Nagata and colleagues,[25] 2017	Takayama Study	Japan	≥35	M/F	29,079	308	16	Self-reported FFQ	Ischemic CVD mortality Stroke mortality	Natto: >5 vs <0.7 g/d	HR 0.71 (0.49-1.04) HR 0.68 (0.52-0.88)	
Yamasaki and colleagues,[13] 2015	Jichi Medical School Cohort Study	Japan	19-93	M	4,309	528 108 207	11.4	Self-reported FFQ	All-cause mortality CVD mortality Cancer mortality	Soy: Almost daily vs 1-2 times/wk	HR 1.55 (1.19-2.03) HR 1.39 (0.78-2.41) HR 1.39 (0.88-2.19)	1, 5, 21, 38, 45-47, 51
				F	6,757	354 90 139			All-cause mortality CVD mortality Cancer mortality		HR 0.81 (0.51-1.30) HR 0.62 (0.27-1.42) HR 0.77 (0.34-1.73)	1, 5, 21, 38, 45-47, 51, 55

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Table 1. Studies on the association of soy/soy products and soy-specific foods intakes with mortality from all-cause, total, and specific cancers and cardiovascular diseases (CVDs) (*continued*)

Author(s), reference, y	Study name	Country	Age range, y	Sex	Sample size	Cases	Follow-up, y	Exposure assessment	Outcome	Comparison	OR[a], RR[b], or HR[c] (95% CI)[d]	Adjustment[e]
Talaei and colleagues,[14] 2014	Singapore Chinese Health Study	China	45-74	M/F	63,257	2,697 1,298	14.7	Self-reported FFQ	CHD[l] mortality Stroke mortality	Tofu: Q4 vs Q1 >148.45 vs <52 g/d	HR 1.04 (0.92-1.18) HR 1.00 (0.83-1.20)	1, 4, 5, 8, 10, 21, 22, 33-38, 45-49
				M	26,834	2,702			CVD mortality		HR 1.11 (0.98-1.25)	
				F	33,464	2,078			CVD mortality		HR 0.96 (0.83-1.12)	
Conroy and colleagues,[15] 2013	Multiethnic Cohort	United States	≥50	F	3,842	804 376	14	Self-reported FFQ	All-cause mortality Breast cancer mortality	Soy products: T3 vs T1 ≥3.1 vs 0 g/1,000 kcal	HR 1.03 (0.81-1.33) HR 1.03 (0.71-1.50)	1, 3, 10, 11, 14, 15, 16, 21, 22, 45, 47
Yang and colleagues,[16] 2013	Shanghai Women's Health Study	China	40-70	F	444	318	3	Self-reported FFQ	Lung cancer mortality	Soy: 90th vs 50th percentile >26.4 vs <18.7 g/d	HR 0.93 (0.75-1.14)	1, 5, 10, 11, 18-23, 25, 40, 42, 45, 50, 55
Kokubo and colleagues,[17] 2007	Japan Public Health Center	Japan	40-59	M	19,466	175	12.5	Self-reported FFQ	Ischemic CVD Mortality	Soy: ≥5 vs ≤2 times/wk Miso soup: ≥3 vs ≤1 time/d Soybean: ≥3 vs <1 time/wk	HR 0.90 (0.56-1.45) HR 0.86 (0.53-1.40) HR 1.34 (0.82-2.17)	1, 2, 5, 8, 10, 21-24, 27, 32, 38, 43, 45-47
				F	20,984	57					HR 0.31 (0.13-0.74) HR 0.82 (0.33-2.01) HR 1.22 (0.57-2.61)	1, 2, 5, 8, 10, 21-24, 27, 32, 38, 43, 45, 46, 47, 55
Sakauchi and colleagues,[18] 2007	Japan Collaborative Cohort Study	Japan	40-79	F	3,004	77	13.3	Self-reported FFQ	Ovarian cancer mortality	Tofu: every day vs ≤1-2 time/wk	HR 0.61 (0.26-1.45)	1, 5, 8, 21, 44, 54, 55

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Table 1. Studies on the association of soy/soy products and soy-specific foods intakes with mortality from all-cause, total, and specific cancers and cardiovascular diseases (CVDs) (*continued*)

Author(s), reference, y	Study name	Country	Age range, y	Sex	Sample size	Cases	Follow-up, y	Exposure assessment	Outcome	Comparison	OR[a], RR[b], or HR[c] (95% CI)[d]	Adjustment[e]
Ho and colleagues,[19] 2006	—	China	>60	M	13,609	10,415	10	Self-reported FFQ	All-cause mortality	Soy: ≥4 times/wk vs <1/mo	OR 0.77 (0.62-0.95)	1, 5, 6, 8, 23, 30, 38, 41, 45
						3,990			Cancer mortality		OR 0.75 (0.59-0.97)	
						1,403			Lung cancer mortality		OR 0.76 (0.54-1.05)	
						281					OR 0.40 (0.23-0.71)	
						458			Gastric cancer mortality		OR 0.66 (0.40-1.08)	
						524					OR 0.88 (0.52-1.47)	
						115			Colorectal cancer mortality		OR 0.59 (0.20-1.72)	
						2,637					OR 0.72 (0.55-0.94)	
						941			Liver cancer mortality		OR 0.92 (0.63-1.33)	
						1,060					OR 0.61 (0.42-0.88)	
									Prostate cancer mortality			
									CVD mortality			
									Stroke mortality			
									IHD[m] mortality			
				F	15,973	8,991			All-cause mortality		OR 0.66 (0.54-0.81)	
						2,647			Cancer mortality		OR 0.72 (0.55-0.95)	
						765			Lung cancer mortality		OR 0.71 (0.46-1.10)	
						153					OR 1.19 (0.35-4.12)	
						412			Gastric cancer mortality		OR 0.47 (0.28-0.81)	
						212					OR 0.81 (0.34-1.91)	
						161			Colorectal cancer mortality		OR 0.66 (0.25-1.73)	
						2,819					OR 0.65 (0.50-0.83)	
						1,219			Liver cancer mortality		OR 0.73 (0.52-1.03)	
						956					OR 0.60 (0.42-0.87)	
									Breast cancer mortality			
									CVD mortality			
									Stroke mortality			
									IHD mortality			

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Table 1. Studies on the association of soy/soy products and soy-specific foods intakes with mortality from all-cause, total, and specific cancers and cardiovascular diseases (CVDs) (*continued*)

Author(s), reference, y	Study name	Country	Age range, y	Sex	Sample size	Cases	Follow-up, y	Exposure assessment	Outcome	Comparison	OR[a], RR[b], or HR[c] (95% CI)[d]	Adjustment[e]
Khan and colleagues,[20] 2004	—	Japan	>40	M	1,524	155	14	Dietary habit questionnaire	Cancer mortality	Tofu: daily or weekly vs monthly or yearly	RR 1.20 (0.70-2.10)	1, 45
						41			Lung cancer mortality		RR 0.60 (0.30-1.30)	
						36			Gastric cancer mortality		RR 3.60 (0.50-26.0)	
						15			Colorectal cancer mortality		RR 1.50 (0.20-11.2)	
						155			Cancer mortality	Miso soup: daily or weekly vs monthly or yearly	RR 0.40 (0.10-1.10)	
						36			Gastric cancer mortality		RR 0.20 (0.10-0.80)	

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Table 1. Studies on the association of soy/soy products and soy-specific foods intakes with mortality from all-cause, total, and specific cancers and cardiovascular diseases (CVDs) (*continued*)

Author(s), reference, y	Study name	Country	Age range, y	Sex	Sample size	Cases	Follow-up, y	Exposure assessment	Outcome	Comparison	OR[a], RR[b], or HR[c] (95% CI)[d]	Adjustment[e]
				F	1,637	89 15 14			Cancer mortality Gastric cancer mortality Colorectal cancer mortality	Tofu: daily or weekly vs monthly or yearly	RR 1.40 (0.60-3.40) RR 1.10 (0.10-8.50) RR 0.90 (0.10-6.90)	1, 45, 56-58
Kurozawa and colleagues,[21] 2004	Japan Collaborative Cohort Study	China	40-59	M	17,094	21	10	Self-reported FFQ	HCC[n] mortality in persons without a history of liver disease	Tofu: daily vs ≤1-2/wk	HR 2.01 (0.67-6.01)	-
			60-79	M	12,601	52					HR 1.12 (0.55-2.29)	
			40-59	M	17,856	22				Miso soup: ≥2 servings/d vs <1 servings/d	HR 4.36 (0.99-19.3)	
			60-79	M	13,069	56					HR 1.12 (0.43-2.91)	
			40-59	M	1,384	31			HCC mortality in persons with a history of liver disease	Tofu: daily vs ≤1-2/wk	HR 0.28 (0.06-1.30)	
			60-79	M	1,300	56					HR 0.63 (0.31-1.25)	
			40-59	M	1,453	36				Miso soup: ≥2 servings/d vs <1 servings/d	HR 0.97 (0.35-2.71)	
			60-79	M	1,351	58					HR 0.72 (0.30-1.71)	
			40-59	F	24,952	6			HCC mortality in persons without a history of liver disease	Tofu: daily vs ≤1-2/wk	HR 0.52 (0.06-4.43)	

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Table 1. Studies on the association of soy/soy products and soy-specific foods intakes with mortality from all-cause, total, and specific cancers and cardiovascular diseases (CVDs) (*continued*)

Author(s), reference, y	Study name	Country	Age range, y	Sex	Sample size	Cases	Follow-up, y	Exposure assessment	Outcome	Comparison	OR[a], RR[b], or HR[c] (95% CI)[d]	Adjustment[e]
			60-79	F	17,827	21					HR 1.25 (0.40-3.90)	
			40-59	F	25,551	8				Miso soup: ≥2 serv/d vs <1 servings/d	HR 0.31 (0.03-3.12)	
			60-79	F	18,245	20					HR 0.17 (0.04-0.67)	
			40-59	F	1,256	8			HCC mortality in persons with a history of liver disease	Tofu: daily vs ≤1-2/wk	HR 0.84 (0.12-6.07)	
			60-79	F	1,449	40					HR 0.94 (0.42-2.07)	
			40-59	F	1,284	7				Miso soup: ≥2 servings/d vs <1 serving/d	HR 0.77 (0.09-6.33)	
			60-79	F	1,489	43					HR 1.25 (0.44-3.57)	
Nagata and colleagues,[22] 2002	Takayama Study	Japan	≥35	M	14,427	1,163 400 308	7	Self-reported FFQ	All-cause mortality Cancer mortality CVD mortality	Soy products: Q5 vs Q1 >140.4 vs <52.25 g/d	HR 0.83 (0.69-1.01) HR 0.89 (0.64-1.22) HR 0.78 (0.55-1.12)	1, 7, 8, 21, 22, 38, 39, 45-47
				F	17,125	899 253 327			All-cause mortality Cancer mortality CVD mortality	>125.85 vs <49.35 g/d	HR 0.83 (0.68-1.02) HR 0.79 (0.53-1.18) HR 0.90 (0.63-1.28)	1, 5, 7, 8, 21, 22, 38, 45-47, 52, 53

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Table 1. Studies on the association of soy/soy products and soy-specific foods intakes with mortality from all-cause, total, and specific cancers and cardiovascular diseases (CVDs) (*continued*)

Author(s), reference, y	Study name	Country	Age range, y	Sex	Sample size	Cases	Follow-up, y	Exposure assessment	Outcome	Comparison	OR[a], RR[b], or HR[c] (95% CI)[d]	Adjustment[e]
Nagata and colleagues,[23] 2002	Takayama Study	Japan	≥35	M	13,880	91	7	Self-reported FFQ	Gastric cancer mortality	Soy products: T3 vs T1 >112.8 vs <67.65 g/d	HR 0.50 (0.26-0.93)	1, 21, 22, 26, 32, 45
				F	16,424	40					HR 0.53 (0.23-1.22)	1, 7, 21, 22, 39, 53

[a]OR=odds ratio.
[b]RR=relative risk.
[c]HR=Hazard ratio.
[d]Effect sizes were presented for the highest vs lowest categories of soy/soy products or soy-specific foods intakes.
[e]Adjustments: 1=Age, 2=sex, 3=ethnicity, 4=dialect, 5=education, 6=job, 7=marital status, 8=physical activity, 9=residential area, 10=years between cohort entry and diagnosis, 11=stage at diagnosis, 12=Non-Hodgkin lymphoma type, 13=comorbidity, 14=cardiovascular comorbidity, 15=hormone receptor status, 16=treatment type, 17=steroid treatment, 18=surgery, 19=radiotherapy, 20=chemotherapy, 21=body mass index, 22=intake of energy, 23=fruits, 24=vegetables, 25=nonsoy vegetables, 26=rice, 27=fish, 28=meat, 29=milk, 30=dairy products, 31=sodium, 32=salt, 33=dietary fiber, 34=saturated fatty acids, 35=monounsaturated fatty acids, 36=n-3 polyunsaturated fatty acids, 37=n-6 polyunsaturated fatty acids, 38=alcohol, 39=coffee, 40=vitamin supplements, 41=Chinese tea, 42=use of nonsteroidal anti-inflammatory drugs, 43=hypercholesterolemia drugs, 44=history of sex hormone use, 45=smoking status, 46=history of hypertension, 47=diabetes, 48=coronary heart disease, 49=stroke, lung cancer in first-degree relatives, 51=levels of high-density lipoprotein cholesterol, 52=hysterectomy, 53=age at menarche, 54=number of pregnancies, 55=menopausal status, 56=health status, 57=health education. 58=health screening.
[f]M=male.
[g]Q=quartile or quintile.
[h]F=female.
[i]FFQ=food frequency questionnaire.
[j]NHL=non-Hodgkin's lymphoma.
[k]T=tertile.
[l]CHD=coronary heart disease.
[m]IHD=ischemic heart disease.
[n]HCC=hepatocellular carcinoma.

Table 2. Studies on the association between soy isoflavones intake and mortality from all-cause, total, and specific cancers and cardiovascular disease (CVDs)

Author(s), reference, y	Study name	Country	Age range, y	Sex	Sample size	Cases	Follow-up, y	Exposure assessment	Outcome	Comparison	OR[a] or HR[b] (95% CI)[c]	Adjustment[d]
Zhang and colleagues,[24] 2017	Breast Cancer Family Registry	United States, Canada, and Australia	≥18	F[e]	6,235	1,224	9.4	Self-reported FFQ[f]	All-cause mortality	Q[g]4 vs Q1 ≥1.494 vs <0.342 mg/d	HR 0.79 (0.64-0.97)	1, 3, 5, 7, 9, 14, 20-22, 29, 33, 39
Nagata and colleagues,[25] 2017	Takayama Study	Japan	≥35	M[h]/F	29,079	1,678	16	Self-reported FFQ	CVD mortality	Q4 vs Q1 >55.45 vs<27.25 mg/d	HR 0.91 (0.75-1.09)	1, 2, 5-7, 20, 22-24, 28, 30, 32, 39-41
Talaei and colleagues,[14] 2014	Singapore Chinese Health Study	China	45-74	M/F	63,257	2,697 1,298	14.7	Self-reported FFQ	CHD[i] mortality Stroke mortality	Q4 vs Q1 >25.6 vs <9.65 mg/d	HR 0.99 (0.88-1.12) HR 0.97 (0.81-1.16)	1, 4, 5, 7, 9, 20, 22, 29-33, 39-43
				M	26,834	2,702			CVD mortality		HR 1.05 (0.93-1.19)	
				F	33,464	2,078	14.7		CVD mortality		HR 0.92 (0.80-1.07)	
Conroy and colleagues,[15] 2013	Multiethnic Cohort	United States	≥50	F	3,842 3,842	804 376	14	Self-reported FFQ	All-cause mortality Breast cancer mortality	T[j]3 vs T1 ≥5.5 vs 2.5 mg/1,000 kcal	HR 0.99 (0.82-1.20) HR 0.95 (0.71-1.28)	1, 3, 9, 10, 12-14, 20, 22, 39, 41
					1,748	113			Breast cancer mortality in women with ER[k]+		HR 1.01 (0.59-1.73)	
					494	107			Breast cancer mortality in women with ER−		HR 0.96 (0.54-1.72)	

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Table 2. Studies on the association between soy isoflavones intake and mortality from all-cause, total, and specific cancers and cardiovascular disease (CVDs) (*continued*)

Author(s), reference, y	Study name	Country	Age range, y	Sex	Sample size	Cases	Follow-up, y	Exposure assessment	Outcome	Comparison	OR[a] or HR[b] (95% CI)[c]	Adjustment[d]
Yang and colleagues,[16] 2013	Shanghai Women's Health Study	China	40-70	F	444	318	3	Self-reported FFQ	Lung cancer mortality	90th vs 50th percentile >45.7 vs <32.2 mg/d	HR 0.97 (0.78-1.20)	1, 5, 9, 10, 17-20, 22, 23, 25, 35, 36, 39, 44, 48
Kang and colleagues,[26] 2012	—	China	>30	F	288	124	6	FFQ	Breast cancer mortality	>35.30 vs <8.45 mg/d	HR 0.25 (0.09-0.54)	1, 5, 11, 13, 16, 33, 38,39, 48
Nechuta and colleagues,[27] 2012	Shanghai Breast Cancer Survival Study	China	25-70	F	4,856	466	7.4	FFQ	All-cause mortality	≥10.0 vs <4 mg/d	HR 0.84 (0.54-1.33)	1, 3, 5, 7, 11, 13, 15, 18-20, 26, 39, 47, 48
						405			Breast cancer mortality		HR 0.75 (0.47-1.20)	
	Life after Cancer Epidemiology and Women's Healthy Eating & Living	United States	>18	F	4,658	705			All-cause mortality		HR 0.93 (0.69-1.24)	
						476			Breast cancer mortality		HR 0.84 (0.59-1.19)	
	After Breast Cancer Pooling Project				9,514	534			Breast cancer mortality in women with ER+		HR 0.93 (0.67-1.28)	
						326			Breast cancer mortality in women with ER+		HR 0.67 (0.43-1.05)	
						382			Breast cancer mortality in premenopausal women		HR 0.97 (0.66-1.43)	
						467			Breast cancer mortality in postmenopausal women		HR 0.78 (0.54-1.14)	

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Table 2. Studies on the association between soy isoflavones intake and mortality from all-cause, total, and specific cancers and cardiovascular disease (CVDs) (*continued*)

Author(s), reference, y	Study name	Country	Age range, y	Sex	Sample size	Cases	Follow-up, y	Exposure assessment	Outcome	Comparison	OR[a] or HR[b] (95% CI)[c]	Adjustment[d]
Zhang and colleagues,[33] 2012	—	China	>35	F	616	79	4.3	FFQ	Breast cancer mortality	Q4 vs Q1 >28.83 vs <7.56 mg/d	HR 0.62 (0.42-0.90)	1, 5, 11, 13, 16, 18, 19, 33, 39, 44, 48
					378	35			Breast cancer mortality in women with ER+		HR 0.59 (0.40-0.93)	1, 5, 11, 16, 18, 19, 33, 39, 44, 48
					238	44			Breast cancer mortality in women with ER−		HR 0.78 (0.47-0.98)	
Chan and colleagues,[28] 2012	—	China	>50	M/F	127 127	8 3	2.5	FFQ: interview	All-cause mortality CVD mortality	>6.9 vs <6.9 mg/d	OR 0.30 (0.05-1.58) OR 0.48 (0.04-4.57)	—
Kang and colleagues,[29] 2010	—	China	29-72	F	524	76	5.1	FFQ: interview	Premenopausal breast cancer mortality	Q4 vs Q1 > 42.3 vs < 15.2 mg/d	HR 1.05 (0.78-1.71)	1, 11, 13, 18, 19
						78			Postmenopausal breast cancer mortality		HR 0.88 (0.56-1.24)	
Kokubo and colleagues,[17] 2007	Japan Public Health Center	Japan	40-59	M	19,466	175	12.5	Self-reported FFQ	Ischemic CVD mortality	Q5 vs Q1 ≥39.6 vs ≤16.4 mg/d	HR 1.27 (0.66-2.43)	1, 2, 5, 7, 9, 20, 22-24, 27, 28, 33, 37,39-41
				F	20,984	57				≥37.7 vs ≤16.2 mg/d	HR 0.87 (0.29-2.52)	1, 2, 5, 7, 9, 20, 22-24, 27, 28, 33, 37, 39, 40, 41, 48

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Table 2. Studies on the association between soy isoflavones intake and mortality from all-cause, total, and specific cancers and cardiovascular disease (CVDs) (*continued*)

Author(s), reference, y	Study name	Country	Age range, y	Sex	Sample size	Cases	Follow-up, y	Exposure assessment	Outcome	Comparison	OR[a] or HR[b] (95% CI)[c]	Adjustment[d]
Boyapati and colleagues,[30] 2005	Shanghai Breast Cancer Study	China	25−64	F	1,455	296	5.2	Soy isoflavones: interview	Breast cancer survival	T3 vs T1 N/R[l]	HR 1.06 (0.79-1.42)	1, 10, 13, 18, 22
Nagata and colleagues,[22] 2002	Takayama Study	Japan	≥35	M	14,427	1163	7	Self-reported FFQ	All-cause mortality	Q5 vs Q1 >60.6 vs <23.8 mg/d	HR 0.88 (0.72-1.06)	1, 6, 7, 20, 22, 33, 34, 39-41
				F	17,125	899			All-cause mortality	>55.35 vs <22.75 mg/d	HR 0.94 (0.76-1.15)	1, 5-7, 20, 22, 33, 39-41, 45,46

[a]OR=odds ratio.
[b]HR=Hazard ratio.
[c]Effect sizes were presented for the highest vs lowest categories of soy isoflavones intake.
[d]Adjustments: 1=Age, 2=sex, 3=race/ethnicity, 4=dialect, 5=education, 6=marital status, 7=physical activity, 8=residential area, 9=years between cohort entry and diagnosis, 10=stage at diagnosis, 11=TNM stage, 12=cardiovascular co-morbidity, 13=hormone receptor status, 14=treatment type, 15=hormonal therapy, 16=tamoxifen use, 17=surgery, 18=radiotherapy, 19=chemotherapy, 20=body mass index, 21=Health Eating Index, 22=intake of energy, 23=fruits, 24=vegetables, 25=nonsoy vegetables, 26=cruciferous vegetable, 27=fish, 28=salt, 29=dietary fiber, 30=saturated fatty acids, 31=monounsaturated fatty acids, 32=polyunsaturated fatty acids, 33=alcohol, 34=coffee, 35=vitamin supplements, 36=use of nonsteroidal anti-inflammatory drugs, 37=hypercholesterolemia drugs, 38=oral contraceptive use, 39=smoking status, 40=history of hypertension, 41=diabetes, 42=coronary heart disease, 43=stroke, 44=cancer in first-degree relatives, 45=hysterectomy, 46=age at menarche, 47=parity, 48=menopausal status.
[e]F=female.
[f]FFQ=food frequency questionnaire.
[g]Q=quartile or quintile.
[h]M=male.
[i]CHD=coronary heart disease.
[j]T=tertile.
[k]ER=estrogen receptor.
[l]N/R=not reported.

Table 3. Studies on the association between soy protein intake and mortality from all-cause, total, and specific cancers and cardiovascular diseases (CVD)

Author(s), reference, y	Study name	Country	Age range, y	Sex	Sample size	Cases	Follow-up, y	Exposure assessment	Outcome	Comparison	OR[a], RR[b], or HR[c] (95% CI)[d]	Adjustment[e]
Nagata and colleagues,[25] 2017	Takayama Study	Japan	≥35	M[f]/F[g]	29,079	1,678 677 308	16	Self-reported FFQ[h]	CVD mortality Stroke mortality IHD[i] mortality	Q[j]4 vs Q1 >16.1 vs <7.85 g/d	HR 0.87 (0.73-1.04) HR 0.75 (0.57-0.99) HR 0.81 (0.53-1.24)	1, 2, 4, 5, 8, 17, 19-21, 25, 28, 30, 36-38
Talaei and colleagues,[14] 2014	Singapore Chinese Health	China	45-74	M/F	63,257	2,697 1,298	14.7	Self-reported FFQ	CHD[k] mortality Stroke mortality	Q4 vs Q1 >8 vs <3.25 g/d	HR 1.06 (0.93-1.20) HR 1.02 (0.85-1.23)	1, 3, 4, 8, 9, 17, 19, 26-31, 36-40
				M	26,834	2,702			CVD mortality		HR 1.16 (1.03-1.31)	
				F	33,464	2,078			CVD mortality		HR 0.95 (0.81-1.10)	
Kang and colleagues,[26] 2012	—	China	>30	F	288	124	6	FFQ	Breast cancer mortality	>15.78 vs <4.55 g/d	HR 0.38 (0.17-0.86)	1, 4, 11, 13, 31, 35, 36, 43
Zhang and colleagues,[33] 2012	—	China	>35	F	616	79	4.3	FFQ	Breast cancer mortality	Q4 vs Q1 >13.03 vs <2.12 g/d	HR 0.71 (0.52-0.98)	1, 4, 11-13, 15, 16, 31, 36, 41, 43
					378	35			Breast cancer mortality in women with ER+[l]		HR 0.66 (0.44-0.93)	1, 4, 11-13, 15, 16, 31, 36, 41, 43
					238	44			Breast cancer mortality in women with ER−[m]		HR 0.77 (0.53-1.00)	

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Table 3. Studies on the association between soy protein intake and mortality from all-cause, total, and specific cancers and cardiovascular diseases (CVD) (*continued*)

Author(s), reference, y	Study name	Country	Age range, y	Sex	Sample size	Cases	Follow-up, y	Exposure assessment	Outcome	Comparison	OR[a], RR[b], or HR[c] (95% CI)[d]	Adjustment[e]
Shu and colleagues,[31] 2009	Shanghai Breast Cancer Survival Study	China	25-70	F	5,033	444 534	3.9	Self-reported FFQ	All-cause mortality Relapse/breast cancer mortality	Q4 vs Q1 >15.31 vs ≤5.31 g/d	HR 0.67 (0.51-0.88) HR 0.66 (0.52-0.84)	1, 4, 8, 11-17, 22-24, 33, 34, 43
					3,180	202			Relapse/breast cancer mortality in women with ER+		HR 0.65 (0.46-0.92)	
					1,772	224			Relapse/breast cancer mortality in women with ER−		HR 0.76 (0.53-1.08)	
Boyapati and colleagues,[30] 2005	Shanghai Breast Cancer Study	China	25-64	F	1,458	297	5.2	FFQ: Interview	Breast cancer survival	T[n]3 vs T1 N/R[o]	HR 0.99 (0.73-1.33)	1, 10, 12, 15, 19
					528	107			Breast cancer survival in women with ER+		HR 1.09 (0.62-1.91)	
					259	53			Breast cancer survival in women with ER−		HR 0.75 (0.29-1.89)	

(*continued on next page*)

Table 3. Studies on the association between soy protein intake and mortality from all-cause, total, and specific cancers and cardiovascular diseases (CVD) (*continued*)

Author(s), reference, y	Study name	Country	Age range, y	Sex	Sample size	Cases	Follow-up, y	Exposure assessment	Outcome	Comparison	OR[a], RR[b], or HR[c] (95% CI)[d]	Adjustment[e]
Zhang and colleagues,[32] 2003	Shanghai Women's Health Study	China	40-70	F	64,915	19	2.5	FFQ: interview	CHD death	Q4 vs Q1 ≥11.19 vs <4.50 g/d	RR 0.73 (0.15-3.58)	1, 4, 6-8, 17-21, 26, 27, 31, 36, 37, 43

[a]OR=odds ratio.
[b]RR=relative risk.
[c]HR=Hazard ratio.
[d]Effect sizes were presented for the highest vs lowest categories of soy protein intake.
[e]Adjustments: 1=Age, 2=sex, 3=dialect, 4=education, 5=marital status, 6=income, 7=season of recruitment, 8=physical activity, 9=years between cohort entry and diagnosis, 10=stage of disease, 11=TNM stage, 12=hormone receptor status, 13=tamoxifen use, 14=surgery, 15=radiotherapy, 16=chemotherapy, 17=body mass index, 18=waist-to-hip ratio, 19=intake of energy, 20=fruits, 21=vegetables, 22=cruciferous vegetable intake, 23=fish, 24=meat, 25=salt, 26=dietary fiber, 27=total fat, 28=saturated fatty acids, 29=monounsaturated fatty acids, 30=polyunsaturated fatty acids, 31=alcohol, 32=coffee, 33=tea, 34=vitamin supplements, 35=oral contraceptive use, 36=smoking status, 37=history of hypertension, 38=diabetes, 39=coronary heart disease, 40=stroke, 41=cancer in first-degree relatives, 42=age at menarche, 43=menopausal status.
[f]M=male.
[g]F=female.
[h]FFQ=food frequency questionnaire.
[i]IHD=ischemic heart disease.
[j]Q=quartile or quintile.
[k]CHD=coronary heart disease.
[l]ER+=positive estrogen receptor status.
[m]ER+=negative estrogen receptor status.
[n]T=tertile.
[o]N/R=not reported.

Table 4. Quality assessment of prospective studies included in the current systematic review and meta-analysis based on Newcastle-Ottawa scale (NOS)[47]

	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Energy adjustment	Controls for any additional factor	Assessment of outcome	Follow up long enough	Adequacy of follow up of cohorts	Total
Nagata and colleagues,[22] 2002a	•	•		•	•	•	•		•	7
Nagata and colleagues,[23] 2002b	•	•		•	•	•	•		•	7
Zhang and colleagues,[32] 2003	•	•		•	•	•	•		•	7
Kurozawa and colleagues,[21] 2004	•	•		•		•	•	•	•	7
Khan and colleagues,[20] 2004	•	•		•		•	•	•	•	7
Boyapati and colleagues,[30] 2005	•	•		•	•	•	•		•	7
Ho and colleagues,[19] 2006	•	•	•	•		•	•	•	•	8
Kokubo and colleagues,[17] 2007	•	•		•	•	•	•	•	•	8
Sakauchi and colleagues,[18] 2007	•	•		•		•	•	•	•	7
Shu and colleagues,[31] 2009	•	•		•		•	•		•	6
Kang and colleagues,[29] 2010	•	•		•		•	•		•	6
Nechuta and colleagues, 2012	•	•		•		•	•		•	6
Zhang and colleagues,[33] 2012	•	•		•		•	•		•	6
Chan and colleagues,[28] 2012		•	•	•			•		•	5
Kang and colleagues,[26] 2012	•	•		•		•	•		•	6
Conroy and colleagues,[15] 2013	•	•		•		•	•	•	•	7
Yang and colleagues,[16] 2013	•	•		•	•	•	•		•	7
Yamasaki and colleagues,[13] 2015	•	•		•		•	•	•	•	7
Talaei and colleagues,[14] 2014	•	•		•	•	•	•	•	•	7
Nagata and colleagues,[25] 2017	•	•		•	•	•	•	•	•	8
Nguyen and colleagues,[11] 2018	•	•		•		•	•	•	•	8
Leo and colleagues,[12] 2016	•	•		•		•	•		•	6
Zhang and colleagues,[24] 2017	•	•		•	•	•	•	•	•	8