Food & Function

REVIEW

View Article Online
View Journal | View Issue

Cite this: *Food Funct.*, 2018, **9**, 2576

Soy product consumption and the risk of all-cause, cardiovascular and cancer mortality: a systematic review and meta-analysis of cohort studies

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Currently, the association of soy intake with total- and cause-specific mortality is inconsistent. The aim of this study was to systematically review cohort studies on the association between the consumption of soy products and mortality from all-causes, cardiovascular disease (CVD), and cancer. We conducted a systematic search of the PubMed/Medline, ISI Web of Knowledge and Embase electronic databases up to October 2016. Prospective cohort studies that examined the association of soy products with the risk of all-cause, CVD and cancer mortality using the relative risk (RR) or Hazard Ratio (HR) with 95% CIs were considered. Random-effect models were used to pool the study results and heterogeneity was examined using the I^2 index and Q test. Finally, 7 studies were included for the meta-analysis; three studies reported the risk of all-cause mortality. Four studies assessed the risk of mortality from CVD and cancer. In total, 39 250 deaths were reported among 627 209 participants in a 7 to 18-year follow-up. A high consumption of soy products was not significantly associated with a lower risk of mortality from all-causes (HR: 0.96, 95% CI: 0.90, 1.02, I^2: 38.5%, and $P_{heterogeneity}$ = 0.14), CVD (HR: 0.95, 95% CI: 0.82, 1.10, I^2: 49.9%, and $P_{heterogeneity}$ = 0.07), and cancer (HR: 0.98, 95% CI: 0.92, 1.05, I^2: 0%, and $P_{heterogeneity}$ = 0.75). These findings indicated no significant association between a high intake of soy products and all-cause, CVD, and cancer mortality. Further studies are needed to clarify the association between the types of soy products and the risk of mortality.

Received 17th October 2017,
Accepted 13th March 2018

DOI: 10.1039/c7fo01622k

rsc.li/food-function

1. Introduction

The prevalence of chronic diseases is dramatically increasing across the world. According to the World Health Organization (WHO), approximately 60% of all reported deaths in 2001 were due to chronic diseases, such as cardiovascular disease (CVD), diabetes, and cancers. The WHO also predicted that by 2020, chronic diseases will contribute to 75% of all deaths.[1] The primary causes of mortality from chronic diseases are related to lifestyle (dietary intake, physical activity, smoking, and psychological stress), particularly dietary habits and food choices.[2] In Japan and the Mediterranean countries, the mortality rates from CVD are relatively low,[2,3] which may be related to lifestyle, including the dietary intakes of these populations.[4]

Soy protein is the main source of protein in many East Asian countries. It contains phytoestrogens, which are known as isoflavones, such as daidzein, genistein, glycitein, and biochanin A, proteins, vitamin E, fiber, and saponins.[5] Earlier studies have examined the association of these components with chronic conditions and mortality.[6–13] Soy products are classified into non-fermented and fermented soy products.[14] Based on evidence, high consumption of non-fermented soy products (tofu and soy protein) can lower the risk of all-cause[15] and cancer[14] mortality. However, fermented soy products (natto and miso) can cause a higher risk;[16,17] thus, the types of soy can play key roles in the risk of diseases and mortality.

Controlled clinical trials have shown that soy intake can affect the endothelial function, lipid profile, glycemic status,

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and arterial stiffness.[9,18] In addition, in populations that consumed high amounts of soy protein or soy products, the occurrence of some types of cancers was low.[19,20] Thus, soy intake might be associated inversely with cancer mortality.[11,14,21,22]

While some studies have indicated that there is an inverse association between the consumption of soy protein or products and mortality,[11,14,23] others have not obtained an association.[24–27] Furthermore, after considering the participant characteristics, such as gender and age range, or cause of mortality, different findings have been observed.[21,22,28,29] Thus, the relationship between the soy protein or product intake and death remains controversial. To the best of our knowledge, there is no systematic review to summarize the earlier findings in this regard. Therefore, the aim of this study was to systematically review findings on the association between the soy product intake and mortality from all-causes, CVD, and cancer in the prospective cohort studies on adult populations, and to perform a meta-analysis, if possible.

2. Methods

2.1. Databases and search strategy

The present meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines.[30] We searched PubMed/Medline, ISI Web of Knowledge and Embase electronic databases with no language restriction until October 2016. The keywords we used in this search were as follows: (Soy OR Natto OR Tempeh OR Miso OR Tofu OR legumes OR "Glycine max" OR "Bean curd" OR "Plant protein" OR "Vegetable protein") AND (Mortality OR death OR fatal).

The reference lists of all relevant papers and review articles were examined to identify studies not found by a search of the electronic databases. Two investigators (N.N and A.E) independently searched and entered the studies into the Endnote program; duplicated studies were removed. After screening the possible relevant publications by the title and abstract, the full texts of the eligible papers were assessed by each reviewer independently.

2.2. Inclusion and exclusion criteria

Studies were included for the current systematic review if: (I) they were of a prospective cohort design, (II) they examined the consumption of soy protein or soy products as exposure, (III) their primary outcome was the occurrence of death (all-cause, CVD and cancer mortality), (IV) they reported relative risks (RRs) or hazard ratios (HRs) with 95% Confidence Intervals (CIs) for the highest *vs.* lowest category of soy consumption, and (V) they included healthy subjects (individuals suffering from neither cancer or CVD at the baseline). Studies with (I) other designs (case-control, cross-sectional studies, *etc.*) along with (II) animals, (III) *in vitro* studies and (IV) the grey literature (dissertations, interviews, book chapters, and abstracts in conferences) and also narrative reviews or systematic review papers were not included. Studies on (V) the effects of dietary habits, plant proteins or beans that did not report RRs/or HRs for soy protein or soy products separately, were also excluded.

2.3. Data extraction

The investigators (N.N and P.S) used a pre-designed extraction sheet to extract data from the full-text of the papers. Name of the first author, publication year, country, age range, gender, sample size, incidence of death, duration of follow-up, person-year, exposure, comparison categories, OR or RR (95% CI) as well as the method of exposure assessment, outcome, and comparison *vs.* the reference group (highest to the lowest intake), and covariates adjusted for in the statistical analyses were extracted. The data were extracted separately from the studies that reported distinct results for men and women, different age ranges, specific causes of mortality (cancer, CVD, and all-cause). If an included study reported several risk estimates, the HRs which were adjusted for the most confounding factors were extracted. For duplicated publications, the most recent paper with the most complete data (larger population and longer duration of follow-up) was included in this study.

2.4. Quality assessment

To determine the methodological quality of the studies, the Newcastle–Ottawa quality assessment scale[31] was completed by two independent reviewers (N.N and A.E) for each eligible paper. The Newcastle–Ottawa scale contains eight items about selection, comparability, and exposure; the scale ranges from zero to nine. The selection section contains four items: (1) representativeness of the exposed and (2) the non-exposed cohorts, (3) ascertainment of exposure, and (4) demonstration that interests outcome was not present at the baseline. In the next section, comparability of the cohorts according to the design or analysis controlled for confounders are assessed (1 item). The third section is dedicated to the outcome and contains three items, including (1) assessment of the outcome, (2) sufficiency of the follow-up duration, and (3) acceptability of lost to follow-up (less than 20%). Any study can be obtained as a maximum of one star for each numbered item in the selection and outcome categories. However, a maximum of two stars can be dedicated to the comparability section. In the present study, papers with a score of 7 or greater were considered to be high-quality studies. The scores for the quality assessment of each paper are presented in Table 2.

Any discrepancies between the two investigators in each aforementioned procedure were resolved by discussion.

2.5. Data synthesis and statistical analysis

To examine the association between the consumption of soy (highest *vs.* lowest category) and all-cause, CVD, and cancer mortality, the RRs or HRs (with 95% CIs) were extracted from the eligible papers and the log HRs and standard errors (Standard Error = (upper level − lower level)/3.92) were calculated. The different types of soy foods (tofu, miso, soy protein, natto, and total soy products) were reported in some included prospective studies. Based on the previous study,[32] soy foods were prioritized as follows: (1) total soy foods, (2) tofu, (3) soy

milk, (4) soy protein, (5) miso (soy paste soup) and (6) natto. Whenever possible, we classified different soy foods into fermented (miso and natto) and non-fermented (tofu, soy protein, and soy milk) soy products and examined the association between the different types of soy food products and mortality. Based on the aforementioned ranking, the main type of soy was considered for statistical analysis to estimate the effects of soy products on the risk of mortality.

RRs or HRs for all-cause mortality, CVD and cancer mortality were pooled with random-effect models using the DerSimonian & Laird method.[33] Heterogeneity was examined using Cochran's Q test and the I-square (I^2) index. The I^2 values lower than 25%, between 25 and 50%, 51–75% and greater than 75% were considered as low, moderate, severe and highly severe heterogeneity, respectively.[34] To identify the sources of heterogeneity, whenever possible (at least two studies in each subgroup), the potential sources of heterogeneity for each outcome (all-cause, CVD, cancer, and specific-cancer mortality) were assessed according to the following categories: the type of soy food (fermented and non-fermented), gender (men/women), duration of follow-up (less or ≥10 years), study quality (less or ≥score of 6) and energy adjustment (adjusted and non-adjusted). The robustness of the findings was checked using sensitivity analysis. The analysis was repeated after excluding one prospective study at a time to determine the influence of each study on the pooled effect size. To evaluate the publication bias, a funnel plot and also Egger's regression test[5] were used. All data analyses were performed using Stata 12.0 software (Stata Corp LP, College Station, TX).

3. Results

3.1. Literature search

After systematic searching, we identified 1877 papers (including 674 duplications). Three eligible papers were also found by hand searching. After screening, 13 cohort studies were obtained. As there were insufficient studies on each specific cancer, they were not included for the meta-analysis and quantitative synthesis was performed on 7 studies (Fig. 1). Nagata

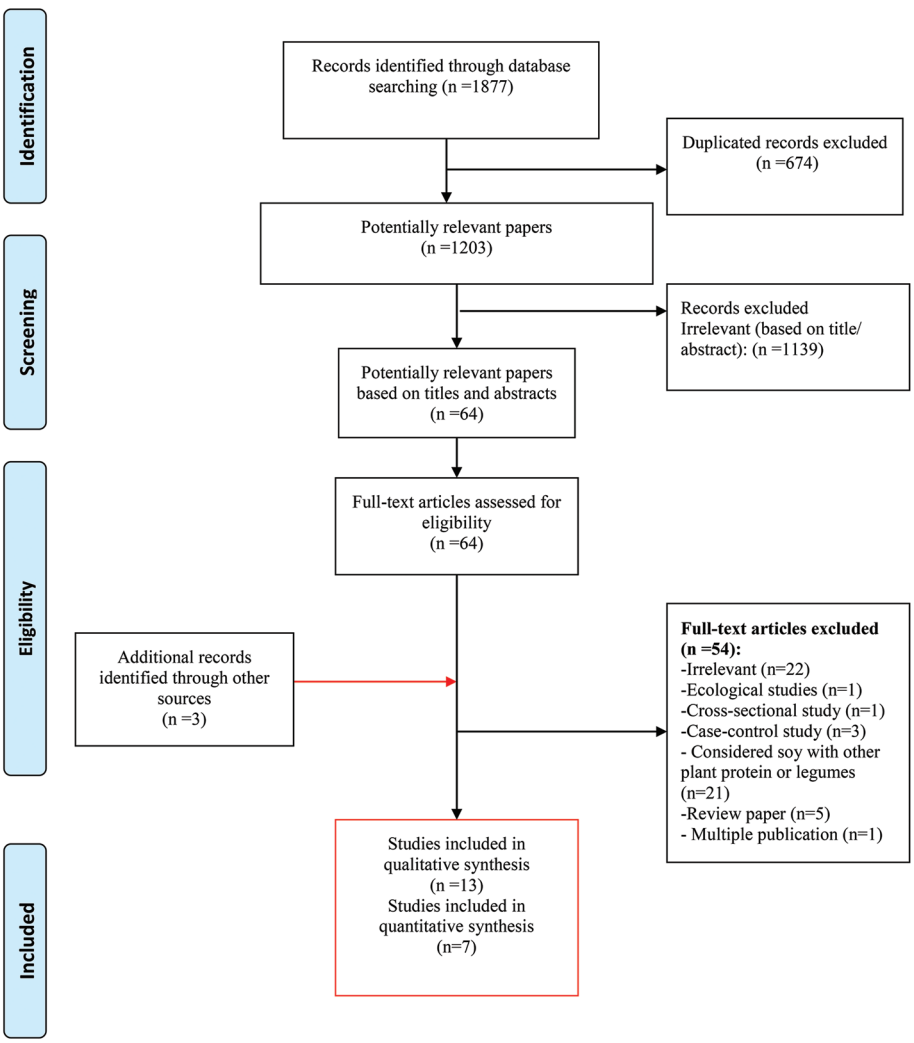

Fig. 1 Flowchart of the screening steps to identify the eligible studies.

et al. published two papers[14,23] and examined the association between the total soy product consumption and CVD mortality. However, we included the data from their most comprehensive study[35] and excluded their preliminary findings.

3.2. Study characteristics

The characteristics of the 13 cohort studies[11,14,15,21–29,36] included in the current systematic review are presented in Table 1. The selected papers were published between 1990[36] and 2016.[23] Except for one study[27] that investigated soy consumption in Chinese people residing in Singapore, all the included cohort studies were from Japan. The sample size in the included studies ranged from 3155 to 265 118 people. The mean age in the study population was between 30[24] and 69.5[29] years. All the included studies,[11,14,15,21,22,24–26,28,29] except three,[23,27,36] reported the effect size for each gender, separately. One study included only women. It reported the association between soy and ovarian cancer.[11]

To determine the consumption of dietary soy, most studies used a food frequency questionnaire (FFQ). Khan *et al.* used a dietary questionnaire like an FFQ containing 37 dietary items.[28]

Overall, there were 39 250 deaths among 627 209 participants during 7–18 years of follow-up. The papers examined the association with mortality from all causes (n = 3),[15,22,24] CVD (n = 4),[21–23,27] and cancer (n = 4).[14,22,24,28] Six studies reported the RRs or HRs for specific-cancer mortality: ovarian (n = 1),[11] hepatocellular carcinoma (n = 1),[29] stomach (n = 2),[15,25] lung (n = 1),[26] colon (n = 1)[36] and rectum cancers (n = 1).[36] The reported deaths from all causes, CVD and cancer were 18 983, 6241 and 14 026, respectively. In the included studies,[11,14,15,21–29,36] soy protein (n = 4),[21–23,27] soy products (n = 4),[14,15,22,36] natto (n = 1),[23] tofu (n = 6),[11,25–29] and miso (n = 5),[21,24,26,28,29] fermented and non-fermented (n = 1)[14] were examined.

Based on the Newcastle–Ottawa checklist, the scores of the methodological quality for all cohort studies,[11,14,15,21–23,25–28] except three[24,29,36] were more than 7.

3.3. Findings of a systematic review

Six cohort studies reported the association of soy and specific cancer.[11,15,25,26,29,36] Among them, two showed an inverse association. Kurozawa *et al.* reported an inverse association between the miso intake and hepatocellular cancer in women aged 60–79 years old.[29] Additionally, in the study by Nagata *et al.*, both total and non-fermented soy products were linked with a lower risk of stomach cancer in men only.[15] No significant link was reported in the remaining papers.[11,25,26,36]

3.4. Findings from the meta-analysis on soy or soy product consumption and the risk of all-cause mortality

Based on the meta-analysis of the six effect sizes derived from 3 studies,[14,22,24] which were obtained from three studies with a total number of 18 992 deaths among 141 335 people, we did not find any significant association between the high consumption of different types of soy foods and the risk of all-cause mortality (overall HR: 0.96; 95% CI: 0.90, 1.02) (Fig. 2). However, moderate heterogeneity was found (I^2 = 38.5% and $P_{\text{heterogeneity}}$ = 0.14).

The sensitivity analysis indicated that excluding any of the studies did not change the overall effect size considerably. Furthermore, no evidence for publication bias was seen (P = 0.86).

3.5. Findings from the meta-analysis on soy or soy product consumption and the risk of CVD mortality

Based on the six effect sizes from four studies,[21,23,27] we found that there was no significant association between the high intake of different types of soy foods and the risk of CVD mortality (overall HR: 0.95, 95% CI = 0.82, 1.10, I^2 = 49.9%; $P_{\text{heterogeneity}}$ = 0.75) (Fig. 3). When we analyzed the data separately with fermented (n = 3) and non-fermented soy products (n = 5), we found a significant inverse association between the consumption of fermented soy products and CVD mortality (0.84; 95% CI: 0.73, 0.97); however, there was no significant association between the intake of non-fermented soy products and the risk (0.87; 95% CI: 0.62, 1.22) (Table 3).

Using sensitivity analysis, we found that no single study had a considerable impact on the overall effect size. Egger's regression test showed no publication bias (P = 0.40).

3.6. Findings from the meta-analysis on soy or soy product consumption and the risk of total cancer mortality

As presented in Fig. 4, there was no significant association between the consumption of soy/or soy products and the risk of total cancer mortality (HR: 0.98; 95% CI: 0.92, 1.05, I^2 = 0%; $P_{\text{heterogeneity}}$ = 0.75). Stratified analysis based on the type of soy food and gender revealed no significant alteration in the findings (Table 3). Based on the sensitivity analysis, no single study had any considerable impact on the pooled effect size. Moreover, no evidence for publication bias was observed (P = 0.46).

In the sub-group analysis based on fermented *vs.* non-fermented soy products, two studies[21,28] reported the RR for CVD-mortality and total cancer-mortality in both fermented and non-fermented soy products. These two studies were included in both sub-groups. Due to overlapping in the sample sizes of the subgroups, it was not reasonable to have p-values for fermented *vs.* non-fermented soy foods (Table 3).

4. Discussion

Based on the present meta-analysis of cohort studies, we found that a highest intake of total soy foods was not associated with a lower risk of mortality from all causes, CVD and cancers compared with a low intake of soy food. To the best of our knowledge, this is the first meta-analysis that summarized the findings from prior studies on the association of soy intake and mortality.

Our findings were in line with the previous meta-analysis by Kim *et al.*[37] They showed no significant association between

Table 1 Main characteristics of the studies examined the association of soy protein or soy product intake with all-cause, CVD and cancer and other-cause mortality

First author (year)	Cohort name	Age range	Gender	Sample size	Cases	Duration follow-up (*y*)	Person-year	Exposure assessment	Outcome (ascertainment)	Comparison	OR or RR (95% CI)	Adjustments[a]
Nagata *et al.* (2016)	Takayama study	≥40	M/F	29 079	1678	16	—	FFQ, 169-item	Total CVD mortality	Q4 *vs.* Q1 (median: 19 *vs.* 6 g day^{-1})	0.89 (0.77, 1.03)	1, 2, 4, 5, 8, 10, 13, 15, 19, 29
								Total soy protein				
					1678			Natto	CVD (ICD-10: I00–I99), IHD (ICD-9 codes 410–414 and ICD-10 codes I20–I25), total stroke (ICD-9 codes 430–438 and ICD-10 codes I60–I69), ischemic stroke (ICD-9 codes 434 and ICD-10 codes I63 and I69.3)	Q4 *vs.* Q1 (median: 7.3 *vs.* 0 g day^{-1})	0.84 (0.72, 0.98)	
					1678			Other than natto		Q4 *vs.* Q1 (median: 18.1 *vs.* 5.7 g day^{-1})	0.88 (0.76, 1.02)	
Yamasaki *et al.* (2015)	Jichi Medical School Study (JMS)	19–93	M	4309	528	11.8	50 822	FFQ, 30-item	All-cause mortality	Almost daily *vs.* rarely	1.55 (1.19, 2.03)	1, 2, 3, 4, 5, 6, 7, 8, 9
					108				CVD mortality		1.39 (0.78, 2.41)	
					207			Soy protein	Cancer mortality		1.39 (0.88, 2.19)	
					202				Other cause death (ICD-10 (I00–I99, C00-C97, D00-D48, J00-J99, K00-K93, V01-Y89))		1.82 (1.21, 2.77)	
			F	6757	354		80 629				0.81 (0.51, 1.30)	
					90						0.62 (0.27, 1.42)	
					139						0.77 (0.34, 1.73)	
					121						1.09 (0.48, 2.50)	
			M	4309	528		50 821	Soy product	All-cause mortality	Almost daily to 1–4 times per week	1.11 (0.93, 1.32)	
					119				CVD mortality		1.18 (0.84, 1.75)	
					207				Cancer mortality		1.14 (0.85, 1.53)	
					202				Other cause death (ICD-10 (I00–I99, C00-C97, D00-D48, J00-J99, K00-K93, V01-Y89))		1.04 (0.77, 1.40)	
			F	6757	354		80 629				1.06 (0.85, 1.33)	
					94						1.03 (0.66, 1.61)	
					139						1.10 (0.77, 1.58)	
					121						1.06 (0.71, 1.57)	

Table 1 *(Contd.)*

First author (year)	Cohort name	Age range	Gender	Sample size	Cases	Duration follow-up (y)	Person-year	Exposure assessment	Outcome (ascertainment)	Comparison	OR or RR (95% CI)	Adjustments[a]
Talaei *et al.* (2014)	Singapore Chinese Health study	45–74	M/F	60 298	3920	14.7	851 674	FFQ, 165-item	CVD mortality (ICD-9, codes 390–459); CHD mortality (ICD-9, codes 410–414); stroke mortality (ICD-9, codes 430–438)	Q4 *vs.* Q1 (median: 9.8 *vs.* 2.2 g day^{-1})	1.00 (0.91, 1.09)	1, 10, 11, 12, 4, 8, 13, 21, 14, 3, 15, 16, 17, 18, 19
								Soy protein				
								Tofu		Q4 *vs.* Q1 (median: 197 *vs.* 42.8 g day^{-1})	1.01 (0.92, 1.10)	
Sakauchi *et al.* (2007)	Japan Collaborative Cohort Study (JACC)	40–79	F	64 327	64	13.3	—	FFQ, 32-item	Ovarian cancer mortality (ICD10 code C56)	Almost every day *vs.* ≤1–2 times per week	0.61 (0.26, 1.45)	1, 9, 22, 23, 8, 13, 4
								Tofu				
Kokubo *et al.* (2007)	Japan Public Health Center-Based study (JPHC)	40–59	M	19 466	175	12.5	239 088	FFQ, 44-item	Ischemic CVD mortality (ICD-10 codes I21–I23 and I46 for myocardial infarctions and I60–I61, I63, and I693 for cerebral infarctions)	≥5 days per week *vs.* 0–2 days per week	0.90 (0.56, 1.45)	1, 10, 2, 3, 8, 15, 16, 24, 4, 13, 30, 19, 9, 31
								FFQ, 147-item				
			F	20 984	57		260 465	Soy protein			0.31 (0.13, 0.74)	
			M	19 466	175		239 087	Miso soup			0.86 (0.53, 1.40)	
			F	20 984	57		260 465				0.82 (0.33, 2.01)	
Iso *et al.* (2007)	Japan Collaborative Cohort Study (JACC)	30	M	42 696	9452	—		Miso soup	All-cause mortality	≥2 per day *vs.* ≤1 per two day	0.95 (0.9, 1.01)	1, 35
			F	58 494	6596						0.98 (0.92, 1.04)	
			M	42 696	9452				Cancer Mortality		0.99 (0.9, 1.08)	
			F	58 494	2156						0.96 (0.86, 1.07)	
Kurozawa *et al.* (2004)	Japan Collaborative Cohort Study (JACC)	40–59	M	17 094	21	9–11	—	FFQ, 33-item	Hepatocellular carcinoma (HCC) (ICD-10 code C22.0)	Almost every day *vs.* ≤1–2 per week	2.01 (0.67, 6.01)	—
			F	24 952	6						0.52 (0.06, 4.43)	
		60–79	M	12 601	52			Tofu			1.12 (0.55, 2.29)	
			F	17 827	21						1.25 (0.4, 3.90)	
		40–59	M	17 852	22			Miso soup		2 serving per day *vs.* <serving per day	4.36 (0.99, 19.33)	
			F	25 551	8						0.31 (0.03, 3.12)	
		60–79	M	13 069	56						1.12 (0.43, 2.91)	
			F	18 245	20						0.17 (0.04, 0.67)	

Table 1 *(Contd.)*

First author (year)	Cohort name	Age range	Gender	Sample size	Cases	Duration follow-up (y)	Person-year	Exposure assessment	Outcome (ascertainment)	Comparison	OR or RR (95% CI)	Adjustments[a]
Khan *et al.* (2004)	Hokkaido	≥40	M	1522	155	18	—	Dietary factor, 37-item	Cancer mortality (ICD-9)	≥several times per week *vs.* ≤several times per month	1.2 (0.7–2.1)	M: 1, 2; F: 1, 2, 26, 27, 28
								Tofu				
			F	1633	89						1.4 (0.6, 3.4)	
			M	1522	155			Miso soup			0.4 (0.1, 1.1)	
			F	1633	89						—	
Nagata *et al.* (a) (2002)	Takayama study	>35	M	13 355	1163	7	201 160	FFQ, 169-item	All-cause mortality	Q5 *vs.* Q1 (166.4 *vs.* 40.6 g day^{-1})	0.83 (0.69, 1.01)	1, 19, 29, 8, 2, 3, 30, 13, 15, 16
					400				Cancer mortality (ICD-10 codes C00-D48)		0.89 (0.64, 1.22)	
					308				Cardiovascular (ICD-10 codes I00-I99)		0.78 (0.55, 1.12)	
					455				Other mortality		0.85 (0.61, 1.17)	
			F	15 724	899			Total soy product	All-cause mortality		0.83 (0.68, 1.02)	
					253				Cancer mortality (ICD-10 codes C00-D48)		0.79 (0.53, 1.18)	
					327				Cardiovascular (ICD-10 codes I00-I99)		0.90 (0.63, 1.28)	
					319				Other mortality		0.79 (0.57, 1.11)	
Nagata *et al.* (b) (2002)	Takayama study	≥35	M	13 880	91	7	94 280	FFQ, 169-item total soy product	Stomach cancer mortality (ICD-9 code 151 or the ICD-10 code C16)	High *vs.* low (median: 140 *vs.* 49.7 g day^{-1})	0.5 (0.26, 0.93)	1, 19, 2, 8, 1
					81			Fermented soy product		High *vs.* low (median: 30.9 *vs.* 8.9 g day^{-1})	1.05 (0.57, 1.93)	
					81		94 279	Non-fermented soy product		High *vs.* low (median: 112 *vs.* 36.7 g day^{-1})	0.49 (0.26, 0.92)	
			F	16 424	40		114 670			High *vs.* low (median: 126.9 *vs.* 46.7 g day^{-1})	0.53 (0.23, 1.22)	1, 29, 19, 32, 8, 30
					40		114 671			High *vs.* low (median: 30.9 *vs.* 8.9 g day^{-1})	0.56 (0.25, 1.24)	
					40					High *vs.* low (median: F: 102 *vs.* 35.3 g day^{-1})	0.51 (0.22, 1.18)	

Table 1 *(Contd.)*

First author (year)	Cohort name	Age range	Gender	Sample size	Cases	Duration follow-up (*y*)	Person-year	Exposure assessment	Outcome (ascertainment)	Comparison	OR or RR (95% CI)	Adjustments[a]
Ngoan *et al.* (2002)	Fukuoka study	>15	M	5711	73	10–13	139 390	FFQ, 25-item	Stomach cancer mortality (ICD-9 coded 151.2, 151.3, 151.4, 151.8, 151.9)	High to low (>2 *vs.* <2–4 per week)	0.9 (0.4, 1.8)	—
			F	7042	34						0.8 (0.3, 2.2)	
			M	5705	75			Tofu Miso soup		(≥a day *vs.* ≤2–4 times per month)	1.4 (0.7, 3.2)	
			F	7111	37						0.7 (0.2, 3.4)	
Ozasa *et al.* (2002)	Japan Collaborative Cohort Study (JACC)	40–79	M	42 940	336	7–9	265 971	FFQ, 32-item	Lung cancer mortality (ICD-10 code C34)	Almost every day *vs.* ≤1–2 week	0.83 (0.63, 1.08)	1, 33, 2, 34, 35
			F	55 308	91		358 590				0.85 (0.52, 1.37)	
Hirayama *et al.* (1990)	—	Not clear	M/F	265 118	Not reported	Not clear	Not clear	Tofu Soybean past soup	Colon	Non-daily *vs.* daily	1.13 (0.97, 1.32)	1, 10
									Rectum		1.04 (0.89, 1.21)	

[a] Adjustments were: 1 = age, 2 = smoking status, 3 = drinking status, 4 = education level, 5 = hypertension, 6 = presence of diabetes, 7 = high-density lipoprotein cholesterol, 8 = body mass index, 9 = menopause, 10 = sex, 11 = dialect, 12 = year of interview, 13 = physical activity, 14 = cigarettes per day, 15 = history of diabetes, 16 = history of hypertension, 17 = history of coronary disease, 18 = stroke, 19 = total energy intake, 20 = fiber intake, 21 = smoking duration, 22 = number of pregnancies, 23 = history of sex hormone, 24 = medication use for hypercholesterolemia, 25 = dietary intake of fruits, vegetables, salt, and fish, 26 = health status, 27 = health education, 28 = health screening, 29 = marital status, 30 = coffee intake, 31 = salt and rice, 32 = age at menarche, 33 = parents' history of lung cancer, 34 = smoking index, 35 = time since quitting smoking.

Table 2 The score for the risk of bias assessment in the included papers

Author name	Selection	Comparability	Outcome	Total score
Nagata *et al.* (2016)	4	2	3	**9**
Yamasaki *et al.* (2015)	3	2	3	**8**
Talaei *et al.* (2014)	4	2	2	**8**
Sakauchi *et al.* (2007)	4	2	3	**9**
Kokubo *et al.* (2007)	4	2	2	**8**
Iso *et al.* (2007)	3	1	2	**6**
Kurozawa *et al.* (2004)	3	1	2	**6**
Khan *et al.* (2004)	3	2	2	**7**
Nagata *et al.* (2002)	3	2	2	**7**
Nagata *et al.* (2002)	3	1	2	**7**
Ngoan *et al.* (2002)	3	1	3	**7**
Ozasa *et al.* (2002)	3	2	3	**8**
Hirayama *et al.* (1990)	2	1	2	**5**

the dietary isoflavone intake and the risk of all-cause mortality.[37] However, based on the study by Grosso *et al.*, there was an inverse association between the total flavonoid intake and all-cause mortality.[38] Differences in the findings can be related to different exposures. In our meta-analysis, soy productions and not their effective components were examined.

In addition, most studies on CVD have indicated the null effects of soy products on mortality from CVD.[21–23,27] However, the study by Nagata *et al.* revealed an inverse association between the natto intake and CVD mortality. They also reported that high consumption of total soy protein was not associated inversely with the risk.[23] The current meta-analysis reached similar findings. Nattokinase plays a main role in reducing thrombosis. Nattokinase is a potent anti-coagulant protein. This enzyme can reduce thrombosis and is used for the treatment of cardiovascular diseases. Throughout the fermentation of soybeans, nattokinase is generated by the bacterium *Bacillus subtilis* to produce natto.[39] Moreover, it was reported that supplementation with nattokinase can decrease blood pressure and may increase the markers of fibrinolysis and anticoagulation.[23]

Our findings on the effects of fermented soy products on CVD mortality can be partially interpreted based on this possible mechanism.

Similar to our findings, the previous study[5] showed that neither soy products nor isoflavone extracts are linked with the

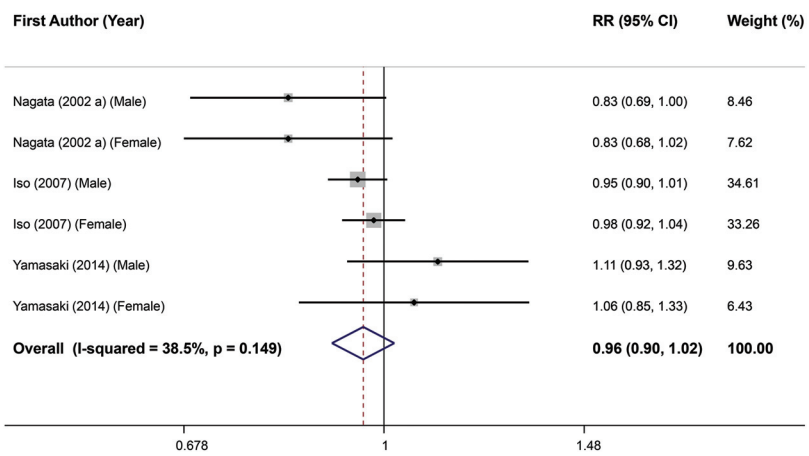

Fig. 2 Forest plot of the association between the soy intake and the risk of all-cause mortality.

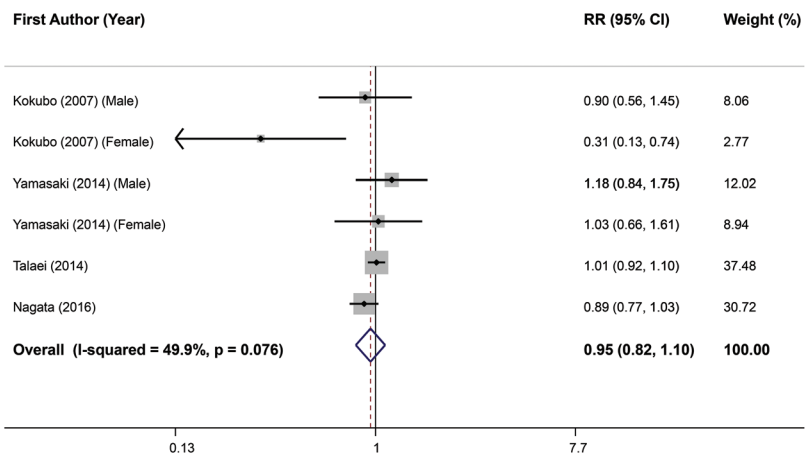

Fig. 3 Forest plot of the association between the soy intake and the risk of CVD mortality.

Table 3 Subgroup analysis for the association of soy intake with all-cause, CVD and cancer mortality

Outcome	No. effect size	Pooled effect size (95% CI)	I^2	Q test	$P_{between}$
All-cause mortality					
Gender					
Men	3	0.95 (0.90, 1.00)	59.3	0.08	0.62
Women	3	0.97 (0.92, 1.03)	32.8	0.22	
CVD mortality					
By the type of soy food					
Fermented	3	0.84 (0.73, 0.97)	0	0.99	—
Non-fermented	5	0.87 (0.62, 1.22)	59.1	0.04	
Energy adjustment					
Adjusted	3	0.93 (0.82, 1.06)	7.7	0.33	0.42
Non-adjusted	3	0.99 (0.91, 1.08)	72.2	0.02	
Gender					
Men	2	1.07 (0.80, 1.43)	0	0.37	0.52
Women	2	0.80 (0.54, 1.19)	82.8	0.01	
Both	2	0.96 (0.85, 1.08)	52.6	0.14	
Total cancer mortality					
By the type of soy food					
Fermented	3	0.97 (0.90, 1.05)	13.3	0.31	—
Non-fermented	4	1.23 (0.91, 1.66)	0	0.65	
Gender					
Men	4	1.00 (0.92, 1.09)	0	0.62	0.58
Women	4	0.96 (0.87, 1.07)	0	0.53	

risk factors of CVD. However, they reported that the soy protein isolate had substantial positive effects on diastolic blood pressure and the levels of low density lipoprotein cholesterol. Moreover, Mink *et al.* showed no association between the isoflavone intake and CVD mortality in a cohort study on postmenopausal women.[40] Kokubo *et al.* also revealed no association between the isoflavone intake and CVD mortality in Japanese women.[21] However, they found an inverse association between the isoflavone intake and the risk of cerebral and myocardial infarctions only in women.[21] Additionally, in the study by Talaei *et al.*, it was revealed that there was no significant association between the dietary isoflavone intake and the risk of mortality from CVD and stroke.[27] Our results contradicted a recent meta-analysis in which soy consumption was inversely associated with the risk of CVD (16%), stroke (18%), and coronary heart disease risk (17%).[12] However, some isoflavones are associated with a higher risk of mortality. Based on the National Health and Nutrition Examination Survey, higher urinary levels of total enterolignans were associated with a lower risk of mortality from CVD. However, there were positive associations between the higher urinary levels of total isoflavones and daidzein with CVD death.[41] Differences in the gender, individual characteristics and, types of soy products might explain the contradictory findings.

The present study indicated no association between soy and cancer mortality. However, Shu *et al.* showed an inverse association between the soy isoflavone intake and mortality from breast cancer.[42] Differences in the findings may be explained by the type of exposure (soy *vs.* isoflavone), the type of cancer, the amount of soy intake, dietary assessment methods used (FFQ and other questionnaires), the number of dietary items particularly soy products in dietary assessment tools, differences in the food composition tables among various societies, and the adjustments made for various confounding factors. Additionally, in the two aforementioned studies, the effects of isoflavones, the main component of soy, were examined, which might result in different findings.

The two meta-analyses reported the association between flavonoids and mortality.[37,38] Based on a meta-analysis, there was an inverse association between the high intake of total flavonoids and all-cause, and CVD mortality. Among the flavonoid classes, significant links were observed for the consumption of flavones, flavonols, anthocyanidins, flavanones, and proanthocyanidins.[38] Additionally, Kim *et al.* in a meta-analysis found a link between the dietary flavonoid intake and mortality from all-causes and CVD. They reported that all classes of flavonoids, except flavonols and isoflavones, indicated inverse associations.[37]

There are limited studies for the association of soy products and each type of cancer. Therefore, they were not included in

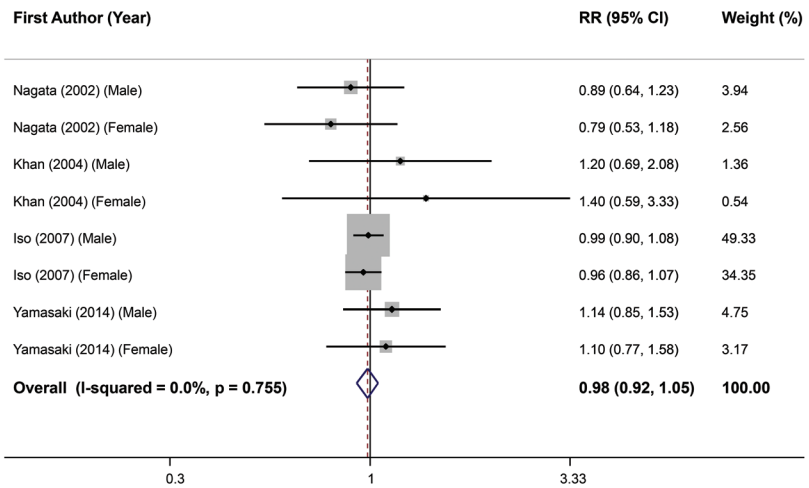

Fig. 4 Forest plot of the association between the soy intake and the risk of total cancer mortality.

the meta-analysis. It is not clear which component in fermented and non-fermented soy products is involved in mortality and, thus the mechanism remains uncertain.

Salt plays the main role in stomach cancer; however, two studies[15,25] on stomach cancer mortality did not adjust findings for this confounder. Therefore, this issue can affect the results. The potential protective influence of soy intake in some studies may be due to its components. Soy contains phytoestrogens known as isoflavones, vitamin E and fiber.[23] These components particularly isoflavones have indicated anti-proliferative, anti-oxidative, anti-inflammatory and anti-angiogenic properties.[16,17]

It is noticeable that all studies included in this meta-analysis were from Japan and China; no studies from Europe or the United States on the association between the soy intake and mortality have been published. One explanation is that soy intake is not common in other geographical locations; therefore, there are few studies that have examined the long-term effects of soy products on chronic diseases. Furthermore, there are wide variations in the amount and types of soy products consumed between East Asia and the Western countries. On the other hand, in Western countries the types of soy products (soy milk and energy bars) are different from those of Asians (miso, tofu, and natto).[23] It is worth noting that the dietary pattern and other cultural and social factors in Asian populations are widely different from those in Western populations. Therefore, the results of the studies on the Western countries are likely to be different.

Although all cohort studies except one were from Japan, a considerable heterogeneity was observed. Due to limited studies in each type of mortality, we could perform subgroup analysis for only a few parameters. Stratifications by gender and the type of soy food reduced the heterogeneity in total cancer mortality. However, it remained considerable in all-cause and CVD mortality. Limited numbers of studies, differences in the type and the amount of soy intake, and the genetic and participants' characteristics can be involved in the heterogeneity.

The differences in dietary assessment tools can also affect the results. All the included studies had used FFQs for dietary assessment. However, the number of food items were different across the studies. Some studies have used comprehensive FFQs, while others have applied short FFQs to assess dietary intake. For instance, in three studies[14,15,23] FFQs with the most dietary items (169 items) were used, while Ngoan *et al.* used a FFQ with only 25 items.[25] FFQs with more items can estimate energy intake more precisely than the short one and it can reduce the probability of bias. Accordingly, this parameter can partially involve in different results.

One important factor in the interpretation of the findings is the adjustment for covariates. Although dietary habits play the main role in the occurrence of diseases and mortality, only total energy intake was controlled in most studies. Due to insufficient studies for all-cause and total cancer mortality in each subgroup of energy adjustment, we could not compare its effects. However, we found no considerable differences in the association between the soy intake and CVD mortality in studies in which energy intake was adjusted or not.

Moreover, differences in the dietary assessment tools can affect the results. The qualitative and semi-quantitative FFQs reflects different findings on dietary intake. The included studies used the FFQ with various numbers of food items. Considering the FFQ with more semi-quantitative items in particular for soy products can clarify the association much better than a qualitative dietary questionnaire with less food items. Accordingly, this parameter can be involved in different results.

There were some limitations in the present study. Due to the limited studies for each type of soy product, we did not differentiate between soy foods. The subgroup analyses were done on a few studies, in which this issue limited the identification of effective parameters. In addition, due to limited studies, we could not conduct a dose–response analysis.

In conclusion, we found that a high intake of total soy foods was not associated with a lower risk of mortality from all causes, CVD, and cancer. Further cohort studies are needed to shed light on the association between the different types of soy food products and mortality in various societies.

Author contribution

The authors' responsibilities were as follows: B. L and A. E designed the research; N. N and A. E conducted systematic research; N. N and P. S extracted the data; N. N and P. S analyzed the data; N. N, P. S, B. L and A. E wrote the manuscript; B. L and A. E had the primary responsibility for the final content of the manuscript; and all authors read and approved the final manuscript.

Funding

There was no financial support.

Conflicts of interest

All authors declared no conflicts of interest.

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