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Soy and Isoflavone Consumption and Multiple Health Outcomes: Umbrella Review of Systematic Reviews and Meta-Analyses of Observational Studies and Randomized Trials in Humans

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Scope: To assess the existing evidence of associations between consumption of soy and isoflavone and multiple health outcomes.
Methods and results: This is an umbrella review of meta-analyses and systematic reviews of randomized trials and observational studies in humans. 114 Meta-analyses and systematic reviews are identified with 43 unique outcomes. Soy and isoflavone consumption seems more beneficial than harmful for a series of health outcomes. Beneficial associations are identified for cancers, cardiovascular disease, gynecological, metabolic, musculoskeletal, endocrine, neurological, and renal outcomes, particularly in perimenopausal women. Harmful association is only found for gastric cancer (RR: 1.17, 95% CI: 1.02–1.36) for high intake of miso soup (1–5 cups per day) in male.
Conclusion: Generally, soy and isoflavone consumption is more beneficial than harmful. The results herein support promoting soy intake as part of a healthy diet. Randomized controlled trials are necessary to confirm this finding.

1. Introduction

Soybean (*Glycine max*), which was first domesticated in the Northeastern China around 1100 B.C.,[1] is one of the most important crop plants for seed protein and oil content, and for its capacity to fix atmospheric nitrogen through symbioses with soil-borne microorganisms.[2] It is a rich source of bioactive compounds, some with potentially therapeutic antihyperlipidemic,[3] antihyperglycaemic,[4] antihypertensive,[5] antioxidant,[6] anti-inflammatory,[7] anticancer,[8] antiobesity,[9] and neuroprotective[10] activities that support the biological plausibility for observational associations. As key active compounds, isoflavones (genistein, daidzein, and glycitein) are changed in the body to phytoestrogens, which are bioactive compounds with mildly estrogenic properties.[11] Although processed soy food products (such as soy milk, tofu, miso, natto) have been an integral part of regular diets in Asia (e.g., China, Japan, and Korea) for centuries, the consumption of this food in the West is recent.[12] Evidence from clinical trials show that the consumption of soy protein decreases serum cholesterol concentrations in humans.[13] Accordingly, the U.S. Food and Drug Administration (FDA) authorized the use on food labels of health claims associated with soy protein and the reduced risk of coronary heart disease by lowering blood cholesterol levels.[14]

Recent epidemiological studies have explored the associations between consumption of soy and isoflavone and a wide series of outcomes (including mortality, cancers, cardiovascular disease, gynecological, metabolic, musculoskeletal, endocrine, neurological, and renal outcomes).[15] Most of these studies were not interventional in design, dependent on evidence from cohort, case-control or cross-sectional studies and frequently generalized by outcome through meta-analysis and systematic review. There have been conflicting conclusions if soy and isoflavone consumption is good or damaging to health, and the roles of soy and isoflavone were different among various health outcomes.[16] Newly discovered associations often have inflated effects compared with the true effects.[17] Inherent biases in study, for example, reporting bias and residual confounding may overinflate the magnitudes of the observed effects.[17] Both randomized controlled trials (RCTs) and observational studies have strengths and weaknesses, and including information from observational studies, may improve the inference based on only RCTs.[18]

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To provide a summary of the breadth and validity of the potential causal associations of soy and isoflavone with multiple various health outcomes, we did this umbrella review of the evidence from meta-analyses and systematic reviews of randomized trials and observational studies in humans. This method could assist evaluate the existing evidence for any benefit or harm that can be associated to increased intake of soy and isoflavone and provide decision makers with evidence about this subject.[19]

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2. Experimental Section

2.1. Umbrella Review Methods

Umbrella reviews give a ready way for decision makers in healthcare to achieve a clear understanding of a broad topic field, which assemble together multiple meta-analyses and systematic reviews on the same condition. Integration of evidence from many meta-analyses and systematic reviews may be extended across many diseases.[20,21]

2.2. Literature Search

Cochrane Database of Systematic Reviews, Medline, Embase, and Web of Science were searched from the inception to January 2019 for meta-analyses and systematic reviews that study the correlation between consumption of soy and isoflavone and multiple outcomes in humans. The following search strategy was used: (soy or isoflavone) AND (meta-analysis or systematic review), by truncated terms in all fields. References from each eligible articles were also checked. Discussions were used to resolve potential discrepancies.

2.3. Eligibility Criteria

Studies were eligible for the umbrella review: meta-analyses and/or systematic reviews of randomized trials or observational studies evaluating dietary or supplementary soy or isoflavone in humans. Participants may be healthy or having preexisting illness, male or female, or perimenopausal. Articles were excluded if published in a language other than English, included animal studies, or laboratory researches. Studies that assessed the exposure to phytoestrogen were also excluded. If an article gave different meta-analyses for two or more suitable outcomes or type of clinical setting, each of them were included separately. When two or more meta-analyses and/or systematic reviews were published within 2 years, the one including the most studies was selected. The final tier was a higher AMSTAR score. Any articles with comparisons of soy or isoflavone consumption were included, including any versus none, high versus low, and any dose responses. Appraisal of individual component studies was over the range of this umbrella review.

2.4. Data Extraction

Two authors (Li and Zhou) independently extracted data separately from eligible articles. From each eligible meta-analyses and/or systematic reviews, data were extracted on journal, population, publication year, the first author, and outcome examined. The soy type, units of soy or isoflavone, number of total participants, number of cases, number of control, number of each type of study (RCTs, case-control, cohort, cross-sectional) were also abstracted. Moreover, the estimated summary effect was extracted (RR, relative risk; OR, odds ratio; SMD, standardized mean difference; WMD, weighted mean difference; ME, mean estimate; MD, mean difference; ES, effect size), along with the 95% confidence intervals (CIs). Finally, Egger's test, the type of effect model, and dose-response analyses were extracted. Any discrepancies were resolved by discussion about the extracted data.

2.5. Evaluation of the Methodological Quality and Grading of Evidence

The eleven items Assessment of Multiple Systematic Reviews (AMSTAR) checklist[22] was used to assess reporting and methodological quality of systematic reviews and meta-analyses. The grading of recommendations, assessment, development, and evaluation (GRADE)[23] is a method of assessing the certainty in evidence and the strength of recommendations in health care.

2.6. Data Analysis

The estimated summary effect along with the 95% CI were extracted from every eligible meta-analysis and systematic review. Cochran's q-test and the I^2 statistic was used to assess the heterogeneity between studies. Egger's test was used to calculate the publication bias, in which a p-value less than 0.10 was considered significant. If dose-response meta-analyses were not available, no reanalysis was done since the primary articles were not checked.

3. Results

3.1. Characteristics of Studies

As shown in **Figure 1**, the search strategy found 949 articles, after following the selection process, 114 meta-analyses and

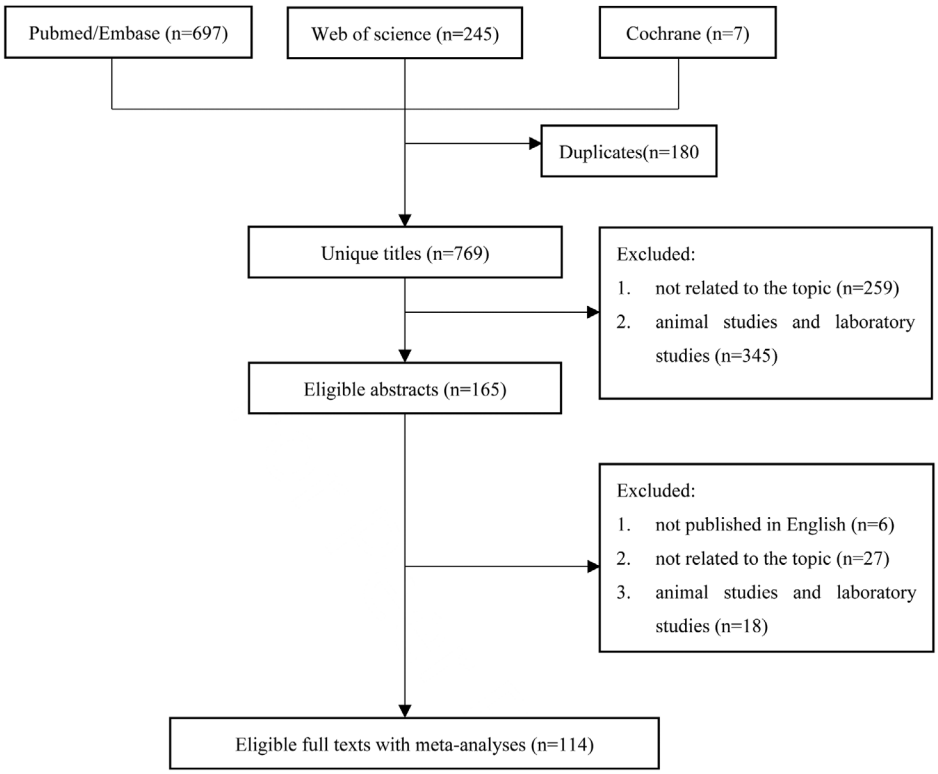

Figure 1. Flowchart of the selection process.

systematic reviews of randomized trials and observational studies with 43 unique health outcomes (**Figure 2**). A wide range of outcomes were present: cancer (n = 35), cardiovascular disease (CVD) (n = 28), gynecological outcomes (n = 18), musculoskeletal outcomes (n = 12), metabolic disease (n = 11), endocrine outcomes (n = 4), neurological outcomes (n = 3), renal outcomes (n = 2), and mortality (n = 1) (Figure 2). The association between soy and isoflavone consumption and cancer outcomes are presented in **Table 1**. **Table 2** presents the associations between consumption of soy and isoflavone and mortality and CVD. The associations between soy and isoflavone consumption and gynecological, metabolic, musculoskeletal, endocrine, neurological, and renal outcomes are presented in **Table 3**. **Table 4** presents the assessments of AMSTAR scores and GRADE classification.

3.2. Mortality

No association was found between soy consumption and risk of mortality from all-causes, CVD, and cancer.[24] When analyzed the data separately with fermented and non-fermented soy products, a significant inverse association was found between the consumption of fermented soy products (miso and natto) and CVD mortality (0.84; 95% CI: 0.73, 0.97).[24]

3.3. Cancer

High intake of soy was related to a reduced cancer risk of ovarian,[25] prostate,[26] gastric,[27] colorectal,[28] lung,[29] and breast.[30] Considering the different types of soy, high consumption of non-fermented soy (tofu, soy protein, and soy milk) was related to a reduced risk of gastric cancer.[27] Isoflavone intake was related to a lower risk of colorectal[28] and endometrial cancer.[31]

Conversely high consumption of miso soup was associated with gastric cancer risk in male (the highest versus the lowest category: RR: 1.17, 95% CI: 1.02–1.36). In dose-response meta-analysis,[27] in male, the RRs (95% CI) for 1, 3, and 5 cups per day intake of miso soup were 1.14 (1.00–1.29), 1.29 (1.06–1.56), and 1.31 (1.06–1.62), respectively. Thus, in male, miso soup intake (1–5 cups per day) was significantly associated with gastric cancer risk.[27]

There was no relationship of high intake of isoflavones with gastric cancer[32] and breast cancer.[30]

3.4. Cardiovascular Disease

Soy consumption was inversely associated with the risk of CVD, stroke, and coronary heart disease risk.[33] However, there were no associations between isoflavones consumption and risk of CVD, stroke, and coronary heart disease.[33] A Bayesian meta-analysis of RCTs indicates that exposure to isoflavones can modestly, but significantly, improve endothelial function as measured by flow-mediated dilation.[34] In addition, soy protein intake more than 25 g per day or isoflavone intake more than 100 mg per day has blood pressure-lowering effects in postmenopausal women.[35] Moreover, soy proteins exert beneficial effects on the serum lipid profile (LDL-cholesterol, HDL-cholesterol, triglyceride and total cholesterol),[36] and the effect was stronger in hypercholesterolaemic subjects.[36] Whereas

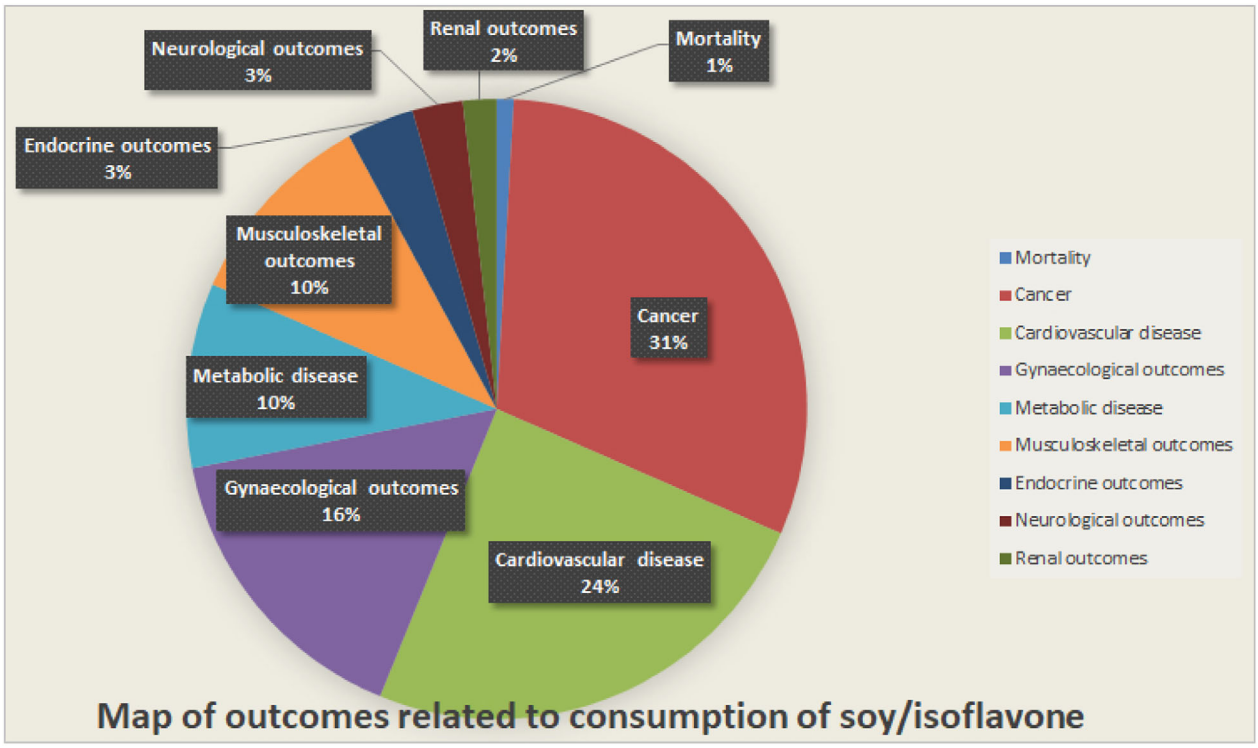

Figure 2. Map of outcomes related to consumption of soy and isoflavone.

isoflavone supplementation had no effects on the lipid profile[36] or plasma lipoprotein(a) concentrations.[37]

3.5. Gynecological Outcomes

Soybean isoflavones significantly reduced menopausal hot flash frequency and severity in perimenopausal and postmenopausal women,[38] but it showed slight and slow effects in attenuating menopausal hot flashes compared with estradiol.[39] A daily dose of more than 54 mg isoflavone could decrease the endometrial thickness for 0.26 mm.[40] It may also improve subjective symptoms and objective signs of vaginal atrophy in menopause.[41] Besides, isoflavone intake may cause a small increase in breast density in premenopausal women.[42]

3.6. Metabolic Outcomes

Soy products and isoflavones may reduce risk of type 2 diabetes mellitus (T2DM)[43] and BMI in obese subjects.[44] There seems to be beneficial associations between soy protein supplementation and clinical indices in T2DM and metabolic syndrome.[45] Soy isoflavones also played an important role in improving glucose metabolism in menopausal women.[46]

3.7. Musculoskeletal Outcomes

No association was found between isoflavones consumption and risk of osteoporotic vertebral fracture in postmenopausal women.[47] However, isoflavone treatments exert a moderately beneficial effect against estrogen-deficient bone loss in women.[48] It also moderately decreased the bone resorption marker deoxypyridinoline, but did not affect bone formation markers bone alkaline phosphatase and osteocalcin in menopausal women.[49]

3.8. Endocrine Outcomes

Isoflavone-rich soy products decrease follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in premenopausal women and may increase estradiol in postmenopausal women.[50] Neither soy foods nor isoflavone supplements alter measures of reproductive hormones in men.[51] No effect was found on the thyroid hormones and only very modestly raises thyroid stimulating hormone (TSH) levels, the clinical significance, if any, of the rise in TSH is unclear.[52]

3.9. Neurological Outcomes

Soy isoflavone supplementation seems to have a positive effect on improving summary cognitive function and visual memory in postmenopausal women.[53] Greater benefits were seen in women who are less than 10 years postmenopause and supplemented for less than 6 months.[54] The dose and duration efficacy was found to be 60–116 mg per day for at least 12 weeks.[54] Soy was also found to have a beneficial effect on depression and anxiety in menopausal women.[55]

Table 1. Associations between soy and isoflavone consumption and cancer outcomes.

Outcome	Category	Study	No. of cases/total	MA metric	Estimates	95% CI	No. of studies in MA	Cohort	Case control	Effects model	I^2 [%]	Egger test *p*-value
Significant associations												
Ovarian cancer	Soy	[25]	1912/163 879	OR[a)]	0.52	0.42–0.66	4	2	2	Fixed	0.0	NA
Gastric cancer	NFS	[27]	1022/80 573	RR[a)]	0.63	0.50–0.79	4	4	0	Random	0.0	0.72
Prostate cancer	Soy	[26]	21 612/266 699	RR[b)]	0.71	0.58–0.85	30	8	22	Random	68.9	0.05
Colorectal cancer	Iso	[28]	6609/148 210	RR[a)]	0.76	0.69–0.83	8	4	4	Fixed	0	NA
Gastric cancer	Soy	[27]	5800/517 106	RR[a)]	0.78	0.62–0.98	7	7	0	Random	47.5	0.11
Colorectal cancer	Soy	[28]	7659/266 895	RR[a)]	0.79	0.69–0.89	14	4	10	Random	46.2	NA
Endometrial cancer	Iso	[31]	7067/178 947	OR[a)]	0.81	0.74–0.89	13	3	10	Fixed	11.7	0.14
Lung cancer	Soy	[29]	6811/231 494	OR[a)]	0.83	0.72–0.96	11	4	7	NA	NA	0.10
Breast cancer	Soy	[30]	8041/409 970	RR[a)]	0.87	0.76–1.00	6	6	0	Fixed	0.0	NA
Gastric cancer	MS	[27]	1484/72 083	RR[a)]	1.17	1.02–1.36	4	4	0	Random	0.0	0.18
Non-significant associations												
Breast cancer	Iso	[30]	11 169/648 913	RR[a)]	0.99	0.91–1.09	11	11	0	Fixed	27.0	0.08
Gastric cancer	Iso	[32]	3873/596 553	OR[a)]	0.97	0.87–1.09	12	6	6	Fixed	27.5	NA

MA, meta-analysis; CI, confidence interval; Iso, isoflavones; NFS, nonfermented soy; MS, miso soup; RR, relative risk; OR, odds ratio; NA, not available.[a)]highest versus lowest/none; [b)]any versus none.

3.10. Renal Outcomes

Soy protein containing isoflavones intake was associated with a lower risk of chronic kidney disease.[56] It also could maintain the nutritional status in dialysis patients, though no significant change in C reactive protein, blood urea nitrogen, and serum phosphorus was detected.[56]

3.11. Side Effects

Gastrointestinal complaints were commonly reported side effects in participants taking any source of soy and/or isoflavones, and meta-analysis of studies reporting dropouts due to gastrointestinal problems did not suggest a statistically significant difference between intervention and control arms.[42,50]

3.12. Heterogeneity

Approximately, 40% of the meta-analyses presented moderate-to-high (I^2 25–75%) heterogeneity; 32% had low heterogeneity, with $I^2 < 25\%$; and 23% had very high heterogeneity, with $I^2 > 75\%$. The remaining 5% of the included articles did not give the heterogeneity of the meta-analyses and could not be reanalyzed.

3.13. Publication Bias

Evidence for small-study effects was evaluated by use of the Egger's test. Of the 114 meta-analyses and systematic reviews, three articles showed statistical evidence for publication bias including CVD, stroke, and T2DM. Meta-analyses on prostate cancer showed borderline significant ($p = 0.05$) publication bias. The remaining 110 articles did not give significant publication bias.

3.14. AMSTAR and GRADE Classification

Table 4 presented the assessments of AMSTAR and GRADE classification. The median AMSTAR score was 8 out of 11 (range 6–10, interquartile range 7–9). Evaluating the quality of evidence, about 16% of the articles were ranked as "very low," 24% as "low," 33% as "moderate," and 27% as "high."

4. Discussion

4.1. Main Findings and Interpretation

We identified 114 meta-analyses and systematic reviews of randomized trials and observational studies with 43 unique health outcomes in our umbrella review to assess the existing evidence for associations between consumption of soy and isoflavone and multiple health outcomes. We also compiled these evidences and came to a conclusion on the overall effects of soy and isoflavone intake on health: In general, soy and isoflavone intake seems more beneficial than harmful.

Soy consumption and CVD was one of the most noticeable associations found in this review. Soy consumption could significantly decrease the risk of CVD, stroke, and coronary heart disease risk. More than 100 years ago, Alexander I. Ignatowski published his pioneering work that the cholesterol-lowering effects of soy protein as compared with animal protein have been recognized in rabbits.[57,58] On this issue, the first meta-analysis by Anderson et al. found that the consumption of soy protein rather than animal protein significantly decreased serum

Table 2. Associations between soy and isoflavone consumption and mortality and cardiovascular disease.

Outcome	Category	Study	No. of cases/total	MA metric	Estimates	95% CI	No. of studies in MA	Cohort	Case control	RCT	Effects model	I^2 [%]	Egger test *p*-value
Mortality													
Significant associations													
CVD mortality	FS	[24]	1910/69 529	RR[a)]	0.84	0.73–0.97	3	3	0	0	Random	0.0	NA
Non-significant associations													
All-causes mortality	Soy	[24]	18 992/141 335	RR[b)]	0.96	0.90–1.02	3	3	0	0	Random	38.5	0.86
CVD mortality	Soy	[24]	6028/140 893	RR[b)]	0.95	0.82–1.10	4	4	0	0	Random	49.9	0.40
Cancer mortality	Soy	[24]	12 802/144 490	RR[b)]	0.98	0.92–1.05	4	4	0	0	Random	0.0	0.46
Cardiovascular outcomes													
Significant associations													
CVD	Soy	[33]	17 269/492 676	RR[b)]	0.83	0.75–0.93	17	10	7	0	Random	71.4	0.02
Stroke	Soy	[33]	6265/373 928	RR[b)]	0.82	0.68–0.99	11	7	4	0	Random	78.8	0.01
Coronary heart disease	Soy	[33]	10 806/441 140	RR[b)]	0.83	0.72–0.95	12	8	4	0	Random	64.6	0.30
Endothelial function	Iso	[34]	1281[#]	ME[c)]	1.98%	0.07–3.97	17	0	0	17	Bayesian	NA	NA
Systolic blood pressure	Soy	[35]	1551[#]	WMD[d)]	−4.62 mmHg	−8.42, −0.81	12	0	0	12	Random	69.2	0.51
Diastolic blood pressure	Soy	[35]	1551[#]	WMD[d)]	−1.63 mmHg	−2.85, −0.41	12	0	0	12	Random	25.1	0.17
Systolic blood pressure	Iso	[35]	1551[#]	WMD[e)]	−5.47 mmHg	−8.42, −2.51	12	0	0	12	Random	54.5	0.51
Diastolic blood pressure	Iso	[35]	1551[#]	WMD[e)]	−2.03 mmHg	−3.35, −0.72	12	0	0	12	Random	0.0	0.17
LDL cholesterol	Soy	[36]	1687/1679*	WMD[c)]	−4.83 mg dL^{-1}	−7.34, −2.31	35	0	0	35	Random	97.0	NA
HDL cholesterol	Soy	[36]	1659/1651*	WMD[c)]	1.40 mg dL^{-1}	0.58, 2.23	35	0	0	35	Random	95.0	NA
TC	Soy	[36]	1630/1617*	WMD[c)]	−5.33 mg dL^{-1}	−8.35, −2.30	35	0	0	35	Random	99.0	NA
TAG	Soy	[36]	1502/1496*	WMD[c)]	−4.92 mg dL^{-1}	−7.79, −2.04	35	0	0	35	Random	92.0	NA
Plasma lipoprotein(a)	Iso	[37]	489/484*	SMD[c)]	0.08	−0.05, 0.20	10	0	0	10	Random	0.0	0.63
Non-significant associations													
CVD	Iso	[33]	10 766/375 830	RR[b)]	0.98	0.88–1.10	8	8	0	0	Random	63.3	NA
Stroke	Iso	[33]	6184/319 674	RR[b)]	1.00	0.81–1.23	6	6	0	0	Random	76.0	NA
Coronary heart disease	Iso	[33]	6669/308 998	RR[b)]	0.96	0.86–1.07	7	7	0	0	Random	27.1	NA
Endothelial function	Soy	[34]	1281[#]	ME[c)]	0.72%	−1.39, 2.90	17	0	0	17	Bayesian	NA	NA

MA, meta-analysis; CI, confidence interval; RCT, randomized controlled trial; FS, fermented soy; Iso, isoflavones; RR, relative risk; OR, odds ratio; SMD, standardized mean difference; WMD, weighted mean difference; ME, mean estimate; NA, not available; CVD, cardiovascular disease; TAG, triglyceride; TC, total cholesterol. [a)] not available; [b)] highest versus lowest/none; [c)] any versus none; [d)] 25 g per day versus none; [e)] 100 mg per day versus none. *cases/control; [#] participants.

concentrations of total cholesterol, LDL cholesterol, and triglycerides without significantly affecting serum HDL cholesterol concentrations.[13] Accordingly, the FDA approved a food-labeling health claim for soy protein (25 g per day) for prevention of coronary heart disease in 1999.[14] Later, in 2006, the American Heart Association (AHA) reported a modest effect of soy foods on LDL cholesterol: a reduction by approximately 3%, and stated that the benefit was very small relative to the large amount of soy protein tested, which averaged 50 g per day, about half the usual total daily protein intake.[59] Recently, a meta-analysis of 46 studies identified by the FDA demonstrates that soy protein decreases circulating LDL, by approximately 3–4%, and total cholesterol concentrations in adults.[60] The mechanism responsible for the plasma cholesterol reduction remains an open question.[61] One mechanism of action of the intrinsic cholesterol-lowering effect of soy protein has been proposed to relate to the peptides formed from the digestion of soy protein upregulate hepatic LDL receptors.[61,62] Another mechanism is that soy foods potentially reduce cholesterol via substitution or replacement effects.[63] In addition, subgroup analysis according to locations showed a significant inverse relationship of soy intake in Asians but not in Westerners. These findings may be partly explained by the much higher intake of soy in Asians[64,65] and much lower prevalence of S-equol producers in Westerners[66]: only 20–30% of Westerners produce S-equol in contrast to 50–70% in Asians.[66] S-equol is a metabolite of dietary soy isoflavone daidzein by gut microbiome and possesses the most antiatherogenic properties among all isoflavones.[67,68] However, it is worth noting that isoflavones failed to show their benefit neither of CVD, stroke or coronary heart disease nor of the lipid profile in the umbrella review. The discrepancy may be due to other components,[69] such as high content of polyunsaturated fats,[70] fiber,[71] vitamins,[72] and minerals[73] and low content of saturated fat,[74] in the soy foods.[59]

Beneficial associations were identified between soy intake and diverse cancers: ovarian cancer,[25] prostate cancer,[26] gastric cancer,[27] colorectal cancer,[28] lung cancer,[29] and breast cancer,[30] and between isoflavone consumption and colorectal cancer[28] and endometrial cancer.[31] Interestingly, in most observational studies, cancer risk reduction was more frequently

Table 3. Associations between soy and isoflavone consumption and gynecological, metabolic, musculoskeletal, endocrine, neurological, and renal outcomes.

Outcome	Category	Study	No. of cases/control	MA metric	Estimates	95% CI	No. of studies in MA	Cohort	Case control	RCT	Effects model	I^2 [%]	Egger test *p*-value
Significant associations													
Hot flash frequency	Iso	[38]	602/594	MD[a)]	20.6%	−28.38, −12.86	13	0	0	13	Random	67	0.23
Hot flash severity	Iso	[38]	538/450	MD[a)]	26.2%	−42.23, −10.15	9	0	0	9	Random	86.0	0.49
Endometrial thickness	Iso	[40]	494/490	SMD[b)]	−0.26	−0.45, −0.07	10	0	0	10	Random	47.0	0.62
Maturation value	Iso	[41]	262/232	SMD[a)]	0.072	−0.42, 0.57	7	0	0	7	Random	85.2	0.06
Vaginal dryness	Iso	[41]	262/232	SMD[a)]	−0.204	−0.28, −0.13	7	0	0	7	Random	0.0	0.06
Breast density	Iso	[42]	257/262	MD[a)]	1.83%	0.25–3.40	5	0	0	5	Random	0.0	NA
T2DM	Soy	[43]	7589/335 230*	RR[c)]	0.77	0.66–0.91	19	14	5[#]	0	Random	91.6	0.03
Body weight	Soy	[44]	325/325	MD[a)]	0.80	0.15–1.45	8	0	0	8	Random	38.7	NA
Bone mineral density	Iso	[48]	1413/1357	WMD[a)]	0.01	0.01–0.02	26	0	0	26	Random	90.0	NA
Deoxypyridinoline	Iso	[49]	457/430	WMD[c)]	−18.01%	−28.39, −7.64	10	0	0	10	Random	73.0	0.58
BAP	Iso	[49]	622/588	WMD[a)]	8.01%	−4.15, 20.18	10	0	0	10	Random	98.0	0.60
Osteocalcin	Iso	[49]	201/179	WMD[a)]	10.33%	−3.07, 23.73	8	0	0	8	Random	69.0	0.36
FSH	Iso	[50]	68/73	SMD[a)]	−0.45	−0.79, −0.11	7	0	0	7	Random	0	NA
LH	Iso	[50]	69/73	SMD[a)]	−0.34	−0.68, −0.01	7	0	0	7	Random	0	NA
TSH	Soy	[52]	NA	WMD[a)]	0.248	0.001, 0.494	18	0	0	18	Random	80.3	0.07
Cognitive function	Iso	[53]	515/509	SMD[a)]	0.08	0.02–0.15	10	0	0	10	Random	61.3	NA
Visual memory	Iso	[53]	515/509	SMD[a)]	0.10	0.02–0.18	10	0	0	10	Random	2.0	NA
Serum creatinine	Soy	[56]	74/75	MD[a)]	−0.05	−0.10, −0.00	6	0	0	6	Fixed	7.0	NA
Non-significant associations													
Vertebral fracture	Iso	[47]	193/223	OR[a)]	0.44	0.12–1.63	3	0	0	3	Random	69.2	NA
Testosterone	Soy/iso	[51]	346/339	ES[a)]	0.05	−0.06, 0.15	15	0	15	0	Random	14.6	NA
Free triiodothyronin	Soy	[52]	NA	WMD[d)]	0.027	−0.052, 0.107	18	0	0	18	Random	55.6	0.37
Free thyroxine	Soy	[52]	NA	WMD[d)]	−0.003	−0.018, 0.011	18	0	0	18	Random	87.6	0.22

MA, meta-analysis; CI, confidence interval; RCT, randomized controlled trial; Iso, isoflavones; OR, odds ratio; RR, relative risk; MD, mean difference; SMD, standard mean differences; WMD, weighted mean difference; ES, effect size; NA, not available; T2DM, type 2 diabetes mellitus; BAP, bone alkaline phosphatase; TSH, thyroid stimulating hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.[a)] any versus none; [b)] more than 54 mg versus none; [c)] highest versus lowest/none; [d)] not available. [#] Cross-sectional; *cases/participants.

found with soy but not isoflavone consumption.[75–78] However, debates remain about these beneficial associations from observational epidemiologic studies. Two small RCTs supported the value of soy/isoflavone for prostate cancer risk reduction.[79,80] Whereas, a phase III double-blind RCT including 303 men in 12 Canadian centers for 3 years does not support the hypothesis that combinations of vitamin E, selenium, and soy prevent progression from high-grade prostatic intraepithelial neoplasia to prostate cancer.[81] In addition, a double-blind RCT including 177 men at seven U.S. centers for up to 2 years found that soy protein consumption following radical prostatectomy did not reduce biochemical recurrence of prostate cancer at high risk of prostate-specific antigen failure.[82] Furthermore, a phase IIB double-blind RCT including 126 women at two U.S. centers found a 6-month intervention of mixed soy isoflavones in healthy, high-risk adult Western women did not reduce breast epithelial proliferation, suggesting a lack of efficacy for breast cancer prevention and a possible adverse effect in premenopausal women.[83] Recently, a double-blind RCT including 350 postmenopausal women in U.S. center found that 3-year isoflavone soy protein supplementation has no effect on endometrial thickness or on the rates of endometrial hyperplasia and cancer in postmenopausal women.[84] Finally, a prospective study in Takayama, Japan including 13 894 men and 16 327 women exhibited the weak benefit of soy foods only among women.[85] The following mechanisms of anticancer have been proposed: 1) high plasma isoflavones levels may inhibit the growth of cancer[86–88]; 2) soy supplementation alters cancer-related gene expression[89]; 3) soy isoflavones may contend with endogenous estrogens in binding to ERs and may regulate estrogen levels through increasing clearance and lowering bioavailability[90,91]; 4) soybean protein have the antioxidant and antiproliferative activities[92]; 5) soy isoflavones can regulate multiple signaling pathways included in neoplastic transformation.[93–95]

High intake of miso soup (1–5 cups per day) in male might increase the risk of gastric cancer.[27] As one kind of fermented soy food, miso soup is the most basic soup in Japan, the concentration of salt in miso soup is 0.5–1.2%.[96] In 2004, Tsugane and colleagues conducted a population-based prospective study of 18 684 men and 20 381 women aged 40–59 years in Japan, they found

Table 4. Assessments of AMSTAR scores and GRADE classification.

Outcome	Category	Work/reference	AMSTAR	GRADE
Mortality				
All-causes mortality	Soy	[24]	9.0	Low
CVD mortality	Fermented Soy	[24]	9.0	Low
CVD mortality	Soy	[24]	9.0	Low
Cancer mortality	Soy	[24]	9.0	Low
Cancer outcomes				
Ovarian cancer	Soy	[25]	8.5	Low
Gastric cancer	Nonfermented soy	[27]	9.5	Moderate
Gastric cancer	Soy	[27]	9.5	Moderate
Gastric cancer	Miso soup	[27]	9.5	Moderate
Gastric cancer	Isoflavones	[32]	8	Low
Prostate cancer	Soy	[26]	9.5	Very low
Colorectal cancer	Isoflavones	[28]	6.0	Low
Colorectal cancer	Soy	[28]	6.0	Low
Endometrial cancer	Isoflavones	[31]	7.0	Low
Lung cancer	Soy	[29]	6.0	Very low
Breast cancer	Soy	[30]	9.0	Low
Breast cancer	Isoflavones	[30]	9.0	Low
Cardiovascular outcomes				
CVD	Soy	[33]	8.5	Very low
CVD	Isoflavones	[33]	8.5	Very low
Coronary heart disease	Soy	[33]	8.5	Very low
Coronary heart disease	Isoflavones	[33]	8.5	Very low
Stroke	Soy	[33]	8.5	Very low
Stroke	Isoflavones	[33]	8.5	Very low
Endothelial function	Isoflavones	[34]	7.0	High
Endothelial function	Soy	[34]	7.0	High
Systolic blood pressure	Soy	[35]	6.0	High
Systolic blood pressure	Isoflavones	[35]	6.0	High
Diastolic blood pressure	Soy	[35]	6.0	High
Diastolic blood pressure	Isoflavones	[35]	6.0	High
LDL cholesterol	Soy	[36]	8.0	Moderate
HDL cholesterol	Soy	[36]	8.0	Moderate
Total cholesterol	Soy	[36]	8.0	Moderate
Triglyceride	Soy	[36]	8.0	Moderate
Plasma lipoprotein(a)	Isoflavones	[37]	9.0	High
Gynecological outcomes				
Hot flash frequency	Isoflavones	[38]	9.0	High
Hot flash severity	Isoflavones	[38]	9.0	High
Endometrial thickness	Isoflavones	[40]	8.0	Moderate
Maturation value	Isoflavones	[41]	7.0	Moderate
Vaginal dryness	Isoflavones	[41]	7.0	Moderate
Breast density	Isoflavones	[42]	8.5	Moderate
Metabolic outcomes				
T2DM	Soy	[43]	9.0	Very low
Body weight	Soy	[44]	7.5	Moderate
Musculoskeletal outcomes				
Vertebral fracture	Isoflavones	[47]	6.5	Low
Bone mineral density	Isoflavones	[48]	9.5	High

(*Continued*)

Table 4. Continued.

Outcome	Category	Work/reference	AMSTAR	GRADE
Deoxypyridinoline	Isoflavones	[49]	10	High
BAP	Isoflavones	[49]	10	High
Osteocalcin	Isoflavones	[49]	10	High
Endocrine outcomes				
FSH	Isoflavones	[50]	8.0	Moderate
LH	Isoflavones	[50]	8.0	Moderate
TSH	Soy	[52]	8.0	Moderate
Testosterone	Soy/isoflavones	[51]	8.5	Low
Free triiodothyronin	Soy	[52]	8.0	Moderate
Free thyroxine	Soy	[52]	8.0	Moderate
Neurological outcome				
Cognitive function	Isoflavones	[53]	8.5	High
Visual memory	Isoflavones	[53]	8.5	High
Renal outcome				
Serum creatinine	Soy	[56]	7.5	Moderate

AMSTAR, a measurement tool to assess systematic reviews; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus; BAP, bone alkaline phosphatase; TSH, thyroid stimulating hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

a dose-dependent increased risks of gastric cancer with the intake of highly salted foods, for example, pickled vegetables, miso soup, and dried or salted fish in men.[96] Accordingly, in Japan, reducing the consumption of miso soup is recommended in order to decrease dietary salt intake.[97] The mechanism by which miso soup can cause gastric cancer has been discussed in previous studies. Early in 1994, a cross-sectional analysis in an ecological study found that the consumption of both miso soup and pickled vegetable was associated with *Helicobacter pylori* infection,[98] which is considered to play an etiologic role in atrophic gastritis, duodenal ulcer, and gastric cancer. In addition, salt intake is known to cause gastritis, and it enhances the carcinogenic effects of known gastric carcinogens, for example, *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (MNNG) when coadministered in experimental studies with rats.[99,100] Furthermore, It has been suggested that salt intake is strongly associated with intestinal metaplasia and potentiates the effects of carcinogens.[101]

Soy and isoflavone consumption was more often associated with benefit especially in perimenopausal women. Estrogen deficiency in the postmenopausal woman results in numerous symptomatic and asymptomatic manifestations, including vasomotor symptoms, osteoporosis, heart disease, bladder, and vaginal symptoms, and CVD.[102] Postmenopausal estrogen therapy has been posited to have some beneficial effects on aging processes, but its use has risks.[103,104] Since soy contains isoflavones (genistein, daidzein, and glycitein) which are changed in the body to phytoestrogens, which are bioactive compounds with mildly estrogenic properties,[11] it has been widely used in the United States in perimenopausal women. However, even though isoflavones are categorized as phytoestrogens, due to their preferential binding to and transactivation of estrogen receptor beta in contrast with estrogen receptor alpha, they are also categorized as selective estrogen receptor modulators,[105] which means isoflavones exert estrogen-like effects in some but not all estrogen-sensitive tissues.[106,107] Meta-analysis revealed that soybean isoflavones statistically significantly reduced the frequency and severity of hot flashes by 20.6% ($p < 0.00001$) and 26.2% ($p = 0.001$), respectively, compared with placebo.[38] However, a time interval of 13.4 weeks was required for soy isoflavones to gain half of its maximal effects, much longer than estradiol, which only needed 3.09 weeks.[39] Accordingly, treatment intervals of 12 weeks are not long enough for soy isoflavones, which need at least 48 weeks to gain 80% of their maximum effects.[39] As a result, soy isoflavones present slight and slow effects in reducing menopausal hot flashes contrasted with estradiol.[39]

Reported adverse events and gastrointestinal complaints were predominantly mild.[42,50] Early in 1960, a case report of probable gastrointestinal reaction to soybean milk in an infant, who had a family history of allergy, published in the *New England Journal of Medicine*.[108] Later, the allergen is identified.[109] Recently, a systematic review of 43 human studies and 62 animal studies by the European Food Safety Authority concluded that no harmful effect of isoflavones from food supplements has been observed on mammary gland, uterus, and thyroid in peri- and postmenopausal women.[110]

4.2. Strengths and Limitations

This umbrella review systematically collects and evaluates information from multiple meta-analyses and systematic reviews on all clinical outcomes for soy and isoflavone consumption.[111] In addition, we systematic search four scientific databases by a strong search strategy with eligible criteria and data extraction by two authors. Besides, we analyzed the extent of publication bias and heterogeneity. Furthermore, the quality of included systematic reviews was evaluated by AMSTAR,[22] and the categorization of the evidence was assessed by GRADE[23] classification. However, there are also some limitations that need to be discussed as well. First, this umbrella review depended on published

systematic reviews and meta-analyses. As a result, the quality is directly associated to the quality of the included articles. Second, even though the total number of included studies in the meta-analysis was large, the number of included studies for other associations was small, potential publication bias should be considered. Third, a form of reverse causation may occur through reporting bias. Fourth, some health-related outcomes were inadequately covered, and we have highlighted this gap. Finally, no reanalysis was done since we did not check the primary articles when dose-response meta-analyses were not available.

5. Conclusions

Associations between soy and isoflavone consumption and multiple various health outcomes were explored in a lot of meta-analyses. Based on our umbrella review, soy and isoflavone consumption was more beneficial than harmful for a series of health outcomes. Beneficial associations were identified for cancers, CVD, gynecological, metabolic, musculoskeletal, endocrine, neurological, and renal outcomes, most especially in perimenopausal women. However, high intake of miso soup (1–5 cups per day) in male should be warned because of potential risk of gastric cancer. Generally, intake of soy and isoflavone was more beneficial than harmful. Our results support that promote soy intake as part of a healthy diet. Robust RCTs are necessary to confirm this finding.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

health, isoflavones, meta-analysis, soy, systematic review, umbrella review

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