


# Effects of soy isoflavones on cognitive function: a systematic review and meta-analysis of randomized controlled trials

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**Context:** The results of preclinical and observational studies support the beneficial effect of soy isoflavones on cognition. **Objective:** This review aimed to evaluate the effects of soy isoflavones on cognition in adults. **Data Sources:** The PUBMED, EMBASE, Ovid Medline, Cochrane Library, and clinicaltrials.gov databases were searched. **Study Selection:** Two researchers independently screened 1955 records, using the PICOS criteria: participants were adults; intervention was dietary sources with soy isoflavones or isolated soy isoflavones; comparator was any comparator; outcome was cognitive function; study type was randomized controlled trials (RCTs). A third researcher was consulted to resolve any discrepancies. Sixteen RCTs were included and their quality assessed. **Data Extraction:** Information on study design, characteristics of participants, and outcomes was extracted. PRISMA guidelines were followed. **Data Analysis:** A random-effects meta-analysis was used to pool estimates across studies. In the 16 RCTs (1386 participants, mean age = 60 y), soy isoflavones were found to improve overall cognitive function (standardized mean difference [SMD], 0.19; 95% confidence interval [CI], 0.07–0.32) and memory (SMD, 0.15; 95%CI, 0.03–0.26). **Conclusion:** The results showed that soy isoflavones may improve cognitive function in adults. **Systematic Review Registration:** PROSPERO registration no. CRD42018082070.

## INTRODUCTION

Dementia affects 5 million Americans.<sup>1</sup> In the United States alone, total costs for patients with dementia were \$259 billion in 2017, and are predicted to increase to \$1.1 trillion by 2050.<sup>1</sup> Effective prevention strategies for dementia is of critical importance given that a delayed onset of 5 years reduces the degree of dementia

prevalence by 41%.<sup>2</sup> Dietary intervention may significantly contribute to the prevention of dementia. Observational studies have shown the Dietary Approaches to Stop Hypertension (DASH) diet, Mediterranean diet (MedDiet), and similar dietary patterns to be associated with better cognitive function.<sup>3–6</sup> A post-hoc analysis of the Prevención con Dieta Mediterránea (PREDIMED) study revealed that the

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MedDiet improved cognitive function among the older population.<sup>7,8</sup> The National Academy of Medicine emphasizes the need to identify nutrients and food associated with cognitive benefits, which could be added to the DASH diet or the MedDiet to develop a comprehensive dietary intervention for cognitive decline and dementia.<sup>9</sup>

Soy isoflavones (ISFs) are phytoestrogens, which are thought to exert beneficial effects on cognition function through their estrogen-like activity. Preclinical studies highlight the importance of ISFs in several Alzheimer's disease-like pathologies, including removing amyloid  $\beta$ <sup>10</sup> and decreasing tau phosphorylation.<sup>11</sup> Additionally, ISFs exert anti-inflammatory and anti-oxidative effects,<sup>12</sup> and inhibit the mitochondrial apoptotic pathway, which leads to Alzheimer's disease.<sup>13</sup> It is unsurprising that animal studies have shown that ISFs improve cognitive function.<sup>10,11,13</sup>

In human research, some observational studies have highlighted the cognitive benefits of ISFs.<sup>14–18</sup> Since the early 2000s, randomized controlled trials (RCTs) have been conducted to explore the effect of ISFs on cognition, with inconsistent results.<sup>19–25</sup> Additionally, some systematic reviews have reported inconclusive results regarding the effect of ISFs on cognition.<sup>26–29</sup> Cheng et al<sup>30</sup> conducted a meta-analysis of the effects of ISFs in postmenopausal women, which indicated that ISFs improve cognitive function in this group. However, trials that included men or young women, some of which suggested positive effects of ISFs on cognition,<sup>32,34</sup> were not included in their analysis,<sup>23,31–34</sup> In addition, they failed to capture all of the trials involving postmenopausal women,<sup>22,35</sup> and they included a study of red clover, which only contains 2% soy isoflavones.<sup>36</sup>

The primary aim of this systematic review and meta-analysis was to determine the effect of ISFs on overall and domain-specific cognitive functions by systematically and quantitatively summarizing the results of RCTs that have explored ISFs in adults (both men and women). The secondary aim was to evaluate any adverse effects of ISFs within these RCTs. With the above information, the potential role of ISFs in preventing cognitive decline and dementia was then further discussed.

## MATERIALS AND METHODS

### Literature search

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines ([Appendix S1](#) in the Supporting Information

online) and the protocol was registered with PROSPERO (CRD42018082070).<sup>37</sup> The databases PubMed, EMBASE through Embase.com, Ovid Medline, Cochrane Central Register of Controlled Trials, and clinicaltrials.gov were searched from inception through June 2018 by 2 investigators (C.C. and R.B.). One or more textual or MESH terms were used for isoflavones (isoflavone, genistein, daidzein, equol, soy, soya), cognitive factors (dementia, cognition, cognitive, memory, executive function, spatial, attention, brain, neuron, neuropsychological, Alzheimer's disease), and RCTs (randomized, trial, human, placebo, epidemiological studies, intervention) ([Table S1](#) in the Supporting Information online). The search terms were devised by 3 investigators (R.B., C.C., B.S., and A.S.) and confirmed by a librarian. Reference lists of included articles and related systematic reviews were reviewed to identify additional articles, and 2 ongoing and 2 unpublished trials were identified via clinicaltrials.gov ([Table S2](#) in the Supporting Information online). The principal investigators of these 4 trials were contacted.

### Study selection

A 2-stage screening process consisting of a title and abstract scan and a full-text review was used to determine the eligibility of articles. Both stages followed the same process. Each article was independently reviewed by 2 investigators (C.C. and R.B.). Discrepancies were discussed with another investigator (A.S.). Studies were selected in accordance with the PICOS (population, intervention, comparison, outcome, and study design) criteria shown in [Table 1](#). The search was restricted to English-language articles only. The quality of included articles was graded by 2 investigators (C.C. and R.B.), using the Cochrane Risk of Bias tool from the *Cochrane Handbook for Systematic Reviews of Interventions*.<sup>38</sup> Quality of trials was assessed in accordance with the following 7 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases.<sup>38</sup> Study quality was evaluated in line with the Jadad scale.<sup>39,40</sup> Jadad score calculation was based on random sequence generation, randomization, blinding, and incomplete outcome data. A Jadad score  $\geq 4$  indicated a high-quality study, and a score  $< 4$  indicated a lower-quality study. Discrepancies were discussed with another investigator (A.S.).

### Data extraction and data synthesis

Two investigators (C.C. and R.B.) independently extracted the data from each article. Any disagreements

**Table 1 PICOS criteria for inclusion of studies**

Parameter	Inclusion criterion
Participants	Adults $\geq 18$ years
Intervention	Dietary-based (eg, soy) with isoflavones or isolated isoflavones
Comparison	Any
Outcome	Cognitive function (including global cognition, executive function, processing speed, attention, language, verbal memory, and visual memory)
Study design	Randomized controlled trial

were resolved through discussion with another investigator (A.S.). The data extracted included the following information: study design, duration of the trial, number of participants, age, participants' characteristics (eg, postmenopausal), the source of isoflavones, intervention in control group, dose and constituents of the ISF, and any changes across the neuropsychological batteries. If the mean and standard deviation of the change from baseline were unavailable, the mean and standard deviation of the preintervention (b) and post-intervention (a) performance were extracted. Then, the mean of change (c) was calculated by  $\bar{X}_c = \bar{X}_a - \bar{X}_b$ , and the standard deviation of change was calculated by  $S_c = \sqrt{S_a^2 + S_b^2 - 2 * corr * S_a * S_b}$ .<sup>41</sup> Next, *corr* was calculated according to the method described in the Cochrane Handbook,<sup>38</sup> applying the data used in the study by Woo et al,<sup>35</sup> since this was the largest trial to provide adequate data.<sup>41</sup> The mean and standard deviation of the postintervention performance was used to represent the change when studies did not provide measurements of preintervention performance. The rationale was the assumption that the distributions of preintervention performance should not differ between the intervention and control groups owing to the randomization.

The standardized mean difference (SMD) was used to standardize the results, as represented by  $SMD = \frac{\bar{X}_{treatment} - \bar{X}_{control}}{S_{pooled}}$ , where  $S_{pooled} = \sqrt{\frac{(n_{treatment}-1)*S_{treatment}^2 + (n_{control}-1)*S_{control}^2}{n_{treatment} + n_{control}}}$ .<sup>41</sup> Tests with lower scores, representing better performance (eg, time to complete the neuropsychological batteries), were multiplied by  $-1$  so that positive values signified improvement.

Neuropsychological batteries were grouped by cognitive domains, ie, global cognition, executive function, psychomotor speed, attention/working memory, language, visuospatial reasoning, and memory (ie, learning, recall, and/or recognition of novel material), based primarily on traditional cognitive domain membership in the neuropsychological literature (Table S3 in the Supporting Information online).

The effect of ISFs on cognition was synthesized by calculating the overall and domain-specific SMD using the random-effects method. A summary SMD was calculated for each study and then added to a pooled SMD.<sup>30</sup> The robustness of results was tested using the 3-level method to account for the dependence within studies and neuropsychological tests.<sup>42</sup> For subgroup analysis, the SMD with 95% confidence interval (CI) was calculated for each stratum (ie, duration of trials [ $\geq 6$  vs  $< 6$  mo], the dose of ISFs [ $\geq 100$  vs  $< 100$  mg/d], age [ $\geq 60$  vs  $< 60$  y], region [Asia vs other regions], and the study population [postmenopausal women only vs others]), and a Wald test was performed to compare the means. The adverse events were summarized. The heterogeneity was assessed by a  $\chi^2$  test, and the corresponding  $I^2$  statistic was reported. A funnel plot was generated to identify potential publication bias. All tests were two-sided. A *P* value  $< 0.05$  was considered statistically significant. Subgroup analyses were assessed using the Bonferroni correction for multiple comparisons. The analysis was conducted using the metafor package in R.<sup>43</sup>

## RESULTS

After the search of the databases, 1955 records were identified. Following the removal of duplicates, 1537 were retained. After excluding 1521 studies that did not meet the inclusion criteria (Figure 1), 16 remained. The risk of bias of the included RCTs is summarized in Table S4 in the Supporting Information online. All the RCTs used randomization, but most RCTs<sup>20-24,31,32,34,44</sup> did not describe the methods used for the random sequence generation or allocation concealment in their reports. Regarding blinding, most RCTs used placebos that were similar to the interventions, and only some RCTs<sup>32,33,35,45</sup> reported that they also performed blinding of the outcome assessors. In some RCTs,<sup>20,21,24,34,45,46</sup> the loss-to-follow-up rate differed between the intervention group and control group. The study characteristics are summarized in Table 2<sup>19-23,25,31-35,44-47</sup>. For the 16 studies selected, there were 1386 participants (mean age = 60 y, 21.8% Asians), of which 1252 were postmenopausal women, 27 were premenopausal women, and 107 were men. Two trials were conducted in Asian countries, and 14 trials in non-Asian regions. The median duration of intervention was 17 weeks (range 6–130 wk). The sample size varied from 27 to 313. Two trials recruited both men and women. Twelve trials were women-only, and 2 trials were men-only. Seven trials were conducted in individuals aged 60 years or older. The dose of ISFs ranged from 60 to 160 mg/d. The dose of daidzein and genistein ranged from 16 to 63 mg/d and from 12 to 64 mg/d, respectively.

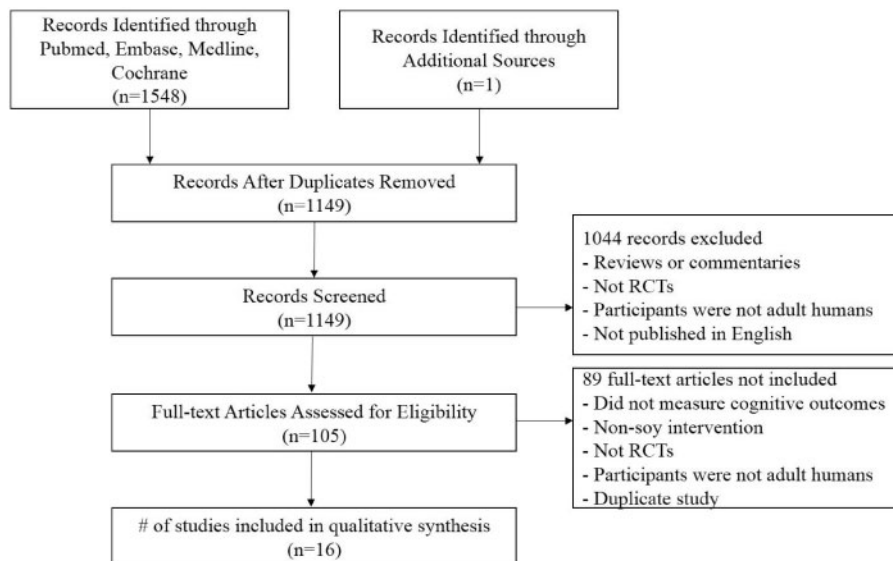


Figure 1 Flow diagram of the literature selection process. Abbreviation: RCT, randomized controlled trial.

The summary effect for each cognitive domain is shown in Table 3. The overall SMD was 0.19 (Figure 2; 95%CI, 0.07–0.32). A statistically significant effect was observed for memory (Figure 3; SMD, 0.15; 95%CI, 0.03–0.26), but not for other domains (Figures S1–S6 in the Supporting Information online). Similar results were shown by the 3-level method (Table S5 in the Supporting Information online). Subgroup analysis showed no statistically significant difference by duration of intervention (<6 vs ≥6 mo), dose (<100 vs ≥100 mg/d), age (<60 vs ≥60 y), region (Asia vs others), or study population (postmenopausal vs others) with a consideration of the Bonferroni correction (Figure 4).  $I^2$  was 53.1% for the language domain, which indicated moderate heterogeneity. For other domains,  $I^2$  was smaller than 40%. There was no strong indication of publication bias (Figure S7 in the Supporting Information online).

The dropout rate and adverse events were summarized (Table S6 in the Supporting Information online). The dropout rate ranged from 0% to 24%. Adverse events were reported by 7 trials and missing in 9 trials. Two studies<sup>45,46</sup> collected data on adverse events by different systems, such as the gastrointestinal system and gynecological system. No serious adverse events were reported, and other adverse events were similar, between the treatment group and placebo group. The Jadad scores were reported in each trial (Table S6 in the Supporting Information online). The detailed results of each trial are described in Tables S7 and S8 in the Supporting Information online.

## DISCUSSION

The results of the present meta-analysis show that ISFs improve cognitive function in adults. This effect is

pronounced in the domain of memory. According to the RCTs that reported adverse events in their study, no serious adverse effects were found.

Several systematic reviews summarized the findings from RCTs regarding the effects of ISFs on cognitive function.<sup>26–29</sup> The recent reviews<sup>26,28,29</sup> made more promising conclusions than the older reviews.<sup>27</sup> One earlier meta-analysis indicated that ISFs improve cognitive function in postmenopausal women,<sup>30</sup> despite the fact that some trials involving postmenopausal women were missed<sup>22,35</sup> and a trial concerning red clover, whose major ingredients are non-soy isoflavones (ie, biochanin A and formononetin) was included.<sup>36</sup> The present meta-analysis confirmed the findings of this earlier meta-analysis in relation to postmenopausal women and extended its results by including trials involving men and premenopausal women.<sup>23,31–34</sup> An overall cognitive benefit of ISFs has been observed. The cognitive benefits were observed not only for postmenopausal women, but also for premenopausal women and men.

Preclinical studies indicate that ISFs have significant roles in important Alzheimer's disease pathologies. ISFs can reduce the level of inflammation and oxidative stress, which alleviates cognitive impairment.<sup>48</sup> In addition, ISFs promote clearance of amyloid  $\beta$  protein ( $A\beta$ ) via peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ )/apolipoprotein E (ApoE) activation.<sup>10</sup> One ongoing RCT aimed to determine whether ISFs accelerate the degradation of  $A\beta$ .<sup>49</sup> Furthermore, ISFs decrease tau phosphorylation, which causes the formation of neurofibrillary tangles.<sup>11</sup> Besides this, ISFs suppress the mitochondrial apoptotic pathway.<sup>13</sup> The mitochondrial apoptotic pathway leads to neuronal cell death,

Table 2 Characteristics of the included trials<sup>19–23,25,31–35,44–47</sup>

First author, y	#Participants (#F/#M)	Mean age, y	Participants' characteristics	Country	Duration of trial, wk	Dose of ISFs, mg/d	Constituents of ISFs	Comparisons	Study design	Cognitive outcomes
Basaria et al (2009) <sup>25</sup>	84 (84/0)	56	Postmenopausal	USA	12	160	64 mg genistein, 63 mg daidzein, 34 mg glycitein	Whole-milk protein	DB, PC, P	Psychomotor speed; executive function; language; visuospatial reasoning
Casini et al (2006) <sup>22</sup>	77 (77/0)	50	Postmenopausal	Italy	26	60	24 mg genistein, 24 mg daidzein, 12 mg glycitein	Placebo tablet	DB, PC, CO	Psychomotor speed; attention/working memory; visuospatial reasoning
Duffy et al (2003) <sup>21</sup>	33 (33/0)	50–65	Postmenopausal	UK	12	60	N/A	Lactose tablet	DB, PC, P	Executive function; attention/working memory; language
File et al (2001) <sup>34</sup>	27 (27/0)	26	Healthy	UK	10	100	N/A	Low-soy diet	P	Executive function; language
File et al (2005) <sup>20</sup>	50 (50/0)	58	Postmenopausal	UK	6	60	N/A	Placebo capsule	DB, PC, P	Memory; attention/working memory; language
Fournier et al (2007) <sup>24</sup>	79 (79/0)	56	Postmenopausal	USA	16	70	33 mg genistein, 30 mg daidzein, 7 mg glycitein	Cow's milk	DB, PC, P	Memory; attention/working memory; visuospatial reasoning
Gleason et al (2009) <sup>31</sup>	30 (15/15)	74	Postmenopausal women and men	USA	26	100	Glycitein	Placebo tablet	DB, PC, P	Psychomotor speed; memory; executive function; language; visuospatial reasoning
Gleason et al (2015) <sup>23</sup>	59 (34/25)	76	Alzheimer's disease, postmenopausal women and men	USA	26	100	85 mg daidzein and genistein, 15 mg others	Placebo capsule	DB, PC, P	Psychomotor speed; memory; global cognition; executive function; language;
Henderson et al (2012) <sup>19</sup>	313 (313/0)	61	Postmenopausal	USA	130	91	77 mg daidzein and genistein, 14 mg others	Milk protein–matched placebo	DB, PC, P	Visuospatial reasoning; psychomotor speed; memory; global cognition; executive function; attention/working memory; language; visuospatial reasoning
Ho et al (2007) <sup>45</sup>	176 (176/0)	64	Postmenopausal	China	26	80	52 mg genistein, 36 mg daidzein, 3 mg glycitein	Placebo capsules	DB, PC, P	Psychomotor speed; memory; global cognition; executive function; language;
Kreijkamp-Kaspers et al (2004) <sup>46</sup>	175 (175/0)	67	Postmenopausal	Netherlands	52	99	N/A	Whole-milk protein	DB, PC, P	Visuospatial reasoning; psychomotor speed; memory; global cognition; executive function; attention/working memory; language

(continued)

Table 2 Continued

First author, y	#Participants (#F/#M)	Mean age, y	Participants' characteristics	Country	Duration of trial, wk	Dose of ISFs, mg/d	Constituents of ISFs	Comparisons	Study design	Cognitive outcomes
Kritz-Silverstein et al (2003) <sup>47</sup>	53 (53/0)	61	Postmenopausal	USA	26	110	52 mg genistein, 41 mg daidzein, 6 mg glycitein	Placebo pills	DB, PC, P	Psychomotor speed; memory; executive function; language
Santos-Galduroz et al (2010) <sup>44</sup>	36 (36/0)	56	Postmenopausal	Brazil	17	80	N/A	Placebo capsules	DB, PC, P	Psychomotor speed; memory; executive function; attention/working memory
Sharma et al (2009) <sup>33</sup>	33 (0/33)	69	Prostate cancer	USA	12	160	60.8 mg genistein, 16 mg daidzein, 3.2 mg glycitein	Whole-milk protein	DB, PC, P	Psychomotor speed; memory; language; visuospatial reasoning
Thorp et al (2009) <sup>32</sup>	34 (0/34)	40	Healthy	Australia	6	116	52 mg genistein, 36 mg daidzein, 3 mg glycitein	Placebo capsules	DB, PC, CO	Psychomotor speed; memory; executive function; attention/working memory; language; visuospatial reasoning
Woo et al (2003) <sup>35</sup>	127 (127/0)	57	Postmenopausal	China	13	100	12 mg genistein, 68 mg daidzein, 36 mg glycitein	No treatment	DB, P	Psychomotor speed; memory; global cognition; executive function

Abbreviations: CO, crossover design; DB, double-blind; P, parallel design; PC, placebo-controlled.

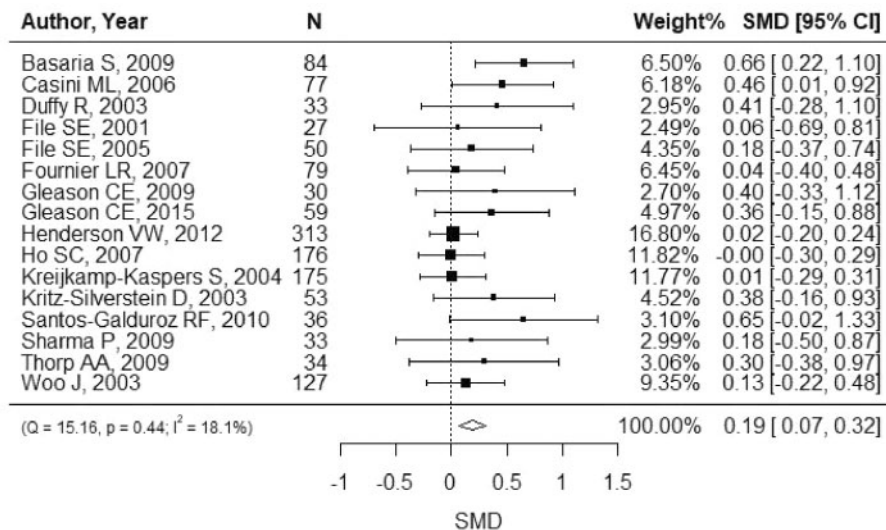


Figure 2 Overall standardized mean difference (SMD). The SMD with 95% confidence interval (CI) is displayed for each study. The weight was calculated using the inverse-variance weighting method. A random-effects model was used to calculate the summary SMD.

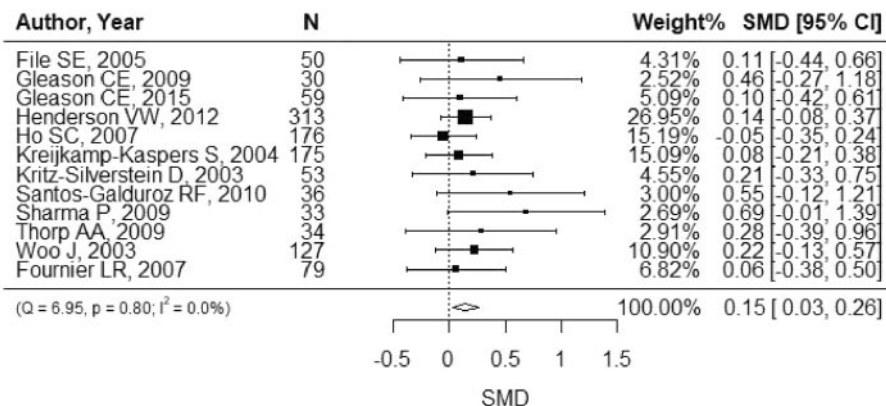


Figure 3 Standardized mean difference (SMD) for memory. The SMD with 95% confidence interval (CI) is displayed for each study. The weight was calculated using the inverse-variance weighting method. A random-effects model was used to calculate the summary SMD.

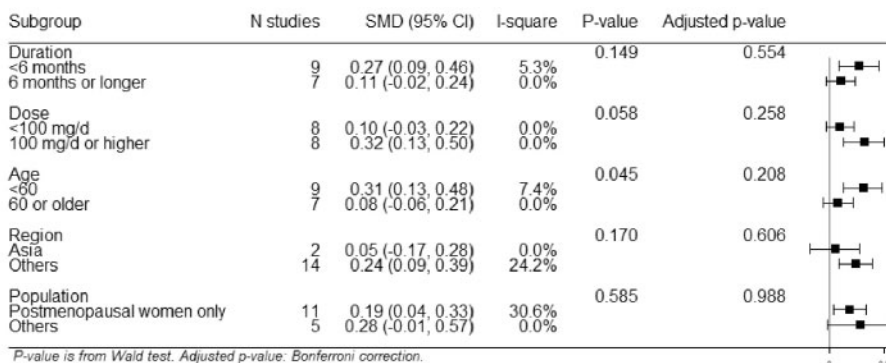


Figure 4 Subgroup analysis by duration, dose, age, region, and population. The SMD with 95% confidence interval (CI) was calculated for each subgroup. The P value was based on the Wald test.

which contributes to Alzheimer's disease.<sup>13</sup> Through these mechanisms, ISFs can protect the brain and lower the risk of dementia.

The selective binding of ISFs to estrogen receptor beta (ER $\beta$ ) contributes to the cognitive benefits of ISFs. Estrogen has pervasive effects on brains. However, the

**Table 3 Effect of soy isoflavones on cognition by domains**

Domain	No. of studies	Test type, n	SMD (95%CI)	P value	I <sup>2</sup> statistic (P value)
<b>All domains<sup>a</sup></b>	16	79	<b>0.19 (0.07–0.32)</b>	<0.01	18.1% (0.44)
Global cognition	5	2	0.04 (–0.10 to 0.17)	0.59	0.0% (0.64)
Executive function	11	13	0.05 (–0.07 to 0.17)	0.39	0.0% (0.89)
Psychomotor speed	12	8	0.03 (–0.08 to 0.15)	0.57	0.0% (0.94)
Attention/working memory	8	9	0.08 (–0.11 to 0.27)	0.41	33.9% (0.25)
Language	12	11	0.10 (–0.10 to 0.29)	0.33	53.1% (0.03)
Visuospatial reasoning	8	8	0.05 (–0.08 to 0.19)	0.45	0.0% (0.16)
<b>Memory<sup>b</sup></b>	12	28	<b>0.15 (0.03–0.26)</b>	0.01	0.0% (0.80)

<sup>a</sup>An effect size >0 indicates that the intervention group exhibited more positive effects than the control group.

<sup>b</sup>The difference in cognitive function between the control and intervention groups was found to be statistically significant at a P <0.05 level.

Abbreviations: SMD, standardized mean difference; CI, confidence interval.

included RCTs failed to show the cognitive benefits of hormone replace therapy in postmenopausal women.<sup>50</sup> Unlike estrogens, which bind to ER alpha (ER $\alpha$ ) and ER $\beta$ , ISFs selectively bind to ER $\beta$ . ER $\beta$ s are highly expressed in the brain, especially in the hippocampus and prefrontal cortex.<sup>51</sup> In the current meta-analysis, the effect of ISFs was pronounced in the domain of memory. Memory is highly related to the hippocampus and prefrontal cortex. It suggests that ISFs benefit cognition via selective binding to ER $\beta$ .

The RCTs included in this review did not show any severe adverse effect. One previous concern about ISFs was that they might pose risks to cognitive function. This finding was highlighted by 3 particular observational studies, ie, the Honolulu-Asia Aging Study (HAAS)<sup>52</sup> and studies in China<sup>53</sup> and Indonesia,<sup>54</sup> which revealed that the intake of tofu, which is made from soy and contains ISFs, is inversely associated with cognitive function. However, several points are worthy of note. HAAS was primarily focused on cardiovascular disease, and the findings concerning cognition were secondary. The baseline cognitive function was not measured, and the high-tofu-intake group had a less preferable profile regarding age, education, and ApoE4. The Chinese study was cross-sectional, and it may have been confounded by the participants' overall health status and total energy intake.<sup>53</sup> Compared to those with worse cognitive function, those with better cognitive function were much younger and more educated, and had a higher intake of both meat and vegetables. The Indonesian study was also cross-sectional. the authors of this study reported another soy product, tempeh, which was found to be associated with better memory.<sup>54</sup> Moreover, their later analysis showed that tofu and tempeh consumption is associated with better recall.<sup>16</sup> In fact, observational studies that aimed to evaluate the association between dietary intake of ISFs/soy and cognition showed no adverse effect, and rather, an improvement in cognitive function.<sup>14–18</sup> Therefore, current evidence does not support the proposition that ISFs negatively affect cognition.

The other concern about ISFs is that their estrogen-like effects may increase the risk of cancer. However, epidemiological studies have shown that ISFs and soy do not increase the risk of breast, endometrial, or prostate cancer.<sup>55–57</sup> Instead, soy intake is associated with decreased risk of breast cancer,<sup>58</sup> and is beneficial to breast cancer survivors, especially estrogen receptor-negative breast cancer patients.<sup>59,60</sup> The North American Menopause Society recommends that midlife women should increase their dietary intake of soy and isoflavone products.<sup>58</sup> In the prostate, ISFs exhibit an anticarcinogenic effect through their antiproliferative, anti-invasive, and pro-apoptotic activities.<sup>57</sup> Overall, current evidence shows no adverse effects in relation to ISFs.

Equol, a metabolite formed from ISFs by gut microbiota, may have greater cognitive benefit than ISFs themselves.<sup>61</sup> This is because, compared to ISFs, equol possesses higher antioxidant properties, greater or similar affinity to ER $\beta$ , longer bioavailability, and the ability to increase mitochondrial activities.<sup>62–66</sup> Equol cannot be produced unless one consumes ISFs, yet not all individuals can convert daidzein to equol. The ability to convert daidzein to equol is determined by the presence of specific bacteria in the gut,<sup>67</sup> not by genetics.<sup>68,69</sup> Interestingly, it is reported that 40%–70% of Asians can produce equol, in contrast to 20%–30% of westerners.<sup>65</sup> A recent cross-sectional study of 152 elderly subjects in Japan reported that equol-producers had significantly better cognition and lower prevalence of mild cognitive impairment than non-producers.<sup>70</sup> Two RCTs conducted in western countries that examined the effect of ISFs on cognition, also revealed that the equol-producers in these studies tended to have better cognitive outcomes in their post-hoc analyses.<sup>19,23</sup> The results did not reach statistical significance, however, mainly due to the small percentages of equol-producers in these trials (ie, <25%). Since equol is now available as nutraceutical and pharmaceutical supplements, future research in this area is warranted to evaluate the cognitive effects of equol.



Some variances were observed across the included RCTs. First, the ISF dose varied across trials. The dose-response relationship has been reported in relation to the effect of ISFs on hot flashes<sup>71</sup> and osteoporosis<sup>72</sup> among postmenopausal women. An in-vivo study also showed the dose-effect relationship of ISFs in terms of reducing neuroinflammation in rats.<sup>73</sup> In the present review, high-dose trials showed slightly better results than low-dose trials, suggesting a potential dose-response effect of ISFs. Second, the different constituents of ISFs may influence the effectiveness of the dose. Higher ratios of aglycones and glucosides (ie, two major chemical forms of ISFs) may increase the absorption of ISFs.<sup>74</sup> Compared to daidzein, genistein has stronger digestibility and affinity for ER $\beta$ .<sup>75</sup> Third, trials had various durations – a factor that may also influence the results. The subgroup analysis revealed no differences in the results of the short-duration vs long-duration trials. Yet, it is possible that the durations were too short to show a difference, as the longest duration of all the trials was 2 years. Fourth, study populations were different. The subgroup analysis suggested that younger individuals might gain more cognitive benefits from soy isoflavones than older individuals, although the results did not reach statistical significance after adjusting for multiple comparisons. All these variances should be considered while interpreting results.

There were several gaps in the current literature. First, the evidence on men is sparse. Observational studies showed an overall cognitive benefit of ISFs in both men and women.<sup>14,15,18</sup> More trials are needed to confirm this observation. Second, trials of longer duration are critically needed. The longest duration trial was the Women's Isoflavone Soy Health (WISH) trial, which administered ISFs for 2.5 years.<sup>19</sup> The evidence from one observational study supports the long-term effect by highlighting the cognitive benefits of ISFs with a follow-up of 15 years.<sup>15</sup> Third, more observational studies are needed regarding the association between ISFs and dementia. One cohort showed that high-soy intake was associated with lower dementia risk,<sup>14</sup> though further studies are needed to confirm this proposition.

The National Academy of Medicine recently reviewed strategies for preventing dementia. They highlighted dietary interventions, especially the MedDiet and DASH diet. Observational studies of the MedDiet and DASH diet revealed promising results for reducing dementia risk.<sup>6</sup> The post-hoc analysis of the PREDIMED trial found that the MedDiet group had better performance in global cognition, memory, and psychomotor speed than the control group.<sup>7,8</sup> The National Academy of Medicine also emphasized the need to identify components that should be included in dietary interventions for dementia. Many trials have

been conducted with a focus on effective intervention components, yet the current knowledge remains limited. RCTs failed to show that marine omega-3 fatty acids improve cognitive function.<sup>76,77</sup> For vitamin interventions, current evidence only noted some benefits of vitamin B12 plus folic acid, and did not show any beneficial effect for vitamins A, D, or E.<sup>78,79</sup> Regarding plant extracts, the findings of a recent RCT of 40 participants indicated that curcumin improved cognitive function, and decreased amyloid and tau accumulation in the brain.<sup>80</sup> The present study suggests that ISFs should be considered as an intervention for cognitive decline and dementia through a comprehensive evaluation of ISFs. ISFs are available as dietary supplements, which can be incorporated into the DASH diet and MedDiet. Overall, ISFs have the potential to improve cognitive function and reduce the risk of dementia as a component of dietary interventions.

The results should be interpreted in light of their strengths and weaknesses. The present study is the first systematic review and meta-analysis to quantitatively assess the cognitive effect of ISFs in both men and women. Besides this, the robustness of the results was tested by conducting multiple subgroup analyses and using two methods of meta-analysis (traditional and 3-level methods). The present study is not without limitations. Most trials involved a small sample size. The subgroup analysis should be interpreted with caution on account of the small number of studies in certain strata; for example, only 2 trials were performed in Asia. More research is needed before these findings can be generalized to the Asian population. Nevertheless, the present study informs future dietary interventions aimed at reducing cognitive decline and dementia by comprehensively evaluating the cognitive benefits of ISFs and corresponding adverse events.

## CONCLUSION

In adults, ISFs improve cognitive function. In the RCTs included in this review, ISF groups were associated with better performance in neuropsychological batteries than the control groups and no severe adverse effects were reported. These findings support the potential of ISFs to reduce the risk of cognitive decline and dementia. ISFs can be considered as a component of future dietary interventions for cognitive decline and dementia.

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*Author contributions.* C.C., R.B., and A.S. conceptualized and planned the study, including production of the search strategy. C.C., R.B., and A.S. undertook the study

selection, and assessed the quality of the studies. C.C., R.B., B.S., and A.S. performed the data extraction. C.C. performed the data analysis and synthesis. Data interpretation was discussed and executed by all authors. C.C. drafted the manuscript, which was critically reviewed by R.B., B.S., M.I., A.H., C.K., B.L., H.A., O.L., C.M., Y.M., L.K., and A.S. All authors read and approved the final manuscript.

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## Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

[Table S1 Search strategies in EMBASE](#)

[Table S2 Ongoing or unpublished trials](#)

[Table S3 Cognitive tests in each cognitive domain](#)

[Table S4 Quality assessment of the included studies](#)

[Table S5 The effect of soy isoflavones on cognition by domains \(using the 3-level method\)](#)

[Table S6 Adverse events and Jadad scores reported by 16 studies](#)

[Table S7 The availability of results](#)

[Table S8 Detailed results of ISFs vs control provided by 16 studies](#)

[Figure S1 Standardized mean difference \(SMD\) in global cognition.](#) The weight was calculated using the inverse-variance weighting method. A random-effects model was used to calculate the summary SMD

[Figure S2 Standardized mean difference \(SMD\) in executive function.](#) The weight was calculated using the inverse-variance weighting method. A random-effects model was used to calculate the summary SMD

[Figure S3 Standardized mean difference \(SMD\) in psychomotor speed.](#) The weight was calculated using the inverse-variance weighting method. A random-effects model was used to calculate the summary SMD

[Figure S4 Standardized mean difference \(SMD\) in attention/working memory.](#) The weight was calculated using the inverse-variance weighting method. A random-effects model was used to calculate the summary SMD

[Figure S5 Standardized mean difference \(SMD\) in language.](#) The weight was calculated using the inverse-variance weighting method. A random-effects model was used to calculate the summary SMD

[Figure S6 Standardized mean difference \(SMD\) in visuospatial reasoning.](#) The weight was calculated using the inverse-variance weighting method. The summary SMD was calculated using the 3-level random effects model

[Figure S7 Funnel plot](#)

[Appendix S1 PRISMA checklist](#)

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