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Beneficial effect of soy isoflavones and soy isoflavones plus soy protein on serum concentration of C-reactive protein among postmenopausal women: An updated systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: Scientists suggest that soy isoflavones or the combination of soy isoflavones and soy protein may have beneficial effects on inflammation. Thus, the present study aims at conducting a systematic review and meta-analysis on randomized controlled trials (RCTs) in which the effect of soy isoflavones and the combination of soy isoflavones and soy protein on serum concentration of C-reactive protein (CRP) among postmenopausal women is assessed.

Methods and materials: A literature searching was done to identify a breadth of related references in PubMed, Scopus, ISI Web of Science, Cochrane Library, and Clinicaltrials.gov up to December 2020. The mean change from baseline in the CRP concentrations and its standard deviation (SD) for both intervention and comparison groups were used to calculate the effect size. The summary of the overall effects and heterogeneity was estimated by using the DerSimonian and Laird random effects model. The protocol was registered in PROSPERO (No. CRD42020166053).

Results: This study considered 23 articles for systematic review and 19 articles for meta-analysis. The overall effect presented a non-significant effect of soy isoflavones on serum CRP concentrations (WMD = 0.08 mg/L, 95 % CI: -0.08, 0.24; p = 0.302) and the overall effect of the combination of soy isoflavones and soy protein indicated non-significant effect in serum levels of CRP (WMD= -0.02 mg/L 95 % CI: -0.12, 0.08; p = 0.715).

Conclusion: Published RCTs did not provide strong evidence regarding beneficial effect of soy isoflavones or the combination of soy isoflavones and soy protein on serum CRP concentration among postmenopausal women.

1. Introduction

Local inflammation starts in fourth decade of life and increases during aging.[1] The enhancement of proinflammatory cytokines causes oxidative stress and results in damage to various intracellular components such as regulatory and structural proteins, DNA, and lipids.[2] C-reactive protein (CRP) considers as a hepatically-produced acute phase reactant protein. Its serum concentration is associated with inflammation[3] and the high serum level of CRP is a predictor of ischemic stroke and first myocardial infarction in humans.[4,5] According to Women's Health Study, postmenopausal women with the highest CRP concentration at baseline had a 7-fold enhancement in myocardial infarction risk and 5-fold enhancement in any vascular event.[6] Thus, it seems that high serum level of CRP can predict cardiovascular events especially among postmenopausal women.

Beside the enhancement of inflammation, a reduction in endogenous

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estrogen is also a reason for cardiovascular disease (CVD) among postmenopausal women.[7] Hormone replacement therapy (HRT) has favorable effects on endothelial function, antioxidant protection, blood lipids and lipoprotein concentrations, and vascular reactivity.[8,9] Despite the positive effects of estrogen therapy on clinical markers, the benefits of HRT for postmenopausal women remain controversial.[10] Polyphenolic isoflavones such as genistein and daidzein are presented in soy and structurally are similar to estradiol[11] and therefore they can bind to estrogen receptor β in vascular wall[12–16].

Animal experiments and cell studies propose that in addition to soy isoflavones the genistein and daidzein have anti-inflammatory and lipid lowering effects.[17,18] Scientists suggest that soy isoflavones may reduce inflammatory mediators through the inhibition of tyrosine kinase.[19,20] Besides soy isoflavones, soy protein is recommended as a food for cardiovascular protection due to its favorable impact on blood pressure and cholesterol.[21,22] Some studies have indicated that substitution of animal protein with soy protein might reduce circulating levels of inflammatory mediators[23,24].

Previous information regarding soy consumption and inflammatory mediators among postmenopausal women is far from conclusive. Some randomized clinical trials (RCTs) support the effectiveness of soy food consumption on proinflammatory cytokine reduction,[25–29] while others do not.[30–36] A meta-analysis of 14 trials conducted in 2011 examined soy isoflavones effect on serum concentration of CRP among postmenopausal women and their results proposed non-significant effect of soy isoflavones on CRP.[37]

It should be noted that we performed an updated systematic review and meta-analysis to report a summary of RCTs exploring the effect of soy isoflavones and soy isoflavones plus soy protein on CRP.

2. Materials and methods

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklists were used for all steps of conducting the present systematic review and meta- analysis.[38] The protocol was registered in PROSPERO (No. CRD42020166053).

2.1. Literature search

In order to identify RCTs, a literature search was conducted using PubMed, Scopus, and ISI Web of Science, Cochrane Library, and Clinicaltrials.gov up to December 2020 exploring the effect of soy isoflavones, and soy isoflavones plus soy protein on serum concentration of CRP among postmenopausal women. These databases were searched by following related medical subject heading (MeSH) and non-MeSH terms for the most important inflammatory mediators, soy and clinical trial: "C-Reactive Protein", "Protein-C Reactive", "CRP", "Tumor Necrosis Factor-alpha", "Tumor Necrosis Factor", "Tumor Necrosis Factorα", "TNFα", "TNF-α", "Cachectin", "Cachexin", "Interleukin-6", "Interleukin6", "IL6", "IL-6", "E-Selectin", "E-Selectin", "Selectin E", "SelectinE", "ESelectin", "Intercellular Adhesion Molecule-1", "Intercellular Adhesion Molecule1", "Intercellular Adhesion Molecule", "ICAM-1", "ICAM1", "Vascular Cell Adhesion Molecule-1", "Vascular Cell Adhesion Molecule1", "Vascular Cell Adhesion Molecule", "VCAM-1", "VCAM1", Inflammat, "Soy", "Soy Foods", "Soy Food", "Soy, Food", "Soy, Foods", "Soyfood", "Soyfoods", "Foods Soy", "Soy Cheese", "Soy Cheeses", "Soy Sauce", "Soysauce", "Soy Bean Curd", "Texturized Soy Protein", "Texturized Soy Proteins", "Texturized Vegetable Protein", "Soya", "Natto", "Tempeh", "Tofu", "Miso", "Soy Milk", "Milk Soy", "Milk, Soy", "Soy Beverage", "Soy Beverages", "Soy, Beverage", "Soybeans", "Soybean", "Soy Bean", "Soy Beans", "Glycine max", "Soybean Proteins", "Soy Bean Proteins", "Soy Protein", "Soy Proteins", "Proteins Soy", "Protein Soy", "Genistein", "Soy Products", "Isoflavones", "Isoflavone", "Homoisoflavones", "3-Benzylchroman-4-Ones", "3-Benzylidene-4-Chromanones", "Phytoestrogens", "Phytoestrogen", "Phyto-Estrogen", "Plant Estrogen", "Plant Estrogens", "Equol", "Clinical Trials", "Clinical Trial", "RCT". Boolean operators, quotation marks, parentheses, and asterisks were used to create our search strategy. Through searching databases based on just CRP a few articles might be missed, therefore; we also applied key words related to the most important inflammatory mediators. All found papers by systematic search were imported to reference manager software (EndNote X7) and two reviewers (M.H and A.Gha) separately checked titles and abstracts of exported papers in order to identify the relevant RCTs. Reference list of relevant reviews and included RCTs were hand searched to find any other relevant RCTs. There wasn't any restriction on publication time and any discrepancies were solved through consulting with a third investigator (A.Gho).

2.2. Eligibility criteria for study

PICOS (Patient/Population, Intervention, Comparison, Outcome, Study types) framework was used as inclusion criteria for this systematic review and meta-analysis. Original investigations with RCT design conducted among postmenopausal women were considered for inclusion in this study. To be inclusion, trials should report the effects of soy isoflavones or soy isoflavones plus soy protein on serum concentration of CRP. After reading the full texts of retrieved studies, RCTs with following criteria were not taken into account in this systematic review and meta-analysis: 1) taking other nutrient supplements beside soy in intervention group; 2) being done trials without comparison group; 3) not reporting information related to serum concentration of CRP at baseline or after intervention and any data for computing it; 4) reporting serum concentration of CRP in figures; 5) not reporting the dose of soy isoflavones and soy protein in natural soy product. In addition, our study was restricted to the articles published in English.

2.3. Data extraction

Two independent authors (M.H and A.Gha) done data extraction to elicit the following information: the author's first name, the year of publication, the country where RCTs were conducted, body mass index (BMI), sample size, trial design, age range and/or mean, soy isoflavones and soy protein dose and source, intervention duration, placebo kind, subjects' health status, mean of serum concentration of CRP and its corresponding standard deviation (SD) before and after intervention. Any discrepancies in this stage also were resolved through consulting with a third reviewer (A.Gho). We converted all CRP measurements into the same unit (mg/L). Studies which had more than one intervention or comparison group were included separately.

2.4. Quality assessment

Two reviewers (M.H and A.Gho) separately assessed the quality of included trials by Cochrane Collaboration's tool.[39] Following items are included in this tool for risk of bias assessment: I) selection bias: A) random sequence generation, B) allocation concealment; II) reporting bias; III) performance bias; IV) detection bias; IV) attrition bias. Each item was judged as "unclear risk of bias", "high risk of bias," or "low risk of bias". We considered included RCTs as "good" quality if they had the least low risk of bias for three criteria, as "fair" if they had low risk for two criteria, and "weak" if they had low risk for less than two criteria.[39]

2.5. Data synthesis and statistical analysis

The current meta-analysis was performed by extracting mean differences (MDs) and their SDs for CRP (mg/l). Additionally, the values were calculated using the data extracted from the included articles in which MDs and SDs weren't reported. Based on Cochrane Handbook,[40] the mean change from baseline in the CRP concentrations and its SD for both intervention and comparison groups were used to calculate the effect size. In order to estimate the mean of CRP concentration, Hozo's method[41] was used. Moreover, SDs were obtained from multiplying

standard errors (SEs) divided by square root of the sample size in studies which reported SEs. The summary of the overall effects and heterogeneity was estimated by using the DerSimonian and Laird random effects model,[42] if a heterogeneity test was statistically significant. Statistical heterogeneity of intervention effects was measured using Cochran's Q test and I-squared statistic. Heterogeneity was considered substantial if p-value was ≤0.10 in Cochran's Q test or value of the I-squared statistic was ≥50 %.[43]

Subgroup analyses were performed to explore sources of heterogeneity which included soy isoflavones dose, soy protein dose, trial design, intervention duration, mean of baseline CRP concentration, health status of participants, sample size, geographical region, age of participants, BMI, quality assessment of articles and year of study publication. Meta-regression was used to examine the impact of moderator variables on effect sizes and to compute adjusted effect of soy isoflavones dose and soy protein dose on effect sizes after controlling for other variables. Visual inspection of Begg's funnel plot, Begg's rank correlation, and Eggar's weighted regression tests were used to assess the presence of publication bias in the meta-analysis.[44,45] Sensitivity analysis was conducted using the leave-one out method to specify the effect of each study on the overall effect size. Ninety-five percent confidence intervals were provided for all calculated effect sizes. All analyses were performed using STATA version15 (Stata Corp, Collage Station, TX).

3. Results

3.1. Study selection

Systematic search of databases retrieved 4387 articles. By removing duplicate papers, 2955 articles remained for reading title and abstract. Among these articles, 2833 were excluded from investigations, thus 122 RCTs remained for reading full text. Likewise, 99 articles were excluded due to the following reasons: ninety-two articles did not measure CRP or not conducted among postmenopausal women, there was a non-English article, five articles reported using other nutrients beside soy intervention, and CRP unit was not reported in one article (Fig. 1). Therefore, 23 papers remained eligible for being investigated in this systematic review (Table 1).[24–36,46–55] Concerning the data inadequacy in four articles,[28,32,50,55] nineteen articles were finally included in this meta-analysis.[24–27,29–31,33–36,46–49,51–54]

3.2. Study characteristics

By conducting this study, we found that ten articles assessed the effect of soy isoflavones,[27,28,30,33,34,46–48,51,55] nine articles assessed the effect of soy isoflavones plus soy protein,[24–26,31,32,35,50,53,54] and four articles assessed the effect of both soy isoflavones and soy isoflavones plus soy protein.[29,36,49,52] Participants involved in seven articles received soy isoflavones plus soy protein by taking natural soy products.[24–26,29,31,50,54] That is to say, seven articles had two

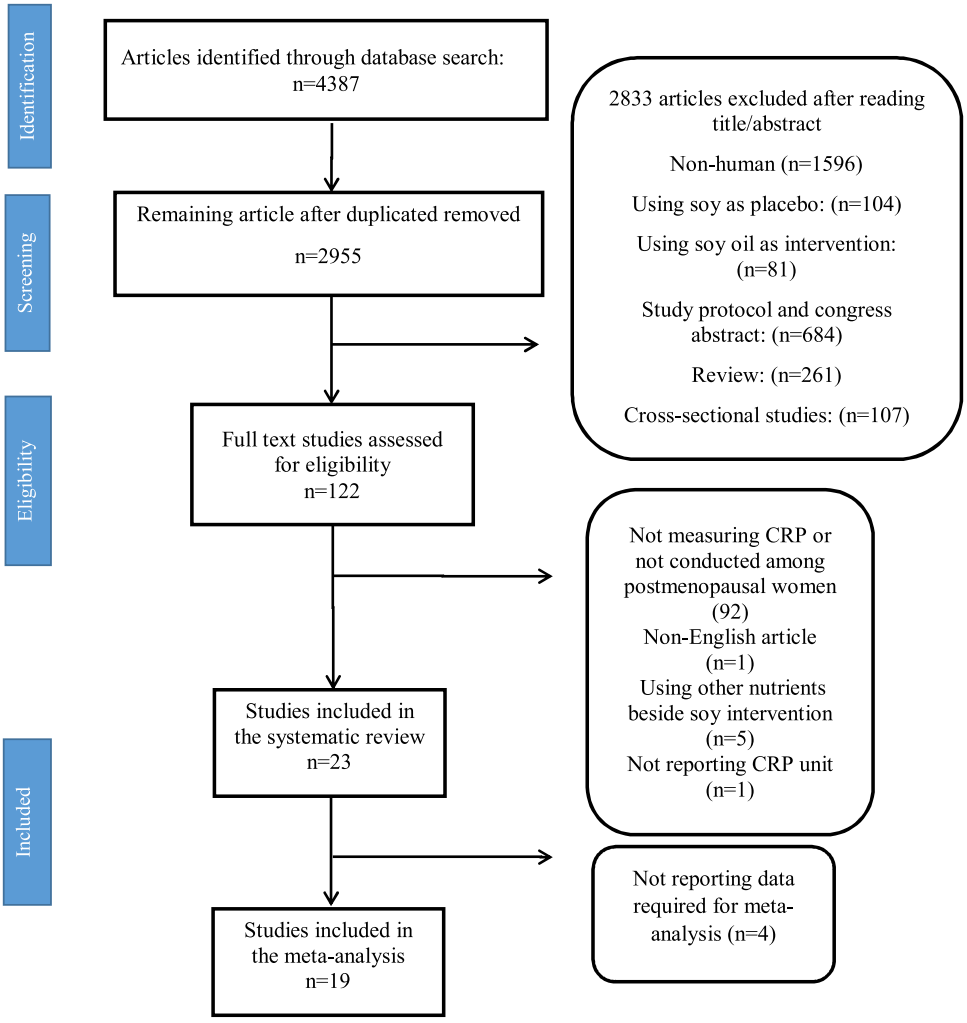

Fig. 1. Flowchart of study selection process.

Table 1
Randomized controlled trial studies included in the systematic review and meta-analysis.

Code Author year country	Subjects	Age and BMI* (mean ± SD)	RCT[Δ]	Intervention	Placebo	Duration (week)	Results
1.1 Acharjee, S. 2015 Israel [25]	Healthy postmenopausal women without metabolic syndrome N = 49	Age: 54.6 ± 5.8 BMI: 24.6 ± 3.8	Randomized, controlled, crossover trial	0.5 cups/day soy nuts (containing 25 g of soy protein and 101 mg of aglycone isoflavones)	Non soy protein	8	CRP[†] decreased significantly
1.2 Acharjee, S. 2015 Israel [25]	Healthy postmenopausal women with metabolic syndrome N = 11	Age: 54.1 ± 6.5 BMI: 31.8 ± 4.6	Randomized, controlled, crossover trial	0.5 cups/day soy nuts (containing 25 g of soy protein and 101 mg of aglycone isoflavones)	Non soy protein	8	CRP decreased significantly
2.1 Aubertin-Leheudre, M. 2007 Canada [30]	Obese postmenopausal women N = 20	Age: 58 ± 5 BMI: 30 ± 5	Randomized, double-blind, controlled trial	70 mg/day isoflavones (44 mg of diadzein, 16 mg of glycitein, and 10 mg of genistein)	N/M[‡]	24	CRP did not change significantly
2.2 Aubertin-Leheudre, M. 2007 Canada [30]	Obese postmenopausal women N = 20	Age: 58 ± 5 BMI: 30 ± 5	Randomized, double-blind, controlled trial	70 mg/day isoflavones (44 mg of diadzein, 16 mg of glycitein, and 10 mg of genistein)	N/M[‡]	48	CRP did not change significantly
3.1 Azadbakht, L. 2007 Iran [26]	Postmenopausal women with the metabolic Syndrome N = 42	Age: 57 ± 1.94 BMI: 28 ± 1.29	Randomized cross-over clinical trial	30 g/day soy nut (containing 11.25 g/ day protein with 84 mg/day isoflavones)	Red meat	8	CRP decreased significantly
3.2 Azadbakht, L. 2007 Iran [26]	Postmenopausal women with the metabolic Syndrome N = 42	Age: 57 ± 1.94 BMI: 28 ± 1.29	Randomized cross-over clinical trial	30 g/day soy protein (containing 15 g/day protein with 102 mg/ day isoflavones)	Red meat	8	CRP decreased significantly
4.1 Bakhtiari, A 2019 Iran [31]	Older women with metabolic syndrome N = 50	Age: 63.8 ± 2.82 BMI: N/M	Randomized, single-blind, controlled clinical trial	35 g/day roasted soy-nut (containing 92.5 mg isoflavines and 13.8 g protein)	Nothing	12	CRP did not change significantly
4.2 Bakhtiari, A 2019 Iran [31]	Older women with metabolic syndrome N = 50	Age: 63.8 ± 2.82 BMI: N/M	Randomized, single-blind, controlled clinical trial	35 g/day textured soy protein (containing 117.2 mg isoflavines and 18.2 g protein)	Nothing	12	CRP did not change significantly
5 Christie, D. R. 2010 England [32]	Healthy postmenopausal white and African American women N = 33	Age: 54.4 ± 3.3 BMI: 35.3 ± 6.0	Randomized, double-blind, controlled trial	soy shakes (containing 20 g soy protein plus 160 mg isoflavones)	Casein without isoflavones	12	CRP did not change significantly
6 Colacurci, N. 2005 Italy [33]	Healthy postmenopausal women N = 57	Age: 55.4 ± 3.7 BMI: 25.6 ± 1.6	Randomized, single-blind, controlled clinical trial	60 mg/day isoflavones (30 mg genistein and 30 mg daidzein)	N/M	24	CRP did not change significantly
7 D'Anna, R. 2005 Italy [34]	Healthy Postmenopausal women N = 55	Age: 50–60 BMI: N/M	Randomized, double-blind, controlled trial	54 mg/day genistein	N/M	24	CRP did not change significantly
8 Gonźalez, S 2007 UK [46]	Postmenopausal women with diet-controlled type 2 diabetes N = 26	Age: N/M BMI: 30.7 ± 5.5	Randomized, double-blind, placebo-controlled, crossover	132 mg/day isoflavones (53 % genistein, 37 % daidzein, and 10% glycitein)	Microcrystalline cellulose	12	CRP did not change significantly
9 Greany, K. A. 2007 USA [35]	Healthy Postmenopausal women N = 34	Age: 57.7 ± 6.0 BMI: 25.0 ± 4.3	Randomized, placebo-controlled, crossover	soy protein isolated (26 ± 5 g protein containing 44 ± 8 mg isoflavones per day)	Milk protein	6	CRP did not change significantly
10 Hall, W. L		Age: 57.7 ± 5.4 BMI: 25 ± 2.9	Randomized, double-blind,	50 mg/day isoflavones	cereal bars	8	CRP decreased significantly in

(continued on next page)

Table 1 (*continued*)

Code Author year country	Subjects	Age and BMI* (mean ± SD)	RCT[Δ]	Intervention	Placebo	Duration (week)	Results
2005 UK 27	Healthy postmenopausalwomen N = 113		placebo-controlled, crossover				intervention group
11 Lebon, J. 2014 Canada 28	Overweight and obese postmenopausal women N:29	Age: 59.5 ± 4.5 BMI: 29.5 ± 3.8	Randomized, double-blind, controlled trial	70-mg/day daily dose of isoflavones (containing 44 mg of daidzein, 16 mg of glycitein, and 10 mg of genistein)	cellulose	24	CRP decrease significantly
12.1 Jenkins, D. J 2002 Canada 24	Postmenopausal women N = 18	Age: N/M BMI: N/M	Randomized crossover trial	Low isoflavone soy protein foods (supplied 10 mg/day isoflavones and 52 g/day soy protein)	Regular diet	4	CRP did not change significantly
12.2 Jenkins, D. J 2002 Canada 24	Postmenopausal women N = 18	Age: N/M BMI: N/M	Randomized crossover trial	High isoflavone soy protein foods (supplied 73 mg/day isoflavones and 50 g/day soy protein)	Regular diet	4	CRP did not change significantly
13.1 Liu, Z. M. 2014 Hong Kong 29	Healthy postmenopausal women N = 180	Age: 57.6 ± 5.3 BMI: 23.2 ± 3.5	Randomized, double-blind, controlled trial	40 g low-fat milk powder + 63 mg daidzein	40 g low-fat milk powder	24	CRP did not change significantly
13.2 Liu, Z. M. 2014 Hong Kong 29	Healthy postmenopausal women N = 180	Age: 57.6 ± 5.3 BMI: 23.2 ± 3.5	Randomized, double-blind, controlled trial	40 g/day soy flour (containing 12.8 g protein and 49.8 mg total isoflavones (23.2 mg daidzein and 19.4 mg genistein))	40 g low-fat milk powder	24	CRP decreased significantly in intervention group
14.1 Liu, Z. M. 2012 Hong Kong 36	Prediabetes postmenopausal women N = 120	Age: 56.4 ± 4.7 BMI: 24.1 ± 3.8	Randomized, double-blind, controlled trial	15-g/day soy protein and 100-mg isoflavone (35 mg daidzin, 59 mg genistin and 4 mg	15 g/day milk protein	12	CRP did not change significantly
14.2 Liu, Z. M. 2012 Hong Kong 36	Prediabetes postmenopausal women N = 120	Age: 56.4 ± 4.7 BMI: 24.1 ± 3.8	Randomized, double-blind, controlled trial	15-g/day soy protein and 100-mg isoflavone (35 mg daidzin, 59 mg genistin and 4 mg	15 g/day milk protein	24	CRP did not change significantly
14.3 Liu, Z. M. 2012 Hong Kong 36	Prediabetes postmenopausal women N = 120	Age: 56.4 ± 4.7 BMI: 24.1 ± 3.8	Randomized, double-blind, controlled trial	100-mg isoflavone (35 mg daidzin, 59 mg genistin and 4 mg glycitin)	15 g/day milk protein	12	CRP did not change significantly
14.4 Liu, Z. M. 2012 Hong Kong 36	Prediabetes postmenopausal women N = 120	Age: 56.4 ± 4.7 BMI: 24.1 ± 3.8	Randomized, double-blind, controlled trial	100-mg isoflavone (35 mg daidzin, 59 mg genistin and 4 mg glycitin)	15 g/day milk protein	24	CRP did not change significantly
15 Llaneza, P. 2011 Spain 47	Obese postmenopausal women N = 87	Age: 56.1 ± 3.51 BMI: 35.2 ± 4.78	Single blind randomized clinical trial	80 mg/day isoflavone (60.8 mg of genistein, 16 mg of daidzein and 3.2 mg of glicitein)	Nothing	24	CRP did not change significantly
16.1 Llaneza, P. 2012 Spain 48	Obese postmenopausal women N = 65	Age: 56.7 ± 3.5 BMI: 30.6 ± 4.7	Single blind randomized clinical trial	80 mg of isofl avones (60.8 mg genistein, 16 mg daidzein and 3.2 mg glicitein)	Nothing	24	CRP did not change significantly
16.2 Llaneza, P. 2012 Spain 48	Obese postmenopausal women N = 65	Age: 56.7 ± 3.5 BMI: 30.6 ± 4.7	Single blind randomized clinical trial	80 mg of isofl avones (60.8 mg genistein, 16 mg daidzein and 3.2 mg glicitein)	Nothing	48	CRP did not change significantly
16.3 Llaneza, P. 2012 Spain 48	Obese postmenopausal women N = 65	Age: 56.7 ± 3.5 BMI: 30.6 ± 4.7	Single blind randomized clinical trial	80 mg of isofl avones (60.8 mg genistein, 16 mg daidzein and 3.2 mg glicitein)	Nothing	72	CRP did not change significantly
16.4 Llaneza, P. 2012	Obese postmenopausal women N = 65	Age: 56.7 ± 3.5 BMI: 30.6 ± 4.7	Single blind randomized clinical trial	80 mg of isoflavones (60.8 mg genistein, 16 mg daidzein and 3.2 mg glicitein)	Nothing	96	CRP did not change significantly

(*continued on next page*)

Table 1 (*continued*)

Code Author year country	Subjects	Age and BMI* (mean ± SD)	RCT[Δ]	Intervention	Placebo	Duration (week)	Results
Spain [48]							
17.1 Mangano, K. M. 2013 USA [49]	Healthy older women N = 47	Age: 73 ± 5.7 BMI: 29.3 ± 6.9	Randomized, double-blind, placebo-control, clinical trial	18 g/day soy protein and isoflavone tablets (105 mg/d isoflavone)	Maltodextrin and animal protein	48	CRP did not change significantly
17.2 Mangano, K. M. 2013 USA [49]	Healthy Older women N = 48	Age: 73 ± 5.7 BMI: 29.3 ± 6.9	Randomized, double-blind, placebo-control, clinical trial	105 mg/d isoflavone	Maltodextrin and animal protein	48	CRP did not change significantly
18.1 Nasca, M. M. 2008 USA [50]	Healthy postmenopausal women N = 48	Age: N/M BMI:N/M	Randomized, placebo-controlled, crossover	0.5 cups of soy nuts (containing 25 g soy protein and 101 mg aglycone Isoflavones)	Control diet	8	CRP did not change significantly
18.2 Nasca, M. M. 2008 USA [50]	Hypertension postmenopausal women N = 12	Age: N/M BMI:N/M	Randomized, placebo-controlled, crossover	0.5 cups of soy nuts (containing 25 g soy protein and 101 mg aglycone Isoflavones)	Control diet	8	CRP did not change significantly
19 Riesco, E. 2012 Canada [51]	Overweight or obese postmenopausal women N = 52	Age: 56.2 (52.7−59.7)[Φ] BMI:28.8 (25.2 −34.2)	Randomized, double-blind, placebo-control, clinical trial	70 mg/day soy isoflavones	cellulose	24	CRP did not change significantly
20.1 Ryan-Borchers, T. A. 2006 USA [52]	Healthy postmenopausal women N = 37	Age: 55.4 ± 3.9 BMI: 27.5 ± 4.9	double-blind, placebo-controlled trial	706 mL soymilk/ d (containing 71.6 mg isoflavones and 18 g/ day soy protein)	Cow milk	16	CRP did not change significantly
20.2 Ryan-Borchers, T. A. 2006 USA [52]	Healthy postmenopausal women N = 34	Age: 55.4 ± 3.9 BMI: 27.5 ± 4.9	double-blind, placebo-controlled trial	71.6 mg/day isoflavones	Maltodextrin	16	CRP did not change significantly
21 Törmälä, R. 2008 Finland [53]	Healthy postmenopausal women using tibolone N = 36	Age: 57.7 ± 0.8 BMI: 24.6 ± 5.3	Randomized, placebo-controlled, crossover	52 g/day of soy protein containing 63 mg of genistein, 43 mg of daidzein and 6 mg of glycitein, altogether 112 mg of isoflavones	Milk protein	8	CRP did not change significantly
22 van Nielen, M. 2014 Netherlands [54]	Postmenopausal women with abdominal obesity N:15	Age: 61 ± 5 BMI: N/M	Single-blind randomized crossover trial	soy nuts (containing 30 g/d soy protein and 48 mg/d isoflavones)	Meat protein	24	CRP did not change significantly
23 Yildiz, M. F. 2005 Turkey [55]	Healthy postmenopausal women N = 40	Age: 49.5 ± 3.0 BMI: 26.9 ± 2.3	Single blind randomized clinical trial	40 mg/day of genistein,	Nothing	24	CRP did not change significantly

[†] : CRP: C-reactive protein.
[*] : BMI: Body Mass Index.
[‡] : N/M: Not mention.
[Δ] : RCT: Randomized clinical trial.
[Φ] : means (95 % confidence interval).

intervention groups and one comparison group[24,26,29,31,36,49,52] and one article had two intervention groups and two comparison groups,[25] therefore; we considered every article as two separate articles and separate effect sizes were calculated. In three studies by Llaneza, P et al.,[48] Liu Z, M et al.,[36] and Aubertin-Leheudre, M et al.,[30] CRP concentration was reported in regular periods over intervention duration, so we calculated separate effect sizes for each treatment duration which CRP concentration was reported. Altogether, a total of 33 datasets (17 datasets for soy isoflavones and 16 datasets for soy isoflavones plus soy protein) from 19 studies with 1407 subjects were analyzed in our meta-analysis.

Among twenty-three articles, nine articles were done by cross-over

design,[24–2735,46,50,53,54] and fourteen articles were done by parallel design.[28–34,36,47–49,51,52,55] Soy isoflavones dose ranged from 10 mg/day to 160 mg/day and treatment duration varied from four to 96 weeks. Also, with regards to the subjects' health status, thirteen RCTs indicated soy supplements effects on healthy postmenopausal women,[24,25,27,29,32–35,49,50,52,53,55] five RCTs indicated soy supplements effects on obese or overweight women,[28,30,47,48,51] one article indicated soy supplements effects on postmenopausal women with abdominal obesity,[54] two RCTs indicated soy supplements effects on postmenopausal women with metabolic syndrome,[26,31] and two RCTs indicated soy supplements effects on patients with diabetes[46] or prediabetes.[36]

3.3. Risk of bias assessment

Out of the twenty-three RCTs included in this study, one RCT was scored as "weak"[24] seven RCTs as "fair",[25,26,35,49,50,53,55] and fifteen RCTs as "good".[27–34,36,46–48,51,52,54] According to blinding of participants and personals and outcome assessors, eight trials,[24–2631,35,50,53,55] and four trials[24,50,53,55] displayed high risk of bias respectively. Lack of allocation concealment was the source of risk of bias in five studies.[24,30,46,49,50] One study[49] and four studies[24,27,32,49] were considered as high risk of bias regarding incomplete outcome data and selective reporting, respectively. For further details, Table 2 presents the quality assessment of included RCTs.

3.4. Findings of the meta-analysis

Twelve studies with seventeen effect sizes evaluated soy isoflavones effects on serum CRP concentrations (Fig. 2). The overall effect suggested a non-significant effect on serum CRP concentrations after supplementation with soy isoflavones compared with comparison group (WMD = 0.08 mg/L, 95 % CI: -0.08, 0.24; p = 0.302). There was a substantial heterogeneity between studies (Cochrane's Q test, $p < 0.001$; $I^2 = 87.0$ %). Sensitivity analysis showed that excluding each trial from the overall analysis did not reveal a significant change in overall effect size of soy isoflavones on CRP concentration. Subgroup analysis based on most studied variables could not diminish the heterogeneity among studies (Table 3). Subgroup analyses revealed no significant change in circulatory levels of CRP following soy isoflavones intake compared with comparison group in each subgroup (except cross-over design).

The overall effect of soy isoflavones plus soy protein on serum CRP is shown in Fig. 3. Eleven studies with sixteen effect sizes assessed the effect of soy isoflavones plus soy protein on serum CRP levels. The overall estimates indicated a non-significant effect on serum levels of CRP following soy isoflavones plus soy protein intake in comparison with control group (WMD= −0.02 mg/L 95 % CI: −0.12, 0.08; p = 0.715) with high heterogeneity (Cochrane's Q test, $p < 0.001$, $I^2 = 84.9$ %). Sensitivity analysis showed that excluding each trial from the overall analysis did not reveal a significant change in overall effect size of soy isoflavones plus soy protein on CRP concentration. The between-group heterogeneity was not significant in trials using soy isoflavones >100 mg/d (Cochrane's Q test, p = 0.600, $I^2 = 0.00$ %), in trials with parallel design (Cochrane's Q test, p = 0.074, $I^2 = 53.7$ %), in trials performed with study duration>56 day (Cochrane's Q test, p = 0.074, $I^2 = 47.9$ %) and in trials conducted in healthy people (Cochrane's Q test, p = 0.330, $I^2 = 13.2$) (Table 4). In subgroup analysis based on BMI, it was indicated that soy isoflavones plus soy protein could increase CRP levels in people with BMI ≤ 26 (p = 0.045), but a non-significant reduction was observed in people with BMI > 26 (p = 0.121). However, in subgroup analysis revealed no significant change in circulatory levels of CRP following soy isoflavones plus soy protein intake compared with comparison group in other subgroups (Table 4).

3.5. Meta-regression analysis and publication bias

Meta-regression analysis was used to explore possible sources of heterogeneity and to find characteristics of participants or trials with effective treatment effects. The result of univariate meta-regression analysis didn't show a significant linear association between soy isoflavones dose and effect size of soy isoflavones effect on CRP levels (Coefficient= −0.0004, 95 % CI: −0.03, 0.03; P = 0.977). Similarly, after adjustment for trial design, intervention duration, baseline CRP, participants' health status, sample size, geographical region, age, BMI, quality assessment, and publication year of article, dose of soy isoflavones did not have any linear association with effect size of soy isoflavones effect on CRP levels (Coefficient = 0.009, 95 % CI: -0.11, 0.13; P = 0.847). We also didn't find a significant association between other studied variables and effect size in univariate meta-regression analysis. Regarding RCTs which indicated soy isoflavones effect, funnel plot was

Table 2
Quality of bias assessment of the included studies according to the Cochrane guidelines.

Author name, year of publication, references	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall quality
Acharjee, 2015 [25]	U	U	H	U	L	L	Fair
Aubertin-Leheudre, 2007[30]	U	H	L	U	L	L	Good
Azadbakht, 2007[26]	U	U	H	U	L	L	Fair
Bakhtiari, 2019[31]	L	L	H	L	L	L	Good
Christie, 2010[32]	L	L	L	U	L	H	Good
Colacurci, 2005[33]	L	U	U	U	L	L	Good
D'Anna, 2005[34]	U	U	L	U	L	L	Good
Gonźalez, 2007[46]	L	H	U	U	L	L	Good
Greany, 2008[35]	U	U	H	U	L	L	Fair
Hall, 2005[27]	L	U	L	U	L	H	Good
Jenkins, 2002[24]	U	H	H	H	L	H	Weak
Lebon, 2014[28]	L	U	L	L	U	L	Good
Liu, 2014[29]	L	L	L	L	L	L	Good
Liu, 2012[36]	L	U	L	L	L	L	Good
Llaneza, 2011[47]	L	U	L	L	L	L	Good
Llaneza, 2012[48]	U	H	L	L	L	U	Good
Mangano, 2013[49]	L	U	L	U	H	H	Fair
Nasca, 2008[50]	U	H	H	H	L	L	Fair
Riesco, 2012[51]	U	L	L	L	L	L	Good
Ryan-Borchers, 2006[52]	L	U	L	U	L	L	Good
Törmälä, 2008[53]	U	U	H	H	L	L	Fair
van Nielen, 2014[54]	L	U	L	L	L	L	Good
Yildiz, 2005[55]	U	U	H	H	L	L	Fair

L, low risk of bias; H, high risk of bias; U, unclear risk of bias.

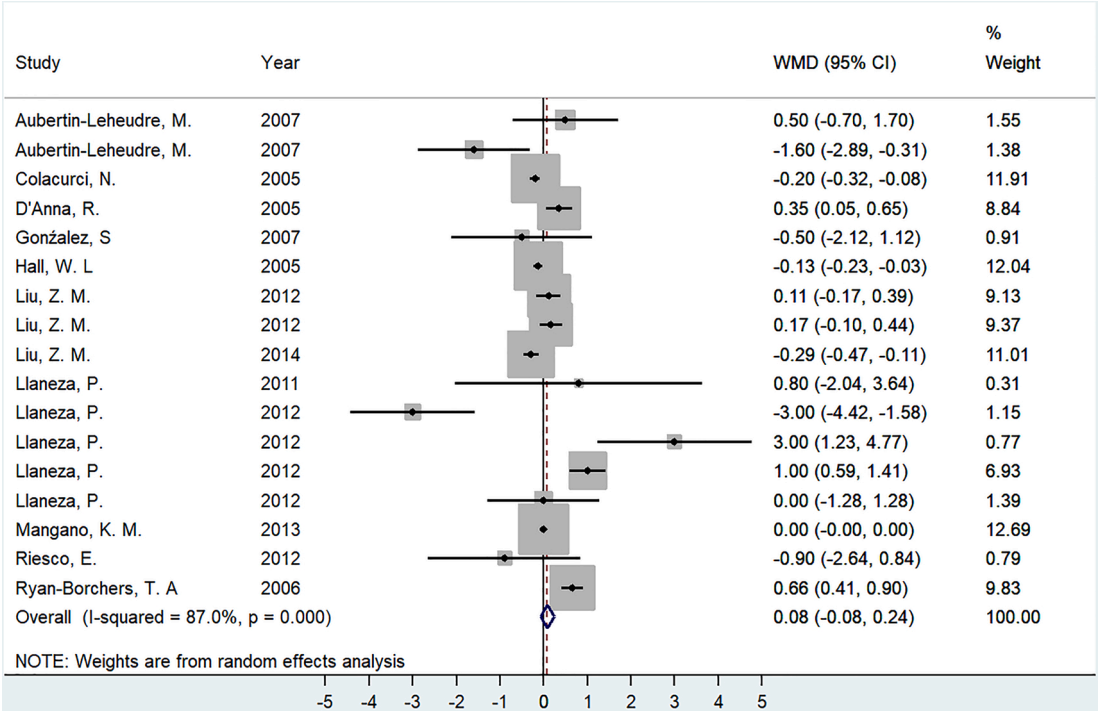

Fig. 2. Forest plot of the effect of soy isoflavones consumption on serum CRP concentrations.

Table 3
Results of subgroup analyses for studies evaluating the effect of soy isoflavones on serum CRP.

	Subgroup	No. of trial	Change in CRP (95% CI)	P-value	I^2 (%)	$P_{heterogeneity}$
Total	–	17	0.08 (−0.08, 0.24)	0.302	87.0	<0.001
Isoflavones dose (mg)	≤80 mg/d	13	0.07 (−0.22, 0.37)	0.627	89.6	<0.001
	>80 mg/d	4	0.00 (−0.002, 0.002)	0.967	0.00	0.475
Trial design	Parallel	15	0.12 (−0.08, 0.32)	0.243	88.0	<0.001
	Cross-over	2	−0.13 (−0.24, −0.80)	0.013	0.00	0.655
Intervention duration	≤168 day	13	0.04 (−0.09, 0.17)	0.541	81.8	<0.001
	>168 day	4	−0.17 (−2.37, 2.03)	0.881	93.6	<0.001
Baseline CRP (mg/l)	≤3 mg/l	12	0.11 (−0.05, 0.28)	0.174	90.4	<0.001
	>3 mg/l	5	−0.47 (−1.38, 0.44)	0.312	37.9	0.168
Health status	Healthy	5	0.08 (−0.09, 0.26)	0.336	92.2	<0.001
	At risk/disease	12	0.0 (-0.47, 0.41)	0.887	84.7	<0.001
Sample size	≤33	12	0.15 (−0.12, 0.42)	0.106	89.4	<0.001
	>33	5	−0.06 (−0.24, 0.11)	0.671	63.9	0.026
Geographical region	Americas	5	0.02 (−0.53, 0.57)	0.941	88.8	<0.001
	Europe	9	0.12 (−0.23, 0.47)	0.516	88.2	<0.001
	Asia	3	−0.02 (−0.33, 0.30)	0.912	81.0	0.005
Age	≤57 year	9	0.24 (−0.20, 0.67)	0.288	91.3	<0.001
	>57 year	6	−0.14 (−0.31, 0.02)	0.094	79.2	<0.001
	Unknown	2	0.31 (−0.02, 0.65)	0.068	2.2	0.312
BMI	≤29	8	0.01 (−0.13, 0.15)	0.923	88.2	<0.001
	>29	8	−0.02 (−1.16, 1.12)	0.970	85.7	<0.001
	Unknown	1	0.35 (0.18, 0.65)	0.021	–	–
Quality assessment	Good	16	0.08 (−0.16, 0.33)	0.520	87.5	<0.001
	Fair or weak	1	0.00 (−0.076, 0.002)	0.981	–	–
Publication year of article	≤2010	7	0.07 (−0.24, 0.37)	0.678	89.0	<0.001
	>2010	10	0.09 (−0.20, 0.38)	0.541	86.1	<0.001

CRP: C-reactive protein, BMI: body Mass index, g/d: gram per day, mg/l: milligram per liter, mg/d: milligram per day, CI: confidence interval.

not visually symmetric, but there was not any evidence of publication bias (Egger test p-value = 0.869 and Begg test p-value = 0.805) (Fig. 4).

Although, univariate meta-regression analysis did not show a significant linear association between soy isoflavones dose of combination of soy isoflavones plus soy protein dose and studied effect size (Coefficient= −0.008, 95 % CI: −0.02, 0.001; P = 0.082). Also, after adjustment for other variables, no significant association between dose of soy isoflavones and studied effect size was observed (Coefficient= −0.005, 95 % CI: −0.02, 0.01; P = 0.447). Although the funnel plot was not visually symmetric for the studies included in meta-analysis of soy isoflavones plus soy protein (Fig. 5), the results from the Egger and Begg tests did not show evidence of publication bias (Egger test p-value = p = 0.832 and Begg test p-value = 0.418).

4. Discussion

As far as we know, this is the first meta-analysis which reported the effect of soy products based on soy isoflavones and the combination of

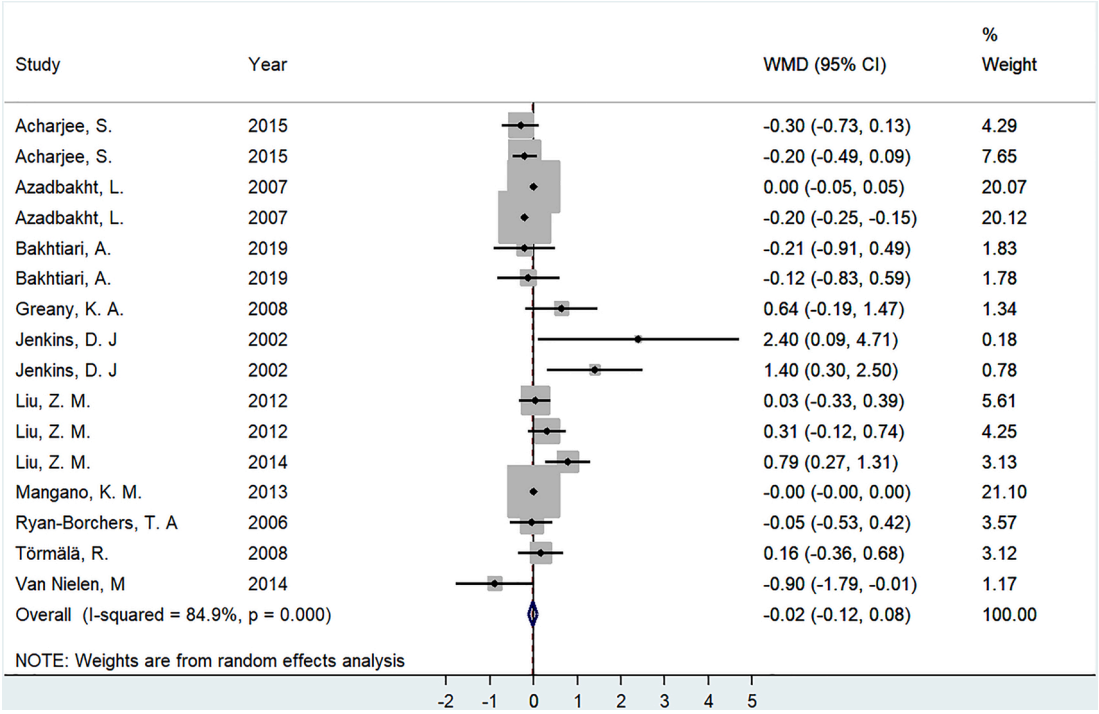

Fig. 3. Forest plot of the effect of soy isoflavones plus soy protein consumption on serum CRP concentrations.

Table 4
Subgroup analyses for studies evaluating the effect of soy isoflavones plus soy protein on serum CRP.

	Subgroup	No. of trial	Change in CRP (95% CI)	P-value	I^2 (%)	$P_{heterogeneity}$
Total	–	16	−0.02 (−0.12, 0.08)	0.715	84.9	<0.001
Isoflavones dose (mg)	≤100 mg/d	9	0.23 (−0.12, 0.57)	0.196	79.9	<0.001
	>100 mg/d	7	−0.001 (−0.004, 0.002)	0.622	0.00	0.600
Protein dose (g)	≤18 g/d	8	−0.01 (−0.12, 0.09)	0.812	91.1	<0.001
	>18 g/d	8	−0.07 (−0.32, 0.46)	0.730	65.1	0.005
Trial design	Parallel	7	0.10 (−0.10, 0.30)	0.321	53.7	0.074
	Cross-over	9	−0.07 (−0.24, 0.10)	0.419	90.0	<0.001
Intervention duration	≤56 day	9	−0.07 (−0.24, 0.10)	0.419	84.9	<0.001
	>56 day	7	0.10 (−0.10, 0.30)	0.321	47.9	0.074
Baseline CRP (mg/l)	≤2.5 mg/l	8	0.11 (−0.10, 0.32)	0.313	67.2	0.003
	>2.5 mg/l	8	−0.09 (−0.26, 0.09)	0.330	84.0	<0.001
Health status	Healthy	5	0.004 (−0.13, 0.12)	0.947	13.2	0.330
	At risk/disease	11	0.011(−0.15, 0.17)	0.892	84.3	<0.001
Sample size	≤35	8	−0.05 (−0.31, 0.21)	0.705	58.0	0.020
	>35	8	0.0 (−0.12, 0.20)	0.615	86.8	<0.001
Geographical region	Americas	5	0.38 (−0.1, 0.87)	0.130	68.6	0.013
	Europe	2	−0.31 (−1.34, 0.73)	0.562	75.4	0.044
	Asia	9	−0.03 (−0.18, 0.11)	0.643	83.9	<0.001
Age	≤58 year	8	0.11 (−0.13, 0.36)	0.372	59.1	0.017
	>58 year	6	0.06 (−0.43, 0.55)	0.799	66.1	0.011
	Unknown	2	−0.10 (−0.30, 0.10)	0.317	97.0	<0.001
BMI	≤26	8	0.36 (0.01, 0.72)	0.045	65.8	0.005
	>26	7	−0.08 (−0.18, 0.02)	0.121	91.3	<0.001
	Unknown	1	−0.90 (−1.79, −0.02)	0.048	–	–
Quality assessment	Good	7	0.06 (−0.26, 0.38)	0.713	57.9	0.027
	Fair or weak	9	−0.05 (−0.16, 0.06)	0.351	90.5	<0.001
Publication year of article	≤2010	7	0.02 (−0.17, 0.21)	0.833	87.7	<0.001
	>2010	9	−0.01 (−0.20, 0.18)	0.908	58.2	0.014

CRP: C-reactive protein, BMI: body Mass index, g/d: gram/day, mg/l: milligram per liter, mg/d: milligram per day, CI: confidence interval.

soy isoflavones and soy protein on serum CRP levels among postmenopausal women.

Our systematic review contains 23 articles which studied the effects of soy isoflavones and soy isoflavones plus soy protein on serum CRP concentration. Meta-analysis contains 19 articles with 33 datasets and its results indicated that soy isoflavones and soy isoflavones plus soy protein could not change CRP concentration among postmenopausal women. Our meta-analysis results confirm the result of a meta-analysis in year 2011[37] which reported the effect of overall soy products. Furthermore, these results revealed that new published papers with longer treatment duration, using higher dose of soy isoflavones or soy protein, and more sample size could not change the non-significant effect of soy products on serum CRP levels in previous article. The results of another meta-analysis regarding soy effects on postmenopausal

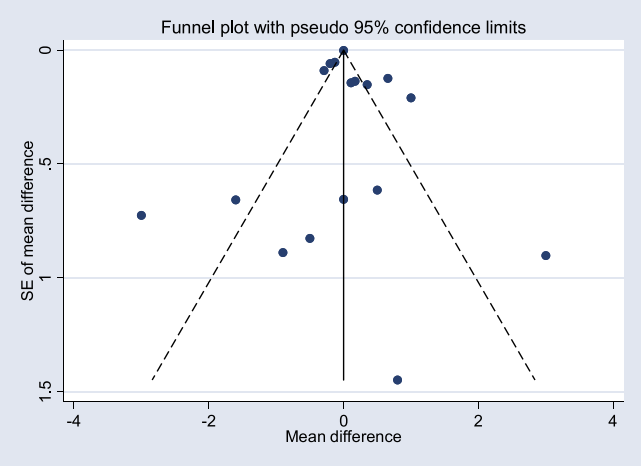

Fig. 4. Funnel plots for the studies of the effects of soy isoflavones consumption on serum CRP concentrations.

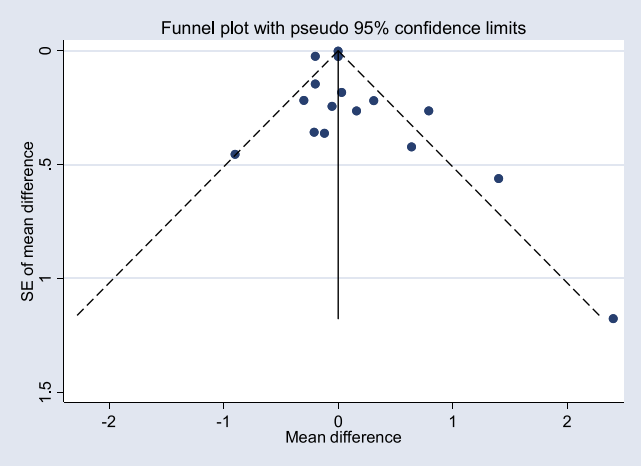

Fig. 5. Funnel plots for the studies of the effects of soy isoflavones plus soy protein consumption on serum CRP concentrations.

women revealed beneficial effects of soy products on lipid profile.[56]

There was a considerable heterogeneity between included studies even in most subgroup analyses. The probable reasons might be related to discrepancies in the ability of study papulation in metabolization and absorption of isoflavones, participants' intestinal flora, dietary habit and genetic background of the participants. However, CRP distributions and the methods used in the data process were seldom reported in each trial, which potentially might result in heterogeneity.

There was no significant change in serum levels of CRP in subgroup analysis based on dose, age, intervention duration, baseline CRP level, BMI, sample size, geographical region, quality assessment, publication year, and health status. Dose response analysis revealed no association of higher dose of soy isoflavones with isoflavones effect on CRP levels.

Review articles revealed that some nutrients might have changed inflammatory mediators.[57,58] Results of vitro,[59] human[60] and animal[61] studies have indicated that soy products can reduce the activity of nuclear factor-κB (NF-κB) as cytokine-induced signal transduction thereby decreases the concentration of pro-inflammatory cytokine. Furthermore, new evidence suggested that IL-6 by activating NF-κB is able to induce CRP expression.[62] Therefore, in participants with health condition who enhance IL-6 levels, soy products by inhibition of IL-6 effect on NF-κB and CRP expression can reduce CRP levels, but these results were not confirmed in our meta-analysis.

The absence of a significant effect in this study might have been due to: baseline CRP concentration, equol-producer status and duration of intervention. In this study, CRP levels in most included articles were in normal range, therefore; non-significant effect might be due to low levels of CRP.

Equol is an isoflavandiol estrogen produced by the action of intestinal bacteria on daidzein.[63] Although equol has the superior antioxidant activity in comparison with other isoflavones, most people are not able to produce equol. In a study by Acharjee et al., [25] it was revealed that taking soy products causes no significant changes in blood CRP levels among equol non-producing women, but equol-producers indicated a significant reduction. Most articles in our meta-analysis did not report any information regarding equol production in participants and we could not perform subgroup analysis based on equol non-producers and equol-producers.

According to the results obtained from subgroup analysis for soy isoflavones effect on CRP, there was a greater, although not significant, reduction among trials with a duration longer than 168 days compared with those with a duration shorter than 168 days. Therefore, it is possible that a longer period is required to produce a significant reduction.

Our systematic review and meta-analysis have several limitations. First of all, most articles did not have any information related to equal production among participants; therefore, we did not assess whether equal production could change non-significant effect of soy products on CRP to significant effect among elderly subjects. Secondly, participants' dietary habits were not reported in any article. Since, the dietary habits might change intestinal flora and the absorbed absorption amount of isoflavones, not considering the confounding effect of dietary habits is an important problem. Thirdly, most articles did not have any information regarding medicine used by participants. Some medicine might have anti-inflammatory effect and change the results. Fourthly, trials included in this meta-analysis had small or moderate sample size. Small sample size does not have an adequate statistical power to detect a significant effect in trials and in the meta-analysis. Fifthly, no article measured serum levels of isoflavones; therefore, the actual absorbed values of isoflavones were not clarified. Sixthly, even though changes in fat mass are very important factor in inflammatory mediators levels, most RCTs did not report any information related to changes in body-composition. Seventhly, we did not include non-English articles.

Our meta-analysis had a number of strengths in comparison with previous meta-analysis. Firstly, a large number of studies were included in meta-analysis; therefore, we could conduct subgroup analysis based on dose, trial design, health status, age, intervention duration, baseline CRP level, sample size, geographical region, BMI, quality assessment, and publication year. Secondly, we included RCTs which used only soy products in form of supplements or natural soy products and we excluded studies with other food supplements beside soy products. Thirdly, our meta-analysis included 19 trials from different countries; therefore, we limited the differences in lifestyles in this study. Fourthly, we reported the effect of soy isoflavones or the combination of soy isoflavones and soy protein separately with sufficient effect sizes. Fifthly, in the current study, we used a broad search terms to find all published studies by systematic search across multiple databases and also made contact with corresponding authors for clarification and additional data, which caused to reduce the potential misclassification and publication bias. Sixthly, our study was limited to RCTs and most of them were double-blinded which had highest quality in comparison with other papers. Seventhly, we did not have any limitation on publication time.

In conclusion, according to our study results, published RCTs did not provide strong evidence regarding beneficial effect of soy isoflavones or the combination of soy isoflavones and soy protein on CRP concentration among postmenopausal women. Future studies should report soy effect among equol producers and non-producers and assess intestinal microbial composition.

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Declaration of Competing Interest

No conflict of interest.

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