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REVIEW ARTICLE

Effect of soy isoflavones on circulating C-reactive protein in postmenopausal women: meta-analysis of randomized controlled trials

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Abstract

Strong evidence suggests that C-reactive protein (CRP) is a novel risk factor for cardiovascular disease. We aimed to examine the effect of soy isoflavones on circulating CRP concentrations in postmenopausal women by conducting a meta-analysis of randomized controlled trials. We performed a literature search using PubMed, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov databases in December 2010 for randomized controlled trials conducted in postmenopausal women, using soy foods with isoflavones or isoflavone extracts as treatment, and with a report of CRP change. A meta-analysis was performed using a fixed-effects model or a random-effects model to calculate the combined effect size. In addition, subgroup and metaregression analyses were carried out to examine the influences of study designs and participant characteristics on the effect estimates. A pooled analysis of 14 trials showed a slight, but not significant, reduction of 0.17 mg/L (95% CI, −0.38 to 0.04; $P = 0.12$) in CRP concentrations among postmenopausal women with soy isoflavone intervention compared with controls. No substantial heterogeneity was observed. Subgroup analyses showed that soy isoflavones significantly lowered CRP by 0.70 mg/L (95% CI, −1.17 to −0.23; $P = 0.003$) among women with baseline CRP concentrations greater than 2.2 mg/L. No significant changes in CRP were observed in the other subgroups. Metaregression analysis further revealed that baseline CRP was a potential effect modifier of isoflavone treatment in lowering CRP. The present meta-analysis found insufficient evidence that soy isoflavones significantly reduce CRP concentrations in postmenopausal women. However, soy isoflavones may produce a significant reduction in CRP among postmenopausal women with elevated CRP.

Key Words: Isoflavones – C-reactive protein – Postmenopausal women – Meta-analysis.

A large body of evidence suggests that C-reactive protein (CRP), one important marker of inflammation, is a novel risk factor and predictor of cardiovascular disease,[1,2] which remains the no. 1 killer among men and women in the United States.[3] The large Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial[4] has documented that, in healthy people without hyperlipidemia but with elevated CRP, rosuvastatin intervention lowered both low-density lipoprotein (LDL) cholesterol levels and CRP concentrations and significantly reduced the incidence of major cardiovascular events. This raises hopes that CRP-lowering interventions as a novel strategy may prevent cardiovascular disease.

Soy, which has been habitually consumed in Asia for hundreds of years, has received increasing scientific interest for its potential cardioprotective effects in general populations, particularly in postmenopausal women who are at increased risk of heart disease. The Shanghai Women's Health Study[5] and the Japan Public Health Center-Based Study[6] have added evidence to the strong hypothesis that dietary isoflavone consumption is associated with a significantly lower risk of cardiovascular disease in women. Furthermore, numerous clinical trials have documented the beneficial effects of soy isoflavones on lipid profiles, blood pressure, and vascular endothelial function.[7-9]

Evidence from cell studies and animal experiments[10-12] suggests that soy isoflavones may also exert anti-inflammatory effects, indicating a possible CRP-lowering role of isoflavones. A cross-sectional study in US adults has observed that isoflavone intake is inversely associated with CRP concentrations.[13] Clinical trials assessing the effect of isoflavones on CRP, however, yielded mixed results. Some observed that isoflavone intervention was associated with CRP reductions, whereas most suggested no effect. Notably, the sample sizes

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of these trials were relatively small, resulting in insufficient statistical power to detect a significant difference.

We therefore aimed to examine the effect of soy isoflavones on circulating CRP in postmenopausal women by conducting a meta-analysis of randomized controlled trials to increase the sample size and therefore enhance the statistical power and provide more precise estimates.

METHODS

Literature search

We attempted to follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[14] guidelines in the report of this meta-analysis. We searched PubMed, the Cochrane Central Register of Controlled Trials, and the ClinicalTrials.gov databases through December 2010 for relevant studies, using the terms *soybeans*, *soy foods*, *soy*, and *isoflavones* in combination with *C-reactive protein* and *inflammation*. We restricted our search to published studies concerning the effect of soy isoflavones on CRP. Non-English articles were translated when necessary. In addition, we manually searched the reference lists of original articles and recent reviews. We did not contact the authors for additional information. No attempt was made to identify unpublished studies.

Study selection

Studies were included if they (1) were randomized controlled trials of soy isoflavone extracts or soy foods containing isoflavones and had a control or a comparison arm, (2) were conducted in postmenopausal women, and (3) reported the net changes of CRP and their corresponding SDs or available data to calculate these values. The studies were excluded if the participants used hormone therapy or statins during the intervention because previous systematic reviews have clearly shown that hormone therapy can result in a significant rise in CRP[15] and all statins are effective in lowering CRP.[16,17]

Data extraction and quality assessment

We recorded study characteristics as follows: first author's name, publication year, and country of origin; design details, including whether parallel or crossover and open, single-blinding, or double-blinding; study duration; number of participants; daily dose of isoflavones, placebo, and other treatment intervention. We also recorded the following participant characteristics: health status; mean age or age range; body mass index; tobacco and alcohol use; and baseline mean LDL cholesterol and CRP concentrations. The data for CRP were converted into the same unit (mg/L). If more than one time point for follow-up was reported, we used the data from the longest follow-up. If one study included two independent strata, it was treated as two trials. The Jadad[18] scale was used to assess the methodological quality of each included trial. This instrument assigned scores for reported randomization, blinding, and withdrawals. Two of the authors (J.-Y.D. and L.-Q.Q.) independently performed the literature search, data extraction, and quality assessment. Any disagreements were resolved through discussion.

Data synthesis and analysis

The mean baseline CRP value for each trial was calculated by combining the mean values from the intervention and control groups, weighted by the number of participants. For parallel trials, the net changes were calculated by the difference (intervention minus control) of the changes (final values minus baseline values) of the mean values. For crossover trials, the net changes were calculated as the mean difference of values at the end of the intervention and control periods. Standard errors, CIs, and P values were converted to SDs for the analyses. The SDs for changes from baseline in each group were obtained. If not given, we imputed the missing SDs using the method of Follmann et al,[19] in which a correlation coefficient of 0.5 was assumed.

The homogeneity of the effect size among the studies was tested using the Q test at the $P < 0.10$ level of significance. We also calculated the I^2 statistic, which describes the proportion of total variation in study estimates that is caused by heterogeneity.[20] If a heterogeneity test is statistically significant, the random-effects model is advocated; otherwise, the fixed-effects model is appropriate.

To explore the possible influences of study designs and participant characteristics on net CRP change, we further conducted prespecified subgroup analyses stratified by study design (parallel or crossover), the duration of intervention, source and daily dose of isoflavones, and baseline CRP. Sensitivity analysis was conducted to investigate the influence of a single study on the overall effect estimate by omitting one study in each turn. We also performed a metaregression analysis to examine the quantitative influence of these variables on the effect sizes and to explore possible sources of heterogeneity across studies.

Potential publication bias was assessed using Begg funnel plots and the Egger regression test[21] at the $P < 0.10$ level of significance. All analyses were performed using STATA version 10.0 (Stata Corp., College Station, TX). $P < 0.05$ was considered statistically significant, except where otherwise specified.

RESULTS

Search results and study selection

We initially identified 864 potentially eligible studies, most of which were excluded because they were not randomized controlled trials or because the interventions were not relevant to our analysis. After assessing the full text of the 44 potentially relevant articles, we yielded 13 eligible articles,[22-34] including 14 trials for analysis. The main reasons for exclusion were as follows: 18 trials enrolled men or premenopausal women, and 9 studies did not report CRP data. In one trial, isoflavones were given as a part of the intervention,[35] and two trials enrolled postmenopausal women who used hormone therapy during the intervention.[36,37] We excluded another trial[38] because the data were reported as interquartile range and the baseline CRP substantially differed between treatment and control groups (34.1 vs 11.7 mg/L). A flowchart showing the study selection is presented in Figure 1.

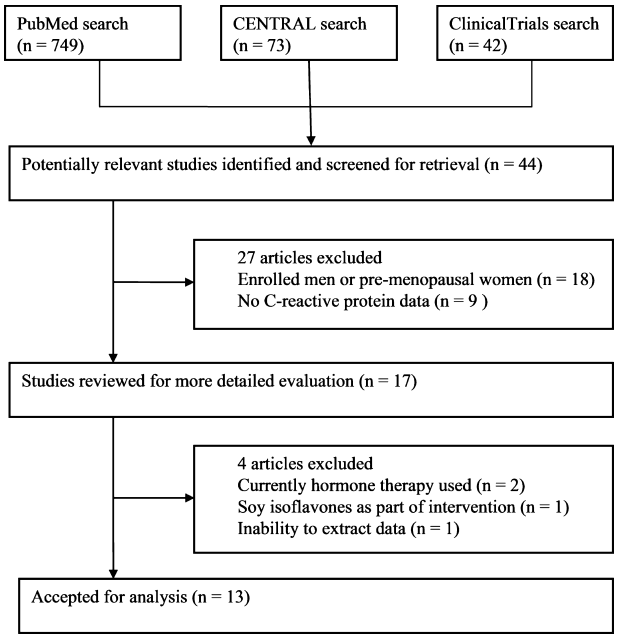

FIG. 1. Flow chart of study selection. CENTRAL, Cochrane Central Register of Controlled Trials.

Study characteristics

The characteristics of the studies and participants for the 14 trials that met the inclusion criteria are presented in Table 1. The trials were published between 2004 and 2008. Of the 14 trials, 7 were conducted in the United States, 5 in Europe, 1 in Iran, and 1 in Australia. The sample size varied from 12 to 113, with a sum of 603 and a median of 40. The treatment was double-blinding in seven trials, single-blinding in one trial, and open in six trials. Eight trials were parallel-designed, and the others had a crossover design. The duration of intervention lasted from 6 to 48 weeks, with a median of 12 weeks. Six trials used soy isoflavone extracts, and eight used soy protein, soy milk, or other soy foods containing isoflavones. The dose of isoflavones varied from 34 to 132 mg/day, with a median of 70 mg/day. Most of the control group received placebo or milk products. The quality of these trials ranged from 1 to 5, with a mean of 3.5.

All trials were conducted in postmenopausal women with ages ranging from 44 to 75 years. All trials enrolled apparently healthy women except two,[32] which enrolled women with type 2 diabetes or metabolic syndrome. The mean baseline body mass index varied from 25 to 32 kg/m^2. Most women were nonsmokers, and no women used hormone therapy or statins during the intervention. Baseline LDL cholesterol concentrations were reported in nine trials, and most were in the range between 3.3 and 4.1 mmol/L. Baseline CRP concentrations varied from 1.35 to 5.25 mg/L, with a median of 2.2 mg/L.

Effect of soy isoflavones on CRP

The net changes and corresponding 95% CIs for CRP in each trial and overall are presented in Figure 2. Compared with no intervention (control), soy isoflavone intervention was associated with an average net change in CRP ranging

TABLE 1. *Characteristics of the trials and participants in this meta-analysis*

Author	Year	Country	Study design	Duration, wk	Sample size	Source of isoflavones	Isoflavone dose, mg/day	Control	Jadad scores	Participants	Mean age or age range, y	Mean BMI or BMI range, kg/m^2	Smoking, cigarettes/d	Baseline LDL-C, mmol/L	Baseline CRP, mg/L	Change in CRP, mg/L (treatment vs control)
Teede et al[22]	2004	Australia	R, DB, P, PC	12	50	SPI	118	Casein	4	Healthy PMW	61	25	0	NR	1.7	0.42 vs 0.48
Colacurci et al[23]	2005	Italy	R, Open, P, PC	24	57	Isoflavone extracts	60	Placebo	3	Healthy PMW	55.4	26	0	3.7	1.35	−0.1 vs 0.1
D'Anna et al[24]	2005	Italy	R, DB, P, PC	24	55	Genistein	54	Placebo	4	Healthy PMW	50-60	NR	<10	NR	1.71	0.4 vs 0.05
Hall et al[25]	2005	Europe	R, DB, X, PC	8	113	Isoflavone extracts	50	Placebo	5	Healthy PMW	45-70	20-32	<5	3.59	1.67	−0.01 vs 0.12
Yildiz et al[26]	2005	Turkey	R, SB, P, PC	24	40	Isoflavone extracts	40	Placebo	3	Healthy PMW	50	27	0	3.95	2.8	−1.3 vs 0
Hanson et al[27]	2006	US	R, DB, P	6	27	Soy with isoflavones	85	Soy without isoflavones	4	Healthy PMW	60	26	0	NR	1.44	0.3 vs 0
Lukaczer et al[28]	2006	US	R, Open, P	12	42	Soy protein	34	AHA diet	3	Healthy PMW	54.6	32	NR	4.25	4.05	−1.68 vs −0.22
Ryan-Borchers et al[29]	2006	US	R, DB, P, PC	16	37	Soy milk	71.6	Cow milk	5	Healthy PMW	55.4	28	0	NR	2.75	−0.11 vs −0.05
Aubertin-Leheudre et al[30]	2007	US	R, DB, P, PC	48	20	Isoflavone extracts	70	Placebo	5	Obese healthy PMW	58	30	0	3.36	3.5	−0.3 vs 1.3
Azadbakht et al[31]	2007	Iran	R, Open, X	8	42	Soy protein	80	DASH diet	2	PMW with MS	NR	NR	NR	NR	3.4	−0.1 vs 0
Gonzalez et al[32]	2007	UK	R, DB, X, PC	12	26	Isoflavone extracts	132	Placebo	5	PMW with T2DM	NR	30	NR	3.4	5.25	0.8 vs 1.3
Greany et al[33]	2008	US	R, Open, X	6	34	SPI	44	Milk protein	2	Healthy PMW	57.7	25	0	3.46	2.6	0.35 vs −0.29
Nasca et al[34] (1)	2008	US	R, Open, X	8	48	Soy nut	101	Nonsoy protein	1	Healthy PMW	53.5	25.4	0	3.7	2.2	−0.6 vs 0
Nasca et al[34] (2)	2008	US	R, Open, X	8	12	Soy nut	101	Nonsoy protein	1	Healthy PMW	58.3	28	0	4.2	2	−0.1 vs 0

AHA, American Heart Association; BMI, body mass index; CRP, C-reactive protein; DASH, Dietary Approaches to Stop Hypertension; DB, double-blinding; LDL-C, low-density lipoprotein cholesterol; MS, metabolic syndrome; NR, not reported; P, parallel; PC, placebo-controlled; PMW, postmenopausal women; R, randomized; SB, single-blinding; SPI, soy protein isolate; T2DM, type 2 diabetes mellitus; X, crossover.

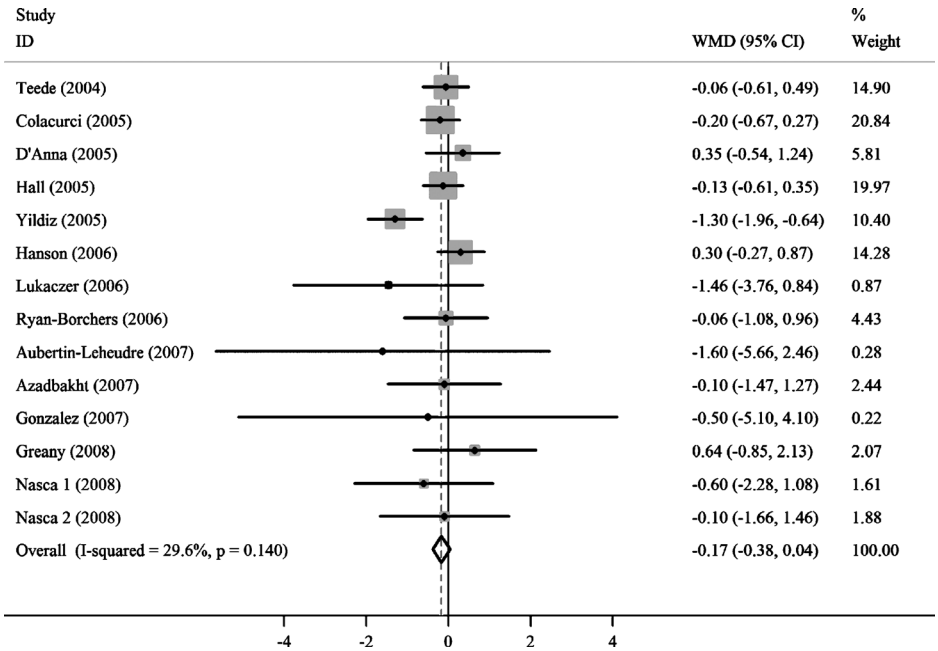

FIG. 2. Pooled effect size of soy isoflavones on C-reactive protein (mg/L) in postmenopausal women. WMD, weighted mean difference.

from −1.60 to 0.64 mg/L. CRP decreased in response to isoflavone intervention in 10 of the 14 trials, but the reduction was statistically significant in only one trial.[26] The overall pooled estimate of the effect of soy isoflavones on CRP was −0.17 mg/L (95% CI, −0.38 to 0.04; P = 0.12). This is equivalent to an 8% reduction in CRP concentrations from baseline. Tests for heterogeneity showed no significant differences in overall combined effect across studies (P = 0.14; I^2 = 29.6%).

Subgroup and sensitivity analyses

Prespecified subgroup analyses were carried out according to study design, intervention duration, source and daily dose of isoflavones, and baseline CRP concentration. Overall, isoflavone intervention produced a significantly greater reduction of 0.70 mg/L (95% CI, −1.17 to −0.23; P = 0.003; n = 7) in CRP among postmenopausal women with a baseline CRP concentration greater than 2.2 mg/L. This is equivalent to a 22% reduction in CRP concentrations from baseline in this group. No significant changes in CRP were observed among the other subgroups (Table 2). In the sensitivity analyses, omitting the trial by Hanson et al[27] resulted in a significant reduction of 0.25 mg/L (95% CI, −0.49 to −0.02) and omitting the trial by Yildiz et al[26] resulted in a small reduction of 0.04 mg/L (95% CI, −0.27 to 0.19), whereas none of the other trials seemed to substantially influence the treatment effect (from −0.20 [95% CI, −0.43 to 0.02] to −0.16 mg/L [95% CI, −0.41 to 0.08]). Further analysis using a random-effects model yielded a similar effect size of −0.18 mg/L (95% CI, −0.49 to 0.12; P = 0.25).

TABLE 2. *Results of subgroup analyses according to trial or participant characteristics*

Group	No. of trials	Net change in CRP, mg/L (95% CI)	P	$P_{heterogeneity}$	I^2, %	$P_{interaction}$
Total	14	−0.17 (−0.38 to 0.04)	0.12	0.14	29.6	
Study design						0.70
Parallel	8	−0.24 (−0.68 to 0.21)	0.30	0.02	58.8	
Crossover	6	−0.12 (−0.52 to 0.29)	0.57	0.92	0	
Study duration, wk						0.27
<12	6	0.04 (−0.29 to 0.37)	0.87	0.74	0	
≥12	8	−0.35 (−0.82 to 0.11)	0.14	0.07	47.3	
Source of isoflavones						0.30
Isoflavone extracts	6	−0.36 (−0.89 to 0.17)	0.18	0.04	57.7	
Soy foods	8	0.04 (−0.29 to 0.37)	0.77	0.70	0	
Isoflavone dose, mg/day						0.36
≤70	7	−0.32 (−0.84 to 0.20)	0.22	0.03	58.2	
>70	7	0.03 (−0.31 to 0.37)	0.87	0.93	0	
Baseline CRP, mg/L						0.04
≤2.2	7	−0.02 (−0.26 to 0.22)	0.87	0.75	0	
>2.2	7	−0.70 (−1.17 to −0.23)	0.003	0.17	34.4	

CRP, C-reactive protein.

Metaregression analysis

Because the tests for heterogeneity often have low power,[39] we used a metaregression analysis to identify the sources of heterogeneity and to assess whether the study or participant characteristics influence the effect estimates. To minimize the likelihood of false-positive results,[40] we carefully selected a small number of covariates: baseline CRP concentration, intervention duration, and the dose of isoflavone. In the univariate metaregression analysis, baseline CRP was significantly associated with the effect estimate ($P = 0.03$) and accounted for 76% of the total between-study variation, whereas the duration and dose were not associated with the net change in CRP ($P = 0.15$ and 0.16 for duration and dose, respectively). The multivariate model showed that the association between baseline CRP and the treatment effect became borderline significant ($P = 0.06$) after adjustment for duration and dose, and this model explained 88% of the total between-study variance. Baseline CRP therefore was considered a potential effect modifier and a major source of heterogeneity among trials.

Publication bias

There were no signs of publication bias when the Begg funnel plot was inspected. The results from the Egger test also did not indicate evidence of publication bias ($P = 0.65$).

DISCUSSION

To our knowledge, this is the first quantitative systematic analysis that evaluates the effect of soy isoflavones on circulating CRP. The present meta-analysis of 14 trials consisting of 603 participants showed a slight, although not significant, reduction of 0.17 mg/L (95% CI, −0.38 to 0.04; $P = 0.12$) in CRP concentrations among postmenopausal women in response to soy isoflavone intake compared with control. No substantial heterogeneity was observed. However, the subgroup analyses showed isoflavones significantly lowered CRP by 0.70 mg/L (95% CI, −1.17 to −0.23; $P = 0.003$) among postmenopausal women with baseline CRP concentrations greater than 2.2 mg/L. Metaregression further revealed that the baseline CRP was borderline significantly associated with effect size and largely contributed to the heterogeneity among trials.

The absence of an intervention effect may be explained by several factors: baseline CRP concentration, duration of intervention, and equol-producer status. Women involved in most trials were apparently healthy, and the baseline CRP concentrations were generally within the reference ranges. Therefore, there may be less room for improvement. In fact, a clinical trial by Chan et al[41] documented that patients who had ischemic stroke with established atherosclerosis and an elevated CRP concentration of 4.6 mg/L experienced a significant CRP reduction of 1.7 mg/L (95% CI, −3.3 to −0.1) in response to isoflavone intervention compared with placebo. In line with their finding, the results from our subgroup and metaregression analyses indicate that baseline CRP concentrations are very likely to modify the magnitude of treatment effect, that is, the higher the baseline concentration, the greater the reduction.

Subgroup analysis according to intervention duration showed a greater, although not significant, reduction among trials with a duration of 12 weeks or longer compared with those with a duration shorter than 12 weeks (−0.35 vs 0.04 mg/L; $P_{interaction} = 0.27$). A longitudinal randomized clinical trial[42] of 4 years in patients with diabetes found that soy protein containing isoflavones significantly decreased CRP compared with control (−1.31 vs −0.33 mg/L; $P_{interaction} = 0.02$). Therefore, it is possible that a longer period is required to produce a significant reduction.

Equol is the metabolite of one soy isoflavone, daidzein. There is rapidly growing interest in equol because of its superior antioxidant activity compared with other isoflavones.[43] It is hypothesized that isoflavones may exert anti-inflammatory activities for their antioxidant properties. If this is true, then the absence of effect in the present study is probably caused by the fact that most women involved in the analysis were from Western countries where only 25% to 30% of the adult populations have the capacities to produce equol.[44] Because 50% to 60% of adults from China, Japan, and Korea are equol-producers,[44] further studies in these populations are warranted to address the effects of equol on cardiovascular risk factors, including CRP.

Despite the insufficient evidence of effect in the present study, biological plausibility exists for the potential CRP-lowering role of isoflavones. It is known that CRP is principally induced by interleukin-6 through a mechanism involving the activation of nuclear factor-κB (NF-κB), a key regulator of proinflammatory mediator synthesis.[45,46] There is consistent evidence that soy isoflavones have the ability to block the nuclear translocation of NF-κB and inhibit its activation.[47,48] Therefore, it is probable that the effects of isoflavones on CRP expression could be mediated, at least partly, through the modulation of the NF-κB–dependent pathway.

The limitations of the present study should be considered. The sample sizes of individual trials included in this meta-analysis were relatively small or moderate. In a randomized controlled trial, randomization helps ensure that the treatment and control groups are similar in all characteristics that may affect the outcome. However, it cannot guarantee that the groups are comparable when the sample size is small, which limits the capacity of randomization to minimize the potential influence of confounding factors. Furthermore, the small sample size resulted in insufficient statistical power to detect a significant effect in individual trials and in the present meta-analysis. Another concern is the biological properties of CRP. As a classical member of acute-phase reactants, CRP rises dramatically during the inflammatory process. Several,[23,25,28] but not all, trials explicitly reported that women with a systematic infection or inflammation were excluded from the study, which may potentially influence the outcome. However, the possibility of this influence is small in our meta-analysis because most trials (12 of 14) enrolled apparently healthy women and the CRP concentrations were generally

within the reference range. In addition, the sources of isoflavones varied among the trials. Because of limited available evidence, we cannot exclude the possibility that the various sources of isoflavones may have impacts on treatment effects, although subgroup analyses did not detect significant differences. Finally, substantial asymmetry has been noted in CRP distribution, and log-transformed data are often used in the statistical analysis. However, the distributions of CRP and the methods used in the data process were seldom reported in individual trials, which potentially resulted in heterogeneity and affected the combined effect size.

Our study also has strengths. No substantial heterogeneity was observed in this meta-analysis. The participants were all postmenopausal women, and most of them were apparently healthy, with cardiovascular risk factors within the reference ranges. The possibility that genetic variation influenced the effect size was small because most of the trials (12 of 14) were conducted in Europe and United States, where women did not habitually consume isoflavones or soy foods and had relatively small differences in genetic susceptibility to isoflavones. Moreover, none of the women used hormone therapy or statins during the intervention, and most of the women were nonsmokers, which further eliminates the influences of these confounding factors. All of these facts help greatly to reduce clinical heterogeneity and assist in achieving reliable and precise results.

In addition to the relatively high degree of internal validity noted previously, we were able to detect factors that potentially modified the effect size and to explore sources of the moderate heterogeneity. With the help of subgroup and meta-regression analyses, we have successfully identified baseline CRP concentration as a potential effect modifier and as a major contributor to the overall between-study variation. Finally, our findings are unlikely to result from publication bias, as indicated by the results of the Begg funnel plot and the Egger test.

CONCLUSIONS

The present meta-analysis found insufficient evidence that soy isoflavones significantly reduce CRP in postmenopausal women. However, soy isoflavones may produce a significant reduction in CRP among postmenopausal women with elevated CRP concentrations. Large-scale long-term studies are warranted to confirm the potential CRP-lowering effect of isoflavones.

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