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Meta-analysis

Effects of non-soy legume consumption on C-reactive protein: A systematic review and meta-analysis

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ABSTRACT

Objectives: Because of conflicting results of presented studies, the aim of this systematic review and meta-analysis of randomized clinical trials (RCTs) was to examine the effect of non-soy legume intake on inflammatory markers and C-reactive protein (CRP).
Methods: We searched Pubmed, ISI Web of Knowledge, SCOPUS, and Google Scholar for relevant studies up to July 2013, using medical subject headings [MeSH] and other related keywords. Nine RCTs were systematically reviewed to examine the effect of non-soy legume consumption on inflammatory markers. Eight studies involving 464 participants were included in the meta-analysis.
Results: The results of the meta-analysis showed that non-soy legume consumption had a trend toward a significant effect on decreasing CRP and high-sensitivity (hs)-CRP concentrations (mean difference (MD) = −0.21; 95% confidence interval [CI], −0.44 to 0.02; $P = 0.068$). There was no overall effect of non-soy legume consumption on CRP or hs-CRP levels in either the parallel or crossover study designs. Our subgroup analysis of CRP type and study design, showed that non-soy legume intake had a significant effect on CRP levels in parallel studies (MD = −1.01; 95% CI, −1.78 to −0.23; $P = 0.011$) and a significant effect on hs-CRP levels (MD = −0.53; 95% CI, −0.95 to −0.11; $P = 0.014$) and in the crossover sub group (MD = −0.68; 95% CI, −1.28 to −0.08; $P = 0.026$).
Conclusions: This review of RCTs showed that non-soy legume consumption may contribute to reductions in CRP and hs-CRP concentrations. However, further controlled clinical trials are needed to investigate the effect of non-soy legume intake on other inflammatory markers.

Introduction

Inflammation may occur in response to acute major trauma, surgery, infections, or atherothrombotic events such as acute coronary syndromes (unstable angina or myocardial infarction), acute stroke, and chronic degenerative diseases such as arthritis [1]. The acute phase protein C-reactive protein (CRP) is a marker of general inflammation, which is elevated in the presence of several chronic diseases, including cardiovascular disease [2]; obesity [3,4]; type 2 diabetes [5]; and components of metabolic syndrome [6], including high blood pressure [7], waist circumference [8], fasting blood glucose [9], high-density lipoprotein cholesterol and triacylglycerols [10].

The effects of dietary components and patterns have been the focus of several studies assessing the interaction between diet and inflammation. These studies include the low glycemic index (LGI) [11] and the Dietary Approach to Stop Hypertension eating pattern diets [12], fruits and vegetables [13], red meat [14], nonhydrogenated vegetable oils [15], soy [16], micronutrients including non-heme iron and magnesium [17], and macronutrients, including ω-3 fatty acids [18] and low- and high-carbohydrate diets [19].

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Non-soy legumes are of interest due to their role in human health as part of LGI diets [20] and favorable effects on blood lipids [21]. Non-soy legumes include beans, lentils, peas, and chickpeas, all of which are sources of dietary fiber and resistant starch. Non-soy legumes are good sources of vegetable proteins; oligosaccharides; dietary fiber; minerals such as potassium, calcium, and magnesium; polyunsaturated fatty acids; and phytochemicals [22].

Although a larger body of evidence investigating the effect of soy consumption on inflammatory biomarkers exists [23–25], less is known about the role of non-soybeans. A recent study showed that the beneficial effects of non–soy-based diets on inflammatory markers is due to their LGI and low glycemic load (LGL) [26]. Low GI diets were associated with improved insulin sensitivity and lower CRP levels [27]. However, studies are limited, and there currently are no published systematic reviews examining the effect of non-soy legume consumption and inflammatory markers. Therefore, we conducted a systematic review and meta-analysis of published randomized clinical trials (RCTs) to determine the effect of non-soy legume consumption on CRP concentrations.

Methods and materials

Search strategy

We searched Pubmed, ISI Web of Knowledge, SCOPUS, and Google Scholar for relevant studies up to July 2013, using various keywords, including "Fabaceae," "bean/s," "gram," "faba," "pea(s)," "lentil," "lupin," "pulses," "legume/s" in combination with "inflammation," "c-reactive protein," "interleukin," "tumor necrosis factor," "insulin," "fasting blood sugar," "HbA_{1c} OR glycosylated hemoglobin," "HOMA-IR OR homeostasis model assessment of insulin resistance," "impaired fasting glucose," "triacylglycerols," "low-density lipoprotein," "high density lipoprotein," "very low-density lipoprotein" in our search because some interventional studies report inflammatory factors as a secondary outcome and the results may not be included in the abstract. Furthermore, a manual search of related articles supplemented the electronic search. There were no non–English-language articles to translate and our findings were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines. This systematic review and meta-analysis protocol is registered in the International Prospective Register of Systematic Reviews website: http://www.crd.york.ac.uk/prospero/index.asp (registration no: CRD42013003683).

Inclusion criteria

We included original trials investigating the effect of non-soy legume-enriched diets that measured at least one inflammatory marker in healthy participants, or in those with cardiovascular risk factors, including obesity, hypercholesterolemia, or insulin resistance. Only a few trials reported inflammatory conditions other than CRP concentrations, but these were excluded from the analysis. Of 212 potentially related clinical trials, nine were eligible for inclusion in this systematic review [3,28–35].

Exclusion criteria

Two reviewers independently reviewed each report. Trials were excluded if they did not employ randomization to allocate participants to treatment conditions, lacked a control group to compare the effect of legume-enriched diets, or were conducted with non-adult populations. We excluded studies of short duration (<1 wk). One study had data on inflammatory markers other than CRP and had a 1-d intervention; therefore it was excluded from the final meta-analysis [28]. Eight studies were included in the meta-analysis [4,29–35].

Data extraction

First author's last name, publication date, number of participants in the intervention and control groups, sex, mean ± SD of age, study design (parallel or crossover), dietary intervention type in experimental and control groups, study duration and mean ± SD of inflammatory markers before and after intervention were extracted by two reviewers. All studies reported the mean ± SD of CRP for both groups. However, one study did not report CRP by study design [29]. Thus, the authors were contacted and were asked to provide the mean ± SD of CRP concentrations in the intervention and control groups [29].

Statistical analysis

The mean change from baseline in CRP concentrations and SD for both intervention and control groups were used to calculate the effect size [36].The unit of analysis for CRP was mg/L. The SD of mean change from baseline in the intervention and control groups was calculated by using a previously described method [36]. We also used this coefficient to calculate the difference in SD between intervention and control groups for crossover studies. The summary of the overall mean difference (MD) with its corresponding SD was determined by employing a previously described method using the random effects model [37], which incorporates between-study variability. Meta-regression and subgroup analyses were performed to check for between-study heterogeneity. Subgroup heterogeneity was evaluated using the fixed effects model. Statistical heterogeneity between studies was evaluated with Cochran's Q test [38]. Sensitivity analysis was also used to explore the extent to which the overall effects depended on a particular study or group of studies. Publication bias was determined by visual inspection of Begg's funnel plots [39]. Formal statistical assessment of funnel plot asymmetry was done with Egger's regression asymmetry test and an adjusted rank correlation test [40]. Additionally, Begg's adjusted rank correlation test was used [40]. Statistical analyses were carried out by the use of Stata, version 11.2 (Stata Corp, College Station, TX, USA). *P*-values ≤ 0.05 were considered statistically significant.

Results

Figure 1 provides a detailed description of the trial selection process. In all, 480 participants between the ages of 20 to 75 y were enrolled in the selected trials. Duration of intervention periods were between 4 and 52 wk. Our primary search yielded 12,946 trials, of which 12,734 did not meet our inclusion criteria. We identified another 212 potentially related studies; however, 203 did not have data on inflammatory markers. Nine studies reported data on the effect of non-soy legume consumption on inflammatory markers [4,28–35]. Characteristics of included RCTs for systematic review are presented in Table 1.

One study did not include data on CRP concentrations and was of short duration (11–14 h); therefore, it was excluded from the meta-analysis [28]. The randomized crossover study provided healthy young adults with an evening meal of brown beans or white bread and evaluated the effect on cardiometabolic risk factors and inflammatory markers following standard breakfast the next day [28]. Two studies included legumes as part of energy-restricted diets. One study [4] used a hypocaloric diet as the control group and a legume-based hypocaloric diet for intervention group. Therefore, the effect of legumes may have been masked due to the effect of energy restriction alone. Another study [29] compared a legume-based diet with diet counseling to determine the ability to reduce energy intake (500 kcal/d) over 8 wk. At 8 wk, neither energy intake nor body weight differed between groups.

Four trials used a parallel design [4,29,31,32], whereas the others used a crossover design [30,33–35]. In three of the included studies, participants consumed a mixture of legumes, including beans, peas, chickpeas, and lentils [4,29,30], whereas one study used different type of bean including navy, pinto, kidney, and black beans during the intervention phase [33]. Two of the included studies substituted wheat flour with lupin flour [31,32], and the last two studies used pinto beans, black eyed-peas [34], or baked navy beans [35] as the dietary intervention. Participants included both men and women, except in one trial [33] where only men were included. Three trials were legume-based diets [4,30,33], whereas the remaining trials incorporated legumes into the habitual diets of participants.

The final meta-analysis included eight studies with 464 participants. Our meta-analysis of these eight trials [4,29–35] (Fig. 2) showed that non-soy legume consumption had a trend toward a significant decrease in CRP and hs-CRP concentrations

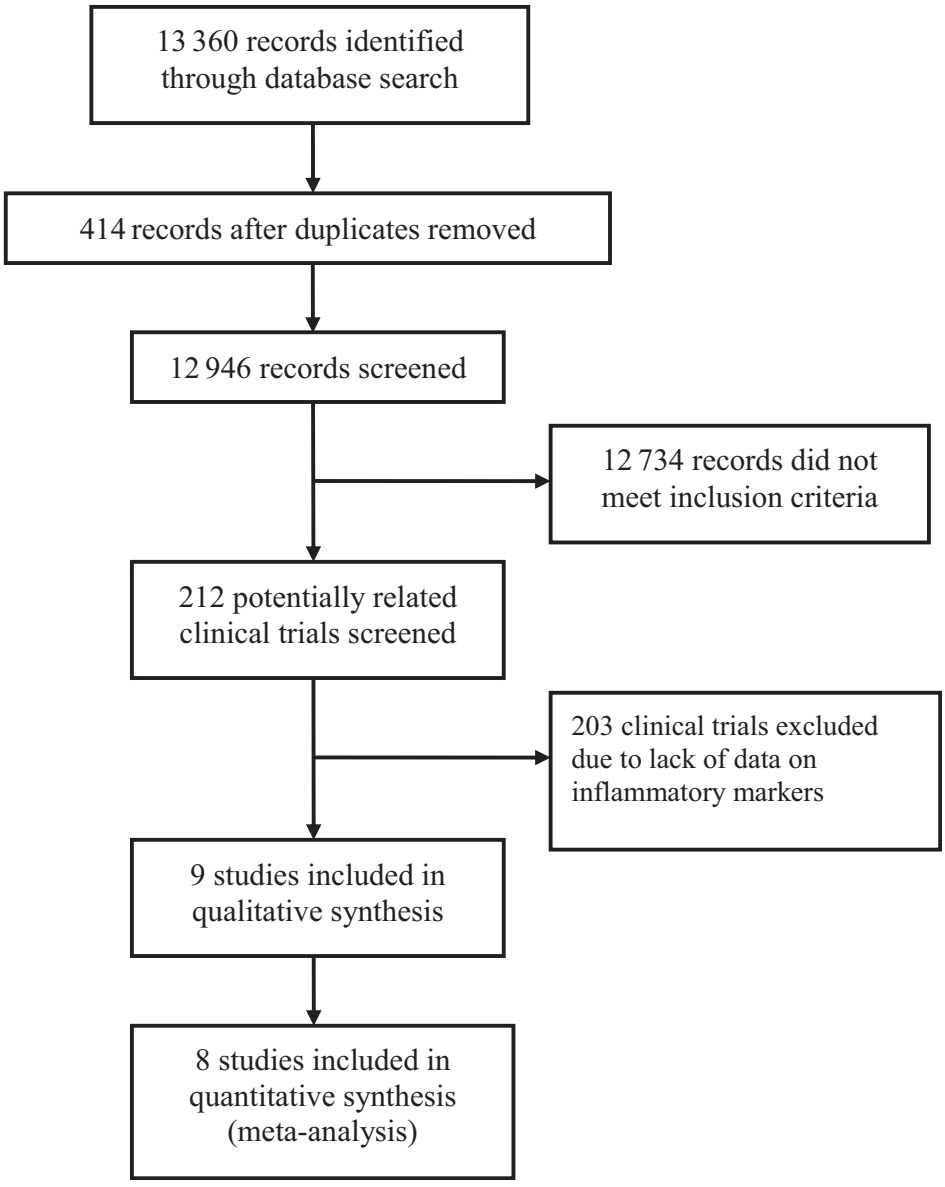

Fig. 1. Flowchart of study selection process.

(MD = −0.21; 95% confidence interval (CI), −0.44 to 0.02; $P = 0.068$; results from fixed-effect model: MD = −0.04; 95% CI, −0.11 to 0.03; $P = 0.216$). We included one study [34] as two separate studies because pinto beans and black-eyed peas were provided to different groups of participants and then compared with control group. However, the heterogeneity among studies was significant (Cochrane Q test, $P < 0.001$, $I^2 = 81.7\%$). To determine the source of heterogeneity, we divided the subgroup analyses according to their design: parallel [4,29,31,32] or crossover [30,33–35]. Subgroup analysis showed that the effect of non-soy legume consumption failed to achieve statistical significance either in the parallel design (MD = −0.69; 95% CI, −1.43 to 0.06; $P = 0.071$; results from the fixed effects model: MD = −0.44; 95% CI, −0.84 to −0.03; $P = 0.035$) (Fig. 3) or in crossover trials (MD = −0.13; 95% MD = −0.38 to 0.11; $P = 0.281$; results from fixed effect model: MD = −0.03; 95% CI, −0.1 to 0.04; $P = 0.37$) (Supplementary Fig. 1). Heterogeneity among parallel studies decreased (Cochrane Q test, $P = 0.141$, $I^2 = 45\%$); however, heterogeneity still remained significant in crossover trials (Cochrane Q test, $P < 0.001$, $I^2 = 88.4\%$). To minimize heterogeneity from the crossover subgroup analysis, we excluded one study [35] because the macro- and micronutrient composition of baked beans in sauce differed from the legumes, which may have contributed to increased heterogeneity (Fig. 3). However, the effect of non-soy legume consumption on CRP and hs-CRP levels failed to reach significance in the crossover trials by using a random effect model (MD = −0.24; 95% CI, −0.53 to 0.04; $P = 0.95$; results from fixed effect model: MD = −0.1; 95% CI, −0.18 to −0.02; $P = 0.014$) and heterogeneity between studies did not diminish (Cochrane Q test, $P < 0.001$, $I^2 = 86.4\%$) (Fig. 3). However, by removing the one study [35], the overall effect significantly decreased (MD = −0.32; 95% CI, −0.58 to −0.06; $P = 0.016$; results from fixed effect model: MD = −0.11; 95% CI, −0.19 to −0.03; $P = 0.005$) (Fig. 3).

We also conducted separate analyses based on the study design and CRP type: CRP or hs-CRP. Our analysis on four studies that examined the effects of non-soy legume intake on CRP levels [4,29,30,33] (Fig. 4) showed that the overall effect was not

Table 1
Characteristics of included randomized controlled trials to the systematic review investigating the effects of non-soy legume on CRP/hs-CRP levels

Author (y)	Participants and sex	Age range or mean of age (y)	Design	Intervention diet (name and composition)	Control diet (name and composition)	Duration	Data presented	Notes about participants	Results
Mollard et al. (2012)	All: 40 (29 F/11 M) Intervention: 19 (13 F/6 M) Control: 21 (16 F/5 M)	All: 35–55 y (45.5±6.32 y) Intervention: 43.5± 29.20 y Control: 47.3 ± 27.03 y	Randomized parallel– without matching	Pulse diet: 5 cups/wk (on average 896 g/wk); including yellow peas, chickpeas, navy beans, and lentils; incorporated into servings of (180–330 kcal) ad libitum diet	Counseling to energy restrict: Reduce energy intake by 2093 kJ/d (500 kcal/d) Carbohydrate: 45%–65%, fat: 20%–35%, protein: 10%–35%	8 wk	CRP (mg/L): All participants: Base = week 1: 4.59 ± 7.20 Week 4: 4.70 ± 5.565 Week 8: 3.52 ± 4.11	Overweight or obese (BMI 27–39.9 kg/m^2)	CRP did not change significantly
Abeysekara et al. (2012)	All:108 (91 F/37 M)	59.7 ± 6.3 y	Randomized single-blind crossover	Pulse-based diet: *150 g dry weight (2 servings) or 250 g wet weight daily Including: Lentils, chickpeas, beans and peas; 25% of meals containing legumes	Habitual diet	8 wk	CRP (nmol/L): (N = 87; 57 F/30 M) Base: 22.7 ± 26.1 After 2 mo: 19.1 ± 24.1	Inactive men and women (participating in moderate aerobic exercise (≤2/wk)	CRP did not change significantly
Hermsdorff et al. (2011)	All: 30 (13 F/17 M) Intervention: 15 Control: 15	36 ± 8 y	Randomized, parallel	Legume-based diet: 4 servings/wk; including lentils, chickpeas, peas, and beans 60 and 90 g (raw), or 160 and 235 g (cooked) Carbohydrate: 53%, protein: 17%, fat: 30% Hypocaloric diets (–30%)	Legume-restricted diet: Carbohydrate: 53%, protein:17%, fat: 30% Hypocaloric diets (–30%)	8 wk	Complement C3 IL-6 TNF-α Homocysteine CRP (mg/l): (N = 15) Base: 2.7 ± 2.4 (1.8-4) After: 1.6 ± 0.9 (1.2-3)	Obese (BMI: 32.5 ± 4.5 kg/m^2)	Complement C3, TNF-α, and CRP decreased significantly IL-6 and homocysteine did not change significantly
Belski et al. (2011)	All: 131 (63 F/68 M) Intervention: 68 (34 F/34 M) Control: 63 (29 F/34 M)	20–71 y Lupin: 46.5 ± 10.1 y Control: 46.7 ± 9.4 y	Randomized, controlled, double-blind parallel	Lupin group including bread, biscuits, and pasta Lupin flour in the lupin products was substituted for wheat flour primarily whole meal (25%–40% by weight) in an ad libitum diet	Control group: Bread, biscuits, and pasta Wheat flour, primarily whole meal in an ad libitum diet	52 wk	hs-CRP (mg/L) Base (N = 68): 2.93 ± 3.27 4 mo (N = 55; 26 F/29 M): 3.12 (2.22–4.01) 12 mo (N = 46;21 F/25 M): 2.56 (1.60–3.51)	Overweight and obese (BMI 27–35 kg/m^2), Healthy	CRP did not change significantly
Hodgson et al. (2010)	All: 88 Intervention: 37 (25 F/12 M) Control: 37 (23 F/14 M)	20–70 y Lupin: 59.0 ± 7.4 y Control: 56.8 ± 8.5 y	Randomized controlled parallel-design	Lupin group: Replace ∼15%–20% of habitual daily energy intake with lupin bread that substitutes 40% of wheat flour with LKF. Provided bread was replaced with usual bread (pasta, rice, and breakfast cereals)	Control group: Replace ∼ 15%–20% of habitual daily energy intake with white bread. Provided bread was replaced with usual bread (pasta, rice, and breakfast cereals)	16-wk	hs-CRP (mg/L): Base (N = 37): 5.01 ± 11.1 After (N = 37): 3.05 (1.96–4.14)	Overweight and obese men and women (BMI 25–35 kg/m^2)	CRP did not change significantly
Hartman et al. (2010)	All: 64 male	35–75 y Mean: 54.5 ± 7.8 y	Randomized crossover feeding trial	High-legume, LGI diet: ∼250 g legumes/d (1.5 cups) including navy, pinto, kidney, and black beans (main source of protein) Fat: 34% (11%–12% saturated fat), protein: 18%, carbohydrate: 50% GI = 38, GL = 84	Healthy American, high-GI diet: Chicken (main source of protein) Fat: 34% (11%–12% saturated fat), protein: 18%, carbohydrate: 50% GI = 69, GL = 152	4 wk	sTNFRI sTNFRII CRP (mg/L): Base (N = 64): 1.28 ± 9.92 After (difference): –0.259 ± 1.032	In global health weight-stable conditions	sTNFRI and CRP decreased significantly and sTNFRII decreased marginally
Winham et al. (2007)	All: 16 (9 F/7 M) 15 for hs-CRP analysis	22–65 y Mean: 43 ±11.62 y	Randomized, crossover 3 × 3 block design	Canned pinto beans Canned black-eyed peas 1/2 cup serving as a part of habitual diet	Canned North Pride brand sliced carrots 1/2 cup serving as a part of habitual diet	8 wk	hs-CRP (mg/L): Pinto (N = 15): Base: 3.4 ± 2.8 After: 3.0 ± 1.936 Black-eyed peas (N = 16): Base: 4.0 ± 5.6 After: 2.9 ± 2.711	generally healthy, mild to moderately insulin-resistant adults (fasting insulin level ≥15 μU/mL)	CRP did not change significantly

Winham et al. (2007)	All: 23 (13 F/10 M) 22 for hs-CRP analysis	24–67 y Mean: 45.9 ± 10.32 y	Un-blinded, 2 × 2 randomized crossover	baked beans (navy beans): a single 1/2 cup serving of vegetarian baked beans as part of habitual diet	canned carrots: a single 1/2 cup serving of carrots as a part of habitual diet	8 wk	hs-CRP (mg/L): Base (N = 22): 2.3 ± 2.34 After: 2.5 ± 2.34	Free-living hypercholesterolemic men and women (200 mg/dL ≤TC ≤ 260 mg/dL)	CRP did not change significantly
Nilsson et al. (2013)	All: 16 (10 F/6 M)	23.8 ± 0.7 y	Randomized crossover	Late evening meal: 101 g uncooked brown beans to provide 35 g available starch	89 g fresh white wheat bread to provide 35 g available starch	11–14 h	sIL-6 sIL-18	Healthy young volunteer with normal weight (22.5 ± 0.6 kg/m^2)	IL-6 and IL-8 decreased significantly

BMI, body mass index; CRP, C-reactive protein; hs, high-sensitivity; GI, glycemic index; GL, glycemic load; IL, interleukin; LGI, low glycemic index; LKF, lupin kernel flour; sIL, serum interleukin; sTNFR, soluble tumor necrosis factor-α receptors; TC, total cholesterol; TNF, tumor necrosis factor

significant (MD = −0.08; 95% CI, −0.28 to 0.12; $P = 0.416$; results from fixed effect model: MD = −0.04; 95% CI, −0.12 to 0.05; $P = 0.408$) and the overall heterogeneity was not significant (Cochrane Q test, $P = 0.106$, $I^2 = 50.9\%$). However, this effect was significant for parallel studies [4,29] (MD = −1.01; 95% CI, −1.78 to −0.23; $P = 0.011$; results from fixed effect model: MD = −1.01; 95% CI, −1.78 to −0.23; $P = 0.011$) and heterogeneity was not significant in this subgroup (Cochrane Q test, $P = 0.95$, $I^2 = 0.0\%$). However, in crossover studies [30,33], the effect of non-soy legume consumption on CRP levels was not significant (MD = −0.02; 95% CI, −0.11 to 0.06; $P = 0.578$; results from fixed effect model: MD = −0.02; 95% CI, −0.11 to 0.06; $P = 0.578$). There was no evidence of heterogeneity between two studies in this subgroup (Cochrane Q test, $P = 0.96$, $I^2 = 0.0\%$).

The analysis on studies that reported the effects of non-soy legume consumption on hs-CRP [31,32,34,35] showed that the overall effect was not significant (MD = −0.37; 95% CI, −0.88 to 0.14; $P = 0.153$; results from fixed effect model: MD = −0.06; 95% CI, −0.17 to 0.06; $P = 0.34$) but heterogeneity between studies was significantly high (Cochrane Q test, $P < 0.001$, $I^2 = 89.4\%$) (Supplementary Fig. 2). When subgroup analysis was assessed on the basis of study design, we found no effect in parallel studies [31,32] (MD = −0.85; 95% CI, −2.85 to 1.15; $P = 0.405$; results from fixed effect model: MD = −0.22; 95% CI, −0.7 to 0.25; $P = 0.36$) (Fig. 5) or in crossover studies [34,35] (MD = −0.37; 95% CI, −1.01 to 0.27; $P = 0.261$; results from fixed effect model: MD = −0.05; 95% CI, −0.16 to 0.07; $P = 0.44$) (Supplementary Fig. 2). Heterogeneity between parallel studies was relatively high but was not statistically significant (Cochrane Q test, $P = 0.108$, $I^2 = 61.3\%$), whreas heterogeneity among crossover studies was significant (Cochrane Q test, $P < 0.001$, $I^2 = 94.2\%$) (Supplementary Fig. 2). When we excluded the aforementioned study [35] (Fig. 5), non-soy legume consumption significantly reduced the risk for high hs-CRP levels (MD = −0.53; 95% CI, −0.95 to −0.11; $P = 0.014$; results from fixed effect model: MD = −0.48; 95% CI, −0.67 to −0.29; $P < 0.001$) and in crossover subgroup (MD = −0.68; 95% CI, −1.28 to −0.08; $P = 0.026$; results from fixed effect model: MD = −0.53; 95% CI, −0.73 to −0.33; $P < 0.001$) (Fig. 5). Furthermore, removing the aforementioned study [35], overall heterogeneity (Cochrane Q test, $P = 0.119$, $I^2 = 48.7\%$) as well as heterogeneity of crossover subgroup was not significant (Cochrane Q test, $P = 0.169$, $I^2 = 47.1\%$).

We used meta-regression to find other possible sources of heterogeneity such as the effect of age, non-soy legume dose, obesity, and insulin resistance. None of these variables were associated with a significant source of heterogeneity. The only source of heterogeneity was due to the excluded study [35]. After removing this study from analysis, the overall effect and results of subgroup analysis were significantly affected. Although there was a slight asymmetry in Begg's funnel plot for studies examining the effect of non-soy legume levels on CRP concentrations (Fig. 6A) and hs-CRP (Fig. 6B), there was no evidence of publication bias based on Begg and Mazumdar, or Egger's test for CRP ($P = 0.174$ and $P = 0.163$, respectively) and hs-CRP ($P = 0.624$ and $P = 0.293$, respectively).

Discussion

Our meta-analysis of eight RCTs showed that non-soy legume consumption had a trend toward a significant reduction of hs-CRP and CRP levels. However, heterogeneity among studies was high. Although between-study variations remained high even after the exclusion of one study that intervened with baked beans [35], non-soy legume intake reached reduced hs-CRP and

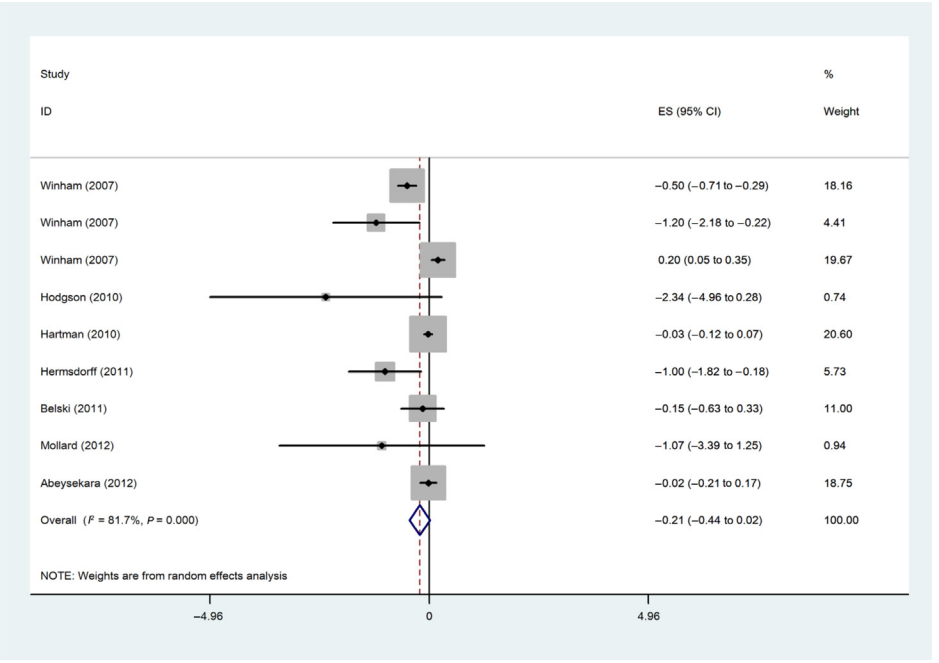

Fig. 2. Forest plot demonstrating weighted mean differences with 95% CI for all eligible studies (ES) investigating the effects of non-soy legume consumption on CRP/hs-CRP levels.

CRP levels. Subgroup analysis based on the study design and CRP type (CRP and hs-CRP) showed that non-soy legume consumption significantly decreased CRP levels in parallel design trials [4,29]. In crossover studies, after removing the study that used baked beans [35], hs-CRP concentration were substantially reduced by non-soy legume intake [34].

The two parallel studies [4,29] incorporated several sources of legumes to the habitual diet and included advice on energy-reducing intake in overweight and obese participants. Two other studies [31,32] used bread- and cereal-based food products in which wheat flour was partially substituted with lupin flour. In only one study [4] were CRP levels significantly

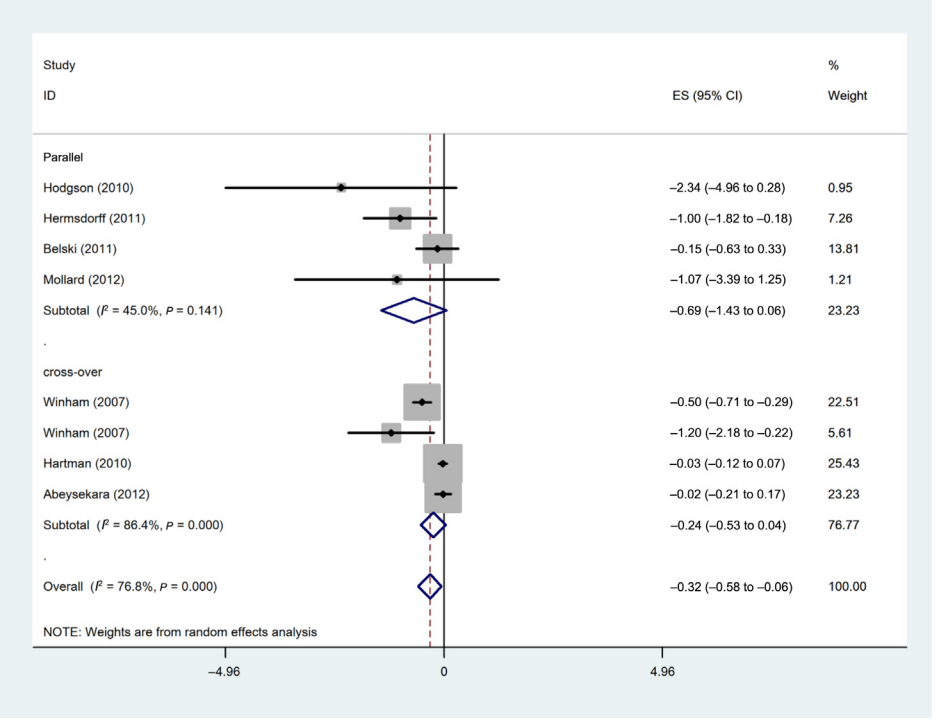

Fig. 3. Forest plot demonstrating weighted mean differences with 95% CI for subgroup analysis based on design of study (parallel and crossover; Winham study excluded from crossover subgroup) investigating the effects of non-soy legume consumption on CRP/hs-CRP levels.

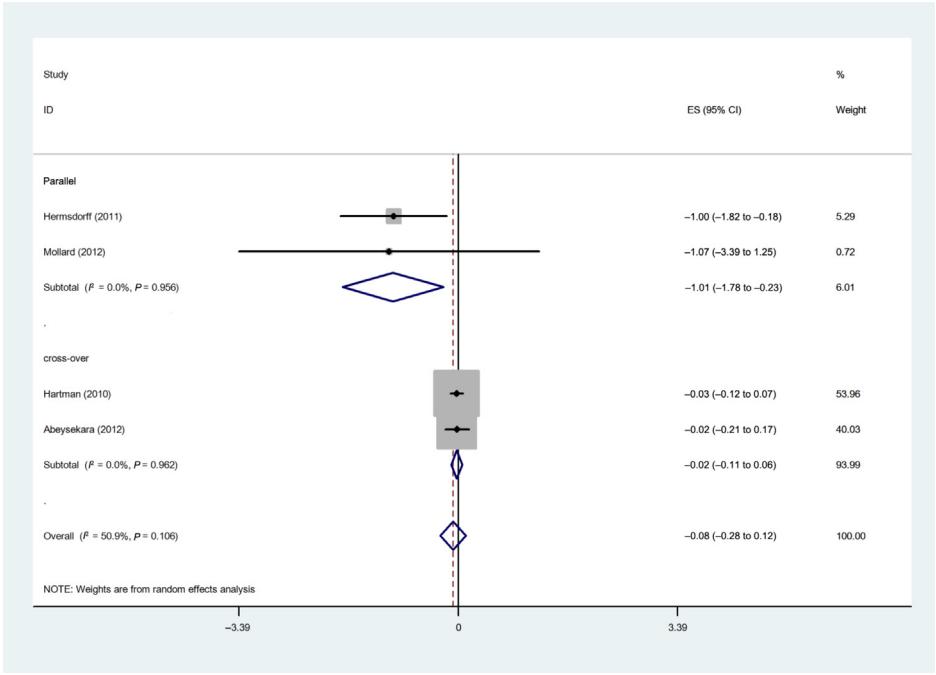

Fig. 4. Forest plot demonstrating weighted mean differences with 95% CI for subgroup analysis based on design of study (parallel and crossover) investigating the effects of non-soy legume consumption on CRP levels.

decreased, and remained significant even after adjusting for weight loss. It appears that there is an additive or synergistic effect and more favorable effect on inflammatory markers when a variety of legumes are consumed.

Two studies [30,33] investigated the effects of a pulse-based diet on CRP levels, using a crossover study design. In the hs-CRP subgroup [34,35], one study used only baked beans alone for the intervention. Due to a high level of interstudy variation in this subgroup, that study was excluded, which showed that that pinto beans and black-eyed peas significantly decreased hs-CRP concentration in our meta-analysis compared with studies investigating the effects of a legume-enriched diet on CRP levels [30,33]. However, among crossover studies, CRP significantly decreased in one trial [33], whereas other studies did not result in a reduction of CRP or hs-CRP concentrations [30,34,35].

There are several components of non-soy legume consumption that may explain their effects on markers of inflammation (i.e., CRP), including total dietary fiber (soluble and insoluble

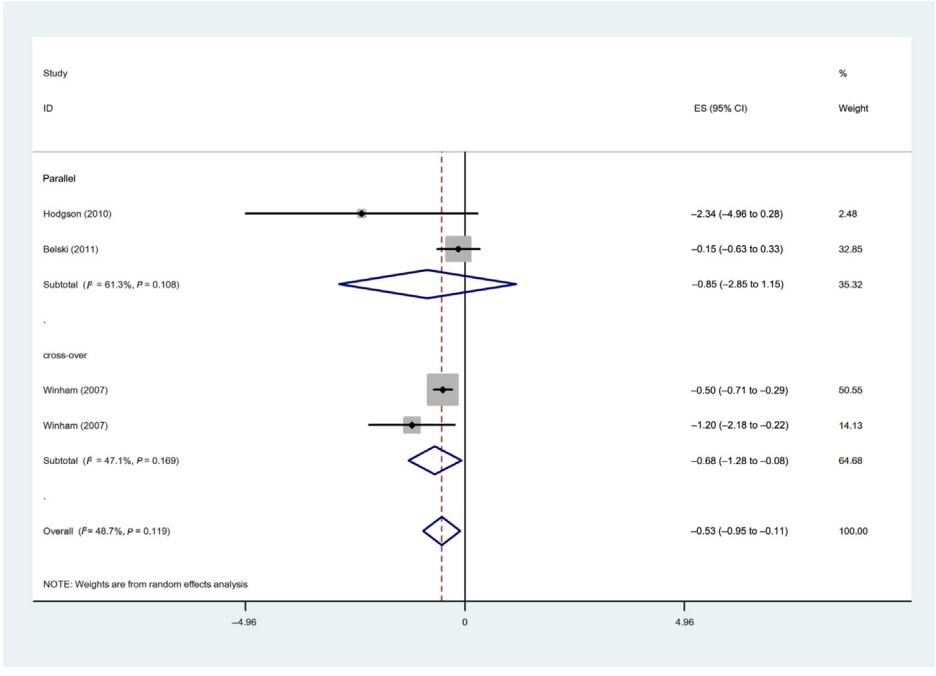

Fig. 5. Forest plot demonstrating weighted mean differences with 95% CI for subgroup analysis based on design of study (parallel and crossover; Winham study excluded from crossover subgroup) investigating the effects of non-soy legume consumption on hs-CRP levels.

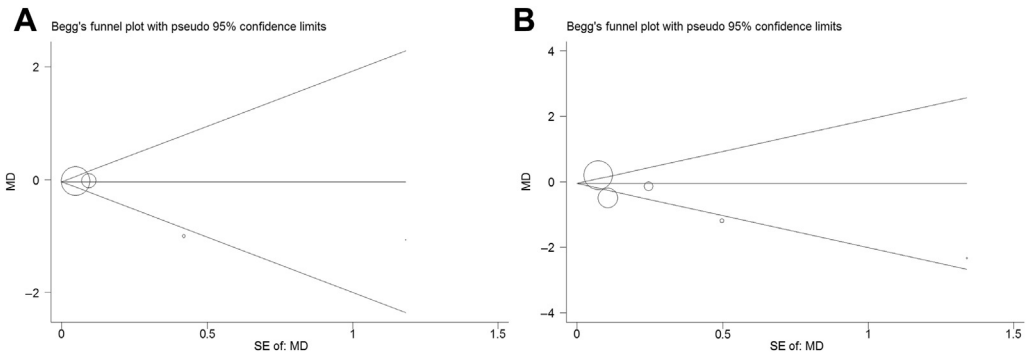

Fig. 6. Begg's funnel plots (with pseudo 95% CIs) of the difference in means (DMs) versus the SEs of the mean differences (MDs) for studies that investigating the effect of non-soy legume consumption on CRP (A) and hs-CRP (B).

fiber), resistant starch, high magnesium content, L-arginine, and polyunsaturated fatty acids. Furthermore, non-soy legumes may have beneficial effects on body weight and therefore may directly reduce inflammation. Dietary fiber intake is inversely associated with CRP levels and interleukin (IL)-6, and soluble fiber with tumor necrosis factor receptor II (sTNFRII) [41]. Dietary fiber and resistance starch may attenuate inflammatory markers by slowing glucose absorption, and modulating inflammatory cytokine response and production of antiinflammatory cytokines by gut microflora [42]. Due to the microvascular effect of magnesium, this mineral is important for endothelial function and contributes to endothelial growth and nitric oxide synthesis [43]. Legumes are also a good source of L-arginine (precursor of nitric oxide) and polyunsaturated fatty acids which have anti-inflammatory effects [44,45].

The LGI and LGL of non-soy legumes also may contribute to their effects on inflammation [27,41,43–46]. Several observational studies have reported an inverse association between LGI and LGL diets and inflammatory markers [27,44]. After 4 to 6 h of high GI meal consumption, the counter-regulatory hormones increased plasma levels of glucose and free fatty acids, which in turn may contribute to insulin resistance. It has been proposed that hyperglycemia and insulin resistance are risk factors for inflammation and oxidative stress [46]. The significant inverse relation of a hypocaloric diet enriched with legumes (L-diet) on weight loss was previously reported [47], and it was suggested that the effect of L-diet may be mediated via its effect on reducing fat mass reduction and increasing insulin sensitivity. The components of legumes may help promote healthy body weight through their effect on satiety [22,48]. The useful effects of weight loss on reducing inflammatory markers are well known [45].

There are few reports on the effects of non-soy legume consumption on inflammatory markers other than CRP. We could not perform a meta-analysis for other inflammatory markers, including IL-6 (reported in two studies [4,28]), TNF-α (reported in one study [4]), complement C3 (reported in one study [4]), sTNFRI and sTNFRII (reported in one study [33]), and homocysteine (reported in one study [4]). One trial [4] reported a significant reduction in plasma levels of TNF-α and complement C3 following consumption of a legume-based hypocaloric diet, whereas plasma concentrations of IL-6 and homocysteine were not significantly improved. One study [33] demonstrated that a legume-enriched, LGI diet contributed to a modest decrease in TNFRII concentrations after 4 wk. Due to particular design of study and lack of data about CRP and hs-CRP, one study was omitted from the meta-analysis. A crossover study [28] showed that consuming brown beans at an evening meal significantly reduced IL-6 and IL-18 concentrations 3 h after a standardized breakfast the next morning ($P < 0.05$). We failed to determine the effective dose of non-soy legumes on reducing inflammatory markers, perhaps due to small sample size and short duration of available trials. Further subgroup analysis based on study duration and meta-regression did not eliminate interstudy heterogeneity.

To the best of our knowledge, there are no reviews examining the effect of non-soy legume intake on inflammatory markers, or in relation to subgroup analyses, including study design, duration, and dose. Similar reviews and the effects of non-soy legumes were assessed as a component of Mediterranean diet [49] and other dietary patterns [50]. Furthermore, the effects of study design, study duration, and dose of non-soy legume consumption during intervention period on overall effect and between-study heterogeneity were assessed for the first time.

However, it seems that larger prospective studies are needed to determine the dose–response effect of non-soy legume consumption on inflammation. Although a meta-analysis can be performed on just two studies [51], very few trials focusing on non-soy legumes and inflammation (CRP) met the inclusion criteria. We could only include eight studies in this meta-analysis. Therefore, more RCTs with larger sample sizes, including a variety of non-soy legumes, and longer follow-up and duration are merited. The studies included in our meta-analysis had relatively small sample size (data of only 464 participants was available for analysis) and of short duration. In our meta-analysis, we included one study of 4-wk duration [33], which was sufficient to reduce CRP concentrations. Among the other included studies, five were 8 wk [3,29,30,34,35], one was 16 wk [32], and one was 52 wk in duration [31]. Except for one study [4], most did not show a significant reduction in CRP levels. Therefore, additional RCTs are needed to assess the effects of non-soy legume consumption on inflammatory markers.

In conclusion, the results of the current meta-analysis of RCTs showed a trend toward a reduction of CRP and hs-CRP concentrations after non-soy legume consumption. Additional RCTS of longer duration, with an appropriate dose and including a variety of non-soy legumes on several inflammatory markers is warranted.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.nut.2014.10.018

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