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Review

A systematic review and meta-analysis of the effects of soy on serum hs-CRP

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SUMMARY

Background & aim: The results of studies about the effect of soy products on serum highly sensitive C-reactive protein (hs-CRP) are inconsistent. The aim of this systematic review and meta-analysis of randomized clinical trials (RCTs) was to investigate the effect of soy products intake on serum hs-CRP concentration.
Methods: We searched PubMed, EMBASE, Science Direct, ISI Web of Science, Google Scholar and Cochrane Central Register of Controlled Trials up to December 2016 without language restrictions. Random-effect model was used for quantitative data synthesis.
Results: Thirty-six studies were included in our analyses. A meta-analysis revealed a non-significant reduction in serum hs-CRP concentrations following soy products consumption, −0.19 (mg/L) (95% CI: −0.49 to 0.09; $I^2 = 95.6\%$). Subgroup analyses suggested that natural soya products may reduce plasma levels of CRP by −0.18 mg/L (95% CI: −0.28 to −0.08; I^2: 11.6) in comparison to other source of isoflavones (soya extracts, supplements). Moreover, the effect was stronger among subjects with baseline hs-CRP concentrations of less than 2.52 mg/L, −0.15 (95% CI: −0.27 to −0.02; I^2: 34.6). A meta-regression analysis revealed that dosage of isoflavones seems to be a strong predictor of the effect of soya on serum hs-CRP levels.
Conclusion: Present review of RCTs published up to December 2016 did not provide strong evidence regarding the beneficial effect of soya products consumption on blood hs-CRP concentrations. However, it appears that natural soya products may reduce plasma levels of hs-CRP in comparison to other source of isoflavones. Large and well-designed studies are recommended to confirm this conclusion.
Systematic review registration: PROSPERO CRD42018069371.

1. Introduction

Chronic low grade inflammation characterized by the increase in circulating levels of pro-inflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF)-alpha, and highly sensitive C-reactive protein (hs-CRP) [1], plays a crucial role in the pathology of numerous age-related chronic abnormalities such as cardiovascular disease (CVD), type 2 diabetes, metabolic syndrome (MetS) and non-alcoholic fatty liver disease (NAFLD) [2]. Among inflammatory markers, hs-CRP has been proposed as a potent predictor of cardiovascular disease [1], suggesting that a novel, safe and effective method for lowering hs-CRP concentration reduce the rate of CVD with significant anti-inflammatory effect.

Recently, numerous epidemiological studies have focused on the interaction between diet and inflammation [3,4]. A large body of

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evidence has examined the effects of diet on serum levels of inflammatory markers [5–7]. Recent investigations in this field have mainly focused on nutrients, dietary patterns [8] and dietary components such as soy foods [9]. Soy foods contain several components, notably, phytoestrogens, polyunsaturated fat and fiber that have been identified as factors with inflammation-modulating capabilities [10]. Soy products have been consumed by Asian countries for hundreds of years, where cardio-metabolic risks are lowest [11]. According to the American Heart Association recommendations, daily consumption of 25 g or more of phytoestrogen-rich soy protein along with a healthy diet reduces the risk of CVD [12]. Many soy foods are a source of isoflavones that belong to one of the main phytoestrogen classes [13]. Genistein, daidzein and glycitein are the most abundant soy isoflavones [14]. Soy isoflavones have a chemical structure similar to natural estrogens and exert both weak estrogenic and anti-estrogenic effects [15]. In fact, genistein and daidzein are selective estrogen receptor modulators [16].

Numerous studies have investigated the effect of soy consumption on cardio-metabolic risk factors, especially on blood cholesterol levels [17,18]; however, less is known about the role of these products on inflammatory markers. In animal models, in vitro and in vivo data support isoflavones' ability to reduce pro-inflammatory cytokines [19,20]. Nevertheless, the results of randomized controlled trials (RCTs) in relation to the role of soy products in inflammatory processes are inconsistent [17,21], mainly due to differences in the type of soy products (whole soy foods or isolated soy components), baseline levels of inflammatory markers, isoflavone metabolizing phenotypes, small sample sizes, etc. On the other hand, health benefits of soy depend on isoflavone bioavailability [22]. In this regard, previous studies have reported that the effects of isoflavones on inflammatory markers, blood pressure, lipid levels and adhesion molecules [23] are only significant in subjects with ability to metabolize daidzein to equol, defined as "equol producers" [24].

Therefore, discrepancies between the results of human and animal trials can arise from the fact that approximately 30%–60% of human adults are equol producers, while all tested animals can produce equol [25]. Thus, equol, which is biologically more potent compared with other isoflavones, might exert additional health benefits among equol producers [26]. In 2011, a meta-analysis that included 14 trials examined the effect of soy isoflavones on circulating hs-CRP in postmenopausal women and found insufficient evidence regarding hs-CRP-reducing effects of soy isoflavones [27]. Moreover, this analysis omitted studies which included men, subjects with various health statuses, and other inflammatory markers [27]. In addition, a number of newly published papers are recently available considering the association between soy products and inflammatory markers which raises a need for a new, more extensive review. Although the overall purpose of this study was to synthesize the evidence from randomized controlled trials (RCTs) by performing a meta-analysis to evaluate the effects of soya products on inflammatory markers (hs-CRP, TNF-α, IL-6, adhesion molecules and other ILs), due to the large number of studies which were found and also the high volume of results, in the present study we aimed to systematically review RCTs that investigated the effect of soy products on hs-CRP and if possible, quantify the association using meta-analysis on qualified published papers with special regard to find major sources of heterogeneity between studies.

2. Materials and methods

2.1. Literature search

The current study was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines [28]. Overall purpose of our study was to synthesize the evidence from RCTs by performing a meta-analysis to evaluate the effects soya products on inflammatory markers (CRP, TNF-α, IL-6, adhesion molecules and other ILs). However, due to the large number of found studies and high volume of results, in present study we tried to systematically review RCTs that investigated the effect of soy products on CRP and if possible to conduct a meta-analysis. Therefore, we will report the results about other inflammatory markers within our next publications. Therefore, search strategy contained all of key words in this regard. We conducted a literature search in PubMed, EMBASE, Science Direct, ISI Web of Science, Google Scholar and Cochrane Central Register of Controlled Trials up to December 2016 to identify RCTs examining the effect of soya products on circulating hs-CRP levels. No language or time restriction was made. The primary search strategy contained all key words in this regard. We used the following medical subject heading (MeSH) terms and/or text words in the search strategy: 'Soy Foods', 'Natto', 'Soy Cheese', 'Tempeh', 'Texturized Soy Protein', 'Texturized Vegetable Protein', 'Tofu', 'Soy Bean Curd', 'Miso', 'Soy Sauce', 'Soybean Proteins', 'Soya', 'Soy Protein', 'Genistein', 'Equol', 'Soy', 'Soy milk', 'Soy Beverages', 'Phytoestrogens', 'Isoflavones', 'Isoflavone Derivatives', 'Homoisoflavones', '3-Benzylchroman-4-Ones', '3-Benzylidene-4-Chromanones', 'Glycine max' in combination with 'C-reactive protein', 'Tumor Necrosis Factor-alpha', 'Cytokine', 'Interleukin', 'IL-6', 'Cachectin', 'Inflammation', 'Adhesion molecules', 'Thrombosis', 'Thromboses', 'Thrombus', 'Adhesion molecules', 'VCAM', 'ICAM', 'Selectin' 'Atherosclerosis', 'Atherosclerosis', 'Atherogenesis', 'Fasting glucose', 'Triglycerides', 'Triacylglycerols', 'Lipoproteins, LDL', 'Low-density lipoprotein', 'LDL', 'Lipoproteins, HDL', 'High density lipoprotein', 'Heavy Lipoproteins', 'Lipoproteins, VLDL', 'VLDL Lipoproteins', 'Prebeta-Lipoproteins', 'Insulin', 'Fasting blood sugar', 'Hemoglobin A, Glycosylated', 'HbA1c', and 'Glycosylated hemoglobin'. Since inflammatory factors might be regarded as secondary outcomes of studies, we also applied keywords related to blood lipids, glucose, adhesion molecules and thrombosis factors. The reference lists of eligible articles was searched. Authors were contacted for further information and data that were not presented in the manuscripts. The protocol of this study is registered in an international prospective register of systematic reviews [PROSPERO (www.crd.york.ac.uk/Prospero), (registration no: CRD42018069371).

2.2. Study selection

A selection process in accordance with inclusion and exclusion criteria was independently conducted by two investigators (MK and JM). Identified studies were enrolled in the current systematic review and meta-analysis if they met the following criteria: 1) RCTs were written in English; 2) evaluated the effects of soy, soy products or isoflavones on hs-CRP; 3) reported net change values or available sufficient data to calculate this value; 4) provided the source and dose of soya products intake.

All RCTs were included according to above criteria regardless of participants' health status.

After reading abstracts and full texts of retrieved articles, we did not consider studies in which soy products intake was mixed with other dietary treatments. Trials without a control group or comparison arm were excluded. Moreover, interventions were excluded if they did not provide means and corresponding standard deviation (SD) changes in plasma concentrations of the outcomes of interest or any data for computing them. Since we wanted to report the effects of habitual intake of soya products, we ignored studies of short duration (<1 wk).

2.3. Data extraction and quality assessment

Data extraction and quality assessment were conducted by two independent authors (MK and JM) and discrepancies were resolved through discussion with a third reviewer (MAJ). The following information from each study was extracted: the first author's last name, publication year, country of origin, number of participants, study design (crossover or parallel and other details), participants' gender, age range and/or mean, source and daily amount of isoflavones and soya products consumed in the intervention, control and other arms, duration of the follow-up, participants' baseline health status, changes in body mass index or weight, dietary modifications, and mean change in outcome values and their corresponding standard deviation. All measurements were converted to the same unit (mg/L). If there was more than one time point for follow up, data from the longest follow-up was considered. Studies with multiple independent strata were included separately.

The quality of included studies was assessed by Cochrane Collaboration's tool for assessment of risk of bias tool [29]. This instrument includes the following criteria: the generation of the allocation sequence, allocation concealment, blinding, blinding outcome data, incomplete outcome data, and selective reporting. Each individual investigation that was included in the meta-analysis was classified as “good” quality if it was low risk for at least three items, “fair” if it was low risk for two items, and “weak” if it was low risk for less than two items [29].

2.4. Data synthesis

We used mean change from baseline in hs-CRP concentrations for both intervention and control groups to calculate effect size in accordance with recommendation of the Cochrane Handbook. The method of Hozo et al. [30] was used if median and range (or 95% confidence interval [CL]) was reported. Standard errors were converted to SDs by multiplying SEM by the square root of the sample size [4]. For studies that didn't provide SDs, a correlation coefficient of 0.5 was considered for the missing SDs based on the method of Follmann et al. [31]. A multiplication factor of 0.105 was used to convert levels, respectively, from nmol/L to mg/L.

2.5. Statistical methods

For each meta-analysis, weighted means and their corresponding SDs were determined following Der Simonian and Laird [32] and by using the random effects model if a heterogeneity test was statistically significant. Statistical heterogeneity between studies was evaluated with Cochran's Q test and I square [33]. Meta-regression and subgroup analyses were conducted to check for the specific source of heterogeneity. Sensitivity analysis also was used to explore the extent to which inferences might depend on a particular study or a number of publications.

We performed subgroup analyses according to sources of interventions (natural soy products, soya extracts or supplements, soya protein and isoflavone together), isoflavone dosages ($\leq$70 mg/day or more), study duration ($\geq$84 day or less), study subjects (women only, men only or both), health status of subjects (healthy, at risk, patient), sample size ($\leq$42 or more), quality of included studies using Cochrane Collaboration's tool (good, fair, poor), mean baseline hs-hs-CRP concentration ($\leq$2.53 or more), geographical region (Asia or non-Asia) and study design (parallel or cross-over) to explore possible source of heterogeneity among studies.

Publication bias was discovered by looking over Begg's funnel plots [34]. Formal statistical assessment of funnel plot asymmetry was incorporated with Egger's regression asymmetry test and Begg's adjusted rank correlation test [35]. Statistical analyses were carried out by using Stata 14.2 (Stata Corp, College Station, TX). For all effect sizes, 95% confidence intervals were presented.

3. Results

3.1. Flow of studies

Our search retrieved 3446 papers. Most of these published studies were excluded after reading abstracts since they were not relevant. In brief, 537 papers did not meet the inclusion criteria and were excluded, containing review or editorial articles (n = 84), non-human studies, genetic, or molecular studies (n = 356), not RCT (n = 17) and inappropriate intervention (n = 80). After assessing the full text of 76 potentially related papers, 44 publications [36–79] were eligible according to our inclusion criteria. In this step, the most important reasons for exclusion were as follows: seven studies [23,80–85] did not report data required for meta-analysis, and two exclusions [86,87] were due to the administration of soy intake which was mixed with other dietary regimens. We found eight papers [88–95] which enrolled women who used hormone replacement therapies (HRT) and statins during the intervention; these studies were removed. Two studies [96,97] were excluded because they were of extremely short duration (<1 wk). Eleven trials [98–108] were removed because their outcomes were inflammatory markers other than hs-CRP. Two exclusions [109,110] were due to administration of energy restriction in both intervention and control groups and there was significant weight reduction at the end of study. The flowchart for the selection of articles is given in Fig. 1. In all, 44 clinical trials [36–79] were included in the present systematic review, and, of these, eight trials were excluded because they had very high or low baseline hs-CRP concentrations compared with the other studies [44,46,52,54,59,61,68,75] (see Fig. 2).

3.2. Study characteristics

Characteristics and the main outcomes of the 44 RCTs included in the systematic review are summarized in Table 1. The trials were published between 2003 and 2016. Of all the identified studies, 16 studies were conducted in the United States [38,43,44,47,49,52,60–63,66,70–72,75,76], five in Iran [37,41,65,69,73], four in the United Kingdom [64,68,74,79], three in Canada [45,56,77], three in Italy [39,42,53], two each in Brazil [36,46], Germany [40,51] and Spain [58,59], and one each in Korea [55], Turkey [54], China [57], Europe generally [67], Australia [50], Finland [78], and The Netherlands [48]. Twenty-eight studies used a parallel design [36–62,64], whereas the rest used a crossover design [63,65–79]. The number of participants enrolled in studies ranged from 12 [76] to 180 [57], with a total of 2607 (aged 20–77 years; mean baseline BMI between 21.8 and 37.3 kg/m^2). Twenty-nine studies recruited only females [37–39,43,45,46,48–50,53,54,56–62,65–70,73,74,76,78,79], six only males [36,47,51,53,63,65,77] and nine used both sexes [40–42,44,52,55,71,72,75]. Selected trials assessed effects of the intervention among healthy participants [38–40,48–51,53,54,60–62,67,72,76,77], overweight/obese [43,45,55,56,58,59,63,68,70,75], patients with diabetes [64,65,79], hypothyroidism [74], metabolic syndrome [37,46,64,65,69,71], participants with risk factors of CVD [36,42,57,76], subjects with diabetic nephropathy [41,73] and hemodialysis [44,52], women with and without a history of breast cancer or those who treated for breast cancer [66,78], and men with androgen deprivation therapy [47]. Of the 51 trials, 13 used

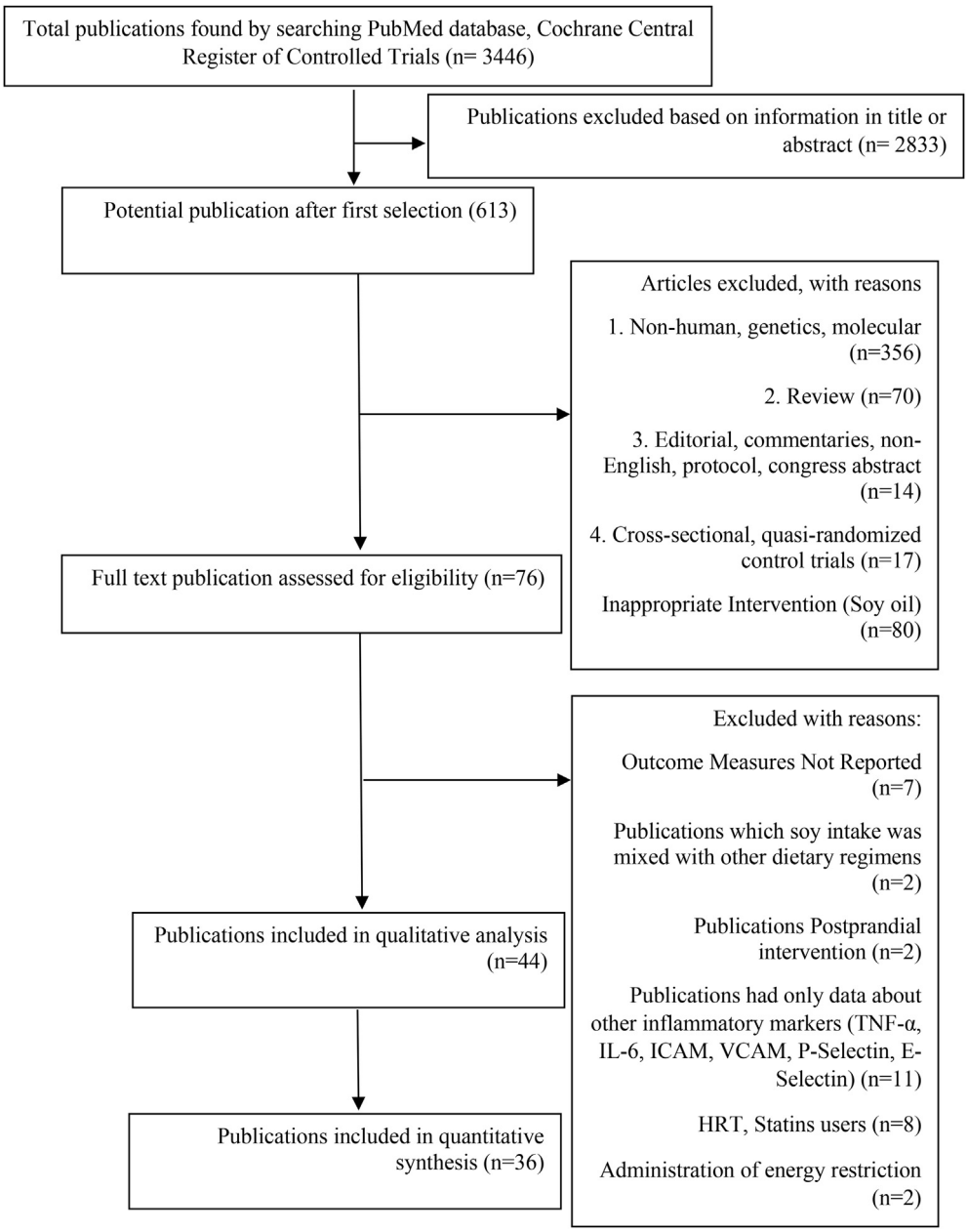

Fig. 1. Flow diagram of screened, excluded and analyzed publications.

natural soy products (soya milk, whole soya beans, soya nuts, etc) containing isoflavones [36,37,42,46,49,57,62,63,65,69,71,73,76], 18 used soy protein [37,38,40,41,44,47,50–52,55,60,64,66,69,70,72,75,77], 14 investigated 'processed' soya (soya extracts, supplements) [39,43,45,48,49,53,54,56–59,67,78,79] and four examined soya protein and isoflavone together [36,61,68,74]. In total, 43 datasets from 36 studies for hs-CRP were analyzed, including seven studies with different treatment groups or with different sources of subjects.

3.3. Risk of bias assessment

Of the 44 studies included in the systematic review, 27 studies were rated as "good" [36–39,43,44,47–50,52–60,64,67,68,70,72,74,78,79], 11 studies as "fair" [41,42,45,46,51,61–63,66,69,77] and six studies as "poor" [40,65,71,73,75,76]. There was unclear risk of bias according to all key domains selected for methodological quality assessment. Five studies did not describe any procedure used to conceal the allocation [37,43,58,65,79]. Nine studies had a high risk of bias according to blinding of participants and personnel [37,41,46,52,65,66,69,71,73]. Lack of blinding of assessors or analysts and incomplete outcome data were source of bias in three studies [41,69,71] and one [61] study, respectively. Bias associated with selective outcome reporting seemed likely in 17 studies [36,40,42,45,47,48,50,61,65,67,68,71,73,75–78]. Table 2 shows more details of the quality of bias assessment of included trials.

3.4. Pooled estimate of the effect of soya consumption on hs-CRP concentration

Soya products intake resulted in a significant reduction in serum hs-CRP concentration of 0.589 mg/L (95% CI −0.636 to −0.542; $p < 0.001$) only in a fixed effects model and with high heterogeneity (Cochrane's Q test, $p < 0.001$, $I^2 = 95.6\%$). Our preliminary analysis

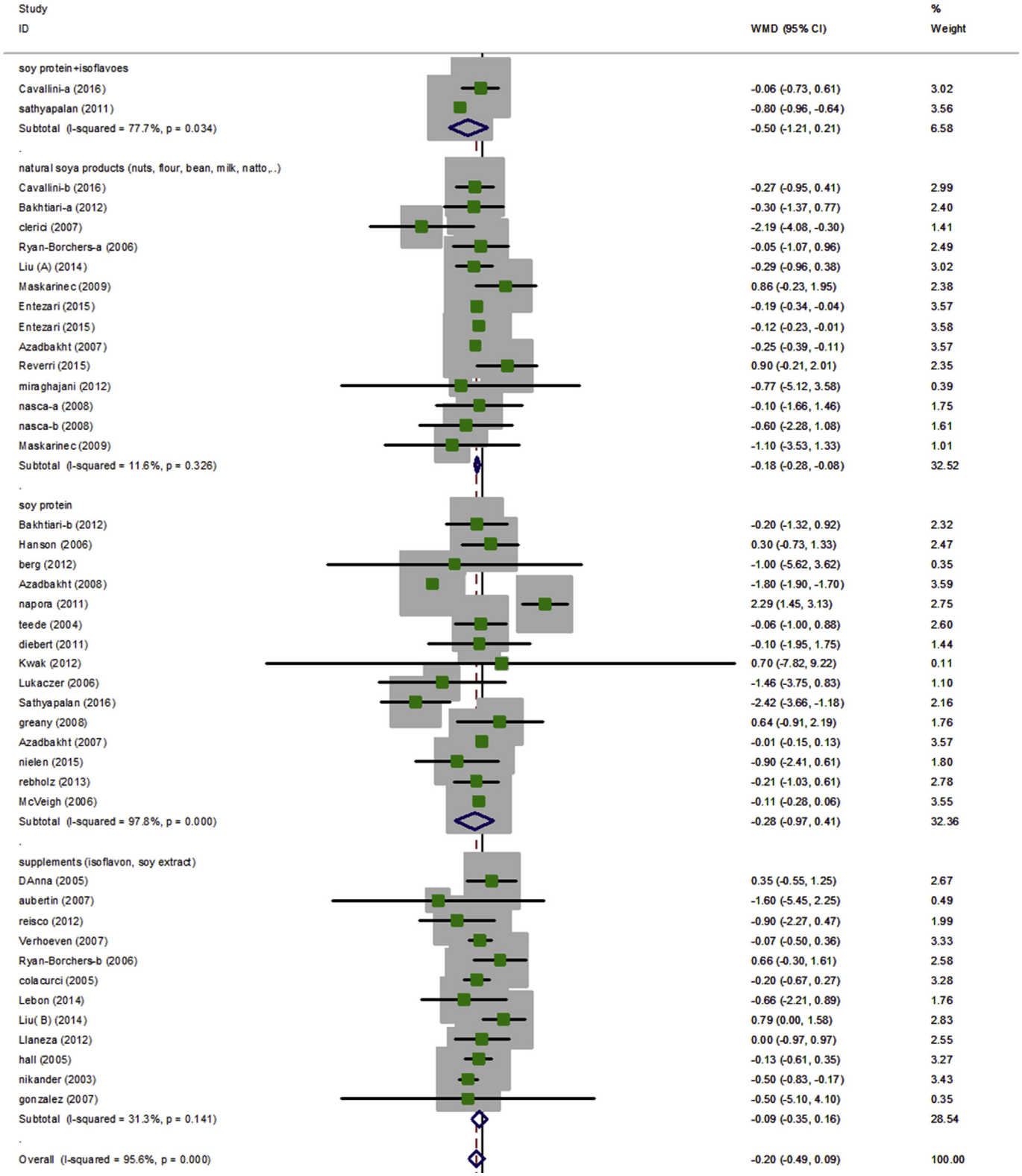

Fig. 2. Forest plot showing the Pooled effect size of soy products on C-reactive protein (mg/L) levels and subgroup analysis based on source of isoflavones, using random effects model.

Table 1
Characteristics of the trials and participants in this systematic review and meta-analysis.

Author	Year	Study design	Country	Sample size	Participants	Mean age or age range, y	Diet		Duration, day	Dose of isoflavones
							Intervention	Control		
Cavallini et al. [36]	2016	Parallel	Brazil	32	Hypercholesterolaemic	46.7	Isoflavone-supplemented probiotic soy product	Unfermented soy product	42	102.50
Cavallini et al. [36]	2016	Parallel	Brazil	32	Hypercholesterolaemic	45.7	fermented soy product	Unfermented soy product	42	16.08
Sathyapalan et al. [64]	2016	Parallel	UK	171	Men with Diabetes type 2 and low testosterone levels	52	Isolated soy protein powder	15 gr isoflavone-free soy protein	90	66.00
Entezari et al. [65]	2015	Cross-over	Iran	30	Diabetes type 2	45.7	Soybean flour fortified bread	Habitual diet	42	
Entezari et al. [65]	2015	Cross-over	Iran	30	Diabetes type 2	45.7	Soybean flour fortified bread	Habitual diet	42	
Reverri et al. [71]	2015	Cross-over	USA	17	Metabolic syndrome	56	Snacks consisted of soy nuts	Macronutrient-matched control snack (cookies developed and baked)	28	101.00
Tomayko et al. [44]	2015	Parallel	USA	27	Maintenance hemodialysis	52.9	Soy protein	Whey protein	168	40
Lebon et al. [56]	2014	Parallel	Canada	34	Overweight and obese postmenopausal women	59.4	Isoflavone supplement	Capsule cellulose	180	70.00
Liu et al. [57]	2014	Parallel	China	180	Postmenopausal, prehypertensive, hypercholest	46–65	Soya flour	Low-fat milk powder	180	49.00
Liu et al. [57]	2014	Parallel	China	180	Postmenopausal, prehypertensive, hypercholest	46–65	Low-fat milk powder+ 63 mg daidzein	Low-fat milk powder	180	63.00
Nielen et al. [70]	2014	Cross-over	USA	15	Abdominal obesity	61	Soy protein	A high-protein diet of mixed, non-soy sources	28	
Mangano et al. [61]	2013	Parallel	USA	47	Ambulatory women	73	Isolates soy protein and isoflavone tablt	Control protein mix (consisting of 50% sodium caseinate, 25% whey, and 25% egg white protein) and placebo tablets	365	105
Rebholz et al. [72]	2013	Cross-over	USA	102	Healthy	46	Soy bean protein	Placebo	56	89.30
Bakhtiari et al. [37]	2012	Parallel	Iran	50	Metabolic syndrome	64	Soy nut	Group received nothing	84	
Bakhtiari et al. [37]	2012	Parallel	Iran	50	Metabolic syndrome	64.3	Textured soy protein	Group received nothing	84	
Berg et al. [40]	2012	Parallel	Germany	30	Healthy	23.6	Soy based protein supplementation	Without supplement	42	
Kwak et al. [55]	2012	Parallel	Korea	64	Overweight/obese subjects	37.6	Black soy peptide	Casein	84	
Llaneza et al. [58]	2012	Parallel	Spain	65	Postmenopausal women (obese, overweight, normal body weight)	57.6	Physical exercise and Mediterranean diet program + daily oral intake of a soy isoflavone extract	Physical exercise and Mediterranean diet program	730	80.00
Miraghajani et al. [73]	2012	Cross-over	Iran	25	Diabetic nephropathy	51	Soy milk	Cow's milk	28	
Reisco et al. [45]	2012	Parallel	Canada	52	Overweight or obese	58.1	Soy extract isoflavone	Placebo	180	70.00
Simao et al. [46]	2012	Parallel	Brazil	30	Metabolic syndrome	47.9	Soybean	Usual diet	90	50
Diebert et al. [51]	2011	Parallel	Germany	22	Healthy	55.8	Soy–yogurt–honey	Lifestyle education	84	
Llaneza et al. [59]	2011	Parallel	Spain	70	Healthy obese postmenopausal	56.8	Isoflavone extracts	1200 kcal diet and exercise	180	80

(*continued on next page*)

Table 1 (*continued*)

Author	Year	Study design	Country	Sample size	Participants	Mean age or age range, y	Diet		Duration, day	Dose of isoflavones
							Intervention	Control		
Napora et al. [47]	2011	Parallel	USA	33	Men with Androgen deprivation therapy	69.1	Soy protein consisting of 160 mg of total isoflavones	Whole milk protein	84	160.00
Sathyapalan et al. [74]	2011	Cross-over	UK	60	Subclinical hypothyroidism	57.2	High-dose phytoestrogen (30 g soy protein with 16mgphytoestrogens, representative of a vegetarian diet) supplementation	Low-dose phytoestrogen (30 g soy protein with 2 mg phytoestrogens, representative of a Western diet)	56	16.00
Zemel et al. [75]	2011	Cross-over	USA	19	Obese/overweight	31	Soy protein isolated	Dairy smoothies were milk based	28	10 g soy pro
Chiristie et al. [68]	2010	Cross-over	UK	33	Postmenopausal nondiabetic obese	54.8	Daily shake supplement containing either soy protein plus isoflavones	Isocaloric casein placebo containing no isoflavones	90	160
Maskarinec et al. [62]	2009	Parallel	USA	168	Premenopausal healthy overweight women	43	Soy products	Regular diet	730	50.00
Maskarinec et al. [63]	2009	Cross-over	USA	20	Healthy	58.7	Soy products	Regular diet	90	70.00
Azadbakht et al. [41]	2008	Parallel	Iran	41	Type 2 diabetic patients with nephropathy	62	Textured soy protein (35% animal proteins, 35% textured soy protein, and 30% vegetable proteins)	Diet with 0.8 g protein/kg body weight containing 70% animal and 30% vegetable proteins	1464	41.50
Greany et al. [66]	2008	Cross-over	USA	34	With and without a history of breast cancer	57.7	Isoflavone-containing soy protein isolate	Milk protein isolate	42	44.00
Nasca-a et al. [76]	2008	Cross-over	USA	12	Hypertension	58.3	Soy nut	TLC diet alone, non-Soy nut	56	101.00
Nasca-b et al. [76]	2008	Cross-over	USA	48	Normotensive	53.5	Soy nut	TLC diet alone, non-Soy nut	56	101.00
Aubertin et al. [43]	2007	Parallel	USA	20	Obese postmenopausal	57.5	Isoflavone supplement	Placebo	180	70.00
Azadbakht et al. [69]	2007	Cross-over	Iran	42	Metabolic syndrome	NR	Isolated soy protein	DASH diet	56	84.00
Azadbakht et al. [69]	2007	Cross-over	Iran	42	Metabolic syndrome	NR	Soy nut	DASH diet	56	102.00
Clerici et al. [42]	2007	Parallel	Italy	60	Hypercholesterolemia	55.1	80 g soy germ pasta	Conventional pasta	28	33.00
Gonzalez et al. [79]	2007	Cross-over	UK	26	Type 2 diabetes	NR	Isoflavone extracts	Placebo	84	132.00
Verhoeven et al. [48]	2007	Parallel	Netherlands	106	Healthy menopausal	57.5	Soy extract	Olive oil	84	50.00
Hanson et al. [38]	2006	Parallel	USA	27	Healthy	59.2	Native phytate/native isoflavone	Low phytate and low isoflavone	42	84.60
Lukaczer et al. [60]	2006	Parallel	USA	42	Postmenopausal women, healthy	55.2	Soya protein	American Heart Association Step 1 diet 0.6 oz of animal protein per day with the allowance of one cup of legumes to be substituted for 3 oz of animal protein per day if desired by the subject	84	34.00
McVeigh et al. [77]	2006	Cross-over	Canada	35	Healthy young men	27.9	High isoflavone soy protein isolate SPI, Soya protein powder supplement	Milk protein isolate	57	61.70
Ryan-Borchers et al. [49]	2006	Parallel	USA	37	Healthy	55.7	Soy milk	Cow milk	112	71.60
Ryan-Borchers et al. [49]	2006	Parallel	USA	34	Healthy	55.9	Isoflavone tablet	Cow milk	112	70.00

Siefker et al. [52]	2006	Parallel	USA	16	Hemodialysis patients	50.3	Soy protein	Whey protein	28	30	
Colacurci et al. [53]	2005	Parallel	Italy	57	Healthy	55.1	Genistein + daidzein	Placebo	180	60.00	
D Anna et al. [39]	2005	Parallel	Italy	55	Healthy, postmenopausal	50–60	Genistein	Placebo	180	54.00	
Hall et al. [67]	2005	Cross-over	Europe	113	Healthy	57.7	Isoflavone-enriched cereal bars	Placebo cereal bars	56	50.00	
Yildiz et al. [54]	2005	Parallel	Turkey	40	Healthy	50	Isoflavone extracts	Placebo	180	40	
Teede et al. [50]	2004	Parallel	Australia	50	Healthy and normotensive	61.5	Soy protein isolate powder	Casein placebo	84	118.00	
Nikander et al. [78]	2003	Cross-over	Finland	56	Treated for breast cancer	54	Isoflavonoid tablets	Placebo tablets	90	114.00	

TLC, Therapeutic life style changes; DASH, Dietary Approaches to Stop Hypertension.

from 36 RCTs by using random effect model showed that intake of soya products have no significant effect on serum hs-CRP level 0.19 (mg/L) (95% CI: −0.49 to 0.09; $p = 0.17$). However, there was significant heterogeneity among studies (Cochrane's Q test, $p < 0.001$, $I^2 = 95.6\%$).

Sensitivity analysis revealed that excluding the trial by Azadbakht et al. [41] could non-significantly increase pooled effect size 0.13 mg/L (95% CI: 0.29 to 0.02; $p = 0.09$) compared with the overall analysis. However, removal of the trial by Napora et al. [47] resulted in a reduction of 0.27 mg/L (95% CI: 0.56 to −0.02; $p = 0.07$) overall effect size. Exclusion of other trials from the overall analysis did not seem to make a significant change in treatment effects of soy products on serum hs-CRP concentration.

3.5. Subgroup analyses

Subgroup analyses were carried out based on the protocol. It was revealed that intake of soya products could reduce hs-CRP by 0.21 mg/L (95% CI: −0.38 to −0.04; $p = 0.017$) in trials of short-term duration (less than 84 days), compared with trials of long-term duration (more than 84 days). The heterogeneity between studies in this subgroup was significant (Cochrane's Q test, $p < 0.001$, $I^2 = 76.6\%$). In studies using natural soya products as treatments, concentration of hs-CRP reduced by 0.18 mg/L (95% CI: −0.28 to −0.08; $p < 0.001$) and heterogeneity was not significant in this subgroup (Cochrane's Q test, $p = 0.326$, $I^2 = 11.6\%$) [2]. On the other hand, trials using supplements did not seem to exert significant effects on serum hs-CRP concentrations −0.1 (95% CI: −0.35 to 0.16; $p = 0.468$). However, no significant heterogeneity was found in this subgroup (Cochrane's Q test, $p = 0.141$, $I^2 = 31.3\%$). Soy also resulted in greater reduction of hs-CRP level 0.91 (95% CI: −1.78 to −0.03; $p < 0.04$) with a significant between-study heterogeneity (Cochrane's Q test, $p < 0.001$, $I^2 = 99\%$) among diseased subjects as the subjects were stratified according to their health status. Subsequent subgroup analysis based on baseline hs-CRP concentration showed that effect is significant −0.15 (95% CI: −0.27 to 0.02; $p = 0.025$) among participants with a baseline hs-CRP concentration lesser than 2.56 mg/L and no heterogeneity was seen in this group (Cochrane's Q test, $p = 0.053$, $I^2 = 34.6\%$) (Figs. 3 and 4). Other sub group analyses showed that soy intake might decrease hs-CRP level only in the studies with a sample size >42 (0.28 (95% CI: −0.56 to −0.00; $p = 0.049$) with a relatively high significant heterogeneity (Cochrane's Q test, $p < 0.001$, $I^2 = 68.4\%$), cross over design (0.26 (95% CI: −0.5 to −0.02; $p = 0.034$)) with a high significant heterogeneity (Cochrane's Q test, $p < 0.001$, $I^2 = 79.6\%$). The lowest rate of quality (0.14 (95% CI: −0.23 to −0.05; $p = 0.002$)) without significant heterogeneity (Cochrane's Q test, $p = 0.616$, $I^2 = 0.0\%$) (Fig. 5), included only female (0.18 (95% CI: −0.33 to −0.02; $p = 0.026$)) with a relatively high significant heterogeneity (Cochrane's Q test, $p < 0.001$, $I^2 = 67.1\%$) and also studies performed in Europe/Asia/Australia (0.38 (95% CI: −0.76 to −0.00; $p = 0.048$) with a substantial heterogeneity (Cochrane's Q test, $p < 0.001$, $I^2 = 97.2\%$). We did not find any significant change in hs-CRP among the other subgroups (Table 3).

3.6. Meta-regression analysis and publication bias

We used a meta-regression analysis to find possible sources of heterogeneity and to assess characteristics of studies with effective treatment effects.

Meta-regression indicated that dose of isoflavones ($p = 0.009$) (Fig. 6) was associated with a greater effect size. However, there was not a significant linear association between baseline hs-CRP concentration ($p = 0.078$), treatment duration ($p = 0.265$) or

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
Cavallini, 2016 [36]	L	L	L	U	L	H	Good
Bakhtiari, 2012 [37]	L	H	H	L	L	L	Good
Entezari, 2015 [65]	U	H	H	U	L	H	weak
Hanson, 2006 [38]	U	U	L	U	L	L	good
D'Anna, 2005 [39]	U	U	L	U	L	L	Good
Hall, 2005 [67]	L	U	L	U	L	H	Good
Berg, 2012 [40]	U	U	U	U	L	H	Weak
Chiristie, 2010 [68]	L	L	L	U	L	H	Good
Greany, 2008 [66]	U	U	H	U	L	L	Fair
Azadbakht, 2007 [69]	U	U	H	H	L	L	Fair
Clerici, 2007 [42]	U	U	L	U	L	H	Fair
Aubertin, 2007 [43]	U	H	L	U	L	L	Good
Tomayko, 2015 [44]	U	U	L	L	L	L	Good
Nielen, 2014 [70]	U	U	L	U	L	L	Good
Reisco, 2012 [45]	U	L	L	U	U	H	Fair
Rebholz, 2013 [72]	L	U	L	L	U	L	Good
Simao, 2012 [46]	U	U	H	U	L	L	Fair
Miraghajani, 2012 [73]	U	U	H	U	L	H	Weak
Zemel, 2011 [75]	U	U	L	U	U	H	Weak
Nasca, 2008 [76]	U	U	U	U	L	H	Weak
Verhoeven, 2007 [48]	L	U	L	U	L	H	Good
McVeigh, 2006 [77]	U	U	L	U	L	H	Fair
Ryan-Borchers, 2006 [49]	L	U	L	U	L	L	Good
Teede, 2004 [50]	L	U	L	U	L	H	Good
Diebert, 2011 [51]	U	U	H	U	L	L	Fair
Siefker, 2006 [52]	U	U	L	U	L	L	Good
Colacurci, 2005 [53]	L	U	U	U	L	L	Good
Nikander, 2003 [78]	L	U	L	U	L	H	Good
Kwak, 2012 [55]	U	U	L	U	L	L	Good
Lebon, 2014 [56]	L	L	L	L	L	U	Good
Liu (A,B), 2014 [57]	L	L	L	L	L	L	Good
Llaneza, 2012 [58]	U	H	L	L	L	U	Good
Llaneza, 2011 [59]	L	U	L	L	L	L	Good
Lukaczer, 2006 [60]	L	U	U	U	L	L	Good
Mangano [61], 2013	L	U	L	U	H	H	Fair
Maskarinec (women), 2009 [62]	U	U	U	L	L	U	Fair
Maskarinec)Men) 2009 [63]	U	U	U	L	L	U	Fair
Sathyapalan, 2016 [64]	L	L	L	L	L	L	Good
Gonzalez, 2007 [79]	L	H	U	U	L	L	Good
Yildiz, 2005 [54]	U	U	L	U	L	L	Good
Napora, 2011 [47]	L	U	L	U	L	H	Good
Azadbakht, 2008 [41]	U	U	H	H	L	L	fair
Reverri, 2015 [71]	U	U	H	H	L	H	weak
Sathyapalan, 2011 [74]	L	U	L	U	L	L	Good

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

sample size (p = 0.089) and effect of soya on serum hs-CRP. After adjustment for duration and baseline hs-CRP concentration in the multivariate model, dose of isoflavone remained a strong predictor of the effect size ($p = 0.024$).

Although visual inspection of the funnel plot suggested a slightly asymmetrical distribution for studies which were included in the meta-analysis (Fig. 7), the results from the Egger test did not indicate evidence of publication bias ($p = 0.133$).

4. Discussion

The result of the present meta-analysis of 36 studies involving 2399 participants did not show significant effects of overall soya products consumption on blood hs-CRP levels. There was significant heterogeneity among studies. However, subgroup analyses based on the source of soya isoflavones suggest that natural soya product reduce plasma levels of hs-CRP. We also observed a significant reduction in serum hs-CRP concentrations among individuals with baseline hs-CRP concentrations lower than 2.52 mg/L. Furthermore, in spite of substantial heterogeneity, soy products may have modest benefits in lowering of serum hs-CRP levels in shorter durations (<84 day) compared to longer duration (>84 day), females compared to males, larger sample sizes (>42) compared to smaller sample sizes (<42), cross over design compared to parallel studies, studies conducted in Europe, Asia and Australia compared to the Americas and also subjects who were influenced by various diseases. Evidence from meta-regression showed that dose of isoflavones appears to significantly influence serum hs-CRP levels.

To the best of our knowledge, this is the first quantitative review that has examined the effect of different types of soy products containing isoflavones on hs-CRP concentration regarding different subgroups among subjects with a wide range of health conditions. In 2011, a meta-analysis [27] on soy isoflavones and circulating C-reactive protein was published consisting of 14 RCTs among 603 postmenopausal women. Dong et al., in a previous meta-analysis [27], did not find sufficient evidence regarding the association between soy isoflavones and hs-CRP concentrations in postmenopausal women. The results of the meta-analysis indicated that a higher baseline hs-CRP concentration may be as a strong modifier of therapeutic effects of soya. In comparison, after examining recently published evidence by conducting a complete search and

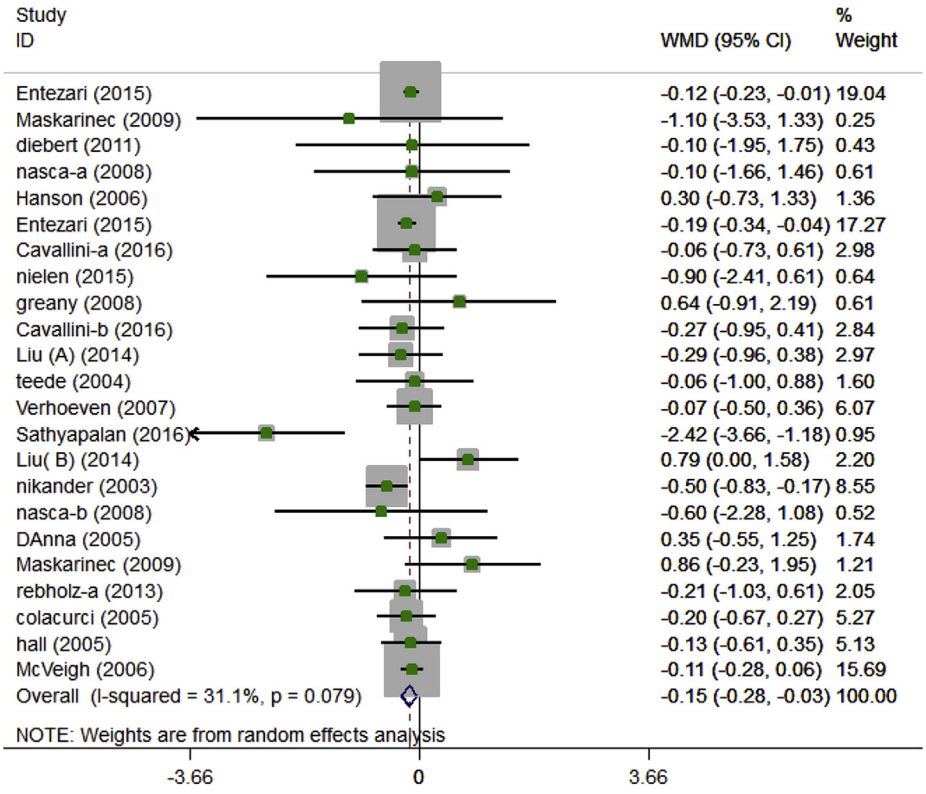

Fig. 3. Forest plot showing the Pooled effect size of soy products on C-reactive protein (mg/L) levels and subgroup analysis based on baseline C-reactive protein concentrations (<2.53), using random effects model.

including all RCTs regardless of health status, the current meta-analysis provides a greater comprehensive review of the literature. Our findings showed that intake of natural soya products seem to be more efficient in improving metabolic abnormalities such as elevated levels of hs-CRP concentration compared with consumption of other processed soya products (soya protein extract or supplements). Similar results were reported in a meta-analysis of RCTs on lipid profile [18], which revealed that the LDL-cholesterol

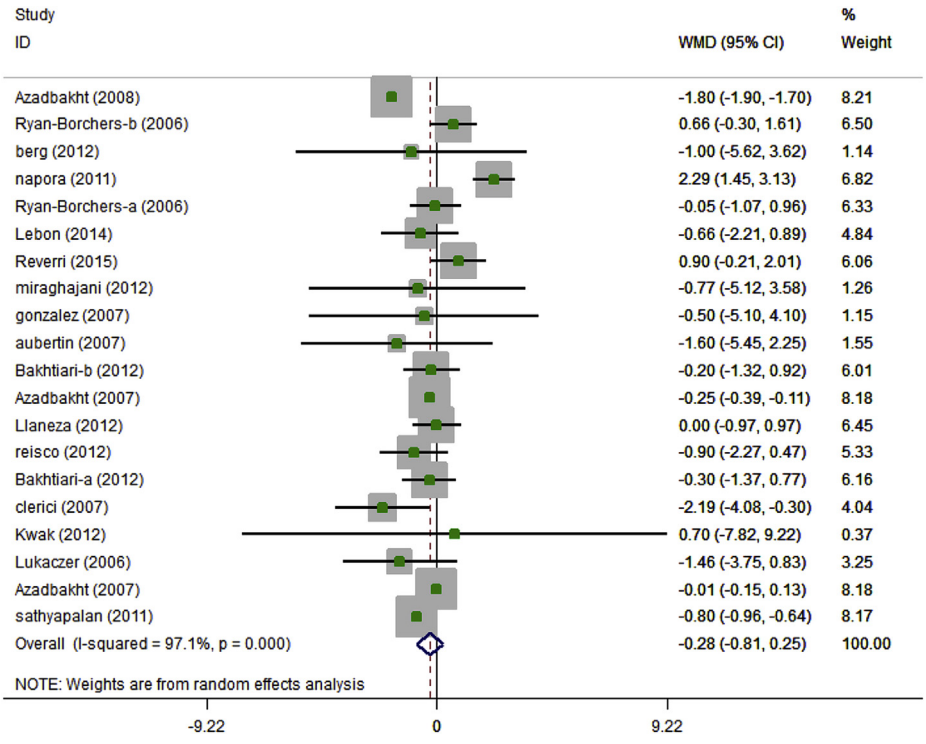

Fig. 4. Forest plot showing the Pooled effect size of soy products on C-reactive protein (mg/L) levels and subgroup analysis based on baseline C-reactive protein concentrations (>2.53), using random effects model.

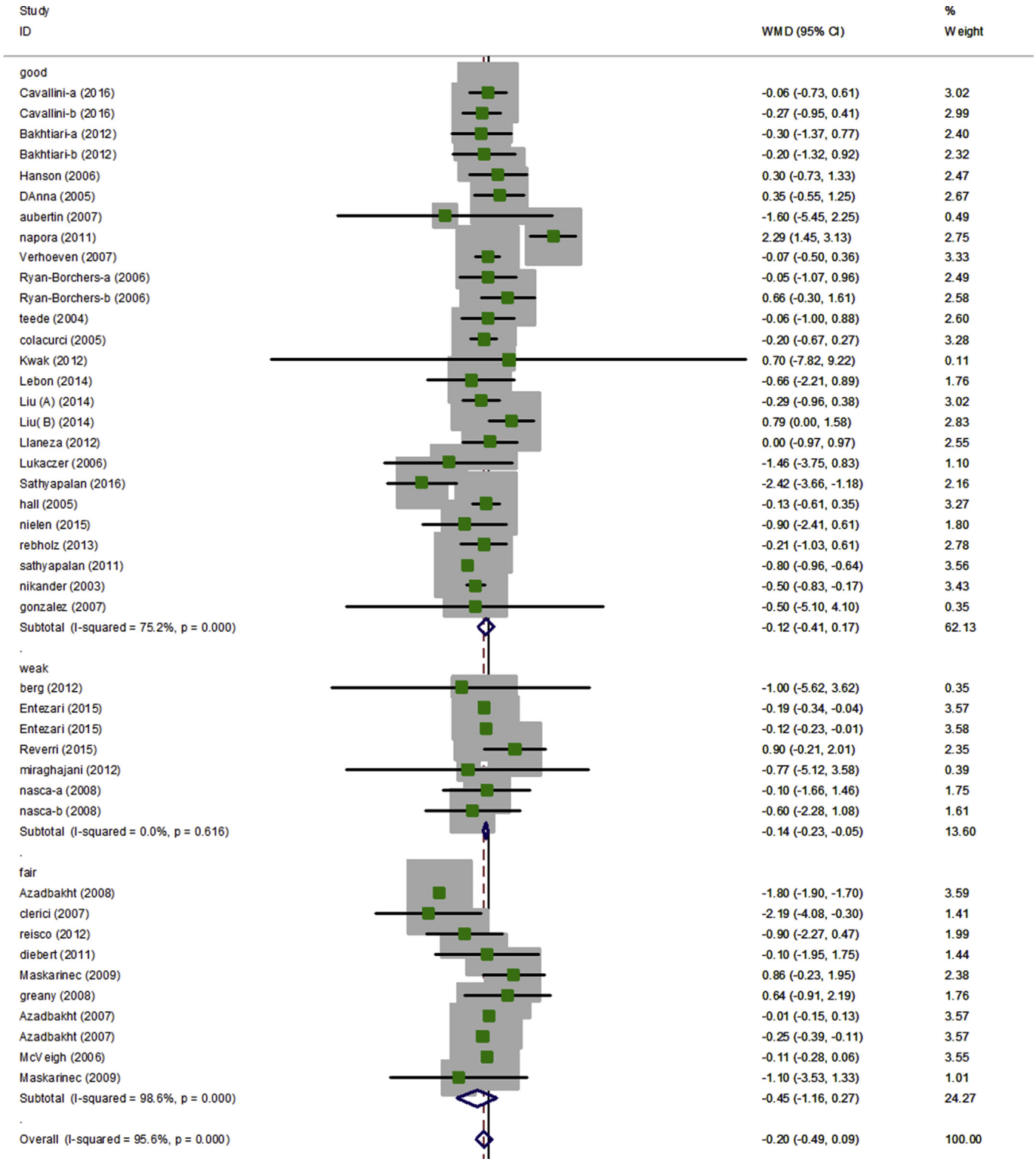

Fig. 5. Forest plot showing the Pooled effect size of soy products on C-reactive protein (mg/L) levels and subgroup analysis based on quality of studies, using random effects model.

lowering effect of whole soy products is three times more efficient than isolated soy components. A possible explanation may be a loss of beneficial ingredients of natural soy products during making of processed soya [111]. Soy products are rich sources of isoflavones [112], poly-unsaturated fats [113] and fiber [114], contributing to the anti-inflammatory health benefits of soy-based products [10].

In vitro [115] and animal studies [116] have suggested that isoflavones can down-regulate cytokine-induced signal transduction (nuclear factor-kB) and thereby reduce pro-inflammatory cytokine levels such as interleukin-6. On the other hand, there is sufficient evidence that IL-6 is able to induce hs-CRP expression by activating the nuclear factor-kB [117]. Therefore, soy

Table 3
Results of subgroup analyses according to intervention or participant characteristics.

Group	No. of trial	Net change in hs-CRP, mg/L (95% CI)	P	$P_{heterogeneity}$	I^2, %
Total	43	−0.20 (−0.49 to 0.09)	0.175	<0.001	95.6
Design					
Parallel	28	−0.20 (−0.64 to 0.24)	0.370	<0.001	96.4
Cross-over	15	−0.26 (−0.5 to −0.02)	0.034	<0.001	79.6
Study duration, day					
<84	19	−0.21 (−0.38 to −0.04)	0.017	<0.001	76.6
≥84	24	−0.22 (−0.78 to 0.34)	0.446	<0.001	93.5
Source of isoflavones					
soy protein + isoflavo	2	−0.50 (−1.21 to 0.21)	0.165	0.034	77.7
natural soya product	14	−0.18 (−0.28 to −0.08)	<0.001	0.326	11.6
Soy protein	15	−0.28 (−0.97 to 0.41)	0.423	<0.001	97.8
supplement	12	−0.1 (−0.35 to 0.16)	0.468	0.141	31.3
Isoflavone dose, mg/day					
≤70	20	−0.41 (−0.89 to 0.06)	0.09	<0.001	96
>70	14	0.05 (−0.22 to 0.32)	0.724	<0.001	71.9
Not reported	9	−0.15 (−0.24 to −0.06)	0.001	0.986	0.0
Baseline hs-CRP, mg/L					
≤2.53	23	−0.15 (−0.27 to −0.02)	0.025	0.053	34.6
>2.53	20	−0.3 (−0.83 to 0.24)	0.277	<0.001	97.1
Health status					
Healthy	14	−0.09 (−0.23 to 0.05)	0.20	<0.001	81.8
At risk	22	−0.04 (−0.32 to 0.24)	0.79	0.916	0.0
disease	7	−0.91 (−1.78 to −0.03)	0.04	<0.001	99
Sample size					
≤ 42	24	−0.10 (−0.54 to 0.32)	0.626	<0.001	97.4
>42	19	−0.28 (−0.56 to −0.00)	0.049	<0.001	68.4
Region					
Americas	32	0.10 (−0.26 to 0.46)	0.576	<0.001	60.5
Europe/Asia/Australia	11	−0.38 (−0.76 to 0.00)	0.048	<0.001	97.2
Quality					
good	26	−0.12 (−0.41 to 0.17)	0.401	<0.001	75.2
Fair	10	−0.45 (−1.16 to 0.27)	0.221	<0.001	98.6
Poor	7	−0.14 (−0.23 to −0.05)	0.002	0.616	0.0
Gender					
Male	7	−0.12 (−0.91 to 0.67)	0.774	<0.001	86.7
Female	30	−0.18 (−0.33 to −0.02)	0.026	<0.001	67.1
Both gender	6	−0.76 (−2.06 to 0.54)	0.251	<0.001	86.5

isoflavones, by acting as weak estrogenic compounds, exhibit anti-inflammatory properties [22].

Findings of the present meta-analysis showed a marked effect of soya products on hs-CRP in the short term and also among participants with basal hs-CRP <2.57 mg/L. Since in our meta-analysis more frequent limitation of soy RCTs with long period design was missing measurement of plasma or urine levels of soy isoflavones, dietary compliance, the absorption of isoflavones and their bioavailability could not be confirmed. So, these measurements should be considered in future long-term studies to draw conclusions about duration of soy intervention.

While a subgroup analysis based on isoflavones dosage did not show similar beneficial effects of soy isoflavones on reducing hs-CRP concentration, we determined a dose–response effect of soya

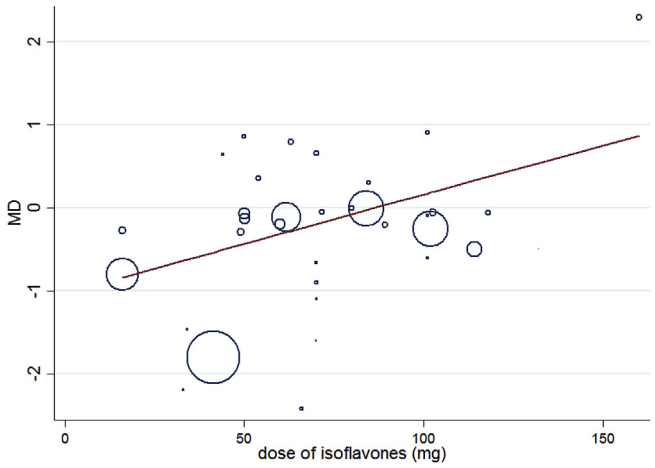

Fig. 6. Meta-regression plot of the effect of dose of isoflavones on soya's effect on C-reactive protein. Values are in mg/L.

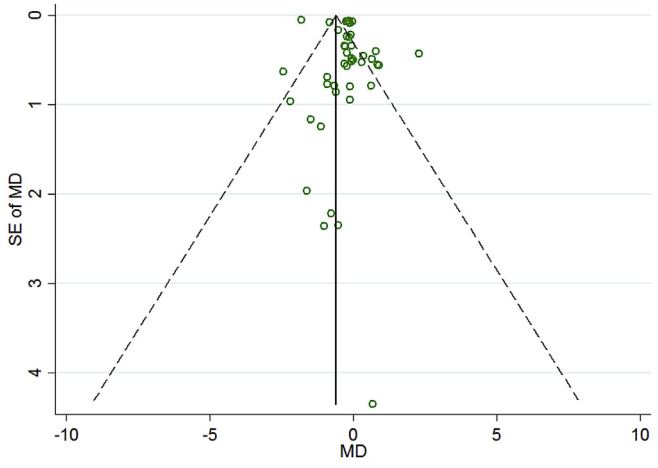

Fig. 7. Begg's funnel plots (with pseudo 95% CIs) of the difference in means (DMs) versus the SEs of the mean differences (MDs) for studies that investigating the effect of soy products on C-reactive protein.

isoflavones on hs-CRP reduction in a meta-regression analysis in a multivariate model. The mean daily intake of isoflavones was about 73 mg in our meta-analysis, which is similar to mean isoflavone consumption in Asian diets (25–50 mg/d) [118,119], but is not seen in Western diets (1–2 mg/day) [120]. Therefore, further prospective studies are warranted to determine the optimal required dose of soy isoflavones for reducing serum hs-CRP concentrations. Subsequent subgroup analysis showed that soy products may not have any effect on serum hs-CRP concentrations among populations in North and South America. There are possibilities for the inconsistent results according to the locations of the included studies. It may be due to differences in food sources of soy among Asian and American consumers [121]. Asian populations consume minimally processed, often fermented soy foods, whereas Americans and other westernized populations consume more processed forms of soy [122]. Thus, the effect of soy on hs-CRP reduction may be product-dependent.

One of the main reasons for insufficient evidence to support soy–inflammation relation in our meta-analysis regardless of subgroup analysis results is probably due to different ability of subjects in metabolizing daidzein to equol [24]. It is noteworthy that only 20–25% of Western populations have the capacity to produce equol [24], whereas about 60% of Asian populations make equol [123]. In the present study, from all of the 44 studies included in our systematic review, only six studies [42,61,66,67,71,77] reported stratified interest outcomes according to equol-producer status and most of them had not prepared any data for computing net change values based on this stratification [61,67,71,77]. Therefore, because of the high heterogeneity in design and definition of equol producers and incomplete data in the reviewed studies in the current meta-analysis, we avoided formal combination of the results in the form of a meta-analysis. However, equol producing status had a non-significant effect on hs-CRP levels in four studies [61,66,67,71,77] and was beneficial in one study [42]. It should be noted that five studies were conducted in Western countries, where the capacity of equol production is low. It seems that equol may mediate protective effects; for example, an RCT that used natural S-equol as a supplement showed a significant reduction in HbA1c, serum low-density lipoprotein cholesterol levels and cardio-ankle vascular index score in overweight and obese patients with predominant effects in equol non-producers [124].

This meta-analysis had several limitations that must be considered in the interpretation of our finding. First, there was substantial heterogeneity among studies even in several different sub-groups. Accordingly, we applied a random-effect model to consider discrepancies across studies. The probable reasons of this heterogeneity may be related to discrepancies in the studies' design, intervention methods, capability of participants to absorb and metabolize isoflavones, genetic background of the participants, and participants' dietary habits [17,125]. Secondly, several included studies in our meta-analysis did not provide any information about using drugs (such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers agents) during the intervention. Since evidence suggest that these therapeutic agents may have direct anti-inflammatory activities [126], neglecting the confounding effect of drug usage is an important issue. Thirdly, hs-CRP change had reported as secondary outcomes in most of the included studies in the present analysis. Thus, decisions about definite conclusions regarding the inflammation-soy relationship is difficult. Fourthly, we excluded studies [44,46,52,54,59,61,66,68] with very high and very low baseline levels of hs-CRP concentrations compared with other studies. However, exclusion of these studies did not change our results. Finally, serum or urine levels of isoflavones were not measured and therefore, actual absorbed values of isoflavones was not clarified in the included studies.

Our meta-analysis had a number of strengths. First of all, since studies with RCT designs are suitable for determining casual inference, quantification of their results can represent greater reliable conclusions. Secondly, the large number of included studies allowed for a comprehensive subgroup analysis. By using subgroup and meta-regression analyses, we could successfully identify possible sources of heterogeneity. Third, including studies with both sexes and stratifying results according to sex showed a considerable benefit of soy intake on hs-CRP level among women. Fourth, participants were not users of hormone therapy or statins during the intervention. Finally, using Egger's test, we did not find any evidence of significant publication bias among studies which were included in meta-analysis.

5. Conclusion

In conclusion, present review of RCTs published up to December 2016 did not provide strong evidence regarding the beneficial effect of soya products consumption on blood hs-CRP concentrations. However, it appears that natural soya products may reduce plasma levels of hs-CRP in comparison to other source of isoflavones (soya extracts, supplements). Moreover, dietary soy isoflavone intake may have a potential beneficial effect among subjects with baseline hs-CRP concentrations of less than 2.52 mg/L. On the other hand, dose of isoflavones seems to be a strong predictor of the effect of soya on serum hs-CRP levels. Therefore, larger and well-designed intervention studies are recommended to confirm the beneficial effects of soy products on inflammatory markers, particularly serum hs-CRP concentration.

Contributors

MK designed this study. MK and JM searched the literature and extracted data. MK and MAJ analyzed data. MK and MAF wrote the first draft of the manuscript and revised it.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

Not required.

Data sharing

No additional data available.

Conflict of interest

None declared.

What is already known on this topic?

Hs-CRP is a strong, independent predictor of CVD risk among both men and women. The results of studies about the effect of soy products on serum hs-CRP are inconsistent.

What this study adds?

It appears that natural soya products may reduce plasma levels of hs-CRP in comparison to other source of isoflavones (soya extracts, supplements). Moreover, dietary soy isoflavone intake may have a potential beneficial effect among subjects with baseline hs-CRP concentrations of less than 2.52 mg/L. On the other hand, dose of isoflavones seems to be a strong predictor of the effect of soya on serum hs-CRP levels. Inclusion of soyfoods in a western diet might play a curial role in regulating inflammation.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.09.007.

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