Effects of phytoestrogen supplementation on intermediate cardiovascular disease risk factors among postmenopausal women: A meta-analysis of randomized controlled trials

Maike Wolters, Gordana M. Dejanovic, Eralda Asllanaj, Kathrin Günther, Hermann Pohlabeln, Wichor Bramer, Jenny Ahrens, Rajini Nagrani, Iris Pigeot, Oscar H. Franco, Wolfgang Ahrens, Taulant Muka, Marija Glisic

DOI
10.1097/GME.0000000000001566

Published in
Menopause

Document version
Accepted manuscript

Online publication date
29 June 2020

Corresponding author
Maike Wolters

Citation
Wolters M, Dejanovic GM, Asllanaj E, Günther K, Pohlabeln H, Bramer W, et al. Effects of phytoestrogen supplementation on intermediate cardiovascular disease risk factors among postmenopausal women: A meta-analysis of randomized controlled trials. Menopause. 2020;27(9):1081-92.

Effects of Phytoestrogen Supplementation on Intermediate Cardiovascular Disease Risk Factors among Postmenopausal Women: a Meta-analysis of Randomized Controlled Trials

Maike Wolters, PhD[1], Gordana M. Dejanovic, MD[2]*, Eralda Asllanaj, MD, DSc[3,4]*, Kathrin Günther, PhD[1], Hermann Pohlabeln, PhD[1], Wichor M. Bramer, MSc[5], Jenny Ahrens, BA[1], Rajini Nagrani, PhD[1], Iris Pigeot, PhD[1], Oscar H. Franco, MD, PhD[6], Wolfgang Ahrens, PhD[1], Taulant Muka, MD, PhD[6], Marija Glisic, MD, PhD[1,6,7]

*denotes equal contribution

[1]Leibniz Institute for Prevention Research and Epidemiology - BIPS, Bremen, Germany
[2]Department of Ophthalmology, University of Novi Sad, Faculty of Medicine, Hajduk Veljkova 1-3, 21000 Novi Sad , Serbia
[3]Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands
[4]Institute for Community Medicine, University of Greifswald, Greifswald, Germany
[5] Medical Library, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands
[6]Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland
[7]Swiss Paraplegic Research, Nottwil, Switzerland

Address correspondence to: Maike Wolters, PhD, Department of Epidemiological Methods and Etiological Research, Leibniz Institute for Prevention Research and Epidemiology - BIPS, Achterstr. 30, 28359 Bremen, Germany. E-mail: wolters@leibniz-bips.de

Short title: Phytoestrogens and Cardiovascular Disease

KEY POINTS

Question

Does phytoestrogen use improve cardiovascular disease (CVD) risk factors in postmenopausal women?

Objective

To determine the effect of phytoestrogen supplementation on CVD risk factors by means of a systematic review and meta-analysis of randomized controlled trials.

Findings

- This meta-analysis shows that phytoestrogen supplementation improves serum triglycerides, total cholesterol, low density lipoprotein, apolipoproteins A-1 and B as well as cell adhesion molecules (intercellular adhesion molecule 1, E-selectin) but not other endothelial function markers, flow mediated diameter, fibrinogen or inflammation markers (high quality of evidence).
- Phytoestrogens have no effect on homocysteine (moderate quality of evidence).
- Use of phytoestrogens may have a modest adverse effect on carotid intima media thickness (CIMT) progression particularly in postmenopausal women at increased risk of developing atherosclerosis (low quality of evidence).

Meaning

Phytoestrogen supplementation may be useful to improve the CVD risk profile in postmenopausal women but caution is indicated in women with an increased risk of developing atherosclerosis.

ABSTRACT

Importance: Phytoestrogens are becoming popular constituents of human diets and are increasingly used by postmenopausal women.

Objective: Our study aims to determine the effects of phytoestrogen supplementation on intermediate cardiovascular disease (CVD) risk factors in postmenopausal women.

Evidence review: Five electronic databases (Medline, EMBASE, Web of Science, Cochrane CENTRAL, Google Scholar) were systematically searched to identify eligible studies, i.e. randomized controlled trials (RCTs) that assessed the association of phytoestrogen supplementation with CVD risk factors (serum lipids, homocysteine, fibrinogen, markers of inflammation, oxidative stress and endothelial function, carotid intima media thickness (CIMT)) in postmenopausal women. Data were extracted by two independent reviewers using a pre-defined data collection form.

Findings: In total, 56 RCTs were identified, including 4,039 individual postmenopausal women. There was substantial heterogeneity in quality across studies. Twenty six (46%) RCTs showed poor quality and there was an indication of publication bias presence for some of the biomarkers. Results are reported in pooled mean difference [95% CI] of changes. Use of phytoestrogens was associated with a decrease in serum total cholesterol (−0.27 mmol/L [−0.41 to −0.13]), low density lipoprotein (−0.25 mmol/L [−0.37 to −0.13]), triglycerides (−0.20 mmol/L [−0.28 to −0.11]) and apolipoprotein B (−0.13 g/L [−0.23 to −0.03]) and with an increase in serum apolipoprotein A-1 (0.04 g/L [0.02 to 0.07]. Also, phytoestrogen supplementation was associated with a decrease in serum intercellular adhesion molecule 1 (−18.86 ng/mL [−30.06 to −7.65]) and E-selectin (−2.32 ng/mL [−4.05 to −0.59]). There was no association observed between phytoestrogen supplementation and inflammatory markers, fibrinogen, homocysteine or other endothelial function markers. In contrast, use of phytoestrogens was associated with an increase in CIMT (9.34 μm [95% CI, 0.39 to 18.29]). Effect estimates of phytoestrogen supplementation on oxidative stress could not be pooled.

Conclusions and Relevance: Phytoestrogen supplementation seems to modestly improve the CVD risk profile of postmenopausal women by influencing blood lipids and parameters of endothelial function. In women with an increased risk of atherosclerosis, although modest, a harmful effect on CIMT progression may be present.

However, because of limited quality and the heterogeneous nature of the current evidence, additional rigorous studies are needed to explore the role of phytoestrogens in menopausal cardiovascular health.

Key words: cardiovascular diseases; risk markers; lipids, menopause; meta-analysis; phytoestrogens; vascular function

INTRODUCTION AND OBJECTIVE

Increasing numbers of women use phytoestrogen supplements.[1,2] Phytoestrogens, plant-derived estrogen-like compounds, may cause organ-specific (anti-)estrogenic effects and may modify estrogen-dependent signaling pathways.[2,3] High levels of estrogen in postmenopausal women, as well as use of menopausal hormone therapy (MHT), were associated with adverse changes in cardiometabolic health [including cardiovascular disease (CVD)],[4-6 7] raising a concern regarding potential cardiovascular consequences of phytoestrogens in aging women.[2,3]

Although favorable cardiovascular health effects have been ascribed to phytoestrogens by positively altering the levels of cardiovascular risk factors such as lipids, blood pressure and inflammation and atherosclerosis,[8-10] the evidence has been inconsistent. Various meta-analyses have attempted to summarize the evidence from randomized controlled trials (RCTs) to quantify the association between phytoestrogen supplementation and CVD risk factors. However, the majority of previous meta-analyses were limited by: (i) focusing on heterogeneous interventions (e.g. phytoestrogens plus exercise)[11] or solely one outcome,[12] (ii) including specific types of phytoestrogens: isoflavones,[13] flaxseed[14] or soy products only,[15-17] and (iii) inclusion of heterogeneous populations in terms of menopausal status or sex[12,16,17] making interpretation of results challenging.

Therefore, we conducted a systematic review and meta-analysis of RCTs evaluating the association of phytoestrogen supplementation with CVD risk factors in postmenopausal women.

METHODS

Data Sources and Search Strategy

The current review was conducted following a standardized protocol registered in PROSPERO (**ID No. CRD42019121110**) and in accordance with the PRISMA Statement[18] and the Cochrane Handbook for Systematic Reviews of Interventions.[19] An experienced information specialist (WMB) searched four bibliographic databases: Medline ALL via Ovid (from 1946), EMBASE via embase.com (from 1974), Web of Science Core Collection (from 1900), Cochrane CENTRAL via Wiley (from 1996) from inception until January 23, 2020 (date last searched). Additionally we downloaded the first 200 results from the search engine Google Scholar. The

searches combined terms related to (i) supplementation such as “phytoestrogen”, “red clover”, “soybean” etc. and (ii) CVD risk factors (e.g. lipoproteins, inflammation markers) and were filtered to include human studies only. Further, the reference lists of the included studies and relevant reviews were searched for eligible studies. Details on the search strategy are provided in **Supplementary Table 1**.

Study Selection, Eligibility Criteria and Data Extraction

Detailed inclusion and exclusion criteria can be found in the review protocol (PROSPERO ID No.CRD42019121110). In brief, RCTs were eligible for inclusion if they: (i) were conducted among postmenopausal women and (ii) investigated associations of phytoestrogen supplementation with any of the following outcomes: serum lipids, inflammatory markers, coagulation system/fibrinolysis markers, homocysteine, markers of oxidative stress, markers of endothelial dysfunction and vascular function and carotid atherosclerosis. Exclusion criteria were: (i) RCTs investigating phytoestrogen supplementation in combination with dietary restrictions or other interventions, (ii) inappropriate study population (premenopausal women or men) and (iii) articles with incomplete information.

Based on these criteria, titles and abstracts were independently evaluated by two reviewers. The full-texts of potentially eligible studies were afterwards assessed by two independent reviewers and any disagreement was settled by reaching a consensus or by consulting a third reviewer. Two authors independently extracted the relevant information using a pre-defined data extraction form.

Assessing the Quality of Evidence

The quality of included RCTs was assessed by two independent reviewers using the Cochrane Collaboration’s tool.[19] Detailed information on the assessment of study quality and risk of bias is provided in **Supplementary Table 2**. Furthermore, we applied the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rate the overall quality of the evidence for risk of bias, publication bias, imprecision, inconsistency, indirectness, and magnitude of effect.[20]

Data Synthesis and Statistical Analysis

Treatment effects were defined as the pre-post differences in outcomes between phytoestrogen supplementation and control at the end of the trial. All outcomes were continuous; therefore the mean differences [intervention minus control] of the treatment effects in CVD risk factors were presented as summary outcome measures. For data reported as medians, ranges, or 95% confidence intervals (CI), we calculated means and standard deviations using previously described method.[21] Units of measurement were converted to SI units where appropriate. Random-effect models were used to obtain estimates of weighted mean differences (WMDs) and 95% CIs. For RCTs with cross-over design we used the data from the first period only. Fixed effect models as shown in the forest plots were applied to report the estimates for sensitivity analyses. Heterogeneity was assessed using the Cochrane χ2 statistic and the I^2 statistic and was determined as ($I^2 \leq 25\%$), moderate ($25\% < I^2 < 75\%$), or high ($I^2 \geq 75\%$).[22]

Study characteristics including geographic location, number of participants, duration of intervention, type of supplement's administration, baseline age and years since menopause onset, body mass index (BMI), smoking status, women's health status, hyperlipidemia and study quality were pre-specified as characteristics for assessment of heterogeneity and were evaluated using stratified analyses and random-effects meta-regression if eight or more studies were included in the meta-analysis.[23] We performed a leave-one-out sensitivity analysis iteratively by removing one study at a time to confirm that the findings were not influenced by any single study. Asymmetry was assessed by Egger's test and publication bias was evaluated through a funnel plot. All statistical analyses were conducted with STATA, Release 14 (Stata Corp, College Station, Texas, USA). The trials that could not be quantitatively pooled were descriptively summarized.

RESULTS

Study Identification and Selection

Based on the search strategy, 13,780 citations were identified of which 142 were selected for detailed full text evaluation. Of those, 65 studies based on 56 unique RCTs met the inclusion criteria and were included in our systematic review (**Figure 1)**. Among these (i) 42 RCTs investigated serum lipids [total cholesterol (TC), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), triglycerides (TG), apolipoprotein A-1 and B (Apo A-1/B), lipoprotein a (LPa)], (ii) 10 RCTs investigated inflammatory markers [C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor α (TNF-α)], (iii) 4 hemostatic factors

(fibrinogen), (iv) 5 homocysteine, (v) 7 endothelial metabolites and 8 cell adhesion molecules [intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), E-selectin, P-selectin, nitric oxide products (NOx), Endothelin-1], (vi) 4 vascular function [flow mediated diameter (FMD)], (vii) 3 studied carotid intima media thickness (CIMT) (**Table 1, Supplementary Table 3)** and 7 RCTs investigated the association of phytoestrogen supplementation and oxidative stress (**Supplementary Table 4**).

Characteristics of Included Studies

The review included 4,039 postmenopausal women from 56 RCTs. Seventeen RCTs were conducted in North America, 12 in Europe, 15 in Asia-Pacific, 9 in South America, and 9 in Middle East. The sample size ranged from 16 to 325 women (median 50.5 women) and the duration of the interventions from 2 to 113 weeks (median duration 12 weeks). The majority of RCTs included healthy women (n=41), while the rest of RCTs recruited women with different health conditions [e.g. type 2 diabetes (T2D)]. Most of the RCTs (n=44) investigated dietary soy products or isoflavones from soy, 4 trials reported on interventions with red clover and 1 study examined a combination of soy extract with black cohosh extract. Five trials examined isolated isoflavones without specifying the source, 2 studied flaxseed lignans and 1 trial studied lignans from sesame (**Supplementary Table 5**).

Inflammation Markers, Serum Lipids, Fibrinogen and Homocysteine

Based on findings from 40 RCTs[24-65] including 3,069 women, phytoestrogen supplementation, compared to placebo, was associated with a moderate decrease in TC, LDL and TG with pooled mean differences of changes of −0.27 mmol/L [95%CI: −0.41 to −0.13], −0.25 mmol/L [−0.37 to −0.13] and −0.20 mmol/L [95%CI: −0.28 to −0.11], respectively. Based on 12 RCTs[25,31,36,41,46,49,50,57,61,62,65,66] including 985 women, serum Apo A-1 increased (0.04 mmol/L [95%CI: 0.02 to 0.07]) whereas Apo B decreased (−0.13 mmol/L [95%CI: −0.22 to −0.03]), in the phytoestrogen arm as compared to controls. There were no significant associations between phytoestrogen supplementation and serum Lp(a) or HDL. Also, no statistically significant associations were observed between phytoestrogen supplementation and serum CRP[24,25,44,66-72], TNF-α[70,73-75], IL-6[70,73,74], fibrinogen[25,30,66,76] or homocysteine[56,67,68,77,78] (**Figure 2, Supplementary Figures 1-6**).

Cell Adhesion Molecules, Endothelial Metabolites, Vascular Function, and Carotid Atherosclerosis

Based on findings from 5 RCTs including 583[30,68-70,79] and 651[30,68,69,72,79] women, respectively, phytoestrogen supplementation was associated with a decrease in serum ICAM-1 (−18.86 ng/mL [95%CI: −30.06 to −7.65]) and E-selectin (−2.32 ng/mL [95%CI: −4.05 to −0.59]) as compared to placebo. While, no associations were observed between phytoestrogen supplementation and the other endothelial function markers: VCAM-1, Endothelin-1[69,80] and NOx.[72,80] Furthermore, based on 3 unique RCTs[44,81,82] including 688 women, use of phytoestrogens was associated with a modest increase in CIMT (9.34 µm/year [95%CI: 0.39 to 18.29]) whereas no association with FMD[42,83-85] was observed (**Figure 3, Supplementary Figure 7**).

Oxidative Stress

Seven RCTs investigated the effect of lignans[86 59] and soy derived phytoestrogens[54 73 77,87,88] on oxidative stress markers (**Supplementary Table 4**); yet, we were not able to pool the estimates because different markers were reported. The protein-rich soy bean intervention resulted in a significant increase in paraoxonase 1 (PON-1) activity as compared with whey protein.[54] Also, the textured soy protein intervention improved total antioxidant capacity and malondialdehyd compared to no intervention,[87] whereas no beneficial effects on oxidative stress parameters like plasma lipid peroxidation, catalase or glutathion peroxidase were observed after isolated isoflavones[77] and after one soy milk intervention.[73] Another soy milk intervention resulted in improved total antioxidant capacity.[88] Lignan-rich sesame seed powder resulted in an increase of serum γ-tocopherol and of the ratio of α- and γ-tocopherol to TC and a decrease in the levels of thiobarbituric acid reactive substances (TBARS) in oxidized LDL as compared to rice powder whereas the lag time of LDL oxidation did not change after either treatment.[59]

Sensitivity Analyses and Assessments of Bias, Study Quality and Heterogeneity

There was substantial heterogeneity in quality across the available studies with 26 (46%) and 21 (38%) of the included RCTs demonstrating poor and fair quality, respectively (**Supplementary Table 2**). Further, **Figures 2-4** indicate the overall quality of evidence based on the GRADE approach and taking into account the risk of bias, study design, consistency and directness of findings.[20] All analyses except a single one (on the association between phytoestrogen supplementation and IL-6) showed high between study heterogeneity; with an I^2 estimate exceeding 75% ($p < 0.001$ for the Cochrane χ2 statistic) (**Supplementary Figures 1-7**). The heterogeneity between the investigated parameters was barely explained using “meta regression method”.

However, the factors such as age, time since menopause onset, smoking status, type of phytoestrogen administration, sample size, and study quality are suggested to be the sources of heterogeneity regarding the association of phytoestrogen supplementation with TC, LDL, TG and Apo A-1. In subgroup analyses, we found significant reductions for TC, TG and LDL for studies lasting longer than 8 weeks while in shorter trials there was no such effect. However, meta-regression analysis is suggesting that this criterion was not the source of heterogeneity between the studies (**Supplementary Table 6**). Although overall there was no association between phytoestrogen supplementation and serum high sensitivity CRP, when stratified the analysis by median age of trial participants and study location, in women above the median age of 55.7 years and in studies from Middle East, phytoestrogen supplementation was associated with a significant decrease in serum hs-CRP. Also, serum Lp(a) increased in women >5.3 years since menopause onset [pooled mean difference of changes 0.50 g/L (**Supplementary Table 6**) while in the main analysis we found no association, however, this result was based on estimates from a single RCT.[57]

Leave-one-out sensitivity analysis showed that the pooled estimates were not influenced by any specific study included (**Supplementary Figures 8-15)** except in the case of Apo A-1 where the significant overall estimate might be driven by three RCTs[36,50,57] indicating no consistency (**Supplementary Figure 14**). The funnel plots for the analyses of the association of phytoestrogen supplementation and TG and CRP were asymmetrical, with Egger's *p* values of 0.04 and 0.002 for CRP and TG respectively, indicating the presence of publication bias (**Supplementary Figures 16-23**). The remaining plots involving a minimum of eight studies remained symmetrical with non-significant Egger's *p* values ($p>0.05$).

DISCUSSION

We conducted an extensive systematic review of the benefits of phytoestrogens across a broad range of CVD risk factors in postmenopausal women. Our findings suggest that beneficial effects of phytoestrogens in CVD could be mediated via improvements in some serum lipids and cell adhesion molecules. Regardless of an increase in CIMT with phytoestrogen supplementation, it has to be noted that the observed effect size could be considered small and that the corresponding studies were of low quality. Hence, the evidence provided by these studies probably falls behind the evidence for cardiovascular benefits of phytoestrogens in aging women.

Based on the GRADE approach, there was in general high quality of evidence that phytoestrogen supplementation improves serum TC, LDL, TG, Apo A-1 and Apo B. Also, the cholesterol-lowering effect of phytoestrogens was more apparent in postmenopausal women with high initial cholesterol concentrations, indicating that women with dyslipidemia may benefit the most from phytoestrogen supplements. Based on high quality evidence we did not detect an increase of HDL following phytoestrogen supplementation, yet, we found an increase of Apo A-1 which plays a vital role in reverse cholesterol transport and cellular cholesterol homeostasis[89]. Also, based on moderate quality evidence phytoestrogens did not decrease serum Lp(a) which is in accordance with a recent meta-analysis on supplemental soy isoflavone intake[13]. There was moderate and high quality of evidence for improvement in serum E-selectin and ICAM-1 respectively, and high quality evidence of no effect on VCAM-1. The largest crossover trial found differences in the VCAM-1 response by estrogen receptor (ER) β AluI genotype. There was a significant VCAM-1 response after both isoflavone and placebo treatments in women with the AA genotype, but not with the GG or GA genotypes,[69] indicating that single-nucleotide polymorphisms in ERs may cause the variability in response to isoflavones.[90,91]

Although the evidence for a modest disadvantageous effect of phytoestrogens on CIMT was of low quality,[44,81,82] these results may warrant some attention as they are in line with the so called "timing hypothesis". This hypothesis suggests that the vasoprotective effects of estradiol may be age-dependent and could be lost after a prolonged period of hypoestrogenicity.[92-94 95,96] To support this hypothesis: in a single trial phytoestrogen supplementation reduced subclinical atherosclerosis in healthy younger postmenopausal women (median age, 53 years; <5 years postmenopausal) at low CVD risk.[82] While two trials included in this analysis were conducted in women who were around 13 years[81] and 9 years[44] after menopause onset (and diagnosed with T2D and prehypertension) - both reported no effect of phytoestrogen supplements on CIMT. However, individuals with diabetes are at increased risk of developing atherosclerosis, while T2D can also alter the expression of ERβ (the main phytoestrogen binding receptor)[97] which may have also influenced our pooled estimate.

High quality of evidence did not indicate changes in FMD and serum NOx while moderate quality of evidence showed no changes in endothelin-1 with phytoestrogen intervention. Women included in our meta-analysis had relatively high mean baseline FMD ranging between 8.6 and 13.7%, and although previous evidence suggested that isoflavones may be beneficial in women with decreased FMD only [98] due to small number of

trials reporting on FMD we were not able to stratify the analyses by median baseline FMD. Similarly, due to limited number of trials we were not able to further explore the null findings observed in serum NOx and enothelin-1.

There was moderate quality of evidence that phytoestrogen supplementation did not change inflammatory markers and homocysteine and high quality evidence that there was no effect on fibrinogen levels. Yet, in subgroup analyses, serum CRP decreased in older women (above median age of 55.7 years) and in trials conducted in Middle East. It may be that the phytoestrogen supplementation is beneficial in elderly women who usually have higher CRP levels[99] and that a prolonged exposure to phytoestrogens (such as in areas where phytoestrogens are a part of regular diet) may play an important role in modifying this association. In line with our hypothesis, a previous meta-analysis indicated a beneficial role of soy isoflavones in decreasing CRP in women with elevated baseline CRP levels[11] while in our study only 3 out of 11 RCTs included women with elevated serum CRP levels (mean >3 mg/L).

The beneficial role of phytoestrogen supplementation on markers of oxidative stress was inconsistent and the quality of evidence was only moderate. Yet, in vitro and animal studies identified various mechanisms supporting a role of phytoestrogens in improving antioxidant status mostly by their action as free radical scavengers[100] as well as by increasing mitochondrial glutathione and gene expression of anti-oxidative enzymes.[101,102] Thus oxidative stress remains an important factor contributing to increased CVD risk in aging women and merits further investigation.

Strengths and Weaknesses

This review was conducted in accordance with the Cochrane guidelines[103] and we used the Cochrane risk of bias tool[104] and the GRADE[104] approach to rate the quality of the evidence. In order to identify as many relevant studies as possible and reduce the risk of publication bias, a highly sensitive search strategy was used and additional resources were searched including the reference list of included trials and relevant systematic reviews. Nevertheless, this study has a number of limitations. First, although conventional funnel plots and Egger test estimates indicated only a minimal publication bias, these methods are limited by their qualitative nature. We can therefore not exclude that measured or unmeasured publication bias limits our findings. Second, study quality, women's age, time since menopause onset and smoking status contributed to the

heterogeneity of findings. Yet, the number of available studies in some analyses was small (n≤3), precluding our ability to investigate the sources of the observed heterogeneity. Further, the supplements provided to trial participants may vary in quality and composition; also no RCTs matching our search criteria were found after 2015. Moreover, the formulation and quality of newer supplements may differ as compared to the supplements used ≥4 years ago. The capacity of individuals to produce equol (by gut microbiome) may be one of the most important determinants of phytoestrogen effectiveness.[105] For example, Asian individuals have greater ability than non-Asians to produce equol (a metabolite of isoflavone called daidzein)[106]. Also, emerging evidence has suggested an association between equol-producer status, genetic factors (ER polymorphism), and vascular function.[107] The existing trials did not properly address this issue; thus, it is necessary that future trials investigate how phytoestrogen metabolites in serum/urine (as a proxy of phytoestrogen bioactivity) contribute to any effects of phytoestrogens on women's health. Also, the effect of phytoestrogen supplementation may depend on the level of dietary intake: The mean intake of isoflavones in postmenopausal women may vary from 0.779 mg/day in USA[108] to 11.3–41.3 mg/day in Japan.[109] Although we used the study location as an indicator of dietary habits, a comprehensive assessment of women's dietary habits is necessary in order to distinguish women who are regularly consuming phytoestrogen rich food. Lastly, our study did not include the major CVD endpoints because corresponding RCTs on clinical CVD endpoints are not available. However, the included outcomes (i.e. CRP, homocysteine, serum lipids, CIMT) may be considered as proxies of CVD risk.[110-112] Nevertheless, the risk of a fatal CVD event depends on several influences including genetic factors and lifestyle behaviours which can strongly increase or reduce an individual's cardiovascular risk.[113]

Our search identified three reviews of clinical trials conducted in postmenopausal women that reported improvements in blood lipids[114] with flaxseed and improvements in serum homocysteine, lipids[14] and FMD[98] with isoflavone supplementation. This meta-analysis strictly included trials that studied phytoestrogen interventions alone in comparison with controls, whereas the earlier meta-analyses included also trials with combined interventions (e.g. soy isoflavones and low-fat diet). Thus, those earlier studies left unclear whether the beneficial effects observed in these studies were enhanced by beneficial lifestyle changes or whether they can be attributed to flaxseed and isoflavones alone. Also, those reviews did not use the GRADE approach to rate the quality of the evidence and therefore the strength of the evidence published previously was unclear.

Implications for future research

In **Figure 4** we present the overall findings, quality of evidence and factors which may have influenced the observed associations. Herewith we provide hints for the directions future research may take. In particular, to study the effects of phytoestrogens on cardiovascular health in aging women, well-designed clinical trials should: (i) compare the effectiveness of three major types of phytoestrogens (isoflavones, lignans, coumestans) with placebo for a sufficiently long duration of at least 1 year in healthy and in women with impaired cardio-metabolic health, (ii) consider a broad spectrum of intermediate CVD risk factors, (iii) evaluate the ER polymorphism, equol producing status and measure blood and urine phytoestrogen metabolites as a proxy of their bioavailability and (iv) carefully examine and dietary habits of postmenopausal women at baseline and during the follow-up.

CONCLUSIONS

This meta-analysis of clinical trials suggests that phytoestrogen supplementation improves the CVD risk profile in postmenopausal women, particularly by beneficially influencing blood lipids and some parameters of endothelial function while such association could not be observed for plasma fibrinogen and FMD. However, although modest, a deleterious effect on CIMT progression may be present in particular in postmenopausal women at increased risk of developing atherosclerosis. Due to the limited quality of the evidence we cannot draw firm conclusions on how phytoestrogens may affect inflammatory markers, homocysteine and oxidative stress. Therefore, future rigorous clinical trials are needed to further explore the potential of phytoestrogens in improving menopausal health.

Funding/support: None reported.
Financial disclosure/conflicts of interest: None reported.

Author's contribution

Study concept and design: TM, MG and OHF; Acquisition, collection, analysis, or interpretation of data: MW, GMD, EA, HP, MG, WA, IP, WMB, KG, HP, RN, JA, OHF; drafting of the manuscript: MW, MG; Critical revision of the manuscript: TM, WA, IP, WMB, GMD, EA, KG, HP, RN, JA, OHF. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Acknowledgments
We would like to thank the *24-design.com* for help with the design of the figures.

Supplemental digital content is available for this article. Direct URL citationsareprovidedinthe HTMLandPDFversionsofthisarticleonthe journal's Website (www.menopause.org).

References

1. Vashisht A, Domoney CL, Cronje W, Studd JW. Prevalence of and satisfaction with complementary therapies and hormone replacement therapy in a specialist menopause clinic. *Climacteric : the journal of the International Menopause Society.* 2001;4(3):250-256.
2. Chen MN, Lin CC, Liu CF. Efficacy of phytoestrogens for menopausal symptoms: A meta-analysis and systematic review. *Climacteric : the journal of the International Menopause Society.* 2015;18(2):260-269.
3. Talaei M, Pan A. Role of phytoestrogens in prevention and management of type 2 diabetes. *World J Diabetes.* 2015;6(2):271-283.
4. Glisic M, Mujaj B, Rueda-Ochoa OL, et al. Associations of endogenous estradiol and testosterone levels with plaque composition and risk of stroke in subjects with carotid atherosclerosis. *Circulation research.* 2018;122(1):97-105.
5. O'Reilly MW, Glisic M, Kumarendran B, et al. Serum testosterone, sex hormone-binding globulin and sex-specific risk of incident type 2 diabetes in a retrospective primary care cohort. *Clin Endocrinol (Oxf).* 2019;90(1):145-154.
6. Muka T, Nano J, Jaspers L, et al. Associations of steroid sex hormones and sex hormone-binding globulin with the risk of type 2 diabetes in women: A population-based cohort study and meta-analysis. *Diabetes.* 2017;66(3):577-586.
7. Oliver-Williams C, Glisic M, Shahzad S, et al. The route of administration, timing, duration and dose of postmenopausal hormone therapy and cardiovascular outcomes in women: A systematic review. *Human reproduction update.* 2019;25(2):257-271.
8. Rietjens I, Louisse J, Beekmann K. The potential health effects of dietary phytoestrogens. *British journal of pharmacology.* 2017;174(11):1263-1280.
9. Yan Z, Zhang X, Li C, Jiao S, Dong W. Association between consumption of soy and risk of cardiovascular disease: A meta-analysis of observational studies. *European journal of preventive cardiology.* 2017;24(7):735-747.
10. Lou D, Li Y, Yan G, Bu J, Wang H. Soy consumption with risk of coronary heart disease and stroke: A meta-analysis of observational studies. *Neuroepidemiology.* 2016;46(4):242-252.
11. Dong JY, Wang P, He K, Qin LQ. Effect of soy isoflavones on circulating c-reactive protein in postmenopausal women: Meta-analysis of randomized controlled trials. *Menopause.* 2011;18(11):1256-1262.
12. Qin Y, Niu K, Zeng Y, et al. Isoflavones for hypercholesterolaemia in adults. *The Cochrane database of systematic reviews.* 2013(6):Cd009518.
13. Simental-Mendia LE, Gotto AM, Jr., Atkin SL, Banach M, Pirro M, Sahebkar A. Effect of soy isoflavone supplementation on plasma lipoprotein(a) concentrations: A meta-analysis. *Journal of clinical lipidology.* 2018;12(1):16-24.
14. Li J, Liu Y, Wang T, Zhao L, Feng W. Does genistein lower plasma lipids and homocysteine levels in postmenopausal women? A meta-analysis. *Climacteric.* 2016;19(5):440-447.
15. Tokede OA, Onabanjo TA, Yansane A, Gaziano JM, Djousse L. Soya products and serum lipids: A meta-analysis of randomised controlled trials. *Br J Nutr.* 2015;114(6):831-843.
16. Beavers DP, Beavers KM, Miller M, Stamey J, Messina MJ. Exposure to isoflavone-containing soy products and endothelial function: A bayesian meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis.* 2012;22(3):182-191.
17. Khodarahmi M, Jafarabadi MA, Moludi J, Abbasalizad Farhangi M. A systematic review and meta-analysis of the effects of soy on serum hs-crp. *Clin Nutr.* 2019;38(3):996-1011.
18. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: The prisma statement. *PLoS medicine.* 2009;6(7):e1000097.
19. Higgins JPT GSe. Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated march 2011]. The cochrane collaboration, 2011. Available from www.Handbook.Cochrane.Org. .

20. Schünemann H BJ, Guyatt G, Oxman A, editors. Grade handbook for grading quality of evidence and strength of recommendations. Updated october 2013. The grade working group, 2013. Available from guidelinedevelopment.Org/handbook. 2013.
21. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC medical research methodology.* 2005;5:13.
22. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ (Clinical research ed).* 2003;327(7414):557-560.
23. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: A comparison of methods. *Statistics in medicine.* 1999;18(20):2693-2708.
24. Aubertin-Leheudre M, Lord C, Khalil A, Dionne IJ. Effect of 6 months of exercise and isoflavone supplementation on clinical cardiovascular risk factors in obese postmenopausal women: A randomized, double-blind study. *Menopause.* 2007;14(4):624-629.
25. Bakhtiary A, Yassin Z, Hanachi P, et al. Evaluation of the oxidative stress and glycemic control status in response to soy in older women with the metabolic syndrome. *Iran Red Crescent Med J.* 2011;13(11):795-804.
26. Basaria S, Wisniewski A, Dupree K, et al. Effect of high-dose isoflavones on cognition, quality of life, androgens, and lipoprotein in post-menopausal women. *J Endocrinol Invest.* 2009;32(2):150-155.
27. Beavers KM, Serra MC, Beavers DP, Hudson GM, Willoughby DS. The lipid-lowering effects of 4 weeks of daily soymilk or dairy milk ingestion in a postmenopausal female population. *J Med Food.* 2010;13(3):650-656.
28. Blum A, Lang N, Vigder F, et al. Effects of soy protein on endothelium-dependent vasodilatation and lipid profile in postmenopausal women with mild hypercholesterolemia. *Clin Invest Med.* 2003;26(1):20-26.
29. Campbell SC, Khalil DA, Payton ME, Arjmandi BH. One-year soy protein supplementation does not improve lipid profile in postmenopausal women. *Menopause.* 2010;17(3):587-593.
30. Colacurci N, Chiàntera A, Fornaro F, et al. Effects of soy isoflavones on endothelial function in healthy postmenopausal women. *Menopause.* 2005;12(3):299-307.
31. Chiechi LM, Secreto G, Vimercati A, et al. The effects of a soy rich diet on serum lipids: The menfis randomized trial. *Maturitas.* 2002;41(2):97-104.
32. Choquette S, Riesco E, Cormier E, Dion T, Aubertin-Leheudre M, Dionne IJ. Effects of soya isoflavones and exercise on body composition and clinical risk factors of cardiovascular diseases in overweight postmenopausal women: A 6-month double-blind controlled trial. *Br J Nutr.* 2011;105(8):1199-1209.
33. Curtis PJ, Dhatariya K, Sampson M, Kroon PA, Potter J, Cassidy A. Chronic ingestion of flavan-3-ols and isoflavones improves insulin sensitivity and lipoprotein status and attenuates estimated 10-year cvd risk in medicated postmenopausal women with type 2 diabetes: A 1-year, double-blind, randomized,controlled trial. *Diabetes Care.* 2012;35(2):226-232.
34. Dodin S, Lemay A, Jacques H, Légaré F, Forest JC, Mâsse B. The effects of flaxseed dietary supplement on lipid profile, bone mineral density, and symptoms in menopausal women: A randomized, double-blind, wheat germ placebo-controlled clinical trial. *J Clin Endocrinol Metab.* 2005;90(3):1390-1397.
35. Dewell A, Hollenbeck CB, Bruce B. The effects of soy-derived phytoestrogens on serum lipids and lipoproteins in moderately hypercholesterolemic postmenopausal women. *J Clin Endocrinol Metab.* 2002;87(1):118-121.
36. Garrido A, De la Maza MP, Hirsch S, Valladares L. Soy isoflavones affect platelet thromboxane a2 receptor density but not plasma lipids in menopausal women. *Maturitas.* 2006;54(3):270-276.
37. Hall WL, Vafeiadou K, Hallund J, et al. Soy-isoflavone-enriched foods and markers of lipid and glucose metabolism in postmenopausal women: Interactions with genotype and equol production. *Am J Clin Nutr.* 2006;83(3):592-600.

38. Hale G, Paul-Labrador M, Dwyer JH, Merz CN. Isoflavone supplementation and endothelial function in menopausal women. *Clinical endocrinology.* 2002;56(6):693-701.
39. Hidalgo LA, Chedraui PA, Morocho N, Ross S, San Miguel G. The effect of red clover isoflavones on menopausal symptoms, lipids and vaginal cytology in menopausal women: A randomized, double-blind, placebo-controlled study. *Gynecol Endocrinol.* 2005;21(5):257-264.
40. Howes JB, Tran D, Brillante D, Howes LG. Effects of dietary supplementation with isoflavones from red clover on ambulatory blood pressure and endothelial function in postmenopausal type 2 diabetes. *Diabestes Obes Metab.* 2003;5(5):325-332.
41. Jassi HK, Jain A, Arora S, Chitra R. Effect of soy proteins vs soy isoflavones on lipid profile in postmenopausal women. *Indian J Clin Biochem.* 2010;25(2):201-207.
42. Katz DL, Evans MA, Njike VY, et al. Raloxifene, soy phytoestrogens and endothelial function in postmenopausal women. *Climacteric.* 2007;10(6):500-507.
43. Kim J, Lee H, Lee O, et al. Isoflavone supplementation influenced levels of triglyceride and luteunizing hormone in korean postmenopausal women. *Arch Pharmacal Res.* 2013;36(3):306-313.
44. Liu ZM, Ho SC, Chen YM, et al. Whole soy, but not purified daidzein, had a favorable effect on improvement of cardiovascular risks: A 6-month randomized, double-blind, and placebo-controlled trial in equol-producing postmenopausal women. *Mol Nutr Food Res.* 2014;58(4):709-717.
45. Liu ZM, Ho SC, Chen YM, Ho YP. The effects of isoflavones combined with soy protein on lipid profiles, c-reactive protein and cardiovascular risk among postmenopausal chinese women. *Nutr Metab Cardiovasc Dis.* 2012;22(9):712-719.
46. Nikander E, Tiitinen A, Laitinen K, Tikkanen M, Ylikorkala O. Effects of isolated isoflavonoids on lipids, lipoproteins, insulin sensitivity, and ghrelin in postmenopausal women. *J Clin Endocrinol Metab.* 2004;89(7):3567-3572.
47. Nestel PJ, Pomeroy S, Sally K, et al. Isoflavones from red clover improve systemic arterial compliance but not plasma lipids in menopausal women. *J Clin Endocrinol Metab.* 1999;84(3):895-898.
48. Maesta N, Nahas EAP, Nahas-Neto J, et al. Effects of soy protein and resistance exercise on body composition and blood lipids in postmenopausal women. *Maturitas.* 2007;56(4):350-358.
49. Ma D, Taku K, Zhang Y, Jia M, Wang Y, Wang P. Serum lipid-improving effect of soyabean β-conglycinin in hyperlipidaemic menopausal women. *Br J Nutr.* 2013;110(9):1680-1684.
50. Okamura S, Sawada Y, Satoh T, et al. Pueraria mirifica phytoestrogens improve dyslipidemia in postmenopausal women probably by activating estrogen receptor subtypes. *Tohoku J Exp Med.* 2008;216(4):341-351.
51. Rios DRA, Rodrigues ET, Cardoso APZ, Montes MBA, Franceschini SA, Toloi MRT. Lack of effects of isoflavones on the lipid profile of brazilian postmenopausal women. *Nutrition.* 2008;24(11-12):1153-1158.
52. Terzic M, Micic J, Dotlic J, Maricic S, Mihailovic T, Knezevic N. Impact of phytoestrogens on serum lipids in postmenopausal women. *Geburtshilfe Frauenheilkd.* 2012;72(6):527-531.
53. Steinberg FM, Guthrie NL, Villablanca AC, Kumar K, Murray MJ. Soy protein with isoflavones has favorable effects on endothelial function that are independent of lipid and antioxidant effects in healthy postmenopausal women. *Am J Clin Nutr.* 2003;78(1):123-130.
54. Shidfar F, Ehramphosh E, Heydari I, Haghighi L, Hosseini S, Shidfar S. Effects of soy bean on serum paraoxonase 1 activity and lipoproteins in hyperlipidemic postmenopausal women. *Int J Food Sci Nutr.* 2009;60(3):195-205.
55. Teede HJ, Dalais FS, Kotsopoulos D, et al. Dietary soy containing phytoestrogens does not activate the hemostatic system in postmenopausal women. *J Clin Endocrinol Metab.* 2005;90(4):1936-1941.

56. Turhan N, Duvan C, Bokan F, Onaran Y. Effect of isoflavone on plasma nitrite/nitrate, homocysteine, and lipid levels in turkish women in the early postmenopausal period: A randomized controlled trial. *Turk J Med Sci.* 2009;39(3): 367-375.
57. Wangen KE, Duncan AM, Xu X, Kurzer MS. Soy isoflavones improve plasma lipids in normocholesterolemic and mildly hypercholesterolemic postmenopausal women. *Am J Clin Nutr.* 2001;73(2):225-231.
58. Wu J, Oka J, Higuchi M, et al. Cooperative effects of isoflavones and exercise on bone and lipid metabolism in postmenopausal japanese women: A randomized placebo-controlled trial. *Metab Clin Exp.* 2006;55(4):423-433.
59. Wu WH, Kang YP, Wang NH, Jou HJ, Wang TA. Sesame ingestion affects sex hormones, antioxidant status, and blood lipids in postmenopausal women. *J Nutr.* 2006;136(5):1270-1275.
60. Yildiz MF, Kumru S, Godekmerdan A, Kutlu S. Effects of raloxifene, hormone therapy, and soy isoflavone on serum high-sensitive c-reactive protein in postmenopausal women. *Int J Gynecol Obstet.* 2005;90(2):128-133.
61. Zhang T, Chi XX. The effect of genistein on lipid levels and ldlr, lxralpha and abcg1 expression in postmenopausal women with hyperlipidemia. *Diabetology & metabolic syndrome.* 2019;11:111.
62. Ye YB, Wang ZL, Zhuo SY, et al. Soy germ isoflavones improve menopausal symptoms but have no effect on blood lipids in early postmenopausal chinese women: A randomized placebo-controlled trial. *Menopause.* 2012;19(7):791-798.
63. Nahas EA, Nahas-Neto J, Orsatti FL, Carvalho EP, Oliveira ML, Dias R. Efficacy and safety of a soy isoflavone extract in postmenopausal women: A randomized, double-blind, and placebo-controlled study. *Maturitas.* 2007;58(3):249-258.
64. Braxas H, Rafraf M, Karimi Hasanabad S, Asghari Jafarabadi M. Effectiveness of genistein supplementation on metabolic factors and antioxidant status in postmenopausal women with type 2 diabetes mellitus. *Can J Diabetes.* 2019;43(7):490-497.
65. Barrasa GRR, Gonzalez Canete N, Boasi LEV. Age of postmenopause women: Effect of soy isoflavone in lipoprotein and inflammation markers. *J Menopausal Med.* 2018;24(3):176-182.
66. Dodin S, Cunnane SC, Mâsse B, et al. Flaxseed on cardiovascular disease markers in healthy menopausal women: A randomized, double-blind, placebo-controlled trial. *Nutrition.* 2008;24(1):23-30.
67. D'Anna R, Baviera G, Corrado F, Cancellieri F, Crisafulli A, Squadrito F. The effect of the phytoestrogen genistein and hormone replacement therapy on homocysteine and c-reactive protein level in postmenopausal women. *Acta Obstet Gynecol Scand.* 2005;84(5):474-477.
68. Greany KA, Nettleton JA, Wangen KE, Thomas W, Kurzer MS. Consumption of isoflavone-rich soy protein does not alter homocysteine or markers of inflammation in postmenopausal women. *Eur J Clin Nutr.* 2008;62(12):1419-1425.
69. Hall WL, Vafeiadou K, Hallund J, et al. Soy-isoflavone-enriched foods and inflammatory biomarkers of cardiovascular disease risk in postmenopausal women: Interactions with genotype and equol production. *Am J Clin Nutr.* 2005;82(6):1260-1268.
70. Hallund J, Tetens I, Bugel S, Tholstrup T, Bruun JM. The effect of a lignan complex isolated from flaxseed on inflammation markers in healthy postmenopausal women. *Nutr Metab Cardiovasc Dis.* 2008;18(7):497-502.
71. Verhoeven MO, Teerlink T, Kenemans P, Zuijdgeest-van Leeuwen SD, van der Mooren MJ. Effects of a supplement containing isoflavones and actaea racemosa l. On asymmetric dimethylarginine, lipids, and c-reactive protein in menopausal women. *Fertility and sterility.* 2007;87(4):849-857.
72. Nikander E, Metsa-Heikkila M, Tiitinen A, Ylikorkala O. Evidence of a lack of effect of a phytoestrogen regimen on the levels of c-reactive protein, e-selectin, and nitrate in postmenopausal women. *J Clin Endocrinol Metab.* 2003;88(11):5180-5185.

73. Beavers KM, Serra MC, Beavers DP, Cooke MB, Willoughby DS. Soymilk supplementation does not alter plasma markers of inflammation and oxidative stress in postmenopausal women. *Nutr Res.* 2009;29(9):616-622.
74. Charles C, Yuskavage J, Carlson O, et al. Effects of high-dose isoflavones on metabolic and inflammatory markers in healthy postmenopausal women. *Menopause.* 2009;16(2):395-400.
75. Ryan-Borchers TA, Park JS, Chew BP, McGuire MK, Fournier LR, Beerman KA. Soy isoflavones modulate immune function in healthy postmenopausal women. *Am J Clin Nutr.* 2006;83(5):1118-1125.
76. Crisafulli A, Altavilla D, Marini H, et al. Effects of the phytoestrogen genistein on cardiovascular risk factors in postmenopausal women. *Menopause.* 2005;12(2):186-192.
77. Brandao LC, Hachul H, Bittencourt LR, Baracat EC, Tufik S, D'Almeida V. Effects of isoflavone on oxidative stress parameters and homocysteine in postmenopausal women complaining of insomnia. *Biol Res.* 2009;42(3):281-287.
78. Reimann M, Dierkes J, Carlsohn A, et al. Consumption of soy isoflavones does not affect plasma total homocysteine or asymmetric dimethylarginine concentrations in healthy postmenopausal women. *J Nutr.* 2006;136(1):100-105.
79. Liu ZM, Ho SC, Chen YM, Woo J. Effect of soy protein and isoflavones on blood pressure and endothelial cytokines: A 6-month randomized controlled trial among postmenopausal women. *J Hypertens.* 2013;31(2):384-392.
80. Hallund J, Bügel S, Tholstrup T, et al. Soya isoflavone-enriched cereal bars affect markers of endothelial function in postmenopausal women. *Br J Nutr.* 2006;95(6):1120-1126.
81. Curtis PJ, Potter J, Kroon PA, et al. Vascular function and atherosclerosis progression after 1 y of flavonoid intake in statin-treated postmenopausal women with type 2 diabetes: A double-blind randomized controlled trial. *Am J Clin Nutr.* 2013;97(5):936-942.
82. Hodis HN, MacK WJ, Kono N, et al. Isoflavone soy protein supplementation and atherosclerosis progression in healthy postmenopausal women: A randomized controlled trial. *Stroke.* 2011;42(11):3168-3175.
83. Evans M, Njike VY, Hoxley M, Pearson M, Katz DL. Effect of soy isoflavone protein and soy lecithin on endothelial function in healthy postmenopausal women. *Menopause.* 2007;14(1):141-149.
84. Liu ZM, Ho SC, Chen YM, et al. Effect of whole soy and purified daidzein on ambulatory blood pressure and endothelial function--a 6-month double-blind, randomized controlled trial among chinese postmenopausal women with prehypertension. *Eur J Clin Nutr.* 2015;69(10):1161-1168.
85. Lissin LW, Oka R, Lakshmi S, Cooke JP. Isoflavones improve vascular reactivity in post-menopausal women with hypercholesterolemia. *Vasc Med.* 2004;9(1):26-30.
86. Hallund J, Ravn-Haren G, Bugel S, Tholstrup T, Tetens I. A lignan complex isolated from flaxseed does not affect plasma lipid concentrations or antioxidant capacity in healthy postmenopausal women. *J Nutr.* 2006;136(1):112-116.
87. Bakhtiari A, Hajian-Tilaki K, Omidvar S, Nasiri-Amiri F. Clinical and metabolic response to soy administration in older women with metabolic syndrome: A randomized controlled trial. *Diabetology & metabolic syndrome.* 2019;11:47.
88. Hanachi P, Golkho S, Ahmadi A, Barantalab F. The effect of soymilk on alkaline phosphatase, total antioxidant levels, and vasomotor symptoms in menopause women. *Iranian Journal of Basic Medical Sciences.* 2007;10(3):162-168.
89. Uehara Y, Saku K. High-density lipoprotein and atherosclerosis: Roles of lipid transporters. *World journal of cardiology.* 2014;6(10):1049-1059.
90. Herrington DM, Howard TD, Hawkins GA, et al. Estrogen-receptor polymorphisms and effects of estrogen replacement on high-density lipoprotein cholesterol in women with coronary disease. *The New England journal of medicine.* 2002;346(13):967-974.

91. Herrington DM, Howard TD, Brosnihan KB, et al. Common estrogen receptor polymorphism augments effects of hormone replacement therapy on e-selectin but not c-reactive protein. *Circulation.* 2002;105(16):1879-1882.
92. Bowling MR, Xing D, Kapadia A, et al. Estrogen effects on vascular inflammation are age dependent: Role of estrogen receptors. *Arteriosclerosis, thrombosis, and vascular biology.* 2014;34(7):1477-1485.
93. Miller AP, Xing D, Feng W, Fintel M, Chen YF, Oparil S. Aged rats lose vasoprotective and anti-inflammatory actions of estrogen in injured arteries. *Menopause.* 2007;14(2):251-260.
94. Williams JK, Anthony MS, Honore EK, et al. Regression of atherosclerosis in female monkeys. *Arteriosclerosis, thrombosis, and vascular biology.* 1995;15(7):827-836.
95. Phillips LS, Langer RD. Postmenopausal hormone therapy: Critical reappraisal and a unified hypothesis. *Fertility and sterility.* 2005;83(3):558-566.
96. Miller VM SL, Hayes SN. . Controversy of hormone treatment and cardiovascular function: Need for strengthened collaborations between preclinical and clinical scientists. *Curr Opin Investig Drugs* 2003(4):1220-1232.
97. Muka T, Vargas KG, Jaspers L, et al. Estrogen receptor beta actions in the female cardiovascular system: A systematic review of animal and human studies. *Maturitas.* 2016;86:28-43.
98. Li SH, Liu XX, Bai YY, et al. Effect of oral isoflavone supplementation on vascular endothelial function in postmenopausal women: A meta-analysis of randomized placebo-controlled trials. *Am J Clin Nutr.* 2010;91(2):480-486.
99. Singh T, Newman AB. Inflammatory markers in population studies of aging. *Ageing research reviews.* 2011;10(3):319-329.
100. Kladna A, Berczynski P, Kruk I, Piechowska T, Aboul-Enein HY. Studies on the antioxidant properties of some phytoestrogens. *Luminescence : the journal of biological and chemical luminescence.* 2016;31(6):1201-1206.
101. Mahn K, Borras C, Knock GA, et al. Dietary soy isoflavone induced increases in antioxidant and enos gene expression lead to improved endothelial function and reduced blood pressure in vivo. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology.* 2005;19(12):1755-1757.
102. Roghani M, Vaez Mahdavi MR, Jalali-Nadoushan MR, et al. Chronic administration of daidzein, a soybean isoflavone, improves endothelial dysfunction and attenuates oxidative stress in streptozotocin-induced diabetic rats. *Phytotherapy research : PTR.* 2013;27(1):112-117.
103. Higgins JPT GSe. Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated march 2011]. *The Cochrane Collaboration,.* 2011.
104. Higgins JP, Altman DG, Gotzsche PC, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *Bmj.* 2011;343:d5928.
105. Lampe JW. Is equol the key to the efficacy of soy foods? *Am J Clin Nutr.* 2009;89(5):1664S-1667S.
106. Patisaul HB, Jefferson W. The pros and cons of phytoestrogens. *Frontiers in neuroendocrinology.* 2010;31(4):400-419.
107. Hong KW, Ko KP, Ahn Y, et al. Epidemiological profiles between equol producers and nonproducers: A genomewide association study of the equol-producing phenotype. *Genes Nutr.* 2012;7(4):567-574.
108. de Kleijn MJ, van der Schouw YT, Wilson PW, Grobbee DE, Jacques PF. Dietary intake of phytoestrogens is associated with a favorable metabolic cardiovascular risk profile in postmenopausal u.S.Women: The framingham study. *J Nutr.* 2002;132(2):276-282.
109. Kokubo Y, Iso H, Ishihara J, et al. Association of dietary intake of soy, beans, and isoflavones with risk of cerebral and myocardial infarctions in japanese populations: The japan public health center-based (jphc) study cohort i. *Circulation.* 2007;116(22):2553-2562.

110. Bots ML. Carotid intima-media thickness as a surrogate marker for cardiovascular disease in intervention studies. *Current medical research and opinion.* 2006;22(11):2181-2190.
111. Glasser SP, Mosher A, Howard G, Banach M. What is the association of lipid levels and incident stroke? *International journal of cardiology.* 2016;220:890-894.
112. Fonseca FA, Izar MC. High-sensitivity c-reactive protein and cardiovascular disease across countries and ethnicities. *Clinics.* 2016;71(4):235-242.
113. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 acc/aha guideline on the primary prevention of cardiovascular disease: A report of the american college of cardiology/american heart association task force on clinical practice guidelines. *J Am Coll Cardiol.* 2019;74(10):e177-e232.
114. Pan A, Yu D, Demark-Wahnefried W, Franco OH, Lin X. Meta-analysis of the effects of flaxseed interventions on blood lipids. *Am J Clin Nutr.* 2009;90(2):288-297.

Figure Legends

Figure 1. Flowchart of randomized controlled trials included in the current review

Figure 2. **The associations between phytoestrogen supplementation and inflammation markers, fibrinogen, homocysteine and blood lipids**

Abbreviations: Apo, apolipoprotein; CPP, C-reactive protein; HDL, high density lipoprotein; IL-6, interleukin-6; LDL, low density lipoprotein; LP(a), lipoprotein a; TC, total cholesterol; TG, triglycerides; TNF-α, tumor necrosis factor α

Quality of evidence was evaluated using Grading of Recommendations Assessment, Development and Evaluation (GRADE):

A (High): We are very confident that the true effect lies close to that of the estimate of the effect; Further research is very unlikely to change our confidence in the estimate of effect; **B (Moderate)**: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; **C (Low)**: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; **D (Very Low)**: We have little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Figure 3. The associations between phytoestrogen supplementation and cell adhesion molecules, endothelial metabolites, vascular function and carotid atherosclerosis

Abbreviations: CIMT, carotid intima media thickness; FMD, flow mediated diameter; ICAM-1, intercellular adhesion molecule 1; Nox, nitric oxide products; VCAM-1, vascular cell adhesion molecule 1

Quality of evidence was evaluated using Grading of Recommendations Assessment, Development and Evaluation (GRADE):

A (High): We are very confident that the true effect lies close to that of the estimate of the effect; Further research is very unlikely to change our confidence in the estimate of effect; **B (Moderate)**: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; **C (Low)**: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; **D (Very Low)**: We have little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Figure 4. Illustrative summary of overall findings

Abbreviations: CIMT, carotid intima media thickness; FMD, flow mediated diameter

Quality of evidence was evaluated using Grading of Recommendations Assessment, Development and Evaluation (GRADE):

A (High): We are very confident that the true effect lies close to that of the estimate of the effect; Further research is very unlikely to change our confidence in the estimate of effect; **B (Moderate)**: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; **C (Low)**: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; **D (Very Low)**: We have little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1]The beneficial effect for lipids refers to total cholesterol, low density lipoprotein, triglycerides, apolipoprotein A-1, apolipoprotein B; [2]The beneficial effect for endothelial function refers to intercellular adhesion molecule 1 and E-selectin

Table Legends

Table 1. Characteristics of the unique RCTs included in the meta-analyses

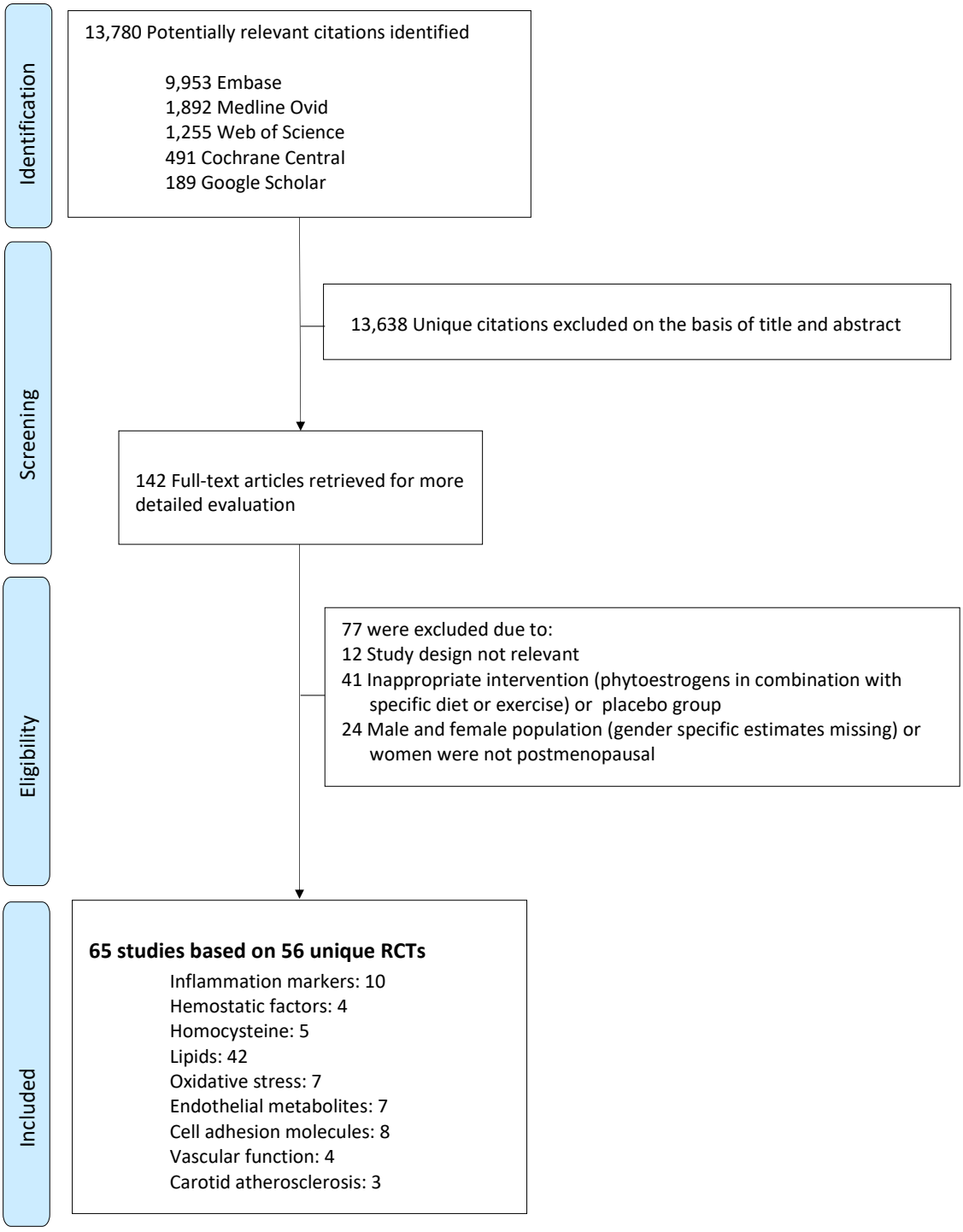
Table 1. Characteristics of the unique RCTs included in the meta-analyses

OUTCOME		Eligible studies		Participants			Location					Intervention characteristics				
												Administration type		Source of phytoestrogens		
		Unique studies, no.	Follow-up duration, median (IQR), weeks	Total	Median (IQR), no.	Age, median (IQR), years	Europe	North America	South America	Asia-Pacific	Middle East	Pills/ tablets	Dietary products	Isofla-vones (Soy or isolated)	Coumestans (Red clover)	Lignans (Flax seed)
Inflammation markers	CRP	10	14 (12-24)	1077	90 (50-179.75)	57.5 (55.7-64.35)	5	3	---	1	1	4	6	8	---	2
	IL-6	3	4 (NA)	139	44 (NA)	54.61 (NA)	1	2	---	---	---	---	3	2	---	1
	TNF-α	4	9 (14.5-15)	163	38 (31.75-6)	56.2 (54.75-59.9)	1	3	---	---	---	---	4	3	---	1
Hemostatic factors	Fibrinogen	4	24 (24-42)	371	58.5 (51.8-149.3)	55.33 (54.8-62.1)	2	1	---	1	---	3	1	3	---	1
Homocysteine	Homo-cysteine	5	16 (7-24)	423	68 (49-128.5)	*53 (NA)	2	1	1	---	1	3	2	5	---	---
Lipids*	TC	40	12 (12-24)	3069	50 (38-90)	55.7 (53.9-58)	5	11	6	12	6	25	24	34	3	3
	TG	39	12(12-24)	3038	52.5 (37-90)	55.7 (53.9-57.9)	4	13	6	11	5	28	22	35	3	3
	Apo A-1/ Apo B	12	12 (12-24)	985	50 (36-90)	53.9 (52.6-56.9)	2	2	2	5	1	8	8	11	0	1
	LP(a)	7	12 (12-24)	832	98 (41-162)	54.9 (52.1-56.9)	3	2	1	1	---	4	4	6	---	1
Cell adhesion molecules	VCAM-1/ ICAM-1	5	8(6-24)	583	94 (53.8-148.5)	56.12 (55.42-59.45)	3	1	---	1	---	2	3	4	---	1

	E-selectin	5	12 (7-24)	651	116.7 (62.3-148.5)	55 (54.58-56.7)	3	1	---	1	---	3	2	5	---	---
Endothelial metabolites	**NO products**	6	10 (7.5-30)	573	91.5 (53-128.5)	57 (52.75-61.75)	5	---	---	---	1	4	2	4	---	2
	Endothelin-1	4	7 (6-38)	427	75.5 (48 -198.7)	59.4 (57.12-62.13)	4	---	---	---	---	---	4	2	---	2
Vascular function	**FMD**	4	6 (4.5-19.5)	442	112 (41-180)	60 (58-61.6)	---	3	---	1	---	2	2	4	---	---
Atherosclerosis	**CIMT**	3	48 (NA)	688	180 (NA)	60.9 (NA)	1	1	---	1	---	---	3	3	---	---

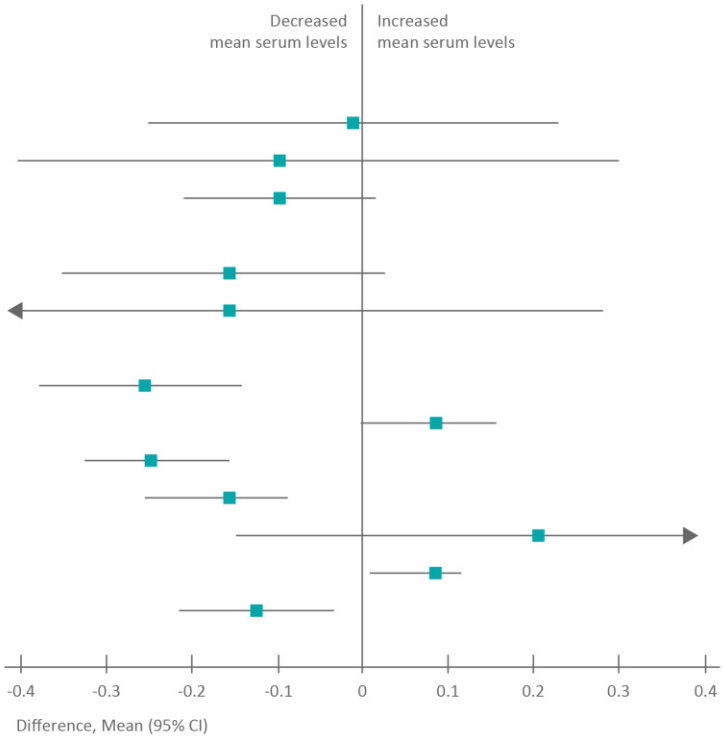
*Study characteristics of HDL and LDL did not vary in comparison to TC therefore are not presented in the table

Abbreviations: Apo, apolipoprotein; CIMT, carotid intima media thickness; CRP, C-reactive protein; FMD, flow mediated diameter; HDL, high density lipoprotein; ICAM-1, intercellular adhesion molecule 1; IL-6, interleukin 6; IQR, interquartile range; LDL, low density lipoprotein; Lp(a), lipoprotein a; NA, not available; no., number; TC, total cholesterol; TG, triglycerides; TNF-α, tumor necrosis factor α; VCAM-1, vascular cell adhesion molecule 1


Identification
13,780 Potentially relevant citations identified
9,953 Embase
1,892 Medline Ovid
1,255 Web of Science
491 Cochrane Central
189 Google Scholar
Screening
13,638 Unique citations excluded on the basis of title and abstract
142 Full-text articles retrieved for more detailed evaluation
Eligibility
77 were excluded due to:
12 Study design not relevant
41 Inappropriate intervention (phytoestrogens in combination with specific diet or exercise) or placebo group
24 Male and female population (gender specific estimates missing) or women were not postmenopausal
Included
65 studies based on 56 unique RCTs
Inflammation markers: 10
Hemostatic factors: 4
Homocysteine: 5
Lipids: 42
Oxidative stress: 7
Endothelial metabolites: 7
Cell adhesion molecules: 8
Vascular function: 4
Carotid atherosclerosis: 3

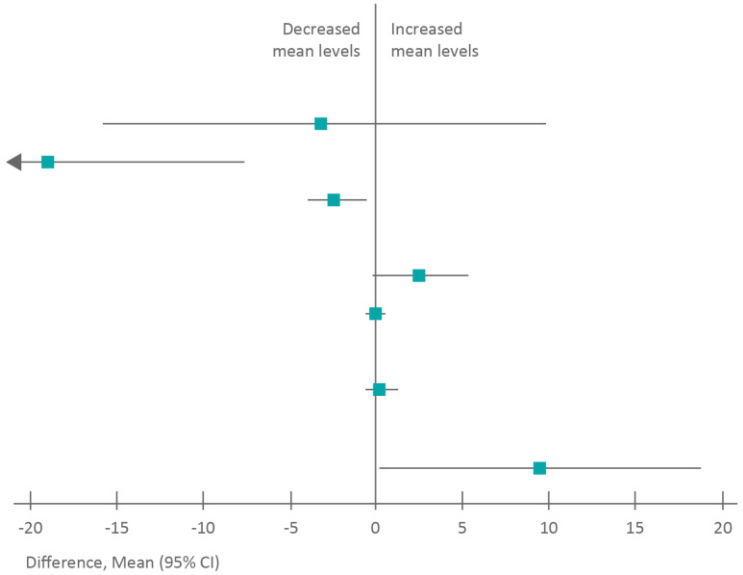
Outcome	No. of estimates included in analysis	No. of women in intervention arm	No. of women in control arm	Difference, Mean (95 % CI)	Quality of evidence
Inflammation markers					
CRP, mg/L	12	640	652	-0.01 (-0.26; 0.23)	B
TNF-α	5	103	79	-0.10 (-0.51; 0.30)	A
IL-6, ng/L	3	70	69	-0.10 (-0.21; 0.02)	A
Haemostatic factors					
Fibrinogen, g/L	5	194	202	-0.17 (-0.36; 0.03)	A
Homocysteine, µmol/L	5	217	206	-0.17 (-0.63; 0.29)	B
Lipids					
TC, mmol/L	439	1,683	1,705	**-0.27 (-0.41; -0.13)**	A
HDL, mmol/L	50	1,808	1,724	0.09 (-0.00; 0.18)	A
LDL, mmol/L	51	1,724	1,740	**-0.25 (-0.37; -0.13)**	B
TG, mmol/L	48	1,669	1,688	**-0.20 (-0.28;- 0.11)**	B
LP(a), g/L	8	421	429	0.22 (-0.15; 0.58)	B
Apo A-1, g/L	17	545	568	**0.04 (0.02; 0.07)**	A
Apo B, g/L	17	545	568	**-0.13 (-0.22; -0.03)**	A

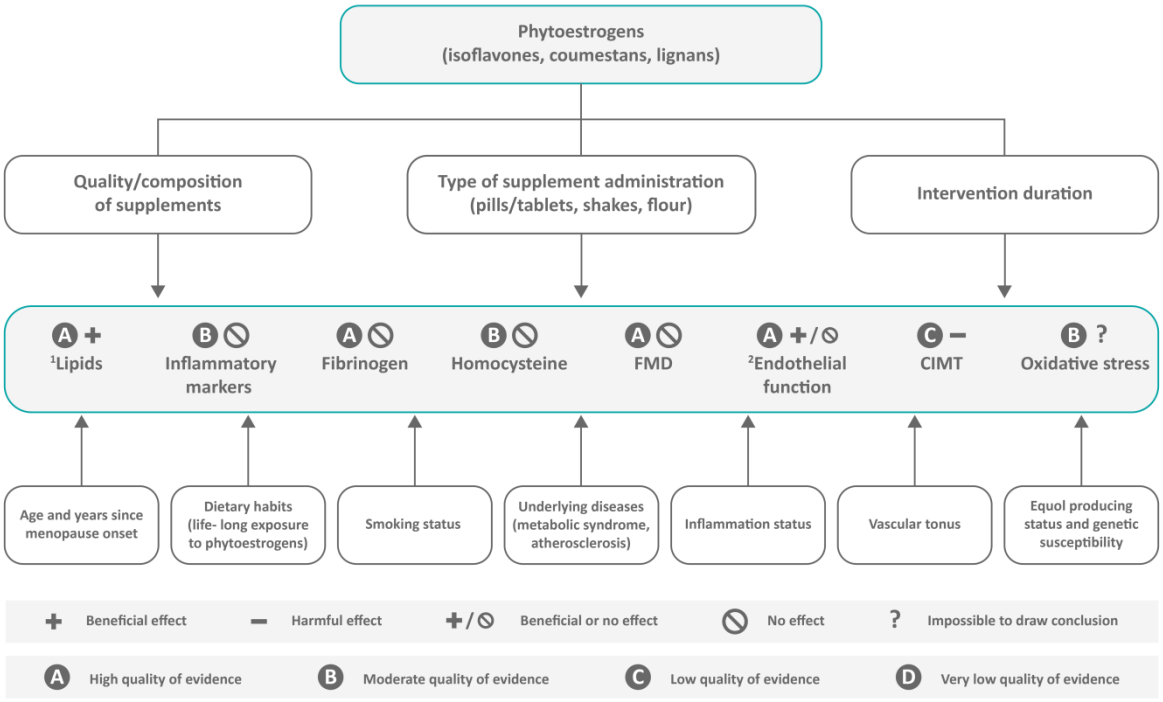
*Statistically significant results are bold; Difference in mean is pooled using random effect model



Outcome	No. of estimates included in analysis	No. of women in intervention arm	No. of women in control arm	Difference, Mean (95 % CI)	Quality of evidence
Cell adhesion molecules					
VCAM-1, ng/mL	6	322	321	-3.41 (-16.73; 9.90)	A
ICAM-1, ng/mL	6	322	261	**-18.86 (-30.06; -7.65)**	A
E-selectin, ng/mL	6	356	355	**-2.32 (-4.05; -0.59)**	B
Endothelial metabolites					
NOx, µmol/L	6	287	286	2.67 (-0.03; 5.36)	A
Endothelin-1, pg/mL	4	214	213	0.07 (-0.09; 0.22)	B
Vascular function					
FMD, %	7	288	288	0.28 (-0.68; 1.25)	A
Atherosclerosis					
Mean CIMT, µm/year	4	389	389	**9.34 (0.39; 18.29)**	C

*Statistically significant results are bold; Difference in mean is pooled using random effect model




Phytoestrogens
(isoflavones, coumestans, lignans)
Quality/composition of supplements
Type of supplement administration (pills/tablets, shakes, flour)
Intervention duration
A +
[1]Lipids
B ⊘
Inflammatory markers
A ⊘
Fibrinogen
B ⊘
Homocysteine
A ⊘
FMD
A +/⊘
[2]Endothelial function
C −
CIMT
B ?
Oxidative stress
Age and years since menopause onset
Dietary habits (life- long exposure to phytoestrogens)
Smoking status
Underlying diseases (metabolic syndrome, atherosclerosis)
Inflammation status
Vascular tonus
Equol producing status and genetic susceptibility
+ Beneficial effect
− Harmful effect
+/⊘ Beneficial or no effect
⊘ No effect
? Impossible to draw conclusion
A High quality of evidence
B Moderate quality of evidence
C Low quality of evidence
D Very low quality of evidence

Supplementary Material to

Effects of Phytoestrogen Supplementation on Intermediate Cardiovascular Disease Risk Factors among Postmenopausal Women: a Meta-analysis of Randomized Controlled Trials

Link to registered PROSPERO protocol: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=121110

Supplementary Table 1. Search strategy used in current review

Embase.com

('phytoestrogen'/exp OR 'soybean'/de OR 'soybean extract'/de OR 'soybean protein'/de OR 'soybean oil'/de OR 'soybean meal'/de OR 'soybean milk'/de OR 'red clover'/de OR 'red clover extract'/de OR 'isoflavone'/de OR 'isoflavone derivative'/de OR 'daidzein'/de OR 'genistein'/de OR 'soy food'/de OR (phytoestrogen* OR phytooestrogen* OR phyto-estrogen* OR phyto-oestrogen* OR soybean* OR soy OR 'red clover' OR Trifolium OR Isoflavon* OR daidzein OR genistein* OR flaxseed OR ((herb* OR plant*) NEAR/6 (estrogen* OR estrogen*)) OR tofu):ab,ti) AND ('diabetes mellitus'/exp OR 'cardiovascular disease'/de OR 'heart failure'/de OR 'congestive heart failure'/de OR 'heart disease'/de OR 'coronary artery disease'/de OR 'ischemic heart disease'/exp OR 'cerebrovascular accident'/de OR 'atherosclerotic cardiovascular disease'/de OR 'brain ischemia'/exp OR 'insulin response'/exp OR 'glucose blood level'/exp OR 'insulin blood level'/exp OR hyperinsulinism/exp OR 'lipid blood level'/exp OR (inflammation/de AND (marker/de OR 'C reactive protein'/exp OR cytokine/de OR fibrinolysis/exp OR 'tumor necrosis factor alpha'/exp)) OR 'chronic inflammation'/exp OR atherosclerosis/de OR 'atherosclerotic plaque'/de OR 'carotid atherosclerosis'/exp OR 'coronary artery atherosclerosis'/exp OR obesity/de OR 'body mass'/de OR 'abdominal obesity'/de OR 'mortality'/exp OR 'oxidative stress'/de OR 'reactive oxygen metabolite'/de OR 'lipid peroxidation'/de OR 'isoprostane derivative'/de OR 'malonaldehyde'/de OR 'lipoxygenase'/de OR 'myeloperoxidase'/de OR (diabet* OR ((cardiovascular OR coronar*) NEAR/3 (disease* OR event*)) OR cvd OR cvds OR ((ischemi* OR ischaemi* OR fail* OR insufficien*) NEAR/3 (heart OR cardia*)) OR (cerebrovascular* NEAR/3 accident*) OR cva OR stroke* OR (brain NEAR/3 (ischemi* OR ischaemi*)) OR ((glucose OR sugar OR insulin* OR lipid* OR cholester* OR triacylglycerol* OR triglyceride*) NEAR/6 (level* OR blood OR serum OR plasma* OR concentration*)) OR glucosaem* OR glucosem* OR glycaem* OR glycem* OR hyperinsulin* OR hypoinsulin* OR insulinaem* OR insulinem* OR (insulin NEAR/3 (response OR dependen* OR resistan* OR sensitiv*)) OR hypercholesterol* OR (inflammat* NEAR/3 (chronic* OR marker* OR biomarker* OR interleukin* OR crp OR 'c reactive' OR cytokine* OR fibrinolys* OR fibrinogenlys* OR 'tumor necrosis factor' OR tnf)) OR atherosclero* OR obes* OR 'body mass' OR bmi OR mortalit* OR (oxidative NEAR/3 stress*) OR (reactive NEAR/3 oxygen* NEAR/3 (metabolite* OR species)) OR (lipid* NEAR/3 (peroxidat* OR autooxidat* OR autoxidat*)) OR lipoperoxidat* OR lipo-peroxidat* OR isoprostan* OR malonaldehyde* OR lipoxygenase* OR myeloperoxidase*):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim)

Medline Ovid

(exp "Phytoestrogens"/ OR "Soybeans"/ OR exp "Soybean Proteins"/ OR exp "Soy Foods"/ OR "Trifolium"/ OR exp "Isoflavones"/ OR (phytoestrogen* OR phytooestrogen* OR phyto-estrogen* OR phyto-oestrogen* OR soybean* OR soy OR "red clover" OR Trifolium OR Isoflavon* OR daidzein OR genistein* OR flaxseed OR ((herb* OR plant*) ADJ6 (estrogen* OR estrogen*)) OR tofu).ab,ti.) AND (exp "Diabetes Mellitus"/ OR "Cardiovascular Diseases"/ OR "Heart Failure"/ OR "Heart Diseases"/ OR exp "Coronary Artery Disease"/ OR exp "Myocardial Ischemia"/ OR exp "Stroke"/ OR "Atherosclerosis"/ OR exp "Brain Ischemia"/ OR "Insulin Resistance"/ OR glucose/bl OR insulin/bl OR exp Hyperinsulinism/ OR lipids/bl OR (inflammation/ AND (biomarkers/ OR "C-Reactive Protein"/ OR cytokines/ OR fibrinolysis/ OR "Tumor Necrosis Factor-alpha"/)) OR "Plaque, Atherosclerotic"/ OR "Carotid Artery Diseases"/ OR exp obesity/ OR "Body Mass Index"/ OR "mortality"/ OR mortality.xs. OR Oxidative Stress/ OR Reactive Oxygen Species/ OR Lipid Peroxidation/ OR Isoprostanes derivative/ OR Malondialdehyde/ OR Lipoxygenase/ OR (diabet* OR ((cardiovascular OR coronar*) ADJ3 (disease* OR event*)) OR cvd OR cvds OR ((ischemi* OR ischaemi* OR fail* OR insufficien*) ADJ3 (heart OR cardia*)) OR (cerebrovascular* ADJ3 accident*) OR cva OR stroke* OR (brain ADJ3 (ischemi* OR ischaemi*)) OR ((glucose OR sugar OR insulin* OR lipid* OR cholester* OR triacylglycerol* OR triglyceride*) ADJ6 (level* OR blood OR serum OR plasma* OR concentration*)) OR glucosaem* OR glucosem* OR glycaem* OR glycem* OR hyperinsulin* OR hypoinsulin* OR insulinaem* OR insulinem* OR (insulin ADJ3 (response OR dependen* OR resistan* OR sensitiv*)) OR hypercholesterol* OR (inflammat* ADJ3 (chronic* OR marker* OR biomarker* OR interleukin* OR crp OR "c reactive" OR cytokine* OR fibrinolys* OR fibrinogenlys* OR "tumor necrosis factor" OR tnf)) OR atherosclero* OR obes* OR "body mass" OR bmi OR mortalit*).ab,ti.) NOT (exp animals/ NOT humans/) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt.

Cochrane

((phytoestrogen* OR phytooestrogen* OR phyto-estrogen* OR phyto-oestrogen* OR soybean* OR soy OR 'red clover' OR Trifolium OR Isoflavon* OR daidzein OR genistein* OR flaxseed OR ((herb* OR plant*) NEAR/6 (estrogen* OR estrogen*)) OR tofu):ab,ti) AND ((diabet* OR ((cardiovascular OR coronar*) NEAR/3 (disease* OR event*)) OR cvd OR cvds OR ((ischemi* OR ischaemi* OR fail* OR insufficien*) NEAR/3 (heart OR cardia*)) OR (cerebrovascular* NEAR/3 accident*) OR cva OR stroke* OR (brain NEAR/3 (ischemi* OR ischaemi*)) OR ((glucose OR sugar OR insulin* OR lipid* OR cholester* OR triacylglycerol* OR triglyceride*) NEAR/6 (level* OR blood OR serum OR plasma* OR concentration*)) OR glucosaem* OR glucosem* OR glycaem* OR glycem* OR hyperinsulin* OR hypoinsulin* OR insulinaem* OR insulinem* OR (insulin NEAR/3 (response OR dependen* OR resistan* OR sensitiv*)) OR hypercholesterol* OR (inflammat* NEAR/3 (chronic* OR marker* OR biomarker* OR interleukin* OR crp OR 'c reactive' OR cytokine* OR fibrinolys* OR fibrinogenlys* OR 'tumor necrosis factor' OR tnf)) OR atherosclero* OR obes* OR 'body mass' OR bmi OR mortalit* OR (oxidative NEAR/3 stress*) OR (reactive NEAR/3 oxygen* NEAR/3 (metabolite* OR species)) OR (lipid* NEAR/3 (peroxidat* OR autooxidat* OR autoxidat*)) OR lipoperoxidat* OR lipo-peroxidat* OR isoprostan* OR malonaldehyde* OR lipoxygenase* OR myeloperoxidase*):ab,ti)

Web of science

TS=(((phytoestrogen* OR phytooestrogen* OR phyto-estrogen* OR phyto-oestrogen* OR soybean* OR soy OR "red clover" OR Trifolium OR Isoflavon* OR daidzein OR genistein* OR flaxseed OR ((herb* OR plant*) NEAR/5 (estrogen* OR estrogen*)) OR tofu)) AND ((diabet* OR ((cardiovascular OR coronar*) NEAR/2 (disease* OR event*)) OR cvd OR cvds OR ((ischemi* OR ischaemi* OR fail* OR insufficien*) NEAR/2 (heart OR cardia*)) OR (cerebrovascular* NEAR/2 accident*) OR cva OR stroke* OR (brain NEAR/2 (ischemi* OR ischaemi*)) OR ((glucose OR sugar OR insulin* OR lipid* OR cholester* OR triacylglycerol* OR triglyceride*) NEAR/5 (level* OR blood OR serum OR plasma* OR concentration*)) OR glucosaem* OR glucosem* OR glycaem* OR glycem* OR hyperinsulin* OR hypoinsulin* OR insulinaem* OR insulinem* OR (insulin NEAR/2 (response OR dependen* OR resistan* OR sensitiv*)) OR hypercholesterol* OR (inflammat* NEAR/2 (chronic* OR marker* OR biomarker* OR interleukin* OR crp OR "c reactive" OR cytokine* OR fibrinolys* OR fibrinogenlys* OR "tumor necrosis factor" OR tnf)) OR atherosclero* OR obes* OR "body mass" OR bmi OR mortalit* OR (oxidative NEAR/3 stress*) OR (reactive NEAR/3 oxygen* NEAR/3 (metabolite* OR species)) OR (lipid*

NEAR/3 (peroxidat* OR autooxidat* OR autoxidat*)) OR lipoperoxidat* OR lipo-peroxidat* OR isoprostan* OR malonaldehyde* OR lipoxygenase* OR myeloperoxidase*)) AND human*) AND DT=(article)
Google scholar phytoestrogens|soybean|soy|"red clover"|Trifolium|Isoflavones diabetes|"cardiovascular|coronary disease|event"|"ischemic heart"|cva|stroke|"brain|heart|cardiac ischemia"|obesity|"body mass"|bmi|mortality

Supplementary Table 2. Risk of bias assessment of the randomized controlled trials (RCT) based on the Cochrane Collaboration's tool

Lead author, year of publication	Random sequence generation	Allocation concealment[1]	Selective reporting	Blinding of participants/ personnel	Blinding of outcome assessment[2]	Incomplete outcome	Other bias	Study[3] quality
Aubertin-Leheudre et al, 2007**(1)**	?	?	+	+	+	+	-	Poor
Bakhtiary et al, 2012, 2019**(2, 3)**	+	+	+	+	+	+	-	Fair
Barrasa at al, 2018**(4)**	?	?	+	+	+	+	+	Fair
Basaria et al, 2009 (lipids)**(5)**	+	+	+	+	+	+	+	Good
Beavers et al, 2009**(6)** et 2010**(7)**	?	?	+	+	+	+	-	Poor
Blum et al, 2003**(8)**	?	?	+	+	+	+	-	Poor
Brandao et al. 2009**(9)**	?	?	+	+	+	+	+	Fair
Braxas et al, 2019**(10)**	+	+	+	+	+	+	+	Good
Campbell et al. 2010**(11)**	?	+	+	+	+	+	+	Good
Charles et al, 2009**(12)**	+	+	+	+	+	+	+	Good
Chieci et al, 2002**(13)**	?	?	+	-	+	+	+	Poor
Choquette et al, 2011**(14)**	?	?	+	+	+	+	-	Poor
Chrisafulli et al, 2005**(15)**	?	?	+	+	+	+	+	Fair
Colacurci et al, 2005**(16)**	+	+	+	?	+	+	-	Poor

Curtis et al, 2012**(17)** and 2013**(18)**	?	?	+	+	+	+	-	Poor
D'Anna et al, 2005**(19)**	?	?	+	+	+	+	+	Fair
Dewell et al, 2002**(20)**	?	?	+	+	+	+	-	Poor
Dodin et al, 2005**(21)** and 2008**(22)**	+	+	+	+	+	+	+	Good
Evans et al, 2007**(23)**	+	+	+	+	+	+	-	Fair
Garrido et al, 2006**(24)**	?	?	+	+	+	+	-	Poor
Greany et al, 2008**(25)**	?	?	-	+	+	+	-	Poor
Hale et al, 2002**(26)**	?	?	+	+	+	+	-	Poor
Hall et al, 2005**(27)** and 2006**(28)**	?	?	+	+	+	+	-	Poor
Hallund et al, 2006 (1)**(29)** and 2008**(30)**	?	?	+	+	+	+	-	Poor
Hallund et al, 2006 (2)**(31)**	?	?	+	+	+	+	-	Poor
Hanachi et al. 2007**(32)**	?	?	-	-	+	+	-	Poor
Hidalgo et al, 2005**(33)**	?	?	+	+	+	+	+	Fair
Hodis et al, 2011**(34)**	+	+	+	+	+	+	+	Good
Howes et al, 2003**(35)**	?	?	+	+	+	+	-	Poor
Jassi et al, 2010**(36)**	?	?	+	+	+	+	+	Fair
Katz et al, 2007**(37)**	+	+	+	+	+	+	-	Fair

Kim et al, 2013**(38)**	?	?	+	+	+	+	+	Fair
Lissin et al. 2004**(39)**	?	?	+	+	+	+	-	Poor
Liu et al, 2012**(40)**, 2013**(41)** and 2014**(42)**	+	+	+	+	+	+	-	Fair
Liu et al, 2015**(43)**	+	?	+	+	+	+	-	Fair
Ma et al, 2013**(44)**	+	+	+	+	+	+	+	Good
Maesta et al, 2007**(45)**	?	?	+	+	+	+	-	Poor
Nahas et al, 2007**(46)**	+	+	+	+	+	+	+	Good
Nestel et al, 1999**(47)**	?	?	+	+	+	+	-	Poor
Nikander et al, 2003**(48)** and 2004**(49)**	+	+	+	+	+	+	-	Fair
Okamura et al. 2008**(50)**	?	?	+	+	+	+	+	Fair
Reimann et al, 2006**(51)**	?	?	+	+	+	+	-	Poor
Rios et al, 2008**(52)**	?	+	+	+	+	+	-	Poor
Ryan-Borchers et al, 2006**(53)**	+	+	+	+	+	+	-	Fair
Shidfar et al, 2009**(54)**	?	?	+	+	+	+	-	Poor
Steinberg et al, 2003**(55)**	?	?	+	+	+	+	+	Fair
Teede et al, 2005**(56)**	+	+	+	+	+	+	-	Fair
Terzic et al, 2012**(57)**	+	+	+	+	+	+	+	Good

Turhan et al, 2009**(58)**	+	+	+	+	+	+	-	Fair
Verhoeven et al, 2007**(59)**	+	+	+	+	+	+	-	Fair
Wangen et al, 2001**(60)**	?	?	+	-	+	+	-	Poor
Wu J et al, 2006**(61)**	?	?	+	+	+	+	-	Poor
Wu WH et al, 2006**(62)**	?	?	+	-	+	+	-	Poor
Ye at al, 2012**(63)**	+	?	-	+	+	+	+	Fair
Yildiz et al, 2005**(64)**	?	?	+	-	+	+	-	Poor
Zhang et al, 2019**(65)**	+	?	+	+	+	+	-	Fair

Risk of bias assessment of the randomized controlled trials (RCT) based on Cochrane risk of bias tool. The Cochrane Collaboration's tool evaluates seven possible sources of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Risk of bias of each item was judged as low (+), high (-) or unclear (?).
[1]In case of clearly explained randomization procedure in a double blind trial, even if the allocation is not mentioned or described we have considered that the study has low risk of bias in this domain
[2]In case that blinding procedure or outcome was not sufficiently described we have considered studies to have low risk of bias in this domain as the outcome measurement was not likely to be influenced by lack of blinding (biomarkers are measured in blood using standardized laboratory measurements)
[3]Thresholds for Converting the Cochrane Risk of Bias Tool to AHRQ Standards (Good, Fair, and Poor)
Good quality: All criteria met (i.e. low risk for each domain)
Fair quality: One criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was unlikely to have biased the outcome, and there is no known important limitation that could invalidate the results. Poor quality: One criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was likely to have biased the outcome, and there are important limitations that could invalidate the results. Poor quality: Two or more criteria listed as high or unclear risk of bias

Supplementary Table 3. Baseline and end-study estimates of RCTs included in the meta-analysis

Lead Author, publication date	Intervention	Outcome	Intervention Group			Control Group		
			No. of Participants	Baseline mean ± SD	End study mean ± SD	No. of Participants	Baseline mean ± SD	End study mean ± SD
Aubertin-Leheudre et al, 2007(1)	Isoflavones, 70 mg/d	CRP, mg/L	10	4.5±3.9	6.3±2.9	10	2.5±3.5	3.8±2.1
		LDL, mmol/L		3.31±0.79	3.29±0.59		3.41±0.80	3.39±0.53
		TG, mmol/L		1.31±0.77	1.31±0.64		1.43±0.68	1.55±1.07
		TC, mmol/L		5.4±0.82	5.26±0.54		5.63±0.77	5.54±0.83
		HDL/TC, mmol/L		3.82±1.18	4.01±1.13		3.81±1.14	5.54±0.83
		HDL, mmol/L		1.48±0.31	1.37±0.25		1.55±0.32	1.44±0.38
Bakhtiary et al, 2012(2) and 2019(3)	Soy nut, 35 g/d	Fibrinogen, g/L	25	3.17±0.34	2.98±0.29	25	3.14±0.43	3.06±0.3
		CRP, mg/L		3.2±1.8	2.9±1.9		3.0±2.28	3.0±1.54
		TC, mmol/l		5.95±0.65	5.19±0.61		6.03±0.62	5.81±0.62
		TG, mmol/L		2.39±0.45	2.26±0.48		2.4±0.55	2.35±0.56
		HDL, mmol/L		1.14±0.17	1.20±0.15		1.14±0.19	1.13±0.20
		LDL, mmol/L		3.98±0.73	3.39±0.65		3.94±0.65	3.92±0.77
		Apo A-1, g/L		1.8±1.02	2±1.0		1.6±1.0	1.6±0.9
		Apo B, g/L		1.5±0.48	1.2±0.4		1.5±0.8	1.6±0.7
	Textured soy protein, 35 g/d	Fibrinogen, g/L		3.17±0.43	3.02±0.31			
		CRP, mg/L		3.1±2.16	2.9±1.9			
		TC,mmol/L		5.93±0.72	5.31±0.69			
		TG, mmol/L		2.39±0.48	2.26±0.49			
		HDL, mmol/L		1.11±0.12	1.16±0.11			
		LDL, mmol/L		4±0.74	3.48±0.7			
		Apo A-1, g/L		1.8±1.1	1.9±1			
		Apo B, g/L		1.5±0.5	1.2±0.5			
	Soy nut, 35 g/d	MDA, µmol/l	25	4.9±3.12	4.2±3.03	25	5.3±2.42	5.3±2.17
		TAC, µmol/l		1302.0±392.83	1516.3±343.81		1305.1±347.19	1350.2±410.32
	Textured soy protein, 35 g/d	MDA, µmol/l		4.9±1.47	4.3±1.65			
		TAC, µmol/l		1305.3±392.92	1503.4±305.53			
Barrasa et al, 2018(4)	Soy isoflavone extract, 100 mg	TC, mmol/L	20	5.13±0.68	5.00±0.58	15	4.87±0.62	5.01±0.56
		LDL, mmol/L		3.10±0.94	2.92±0.77		2.97±0.50	3.10±0.50
		HDL, mmol/L		1.30±0.43	1.37±0.27		1.18±0.38	1.12±0.38
		TG, mmol/L		1.53±0.39	1.51±0.27		1.53±0.35	1.58±0.26
		APO A1, g/L		1.56±0.35	1.58±0.46		1.40±0.32	1.37±0.30

		Apo B, g/L		1.22±0.34	1.07±0.34		1.09±0.30	1.29±0.38
		sP-selectin, ng/mL		44.4±7.2	42.8±7.5		42.6±9.9	43.1±10.3
Basaria et al, 2009(5)	Soy isoflavones, 140 mg	TC, mmol/L	38	5.48±0.14	5.4±0.16	46	5.69±0.14	5.63±0.14
		HDL, mmol/L		1.88±0.07	1.77±0.08		2.02±0.07	2.03±0.07
		TG, mmol/L		1.03±0.09	1.10±0.10		0.99±0.07	0.95±0.07
		LDL, mmol/L		3.15±0.12	3.12±0.13		3.21±0.11	3.17±0.11
Beavers et al, 2009(6) and 2010(7)	Soymilk, 90 mg	Superoxide dismutase levels, SOD	16	1.26 ± 0.62	1.25 ± 0.46	15	1.17 ± 0.30	1.09 ± 0.38
		Cyclooxygenase-2, Cox-2		1.78 ± 1.39	1.74 ± 1.23		1.16 ± 1.06	1.08 ± 0.96
		Glutathione peroxidase, GPx		146.31 ± 35.05	140.24 ± 32.31		137.12 ± 26.74	137.46 ± 33.54
		Tumor necrosis factor α, TNF-α		2.79 ± 0.93	2.71 ± 1.01		2.99 ± 1.20	3.53 ± 0.85
		IL-1β		0.78 ± 0.38	0.73 ± 0.29		0.74 ± 0.22	0.77 ± 0.22
		IL-6		2.27 ± 1.16	2.10 ± 0.78		2.22 ± 1.29	2.48 ± 1.63
		TC, mmol/L	16	4.95±0.74	5.07±0.91	16	5.38±0.61	5.52±1.05
		TG, mmol/L		1.17±0.90	1.19±0.82		1.28±0.93	1.27±0.71
		LDL, mmol/L		2.76±0.63	2.88±0.79		2.99±0.52	3.17±0.87
		HDL, mmol/L		1.63±0.31	1.62±0.34		1.73±0.45	1.76±0.40
Blum et al, 2003(8)	Isolated soy protein, 25 g/d	TC, mmol/L	24	6.99 ±0.82	6.25±0.93	24	6.99 ±0.82	6.18±0.83
		LDL, mmol/L		4.62±0.74	3.7±0.74		4.54±0.74	3.57±0.74
		HDL,mmol/L		1.56±0.46	1.53±0.34		1.56±0.46	1.60±0.39
Brandao et al, 2009(9)	Isoflavones, 80 mg/d	Hcy, µmol/L	19	10.94±1.85	10.41±2.24	19	12.46±3.0	11.22±2.65
		Superoxide dismutase activity (SOD), U/mg Hb		13.8±2.13	10.49±2.63		13.93±1.83	11.73±3.29
		TBARS, nmol/mL		2.63±0.56	1.63±0.63		2.61±1.11	1.99±0.71
		Catalase activity, U/mg Hb		83.27±28.8	106.69±18.0		81.64 ±23.61	110.81±16.74
		Total glutathione, µmol /g Hb		6.32 ±1.17	7.16±0.91		6.01±1.02	6.88±0.98
Braxas et al, 2019(10)	Genistein, 54 mg/d	TC, mmol/L	30	4.83±1.28	4.58±1.1	30	4.92±0.92	4.89±1.06
		TG, mmol/L		2.23±0.86	1.83±0.59		2.21±0.72	2.2±0.88
		HDL, mmol/L		0.85±0.29	0.96±0.28		0.87±0.23	0.89±0.18
		LDL, mmol/L		3.64±1.07	3.55±1.08		3.73±0.96	3.7±0.97
		TAC, mmol		1.37±0.21	1.57±0.32		1.44±0.33	1.40±0.27
		MDA, µmol/L		2.58±0.52	2.16±0.43		2.46±0.46	2.43±0.51
Campbell et	Soy protein	TC, mmol/L	35	5.97 ±0.93	6.27 ±0.95	27	6.13 ±0.91	6.57 ±0.93

al, 2010(11)	isoflavones 60 mg/d	TG, mmol/L		1.34 ±0.70	1.53 ±0.71		1.48 ±0.69	1.69 ±0.69
		HDL, mmol/L		1.47 ±0.38	1.56 ±0.38		1.49 ±0.36	1.62 ±0.38
		LDL, mmol/L		3.88 ±0.90	4.01 ±0.90		3.94 ±0.87	4.16 ±0.89
Charles et al, 2009(12)	Soy isoflavones, 160 mg/d	IL-6, pg/mL	32	2.18±1.75	2.12±1.53	43	1.61±0.98	1.56±0.92
		TNF-α, pg/mL		1.93±1.53	1.72±1.24		0.61±0.07	0.66±0.66
		Adiponectin, µg/mL		18.6±9.45	20.6±8.71		19.7±7.15	19.2±8.26
		Leptin, ng/mL		25.9±16.8	28.6±16.7		25.2±18.6	25.8±18.7
Chrisafulli et al, 2005(15)	Genistein, 54 mg/d	Fibrinogen, g/L	30	3.6± 0.66	3.18 ±0.66	30	3.7±0.28	3.83 ±0.22
		platelet (PLT) count ,mmc		228 286 ± 54142	244 428 ±73172		232 333 ±87747	235 100 ±43895.5
Chieci et al, 2002(13)	Soy diet, 60 mg isoflavones	TC, mmol/L	24	-0.22±0.79		43	-0.07±0.52	
		HDL, mmol/L		-0.05±0.18			-0.09±0.16	
		LDL, mmol/L		-0.16±0.71			0.008±0.50	
		TG, mmol/L		-0.04±0.53			0.041±0.26	
		APO A1, g/L		-0.344±0.34			-0.42±0.29	
		Apo B, g/L		-0.111±0.22			-0.092±0.13	
Choquette et al, 2011(14)	Isoflavones, 70 mg/d	TC,mmol/L	23	5.4±0.88	5.32±0.7	22	5.58±0.86	5.64±0.78
		HDL,mmol/L		1.49±0.34	1.45±0.29		1.57±0.32	1.53±0.36
		LDL, mmol/L		3.24±0.75	3.25±0.65		3.34±0.81	3.45±0.65
		TG,mmol/L		1.47±0.67	1.34±0.59		1.44±0.73	1.44±0.89
Colacurci et al, 2005(16)	Genistein 60 mg/d, Daidzein 30 mg/d	Prothrombin, V/min	29	0.05 ± 0.03	0.04 ± 0.03	28	0.04 ± 0.01	0.04 ± 0.02
		Fibrinogen, g/L		2.85 ± 0.6	2.81 ± 0.35		2.78 ± 0.56	2.86 ± 0.68
		Plasminogen activator inhibitor-1, PAI-1, ng/mL		21.2 ± 3.8	20.5 ± 2.9		22.1 ± 3.3	24.2 ± 3.4
		D-dimer, ng/mL		108.6 ± 64.7	104.0 ± 71.4		105.8 ± 69.2	109.3 ± 76.0
		vWf, IU/dL		91.3 ± 4.7	89.0 ± 5.2		90.9 ± 5.0	93.4 ± 4.8
		sE-selectin, ng/mL		89.0 ± 49.3	54.9 ± 33.8		92.3 ± 52.3	87.6 ± 56.9
		P-selectin, ng/mL		186.3 ± 74.5	147.0 ± 79.4		179.7 ± 78.3	185.2 ± 76.0
		sVCAM-1, ng/mL		590.2 ± 163.6	529.1 ± 167.5		605.3 ± 159.4	618.0 ± 152.7
		sICAM-1, ng/mL		343.1 ± 96.4	282.6 ± 82.4		338.6 ± 80.5	334.0 ± 87.3
		HDL, mmol/L		1.6±0.5	1.5±0.6		1.5±0.5	1.5±0.4
		LDL, mmol/L		3.7±0.3	3.8±0.4		3.6±0.4	3.6±0.3
		TG, mmol/L		1.5±0.6	1.7±0.5		1.6±0.8	1.7±0.9
		LP(a), mg/dL		10.2±4.8	9.9±4.5		10.9±5.1	11.2±4.3
Curtis et al, 2012(17) and	Flavonoids plus 100 mg isoflavones	NO, µmol/L	47	49.5 ±26.05	45.4±20.57	46	43.3 ± 19.7	41.1 ± 20.4
		ET-1, pg/mL		1.6 ± 0.69	1.7 ± 0.69		1.6 ± 0.68	1.5 ± 0.68

2013(18)		NO:ET1		38.8 ± 26.7	33.3 ± 19.9		35.3 ±25.8	32.7 ± 21.7
		Angiotensin-converting enzyme, ACE,mg/mL		125.9±227.6	127.6±218.7		95.7±130.2	94.3±137.0
		CIMT, mean, mm		0.75±0.14	0.76±0.14		0.75±0.14	0.74±0.14
		TG, mmol/L		1.44±0.62	1.46±0.62		1.69±0.81	1.81±1.02
		LDL, mmol/L		2.21±0.48	2.10±0.48		2.20±0.68	2.24±0.61
		TC, mmol/L		4.26±0.62	4.22±0.69		4.29±0.75	4.35±0.75
		HDL, mmol/L		1.40±0.34	1.45±0.34		1.34±0.34	1.35±0.41
		Pulse wave velocity, PWV, m/s^2	18	8.9±2.74	8.8±1.37	17	9.5±2.71	10.1±2.71
Dodin et al, 2005(21)	Flaxseed, 40 g/d	TC, mmol/L	85	5.67±0.75	5.66±0.72	94	5.78±0.71	5.96±0.72
		LDL, mmol/L		3.43±0.69	3.45±0.67		3.5±0.64	3.64±0.67
		HDL, mmol/L		1.72±0.33	1.68±0.35		1.74±0.39	1.77±0.38
		TG, mmol/L		1.12±0.45	1.15±0.53		1.16±0.57	1.17±0.72
Dodin et al, 2008(22)	Flaxseed, 40 g/d	Fibrinogen, g/L	85	+0.08±0.53		94	+0.04±0.56	
		CRP, mg/L		0.07±1.77			0.16±1.92	
		ApoA-1, g/L		0.07±0.24			0.18±0.27	
		APO B, g/L		0.03±0.13			0.07±0.18	
		LP(a), g/L		0.04±0.07			0.06±0.1	
D'Anna et al, 2005(19)	Genistein, 54 mg/d	Hcy, µmol/L	30	11.36±2.14	10.72±2.39	30	11.26±1.81	11.5±2.28
		CRP, mg/L		1.73±1.70	2.13±2.34		1.69±1.15	1.74±1.16
Dewell et al, 2002(20)	Isoflavones, 150 mg	TC, mmol/L	20	6.8±0.89	6.5±0.96	16	6.3±2.0	6.4±1.6
		HDL,mmol/L		1.2±0.45	1±0.48		1.2±0.4	1±0.4
		LDL, mmol/L		5.6±0.89	5.5±0.96		5.1±2.0	5.3±1.6
		TG, mmol/L		0.8±0.45	1.2±0.48		1.3±0.8	1.3±0.8
Evans et al, 2007(23)	Soy protein, 25 g/d	FMD, %	22	8.60 ± 7.20	5.51 ± 10.11	22	8.60 ± 7.20	4.53±7.84
	Soy protein, 25 g/d + soy lecithin	FMD, %		8.60 ± 7.20	7.50 ±9.85		8.60 ± 7.20	4.53±7.84
	Soy lecithin, 20g/d	FMD, %		8.60 ± 7.20	5.35 ±6.13		8.60 ± 7.20	4.53±7.84
Garrido et al, 2006(24)	Isoflavones	TC, mmol/L	15	5.5±1	5.8±0.7	14	4.8±0.5	4.8±0.6
		HDL,mmol/L		1.4 ± 0.3	1.8±0.4		1.8±0.6	1.7±0.2
		LDL, mmol/L		3.4±0.4	3.7±0.3		2.9±0.3	3.1±0.4
		TG, mmol/L		1.3±0.2	1.4±0.2		1.4±0.2	1.4±0.2
		Apo A-1, g/L		1.2±0.6	1.5±0.5		1.3±0.5	1.1±0.4
		APO B, g/L		1.86±0.2	1.8±0.2		1.78±0.1	1.82±0.2
Greany et al, 2008(25)	Isoflavone-containing	CRP, mg/L	34	2.6±3.3	2.95±3.83	34	2.6±3.3	2.31±2.21
		Hcy, µmol/L		10.4±3.2	9.59±2.23		10.4±3.2	9.46±2.43

	soy protein isolate, 44 mg/d	sE-selectin, ng/mL		37.6±19.6	35.4±14.6		37.6±19.6	35.7±13.6
		sVCAM-1, ng/mL		854±176	823±152		854±176	816±151
		sICAM-1, ng/mL		211±40	214±38		211±40	211±33
Hall et al, 2005(27) and 2006(28)	Cereal bars, 100 mg isoflavones	CRP, mg/L	117	1.71±1.89	1.70±1.89	117	1.64±1.73	1.76±1.83
		vWF, IU/dL		104.96±53.77	105.46±53.07		103.27±49.46	99.99±39.92
		MCP-1, ng/mL		259.36±95.93	260.43±101.23		262.4±85.74	260.49±106.17
		sE-selectin, ng/mL		42.14±15.41	42.17±15.82		40.67±15.05	41.26±15.17
		sICAM-1, ng/mL		215.04±51.6	220.4±52.77		217.45±52.21	217.78±48.28
		sVCAM-1, ng/mL		504.79±134.39	503.48±146.66		498.14±129.0	499.76±135.88
		ET-1, pg/mL		1.15±0.39	1.20±0.43		1.15±0.39	1.21±0.40
		TC, mmol/L		6.03±1.32	6.13±1.34		5.96±1.19	6.10±1.22
		LDL, mmol/L		3.88±1.11	3.84±1.11		3.81±1.02	3.83±1.04
		HDL, mmol/L		1.60±0.39	1.74±0.47		1.62±0.35	1.71±0.41
		TG, mmol/L		1.21±0.50	1.22±0.48		1.19±0.46	1.22±0.52
		LP(a)		226.2±265.3	216.40±244.45		227.38±250.27	233.68±264.44
Hale et al, 2002(26)	Soy isoflavones 80 mg /d	TC, mmol/L	16	0.39±0.71		16	0.22±0.62	
		LDL, mmol/L		-0.03±0.99			0.12±0.66	
		HDL, mmol/L		0.01±0.2			0.013±0.21	
		TG, mmol/L		-0.01±0.43			-0.19±0.44	
Hallund et al, 2006(1)(29)	Lignan complex, 500 mg/d	NOx, µmol/L	22	16.69±8.5	20.55±12.4	22	16.58±8.5	20.26±13.09
		ET-1, ng/L		12.7±3.7	12.66±3.3		13.17±3.4	12.03±3.14
		NOx:ET-1, µmol/ng		1.47±0.94	1.74±0.94		1.36±0.8	1.8±1.27
		ADMA, µmol/L		0.47±0.05	0.48±0.05		0.48±0.05	0.48±0.05
		Arginine, µmol/L		89.65±14.49	92.92±15.8		89.38±11.5	91.1±14.1
		SDMA, µmol/L		0.52±0.05	0.52±0.09		0.51±0.05	0.5±0.09
[1]Hallund et al, 2008(30)	Lignan complex, 500 mg/d	CRP, mg/L	22	1.11±0.36	0.98±0.23	22	0.96±0.25	1.14±0.23
		IL-6, ng/L		1.36±0.28	1.21±0.15		1.21±0.15	1.16±0.23
		Tumor necrosis factor α, TNF-α, ng/L		1.11±0.14	1.09±0.12		1.13±0.15	1.08±0.1
		sICAM-1, ng/mL		210.5±18.5	214.5±16		209.5±14	217.25±13.75
		sVCAM-1, ng/mL		357.25±18.25	361±40.5		360.75±29.25	367±27
		Monocyte chemoattractant protein-		242.25±25.75	234.75±26.25		260±20	227.25±23.25

		1, MCP-1, ng/L						
Hallund et al, 2006(2)(31)	Isoflavones, 50 mg/d	Sum of nitrite and nitrate, NOx, µmol/L	28	27.7±14.3	31.1±16.9	28	25.4±7.95	20.4±5.8
		ET-1, ng/L		1.23±0.3	1.24±0.4		1.1±0.3	1.27±0.4
		NOx:ET-1, µmol/ng		25.1±17.5	31.1±29.2		24.8±9.5	18.5±10.1
Hanachi et al, 2007(32)	Soy protein, 12.5 g/d	Total antioxidant capacity	15	NA	1379.11±87.4	10	NA	642.88±66.9
[3]Hidalgo et al, 2005(33)	Isoflavones, 90 mg	TC, mmol/L	53	5.8±0.97	5.5±0.83	53	5.8±0.97	5.7±0.88
		HDL, mmol/L		1.03±0.30	1.03±0.25		1.03±0.30	1.06±0.26
		LDL, mmol/L		3.8±0.8	3.35±1.02		3.8±0.8	3.6±0.91
		TG, mmol/L		2.25±0.88	2.04±0.82		2.25±0.88	2.74±1.88
		Lp(a), mg/dl		41.2±36.9	22.8±26.9		41.2±36.9	20.5±25.8
Hodis et al, 2011(34)	Soy protein, 25 g/d	CIMT, mean, µm/year	162	+4.77±8.99		163	+5.68±8.96	
Howes et al, 2003(35)	Isoflavones, 50 mg	TG, mmol/L	16	0.11±2.21		16	0.5±1.84	
		TC, mmol/L		0.26±0.86			1.16±1.79	
		HDL, mmol/L		0.05±NA			0.06±0.23	
		LDL, mmol/L		-0.05±0.99			0.62±0.89	
Jassi et al, 2010(36)	Soy protein 30 g/d containing 60 mg of isoflavones	TC, mmol/L	25	4.95±0.36	4.39±0.35	25	4.69±0.71	4.66±0.66
		TG, mmol/L		1.75±0.22	1.34±0.21		1.76±0.17	1.84±0.24
		HDL, mmol/L		1.06±0.15	1.25±0.21		1.06±0.16	1.10±0.18
		LDL, mmol/L		3.09±0.37	2.50±0.42		2.83±0.76	2.74±0.73
		Apo A1, g/L		1.29±0.15	1.31±0.15		1.3±0.05	1.31±0.05
	Soy isoflavones 60 mg/d	Apo B, g/L		1.39±0.2	1.29±0.2		1.41±0.2	1.42±0.2
		TC, mmol/L	25	4.80±0.52	4.87±0.63			
		TG, mmol/L		1.73±0.20	1.48±0.25			
		HDL, mmol/L		1.13±0.18	1.16±0.18			
		LDL, mmol/L		2.87±0.63	2.78±0.69			
		Apo A1, g/L		1.29±0.15	1.37±0.2			
		Apo B, g/L		1.46±0.2	1.37±0.15			
Katz et al, 2007(37)	Soy isoflavones, 65 mg genistin and daidzin	FMD, %	22	9.6±6.4	8.3±7.7		9.6±6.4	9.51±4.4
		Stimulus adjusted response measure, SARM		0.1±0.1	0.0±0.1		0.1±0.1	0.1±0.0
		TC, mmol/L		5.8±1.03	5.47±0.92		5.8±1.03	5.39±0.64
		TG, mmol/L		1.08±0.46	1.02±0.48		1.08±0.46	0.86±0.33
		HDL, mmol/L		1.69±0.40	1.62±0.39		1.69±0.40	1.67±0.36

		LDL, mmol/L		3.62±0.91	3.4±0.84		3.62±0.91	3.34±0,59
		LDL/HDL ratio		0.06±0.02	0.06±0.02		0.06±0.02	0.05±0.02
Kim et al, 2013(38)	Isoflavones, 70 mg/d	TC, mmol/L	42	5.13±0.85	4.93±0.97	43	5.48±1.03	5.24±0.90
		TG, mmol/L		1.26±0.71	1.08±0.66		1.27±0.66	1.36±0.97
		LDL, mmol/L		2.96±0.7	2.86±0.73		3.25±0.92	3.16±0.81
		HDL, mmol/L		1.49±0.36	1.48±0.38		1.52±0.37	1.54±0.40
Lissin et al, 2004	Isoflavones, 90 mg/d	FMD, %	20	+3.4±8.9		20	-0.6±7.6	
Liu et al, 2015(43)	Whole soy, 40g/d	FMD, %	90	13.73± 7.11	13.56± 5.53	90	11.54±7.25	12.82±5.27
		FMD, cm		0.42±0.19	0.44±0.17		0.37±0.21	0.42±0.16
		Arterial stiffness index, AASI		0.498± 0.174	0.495± 0.179		0.505± 0.154	0.517± 0.173
	Daidzein, 63mg/d	FMD, %	90	12.06±6.69	13.19±6.17			
		FMD, cm		0.37±0.19	0.41±0.18			
		Arterial stiffness index, AASI		0.485± 0.168	0.496± 0.180			
Liu et al, 2014(42)	Whole soy, 40g/d d	Hs-CRP,mg/L	90	1.74±2.04	1.41±1.96	90	1.69±2.27	1.65±2.73
		TG, mmol/L		1.21±0.51	1.12±0.44		1.39±0.69	1.48±0.7
		TC, mmol/L		5.62±0.92	5.55±0.85		5.69±0.97	5.86±0.92
		HDL, mmol/L		1.66±0.3	1.66±0.31		1.71±0.35	1.71±0.34
		LDL, mmol/L		3.64±0.86	3.48±0.79		3.57±0.85	3.67±0.84
		LDL/HDL ratio		2.27±0.72	2.18±0.66		2.17±0.63	2.24±0.68
		CIMT mean, mm		0.703±0.127	0.689±0.124		0.745±0.110	0.730±0.107
		CIMT max, mm		0.887±0.144	0.874±0.141		0.9250.125	0.911±0.125
	Daidzein, 63mg/d	hs-CRP, mg/L	90	1.26±1.15	2.01±3.26			
		TG, mmol/L		1.39±0.74	1.28±0.6			
		TC, mmol/L		5.54±0.94	5.76±0.91			
		HDL, mmol/L		1.66±0.38	1.64±0.35			
		LDL, mmol/L		3.48±0.84	3.64±0.83			
		LDL/HDL ratio		2.19±0.67	2.31±0.69			
		CIMT mean, mm		0.712±0.128	0.709±0.142			
		CIMT max, mm		1.147±2.181	0.896±0.171			
Liu et al, 2012(40) and	Whole soy, 15g/d	sICAM-1, ng/mL	60	408.6±246.0	364.2±215.0	60	371.9±207.2	388.8±222.0

2013(41)		sVCAM-1, ng/mL		543.7±243.8	532.7±262.0		551.8±196.1	519.6±224.7
		E-selectin, ng/mL		30.3±9.2	27.3±9.2		29.2±9.6	28.6±9.8
		TC, mmol/L		5.83±0.94	5.67±0.87		5.63±0.93	5.43±0.92
		TG, mmol/L		1.35±0.79	1.39±1.02		1.3±0.7	1.28±0.74
		HDL, mmol/L		1.66±0.37	1.64±0.37		1.65±0.3	1.58±0.3
		LDL, mmol/L		3.94±0.9	3.82±0.85		3.81±0.88	3.68±0.82
		LDL/HDL ratio		2.5±0.82	2.47±0.85		2.39±0.74	2.42±0.71
	Isoflavones, 100 mg/d	sICAM-1, ng/mL	60	396.7±217.9	398.3±225.4	60	371.9±207.2	388.8±222.0
		sVCAM-1, ng/mL		556.0±208.5	540.9±207.7		551.8±196.1	519.6±224.7
		E-selectin, ng/ml		28.3±9.3	27.9±10.3		29.2±9.6	28.6±9.8
		TC, mmol/L		5.38±0.73	5.36±0.82		5.63±0.93	5.43±0.92
		TG, mmol/L		1.27±1.19	1.3±0.96		1.3±0.7	1.28±0.74
		HDL, mmol/L		1.6±0.31	1.55±0.26		1.65±0.3	1.58±0.3
		LDL, mmol/L		3.55±0.67	3.62±0.71		3.81±0.88	3.68±0.82
		LDL/HDL ratio		2.28±0.55	2.39±0.56		2.39±0.74	2.42±0.71
Ma et al, 2013(44)	Soybean β-conglycinin, 2,3 g/d	TG, mmol/L	30	3.23±1.4	1.99±0.85	30	3.79±1.32	3.84±1.26
		TC, mmol/L		6.43±1.06	6.22±0.97		6.43±0.81	6.72±0.77
		LDL mmol/L		3.91±0.95	3.39±0.58		3.68±0.69	3.87±0.86
		HDL mmol/L		1.21±0.29	1.23±0.26		1.17±0.26	1.22±0.28
		Apo A-1, g/L		1.5±0.14	1.61±0.19		1.54±0.09	1.69±0.21
		Apo B, g/L		1.13±0.13	0.98±0.13		1.09±0.09	1.15±0.13
	Soybean β-conglycinin 4,6 g/d	TG, mmol/L	30	3.2±0.74	2.41±0.78			
		TC, mmol/L		6.53±0.73	6.36±0.82			
		LDL, mmol/L		3.91±0.58	3.45±0.56			
		HDL, mmol/L		1.20±0.36	1.16±0.14			
		Apo A-1, g/L		1.52±0.15	1.68±0.24			
		Apo B, g/L		1.16±0.1	1.04±0.22			
Maesta et al, 2007(45)	Soy protein, 25 g/d	TC, mmol/L	10	5.95±0.71	5.2 ±0.76	11	5.76±0.98	5.57±0.93
		HDL, mmol/L		1.62±0.34	1.57±0.39		1.32±0.25	1.28±0.22
		LDL mmol/L		3.71±0.72	3.09±0.79		3.56±0.7	3.3±0.52
		TG, mmol/L		1.34±0.52	1.17±0.5		1.93±0.71	1.72±0.65
Nahas et al, 2007(46)	Soy extract, 40 mg/d	TG, mmol/L	40	1.72±0.73	1.56±0.57	40	1.66±0.88	1.92±0.83
		TC, mmol/L		5.56±0.92	5.62±1.03		5.37±0.97	5.44±0.97
		LDL, mmol/L		3.47±0.82	3.51±0.88		3.26±0.82	3.29±0.98

		HDL, mmol/L		1.30±0.27	1.35±0.21		1.35±0.34	1.29±0.38
Nestel et al, 1999(47)	Red clover isoflavones, 40 mg/d	TC, mmol/L	16	5.96±0.98	5.94±0.93	16	5.96±0.98	6.11±0.82
		HDL, mmol/L		1.57±0.25	1.68±0.27		1.57±0.25	1.6±0.23
		LDL, mmol/L		3.81±0.89	3.77±0.94		3.81±0.89	4±0.82
		TG, mmol/L		1.22±0.49	1.09±0.3		1.22±0.49	1.1±0.41
	Red clover isoflavones, 48 g/d	TC, mmol/L	16	5.96±0.98	5.91±0.64			
		HDL, mmol/L		1.57±0.25	1.67±0.24			
		LDL, mmol/L		3.81±0.89	3.76±0.72			
		TG, mmol/L		1.22±0.49	1.05±0.36			
NIkander et al, 2003(48) and 2004(49)	114 mg Isoflavones	CRP, mg/L	56	1.16±1.03	1.10±0.91	56	1.1±0.79	1.1±0.84
		E-Selectin, ng/mL		45.4±20.6	42.6±18.3		42.7±17.5	41.3±17.3
		NO_x, µmol/L		23.1±16.5	25.5±16.5		22.7±10	25.8±16.5
		TC, mmol/L		5.88±0.97	6.02±1.46		5.83±1.04	5.91±1.13
		LDL, mmol/L		3.87±0.93	4.08±1.17		3.80±1.17	3.74±0.86
		HDL, mmol/L		1.78±0.45	1.76±0.39		1.76±0.38	1.76±0.39
		TG, mmol/L		1.22±0.57	1.24±0.59		1.25±0.53	1.26±0.65
		Apo B, g/L		1.10±0.24	1.13±0.33		1.12±0.27	1.10±0.28
		Apo A-1, g/L		1.58±0.23	1.58±0.22		1.55±0.17	1.56±0.26
		LP(a), mg/dL		17.21±20.48	17.9±23.32		17.58±22.17	16.28±20.08
Okamura et al, 2008(50)	Pueraria Mirifica, 20 mg/kg of miroestrol and 1 mg/kg or less of isoflavonoids	HDL, mmol/L	12	1.6±0.1	2.1±0.1	7	1.6±0.1	1.6±0.1
		LDL, mmol/L		2.9±0.3	2.3±0.2		3.1±0.2	3.3±0.1
		LDL:HDL ratio		1.9±0.7	1.1±0.3		2±0.7	2.2±0.7
		Apo A-1, g/L		1.46±0.06	2.03±0.07		1.35±0.05	1.41±0.07
		Apo B, g/L		0.86±0.04	0.77±0.04		0.86±0.08	0.91±0.08
Ryan-Borchers et al, 2006(53)	Soymilk group: 706 mL soymilk/d containing 71.6±3.1 mg isoflavones/d	Interferon-γ, IFN-γ, pg/mL	18	10.1±19.32	25.7±19.5	19	8.4 ±19.2	13.5 ±19.2
		IL-2, pg/mL		11.3±0.42	11.4±0.42		11.4±0.44	11.5±0.44
		Tumor necrosis factor α, TNF-α, ng/mL		2.45±4.54	2.46±5.09		2.26±4.66	1.98±5.71
	706 mL cow milk/d and isoflavone tablets (70 mg isoflavones/d)	INF-gamma, pg/mL	15	11.4±20.9	24.7±20.1	19	8.4 ±19.2	13.5 ±19.2
		IL-2 pg/mL		11.3±0.39	11.4±0.39		11.4±0.44	11.5±0.44
		Tumor necrosis factor α, TNF-α, ng/mL		1.28±4.65	2.09±5.07		2.26±4.7	1.98±5.8
Reimann et al, 2006(51)	Isoflavones, 50 mg/d	tHcy, µmol/L	89	0.32±0.21		89	0.29±0.26	
		ADMA, mmol/L		-0.02±0.02			0±0.02	
		NOx, µmol/L		1±2.42			-2.6±1.83	

Rios et al, 2008(52)	Purified soy isoflavones (genistein and daidzein at 5% and 12%, respectively)	TC, mmol/L	25	5.30±0.90	5.19±1.1	22	5.77±1.52	5.67±1.27
		LDL, mmol/L		3.41±0.81	3.18±1		3.85±1.36	3.49±1.01
		HDL, mmol/L		1.28±0.27	1.39±0.25		1.27±0.22	1.47±0.27
		TG, mmol/L		1.43±0.56	1.5±0.49		1.51±0.71	2.09±1.36
Terzic et al, 2012(57)	Soy containing genistein (39 mg/d) and daidzein (1 mg/d	TC, mmol/L	23	6.89±0.47	5.25±0.41	25	6.87±0.51	7.13±0.49
		TG,mmol/L		3.01±0.39	1.69±0.41		3.1±0.39	3.22±0.39
		LDL, mmol/L		5.18±0.23	3.95±0.3		5.2±0.28	5.39±0.39
		HDL, mmol/L		0.54±0.1	1.73±0.25		0.56±0.09	0.45±0.1
	Red clover containing 4 isoflavones, biochanin A (23 mg/d), daidzein (1 mg/d), formononetin (15 mg/d) and genistein (1 mg/d)	TC, mmol/l	26	6.92±0.47	5.3±0.42			
		TG, mmol/L		3.07±0.44	1.71±0.59			
		LDL, mmol/L		4.97±0.23	3.8±0.31			
		HDL, mmol/L		0.49±0.09	1.68±0.16			
Steinberg et al, 2003(55)	Isolated soy protein, 25 g/d with naturally occurring isoflavones (107.67 mg/d)	TC, mmol/l	28	4.91±0.53	4.82±0.53	28	4.91±0.53	5±0.53
		TG, mmol/L		1.03±0.53	1.04±0.53		1.03±0.53	0.98±0.53
		LDL, mmol/L		2.89±0.53	2.86±0.53		2.89±0.53	2.94±0.53
		HDL, mmol/L		1.55±0.53	1.49±0.53		1.55±0.53	1.61±0.53
Shidfar et al, 2009(54)	Isolated soy protein, 25 g/d with trace amounts of isoflavones (1.82 mg/d)	Paraoxonase 1, PON1	21	50.76±7.58	55.69±4.62	21	52.78±7.56	51.07±8.03
		LDL, mmol/L		4.96±0.38	4.43±0.34		5.07±0.39	4.97±0.32
		HDL, mmol/L		0.95±0.17	1.06±0.09		1.0±0.24	1.0±0.25
		TG, mmol/L		3.56±0.46	3.4±0.48		3.72±0.37	3.68±0.47
		TC, mmol/L		7.54±0.36	7.09±0.45		7.43±0.42	7.51±0.53
		LDL/HDL		5.41±1.31	4.21±0.48		5.38±1.51	5.39±1.77
Teede et al,2005(56)	Soy protein isolate (40 g soy protein/d, 118 mg isoflavones/d)	TC, mmol/L	19	6.2±1.31	5.2±0.31	21	5.8±0.92	5.3±0.92
		LDL, mmol/L		4±0.87	3.3±0.87		3.6±0.92	3.3±0.92
		HDL, mmol/L		1.6±0.44	1.5±0.44		1.6±0.46	1.4±0.46
		LDL/HDL, mmol/L		2.7±0.87	2.4±0.87		2.5±1.38	2.7±1.38
Turhan et al, 2009(58)	2 tablets/d containing Isolated isoflavones 80 mg isoflavones/d (29.8 mg genistein, 7.8	Hcy, µmol/L	45	7.5 ± 1	6.7 ± 0.9	45	8.7 ± 1.8	8.6 ± 1.5
		Nitrite/nitrate, µmol/L		27.8 ± 9.3	33 ± 8.2		25 ± 7.6	24 ± 7.4
		TC, mmol/L		6.82±0.96	6.38±0.77		6.29±0.76	6.45±0.76
		LDL, mmol/L		4.25±0.73	3.81±0.61		4.07±0.65	4.09±0.51
		TG, mmol/L		1.7±0.57	1.36±0.49		1.77±0.73	1.76±0.57

	mg daidzein, and 2.4 mg glycitein per tablet)	HDL, mmol/L		1.54±0.35	1.68±0.33		1.38±0.28	1.43±0.28
		LP(a), mg/dL		29.5±29.5	34±43.3		27.7±21.1	32.1±20.2
[1]**Verhoeven et al, 2007**	50 mg isoflavones and 8 mg deoxyacetein	CRP, mg/L	56	1.22±0.29	1.33±0.46	59	1.06±0.3	1.8±0.3 4
		ADMA, µmol/L		0.464±0.053	0.467±0.052		0.467±0.060	0.467±0.063
		SDMA, µmol/L		0.538±0.070	0.539±0.087		0.539±0.072	0.546±0.064
		Arginine, µmol/L		202±38	204±47		202±38	207±39
Wangen et al, 2001(60)	Isolated soy protein, 65mg/d	TC, mmol/L	18	5.55±0.68	4.99±0.07	18	5.55±0.68	5.09±0.06
		HDL, mmol/L		1.35±0.43	1.38±0.02		1.35±0.43	1.34±0.02
		LDL, mmol/L		3.53±0.81	3.05±0.05		3.53±0.81	3.22±0.05
		TG, mmol/L		1.46±1.29	1.22±0.08		1.46±1.29	1.16±0.08
		LDL/HDL ratio		2.9±1.4	2.49±0.06		2.9±1.4	2.72±0.05
		Apo A-1, g/L		1.17±0.02	1.14±0.02		1.17±0.02	1.11±0.02
		Apo B, g/L		1.08±0.03	0.96±0.02		1.08±0.03	0.98±0.02
		Lp(a), mg/dL		25 ±1	27.2±0.9		25.49±1.12	26.8±0.8
	Isolated soy protein, 132 mg/d	TC, mmol/L		5.55±0.68	4.93±0.06			
		HDL, mmol/L		1.35±0.43	1.36±0.02			
		LDL, mmol/L		3.53±0.81	3.01±0.05			
		TG, mmol/L		1.46±1.29	1.22±0.08			
		LDL/HDL ratio		2.9±1.4	2.51±0.05			
		Apo A-1, g/L		1.17±0.02	1.15±0.02			
		Apo B, g/L		1.08±0.03	0.98±0.02			
		Lp(a), mg/dL		25.49±1.12	27.4±0.8			
Wu WH. et al, 2006(62)	50 g sesame seed powder/d containing lignans, 381 mg/d	TBARS-1 h, mmol/g protein	23	25.1 ± 12.6	19.3 ± 10.7	23	23.2 ±9.1	24.4 ± 13.4
		TBARS-3 h, mmol/g protein		82.5 ±16.8	75.3 ± 18.		83.7 ± 19.3	85.1 ± 20.6
		TC, mmol/L		5.37±0.93	5.05±0.85		5.41±0.91	5.35±0.84
		LDL, mmol/L		3.03±0.97	2.72±0.83		3.19±0.7	3.14±0.73
		HDL, mmol/L		1.33±0.33	1.31±0.33		1.35±0.29	1.33±0.31
		TG, mmol/L		1.07±0.3	1.11±0.46		1.03±0.34	1.17±0.43
		LDL/HDL ratio		2.42±0.68	2.27±0.8		2.45±0.68	2.46±0.82
Wu et J. al, 2006(61)	Isoflavone conjugate, 75 mg/d from soy	TC, mmol/L	33	5.89±0.76	6.02±0.93	33	5.88±0.86	5.98±0.74
		HDL, mmol/L		1.92±0.47	1,96±0.45		1.85±0.39	1.99±0.38
		LDL, mmol/L		3.52±0.71	3.49±0.70		3.59±0.76	3.52±0.70
		TG, mmol/L		0,95±0.43	0.98±0.54		1.16±0.55	0.99±0.37

Ye et al, 2012(63)	Isoflavones from soy germ extract, low-dose: 84 mg/d	TC, mmol/L	30	5.51±0.87	5.61±0.95	30	5.26±0.83	5.37±0.94
		TG mmol/L		1.39±0.59	1.43±0.71		1.47±0.92	1.67±1.61
		LDL mmol/L		3.23±0.65	3.20±0.71		2.99±0.72	2.93±0.76
		HDL mmol/L		1.49±0.34	1.58±0.36		1.50±0.31	1.52±0.34
		Apo A-1, g/L		1.20±0.22	1.20±0.20		1.23±0.20	1.21±0.23
		Apo B100, g/L		1.02±0.15	1.01±0.19		0.95±0.16	0.93±0.19
	Isoflavones from soy germ extract, high-dose: 126 mg/d	TC, mmol/L	30	5.38±1.00	5.56±1.18			
		TG mmol/L		1.26±0.69	1.39±0.76			
		LDL mmol/L		3.07±0.75	2.93±0.80			
		HDL mmol/L		1.59±0.41	1.68±0.44			
		Apo A-1, g/L		1.24±0.27	1.30±0.21			
		Apo B100, g/L		0.93±0.20	0.91±0.22			
Yildiz et al, 2005(64)	Genistein, 40 mg/d from soy	TC, mmol/L	20	5.81±0.12	4.82±0.08	20	5.51±0.07	5.45±0.1
		TG mmol/L		1.73±0.71	1.72±0.55		1.67±0.59	1.73±0.63
		LDL mmol/L		3.98±0.79	3.43±0.92		3.92±0.81	3.95±0.92
		HDL mmol/L		1.25±0.03	1.33±0.06		1.25±0.05	1.18±0.12
Zhang et al, 2019(65)	Genistein, 60 mg/d	TC, mmol/L	77	6.7±1.1	6.1±1.1	83	6.7±1.1	6.6±1.1
		TG, mmol/L		3.0±0.9	2.4±1.1		3.0±1.1	3.0±1.2
		HDL, mmol/L		1.1±0.1	1.2±0.1		1.1±0.2	1.0±0.3
		LDL, mmol/L		5.2±1.0	3.8±0.6		5.3±1.1	5.3±1.4
		Apo-A-1, g/L		1.19±0.03	1.19±0.02		1.19±0.04	1.18±0.02
		Apo-B, g/L		1.02±0.04	0.68±0.06		1.01±0.04	1.00±0.03

Abbreviations: ADMA, asymmetric dimethylarginine; Apo, apolipoprotein; CIMT, carotid intima media thickness; ET-1, Endothelin 1; FMD, flow mediated diameter; Hcy, homocysteine; HDL, high density lipoprotein cholesterol; Hb, hemoglobin; (hs-)CRP, (high sensitive) C-reactive protein; IL, interleukin; LDL, low density lipoprotein cholesterol; Lp(a), lipoprotein a; MCP-1, monocyte chemoattractant protein 1; SD, standard deviation; SDMA, symmetric dimethylarginine; sICAM-1, soluble intracellular adhesion molecule 1; sVCAM-1, soluble vascular cell adhesion molecule 1; TBARS, thiobarbituric acid reactive substances; TG, triglycerides; tHcy; total homocysteine; TC, total cholesterol; U/mg Hb, Units per mg of hemoglobin; vWF, von Willebrand Factor

*For serum lipids units were transformed from mg/dl to mmol/l; The rules for converting cholesterol units of TC (total cholesterol), HDL (high density lipoprotein) and LDL (low density lipoprotein) are the same: To get from mg/dL to mmol/L multiply by 0.02586. Conversion for TG (triglycerides) is calculated differently: to get from mg/dL to mmol/L multiply by 0.01129.

*To calculate the SD from 95% CI we used the following formula: $SD = \sqrt{\mathrm{N}} * (\text{upper limit} - \text{lower limit})/3.92$. If the sample size was small then confidence intervals was calculated using a value from a t distribution. The number 3.92 was replaced with a slightly larger numbers specific to the t distribution, which can be obtained from tables of the t distribution with degrees of freedom equal to the group sample size minus 1(66).
*To calculate the mean and SD from median and interquartile range we used the Hozo formula(67) where **m** was median; **a** was low and **b** was high end of the range. First formula (1) refers to sample size below 25, while second formula (2) refers to sample size above 25.

(1) $\bar{x} = \frac{a + 2m + b}{4} + \frac{a - 2m + b}{4n}$ (2) $\bar{x} = \frac{a + 2m + b}{4}$

For very small samples (up to 15) the best estimator for the variance is the formula 4, in the other cases formula 3 can be used.

(3) $s^2 = \frac{1}{n - 1}\left(a^2 + m^2 + b^2 + \left(\frac{n - 3}{2}\right)\frac{(a + m)^2 + (m + b)^2}{4} - n\left(\frac{a + 2m + b}{4} + \frac{a - 2m + b}{4n}\right)^2\right)$

(4) $s^2 = \frac{1}{12}\left(\frac{(a - 2m + b)^2}{4} + (b - a)^2\right)$

An automatized formula can be found online at http://vassarstats.net/median_range.html

Supplementary Table 4. Descriptive summary of RCTs investigating the associations between phytoestrogen supplementation and oxidative stress

	Lead Author, Publication Year	Dietary Treatment Characteristics		Main findings
		Intervention type	Control type	
Soy derived	Bakthiari et al, 2019(3)	Textured soy protein cooked with tumeric powder and lime or roasted soy-nut, 35 g/d	No intervention	Consumption of soy showed a beneficial effect in elderly women with borderline parameters of Metabolic Syndrome who suffered from a hyperlipidemic, insulin resistance and oxidative stress. Cosumption of soy significantly improved MDA and TAC as indicators of lipid peroxidation and antioxidant activity
	Beavers et al, 2009(6)	Dietary vanilla soy milk containing 90 mg/d of isoflavones	Reduced fat dairy milk	No differences were observed between oxidative stress biomarkers (SOD, GPx and COX-2) by dietary treatment group.
	Brandao et al, 2009(9)	Tablets, 80 mg/d of soybean derived isoflavones	Placebo tablets	Soy isoflavones did not improve oxidative stress parameters (plasma lipid peroxidation, erythrocyte SOD and catalase activities and total glutathione) in postmenopausal women complaining on insomnia.
	Hanachi et al, 2007(32)	Daily soymilk consumption containing 12.5 g of soy protein with 13 mg Genistein and 4.13 mg Daidzein	No intervention	Total antioxidant capacity in control and soymilk consumption group was significantly increased after the intervention period
	Shidfar et al, 2009(54)	Soy beans, 50 g/d soy protein containing 164 mg/d of isoflavones	Whey protein	A significant increase in PON-1 activity and after intervention as compared with the baseline values in soy group.
Lignans	Hallund et al, 2006 (1)(29)	Muffin enriched with lignans (secoisolariciresinol diglucoside, SDG) isolated from flaxseed, 500 mg/d	Placebo muffin	Consumption of lignan complex enriched food did not affect serum lipoprotein oxidation resistance or plasma antioxidant capacity.
	Wu WH et al, 2006(62)	Dietary sesame seed powder containing 381 mg/d of lignans	Rice powder placebo	– The serum γ-tocopherol concentration and the ratio of serum α- or γ-tocopherol to plasma total cholesterol increased significantly after sesame treatment, but did not change after rice, and the values differed significantly between the 2 treatments. – The lag time of LDL oxidation did not change after either treatment. – The levels of TBARS in LDL that was oxidized for 1 and 3 h

	decreased significantly after sesame treatment, but not after rice, and the values differed significantly between the 2 treatments.

Abbreviations: COX-2: cyclooxygenase-2; GPx,: glutathione peroxidase; LDL: low density lipoprotein cholesterol; MDA: malondialdehyde; PON-1: paraoxonase 1; SOD:superoxide dismutase; TAC: total antioxidant capacity; TBARS: thiobarbituric acid reactive substances

Supplementary Table 5. Characteristics of RCTs included in meta-analysis

Lead Author, Publication Date	Location	Study design	Sample size	Duration (weeks)	Diet / Supplement		Mean age, y	Mean BMI, kg/m^2	Health status	Years since menopause
					Intervention	Control				
Aubertin-Leheudre et al, 2007(1)	Canada	P	22	24	Capsule; Isoflavones ,70 mg/d, extracted from soy	Placebo capsule	66±5	23.62±2.11	Obese, otherwise healthy non-smokers	NA
Bakhtiary et al, 2012(2) and 2019(3)	Iran	P	75	12	Dietary intake; Group I: Textured soy protein 35 g/d, isoflavones 96.2 mg/d; Group II: Soy nut 35 g/d, isoflavones, 117.2 mg/d	Nothing	64.35±2.86	28±4.03	Metabolic syndrome, non-smokers	15.9
Barrasa et al, 2018(4)	Chile	P	35	12	Capsule; Soyextract withIsoflavones 100 mg/d	Placebo capsule with starch	64.74	32.13	No major illness, non-smokers	NA
Basaria et al, 2009(5)	USA	P	84	12	Powder soy protein 20 g/d containing 160 mg of total isoflavones	Whole milk protein	56	25.9	Healthy	5.6
Beavers et al, 2009(6) and 2010(7)	USA	P	31	4	Vanilla soy milk; Isoflavones, 90 mg/d	Reduced-fat dairy milk	54.4	25.8	Healthy non-smokers; markers were measured after downhill run-walk test	NA
Blum et al, 2003(8)	Israel	CO	24	6	Dietary; Isolated soy protein, 25 g/d	Milk protein	55±5	NA	Hypercholesterolemia, non-smokers	NA
Brandao et al, 2009(9)	Brazil	P	38	16	Tablets, 200 mg of *Glycine max/*soybean*;* corresponding to 80 mg/d of	Placebo tablets	50-65	NA	Insomnia	NA

					isoflavone mixture					
Braxas et al, 2019(10)	Iran	P	54	12	Genistein Capsules, 54 mg/d	Placebo capsules, maltodextrin	57.66	31.06	Non-smokers with type 2 diabetes	6.48
Campbell et al, 2010(11)	USA	P	62	48	Dietary; Soy protein provided as snack bar, drink mix or cereal, 25 g/d corresponding to isoflavones 60 mg/d	Casein	54.3	28.03	Healthy	5.4
Charles et al, 2009(12)	USA	P	75	12	Powder; Soy isoflavones (genistein, daizein, glycitein), 160 mg/d	Whole milk protein	56.61±5.81	25.65±5.18	Healthy	9±1.9
Chieci et al, 2002(13)	Italy	P	108	24	Dietary; Isoflavones, 40-60 mg/d from soy	Control diet	53.8	28.4	Healthy	4.8
Choquette et al, 2011(14)	Canada	P	45	24	Pills; Soy isoflavones, 70mg/d	Placebo	58.5	30.1	Overweight/obese, otherwise healthy non-smokers	9.5
Chrisafulli et al, 2005(15)	Italy	P	60	24	Tablets; Genistein, 54 mg/d	Placebo tablets	55.5±6.49	23.5±2.58	Healthy	NA
Colacurci et al, 2005(16)	Italy	P	57	24	Tablet; Genistein 60 mg/d, daidzein 30 mg/d from soy	Placebo tablets	55.15±3.85	25.89±1.79	Healthy non-smokers	NA
Curtis et al, 2012(17) and 2013(18)	UK	P	93	48	27 g flavonoid-enriched chocolate/d [850 mg flavan-3-ols (90 mg epicatechin) + 100 mg isoflavones (aglycone equivalents)/d] derived from soy	Placebo	62.05	32.3	Non-smokers with type 2 diabetes	13.5

D'Anna et al, 2005(19)	Italy	P	55	24	Pills; Genistein, 54 mg/d	Placebo pills	50-60	NA	Healthy	NA
Dewell et al, 2002(20)	USA	P	36	24	Tablets; Soy-derived isoflavones, 150 mg/d	Placebo, maltodextrin	69.4	25	Healthy; moderately hypercholesterolemic	NA
Dodin et al, 2005(21) and 2008(22)	Canada	P	179	48	Dietary; Flaxseed, 40 g/d; 21.071 µg total lignan	Wheat germ placebo	54.7	26.2	Healthy	5.3
Evans et al, 2007(23)	USA	CO	25	4	Dietary powder or granules; included soy protein (SP) containing isoflavones (25 g/d) and soy lecithin (SL) (20 g/d); SP containing isoflavones (25 g/d) and placebo lecithin; placebo protein (50:50 calcium/sodium caseinate) and SL (20 g/d);	Placebo	61.5±8.2	26.34	Healthy non-smokers	9.9
Garrido et al, 2006(24)	Chile	P	29	12	Capsules; Soy isoflavones , approx. 100 mg/d (2 capsules/d containing 23.4±3.4 mg daidzein and 24.1±4.6 mg genistein)	Placebo	53.52±3.52	26.94±2.5	Healthy non-smokers	NA
Greany et al, 2008(25)	USA	CO	34	6	Dietary powder; Soy protein isolate 0.38 g/kg body	Powder; milk protein isolate	55.7±6	25.0±4.3	With and without a history of breast cancer, non-smokers	9.26±6.1

					weight (26±5 g/d) containing 0.64 mg/kg body weight (44±8 mg/d) isoflavones					
Hale et al, 2002(26)	USA	P	32	2	Tablet; Soy isoflavones 80 mg /d	Placebo tablet	57.2	24.9	Healthy non-smokers	NA
Hall et al, 2005(27) and 2006(28)	Europe	CO	117	8	Dietary; Soy isoflavone enriched cereal bars, genistein: daidzein 2:1 ratio, 100mg/d	Cereal bars without isoflavones	57.7±5.4	25±2.9	Healthy non-smokers	NA
Hallund et al, 2006 (1)(29) and 2008(30)	Denmark	CO	22	6	Dietary; Muffin enriched with lignans (secoisolariciresinol diglucoside, SDG) isolated from flaxseed, 500 mg/d	Placebo muffin	61±7	24.1±3.4	Healthy non-smokers	NA
Hallund et al, 2006 (2)(31)	Denmark	CO	28	8	Dietary; Cereal bars with soy isoflavones, 50 mg/d	Cereal bars without isoflavones	57±5	24± 2.6	Healthy	NA
Hanachi et al, 2007(32)	Iran	P	25	12	Soy milk; containing 12.5 g/d soy protein (Genistein 13 mg/d, Daidzein 4.13 mg/d)	Nothing	52.2±4.6	NA	Healthy non-smokers, menopausal symptoms	5.47±3.4
Hidalgo et al, 2005(33)	Ecuador	CO	53	12	Capsules; Red clover: T. pratense-derived isoflavones, 80 mg/d	Placebo capsules	51.3	26.6	Menopausal symptoms	NA
Hodis et al, 2011(34)	USA	P	325	129.6	Dietary; Beverage powder-food packs or food bars; 25 g/d of soy	Placebo; milk protein	60.9	NA	Healthy	NA

					protein with 91 mg aglycon isoflavone equivalents					
Howes et al, 2003(35)	Australia	CO	16	4	Tablets; Red clover, isoflavones approx. 50 mg/d	Placebo tablets	62±8	29.6±4.8	With Type 2 diabetes, non-smokers	11.2±7.6
Jassi et al, 2010(36)	India	P	75	12	Group I : Soy protein (powder) 30 g/d containing 60 mg of isoflavones; Group II: Soy isoflavones 60 mg/d	Casein protein	51.1	23.4	Vasomotor or genito-urinary complaints	2.5
Katz et al, 2007(37)	USA	CO	22	6	Capsules; Soy phytoestrogens containing 65 mg/d genistein and daidzein	Placebo capsules	58.5±7.0	27.6±5.2	Healthy non-smokers	10.33±9.4
Kim et al, 2013(38)	Korea	P	85	12	Capsules; Isoflavones from soy germ, 70mg/d	Placebo capsules	53.6	23.3	Healthy	3.6
Lissin et al, 2004(39)	USA	P	40	6	Tablets; Isoflavones, 90 mg/d (1:1:0.2 genistein : daidzein : glycitein)	Placebo tablets	61.6± 8.4	NA	Healthy non-smokers	12.8± 8.8
Liu et al, 2012(40)**, 2013**(41) **and 2014**(42)	China	P	180	24	Powder; Soy group: 15 g/d of soy protein and 100 mg/d of isoflavones, Iso group: 15 g/d milk protein and 100 mg/d of isoflavones	Milk protein	56.12	24.5	Prediabetic	5.97
Liu et al,	China	P	265	24	Beverage powder;	Low-fat milk	57.9	NA	Prehypertensive	9

2015(43)					Whole soy group: 40 g/d of soy flour, Daidzein group: 40 g/d of low-fat milk powder plus 63 mg/d daidzein	powder				
Ma et al, 2013(44)	China	P	90	12	Tablets; Low and high dose 2,3 g/d and 4,6 g/d of soybean β-conglycinin, respectively	Tablets casein	53.4	24.2	Hyperlipidemic	NA
Maesta et al, 2007(45)	Brazil	P	21	16	Tablets; Soy protein, 25 g/d, containing 50 mg of isoflavones (32 mg genistein, 15 mg daidzein, 3 mg glycitein)	Placebo, maltodextrin	59.5	26.9	Healthy non-smokers	10.6
Nahas et al, 2007(46)	Brazil	P	76	10	Capsules; Soy isoflavone extract, 250 mg/d containing 100 mg/d isoflavones	Placebo	55.7	29.1	Healthy	6.85
Nestel et al, 1999(47)	Australia	CO	18	5	Tablets; Red clover isoflavones, 40 and 80 mg/d	Placebo tablets	55.7	25.2	Healthy non-smokers	NA
Nikander et al, 2003(48) and 2004(49)	Finland	CO	56	12	Tablets; Isoflavone mixture, 114 mg/d	Placebo	54±6	26.25±3.3	History of breast cancer (treatment more than 6 months earlier), with vasomotor symptoms, non-smokers	5.3±5.5
Okamura et al, 2008(50)	Japan	P	19	8	Tablets; Extracts of Pueraria Mirifica, 20 mg/kg of miroestrol and about 1 mg/kg or	Placebo	NA	22.2	Healthy	NA

					less of isoflavonoids (genistein, daidzein, and coumestrol)					
Reimann et al, 2006(51)	Demark, Germany, UK	CO	89	8	Dietary; Cereal bars with soy isoflavones, 50 mg/d, genistein: daidzein ratio of 2:1	Cereal bars without isoflavones	59±5	24.4±3.0	Healthy non-smokers	
Rios et al, 2008(52)	Brazil	P	47	24	Capsule; Purified soy isoflavones (genistein and daidzein at 5% and 12%, respectively)	Placebo	55.7	26.5	Healthy non-smokers	7.9
Ryan-Borchers et al, 2006(53)	USA	P	52	16	Dietary and tablets; Soymilk group: 706 mL soymilk/d containing 71.6±3.1 mg isoflavones/d plus a placebo supplement, Isoflavone supplement group: 706 mL cow milk/d and isoflavone tablets (70 mg isoflavones/d)	Cow milk, 706 mL/d plus a placebo supplement	55.8	27.8	Healthy non-smokers	NA
Shidfar et al, 2009(54)	Iran	P	42	10	Dietary; Soy beans, 50 g/day soy protein containing 164 mg isoflavones/d	Whey protein	55	26.9	Hyperlipidemic, non-smokers	NA
Steinberg et al, 2003(55)	USA	CO	28	6	Powder; Soy^{+} group: Isolated soy protein, 25 g/d with naturally occurring	Total milk protein	54.9	24.6	Healthy	NA

					isoflavones (107.67 mg/d) , Soy^- group: Ethanol-washed isolated soy protein, 25 g/d with trace amounts of isoflavones (1.82 mg/d)					
Teede et al, 2005(56)	Australia	P	40	12	Powder; Soy protein isolate (40 g soy protein/d, 118 mg isoflavones/d)	Casein	59.45	26	Healthy non-smokers	NA
Terzic et al, 2012(57)	Serbia	CO	74	72	Capsules; Soy or red clover-derived phytoestrogens; Soy: containing 2 isoflavones, genistein (39 mg/d) and daidzein (1 mg/d); Red clover: containing 4 isoflavones, biochanin A (23 mg/d), daidzein (1 mg/d), formononetin (15 mg/d) and genistein (1 mg/d)	Nothing	55.7	26.6	Healthy	NA
Turhan et al, 2009(58)	Turkey	P	90	24	Tablets; 2 tablets/d containing Isolated isoflavones 80 mg isoflavones/d (29.8 mg genistein, 7.8 mg daidzein, and 2.4 mg glycitein per tablet)	Placebo tablet	51.5± 4,1	27.1± 3.1	Recently healthy non-smokers	3.6 ±1.7

Verhoeven et al, 2007(59)	The Netherlands	P	115	12	Capsule; 125 mg soy extract (providing 50 mg isoflavones/d, including 24 mg genistein and 21.5 mg daidzein) combined with 100 mg black cohosh extract (providing 8 mg deoxyacetein/d)	Placebo capsules of 2000 mg olive oil	57.5	26.6±2.6	Healthy non-smokers	4
Wangen et al, 2001(60)	USA	CO	18	13	Powder; Isolated soy protein: low dose 65mg/d, high dose 132 mg/d	Placebo powder	56.9±5.8	25.2±3.6	Healthy non-smokers	7.6±4.7
Wu J et al, 2006(61)	Taiwan	CO	24	5	Dietary; 50 g sesame seed powder/d containing lignans, 381 mg/d	Rice powder placebo	59±7	NA	Healthy non-smokers	9.8±7.8
Wu WH et al, 2006(62)	Japan	P	66	24	Capsules; Isoflavone conjugate, 75 mg/d from soy	Placebo capsules; dextrin	54.4	21.1	Healthy non-smokers	3.2
Ye et al, 2012(63)	China	P	90	24	Soy germ isoflavone extract powder; low-dose group with 84 mg/d and high-dose group with 126 mg/d	Placebo	52.27	22.63	Healthy	7.8
Yildiz et al, 2005(64)	Turkey	P	40	24	Tablets; Genistein, 40 mg/d from soy	Placebo	50.0	27.05	Healthy non-smokers	2.65
Zhang et al, 2019(65)	China	P	160	24	Capsules; Genistein 60 mg/d	Placebo capsules	56.9±4.9	22.7±0.8	Hyperlipidemic	NA

Abbreviations: BMI, body mass index; CO, cross-over design; d, day; NA, not available; P, parallel

Supplementary Table 6. Subgroup analyses

Subgroups by study characteristics		Number of studies	[1]Difference, Mean (95 % CI)	[2]I^2 for heterogeneity	[3]P value for heterogeneity
Mean serum CRP change, mg/L					
[a]Median age, y	≤55.7	5	0.05 (-0.40; 0.51)	99.4%	0.61
	>55.7	6	**-0.22 (-0.36; -0.08)**	81.7%	
	Unknown	1	NA	NA	
[b]Median years since menopause onset	≤5.97	5	-0.06 (-0.54;0.43)	99.5%	0.28
	>5.97	3	0.04 (-0.51; 0.58)	88.1%	
	Unknown	4	-0.05 (-0.27;0.17)	93.9%	
[c]Health status	Healthy	6	-0.16 (-0.43; 0.11)	98.7%	0.23
	Unhealthy	6	0.09 (-0.29; 0.48)	98%	
[e]Smoking status	Non-smokers	8	-0.15 (-0.38; 0.09)	98.7%	0.24
	Smokers and non-smokers	4	0.20 (-0.46; 0.86)	98.6%	
[f]Type of administration	Tablet/capsule	4	-0.06 (-0.53; 0.41)	99.1%	0.28
	Diet	8	0.01 (-0.27; 0.29)	98.1%	
[g]Intervention type	Lignans	2	**-0.31 (-0.36; -0.26)**	0%	0.85
	Isoflvones	10	0.03 (-0.28; 0.34)	99.2%	
	Coumestans	0	NA	NA	
[h]Median number of study participants	≤90women	6	0.05 (-0.30; 0.40)	91.5%	0.47
	>90 women	6	-0.07 (-0.46; 0.32)	99.5%	
[i]Intervention duration	≤14 weeks	6	-0.18 (-0.44; 0.08)	98.8%	0.28
	>14 weeks	6	0.16 (-0.26; 0.58)	98.1%	
[i]Intervention duration	≤8weeks	2	0.15 (-0.78; 1.08)	96%	0.82
	>8 weeks	10	-0.04 (-0.35; 0.27)	99.1%	
[j]Median, BMI	≤25	6	0.14 (-0.21; 0.49)	98.6%	0.49
	>25	5	-0.27 (-0.63; 0.09)	98.6%	
	Unknown	1	NA	NA	
[k]Location	Europe	5	-0.17 (-0.44; 0.11)	99.3%	0.23
	North America	3	0.34 (-0.21; 0.89)	58.2%	
	Middle East	2	**-0.25 (-0.47; -0.04)**	0%	
	Asia-Pacific	2	0.25 (-0.81; 1.31)	99.5%	
[l]Study design	Cross-over	4	-0.07 (-0.24; 0.10)	95.2%	0.59
	Parallel	8	-0.01 (-0.50; 0.47)	99.1%	
[m]Study quality	Good	1	NA	NA	0.63
	Fair	8	-0.06 (-0.39; 0.28)	99.3%	
	Poor	3	0.22 (-0.58; 1.02)	92.4%	
Mean serum Total Cholesterol change, mmol/L					
[a]Median age, y	≤55.7	26	**-0.31 (-0.53;-0.09)**	99.6%	0.46
	>55.7	23	**-0.22 (-0.32;-0.12)**	97.1%	
[b]Median years since menopause onset	≤6.85	14	-0.16 (-0.42; 0.11)	99.8%	**0.03**
	>6.85	15	**-0.15(-0.25; -0.05)**	94%	
	Unknown	20	**-0.45 (-0.75; -0.14)**	99.5%	
[c]Health status	Healthy	36	**-0.28 (-0.45; -0.11)**	99.7%	0.09
	Unhealthy	13	**-0.26 (-0.42; -0.09)**	98.2%	
[d]Dyslipidemia	Yes	6	**-0.38 (-0.57; -0.19)**	91.4%	0.29
	No	43	**-0.25 (-0.40; -0.11)**	99.6%	
[e]Smoking status	Non-smokers	28	**-0.24 (-0.43; -0.05)**	99.2%	0.36
	Smokers and non-smokers	21	**-0.33 (-0.52;-0.14)**	99.6%	

[f]**Type of administration**	Tablet/capsule	24	**-0.41 (-0.65;-0.18)**	99.4%	0.46
	Diet	25	**-0.14 (-0.20; -0.07)**	96.6%	
[g]**Intervention type**	Isoflavones	42	**-0.23(-0.38;-0.09)**	99.6%	0.62
	Lignans	2	**-0.19 (-0.22; -0.16)**	0%	
	Coumestans	5	-0.66 (-1.63;0.31)	99.7%	
[h]**Median number of study participants**	≤50women	25	**-0.34 (-0.56; -0.12)**	99.1%	0.44
	>50 women	24	**-0.21 (-0.34; -0.08)**	99.3%	
[i]**Intervention duration, median**	≤12 weeks	27	**-0.20 (-0.29;-0.12)**	96.8%	0.84
	> 12 weeks	22	**-0.35 (-0.59; -0.11)**	99.7%	
[i]**Intervention duration, median**	≤8 weeks	9	-0.06 (-0.015; 0.02)	66%	0.29
	> 8 weeks	40	**-0.31 (-0.46; -0.15)**	99.6%	
[j]**Median, BMI**	≤26	22	-0.12 (-0.21;-0.05)	94.4%	0.28
	>26	21	**-0.46 (-0.69; -0.23)**	99.6%	
	Unknown	6	-0.09 (-0.25; 0.07)	95.8%	
[k]**Location**	Europe	6	-0.67 (-1.43; 0.09)	99.9%	0.18
	North America	12	**-0.10 (-0.18; -0.03)**	90.7%	
	South America	6	-0.26 (-0.60;0.09)	97.4%	
	Middle East	7	**-0.44 (-0.71; -0.18)**	97.5%	
	Asia-Pacific	18	**-0.17 (-0.30; -0.05)**	97%	
[l]**Study design**	Cross-over	13	-0.38(-0.80; 0.05)	99%	0.10
	Parallel	36	**-0.23 (-0.38; -0.09)**	99.5%	
[m]**Study quality**	Poor	19	-0.20 (-0.45; 0.05)	99%	0.14
	Fair	21	**-0.20 (-0.31; -0.08)**	98.1%	
	Good	9	**-0.59 (-1.01;-0.17)**	99.8%	
Mean serum Triglycerides change, mmol/L					
[a]**Median age, y**	≤55.7	27	**-0.32(-0.48; -0.17)**	99.4%	**0.01**
	>55.7	21	-0.03(-0.09;0.04)	98%	
[b]**Median years since menopause onset**	≤6.85	15	-0.13 (-0.25; -0.01)	99.4%	0.11
	>6.85	14	**-0.10 (-0.16; -0.04)**	89.4%	
	Unknown	19	**-0.33 (-0.58; -0.08)**	99.6%	
[c]**Health status**	Healthy	35	**-0.15 (-0.25; -0.05)**	99.4%	0.09
	Unhealthy	13	**-0.31 (-0.46; -0.16)**	98.9%	
[d]**Dyslipidemia**	Yes	6	**-0.48(-0.89; -0.08)**	98.5%	0.16
	No	42	**-0.16 (-0.25; -0.08)**	99.4%	
[e]**Smoking status**	Non-smokers	27	-0.05 (-0.11; 0.00)	92.9%	0.08
	Smokers and non-smokers	21	**-0.37 (-0.53; -0.21)**	99.7%	
[f]**Type of administration**	Tablet/capsule	25	**-0.30 (-0.51; -0.09)**	99.4%	**0.003**
	Diet	23	**-0.09 (-0.17; -0.01)**	99.1 %	
[g]**Intervention type**	Isoflavones	41	**-0.17 (-0.25; -0.08)**	99.3%	0.35
	Lignans	2	-0.04 (-0.15; 0.08)	91%	
	Coumestans	5	-0.54(-1.22;0.14)	99.5%	
[h]**Median number of study participants**	≤50women	23	-0.12 (-0.29; 0.04)	98.9 %	**0.02**
	>50 women	25	**-0.26 (-0.36;-0.16)**	99.4%	
[i]**Intervention duration**	≤12 weeks	26	**-0.24(-0.40; -0.07)**	99.4%	0.06
	>12 weeks	22	**-0.16(-0.26; -0.07)**	99.1%	
[i]**Intervention duration**	≤8 weeks	8	**0.03 (-0.03; 0.10)**	72.7%	0.95
	>8 weeks	40	**-0.24 (-0.34, -0.13)**	99.5%	
[i]**Intervention duration, median**	≤8 weeks	10	-0.20 (-0.39;00)	96.7%	0.29
	> 8 weeks	41	**-0.26 (-0.40;-0.12)**	99.6%	
[j]**Median, BMI**	≤26.2	22	**-0.15 (-0.25; -0.04)**	99.2%	0.05
	>26.2	21	**-0.27(-0.47; -0.07)**	99.4%	
	Unknown	5	-0.07 (-0.22; 0.07)	97.6%	
[k]**Location**	Europe	7	-0.43 (-0.88;0.02)	99.8%	0.06
	North America	12	**0.07 (0.02; 0.12)**	87.1%	
	South America	6	-0.10 (-0.27;0.06)	91.6%	

	Middle East	6	**-0.18 (-0.30; -0.06)**	91.6%	
	Asia-Pacific	17	**-0.26(-0.38; -0.15)**	98.6%	
[l]**Study design**	Cross-over	12	-0.29 (-0.59; 0.01)	99.7%	0.47
	Parallel	36	**-0.16(-0.25; -0.08)**	99%	
[m]**Study quality**	Good	9	**-0.64 (0.98;-0.30)**	99.8%	**0.005**
	Fair	20	**-0.16 (-0.25; -0.07)**	98.7%	
	Poor	19	-0.01 (-0.09; 0.07)	89.4%	
Serum LDL Change, mmol/L					
[a]**Median age, y**	≤55.7	29	**-0.24 (-0.41; -0.07)**	99.6%	0.32
	>55.7	22	**-0.24(-0.42; -0.05)**	99.2%	
	Unknown	1	NA	NA	
[b]**Median years since menopause onset**	≤6.85	15	**-0.09 (-0.18; 00)**	97.7%	0.05
	>6.85	14	**-0.15 (-0.25; -0.04)**	95.6%	
	Unknown	22	**-0.42 (-0.70;-0.15)**	99.6%	
[c]**Health status**	Healthy	38	**-0.22 (-0.35; -0.08)**	99.4%	0.12
	Unhealthy	13	-0.35 (-0.65; -0.04)	99.6%	
[d]**Dyslipidemia**	Yes	6	-0.62 (-0.1.12;-0.11)	99.2%	0.29
	No	45	-0.20 (-0.32;-0.09)	99.4%	
[e]**Smoking status**	Non-smokers	28	**-0.16 (-0.26;-0.07)**	96.2%	**0.02**
	Smokers and non-smokers	23	**-0.34 (-0.55;-0.14)**	99.7%	
[f]**Type of administration**	Tablet/capsule	26	**-0.37 (-0.62; -0.11)**	99.5%	**0.02**
	Diet	25	**-0.13 (-0.19; -0.07)**	97%	
[g]**Intervention type**	Isoflavones	44	**-0.23(-0.35; -0.11)**	99.4%	0.76
	Lignans	2	-0.05 (-0.1; 0.10)	83.9%	
	Coumestans	5	-0.55 (-1.22; 0.12)	99.5%	
[h]**Median number of study participants**	≤50women	26	**-0.29 (-0.51; -0.08)**	98.8%	**0.003**
	>50 women	25	**-0.21 (-0.36; -0.06)**	99.6%	
[i]**Intervention duration**	≤12weeks	28	**-0.23 (-0.32; -0.13)**	97.9%	0.21
	>12weeks	23	**-0.27(-0.50; -0.04)**	99.7%	
[i]**Intervention duration, median**	≤8 weeks	10	-0.20 (-0.39;00)	96.7%	0.29
	> 8 weeks	41	**-0.26 (-0.40;-0.12)**	99.6%	
[j]**Median, BMI**	≤25.9	24	**-0.23 (-0.39; -0.07)**	99.4%	0.21
	>25.9	21	**-0.32 (-0.56; -0.08)**	99.5%	
	Unknown	6	-0.05 (-0.22;0.12)	97%	
[k]**Location**	≤12weeks	28	**-0.23 (-0.32; -0.13)**	97.9%	0.06
	>12weeks	23	**-0.27(-0.50; -0.04)**	99.7%	
	≤8 weeks	10	-0.20 (-0.39;00)	96.7%	
	> 8 weeks	41	**-0.26 (-0.40;-0.12)**	99.6%	
	≤12weeks	28	**-0.23 (-0.32; -0.13)**	97.9%	
[l]**Study design**	Cross-over	13	-0.28 (-0.66;0.10)	99.7%	0.2
	Parallel	38	**-0.22 (-0.34;-0.13)**	99.1%	
[m]**Study quality**	Good	9	**-0.49 (-0.89; -0.09)**	99.9%	**0.009**
	Fair	19	**-0.23 (-0.41; -0.06)**	99.4%	
	Poor	20	**-0.14 (-0.24; -0.04)**	92.5%	
Serum HDL change, mmol/L					
[a]**Meadian age, y**	≤57.9	28	0.12 (-0.07; 0.31)	99.9%	0.24
	>57.9	22	0.03 (-0.03; 0.09)	99.3%	
	Unknown	1	NA	NA	
[b]**Median years since menopause onset**	≤6.85	21	0.01 (-0.05; 0.08)	99.3%	0.39
	>6.85	16	**0.03 0.00; 0.05)**	89.5%	
	Unknown	12	0.18(-0.04; 0.41)	99.9%	
[c]**Health status**	Healthy	37	0.10(-0.03; 0.23)	99.9%	0.81
	Unhealthy	13	0.05 (-0.01; 0.11)	98.6%	
[d]**Dyslipidemia**	Yes	5	0.00 (-0.16; 0.16)	99.1%	0.59
	No	45	0.10 (-0.01; 0.20)	99.9%	
[e]**Smoking status**	Non-smokers	27	**0.04 (0.01; 0.07)**	93.6%	0.08

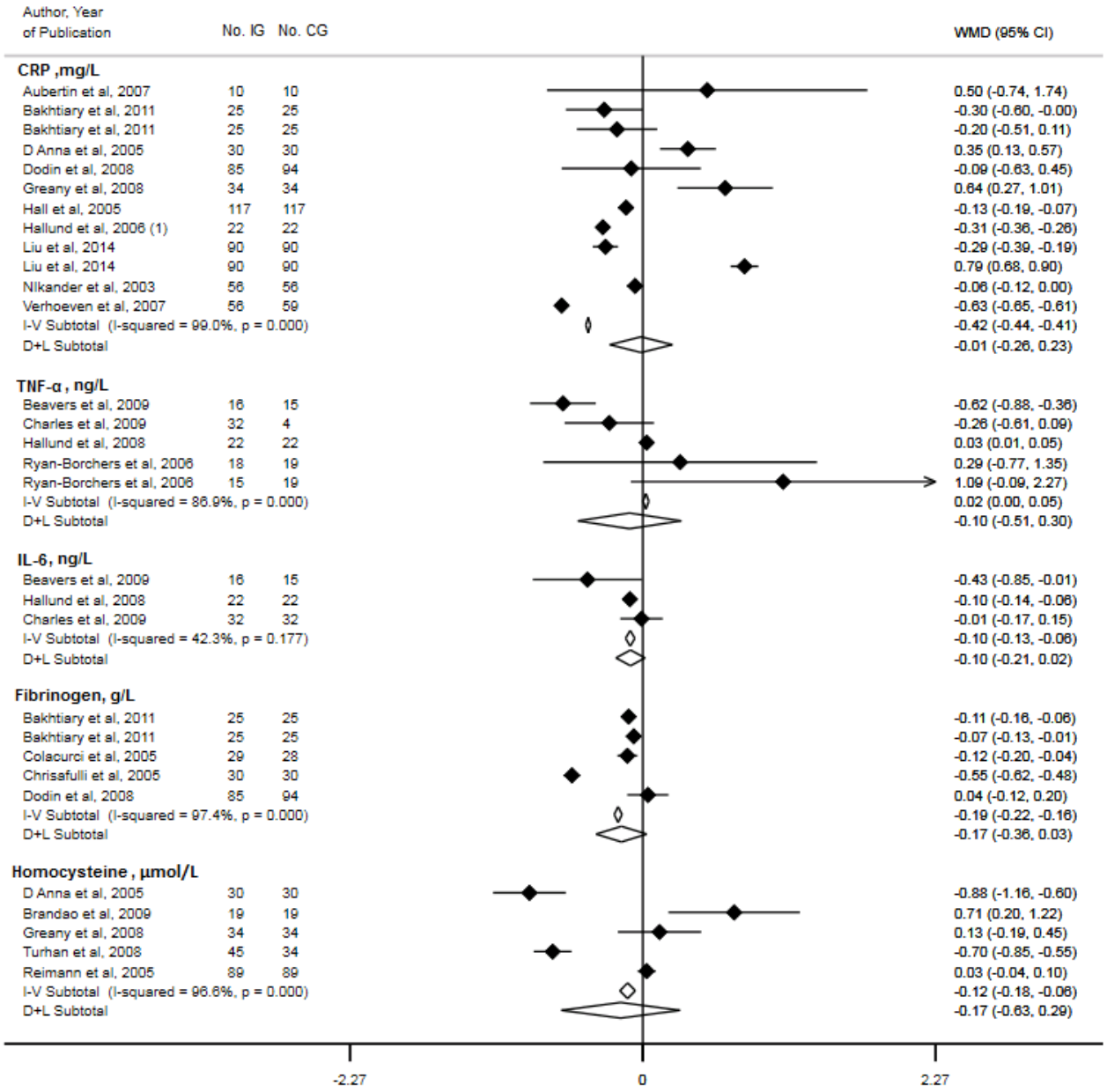
	Smokers and non-smokers	23	0.14 (-0.02;0.30)	99.9%	
[f]**Type of administration**	Tablet/capsule	25	0.16 (-0.02; 0.35)	99.9%	0.49
	Diet	25	0.01 (-0.02; 0.05)	98.2%	
[g]**Intervention type**	Isoflavones	43	0.07 (0.00;0.14)	99.7%	0.90
	Lignans	2	-0.04 (-0.11; 0.03)	83.8%	
	Coumestans	5	0.36 (-0.50; 1.21)	100%	
[h]**Median number of study participants**	≤50women	25	0.12 (-0.03; 0.28)	99.7%	0.04
	>50 women	25	0.06 (-0.07; 0.18)	99.9%	
[i]**Intervention duration**	≤12 weeks	28	0.05 (0.00; 0.10)	99.9%	0.86
	> 12weeks	22	0.13 (-0.04; 0.31)	99.9%	
[i]**Intervention duration**	≤8 weeks	9	0.05 (-0.07;0.17)	98%	0.48
	> 8 weeks	41	0.10 (-0.01: 0.20)	99.9%	
[j]**Median, BMI**	≤25.9	24	0.04 (-0.03; 0.10)	99.4%	0.58
	>25.9	21	0.18(-0.04; 0.39)	99.9%	
	Unknown	5	-0.03 (-0.05; -0.00)	4.57%	
[k]**Location**	Europe	7	0.37 (-0.16;0.91)	100%	0.69
	North America	12	**-0.04 (-0.07; -0.01)**	90.3%	
	South America	6	0.09 (-0.01; 0.20)	96.8%	
	Middle East	6	**0.07 (0.03; 0.12)**	93.8%	
	Asia-Pacific	18	0.06 (0.00; 0.11)	98.9%	
[l]**Study design**	Cross-over	13	0.20 (-0.16; 0.56)	99.9%	0.43
	Parallel	37	0.05 (0.00; 0.09)	99.2%	
[m]**Study quality**	Good	9	0.27(-0.13; 0.67)	99.9%	0.14
	Fair	22	**0.06 (0.01; 0.10)**	97.5%	
	Poor	19	0.03 (-0.02; 0.08)	94.65	
Mean serum Apo A-1 change, g/L					
[a]**Meadian age, y**	≤53.9	8	0.02 (-0.06; 0.09)	96.6%	0.05
	>53.9	8	**0.02 (0.00; 0.04)**	97.2%	
	Unknown	1	NA	NA	
[b]**Median years since menopause onset**	≤7.8	9	-0.01 (-0.03; 0.01)	96.1%	0.18
	>7.8	2	**0.15 (0.04; 0.26)**	0%	
	Unknown	6	0.17(0.02; 0.31)	99.6%	
[c]**Health status**	Healthy	9	0.12(0.07; 0.17)	99.3%	0.26
	Unhealthy	8	-0.04 (-0.07; 0.00)	95.4%	
[d]**Dyslipidemia**	Yes	3	-0.01 (-0.04;0.02)	90.4%	0.15
	No	14	**0.07 (0.02; 0.11)**	99 %	
[e]**Smoking status**	Non-smokers	7	**0.04 (0.02; 0.06)**	93.5%	0.33
	Smokers and non-smokers	10	0.02 (-0.07;0.11)	99.3%	
[f]**Type of administration**	Tablet/capsule	5	**0.14 (0.04; 0.24)**	99.7%	0.27
	Diet	10	-0.00 (-0.03; 0.02)	95.0%	
[g]**Intervention type**	Isoflavones	16	0.05 (0.03 ; 0.08)	99.1%	0.33
	Lignans	1	NA	NA	
	Coumestans	0	NA	NA	
[h]**Median number of study participants**	≤50women	9	**0.10 (0.04; 0.16)**	99.4%	0.31
	>50 women	8	0.00 (-0.02; 0.03)	98.2%	
[i]**Intervention duration**	≤12 weeks	12	**0.07 (0.02; 0.11)**	99.2%	0.16
	> 12weeks	5	0.02 (-0.02; 0.06)	87.5%	
[i]**Intervention duration**	≤8 weeks	1	NA	NA	0.36
	> 8 weeks	16	0.01 (-0.01; 0.02)	96.7%	
[j]**Median, BMI**	≤25.2	9	0.10 (-0.01; 0.21)	91.7%	0.2
	>25.2	7	0.12(-0.02; 0.25)	97.9%	
	Unknown	1	NA	NA	
[k]**Location**	Europe	2	-0.01 (-0.04; 0.03)	7.6%	0.26
	North America	3	**0.03 (0.02; 0.04)**	91.9%	
	South America	2	0.27 (-0.17, 0.71)	96.8%	

	Middle East	2	**0.15 (0.04; 0.26)**	0%	
	Asia-Pacific	8	0.03 (-0.07;0.13)	99.5%	
[l]**Study design**	Cross-over	14	0.07(-0.01; 0.15)	99.1%	**0.39**
	Parallel	3	0.02 (0.01, 0.04)	95.1%	
[m]**Study quality**	Good	4	-0.04 (-0.09; 0.01)	86.7%	0.26
	Fair	10	0.06 (-0.04;0.15)	86.7%	
	Poor	4	**-0.05 (-0.03;-0.07)**	94.6%	
Mean serum Apo B change, g/L					
[a]**Meadian age, y**	≤53.9	8	**-0.09 (-0.16; -0.02)**	94.1%	0.06
	>53.9	8	**-0.18(-0.35; -0.02)**	98.2%	
	Unknown	1	NA	NA	
[b]**Median years since menopause onset**	<7.6	7	-0.03 (-0.08; 0.01)	94.5%	0.19
	≥7.6	4	**-0.18 (-0.31; -0.06)**	97.6%	
	Unknown	6	**-0.22 (-0.30;-0.13)**	99.2 %	
[c]**Health status**	Healthy	9	**-0.07 (-0.11;-0.02)**	95%	0.24
	Unhealthy	8	**-0.20(-0.32; -0.09)**	99.7%	
[d]**Dyslipidemia**	Yes	3	**-0.24 (-0.35; -0.13)**	99.6%	0.08
	No	14	**-0.10 (-0.14; -0.06)**	96.6%	
[e]**Smoking status**	Non-smokers	7	**-0.16 (-0.24;-0.08)**	97.5%	0.41
	Smokers and non-smokers	9	**-0.11 (-0.21; -0.01)**	99.7%	
[f]**Type of administration**	Tablet/capsule	7	**0.18 (-0.30; -0.06)**	99.7%	0.21
	Diet	10	**-0.09 (-0.14; -0.05)**	95.6%	
[g]**Intervention type**	Isoflavones	16	**-0.14 (-0.25; -0.04)**	99.9%	0.25
	Lignans	1	NA	NA	
	Coumestans	0	NA	NA	
[h]**Median number of study participants**	≤50women	9	**-0.17 (-0.25;-0.10)**	97.7%	0.29
	>50 women	8	-0.09 (-0.22; 0.04)	99.8%	
[i]**Intervention duration**	≤12 weeks	12	**-0.16 (-0.22; -0.09)**	99.1%	0.10
	>12weeks	5	-0.08 (-0.28; 0.13)	99.8%	
[i]**Intervention duration**	≤8 weeks	1	NA	NA	0.38
	>8 weeks	16	**-0.14 (-0.24;-0.03)**	99.6%	
[j]**Median, BMI**	≤25.7	9	-0.10 (-0.24; 0.03)	97.5%	0.10
	>25.7	7	**-0.18 (-0.30; -0.05)**	97.5%	
	Unknown	1	NA	NA	
[k]**Location**	Europe	2	0.03 (-0.03;0.09)	47.3%	0.32
	North America	3	**-0.01 (-0.04;0.02)**	34.4%	
	South America	2	-0.22 (-0.47; 0.02)	96.4%	
	Middle East	2	**-0.40 (-0.47; -0.33)**	0%	
	Asia-Pacific	8	**-0.13 (-0.24; -0.02)**	99.7%	
[l]**Study design**	Cross-over	3	0.02 (-0.03; 0.06)	91.3%	0.36
	Parallel	14	**-0.17 (-0.25;-0.08)**	99.5%	
[m]**Study quality**	Good	3	**-0.15 (-0.21; -0.08)**	95.6%	0.37
	Fair	10	**-0.17 (-0.31; -0.04)**	99.7%	
	Poor	4	-0.04 (-0.10; 0.03)	91.7%	
Mean serum LP(a) change, g/L					
[a]**Meadian age, y**	≤54.9	5	0.40 (-0.45; 1.26)	67.5%	0.16
	>54.9	3	0.27 (-0.14; 0.68)	83.8%	
[b]**Median years since menopause onset**	≤5.3	3	0.64 (-0.78; 2.07)	70.7%	0.15
	>5.3	2	**0.50 (0.30; 0.69)**	44.1%	
	Unknown	3	-0.21 (-1.21; 0.79)	63.6%	
[c]**Health status**	Healthy	7	0.13 (-0.23; 0.49)	89.5%	0.33
	Unhealthy	1	NA	NA	
[d]**Dyslipidemia**	Yes	0	NA	NA	NA
	No	8	0.22 (-0.15; 0.58)	89%	

[e]**Smoking status**	Non-smokers	6	0.23 (-0.20; 0.66)	77.4%	0.09
	Smokers and non-smokers	2	0.82 (-1.36; 3.01)	72.8%	
[f]**Type of administration**	Tablet/capsule	4	0.84 (-0.86; 2.54)	77.9%	0.10
	Diet	4	0.20 (-0.19; 0.59)	94%	
[g]**Intervention type**	Isoflavones	7	0.29 (-0.14; 0.72)	75.6%	0.08
	Lignans	1	NA	NA	
	Coumestans	0	NA	NA	
[h]**Median number of study participants**	≤98women	4	0.27 (-0.12; 0.66)	75.8%	0.15
	>98 women	4	0.47 (-0.49; 1.43)	75.6%	
[l]**Intervention duration**	≤12 weeks	5	**0.48 (0.07; 0.88)**	71.7%	0.13
	> 12weeks	3	-0.16 (-0.56; 0.24)	35.7%	
[l]**Intervention duration**	≤8weeks	1	NA	NA	0.34
	> 8 weeks	7	0.31 (-0.08; 0.70)	90.3%	
[j]**Median, BMI**	≤26	4	0.12 (-0.31; 0.56)	83.3%	0.13
	>26	4	0.96 (-0.43; 2.34)	71.4%	
[k]**Location**	Europe	3	0.07 (-1.15; 1.30)	80.3%	0.22
	North America	3	0.32 (-0.10; 0.74)	95.8%	
	South America	1	NA	NA	
	Middle East	1	NA	NA	
	Asia-Pacific	0	NA	NA	
[l]**Study design**	Cross-over	5	**0.48 (0.07; 0.88)**	71.7%	0.13
	Parallel	3	-0.16 (-0.56; 0.24)	35.7%	
[j]**Study quality**	Good	1	NA	NA	0.08
	Fair	4	0.85 (-0.82; 2.51)	74.7%	
	Poor	3	0.27 (-0.14; 0.68)	83.8%	

[1]Mean difference refers to mean difference of changes between treatment groups (subjects using phytoestrogens as compared with the subjects from control/placebo group)
[2]I^2 for heterogeneity was calculated using fixed- effects models
[3]P value for heterogeneity was evaluated using random-effects meta-regression (when ≥8 studies were meta-analyzed).
[a]Median age of women at baseline
[b]Median years since menopause, number of years since menopause onset, unknown: no information
[C]Health status: healthy women vs. women with impaired health status (history of breast cancer, prediabetes etc.)
[d]Dyslipidemia, accounted only for blood lipids measurements
[e]Smoking status; RCTs including only non-smokers vs. RCTs which included participants regardless smoking habits
[f]Type of administration includes tablets/capsules use and other type of administration (shake, powder, flower)
[g]Intervention type: three major types of phytoestrogens: isoflavones, lignans and coumestans
[h]Median number of study participants was calculated for each outcome separately
[j]Median, BMI was calculated for each outcome separately
[k] Location refers to study location
[l]Study design: parallel or cross-over trials
[m]Studies' quality was judged based on criteria to evaluate random sequence generation, allocation concealment, blinding of participants/personnel and outcome assessment, incomplete outcome data and selective reporting

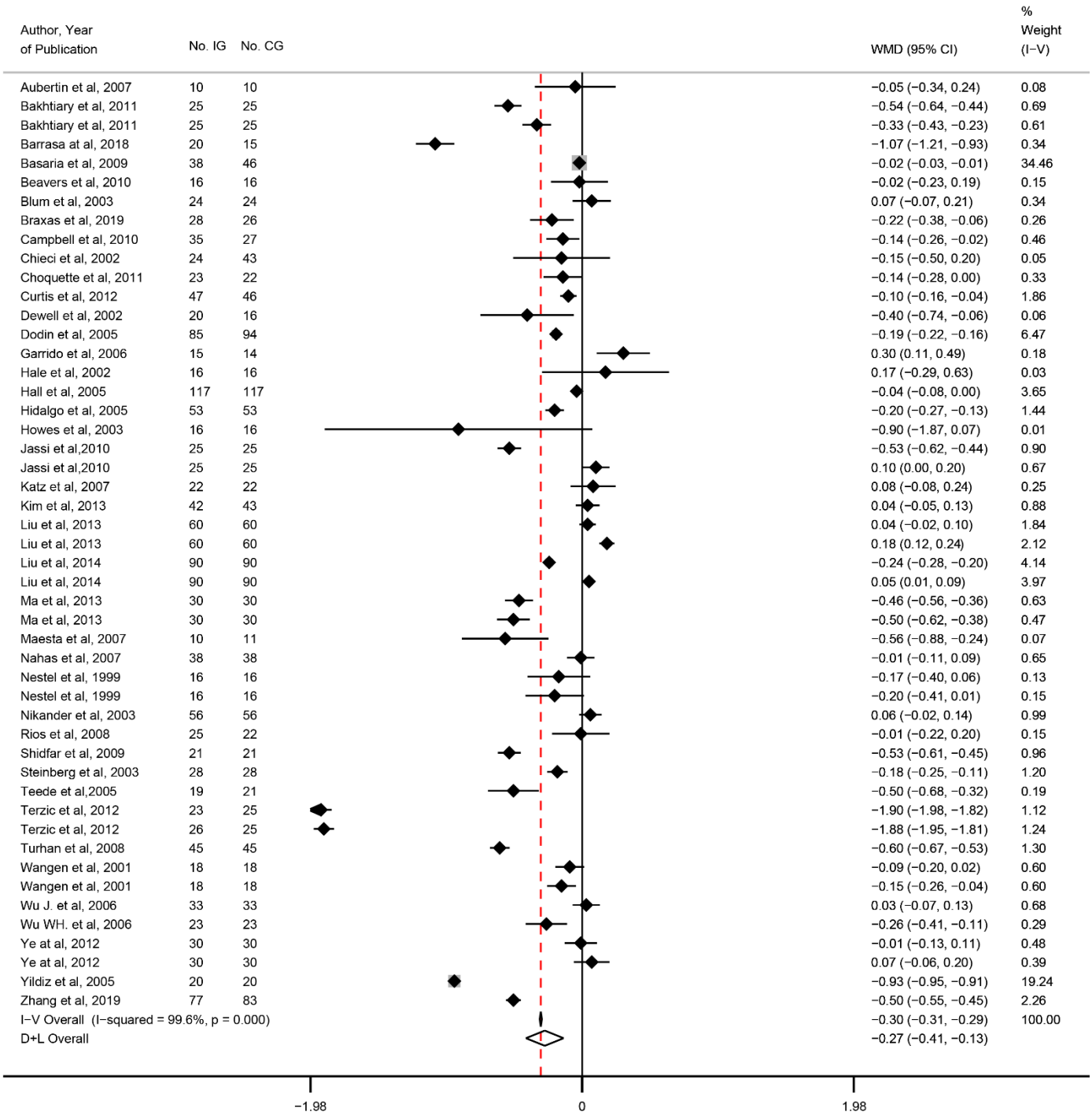
Supplementary Figure 1. The associations between phytoestrogen supplementation and inflammation markers, fibrinogen and homocysteine



I-V fixed effect model; D+L random effect model. I-squared: Higgins's I2 represents the percentage of variation between the sample estimates that is due to heterogeneity rather than to sampling error. WMD, weighted mean difference; Mean difference refers to mean difference of changes between treatment groups. P value comes from Q statistics.

Abbreviations: No. IG, number of women in intervention group; No. CG, number of women in control group; CRP, C-reactive protein; TNF-α, tumor necrosis factor alpha; IL-6, interleukin 6

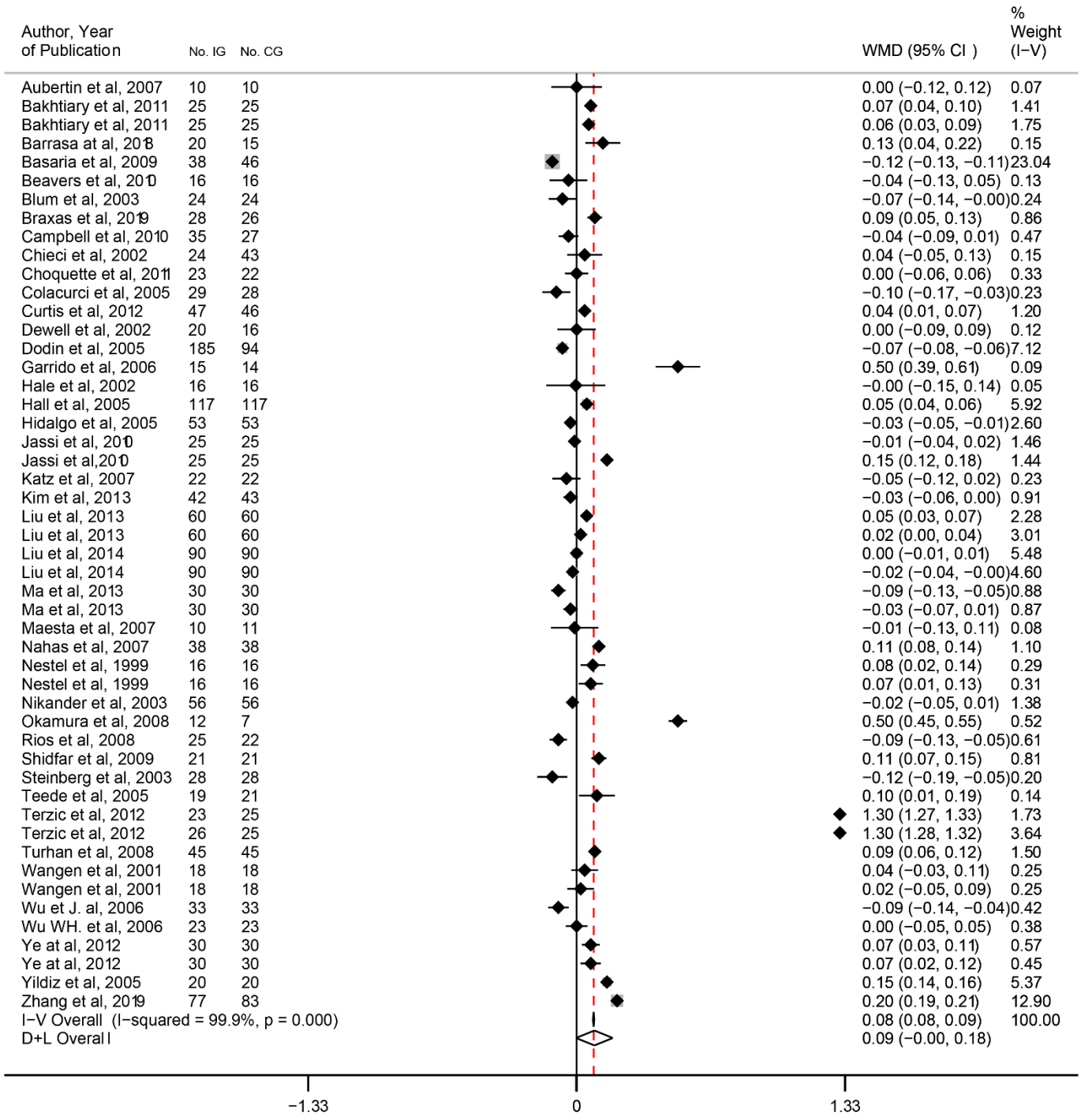
Supplementary Figure 2. The associations between phytoestrogen supplementation and changes in serum total cholesterol, mmol/L



I-V fixed effect model; D+L random effect model. I-squared: Higgins's I2 represents the percentage of variation between the sample estimates that is due to heterogeneity rather than to sampling error. WMD, weighted mean difference; Mean difference refers to mean difference of changes between treatment groups. The size of data markers is proportional to the inverse of the variance of the effect estimate. P value comes from Q statistics.

Abbreviations: No. IG, number of women in intervention group; No. CG, number of women in control group

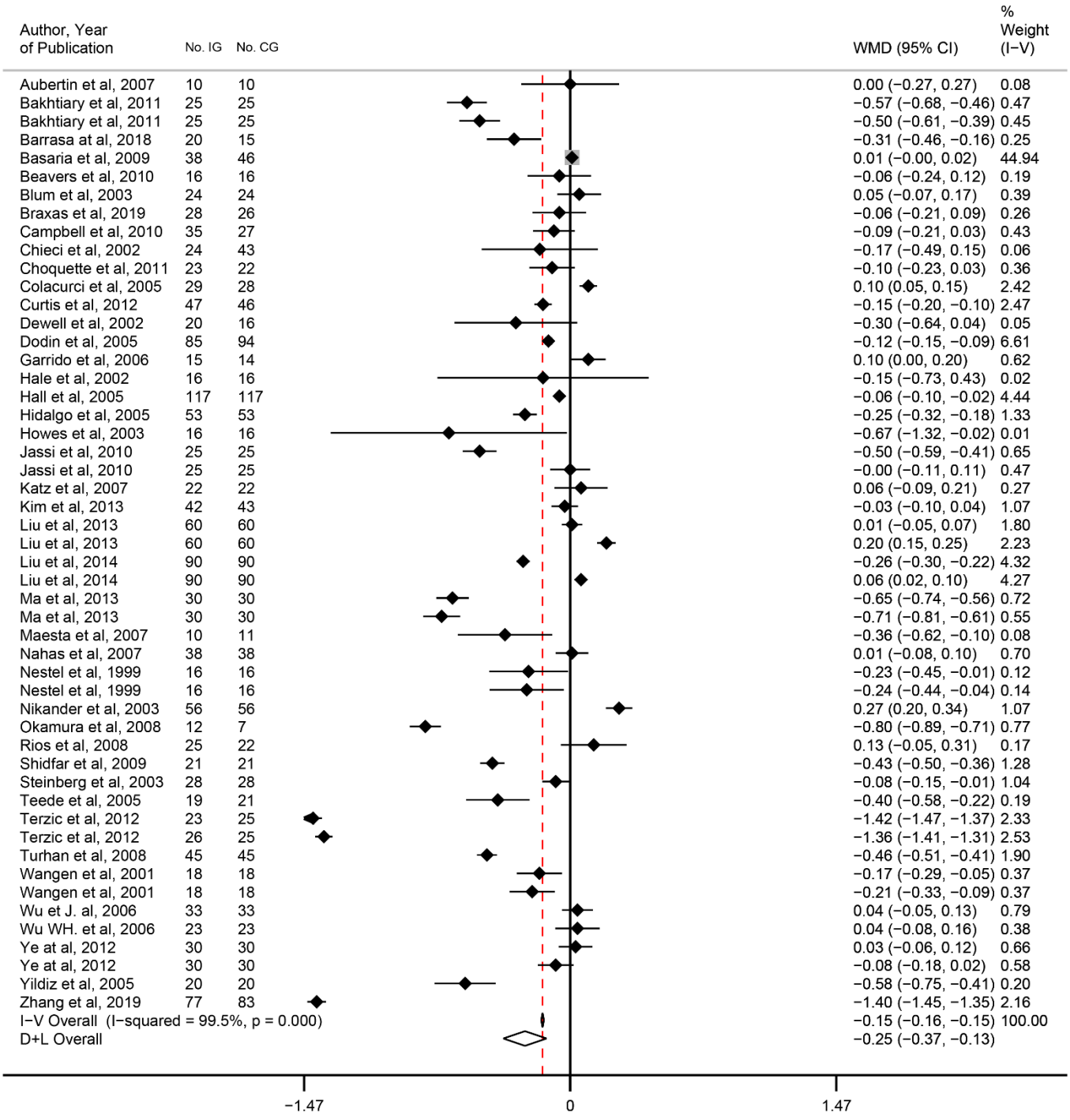
Supplementary Figure 3. The associations between phytoestrogen supplementation and changes in serum high density lipoprotein, mmol/L



I-V fixed effect model; D+L random effect model. I-squared: Higgins's I2 represents the percentage of variation between the sample estimates that is due to heterogeneity rather than to sampling error. WMD, weighted mean difference; Mean difference refers to mean difference of changes between treatment groups. The size of data markers is proportional to the inverse of the variance of the effect estimate. P value comes from Q statistics.

Abbreviations: No. IG, number of women in intervention group; No. CG, number of women in control group

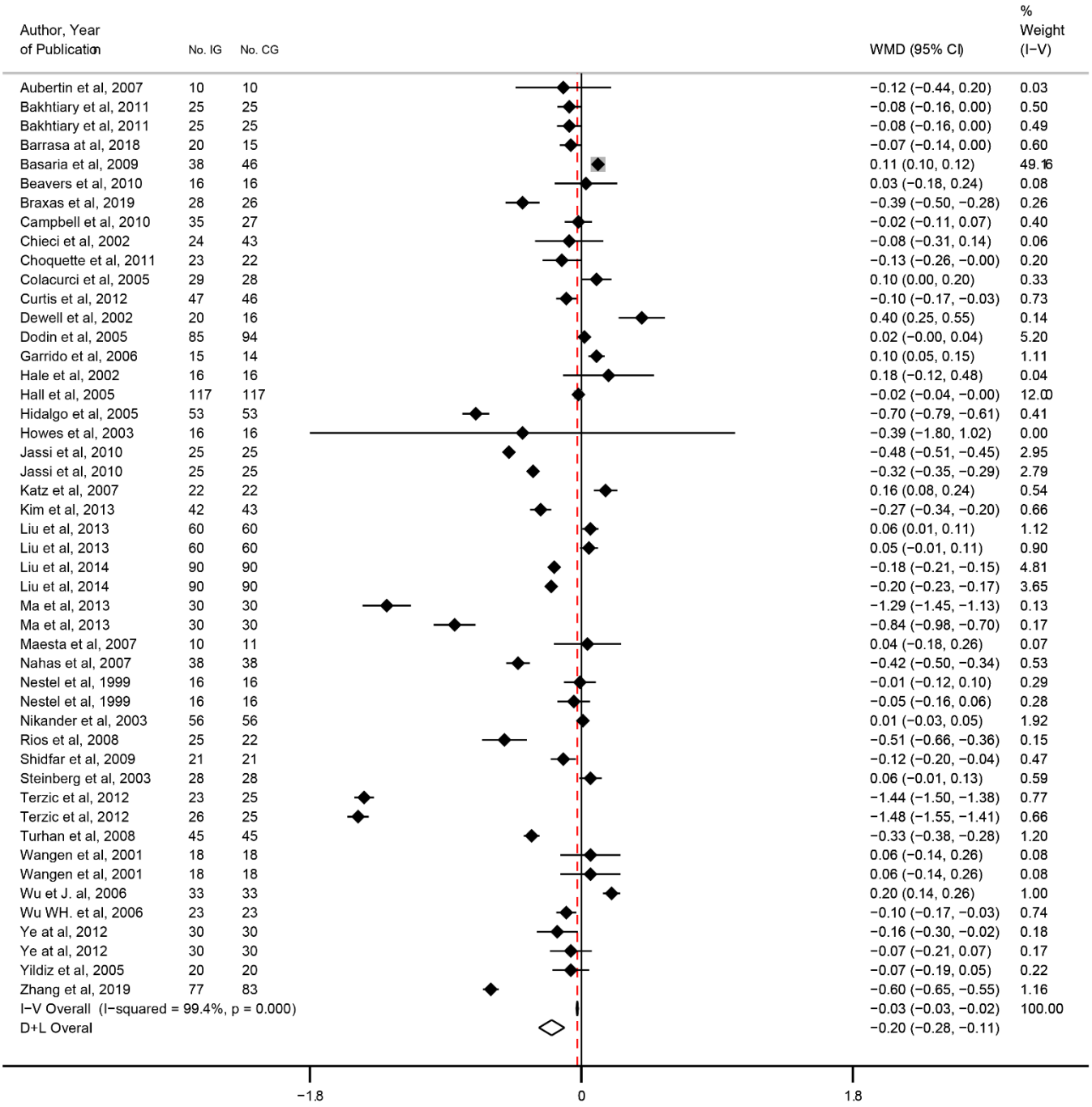
Supplementary Figure 4. The associations between phytoestrogen supplementation and changes in serum low density lipoprotein, mmol/L



I-V fixed effect model; D+L random effect model. I-squared: Higgins's I2 represents the percentage of variation between the sample estimates that is due to heterogeneity rather than to sampling error. WMD, weighted mean difference; Mean difference refers to mean difference of changes between treatment groups. The size of data markers is proportional to the inverse of the variance of the effect estimate. P value comes from Q statistics.

Abbreviations: No. IG, number of women in intervention group; No. CG, number of women in control group

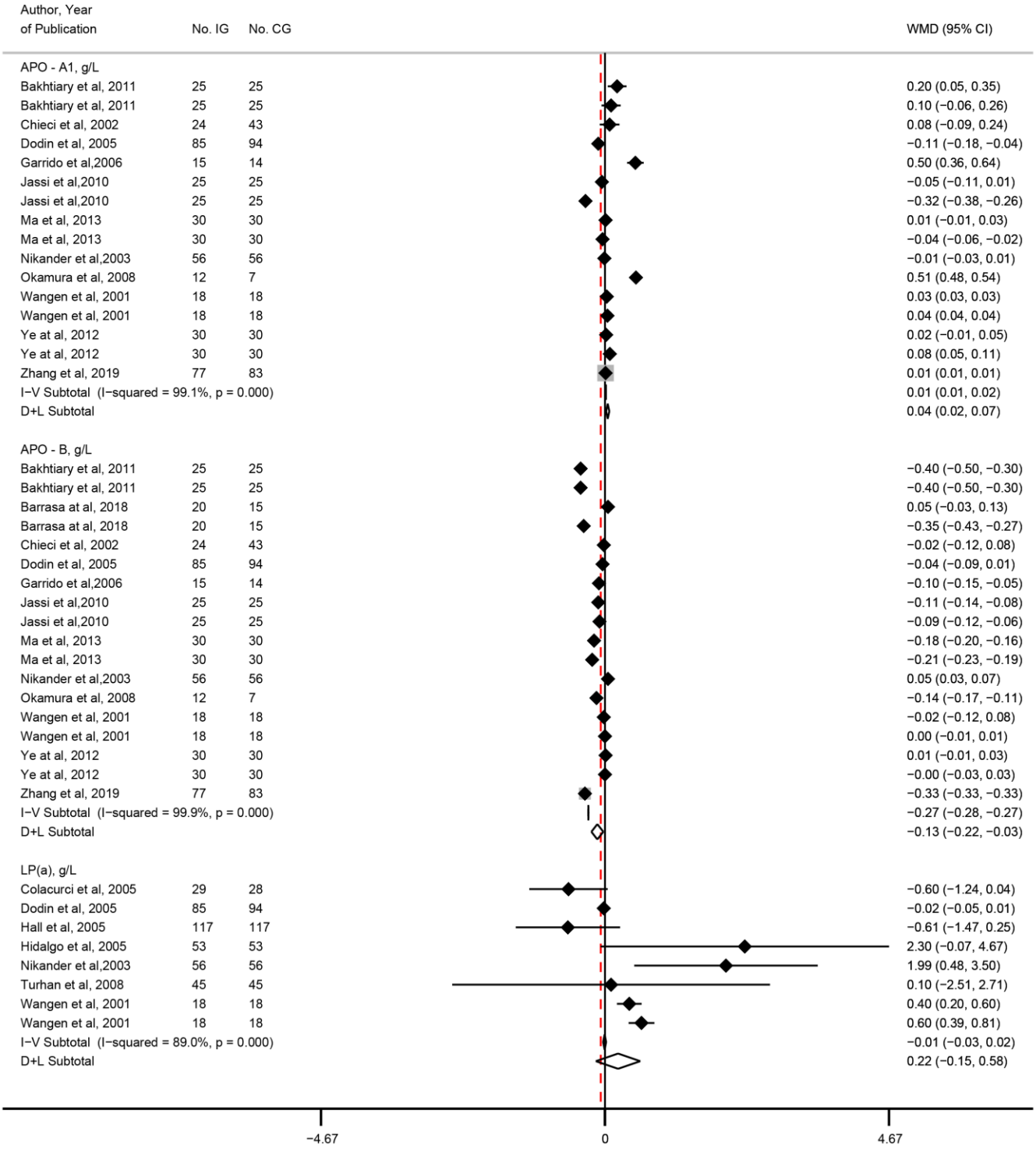
Supplementary Figure 5. The associations between phytoestrogen supplementation and changes in serum triglycerides, mmol/L



I-V fixed effect model; D+L random effect model. I-squared: Higgins's I2 represents the percentage of variation between the sample estimates that is due to heterogeneity rather than to sampling error. WMD, weighted mean difference; Mean difference refers to mean difference of changes between treatment groups. The size of data markers is proportional to the inverse of the variance of the effect estimate. P value comes from Q statistics.

Abbreviations: No. IG, number of women in intervention group; No. CG, number of women in control group

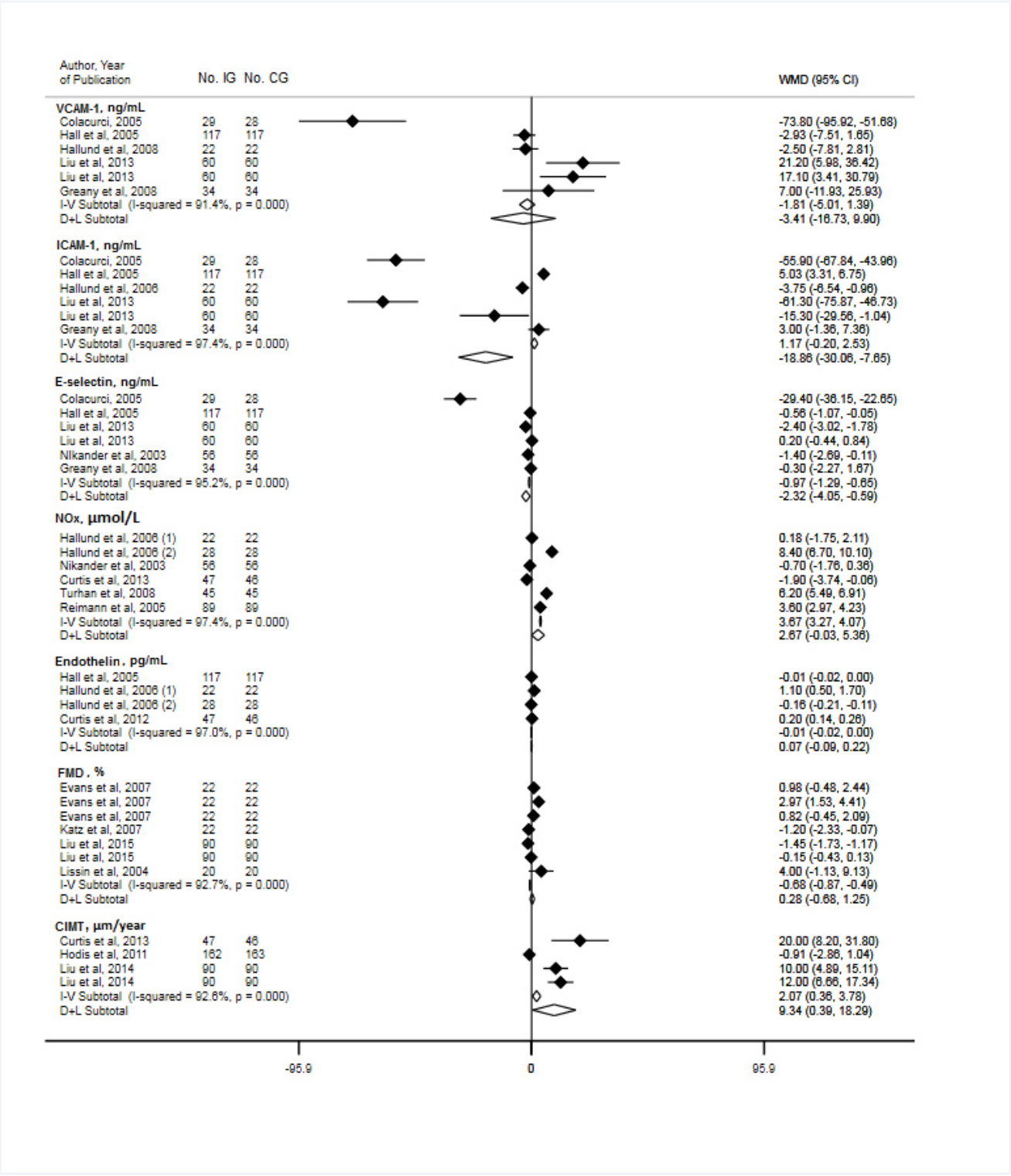
Supplementary Figure 6. The associations between phytoestrogen supplementation and lipoprotein a, apolipoprotein A-1 and apolipoprotein B



I-V fixed effect model; D+L random effect model. I-squared: Higgins's I2 represents the percentage of variation between the sample estimates that is due to heterogeneity rather than to sampling error. WMD, weighted mean difference; Mean difference refers to mean difference of changes between treatment groups. P value comes from Q statistics.

Abbreviations: Apo-A1, apolipoprotein A-1; Apo-B, apolipoprotein B; LP(a), lipoprotein a; No. IG, number of women in intervention group; No. CG, number of women in control group

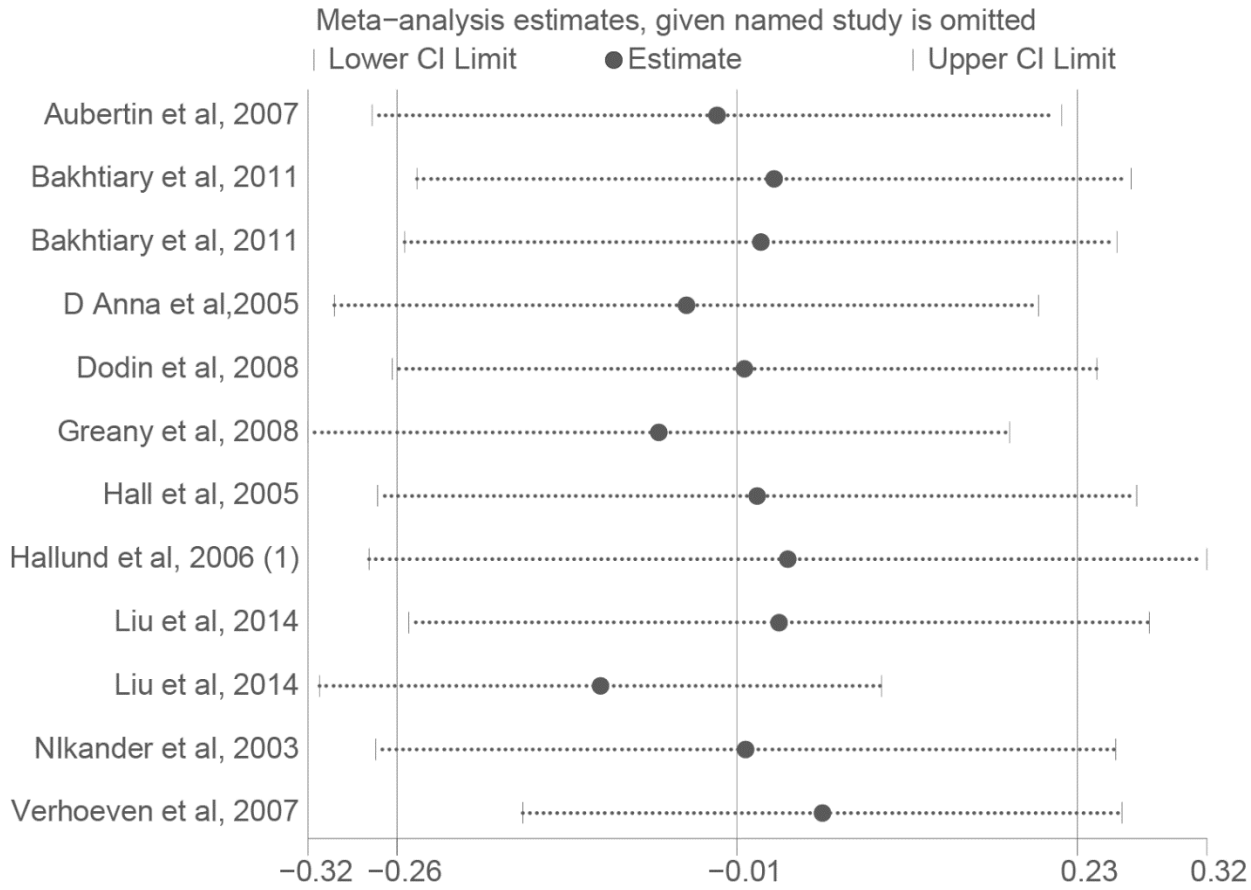
Supplementary Figure 7. The associations between phytoestrogen supplementation and cell adhesion molecules, endothelial metabolites, vascular function and carotid atherosclerosis



I-V fixed effect model; D+L random effect model. I-squared: Higgins's I2 represents the percentage of variation between the sample estimates that is due to heterogeneity rather than to sampling error. WMD, weighted mean difference; Mean difference refers to mean difference of changes between treatment groups. P value comes from Q statistics.

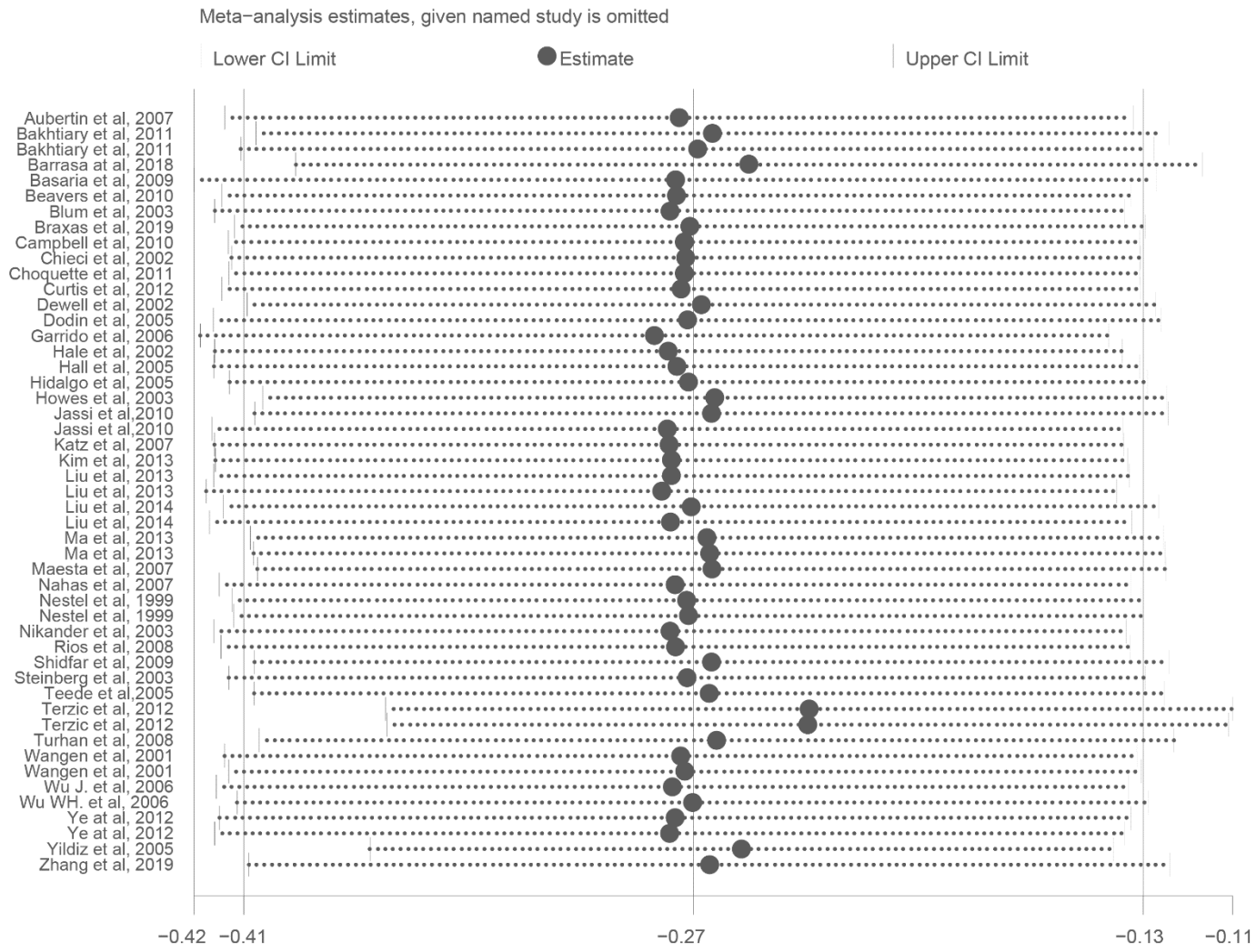
Abbreviations: CIMT, carotid intima media thickness; FMD, flow mediated diameter; ICAM-1, intercellular adhesion molecule; No. IG, number of women in intervention group; No. CG, number of women in control group; NOx, nitric oxide products; VCAM-1, vascular cell adhesion molecule 1

Supplementary Figure 8. Leave-one-out sensitivity analyses: serum C-reactive protein



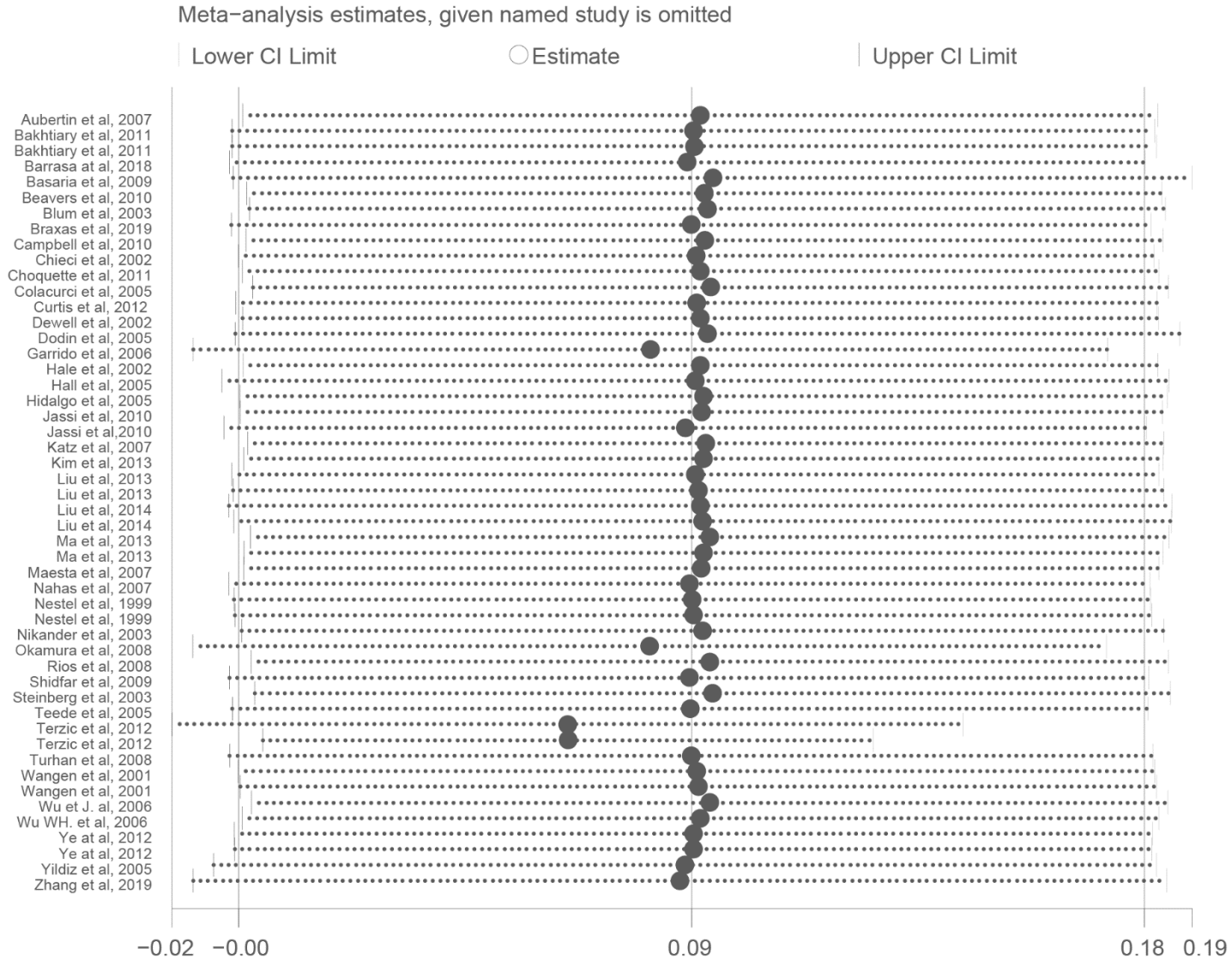
Leave-one-out sensitivity analysis for the effects of phytoestrogen supplementation on serum C-reactive protein as compared to control group. The vertical axis shows the omitted study, and the horizontal axis depicts the pooled non-standardized estimate (circle) when each study is removed, with 95% confidence intervals. The analyses were performed using *metaninf* command in STATA.

Supplementary Figure 9. Leave-one-out sensitivity analyses: serum total cholesterol



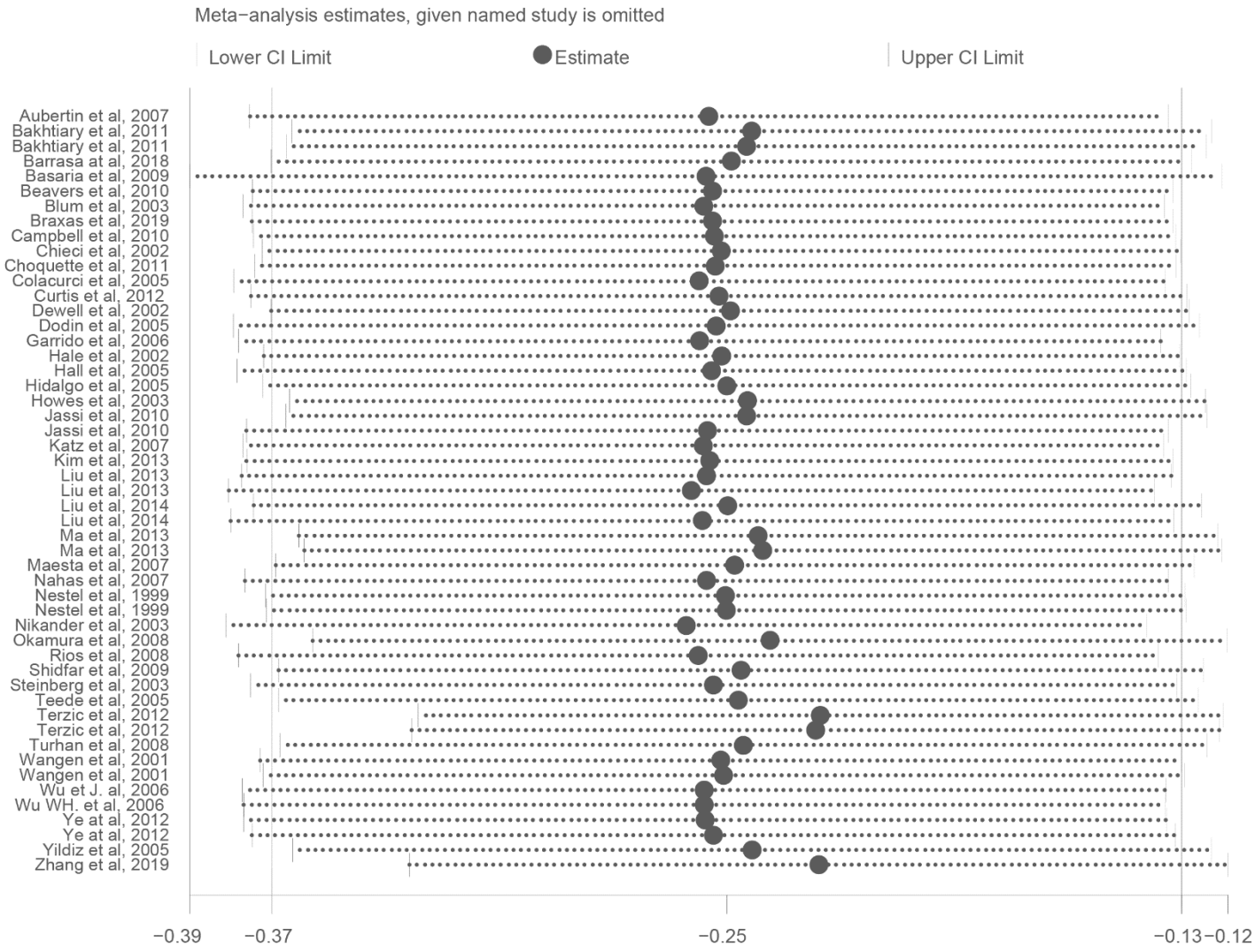
Leave-one-out sensitivity analysis for the effects of phytoestrogen supplementation on serum total cholesterol as compared to control group. The vertical axis shows the omitted study, and the horizontal axis depicts the pooled non-standardized estimate (circle) when each study is removed, with 95% confidence intervals. The analyses were performed using metaninf command in STATA.

Supplementary Figure 10. Leave-one-out sensitivity analyses: serum high-density lipoprotein cholesterol



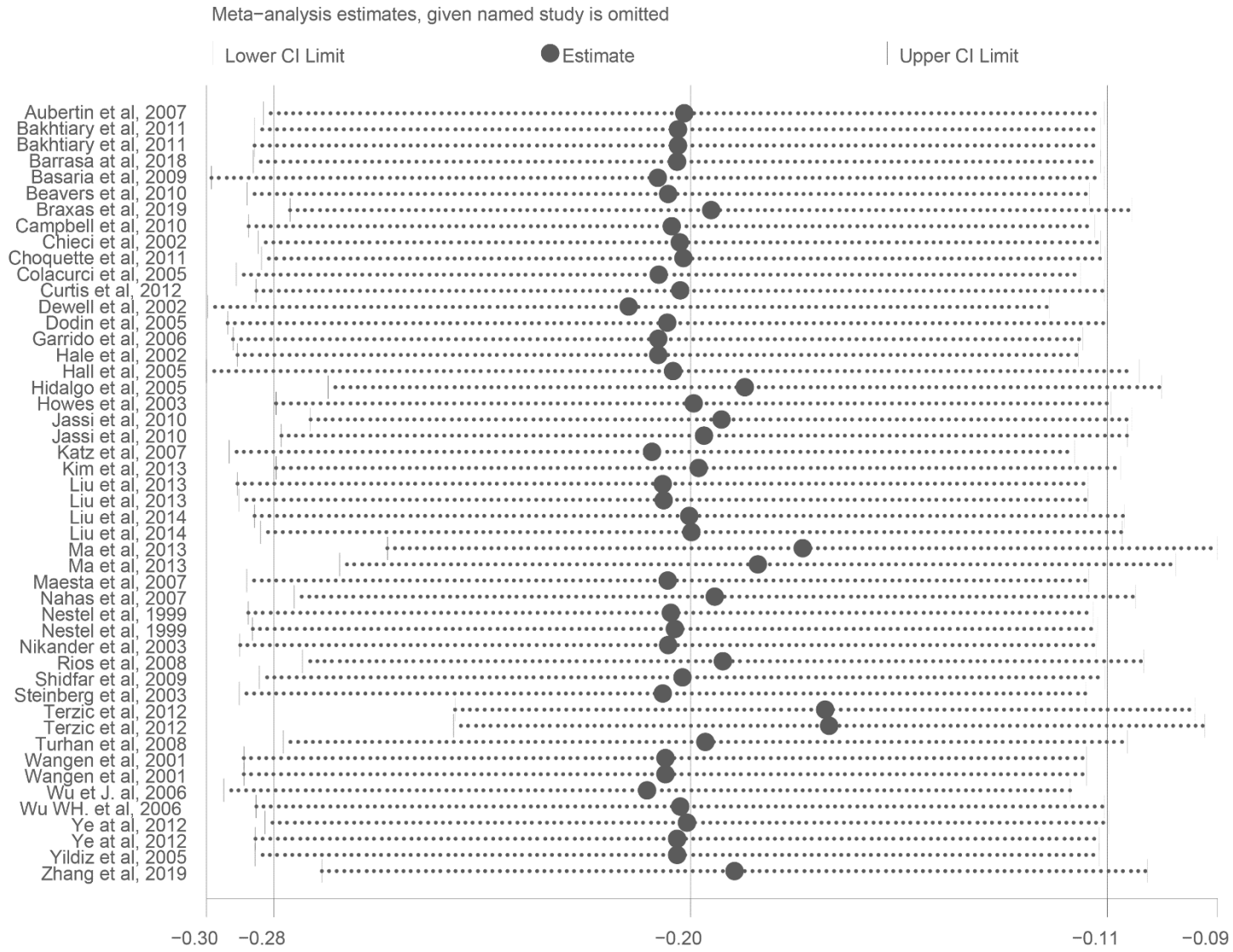
Leave-one-out sensitivity analysis for the effects of phytoestrogen supplementation on serum high-density lipoprotein cholesterol as compared to control group. The vertical axis shows the omitted study, and the horizontal axis depicts the pooled non-standardized estimate (circle) when each study is removed, with 95% confidence intervals. The analyses were performed using metaninf command in STATA.

Supplementary Figure 11. Leave-one-out sensitivity analyses: serum low-density lipoprotein cholesterol



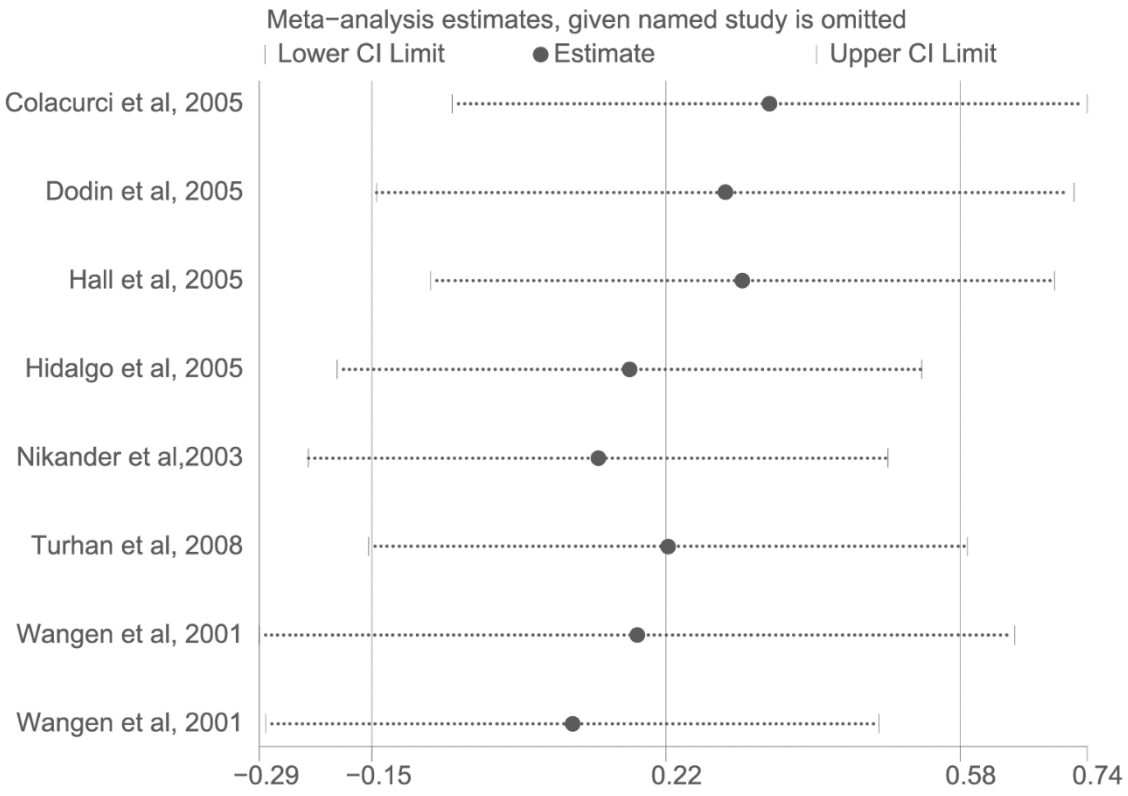
Leave-one-out sensitivity analysis for the effects of phytoestrogen supplementation on serum low-density lipoprotein cholesterol as compared to control group. The vertical axis shows the omitted study, and the horizontal axis depicts the pooled non-standardized estimate (circle) when each study is removed, with 95% confidence intervals. The analyses were performed using metaninf command in STATA.

Supplementary Figure 12. Leave-one-out sensitivity analyses: serum triglycerides



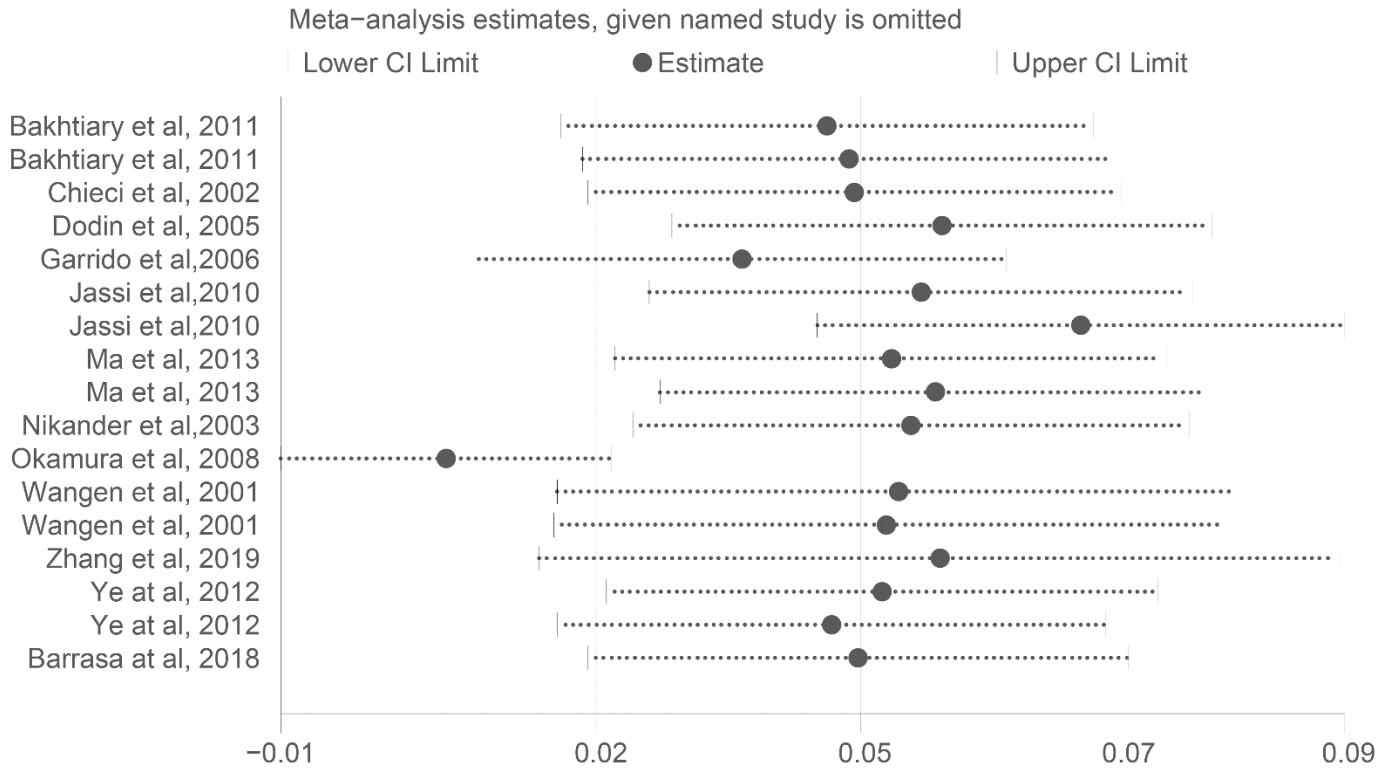
Leave-one-out sensitivity analysis for the effects of phytoestrogen supplementation on serum triglycerides as compared to control group. The vertical axis shows the omitted study, and the horizontal axis depicts the pooled non-standardized estimate (circle) when each study is removed, with 95% confidence intervals. The analyses were performed using metaninf command in STATA.

Supplementary Figure 13. Leave-one-out sensitivity analyses: serum lipoprotein a



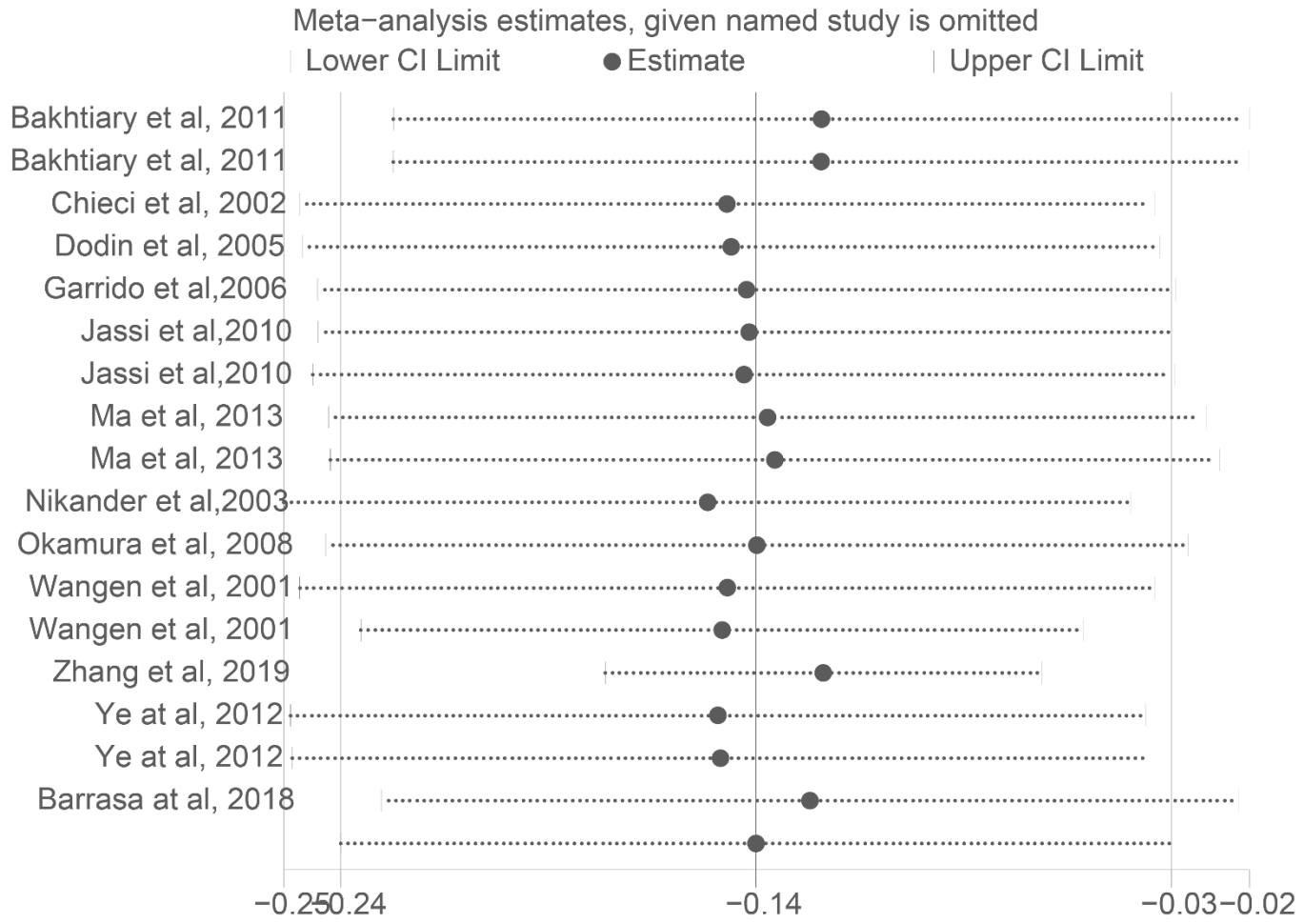
Leave-one-out sensitivity analysis for the effects of phytoestrogen supplementation on serum lipoprotein a as compared to control group. The vertical axis shows the omitted study, and the horizontal axis depicts the pooled non-standardized estimate (circle) when each study is removed, with 95% confidence intervals. The analyses were performed using metaninf command in STATA.

Supplementary Figure 14. Leave-one-out sensitivity analyses: serum apolipoprotein A-1



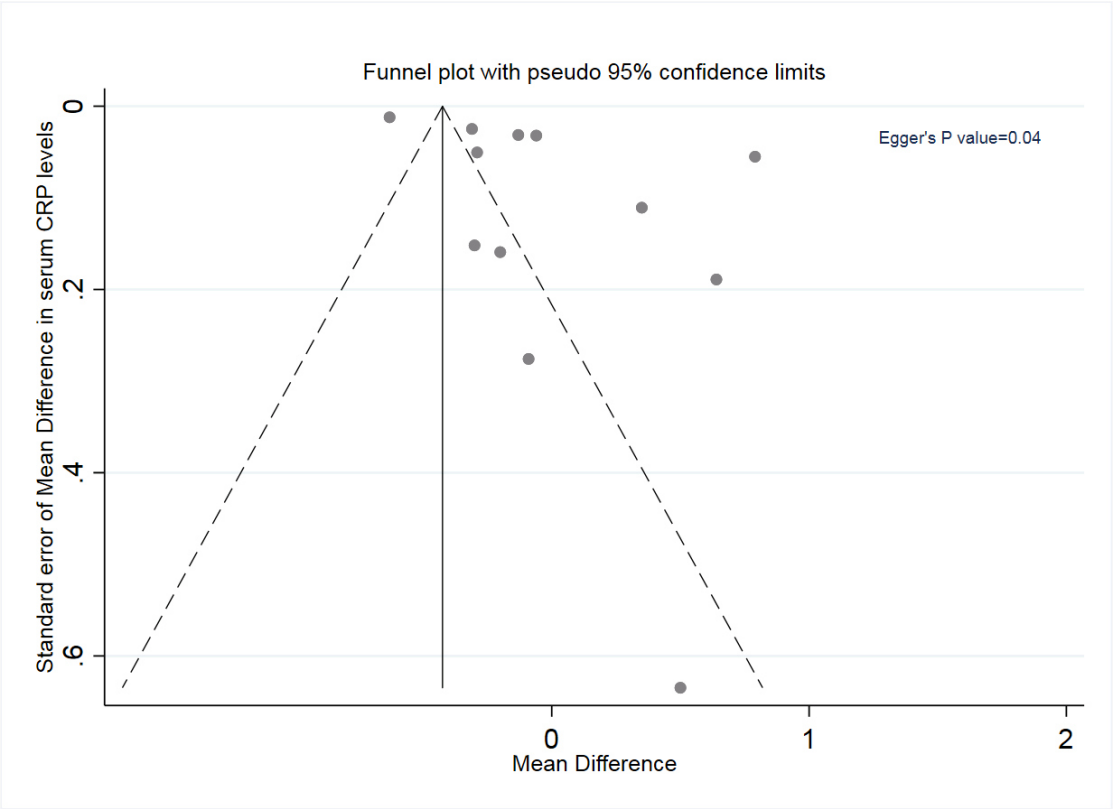
Leave-one-out sensitivity analysis for the effects of phytoestrogen supplementation on serum apolipoprotein A-1 as compared to control group. The vertical axis shows the omitted study, and the horizontal axis depicts the pooled non-standardized estimate (circle) when each study is removed, with 95% confidence intervals. The analyses were performed using metaninf command in STATA.

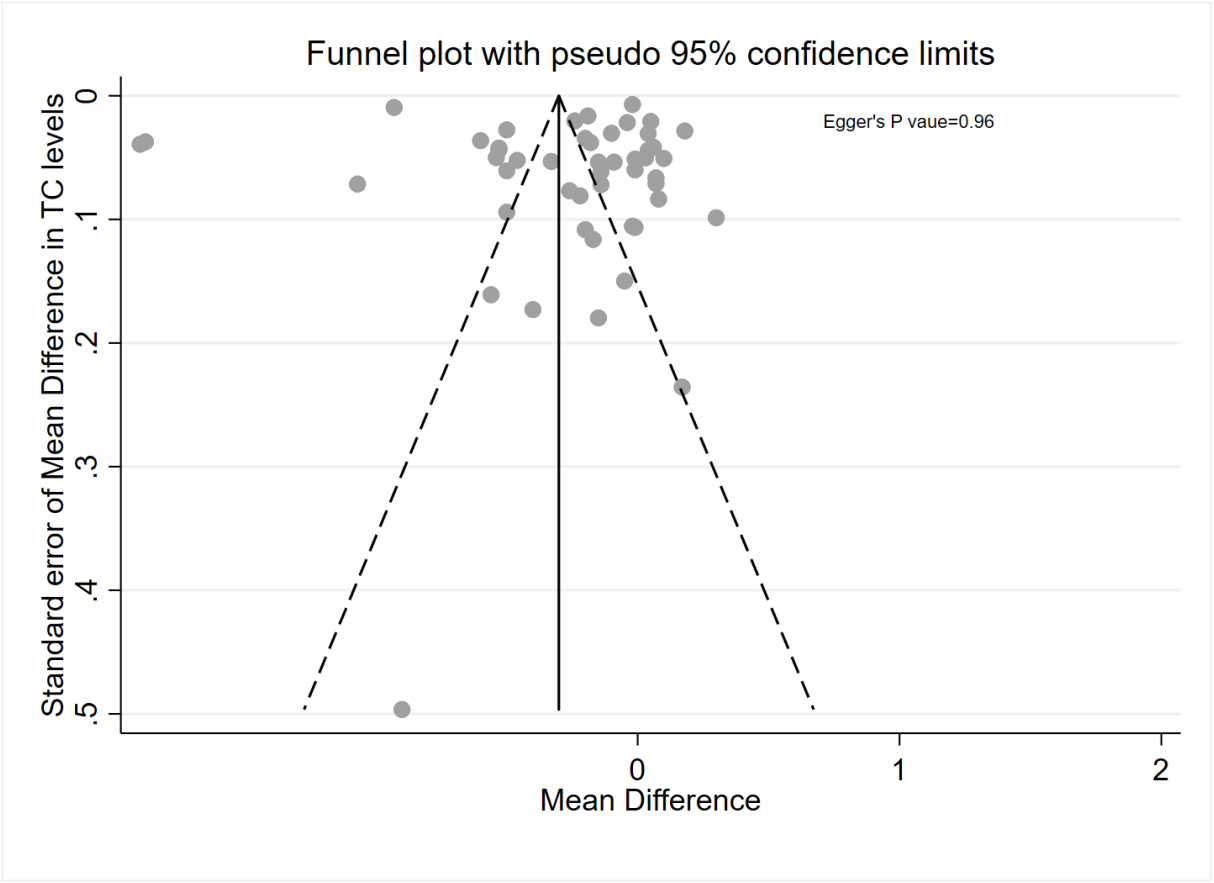
Supplementary Figure 15. Leave-one-out sensitivity analyses: serum apolipoprotein B

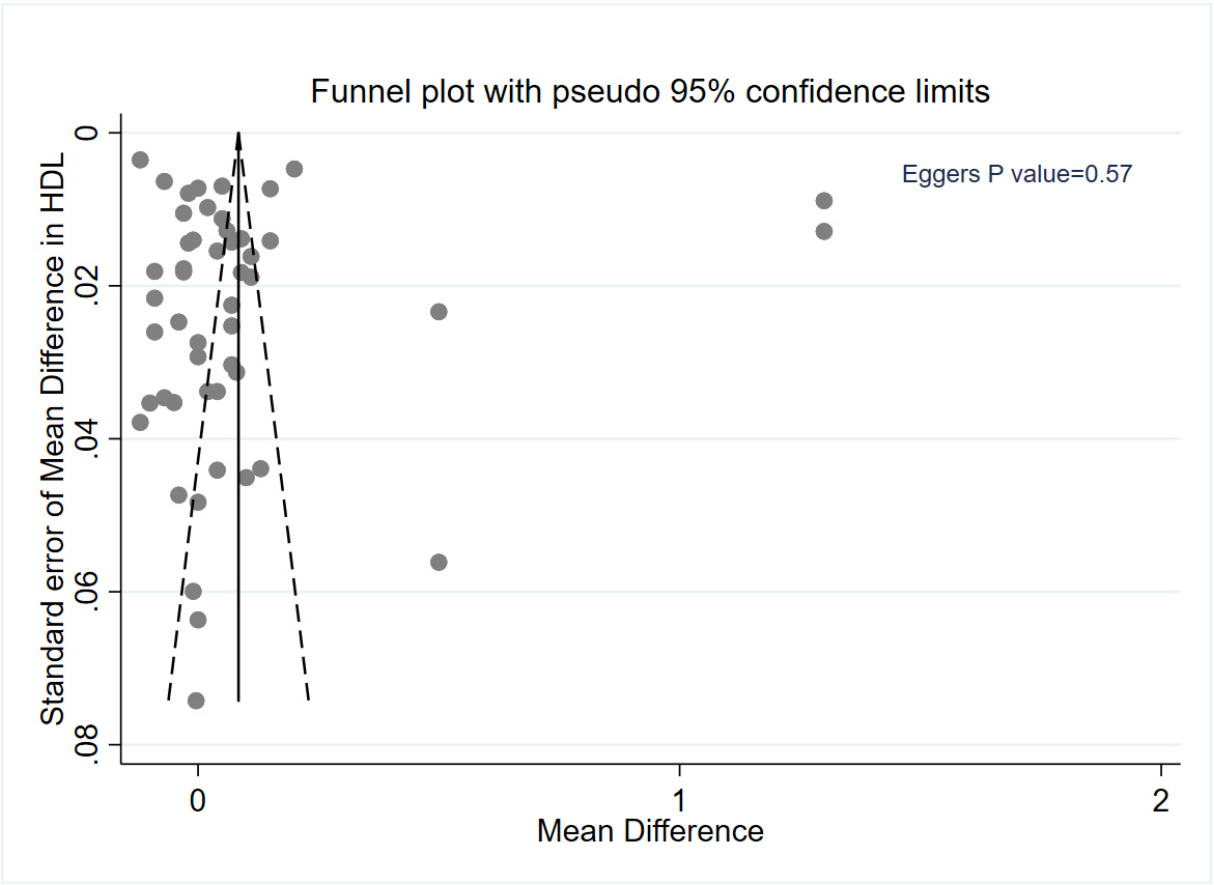


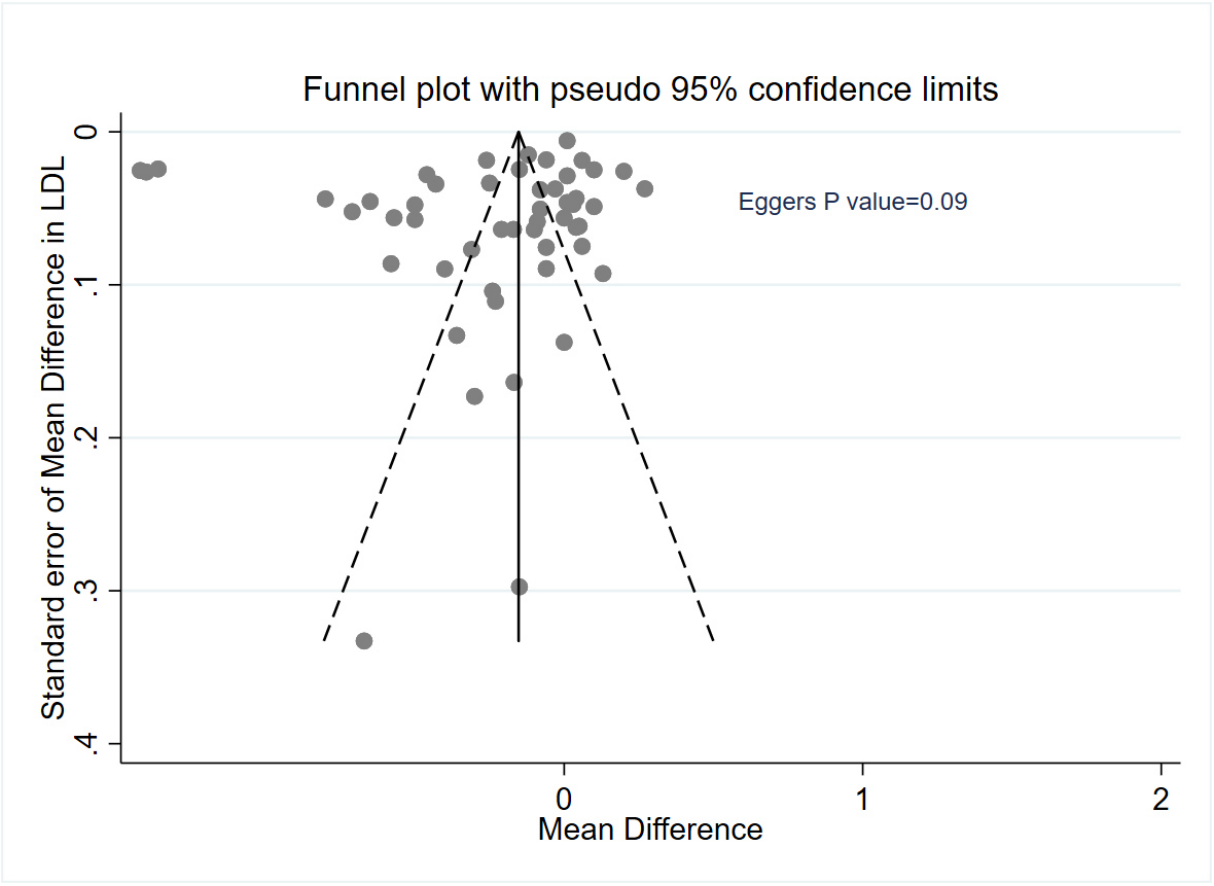
Leave-one-out sensitivity analysis for the effects of phytoestrogen supplementation on serum apolipoprotein B as compared to control group. The vertical axis shows the omitted study, and the horizontal axis depicts the pooled non-standardized estimate (circle) when each study is removed, with 95% confidence intervals. The analyses were performed using metaninf command in STATA.

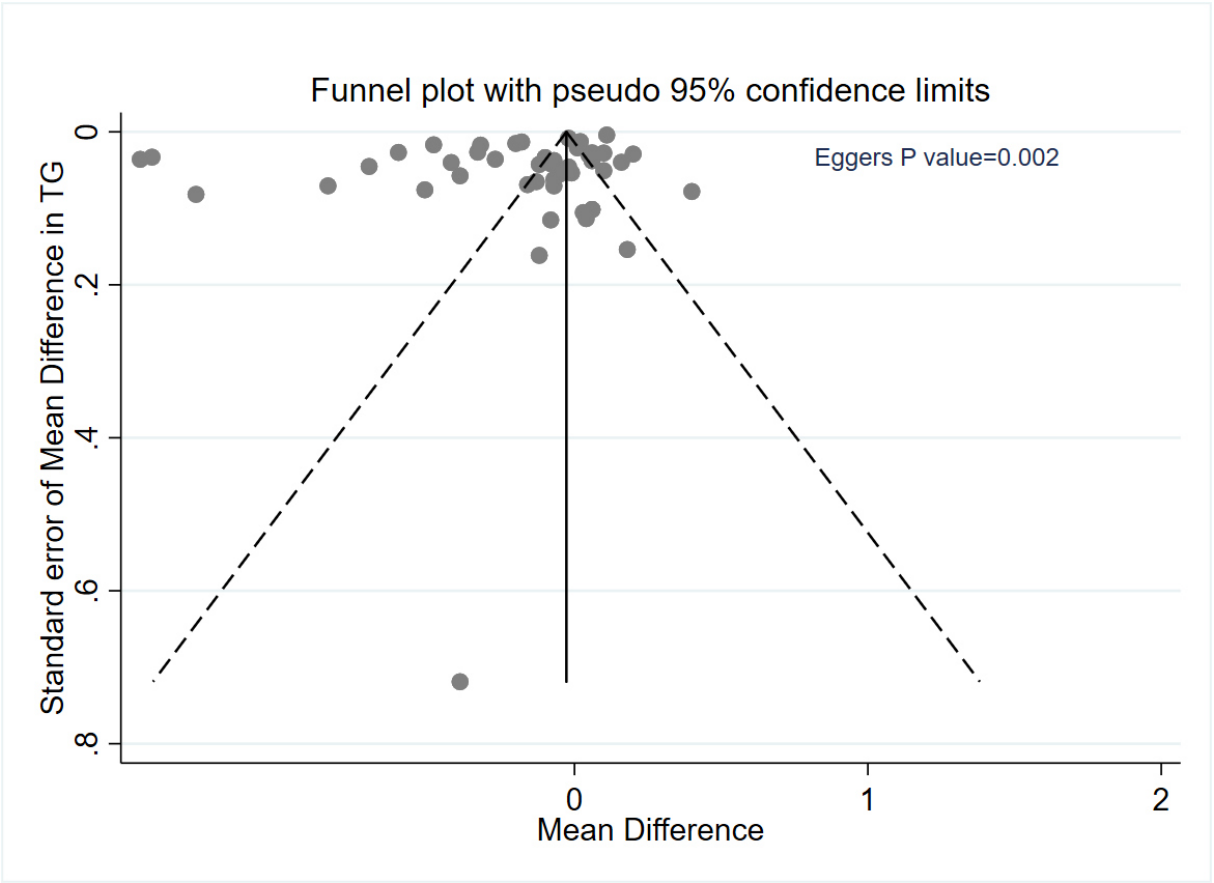
Supplementary Figure 16-23. Publication bias: CRP, TC, HDL, LDL, TG, LP(a), Apo A-1 and Apo B

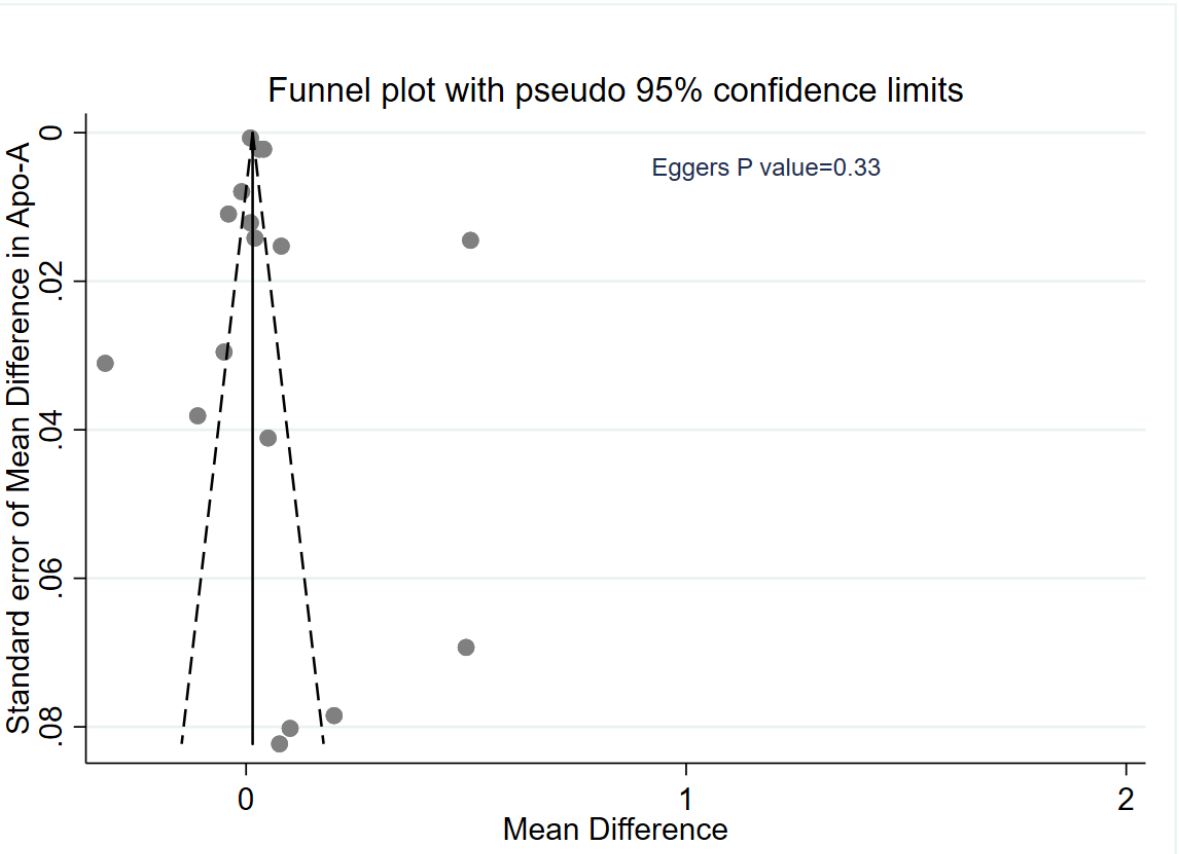


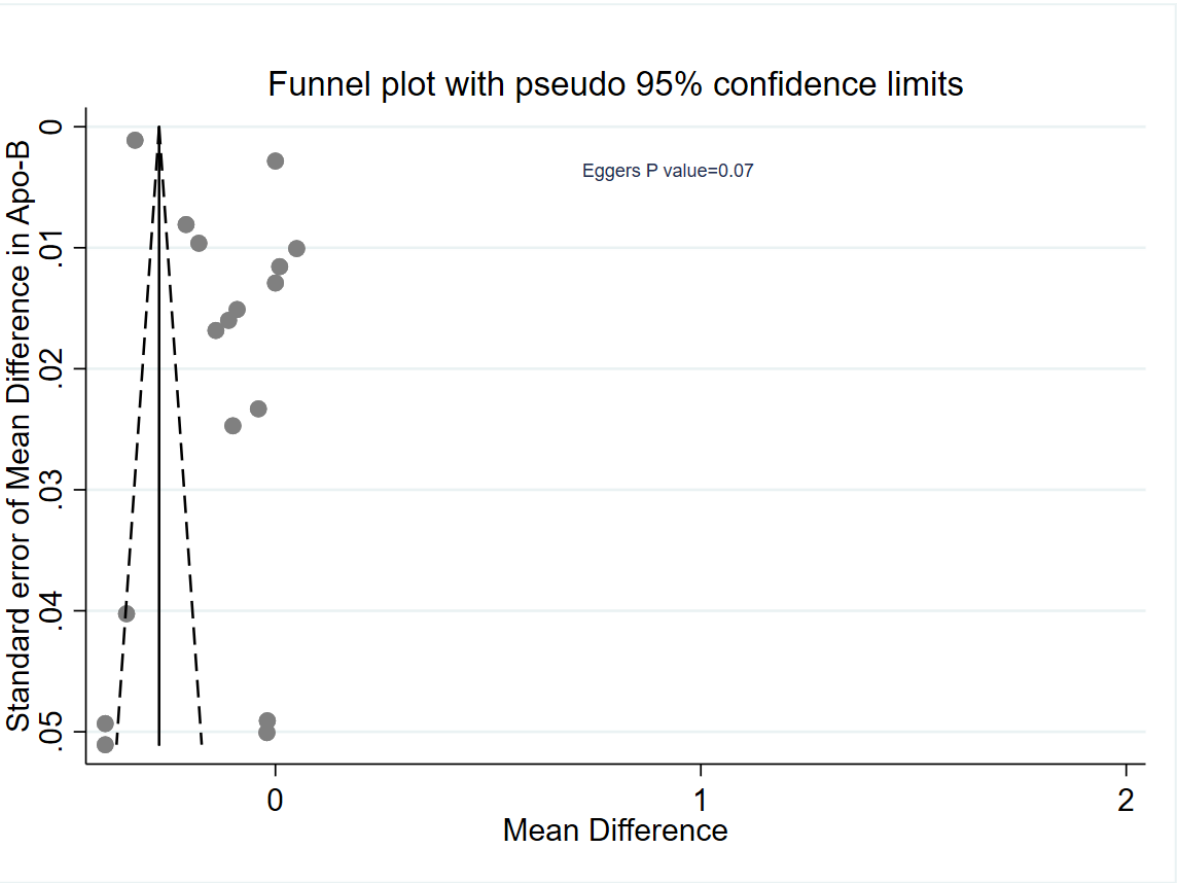

Funnel plot with pseudo 95% confidence limits
Egger's P vaue=0.96
Standard error of Mean Difference in TC levels
0
.1
.2
.3
.4
.5
0
1
2
Mean Difference

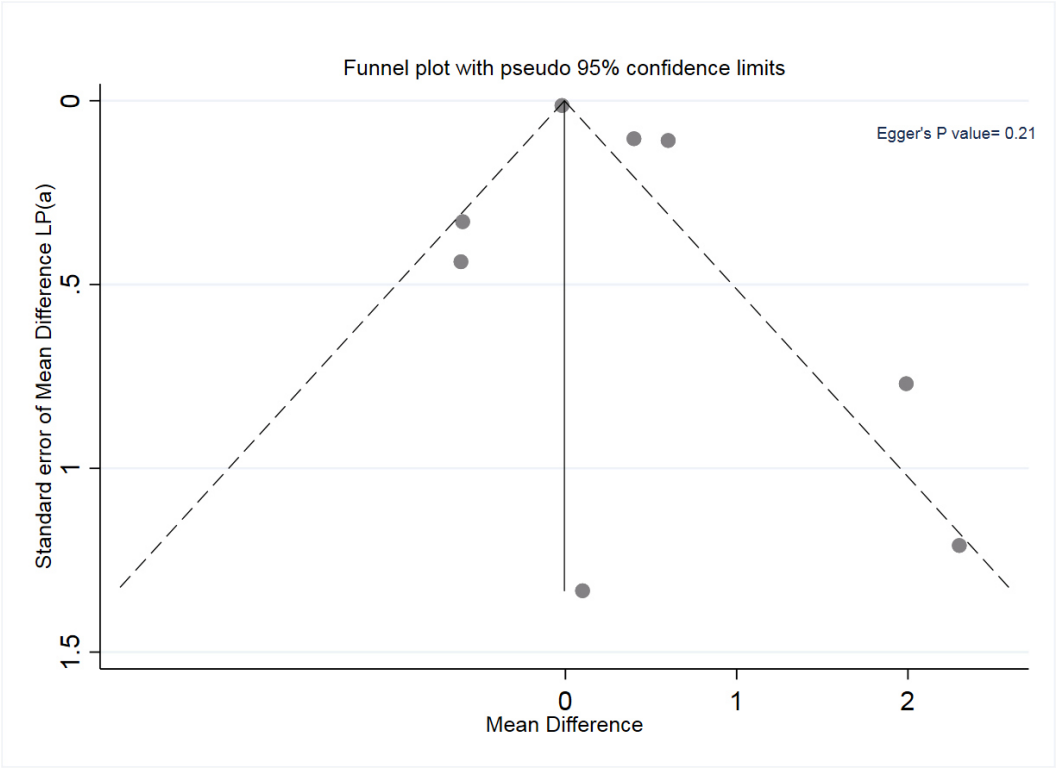

Funnel plot with pseudo 95% confidence limits
Eggers P value=0.57
Standard error of Mean Difference in HDL
0
.02
.04
.06
.08
0
1
2
Mean Difference


Funnel plot with pseudo 95% confidence limits
Eggers P value=0.09
Standard error of Mean Difference in LDL
0
.1
.2
.3
.4
0
1
2
Mean Difference


Funnel plot with pseudo 95% confidence limits
Eggers P value=0.002
Standard error of Mean Difference in TG
0
.2
.4
.6
.8
0
1
2
Mean Difference


Funnel plot with pseudo 95% confidence limits
Eggers P value=0.33
Standard error of Mean Difference in Apo-A
0
.02
.04
.06
.08
0
1
2
Mean Difference


Funnel plot with pseudo 95% confidence limits
Eggers P value=0.07
Standard error of Mean Difference in Apo-B
0
.01
.02
.03
.04
.05
0
1
2
Mean Difference


Funnel plot with pseudo 95% confidence limits
Egger's P value= 0.21
Standard error of Mean Difference LP(a)
0
.5
1
1.5
0
1
2
Mean Difference

References

1. Aubertin-Leheudre M, Lord C, Khalil A, Dionne IJ. Effect of 6 months of exercise and isoflavone supplementation on clinical cardiovascular risk factors in obese postmenopausal women: A randomized, double-blind study. Menopause. 2007;14(4):624-9.
2. Bakhtiary A, Yassin Z, Hanachi P, Rahmat A, Ahmad Z, Halalkhor S, et al. Evaluation of the oxidative stress and glycemic control status in response to soy in older women with the metabolic syndrome. Iran Red Crescent Med J. 2011;13(11):795-804.
3. Bakhtiari A, Hajian-Tilaki K, Omidvar S, Nasiri-Amiri F. Clinical and metabolic response to soy administration in older women with metabolic syndrome: a randomized controlled trial. Diabetology & metabolic syndrome. 2019;11:47.
4. Barrasa GRR, Gonzalez Canete N, Boasi LEV. Age of Postmenopause Women: Effect of Soy Isoflavone in Lipoprotein and Inflammation Markers. J Menopausal Med. 2018;24(3):176-82.
5. Basaria S, Wisniewski A, Dupree K, Bruno T, Song MY, Yao F, et al. Effect of high-dose isoflavones on cognition, quality of life, androgens, and lipoprotein in post-menopausal women. J Endocrinol Invest. 2009;32(2):150-5.
6. Beavers KM, Serra MC, Beavers DP, Cooke MB, Willoughby DS. Soymilk supplementation does not alter plasma markers of inflammation and oxidative stress in postmenopausal women. Nutr Res. 2009;29(9):616-22.
7. Beavers KM, Serra MC, Beavers DP, Hudson GM, Willoughby DS. The lipid-lowering effects of 4 weeks of daily soymilk or dairy milk ingestion in a postmenopausal female population. J Med Food. 2010;13(3):650-6.
8. Blum A, Lang N, Vigder F, Israeli P, Gumanovsky M, Lupovitz S, et al. Effects of soy protein on endothelium-dependent vasodilatation and lipid profile in postmenopausal women with mild hypercholesterolemia. Clin Invest Med. 2003;26(1):20-6.
9. Brandao LC, Hachul H, Bittencourt LR, Baracat EC, Tufik S, D'Almeida V. Effects of isoflavone on oxidative stress parameters and homocysteine in postmenopausal women complaining of insomnia. Biol Res. 2009;42(3):281-7.
10. Braxas H, Rafraf M, Karimi Hasanabad S, Asghari Jafarabadi M. Effectiveness of Genistein Supplementation on Metabolic Factors and Antioxidant Status in Postmenopausal Women With Type 2 Diabetes Mellitus. Can J Diabetes. 2019;43(7):490-7.
11. Campbell SC, Khalil DA, Payton ME, Arjmandi BH. One-year soy protein supplementation does not improve lipid profile in postmenopausal women. Menopause. 2010;17(3):587-93.
12. Charles C, Yuskavage J, Carlson O, John M, Tagalicud AS, Maggio M, et al. Effects of high-dose isoflavones on metabolic and inflammatory markers in healthy postmenopausal women. Menopause. 2009;16(2):395-400.
13. Chiechi LM, Secreto G, Vimercati A, Greco P, Venturelli E, Pansini F, et al. The effects of a soy rich diet on serum lipids: The Menfis randomized trial. Maturitas. 2002;41(2):97-104.
14. Choquette S, Riesco E, Cormier E, Dion T, Aubertin-Leheudre M, Dionne IJ. Effects of soya isoflavones and exercise on body composition and clinical risk factors of cardiovascular diseases in overweight postmenopausal women: A 6-month double-blind controlled trial. Br J Nutr. 2011;105(8):1199-209.
15. Crisafulli A, Altavilla D, Marini H, Bitto A, Cucinotta D, Frisina N, et al. Effects of the phytoestrogen genistein on cardiovascular risk factors in postmenopausal women. Menopause. 2005;12(2):186-92.
16. Colacurci N, Chiàntera A, Fornaro F, De Novellis V, Manzella D, Arciello A, et al. Effects of soy isoflavones on endothelial function in healthy postmenopausal women. Menopause. 2005;12(3):299-307.
17. Curtis PJ, Dhatariya K, Sampson M, Kroon PA, Potter J, Cassidy A. Chronic ingestion of flavan-3-ols and isoflavones improves insulin sensitivity and lipoprotein status and attenuates estimated 10-year CVD risk in medicated postmenopausal women with type 2 diabetes: A 1-year, double-blind, randomized,controlled trial. Diabetes Care. 2012;35(2):226-32.

18. Curtis PJ, Potter J, Kroon PA, Wilson P, Dhatariya K, Sampson M, et al. Vascular function and atherosclerosis progression after 1 y of flavonoid intake in statin-treated postmenopausal women with type 2 diabetes: A double-blind randomized controlled trial. Am J Clin Nutr. 2013;97(5):936-42.
19. D'Anna R, Baviera G, Corrado F, Cancellieri F, Crisafulli A, Squadrito F. The effect of the phytoestrogen genistein and hormone replacement therapy on homocysteine and C-reactive protein level in postmenopausal women. Acta Obstet Gynecol Scand. 2005;84(5):474-7.
20. Dewell A, Hollenbeck CB, Bruce B. The effects of soy-derived phytoestrogens on serum lipids and lipoproteins in moderately hypercholesterolemic postmenopausal women. J Clin Endocrinol Metab. 2002;87(1):118-21.
21. Dodin S, Lemay A, Jacques H, Légaré F, Forest JC, Mâsse B. The effects of flaxseed dietary supplement on lipid profile, bone mineral density, and symptoms in menopausal women: A randomized, double-blind, wheat germ placebo-controlled clinical trial. J Clin Endocrinol Metab. 2005;90(3):1390-7.
22. Dodin S, Cunnane SC, Mâsse B, Lemay A, Jacques H, Asselin G, et al. Flaxseed on cardiovascular disease markers in healthy menopausal women: a randomized, double-blind, placebo-controlled trial. Nutrition. 2008;24(1):23-30.
23. Evans M, Njike VY, Hoxley M, Pearson M, Katz DL. Effect of soy isoflavone protein and soy lecithin on endothelial function in healthy postmenopausal women. Menopause. 2007;14(1):141-9.
24. Garrido A, De la Maza MP, Hirsch S, Valladares L. Soy isoflavones affect platelet thromboxane A2 receptor density but not plasma lipids in menopausal women. Maturitas. 2006;54(3):270-6.
25. Greany KA, Nettleton JA, Wangen KE, Thomas W, Kurzer MS. Consumption of isoflavone-rich soy protein does not alter homocysteine or markers of inflammation in postmenopausal women. Eur J Clin Nutr. 2008;62(12):1419-25.
26. Hale G, Paul-Labrador M, Dwyer JH, Merz CN. Isoflavone supplementation and endothelial function in menopausal women. Clinical endocrinology. 2002;56(6):693-701.
27. Hall WL, Vafeiadou K, Hallund J, Bügel S, Koebnick C, Reimann M, et al. Soy-isoflavone-enriched foods and inflammatory biomarkers of cardiovascular disease risk in postmenopausal women: Interactions with genotype and equol production. Am J Clin Nutr. 2005;82(6):1260-8.
28. Hall WL, Vafeiadou K, Hallund J, Bugel S, Reimann M, Koebnick C, et al. Soy-isoflavone-enriched foods and markers of lipid and glucose metabolism in postmenopausal women: Interactions with genotype and equol production. Am J Clin Nutr. 2006;83(3):592-600.
29. Hallund J, Ravn-Haren G, Bugel S, Tholstrup T, Tetens I. A lignan complex isolated from flaxseed does not affect plasma lipid concentrations or antioxidant capacity in healthy postmenopausal women. J Nutr. 2006;136(1):112-6.
30. Hallund J, Tetens I, Bugel S, Tholstrup T, Bruun JM. The effect of a lignan complex isolated from flaxseed on inflammation markers in healthy postmenopausal women. Nutr Metab Cardiovasc Dis. 2008;18(7):497-502.
31. Hallund J, Bügel S, Tholstrup T, Ferrari M, Talbot D, Hall WL, et al. Soya isoflavone-enriched cereal bars affect markers of endothelial function in postmenopausal women. Br J Nutr. 2006;95(6):1120-6.
32. Hanachi P, Golkho S, Ahmadi A, Barantalab F. The Effect of Soymilk on Alkaline Phosphatase, Total Antioxidant Levels, and Vasomotor Symptoms in Menopause Women. Iranian Journal of Basic Medical Sciences. 2007;10(3):162-8.
33. Hidalgo LA, Chedraui PA, Morocho N, Ross S, San Miguel G. The effect of red clover isoflavones on menopausal symptoms, lipids and vaginal cytology in menopausal women: A randomized, double-blind, placebo-controlled study. Gynecol Endocrinol. 2005;21(5):257-64.
34. Hodis HN, MacK WJ, Kono N, Azen SP, Shoupe D, Hwang-Levine J, et al. Isoflavone soy protein supplementation and atherosclerosis progression in healthy postmenopausal women: A randomized controlled trial. Stroke. 2011;42(11):3168-75.
35. Howes JB, Tran D, Brillante D, Howes LG. Effects of dietary supplementation with isoflavones from red clover on ambulatory blood pressure and endothelial function in postmenopausal type 2 diabetes. Diabestes Obes Metab. 2003;5(5):325-32.

36. Jassi HK, Jain A, Arora S, Chitra R. Effect of soy proteins Vs soy isoflavones on lipid profile in postmenopausal women. Indian J Clin Biochem. 2010;25(2):201-7.
37. Katz DL, Evans MA, Njike VY, Hoxley ML, Nawaz H, Comerford BP, et al. Raloxifene, soy phytoestrogens and endothelial function in postmenopausal women. Climacteric. 2007;10(6):500-7.
38. Kim J, Lee H, Lee O, Lee KH, Lee YB, Young KD, et al. Isoflavone supplementation influenced levels of triglyceride and luteunizing hormone in Korean postmenopausal women. Arch Pharmacal Res. 2013;36(3):306-13.
39. Lissin LW, Oka R, Lakshmi S, Cooke JP. Isoflavones improve vascular reactivity in post-menopausal women with hypercholesterolemia. Vasc Med. 2004;9(1):26-30.
40. Liu ZM, Ho SC, Chen YM, Ho YP. The effects of isoflavones combined with soy protein on lipid profiles, C-reactive protein and cardiovascular risk among postmenopausal Chinese women. Nutr Metab Cardiovasc Dis. 2012;22(9):712-9.
41. Liu ZM, Ho SC, Chen YM, Woo J. Effect of soy protein and isoflavones on blood pressure and endothelial cytokines: A 6-month randomized controlled trial among postmenopausal women. J Hypertens. 2013;31(2):384-92.
42. Liu ZM, Ho SC, Chen YM, Ho S, To K, Tomlinson B, et al. Whole soy, but not purified daidzein, had a favorable effect on improvement of cardiovascular risks: a 6-month randomized, double-blind, and placebo-controlled trial in equol-producing postmenopausal women. Mol Nutr Food Res. 2014;58(4):709-17.
43. Liu ZM, Ho SC, Chen YM, Tomlinson B, Ho S, To K, et al. Effect of whole soy and purified daidzein on ambulatory blood pressure and endothelial function--a 6-month double-blind, randomized controlled trial among Chinese postmenopausal women with prehypertension. Eur J Clin Nutr. 2015;69(10):1161-8.
44. Ma D, Taku K, Zhang Y, Jia M, Wang Y, Wang P. Serum lipid-improving effect of soyabean β-conglycinin in hyperlipidaemic menopausal women. Br J Nutr. 2013;110(9):1680-4.
45. Maesta N, Nahas EAP, Nahas-Neto J, Orsatti FL, Fernandes CE, Traiman P, et al. Effects of soy protein and resistance exercise on body composition and blood lipids in postmenopausal women. Maturitas. 2007;56(4):350-8.
46. Nahas EA, Nahas-Neto J, Orsatti FL, Carvalho EP, Oliveira ML, Dias R. Efficacy and safety of a soy isoflavone extract in postmenopausal women: a randomized, double-blind, and placebo-controlled study. Maturitas. 2007;58(3):249-58.
47. Nestel PJ, Pomeroy S, Sally K, Komesaroff P, Behrsing J, Cameron JD, et al. Isoflavones from red clover improve systemic arterial compliance but not plasma lipids in menopausal women. J Clin Endocrinol Metab. 1999;84(3):895-8.
48. Nikander E, Metsa-Heikkila M, Tiitinen A, Ylikorkala O. Evidence of a lack of effect of a phytoestrogen regimen on the levels of C-reactive protein, E-selectin, and nitrate in postmenopausal women. J Clin Endocrinol Metab. 2003;88(11):5180-5.
49. Nikander E, Tiitinen A, Laitinen K, Tikkanen M, Ylikorkala O. Effects of isolated isoflavonoids on lipids, lipoproteins, insulin sensitivity, and ghrelin in postmenopausal women. J Clin Endocrinol Metab. 2004;89(7):3567-72.
50. Okamura S, Sawada Y, Satoh T, Sakamoto H, Saito Y, Sumino H, et al. Pueraria Mirifica phytoestrogens improve dyslipidemia in postmenopausal women probably by activating estrogen receptor subtypes. Tohoku J Exp Med. 2008;216(4):341-51.
51. Reimann M, Dierkes J, Carlsohn A, Talbot D, Ferrari M, Hallund J, et al. Consumption of soy isoflavones does not affect plasma total homocysteine or asymmetric dimethylarginine concentrations in healthy postmenopausal women. J Nutr. 2006;136(1):100-5.
52. Rios DRA, Rodrigues ET, Cardoso APZ, Montes MBA, Franceschini SA, Toloi MRT. Lack of effects of isoflavones on the lipid profile of Brazilian postmenopausal women. Nutrition. 2008;24(11-12):1153-8.
53. Ryan-Borchers TA, Park JS, Chew BP, McGuire MK, Fournier LR, Beerman KA. Soy isoflavones modulate immune function in healthy postmenopausal women. Am J Clin Nutr. 2006;83(5):1118-25.

54. Shidfar F, Ehramphosh E, Heydari I, Haghighi L, Hosseini S, Shidfar S. Effects of soy bean on serum paraoxonase 1 activity and lipoproteins in hyperlipidemic postmenopausal women. Int J Food Sci Nutr. 2009;60(3):195-205.
55. Steinberg FM, Guthrie NL, Villablanca AC, Kumar K, Murray MJ. Soy protein with isoflavones has favorable effects on endothelial function that are independent of lipid and antioxidant effects in healthy postmenopausal women. Am J Clin Nutr. 2003;78(1):123-30.
56. Teede HJ, Dalais FS, Kotsopoulos D, McGrath BP, Malan E, Gan TE, et al. Dietary soy containing phytoestrogens does not activate the hemostatic system in postmenopausal women. J Clin Endocrinol Metab. 2005;90(4):1936-41.
57. Terzic M, Micic J, Dotlic J, Maricic S, Mihailovic T, Knezevic N. Impact of Phytoestrogens on Serum Lipids in Postmenopausal Women. Geburtshilfe Frauenheilkd. 2012;72(6):527-31.
58. Turhan N, Duvan C, Bokan F, Onaran Y. Effect of isoflavone on plasma nitrite/nitrate, homocysteine, and lipid levels in Turkish women in the early postmenopausal period: a randomized controlled trial. Turk J Med Sci. 2009;39(3): 367-75.
59. Verhoeven MO, Teerlink T, Kenemans P, Zuijdgeest-van Leeuwen SD, van der Mooren MJ. Effects of a supplement containing isoflavones and Actaea racemosa L. on asymmetric dimethylarginine, lipids, and C-reactive protein in menopausal women. Fertility and sterility. 2007;87(4):849-57.
60. Wangen KE, Duncan AM, Xu X, Kurzer MS. Soy isoflavones improve plasma lipids in normocholesterolemic and mildly hypercholesterolemic postmenopausal women. Am J Clin Nutr. 2001;73(2):225-31.
61. Wu J, Oka J, Higuchi M, Tabata I, Toda T, Fujioka M, et al. Cooperative effects of isoflavones and exercise on bone and lipid metabolism in postmenopausal Japanese women: A randomized placebo-controlled trial. Metab Clin Exp. 2006;55(4):423-33.
62. Wu WH, Kang YP, Wang NH, Jou HJ, Wang TA. Sesame ingestion affects sex hormones, antioxidant status, and blood lipids in postmenopausal women. J Nutr. 2006;136(5):1270-5.
63. Ye YB, Wang ZL, Zhuo SY, Lu W, Liao HF, Verbruggen M, et al. Soy germ isoflavones improve menopausal symptoms but have no effect on blood lipids in early postmenopausal Chinese women: A randomized placebo-controlled trial. Menopause. 2012;19(7):791-8.
64. Yildiz MF, Kumru S, Godekmerdan A, Kutlu S. Effects of raloxifene, hormone therapy, and soy isoflavone on serum high-sensitive C-reactive protein in postmenopausal women. Int J Gynecol Obstet. 2005;90(2):128-33.
65. Zhang T, Chi XX. The effect of genistein on lipid levels and LDLR, LXRalpha and ABCG1 expression in postmenopausal women with hyperlipidemia. Diabetology & metabolic syndrome. 2019;11:111.
66. Higgins JPT GSe. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org. .
67. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC medical research methodology. 2005;5:13.