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Phytoestrogen supplementation and body composition in postmenopausal women: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Phytoestrogen-based medications are commonly used by menopausal women, and especially by obese postmenopausal women, to relieve menopausal symptoms. Substitution of animal with soy protein is often used in weight loss regimens, yet the effect of phytoestrogens, the main constituent of soy foods, on body composition is not completely understood. We conducted a systematic review and meta-analysis to investigate the associations between phytoestrogen supplementation and body weight and the main parameters of body composition in postmenopausal women. A literature search was done using 5 electronic databases from inception to April 2018. Randomized controlled trials (RCTs) with postmenopausal women comparing phytoestrogen supplementation followed by usual diet and placebo were included in the present meta-analysis. From 5932 references, we identified 23 RCTs that met our inclusion criteria, with a total of 1880 postmenopausal women. No association was observed between phytoestrogen supplementation and body weight, body mass index, waist and hip circumference, total fat mass or percentage of body fat. However, the use of phytoestrogens supplementation was associated with a slight decrease in waist-hip ratio; the pooled mean difference was −0.01 cm (95%CI: −0.01 to −0.006). In subgroup analysis, we found a modest decrease in body weight with phytoestrogens supplementation compared with placebo in healthy postmenopausal women [pooled mean difference of changes −0.28 kg (95%CI: −0.52 to −0.04)] and in RCTs with a median number of participants of 66 or less [pooled mean difference of changes −0.49 kg (95%CI: −0.87 to −0.11)]. In contrast, phytoestrogen supplementation was associated with increased body weight in postmenopausal women with preexisting metabolic disorders (prediabetes, type 2 diabetes, prehypertension and hyperlipidemia) [pooled mean difference of changes: 0.78 kg (95%CI: 0.53–1.03)]. In addition, there were some indications that some types of phytoestrogens, such as daidzein, but not soy products or isoflavone mix, could lead to modest adverse changes in body composition in menopausal women. Therefore, future studies should investigate the potential adverse effects of phytoestrogen supplementation on body composition among postmenopausal women.

Abbreviations: BMI, body mass index; FM, fat mass; HC, hip circumference; MHT, menopausal hormone therapy; PBF, percentage of body fat; RCT, randomized controlled trial; T2D, type 2 diabetes; WC, waist circumference; WHR, waist to hip ratio

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1. Introduction

Menopause is considered as the end of woman's reproductive life, generally defined as "cessation" of menstrual periods for twelve consecutive months [1]. Menopausal transition is characterized by hormonal disturbances, irregular menstrual periods and presence of menopausal symptoms [1]. The most challenging menopausal symptoms include hot flashes and night sweats, with 50.3%–82.1% of postmenopausal reporting either mild, moderate or severe vasomotor symptoms [2,3]. In women, aging and menopause-induced estrogen deficiency could result in an increase in body weight and may lead to abdominal fat accumulation and decrease in lean mass during menopausal transition [4]. Overweight and obese menopausal women may also tend to have more prevalent [8] and more severe menopausal symptoms [5–8]. Thus, menopausal hormone therapy (MHT) remains the most effective treatment for menopausal vasomotor symptoms [9]. However, given the potentially undesirable health consequences of hormone therapy on cardiovascular health and breast cancer risk, the number of women choosing plant based-therapies as an alternative to treat menopausal symptoms is increasing [10].

The most commonly used herbal therapies may include "over the counter" phytoestrogen supplements, such as dietary soy isoflavones and soy extracts and herbal remedies such as red clover and black cohosh [10]. Phytoestrogens are a group of biologically active plant-derived compounds with estrogen-like properties [11]. Isoflavones (genisten and diadzein) and lignans are the most used phytoestrogens; while isoflavones can be abundantly found in soybeans, lignans are found in legumes, vegetables, fruits, flaxseed and whole grains [11]. Recent meta-analysis of clinical trials showed that specific phytoestrogen supplementation led to relief of menopausal symptoms [10]. Nevertheless, there is inconsistent evidence whether phytoestrogens could additionally help to reduce body weight and counteract the adverse changes that may occur in body composition in women after menopause. While few studies indicated that phytoestrogens may lead to modest improvements in body weight and the other parameters of body composition [12–14], there were few studies raising concerns that phytoestrogens could lead to adverse body composition changes, such as increase in weight [15–18] and body mass index (BMI) [16,18–20]. A meta-analysis of nine randomized trials (conducted in 2013) has suggested that isoflavone supplementation might reduce the body weight [21]. However, this study was limited only to non-Asian postmenopausal women and by investigating only the changes in body weight and not the other parameters of body composition. Furthermore, only trials that investigated solely isoflavone supplementation, and not the other types of phytoestrogens, were included in that review.

Therefore, this comprehensive systematic review and meta-analysis of intervention studies aimed to evaluate the association between phytoestrogen supplementation followed with regular/normocaloric diet and body composition in postmenopausal women.

2. Methods

2.1. Data sources and search strategy

The Cochrane Handbook for Systematic Reviews of Interventions and PRISMA Statement were used to guide the conduct and reporting of this review [22]. A literature search was done using 5 electronic databases (Medline via Ovid, EMBASE, Web of Science Core Collection, Cochrane CENTRAL via Wiley and Google Scholar) from inception to April 2018 (date last searched). Additionally, we searched the reference lists of the included studies and relevant reviews. Details on the search strategy are provided in Supplemental Table 1.

2.2. Study selection and data extraction

Studies were included if they met the following inclusion criteria: (i) were randomized placebo-controlled trials (ii) reported associations of phytoestrogen supplementation with total body weight, total fat mass (FM), percentage of body fat (PBF), BMI, waist circumference (WC), and waist to hip ratio (WHR), (iii) were performed among postmenopausal women and (iv) investigated phytoestrogen supplementation in intervention arm alone. RCTs investigated combination of exposures (e.g. hypocaloric diet or exercise with phytoestrogen supplementation) were not included in this study. Additionally, as we were interested to evaluate overall effect of phytoestrogens on body weight (and not its effect on weight loss), we decided to include RCTs irrespectively of the study aim; therefore, all eligible RCTs that reported baseline and end of study information on outcomes of interest were included in this review. Two reviewers independently evaluated the titles and abstracts according to the inclusion and exclusion criteria. For each potentially eligible study, two reviewers assessed the full-text. In cases of disagreement, a decision was made by consensus or, if necessary, a third reviewer was consulted. A predesigned data extraction form was used to collect relevant information.

2.3. Assessing the risk of bias

The risk of bias within each individual study was evaluated by two reviewers. To assess the quality of RCTs, "The Cochrane Collaboration's tool" for assessing risk of bias was used [23]. Studies were judged to be at lower high risk of bias based on criteria to evaluate random sequence generation, allocation concealment, blinding of participants/personnel and outcome assessment, incomplete outcome data and selective reporting [23]. RCTs were considered to be in low risk of bias, if allocation concealment, blinding of participants and outcome assessors were all coded "*yes*", if a compliance assessment was done, and the number of dropouts and reasons for dropout were reported, otherwise the RCTs were considered to be at high risk of bias. If the risk of bias couldn't be determined in any of the segments (e.g. information not provided) the risk of bias was classified as unknown (Supplemental Table 2).

2.4. Data synthesis and analysis

Summary outcomes measures were presented as mean differences (intervention minus control) of the treatment effects (differences in outcomes at the end of trial) between treatment groups in body weight, BMI, WC, HC, HC, FM and PBF. Estimates of weighted mean differences (WMDs) and 95% CIs were obtained using random-effect model. In case of cross-over trials, the data from the first period only were used. In addition, for sensitivity analysis, the estimates were reported using fixed effect models as shown in the forest plots. Heterogeneity was quantified using the I^2 statistic, classified as low ($I^2 \leq 25\%$), moderate ($I^2 > 25\%$ and $< 75\%$), or high ($I^2 \geq 75\%$) [24]. Additionally, Q-statistic was used to assess the presence of heterogeneity. $P_{Q\ statistic} \geq 0.05$ was considered to indicate no significant heterogeneity among the included studies. Study characteristics including geographic location, "primary" aim of the study, median number of participants, type of phytoestrogens, median duration of intervention, route of phytoestrogen administration, time since menopause onset, and women's health status (healthy vs. women with preexisting chronic disease/non-healthy) were pre-specified as characteristics for assessment of heterogeneity and were evaluated using stratified analyses and random-effects meta-regression, if 10 or more studies were included in the meta-analysis [25]. To assess the influence of each individual study to the overall estimates of the rest of the studies, leave-one-out sensitivity analysis was performed iteratively by removing one study at a time to confirm that the findings were not influenced by any single study. Publication bias was evaluated through a funnel plot and asymmetry was assessed using the Egger's test. All tests were two-tailed and p-values of 0.05 or less was considered as statistically significant. STATA release 14 (Stata Corp, College Station, Texas) was used for all

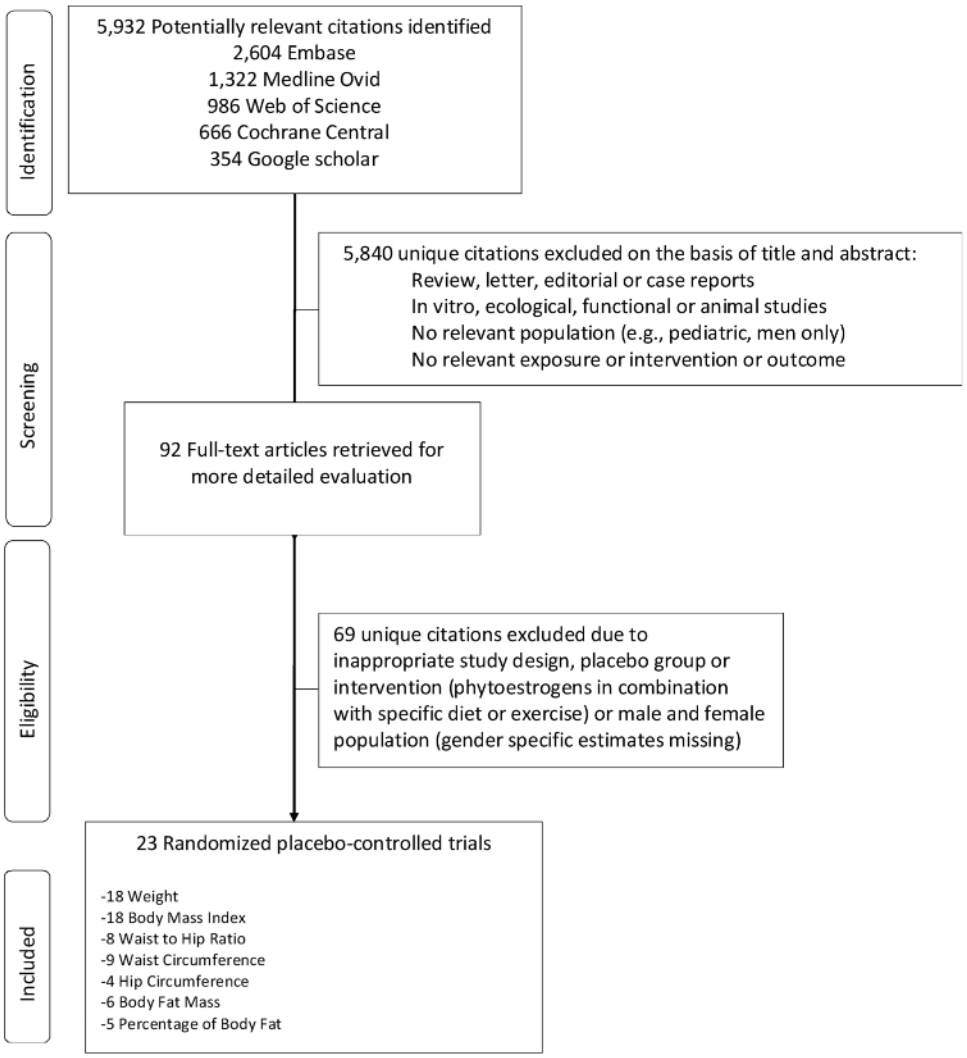

Fig. 1. Flowchart of studies included in this review.

statistical analyses.

3. Results

3.1. Characteristics of included RCTs

Overall 5932 references were identified using the search strategy. After initial screening based on titles and abstracts, the full texts of 92 articles were retrieved and evaluated further. As shown in Fig. 1, after full text assessment, 69 studies were excluded due to inappropriate study design, inappropriate population/exposure studies, or gender specific estimates missing. The remaining 23 RCTs [15–20,26–43] were included in the review and meta-analysis. In total 1880 postmenopausal women (1130 in intervention arm and 750 in placebo arm) were included in the meta-analysis of 23 RCTs. Six trials were done in Asia, 6 in Europe, 5 in North America and 6 in South America. Most of the studies were done among healthy women (n = 19), while four RCTs were conducted in women with metabolic syndrome, type 2 diabetes (T2D), sarcopenic obese, and one RCT in women with prehypertension. All women included in current review were postmenopausal and on average 4.19–15.9 years into menopause, and did not use MHT. The follow-up ranged from 8 to 48 weeks, with majority of RCTs lasting for 24 weeks (n = 11). In nine included RCTs, the effect of phytoestrogen supplementation on parameters of body composition was primarily investigated, while the rest of RCTs investigated the other outcomes (e.g. effect of phytoestrogen supplementation on bone mineral density, menopausal symptoms relief), but reported baseline and end study data on anthropometric parameters of interest. Detailed characteristics of included RCTs are presented in Table 1.

3.2. Association between phytoestrogen supplementation and parameters of body composition

Data from 18 RCTs, including 1692 postmenopausal women, contributed to the meta-analysis on effects of phytoestrogen supplementation on body weight. Consumption of any type of phytoestrogen supplements, as compared to placebo, was not associated with significant decrease in body weight in postmenopausal women [pooled mean difference of changes: −0.14 kg (95%CI: −0.49 to 0.21)] (Fig. 2), in subgroup analysis, a significant decrease in body weight with overall phytoestrogens supplement use as compared to placebo was found in healthy postmenopausal women [pooled mean difference of changes: −0.28 kg (95%CI: −0.52 to −0.04)]. In contrast, phytoestrogen supplementation was associated with increased body weight in postmenopausal women with preexisting health disorders (prediabetes, T2D, prehypertension and hyperlipidemia), [pooled mean difference of changes: 0.78 kg (95%CI: 0.53–1.03)] (Fig. 2).

Based on the findings of 18 RCTs, including 1456 postmenopausal women, overall phytoestrogen supplementation was not associated with BMI changes, [the pooled mean difference of BMI was 0.01 kg/m^2

Table 1
Characteristics of studies included in meta-analysis.

Lead Author, Publication Date	Location	Age group	Intervention form, therapy and daily dosage	Primary outcome of trial	Intervention period	Control	RCT design	Total trial participants	Mean years since menopause	Health status
Arjmandi et al., 2005	USA	< 65	Snack bar, drink mix or cereal, 25 mg of soy protein (60 mg of isoflavones)	Bone's metabolism	48 weeks	Placebo	Parallel	62	5.4	Healthy
[a]Aubertin-Leheudre et al., 2007	Canada	50–70 (66 ± 5)	Capsule, 70 mg isoflavones	Body composition	24 weeks	Placebo	Parallel	18	NA	Sarcopenic obese
Aubertin-Leheudre et al., 2008	Canada	50–70 (66 ± 5)	Capsule, 70 mg isoflavones	Clinical cardiovascular risk factors	24 weeks	Placebo	Parallel	50	6	Obese
[a]Bakhtiary et al., 2011	Iran	60–70 (64.35 ± 2.86)	Powder, Isoflavones, 117.2 mg	Body composition	12 weeks	Placebo	Parallel	50	15.9	Metabolic syndrome
Chiechi et al., 2002	Italy	39–60	Diet, isoflavones, 40–60mg	Serum lipids	24 weeks	Placebo	Parallel	67	4.9	Heathy
[a]Choquette et al., 2011	Canada	50–70 (58.7 ± 5.3)	Capsule, 70 mg isoflavones	Body composition	24 weeks	placebo	Parallel	55	9	Healthy
Colacurci et al., 2005	Italy	55.15 ± 3.85	Tablet, Genistein 60 mg, Daidzein 30 mg	Endothelial function	24 weeks	Placebo	Parallel	60	4.9	Healthy
Colli et al., 2012	Brazil	46–68 (55.2)	Flaxseed extraxt, 100 mg ecoisolariciresinol diglucoside (SDG) or ground whole Flaxseed, 270 mg of SDG	Menopausal symptoms	24 weeks	Placebo	Parallel	53	NA	Healthy
Delmanto et al., 2013	Brazil	> 45	Capsules, soy isoflavones, 100 mg	Mammographic density and breast parenchyma	40 weeks	Placebo	Parallel	80	6.85	Healthy
Engelbert et al., 2016	Germany	50–60	Capsule, Soy isoflavones, 117.4mg	LDL receptors and scavenger receptor CD36	12 weeks	Placebo	Parallel	170	NA	Healthy
Garrido et al., 2006	Chile	45–60 (53.52 ± 3.52)	Capsule, isoflavones, 45 mg	Plasma lipids	12 weeks	Placebo	Parallel	29	1.5	Healthy
Hidalgo et al., 2005	Ecuador	> 40	Capsule, red clover derived isoflavones, 40 mg	Menopausal symptoms	12 weeks	Placebo	Cross-over	53	NA	Healthy
Ho et al., 2007	Hong Kong	48–62 (54.25 ± 3.25)	Capsule, Isoflavones (genistein, daidzein, glycetein), 80 mg	Lipid profile	48 weeks	placebo	Parallel	203	4.13	Healthy
Khaodhiar et al., 2008	USA	38–60 (52.72 ± 5.22)	Capsule, Daidzein, 60mg	Menopausal symptoms	12 weeks	Placebo	Parallel	94	5.1	Healthy
Kim et al., 2013	South Korea	53.5/53.7	Capsules, isoflavones 70mg	Triglycerides and luteunizing hormone	12 weeks	Placebo	Parallel	85	3.6	Healthy
Liu et al., 2010	Hong Kong	48–70 (55.95 ± 4.1)	Flour, Isoflavones, 100 mg	Glycemic control and insulin sensitivity	24 weeks	Placebo: low-fat milk protein	Parallel	180	5.9	Prediabetes/ untreated diabetes
[a]Liu et al., 2013	Hong Kong	48–65	Beverage powder, soy flour 40 g and daidzein, 63mg	Body composition	24 weeks	Placebo	Parallel	180	9	Prehypertensive
[a]Maesta et al., 2006	Brazil	45–70	Tablets, soy protein, 25 g (32 mg genistein, 15 daidzein, 3 g glycitein)	Body composition	16 weeks	Placebo	Parallel	21	10.6	Healthy
[a]Orsatti et al., 2010	Brazil	45–70	Capsules, isoflavones, 100 mg	Body composition	36 weeks	Placebo	Parallel	38	7.07	Healthy
[a]Sites et al., 2007	Italy	55.6	Shakes, 20 g of soy protein + 160 mg of isoflavones	Body composition	24 weeks	Placebo	Parallel	15	4.12	Healthy
Villa et al., 2009	Italy	53.91 (53.92 ± 3.94)	Tablets, 18 mg Genistein	Cardiovascular Risk Factors	24 weeks	Placebo	Parallel	50	NA	Healthy
[a]Weickert et al., 2006	Europe	Mean age 59	Cereal bars, isoflavones, 50mg	Body composition	8 weeks	Placebo	Cross-over	34	NA	Healthy
[a]Wu et al., 2006	Japan	45–60	Capsules Isoflavones,77mg	Body composition	1 year	Placebo	Parallel	66	3.7	Healthy

NA: not available.
[a] RCTs that primarily investigated the association between phytoestrogen supplementation and body composition.

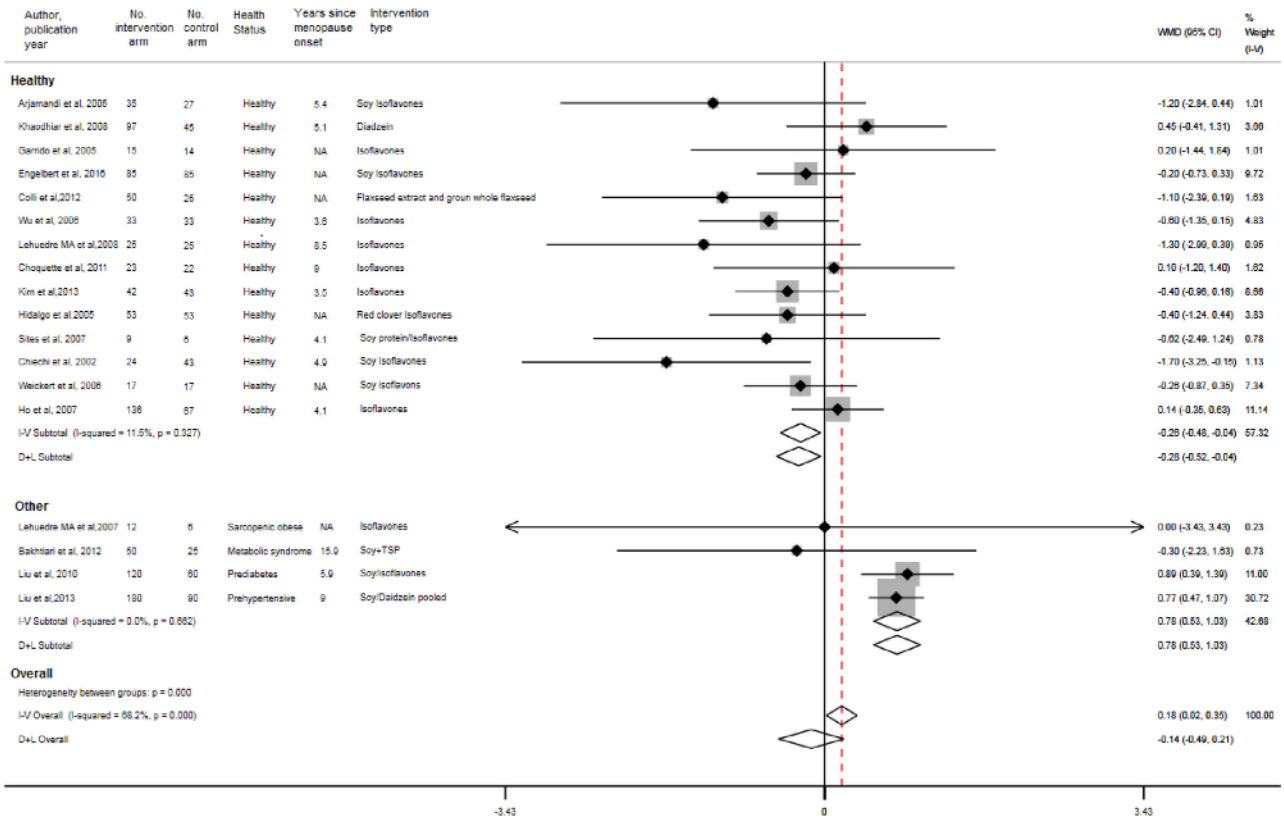

Fig. 2. The association between phytoestrogen supplementation and changes in body weight.
Pooled mean difference is based on 18 RCTs, including 1692 postmenopausal women (1006 in intervention arm and 686 in control arm).
WMD, weighted mean different. Mean difference refers to mean difference of changes between treatment groups. Size of data markers are proportional to the inverse of the variance of the effect estimate. P value comes from Q statistics.

(95%CI: −0.14 to 0.16)] (Fig. 3). In subgroup analysis on health status, the results remained similar, with no significant decrease in mean difference of BMI among healthy and postmenopausal women with pre-existing health conditions (Fig. 3). When stratified by type of phytoestrogen supplements, a significant increase was observed in body weight and BMI change with daidzein [pooled mean difference of changes: 0.92 kg (95%CI: 0.24–1.59)] and [pooled mean difference of changes: 0.35 kg/m^2 (95%CI: 0.17–0.52] respectively. Moreover, a significant decrease of body weight was found with isoflavone mix supplements [pooled mean difference of changes: −0.24 Kg (95%CI: −0.46 to −0.01)] (Table 2).

The data from 8 RCTs including 847 postmenopausal women contributed to the meta-analysis on effects of phytoestrogen supplementation on WHR. Pooled mean WHR change was slightly and significantly decreased, [pooled mean difference of changes of was −0.01 cm (95%CI: −0.01 to −0.006) (Fig. 4).

Data from 9 RCTs, including 824 postmenopausal women and 4 RCTs including 610 postmenopausal women investigated the association between phytoestrogen supplementation and waist and hip circumference changes, respectively. Consumption of any type of phytoestrogen supplements, as compared to placebo, was not associated with a reduction in changes of waist circumference and hip circumference [pooled mean differences of change were: 0.27 cm (95%CI: –0.38 to 0.92) and 0.49 cm (95% CI –0.20 to 1.17)] (Supplemental Figure 1). Furthermore, pooled mean differences based on 6 RCTs, including 421 and 5 RCTs including 573 postmenopausal women showed no association between overall phytoestrogen use and changes in the body fat and percentage of body fat. Pooled mean difference of changes were −0.23 kg (95%CI: −0.74 to 0.28) and −0.26% (95% CI −0.75 to 0.18), respectively (Supplemental Figure 2).

3.3. Assessments of bias, heterogeneity and sensitivity analysis

Two RCTs showed high risk of bias in two domains; however, for most of the RCTs (n = 21), the risk of bias could not be classified in one or more domains (Supplemental Table 2). The four of seven meta-analyses of RCTs showed high between-study heterogeneity, with an I^2 estimate exceeding 75% and $P_{Q\ statistic} < 0.05$, yet, in subgroup analysis by the type of phytoestrogens status, the heterogeneity varied from 0 to 97.2%. In the current systematic review, as shown in the stratified analyses, high heterogeneity might be attributed to the study quality, differences in the methodology of trials and study location. Although I^2 values varied across subgroup analysis, using “meta-regression method”, it was not possible to explain the observed heterogeneity made by any of parameters investigated (the “primary” goal of the study, health status, median years since menopause, route of phytoestrogen administration, type of phytoestrogens, duration of the intervention, number of study participants nor by study location or study quality) (Table 1). However, when stratified by median number of trial participants, in small RCTs with median number of participants ≤66 phytoestrogen supplementation was associated with significant decrease in body weight [pooled mean difference of changes −0.49 kg (95%CI: −0.87 to −0.11)] (Table 2).

In a leave-one out sensitivity analysis, the pooled estimates were not influenced by any single study included in the analyzes (Supplemental Figure 3a–c). For the pooled analyses involving eight or more studies, publication bias was assessed visually using Begg’s funnel plots. The funnel plot for pooled analysis of body weight changes was non-symmetrical with Egger’s p value of 0.005 indicating presence of publication bias. However, funnel plots for pooled analyses reporting changes in BMI and WHR were approximately symmetrical with non-significant Egger’s test estimates for all of these analyses (p values were

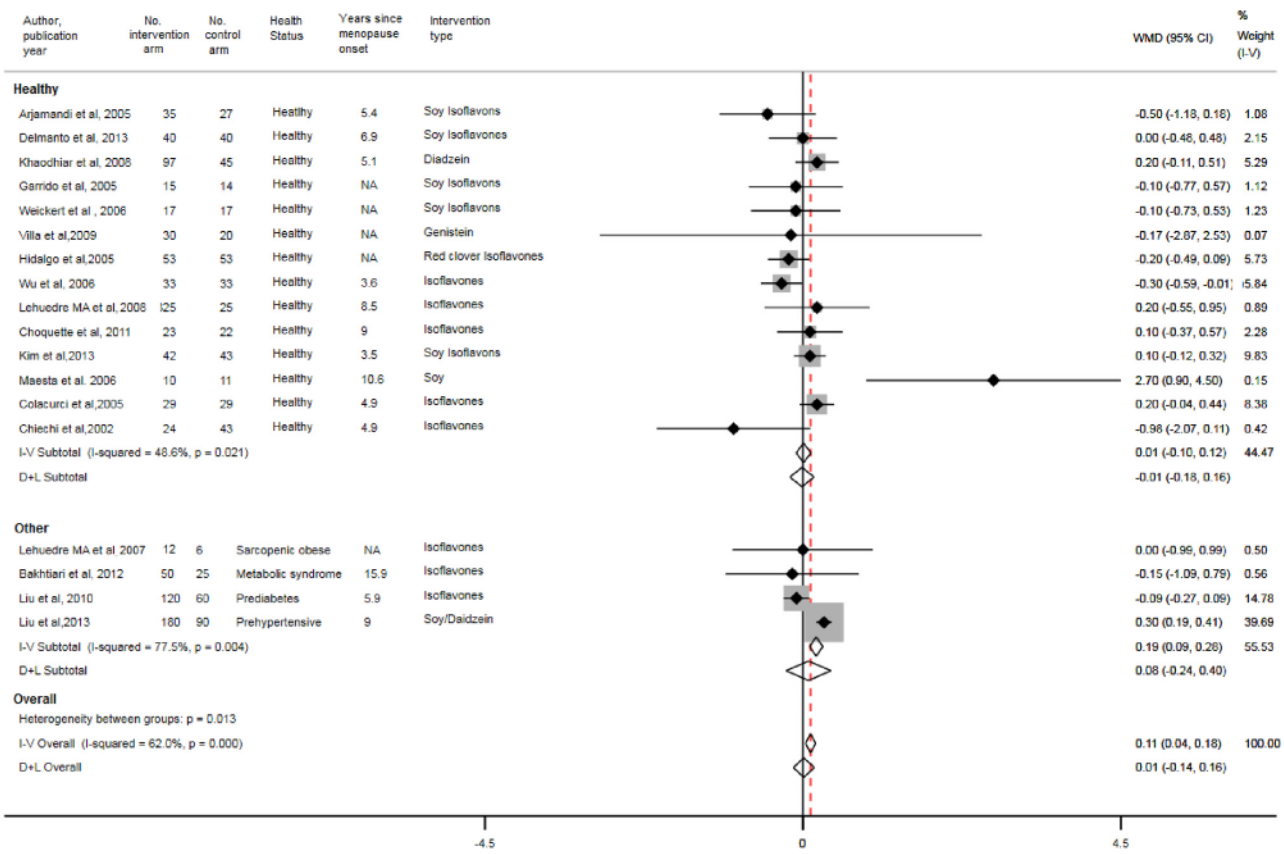

Fig. 3. The association between phytoestrogen intake and changes in BMI.
Pooled mean difference is based on 18 RCTs, including 1456 postmenopausal women (835 in intervention arm and 603 in control arm).
WMD, weighted mean different. Mean difference refers to mean difference of changes between treatment groups. Size of data markers are proportional to the inverse of the variance of the effect estimate. P value comes from Q statistics.

0.19 and 0.97 respectively) (Fig. 5).

4. Discussion

4.1. Summary of evidence

In this systematic review and meta-analysis, phytoestrogen supplementation (compared to placebo and followed by usual diet) was associated with a slight decrease in WHR, and was not associated with changes in body weight, BMI, WC, HC, FM and PBF in postmenopausal women. There was also, an indication that type of phytoestrogens, and health status may play a role in modifying the effect of phytoestrogens in reducing body weight. For instance, a significant decrease in changes of body weight was observed among healthy postmenopausal women and when isoflavone mixture supplements were used. Contrary, body weight was increased in women with underlying metabolic disorders and/or with use of isoflavones rich in daidzein. Furthermore, trials with small sample size showed improved body weight effects in women associated with phytoestrogens, but this effect was not observed in trials with larger samples.

4.2. Interpretation of findings

In contrast to our findings, a meta-analysis published in 2013, reported a significant decrease in body weight with soy isoflavone supplementation [pooled mean difference of −0.52 kg (95%CI: −0.89 to −0.134)] [21]. Although, we did not observe overall significant associations between phytoestrogen supplementation and improvements in body composition parameters, we concluded that type of phytoestrogens and underlying metabolic status of women may play a role in modifying the effectiveness of phytoestrogens in reducing the body weight. There may be several factors that may have yield the differences in our findings on phytoestrogen supplementation and changes in body weight in comparison with previous review. First, we included all types of phytoestrogen supplements, while the prior meta-analysis investigated solely the effect of soy derived phytoestrogens and not the other types of phytoestrogen supplements (e.g. daidzein/genistein enriched formulations, soy products). Second, they included only non-Asian postmenopausal women, while in the current review seventeen non-Asian trials (European, North and South American) and six of Asian trials were included. Finally, the findings of the previous review were based on 9 RCTs and 578 postmenopausal women (272 in intervention trial and 256 in control arm) while we included 23 RCTs and 1880 postmenopausal women (1130 in intervention arm and 750 in placebo arm). Overall, there are some indications that certain types of phytoestrogens may be beneficial in reducing body weight, these findings are supported with experimental data and merit further investigation.

4.3. Biological mechanisms/plausibility

Adipose tissue is highly responsive to estrogen, and both, human and mouse fat tissue express estrogen receptor (ER) α and ERβ [44]. The mechanisms by which dietary soy and phytoestrogens may reduce adiposity are not fully understood. Phytoestrogens may affect the body composition directly binding estrogen receptors (mainly ER α), by mediating the action of hormones thought to be involved in the regulation of body composition (adiponectin, ghrelin, insulin, leptin) or by altering the metabolic activity of adipocytes [45]. Indeed, experimental studies suggested that phytoestrogens could be useful in treating or preventing increased adiposity after menopause onset [46]. Findings

Table 2
The subgroup analyses by study characteristics.

Subgroups by Study Characteristics		Number of studies	[1]Difference, Mean (95% CI)	[2]For heterogeneity	[3]P value for heterogeneity
Phytoestrogen use and mean body weight change					
[a]Primary study goal of the RCT	Body composition	7	−0.04 (−0.68; 0.60)	68.7%	0.59
	Other	11	−0.21 (−0.64; 0.23)	62.3%	
[b]Median years since menopause onset	≤4.1 years	4	−0.23 (−0.6; 0.14)	16.5%	0.87
	> 4.1 years	8	0.07 (−0.51; 0.64)	68.2%	
	Unknown	6	−0.29 (−0.63; 0.04)	0%	
[c]Route of administration	Tablet/capsule	10	−0.17 (−0.82; 0.47)	76.4%	0.52
	Diet	8	−0.17 (−0.42; 0.07)	0%	
[d]Intervention type	Soy products	6	−0.49 (−1.21;0.23)	65.4%	0.83
	Isoflavone mix	10	−0.24(−0.46; −0.01)	0%	
	Daidzein	2	0.92 (0.24; 1.59)	55%	
[e]Median number of study participants	≤66 women	9	−0.49 (−0.87; −0.11)	0%	0.22
	> 66 women	9	0.11 (−0.31; 0.52)	75.2%	
[f]Intervention duration	≤24 weeks	15	−0.10 (−0.51; 0.30)	69.5%	0.9
	> 24 weeks	3	−0.32 (−1.02; 0.37)	53.2%	
[g]Location	Asia	7	0.22 (−0.25; 0.69)	76.8%	0.48
	Europe	4	−0.35 (−0.78; 0.07)	11%	
	North America	4	−0.6 (−1.44; 0.24)	0%	
	South America	3	−0.48 (−1.13; 0.17)	0%	
[h]Risk of bias	High	2	−0.85 (−1.93; 0.22)	0%	0.39
	Low to medium	16	−0.09 (−0.45; 0.27)	69.6%	
Phytoestrogen use and mean Body Mass Index change					
[a]Primary study goal of the RCT	Body composition	7	0.002 (−0.26;0.44)	74.4%	0.49
	Other	11	0.01(−0.13; 0.13)	24.6%	
[b]Median years since menopause onset	≤7.45 years	8	−0.03 (−0.2; 0.14)	53.9%	0.51
	> 7.45 years	4	−0.08 (−0.5; 0.33)	0%	
	Unknown	6	−0.16(−0.40; 0.08)	0%	
[c]Route of administration	Tablet/capsule	10	0.03 (−0.17; 0.23)	47.9%	0.23
	Diet	8	−0.02 (−0.26; 0.22)	73.1%	
[d]Intervention type	Soy products	5	−0.15 (−0.76; 0.47)	68.3%	0.64
	Isoflavone mix	9	0.01 (−0.10; 0.11)	0%	
	Daidzein	2	0.35 (0.17; 0.52)	25.1%	
	Genistein	1	−0.17 (−2.87, −2.53)	NA	
[e]Median number of study participants	≤60 women	9	0.07 (−0.2; 0.35)	36%	0.19
	> 60 women	9	−0.02 (−0.21; 0.17)	75.2%	
[f]Intervention duration	≤20 weeks	9	−0.03 (−0.24; 0.19)	74%	0.31
	> 20 weeks	9	0.05 (−0.16; 0.26)	38.1%	
[g]Location	Asia	5	0.01 (−0.24;0.26)	82.7%	0.48
	Europe	4	−0.06 (−0.51; 0.39)	38.2%	
	North America	5	0.09 (−0.13; 0.31)	0%	
	South America	4	0.1 (−0.44; 0.63)	69.6%	
[h]Risk of bias	High	2	0.18 (−0.06; 0.41)	0%	0.81
	Low to medium	16	−0.01 (−0.17; 0.16)	65.8%	

[1] Mean difference refers to mean difference of changes between treatment groups in body weight and BMI (subjects using phytoestrogens as compared with the subjects from control/placebo group).

[2] For heterogeneity was calculated using fixed- effects models.

[3] P value for heterogeneity was evaluated using random-effects meta-regression (in case that more than 8 studies was meta-analyzed).

[a] Some of RCTs investigated the effect of phytoestrogens on body composition, the others investigated other outcomes but they reported changes in anthropometric parameters at baseline and at the end of the studies.

[b] Median years since menopause, number of years since menopause onset, unknown: no information.

[c] Route of administration includes tablets/capsules use and other routes of administration (shake, powder, flower).

[d] Type of phytoestrogens includes use of soy derived isoflavones/soy protein + isoflavones, extracts of soy isoflavones/isoflavone mixture, daidzein/genistein supplements.

[e] Number of study participants: median number of participants calculated for each outcome separately.

[f] Intervention duration: median intervention duration was calculated for each outcome separately.

[g] Location refers to study location, studies done in Asian ground and the other location (studies done in Europe, America and Australia).

[h] Studies are judged to be at lower high risk of bias based on criteria to evaluate random sequence generation, allocation concealment, blinding of participants/personnel and outcome assessment, incomplete outcome data and selective reporting.

from animal studies reported that fat abundance observed in mice exposed to dietary phytoestrogens correlated with enzymes which could be the key regulators of fatty acid oxidation (AMP-activated protein kinase and Acetyl-CoA carboxylase) [47]. Ovariectomized mice fed with a soy-rich diet have reduced weight and had less adipose deposition than those fed on a soy-free diet [48]. Genistein as the most abundant phytoestrogen in soy food, was extensively studied. Indeed, genistein reversed the truncal fat accumulation in ovariectomized rodent models [44,46]. Moreover, *in vitro* studies using isolated rat adipocytes genistein was found to inhibit the conversion of acetate into lipids, inhibit basal lipogenesis, inhibit the conversion of glucose to lipids more than estradiol, and increase basal lipolysis [49]. Although, genistein may cause adipose changes in mice in concentrations that are within the range of those reported in humans under various nutritional conditions, it is not clear whether genistein could have antilipogenic effects in humans. [44].

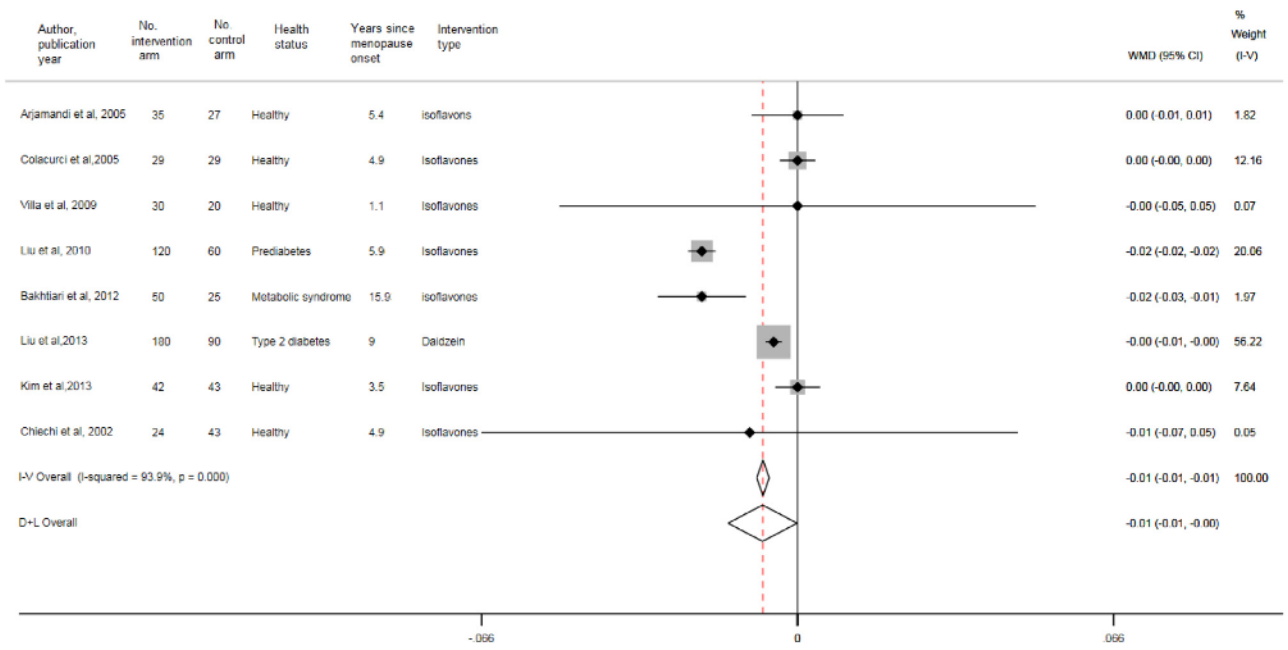

Fig. 4. The association between phytoestrogen supplementation and changes in waist to hip ratio.
Pooled mean difference is based on 8 RCTs, including 847 postmenopausal women (510 in intervention arm and 337 in control arm).
WMD, weighted mean different. Mean difference refers to mean difference of changes between treatment groups. Size of data markers are proportional to the inverse of the variance of the effect estimate. P value comes from Q statists.

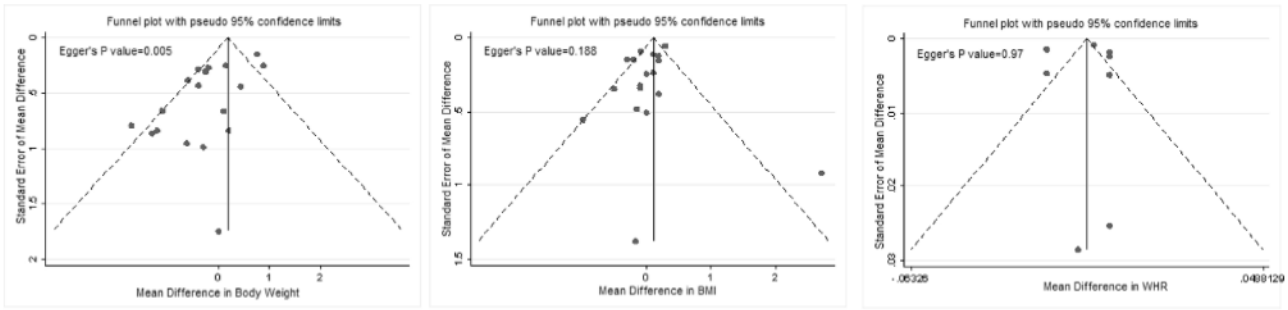

Fig. 5. Funnel plots for RCTs included in the main analysis.
The dotted lines show 95% confidence intervals around the overall summary estimate calculated using a random effect model.

4.4. Strengths and limitations

To our knowledge, this is the first systematic review and meta-analysis including 1880 postmenopausal women to comprehensively address the associations of phytoestrogens with anthropometric parameters in women. Only clinical trials investigating phytoestrogen supplementation following usual/regular diet were included; therefore, studies that combined phytoestrogen supplementation with hypocaloric diets or in combination with exercise were not taken into consideration. Furthermore, we included clinical trials that did not "primary" investigate body composition but have reported outcomes of interest at baseline as well as at the end of trial. In subgroup analysis, those studies which did not primary investigate body composition were excluded and the results remained stable.

However, there are several limitations that need to be mentioned. First, in this study, we found a trend for the possibility of publication for studies investigating body weight changes. Despite the findings of funnel plots and Egger's test, the estimates could indicate minimal publication bias for RCTs investigating BMI and WHR, these approaches are potentially limited by their qualitative nature; therefore, findings on BMI and WHR may have been affected by publication bias as well. Second, the quality of included RCTs in this review was limited because the majority of included RCTs could not be classified in one or more domains, which might have contributed to the heterogeneity that has been observed in the meta-analyses presented in this study (quality and composition of supplements). Furthermore, in included trials women were on average 4.19–15.9 years into menopause. Early postmenopausal period is characterized by pronounced changes in body composition, with an increase in both overall and intra-abdominal adiposity [50]. In fact, in subgroup analysis by median time since menopause, pooled effect on body weight, although non-significant, was larger and in opposite direction compared to women with longer menopause duration. In addition, only four RCTs with more than 100 participants and only four RCT with a duration of the intervention of $\geq$6 months were found, which might undermine the precision of the estimates and may limit the understanding of long-term effects of phytoestrogen supplementation on body composition in women. Considering these observations, the overall results of this study should be interpreted with caution. Finally, most of trials were published before 2013, with only one recent RCT investigating this topic after 2013. Thus, there may be some differences in formulation and quality of supplements of recent data compared to supplements was used $\geq$5 years ago.

4.5. Scientific implications

Inconsistent findings across different trials included in this review may be a consequence of variations in study protocols (differences in dose, duration, route of administration and composition of phytoestrogens used) and baseline characteristics of women studied (various comorbidities, years since menopause onset, the capacity of individuals to produce equol and the genetic susceptibility). Therefore, further well-designed clinical trials should clarify which type and dose of phytoestrogens may have favorable effect on body composition in women, in particular, soy protein isolates, isoflavone mixture and isolated genistein and daidzein effectiveness should be compared. The time since menopause onset, metabolic status and body composition at baseline should be the most important women's characteristics to account for when investigating the association between phytoestrogens and body composition. Additionally, due to variations in phytoestrogen metabolism among individuals, phytoestrogen metabolites (urinary concentrations) shall be measured to reduce measurement errors and address the issue of serum phytoestrogen concentrations over the study period.

4.6. Conclusions

The European Menopause and Andropause Society (EMAS) suggested non-hormonal management of menopausal symptoms as an option for women who cannot or do not wish to take MHT [9]. However, this review raises an important concern regarding the body weight changes with phytoestrogen supplementation. Based on current literature, phytoestrogen supplements followed by usual diet were not associated with changes in body weight. However, the type of phytoestrogens and underlying disease in women may play an important role in modifying the effectiveness of phytoestrogens in reducing body weight and may even lead to increase in body weight. Therefore, until obtaining more evidence in favor of beneficial role of phytoestrogens in reducing body weight, it might be much safer to combine phytoestrogen supplements (especially daidzein rich formulations) with hypocaloric diet/enhanced physical activity to maintain normal body weight during the supplementation period

Contributors

Marija Glisic contributed to analysis and interpretation, drafted and critically revised the manuscript.

Natyra Kastrati contributed to data acquisition, quality assessment and interpretation and critically revised the manuscript.

Juna Musa contributed to data acquisition, quality assessment and interpretation and critically revised the manuscript.

Jelena Milic contributed to interpretation and critically revised the manuscript.

Eralda Asllanaj contributed to interpretation and critically revised the manuscript.

Eliana Portilla Fernandez contributed to interpretation and critically revised the manuscript.

Jana Nano contributed to interpretation and critically revised the manuscript.

Carolina Ochoa Rosales contributed to interpretation and critically revised the manuscript.

Masoud Amiri contributed to interpretation and critically revised the manuscript.

Bledar Kraja contributed to interpretation and critically revised the manuscript.

Arjola Bano contributed to interpretation and critically revised the manuscript.

Wichor M. Bramer contributed to literature search and critically revised the manuscript.

Anton J.M. Roks participated in interpretation of the analyses and critically revised the manuscript.

A.H. Jan Danser participated in interpretation of the analyses and critically revised the manuscript.

Oscar H. Franco contributed to conception and design, contributed to analysis and interpretation and critically revised the manuscript.

Taulant Muka contributed to conception and design, contributed to analysis and interpretation and critically revised the manuscript. All authors gave the final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Conflict of interest

The authors declare that they have no conflict of interest.

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Provenance and peer review

This article has undergone peer review.

Appendix A. Supplementary data

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