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Effect of oral phytoestrogens on endometrial thickness and breast density of perimenopausal and postmenopausal women: a systematic review and meta-analysis

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Highlights

- Phytoestrogens do not affect endometrial thickness compared with placebo.
- Phytoestrogens do not affect endometrial thickness compared with menopausal hormone therapy.
- Compared with placebo, phytoestrogens do not affect breast density.

- Body mass index (BMI) was identified as a confounder (it has a significant inverse association with increased endometrial thickness, $p=0.046$); in contrast, no such correlation was found for age and study duration ($p=0.243$ and $p=0.439$, respectively).

Highlights

- Phytoestrogens did not affect endometrial thickness compared with placebo.
- Phytoestrogens did not affect endometrial thickness compared with MHT.
- Compared with placebo, phytoestrogens did not affect breast density.
- BMI was identified as a confounder (inverse association between BMI and increase of the endometrial thickness, $p=0.046$); in contrast, no such correlation was found for age and study duration ($p=0.243$ and $p=0.439$, respectively).

Abstract

Background: Phytoestrogens constitute an alternative, non-pharmacologic approach for the management of menopausal symptoms. However, few studies have focused on their safety, specifically in relation to endometrial thickness and breast density.

Aim: To systematically search for and quantitatively synthesize the evidence regarding the effect of phytoestrogens on endometrial thickness and breast density in perimenopausal and postmenopausal women.

Methods: Randomized controlled trials (RCTs) examining the effect of phytoestrogens compared with placebo or menopausal hormone therapy (MHT) on endometrial thickness and/or breast density in perimenopausal or postmenopausal

women were searched for in the MEDLINE, CENTRAL and Scopus databases as well as “gray literature” sources until October 31, 2018. Main outcomes were the change from baseline in endometrial thickness and breast density. Statistical analysis was performed with RevMan 5.3, using R language and Open Meta-Analyst software.

Results: The meta-analysis for endometrial thickness included 30 RCTs (with a total of 3,497 women), and that for breast density four RCTs (with a total of 674 women). Phytoestrogens did not affect endometrial thickness compared with placebo [weighted mean difference (WMD) -0.04 mm, 95% confidence interval (CI) -0.18 to 0.11, I^2 66%] or MHT (WMD -1.40 mm, 95% CI -2.98 to 0.18, I^2 84%). In addition, phytoestrogens did not affect breast density compared with placebo [standardized mean difference (SMD) -0.76, 95% CI -1.54 to 0.2, I^2 95%).

Conclusion: Phytoestrogens have no effect on endometrial thickness or breast density, when administered at various doses and for various durations, in perimenopausal and postmenopausal women. However, the high heterogeneity of the studies makes it necessary to conduct RCTs with less risk of systematic error.

Keywords: phytoestrogens; endometrial thickness; breast density; perimenopause; menopause; systematic review.

Introduction

Given the increase in life expectancy, women have to spend 30 years approximately at postmenopausal status [1]. The lack of estrogens leads, among other consequences, to vasomotor (mainly hot flashes and night sweats) and vulvovaginal symptoms (mainly vaginal atrophy and dyspareunia), affecting woman's daily routine and having a negative impact on her quality of life [2]. Menopausal Hormone Therapy (MHT) is the treatment of choice for vasomotor and vulvovaginal symptoms [3]. However, some women cannot receive MHT, because of relative or absolute contraindications or the fear for possible adverse effects on endometrium and breast. Phytoestrogens constitute an alternative non-pharmacological option for the management of menopausal symptoms[4]. Furthermore, they may improve bone mineral density during menopause [5]. However, few studies only focused on their effect on endometrial thickness and breast density [6,7].

The aim of this study was to conduct a systematic review and meta-analysis of studies which refer to the effect of phytoestrogens on endometrial thickness and breast density, in perimenopausal and postmenopausal women who received them for alleviation of menopausal symptoms. By documenting the safety of phytoestrogens in endometrium and breast, more women could use them, especially if they have a contra-indication for MHT.

Materials and Methods

Literature search. Search for studies fulfilling the admission criteria was conducted on the MEDLINE, CENTRAL and Scopus electronic databases from conception until October 31, 2018, without language restrictions, using relevant keywords in both free text and Medical Subject Headings (MeSH terms) format. Search strategy in PubMed

has been combined with an enhanced sensitivity and accuracy filter for randomized control trials (RCTs), designed by the Cochrane Collaboration. The search for grey literature was conducted in repositories, catalogues (EThOS) and websites (OpenGray, GetNet International) as well as conference proceedings of major international congresses. A detailed search strategy is presented in Supplementary Table 1.

Study selection. Selection criteria consisted of RCTs (of parallel or cross-over design) with any duration of treatment that compared any dose of phytoestrogens with placebo or MHT. Studies should report at least one of the predetermined outcomes: endometrial thickness and/or breast density before and after intervention.

Data extraction and quality assessment. Two researchers (EM and CA) independently extracted data from studies, using Microsoft Excel panels. Any disagreement between them have been resolved in consensus with a third researcher (DGG). Data were derived from all studies, in which perimenopausal or postmenopausal women were given any dose of phytoestrogens compared with placebo for any duration and in which endometrial thickness and/or breast density were measured before and after the intervention. The outcomes of the systematic review and meta-analysis were the change from baseline in endometrial thickness (in mm), measured by transvaginal ultrasound and the change in breast density measured by mammography [as a percentage (in two studies) or as BIRADS (Breast Imaging Reporting and Data System) assessment units of the American College of Radiologists (in two studies)].

The revised Rob2.0 Cochrane Risk Assessment Tool for Randomized Controlled Trials was used to evaluate the quality of clinical trials included in the meta-analysis [8]. Two researchers (EM and CA) independently evaluated the risk of a systematic error for both outcomes and any disagreements were resolved in consensus with a third researcher (DGG). The overall risk was considered to be “high” in the presence of high risk in any rating area, “low” if all sectors had a low risk of systematic error and “intermediate” in any other case. Finally, the presence of publication bias for the two outcomes was evaluated by funnel plots.

Data synthesis and analysis. For continuous variables, mean differences (MD) and 95% confidence intervals (CI) were calculated using the inverse-variance random effects model. Since breast density measurements were performed on two different scales, standardized mean differences (SMD) and 95% CIs were calculated using the inverse-variance random effect model. In case the mean differences and the corresponding standard deviations (SD) were not available, e-mails were sent to the authors of the original publications. The procedures suggested by the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0), were always followed [9]. The heterogeneity among the included studies was evaluated with the I^2 index, considering values $>60\%$ as indicative of high heterogeneity. The analyses were performed using the RevMan 5.3 software (Nordic Cochrane Center, Copenhagen, Denmark). Meta-regression analyses were performed using the Open Meta-Analyst software [10]. Egger’s test for publication bias was performed using R language.

Results

Search results and study characteristics. The systematic review and the meta-analysis included 33 RCTs with a total of 4047 patients. Endometrial thickness analysis included 30 RCTs with 3,497 patients and breast density analysis four RCTs with 674 patients. One RCT included both endpoints. The flow diagram of the study selection process is shown in Figure 1.

Characteristics of the included studies and baseline characteristics of the women are summarized in Tables 1-2. From the 33 RCTs, 30 had parallel design and three were cross-over studies. In the latter, only the first part of the study was used. From 30 RCTs relevant to endometrial thickness, 25 compared phytoestrogens with placebo, two compared phytoestrogens with MHT and three compared phytoestrogens with both placebo and MHT. The dose of phytoestrogens ranged from 10 mg (equol) to 270 mg (lignans). The duration of the intervention ranged from eight to 156 weeks. Five RCTs included both premenopausal and postmenopausal women, while the remaining included only postmenopausal women. In three studies, the phytoestrogen metabolite equol was administered as a phytoestrogen source, in one study the *Pueraria mirifica* plant, in three studies the red clover plant, two studies used lignans and the other isoflavones. Participants were advised to maintain their usual eating habits. Endometrial thickness was assessed by transvaginal ultrasound and breast density by mammography.

Effect of phytoestrogens on endometrial thickness. The endometrial thickness meta-analysis included 30 RCTs, of which three compared two different doses of

phytoestrogens with placebo. The two comparisons were treated as two different studies without changing the final number of participants. In two RCTs, the control group received MHT rather than placebo. These studies were included in the meta-analysis that compared MHT with phytoestrogens. The overall effect of phytoestrogens compared with placebo on endometrial thickness is shown in Figure 2. Phytoestrogens did not affect endometrial thickness (WMD -0.04 mm, 95% CI -0.18 to 0.11, I^2 66%). In one study [11], phytoestrogens increased endometrial thickness compared with placebo, in three studies [12–14] phytoestrogens reduced endometrial thickness compared with placebo, and in the other studies no difference was observed. A sensitivity analysis, excluding studies with a daily dose \leq 54 mg, resulted in no effect on endometrial thickness (WMD -0.08 mm, 95% CI -0.28 to 0.12, I^2 75%). A sensitivity analysis, excluding studies with a mean age of $>$ 60 years, resulted in no effect on endometrial thickness (WMD 0.00 mm, 95% CI -0.14 to 0.13, I^2 46%). In a similar way, a sensitivity analysis excluding studies with a duration \leq 12 weeks, resulted in no effect on endometrial thickness (WMD -0.06 mm, 95% CI -0.26 to 0.13, I^2 75%).

The overall effect of phytoestrogens compared with MHT on endometrial thickness is shown in Figure 3. Five RCTs were included in this meta-analysis. Phytoestrogens did not affect endometrial thickness compared with MHT (WMD -1.40 mm, 95% CI -2.98 to 0.18, I^2 84%).

Effect of phytoestrogens on breast density. Four RCTs were included in the breast density meta-analysis. One of these [15] had two parts (comparison of two doses of phytoestrogen with placebo). The two comparisons were treated as two different

studies without changing the final number of participants. Compared with placebo, phytoestrogens did not affect breast density (SMD -0.25, 95% CI -0.60 to 0.11, I^2 80%) (Figure 4).

Meta-regression analysis. Meta-regression analysis was performed to investigate for possible confounders of the effect of phytoestrogens on endometrial thickness, such as BMI, age and study duration. BMI was identified as a confounder (inverse association between BMI and increase of the endometrial thickness, $p=0.046$); in contrast, no such correlation was found for age and study duration ($p=0.243$ and $p=0.439$, respectively) (Supplementary Figures 1-3).

Assessment of publication and systematic bias. Many studies were considered as “high risk”. This was due to allocation concealment violations and attrition bias. A detailed presentation of the systematic error risk assessment of all included studies is given in Supplementary Tables 2 (endometrial thickness) and 3 (breast density). The funnel plot for the endometrial thickness outcome (Figure 5) does not provide evidence for publication bias. Egger’s test ($p=0.151$) also detected no publication bias.

Discussion

The aim of this systematic review and meta-analysis was to investigate the effect of phytoestrogens on endometrial thickness and breast density in perimenopausal and postmenopausal women with vasomotor and other menopausal symptoms. The study provided evidence that phytoestrogens [isoflavones (genistein, daidzein), lignans, equol, S-equol] at different doses, ranging from 10 mg (equol) to 270 mg (lignans), over a period of 8 to 156 weeks do not affect either endometrial thickness or breast

density. In addition, phytoestrogens have no effect on endometrial thickness compared with MHT.

This study provides the most up-to-date and complete data synthesis on the effect of phytoestrogens on endometrial thickness and breast density in perimenopausal and postmenopausal women. The results of the meta-analysis are reassuring about the safety of phytoestrogens on endometrial thickness and breast density up to three years of use and in agreement with the other studies. In the meta-analysis by Liu *et al.* [16], 23 RCTs were included for a total of 2305 women; no effect of phytoestrogens was shown on endometrial thickness as compared with placebo. However, in a subgroup analysis, the administration of phytoestrogens at a daily dose >54 mg reduced the endometrial thickness in postmenopausal women by SMD -0.26 mm, 95% CI -0.45 to -0.07 . In the present meta-analysis there was no effect on endometrial thickness, when only the studies with a dosage of >54 mg were included. This may be due to new studies added and a different classification of studies. Specifically, in the present meta-analysis, Murray *et al.* study [17] was used in the comparison of phytoestrogen with MHT, as it would be wrong to classify it in the comparison of phytoestrogens with placebo. Also, in the meta-analysis by Liu *et al.*, the Penotti *et al.* study was misclassified in the group “ <54 mg”, while the daily dose of phytoestrogens was 72 mg of isoflavone. When only the studies with a mean age of ≤ 60 years were included in the sensitivity analysis, there was no effect on endometrial thickness (WMD -0.00 mm, 95% CI -0.14 to 0.13 , I^2 46%).

The present meta-analysis further evaluated the effect of phytoestrogens compared with MHT on endometrial thickness in perimenopausal and postmenopausal women.

In this comparison, five RCTs were included with 226 patients, who received either phytoestrogens or MHT. The meta-analysis did not reveal a significant effect. Therefore, it is concluded that phytoestrogens are a safe choice, with regard to endometrial thickness, for the treatment of climacteric symptoms in perimenopausal and postmenopausal women.

Four RCTs, with 674 patients, were included in the analysis of breast density. Phytoestrogens did not affect the breast density over a period of three years. It is, therefore, concluded that they can be used safely with regard to breast density. This conclusion is consistent with the study by Hooper *et al.* [18], which studied the effect of isoflavones on breast density of premenopausal and postmenopausal women. This study showed that isoflavones do not affect the breast density, which is one of the most important independent risk factors for developing breast cancer.

The meta-regression analysis showed that the age of the participants and the study duration are not related to the effect of phytoestrogens on endometrial thickness. However, the lower the BMI, the higher the increase of endometrial thickness in the phytoestrogens group. The Kenny *et al.* study [13] was removed from the meta-regression analysis of age, because its average age (73.1 years) greatly increased the heterogeneity of included studies. A meta-regression analysis for possible confounders with regard to breast density was not performed because of the small number of included studies (less than ten).

It is important to recognize some limitations of this meta-analysis. Although there is a large number of clinical trials examining the efficacy and potential adverse effects of

phytoestrogens in perimenopausal and postmenopausal women, there are only few clinical trials examining the effect on endometrial thickness and breast density. Additionally, the included studies are characterized by great heterogeneity in the daily dose of phytoestrogens, the formulation administered and the duration of the studies. These factors result in high heterogeneity in statistical analysis, which gives rise to reservations about the outcome of the study. Another limitation is the high rate of missing data in studies. The high rate of missing data, especially in mean difference values and standard deviations of difference values led, to the use of the final means and final standard deviations, according to the Cochrane Handbook's guidelines for missing data. In some RCTs, final standard deviations were not reported. These values were added by imputation methods from the adjacent studies without affecting the result of the meta-analysis. The small number of studies in the comparison of MHT versus phytoestrogens for endometrial thickness and the comparison of placebo versus phytoestrogens for breast density also limits the strength of the result. With regard to breast density, the existence of two different measurement scales made it necessary to use the standardized mean difference value in the analysis. It is noteworthy, that while Delmanto *et al.* study [19] for breast density did not find statistically significant effect, in our analysis it was found. The risk of systematic error was found to be high in most studies because they did not clearly describe the process of randomization and allocation concealment. In addition, there are high dropout rates and missing data.

In conclusion, phytoestrogens in various types and doses did not affect endometrial thickness or breast density over a maximum use of three years. The high heterogeneity of the studies, mainly regarding types and dose of phytoestrogens,

underlines the necessity of further clinical trials to assess the safety of phytoestrogens on the long term.

Contributors

All authors (Evangelia Mareti, Christina Ampratzi, Dimitrios Vavilis, Irene Lambrinouadaki, Dimitrios G.Goulis) were involved in the search of the literature for appropriate studies, data extraction, statistical analysis and preparation of the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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Conflict of interest

The authors whose names are listed immediately below (Evangelia Mareti, Christina Ampratzi, Dimitrios Vavilis, Irene Lambrinouadaki, Dimitrios G. Goulis) certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership,

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Author's contribution-funding

All authors (Evangelia Mareti, Christina Ampratzi, Dimitrios Vavilis, Irene Lambrinouadaki, Dimitrios G.Goulis) were involved in search of the literature for appropriate studies, data extraction, statistical analysis and preparation of the manuscript.

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Table 1. Baseline characteristics of studies (endometrial thickness).

Id	Study	Year	Country	Population	n	Aim	Control	Phytoestrogens		Age (y)	BMI (kg/m ²)	Duration (w)	Baseline endometrial thickness (mm)	
								Active substance and dose (mg/d)	Source				Control	Phytoestrogens
1	Baber <i>et al.</i> [20]	1998	Australia	Post-menopausal	51	Vasomotor (hot flushes)	Placebo	40 mg isoflavone	Oral tabs (red clover)	54.0	-	12	3.2 ± 1.5	3.2 ± 1.5
2	Upmalis <i>et al.</i> [21]	2000	USA	Peri- and Post-menopausal	122	Vasomotor (hot flushes)	Placebo	50 mg genistein+ daidzein	Oral tabs	54.6	-	12	3.7 ± 2.7	3.5 ± 1.9
3	Hale <i>et al.</i> [22]	2001	USA	Peri- and Post-menopausal	24	Endometrium	Placebo	50 mg isoflavone	Oral tabs	47.1	26.6	12	6.5 ± 1.7	7.1 ± 2.8
4	Chiechi <i>et al.</i> [23]	2002	Italy	Peri- and Post-menopausal	166	Lipids	Placebo, HRT	40-60 mg isoflavone	Diet	53.3	27.9	24	3.6 ± 2.7	3.5 ± 2.1
5	Han <i>et al.</i> [11]	2002	Brazil	Post-menopausal	80	Vasomotor, CVD	Placebo	100 mg isoflavone	Oral caps	48.5	24.9	16	2.6 ± 0.1	3.3 ± 0.1
6	Murray <i>et al.</i> [17]	2003	USA	Post-menopausal	30	Endometrium	MHT	120 mg isoflavone	Oral tabs	55.0	24.9	24	3.6 ± 1.6	3.0 ± 0.7
7	Penotti <i>et al.</i> [12]	2003	Italy	Post-menopausal	62	Vasomotor (hot flushes), Endometrium	Placebo	72 mg isoflavone	Oral tabs	52.5	23.2	24	3.2 ± 1.8	2.6 ± 1.8
8	Sammartino <i>et al.</i> [24]	2003	Italy	Post-menopausal	63	Vasomotor (hot flushes)	Placebo	36 mg genistein	Oral tabs	51.8	25.3	52	3.2 ± 0.5	3.3 ± 0.5
9	Crisafulli <i>et al.</i> [25]	2004	Italy	Post-menopausal	90	Vasomotor (hot flushes)	Placebo, MHT	54 mg isoflavone	Oral tabs	51.7	23.7	48	3.3 ± 1.2	3.2 ± 1.6
10	Woods <i>et al.</i> [26]	2004	UK	Post-menopausal	29	Endometrium	Placebo	80 mg isoflavone	Oral tabs (red clover)	-	-	8	2.4 ± 0.5	2.4 ± 0.9
11	Imhof <i>et al.</i>	2006	Austria	Post-	109	Endometrium,	Placebo	80 mg	Oral caps	54.1	24.7	12	3.4	4.3

	[27]			menopausal		Sex hormones		isoflavone						
12	Kaari <i>et al.</i> [28]	2006	Brazil	Post-menopausal	68	Vasomotor (hot flushes), Endometrium	MHT	120 mg isoflavone	Oral caps	53.8	25.6	24	2.8	3.2
13	Cheng <i>et al.</i> [29]	2007	Sweden	Post-menopausal	51	Vasomotor (hot flushes)	Placebo	60 mg isoflavone	Fruit drink	57.7	24.9	12	2.0 ± 1.0	2.3 ± 1.1
14	Marini <i>et al.</i> [30]	2007	Italy	Post-menopausal	389	BMD	Placebo	54 mg genistein	Oral tabs	54.5	25.1	104	3.2 ± 1.8	3.1 ± 1.5
15	Nahas <i>et al.</i> [31]	2007	Brazil	Post-menopausal	76	Vasomotor (hot flushes)	Placebo	100 mg isoflavone	Oral caps	55.7	29.1	40	3.5 ± 1.2	3.1 ± 1.5
16	Zhang <i>et al.</i> [32]	2007	China	Post-menopausal	100	BMD	Placebo	18 mg genistein+ daidzein	Oral tabs	63.5	-	104	1.8 ± 0.6	1.8 ± 0.6
17	Manonai <i>et al.</i> [33].	2008	Thailand	Post-menopausal	71	Lipids, BMD	Placebo	20, 30, 50 mg isoflavone	Oral caps (Pueraria mirifica)	53.2	24.7	24	4.1 ± 1.4	4.1 ± 1.5
18	D'Anna <i>et al.</i> [34]	2009	Italy	Post-menopausal	389	Vasomotor (hot flushes)	Placebo	54 mg genistein	Oral caps	53.1	23.9	104	3.2 ± 0.1	3.1 ± 0.1
19	Kenny <i>et al.</i> [13]	2009	USA	Post-menopausal	97	BMD	Placebo	105 mg isoflavone	Oral tabs	73.1	28.3	52	3.2 ± 1.0	2.9 ± 0.8
20	Radhakrishnan <i>et al.</i> [35]	2009	India	Post-menopausal	85	Vasomotor, Lipids, BMD	Placebo	75 mg isoflavone	Powder sachs	48.9	25.5	24	3.5 ± 0.7	4.1 ± 1.7
21	Simbalista <i>et al.</i> [36]	2010	Brazil	Peri- and Post-menopausal	38	Vasomotor (hot flushes)	Placebo	46 mg lignans	Bread (flaxseed)	52.3	26.3	12	3.0 ± 3.0	2.4 ± 0.8
22	Evans <i>et al.</i> [37]	2011	Canada	Peri- and Post-menopausal	82	Vasomotor (hot flushes)	Placebo	30 mg genistein	Oral caps	53.5	26.0	12	3.7 ± 1.2	4.3 ± 2.0
23a	Steinberg <i>et al.</i> [14]	2011	USA	Post-menopausal	182	Clinical outcomes	Placebo	80 mg isoflavone	Oral tabs	54.8	25.2	104	2.0 ± 1.2	1.9 ± 1.7
23b	Steinberg <i>et al.</i> [14]	2011	USA	Post-menopausal	180	Clinical outcomes	Placebo	120 mg isoflavone	Oral tabs	54.8	25.2	104	2.0 ± 1.2	1.8 ± 1.0
24a	Colli <i>et al.</i> [38]	2012	Brazil	Post-menopausal	41	Vasomotor (hot flushes)	Placebo	100 mg lignans	Oral caps	54.8	-	24	2.2 ± 1.3	1.9 ± 1.1

24b	Colli <i>et al.</i> [38]	2012	Brazil	Post-menopausal	34	Vasomotor (hot flushes)	Placebo	270 mg lignans	Tablespoon (flaxseed)	54.8	-	24	2.2 ± 1.3	1.8 ± 1.1
25a	Oyama <i>et al.</i> [39]	2012	Japan	Post-menopausal	51	Skin aging	Placebo	10 mg S-equol	Oral tabs (soy germ)	55.2	21.6	12	0.1 ± 0.5	0.2 ± 0.8
25b	Oyama <i>et al.</i> [39]	2012	Japan	Post-menopausal	50	Skin aging	Placebo	30 mg S-equol	Oral tabs (soy germ)	55.2	21.6	12	0.1 ± 0.5	0.2 ± 0.5
26	Colacurci <i>et al.</i> [40]	2013	Italy	Post-menopausal	124	Safety	Placebo	60 mg isoflavone	Oral tabs	55.7	25.0	48	3.5 ± 1.1	3.4 ± 1.0
27	Quaas <i>et al.</i> [41]	2013	USA	Postmenopausal	224	Endometrium	Placebo	154 mg isoflavone	Powder bars	60.5	26.4	156	2.5 ± 0.2	2.4 ± 0.2
28	Carmignani <i>et al.</i> [42]	2015	Brazil	Post-menopausal	60	Urogenital	Placebo, MHT	90 mg isoflavone	Oral powder	52.4	26.3	16	3.9 ± 2.2	4.2 ± 2.3
29	Villa <i>et al.</i> [43]	2017	Italy	Post-menopausal	75	Quality of life	Placebo	80 mg equol	Oral tabs	49.3	23.2	24	4.8 ± 3.1	4.7 ± 3.1
30	Vahiddastjerdi <i>et al.</i> [44]	2018	Iran	Post-menopausal	204	Vasomotor (hot flushes)	Placebo	50 mg isoflavone	Oral tabs	51.7	24.9	12	3.3 ± 2.0	3.4 ± 1.9

Data are given as mean ± SD. BMD: bone mineral density; BMI: body mass index; HRT: hormone replacement therapy SD: standard deviation.

Table 2. Baseline characteristics of studies (breast density).

Id	Study	Year	Country	Population	n	Aim	Control	Phytoestrogens		Age (y)	BMI (kg/m ²)	Duration (w)	Baseline BD Control	Baseline BD Phytoestrogens
								Active substance and dose (mg/d)	Source					
1	Verheus <i>et al.</i> [45]	2008	Netherlands	Post-menopausal	126	Mammographic density	Placebo	99 mg isoflavone	Oral tabs	65.9	26.0	52	15.4%	10.6%
2a	Maskarinec <i>et al.</i> [15]	2009	USA	Post-menopausal	177	Osteoporosis	Placebo	80 mg isoflavone	Oral tabs	54.9	25.1	104	32.0 ± 17.5%	28.9 ± 17.4%
2b	Maskarinec <i>et al.</i> [15]	2009	USA	Post-menopausal	181	Osteoporosis	Placebo	120 mg isoflavone	Oral tabs	54.9	25.1	104	32.0 ± 17.5%	32.3 ± 19.0%
3	Colacurci <i>et al.</i> [40]	2013	Italy	Post-menopausal	124	Safety	Placebo	60 mg isoflavone	Oral tabs	55.7	25.0	52	1.8 ± 0.9	1.9 ± 1.0
4	Delmanto <i>et al.</i> [19]	2013	Brazil	Post-menopausal	66	Mammographic density	Placebo	100 mg isoflavone	Oral tabs	55.7	29.1	40	2.0	1.5

Data are given as mean ± SD. BD: breast density; BMI: body mass index; SD: standard deviation; tabs: tablets.

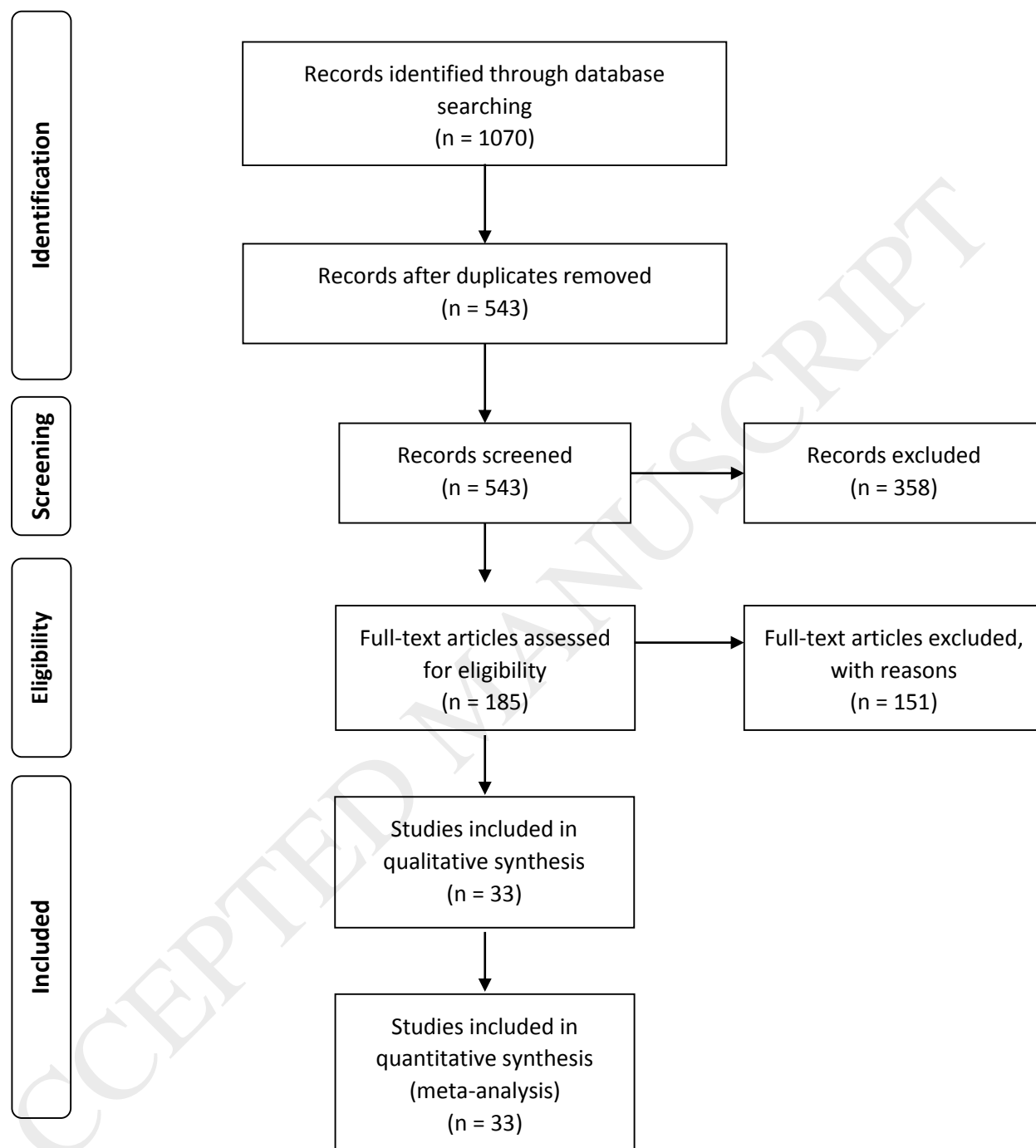


Figure 1. PRISMA study flow diagram.

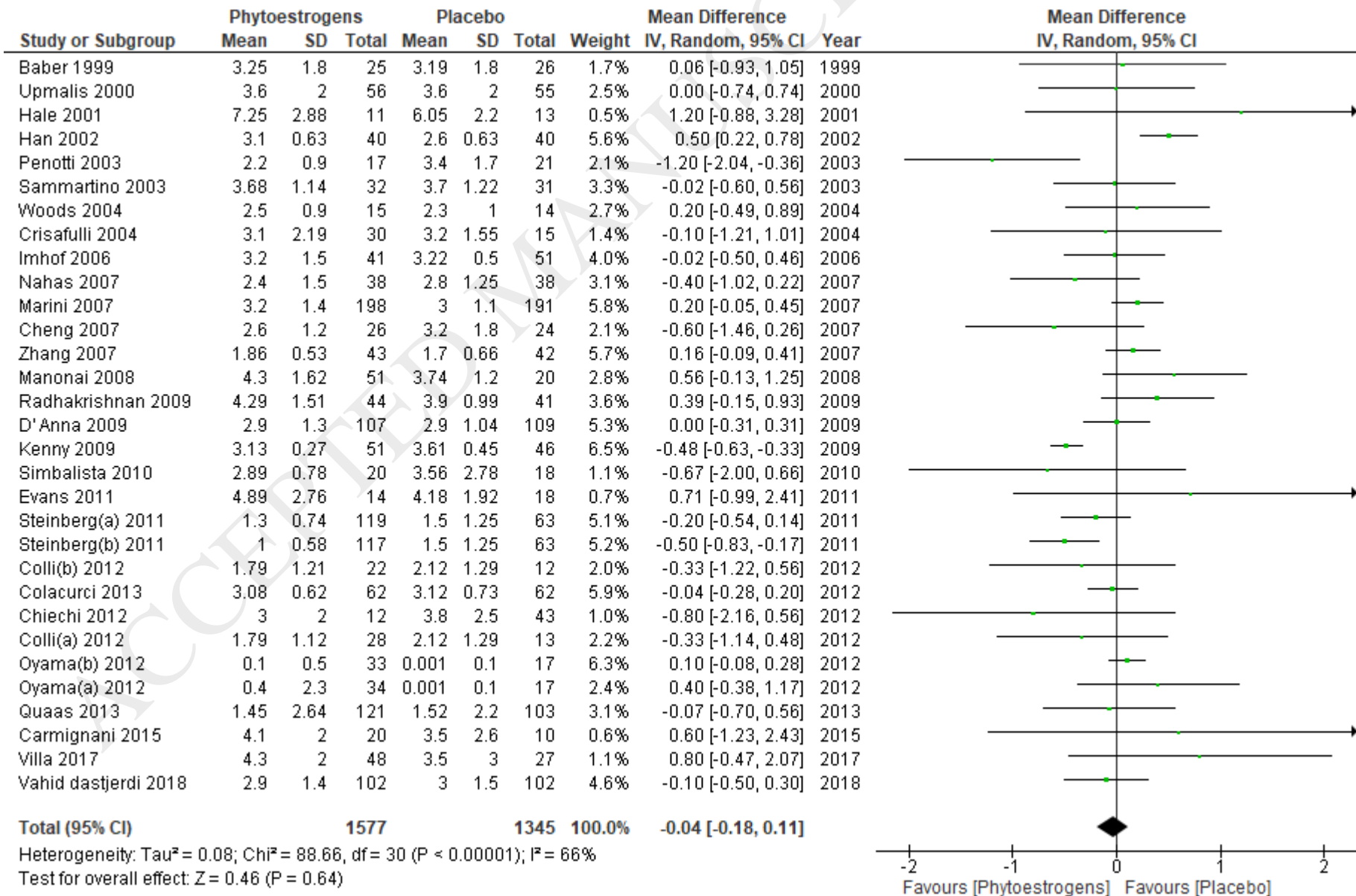


Figure 2. Meta-analysis of the effect of phytoestrogen supplementation on endometrial thickness compared with placebo.

PE: phytoestrogens.

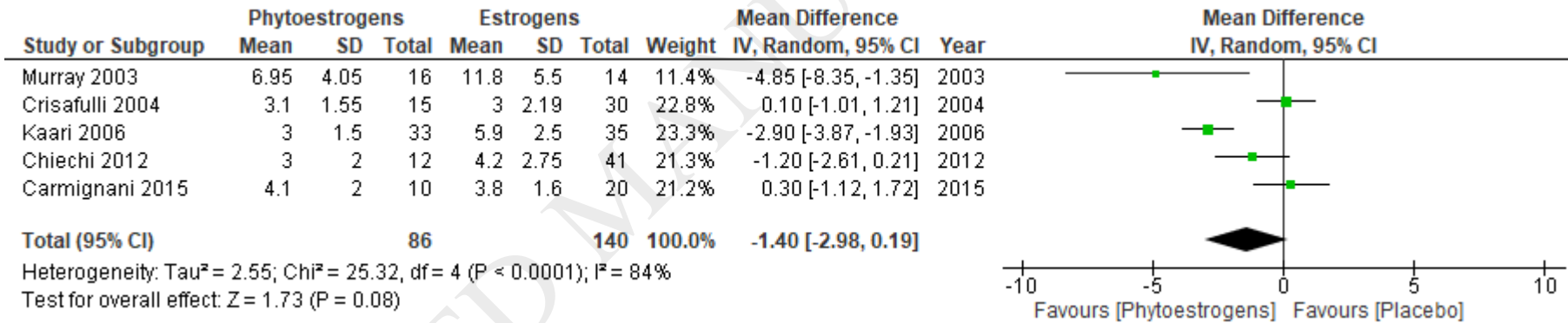


Figure 3. Meta-analysis of the effect of phytoestrogens supplementation on endometrial thickness compared with MHT.

HRT: hormone replacement therapy; PE: phytoestrogens.

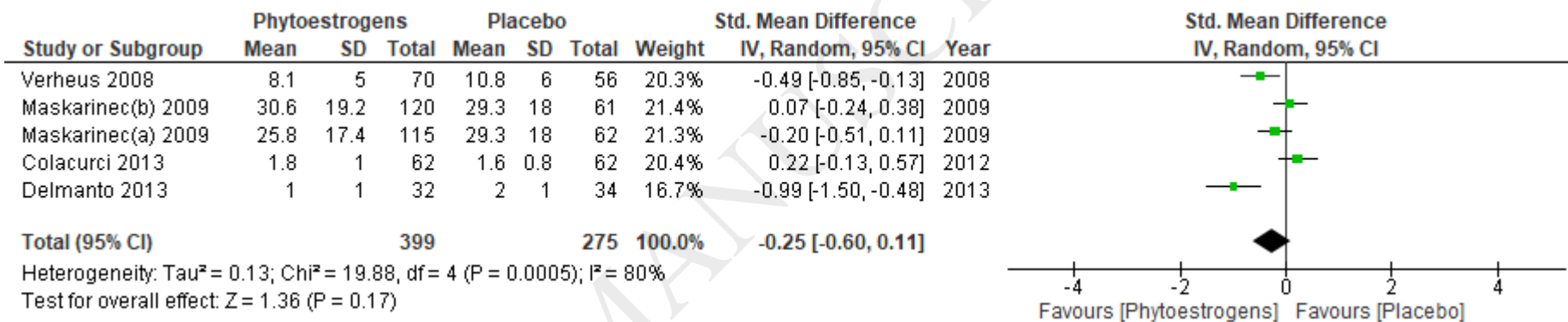


Figure 4. Meta-analysis of the effect of phytoestrogens supplementation on breast density compared with placebo.

PE: phytoestrogens.

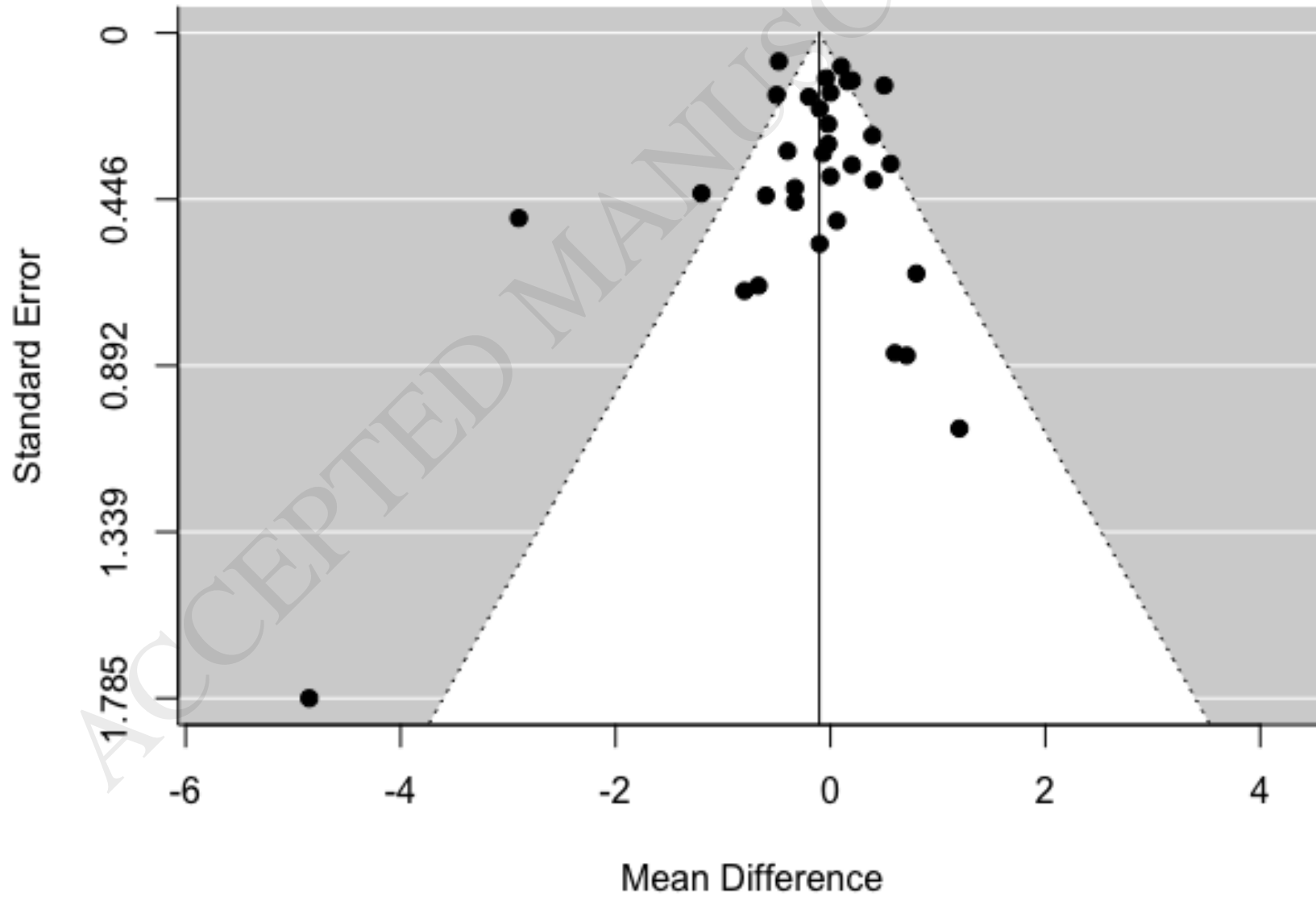


Figure 5. Funnel plot of studies from the endometrial thickness meta-analysis.