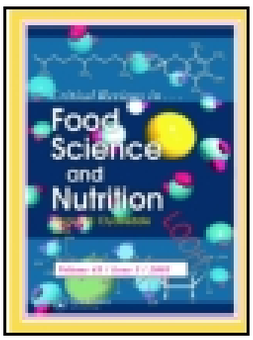

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The effects of isolated soy protein, isolated soy isoflavones and soy protein containing isoflavones on serum lipids in postmenopausal women: A systematic review and meta-analysis

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REVIEW

The effects of isolated soy protein, isolated soy isoflavones and soy protein containing isoflavones on serum lipids in postmenopausal women: A systematic review and meta-analysis

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ABSTRACT

Background: Many randomized controlled trials (RCTs) have assessed the effects of soy products on serum lipids. However, the responsible soy components and the magnitude of effects in healthy or hypercholesterolemic postmenopausal women are unclear. This review assessed the quality of these RCTs and estimated the effects of isolated soy protein, isolated soy isoflavones and soy protein containing isoflavones on total cholesterol (TC), LDL-C, HDL-C, triglycerides (TG), Apolipoprotein (Apo) A-1 and Apo B among postmenopausal women.

Design: Forty-six eligible randomized controlled trials published up to 20 May 2019 were identified from the PubMed, Web of Science and Scopus databases. Weighted mean effect sizes were calculated for net changes in serum lipid concentrations by using random-effect models. Specific subgroup analyses were performed to identify the effect of covariates on serum lipid changes.

Results: Soy consumption was associated with significant decrease in TG (mean differences (MD): −5.04 mg/dl; 95% CI: −9.95, −0.13; P = 0.044), TC (MD: −3.02 mg/dl; 95% CI: −5.56, −0.47; P = 0.02), LDL-C (MD: −3.27 mg/dl; 95% CI: −6.01, −0.53; P = 0.019) and HDL-C (MD: −2.28 mg/dl; 95% CI: −4.27, −0.29; P = 0.025). The reduction in LDL-C, TG and HDL were larger in subjects consuming isolated soy protein than isolated soy isoflavones. There was a significant decrease in serum TG and HDL levels with dosages of >25 grams per day soy protein rather than lower dosages of soy protein. The reductions in Apo A-1 were significantly larger in hypercholesterolemic subjects than in healthy subjects.

Conclusions: Isolated soy protein significantly reduced serum TG, TC, LDL-C, HDL-C and Apo-B levels in postmenopausal women. Isolated soy isoflavones had a significant lowering effect on serum TC and Apo B levels. Soy protein containing isoflavones significantly reduced TG, TC, LDL-C and Apo B levels. Therefore, hyperlipidemia risk reduction with soy products is not uniform and strongly depends on the protein and isoflavone content of soy products, duration and dosage of consumption.

KEYWORDS

Soybean proteins; isoflavones; postmenopause; hyperlipidemias; HDL-C; LDL-C; triglycerides; lipids; lipoproteins; Apo A-1; Apo B; meta-analysis; randomized controlled trials

Introduction

Cardiovascular disease (CVD) is the major cause of death among elderly women (Mendelsohn and Karas 2005). The incidence and prevalence of CVD rise in postmenopausal women presumably due to the reduction in circulating estrogen levels as well as menopause-related atherogenic changes in lipid profiles (American Heart Association 2002; Mendelsohn and Karas 1999). Aside from exogenous estrogen and progesterone in the form of hormone replacement therapy (HRT), soy products approved by US Food and Drug Administration (FDA) health claim, have been reported to be beneficially effective in balancing the side effects versus beneficial effects of HRT as an alternative safe and natural treatment (Erberich et al. 2002; US Department of Health and Human Services 1997). The favorable impact of soy products on health outcomes is mostly due to its components such as protein, polyunsaturated fatty acids, fiber, vitamins, minerals, phytochemicals and isoflavones (ie: genistein, daidzein, and glycitein) (Vitale et al. 2013). They exert their effect by binding to estrogen receptors so as to inhibit and promote the expression of estrogen-sensitive genes (Taylor et al. 2009). Intake of soy products has been suggested to improve serum cholesterol levels, exhibit estrogenic function, stop bone loss and reduce the hot flashes in the postmenopausal women (An et al. 2001; Arjmandi & Smith 2002). However, it has been argued that results from trials of the effect of soy products on blood lipids were too inconsistent to provide exact conclusions in the health

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impacts of soy products. Several studies reported a favorable impact of soy products on plasma levels (Hall et al. 2006; Shidfar et al. 2009; Jassi et al. 2010) However, several trials did not report a beneficial effect on plasma lipids with soy supplementation (Ho et al. 2007; Dewell et al. 2002; Barrasa et al. 2018; Liu et al. 2012). These discrepancies suggest there may be differential blood lipid response to soy intake possibly dependent on the menopause status, age, gender, amount of intake and methods of soy product preparation (ie, soy protein isolate, soy isoflavone isolate, soy protein containing isoflavones). A meta-analysis by Anderson et al found that soy protein reduced low-density-lipoprotein cholesterol (LDL-C) levels by approximately 12.9% and total cholesterol (TC) levels by 9.3% without any changes in high-density lipoprotein cholesterol (HDL-C) levels (Anderson et al. 1995). A recent meta-analysis by Mejia et al also showed that soy protein had significant lowering effect on TC and LDL-C (Blanco Mejia et al. 2019); However, 46 percent of the subjects in the study were postmenopausal women and 37 percent of the subjects were men while our study comprised of postmenopausal women only. In addition, unlike our study which compared the effects of soy protein, soy isoflavones and soy protein containing isoflavones on all lipid factors such as TC, LDL-C, HDL-C, TG, Apo A-1, the study by Blanco Mejia evaluated the effect of mere soy protein on just two lipid factors (TC and LDL-C). To address some of the unsolved questions, we conducted a meta-analysis to systematically evaluate all randomized controlled trials (RCTs) of soy intake for their blood lipid-lowering effect among postmenopausal women.

Method

Search strategy and data sources

Three biomedical literature database, PubMed, Web of Science and Scopus were utilized to search for published reports of RCTs on the effect of soy products on lipid metabolism up to 20 May 2019. The keywords consisted of soya, soybean, soy protein, isoflavones, dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, HDL cholesterol, LDL cholesterol, total cholesterol, triglyceride, triacylglycerol, and VLDL cholesterol. Manual searches were also performed using the reference lists in previous reviews to identify potentially eligible studies not captured by the databases. The search was limited to human subjects, clinical trials and studies published in English.

Study eligibility

Studies were selected for this meta-analysis if they met the following criteria: (i) the duration of intervention was over 2 weeks as it is the required time for blood lipid levels to be stabilized (Grundy and Ahrens 1970); (ii) soy protein isolate, soy isoflavone isolate or soy protein containing isoflavones provided either as supplements or diets enriched with soy products including soy milk, fermented soy products, cereal bars or soy germ; (iii) participants were healthy postmenopausal women or postmenopausal women with dyslipidemia, diabetes mellitus or metabolic syndrome; (iv) participants discontinued HRT at least 3 months before randomization in each study, (v) parallel or crossover RCTs in human beings were conducted; (vi) the outcome included at least one of the following statistics: TC, LDL-C, and HDL-C, TG, Apo A-1 and Apo B; (vii) all data contained the baseline and endpoint values or net changes between them with mean, standard deviation (SD) or standard error (SE) for the experimental and control groups. We excluded literature reviews, cross-sectional studies, nonhuman studies, and studies with inappropriate intervention such as isoflavones or phytoestrogens from other sources rather than soy products, studies with a duration of less than 2 weeks and studies with irrelevant outcomes. Regarding all these criteria, a total of 46 articles including 52 trials were included in the qualitative and quantitative synthesis. Abstracts and complete articles were screened by two independent authors (MM and ED).

Data extraction

The following data were extracted from the studies (i) study characteristics including authors, publication year, study design, dose, and periods of intervention, soy product (soy protein isolate, soy isoflavone isolate or soy protein containing isoflavones), sample size of placebo and experimental group; (ii) participants' information including countries of origin, average ages and physical condition; (iii) study outcomes, including plasma TC, LDL-C, HDL-C, TG, Apo A-1 and Apo B. Plot Digitizer version 2.6.8 was used to extract data from graphs (Plot Digitizer. 2.6.8 ed. Boston 2015). All lipid values were transferred into mg/l and the index of the conversion formula was as follows: (i) 1 mmol/l TG = 88.6 mg/dl TG; (ii) 1 mmol/l TC or LDL or HDL = 38.7 mg/dl TC or LDL or HDL. If the trial included different doses of soy product in the experimental groups, we divided them into two trials with the same control group. If the trial contained several different experimental groups compared with a control group, we only extracted the information on the soy protein, soy isoflavone, soy protein containing isoflavones and control groups. For inaccurate data, we contacted study authors via emails to request their original data. We excluded a study whose author refused to answer the questions (Acharjee et al. 2015).

Risk of bias assessment

Two independent reviewers (MM, and ED) assessed the methodological quality of the included trials using the Cochrane Collaboration risk-of-bias tool (Cochrane Handbook for Systematic Reviews of Interventions 2011). The tool measured the following categories to assess for bias: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, and selective outcome reporting. Trials were classified into three categories including (i) low (proper methods taken to reduce bias), (ii) high (methodological

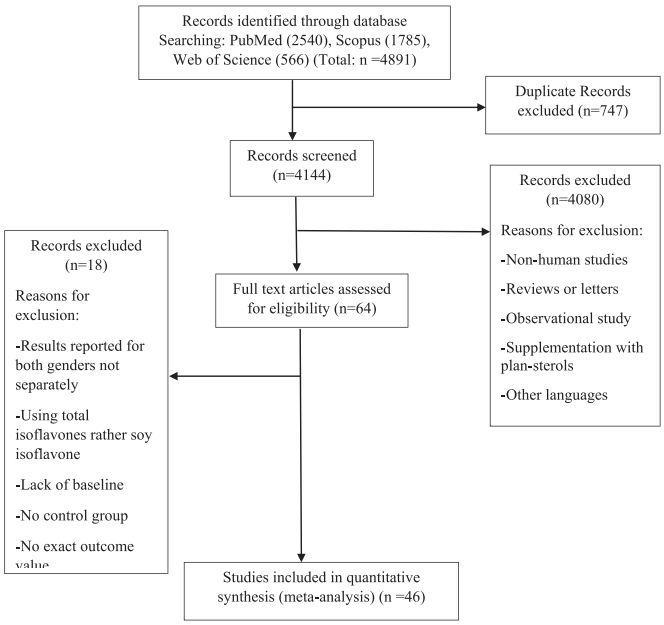

Figure 1. Flow chart literature search.

flaws creating bias), or (iii) unclear (insufficient information provided to determine the bias level). Final assessments were based on agreement among reviewers and confirmed by the third one (LA).

Statistics and analysis

The difference between the change from baseline value for the intervention and control arms was derived from each trial for the endpoints of TC, LDL-C, HDL-C, TG, Apo A-1, and Apo B. If the change from baseline values were not available, we calculated the mean change from baseline to follow-up for each intervention and control group. SEs and confidence intervals (CIs) were converted to SD for the analyses. All serum lipid values were converted to milligrams per deciliter. If more than one-time point for follow-up was reported, we included the value which belonged to the time point with longer duration of follow-up. Heterogeneity in results of the included studies was quantified by Cochran's Q-test at $P < 0.1$ (Cochran 1954). Predefined stratified subgroup analyses were used to investigate potential sources of heterogeneity. Publication bias was analyzed by funnel plot analysis and Egger's regression asymmetry test (Sterne and Egger 2001; Begg and Mazumdar 1994). All of the analyses were performed using STATA version 12.0 (Stata Corporation, College Station, TX, USA) and $P < 0.05$ was considered as significant value.

Results

The literature search yielded 4891 citations of potentially relevant articles of which 747 were duplicate. The remaining 4144 studies were screened on the basis of titles and abstracts, and 64 full-text articles were reviewed in detail. After further sifting, 46 article including 52 trials were selected to complete the meta-analysis. The process is presented in Figure 1. Forty-four articles including 49 trials reported data on TG (Murkies et al. 1995; Teede et al. 2001; Gardner et al. 2001; Van et al. 2001; Jayagopal et al. 2002; Uesugi, Fukui, and Yamori 2002; Dewell, Hollenbeck, and Bruce 2002; Dalais et al. 2003; Nahas et al. 2004; Colacurci et al. 2005; West et al. 2005; Hall et al. 2006; Maesta et al. 2007; Basaria et al. 2009; Campbell et al. 2010; Liu et al. 2012; Kim et al. 2013; Liu et al. 2014; Engelbert et al. 2016; Giolo et al. 2018; Barrasa et al. 2018), 44 articles including 51 trials on TC (Murkies et al. 1995; Teede et al. 2001; Gardner et al. 2001; Van et al. 2001; Dewell, Hollenbeck, and Bruce 2002; Jayagopal et al. 2002; Uesugi, Fukui, and Yamori 2002; Dalais et al. 2003; Nahas et al. 2004; West et al. 2005; Hall et al. 2006; Maesta et al. 2007; Rios et al. 2008; Basaria et al. 2009; Campbell et al. 2010; Liu et al. 2012; Kim et al. 2013; Liu et al. 2014; Engelbert et al. 2016; Giolo et al. 2018; Barrasa et al. 2018), 43 articles including 50 trials on LDL-C (Teede et al. 2001; Gardner et al. 2001; Van et al. 2001; Jayagopal et al. 2002; Uesugi, Fukui, and Yamori 2002; Dewell, Hollenbeck, and Bruce 2002; Dalais et al. 2003; Nahas et al. 2004; Colacurci et al. 2005; West et al. 2005; Hall et al. 2006; Maesta et al. 2007; Rios et al. 2008; Basaria et al. 2009; Campbell et al. 2010; Liu et al. 2012; Kim et al. 2013; Liu et al. 2014; Engelbert et al. 2016; Giolo et al. 2018; Barrasa et al. 2018), 43 articles including 49 trials on HDL-C (Murkies et al. 1995; Teede et al. 2001; Gardner et al. 2001; Van Horn et al. 2001; Jayagopal et al. 2002; Uesugi, Fukui, and Yamori 2002; Dewell, Hollenbeck, and Bruce 2002; Dalais et al. 2003; Nahas et al. 2004; Colacurci et al. 2005; West et al. 2005; Hall et al. 2006; Maesta et al. 2007; Rios et al. 2008; Basaria et al. 2009; Campbell et al. 2010; Liu et al. 2012; Kim et al. 2013; Liu et al. 2014; Engelbert et al. 2016; Giolo and Barrasa 2018), 5 articles on Apo A-1 (Azadbakht et al. 2007; Jassi et al. 2010; Bakhtiary et al. 2010; Maki et al. 2010; Barrasa et al. 2018) and 5 articles on Apo B (Azadbakht et al. 2007; Jassi et al. 2010; Bakhtiary et al. 2010; Maki et al. 2010; Barrasa et al. 2018).

Study characteristics

In total, 46 articles including 52 trials, enrolling 3456 subjects were included, with 1911 participants in the treatment group and 1880 subjects in the control group. Study characteristics are summarized in Table 1. The baseline comorbidity status of the participants varied between studies.

Thirty-one studies enrolled healthy postmenopausal women (Murkies et al. 1995; Teede et al. 2001; Van Horn et al. 2001; Uesugi et al. 2002; Dalais et al. 2003; Steinberg et al. 2003; Murray et al. 2003; Nahas et al. 2004; Kreijkamp-Kaspers et al. 2004; Greany et al. 2004; Colacurci et al. 2005; Hall et al. 2006; Ho et al. 2007; Rios et al. 2008; Basaria et al. 2009; Jassi et al. 2010; Kim et al. 2013; Liu et al. 2014; Engelbert et al. 2016; Barrasa et al. 2018; Giolo et al. 2018) Ten studies enrolled hypercholesterolemic individuals (Gardner et al. 2001; Dewell et al 2002; Blum et al. 2003; Cuevas et al. 2003; Greany et al. 2004; West et al. 2005; Shidfar et al. 2009; Ghafarzadeh and Namdari 2010); two studies included pre-diabetic and diabetic individuals (Jayagopal et al. 2002; Liu et al 2012); three studies enrolled

Table 1. Characteristics of the included studies on the association between soy intake with lipid profile among postmenopausal women.

Author, year, country	Design	Mean age	Health status	PBO	Form of intervention	Intervention	Follow (wk)	No. intervention	No. PBO	Soy protein dose	Isoflavone dose	Exercise
Allen et al., 2007, USA	DB, R, PC	56.4	Healthy	Casein	Powder	Soy protein + Isoflavone	12	107	109	20	160	No
Aubertin-Leheudre et al., 2007, Canada	DB, R, PC	58	Healthy obese	Casein	Capsule	Soy Isoflavone	48	25	25	0	70	No
Basaria et al., 2009, USA	DB, R, PC	56	Healthy	Casein	Powder	Soy protein + Isoflavone	12	38	46	20	160	No
Blum et al., 2002, Israel	DB, R, PC, XO	55	HCH	Casein	Dietary soy	Soy protein + Isoflavone	6	24	24	25	0	No
Blum et al., 2002, Israel	DB, R, PC, XO	55	HCH	Casein	Powder	Soy protein	6	24	24	25	0	No
Campbell et al., 2010, USA	DB, R, PC	56	Heart disease	Casein	Snack bar soy	Soy protein + Isoflavone	48	35	27	25	60	No
Cheng et al., 2004, Taiwan	R, DB, PC	58	Healthy	Esterogen	Capsule	Soy Isoflavone	24	17	11	0	100	No
Colacurci et al., 2005, USA	R, DB, PC	55.4	Healthy	Casein	Tablet	Soy Isoflavone	24	29	29	0	60	No
Cuevas et al., 2003, Chile	DB, R, PC, XO	59	HCH	Casein	Powder	Soy protein + Isoflavone	8	18	18	40	80	No
Dalais et al., 2003, Australia	DB, R, PC	60	Healthy	Casein	Powder	Soy protein + Isoflavone	12	51	40	38	118	No
Dewell et al., 2017, California	DB, R, PC	70	HCH	Casein	Tablet	Soy Isoflavone	24	20	16	0	150	No
Engelbert et al., 2016, Germany	DB, R, PC	59.5	Healthy	Maltodextrin	Capsule	Soy Isoflavone	12	85	85	0	117	No
Ho et al., 2007, China	DB, R, PC	54.1	Healthy	Calcium + Vitamin D	Powder	Soy Isoflavone	12	68	67	0	80	No
Irace et al., 2013, Italy	DB, R, PC	60	MS	Casein	Tablet	Genistein	24	10	10	0	0	No
Jassi et al., 2010, India	DB, R, PC	51.2	Healthy	Casein	Powder	Soy protein + Isoflavone	12	25	25	30	60	No
Jayagopal et al., 2002, UK	DB, R, PC, XO	62.5	T2DM	Cellulose	Powder	Soy protein + Isoflavone	12	16	17	30	132	No
Kim et al., 2013, South Korea	DB, R, PC	53.5	Healthy	Casein	Capsule	Soy Isoflavone	48	42	43	0	70	No
Liu et al., 2014, China	DB, R, PC	58	Healthy	Casein	Powder	Diadzein	24	90	90	0	0	No
Liu et al., 2010, China	DB, R, PC	56.4	Prediabetic	Casein	Powder	Soy protein + Isoflavone	24	60	60	15	100	No
Liu et al., 2010, China	DB, R, PC	56.4	Prediabetic	Casein	Powder	Soy Isoflavone	24	60	60	0	100	No
Llaneza et al., 2010, Spain	R, C	56.6	Healthy	Mediterranean diet	Powder	Soy Isoflavone + Mediterranean diet	96	58	58	0	40	Yes
Rios et al., 2008, Brazil	DB, R, PC	56	Healthy	Casein	Purified soy	Soy Isoflavone	24	25	22	0	40	No
Shidfar et al., 2009, Iran	DB, R, PC	56.6	HCH	Whey	Soy bean	Soy protein + Isoflavone	10	21	21	42	164	No
Teede et al., 2001, Australia	DB, R, PC	61	Healthy	Casein	Powder	Soy protein + Isoflavone	12	50	55	40	118	No
Uesugi et al., 2002, Japan	DB, R, PC	51.8	Healthy	Maltodextrin	Capsule	Soy protein + Isoflavone	4	12	11	16.4	61.8	No
Barrasa et al., 2018, Chile	DB, R, PC	64	Healthy	Starch	Capsule	Soy Isoflavone	12	20	15	0	100	No
Gardner et al., 2001, USA	DB, R, PC	57.7	HCH	Casein	Powder	Soy protein + Isoflavone	16	0	0	42	80	No
Gardner et al., 2001, USA	DB, R, PC	57.7	HCH	Casein	Powder	Soy protein + Isoflavone	16	33	30	42	0	No
Ghafarzadeh and Namdari, 2010, Iran	DB, R, PC	57.7	Healthy	Casein	Capsule	Soy protein	12	50	50	2	0	No
Ghafarzadeh and Namdari, 2010, Iran	DB, R, PC	57.7	HCH	Casein	Capsule	Soy protein	12	50	50	2	0	No
Giolo et al., 2018, Brazil	DB, R, PC	52.7	Healthy	Corn starch	Capsule	Soy Isoflavone	10	17	15	0	100	Yes
Hall et al., 2006, UK	DB, R, PC, XO	57.7	Healthy	Cereal bar	Snack bar soy	Soy isoflavone-enrich-cereal bar	8	117	117	0	59	No
Kreijkamp-Kaspers et al., 2004, Netherland	DB, R, PC	66.7	Healthy	Casein	Powder	Soy protein + Isoflavone	48	100	102	25.6	99	No
Turhan et al., 2009, Turkey	DB, R, PC	51	Healthy	Starch	Tablet	Soy Isoflavone	24	45	45	0	80	No
Maesta et al., 2007, Brazil	R, C	61.3	Healthy	Maltodextrin	Powder	Soy protein + Isoflavone	16	10	11	25	50	No
Maesta et al., 2007, Brazil	R, C	61.3	Healthy	Maltodextrin	Powder	Soy protein + Isoflavone	16	14	11	25	50	Yes
Azadbakht et al., 2006, Iran	R XO	52	MS	Red meat + DASH	Dietary soy	Soy protein	8	42	42	30	84	No
Bakhtiary et al., 2010, Iran	R, C	65	MS	Milk protein	Snack bar soy	Soy protein	12	25	25	35	0	No
Sapbamrer et al., 2013, Thailand	DB, R, PC	55.7	Healthy	Usual diet	Fermented soy	Fermented soy + Usual diet	24	31	29	0	60	No
Manganoa et al., 2013, USA	DB, R, PC	73	Healthy	Maltodextrin	Tablet	Soy Isoflavone	48	34	32	18	35	No
Maki et al., 2010, USA	DB, R, P	51.9	HCH	Casein + Calcium	Powder	Soy protein	4	32	31	25	0	No
Petri et al., 2003, Brazil	DB, R, PC	53.7	Healthy	Placebo	Capsule	Soygerm + Isoflavone	24	25	25	2	60	No
Beavers et al., 2010, USA	B, R, PC	53.8	Healthy	Milk protein	Soy milk	Soymilk	4	16	16	18	0	No
Radhakrishnan et al., 2009, India	DB, R, PC	49.7	Healthy	Casein	Powder	Soy protein + Isoflavone	24	50	50	25	75	No
Van Horn et al., 2001, Chicago	DB, R, PC	66.6	HCH	Oat	Powder	Soy protein + Isoflavone	6	31	31	29	58	No
West et al., 2005, Pennsylvania	DB, R, PC, XO	57.3	HCH	Milk protein	Powder	Soy protein + Isoflavone	6	18	18	25	90	No
Steinberg et al., 2003, California	DB, R, PC, XO	54.1	Healthy	Milk protein	Soy products	Soy protein + Isoflavone	6	28	28	25	107	No
Steinberg et al., 2003, California	DB, R, PC, XO	54.1	Healthy	Milk protein	Soy products	Soy protein	6	28	28	25	0	No
Greany et al., 2004, Minnesota	DB, R, PC, XO	57	HCH	Milk protein	Capsule	Soy protein + Isoflavone	6	37	37	26	44	No
Greany et al., 2004, Minnesota	DB, R, PC, XO	57	Healthy	Milk protein	Capsule	Soy protein + Isoflavone	6	37	37	26	44	No
Murkies et al., 1995, Australia	DB, R, PC	53.8	Healthy	Wheat	Powder	Soy protein + Isoflavone	6	28	30	45	80	No
Murray et al., 2003, North Carolina	DB, R, PC	66.6	Healthy	Estradiol	Powder	Soy protein + Isoflavone	24	8	7	25	120	No

R, randomized; C, controlled; PC, placebo-controlled; Xo, crossover; DB, double-blinded; B, blinded; PBO, placebo; HCH, hypercholesterolemic; MS, metabolic syndrome; T2DM, T2 diabetes mellitus; soy protein dose unit, gram/day; soy isoflavones dose unit, milligram/day.

individuals with metabolic syndrome (Azadbakht et al. 2007; Bakhtiary et al. 2010; Irace et al. 2013) and 1 trial enrolled those with heart disease (Campbell et al. 2010). Fifteen studies were conducted in Asia (Uesugi et al. 2002; Blum et al. 2003; Cheng et al. 2004; Ho et al. 2007; Azadbakht et al. 2007; Shidfar et al. 2009; Turhan et al. 2009; Radhakrishnan et al. 2009; Jassi et al. 2010; Ghafarzadeh and Namdari 2010; Bakhtiary et al. 2010; Liu et al. 2012; Kim et al. 2013; Liu et al. 2014); fourteen trials were performed in North America (Sterne and Egger 2001; Dalais et al. 2003; Blum et al. 2003; Steinberg et al. 2003; Nahas et al. 2004; Cheng et al. 2004; West et al. 2005; Maesta et al. 2007; Allen et al. 2007; Rios et al. 2008; Radhakrishnan et al. 2009; Beavers et al. 2010; Kim et al. 2013; Liu et al. 2014), six trials in South America (Cuevas et al. 2003; Murray et al. 2003; Nahas et al. 2004; Ho et al. 2007; Maesta et al. 2007; Barrasa et al. 2018; Giolo et al. 2018), three in Australia (Murkies et al. 1995; Teede et al. 2001; Dalais et al. 2003) and remainder occurred in Europe (Murkies et al. 1995; Cuevas et al. 2003; Kreijkamp-Kaspers et al. 2004; Ghafarzadeh and Namdari 2010; Sapbamrer et al. 2013; Giolo et al. 2018). Participants were all postmenopausal whose mean ages varied from 49 to 73 years. Dietary interventions lasted from 6 to 96 weeks. Of 46 studies, 38 were parallel randomized controlled trials of which all studies were blinded. Eight articles had a cross-over design (Jayagopal et al. 2002; Blum et al. 2003; Cuevas et al. 2003; Steinberg et al. 2003; Greany et al. 2004; West et al. 2005; Hall et al. 2006; Azadbakht et al. 2007). The dosage of soy protein was from 2 to 45 grams per day. The dosage of soy isoflavones was from 35 to 160 mg per day including genistein (2 to 70 mg), daidzein (4.8 to 93 mg), glycitein (4 to 40 mg). Ten studies provided soy products through the whole diet in the form of soy milk, soy cereal bars, fermented soy, and soybeans (Blum, Steinberg, and Murray 2003; Hall et al. 2006; Azadbakht et al. 2007; Shidfar et al. 2009; Campbell et al. 2010; Bakhtiary et al. 2010; Beavers et al. 2010; Sapbamrer et al. 2013); another 36 studies provided soy supplements in the form of tablet, capsule and powder. Postmenopausal women were given or recommended specific daily amounts of isolated soy protein (Blum et al. 2003; Steinberg et al. 2003; Azadbakht et al. 2007; Ghafarzadeh and Namdari 2010), isolated soy isoflavones (Dewell et al. 2002; Cheng et al. 2004; Colacurci et al. 2005; Ho and Aubertin-Leheudre 2007; Rios et al. 2008; Turhan et al. 2009; Llaneza et al. 2010; Liu et al. 2012; Kim et al. 2013; Liu et al. 2014; Engelbert et al. 2016; Barrasa et al. 2018; Giolo et al. 2018) or soy protein containing isoflavones (Murkies et al. 1995; Teede et al. 2001; Gardner et al. 2001; Van Horn et al. 2001; Jayagopal et al. 2002; Uesugi et al. 2002; Dalais et al. 2003; Nahas et al. 2004; Kreijkamp-Kaspers et al. 2004; West et al. 2005; Maesta et al. 2007; Allen et al. 2007; Shidfar et al. 2009; Basaria et al 2009; Radhakrishnan et al. 2009; Jassi et al. 2010; Beavers et al. 2010; Campbell et al. 2010; Liu et al. 2012). The control groups were diverse, as outlined in Table 1. The outcomes demonstrated that there was non-significant publication bias of TG, TC, LDL-C, HDL-C, Apo A-1 and Apo B (TG Egger's test: $P = 0.897$; TC Egger's test: $P = 0.378$; LDL-C Egger's test: $P = 0.586$; HDL-C Egger's test: $P = 0.188$, Apo A-1 Egger's test: $P = 0.347$, Apo B Egger's test: $P = 0.180$). Given the large heterogeneity in study results, we conducted eight subgroups to analyze the source of heterogeneity, which included the kind of intervention (soy protein, soy isoflavones or soy protein containing isoflavones), the dosage of soy protein, the dosage of soy isoflavones, duration of intervention, continents, health status, kind of soy product (dietary soy or supplement) and physical activity.

Effect of soy products on serum TG levels among postmenopausal women

Forty-nine trials containing 3634 subjects (1831 of them in the treatment group, the remainder in the control group) were used to analyze the effect of soy on plasma TG levels. With a random-effects model, a significant reduction in TG levels between the treatment and control groups were found (mean differences (MD): −5.04 mg/dl; 95% CI: −9.95, −0.13; $P = 0.044$, $I^2 = 90.9\%$; $P_{heterogeneity} < 0.0001$) (Figure 2). Subgroup analysis presented that significant reductions in TG were found in the healthy subjects and subjects with metabolic syndrome (MD: −5.00 mg/dl; 95% CI: −6.77, −3.23; $P < 0.0001$) and (MD: −4.66 mg/dl; 95% CI: −6.56, −2.76; $P < 0.0001$). Similarly, significant changes in TG were detected with the intervention of isolated soy protein and soy protein containing isoflavones (MD: −4.79 mg/dl; 95% CI: −6.59, −2.98; $P < 0.0001$) and (MD: −6.32 mg/dl; 95% CI: −8.45, −4.18; $P < 0.0001$). However, no significant changes in TG were observed with the intervention of isolated soy isoflavones. In the soy protein dosage subgroup, there was a significant decrease in serum TG levels with dosages of >25 grams per day (MD: −6.35 mg/dl; 95% CI: −7.87, −4.82; $P < 0.0001$). In the isoflavone dosage, duration of intervention and kind of intervention, a significant reduction in TG was found in all subgroups (Supplemental Table 2). Moreover, In the subgroup of physical activity, a significant increase in serum TG levels of subjects with physical activity and a significant decrease in subjects without physical activity were found (MD: −5.20 mg/dl; 95% CI: −6.44, −3.95; $P < 0.0001$) and (MD: 17.13 mg/dl; 95% CI: 9.15, 25.11; $P < 0.0001$). Analyses of between-group heterogeneity showed that physical activity, health status, and soy product kind were sources of heterogeneity after subgroup analyses for TG levels (Supplemental Table 2).

Effect of soy products on serum TC levels among postmenopausal women

Fifty-one trials with 1882 subjects in the treatment group and 1851 in the control group reported baseline data and endpoint values regarding plasma TC levels. The forest plot with MD in post-trial TC concentration between intervention and placebo groups and their 95% CIs are shown in Figure 3. Using the random-effects model, the pooled effect size of soy supplementation versus control showed that soy products had a significant effect on plasma TC levels in postmenopausal women (MD: −3.02 mg/dl; 95% CI: −5.56, −0.47; $P = 0.02$, $I^2 = 92.1\%$; P heterogeneity < 0.0001). According to subgroup analyses based on intervention kind, significant changes in TC were observed in all subgroups. Results of categorical analysis based on health

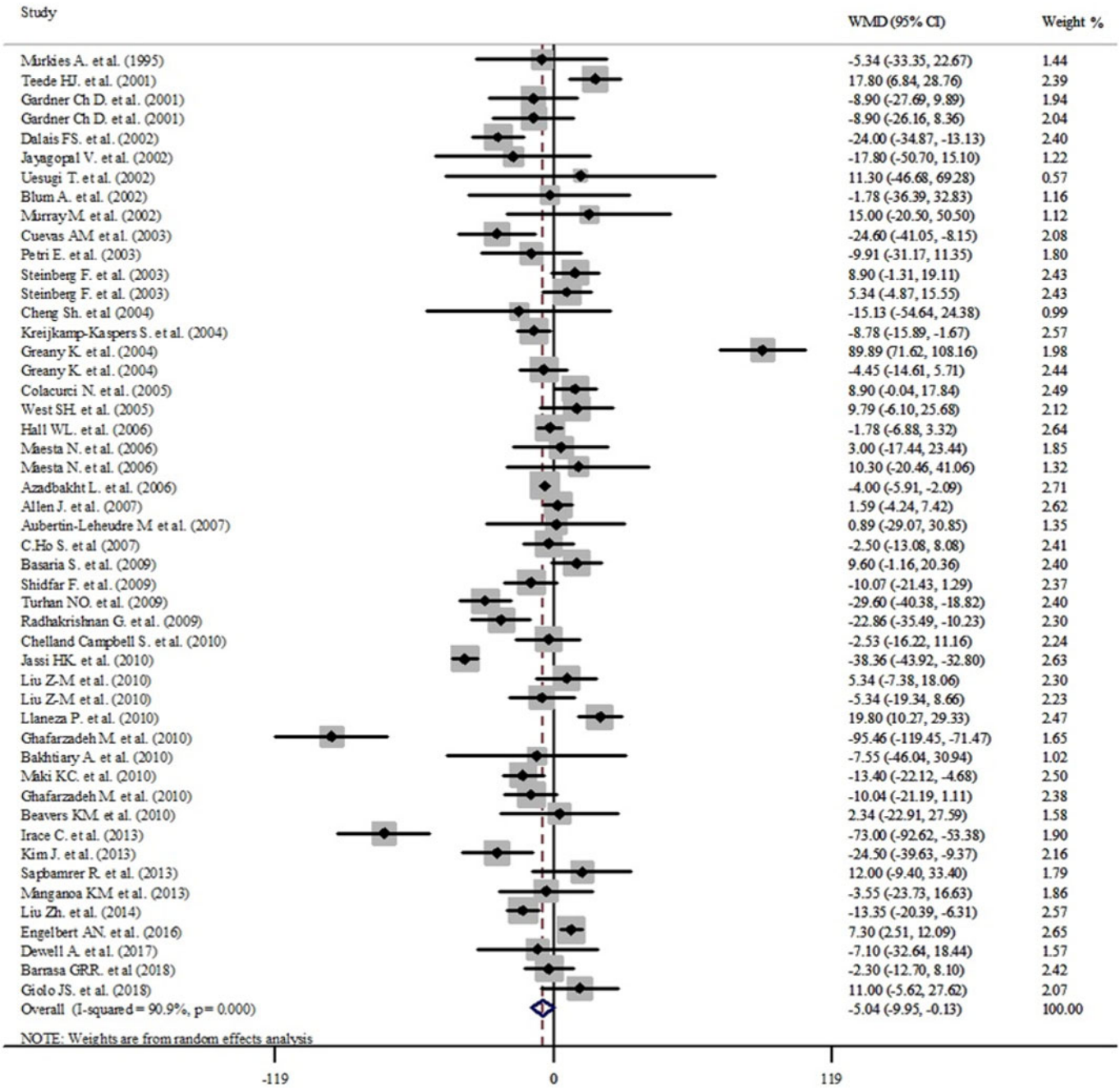

Figure 2. Effect of soy products on TG levels of postmenopausal women.

status, the dosage of soy protein, dosage of soy isoflavone, duration of intervention, physical activity and soy product kind revealed that there was a significant decrease in serum TC levels in subjects of almost all subgroups (Supplemental Table 3). Analyses of between-group heterogeneity showed that physical activity and health status were sources of heterogeneity after subgroup analyses for TC levels.

Effect of soy products on serum LDL-C levels among postmenopausal women

Forty-nine studies representing 1821 participants in the treatment and 1790 in the placebo group reported results for serum LDL-C concentrations. The forest plot with MD in post-trial LDL-C concentration between intervention and placebo groups and their 95% CIs are shown in Figure 4. Overall, there was a significant difference in serum LDL-C between soy intake and control group (MD: −3.27 mg/dl; 95% CI: −6.01, −0.53; P = 0.019, $I^2 = 90.3\%$; $P_{heterogeneity} < 0.0001$). Stratified subgroup analyses revealed that there was a significant decrease in LDL-C levels of subjects consuming isolated soy protein and soy protein containing isoflavones (MD: −5.10 mg/dl; 95% CI: −6.03, −4.01; P < 0.0001) and (MD: −4.10 mg/dl; 95% CI: −5.37, −2.83; P < 0.0001). In a categorical analysis by health status, doses of soy protein, doses of isoflavones and kind of intervention there was a significant decrease in LDL-C

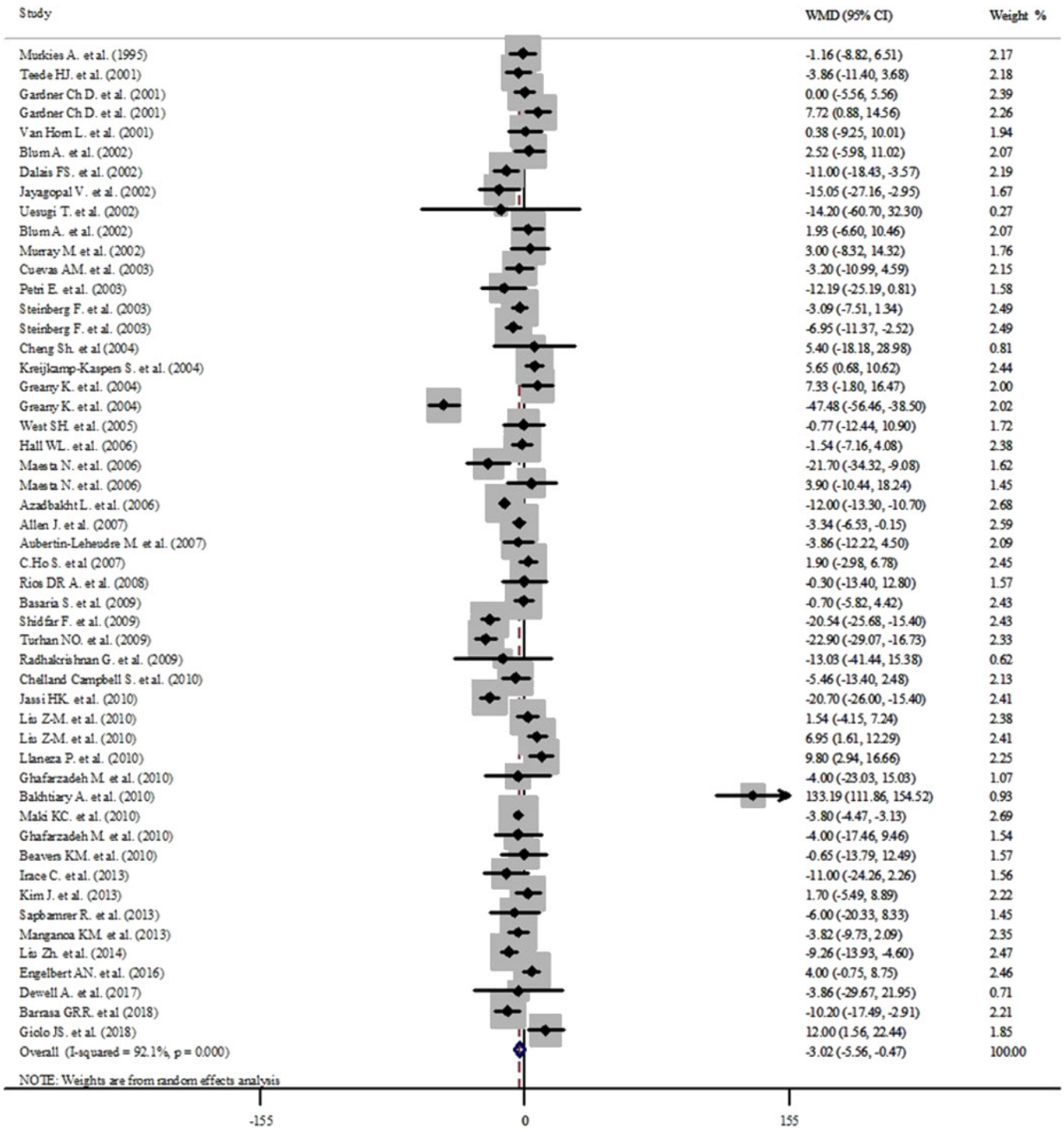

Figure 3. Effect of soy products on TC levels of postmenopausal women.

levels in all subgroups (Supplemental Table 4). In the subgroup of physical activity, an unexpected significant increase in serum LDL-C levels of subjects with physical activity and a significant decrease in subjects without physical activity were found (MD: −4.27 mg/dl; 95% CI: −4.97, −3.58; $P < 0.0001$) and (MD: 10.52 mg/dl; 95% CI: 5.71, 15.34; $P < 0.0001$). Analyses of between-group heterogeneity showed that physical activity and continent were sources of heterogeneity after subgroup analyses for LDL-C levels.

Effect of soy products on serum HDL-C levels among postmenopausal women

Twenty-one trials were selected to perform the analysis. There were 1820 and 1791 subjects in the intervention and control groups, respectively. Using the random-effects model, the net change in HDL levels was (MD: −2.28 mg/dl; 95% CI: −4.27, −0.29; $P = 0.025$, $I^2 = 95.4\%$; $P_{heterogeneity} < 0.0001$) (Figure 5). Results of categorical analysis based on health status revealed that there was a significant increase in

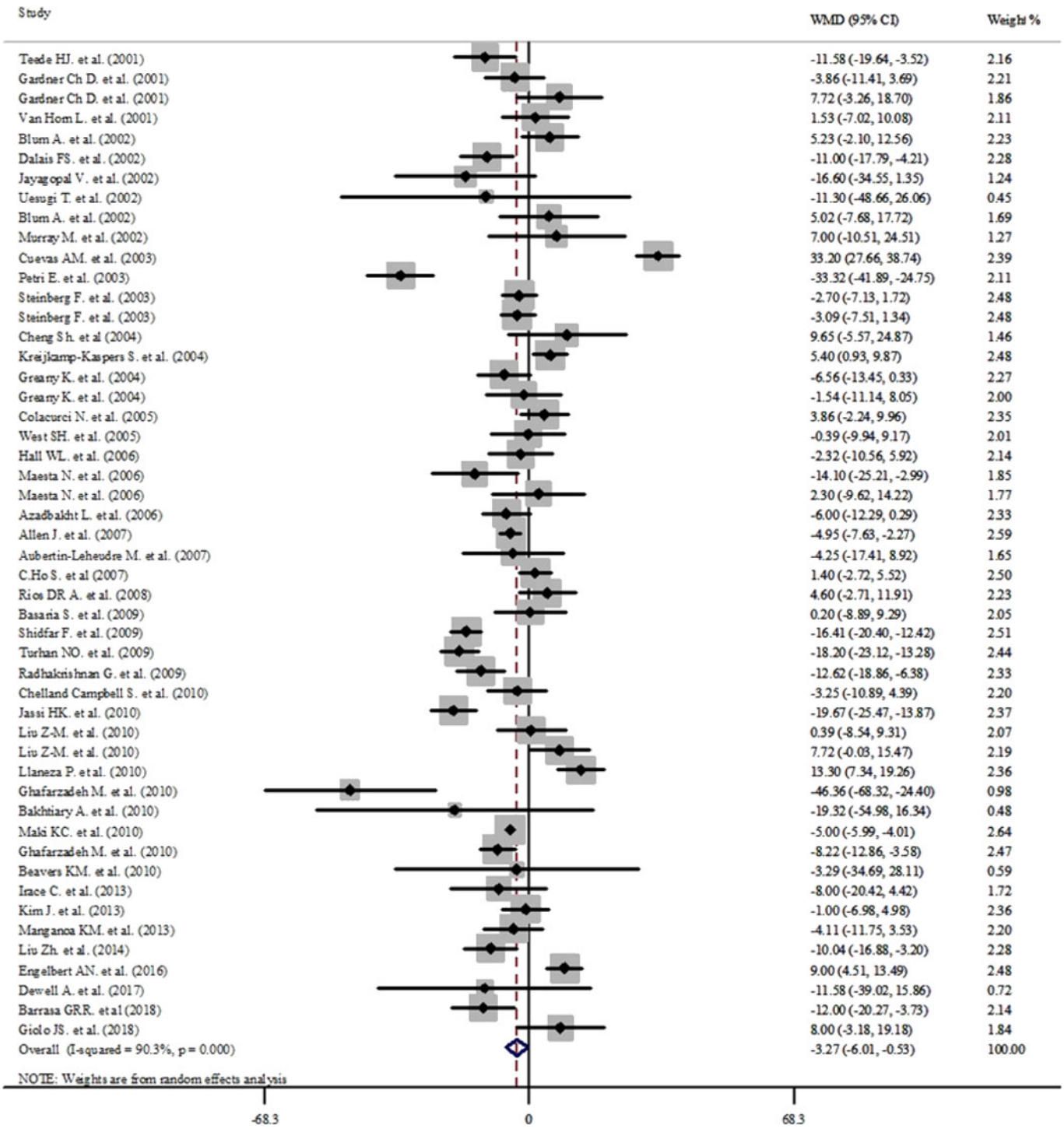

Figure 4. Effect of soy products on LDL-C levels of postmenopausal women.

serum HDL levels of hypercholesterolemic and a significant decrease in healthy subjects (MD: 1.83 mg/dl; 95% CI: 0.81, 2.86; $P < 0.0001$) and (MD: −1.38 mg/dl; 95% CI: −1.92, −0.84; $P < 0.0001$). Subgroup analyses based on intervention suggested that significant changes in HDL were only observed with the intervention of isolated soy protein (MD: −1.20 mg/dl; 95% CI: −2.17, −0.22; $P = 0.016$). Stratified subgroup analyses revealed that a significant increase was observed in HDL levels of subjects in >12 weeks' subgroup (MD: 0.79 mg/dl; 95% CI: −0.17, 1.41; $P = 0.013$). In a categorical analysis by soy protein dosage, subjects consuming higher doses had significantly lower levels of HDL (MD: −0.77 mg/dl; 95% CI: −1.33, −0.21; P= <0.007). A significant increase was observed in HDL levels of subjects consuming >74 mg isoflavones (MD: 0.90 mg/dl; 95% CI: 0.40, 1.40; $P < 0.0001$) whilst there was a significant decrease in the lower dose subgroup (MD: −2.93 mg/dl; 95% CI: −3.61, −2.24; $P < 0.0001$). A large decrease in plasma HDL-C levels was found in subjects consuming soy supplements rather than dietary soy (MD: −0.57 mg/dl; 95% CI: −1.05, −0.09; $P = 0.020$). In the subgroup of physical activity, a significant decrease in HDL-C levels was observed in subjects

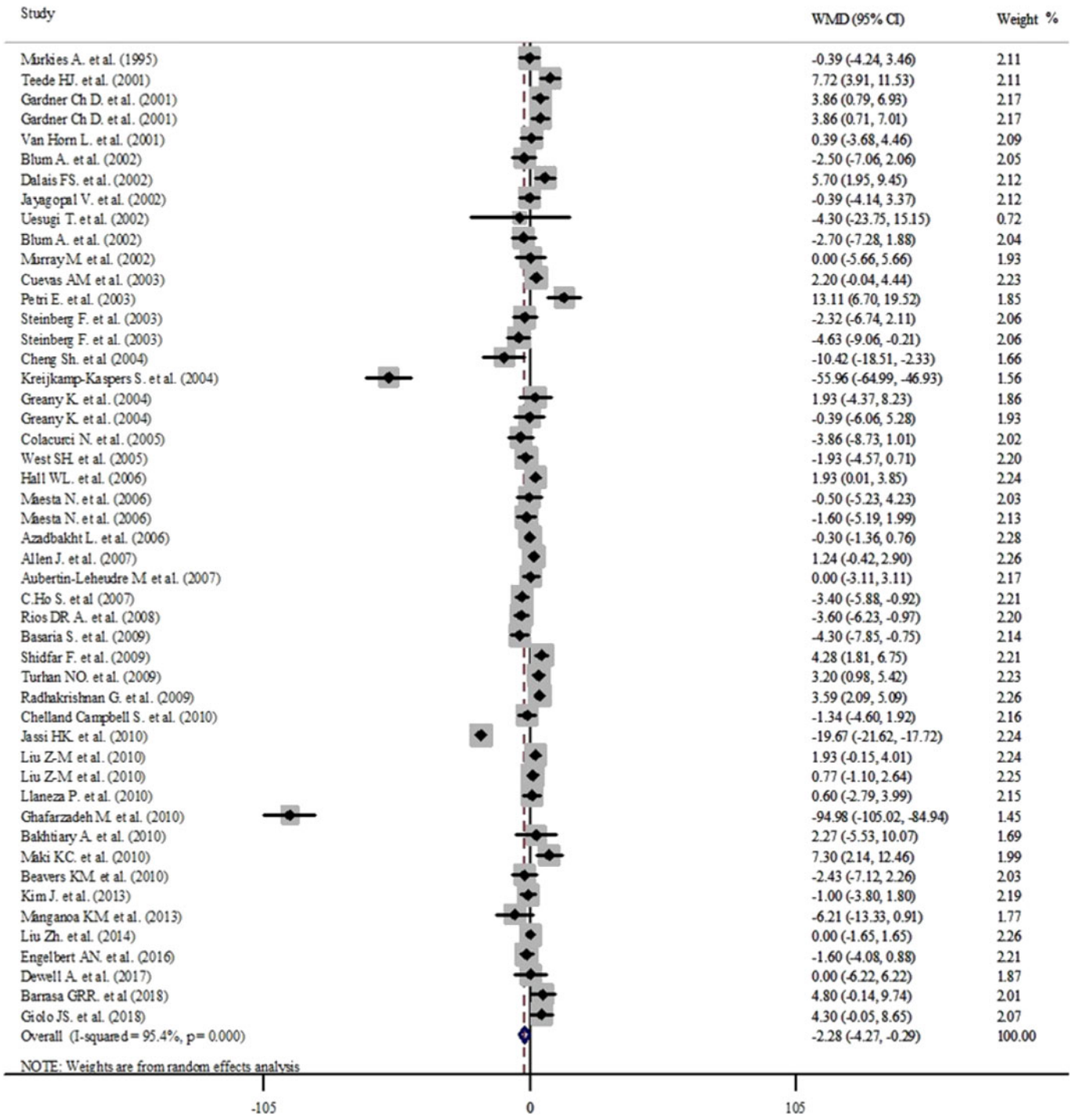

Figure 5. Effect of soy products on HDL-C levels of postmenopausal women.

without physical activity (Supplemental Table 5). Analyses of between-group heterogeneity showed that physical activity, health status, and continent were found to be as sources of heterogeneity after subgroup analyses for HDL levels.

Effect of soy products on serum Apo A-1 levels among postmenopausal women

Five trials containing 282 subjects (144 of them in the treatment group, the remainder in the control group) were used to analyze the effect of soy on plasma Apo A-1 levels. Figure 6 has shown the effects of soy intake on Apo A-1 levels. Results of the meta-analysis showed that soy intake rather than the placebo group had a non-significant effect on Apo A-1 concentration (MD: 0.42 mg/dl; 95% CI: −3.08, 3.92; $P = 0.814$, $I^2 = 58.9\%$; $P_{heterogeneity} = 0.045$). Subgroup analysis suggested that significant reductions in Apo A-1 was found in subjects with hypercholesterolemia (MD: −4.00 mg/dl; 95% CI: −7.60, −0.40; $P = 0.030$). No other effect modifications by other subgroup analyses were observed. Analyses of between-group heterogeneity showed that continent and health status were sources of heterogeneity after subgroup analyses for Apo A-1 levels (Supplemental Table 6).

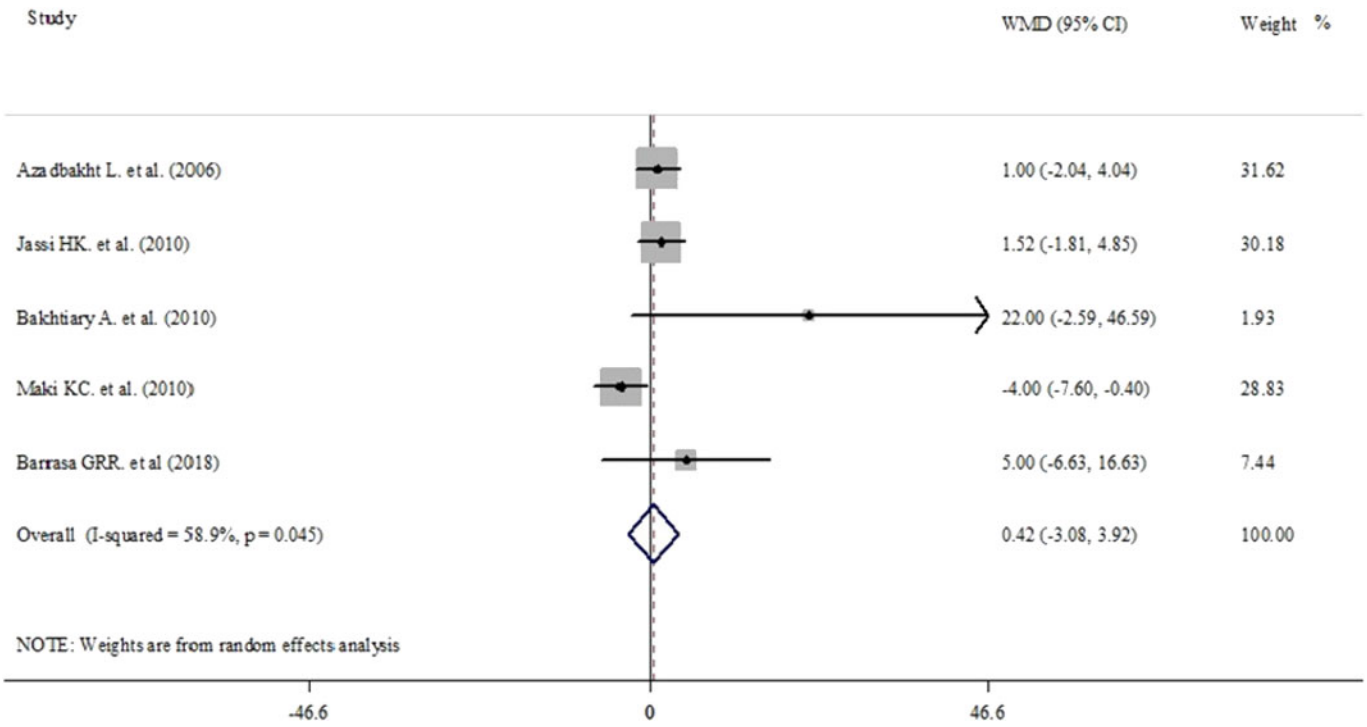

Figure 6. Effect of soy products on Apo A-1 levels of postmenopausal women.

Effect of soy products on serum Apo B levels among postmenopausal women

Five trials containing 282 subjects (144 of them in the treatment group, the remainder in the control group) were used to analyze the effect of soy on plasma Apo B levels. Figure 7 has shown the effects of soy intake on Apo B levels. Results of the meta-analysis showed that soy intake rather than placebo group had a non-significant lowering effect on Apo B concentration (MD: −6.11 mg/dl; 95% CI: −15.05, 2.82; P = 0.180, $I^2 = 93.6\%$; $P_{heterogeneity} < 0.0001$). Results of categorical analysis based on health status, dosage of soy protein and soy isoflavone, duration of intervention, physical activity and soy product kind revealed that there was a significant decrease in serum Apo B levels in subjects of all subgroups (Supplemental Table 7).

Discussion

To the best of our knowledge, the current systematic review and meta-analysis is the first review of RCTs on the efficacy of soy consumption on lipid profiles in postmenopausal women. Results of our meta-analysis support the hypercholesterolemic of soy for the lowering of serum TC levels. Soy intake also favorably affected LDL-C and TG concentrations. Decreases in serum HDL-C concentrations were apparent among postmenopausal women during soy intervention. There was no evidence, however, which suggests that soy-enriched diets or supplements beneficially affected serum Apo A-1 and Apo B levels.

Several meta-analyses on the impact of soy protein on LDL-C reported consistent results. The American Heart Association (AHA) review reported a mean LDL-C reduction of 3% by using isolated soy protein with isoflavones with no dose-effect (Sacks et al. 2006). Moreover, a meta-analysis by Anderson et al. presented a mean LDL-C reduction of 5.5% and a mean TG reduction of 10.7% in parallel studies (Jassi et al. 2010). Furthermore, a meta-analysis by Mejia on 46 trials which is the base of FDA decision to revoke the heart health claim for soy protein, revealed a highly significant reduction of soy protein intake on both TC and LDL-C concentrations (Ho et al. 2007). Results of Zhan et al. meta-analysis also revealed a significant decrease in serum TC, LDL-C, and TG concentrations after consumption of soy protein containing isoflavones (Zhan and Ho 2005). Inconsistent with our outcomes regarding the effects of soy protein containing isoflavones on HDL-C concentrations, a meta-analysis of 23 trials by Zhan et al. reported that the consumption of soy protein containing isoflavones significantly increased serum HDL-C concentrations.

One probable mechanism of the beneficial effect of soy protein on the intrinsic cholesterol-lowering has been attributed to the 7S globulin fraction of soy protein which seems to up-regulate LDL receptors and induce gene expression of several enzymes and proteins which involved in lipid metabolism (Tovar et al. 2002). Moreover, soy peptides may regulate cholesterol homeostasis in Hep G2 cells; 7S β-conglycinin-derived peptides from soybean may decrease the secretion of Apo B from Hep G2 cells. Also, 7S β-conglycinin at high concentration may inhibit C-acetate incorporation into cellular lipids which may result in a remarkable reduction of C-acetate incorporation mainly into free cholesterol but also into cholesterol esters and triglycerides (Lovati et al. 2000). Moreover, among the bioactive peptides derived from soy, lunasin, a peptid with 43 aminoacid with high bioavailability and stability had a potential cholesterol-

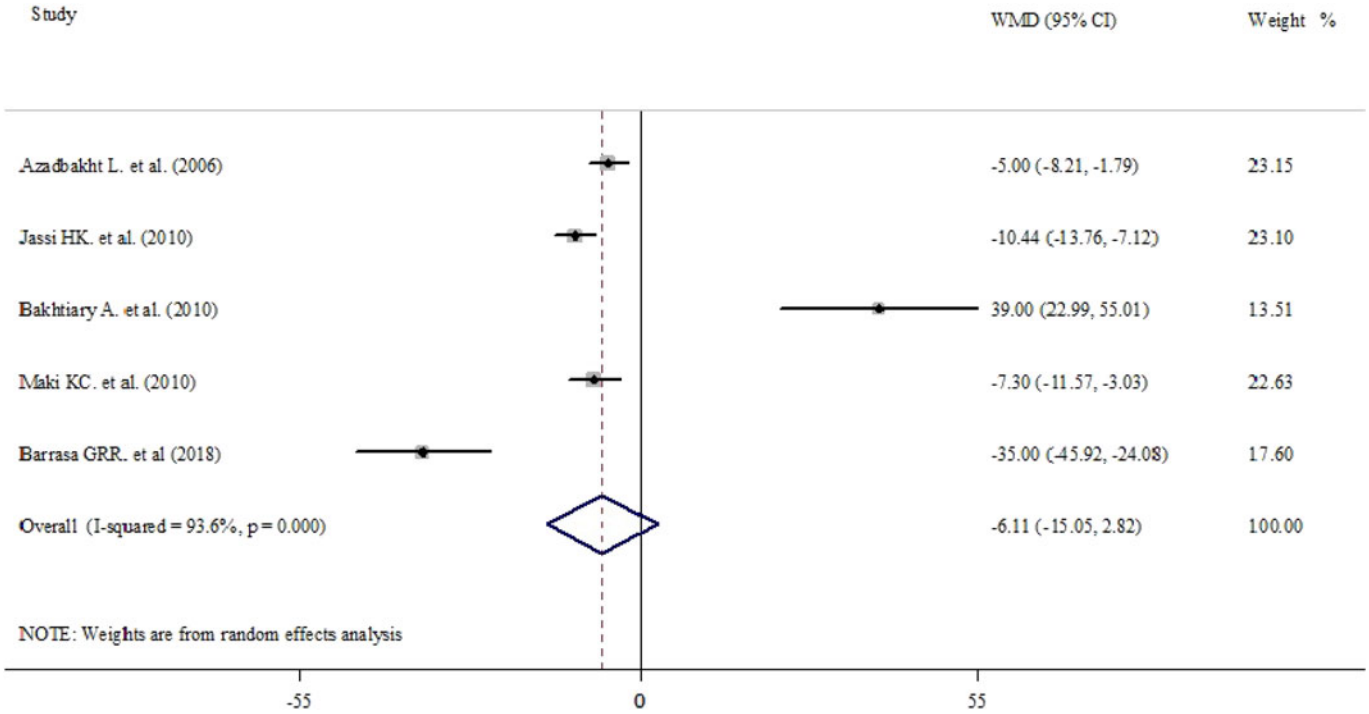

Figure 7. Effect of soy products on Apo B levels of postmenopausal women.

lowering effect specifically (Cicero et al. 2017). Another possible mechanism may be due to the soy isoflavones structural similarities to estrogens and estrogen-receptor-dependent gene expressions which may cause isoflavones to serve as natural selective estrogen receptor modulator and influence the lipid metabolism (Potter 1995).

The subjects included in this meta-analysis varied from healthy individuals to unhealthy ones suffering complication from chronic diseases such as hypercholesterolemia, diabetes, pre-diabetes, metabolic syndrome, and heart disease. Therefore, we conducted a health status subgroup analysis to detect the heterogeneity. In the healthy and hypercholesterolemic subgroups, the soy products showed a statistically significant reduction in TC, LDL-C, TG and Apo B which was consistent with several studies (Shidfar, Turhan 2009). No such effects were found in the subgroups of the other complications which may be due to the few numbers of trials included in those subgroups. An interesting phenomenon was found in HDL group in which we found a significant increase in HDL levels among hypercholesterolemic subjects and a significant reduction in HDL concentrations of healthy individuals. Our outcomes were consistent with the conclusion of Zhan et al. who demonstrated that soy protein containing isoflavones had beneficial effects on HDL-C concentration in a subgroup of postmenopausal women with hypercholesterolemia (Sacks et al. 2006). It is possible that the effects of dietary soy products on HDL-cholesterol concentrations may differ between normal and hypercholesterolemic subjects. It is interesting to point out that a drop in HDL-C cholesterol is common in healthy subjects which may be due to the low-fat diet, as was observed in our study in healthy subgroup (Sanders et al. 2002). On the other hand, it is plausible that isoflavones might affect TGF-β1 concentrations in older individuals with either abnormal concentrations of TGF-β1 or moderate hyperlipidemia (Sanders et al. 2002).

An important contributor to the heterogeneity in our meta-analysis appeared to be the ingredients of soy products. Isolated soy isoflavones significantly decreased Apo B whilst no statistically significant differences were observed in TC, LDL-C, TG, Apo A-1 and HDL-C concentrations in line with several studies (Dewell et al. 2002; Ho et al. 2007; Llaneza et al. 2010) suggesting that soy isoflavones probably play a limited role in modifying serum lipids in postmenopausal women. Additionally, in accordance with a meta-analysis by Anderson et al. consumption of soy protein containing isoflavones showed a statistically significant difference in TC, LDL-C, TG, and Apo B but not in HDL-C and Apo A-1 (Allen et al. 2007). Apo A-1 concentration is an indicator of the number of circulating HDL particles and its changes may result in parallel changes in the HDL-C concentrations. Accordingly, consistent with another study by Jenkins et al. (Jenkins et al. 2002), our results regarding the HDL-C and Apo A-1 response to soy foods could be justified. Consumption of soy protein containing isoflavones also resulted in a significant reduction in all serum lipids including TC, LDL-C, TG, HDL-C, and Apo B except for Apo A-1 levels in accordance with Azadbakht et al. study (Azadbakht et al. 2007). These results indicate that the combination of soy protein and isoflavones probably convey more benefit than does isolated isoflavone alone. One probable explanation for the TC and LDL-C lowering effect of soy protein tends to be related to the 7S globulin fraction of soy protein, which is common to other legume proteins and seems to inhibit hepatic Apo B synthesis. Collectively, it could be inferred that isoflavones may not be the responsible agent for TG and LDL-C lowering effect of soy proteins. The lack of any significant findings for purified

isoflavones suggests that soy isoflavones may require other components found in soy protein to exert their beneficial effects.

Different results may also be due to the duration of supplementation. Our meta-analysis showed that supplementation of more than 12 weeks with soy products significantly improved HDL-C concentrations whereas supplementation of less than 12 weeks could decrease HDL-C levels. This may reflect the idea that soy products may need a longer duration of intervention to exert their improving effect on serum HDL-C. In line with our results, in a meta-analysis by Zhan et al a significant increase in HDL-C was found only in subgroups with intervention periods longer than 12 wk (Zhan and Ho 2005). This may conflict with the article that demonstrated serum lipids changes were minimal, even over a 1-year intervention of soy protein (Mangano et al. 2013). Nahas et al. indicated that 24 wk supplementation with soy germ containing isoflavones as a long-term intervention reduced LDL-C and increased HDL-C significantly (Nahas et al. 2004). Moreover, a study revealed that soy isoflavones can apparently increase HDL-C during 24 wk supplementation (Turhan et al. 2009).

Dose-response effects were observed in available studies. Significant decrease in TG and HDL-C levels were observed in subjects consuming more than 25 grams of soy protein per day which is in line with (Cuevas et al. 2003; Dalais et al. 2003) which suggest that soy protein exerts adverse effects on HDL-C levels with higher doses. However, several studies observed a significant increase in plasma HDL-C responses to soy protein with or without isoflavones at protein dosage of more than 25 g/day (Shidfar et al. 2009; Maki et al. 2010). Based on clinical trials, 74 mg/day of isolated soy isoflavones, half of the 150 mg/day for which there is concern for probable development of endometrial hyperplasia in postmenopausal women, is considered as the "effect level" and the safe upper limit for standard intakes of soy isoflavone for humans (premenopausal and postmenopausal females, and males). The efficiency and safety of soy isoflavones is not well established and evidence from literature is not enough to define the possible its adverse effects. Therefore, the use of isoflavone supplements is not recommended (Sacks et al. 2006; Food Safety Commission 2009). Subgroup analysis in this meta-analysis showed that isolated soy isoflavones intake at doses of lower than 74 mg/day significantly decreased HDL-C levels while a significant increase in HDL-C concentrations of postmenopausal women occurred when exposed to doses of higher than 74 mg/day of soy isoflavones. The previous study by Turhan et al. has also shown that soy isoflavones intake at doses 80 mg/day for 6 months significantly increased HDL-C levels which is in line with our meta-analysis (Turhan et al. 2009). However, several studies found no improvements in HDL-C levels (Dewell et al. 2002; Engelbert et al. 2016). A possible explanation is that isoflavone via estrogenic mechanism is thought to decrease plasma Fasting total homocysteine (tHcy) level, which is found to be an independent risk factor for hyperlipidemia and cardiovascular diseases, in hyperlipidemic and diabetic men and women (Turhan et al. 2009). In the current study, soy dietary supplementation resulted in a significant decrease in HDL-C, whereas no significant reduction was noted with dietary soy intake which may be due to the saponins, polyunsaturated oils, or vegetable proteins in dietary soy products (either individually or in a combined way) (Teede et al. 2001).

Subgroup based on physical activity revealed that the combination of soy products consumption and physical activity training showed a significant increase in TC, LDL-C, HDL-C and TG concentrations. However, significant decreases in the same lipid factors were only seen when subjects were exposed to soy intake alone with no physical activity training.

The weakness of this analysis is that it was based on data involving studies regarding the intrinsic effect of soy products rather than extrinsic effects (displacement) in improving lipid profiles. As reported in a previous meta-analysis by Jenkins et al. the replacement of meat or dairy protein by 13 g of soy protein resulted in a 3.6% LDL-C reduction and a considerable reduction of 6% was achieved at 50 g of soy protein. Besides, this is likely to be more relevant to the uncontrolled real-life situation when soy foods are included as a part of our typical diet (Sanders et al. 2002). Therefore, more trials on this issue are warranted in a population of postmenopausal women. We also noted considerable heterogeneity in the treatment effects. The strengths of this analysis are a large number of trials used; besides we compared the effects of isolated soy protein, isolated soy isoflavones and soy protein containing isoflavones consumption on lipid profile of postmenopausal women through subgroup analysis which to the best of our knowledge was the first time to be considered in a meta-analysis.

Conclusion

In summary, this meta-analysis demonstrates some interesting evidence, suggesting that consumption of soy products is associated with significantly decreased serum TC, LDL-C, HDL-C, TG, and Apo B concentrations. Higher concentrations of isoflavones have larger effects on HDL-C improvements. Longer-term intake of soy products can improve HDL-C concentrations. TG and LDL-C levels were significantly decreased when individuals consumed soy protein or soy protein containing isoflavones rather than isolated soy isoflavones.

Disclosure statement

The authors declare that they have no conflict of interest.

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References

Acharjee, S., J. R. Zhou, T. K. Elajami, and F. K. Welty. 2015. Effect of soy nuts and equol status on blood pressure, lipids and inflammation in postmenopausal women stratified by metabolic syndrome status. *Metabolism* 64 (2):236–43. doi: 10.1016/j.metabol.2014.09.005.

Allen, J. K., D. M. Becker, P. O. Kwiterovich, K. A. Lindenstruth, and C. Curtis. 2007. Effect of soy protein-containing isoflavones on lipoproteins in postmenopausal women. *Menopause* 14 (1):106–14. doi: 10.1097/01.gme.0000229572.21635.49.

American Heart Association. 2002. Heart disease and stroke statistics-2003 update. http://www.americanheart.org/downloadable/heart/10590179711482003HDSStatsBookREV7-03.pdf.

An, J., C. Tzagarakis-Foster, T. C. Scharschmidt, N. Lomri, and D. C. Leitman. 2001. Estrogen receptor β-selective transcriptional activity and recruitment of coregulators by phytoestrogens. *Journal of Biological Chemistry* 276 (21):17808–14. doi: 10.1074/jbc.M100953200.

Anderson, J. W., B. M. Johnstone, and M. E. Cook-Newell. 1995. Meta-analysis of the effects of soy protein intake on serum lipids. *New England Journal of Medicine* 333 (5):276–82. doi: 10.1056/NEJM199508033330502.

Arjmandi, B. H., and B. J. Smith. 2002. Soy isoflavones' osteoprotective role in postmenopausal women: Mechanism of action. *The Journal of Nutritional Biochemistry* 13 (3):130–7. doi: 10.1016/S0955-2863(02)00172-9.

Aubertin-Leheudre, M., C. Lord, A. Khalil, and I. J. Dionne. 2007. Effect of 6 months of physical activity and isoflavone supplementation on clinical cardiovascular risk factors in obese postmenopausal women: A randomized, double-blind study. *Menopause* 14 (4):624–9. doi: 10.1097/gme.0b013e31802e426b.

Azadbakht, L., M. Kimiagar, Y. Mehrabi, A. Esmaillzadeh, M. Padyab, F. B. Hu, and W. C. Willett. 2007. Soy inclusion in the diet improves features of the metabolic syndrome: A randomized crossover study in postmenopausal women. *The American Journal of Clinical Nutrition* 85 (3):735–41. doi: 10.1093/ajcn/85.3.735.

Bakhtiary A., Z. Yassin, P. Hanachi, A. Rahmat, Z. Ahmad, and F. Jalali. 2010. Effects of soy on metabolic biomarkers of cardiovascular disease in elderly women with the metabolic syndrome. *Journal of Family and Reproductive Health*:95–104.

Barrasa, G. R. R., N. González Cañete, and L. E. V. Boasi. 2018. Age of postmenopause women: Effect of soy isoflavone in lipoprotein and inflammation markers. *Journal of Menopausal Medicine* 24 (3):176–82. doi: 10.6118/jmm.2018.24.3.176.

Basaria, S., A. Wisniewski, K. Dupree, T. Bruno, M. Y. Song, F. Yao, A. Ojumu, M. John, and A. S. Dobs. 2009. Effect of high-dose isoflavones on cognition, quality of life, androgens, and lipoprotein in post-menopausal women. *Journal of Endocrinological Investigation* 32 (2):150–5. doi: 10.1007/BF03345705.

Beavers, K. M., M. C. Serra, D. P. Beavers, G. M. Hudson, and D. S. Willoughby. 2010. The lipid-lowering effects of 4 weeks of daily soymilk or dairy milk ingestion in a postmenopausal female population. *Journal of Medicinal Food* 13 (3):650–6. doi: 10.1089/jmf.2009.0171.

Begg, C. B., and M. Mazumdar. 1994. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 50 (4):1088–101. doi: 10.2307/2533446.

Blanco Mejia, S., M. Messina, S. S. Li, E. Viguiliouk, L. Chiavaroli, T. A. Khan, K. Srichaikul, A. Mirrahimi, J. L. Sievenpiper, P. Kris-Etherton, et al. 2019. A meta-analysis of 46 studies identified by the FDA demonstrates that soy protein decreases circulating LDL and total cholesterol concentrations in adults. *The Journal of Nutrition 149* (6):968–81. doi: 10.1093/jn/nxz020.

Blum, A., N. Lang, F. Vigder, P. Israeli, M. Gumanovsky, S. Lupovitz, A. Elgazi, A. Peleg, and M. Ben-Ami. 2003. Effects of soy protein on endothelium-dependent vasodilatation and lipid profile in postmenopausal women with mild hypercholesterolemia. *Clinical and Investigative Medicine* 26 (1):20–6.

Campbell, S. C., D. A. Khalil, M. E. Payton, and B. H. Arjmandi. 2010. One-year soy protein supplementation does not improve lipid profile in postmenopausal women. *Menopause* 17 (3):587–93. doi: 10.1097/gme.0b013e3181cb85d3.

Cheng, S. Y., N. S. Shaw, K. S. Tsai, and C. Y. Chen. 2004. The hypoglycemic effects of soy isoflavones on postmenopausal women. *Journal of Women's Health* 13 (10):1080–6. doi: 10.1089/jwh.2004.13.1080.

Cicero, A. F., F. Fogacci, and A. Colletti. 2017. Potential role of bioactive peptides in prevention and treatment of chronic diseases: A narrative review. *British Journal of Pharmacology* 174 (11):1378–94. doi: 10.1111/bph.13608.

Cochran, W. G. 1954. The combination of estimates from different experiments. *Biometrics* 10 (1):101–29. doi: 10.2307/3001666.

Colacurci, N., A. Chiàntera, F. Fornaro, V. de Novellis, D. Manzella, A. Arciello, V. Chiàntera, L. Improta, and G. Paolisso. 2005. Effects of soy isoflavones on endothelial function in healthy postmenopausal women. *Menopause* 12 (3):299–307. doi: 10.1097/01.GME.0000147017.23173.5B.

Cuevas, A. M., V. L. Irribarra, O. A. Castillo, M. D. Yanez, and A. M. Germain. 2003. Isolated soy protein improves endothelial function in postmenopausal hypercholesterolemic women. *European Journal of Clinical Nutrition* 57 (8):889. doi: 10.1038/sj.ejcn.1601622.

Dalais, F. S., P. R. Ebeling, D. Kotsopoulos, B. P. McGrath, and H. J. Teede. 2003. The effects of soy protein containing isoflavones on lipids and indices of bone resorption in postmenopausal women. *Clinical Endocrinology* 58 (6):704–9. doi: 10.1046/j.1365-2265.2003.01771.x.

Dewell, A., C. B. Hollenbeck, and B. Bruce. 2002. The effects of soy-derived phytoestrogens on serum lipids and lipoproteins in moderately hypercholesterolemic postmenopausal women. *The Journal of Clinical Endocrinology & Metabolism* 87 (1):118–21. doi: 10.1210/jc.87.1.118.

Engelbert, A. K., S. T. Soukup, A. Roth, N. Hoffmann, D. Graf, B. Watzl, S. E. Kulling, and A. Bub. 2016. Isoflavone supplementation in postmenopausal women does not affect leukocyte LDL receptor and scavenger receptor CD36 expression: A double-blind, randomized, placebo-controlled trial. *Molecular Nutrition & Food Research* 60 (9):2008–19. doi: 10.1002/mnfr.201600019.

Erberich, L. C., V. M. Alcântara, G. Picheth, and M. Scartezini. 2002. Hormone replacement therapy in postmenopausal women and its effects on plasma lipid levels. *Clinical Chemistry and Laboratory Medicine* 40 (5):446–51. doi: 10.1515/CCLM.2002.076.

Food Safety Commission. 2009. Fundamental concepts in the safety assessment of foods containing soy isoflavones for the purpose of specified health use. http://www.fsc.go.jp/english/evaluation-reports/newfoods_sphealth/soy_isoflavones.pdf.

Gardner, C. D., K. A. Newell, R. Cherin, and W. L. Haskell. 2001. The effect of soy protein with or without isoflavones relative to milk protein on plasma lipids in hypercholesterolemic postmenopausal women. *The American Journal of Clinical Nutrition* 73 (4):728–35. doi: 10.1093/ajcn/73.4.728.

Ghafarzadeh, M., and M. Namdari. 2010. Effect of soybean diet on serum lipids an lipoproteins of postmenopausal women. *Pakistan Journal of Medical Sciences* 26 (2):407–10.

Giolo, J., J. Costa, J. da Cunha-Junior, A. Pajuaba, E. Taketomi, A. de Souza, D. Caixeta, L. Peixoto, E. de Oliveira, S. Everman, et al. 2018. The effects of isoflavone supplementation plus combined physical activity on lipid levels, and inflammatory and oxidative stress markers in postmenopausal women. *Nutrients* 10 (4):424. doi: 10.3390/nu10040424.

Greany, K. A., J. A. Nettleton, K. E. Wangen, W. Thomas, and M. S. Kurzer. 2004. Probiotic consumption does not enhance the cholesterol-lowering effect of soy in postmenopausal women. *The Journal of Nutrition* 134 (12):3277–83. doi: 10.1093/jn/134.12.3277.

Grundy, S. M., and E. H. Ahrens. 1970. The effects of unsaturated dietary fats on absorption, excretion, synthesis, and distribution of cholesterol in man. *Journal of Clinical Investigation 49* (6):1135–52. doi: 10.1172/JCI106329.

Hall, W. L., K. Vafeiadou, J. Hallund, S. Bugel, M. Reimann, C. Koebnick, H.-J F. Zunft, M. Ferrari, F. Branca, T. Dadd, et al. 2006. Soy-isoflavone-enriched foods and markers of lipid and glucose

metabolism in postmenopausal women: Interactions with genotype and equol production. *The American Journal of Clinical Nutrition* 83 (3):592–600. doi: 10.1093/ajcn.83.3.592.

Ho, S. C., Y. M. Chen, S. S. Ho, and J. L. Woo. 2007. Soy isoflavone supplementation and fasting serum glucose and lipid profile among postmenopausal Chinese women: A double-blind, randomized, placebo-controlled trial. *Menopause* 14 (5):905–12. doi: 10.1097/gme.0b013e318032b2d3.

Irace, C., H. Marini, A. Bitto, D. Altavilla, F. Polito, E. B. Adamo, V. Arcoraci, L. Minutoli, A. Di Benedetto, G. Di Vieste, et al. 2013. Genistein and endothelial function in postmenopausal women with metabolic syndrome. *European Journal of Clinical Investigation* 43 (10):1025–31. doi: 10.1111/eci.12139.

Jassi, H. K., A. Jain, S. Arora, and R. Chitra. 2010. Effect of soy proteins vs soy isoflavones on lipid profile in postmenopausal women. *Indian Journal of Clinical Biochemistry* 25 (2):201–7. doi: 10.1007/s12291-010-0036-8.

Jayagopal, V., P. Albertazzi, E. S. Kilpatrick, E. M. Howarth, P. E. Jennings, D. A. Hepburn, and S. L. Atkin. 2002. Beneficial effects of soy phytoestrogen intake in postmenopausal women with type 2 diabetes. *Diabetes Care* 25 (10):1709–14. doi: 10.2337/diacare.25.10.1709.

Jenkins, D. J., C. W. Kendall, C. J. C. Jackson, P. W. Connelly, T. Parker, D. Faulkner, E. Vidgen, S. C. Cunnane, L. A. Leiter, and R. G. Josse. 2002. Effects of high-and low-isoflavone soyfoods on blood lipids, oxidized LDL, homocysteine, and blood pressure in hyperlipidemic men and women. *The American Journal of Clinical Nutrition* 76 (2):365–72. doi: 10.1093/ajcn/76.2.365.

Kim, J., H. Lee, O. Lee, K. H. Lee, Y. B. Lee, K. D. Young, Y. H. Jeong, and R. Choue. 2013. Isoflavone supplementation influenced levels of triglyceride and luteunizing hormone in Korean postmenopausal women. *Archives of Pharmacal Research* 36 (3):306–13. doi: 10.1007/s12272-013-0059-9.

Kreijkamp-Kaspers, S., L. Kok, D. E. Grobbee, E. H. de Haan, A. Aleman, J. W. Lampe, and Y. T. van der Schouw. 2004. Effect of soy protein containing isoflavones on cognitive function, bone mineral density, and plasma lipids in postmenopausal women: A randomized controlled trial. *Jama* 292 (1):65–74. doi: 10.1001/jama.292.1.65.

Liu, Z. M., S. C. Ho, Y. M. Chen, and Y. P. Ho. 2012. The effects of isoflavones combined with soy protein on lipid profiles, C-reactive protein and cardiovascular risk among postmenopausal Chinese women. *Nutrition, Metabolism and Cardiovascular Diseases* 22 (9):712–9. doi: 10.1016/j.numecd.2010.11.002.

Liu, Z. M., S. C. Ho, Y. M. Chen, S. Ho, K. To, B. Tomlinson, and J. Woo. 2014. 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. *Molecular Nutrition & Food Research* 58 (4):709–17. doi: 10.1002/mnfr.201300499.

Llaneza, P., C. Gonzalez, J. Fernandez-Iñarrea, A. Alonso, M. J. Diaz-Fernandez, I. Arnott, and J. Ferrer-Barriendos. 2010. Soy isoflavones, Mediterranean diet, and physical activity in postmenopausal women with insulin resistance. *Menopause* 17 (2):372–8. doi: 10.1097/gme.0b013e3181ba56fa.

Lovati, M. R., C. Manzoni, E. Gianazza, A. Arnoldi, E. Kurowska, K. K. Carroll, and C. R. Sirtori. 2000. Soy protein peptides regulate cholesterol homeostasis in Hep G2 cells. *The Journal of Nutrition* 130 (10):2543–9. doi: 10.1093/jn/130.10.2543.

Maesta, N., E. A. Nahas, J. Nahas-Neto, F. L. Orsatti, C. E. Fernandes, P. Traiman, and R. C. Burini. 2007. Effects of soy protein and resistance exercise on body composition and blood lipids in postmenopausal women. *Maturitas* 56 (4):350–58.

Maki, K. C., D. N. Butteiger, T. M. Rains, A. Lawless, M. S. Reeves, C. Schasteen, and E. S. Krul. 2010. Effects of soy protein on lipoprotein lipids and fecal bile acid excretion in men and women with moderate hypercholesterolemia. *Journal of Clinical Lipidology* 4 (6):531–42. doi: 10.1016/j.jacl.2010.09.001.

Mangano, K. M., H. L. Hutchins-Wiese, A. M. Kenny, S. J. Walsh, R. H. Abourizk, R. S. Bruno, R. Lipcius, P. Fall, A. Kleppinger, L. Kenyon-Pesce, et al. 2013. Soy proteins and isoflavones reduce interleukin-6 but not serum lipids in older women: A randomized controlled trial. *Nutrition Research* 33 (12):1026–33. doi: 10.1016/j.nutres.2013.08.009.

Mendelsohn, M. E., and R. H. Karas. 1999. The protective effects of estrogen on the cardiovascular system. *New England Journal of Medicine* 340 (23):1801–11. doi: 10.1056/NEJM199906103402306.

Mendelsohn, M. E., and R. H. Karas. 2005. Molecular and cellular basis of cardiovascular gender differences. *Science* 308 (5728):1583–7. doi: 10.1126/science.1112062.

Murkies, A. L., C. Lombard, B. J. G. Strauss, G. Wilcox, H. G. Burger, and M. S. Morton. 1995. Dietary flour supplementation decreases post-menopausal hot flushes: Effect of soy and wheat. *Maturitas* 21 (3):189–95. doi: 10.1016/0378-5122(95)00899-V.

Murray, M. J., W. R. Meyer, B. A. Lessey, R. H. Oi, R. E. DeWire, and M. A. Fritz. 2003. Soy protein isolate with isoflavones does not prevent estradiol-induced endometrial hyperplasia in postmenopausal women: A pilot trial. *Menopause* 10 (5):456–64. doi: 10.1097/01.GME.0000063567.84134.D1.

Nahas, E. P., J. N. Neto, L. De Luca, P. Traiman, A. Pontes, and I. Dalben. 2004. Benefits of soy germ isoflavones in postmenopausal women with contraindication for conventional hormone replacement therapy. *Maturitas* 48 (4):372–80. doi: 10.1016/j.maturitas.2003.09.026.

Potter, S. M. 1995. Overview of proposed mechanisms for the hypocholesterolemic effect of soy. *The Journal of Nutrition* 125 (3 Suppl):606S–11S.

Radhakrishnan, G., N. A. Rashmi, and N. B. Vaid. 2009. Evaluation of isoflavone rich soy protein supplementation for postmenopausal therapy. *Pakistan Journal of Nutrition* 8 (7):1009–17. doi: 10.3923/pjn.2009.1009.1017.

Rios, D. R. A., E. T. Rodrigues, A. P. Z. Cardoso, M. B. A. Montes, S. A. Franceschini, and M. R. T. Toloi. 2008. Lack of effects of isoflavones on the lipid profile of Brazilian postmenopausal women. *Nutrition* 24 (11-12):1153–8. doi: 10.1016/j.nut.2008.06.030.

Sacks, F. M., A. Lichtenstein, L. Van Horn, W. Harris, P. Kris-Etherton, and M. Winston. 2006. Soy protein, isoflavones, and cardiovascular health: An American Heart Association Science Advisory for professionals from the Nutrition Committee. *Circulation* 113 (7):1034–44. doi: 10.1161/CIRCULATIONAHA.106.171052.

Sanders, T. A., T. S. Dean, D. Grainger, G. J. Miller, and H. Wiseman. 2002. Moderate intakes of intact soy protein rich in isoflavones compared with ethanol-extracted soy protein increase HDL but do not influence transforming growth factor β1 concentrations and hemostatic risk factors for coronary heart disease in healthy subjects. *The American Journal of Clinical Nutrition* 76 (2):373–7. doi: 10.1093/ajcn/76.2.373.

Sapbamrer, R., N. Visavarungroj, and M. Suttajit. 2013. Effects of dietary traditional fermented soybean on reproductive hormones, lipids, and glucose among postmenopausal women in northern Thailand. *Asia Pacific Journal of Clinical Nutrition* 22 (2):222.

Shidfar, F., E. Ehramphosh, I. Heydari, L. Haghighi, S. Hosseini, and S. Shidfar. 2009. Effects of soy bean on serum paraoxonase 1 activity and lipoproteins in hyperlipidemic postmenopausal women. *International Journal of Food Sciences and Nutrition* 60 (3):195–205. doi: 10.1080/09637480701669463.

Steinberg, F. M., N. L. Guthrie, A. C. Villablanca, K. Kumar, and M. J. Murray. 2003. Soy protein with isoflavones has favorable effects on endothelial function that are independent of lipid and antioxidant effects in healthy postmenopausal women. *The American Journal of Clinical Nutrition* 78 (1):123–30. doi: 10.1093/ajcn/78.1.123.

Sterne, J. A., and M. Egger. 2001. Funnel plots for detecting bias in meta-analysis: Guidelines on choice of axis. *Journal of Clinical Epidemiology* 54 (10):1046–55. doi: 10.1016/S0895-4356(01)00377-8.

Taylor, C. K., R. M. Levy, J. C. Elliott, and B. P. Burnett. 2009. The effect of genistein aglycone on cancer and cancer risk: A review of in vitro, preclinical, and clinical studies. *Nutrition Reviews* 67 (7):398–415. doi: 10.1111/j.1753-4887.2009.00213.x.

Teede, H. J., F. S. Dalais, D. Kotsopoulos, Y. L. Liang, S. Davis, and B. P. McGrath. 2001. Dietary soy has both beneficial and potentially adverse cardiovascular effects: A placebo-controlled study in men and postmenopausal women. *The Journal of Clinical Endocrinology & Metabolism* 86 (7):3053–60. doi: 10.1210/jc.86.7.3053.

Tovar, A. R., F. Murguía, C. Cruz, R. Hernández-Pando, C. A. Aguilar-Salinas, J. Pedraza-Chaverri, R. Correa-Rotter, and N. Torres. 2002. A soy protein diet alters hepatic lipid metabolism gene expression and reduces serum lipids and renal fibrogenic cytokines in rats with chronic nephrotic syndrome. *The Journal of Nutrition* 132 (9): 2562–9. doi: 10.1093/jn/132.9.2562.

Turhan, N. O., C. I. Duvan, F. Bolkan, and Y. Onaran. 2009. Effect of isoflavone on plasma nitrite/nitrate, homocysteine, and lipid levels in Turkish women in the early postmenopausal period: A randomized controlled trial. *Turkish Journal of Medical Sciences* 39 (3): 367–75.

Uesugi, T., Y. Fukui, and Y. Yamori. 2002. Beneficial effects of soybean isoflavone supplementation on bone metabolism and serum lipids in postmenopausal Japanese women: A four-week study. *Journal of the American College of Nutrition* 21 (2):97–102. doi: 10.1080/07315724.2002.10719200.

US Department of Health and Human Services. 1997. Food and Drug Administration. Food labeling: Health claims; soluble fiber from certain foods and coronary heart disease: Proposed rule. *Federal Register* 62:28234–45.

Van Horn, L., K. Liu, J. Gerber, L. Schiffer, N. Gernhofer, and P. Greenland. 2001. Oats and soy in lipid-lowering diets for women with hypercholesterolemia: Is there synergy? *Journal of the American Dietetic Association* 101 (11):1319–25. doi: 10.1016/S0002-8223(01)00317-0.

Vitale, D. C., C. Piazza, B. Melilli, F. Drago, and S. Salomone. 2013. Isoflavones: Estrogenic activity, biological effect and bioavailability. *European Journal of Drug Metabolism and Pharmacokinetics* 38 (1): 15–25. doi: 10.1007/s13318-012-0112-y.

West, S. G., K. F. Hilpert, V. Juturu, P. L. Bordi, J. W. Lampe, S. A. Mousa, and P. M. Kris-Etherton. 2005. Effects of including soy protein in a blood cholesterol-lowering diet on markers of cardiac risk in men and in postmenopausal women with and without hormone replacement therapy. *Journal of Women's Health* 14 (3):253–62. doi: 10.1089/jwh.2005.14.253.

Zhan, S., and S. C. Ho. 2005. Meta-analysis of the effects of soy protein containing isoflavones on the lipid profile. *The American Journal of Clinical Nutrition* 81 (2):397–408. doi: 10.1093/ajcn.81.2.397.