Soya products and serum lipids: a meta-analysis of randomised controlled trials

Oluwabunmi A. Tokede[1,2]*, Temilola A. Onabanjo[3], Alfa Yansane[2], J. Michael Gaziano[1,2,4] and Luc Djoussé[1,2,4]

[1]*Department of Medicine, Brigham and Women's Hospital, Boston, MA 02120, USA*
[2]*Harvard School of Dental Medicine, Boston, MA 02115, USA*
[3]*Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, NY 10461, USA*
[4]*Massachusetts Veterans Epidemiology and Research Information Center and Geriatric Research, Education and Clinical Center, Boston Veteran Affairs Healthcare System, Boston, MA 02130, USA*

Abstract

Soya proteins and isoflavones have been reported to exert beneficial effects on the serum lipid profile. More recently, this claim is being challenged. The objective of this study was to comprehensively examine the effects of soya consumption on the lipid profile using published trials. A detailed literature search was conducted via MEDLINE (from 2004 through February 2014), CENTRAL (The Cochrane Controlled Clinical Trials Register) and ClinicalTrials.gov for randomised controlled trials assessing the effects of soya on the lipid profile. The primary effect measure was the difference in means of the final measurements between the intervention and control groups. In all, thirty-five studies (fifty comparisons) were included in our analyses. Treatment duration ranged from 4 weeks to 1 year. Intake of soya products resulted in a significant reduction in serum LDL-cholesterol concentration, –4·83 (95 % CI –7·34, –2·31) mg/dl, TAG, –4·92 (95 % CI –7·79, –2·04) mg/dl, and total cholesterol (TC) concentrations, –5·33 (95 % CI –8·35, –2·30) mg/dl. There was also a significant increase in serum HDL-cholesterol concentration, 1·40 (95 % CI 0·58, 2·23) mg/dl. The I^2 statistic ranged from 92 to 99 %, indicating significant heterogeneity. LDL reductions were more marked in hypercholesterolaemic patients, –7·47 (95 % CI –11·79, –3·16) mg/dl, than in healthy subjects, –2·96 (95 % CI –5·28, –0·65) mg/dl. LDL reduction was stronger when whole soya products (soya milk, soyabeans and nuts) were used as the test regimen, –11·06 (95 % CI –15·74, –6·37) mg/dl, as opposed to when 'processed' soya extracts, –3·17 (95 % CI –5·75, –0·58) mg/dl, were used. These data are consistent with the beneficial effects of soya proteins on serum LDL, HDL, TAG and TC concentrations. The effect was stronger in hypercholesterolaemic subjects. Whole soya foods appeared to be more beneficial than soya supplementation, whereas isoflavone supplementation had no effects on the lipid profile.

Key words: Hypercholesterolaemia: Lipids: Nutrition: Prevention: Heart disease

Dyslipidaemia is a primary risk factor for CVD, peripheral vascular disease and stroke. The WHO estimates that over 60 % of CHD and 40 % of ischaemic stroke in developed countries are due to total blood cholesterol levels in excess of the theoretical minimum of 3·8 mmol/l[1]. Reduction of serum LDL-cholesterol by about 5–6 %[2] has the potential to reduce CHD risk by 7–12 %[3], whereas a 3 % increase in HDL-cholesterol has the potential to lower the risk by 6–9 %[4,5]. Fasting serum TAG elevations also increase the risk for CHD[6]. The aggregate changes in these three lipoprotein risk factors can, therefore, potentially reduce CHD risk by 12–20 %[7]. As a result, cholesterol is by far the most studied risk factor for CHD risk[8].

Although what constitutes an optimal dietary regimen remains a matter of controversy, current guidelines recommend diet as a first-line therapy for patients with elevated blood cholesterol concentrations[9]. Among the foods being suggested to lower blood lipids are soya products. A meta-analysis published in 1995 concluded that soya protein intake is effective in reducing total cholesterol (TC), LDL-cholesterol and TAG and in increasing HDL-cholesterol[10]. Following this, in October 1999, the US Food and Drug Administration approved labelling of foods containing soya protein as protective against CHD[11]; the American Heart Association released a similar advisory shortly thereafter[12]. The UK Joint Health Claims Initiative also permitted that 'the inclusion of at least 25 g of soya protein/ d as part of a diet low in saturated fat can help reduce blood cholesterol'. Similar claims were also made in South Africa, the Philippines, Brazil and Indonesia[13]. All these

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presuppose that the hypolipidaemic effects of soya are due to its soya protein content. Soya products in addition, however, contain isoflavones, which have also been subjects of considerable scientific enquiry. Reports of trials investigating the effect of soya isoflavones on blood lipids have not been consistent[14].

Over a 100 randomised controlled trials (RCT) and ten meta-analyses have already been published, which have examined the effects of soya protein and/or isoflavones on lipids. Most of these studies report varying effects of soya proteins and/or soya isoflavones on blood cholesterol. Perhaps the only consensus on the subject is that consumption of soya products may have a more marked hypolipidaemic effect in hypercholesterolaemic individuals than in normocholesterolaemic subjects. Although the ten previously completed meta-analyses have reported beneficial effects of soya protein and/or isoflavone on serum lipids, this favourable effect is being challenged, and a reason may be because some recently completed trials do not report an effect of soya protein on serum lipids. In 2012, the European Food Safety Authority concluded that 'a cause and effect relationship has not been established between the consumption of isolated soya protein and a reduction in blood LDL-cholesterol concentrations'[15]. The last published meta-analysis involved studies completed between 1996 and 2008, and examined mainly the effects of soya proteins on LDL-cholesterol[7].

In the past 6 years, nine additional clinical trials (involving twelve comparisons and 668 people) on the effects of soya products on lipids have been completed. Based on the availability of more recent high-quality trials, the objective of this review was to re-examine the conclusion that soya protein has proven beneficial effects on blood cholesterol. We also assessed the effects of isoflavones and the combined effect of soya protein and isoflavones on blood cholesterol levels. Specifically, we sought to answer the following question: Does habitual consumption of soya products have a beneficial effect on blood cholesterol level, and if it does what are the predictors of this effect?

Methods

Search strategy and study selection

On 3 March 2014, we searched MEDLINE (through February 2014), CENTRAL (The Cochrane Controlled Clinical Trials Register) and the ClinicalTrials.gov website to identify RCT examining the effect of soya products on blood lipid profile. For the MEDLINE search, we used MeSH (major subject heading) terms ('soybeans' OR 'soybean oil' OR 'soybean proteins' OR 'soy isoflavones' OR 'soy milk') AND ('Cholesterol, HDL' OR 'Cholesterol, LDL' OR 'Triglycerides'). The search was limited to the criteria 'clinical trials', 'English', 'human' and 'last 10 years'. We limited to the last 10 years because the last published meta-analyses on this subject was completed in 2008. CENTRAL and the ClinicalTrials.gov website were searched using 'soy' or 'soybeans' as free terms without further restrictions applied to the search. Inspection of the reference list of all identified articles was also conducted. The latter method was repeated until all potentially relevant articles from these sources were

identified. Retrieved studies were included if they met the following criteria: (a) were investigating dietary soya products; (b) had a randomised controlled parallel-arm or cross-over design; (c) included subjects aged 18 years and above; (d) reported 'end of intervention' mean and standard deviation values of lipid measurements for the active (intervention) and control groups; and (e) provided the intake amount of soya products. We *a priori* determined that unpublished materials and conference abstracts will be excluded from the review. One-day trials were also excluded because we wanted to report the effects of habitual intake of soya products. Care was taken not to include data from multiple publications of the same population. Furthermore, we excluded studies in which soya intake was mixed with other dietary treatments.

In a sub-study, we searched MEDLINE (through March 2014), CENTRAL and the ClinicalTrials.gov website to identify RCT examining the effect of soya isoflavone supplementation on blood lipid profile. We used the MeSH terms ('soy isoflavone' OR 'daidzein' OR 'genistein' OR 'glycitein') AND ('Cholesterol, HDL' OR 'Cholesterol, LDL' OR 'Triglycerides'). The search was limited to the criteria 'clinical trials', 'English' and 'human'.

Data extraction and quality assessment

Data were extracted by the lead author and subsequently reviewed by one of the co-authors for accuracy. Extracted data included the study characteristics (first author's name; year of publication; number and age of participants; study design; daily amount of soya product consumed in the active arm; duration of the study; health characteristics of the study population; and location of the study). We also extracted information on the final concentrations of plasma/serum TC, LDL-cholesterol, HDL-cholesterol and TAG in both treatment arms. When the requisite data were not available in the published paper, authors were emailed requesting the appropriate information. All the authors agreed on the eligibility criteria of the included studies. Quality of the studies was evaluated using the validated Jadad score instrument[16] with criteria that included the following: randomisation, adequacy of sequence generation, double blinding and description of drop-outs. The maximum score obtainable was 5.

Data synthesis and statistical analysis

The effect size used in this investigation was the 'difference in means' between the two treatment groups. We utilised plasma/serum cholesterol concentrations obtained at the end of each intervention. Ideally, serum cholesterol concentrations are approximately 3 % higher than the corresponding plasma concentrations[17], but because we were interested in mean differences within each study we analysed plasma and serum concentrations without adjustment for this difference. Studies that reported results in mmol/l were converted to mg/dl using the standard conversion factors (which was a division of the mmol/l value by 0·02586 for TC, LDL and HDL and by 0·01129 for TAG). Estimates of treatment effect on cholesterol in sub-groups defined according to study design features were also carried out. Additional analyses were performed according to the *Cochrane Handbook for Systematic Reviews of Interventions*[18].

Heterogeneity across studies was assessed by the Cochran's Q test, and $P < 0.10$ was considered statistically significant for heterogeneity. The magnitude of heterogeneity was evaluated by the I^2 statistic (percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error). Whenever the test for heterogeneity was statistically significant, the estimate of the difference was calculated using the random effects model, according to DerSimonian & Laird[19]. For the computation of pooled effects, each study was assigned a weight consisting of the reciprocal of its variance. Furthermore, we performed a meta-regression to investigate whether there were any strong predictors of serum lipid changes. The included covariate variables were as follows: (1) initial lipid concentration; (2) duration of intake of soya products (weeks); (3) dose of soya protein consumed measured in grams per day; and (4) study quality (Jadad score). Each coefficient for the meta-regression analysis was estimated using restricted maximum likelihood and the corresponding variances were calculated using the 'Knapp–Hartung' variance estimator. Each meta-regression F test was conducted at the significance level of $\alpha = 0.05$, and all meta-regression analyses were performed using Stata/IC 13.1.

Data synthesis and other analyses were completed using Cochrane Collaboration Review Manager 5[20] and Microsoft Office Excel 2010 package (Microsoft Corporation).

Results

A total of sixty-two articles met our inclusion criteria and their complete texts were downloaded and fully reviewed. A flow chart depicting the selection process is depicted in Fig. 1. Two studies were excluded because there was an inappropriate control group[21,22]; three because they were 1-d trials[23–25]; five exclusions were due to the administration of a mixed test regimen[26–30]; and three studies were excluded due to lack of random assignment of the study groups[31–33]. Other studies were excluded for varying reasons (shown in Fig. 1). In all, thirty-five studies with fifty comparisons were included from our final analyses. Values used for the included studies represent the lipid measurements that correspond to the longest follow-up point. The observed I^2 statistic (percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error) ranged from 92 to 99 %.
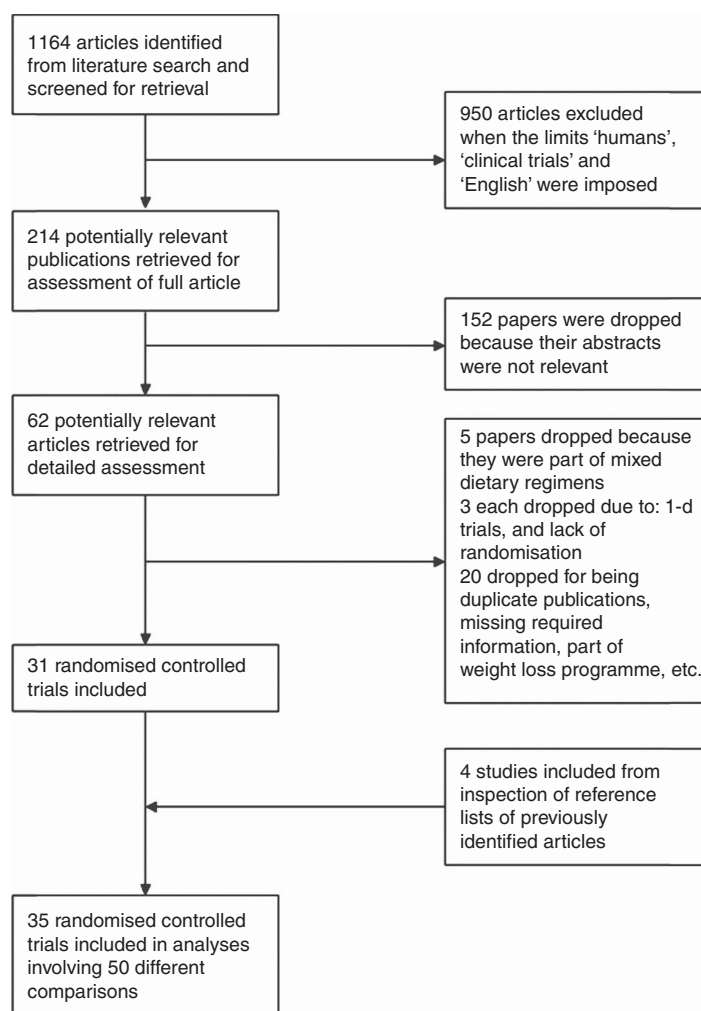

Fig. 1. Study selection process.

In the sub-study examining the effect of soya isoflavone supplementation on blood lipids, our search produced thirty-two results, including four of the studies already included in our primary study. After exclusion of the twenty-one ineligible studies, we had eleven studies[34–44] with fifteen comparison groups.

Study and participant characteristics

The characteristics of the included studies are presented in Table 1. Duration of the studies ranged from 4 weeks to 1 year, with many lasting about 8 weeks. Most RCT were double-blind, described an adequate method of sequence generation and reported details of drop-outs and withdrawals. Overall, twenty-four of the thirty-five studies obtained a Jadad score of ≥3 (high quality).

A total of 2670 subjects (aged 28–83 years and 82 % women) were included in the primary analyses. The average intake of soya protein was 30 g/d (range: 14–50 g/d).

Effects of soya on lipid concentration

Intake of soya products resulted in a significant reduction in serum LDL-cholesterol concentration, –4·83 (95 % CI –7·34, –2·31) mg/dl (Fig. 2). The effect quality test (Cochran's Q) did show significant heterogeneity, and thus the random effects model was used. We also observed statistically significant reduction in serum TAG, –4·92 (95 % CI –7·79, –2·04) mg/dl (Fig. 3), and TC concentrations, –5·33 (95 % CI –8·35, –2·30) mg/dl (Fig. 4). There was also a modest, but highly significant increase in serum HDL-cholesterol concentration, 1·40 (95 % CI 0·58, 2·23) mg/dl (Fig. 5).

For the sub-study in which only isoflavone supplementation was administered as the test regimen, all the results (LDL, HDL, TAG and TC) were non-significant.

Sub-group analyses

LDL reductions also appeared to be more marked in hypercholesterolaemic patients, –7·47 (95 % CI –11·79, –3·16) mg/dl, than in healthy subjects, –2·96 (95 % CI –5·28, –0·65) mg/dl. When natural soya products (soya milk, whole soyabeans and soya nuts) were used as the test regimen, we observed a substantial reduction in serum LDL levels, –11·06 (95 % CI –15·74, –6·37) mg/dl, as opposed to when 'processed' soya (soya extracts, supplements), –3·17 (95 % CI –5·75, –0·58) mg/dl, was used. Intervention with soya protein alone seemed to exert a more positive effect on LDL and TC levels than intervention combining soya protein and isoflavone (Table 2). Studies adjudged to be of higher quality provided more precise estimates. Details of further analyses in sub-groups of studies defined by these study/participant characteristics are shown in Table 2. Sensitivity analyses conducted by excluding studies that used no control group[45], used soya spread as the test diet[46] or that did not have any washout period[47] did not affect the results.

Isoflavone sub-study

The results of the sub-study that focused on the effect of isoflavone supplementation on LDL, HDL, TAG and TC were non-significant (Table 3). Sub-group analyses was also completed for each of these indices using design (cross-over *v.* parallel-arm), duration (≤12 *v.* >12 weeks) and health status (Table 3).

Predictors of the effect of soya on blood lipids

The meta-regression analysis suggested that initial serum LDL, TAG and TC concentrations are strong predictors of the effect of soya on serum LDL, TAG and TC concentrations, respectively (Table 4; Fig. 6–8). Initial HDL concentration did not predict the effect of soya on blood HDL levels. Dose of soya protein, the duration of its consumption and the study quality (Jadad score) also did not predict the effect of soya on blood lipid levels (Table 4).

Discussion

Based on baseline lipid concentrations in the study population, our results show a significant 3 % reduction in serum LDL, 4 % reduction in serum TAG and a 2 % reduction in TC concentrations after an intervention with soya products for a period ranging from 4 to 52 weeks. We also observed a significant 3 % increase in serum HDL concentrations. This beneficial effect seemed stronger in individuals with a higher risk of CHD (hypercholesterolaemic, obese and diabetic subjects). It also appears that consumption of natural soya products is more effective in lowering serum cholesterol than intake of processed soya (e.g. soya protein extract preparations or supplements). LDL reduction was significant in the shorter-duration studies (4–8 weeks), whereas TAG reduction was only significant in the longer-lasting studies (10–52 weeks). Isoflavone supplementation only (i.e. without soya proteins) did not appear to significantly influence the serum lipid profile.

Various mechanisms have been suggested by which soya proteins may exert their lipid-lowering effects. Some have proposed the activation of LDL receptors by essential amino acids from soya protein[48]; others have discussed the possibility of a soya protein-based inhibition of endogenous cholesterol synthesis[49]. Water-soluble fibre and other components of soya may also reduce serum lipid levels[12]. Finally, it has been hypothesised that the substitution of soya for animal protein can result in lower saturated fat and cholesterol intakes, thereby indirectly resulting in a more favourable blood cholesterol levels[50].

As casein has been reported to raise cholesterol levels, the relative increase in cholesterol concentration in the control group may be attributable to the casein content of the milk protein diet fed to the controls; however, when our analysis was restricted to the twenty-two comparisons where non-milk/non-casein-based diets were used as the control diet, the beneficial effect of the soya intervention on serum lipid was even more profound. Change in serum concentration was –6·37 (95 % CI –10·52, –2·22) mg/dl, –9·39 (95 % CI –12·88, –5·90) mg/dl and –9·69 (95 % CI –13·35, –6·04) mg/dl for LDL, TAG and TC, respectively.

Previous meta-analyses have reported on the hypolipidaemic effects of soya proteins[7,51,52], soya isoflavones[53] and soya proteins in combination with soya isoflavones[14]. Our results

Table 1. Characteristics of the included studies

Author	Year	Design	Test/control	Participants	Duration (weeks)	Test	Control	Soya protein (g/d)	Isoflavones (mg)
						Diet		Dose	
Afsaneh Bakhtiary	2012	Parallel	25/25	Met S	12	Soya nuts	Nothing	13·8	117·2
Afsaneh Bakhtiary	2012	Parallel	25/25	Met S	12	Textured soya protein (TSP)	Nothing	18·2	96·2
Liu ZM	2010	Parallel	60/60	Postmenopausal, diabetic	24	Soya protein plus isoflavone powder	Milk protein	15	100
Liu ZM – study 2	2010	Parallel	60/60	Postmenopausal, diabetic	24	Isoflavone powder	Milk protein		100
Santo Antonio	2010	Parallel	11/9	Healthy	4	Soya protein isolate powder	Milk protein	25	0·7
Santo Antonio – 2	2010	Parallel	10/9	Healthy	4	Soya protein isolate powder	Milk protein	25	56·2
Campbell S C	2010	Parallel	35/27	Postmenopausal	52	Soya snack bar or drink mix or cereal	Casein based	25	60
Shidfar F	2009	Parallel	21/21	Hyperlipidaemic/postmenopausal	10	Roasted soyabeans	Whey protein	50	164
Pipe E	2009	X	29	Diabetic type 2; postmenopausal	8	Soya protein beverage	Milk protein	40	88
Tabibi H	2009	Parallel	18/18	Peritoneal dialysis patients	8	Soya flour	Usual diet	14	
Borodin EA	2009	X	28	Hyperlipidaemic	8	Soya protein isolate	50/2	30	
Thorp A	2008	X	91	Healthy	6	Soya protein	Dairy protein beverage	24	71·4
Gardner CD	2007	X	28	Hypercholesterolaemic	4	Whole soyabean	Dairy milk		125
Gardner CD – 2	2007	X	28	Hypercholesterolaemic	4	Soya protein isolate	Dairy milk		39
Hoie L	2007	Parallel	28/28	Hypercholesterolaemic	8	Native non-denatured isolated soya protein	Milk protein	25	
Hoie L – 2	2007	Parallel	32/28	Hypercholesterolaemic	8	Conventional isolated soya protein	Milk protein	25	
Clifton PM	2007	Parallel	37/39	Healthy	6	Soya oil spread	Placebo spread		
Liao Fang-Hsuean	2007	Parallel	15/15	Overweight	8	Soya meal	Traditional meal	45	
Matthan N	2007	X	28	Hypercholesterolaemic	6	Whole soyabean	Animal protein	37·5	
Matthan N – 2	2007	X	28	Hypercholesterolaemic	6	Soya flour	Animal protein	37·5	
Matthan N – 3	2007	X	28	Hypercholesterolaemic	6	Soya milk	Animal protein	37·5	
Ho S	2007	Parallel	68/67	Postmenopausal	52	Isoflavone capsules	Maize starch capsules		80
Ho S – 2	2007	Parallel	68/67	Postmenopausal	52	Isoflavone capsules	Maize starch capsules		40
Aubertin-Leheudre	2007	Parallel	10/10	Obese, postmenopausal	24	Isoflavone capsules	Placebo		70
Allen	2007	Parallel	93/98	Postmenopausal	12	Soya protein powder	Milk protein	20	96
Azadbakht L	2007	X	42	Postmenopausal; Met S	8	Soya nut	Animal protein – red meat		102
Azadbakht L – 2	2007	X	42	Postmenopausal; MetS	8	TSP	Animal protein – red meat	30	84
Welty F	2007	X	48	Postmenopausal	8	Unsalted soya nuts	TLC diet	25	101
Welty F – 2	2007	X	12	Postmenopausal and hypertensive	8	Unsalted soya nuts	TLC diet	25	101
Hall WL	2006	X	117	Postmenopausal	8	Isoflavone-enriched cereal bars	Placebo cereal bars		50
Maesta N	2006	Parallel	10/11	Postmenopausal	16	Soya protein powder supplement	Maltodextrin	25	50
McVeigh B	2006	X	35	Healthy	8	Soya protein powder supplement	Milk protein	32	62
McVeigh B – 2	2006	X	35	Healthy	8	Soya protein powder supplement	Milk protein	32	2
Chen S	2006	Parallel	13/13	Hypercholesterolaemic on haemodialysis	12	Soya protein beverage	Milk protein	30	
Lukaczer D	2005	Parallel	27/26	Postmenopausal	12	Soya protein + phytosterol	AHA standard diet	30	34
Hermansen K	2005	Parallel	49/51	Hypercholesterolaemic	24	Soya supplement (Abalon)	Casein	30	100
Colacurci N	2005	Parallel	29/28	Postmenopausal	24	Isoflavone tablets	Placebo tablet		60
Teede H	2005	Parallel	19/21	Postmenopausal	12	Soya protein supplements	Casein	40	118
Garrido A	2005	Parallel	15/14	Postmenopausal	12	Isoflavone supplement capsule	Placebo capsule		100
Chen S	2005	Parallel	10/9	Hyperlipidaemic on haemodialysis	12	Soya protein isolate beverage	Milk protein	30	
Chen S – 2	2005	Parallel	8/10	Normolipidaemic on haemodialysis	12	Soya protein isolate beverage	Milk protein	30	
Hoie L	2005	Parallel	39/39	Hypercholesterolaemic	8	Soya protein supplement only	Milk protein	25	
Hoie L – 2	2005	Parallel	39/39	Hypercholesterolaemic	8	Soya protein supplement	Milk protein	15	
Kreijkamp-Kaspers	2004	Parallel	88/87	Postmenopausal	52	Soya protein supplement	Milk protein	25·6	99
Wang Y	2004	X	20	Hyperlipidaemic	6	Soya protein minus isoflavone	Milk and meat	50	98
Wang Y	2004	X	20	Hyperlipidaemic	6	Soya protein and isoflavone	Milk and meat	50	6
Wang Y	2004	X	20	Hyperlipidaemic	6	Animal protein plus isoflavone	Milk and meat	50	98
Greany K	2004	X	37	Normocholesterolaemic and hypercholesterolaemic	6	Soya protein powder	Milk protein	26	44
Meyer BJ	2004	X	23	Hypercholesterolaemic and/or hypertensive	5	Whole soyabean extract	Milk protein	30	80
Teixeira S	2004	X	14	Diabetic/nephropathy	8	Soya protein powder	Casein	47	94

Study or sub-group	Soya Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random 95% CI	Mean difference IV, random 95% CI
Afsaneh B 2012	131	25·3	25	151·5	29·8	25	1·5	−20·50 −35·82, −5·18	
Afsaneh B 2012 - study 2	134·5	27·1	25	151·5	29·8	25	1·4	−17·00 −32·79, −1·21	
Allen 2007	137·3	21·3	93	139·6	23·7	98	2·7	−2·30 −8·68, 4·08	
Aubertin-Leheudre 2007	127·2	22·8	10	131·1	20·5	10	1·1	−3·90 −22·90, 15·10	
Azadbakht L 2007	118	3	42	134	3·3	42	3·3	−16·00 −17·35, −14·65	
Azadbakht L 2007 - 2	127	2·4	42	134	3·3	42	3·3	−7·00 −8·23, −5·77	
Borodin EA 2009	0	0	0	0	0	0		Not estimable	
Campbell S C 2010	155·3	5·9	35	161	6·6	27	3·2	−5·70 −8·87, −2·53	
Chen S 2005	111	36·1	10	139·1	29	9	0·6	−28·10 −57·42, 1·22	
Chen S 2005 - 2	97·8	22·8	8	100·7	27·1	10	0·9	−2·90 −25·96, 20·16	
Chen S 2006	137·7	30·2	13	153·9	23·6	13	1·0	−16·20 −37·03, 4·63	
Clifton PM 2007	155·8	34·8	37	175·2	32·1	39	1·5	−19·40 −34·47, −4·33	
Colacurci N 2005	146·9	15·5	29	139·2	11·6	28	2·6	7·70 0·61, 14·79	
Gardner CD 2007	161	20	28	170	24	28	1·9	−9·00 −20·57, 2·57	
Gardner CD 2007 - 2	161	26	28	170	24	28	1·7	−9·00 −22·11, 4·11	
Garrido A 2005	143·1	11·6	15	119·9	15·5	14	2·2	23·20 13·18, 33·22	
Greany K 2004	132·6	1·2	37	128	1·2	37	3·3	4·60 4·05, 5·15	
Hall W 2006	148·5	42·9	117	148·1	40·2	117	2·1	0·40 −10·25, 11·05	
Hermansen K 2005	162·4	27·1	49	170·1	38·7	51	1·7	−7·70 −20·75, 5·35	
Ho S 2007	120·2	28·2	68	121·8	25	67	2·3	−1·60 −10·59, 7·39	
Ho S 2007 - 2	122·7	24·5	68	121·8	25	67	2·4	0·90 −7·45, 9·25	
Hoie L 2005	157	18·6	39	167·4	22·4	39	2·3	−10·40 −19·54, −1·26	
Hoie L 2005 - 2	157	25·1	39	167·4	22·4	39	2·1	−10·40 −20·96, 0·16	
Hoie LH 2007	147	20·1	28	156·2	29·8	28	1·7	−9·20 −22·51, 4·11	
Hoie LH 2007 - 2	152	22·8	32	156·2	29·8	28	1·7	−4·20 −17·77, 9·37	
Kreijkamp-Kaspers 2004	159·8	39·3	88	152·8	28·1	87	2·2	7·00 −3·11, 17·11	
Liao Fang-Hsuean 2007	95·1	16·2	15	110·4	20·6	15	1·7	−15·30 −28·56, −2·04	
Liu ZM - 2010 - study 2	140	27·5	60	142·3	31·7	60	2·1	−2·30 −12·92, 8·32	
Liu ZM 2010	147·7	32·9	60	142·3	31·7	60	1·9	5·40 −6·16, 16·96	
Lukaczer D 2005	157·8	5·4	27	177·1	8·9	26	3·1	−19·30 −23·28, −15·32	
Maesta N 2006	119·5	30·7	10	127·8	20·3	11	0·9	−8·30 −30·79, 14·19	
Matthan N 2007	137·3	23·2	28	140·8	22	28	1·9	−3·50 −15·34, 8·34	
Matthan N 2007 - 2	140·8	20·1	28	140·8	22	28	2·0	0·00 −11·04, 11·04	
Matthan N 2007 - 3	134·6	22·8	28	140·8	22	28	1·9	−6·20 −17·94, 5·54	
McVeigh B 2006	102·5	1·9	35	110·6	1·9	35	3·3	−8·10 −8·99, −7·21	
McVeigh B 2006 - 2	104·8	1·9	35	110·6	1·9	35	3·3	−5·80 −6·69, −4·91	
Meyer B 2004	151·6	8·1	23	153·9	8·1	23	3·0	−2·30 −6·98, 2·38	
Pipe E 2009	107·5	5	29	112·1	4·6	29	3·2	−4·60 −7·07, −2·13	
Santo Antonio 2010	113·1	14·5	11	102·5	12·2	9	1·9	10·60 −1·10, 22·30	
Santo Antonio 2010 - 2	102·8	23·3	10	102·5	12·2	9	1·4	0·30 −16·19, 16·79	
Shidfar F 2009	171·5	13·1	21	192·1	12·5	21	2·5	−20·60 −28·34, −12·86	
Tabibi H 2009	89	30	18	86	33	18	1·0	3·00 −17·60, 23·60	
Teede H 2005	127·6	7·7	19	127·6	7·7	21	3·0	0·00 −4·78, 4·78	
Texeira S 2004	98·6	7·7	14	97·1	7·3	14	2·9	1·50 −4·06, 7·06	
Thorp A 2008	132·6	2·7	91	136·5	2·7	91	3·3	−3·90 −4·68, −3·12	
Wang Y 2004	186	34	20	196	35	20	1·0	−10·00 −31·39, 11·39	
Wang Y 2004 - 2	181	43	20	196	35	20	0·8	−15·00 −39·30, 9·30	
Wang Y 2004 - 3	192	39	20	196	35	20	0·9	−4·00 −26·97, 18·97	
Welty F 2007	142	31	48	143	32	48	1·8	−1·00 −13·60, 11·60	
Welty F 2007 - 2	146	46	12	164	57	12	0·3	−18·00 −59·44, 23·44	
Total (95% CI)			1687			1679	100.0	−4·83 −7·34, −2·31	

Heterogeneity: $\tau^2 = 49\cdot46$; $\chi^2 = 1476\cdot26$, df = 48 ($P < 0\cdot00001$); $I^2 = 97\%$
Test for overall effect: $Z = 3\cdot77$ ($P = 0\cdot0002$)

−100   −50   0   50   100
Favours (soya)   Favours (control)

Fig. 2. Meta-analysis of the effect of soya on LDL-cholesterol. The sizes of the data markers indicate the weight of each study in the analysis. IV, inverse variance. Random–random effects model. Values are in mg/dl.

are consistent with analyses that report the cholesterol-lowering effects of soya protein. We, however, observed no effect of soya isoflavones on serum cholesterol levels and a reduced LDL-lowering effect in studies that administered soya proteins in combination with isoflavones (compared with studies that administered soya proteins alone). Soya protein plus isoflavone test diets, however, had a more positive effect on serum TAG concentrations.

Mean daily intake of soya protein is about 30 g in Japan, 20 g in Korea, 8 g in China and <1 g in the USA[54,55]. The mean

Study or sub-group	Soya group Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random 95% CI
Chen S 2005	185·7	62·6	10	307·9	132·4	9	0·1	−122·20 −217·00, −27·40
Maesta N 2006	103·4	44·3	10	152·5	57·6	11	0·4	−49·10 −92·83, −5·37
Lukaczer D 2005	116·9	11·5	27	158·5	18·6	26	4·3	−41·60 −49·96, −33·24
Hermansen K 2005	132·9	62	49	168·3	106·3	51	0·6	−35·40 −69·35, −1·45
Borodin E A 2009	173	16	28	201	17	28	4·2	−28·00 −36·65, −19·35
Shidfar F 2009	301·2	42·5	21	326	41·7	21	1·1	−24·80 −50·27, 0·67
Texeira S 2004	168·3	25·7	14	193·1	32·8	14	1·4	−24·80 −46·63, 2·97
Aubertin-Leheudre 2007	116	56·7	10	137·3	94·8	10	0·2	−21·30 −89·76, 47·16
Wang Y 2004 - 2	109	45	20	127	47	20	0·9	−18·00 −46·52, 10·52
Ho S 2007	104·4	47	68	121·4	83·4	67	1·3	−17·00 −39·88, 5·88
Campbell SC 2010	135·1	10·7	35	150·2	11·9	27	5·4	−15·10 −20·82, −9·38
Welty F 2007 - 2	114	50	12	128	74	12	0·3	−14·00 −64·53, 36·53
Clifton PM 2007	155·9	70	37	169·2	87·7	39	0·6	−13·30 −48·89, 22·29
Thorp A 2008	147·9	9·7	91	160·3	10·6	91	6·4	−12·40 −15·35, −9·45
Wang Y 2004	116	52	20	127	47	20	0·8	−11·00 −41·72, 19·72
Chen S 2006	156·8	33·7	13	166·5	25·7	13	1·3	−9·70 −32·74, 13·34
Welty F 2007	11·9	83	48	128	97	48	0·6	−9·00 −45·12, 27·12
Afsaneh B 2012	199·8	42·4	25	208·5	49·4	25	1·1	−8·70 −34·22, 16·82
Afsaneh B 2012 - study 2	200·3	43·5	25	208·5	49·4	25	1·0	−8·20 −34·00, 16·60
Chen S 2005 - 2	123·6	31·3	8	130·2	26·9	10	0·9	−6·60 −33·96, 20·76
Ho S 2007 - 2	116·2	63·2	68	121·4	83·4	67	1·1	−5·20 −30·19, 19·79
Azadbakht L 2007 - 2	210	1·7	42	213	1·2	42	6·8	−3·00 −3·63, −2·37
Meyer B 2004	108·1	11·5	23	110·7	11·5	23	5·0	−2·60 −9·25, 4·05
Azadbakht L 2007	212	1·7	42	213	1·2	42	6·8	−1·00 −1·63, −0·37
Pipe E 2009	100·1	8	29	101	7·1	29	6·1	−0·90 −4·79, 2·99
Allen 2007	110·5	43·8	93	110·9	52·4	98	2·7	−0·40 −14·07, 13·27
Liao Fang-Hsuean 2007	80·1	31	15	80·2	32·5	15	1·3	−0·10 −22·83, 22·63
Hoie L 2005	0	0	0	0	0	0		Not estimable
Hoie L 2005 - 2	0	0	0	0	0	0		Not estimable
Hall W 2006	108·1	42·5	117	108·1	46·1	117	3·3	0·00 −11·36, 11·36
Garrido A 2005	124	17·7	15	124	17·7	14	2·9	0·00 −12·89, 12·89
Gardner C D 2007	0	0	0	0	0	0		Not estimable
Gardner C D 2007 - 2	0	0	0	0	0	0		Not estimable
Colacurci N 2005	150·6	44·3	29	150·6	79·7	28	0·7	0·00 −33·64, 33·64
Hoie L H 2007 - 2	0	0	0	0	0	0		Not estimable
Hoie L H 2007	0	0	0	0	0	0		Not estimable
Teede H 2005	0	0	0	0	0	0		Not estimable
Kreijkamp-Kaspers 2004	122·1	52·2	88	121·2	50·6	87	2·3	0·90 −14·33, 16·13
Liu Z M - 2010 - study 2	115·2	85	60	113·4	65·5	60	1·0	1·80 −25·35, 28·95
Santo Antonio 2010 - 2	95·3	25·2	10	92·4	16·4	9	1·7	2·90 −16·04, 21·84
Wang Y 2004 - 3	131	47	20	127	47	20	0·9	4·00 −25·13, 33·13
McVeigh B 2006 - 2	119·6	6·2	35	115·1	6·2	35	6·4	4·50 1·60, 7·40
Matthan N 2007 - 2	136·4	7·1	28	130·2	60·2	28	1·3	6·20 −16·25, 28·65
Greany K 2004	90·3	2·7	37	82·4	2·7	37	6·7	7·90 6·67, 9·13
McVrigh B 2006	123·1	6·2	35	115·1	6·2	35	6·4	8·00 5·10, 10·90
Tabibi H 2009	197·5	131	18	189	130	18	0·1	8·50 −76·76, 93·76
Liu Z M 2010	123·1	90·4	60	113·4	65·5	60	0·9	9·70 −18·55, 37·95
Matthan N 2007 - 3	140·8	86·8	28	130·2	60·2	28	0·5	10·60 −28·53, 49·73
Matthan N 2007	141·7	77·1	28	130·2	60·2	28	0·6	11·50 −24·73, 47·73
Santo Antonio 2010	125·1	23·8	11	92·4	16·4	9	0·9	32·70 15·02, 50·38
Total (95% CI)			1502			1496	100·0	−4·92 −7·79, −2·04

Heterogeneity: $\tau^2 = 31.48$; $\chi^2 = 544.61$, df = 42 ($P < 0.00001$); $I^2 = 92\%$
Test for overall effect: $Z = 3.36$ ($P = 0.0008$)

Mean difference IV, random 95% CI
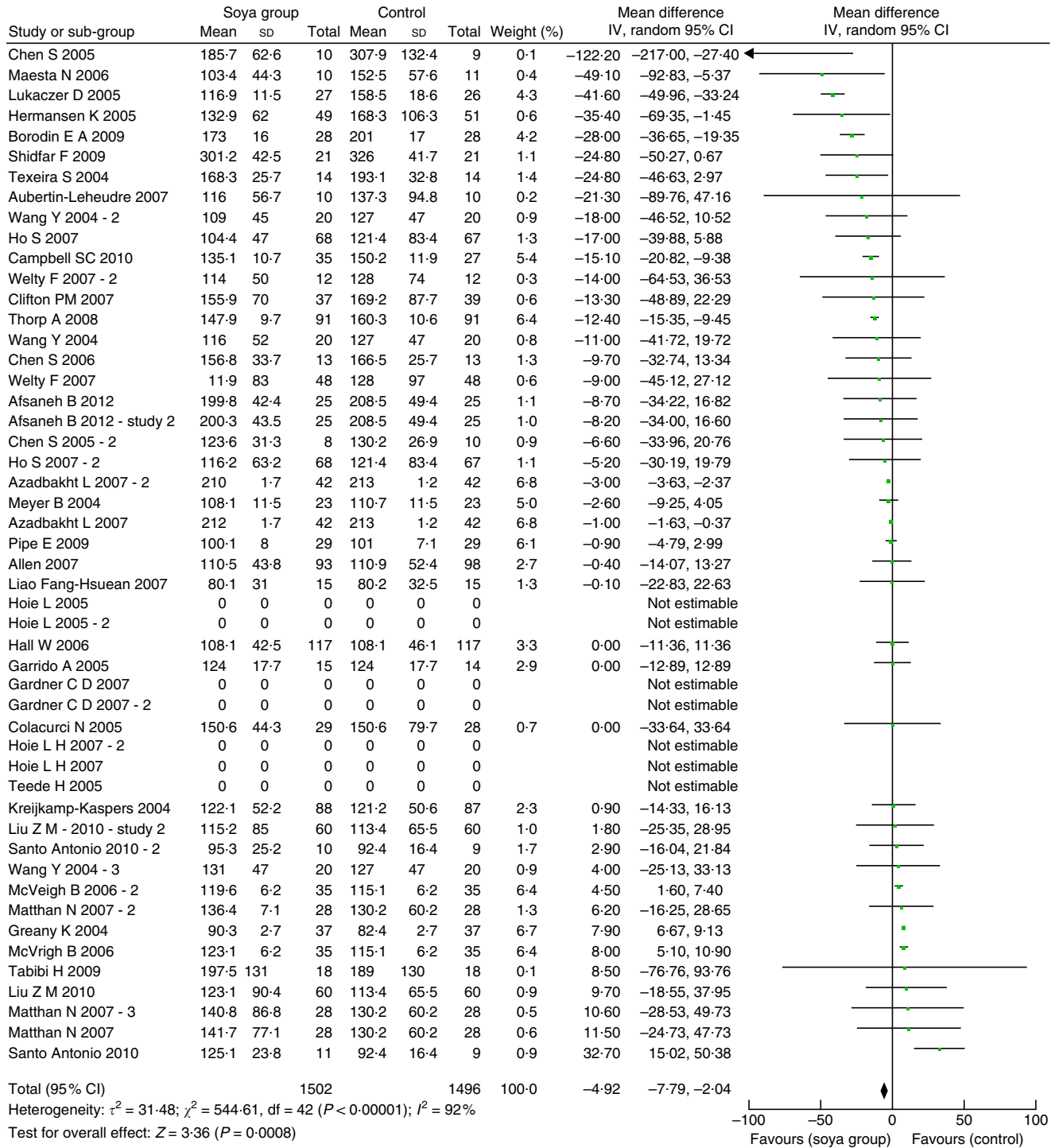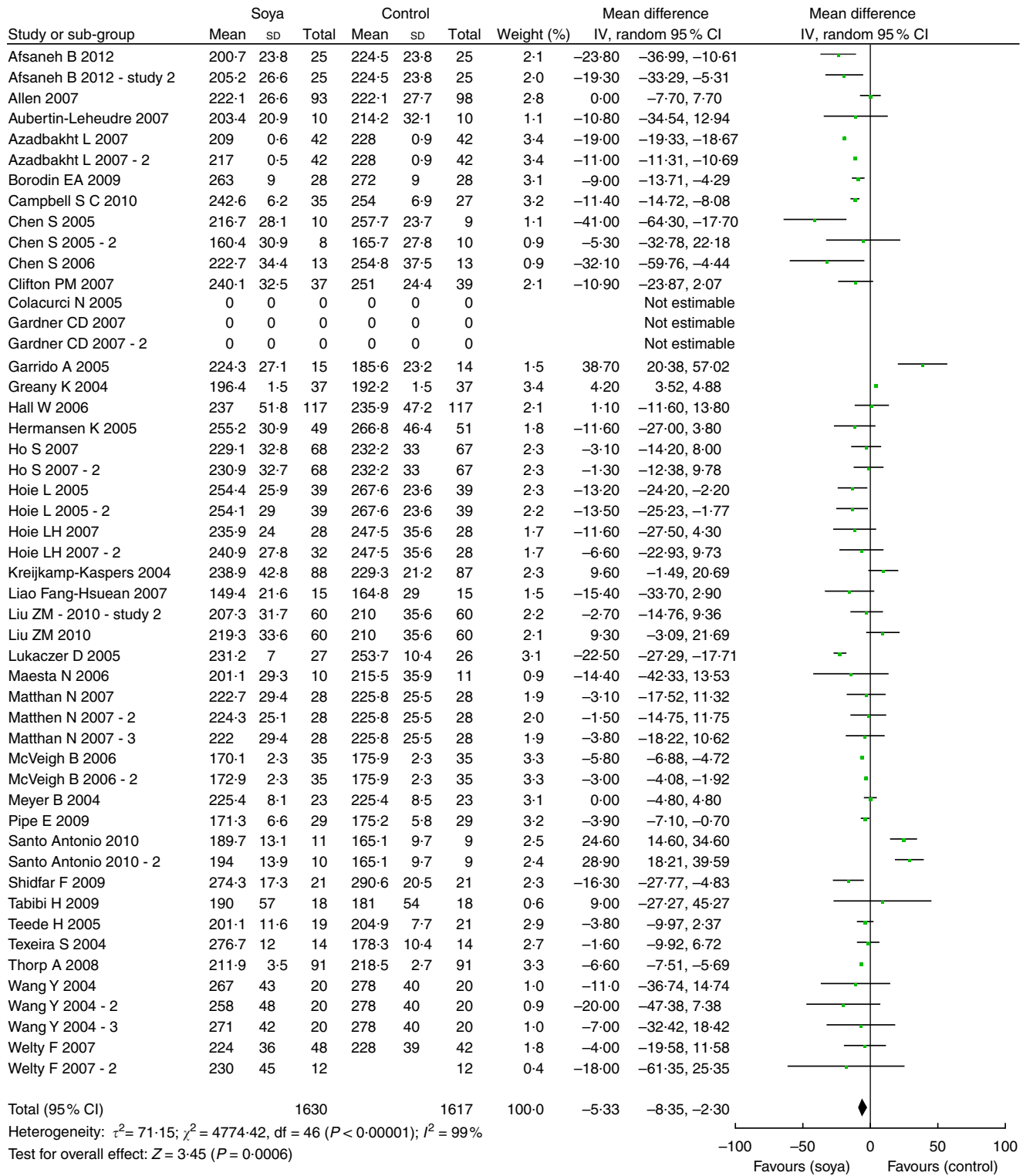−100 −50 0 50 100
Favours (soya group) Favours (control)

Fig. 3. Meta-analysis of the effect of soya on serum TAG. The sizes of the data markers indicate the weight of each study in the analysis. IV, inverse variance. Random–random effects model. Values are in mg/dl.

daily intake by participants in our analyses was 29·8 g (range: 14–50 g). This potentially means that the cholesterol-reducing effects of soya protein may not be realised by most soya consumers. It is important to note, however, that a dose–response effect of soya protein on cholesterol reduction was not observed in our analyses and is yet to be established.

As soyabeans are grown around the world under many different climatic conditions, there is a wide range of soyabean varieties. Unlike in Europe, GM soyabeans have become the predominant type grown in the Americas. When our results were stratified by study location, the studies completed in Europe, Asia and Australia showed highly significant positive effects. Conversely, the studies completed in North/South

Study or sub-group	Soya Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random 95 % CI	Mean difference IV, random 95 % CI
Afsaneh B 2012	200·7	23·8	25	224·5	23·8	25	2·1	−23·80 −36·99, −10·61	
Afsaneh B 2012 - study 2	205·2	26·6	25	224·5	23·8	25	2·0	−19·30 −33·29, −5·31	
Allen 2007	222·1	26·6	93	222·1	27·7	98	2·8	0·00 −7·70, 7·70	
Aubertin-Leheudre 2007	203·4	20·9	10	214·2	32·1	10	1·1	−10·80 −34·54, 12·94	
Azadbakht L 2007	209	0·6	42	228	0·9	42	3·4	−19·00 −19·33, −18·67	
Azadbakht L 2007 - 2	217	0·5	42	228	0·9	42	3·4	−11·00 −11·31, −10·69	
Borodin EA 2009	263	9	28	272	9	28	3·1	−9·00 −13·71, −4·29	
Campbell S C 2010	242·6	6·2	35	254	6·9	27	3·2	−11·40 −14·72, −8·08	
Chen S 2005	216·7	28·1	10	257·7	23·7	9	1·1	−41·00 −64·30, −17·70	
Chen S 2005 - 2	160·4	30·9	8	165·7	27·8	10	0·9	−5·30 −32·78, 22·18	
Chen S 2006	222·7	34·4	13	254·8	37·5	13	0·9	−32·10 −59·76, −4·44	
Clifton PM 2007	240·1	32·5	37	251	24·4	39	2·1	−10·90 −23·87, 2·07	
Colacurci N 2005	0	0	0	0	0	0		Not estimable	
Gardner CD 2007	0	0	0	0	0	0		Not estimable	
Gardner CD 2007 - 2	0	0	0	0	0	0		Not estimable	
Garrido A 2005	224·3	27·1	15	185·6	23·2	14	1·5	38·70 20·38, 57·02	
Greany K 2004	196·4	1·5	37	192·2	1·5	37	3·4	4·20 3·52, 4·88	
Hall W 2006	237	51·8	117	235·9	47·2	117	2·1	1·10 −11·60, 13·80	
Hermansen K 2005	255·2	30·9	49	266·8	46·4	51	1·8	−11·60 −27·00, 3·80	
Ho S 2007	229·1	32·8	68	232·2	33	67	2·3	−3·10 −14·20, 8·00	
Ho S 2007 - 2	230·9	32·7	68	232·2	33	67	2·3	−1·30 −12·38, 9·78	
Hoie L 2005	254·4	25·9	39	267·6	23·6	39	2·3	−13·20 −24·20, −2·20	
Hoie L 2005 - 2	254·1	29	39	267·6	23·6	39	2·2	−13·50 −25·23, −1·77	
Hoie LH 2007	235·9	24	28	247·5	35·6	28	1·7	−11·60 −27·50, 4·30	
Hoie LH 2007 - 2	240·9	27·8	32	247·5	35·6	28	1·7	−6·60 −22·93, 9·73	
Kreijkamp-Kaspers 2004	238·9	42·8	88	229·3	21·2	87	2·3	9·60 −1·49, 20·69	
Liao Fang-Hsuean 2007	149·4	21·6	15	164·8	29	15	1·5	−15·40 −33·70, 2·90	
Liu ZM - 2010 - study 2	207·3	31·7	60	210	35·6	60	2·2	−2·70 −14·76, 9·36	
Liu ZM 2010	219·3	33·6	60	210	35·6	60	2·1	9·30 −3·09, 21·69	
Lukaczer D 2005	231·2	7	27	253·7	10·4	26	3·1	−22·50 −27·29, −17·71	
Maesta N 2006	201·1	29·3	10	215·5	35·9	11	0·9	−14·40 −42·33, 13·53	
Matthan N 2007	222·7	29·4	28	225·8	25·5	28	1·9	−3·10 −17·52, 11·32	
Matthen N 2007 - 2	224·3	25·1	28	225·8	25·5	28	2·0	−1·50 −14·75, 11·75	
Matthan N 2007 - 3	222	29·4	28	225·8	25·5	28	1·9	−3·80 −18·22, 10·62	
McVeigh B 2006	170·1	2·3	35	175·9	2·3	35	3·3	−5·80 −6·88, −4·72	
McVeigh B 2006 - 2	172·9	2·3	35	175·9	2·3	35	3·3	−3·00 −4·08, −1·92	
Meyer B 2004	225·4	8·1	23	225·4	8·5	23	3·1	0·00 −4·80, 4·80	
Pipe E 2009	171·3	6·6	29	175·2	5·8	29	3·2	−3·90 −7·10, −0·70	
Santo Antonio 2010	189·7	13·1	11	165·1	9·7	9	2·5	24·60 14·60, 34·60	
Santo Antonio 2010 - 2	194	13·9	10	165·1	9·7	9	2·4	28·90 18·21, 39·59	
Shidfar F 2009	274·3	17·3	21	290·6	20·5	21	2·3	−16·30 −27·77, −4·83	
Tabibi H 2009	190	57	18	181	54	18	0·6	9·00 −27·27, 45·27	
Teede H 2005	201·1	11·6	19	204·9	7·7	21	2·9	−3·80 −9·97, 2·37	
Texeira S 2004	276·7	12	14	178·3	10·4	14	2·7	−1·60 −9·92, 6·72	
Thorp A 2008	211·9	3·5	91	218·5	2·7	91	3·3	−6·60 −7·51, −5·69	
Wang Y 2004	267	43	20	278	40	20	1·0	−11·0 −36·74, 14·74	
Wang Y 2004 - 2	258	48	20	278	40	20	0·9	−20·00 −47·38, 7·38	
Wang Y 2004 - 3	271	42	20	278	40	20	1·0	−7·00 −32·42, 18·42	
Welty F 2007	224	36	48	228	39	42	1·8	−4·00 −19·58, 11·58	
Welty F 2007 - 2	230	45	12			12	0·4	−18·00 −61·35, 25·35	
Total (95 % CI)			1630			1617	100·0	−5·33 −8·35, −2·30	

Heterogeneity: τ^2 = 71·15; χ^2 = 4774·42, df = 46 (P < 0·00001); I^2 = 99 %
Test for overall effect: Z = 3·45 (P = 0·0006)

−100   −50   0   50   100
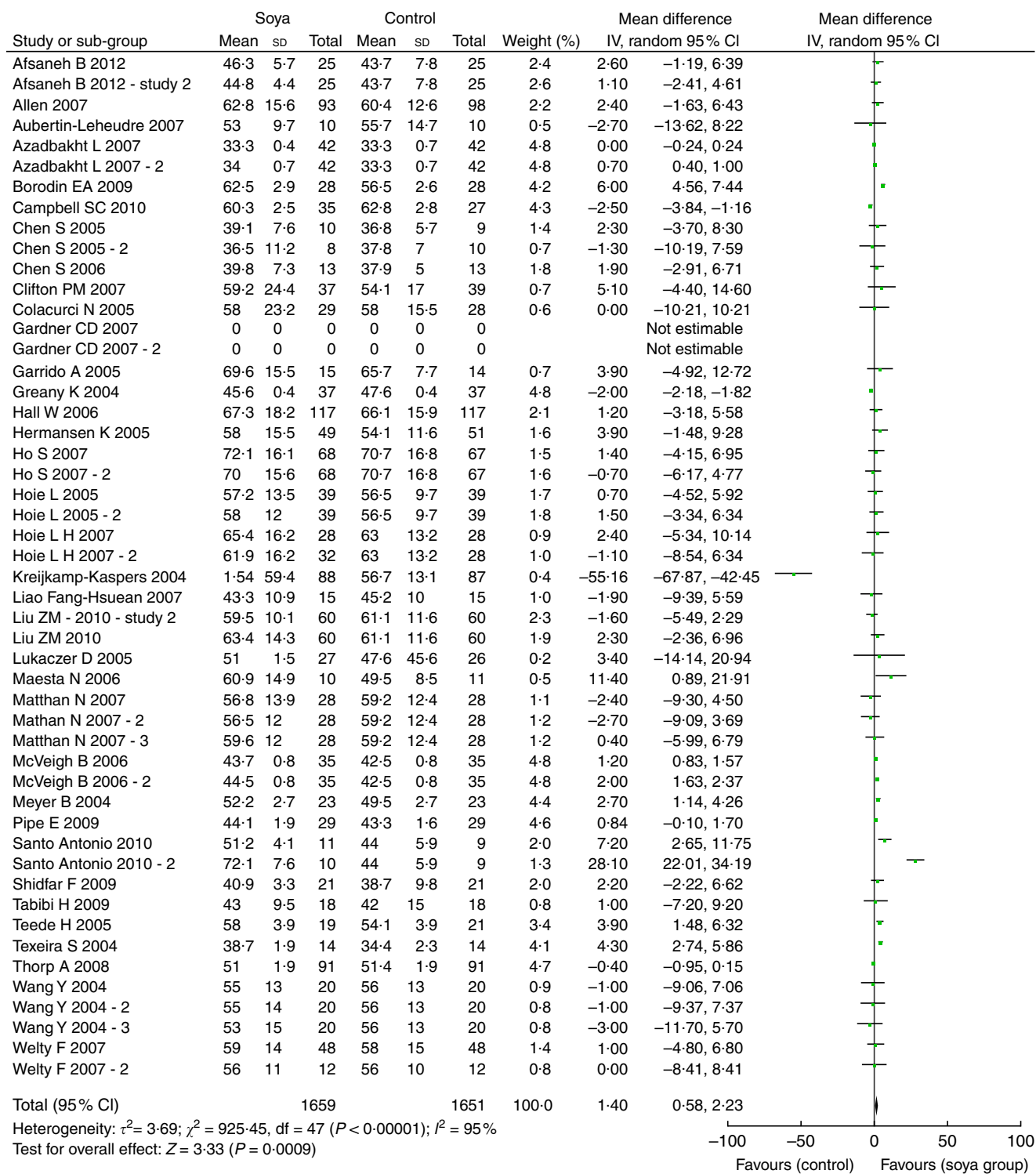Favours (soya)   Favours (control)

Fig. 4. Meta-analysis of the effect of soya on total cholesterol. The sizes of the data markers indicate the weight of each study in the analysis. IV, inverse variance. Random–random effects model. Values are in mg/dl.

America (where >85 % of soyabean produced is GM) showed non-significant results, except for a mild elevation of serum HDL.

In an earlier study, we observed varying effects of flavanols on serum lipids, depending on the matrix with which the flavanols were administered[56]. Consequently, in this analysis, we compared studies that used natural soya products (roasted soyabeans, soya nuts, etc.) with those that used soya extracts or tablets as the test regimen (Table 2). The LDL-cholesterol-lowering effect appeared to be three times stronger when

Study or sub-group	Soya Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, random 95% CI	Mean difference IV, random 95% CI
Afsaneh B 2012	46·3	5·7	25	43·7	7·8	25	2·4	2·60	−1·19, 6·39
Afsaneh B 2012 - study 2	44·8	4·4	25	43·7	7·8	25	2·6	1·10	−2·41, 4·61
Allen 2007	62·8	15·6	93	60·4	12·6	98	2·2	2·40	−1·63, 6·43
Aubertin-Leheudre 2007	53	9·7	10	55·7	14·7	10	0·5	−2·70	−13·62, 8·22
Azadbakht L 2007	33·3	0·4	42	33·3	0·7	42	4·8	0·00	−0·24, 0·24
Azadbakht L 2007 - 2	34	0·7	42	33·3	0·7	42	4·8	0·70	0·40, 1·00
Borodin EA 2009	62·5	2·9	28	56·5	2·6	28	4·2	6·00	4·56, 7·44
Campbell SC 2010	60·3	2·5	35	62·8	2·8	27	4·3	−2·50	−3·84, −1·16
Chen S 2005	39·1	7·6	10	36·8	5·7	9	1·4	2·30	−3·70, 8·30
Chen S 2005 - 2	36·5	11·2	8	37·8	7	10	0·7	−1·30	−10·19, 7·59
Chen S 2006	39·8	7·3	13	37·9	5	13	1·8	1·90	−2·91, 6·71
Clifton PM 2007	59·2	24·4	37	54·1	17	39	0·7	5·10	−4·40, 14·60
Colacurci N 2005	58	23·2	29	58	15·5	28	0·6	0·00	−10·21, 10·21
Gardner CD 2007	0	0	0	0	0	0		Not estimable	
Gardner CD 2007 - 2	0	0	0	0	0	0		Not estimable	
Garrido A 2005	69·6	15·5	15	65·7	7·7	14	0·7	3·90	−4·92, 12·72
Greany K 2004	45·6	0·4	37	47·6	0·4	37	4·8	−2·00	−2·18, −1·82
Hall W 2006	67·3	18·2	117	66·1	15·9	117	2·1	1·20	−3·18, 5·58
Hermansen K 2005	58	15·5	49	54·1	11·6	51	1·6	3·90	−1·48, 9·28
Ho S 2007	72·1	16·1	68	70·7	16·8	67	1·5	1·40	−4·15, 6·95
Ho S 2007 - 2	70	15·6	68	70·7	16·8	67	1·6	−0·70	−6·17, 4·77
Hoie L 2005	57·2	13·5	39	56·5	9·7	39	1·7	0·70	−4·52, 5·92
Hoie L 2005 - 2	58	12	39	56·5	9·7	39	1·8	1·50	−3·34, 6·34
Hoie L H 2007	65·4	16·2	28	63	13·2	28	0·9	2·40	−5·34, 10·14
Hoie L H 2007 - 2	61·9	16·2	32	63	13·2	28	1·0	−1·10	−8·54, 6·34
Kreijkamp-Kaspers 2004	1·54	59·4	88	56·7	13·1	87	0·4	−55·16	−67·87, −42·45
Liao Fang-Hsuean 2007	43·3	10·9	15	45·2	10	15	1·0	−1·90	−9·39, 5·59
Liu ZM - 2010 - study 2	59·5	10·1	60	61·1	11·6	60	2·3	−1·60	−5·49, 2·29
Liu ZM 2010	63·4	14·3	60	61·1	11·6	60	1·9	2·30	−2·36, 6·96
Lukaczer D 2005	51	1·5	27	47·6	45·6	26	0·2	3·40	−14·14, 20·94
Maesta N 2006	60·9	14·9	10	49·5	8·5	11	0·5	11·40	0·89, 21·91
Matthan N 2007	56·8	13·9	28	59·2	12·4	28	1·1	−2·40	−9·30, 4·50
Mathan N 2007 - 2	56·5	12	28	59·2	12·4	28	1·2	−2·70	−9·09, 3·69
Matthan N 2007 - 3	59·6	12	28	59·2	12·4	28	1·2	0·40	−5·99, 6·79
McVeigh B 2006	43·7	0·8	35	42·5	0·8	35	4·8	1·20	0·83, 1·57
McVeigh B 2006 - 2	44·5	0·8	35	42·5	0·8	35	4·8	2·00	1·63, 2·37
Meyer B 2004	52·2	2·7	23	49·5	2·7	23	4·4	2·70	1·14, 4·26
Pipe E 2009	44·1	1·9	29	43·3	1·6	29	4·6	0·84	−0·10, 1·70
Santo Antonio 2010	51·2	4·1	11	44	5·9	9	2·0	7·20	2·65, 11·75
Santo Antonio 2010 - 2	72·1	7·6	10	44	5·9	9	1·3	28·10	22·01, 34·19
Shidfar F 2009	40·9	3·3	21	38·7	9·8	21	2·0	2·20	−2·22, 6·62
Tabibi H 2009	43	9·5	18	42	15	18	0·8	1·00	−7·20, 9·20
Teede H 2005	58	3·9	19	54·1	3·9	21	3·4	3·90	1·48, 6·32
Texeira S 2004	38·7	1·9	14	34·4	2·3	14	4·1	4·30	2·74, 5·86
Thorp A 2008	51	1·9	91	51·4	1·9	91	4·7	−0·40	−0·95, 0·15
Wang Y 2004	55	13	20	56	13	20	0·9	−1·00	−9·06, 7·06
Wang Y 2004 - 2	55	14	20	56	13	20	0·8	−1·00	−9·37, 7·37
Wang Y 2004 - 3	53	15	20	56	13	20	0·8	−3·00	−11·70, 5·70
Welty F 2007	59	14	48	58	15	48	1·4	1·00	−4·80, 6·80
Welty F 2007 - 2	56	11	12	56	10	12	0·8	0·00	−8·41, 8·41
Total (95% CI)			1659			1651	100·0	1·40	0·58, 2·23

Heterogeneity: $\tau^2 = 3{\cdot}69$; $\chi^2 = 925{\cdot}45$, df = 47 ($P < 0{\cdot}00001$); $I^2 = 95\%$
Test for overall effect: $Z = 3{\cdot}33$ ($P = 0{\cdot}0009$)

Favours (control) Favours (soya group)

Fig. 5. Meta-analysis of the effect of soya on HDL-cholesterol. The sizes of the data markers indicate the weight of each study in the analysis. IV, inverse variance. Random–random effects model. Values are in mg/dl.

natural soya products were used. A potential explanation may be the differing levels of bioavailability of the active ingredients.

Soya isoflavones have a biological similarity to mammalian oestrogens, which have been shown to exert cholesterol-lowering effects in humans[57]. Our soya isoflavone sub-study revealed no effects of isoflavone supplementation on serum lipids. In their meta-analysis, Weggemans & Trautwein[58] also reported a lack of efficacy of soya isoflavones on changes in LDL or HDL-cholesterol. In contrast, another study has reported positive effects of isoflavone supplementation on cholesterol

Table 2. Effects of soya proteins on serum lipids by study design, duration, location, health status and quality of study
(Mean differences and 95 % confidence intervals)

	Sub-group	Number of comparisons	LDL (mg/dl) Mean difference	LDL 95 % CI	HDL (mg/dl) Mean difference	HDL 95 % CI	TAG (mg/dl) Mean difference	TAG 95 % CI	Total cholesterol (mg/dl) Mean difference	Total cholesterol 95 % CI
Design	Cross-over only	21	−4·87*	−8·55, −1·19	1·15*	0·15, 2·16	−2·14	−5·34, 1·06	−5·46*	−9·93, −1·00
	Parallel only	29	−4·95*	−9·05, −0·84	1·49	−0·96, 3·95	−8·81*	−17·49, −0·21	−5·50*	−11·15, 0·16
Health status	Hypercholesterolaemic/diabetic/ hypertensive	32	−7·47*	−11·79, −3·16	1·15*	0·18, 2·13	−3·91*	−7·34, −0·47	−9·10	−13·22, −4·98
	Healthy	18	−2·96*	−5·28, −0·65	1·96*	0·48, 3·44	−5·13	−12·70, 2·45	−2·02	−4·99, 0·95
Duration	Shorter duration (4–8 weeks)	30	−5·29*	−8·48, −2·11	1·74*	0·77, 2·72	−1·25	−4·37, 1·86	−4·04*	−7·88, −0·20
	Longer duration (10 weeks to 1 year)	20	−4·38	−9·51, 0·75	0·15	−2·38, 2·67	−12·67*	−21·45, −3·89	−7·54*	−13·39, −1·70
Test regimen	Soya supplement	38	−3·17*	−5·75, −0·58	1·51*	0·47, 2·55	−5·86*	−10·02, −1·70	−4·22*	−7·34, −1·09
	Natural soya (nuts, milk, oil, whole bean, flour)	12	−11·06*	−15·74, −6·37	1·06	−0·27, 2·39	−1·03*	−1·65, −0·40	−9·01*	−16·78, −1·25
	Soya protein plus isoflavone	22	−5·88*	−9·80, −1·97	1·42*	0·34, 2·51	−7·12*	−11·75, −2·48	−4·61*	−8·35, −0·86
	Soya protein only	13	−7·62*	−11·45, −3·78	1·15	−1·09, 3·40	−7·48	−22·77, 7·81	−10·03*	−14·36, −5·71
Jadad score	High (≥3)	31	−4·17*	−6·14, −2·19	1·83*	0·76, 2·90	−6·95*	−12·83, −1·07	−4·27*	−6·77, −1·77
	Low (<3)	19	−6·61*	−12·46, −0·75	0·74	−0·50, 1·98	−2·70	−6·70, 1·30	−7·70*	−13·11, −2·29
Location	Americas	23	−3·21	−7·04, 0·63	1·94*	0·40, 3·48	−3·23	−9·01, 2·56	−1·15	−5·01, 2·71
	Europe/Asia/Australia	27	−6·14*	−9·25, −3·04	1·29*	0·38, 2·19	−6·55*	−9·32, −3·77	−8·62*	−11·81, −5·43

* Significant results.

Table 3. Effects of soya isoflavone on serum lipids
(Mean differences and 95 % confidence intervals)

	Sub-group	LDL (mg/dl) Mean difference	LDL 95 % CI	HDL (mg/dl) Mean difference	HDL 95 % CI	TAG (mg/dl) Mean difference	TAG 95 % CI	Total cholesterol (mg/dl) Mean difference	Total cholesterol 95 % CI
All 15 studies		−0·48	−3·42, 2·46	0·97	−2·93, 1·00	2·49	−5·78, 10·77	−1·08	−4·69, 2·53
Design	Cross-over only	−5·06*	−7·45, −2·67	0·88	0·50, 1·25	2·66	−0·93, 4·39	−3·82	−5·86, −1·79
	Parallel only	2·48	−2·43, 7·39	−3·65	−8·38, 1·08	−3·63	−27·63, 20·38	0·86	−10·48, 12·21
Health status	Hypercholesterolaemic	−6·05*	−8·42, −3·68	1·05*	0·54, 1·56	0·75	−7·55, 9·05	−5·08*	−7·03, −3·12
	Healthy	1·31	−2·83, 5·44	−2·88	−6·05, 0·30	4·57	−6·99, 16·12	0·54	−5·34, 6·43
Duration	Shorter duration (≤12 weeks)	−1·34	−6·39, 3·71	−1·22	−4·95, 2·50	14·29	−2·65, 31·23	0·41	−6·21, 7·03
	Longer duration (>12 weeks)	0·01	−3·71, 3·72	−0·33	−2·41, 1·75	0·12	−5·25, 5·49	−4·35*	−7·18, −1·53

* Significant results.

Table 4. Meta-regression – predictors of the effects of soya on serum lipids
(Coefficients and their standard errors)

	LDL (mg/dl)			HDL (mg/dl)			TAG (mg/dl)			Total cholesterol (mg/dl)		
	Coefficient	SE	P	Coefficient	SE	P	Coefficient	SE	P	Coefficient	SE	P
Initial lipid concentration	−0·13*	0·05*	0·01*	0·02	0·05	0·74	−0·19*	0·05*	<0·01*	−0·19*	0·05*	<0·01*
Duration of study	0·12	0·11	0·25	−0·09	0·05	0·08	−0·26	0·24	0·29	−0·01	0·19	0·96
Dose of test diet	−0·12	0·14	0·38	0·01	0·05	0·79	−0·30	0·31	0·35	−0·19	0·20	0·35

*Significant results.
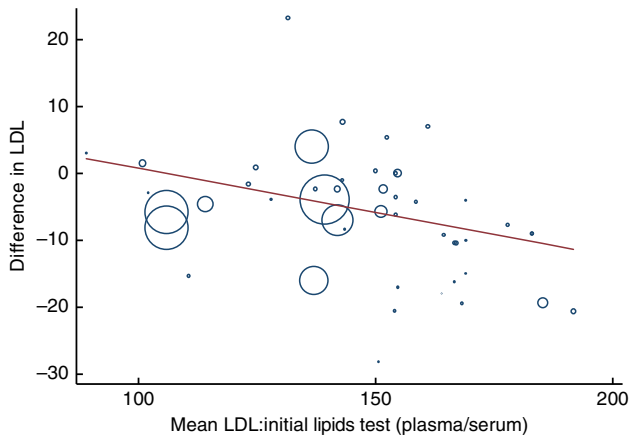
Fig. 6. Meta-regression plot of the effect of initial LDL concentration on soya's effect on LDL-cholesterol. Values are in mg/dl.
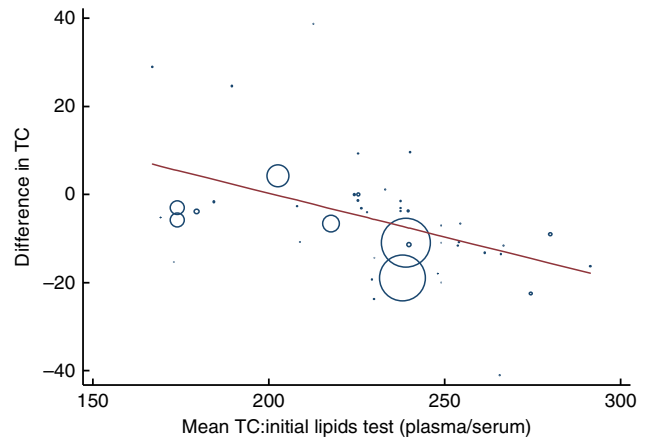
Fig. 8. Meta-regression plot of the effect of initial total concentration (TC) concentration on soya's effect on blood TC level. Values are in mg/dl.
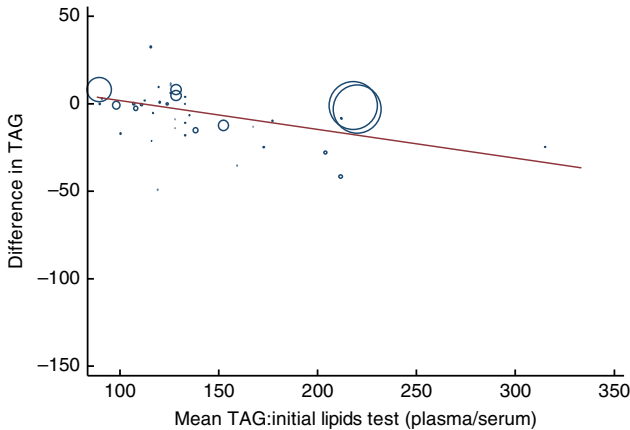
Fig. 7. Meta-regression plot of the effect of initial TAG concentration on soya's effect on blood TAG level. Values are in mg/dl.

In conclusion, our findings showed that an intervention with soya proteins increases serum HDL concentration and lowers serum TAG, LDL and TC concentrations. No effect of isoflavones was observed on serum lipids, and natural soya products appear to have a stronger hypolipidaemic effect on serum cholesterol than soya supplements. Finally, initial LDL, TAG and TC concentrations seem to be strong predictors of the effect of soya on blood lipid levels.

Acknowledgements

and endothelial function[39]. The varying conclusions on the effect of isoflavones may be in part due to the process by which the isoflavones were extracted[59]. Mean isoflavone consumption is 11–47 mg/d in Asian countries and 1–2 mg/d in Western countries[60,61], but the mean daily isoflavone consumption in the included studies was 76 mg.

Although we observed a high level of heterogeneity, we are still confident in the conclusions of these analyses, as our observations are consistent with many of the other previously published reports.

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