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Effect of Plant Protein on Blood Lipids: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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***Background*—**There is a heightened interest in plant-based diets for cardiovascular disease prevention. Although plant protein is thought to mediate such prevention through modifying blood lipids, the effect of plant protein in specific substitution for animal protein on blood lipids remains unclear. To assess the effect of this substitution on established lipid targets for cardiovascular risk reduction, we conducted a systematic review and meta-analysis of randomized controlled trials using the Grading of Recommendations Assessment, Development, and Evaluation system.

***Methods and Results*—**MEDLINE, EMBASE, and the Cochrane Registry were searched through September 9, 2017. We included randomized controlled trials of ≥3 weeks comparing the effect of plant protein in substitution for animal protein on low-density lipoprotein cholesterol, non–high-density lipoprotein cholesterol, and apolipoprotein B. Two independent reviewers extracted relevant data and assessed risk of bias. Data were pooled by the generic inverse variance method and expressed as mean differences with 95% confidence intervals. Heterogeneity was assessed (Cochran Q statistic) and quantified (I^2 statistic). The overall quality (certainty) of the evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation system. One-hundred twelve randomized controlled trials met the eligibility criteria. Plant protein in substitution for animal protein decreased low-density lipoprotein cholesterol by 0.16 mmol/L (95% confidence interval, −0.20 to −0.12 mmol/L; $P<0.00001$; $I^2=55\%$; moderate-quality evidence), non–high-density lipoprotein cholesterol by 0.18 mmol/L (95% confidence interval, −0.22 to −0.14 mmol/L; $P<0.00001$; $I^2=52\%$; moderate-quality evidence), and apolipoprotein B by 0.05 g/L (95% confidence interval, −0.06 to −0.03 g/L; $P<0.00001$; $I^2=30\%$; moderate-quality evidence).

***Conclusions*—**Substitution of plant protein for animal protein decreases the established lipid targets low-density lipoprotein cholesterol, non–high-density lipoprotein cholesterol, and apolipoprotein B. More high-quality randomized trials are needed to improve our estimates.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT02037321. **(*J Am Heart Assoc*. 2017;6: e006659. DOI: 10.1161/JAHA.117.006659.)**

Key Words: animal protein • cholesterol • dyslipidemia • lipids • meta-analysis • protein • soy • systematic review • vegetable protein

Cardiovascular disease (CVD) accounts for ≈48% of deaths attributable to noncommunicable disease worldwide and remains the number one cause of mortality.[1,2] Modification by diet and lifestyle of risk factors, particularly dyslipidemia, remains the cornerstone of therapy, according to major cardiovascular guidelines.[3,4]

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Accompanying Tables S1 through S5 and Figures S1 through S13 are available at http://jaha.ahajournals.org/content/6/12/e006659/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Although the cholesterol-lowering benefit of plant protein sources, such as soy, pulses, and nuts, is well documented, the overall cholesterol-lowering benefit of plant protein in substitution for animal protein (as meat, dairy, and/or egg alternatives) has not been synthesized.
- The available evidence from randomized controlled trials suggests that 1 to 2 servings of plant protein in substitution for animal protein decreases low-density lipoprotein cholesterol, non–high-density lipoprotein cholesterol, and apolipoprotein B by ≈4% in adults with and without hyperlipidemia.
- Because of inconsistency or imprecision in the estimates, the overall quality (certainty) of the evidence is moderate by the Grading of Recommendations Assessment, Development, and Evaluation system, suggesting that more research will refine our estimates.

What Are the Clinical Implications?

- Because the intake of plant protein from soy, nuts, and pulses remains low, there is an opportunity for people to realize the lipid-lowering benefits of sustainable plant-based dietary strategies that substitute plant protein for animal protein.
- Plant protein, especially in combination with other cholesterol-lowering foods (eg, viscous fiber and plant sterols) and/or as an adjunct to lipid-lowering pharmacotherapy, may have a clinically meaningful benefit in helping people to achieve lipid targets and reduce cardiovascular risk.

There has been increasing recent interest in plant-based diets. Vegetarian and vegan dietary patterns and other plant-based dietary patterns, such as the Mediterranean diet, have been established as dietary patterns that improve lipid profiles and reduce risks of CVD.[5–7] Both the Scientific Report of the 2015 Dietary Guidelines Advisory Committee and 2016 Canadian Cardiovascular Society guidelines recently recommended a vegetarian dietary pattern and a Mediterranean dietary pattern for cardiovascular protection.[3,8] The mechanisms by which these dietary patterns improve cardiovascular risk likely include intrinsic and extrinsic pathways. Plant protein sources, such as soy, dietary pulses, and nuts, have all individually shown lipid-lowering advantages through their specific components (specific protein fractions [7s-globulin], viscous fibers, polyunsaturated fatty acids, and plant sterols). Replacement of animal protein with plant protein has also shown advantages through the displacement of saturated fatty acids.[9] The combination allows for meaningful reductions in lipids in systematic reviews and meta-analyses of randomized controlled trials (RCTs).[9–12]

Despite the strong biological plausibility supporting their benefit and endorsement of plant-based diets from recent guidelines, there is still uncertainty as to whether the benefit is attributable to the exchange of plant protein for animal protein or to other aspects of a plant-based dietary pattern. It remains difficult to isolate specific mechanisms,[13–15] and the strength of the evidence supporting the lipid-lowering effects of plant protein remains disputed.[16–19] As a result, many authoritative guidelines do not specifically recommend substituting plant protein for animal protein for lipid-lowering and cardiovascular protection.[20–23] To summarize and evaluate the available evidence, we conducted a systematic review and meta-analysis using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system of the effect of substituting plant protein for animal protein on the established lipid targets for CVD prevention, low-density lipoprotein cholesterol (LDL-C), non– high-density lipoprotein cholesterol (non–HDL-C), and apolipoprotein B (Apo-B), in RCTs.[4,24]

Methods

This study was planned and conducted following the *Cochrane Handbook for Systematic Review of Interventions*.[25] Data were reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[26] The authors declare that all supporting data are available within the article (and its supplementary files).

Literature Search

We searched MEDLINE, EMBASE, and the Cochrane Register through September 9, 2017, for eligible trials. Table S1 shows our detailed search strategy.

Study Selection

We included randomized, long-term, dietary intervention trials in human subjects comparing LDL-C, non–HDL-C, and/or Apo-B parameters between plant and animal protein intervention arms. To be included, studies had to be at least 3 weeks in duration and performed in accordance with the minimum trial follow-up requirement of the US Food and Drug Administration for lipid-lowering health claims.[27] Studies deliberately introducing confounding factors (eg, plant sterols or combined therapeutic interventions) to the plant protein arm were also excluded, including studies applying a broad vegetarian or vegan dietary pattern as opposed to a direct substitution of protein sources. No restrictions were placed on language.

Data Extraction

Study characteristics and results of eligible trials were each extracted by S.S.L. and a coextractor (L.L., S.B.M., S.E.S., E.V., or V.H.). Extracted characteristics include study setting, design, duration, blinding, sample size, participant characteristics, and plant and animal protein diet descriptions. Risk of bias of eligible trials was also assessed by S.S.L. and the same coextractor using the Cochrane risk of bias tool, which categorizes studies as high, low, or unclear risk of bias on the basis of criteria pertaining to selection bias, blinding, incomplete outcome data, and reporting bias.[25] PlotDigitizer version 2.5.1 (Free Software Foundation, Boston, MA) was used to extract data from graphs, where applicable. Any discrepancies in data extraction or risk of bias assessment were reconciled by consensus.

Grading of the Evidence

The overall quality (certainty) of evidence was assessed using the GRADE system,[28–40] which grades evidence as high, moderate, low, or very low quality. RCTs are graded as high-quality evidence by default. Scores can then be downgraded on the basis of the following prespecified criteria: risk of bias (weight of studies shows important risk of bias), inconsistency (substantial unexplained interstudy heterogeneity of I^2 >50%, P<0.10), indirectness (presence of factors that limit the generalizability of the results), imprecision (95% confidence interval [CI] for risk estimates are wide or overlap a minimally important difference of 0.1 mmol/L for LDL-C and non-HDL-C and 0.04 g/L for Apo-B), and publication bias (evidence of small-study effects).

Statistical Analysis

We used Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) for primary analyses and Stata version 13 (StataCorp, College Station, TX) for meta-regression and publication bias tests. Data were pooled using the generic inverse variance method with random-effects models and are expressed as mean differences (MDs) with 95% CIs. All analyses were repeated using fixed-effects models and parametric bootstrapping as sensitivity analyses. Where there were multiple plant or animal protein arms in a single trial, we pooled intervention arms to obtain a single pairwise comparison, to mitigate unit-of-analysis error[25]; where relevant, these arms were assessed separately for subgroup analyses.

Change-from-baseline values were favored, and differences in change-from-baseline values were used, where given; otherwise, we used end-difference values, if reported, or calculated the differences from available data. Non–HDL-C values were calculated by subtracting HDL-C from total cholesterol values, where non–HDL-C values were not directly reported, and the variance sum law was used to derive SDs for non–HDL-C from total cholesterol and HDL-C variance data.[41] In crossover trials, missing variance data were calculated from *t* test *P* values using standard formulas; where *P* values were unavailable, a correlation coefficient of 0.5 was assumed as a conservative estimate and used to impute SE data.[25,42] Where no variance data were available, the average SD of the MDs across all other included trials was used to derive the SEM difference on the basis of the respective trial's sample size.

Interstudy heterogeneity was evaluated by the Cochran Q statistic and quantified using the I^2 statistic. $P<0.10$ was considered significant; an I^2 value of 50% or higher was considered substantial.[25] Potential sources of heterogeneity were investigated by additional sensitivity analyses, in which we recalculated the pooled effect estimate after removing each individual trial, after removing all imputed data, and after imputing alternative correlation coefficients of 0.25 and 0.75. We additionally investigated potential sources of heterogeneity by subgroup analyses. Our a priori subgroups included study design, protein dose, plant and animal protein type, duration of follow-up, and baseline lipid values. A post hoc analysis was also conducted for protein form (ie, whole food or protein isolate product). Between-subgroup differences were assessed using meta-regression with dummy variables.

A post hoc dose-response analysis was conducted using a piecewise linear meta-regression via the mkspline function, to assess potential dose thresholds for the continuous subgroup addressing grams of protein substitution.

Publication bias was assessed by inspection of funnel plots and by the use of Egger and Begg tests. Where publication bias was suspected, Duval and Tweedie nonparametric "trim-and-fill" analyses were also applied to assess the effect of the imputed "missing" studies.[43]

Results

Search Results

Figure 1 shows the trial selection process. Our search identified 3917 reports, of which 3689 were excluded on the basis of review of titles and abstracts. The remaining 228 articles were reviewed in full, of which 104 provided data for 112 trial comparisons for inclusion in our analyses.[44–147]

Trial Characteristics

The Table summarizes characteristics of the included trials. Detailed characteristics are shown in Table S2. In total, 5774 participants (median age, 54 years) were included in this analysis. There were more women versus men overall (≈5:3

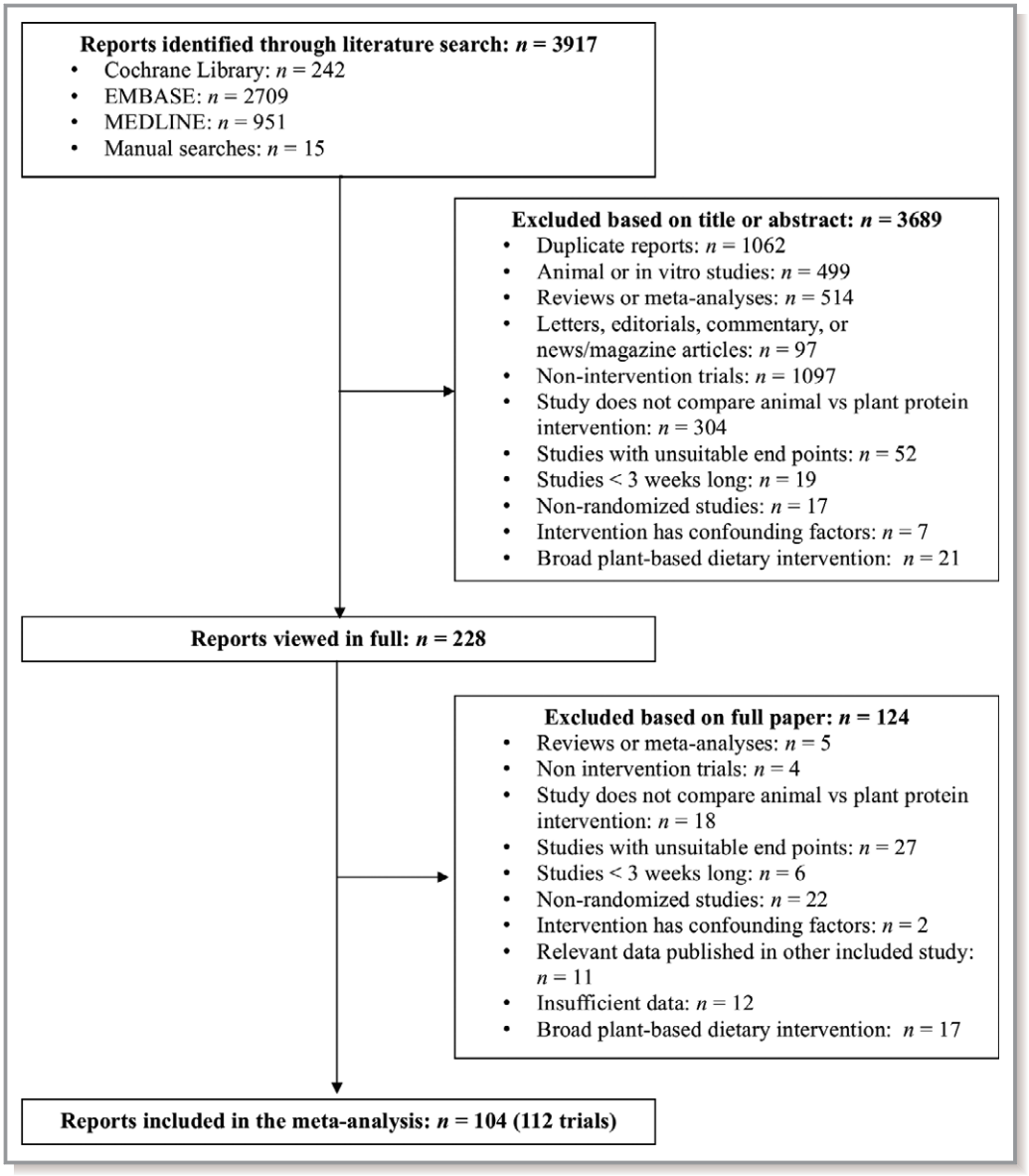

Figure 1. Search summary.

ratio), but this difference is largely attributable to a few large female-only trials, and the median sex ratio in trials was relatively balanced (44% men). Sixty-one trials were crossover, and all but 4 were in outpatient settings. Half of the trials were conducted in the United States and Canada (60 of 112), but trials were also distributed across European (24 trials), Asian (10 trials), Middle-Eastern (9 trials), and South American (3 trials) countries, as well as Australia (6 trials). Of 112 trials, 34 recruited healthy subjects (including healthy postmenopausal women); 51 trials recruited subjects with hyperlipidemia, 4 of which also selected for additional conditions. The remaining 28 trials included participants with various conditions, including renal disease, overweight, obesity, type 2 diabetes mellitus, and hypertension. Average baseline LDL-C, non–HDL-C, and Apo-B measures were 3.81 mmol/L, 4.42 mmol/L, and 1.16 g/L, respectively.

Of 112 trials, 94 used soy as the sole plant protein intervention, and 74 used dairy as the sole animal protein intervention. Other plant protein sources included various pulses, nuts, barley, and seeds; other animal protein sources included meat, fatty fish, and eggs. Seventy-one trials used protein isolate products, 37 used whole foods, and 4 used a combination of the two. The median protein substitution was ≈30 g/d. Trial follow-up ranged from 3 weeks to 4 years, with a median follow-up of 6 weeks. Twenty-five trials obtained funding from publicly funded agencies alone, 22 were supported by industry funding alone, and 55 used a combination of the two.

Table. Summary Table of Characteristics

Trial Characteristics	LDL-C	Non–HDL-C	Apo-B
Trial number, N	108	102	37
Total participants	5582	5401	1506
Trial size (participants)*	32 (4–352)	32 (4–352)	32 (4–130)
Male:female ratio[†‡]	37:63	39:61	51:49
Age, y[‡§]	54 (44–59)	54 (44–59)	54 (43–60)
Inpatient:outpatient setting[†]	4:96	3:97	3:97
Baseline serum level[§‖]	3.7 (3.0–4.2) mmol/L	4.4 (3.8–5.0) mmol/L	1.2 (1–1.4) g/L
Crossover:parallel study design[†]	54:46	54:46	57:43
Amount of substitution, g[§]	29 (23–49)	30 (22–50)	30 (25–50)
Follow-up duration, wks*	6 (3–208)	6 (3–208)	6 (3–52)
Funding sources (agency: industry:agency-industry: NR)[†]	23:19:48:9	23:19:49:10	19:32:43:5
Plant protein source, N	Soy, 91; lupin, 3; legumes, 3; pinto beans, 2; pulses, 2; barley, 1; pea, 1; walnut, 1; various, 4	Soy, 84; legumes, 3; lupin, 3; pinto beans, 2; pulses, 2; barley, 1; pea, 1; walnut, 1; various, 5	Soy, 34; legumes, 1; walnut, 1; various, 1
Animal protein source, N	Dairy, 70; meat, 10; chicken noodle soup, 2; egg, 1; various, 25	Dairy, 64; meat, 10; chicken noodle soup, 2; egg, 1; various, 25	Dairy, 25; meat, 3; egg, 1; various, 8
Protein form, N	Whole food, 38; protein isolate, 72	Whole food, 40; protein isolate, 63	Whole food, 10; protein isolate, 28

Apo-B indicates apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and NR, not reported.
*Values are reported as medians (ranges).
†Values are reported as percentage ratios.
‡Includes baseline data before dropouts, where final data were not available.
§Values are reported as medians (interquartile ranges).
‖Baseline serum-level data correspond to the respective lipid marker for each end point.

Most of our included trials were deemed to be "low risk of bias" or "unclear risk of bias" across most domains by the Cochrane Risk of Bias tool. Of the trials rated has high risk of bias, 3 were for allocation concealment, 3 were for blinding, 14 were for incomplete outcome data, and 5 were for selective outcome reporting; 1 trial was considered to have an alternative high-risk source of bias (substantial macronutrient imbalance in protein interventions for tofu compared with cheese, in the trial by Meredith et al[107]). Detailed risk of bias assessment data can be found in Figure S1.

Effect on LDL-C

Figure 2 and Figures S2 and S3 show the effect of plant protein in substitution for animal protein intake on LDL-C across 108 trials. We found a significant reduction in LDL-C (MD, −0.16 mmol/L [95% CI, −0.20 to −0.12 mmol/L]; $P<0.00001$), with evidence of substantial interstudy heterogeneity ($I^2=55\%$; $P<0.00001$). Fixed-effects model analysis, bootstrap analysis (Table S3), and sensitivity analyses did not alter the direction or significance of the effect estimates. Subgroup analyses were nonsignificant and failed to explain heterogeneity (Figure S4). Post hoc subgroup analyses (Figure S5) failed to identify significant effect modification by protein form on LDL-C, and post hoc dose-response analyses (Table S4) did not find a dose threshold for LDL-C in continuous subgroup analyses.

Effect on Non–HDL-C

Figure 2 and Figures S6 and S7 show the effect of plant protein in substitution for animal protein intake on non–HDL-C across 102 trials. We found a significant reduction in non–HDL-C (MD, −0.18 mmol/L [95% CI, −0.22 to −0.14 mmol/L]; $P<0.00001$), with evidence of substantial interstudy heterogeneity ($I^2=52\%$; $P<0.00001$). Fixed-effects model analysis, bootstrap analysis (Table S3), and sensitivity analyses did not alter the direction or significance of the effect estimates. Subgroup analyses, however, did reveal a greater reduction in non-HDL-C in trials with higher baseline non-HDL-C levels (between-subgroup difference, −0.09 mmol/L [95% CI, −0.17 to −0.01 mmol/L]; $P=0.03$), with a residual $I^2=43\%$

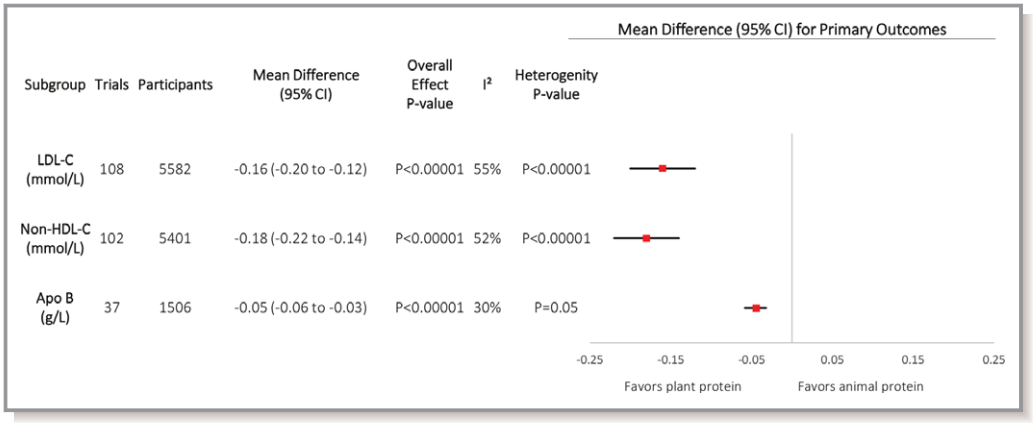

Figure 2. Primary analyses. Pooled effect estimates for each end point (squares) shown. Paired analyses were applied to all crossover trials. Data are expressed as mean differences (95% confidence intervals [CIs]), using generic inverse-variance random-effects models. Interstudy heterogeneity was tested using the Cochran Q statistic (χ^2) at a significance level of $P<0.10$ and quantified by I^2; levels of ≥50% represented substantial heterogeneity. All outcomes had significant pooled effect estimates. Heterogeneity was significant and substantial for low-density lipoprotein cholesterol (LDL-C) and non–high-density lipoprotein cholesterol (HDL-C), and significant but not substantial for apolipoprotein B (Apo-B).

(Figure S8). Post hoc subgroup analyses (Figure S5) failed to identify significant effect modification by protein form on non–HDL-C, and post hoc dose-response analyses (Table S4) did not find a dose threshold in continuous subgroup analyses.

Effect on Apo-B

Figure 2 and Figures S9 and S10 show the effect of plant protein in substitution for animal protein intake on Apo-B across 37 trials. We found a significant reduction in Apo-B by plant protein (MD, −0.05 g/L [95% CI, −0.06 to −0.03 g/L]; $P<0.00001$), with evidence of moderate interstudy heterogeneity ($I^2=30\%$; $P=0.05$). Fixed-effects model analysis, bootstrap analysis (Table S3), and sensitivity analyses did not alter the direction or significance of the effect estimates. Subgroup analyses also did not explain the heterogeneity (Figure S11). However, removal of the 2007 study by Azadbakht et al[51] modified heterogeneity from significant to nonsignificant ($I^2=21\%$; $P=0.14$). Post hoc subgroup analyses (Figure S5) failed to identify significant effect modification by protein form on non–HDL-C, and post hoc dose-response analyses (Table S4) did not find a dose threshold in continuous subgroup analyses.

Publication Bias

Figure S12 shows the funnel plots used to evaluate publication bias; on visual inspection, there was no evidence of asymmetry or small-study effects for any outcome. The Egger test identified significant publication bias for LDL-C ($P=0.03$), but the Begg test was nonsignificant. The Egger and Begg tests were nonsignificant across all other end points. Trim-and-fill analyses were conducted for LDL-C, with data for 8 additional studies imputed to adjust for funnel plot asymmetry (Figure S13). There was no evidence of meaningful small-study effects. The direction, significance, and size of the pooled effect estimate after inclusion of the imputed studies were not significantly altered (MD, −0.18 mmol/L [95% CI, −0.21 to −0.14 mmol/L]; $P<0.001$).

GRADE Assessment

Table S5 shows a summary of the GRADE assessments for each end point. The evidence for both LDL-C and non–HDL-C was rated moderate quality, on the basis of a downgrade for inconsistency in both analyses. The evidence for Apo-B was rated moderate quality, on the basis of a downgrade for imprecision.

Discussion

We conducted a systematic review and meta-analysis of 112 RCTs assessing the effect of plant protein versus animal protein on established lipid targets for CVD prevention in 5774 adult participants with and without hyperlipidemia. Plant protein substitution for animal protein led to modest reductions in LDL-C (−0.16 mmol/L or ≈4%; 95% CI, ≈3%–5%), non–HDL-C (−0.18 mmol/L or ≈4%; 95% CI, ≈3%–5%), and Apo-B (−0.05 g/L or ≈3%; 95% CI, 2%–5%). On the basis of

studies finding a one-to-one relationship between LDL-C and cardiovascular risk reductions, these findings would translate to a 4% risk in major cardiovascular events.[148,149]

Findings in Relation to the Literature

Our findings are supported by other systematic reviews and meta-analyses of the effect of individual sources of plant protein in substitution for different macronutrients (not just animal protein) on blood lipids. We showed, in an updated analysis of an American Heart Association analysis, that soy protein produced similar decreases in LDL-C (≈4%) in RCTs involving participants with and without hyperlipidemia.[9] An individual patient-level pooled analysis of RCTs showed that tree nuts decrease LDL-C by ≈7%, along with other lipid end points.[10] A systematic review and meta-analysis of the effect of dietary pulses on established lipid targets showed an LDL-C–lowering effect of ≈5% and a tendency for a non–HDL-C–lowering effect.[12]

Our findings are also aligned with previous evidence related to plant protein as part of plant-based dietary patterns. A systematic review of 13 observational studies and 14 RCTs trials demonstrated the lipid-lowering benefits of plant-based diets,[6] and a recent systematic review and meta-analysis of 11 RCTs found significant reductions in LDL-C and non–HDL-C following a vegetarian diet.[150] We have shown that the Portfolio diet, which combines cholesterol-lowering foods (including plant protein from soy, pulses, and nuts) along with viscous fibers and plant sterols, produces LDL-C reductions comparable to lovastatin (−28.6% versus −30.9%) over 4 weeks when all foods were provided.[151] There were more modest reductions of 10% to 15% (with greater reductions seen with greater adherence) when the diet was administered as dietary advice under free living conditions over 6 months.[152] Our Eco-Atkins trial also found greater reductions in LDL-C with a vegan low-carbohydrate ("Eco-Atkins") diet that emphasizes plant proteins, compared with a high-carbohydrate, low-fat, lacto-ovo vegetarian diet (treatment difference, −0.49 mmol/L).[153]

Furthermore, studies have found an association between plant-based diets and cardiovascular disease. The PREDIMED (Prevención con Dieta Mediterránea) trial showed that a predominantly plant-based Mediterranean diet supplemented with nuts as a source of plant protein decreases major cardiovascular events.[154] Prospective cohort studies offer further support showing that dietary patterns high in plant proteins, such as Mediterranean and vegetarian dietary patterns, are associated with reduced cardiovascular events.[155–158] An analysis of the Harvard cohorts found that low-carbohydrate and high-protein diets were associated with increased mortality, but inversely correlated with mortality and particularly CVD mortality when based on plant protein.[159] Other prospective cohort studies have also shown that plant-based diets are associated with a mortality benefit.[160] On the other hand, increased intake of animal protein sources has been associated with negative health outcomes. A pooled analysis of the Harvard cohorts found that red meat consumption was associated with increased risks of total, cardiovascular, and cancer mortality.[161] Other large, prospective, cohort studies have found an association between animal protein sources and disease or mortality.[162–164]

There are several mechanisms by which plant protein may exert a lipid-lowering effect. One explanation is that the plant protein source acts as a vehicle for other established antiatherogenic agents, such as plant sterols or soluble fiber; similarly, the displaced animal protein source could also act as a vehicle for hypercholesterolemic agents, such as saturated fat and cholesterol.[13–15,24] Interestingly, our post hoc subgroup analyses did not find a significant difference between protein isolate products and whole food sources for any given end point, suggesting that the cholesterol-lowering effects are at least, in part, attributable to the plant protein itself rather than just the associated nutrients.

An alternative explanation relates to the amino acid breakdown encountered in plant proteins versus animal proteins; in particular, lysine, which is more prevalent in animal proteins, has been shown to increase cholesterol levels in animal models, whereas arginine, which is found more in plant proteins, has been found to have the opposite effect.[165–167] The cholesterol-lowering effect of arginine has also been demonstrated in a 5-week arginine feeding trial in humans,[168] but otherwise there are limited human studies investigating this subject. Proposed mechanisms for these effects involve bile acid production and binding of hepatic LDL receptors.[166,169]

A Priori Subgroup Analyses

Our results appear to be robust to different trial conditions. Similar to a previous meta-analysis by Anderson et al,[170] we did find that increased baseline values amplified the effects seen in non–HDL-C reduction. However, our overall analyses indicate that the lipid-lowering effects of plant protein apply to both hypercholesterolemic and normal subjects, because the normocholesterolemic subgroup also showed a significant improvement in non–HDL-C, and similar subgroup analyses in LDL-C and Apo-B were nonsignificant. The beneficial effects otherwise held across a range of ages and health statuses, and all other subgroup analyses were nonsignificant.

Strengths and Limitations

Our systematic review and meta-analysis has several strengths and limitations. The strengths include the identification of all available evidence through a systematic search strategy, the inclusion of RCTs that provide the greatest

protection against bias, quantitative syntheses of the data, and assessment of the overall quality of the evidence using the GRADE system.

The limitations of our systematic review and meta-analysis relate to inconsistency in the treatment effects and imprecision. Evidence of unexplained inconsistency in treatment effects was seen for 2 of the established therapeutic lipid end points. There was substantial interstudy heterogeneity in our LDL-C and non–HDL-C analyses, which was not fully explained by sensitivity or subgroup analyses. Evidence of imprecision was seen in Apo-B, because the 95% CI for effect estimates for Apo-B overlapped the prespecified minimally important difference of 0.04 g/L. Apo-B also showed evidence of moderate interstudy heterogeneity; however, the statistical significance of heterogeneity was eliminated by the removal of the 2007 study by Azadbakht et al.[51] We also considered downgrading for indirectness of the evidence. A relatively large proportion of the available trials evaluated soy as the sole plant protein source (94 of 112 trials) and/or dairy as the sole animal protein source (74 of 112 trials). Subgroup analyses, however, did not reveal evidence of significant effect modification by protein sources across any of the 3 end points, which suggests that the effects seen apply across varying plant and animal protein sources. Several plant protein sources, however, were not evaluated, including wheat (gluten), rice, and other grains. In addition, there were limited studies with extended follow-up duration, which would help assess issues of long-term adherence.

Taking into account these strengths and limitations, the evidence was assessed by the GRADE system as moderate quality for a cholesterol-lowering effect of plant protein in substitution for animal protein across LDL-C, non–HDL-C, and Apo-B markers.

Implications

Current adult protein intakes average ≈80 to 100 g/d in the United States and Europe. Of this intake, ≈30% is from plant protein sources.[171,172] The median intervention of 30 g protein substitution per day across trials included in our analyses reflects the substitution of 1 to 2 servings of meat for plant protein substitutes or 3 250-mL cups of dairy milk for soy milk. This additional substitution would mean a shift to diets with >50% plant protein, which can be attained by following healthy dietary patterns, such as vegetarian, Mediterranean, and Portfolio dietary patterns.[173–175] Given the low current consumption of plant protein-rich foods, such as soy and pulses, in Canada and the United States, there remains a significant opportunity to realize the benefits of making such dietary changes.[176–178]

Although the reductions in LDL-C, non–HDL-C, and Apo-B on their own were modest (<5%), plant protein can still contribute to meaningful reductions in lipids. On the basis of the evidence from the Portfolio diet, the lipid-lowering effects of individual food components, which include plant protein from soy, pulses, and nuts, are additive, such that the LDL-C–lowering effect (≈5%–10%) of each of the 4 components of the Portfolio diet food can be summed to achieve meaningful reductions.[3,147,148] Several large trials and cohort studies have shown that such reductions are associated with improved cardiovascular outcomes.[179–185] The 2016 Canadian Cardiovascular Guidelines further highlighted the superior predictive value for CVD of non–HDL-C and Apo-B, both of which were reduced by plant protein.[3] The implication is that plant protein as part of a comprehensive lipid-lowering dietary pattern alone or as an add-on to other lipid-lowering therapy can help people achieve their lipid targets and reduce CVD risk.

Despite the existing evidence for benefit, current dietary guidelines do not wholly reflect the demonstrated benefits of plant protein versus animal protein and tend to place animal sources of protein on the same level as plant sources.[20–22] In particular, the 2015 to 2020 Dietary Guidelines for Americans recommend seafood, meats, poultry, eggs, nuts, seeds, and soy products indiscriminately as options for protein sources and suggest that the vegetarian dietary patterns described are only for those already following a vegetarian diet (which is incongruent with the Scientific Report of the 2015 Dietary Guidelines Advisory Committee on which the the 2015 to 2020 Dietary Guidelines for Americans is based).[8,22,23]

Conclusions

In conclusion, our aggregate analyses demonstrate a benefit of plant protein in substitution for animal protein on established lipid targets for CVD prevention in adults with and without hyperlipidemia. To our knowledge, this is the first systematic review and meta-analysis to directly evaluate the effects of plant protein as well as plant for animal protein replacement. These findings presents an opportunity for patients, clinicians, and guidelines to exploit the lipid-lowering benefits of a sustainable plant-based dietary strategy that is associated with improved overall health outcomes. Our confidence in the evidence for the LDL-C–, non–HDL-C–, and Apo-B–lowering effects of plant protein, however, is limited by inconsistency for LDL-C and non–HDL-C and imprecision for Apo-B. Further large, high-quality, randomized controlled trials investigating plant protein sources beyond soy, particularly in young and healthy participants, would be useful to help better understand the role of plant protein in cardiovascular risk reduction.

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Author Contributions

All authors had full access to all of the data (including statistical reports and tables) in this study and take full responsibility for the integrity of the data and the accuracy of the data analysis. Conception and design: Li and Sievenpiper. Analysis and interpretation of the data: Li, Blanco Mejia, de Souza, Leiter, Kendall, Jenkins, and Sievenpiper. Drafting of the article: Li. Critical revision of the article for important intellectual content: Li, Lytvyn, Blanco Mejia, Stewart, Viguiliouk, Ha, de Souza, Leiter, Kendall, Jenkins, and Sievenpiper. Final approval of the article: Li, Lytvyn, Blanco Mejia, Stewart, Viguiliouk, Ha, de Souza, Leiter, Kendall, Jenkins, and Sievenpiper. Statistical expertise: de Souza. Attainment of funding: Kendall, Jenkins, and Sievenpiper. Administrative, technical, or logistic support: Blanco Mejia. Collection and assembly of data: Li, Lytvyn, Blanco Mejia, Stewart, Viguiliouk, and Ha. Guarantor: Sievenpiper.

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He serves as an unpaid scientific advisor for the Food, Nutrition, and Safety Program (FNSP) and the Technical Committee on Carbohydrates of the International Life Science Institute (ILSI) North America. He is a member of the International Carbohydrate Quality Consortium (ICQC), Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the EASD, and Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. His wife is an employee of Unilever Canada. No competing interests were declared by Li, Blanco Mejia, Stewart, Viguiliouk, and Leiter. There are no patents, products in development, or marketed products to declare.

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SUPPLEMENTAL MATERIAL

Table S1. Search Strategy.

	Medline	EMBASE	Cochrane
1	(Exp diet, vegetarian/ OR vegetarian*.mp. OR vegan*.mp. OR exp vegetable proteins/ OR (vegetable* adj1 protein*).mp. OR (plant* adj1 protein*).mp. OR (plant* adj1 food*).mp. OR (plant* adj1 based).mp. OR exp Fabaceae/ OR exp soybean proteins/ OR soy*.mp. OR tofu*.mp. OR natto*.mp. OR tempeh*.mp. OR miso*.mp. OR lentil*.mp. OR bean*.mp. OR legume*.mp. OR (meat* adj1 analog*).mp.) OR lactoovo*.mp. OR lacto-ovo*.mp. OR ovolacto*.mp. OR ovo-lacto*.mp. OR lactoveg*.mp. OR lacto-veg*.mp. OR ovoveg*.mp. OR ovo-veg*.mp.	(Exp vegetarian diet/ OR exp vegetarian/ OR vegetarian*.mp. OR vegan*.mp. OR exp vegetable protein/ OR (vegetable* adj1 protein*).mp. OR (plant* adj1 protein*).mp. OR (plant* adj1 food*).mp. OR (plant* adj1 based).mp. OR exp Fabaceae/ OR soy*.mp. OR tofu*.mp. OR natto*.mp. OR tempeh*.mp. OR miso*.mp. OR lentil*.mp. OR bean*.mp. OR legume*.mp. OR (meat* adj1 analog*).mp. OR lactoovo*.mp. OR lacto-ovo*.mp. OR ovolacto*.mp. OR ovo-lacto*.mp. OR lactoveg*.mp. OR lacto-veg*.mp. OR ovoveg*.mp. OR ovo-veg*.mp.)	(Exp diet, vegetarian/ OR vegetarian*.mp. OR vegan*.mp. OR exp vegetable proteins/ OR (vegetable* adj1 protein*).mp. OR (plant* adj1 protein*).mp. OR (plant* adj1 food*).mp. OR (plant* adj1 based).mp. OR exp Fabaceae/ OR exp soybean proteins/ OR soy*.mp. OR tofu*.mp. OR natto*.mp. OR tempeh*.mp. OR miso*.mp. OR lentil*.mp. OR bean*.mp. OR legume*.mp. OR (meat* adj1 analog*).mp.) OR lactoovo*.mp. OR lacto-ovo*.mp. OR ovolacto*.mp. OR ovo-lacto*.mp. OR lactoveg*.mp. OR lacto-veg*.mp. OR ovoveg*.mp. OR ovo-veg*.mp.
		AND	
	(omnivor*.mp. OR (conventional adj3 diet*).mp. OR (normal adj3 diet*).mp. OR (regular adj3 diet*).mp. OR (mixed adj3 diet*).mp. OR exp egg proteins, dietary/ OR exp milk proteins/ OR exp meat/ OR exp eggS/ OR exp dairy products/ OR exp milk/ OR (meat* adj1 protein*).mp. OR (meat* adj1 product*).mp. OR (animal* adj1 protein*).mp. OR (animal* adj1 product*).mp. OR (fish* adj1 protein*).mp. OR (fish* adj1 product*).mp. OR (poultry adj1 protein*).mp. OR (poultry adj1 product*).mp. OR (chicken* adj1 protein*).mp. OR (chicken* adj1 product*).mp. OR (egg* adj1 protein*).mp. OR (egg* adj1 product*).mp. OR (milk adj1 protein*).mp. OR (milk adj1 product*).mp. OR (dairy adj1 protein*).mp. OR (dairy adj1 product*).mp.)	(exp omnivore/ OR omnivor*.mp. OR (conventional adj3 diet*).mp. OR (normal adj3 diet*).mp. OR (regular adj3 diet*).mp. OR (mixed adj3 diet*).mp. OR exp Meat/ OR exp egg/ OR exp dairy product/ OR (meat* adj1 protein*).mp. OR (meat* adj1 product*).mp. OR (animal* adj1 protein*).mp. OR (animal* adj1 product*).mp. OR (fish* adj1 protein*).mp. OR (fish* adj1 product*).mp. OR (poultry adj1 protein*).mp. OR (poultry adj1 product*).mp. OR (chicken* adj1 protein*).mp. OR (chicken* adj1 product*).mp. OR (egg* adj1 protein*).mp. OR (egg* adj1 product*).mp. OR (milk adj1 protein*).mp. OR (milk adj1 product*).mp. OR (dairy adj1 protein*).mp. OR (dairy adj1 product*).mp.)	(omnivor*.mp. OR (conventional adj3 diet*).mp. OR (normal adj3 diet*).mp. OR (regular adj3 diet*).mp. OR (mixed adj3 diet*).mp. OR exp egg proteins, dietary/ OR exp milk proteins/ OR exp meat/ OR exp eggS/ OR exp dairy products/ OR exp milk/ OR (meat* adj1 protein*).mp. OR (meat* adj1 product*).mp. OR (animal* adj1 protein*).mp. OR (animal* adj1 product*).mp. OR (fish* adj1 protein*).mp. OR (fish* adj1 product*).mp. OR (poultry adj1 protein*).mp. OR (poultry adj1 product*).mp. OR (chicken* adj1 protein*).mp. OR (chicken* adj1 product*).mp. OR (egg* adj1 protein*).mp. OR (egg* adj1 product*).mp. OR (milk adj1 protein*).mp. OR (milk adj1 product*).mp. OR (dairy adj1 protein*).mp. OR (dairy adj1 product*).mp.)
		AND	
	(exp lipoproteins/ OR exp cholesterol/ OR exp hyperlipidemias/ OR (lipid or lipids).mp. OR (cholesterol or cholesterols).mp. OR hdl.mp. OR ("high density lipoprotein" or "high density lipoproteins").mp. OR ldl.mp. OR ("low density lipoprotein" or "low density lipoproteins").mp. OR apolipoprotein*.mp. OR (hyperlipemia* or hyperlipaemia*).mp. OR (hyperlipidemia* or hyperlipidaemia*).mp. OR (lipidemia* or lipidaemia*).mp. OR (lipemia* or lipaemia*).mp. OR (lipemic or lipaemic).mp.)	(exp lipoproteins/ OR exp cholesterol/ OR exp hyperlipidemias/ OR (lipid or lipids).mp. OR (cholesterol or cholesterols).mp. OR hdl.mp. OR ("high density lipoprotein" or "high density lipoproteins").mp. OR ldl.mp. OR ("low density lipoprotein" or "low density lipoproteins").mp. OR apolipoprotein*.mp. OR (hyperlipemia* or hyperlipaemia*).mp. OR (hyperlipidemia* or hyperlipidaemia*).mp. OR (lipidemia* or lipidaemia*).mp. OR (lipemia* or lipaemia*).mp. OR (lipemic or lipaemic).mp.)	(exp lipoproteins/ OR exp cholesterol/ OR exp hyperlipidemias/ OR (lipid or lipids).mp. OR (cholesterol or cholesterols).mp. OR hdl.mp. OR ("high density lipoprotein" or "high density lipoproteins").mp. OR ldl.mp. OR ("low density lipoprotein" or "low density lipoproteins").mp. OR apolipoprotein*.mp. OR (hyperlipemia* or hyperlipaemia*).mp. OR (hyperlipidemia* or hyperlipidaemia*).mp. OR (lipidemia* or lipidaemia*).mp. OR (lipemia* or lipaemia*).mp. OR (lipemic or lipaemic).mp.)
2	limit 1 to animals	limit 1 to animals	1 not (exp infant formula/ OR exp milk, human/)
3	limit 2 to human	limit 2 to human	
4	2 not 3	2 not 3	
5	1 not 4	1 not 4	
6	5 not (exp infant formula/ OR exp milk, human/)	5 not (exp breast milk/ or exp infant formula/)	

For all databases, the original search date was December 6, 2016; updated search was performed on September 10, 2017.

Table S2. Full Table of Characteristics.

Study, year	Participants	Mean Age (SD or range), y *	Mean BMI or Body Weight (SD) †	Setting	Design	Plant Protein Source	Animal Protein Source ‡	Food Form §	Amount of substitution ‖	Background Diet ¶	Energy Balance	Follow-up	Funding #
Abd-Mishani et al. 2014 [1]	24 DM2 (6M,18W)	61.7 (6)	74.5 (7.1) kg	OP, Iran	C	Pulses	Meat	Whole	2 servings pulses 3d/wk	(55:30:15)	Neutral	8 wks	Agency
Abete et al. 2009 [2]**	26 O (26M)	38 (35.7)	31.8 (3) kg/m²	OP, Spain	P	Legumes	Meat, Fatty fish	Whole	Legumes 4d/wk	(53:30:17)	Negative	8 wks	Agency
Ahmed et al. 2011 [3]	27 CKD (4M,23W)	46 (12)	25.6 (4.6) kg/m²	OP, Brazil	P	Soy	Various	Protein	0.8g/kg	Nephropathy diet	Negative	8 wks	N/A
Allen et al. 2007 [4]**	191 PM (191W)	56.8 (5.6)	27.9 (4.7) kg/m²	OP, USA	P	Soy	Dairy	Protein	20g	LF	Neutral	12 wks	Agency & Industry
Appt et al. 2008 [5]	32 PM (32W)	57.7 (4.5)	24.6 (3.2) kg/m²	OP, USA	C	Soy	Dairy	Protein	52g	Habitual	Neutral	8 wks	Agency & Industry
Ashton et al. 2000 [6]	42 N (42M)	45.8 (7.8)	26.2 (3.3) kg/m²	OP, Australia	C	Soy	Lean meat	Whole	290g tofu	Plant-based diet (44:32:17)	Neutral	4 wks	N/A
Azadbakht et al. 2003 [7]	14 DM2,CKD (10M,4W)	62.5 (12.1)	26.6 (4) kg/m²	OP, Iran	C	Soy	Various	Protein	35%	Nephropathy diet	Neutral	7 wks	Agency
Azadbakht et al. 2007 [8]	42 MS,PM (42W)	PM	N/A	OP, Iran	C	Soy	Red meat	Whole & protein	11-15g	DASH	Neutral	8 wks	Agency
Azadbakht et al. 2008 [9]	41 DM2,CKD (18M,23W)	62 (12)	N/A	OP, Iran	P	Soy	Various	Protein	35%	Nephropathy diet	Neutral	4 y	N/A
Bahr et al. 2013 [10]	33 HC (15M,18W)	49.5 (13.4)	28 (5.9) kg/m²	OP, Germany	C	Lupin	Dairy	Protein	20g	Habitual	Neutral	8 wks	Agency & Industry
Bahr et al. 2014 [11]	68 HC (28M,40W)	56.9 (10.7)	26.5 (2.7) kg/m²	OP, Germany	C	Lupin	Dairy	Protein	20g	Habitual	Neutral	4 wks	Agency & Industry
Bakhit et al. 1994 [12] (Cotyledon)	21 HC (21M)	43 (14)	27.1 (3) kg/m²	OP, USA	C	Soy	Dairy	Protein	25g	LF, LC (55:30:15)	Neutral	4 wks	Industry
Bakhit et al. 1994 [12] (Cellulose)	21 HC (21M)	43 (14)	27.1 (3) kg/m²	OP, USA	C	Soy	Dairy	Protein	25g	LF, LC (55:30:15)	Neutral	4 wks	Industry
Basaria et al. 2009 [13]	84 PM (84W)	55.7 (10.8)	26 (5.2) kg/m²	OP, USA	P	Soy	Dairy	Protein	20g	Habitual	Neutral	12 wks	N/A
Baum et al. 1998 [14]	66 PM (66W)	60.9 (8)	28.2 (5.3) kg/m²	OP, USA	P	Soy	Dairy	Protein	40g	NCEP Step 1	Neutral	24 wks	Agency & Industry

Table S2. Full Table of Characteristics (Continued).

Study, year	Participants	Mean Age (SD or range), y *	Mean BMI or Body Weight (SD) †	Setting	Design	Plant Protein Source	Animal Protein Source ‡	Food Form §	Amount of substitution ‖	Background Diet ¶	Energy Balance	Follow-up	Funding #
Beavers et al. 2010 [15]	32 N,PM (32W)	54.4 (3.3)	25.8 (3.8) kg/m²	OP, USA	P	Soy	Dairy	Whole	18g	Habitual	Neutral	4 wks	Industry
Blum et al. 2003 [16]	24 HC,PM (24W)	55 (5)	N/A	OP, Israel	C	Soy	Dairy	Protein	25g	Habitual	Neutral	6 wks	Industry
Borodin et al. 2009 [17]	28 HC,O (9M,19W)	50 (10.6)	29 (3.9) kg/m²	OP, Russia	C	Soy	Dairy	Protein	30g	Habitual	Neutral	2 mos	Industry
Bricarello et al. 2004 [18]	60 HC (15M,45W)	56 (7.7)	24.9 (2.3) kg/m²	OP, Brazil	C	Soy	Dairy	Whole	25g	NCEP TLC	Neutral	6 wks	Agency & Industry
Burns-Whitmore et al. 2014 [19]	20 N (4M,16W)	38 (3)	23 (4.5) kg/m²	OP, USA	C	Walnut	Egg (Standard, N3 FA)	Whole	28g walnut 6x/wk	Habitual	Neutral	8 wks	Agency & Industry
Campbell et al. 2010 [20]	62 HC,PM (62W)	54.3 (33.2)	28 (5.2) kg/m²	OP, USA	P	Soy	Dairy	Protein	25g	Habitual	Neutral	1 y	Agency & Industry
Chen et al. 2005 (HC) [21]	19 HC,CKD (5M,14W)	63.6 (9.4)	24 (2.1) kg/m²	OP, Taiwan	P	Soy	Dairy	Protein	30g	Hemodialysis diet	Neutral	12 wks	Agency & Industry
Chen et al. 2005 (N) [21]	18 CKD (5M,13W)	59.5 (11.9)	21.3 (5) kg/m²	OP, Taiwan	P	Soy	Dairy	Protein	30g	Hemodialysis diet	Neutral	12 wks	Agency & Industry
Chen et al. 2006 [22]	26 HC,CKD (19M,7W)	58.6 (11.4)	23.1 (2.7) kg/m²	OP, Taiwan	P	Soy	Dairy	Protein	30g	Hemodialysis diet	Neutral	12 wks	Agency
Crouse et al. 1999 [23]**	146 HC (94M,62W)	52 (11)	26 (3) kg/m²	OP, USA	P	Soy	Dairy	Protein	25g	NCEP Step 1	Neutral	9 wks	Agency & Industry
Cuevas et al. 2003 [24]	18 HC,PM (18W)	59 (47-70)	29.3 (3.4) kg/m²	OP, Chile	C	Soy	Dairy	Protein	40g	NCEP Step 1	N/A	4 wks	Agency & Industry
Dent et al. 2001 [25]	69 PeriM (69W)	50.2 (3.6)	24.1 (3.2) kg/m²	OP, USA	P	Soy	Dairy	Protein	40g	Habitual	Neutral	24 wks	Agency & Industry
Duane et al. 1999 [26]	8 N (8M)	60.3 (11.9)	26.3 (4) kg/m²	IP, USA	C	Soy	Various	Whole	>75%	American diet	Neutral	6-7 wks	Agency
Dunn et al. 1986 [27]	12 N (12M)	31.8 (6.4)	24.9 (4.6) kg/m²	OP, USA	C	Soy	Dairy	Whole	26.7g	Habitual	Neutral	3 wks	N/A
Finley et al. 2007 (N) [28]	40 N (20M,20W)	37.4 (10.1)	24.5 (2.8) kg/m²	OP, USA	P	Pinto beans	Chicken noodle soup	Whole	130g pinto beans	Habitual	Neutral	12 wks	Agency
Finley et al. 2007 (Pre-MS) [28]	40 Pre-MS (20M,20W)	42.4 (9.9)	32.8 (3.8) kg/m²	OP, USA	P	Pinto beans	Chicken noodle soup	Whole	130g pinto beans	Habitual	Neutral	12 wks	Agency

Table S2. Full Table of Characteristics (Continued).

Study, year	Participants	Mean Age (SD or range), y *	Mean BMI or Body Weight (SD) †	Setting	Design	Plant Protein Source	Animal Protein Source ‡	Food Form §	Amount of substitution ‖	Background Diet ¶	Energy Balance	Follow-up	Funding #
Gardner et al. 2001[29]	94 HC,PM (94W)	59.1 (6.9)	26.3 (4.4) kg/m²	OP, USA	P	Soy	Dairy	Protein	42g	Habitual	Neutral	12 wks	Agency & Industry
Gardner et al. 2007 [30]	28 HC (6M,22W)	52 (9)	26 (4) kg/m²	OP, USA	C	Soy	Dairy	Whole & protein	25g	Habitual	Positive	4 wks	Agency & Industry
Giovannetti et al. 1986 [31] (N)	12 N (12W)	22.1 (2.1)	59.5 (8) kg	OP, Canada	C	Soy	Dairy	Protein	88%	(44:38:18)	Neutral	4 wks	Agency & Industry
Giovannetti et al. 1986 [31] (LF)	12 N (12W)	22.1 (2.1)	59.5 (8) kg	OP, Canada	C	Soy	Dairy & meat	Protein	88%	(59:23:18)	Neutral	4 wks	Agency & Industry
Goldberg et al. 1982 [32] (N)	4 N (3M,1W)	36.8 (16.1)	N/A	OP, USA	C	Soy	Dairy & meat	Protein	75%	(40:40:20)	Neutral	6 wks	Agency & Industry
Goldberg et al. 1982 [32] (HC)	12 HC (7M,5W)	43.6 (12.2)	N/A	OP, USA	C	Soy	Dairy & meat	Protein	75%	(40:40:20)	Neutral	6 wks	Agency & Industry
Greany et al. 2004 [33]	37 PM (37W)	57.5 (13.4)	25.4 (6.7) kg/m²	OP, USA	C	Soy	Dairy	Protein	0.4g/kg	Habitual	Neutral	6 wks	Agency & Industry
Haub et al. 2005 [34]	21 N (21M)	65 (5)	28.2 (2.6) kg/m²	OP, USA	P	Soy	Beef products	Whole	0.6g/kg	Plant-based diet	Neutral	12 wks	Agency & Industry
Hermansen et al. 2001 [35]	20 DM2 (14M,6W)	63.6 (7.5)	30.2 (4.1) kg/m²	OP, Denmark	C	Soy	Dairy	Protein	50g	(~42:29:26)	Neutral	6 wks	Agency & Industry
Hill et al. 2015 [36]††	62 O,MS (28M,34W)	45.8 (21.4)	34.8 (3.7) kg/m²	OP, USA	P	Lean beef	Various	Whole	67%	DASH or (45:27:27)	Neutral 5 wk, Negative 18 wk	6 mos	Agency & Industry
Hoie et al. 2005 [37]- A double-blind placebo-controlled….	116 HC (54M,62W)	55.2 (9.5)	76.9 (12.4) kg	OP, Germany	P	Soy	Dairy	Protein	25g	Habitual	Neutral	8 wks	N/A
Høie et al. 2005 [38]- Lipid Lowering…	117 HC (63M,54W)	53.6 (9.6)	76.3 (12.5) kg	OP, Germany	P	Soy	Dairy	Protein	15g, 25g	Habitual	Neutral	8 wks	N/A
Hoie et al. 2007 [39]	88 HC (34M,54W)	54.6 (9.6)	75.2 (12.5) kg	OP, Germany	P	Soy	Dairy	Protein	25g	Habitual	Neutral	8 wks	Industry
Hosseinpour-Niazi et al. 2014 [40]	31 DM2 (7M,24W)	58.1 (33.4)	27.8 (3.3) kg/m²	OP, Iran	C	Non-soy legumes	Meat	Whole	2 servings legumes 3x/wk	NCEP TLC	Neutral	8 wks	Agency

Table S2. Full Table of Characteristics (Continued).

Study, year	Participants	Mean Age (SD or range), y *	Mean BMI or Body Weight (SD) †	Setting	Design	Plant Protein Source	Animal Protein Source ‡	Food Form §	Amount of substitution ‖	Background Diet ¶	Energy Balance	Follow-up	Funding #
Huff et al. 1984 [41]	5 HC (5M)	49 (11.2)	82 (15.7) kg	OP, Canada	C	Soy	Various	Whole	41g	(49:37:15)	Negative	6 wks	Agency
Jenkins et al. 1989 [42]	11 O (11W)	38 (13.3)	32.8 (4.1) kg/m²	OP, Canada	C	Soy	Various	Protein	17.4g	1000kcal diet	Negative	4 wks	Agency & Industry
Jenkins et al. 2002 [43]	41 HC,PM (23M,18W)	62 (12.8)	25.3 (3.2) kg/m²	OP, Canada	C	Soy	Dairy	Whole & protein	50-52g	NCEP Step 2	Neutral	4 wks	Agency & Industry
Jenkins et al. 2010 [44]	23 HC,PM (7M,16W)	57 (9.6)	26 (4.8) kg/m²	OP, Canada	C	Barley	Dairy	Whole	30g/2000kcal	LF, LC, plant-based diet	Neutral	4 wks	Agency & Industry
Kestin et al. 1989 [45]	26 N (26M)	44 (10)	25.5 (3.2)	OP, Australia	P §§	Various	Meat	Whole	60%	Plant-based diet	Neutral	6 wks	Agency & Industry
Kjolbaek et al. 2017 [46]	113 O (60M:91F)	42.4	33.1	OP, Denmark	P	Soy	Dairy	Protein	45g	Habitual	Neutral	24 wks	Agency & Industry
Kreijkamp-Kaspers et al. 2004 [47]	175 PM (175W)	66.6 (4.7)	26.2 (3.8) kg/m²	OP, Netherlands	P	Soy	Dairy	Protein	25.6g	Habitual	Neutral	1 y	Agency & Industry
Kurowska et al. 1997 [48]	34 HC (17M,17W)	55 (11)	N/A	OP, Canada	C	Soy	Dairy	Whole	31g	Habitual	Neutral	4 wks	Industry
Laidlaw et al. 1985 [49]	19 HC (19M)	47.4 (11.3)	81.5 (11.7) kg	OP, Canada	C	Soy	Dairy	Protein	18.4g	Habitual	Neutral	8 wks	Agency & Industry
Laurin et al. 1991 [50]**	9 FHC (6M,4W)	8 (3)	16.7 (2.6) kg/m²	OP, Canada	C	Soy	Dairy	Protein	35%	LC (52:28:20)	Neutral	4 wks	Agency
Li et al. 2016 [51]	34 O (11M:23F)	53.5 (3.2)	30.9 (0.7) kg/m²	OP, USA	P	Legumes	Meat	Whole	30%	(55:25:20)	Negative	12 wks	Agency & Industry
Liao et al. 2007 [52]	30 O (6M,24W)	33.4 (10.8)	29.8 (3.4) kg/m²	OP, Taiwan	P	Soy	Various	Whole	30g	(60:25:15)	Negative	8 wks	Industry
Lichenstein et al. 2002 [53] (No IF)	42 HC (18M,24W)	62.7 (8.8)	26.6 (3.4) kg/m²	OP, USA	C	Soy	Dairy & meat	Protein	50g/2000kcal	(46.5:37:16)	Neutral	6 wks	Agency & Industry
Lichenstein et al. 2002 [53] (IF)	42 HC (18M,24W)	62.7 (8.8)	26.6 (3.4) kg/m²	OP, USA	C	Soy	Dairy & meat	Protein	50g/2000kcal	(46.5:37:16)	Neutral	6 wks	Agency & Industry
Liu et al. 2012 [54]	180 Pre-DM2,PM (180W)	56.2 (4.4)	24.4 (3.7) kg/m²	OP, China	P	Soy	Dairy	Protein	15g	Habitual	Neutral	6 mos	Agency & Industry

Table S2. Full Table of Characteristics (Continued).

Study, year	Participants	Mean Age (SD or range), y *	Mean BMI or Body Weight (SD) †	Setting	Design	Plant Protein Source	Animal Protein Source ‡	Food Form §	Amount of substitution ‖	Background Diet ¶	Energy Balance	Follow-up	Funding #
Liu et al. 2014 [55]	270 PM (270W)	57.9 (5.1)	N/A	OP, China	P	Soy	Dairy	Whole	12.8g	Habitual	Neutral	6 mos	Agency
Lovati et al. 1987 [56]	12 HC (5M,7W)	45 (12.5)	61.4 (1.7) kg	OP, Italy	C	Soy	Dairy & meat	Protein	N/A	LF (54:26:20)	Neutral	4 wks	Agency & Industry
Ma et al. 2005 [57]	159 HC (70M,89W)	56.6 (8.4)	28.9 (4.3) kg/m²	OP, USA	P	Soy	Dairy	Protein	31.5g	Habitual	Neutral	5 wks	Industry
Ma et al. 2011 [58]	90 HC (26M,64W)	51.7 (10.6)	23.6 (3.3) kg/m²	OP, China	P	Soy	Dairy	Protein	18g	Habitual	Neutral	8 wks	Industry
Maki et al. 2010 [59]	58 HC (26M,32W)	50.8 (12)	27.7 (4.8) kg/m²	OP, USA	P	Soy	Dairy	Protein	25g	NCEP TLC	Neutral	4 wks	Industry
Markova et al. 2015 [60]‡‡	37 DM2 (24M,13W)	64.3 (6.1)	30.5 (3.6) kg/m²	OP, Germany	P	Pulses	Dairy & meat	Whole	>65-70%	(40:30:30)	Neutral	6 wks	N/A
Matthan et al. 2007 [61]	28 HC (2M,26W)	65 (6)	27 (3) kg/m²	OP, USA	C	Soy	Various	Whole	37.5g	NCEP TLC	Neutral	6 wks	Agency
McVeigh et al. 2006 [62]	35 N (35M)	27.9 (5.7)	25.4 (3) kg/m²	OP, Canada	C	Soy	Dairy	Protein	32g	Habitual	Neutral	57 d	Agency & Industry
Mercer et al. 1987 [63]	33 N (23M,10W)	46.7 (10.8)	N/A	OP, Canada	C	Soy	Dairy	Protein	19g	Habitual	Neutral	6 wks	Agency
Meredith et al. 1989 [64]	10 N (10W)	27.3 (6.3)	22.5 (2.6) kg/m²	OP, USA	C	Soy	Dairy	Whole	22g	Plant-based diet	Neutral	3 wks	Agency
Meyer et al. 2004 [65]	23 HC and/or HTN (13M,10W)	54 (8.6)	26.2 (2.9) kg/m²	OP, Australia	C	Soy	Dairy	Whole	>30g	Habitual	Neutral	5 wks	Agency & Industry
Miraghajani et al. 2013 [66]	25 DM2,CKD (10M,15W)	51 (10)	28 (4) kg/m²	OP, Iran	C	Soy	Dairy	Whole	2.5g	Nephropathy diet	Neutral	4 wks	Agency
Napora et al. 2011 [67]	33 ADT (33M)	69.1 (9.3)	29.4 (5.3) kg/m²	IP, USA	P	Soy	Dairy	Protein	20g	Habitual	Neutral	12 wks	N/A
Onning et al. 1998 [68]	22 N (11M,11W)	31.5 (23-54)	(20-25)) kg/m²	OP, Sweden	P	Soy	Dairy	Whole	22.5g-30g	Habitual	Neutral	4 wks	Agency
Padhi et al. 2015 [69]	213 HC (78M,135W)	55 (8.8)	28 (4.6) kg/m²	OP, Canada	P	Soy	Dairy	Whole	12.5g, 25g	Habitual	Neutral	6 wks	Agency & Industry

Table S2. Full Table of Characteristics (Continued).

Study, year	Participants	Mean Age (SD or range), y *	Mean BMI or Body Weight (SD) †	Setting	Design	Plant Protein Source	Animal Protein Source ‡	Food Form §	Amount of substitution ‖	Background Diet ¶	Energy Balance	Follow-up	Funding #
Pipe et al. 2009 [70]**	29 DM2,PM (16M,13W)	60.1 (9.6)	29.6 (4.1) kg/m²	OP, Canada	C	Soy	Dairy	Protein	40g	Habitual	Neutral	57 d	Agency & Industry
Potter et al. 1993 [71]	25 HC (25M)	61 (48-78)	30.2 (6.7) kg/m²	IP, USA	C	Soy	Dairy	Protein	50g	(55:<30:15)	Neutral	4 wks	Industry
Puska et al. 2002 [72]	52 HC (31M,21W)	55.8 (35-70)	N/A	OP, Finland	P	Soy	Dairy	Protein	52g	Habitual	Neutral	6 wks	Industry
Puska et al. 2004 [73]**	132 HC (77M,66W)	Median 58 (30-70)	27 (9.1) kg/m²	OP, Finland	P	Soy	Dairy	Protein	41.4g	Habitual	Neutral	8 wks	Agency & Industry
Roughead et al. 2005 [74]	13 PM (13W)	59.9 (5)	26 kg/m²	OP, USA	C	Soy	Meat	Protein	25g	(55:30:15)	Neutral	7 wks	Agency & Industry
Santo et al. 2008 [75]	30 N (30M)	24.2 (2.3)	23.8 (3.7) kg/m²	OP, USA	P	Soy	Dairy	Protein	25g	Habitual	N/A	4 wks	Industry
Shidfar et al. 2009 [76]	42 HC,PM (42W)	55 (4.8)	27 (3.1) kg/m²	OP, Iran	P	Soy	Dairy	Whole	50g	Habitual	Neutral	10 wks	N/A
Shige et al. 1998 [77]	11 N (11M)	32.6 (6.4)	24.6 (2.8) kg/m²	OP, Japan	C	Soy	Dairy	Protein	20g	Japanese diet	Neutral	3 wks	Industry
Sirtori et al. 1977 [78]	20 HC (10M,10W)	(22-68)	N/A	IP, Italy	C	Soy	Various	Protein	55%	LF, LC, HPUFA	N/A	3 wks	Agency & Industry
Sirtori et al. 1999 [79]	21 HC (8M,13W)	51.9 (13.5)	24.4 (3.6) kg/m²	OP, Italy	C	Soy	Dairy	Whole	35g	LC, HPUFA	Neutral	4 wks	Agency
Sirtori et al. 2002 [80]	20 FHC (4M,16W)	59.5 (8.4)	24.2 (3.5) kg/m²	OP, Italy	C	Soy	Dairy	Whole	25g	LC, HPUFA	Neutral	4 wks	Agency & Industry
Steele et al. 1992 [81]	32 N (15M,17W)	42.2 (16.2)	N/A	OP, Australia	C	Soy	Dairy	Whole	>16.5g	Habitual	Neutral	4 wks	Agency
Steinberg et al. 2003 [82]	28 PM (28W)	54.9 (5.3)	24.6 (3.2) kg/m²	OP, USA	C	Soy	Dairy	Protein	25g	Habitual	Neutral	6 wks	Industry
Sucher et al. 2017 [83]	37 DM2 (24M:13F)	64.3 (6.3)	30.2 (3.9) kg/m²	OP, Germany	P	Pea	Dairy & meat	Whole	72%	(40:30:30)	Neutral	6 wks	Agency & Industry
Tabibi et al. 2010 [84]	36 CKD (18M,18W)	52 (15)	26 (5) kg/m²	OP, Iran	P	Soy	Meat	Whole	14g	Habitual	Neutral	8 wks	Agency
Takahira et al. 2011 [85]	46 O (11M,35W)	55.5 (12.4)	29.2 (4) kg/m²	OP, Japan	P	Soy	Dairy	Protein	12g	Habitual	Neutral	20 wks	Agency

Table S2. Full Table of Characteristics (Continued).

Study, year	Participants	Mean Age (SD or range), y *	Mean BMI or Body Weight (SD) †	Setting	Design	Plant Protein Source	Animal Protein Source ‡	Food Form §	Amount of substitution ‖	Background Diet ¶	Energy Balance	Follow-up	Funding #
Teede et al. 2001 [86]	179 N,PM (96M,83W)	60.5 (9.6)	25.5 (2.6) kg/m²	OP, Australia	P	Soy	Dairy	Protein	40g	Habitual	Neutral	3 mos	Agency
Teixeira et al. 2000 [87]	81 HC (81M)	45.4 (11.4)	27.4 (3.7) kg/m²	OP, USA	P	Soy	Dairy	Protein	20g, 30g, 40g, 50g	NCEP Step 1	Neutral	6 wks	Agency & Industry
Teixeira et al. 2004 [88]	14 DM2,CKD (14M)	(53-73)	29.8 (3) kg/m²	OP, USA	C	Soy	Dairy	Protein	0.5g/kg	1g protein/kg, LF, LC	Neutral	8 wks	Agency & Industry
Thorp et al. 2008 [89]	91 HC (34M,57W)	52.7 (1)	27.3 (4.5) kg/m²	OP, Australia	C	Soy	Dairy	Protein	12g, 24g	Habitual	Neutral	6 wks	Agency & Industry
Tonstad et al. 2002 [90]	130 HC,PM (108M,22W)	52.5 (8.4)	25.3 (2.1) kg/m²	OP, Norway	P	Soy	Dairy	Protein	30g, 50g	AHA Step 1	Neutral	16 wks	Industry
Van Horn et al. 2001 [91] (Oats)	64 HC,PM (64W)	66.6 (10.3)	26.9 (3.8) kg/m²	OP, USA	P	Soy	Dairy	Protein	29g	NCEP Step 1	Neutral	6 wks	Industry
Van Horn et al. 2001 [91] (Wheat)	63 HC,PM (63W)	66.6 (10.3)	26.9 (3.8) kg/m²	OP, USA	P	Soy	Dairy	Protein	29g	NCEP Step 1	Neutral	6 wks	Industry
van Nielen et al. 2014 [92]	15 O,PM (15W)	61 (5)	Waist circumference: 90 (10) cm	OP, Netherlands	C	Soy	Dairy & meat	Whole	30g	(49:21:30)	Neutral	4 wks	Industry
van Raaij et al. 1981 [93]**	69 N (46M,30W)	(18-28)	N/A	OP, Netherlands	P	Soy	Dairy	Protein	65%	Western diet	Neutral	4 wks	Agency & Industry
van Raaij et al. 1982 [94]**	57 N (32M,29W)	46 (9)	N/A	OP, Netherlands	P	Soy	Dairy	Protein	60%	Western diet	Negative	4 wks	Agency & Industry
Vega-Lopez et al. 2010 [95]	30 HC (9M,21W)	61.8 (6.5)	26.7 (3.2) kg/m²	OP, USA	C	Various (Low Lys:Arg)	Various (High Lys:Arg)	Whole	>75%	(50:30:20)	Neutral	5 wks	Agency
Vigna et al. 2000 [96]	77 PM (77W)	53.4 (3.3)	25.9 (3.5) kg/m²	OP, Italy	P	Soy	Dairy	Protein	40g	Habitual	Neutral	12 wks	Industry
Weisse et al. 2010 [97]	43 HC (20M,23W)	43.9 (11.8)	25.9 (4.5) kg/m²	OP, Germany	P	Lupin	Dairy	Protein	35g	Habitual	Neutral	6 wks	Agency
West et al. 2005 [98]	32 HC,PM (14M,18W)	58 (5.2)	26.3 (3.1) kg/m²	OP, USA	C	Soy	Dairy	Protein	25g	NCEP Step 1, HF	N/A	6 wks	Industry

Table S2. Full Table of Characteristics (Continued).

Study, year	Participants	Mean Age (SD or range), y *	Mean BMI or Body Weight (SD) †	Setting	Design	Plant Protein Source	Animal Protein Source ‡	Food Form §	Amount of substitution ‖	Background Diet ¶	Energy Balance	Follow-up	Funding #
Wheeler et al. 2002 [99]	17 DM2,CKD (14M,3W)	56 (12.4)	33.1 (5.8) kg/m²	OP, USA	C	Legumes	Dairy & meat	Whole	60%	(53:30:17)	Neutral	6 wks	Agency & Industry
Wiebe et al. 1984 [100]	8 N (8M)	21 (3.2)	N/A	OP, Canada	C	Various	Dairy	Whole	55%	Western diet	Neutral	3 wks	Agency
Wofford et al. 2012 [101]**	352 N (205M,147 W)	47.7 (10.4)	29.3 (4.5) kg/m²	OP, USA	C	Soy	Dairy	Protein	40g	Habitual	Neutral	8 wks	Agency & Industry
Wolfe et al. 1981 [102]	7 HC (7M)	41.9 (10.8)	76 (13.2) kg	OP, Canada	C	Soy	Dairy & meat	Protein	47g	Habitual, LC	Neutral	7 wks	Agency & Industry
Wolfe et al. 1985 [103]	5 HC (2M,3W)	56 (8.9)	84 (13.4) kg	OP, Canada	C	Soy	Dairy & meat	Protein	72g	Habitual, LC	Neutral	5 wks	Agency & Industry
Wong et al. 1998 [104] (N)	13 N (13M)	35.5 (7.2)	N/A	OP, USA	C	Soy	Dairy & meat	Protein	>75%	NCEP Step 1	Neutral	5 wks	Agency & Industry
Wong et al. 1998 [104] (HC)	13 HC (13M)	41.4 (7.8)	N/A	OP, USA	C	Soy	Dairy & meat	Protein	>75%	NCEP Step 1	Neutral	5 wks	Agency & Industry

ADT = androgen deprivation therapy, C = crossover, CKD = chronic kidney disease, DM2 = diabetes mellitus, FHC = familial hypercholesterolemia, HC = hypercholesterolemic, HF = high fibre, HPUFA = high polyunsaturated fat:saturated fat ratio, HTN = hypertension, IF = isoflavones, IP = inpatient, LC = low cholesterol, LF = low fat, LOV = lacto-ovo-vegetarian, N = normal, N/A = data not available, NP = not published, M = men, MS = metabolic syndrome, O = overweight/obese, OP = outpatient, P = parallel, PM = post-menopausal, Peri-M = peri-menopausal, W = women

* Mean age and SD or range were used as available; where unavailable, post-menopausal (PM) was used for Azadbakht et al. 2007[8], and median age and range were used for Puksa et al. 2004[73].

† Baseline BMI values (kg/m2). Baseline body weight (kg) values are only reported when no data on body weight were available. Waist circumference (cm) was used for the study by van Nielen et al. 2014[92] as neither were available.

‡ Animal protein source. Multiple animal protein intervention arms within the same trial are separated by a comma.

§ Food form indicates whether test foods were in the form of whole foods (whole) and/or isolated protein supplements (protein).

‖ Amount of protein substitution, per day unless otherwise indicated. Where data for grams of substitution was unavailable, grams/2000kcal, percentage protein replacement, grams per kilogram body weight, or serving sizes were used as available. Studies describing replacement of "most" protein are displayed as >75%. Multiple dosage levels within the same trial are separated by a comma.

¶ Background diet as described by study protocol. Where specific diets were not indicated, dietary breakdowns are listed as energy from (carbohydrate:fat:protein) where given, and where no information was given habitual diets were assumed. NCEP Step 1 diet has <30% fat, <1/3 saturated fat, and <300mg cholesterol. NCEP Step 2 diet has <30% fat, <1/4 saturated fat, and <200mg cholesterol. Nephropathy diet contains 0.8g protein/kg body weight. Hemodialysis diet contains 35%F, 1.2g protein/kg body weight, and 32-35kcal/kg body weight. Plant-based diet includes vegetarian, lacto-vegetarian, and lacto-ovo-vegetarian.

Agency funding consists of funding from government, university, or not-for-profit health agency sources. The following studies had declared conflicts of interest: Gardner et al 2007[30], Haub et al 2005[34], Hermansen et al 2001[35], Jenkins et al 2010[44], Maki et al 2010[59], Mercer et al 1987[63], Padhi et al 2015[69], Tonstad et al 2002[90], and West et al 2005[98]. None of the other studies declared any conflicts of interest.

** Includes baseline data before drop-outs where final data were not available for study characteristics

†† For Hill et al. 2015[36], the background diet followed the DASH diet except for one arm of the animal protein arm which had increased protein content

‡‡ The data from Markova et al. 2015 [60] are not yet published; BMI data from this study describe the first 30 patients enrolled

§§ Kestin et al. 1989 [45] used an incomplete crossover design with three arms

Table S3. Bootstrap Analyses.

LDL-C
Total (95% CI): -0.16 [-0.20, -0.12] Heterogeneity: $Chi^2 = 235.60$, df = 107 ($P < 0.0001$); $I^2 = 55\%$ Test for overall effect: Z = -8.597 ($P < 0.0001$) Modified $H^2 = 1.218$ $tau^2 = 0.0160$
non-HDL-C
Total (95% CI): -0.18 [-0.22, -0.14] Heterogeneity: $Chi^2 = 209.96$, df = 101 ($P < 0.0005$); $I^2 = 51\%$ Test for overall effect: Z = -8.463 ($P < 0.0005$) Modified $H^2 = 1.035$ $tau^2 = 0.0164$
ApoB
Total (95% CI): -0.05 [-0.06, -0.03] Heterogeneity: $Chi^2 = 51.36$, df = 36 ($P = 0.05$); $I^2 = 30\%$ Test for overall effect: Z = -6.587 ($P < 0.0005$) Modified $H^2 = 0.449$ $tau^2 = 0.0004$

Data are expressed in mmol/L for LDL-C and non-HDL-C, and g/L for ApoB. Paired analyses were applied to all crossover trials. Data are expressed as MDs with 95% CIs, using generic inverse-variance random-effects models. Inter-study heterogeneity was tested using the Cochran Q statistic (chi-square) at a significance level of $P<0.10$.

Table S4. Post-Hoc Dose Response.

LDL				
Dose threshold, grams AP replaced with PP	**Dose ranges, grams AP replaced with PP**	**β (95% CIs) ***	**Residual I2 †**	**p-value**
15	≤15	0.003 (-0.020, 0.026)	57.58%	0.704
	>15	-0.002 (-0.004, 0.001)		
25	≤25	0.001 (-0.008, 0.011)	57.57%	0.535
	>25	-0.002 (-0.005, 0.001)		
35	≤35	-0.001 (-0.007, 0.005)	57.59%	0.846
	>35	-0.002 (-0.006, 0.002)		
45	≤45	-0.002 (-0.006, 0.002)	57.47%	0.744
	>45	-0.001 (-0.006, 0.005)		
55	≤55	-0.002 (-0.005, 0.001)	57.03%	0.512
	>55	0.001 (-0.007, 0.009)		
Non-HDL				
Dose threshold, grams AP replaced with PP	**Dose ranges, grams AP replaced with PP**	**β (95% CIs) ***	**Residual I2 †**	**p-value**
15	≤15	0.006 (-0.018, 0.029)	44.61%	0.685
	>15	0.001 (-0.002, 0.003)		
25	≤25	0.002 (-0.007, 0.010)	42.15%	0.839
	>25	0.001 (-0.002, 0.003)		
35	≤35	-0.001 (-0.007, 0.005)	44.29%	0.462
	>35	0.002 (-0.002, 0.006)		
45	≤45	-0.002 (-0.006, 0.002)	45.25%	0.112
	>45	0.005 (-0.001, 0.010)		
55	≤55	-0.001 (-0.004, 0.002)	45.16%	0.076
	>55	0.007 (0, 0.015)		
Apo B				
Dose threshold, grams AP replaced with PP	**Dose ranges, grams AP replaced with PP**	**β (95% CIs) ***	**Residual I2 †**	**p-value**
15	≤15	0.001 (-0.006, 0.008)	37.42%	0.836
	>15	0 (-0.001, 0.001)		
25	≤25	0 (-0.003, 0.003)	37.42%	0.922
	>25	0 (-0.001, 0.001)		
35	≤35	0 (-0.002, 0.002)	37.42%	0.899
	>35	0 (-0.001, 0.001)		
45	≤45	0 (-0.002, 0.001)	36.88%	0.615
	>45	0.001 (-0.001, 0.002)		
55	≤55	0 (-0.001, 0.001)	36.11%	0.519
	>55	0.001 (-0.002, 0.003)		

AP = animal protein; PP = plant protein

* β is the slope derived from the piecewise linear meta-regression analyses and represents the treatment effect on LDL-C for doses above and below each dose-threshold representing grams animal protein replaced with plant protein

† The residual I^2 value indicates heterogeneity unexplained by each dose-threshold.

Table S4. GRADE Assessment.

Quality assessment							№ of patients		Effect	Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Plant protein**	**Animal protein**	**Absolute (95% CI)**	
Effects of vegetable protein compared to animal protein intake on LDL-C										
108	randomised trials	not serious	serious [1]	not serious	not serious	potential publication bias [2]	3637	3764	MD **0.16 mmol/L lower** (0.2 lower to 0.12 lower)	⊕⊕⊕⊖ MODERATE due to inconsistency
Effects of vegetable protein compared to animal protein intake on non-HDL-C										
102	randomised trials	not serious	serious [1]	not serious	not serious	none	3502	3643	MD **0.18 mmol/L lower** (0.22 lower to 0.14 lower)	⊕⊕⊕⊖ MODERATE due to inconsistency
Effects of vegetable protein compared to animal protein intake on apo B										
37	randomised trials	not serious	not serious	not serious	serious [3]	none	937	1083	MD **0.05 g/L lower** (0.06 lower to 0.03 lower)	⊕⊕⊕⊖ MODERATE due to imprecision

CI: Confidence interval; MD: Mean difference

1. Significant (P<0.05) and substantial (I-squared>50%) heterogeneity
2. Egger's test for publication bias was significant (P<0.05). However, significance is dependent upon one study with missing variance data, and additional Duval and Tweedie trim-and-fill analyses did not substantially alter the effect size or significance. Therefore there was no further downgrading.
3. 95% CI for risk estimates overlap a minimally important difference of 0.04g/L for apolipoprotein B

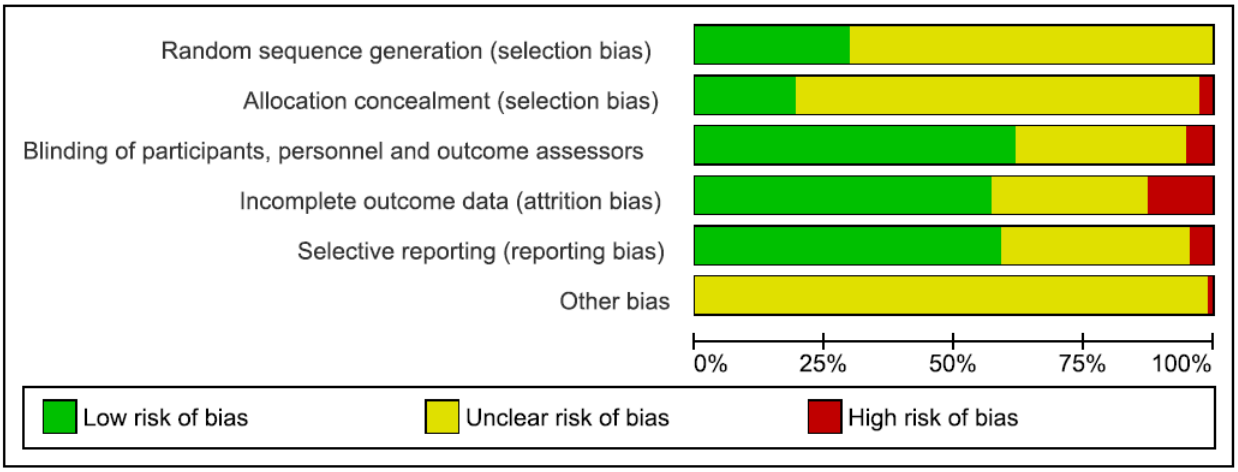

Figure S1. Cochrane Risk of Bias. Risk of bias assessment using Cochrane Risk of Bias Tool.

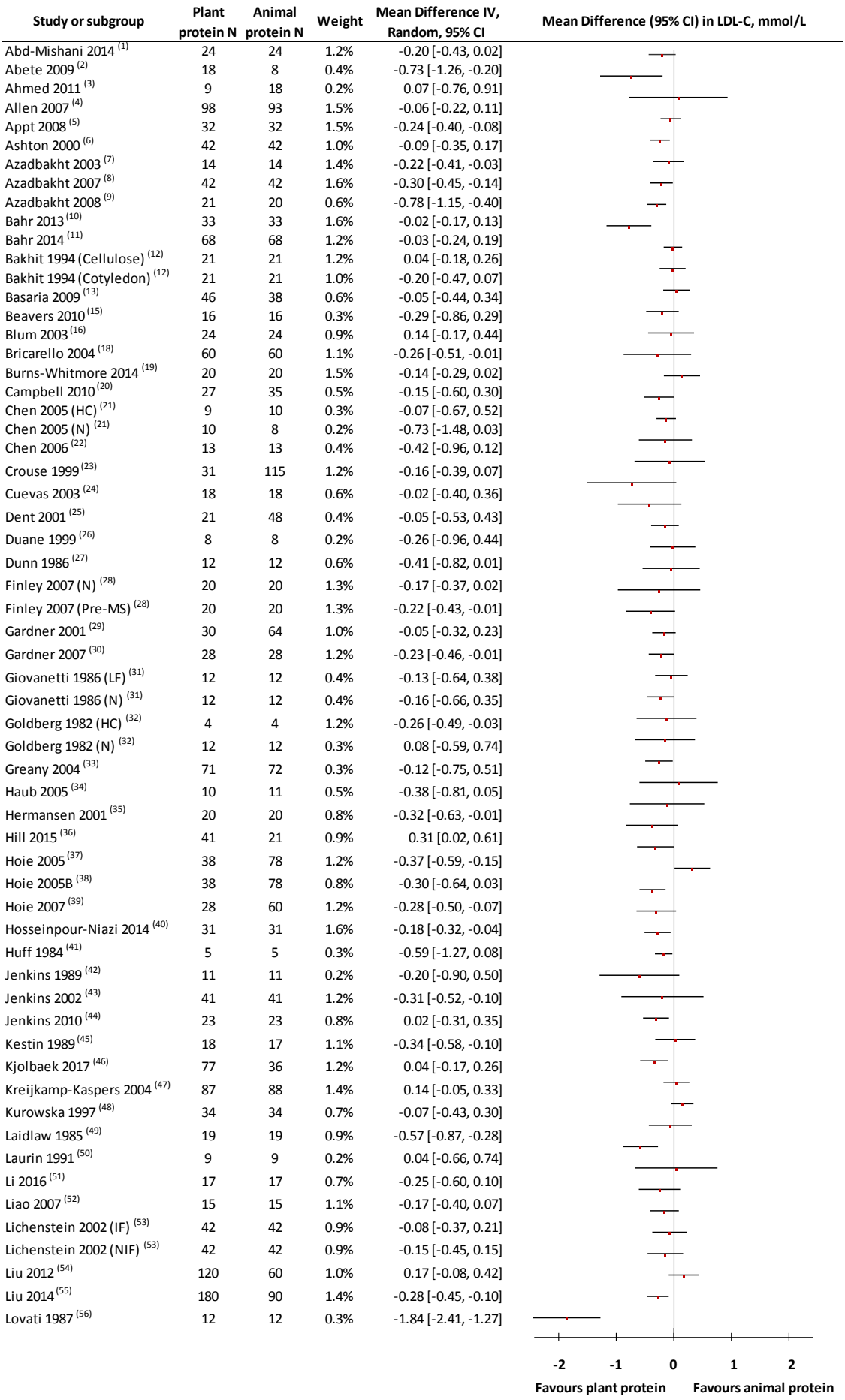

Figure S2. LDL-C Forest Plot, random-effects model.

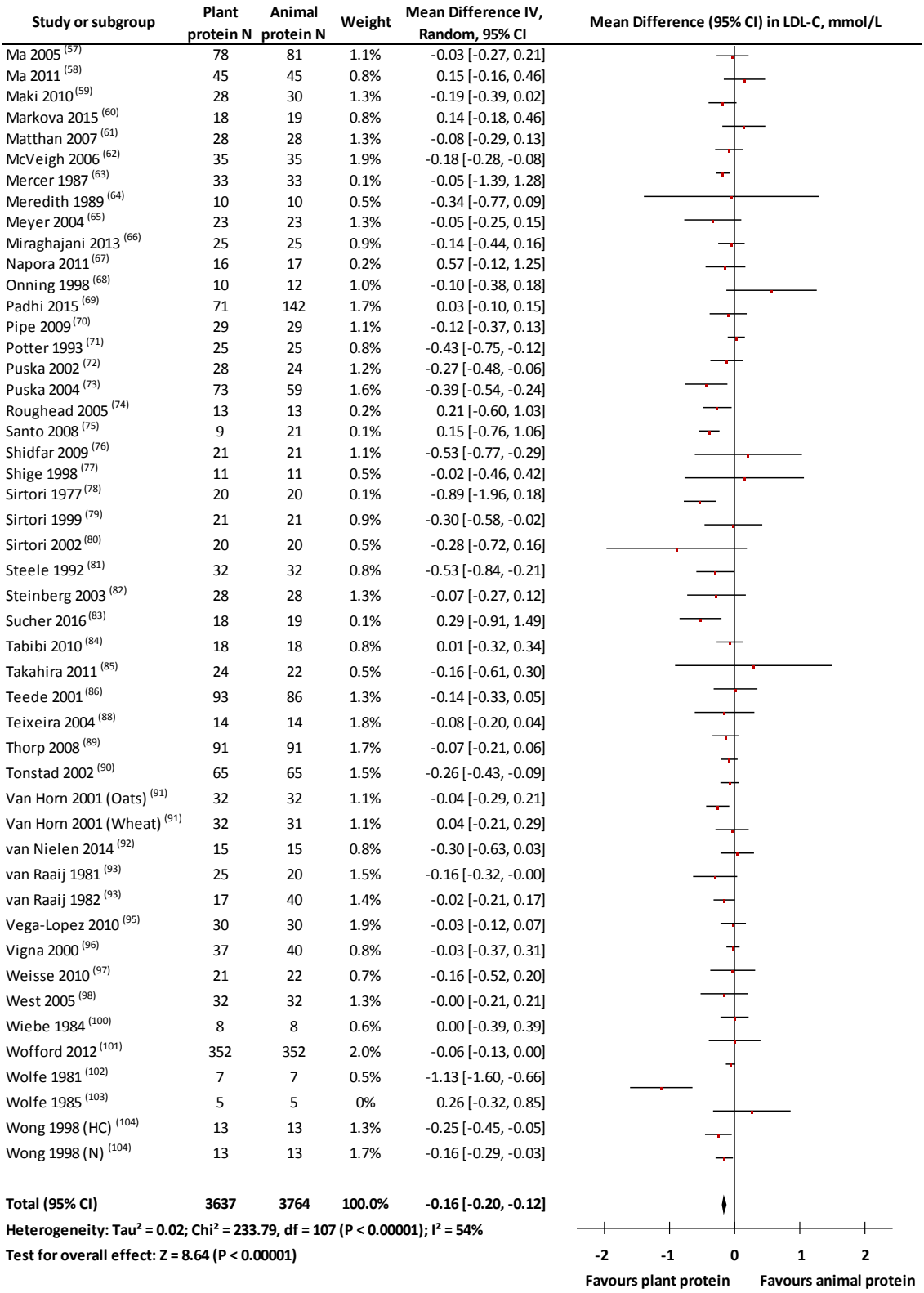

Figure S2 (Continued). LDL-C Forest Plot, random-effects model. HC=hypercholesterolemic; IF=isoflavones; LF=low-fat; N=normal; NIF=no isoflavones; Pre-MS=pre-metabolic syndrome. The pooled effect estimate (diamond) is shown. Paired analyses were applied to all crossover trials. The studies by Duane et al. 1999 [26], Lovati et al. 1987 [56], Sirtori et al. 2002 [80], and Van Horn et al. 2001 [91] were missing variance data, which were imputed using the average standard of the mean differences across included trials based on the respective trial's sample size. Data are expressed as MDs with 95% CIs, using generic inverse-variance random-effects models. Inter-study heterogeneity was tested using the Cochran Q statistic (chi-square) at a significance level of $P<0.10$ and quantified by I^2, levels of ≥50% represented substantial heterogeneity.

Study or subgroup	Plant protein N	Animal protein N	Weight	Mean Difference IV, Fixed, 95% CI
Abd-Mishani 2014 [1]	24	24	0.9%	-0.20 [-0.43, 0.02]
Abete 2009 [2]	18	8	0.2%	-0.73 [-1.26, -0.20]
Ahmed 2011 [3]	9	18	0.1%	0.07 [-0.76, 0.91]
Allen 2007 [4]	98	93	1.7%	-0.06 [-0.22, 0.11]
Appt 2008 [5]	32	32	1.8%	-0.24 [-0.40, -0.08]
Ashton 2000 [6]	42	42	0.7%	-0.09 [-0.35, 0.17]
Azadbakht 2003 [7]	14	14	1.3%	-0.22 [-0.41, -0.03]
Azadbakht 2007 [8]	42	42	1.9%	-0.30 [-0.45, -0.14]
Azadbakht 2008 [9]	21	20	0.3%	-0.78 [-1.15, -0.40]
Bahr 2013 [10]	33	33	2.0%	-0.02 [-0.17, 0.13]
Bahr 2014 [11]	68	68	1.0%	-0.03 [-0.24, 0.19]
Bakhit 1994 (Cellulose) [12]	21	21	1.0%	0.04 [-0.18, 0.26]
Bakhit 1994 (Cotyledon) [12]	21	21	0.6%	-0.20 [-0.47, 0.07]
Basaria 2009 [13]	46	38	0.3%	-0.05 [-0.44, 0.34]
Beavers 2010 [15]	16	16	0.1%	-0.29 [-0.86, 0.29]
Blum 2003 [16]	24	24	0.5%	0.14 [-0.17, 0.44]
Bricarello 2004 [18]	60	60	0.7%	-0.26 [-0.51, -0.01]
Burns-Whitmore 2014 [19]	20	20	1.8%	-0.14 [-0.29, 0.02]
Campbell 2010 [20]	27	35	0.2%	-0.15 [-0.60, 0.30]
Chen 2005 (HC) [21]	9	10	0.1%	-0.07 [-0.67, 0.52]
Chen 2005 (N) [21]	10	8	0.1%	-0.73 [-1.48, 0.03]
Chen 2006 [22]	13	13	0.2%	-0.42 [-0.96, 0.12]
Crouse 1999 [23]	31	115	0.9%	-0.16 [-0.39, 0.07]
Cuevas 2003 [24]	18	18	0.3%	-0.02 [-0.40, 0.36]
Dent 2001 [25]	21	48	0.2%	-0.05 [-0.53, 0.43]
Duane 1999 [26]	8	8	0.1%	-0.26 [-0.96, 0.44]
Dunn 1986 [27]	12	12	0.3%	-0.41 [-0.82, 0.01]
Finley 2007 (N) [28]	20	20	1.2%	-0.17 [-0.37, 0.02]
Finley 2007 (Pre-MS) [28]	20	20	1.1%	-0.22 [-0.43, -0.01]
Gardner 2001 [29]	30	64	0.6%	-0.05 [-0.32, 0.23]
Gardner 2007 [30]	28	28	0.9%	-0.23 [-0.46, -0.01]
Giovanetti 1986 (LF) [31]	12	12	0.2%	-0.13 [-0.64, 0.38]
Giovanetti 1986 (N) [31]	12	12	0.2%	-0.16 [-0.66, 0.35]
Goldberg 1982 (HC) [32]	4	4	0.9%	-0.26 [-0.49, -0.03]
Goldberg 1982 (N) [32]	12	12	0.1%	0.08 [-0.59, 0.74]
Greany 2004 [33]	71	72	0.1%	-0.12 [-0.75, 0.51]
Haub 2005 [34]	10	11	0.2%	-0.38 [-0.81, 0.05]
Hermansen 2001 [35]	20	20	0.5%	-0.32 [-0.63, -0.01]
Hill 2015 [36]	41	21	0.5%	0.31 [0.02, 0.61]
Hoie 2005 [37]	38	78	1.0%	-0.37 [-0.59, -0.15]
Hoie 2005B [38]	38	78	0.4%	-0.30 [-0.64, 0.03]
Hoie 2007 [39]	28	60	1.0%	-0.28 [-0.50, -0.07]
Hosseinpour-Niazi 2014 [40]	31	31	2.3%	-0.18 [-0.32, -0.04]
Huff 1984 [41]	5	5	0.1%	-0.59 [-1.27, 0.08]
Jenkins 1989 [42]	11	11	0.1%	-0.20 [-0.90, 0.50]
Jenkins 2002 [43]	41	41	1.0%	-0.31 [-0.52, -0.10]
Jenkins 2010 [44]	23	23	0.4%	0.02 [-0.31, 0.35]
Kestin 1989 [45]	18	17	0.8%	-0.34 [-0.58, -0.10]
Kjolbaek 2017 [46]	77	36	1.0%	0.04 [-0.17, 0.26]
Kreijkamp-Kaspers 2004 [47]	87	88	1.3%	0.14 [-0.05, 0.33]
Kurowska 1997 [48]	34	34	0.4%	-0.07 [-0.43, 0.30]
Laidlaw 1985 [49]	19	19	0.5%	-0.57 [-0.87, -0.28]
Laurin 1991 [50]	9	9	0.1%	0.04 [-0.66, 0.74]
Li 2016 [51]	17	17	0.4%	-0.25 [-0.60, 0.10]
Liao 2007 [52]	15	15	0.8%	-0.17 [-0.40, 0.07]
Lichenstein 2002 (IF) [53]	42	42	0.6%	-0.08 [-0.37, 0.21]
Lichenstein 2002 (NIF) [53]	42	42	0.5%	-0.15 [-0.45, 0.15]
Liu 2012 [54]	120	60	0.7%	0.17 [-0.08, 0.42]
Liu 2014 [55]	180	90	1.5%	-0.28 [-0.45, -0.10]
Lovati 1987 [56]	12	12	0.1%	-1.84 [-2.41, -1.27]

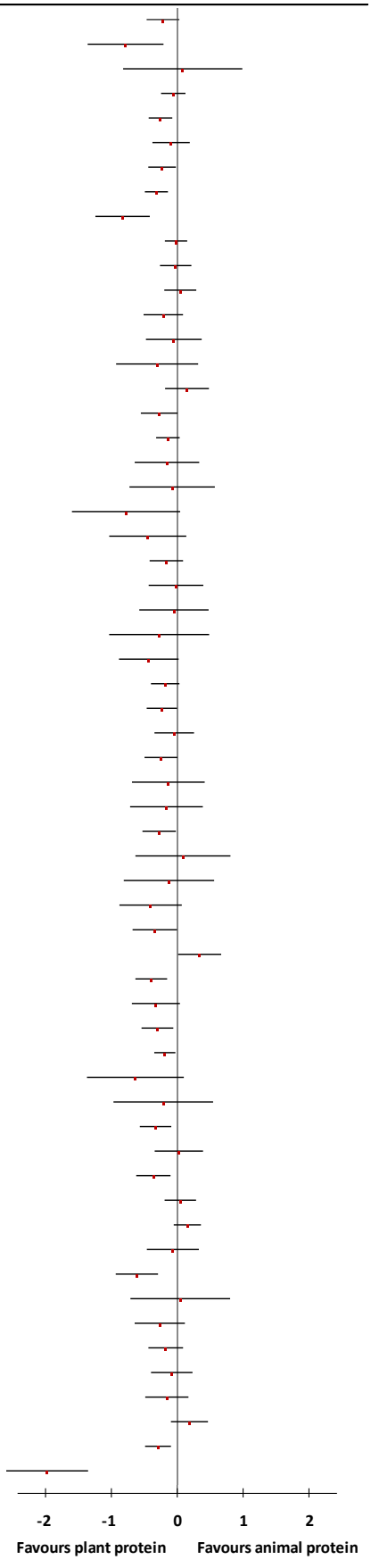

Figure S3. LDL-C Forest Plot, fixed-effects model.

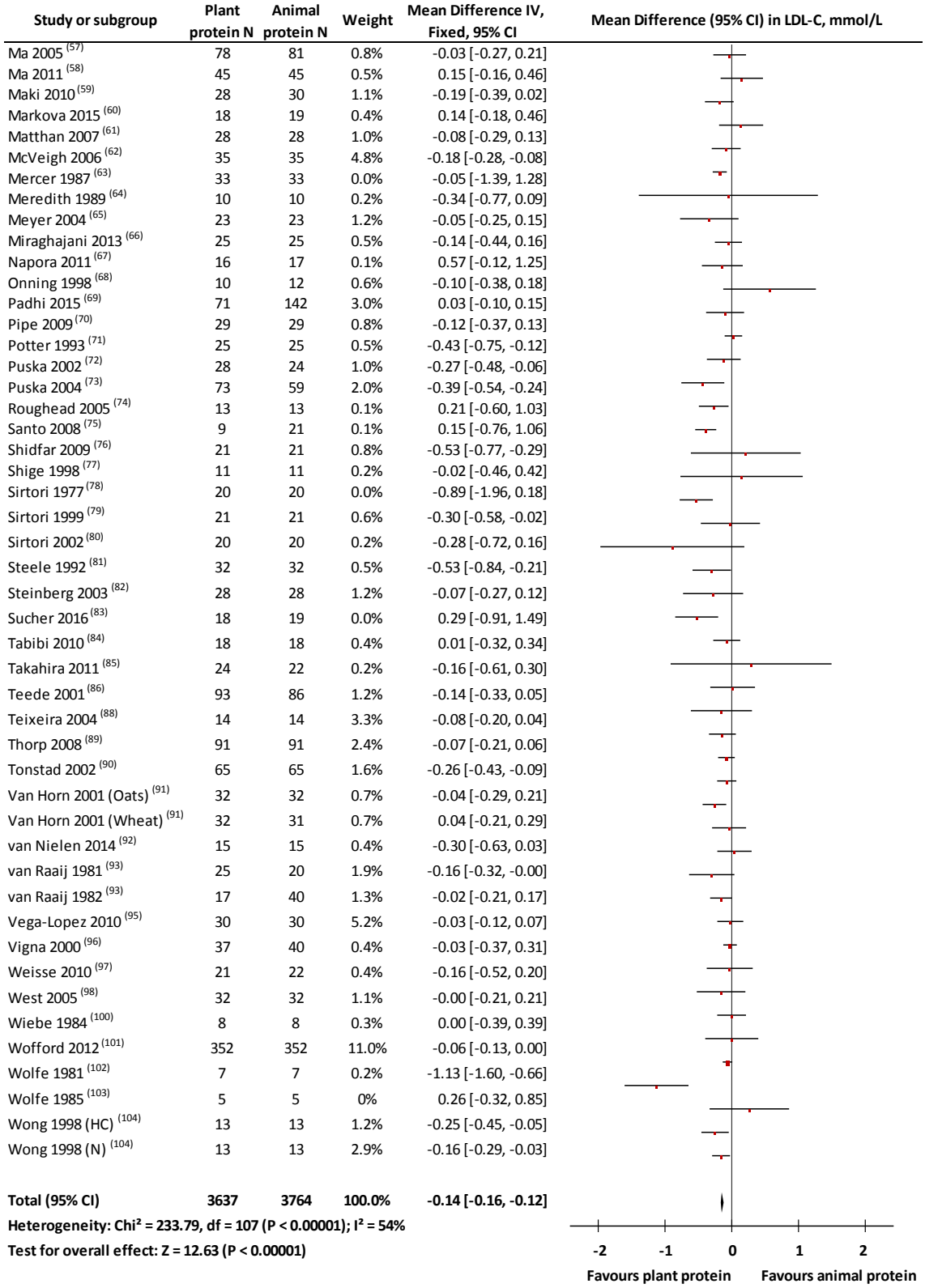

Figure S3 (Continued). LDL-C Forest Plot, fixed-effects model. HC=hypercholesterolemic; IF=isoflavones; LF=low-fat; N=normal; NIF=no isoflavones; Pre-MS=pre-metabolic syndrome. The pooled effect estimate (diamond) is shown. Paired analyses were applied to all crossover trials. The studies by Duane et al. 1999 [26], Lovati et al. 1987 [56], Sirtori et al. 2002 [80], and Van Horn et al. 2001 [91] were missing variance data, which were imputed using the average standard of the mean differences across included trials based on the respective trial's sample size. Data are expressed as MDs with 95% CIs, using generic inverse-variance fixed-effects models. Inter-study heterogeneity was tested using the Cochran Q statistic (chi-square) at a significance level of P<0.10 and quantified by I^2, levels of ≥50% represented substantial heterogeneity.

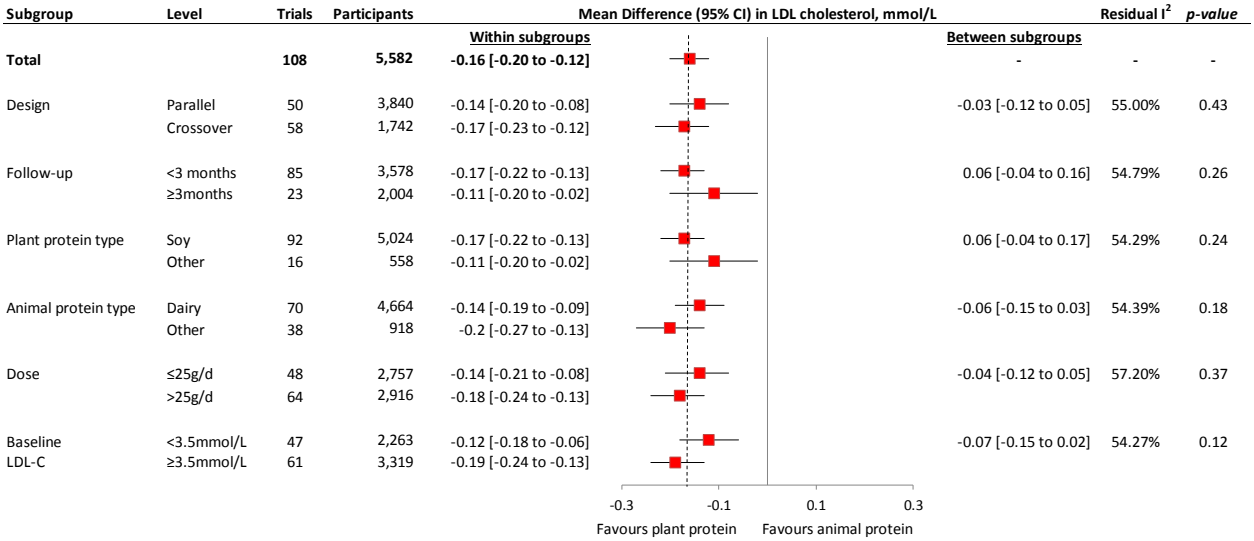

Figure S4. LDL-C Visual Subgroup. Point estimates for each subgroup level (squares) are the pooled effect estimates. The dashed line represents the pooled effect estimate for the overall (total) analysis. The residual I^2 value indicates the interstudy heterogeneity unexplained by the subgroup. Statistically significant pairwise subgroup effect modification by meta-regression analyses at $P < 0.05$.

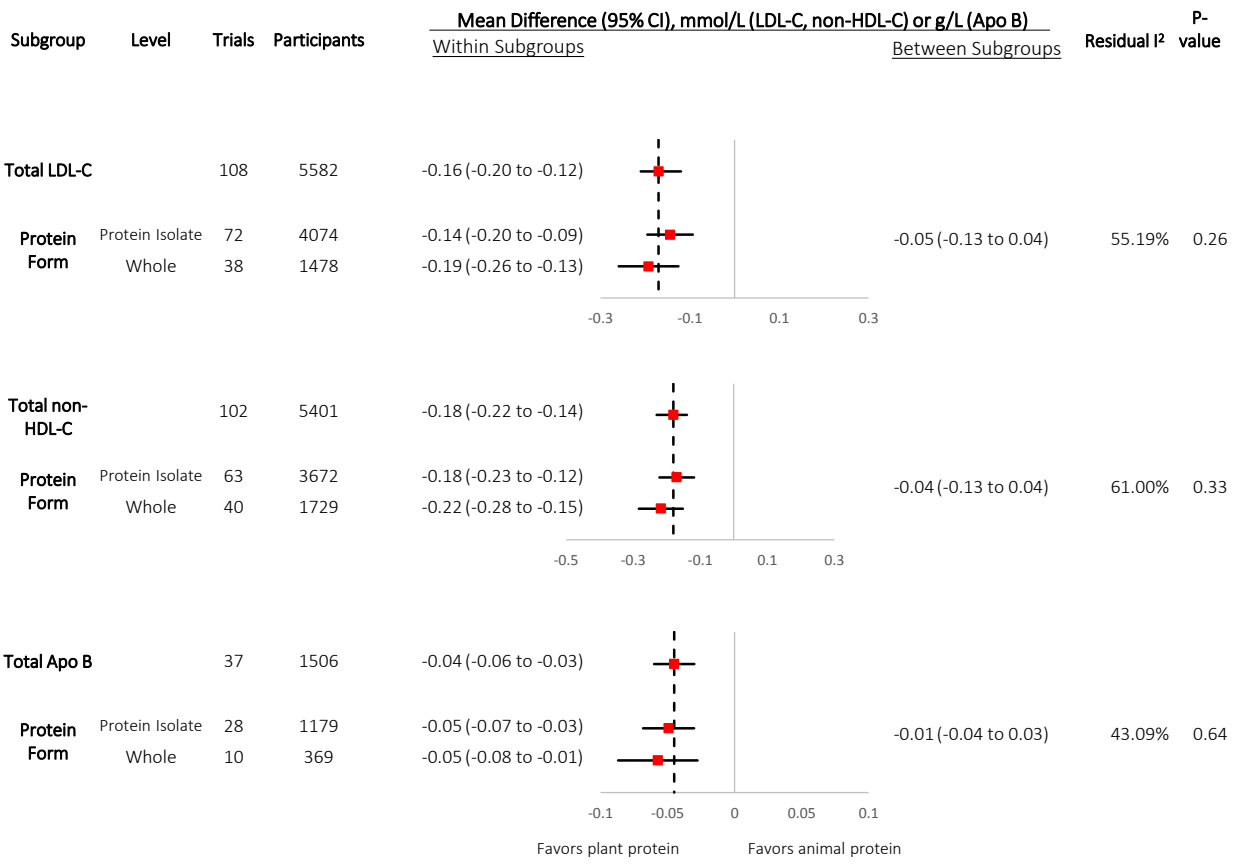

Figure S5. Post-Hoc Subgroups. Point estimates for each subgroup level (squares) are the pooled effect estimates. The dashed line represents the pooled effect estimate for the overall (total) analysis. The residual I^2 value indicates the interstudy heterogeneity unexplained by the subgroup. Statistically significant pairwise subgroup effect modification by meta-regression analyses at $P < 0.05$.

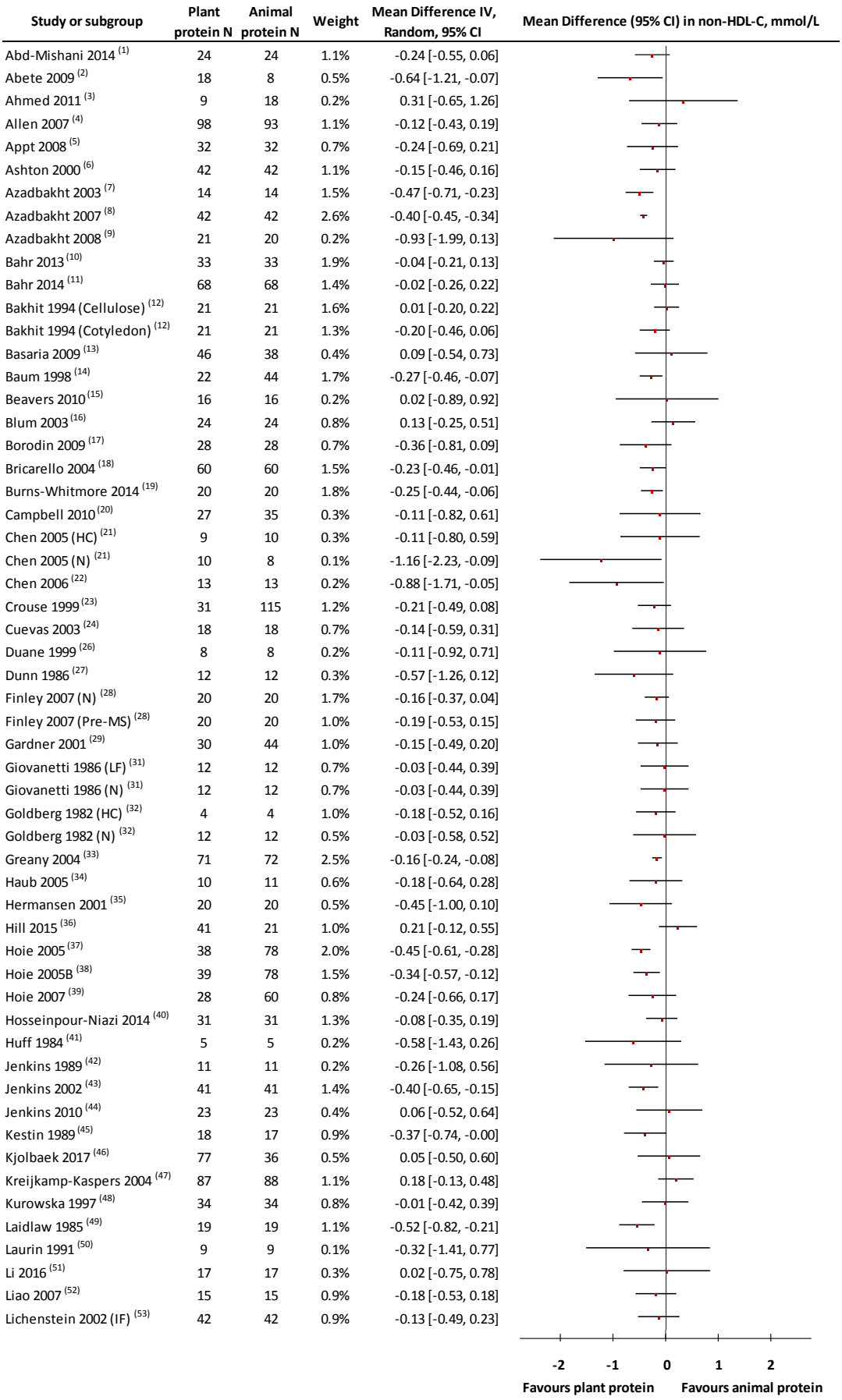

Figure S6. Non-HDL-C Forest Plot, random-effects model.

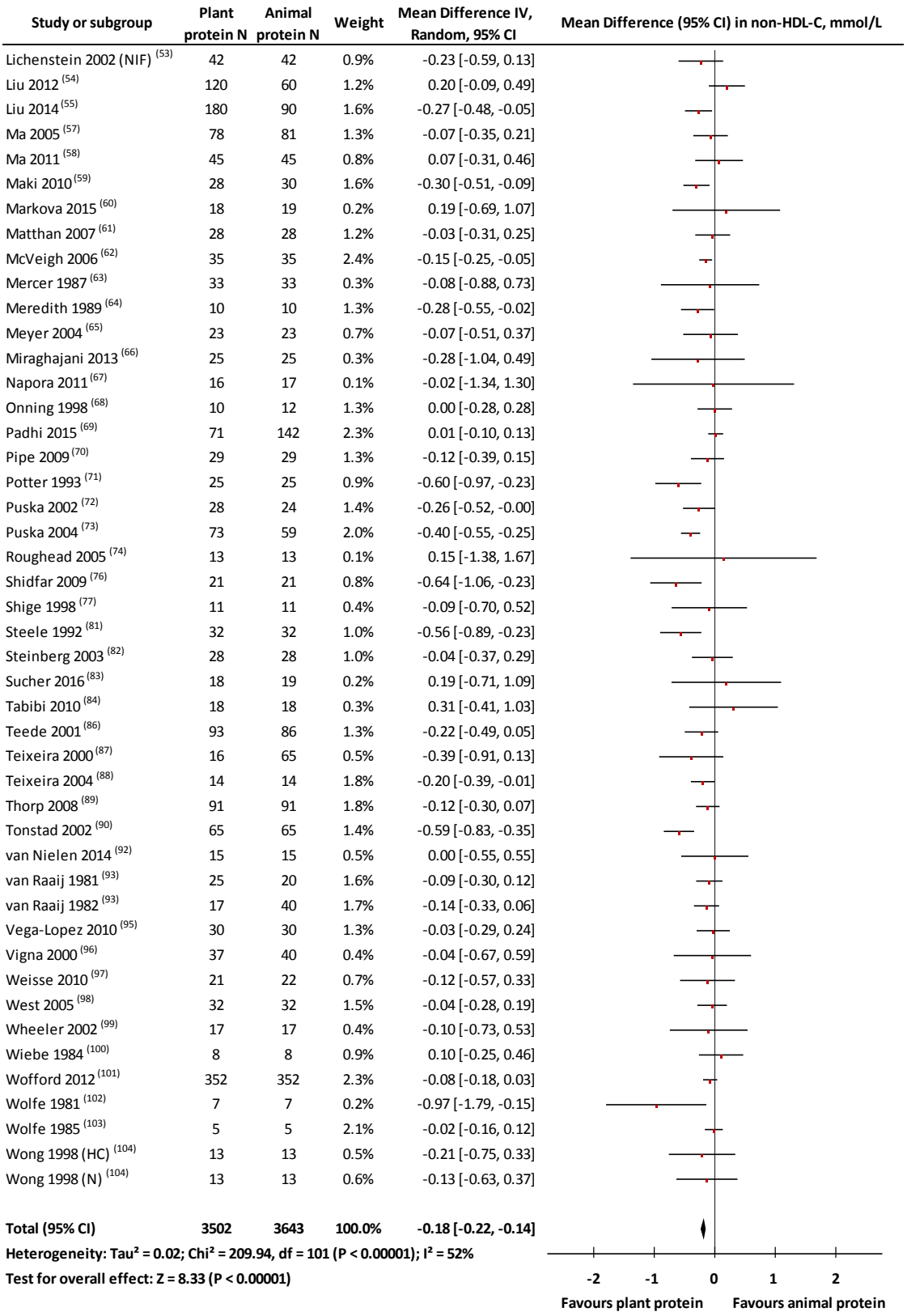

Figure S6 (Continued). Non-HDL-C Forest Plot, random-effects model. HC=hypercholesterolemic; IF=isoflavones; LF=low-fat; N=normal; NIF=no isoflavones; Pre-MS=pre-metabolic syndrome. The pooled effect estimate (diamond) is shown. Paired analyses were applied to all crossover trials. The study by Duane et al. 1999 [26] was missing variance data, which was imputed using the average standard of the mean differences across included trials based on the respective trial's sample size. Data are expressed as MDs with 95% CIs, using generic inverse-variance random-effects models. Inter-study heterogeneity was tested using the Cochran Q statistic (chi-square) at a significance level of P<0.10 and quantified by I^2, levels of ≥50% represented substantial heterogeneity.

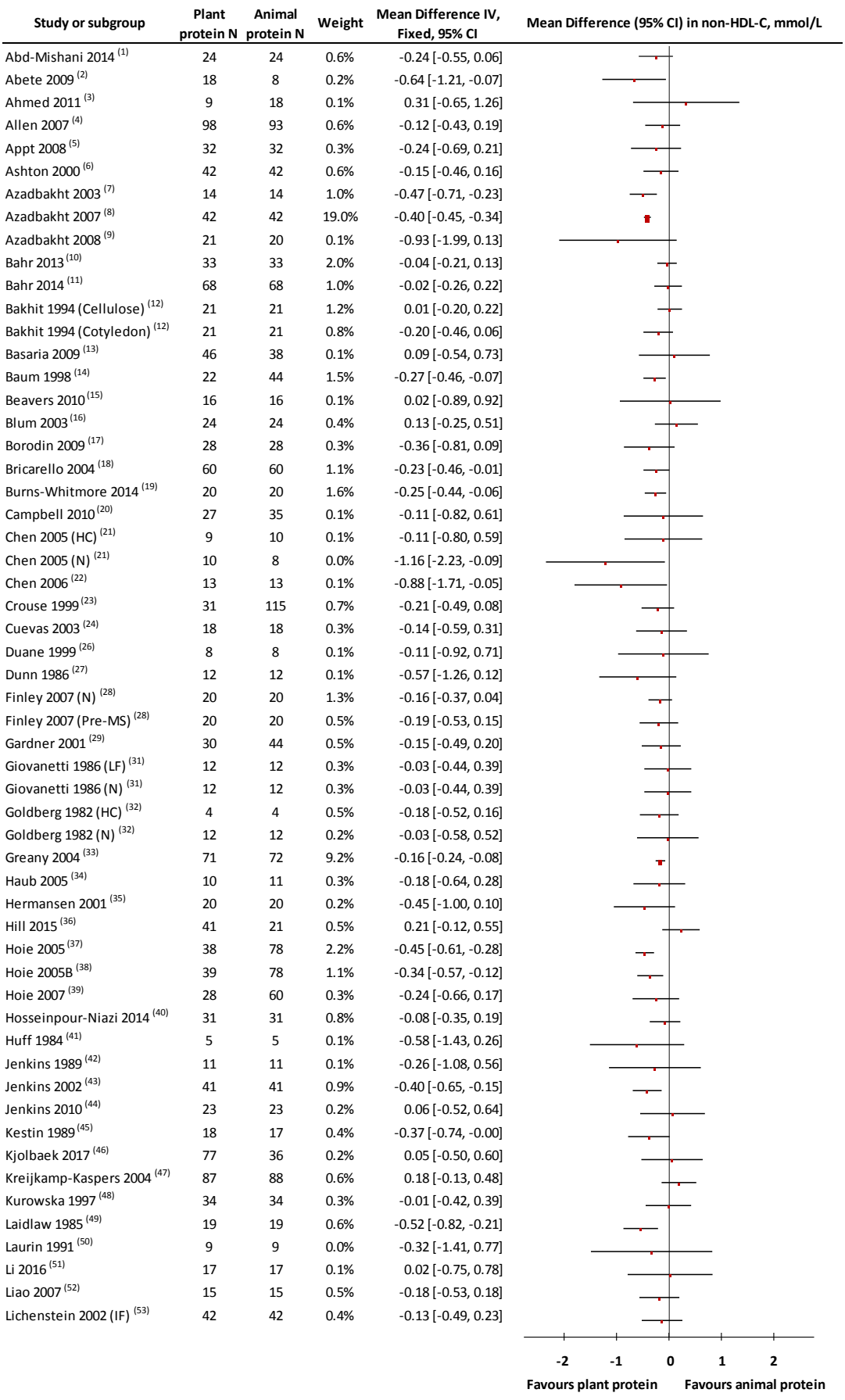

Figure S7. Non-HDL-C Forest Plot, fixed-effects model.

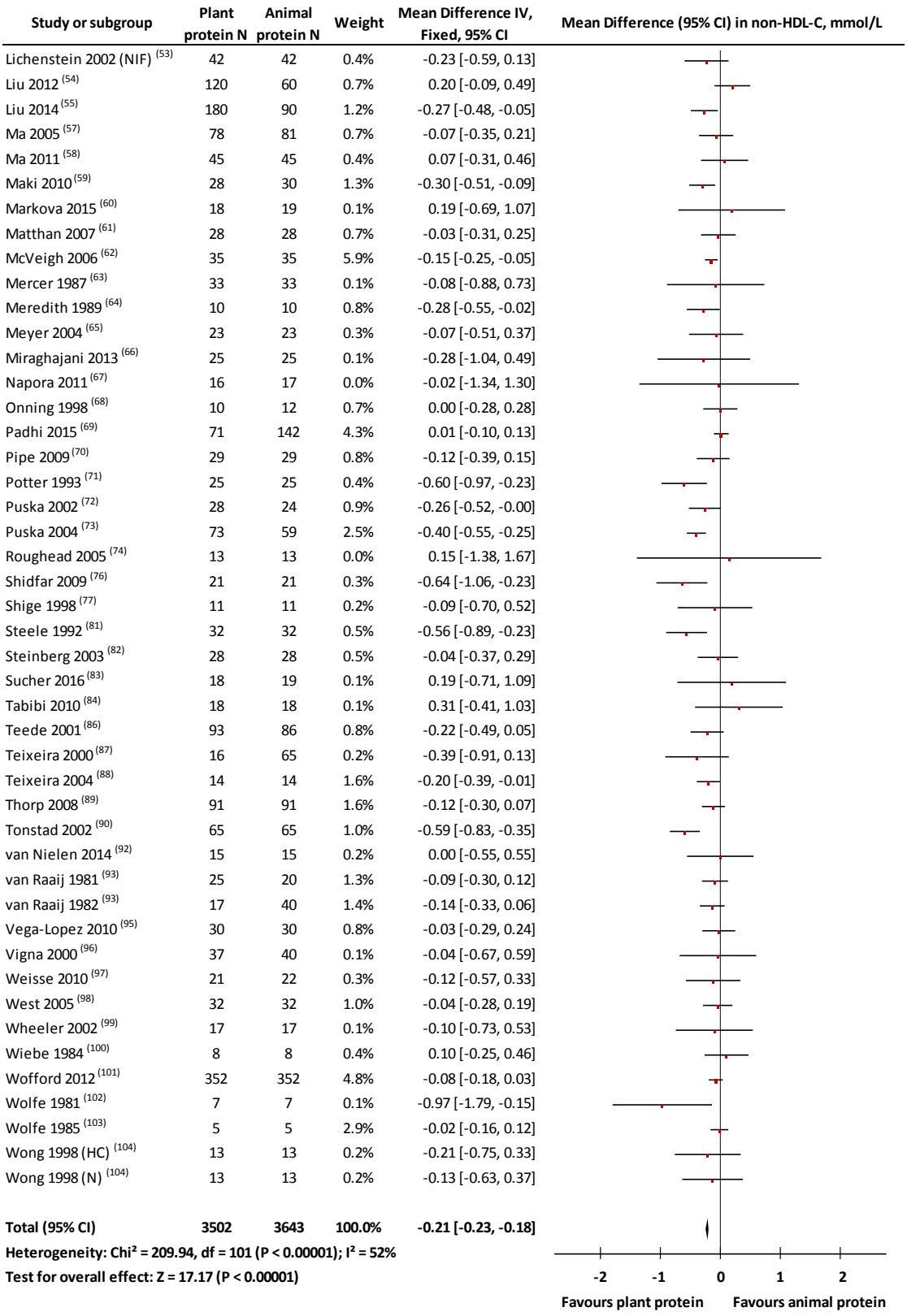

Figure S7 (Continued). Non-HDL-C Forest Plot, fixed-effects model. HC=hypercholesterolemic; IF=isoflavones; LF=low-fat; N=normal; NIF=no isoflavones; Pre-MS=pre-metabolic syndrome. The pooled effect estimate (diamond) is shown. Paired analyses were applied to all crossover trials. The study by Duane et al. 1999 [26] was missing variance data, which was imputed using the average standard of the mean differences across included trials based on the respective trial's sample size. Data are expressed as MDs with 95% CIs, using generic inverse-variance fixed-effects models. Inter-study heterogeneity was tested using the Cochran Q statistic (chi-square) at a significance level of P<0.10 and quantified by I^2, levels of ≥50% represented substantial heterogeneity.

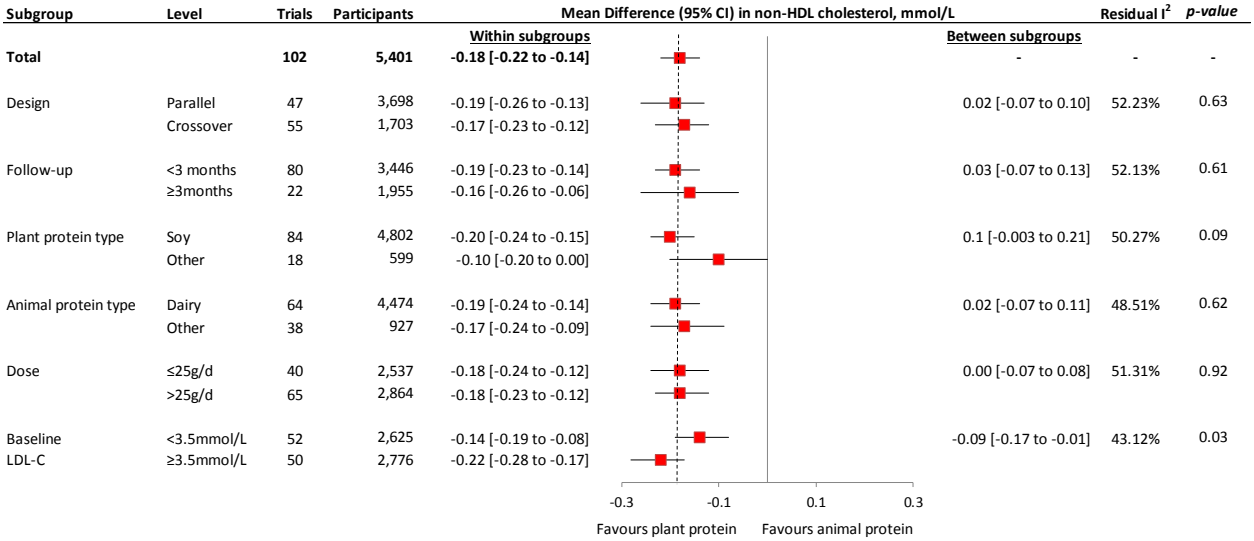

Figure S8. Non-HDL-C Visual Subgroup. Point estimates for each subgroup level (squares) are the pooled effect estimates. The dashed line represents the pooled effect estimate for the overall (total) analysis. The residual I^2 value indicates the interstudy heterogeneity unexplained by the subgroup. Statistically significant pairwise subgroup effect modification by meta-regression analyses at $P < 0.05$.

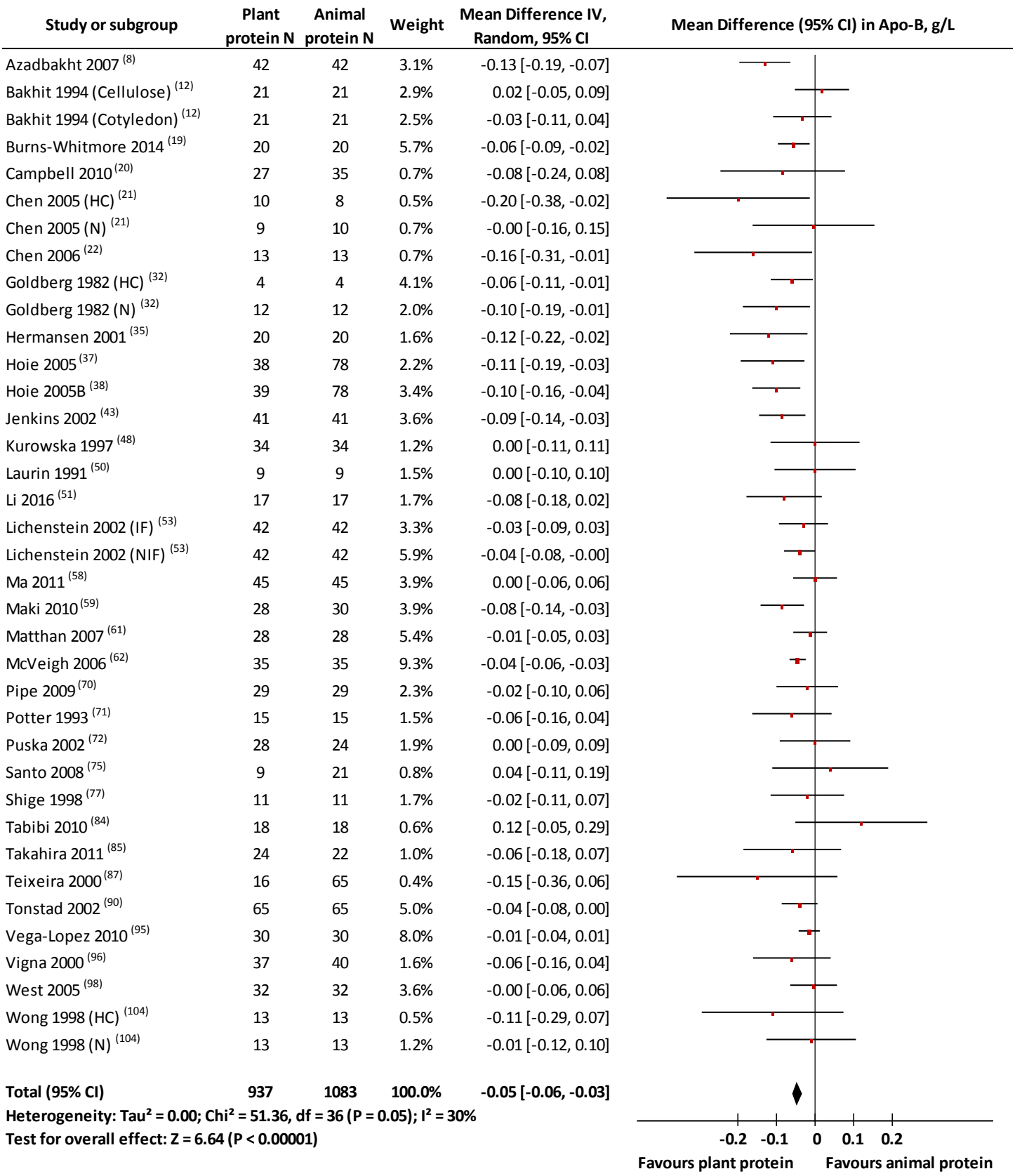

Figure S9. Apo-B Forest Plot, random-effects model. HC=hypercholesterolemic; IF=isoflavones; LF=low-fat; N=normal; NIF=no isoflavones. The pooled effect estimate (diamond) is shown. Paired analyses were applied to all crossover trials. Data are expressed as MDs with 95% CIs, using generic inverse-variance random-effects models. Inter-study heterogeneity was tested using the Cochran Q statistic (chi-square) at a significance level of P<0.10 and quantified by I^2, levels of ≥50% represented substantial heterogeneity.

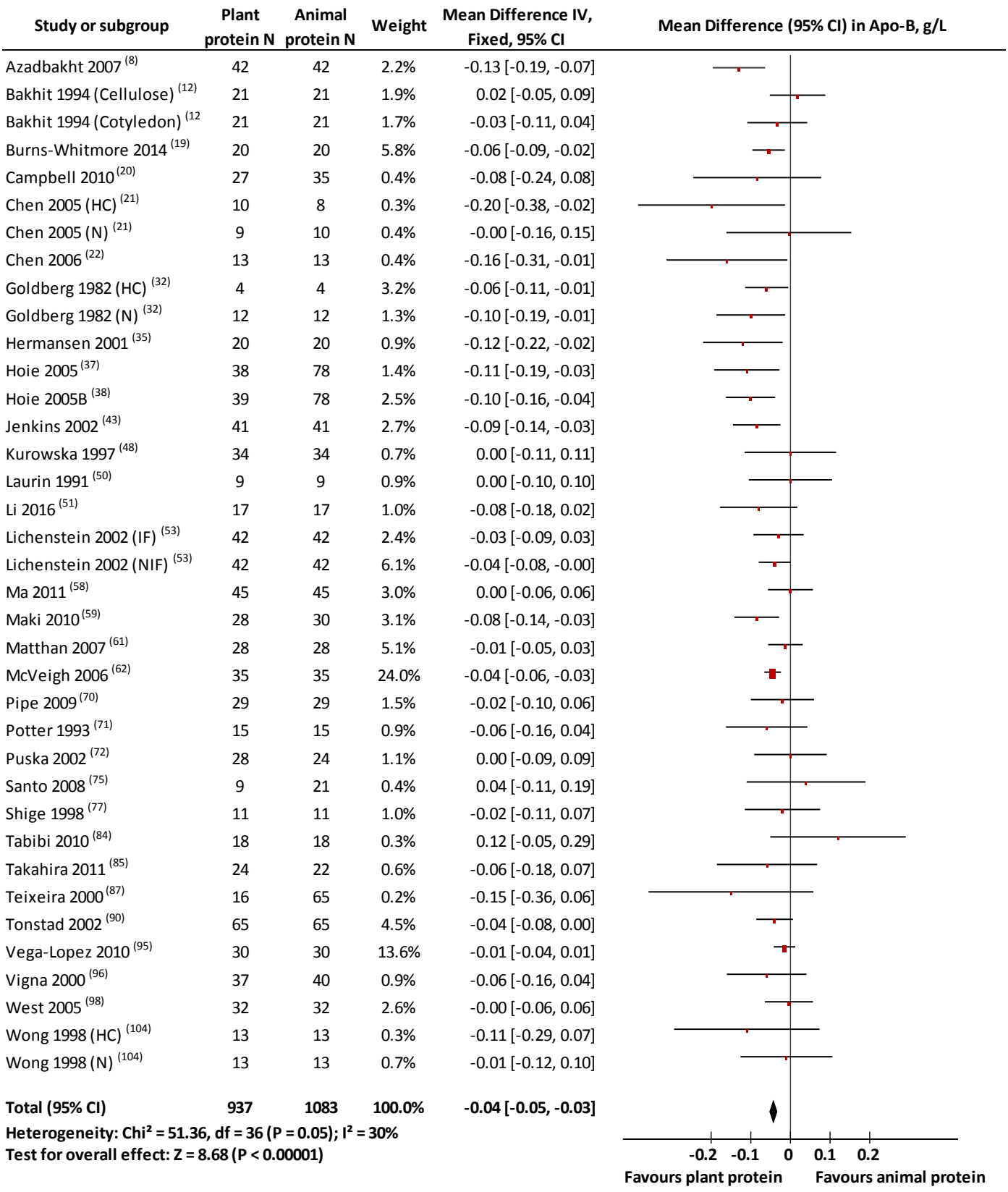

Figure S10. Apo-B Forest Plot, fixed-effects model. HC=hypercholesterolemic; IF=isoflavones; LF=low-fat; N=normal; NIF=no isoflavones. The pooled effect estimate (diamond) is shown. Paired analyses were applied to all crossover trials. Data are expressed as MDs with 95% CIs, using generic inverse-variance fixed-effects models. Inter-study heterogeneity was tested using the Cochran Q statistic (chi-square) at a significance level of P<0.10 and quantified by I^2, levels of ≥50% represented substantial heterogeneity.

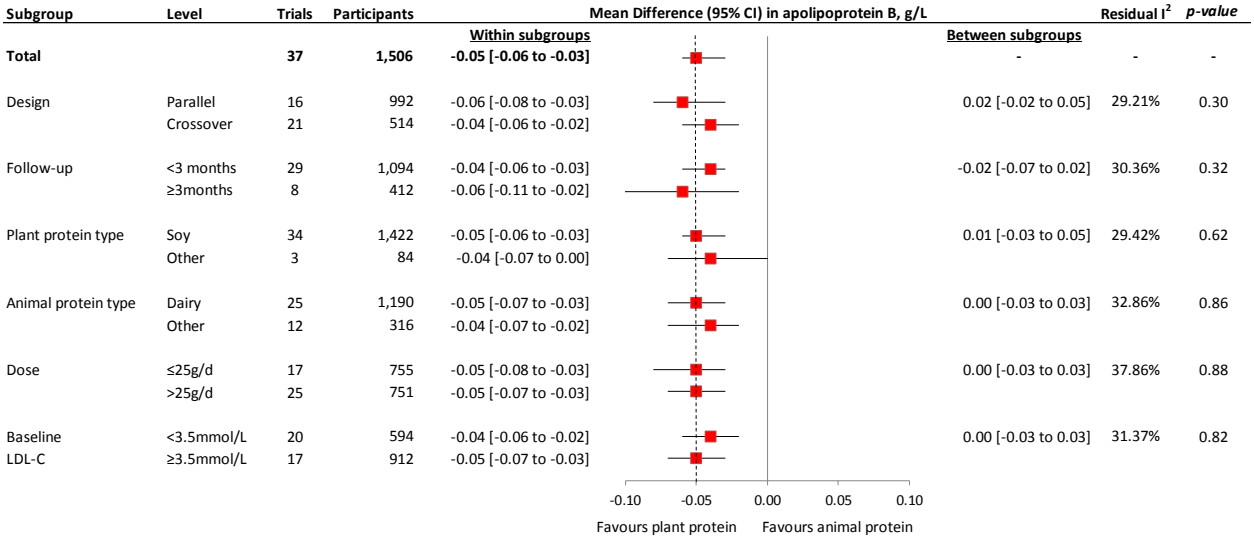

Figure S11. Apo-B Visual Subgroup. Point estimates for each subgroup level (squares) are the pooled effect estimates. The dashed line represents the pooled effect estimate for the overall (total) analysis. The residual I^2 value indicates the interstudy heterogeneity unexplained by the subgroup. Statistically significant pairwise subgroup effect modification by meta-regression analyses at $P < 0.05$.

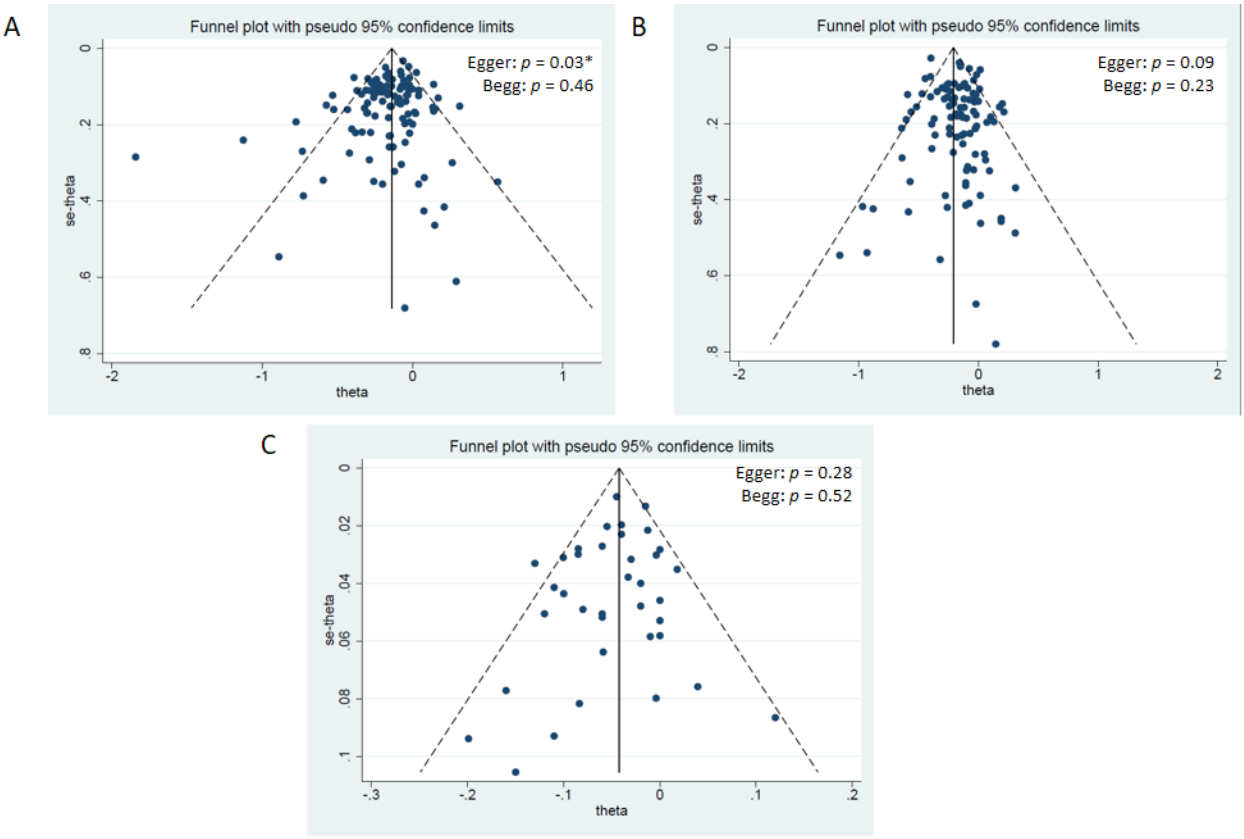

Figure S12. Funnel Plots. Publication bias funnel plots for LDL (A), non-HDL (B), and apolipoprotein B (C). The solid line represents the pooled effect estimate expressed as the weighted mean difference (MD) of each analysis, and dashed lines represent pseudo-95% confidence limits. Circles represent effect estimates of included trials. p-values of Egger and Begg tests for publication bias are shown at top right for each analysis. *Statistically significant ($p < 0.05$).

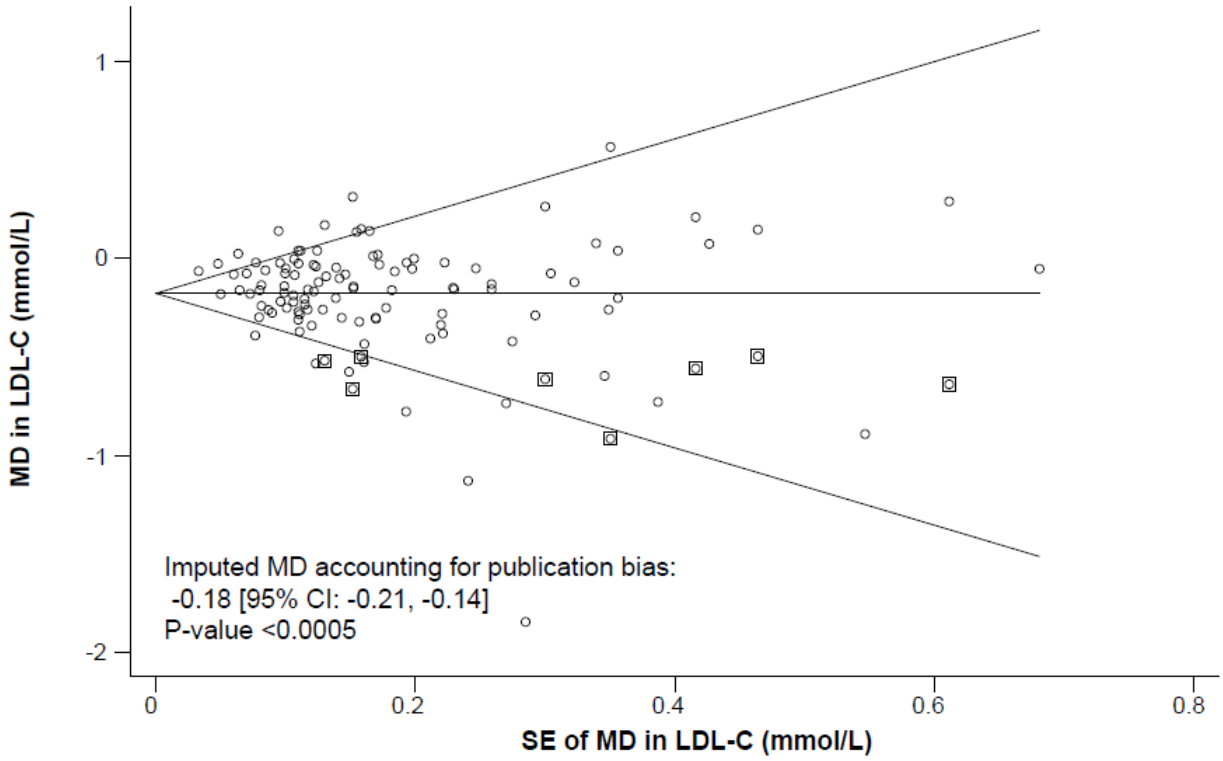

Figure S13. LDL-C Trim-And-Fill Funnel Plot. The horizontal line represents the pooled effect estimate expressed as a mean difference. The diagonal lines represent the pseudo 95% CIs of the mean difference. The clear circles represent effect estimates for each included study.

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