EFFECT OF TREE NUTS ON METABOLIC SYNDROME CRITERIA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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EFFECT OF TREE NUTS ON METABOLIC SYNDROME CRITERIA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Running Title: Tree Nuts and Metabolic Syndrome

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ABSTRACT

Background: Chronic disease guidelines support tree nut consumption alone or as part of the Mediterranean, Dietary Approaches to Stop Hypertension (DASH), or Portfolio dietary patterns to reduce cardiovascular risk, based on their favourable LDL-C lowering effect. The effects of nuts on metabolic risk factors other than LDL-C, however, remain uncertain. We conducted a systematic review and meta-analysis of the effect of tree nuts on criteria metabolic syndrome components to provide a broader evidence summary to inform dietary guidelines.

Methods: We searched MEDLINE, EMBASE, CINAHL, and the Cochrane Library (through March 19, 2013). We included relevant randomized controlled trials (RCTs) of ≥ 3 weeks reporting at least 1 criterion of metabolic syndrome.Two or more independent reviewers extracted all relevant data. Data were pooled using the generic inverse variance method using random effects models and expressed as mean differences (MD) with 95% confidence intervals (CI). Heterogeneity was assessed by Chi^2 and quantified by I^2. Study quality was assessed.

Results: Eligibility criteria were met by 39RCTsincluding1,676 participants who were otherwise healthy or had dyslipidemia, metabolic syndrome or diabetes mellitus. Tree nut interventions lowered triglycerides compared with control diet interventions (MD=-0.07 mmol/L [95%CI, -0.11, -0.04 mmol/L]), but had no effects on waist circumference, HDL-C, blood pressure, or fasting blood glucose with the direction of effect favouring tree nuts for all except HDL-C.

Limitations: Most of the trials were of short duration (<12 weeks) and of poor quality (MQS<8). Substantial unexplained heterogeneity remained in most analyses.

Conclusion: Pooled analyses show a net benefit of tree nuts for metabolic syndrome with decreases in triglycerides across nut types and no adverse effects on other criteria. Longer and higher quality trials are needed.

Protocol Registration: ClinicalTrials.gov identifier, NCT01630980

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Key words: systematic review, meta-analysis, randomized trials, tree nuts, metabolic syndrome.

Strengths and limitations of this study

- This is the first systematic review and meta-analysis to look at the effect of tree nuts on metabolic syndrome criteria.
- This systematic review and meta-analysis involved a large number of trials (36 RCTs) in participants with a range of metabolic conditions.
- Most of the trials (69.4%) were of low quality (MQS<8).
- Most of the trials (66.7%) were of short duration (<12 weeks).
- Substantial inter-study heterogeneity remained unexplained.

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INTRODUCTION

Dietary patterns including tree nuts have received particular attention for their cardiovascular benefits, andthe Food and Drug Administration (FDA) have granted a qualified health claim to tree nuts for cardiovascular risk reduction.[1] General dietary guidelines[2] and heart health guidelines[3 4]also continue to recommend tree nuts alone or as part of the Mediterranean, Portfolio, and Dietary Approaches to Stop Hypertension (DASH) dietary patterns for cardiovascular disease prevention and management.

Although these recommendations are based primarily on the LDL-C lowering benefits of tree nuts, the cardiovascular risk reduction seen with tree nuts is beyond that which would be predicted by this effect alone. The Prevención con Dieta Mediterránea (PREDIMED) trial showed that despite no significant effect on LDL-C early on in the trial[5] a Mediterranean diet supplemented with mixed nuts (30g/day) compared with a low-fat control diet reduced major cardiovascular events by 30% in high cardiovascular risk participants.[6] Nut consumption of >3servings/week was also associated with other metabolic advantages such as a decreased risk of obesity, MetS, and diabetes.[7] Individual large trials of tree nuts have also shown that nuts improve criteria of the metabolic syndrome: waist circumference,[8 9] triglycerides,[5 10-12] HDL-C,[13-18] blood pressure[5 8] and glycemic control.[19-22]

The overall evidence for these additional metabolic benefits, however, remains uncertain. Guidelines have not recommended tree nuts directly for managing these risk factors. Although the Canadian Diabetes Association 2013 clinical practice guidelines for nutrition therapy[23] did acknowledge some of these metabolic benefits, the evidence was deemed insufficient for making a recommendation. Tree nut consumption was recommended only in so far as part of Mediterranean or DASH dietary patterns.[23] To synthesize the evidence on which recommendations are based for the metabolic benefits of tree nuts beyond LDL-C lowering, we conducted a systematic review and meta-analysis of randomized controlled dietary trials of the effect of tree nuts on criteria of the metabolic syndrome.

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METHODS

Protocol and Registration

We followed the guidelines of the Cochrane Handbook for Systematic Reviews of Intervention for the planning and conduct of this meta-analysis.[24] Reporting of results followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[25] The review protocol is available at ClinicalTrials.gov (registration number: NCT01630980).

Study Selection

We searched MEDLINE, EMBASE, CINAHL, and the Cochrane Library (through March 19, 2013) to identify randomized controlled dietary trials of tree nuts. Details of the search strategy are presented in **Appendix Table 1**. The electronic database searches were supplemented by manual searches of the reference list of included trials and reviews. No language restriction was used.

We included randomized dietary trials that reported the effect of diets rich in tree nuts (almonds, Brazil nuts, cashews, hazelnuts, macadamia nuts, pecans, pine nuts, pistachios, walnuts and mixed nuts)[1]as a whole compared to diets without tree nuts, but matched for energy, on at least 1 of the 5 criteria of the MetS: waist circumference, triglycerides, high-density lipoprotein cholesterol (HDL-C), blood pressure and fasting blood glucose. Included trials were ≥ 3 weeks duration, a duration that satisfies the minimum follow-up requirement for lipid-lowering health claims by the FDA used in the scientific evaluation of lipid-lowering health claims.[26] We excluded trials that incorporated tree nuts as paste, oil or skin nuts into the treatment diets and also those trials that added tree nuts as part of a dietary pattern and did not have a matched control group. The former exclusion intended to eliminate contamination from the other nutritional aspects, and to isolate the effect of tree nuts. Where multiple intervention or control groups were presented, we only included those groups which allowed us to isolate the effect of tree nuts.When multiple publications existed for the same trial, data from the most recent report were included. Publications including additional

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relevant data were used as companion reports. The MetS endpoints were selected according to the 2009 harmonized definition for MetS.[27]

Data Extraction

Studies that met the inclusion criteria were extracted in full by 2independent reviewers (SBM and one of EV, LSA, VH or AM) for study characteristics and data for endpoints. Study characteristics included: study design (crossover or parallel), participant characteristics, comparator, nut dose, nut type, duration of follow-up, dietary adherence measures, macronutrient profile, statistical analysis and funding souces. All disagreements amongst reviewers were resolved by consensus.

The Heyland Methological Quality Score (MQS) was used for assessment of study quality.[28] Scores from 0-2 points were given for each of the following evaluated criteria: methods (randomization, blinding and analysis), sample (selection, compatibility and follow-up), and intervention (protocol, co-intervention and crossovers). This scale gave a maximum MQS of 13 points. Studies with a score of ≥8 were considered of high quality.

The Cochrane Collaboration Risk of Bias Tool was used to assess the study risk of bias.[24] Trials were classified as “unclear risk of bias” when insufficient information was provided to permit judgment, “high risk of bias” when the methodological flaw was likely to have affected the true outcome and “low risk of bias” when a methodological flaw was deemed inconsequential to determine the true effect within a study. As blinding of participants in dietary trials is difficult to achieve, we scored the trials based on the intensity of the dietary advice given to the randomized groups. If treatment intensity was judged to be more intensive in one intervention over another, then trials were classified as “high risk”. If both interventions were emphasized equally, then trials were classified as “low risk of bias”.

Means (SD) for baseline values, end values, change-from baseline differences, end-differences, and mean differences were recorded for primary endpoints (waist circumference, triglycerides, HDL-C, blood pressure and fasting blood glucose). Reported t-values or F-statistics, and p-values for differences were also recorded. Missing information

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for any endpoint data or study details were requested directly from authors. Where SDs were not reported or given directly by authors, we attempted to calculate these missing SDs from the available statistics using methods recommended by the Cochrane Collaboration.[24] If this was not possible, then we imputed these missing SDs using a pooled correlation coefficient derived from a meta-analysis of correlation coefficients from those trials reporting sufficient data.[24] These correlation coefficients were then transformed into z-scores ± and meta-analyzed using inverse-variance weighing. The pooled effect estimate from the z-scores was then back transformed to impute the missing SDs.We used a derived pooled correlation coefficient of 0.664 for triglycerides, 0.903 for HDL-C, 0.282 for systolic blood pressure, 0.604 for diastolic blood pressure and 0.658 for fasting blood glucose.

Statistical Analyses

Data were analyzed using Review Manager (RevMan) 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark)[29] for primary analyses and Stata (version 12, College Station, USA)[30]for subgroup analyses. Pooled analyses were conducted using the Generic Inverse Variance method with random effects models. Data were expressed as mean differences (MD) with 95% CI and considered significant at $P<0.05$. Paired analyses were applied to all crossover trials.[31] In cases where there were multiple intervention or control groups, we combined either intervention or control groups to create single pairwise comparisons with the aim of diminishing the unit-of-analysis error.[24]

The presence of between-studies-heterogeneity was assessed (Cochran Q-statistic; significant at $P<0.10$) and quantified (I^2). An I^2 ≥50% indicated "substantial" heterogeneity and ≥75% indicated "considerable" heterogeneity.[24] Analyses were stratified by participant health status: otherwise healthy, dyslipidemia, MetS criteria and type 2 diabetes based on trial entry criteria. Sources of heterogeneity were explored using sensitivity analyses and *a priori* subgroup analyses for baseline values (according to MetS diagnostic criteria[27]), absolute fiber intake (treatment diet <25 g/d vs. ≥25 g/d[23] and change in [within and between the diets]), absolute saturated fatty acid (SFA) intake (treatment diet <7% vs. ≥7% of total

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energy[23] and change in [within and between the diets]), tree nut dose (<50 vs. ≥50 g/day), tree nut type (almonds, Brazil nuts, cashews, hazelnuts, macadamia nuts, pecans, pine nuts, pistachios, walnuts and mixed nuts),duration of follow-up (3< vs. ≥3 months), study design (crossover vs. parallel), and study quality (MQS <8 vs. ≥8). *Post-hoc* subgroup analyses were conducted for the difference in percent carbohydrate intake between the control and intervention arm (carbohydrate displacement). The significance of between-subgroup differences were assessed using meta-regression (P<0.05). To determine if any single trial exerted an undue influence on the overall results, sensitivity analyses were preformed, in which each individual trial was removed from the meta-analysis, and the effect size re-calculated with the remaining trials. Publication bias was assessed by visual inspection of funnel plots and formally complemented by Begg's and Egger's tests.

RESULTS

Trial Selection

Figure 1shows flow of studies through the search and selection process. We identified a total of 2,190reports, from which 701reports were duplicates and 1,367reports were deemed irrelevant (determined by review of title and abstract). The remaining 120 reports were reviewed in full, of which 81reports were excluded for not meeting inclusion criteria. A total of 39 reports on 38trials[8-22 32-52] as well as 3 companion reports[53-55] that addressed at least one criterion of the metabolic syndrome (waist circumference(12 trials, n=813),triglycerides (37 trials, n=1,515), HDL-C (36 trials, n=1,607), blood pressure (16 trials, n=955), and fasting blood glucose (18 trials, n=957) were included).

Trial Characteristics

Table 1 presents characteristics of the included trials. There were 38 trials involving38 comparisons in1706 participants. Eleven trials (30.6%)[10 12 14 16 32 34 36 41 45 51]reported otherwise healthy participants. Two of these trials contained a minority of participants with dyslipidemia who had been classified as otherwise healthy[38 45]. Nine trials

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(25%)[8 18-21 37 39 46 47] were conducted in participants with type 2 diabetes or a mix of patients with overweight and type 2 diabetes in one case[8]. The remaining trials were conducted in people with dyslipidemia (8 trials [22.2%][13 15 17 33 35 40 43 44]), or with criteria of MetS (8 trials [22.2%]:overweight 3 trials[9 11 52], full MetS [4 trials[22 42 49 50]], and prediabetes [1 trial[48]]).Median age for participants was 50.2 years (IQR:43.7 to 55.5 years). Median body weight for participants was 81.7 kg (IQR: 72.1 to 95.3 kg).

Most trials (19[52.8%]) were conducted in the United States of America. The rest were conducted in various countries: 3 trials (8.3%) in Australia; 2 trials (5.6%) each in Canada, Spain, Iran, and New Zealand; and 1 trial (2.8%) each in Japan, Turkey, Italy, China, Taiwan and South Africa. A similar number of trials used parallel (19trials [52.8%]) and crossover (17 trials [47.2%]) designs. All trials were conducted in an outpatient setting.

Control diets included usual diets, (8 trials, 22.2%), a National Cholesterol Education Program (NCEP) step 1 diet (5 trials, 13.9%), an average American Diet (3 trials, 8.3%), a low fat diet (2 trials, 5.6%), among others. Twenty-two trials (61%) provided test food supplements, 11 trials (31%) provided all study foods under metabolic feeding control conditions, and 3 trials provided dietary advice (8%). Four trials (11.1%) used a control diet in which a muffin or pretzel[11 15 20] or cheese sticks[19] were exchanged for nuts. The test and control diets were matched for energy in all cases; however 2 of the trials[11 52] featured a negative energy balance tree nut diet compared with a matched negative energy balance control diet. Tree nut types included almonds (11 trials, 30.6%), cashews (2 trials, 5.6%), hazelnuts (2 trials, 5.6%), macadamia nuts (3 trials, 8.3%), pecans (2 trials, 5.6%), pistachios (5 trials, 12.8%), walnuts (10 trials, 27.8%), and mixed nuts (2 trials, 5.6%). We were unable to find studies on Brazil nuts or pine nuts. Median nut dose intake was 53 g/d (IQR: 42 to 72.5 g/d). Median follow-up was 7 weeks (IQR 4 to 12 weeks).

Macronutrient profiles varied across studies and between treatment and control groups, median values reported for carbohydrate intake were 47% (IQR: of 44 to 52.3%) for the treatment group and 50.5% (IQR: 46 to 56.8%) for the control group. Median values for fat intake were 36.5% (IQR: 31.8 to 39%) and 30.5% (IQR: 28.3 to 34.8%) for tree nut and

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control group respectively. Median values for protein intake were 16% (IQR: 15 to 18%) and 17% (IQR: 15 to 19%) for tree nut and control group correspondingly.

Appendix Table 2 and Appendix Figure 1 present the assessment and summary of the risk of bias by using The Heyland MQS and The Cochrane Risk of Bias Tool. The Heyland MQS ranged from 3 to 9. Twenty-five trials (69.4%) were considered to be low quality (MQS <8) and 11 trials (30.6%) high quality (MQS ≥8). The main contributors of low scores were blinding of participants and crossovers between intervention treatments, followed by sample comparability and follow up. The Cochrane Risk of Bias Tool showed that in our study, blinding of participants and personnel was considered mainly "low risk of bias" (blinding of participants and crossovers in our included dietary trials are not feasible) and that a few studies were considered "high risk of bias" due to incomplete outcome data and selective reporting.

Most of the trials reported research funding from an agency 27/36(75%), while others were funded from a combination of agency and industry 5/36(13.9%).One trial (2.8%) was funded exclusively by industry. Three trials[18 40 47] did not report their funding source (8.3%).

Waist Circumference

Appendix Figure 2 presents data on the effect of tree nuts on waist circumference**.** Tree nuts did not significantly decrease waist circumference in the overall analyses (MD, -0.91 cm [95% CI, -1.99, 0.18 cm]) with evidence of significant heterogeneity (I^2=65%, P<0.001). Stratification by health status failed to demonstrate a significant effect for any of the sub samples. Sensitivity analyses did not alter the results (data not shown).

Appendix Table 3-A and Appendix Figure 3 present the a priori continuous and categorical subgroup analyses, respectively, for waist circumference. There was evidence of statistically significant effect modification by the difference in SFA intake in the categorical subgroup analyses (P<0.05) and by the difference in carbohydrate intake in the continuous subgroup analyses (P<0.05) between tree nut and control interventions. Trials in which tree nuts displaced more SFA leading to larger differences between the tree nut and control

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interventions were more likely to favor the control diet. Trials with lower carbohydrate intakes in the tree nut intervention arms showed larger reductions in waist circumference.

Triglycerides

Figure 2 presents data on the effect of tree nuts on triglycerides. Tree nuts showed a significant triglyceride-lowering effect (MD, -0.07mmol/L, [95% CI, -0.09, -0.04 mmol/L]) in the overall analysis without evidence of significant heterogeneity (I^2=21%, P=0.13). The same effect was seen with evidence of significant heterogeneity (I^2=48%, P=0.03) in the subsample of participants who were otherwise healthy (MD, -0.07 mmol/L [95% CI, -0.11, -0.04 mmol/L]) and without evidence of heterogeneity in the subsample of participants with MetScriteria(MD, -0.09 mmol/L [95% CI, -0.18, 0.00 mmol/L]). Although the reductions were not statistically significant in people with dyslipidemia or diabetes, they did not significantly differ from the reductions in participants who were otherwise healthy or with MetS. Sensitivity analyses did not alter the results (data not shown).

Appendix Table 3-B and Appendix Figure 4 present data from the a priori continuous and categorical subgroup analyses, respectively, for triglycerides. There was significant effect modification by nut type in categorical analyses (P<0.05). Pairwise comparisons showed that pecan, walnut, and pistachio interventions all significantly decreased triglycerides more than almond interventions (P<0.05). No other subgroup analyses were statistically significant.

HDL-C

Appendix Figure 5 presents the effect of tree nuts on HDL-C**.** Tree nuts did not significantly affect HDL-C in the overall analysis (MD, 0.00 mmol/L [95% CI, -0.01, 0.01 mmol/L]) with evidence of considerable heterogeneity (I^2=87%, P=<0.001). Stratification by health status failed to demonstrate a significant effect for any of the subsamples. Sensitivity analyses did not alter the results (data not shown).

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Appendix Table 3-C and Appendix Figure 6 present the a priori continuous and categorical subgroup analyses, respectively, for HDL-C. None of the subgroup analyses were significant.

Blood Pressure

Appendix Figures 7-A and 7-B present the effect of tree nuts on systolic and diastolic blood pressure, respectively. Tree nuts did not significantly decrease either systolic (MD, -0.24mmHg [95% CI, -1.93, 1.45 mmHg]) or diastolic blood pressure (MD, 0.02mmHg [95% CI, -0.49, 0.54 mmHg]) in the overall analysis with evidence of substantial heterogeneity in the systolic blood pressure analysis (I^2=53%, P<0.01). Stratification by health status failed to demonstrate an effect for any of the subsamples. Sensitivity analyses did not alter the results (data not shown).

Appendix Tables 3D and 3E present the a priori continuous subgroup analyses and **Appendix Figures8-A and 8-B** present the a priori categorical subgroup analyses for systolic and diastolic blood pressure, respectively. There was evidence of statistically significant effect modification by fibre intake in both the continuous and categorical subgroup analyses and by the difference in carbohydrate intake in the continuous subgroup analyses, both for systolic blood pressure (P<0.05 and P<0.01 respectively) between tree nut and control interventions. Trials with higher fibre intakes in the tree nut intervention arms showed larger reductions in systolic blood pressure. Trials in which tree nuts displaced more carbohydrates leading to larger differences between the tree nut and control interventions were more likely to favor the Tree nut diet in systolic blood pressure. Change in SFA or fibre intake in the tree nut intervention arms also explained the heterogeneity in the overall analyses reducing the residual-I^2 to 0%. No other subgroup analyses were statistically significant for either systolic or diastolic blood pressure.

Fasting Blood Glucose

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Appendix Figure 9 presents the effect of tree nuts on fasting blood glucose. Tree nuts did not significantly decrease fasting blood glucose in the overall analysis (MD, -0.02 mmol/L [95% CI, -0.16, 0.11mmol/L]), with evidence of significant heterogeneity (I^2=57%, p<0.01). Stratification by health status failed to demonstrate an effect for any of the subsamples. Sensitivity analyses did not alter the results (data not shown).

Appendix Table 3-F and Appendix Figure 10 present a priori continuous and categorical subgroup analyses, respectively, for fasting blood glucose. There was evidence that the attained difference in SFA intake between tree nut and control interventions (in both continuous and categorical subgroup analyses (P<0.05)) influenced the effect of nuts on blood glucose. Trials in which tree nuts displaced less SFA leading to smaller differences in SFA between the tree nut and control interventions were more likely to favor the control diet.

Publication Bias

Appendix Figure 11presents the funnel plots for publication bias for each endpoint. Visual inspection of the funnel plots revealed some evidence of asymmetry in several of the endpoints. There were more small trials with larger effect estimates favoring tree nuts than control for waist circumference, which argues that the “small-study” effect was actually not a source of potential bias (i.e. 2 smaller studies that favoured control were published). On the other hand, there were more small trials with larger effect estimates favoring control than tree nuts for triglycerides. Egger’s test confirmed these small study effects for triglycerides (P<0.05). No other evidence of small study effects was detected by Egger’s test and Begg’s tests.

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis to look at the effect of tree nuts on criteria of the MetS. Our systematic review and meta-analysis included 36 randomized trials in 1691 participants who were otherwise healthy or met MetS criteria, dyslipidemia, or type 2 diabetes. Tree nut consumption at a median dose of ~50g/day was

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found to decrease triglycerides significantly by ~0.07 mmol/L over a median follow-up of 7-weeks. No adverse effects were seen on waist circumference, HDL-C, blood pressure or fasting blood glucose. However the direction of effect favored tree nuts in the case of waist circumference, blood pressure, and fasting blood glucose, suggesting an overall net metabolic benefit.

Results in relation to other studies

Our findings of a reduction in triglycerides without the expected reciprocal increase in HDL-C are in accordance with previous evidence. Although Sabate et al[56] did not show a triglyceride lowering effect of nut interventions (nonspecific to tree nuts) in overall pooled analyses in an patient-level meta-analysis of controlled feeding trials, he did show that nut interventions lowered triglycerides when analyses were restricted to a subsample of participants with baseline triglycerides ≥1.7mmol/L, without an increase in HDL-C. A triglyceride benefit has also been seen in individual trials and meta-analyses of trials investigating the effect of a Mediterranean dietary pattern containing tree nuts in people with diabetes.[57 58]This triglyceride-lowering effect, however, was accompanied by an HDL-C increasing effect.[57 58]Our findings add to these data by showing a similar triglyceride-lowering effect, especially for walnuts, pistachios, and pecans, in the absence of an HDL-C increasing effect, across all subsamples of participants, without differences in triglycerides by baseline levels. The lipid benefits of tree nuts can be attributed to numerous cardioprotective nutrients.[59] The fibre content and high unsaturated fat content with its ability to displace high glycemic index carbohydrate from the diet and so effect a lower glycemic load diet are likely the main factors in lowering triglycerides.

The lack of effect we observed on waist circumference reinforces the view that tree nuts do not have an adverse effect on body weight. Dietary guidelines have raised concerns about the potential of tree nuts to contribute to weight gain,[2] owing to their high energy density; however prospective cohort studies and randomized trials have shown the opposite. A pooled analysis of Harvard cohorts showed an increase in one serving per day of nuts was

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associated with significant weight loss.[60] Controlled trials of tree nuts alone or as part of Mediterranean,[57 58 61] Portfolio,[62] or DASH[63] dietary patterns have shown neutral or weight loss effects, and no influence on body fat mass or body fat percentage.[64] Dietary patterns that incorporated nuts have reported weight loss under isocaloric conditions or no weight gain under hypercaloric feeding conditions,[65] perhaps because of themetabolically-available energy from nuts is less than the calculated value, as incomplete digestion of nuts leading to energy excretion in the feces.[66] Our findings further suggest that tree nuts do not have a significant effect on the most metabolically adverse weight gain involving an increase in waist circumference. We observed a tendency for a reduction in waist circumference, especially where nuts displaced high glycemic index carbohydrate to effect a lower-glycemic load diet (as opposed to where tree nuts were used to displace saturated fat). These data suggest that the inclusion of a greater number of long-term trials in which tree nuts are used to displace high-glycemic index carbohydrate to effect a low-glycemic load diet may yet demonstrate a waist circumference benefit in future meta-analyses.

We were surprised not to see an improvement in blood pressure and fasting blood glucose. Individual trials have shown evidence of improvements in blood pressure[5 8] and other aspects of glycemic control.[19-22] An evidence-based review for the 2013 CDA guidelines also found evidence to support small improvements in overall glycemic control in people with diabetes.[67] A blood pressure-decreasing effect of tree nuts has also been seen in the context of Portfolio[62] and DASH[63 68 69] dietary patterns across a range of participant types. The same is true for improvements in long-term glycemic control as assessed by HbA1c for tree nuts as part of Mediterranean[57 58 61] and DASH[63] dietary patterns in people with diabetes. The inability of tree nuts to decrease fasting blood glucose in our analyses may relate to the proposed displacement mechanism by which tree nuts reduce the glycemic load of the diet, as this mechanism would be expected to improve long-term glycemic control through a reduction in postprandial glycaemia, which was not assessed. As elevated the blood pressure in the metabolic syndrome often relates to the underlying insulin resistance, the lack of effect on BP may also be explained by a lack of trials using tree nuts to displace

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high-glycemic index carbohydrate to decrease the low-glycemic load of the diet (trials taking advantage of this mechanism were more likely to show reductions than trials that did not in subgroup analyses). Alternatively, it may be explained by the need for tree nuts to be combined with the other aspects of a DASH diet, which collectively result in larger amounts of potassium, calcium, magnesium, dietary fibre, and protein.

Limitations

There are some limitations to our work. First, the majority of trials (69.4%) were of low quality (MQS<8). Factors that contributed the most to low quality scores were incomplete outcome data and poor reporting. However, in our a priori subgroup analyses there was no effect modification by study quality. Second, the risk of bias remains uncertain for most of the available trials owing to poor reporting. This point is particularly concerning given that the majority of the trials were conducted after the Consolidated Standards of Reporting Trials (CONSORT) guidelines were first reported in 1993 and published in 1996.[70] Third, the majority of the available trials were <3 months, which is perhaps, too short a time to observe an effect for some outcomes (waist circumference, fasting glucose). This also made it difficult to assess the sustainability of the observed effects over the long term. We did not, however, observe significant effect modification by follow-up in categorical or continuous subgroup analyses for any of the endpoints. Finally, our analyses were complicated by significant unexplained heterogeneity for waist circumference, HDL-C, and fasting blood glucose, which we attempted to accommodate using of random effects models, remains a source of uncertainty in the summary effect estimates for these endpoints.

Practical Implications

Tree nuts are a high-energy food that contain cardioprotective nutrients.[59] Even though the median fat intake (36%) of the tree nut containing diets was above that recommended (20-35%) by dietary guidelines,[23] a beneficial effect was seen when compared to a control diet that tended to meet macronutrient recommendations. The median

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dose of ~50g/day tree nuts can be easily integrated as a snack, into a dietary pattern or as a substitution for animal fats or carbohydrates. No increase in side effects compared with control diets were reported in any of the trials, suggesting diets which emphasize tree nuts are as safe as conventional diets (except in individuals with tree nut allergies).

Conclusion

In conclusion, our pooled analyses indicate that daily tree nut consumption has an overall net metabolic benefit, through decreasing triglycerides while preserving waist circumference, HDL-C, blood pressure and fasting blood glucose in people who are otherwise healthy or have dyslipidemia, criteria of the MetS, or type 2 diabetes. These data support recommendations to consume tree nuts alone or as part of heart healthy dietary patterns such as the Mediterranean, Portfolio, Vegetarian, and DASH as a means for improving metabolic control.[63 71-74] Our conclusions are limited by the small sizes, short duration, poor quality of the majority of trials, and the presence of significant unexplained heterogeneity in our analyses. These limitations highlight the need for larger, longer, high quality trials. Trials in which tree nuts are used to displace high-glycemic index carbohydrate to decrease the glycemic load of the diet will be especially relevant to understand the role of tree nuts in reducing cardiometabolic risk associated with the metabolic syndrome.

Contributions

Conception and design: S Blanco Mejia, CWC Kendall, LS Augustin, JL Sievenpiper.

Analysis or interpretation of the data: S Blanco Mejia, CWC Kendall, E Viguiliouk, LS Augustin, V Ha, A Cozma, A Mirrahimi, A Maroleanu, L Chiavaroli, LA Leiter, RJ de Souza, DJA Jenkins, JL Sievenpiper.

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Transparency declaration

The manuscript's guarantors affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Ethical Approval

Not required.

Potential Conflicts of Interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: **SBM, LSA, AC, EV and LAL,** no conflicts of interest related to this paper. **CWCK** has received consultant fees, honoraria, travel funding, or research support from or served on the scientific advisory board for the CIHR, Calorie Control Council, The Coca Cola Company (investigator initiated, unrestricted), Abbott Laboratories, Advanced Food Materials Network, Almond Board of California, American Peanut Council, American Pistachio Growers, Barilla, California Strawberry Commission, Canola Council of Canada, Danone, General Mills, Hain Celestial, International Tree Nut Council, Kellogg, Loblaw Brands Ltd, Oldways, Orafti, Paramount Farms, Pulse Canada, Saskatchewan Pulse Growers, Solae and Unilever. **VH, AM, LC** have received research support from the Canadian Institutes of health Research (CIHR). **RJdS** has received research support from the Canadian Institutes of Health Research (CIHR), Calorie Control Council, and The Coca-Cola Company (investigator initiated, unrestricted). He has served as an external resource person to the World Health Organization's (WHO) Nutrition Guidelines Advisory Group (NUGAG), and was

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the lead author of systematic reviews and meta-analysis commissioned by the WHO of saturated and trans fatty acids and health outcomes. The WHO paid for his travel and accommodation to attend the 5th NUGAG Meeting in Hangzhou, China (4-7 Mar, 2013), and the 6th NUGAG Meeting in Copenhagen, Denmark (21-24 Oct, 2013). **DJAJ** has received consultant fees, honoraria, travel funding, or research support from or served on the scientific advisory board for the CIHR, Canadian Foundation for Innovation (CFI), Ontario Research Fund (ORF), and Advanced Foods and Material Network (AFMNet) Calorie Control Council, The Coca Cola Company (investigator initiated, unrestricted), Barilla, Solae, Unilever, Hain Celestial, Loblaws Supermarkets, Inc., Sanitarium Company, Herbalife International, Pacific Health Laboratories, Inc., Metagenics/MetaProteomics, Bayer Consumer Care, Oldways Preservation Trust, The International Tree Nut Council Nutrition Research & Education, The Peanut Institute, Procter and Gamble Technical Centre Limited, Griffin Hospital for the development of the NuVal System, Soy Advisory Board of Dean Foods, Alpro Soy Foundation, Nutritional Fundamentals for Health, Pacific Health Laboratories, Kellogg's, Quaker Oats, The Coca-Cola Sugar Advisory Board, Pepsi Company, Agrifoods and Agriculture Canada (AAFC), Canadian Agriculture Policy Institute (CAPI), The Almond Board of California, The California Strawberry Commission, Orafti, the Canola and Flax Councils of Canada, Pulse Canada, the Saskatchewan Pulse Growers, and Abbott Laboratories. **JLS** has received research support from the Canadian Institutes of health Research (CIHR), Calorie Control Council, The Coca-Cola Company (investigator initiated, unrestricted grant), Pulse Canada, and The International Tree Nut Council Nutrition Research & Education Foundation. He has received travel funding, speaker fees, and/or honoraria from the American Heart Association (AHA), American College of Physicians (ACP), American Society for Nutrition (ASN), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), Canadian Diabetes Association (CDA), Canadian Nutrition Society (CNS), Calorie Control Council, Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD), International Life Sciences Institute (ILSI) North America, International Life

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Data Sharing

No additional data available.

Contributorship

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Table 1

Study, year (Reference)	Participants	Mean Age (SD or range), y	Mean Body Weight or BMI (SD or range)§	Setting	Design	Feeding Control	Nut type	Nuts Dose (g/d)‖	Comparator	Diet ††	Energy Balance	Follow-Up	MQS §§	Funding Sources ‖‖
Sabate et al, 1993 (32) Walnut Control	18 (18 M)	30	73	OP, USA	Crossover	Met	Walnut	84	NCEP Step 1 diet	55:31:14 56:30:14	Isocaloric	4 wks	6	Agency
Chisholm et al, 1998 (13) Walnut Control	16 HLP	45 (6.8)	28.4 (4.3)	OP, New Zealand	Crossover	DA	Walnut	78	Low Fat Diet	40:38:17 46:30:19	Isocaloric	4 wks	4	Agency
Spiller et al, 1998 (33) Almond Control	30 HLP	53 (10)	66 (13)	OP, Italy	Parallel	Supp	Almond	100	Matched macronutrient diet	45:39:16 47:36:17	Isocaloric	4 wks	6	Agency
Curb et al, 2000 (10) Macadamia Control Control	30 (15 M, 15 W)	35.25 (18-53)	23 (19.1 - 28.3)	OP, USA	Crossover	Met	Macadamia	46	AHA AAD	48:35:17 54:30:16 48:35:17	Isocaloric	4 wks	4	Agency-Industry
Morgan et al, 2000 (34) Pecan Control	19 (4 M, 15 W)	37 (12) 45(10)	24 (5) 24 (4)	OP, USA	Parallel	Supp	Pecan	68	Self-selected diet	45:43:12 46:36:18	Isocaloric	8 wks	6	Agency
Zambon et al, 2000 (35) Walnut Control	49 HC (26 M, 23 W)	56 (11)	70.6 (12.1)	OP, Spain	Crossover	Supp	Walnut	48.5	Mediterranean diet	48:34:18 50:31:19	Isocaloric	6 wks	6	Agency
Rajaram et al, 2001 (14) Pecan Control	23 (14 M, 9 W)	25-55	74.4 (16.7)	OP, USA	Crossover	Met	Pecan	72	NCEP Step 1 diet	47:40:13 57:28:15	Isocaloric	4 wks	8	Agency
Iwamoto et al, 2002 (36) Walnut Control	40 (20 M, 20 W)	23.8 (3.1)‡ 23.6 (4.6)‡	22.2 (0.5) 20.7 (0.5)	OP, Japan	Crossover	Met	Walnut	52¶	Average Japanese Diet	60:26:14 62:24:14	Isocaloric	4 wks	8	Agency
Jenkins et al, 2002 (15) Almond Control	27 HLP (15 M, 12 W)	64 (9)	71.2 (2.5) 71.0 (2.4)	OP, Canada	Crossover	Supp	Almond	73	NCEP Step 2 diet + Muffin	47:36:17 57:26:18	Isocaloric	4 wks	6	Agency
Lovejoy et al, 2002 (37) High Fat Almond Low Fat Almond High Fat Control Low Fat Control	30 DM2 (13 M, 17 W)	53.8 (10.4)	33.0 (5.5)	OP, USA	Crossover	Met	Almond Almond	85¶	High Fat diet Low Fat diet	48:37:15 60:25:15 48:37:15 60:25:15	Isocaloric	4 wks	5	Agency
Sabate et al, 2003 (38) High-Almond Low-Almond Control	25 NL-HC (14 M, 11 W)	41 (13)	N/A	OP, USA	Crossover	Met	Almond Almond	83 42	NCEP Step 1 diet	46:39:14 35:51:14 56:30:14	Isocaloric	4 wks	5	Agency-Industry
Wien et al, 2003 (8) Almond Control	65 OW/DM2 (28 M, 37 W)	53 (2) 57 (2)	113 (5) 114 (5)	OP, USA	Parallel	Supp	Almond	84	CHO-LCD	53:18:29 32:39:29	Isocaloric	24 wks	8	Agency
Tapsell et al, 2004 (39) Walnut Control	37 DM2	57.7 (9) 59.3 (7.1)	87.6 (12.8) 81.9 (11.2)	OP, Australia	Parallel	Supp	Walnut	30	Modified Fat	44:32:22 41:33:23	Isocaloric	6 months	6	Agency
Tamizifar et al, 2005 (40) Almond Control	30 HC (17 M, 13 W)	56 (6.1)	63 (8.9)	OP, Iran	Crossover	Supp	Almond	25	NCEP Step 1 diet	47:37:17 45:29:15	Isocaloric	4 wks	5	N/A
Kocyigit et al, 2006 (16) Pistachio Control	44 (24 M, 20 W)	32.8 (6.7)	24.2 (6.1) 24.6 (5.6)	OP, Turkey	Parallel	DA	Pistachio	69	Regular diet	N/A	Isocaloric	3 wks	8	Agency
Kurlandsky et al, 2006 (41) Almond Almond + Dark Chocolate Dark chocolate Control	47 (47 W)	41.8 (11.7) 46.2 (7.8) 36.5 (11.9) 51.3 (6.3)	25.3 (3.5) 27.2 (4.2) 23.9 (3.3) 26.1 (4.1)	OP, USA	Parallel	Supp	Almond Almond	60	NCEP ATP III diet + Chocolate NCEP ATP III diet	51:34:15 46:39:15 55:30:15 57:27:16	Isocaloric	6 wks	5	Agency-Industry
Schutte et al, 2006 (53)* Walnut Cashew Control	62 MetS	45.5 45.7 44.4	35.9 34.7 35.5	OP, South Africa	Parallel	Met	Walnut Cashew	85.5	Control diet	47:36:17 47:36:17 50:33:18	Isocaloric	8 wks	7	Agency-Industry
Mukuddem-Petersen et al, 2007 (42) Walnut Cashew Control	64 MetS	45 (10)	107 99 106	OP, South Africa	Parallel	Met	Walnut Cashew	85.5¶	Habitual diet	49:35:16 44:37:19 47:33:20	Isocaloric	8 wks	7	Agency-Industry
Sheridan et al, 2007 (17) Pistachio Control	15 HC	60 (11.2)	175 (26)	OP, USA	Crossover	Supp	Pistachio	35	Regular diet	52:31:17 53:31:16	Isocaloric	4 wks	6	Agency

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Table 1 Cont'd

Study, year (Reference)	Participants	Mean Age (SD or range), y	Mean Body Weight or BMI (SD or range)§	Setting	Design	Feeding Control	Nut type	Nuts Dose (g/d)‖	Comparator	Diet ††	Energy Balance	Follow-Up	MQS §§	Funding Sources ‖‖
Gebauer et al, 2008 (43)														
1 PD	28 HLP (10 M, 18 W)	48 (7.9)	76.6 (13.2)	OP, USA	Crossover	Met	Pistachio	37	NCEP Step 1 diet	53:34:16	Isocaloric	4 wks	5	Agency
2 PD							Pistachio	74		57:29:16				
Control										62:25:15				
Griel et al, 2008 (44)														
Macadamia	25 HC	50.2 (8.4)	26.3 (3.3)	OP, USA	Crossover	Met	Macadamia	42.5**	AAD	50:33:19	Isocaloric	5 wks	8	Agency-Industry
Control										52:33:17				
Jenkins et al, 2008 (54)*														
Almond	27 HLP (15 M, 12 W)	64 (9)	71.2 (2.5)	OP, Canada	Crossover	Supp	Almond	73	NCEP Step 2 diet + Muffin	47:36:17	Isocaloric	4 wks	6	Agency
Control			71.0 (2.4)							57:26:18				
Rajaram et al, 2009 (45)														
Walnut	25 NL-HLP (14 M, 11 W)	23-65	71.9 (15.5)	OP, USA	Crossover	Met	Walnut	42.5	AAD	60:31:15	Isocaloric	4 wks	5	Agency
Control			71.7 (15.5)							57:30:14				
Tapsell et al, 2009 (46)														
Walnut	35 DM2†	54 (8.7)	92.3 (15.7)	OP, Australia	Parallel	Supp	Walnut	30	Low Fat diet	42:29:24	Isocaloric	12 months	7	Agency
Control			93.4 (3)							41:34:20				
Li et al, 2010 (11)														
Almond	52 OW†	45.4 (2.0)	86 (26.8)	OP, USA	Parallel	Supp	Pistachio	53	Pretzel	55:30:15	Hypocaloric	12 wks	7	Agency
Control		47.3 (2.3)	85.5 (40.2)							65:20:15	Hypocaloric			
Ma et al, 2010 (47)														
Walnut	22 DM2†	58.1 (9.2)	89 (15.5)	OP, USA	Crossover	Supp	Walnut	56	Ad libitum diet	39:44:17	Isocaloric	8 wks	5	N/A
Control										43:38:19				
Torabian et al, 2010 (12)														
Walnut	87 (38 M, 49 W)	54 (10.2)	75.6 (13.2)	OP, USA	Crossover	Supp	Walnut	46	Habitual diet	N/A	Isocaloric	6 months	6	Agency
Control														
Wien et al, 2010 (48)														
Almond	65 PD (17 M, 48 W)	53 (9)	82.9 (14.4)	OP, USA	Parallel	Supp	Almond	58	AAD	42:39:19	Isocaloric	16 wks	9	Agency
Control		54 (11)	80.5 (14.4)							48:30:21				
Wu et al, 2010 (49)														
Walnut	189 MetS	48.2 (8.4)	72.2 (11.4)	OP, USA	Parallel	Supp	Walnut	30	AHA	48:37:15	Isocaloric	12 wks	9	Agency
Control		48.6 (8)	70.6 (10.9)							51:34:15				
Casas-Agustench et al, 2011 (50)														
Mixed Nuts	50 MetS (28 M, 22 W)	52.9 (8.4)	31.6 (2.8)	OP, Spain	Parallel	Supp	Mixed Nuts	30	Prudent diet	41:36:19	Isocaloric	12 wks	6	Agency
Control		50.6 (8.4)	30.0 (3.3)							42:36:19				
Cohen et al, 2011 (19)														
Almond	13 DM2 (7 M, 6 W)	66 (11.9)	96.1 (40.4)	OP, USA	Parallel	Supp	Almond	28	Cheese sticks	N/A	Isocaloric	12 wks	7	Agency
Control			105.1 (32.1)											
Jenkins et al, 2011 (20)														
Mixed Nuts	79 DM2 (52 M, 27 W)	63 (9)	80 (15)	OP, Canada	Parallel	Supp	Mixed nuts	75¶	NCEP Step 2 diet + Muffin	41:41:18	Isocaloric	12 wks	8	Agency
Control		61 (10)	83 (15)							46:35:19				
Li et al, 2011 (21)														
Almond	20 DM2 (9 M, 11 W)	58 (8.9)	26 (3.1)	OP, Taiwan	Crossover	Met	Almond	56	NCEP step 2 diet	47:37:17	Isocaloric	4 wks	5	Agency
Control										57:27:17				
Tey et al, 2011 (51)														
Hazelnut	61	38.9 (14.3)	72 (11.1)	OP, New Zealand	Parallel	Supp	Hazelnut	42	Regular diet	45:39:16‡‡	Isocaloric	12 wks	9	Agency
Control		36.1 (15.2)	67.3 (9.5)							50:33:17				
Darvish Damavandi et al, 2012 (18)														
Cashew	43 DM2 (9 M, 34 W)	51 (7.9)	72.1 (13.1)	OP, Iran	Parallel	Supp	Cashew	30	Regular diet	53:32:16	Isocaloric	8 wks	3	N/A
Control		56 (5.7)	71.9 (9.7)							57:27:16				
Foster et al, 2012 (52)														
Almond	123 OW (11 M, 112 W)	47 (12)	94 (13.1)	OP, USA	Parallel	Supp	Almond	56	Nut free diet	N/A	Hypocaloric	18 months	9	Agency
Control		46.7 (13)	91.5 (11.9)								Hypocaloric			
Wang et al, 2012 (22)														
Pistachios	86 MetS	51.9 (8.8)	28.1 (3.2)	OP, China	Parallel	Supp	Pistachio	42	AHA Step 1 diet	N/A	Isocaloric	12 wks	5	Industry
High pistachios		51.8 (9.4)	28 (4.5)				Pistachio	70						
Control		50.7 (9.9)	28 (4.4)											
West et al, 2012 (55)*														
1 Pistachio	28 HLP (10 M, 18 W)	48 (7.9)	76.6 (13.2)	OP, USA	Crossover	Met	Pistachio	37	NCEP Step 1 diet	53:34:16	Isocaloric	4 wks	5	Agency
2 Pistachio							Pistachio	74		57:29:16				
Control										62:25:15				
Somerset et al, 2013 (9)														
Macadamia	64 OW (10 M, 54 W)	43.7 (8.4)	95 (14.7)	OP, Australia	Parallel	DA	Macadamia	46	Regular diet	36:38:21	Isocaloric	10 wks	9	Agency
Control		43.2 (10.9)	99.6 (15.2)							41:38:17				

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Table 1. Characteristics of RCTs Investigating the effect of Tree Nuts on Criteriaof the MetS

MetS: metabolic syndrome; DM2: type 2 diabetes mellitus; OW: overweight; HLP: hyperlipidemic; NL-HLP: normal to mildly hyperlipidemic; HC: Hypercholesterolemic; NL-HC: normal to hypercholesterolemic; M: men; W: women; BMI: body mass index; OP: out-patient; IP: In-patient; USA: United States of America; SUPP: supplement; Met: metabolic; DA: dietary advice; N/A: not available; AHA: American Heart Association; AAD: Average American Diet; NCEP: National Cholesterol Education Program; CHO-LCD: Self-selected Complex Carbohydrate diet; WKS: weeks; MQS: Heyland Methodological Quality Score.

* Companion reports: Jenkins et al, 2008 for Jenkins et al, 2002; Schutte et al, 2006 for Mukuddem-Petersen et al, 2007; Wang et al, 2012 for Gebauer et al, 2008.

† Baseline characteristics were given based on the number of randomized participants for Li et al, 2010 n=70; Ma et al, 2010 n=24; Zambon et al, 2000 n=55 and for recruited subjects for Tapsell et al. 2009 (n=50).

‡ Mean age was given separetly for men and women.

§ Body weight is reported in kg and BMI is reported in kg/m2. BMI is reported only when no data on weight were available.

‖ Nut dose is given based on grams (g) per day, 1oz = 28 g.

¶ Median was taken from a range given. Iwamoto et al, 2010 range 50-54 g/d; Jenkins et al, 2011 range 50-75 g/d; Lovejoy et al, 2002 range 57-113 g/d; Mukuddem-Petersen et al, 2007 range 63-108 g/d; Torabian et al, 2010 range 28-64 g/d; Zambon et al, 2000 range 41-56 g/d.

** Based on 2100 kcal.

†† Energy from carbohydrate:fat:protein.

‡‡ Values for carbohydrates are given in geometric means.

§§ Trials with scores ≥8 were considered to be of high quality.

‖‖ Agency funding is that from government, university, or not-for-profit health agency sources.

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FIGURE LEGENDS

Figure 1. Summary of evidence search and selection

Figure 2. Forest plot of the RCTs investigating the effect of Tree Nuts on Triglycerides. Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia, metabolic syndromecriteria, diabetes and their combination (total). Paired analyses were applied to all crossover trials (15) and one substudy. Data are expressed as mean differences (MD) with 95% CI, using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using the Cochrane's Q statistic (I^2) at a significance level of $P<0.10$ and quantified by I^2, levels ≥50 % considerable heterogeneity and ≥75%, substantial heterogeneity. TG = Triglycerides, mmol/L = mill moles per liter, A = Almond, AC = Almond + Chocolate, HF = High Fat, LF = Low Fat.

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Figure 1. Summary of evidence search and selection

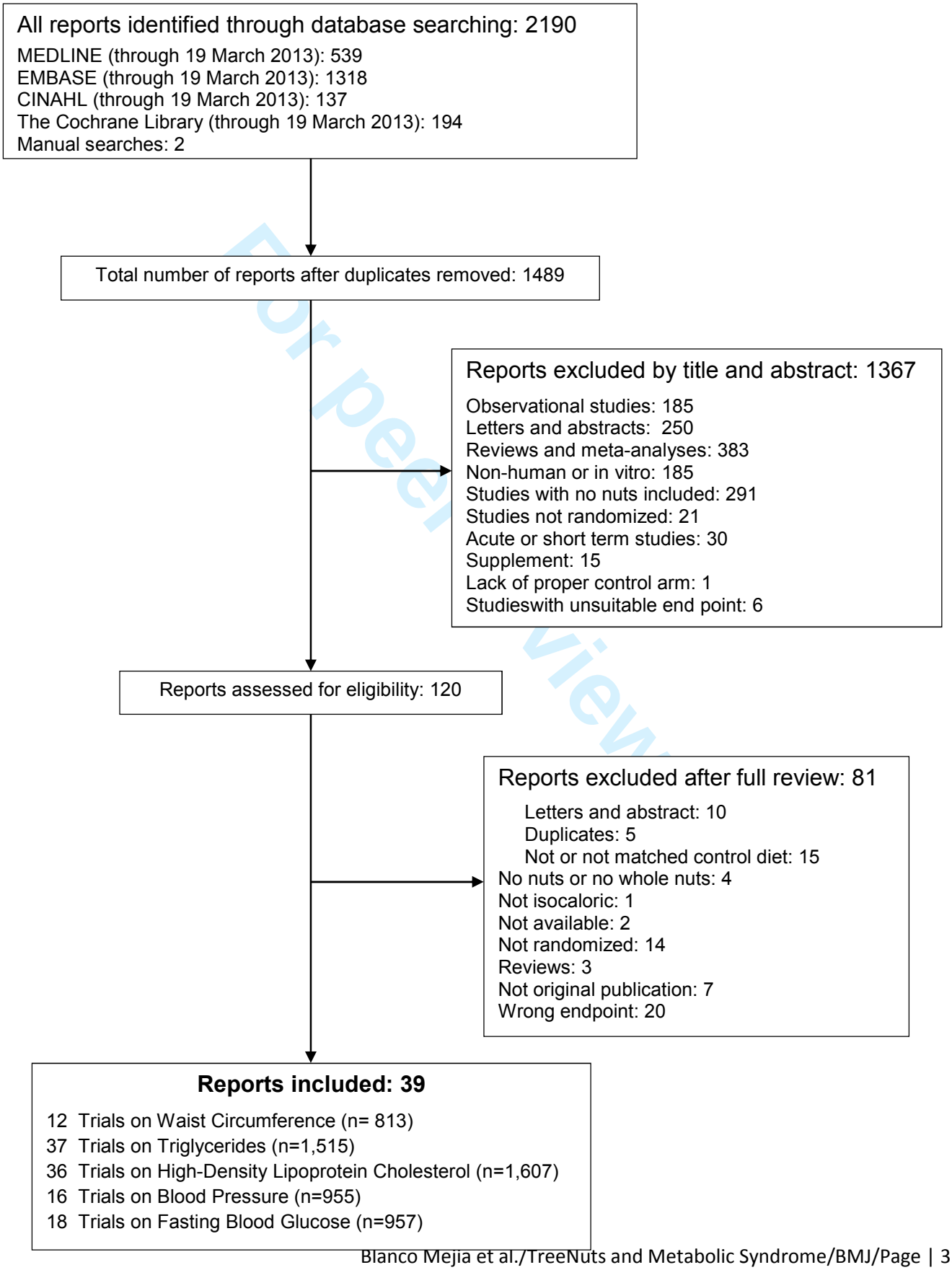

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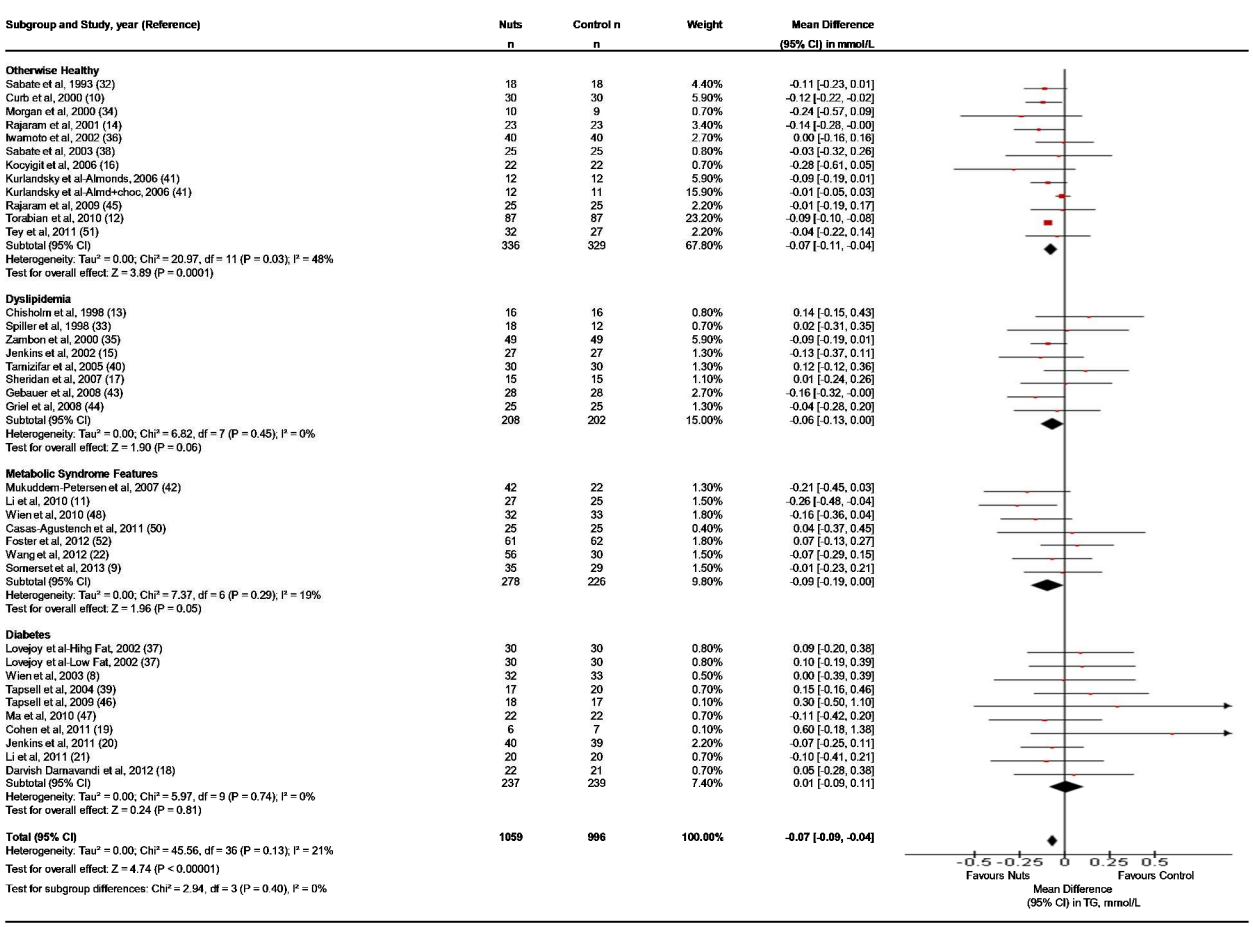
Figure 2. Forest plot of the RCTs investigating the effect of Tree Nuts on Triglycerides



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Appendix Table 1. Search Strategy for Studies Assessing the Effect of Tree Nut consumption on Metabolic Syndrome Criteria in RCTs.

Database	SearchPeriod	Search
MEDLINE	1946 to March Week 1 2013	1. exp nut/ Or nuts.mp. Or nut.mp. Or expbertholletia/ Or walnut*.mp. Or expJuglans/ Or almond*.mp. Or expPrunus/ Or pecan*.mp. Or expCarya/ Or pistachio*.mp. Or expPistacia/ Or cashew*.mp. Or expAnacardium/ Or hazelnut*.mp. Or expCorylus/ Or macadamia*.mp. Or exp Macadamia/ 2. ogtt.mp. Or exp Glucose Tolerance Test/ Or "glucose tolerance test".mp. Or hba1c.mp. Or fructosamine*.mp. Or expFructosamine/ Or insulin*.mp. Or exp Insulin/ Or glycemia*.mp. Or glycaemia*.mp. Or hyperinsulin*.mp. Or expHyperinsulinism/ Or dysglycemia*.mp. Or dysglycaemia*.mp. Or gly* albumin.mp. Or expHemoglobin A, Glycosylated/ Or "blood glucose".mp. Or exp Blood Glucose/ Or hyperglycemia*.mp. Or 39. hyperglycaemia*.mp. Or expHyperglycemia/ Or "homeo* model assessment".mp. Or homa.mp. Or diabetes.mp. Or exp Diabetes Mellitus/ 3. exp Hypertension/ Or exp Blood Pressure/ Or "systolic blood pressure".mp. Or "diastolic blood pressure".mp. Or hypertension.mp. Or SBP.mp. Or DBP.mp. Or "mean arterial pressure".mp. 4. exp Triglycerides/ Or exp Hypertriglyceridemia/ Or hypertriglyceridemia*.mp. Or triglyceride*.mp. Or triacylglycerol*.mp. Or dyslipidemia*.mp. Or dyslipidaemia*.mp. Or exp Dyslipidemias/ 5. exp Cholesterol, HDL/ Or "high density lipoprotein cholesterol".mp. Or hdl.mp. 6. "abdominal obesity".mp. Or exp Obesity, Abdominal/ Or "waist circumference".mp. Or exp waist circumference/ Or "abdominal fat*".mp. Or exp Abdominal Fat/ 7. exp Insulin Resistance/ Or "metabolic syndrome".mp. 8. 1 and (2 or 3 or 4 or 5 or 6 or 7) 9. limit 8 to animals† 10. 8 not 9
EMBASE	1946 to 2013 Week 11	1. exp nut/ Or nuts.mp. Or nut.mp. Or expbertholletia/ Or walnut*.mp. Or expJuglans/ Or almond*.mp. Or expPrunus/ Or pecan*.mp. Or expCarya/ Or pistachio*.mp. Or expPistacia/ Or cashew*.mp. Or expAnacardium/ Or hazelnut*.mp. Or expCorylus/ Or macadamia*.mp. Or exp Macadamia/ 2. ogtt.mp. Or exp Glucose Tolerance Test/ Or "glucose tolerance test".mp. Or hba1c.mp. Or fructosamine*.mp. Or expFructosamine/ Or insulin*.mp. Or exp Insulin/ Or glycemia*.mp. Or glycaemia*.mp. Or hyperinsulin*.mp. Or expHyperinsulinism/ Or dysglycemia*.mp. Or dysglycaemia*.mp. Or gly* albumin.mp. Or expHemoglobin A, Glycosylated/ Or "blood glucose".mp. Or exp Blood Glucose/ Or hyperglycemia*.mp. Or 39. hyperglycaemia*.mp. Or expHyperglycemia/ Or "homeo* model assessment".mp. Or homa.mp. Or diabetes.mp. Or exp Diabetes Mellitus/ 3. exp Hypertension/ Or exp Blood Pressure/ Or "systolic blood pressure".mp. Or "diastolic blood pressure".mp. Or hypertension.mp. Or SBP.mp. Or DBP.mp. Or "mean arterial pressure".mp. 4. exp Triglycerides/ Or exp Hypertriglyceridemia/ Or hypertriglyceridemia*.mp. Or triglyceride*.mp. Or triacylglycerol*.mp. Or dyslipidemia*.mp. Or dyslipidaemia*.mp. Or exp Dyslipidemias/ 5. exp Cholesterol, HDL/ Or "high density lipoprotein cholesterol".mp. Or hdl.mp. 6. "abdominal obesity".mp. Or exp Obesity, Abdominal/ Or "waist circumference".mp. Or exp waist circumference/ Or "abdominal fat*".mp. Or exp Abdominal Fat/ 7. exp Insulin Resistance/ Or "metabolic syndrome".mp. 8. 1 and (2 or 3 or 4 or 5 or 6 or 7) 9. limit 8 to animals† 10. 8 not 9

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CINHAL	1982 to 19 March 2013	1. (MH "Nuts+) Or "pistachio" Or "hazelnut" Or "macadamia" Or "brazil nut" Or "brazil nuts" Or "pine nut" Or "pine nuts". 2. "ogtt" Or (MM "Hemoglobin A, Glycosylated") Or "HbA1c" Or "fructosamine" Or "Insulin" Or "glycemia" Or "hyprinsulin" Or "dysglycemia" Or "gly* albumin" Or "blood glucose" Or "hyperglycemia" Or "homa" Or (MH "Diabetes Mellitus") Or "diabetes mellitus". 3. (MH "Hypertension") Or "hypertension" Or "SBP" Or "DBP" Or "mean arterial pressure" Or "MAP". 4. "triglycerides" Or "hypertriglyceridemia" Or "TG" Or "TAG" Or "dyslipidemia". 5. "HDL" Or (MH "Lipoproteins, HDL Cholesterol") Or "hypercholesterolemia". 6. "abdominal obesity" Or "abdominal fat" Or "waist circumference". 7. "Insulin resistance" Or "metabolic syndrome". 8. 1 and (2 or 3 or 4 or 5 or 6 or 7).
The Cochrane Library	Through March 19th 2013	1. nuts.mp. Or nut.mp. Or brazil nut.mp. Or brazil nuts.mp. Or pine nut.mp. Or walnut*.mp. Or almond*.mp. Or pecan*.mp. Or pistachio*.mp. Or cashew*.mp. Or hazelnut*.mp. Or macadamia.mp. 2. ogtt.mp. Or hba1c.mp. Or fuctosamine*.mp. Or Insulin*.mp. Or glycemia.mp. Hyperinsulin*.mp. Or dysglycemia.mp. Or gly* albumin.mp. Or exp Blood Glucose/ Or blood glucose.mp. Or expHyperglycemia/ Or homa.mp. Or exp Diabetes Mellitus/ Or diabetes mellitus.mp. 3. hypertension.mp. Or /blood pressure.mp. Or systolic blood pressure.mp. Or diastolic blood pressure.mp. Or hypertension.mp. Or SBP.mp. Or DBP.mp. Or mean arterial pressure.mp. Or MAP.mp. 4. triglycerides.mp. Or hypertriglyceridemia.mp. Or TG.mp. Or triacylglycerol*.mp. Or TAG.mp. Or dyslipidemia.mp. 5. HDL.mp. Or HDL cholesterol.mp. Or hypercholesterolemia.mp. 6. abdominal obesity.mp. Or abdominal fat.mp. 7. insulin resistance.mp. Or metabolic syndrome.mp. 8. 1 and (2 or 3 or 4 or 5 or 6 or 7)

* The symbol at the end of each search term is used in order to capture all possible endings with that word.
Original search date for all databases was May 25th 2012; update search date for all databases was March 19th 2013.
† Searches were limited to animals and then extracted from the general search.

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Appendix Table 2 – Study Quality Assessment by Using the Heyland MQS*

Study, Year (Reference)	Design†			Sample‡			Intervention§			MQS (n/13)
	Randomization (n/2)	Blinding (n/1)	Analysis (n/2)	Selection (n/1)	Comparability (n/1)	Follow-up (n/1)	Protocol (n/1)	Co-interventions (n/2)	Crossovers (n/2)	
Sabate et al, 1993 (32)	1	0	0	1	1	0	1	2	0	6
Chisholm et al, 1998 (13)	1	0	0	0	1	0	0	2	0	4
Spiller et al, 1998 (33)	1	0	0	1	1	0	1	2	0	6
Curb et al, 2000 (10)	1	0	0	0	1	0	0	2	0	4
Morgan et al, 2000 (34)	1	0	0	1	1	0	1	2	0	6
Zambon et al, 2000 (35)	2	0	0	0	1	0	1	2	0	6
Rajaram et al, 2001 (14)	2	0	0	1	1	1	1	2	0	8
Iwamoto et al, 2002 (36)	1	0	2	0	1	1	1	2	0	8
Jenkins et al, 2002 (15)	1	0	0	1	1	0	1	2	0	6
Lovejoy et al, 2002 (37)	1	1	0	0	1	0	0	2	0	5
Sabate et al, 2003 (38)	1	0	0	0	1	0	1	2	0	5
Wien et al, 2003 (8)	2	0	2	0	1	0	1	2	0	8
Tapsell et al, 2004 (39)	1	0	2	1	1	0	0	1	0	6
Tamizifar et al, 2005 (40)	1	0	0	0	1	0	1	2	0	5
Kocyigit et al, 2006 (16)	1	0	2	0	1	1	1	2	0	8
Kurlandsky et al, 2006 (41)	1	0	0	0	1	0	1	2	0	5
Schutte et al, 2006 (53)	2	0	0	1	1	0	1	2	0	7
Mukuddem-Petersen et al, 2007(42)	2	0	0	1	1	0	1	2	0	7
Sheridan et al, 2007 (17)	1	0	0	1	1	0	1	2	0	6
Gebauer et al, 2008 (43)	1	0	0	1	1	0	1	1	0	5
Griel et al, 2008 (44)	1	0	2	0	1	1	1	2	0	8
Jenkins et al, 2008 (54)	1	0	0	1	1	0	1	2	0	6
Rajaram et al, 2009 (45)	1	0	0	1	1	0	0	2	0	5
Tapsell et al, 2009 (46)	2	0	0	1	1	0	1	2	0	7
Li et al, 2010 (11)	2	0	0	1	1	0	1	2	0	7
Ma et al, 2010 (47)	1	0	0	1	1	0	1	1	0	5
Torabian et al, 2010 (12)	1	0	0	1	1	0	1	2	0	6
Wien et al, 2010 (48)	2	0	2	1	1	0	1	2	0	9
Wu et al, 2010 (49)	2	0	2	1	1	0	1	2	0	9
Casas-Agustench et al, 2011 (50)	1	0	0	1	1	0	1	2	0	6
Cohen et al, 2011 (19)	1	0	2	0	1	1	0	2	0	7
Jenkins et al, 2011 (20)	1	0	2	1	1	0	1	2	0	8
Li et al, 2011 (21)	1	0	0	0	1	0	1	2	0	5
Tey et al, 2011 (51)	2	0	2	1	1	0	1	2	0	9
DarvishDamavandi et al, 2012 (18)	1	0	0	0	0	0	1	1	0	3

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Foster et al, 2012 (52)	2	0	2	0	1	1	1	2	0	9
Wang et al, 2012 (22)	1	0	0	0	1	0	1	2	0	5
West et al, 2012 (55)	1	0	0	1	1	0	1	1	0	5
Somerset et al, 2013 (9)	1	0	2	1	1	1	1	2	0	9

MQS=Heyland Methodological Quality Score; n/ = total score per category and total MQS score.

* The Heyland MQS assigns a score of 0 or 1 or from 0 to 2 over 9 categories of quality related to study design, sampling procedures, and interventions, for a total of 13 points. Trials that scored ≥8 were considered to be of higher quality (11).

† Randomization was scored 2 points for being randomized with the methods described, 1 point for being randomized without the methods described, or 0 points for being neither randomized nor having the methods described. Blinding was scored 1 point for being double-blind or 0 points for "other." Analysis was scored 2 points for being intention-to-treat; all other types of analyses scored 0 points.

‡ Sample selection was scored 1 point for being consecutive eligible or 0 points for being preselected or indeterminate. Sample comparability was scored 1 point for being comparable or 0 points for not being comparable at baseline. Follow-up was scored 1 point for being 100% or 0 points for <100%.

§ Treatment protocol was scored 1 point for being reproducibly described or 0 points for being poorly described. Co-interventions were scored 2 points for being described and equal, 1 point for being described but unequal or indeterminate, or 0 points for not being described. Treatment crossovers (where participants were switched from the control treatment to the experimental treatment) were scored 2 points for being <10%, 1 point for being >10%, and 0 points for not being described.

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Appendix Table 3. A priori subgroup analyses of continuous variables for criteria of the Metabolic Syndrome

A. Waist Circumference

Subgroups	No. of Trials	N	β [95% CI]	Residual I^2 (%)	P-value
Nuts Dose (g/d)	12	813	-0.020 [-0.099, 0.060]	66.8	0.60
Duration (weeks)	12	813	-0.136 [-0.451, 0.179]	64.4	0.36
Saturated Fat (%)	11	727	0.178 [-0.385, 0.741]	69	0.49
Change in Saturated Fat (%)	9	551	0.633 [-0.463, 1.729]	48.6	0.21
Difference in Saturated Fat (%)	11	727	0.764 [-0.852, 2.380]	70.4	0.31
Fiber Intake (g/d)	11	786	0.006 [-0.206, 0.217]	70.8	0.95
Change in Fiber Intake (g/d)	7	637	0.022 [-0.374, 0.418]	67.1	0.89
Difference in Fiber Intake (g/d)	11	721	-0.050 [-0.343, 0.243]	71	0.71
Baseline (cm)	10	727	-0.006 [-0.071, 0.059]	70.7	0.84
Difference in Carbohydrate intake (%/d)	11	727	0.255 [0.062, 0.448]	41.4	0.02

B. Triglycerides

Subgroups	No. of Trials	N	β [95% CI]	Residual I^2 (%)	P-value
Nuts Dose (g/d)	37	1523	-0.001 [-0.003, 0.001]	19.7	0.35
Duration (weeks)	37	1523	0.002 [-0.001, 0.005]	17.5	0.15
Saturated Fat (%)	32	1162	0.006 [-0.008, 0.020]	0	0.41
Change in Saturated Fat (%)	17	786	-0.003 [-0.026, 0.021]	0	0.81
Difference in Saturated Fat (%)	32	1162	0.005 [-0.011, 0.020]	0	0.53
Fiber Intake (g/d)	29	1024	-0.001 [-0.006, 0.004]	0	0.70
Change in Fiber Intake (g/d)	13	594	-0.003 [-0.014, 0.008]	0	0.60
Difference in Fiber Intake (g/d)	28	1008	0.001 [-0.008, 0.010]	0	0.81
Baseline (mmol/L)	29	1151	0.093 [0.000, 0.187]	4.4	0.05
Difference in Carbohydrate intake (%/d)	32	1170	0.003 [-0.005, 0.011]	0.0	0.51

C. High-Density Lipoprotein Cholesterol

Subgroups	No. of Trials	N	β [95% CI]	Residual I^2 (%)	P-value
Nuts Dose (g/d)	36	1613	-0.001 [-0.002, 0.001]	87	0.4
Duration (weeks)	36	1613	0.000 [-0.002, 0.002]	87	0.91
Saturated Fat (%)	32	1321	0.004 [-0.008, 0.015]	84.7	0.50
Change in Saturated Fat (%)	17	926	0.008 [-0.011, 0.026]	79.7	0.4
Difference in Saturated Fat (%)	32	1321	0.000 [-0.008, 0.009]	84.6	0.95
Fiber Intake (g/d)	30	1137	-0.000 [-0.004, 0.004]	89.1	0.97
Change in Fiber Intake (g/d)	14	734	-0.000 [-0.007, 0.007]	85.6	0.97
Difference in Fiber Intake (g/d)	29	1177	0.002 [-0.003, 0.007]	87.3	0.33
Baseline (mmol/L)	30	1271	0.030 [-0.103, 0.163]	88.5	0.65
Difference in Carbohydrate intake (%/d)	33	1359	-0.001 [-0.006, 0.004]	83.1	0.78

D. Systolic Blood Pressure

Subgroups	No. of Trials	N	β [95% CI]	Residual I^2 (%)	P-value
Nuts Dose (g/d)	16	955	-0.076 [-0.188, 0.037]	55.1	0.17
Duration (weeks)	16	955	-0.031 [-0.160, 0.097]	55.6	0.61
Saturated Fat (%)	14	746	0.791 [-0.091, 1.672]	54.8	0.07
Change in Saturated Fat (%)	10	621	-0.333 [-1.115, 0.449]	0	0.36
Difference in Saturated Fat (%)	14	746	-1.261 [-2.666, 0.145]	44.7	0.07
Fiber Intake (g/d)	14	746	-0.273 [-0.522, -0.023]	48.1	0.04
Change in Fiber Intake (g/d)	7	490	-0.008 [-0.248, 0.233]	0	0.94
Difference in Fiber Intake (g/d)	14	746	-0.291 [-0.698, 0.117]	52.5	0.15
Baseline (mmHg)	13	786	-0.108 [-0.442, 0.226]	59.7	0.49
Difference in Carbohydrate intake (%/d)	14	746	0.546 [0.194, 0.895]	24	< 0.01

E. Diastolic Blood Pressure

Subgroups	No. of Trials	N	β [95% CI]	Residual I^2 (%)	P-value
Nuts Dose (g/d)	16	955	-0.012 [-0.042, 0.019]	14.82	0.43
Duration (weeks)	16	955	0.014 [-0.029, 0.057]	15.3	0.50
Saturated Fat (%)	14	746	0.047 [-0.273, 0.367]	21.5	0.75
Change in Saturated Fat (%)	10	621	-0.275 [-0.703, 0.152]	0	0.18
Difference in Saturated Fat (%)	14	746	-0.064 [-0.335, 0.201]	20	0.61
Fiber Intake (g/d)	14	746	-0.070 [-0.164, 0.023]	12.2	0.13
Change in Fiber Intake (g/d)	7	490	0.057 [-0.075, 0.188]	0	0.32
Difference in Fiber Intake (g/d)	14	746	-0.023 [-0.146, 0.101]	20.7	0.70
Baseline (mmHg)	13	786	0.047 [-0.153, 0.246]	25.5	0.62
Difference in Carbohydrate intake (%/d)	14	746	0.052 [-0.049, 0.152]	13.5	0.28

F. Fasting Glucose

Subgroups	No. of Trials	N	β [95% CI]	Residual I^2 (%)	P-value
Nuts Dose (g/d)	18	955	0.005 [-0.006, 0.015]	58.1	0.35
Duration (weeks)	18	955	0.004 [-0.027, 0.035]	59	0.78
Saturated Fat (%)	15	746	0.028 [-0.053, 0.109]	52.4	0.46
Change in Saturated Fat (%)	9	621	-0.145 [-0.353, 0.064]	48.1	0.15
Difference in Saturated Fat (%)	15	746	-0.097 [-0.265, 0.072]	50.4	0.24
Fiber Intake (g/d)	14	746	0.001 [-0.028, 0.031]	57.9	0.92
Change in Fiber Intake (g/d)	6	490	0.005 [-0.035, 0.045]	42.1	0.74
Difference in Fiber Intake (g/d)	14	746	0.000 [-0.038, 0.038]	57.9	0.99
Baseline (mmol/L)	18	786	-0.070 [-0.186, 0.045]	53.9	0.21
Difference in Carbohydrate intake (%/d)	16	746	0.022 [-0.030, 0.074]	54.5	0.38

N: number of participants in each subgroup.

Residual I^2 was reported as a percent value, where I^2 ≥50% indicated "substantial" heterogeneity and ≥75% indicated "considerable" heterogeneity. P-value significance for heterogeneity was set as $p < 0.10$.

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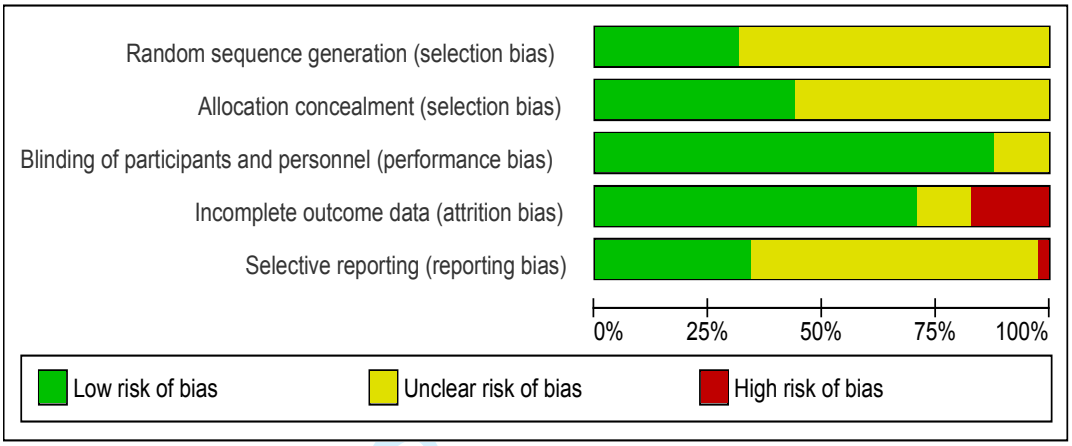
Appendix Figure 1. Cochrane risk of bias.



Review authors' judgements about each risk of bias item presented as percentages across all included studies.

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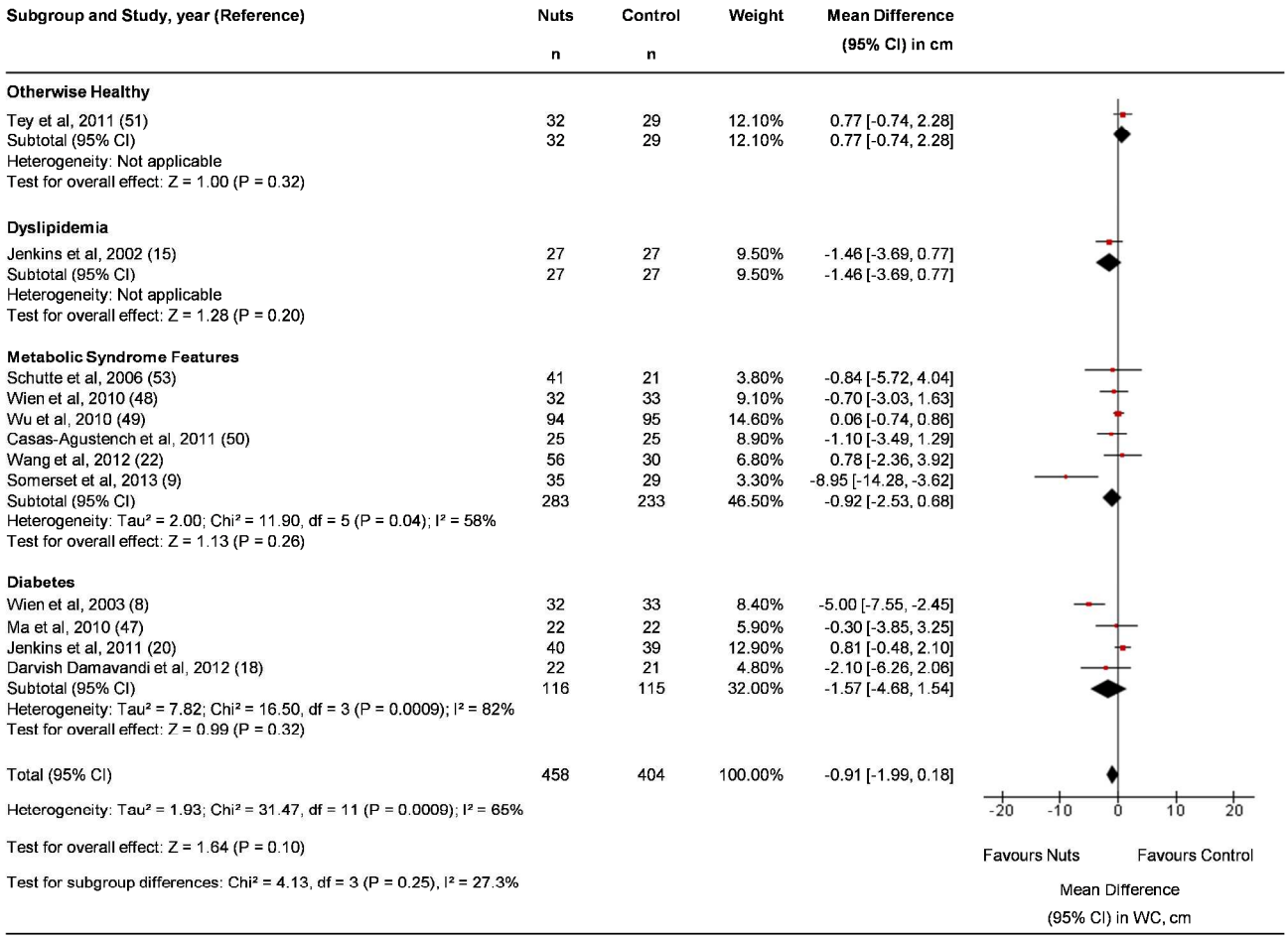
Appendix Figure 2. Forest plot of the RCTs of the effect of Tree Nuts on Waist Circumference



Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia, metabolic syndrome criteria, diabetes and their combination (total). Paired analyses were applied to all crossover trials (2). Data are expressed as mean differences (MD) with 95% CI, using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using the Cochrane's Q statistic (I^2) at a significance level of P<0.10 and quantified by I^2, levels ≥50 % represent considerable heterogeneity and ≥75%, substantial heterogeneity. WC = waist circumference, cm = centimeters.

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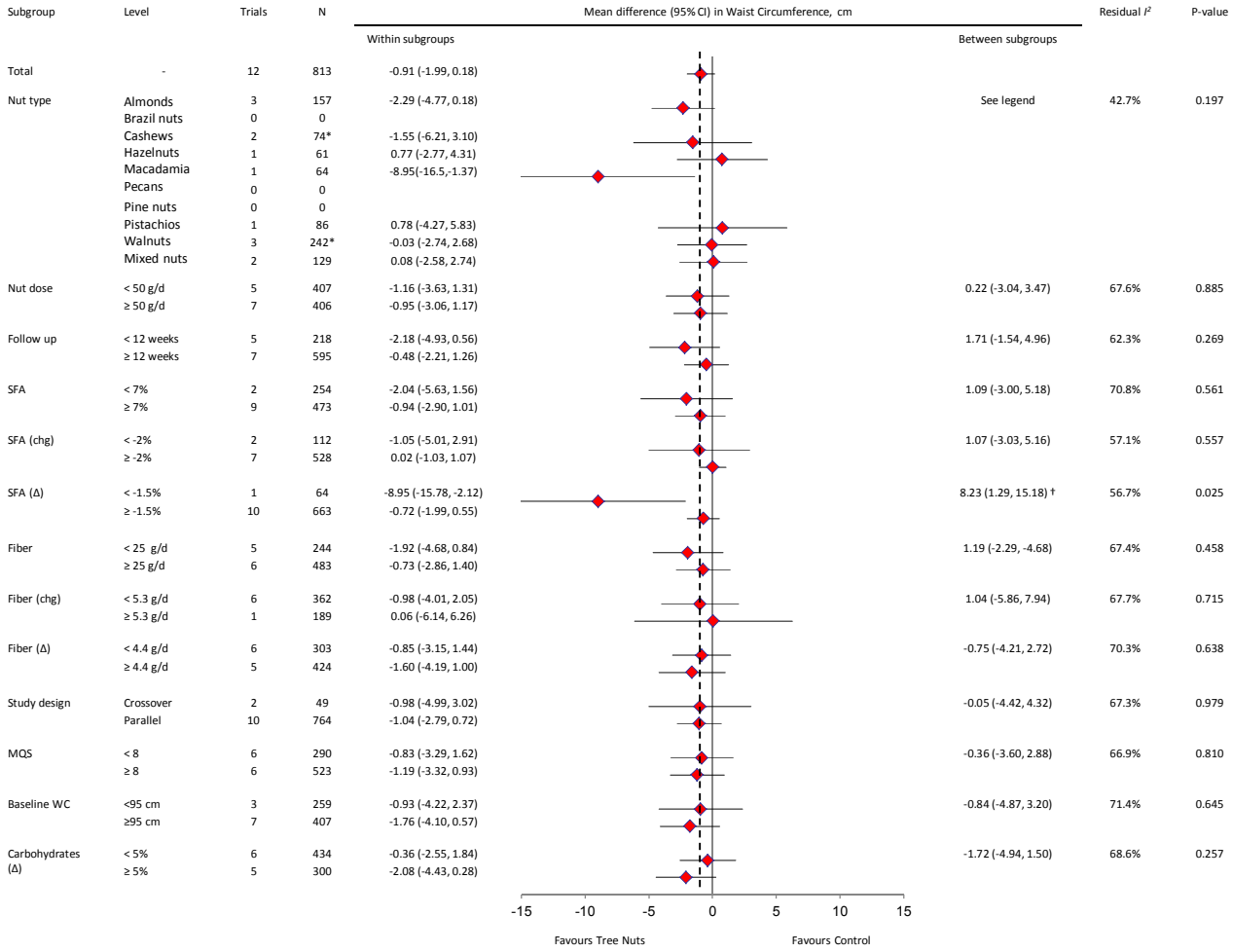
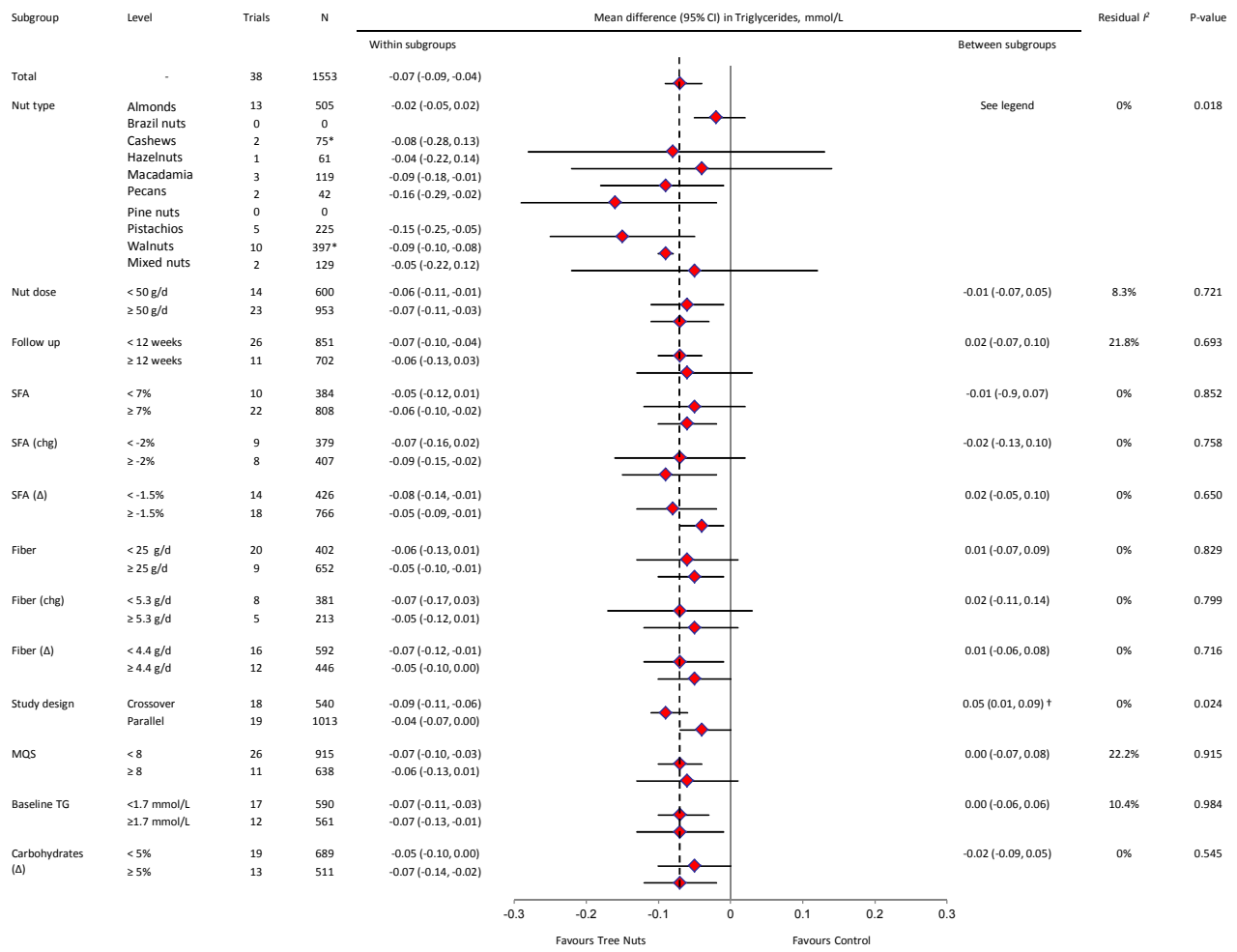
Appendix Figure 3. Forest plot of subgroup analyses for categorical variables for Waist Circumference



Point estimates for each subgroup level are the pooled effect estimates and are represented by diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value indicates the interstudy heterogeneity unexplained by the subgrouping. Pairwise between-subgroup mean differences (95% CIs) for nut type are not shown due to lack of statistical significance between groups. SFA = Saturated Fatty Acids, SFA (chg) = change within treatment diet for SFA, SFA (Δ) = difference between groups for SFA, Fiber (chg) = change within treatment diet for Fiber, Fiber (Δ) = difference between groups for SFA, MQS = Heyland Methodological Quality Score, WC = waist circumference, Carbohydrates (Δ)= difference between groups for carbohydrates.

* Both nut types were studied within the same trial, for the sole purposes of number of participants, the control group was divided in half.

Appendix Figure 4. Forest plot of subgroup analyses for categorical variables for Triglycerides.

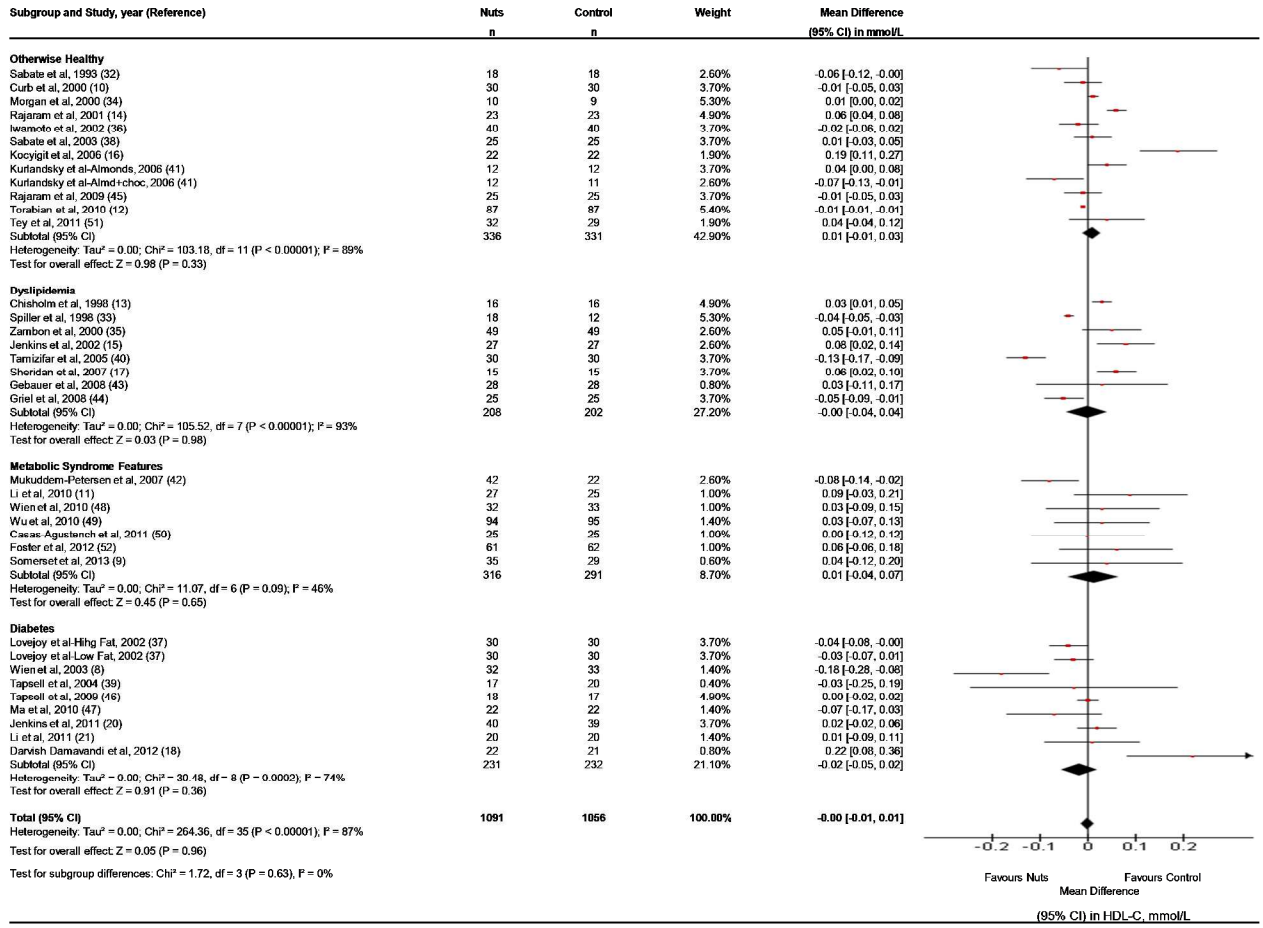


Point estimates within each subgroup level are the pooled effect estimates and are represented by diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value indicates the interstudy heterogeneity unexplained by the subgrouping. Significant pairwise between-subgroup mean differences (95% CIs) for nut types as follows: almonds vs. walnuts -0.07 mmol/L (-0.11, -0.04 mmol/L)†, almonds vs. pistachio -0.13 mmol/L (-0.24, -0.03 mmol/L)†, almonds vs. pecan -0.14 mmol/L (-0.28, -0.001 mmol/L) †ll others non-significant (P>0.05),. SFA = Saturated Fatty Acids, SFA (chg) = change within treatment diet for SFA, SFA (Δ) = difference between groups for SFA, Fiber (chg) = change within treatment diet for Fiber, Fiber (Δ) = difference between groups for SFA, MQS = Heyland Methodological Quality Score, TG = Triglycerides.

* Both nut types were studied within the same trial, for the sole purposes of number of participants, the control group was divided in half.

† Statistically significant pairwise subgroup effect modification by meta-regression analysis (p< 0.05)

Appendix Figure 5. Forest plot of the RCTs investigating the effect of Tree Nuts on HDL-C.



Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia, metabolic syndrome criteria, diabetes and their combination (total). Paired analyses were applied to all crossover trials (15) and one substudy. Data are expressed as mean differences (MD) with 95% CI, using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using the Cochrane's Q statistic (I^2) at a significance level of P<0.10 and quantified by I^2, levels ≥50 % represent considerable heterogeneity and ≥75%, substantial heterogeneity. HDL-C = High-Density Lipoprotein Cholesterol, mmol/L = millimoles per liter, A = Almond, AC = Almond + Chocolate, HF = High Fat, LF = Low Fat.

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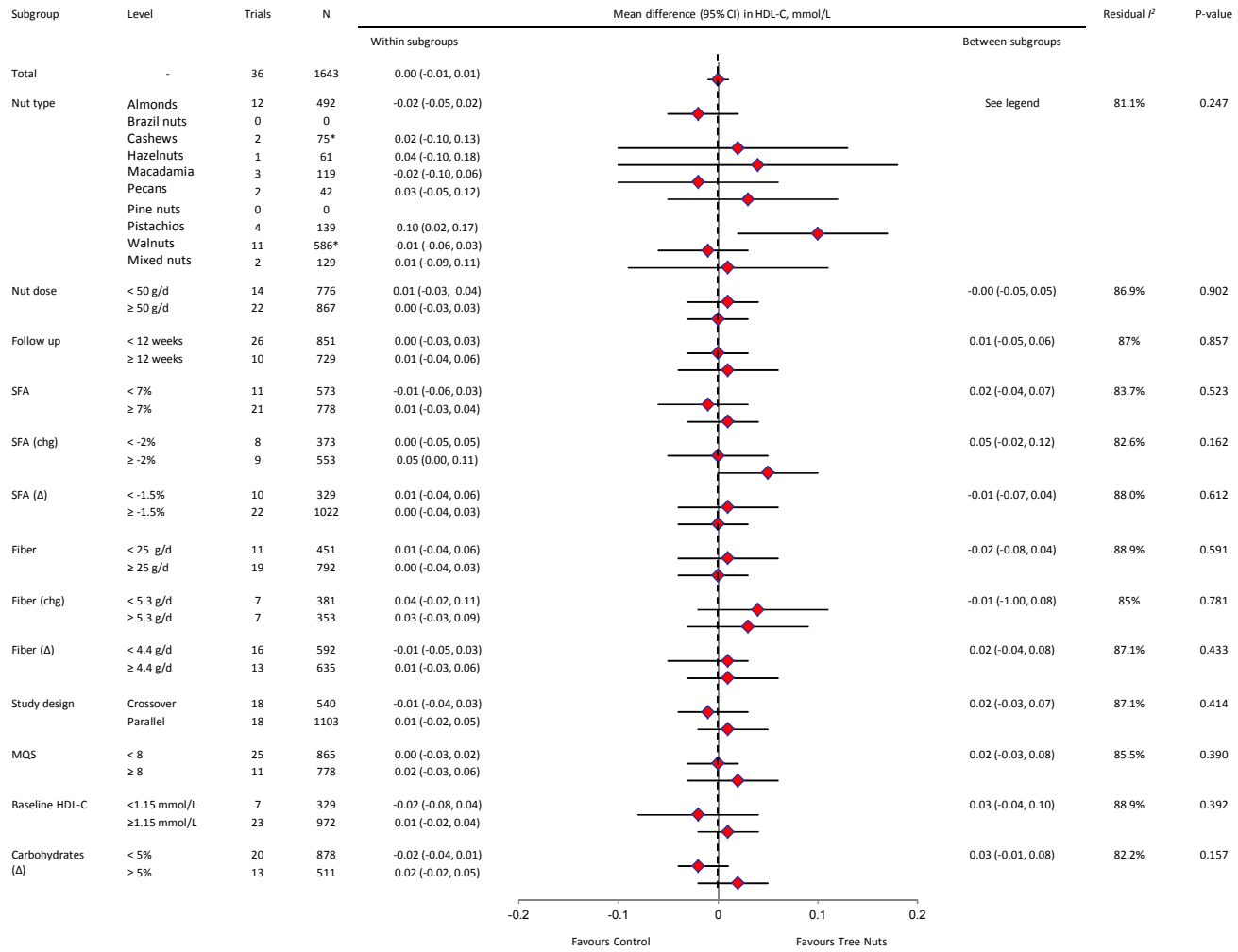
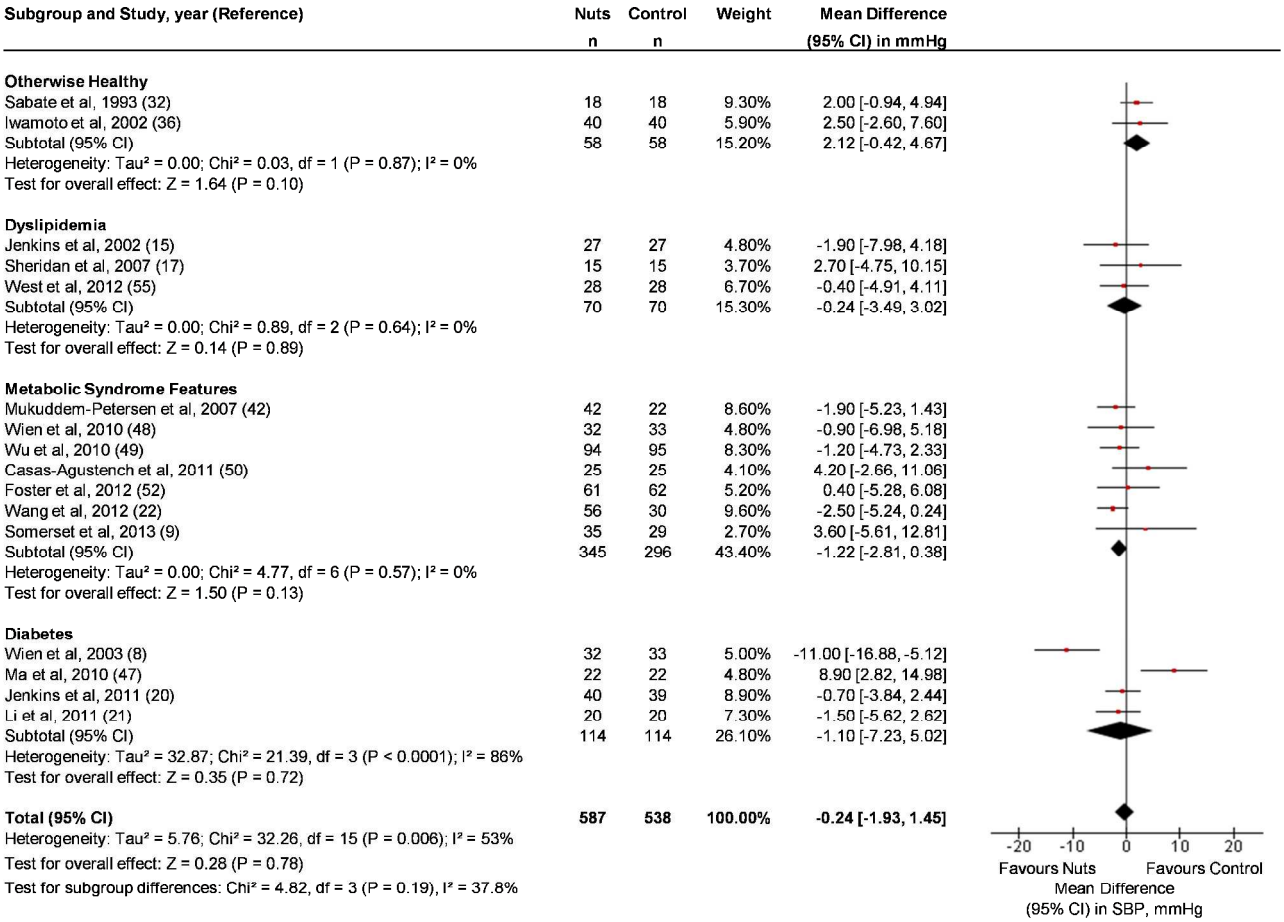
Appendix Figure 6. Forest plot of subgroup analyses for categorical variables for HDL-C.



Point estimates for each subgroup level are the pooled effect estimates and are represented by diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value indicates the interstudy heterogeneity unexplained by the subgrouping. Pairwise between-subgroup mean differences (95% CIs) for nut type are not shown due to lack of statistical significance between groups. SFA = Saturated Fatty Acids, SFA (chg) = change within treatment diet for SFA, SFA (Δ) = difference between groups for SFA, Fiber (chg) = change within treatment diet for Fiber, Fiber (Δ) = difference between groups for SFA, MQS = Heyland Methodological Quality Score, HDL-C = high-density lipoprotein cholesterol.

* Both nut types were studied within the same trial, for the sole purposes of number of participants, the control group was divided in half.

Appendix Figure 7A. Forest plot of the RCTs investigating the effect of Tree Nuts on Systolic Blood Pressure.



Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia, metabolic syndrome criteria, diabetes and their combination (total). Paired analyses were applied to all crossover trials (7). Pooled effects are mean differences (MD) with 95% CI, using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using the Cochrane's Q statistic (I^2) at a significance level of P<0.10 and quantified by I^2, levels ≥50 % represent considerable heterogeneity and ≥75%, substantial heterogeneity. SBP = Systolic Blood Pressure, mmHg = millimeters of mercury.

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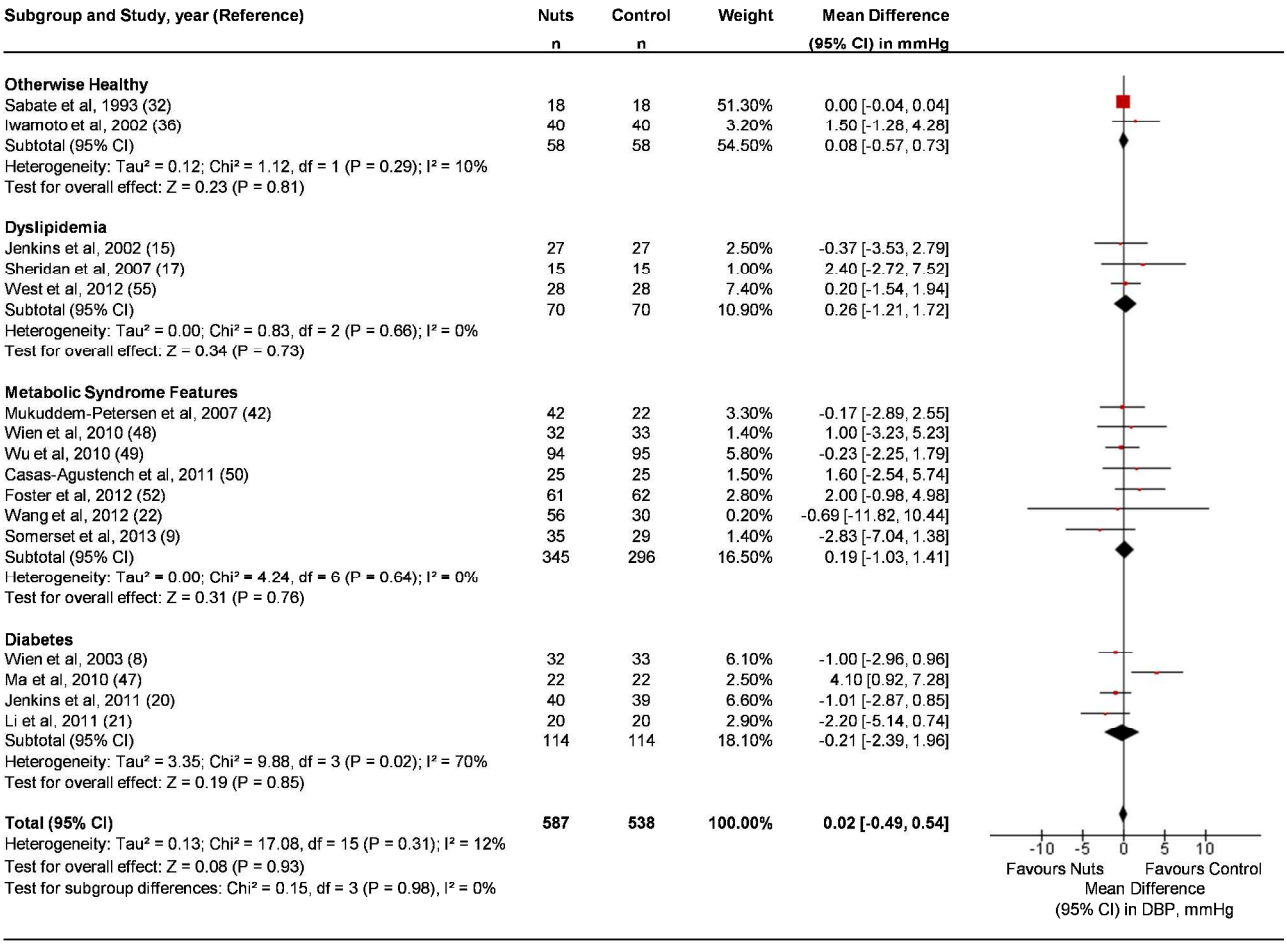
Appendix Figure 7B. Forest plot of the RCTs investigating the effect of Tree Nuts on Diastolic Blood Pressure.



Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia, metabolic syndrome criteria, diabetes and their combination (total). Paired analyses were applied to all crossover trials (7). Pooled effects are mean differences (MD) with 95% CI, using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using the Cochrane's Q statistic (I^2) at a significance level of P<0.10 and quantified by I^2, levels ≥50 % representing considerable heterogeneity and ≥75%, substantial heterogeneity. SBP = Systolic Blood Pressure, mmHg = millimeters of mercury.

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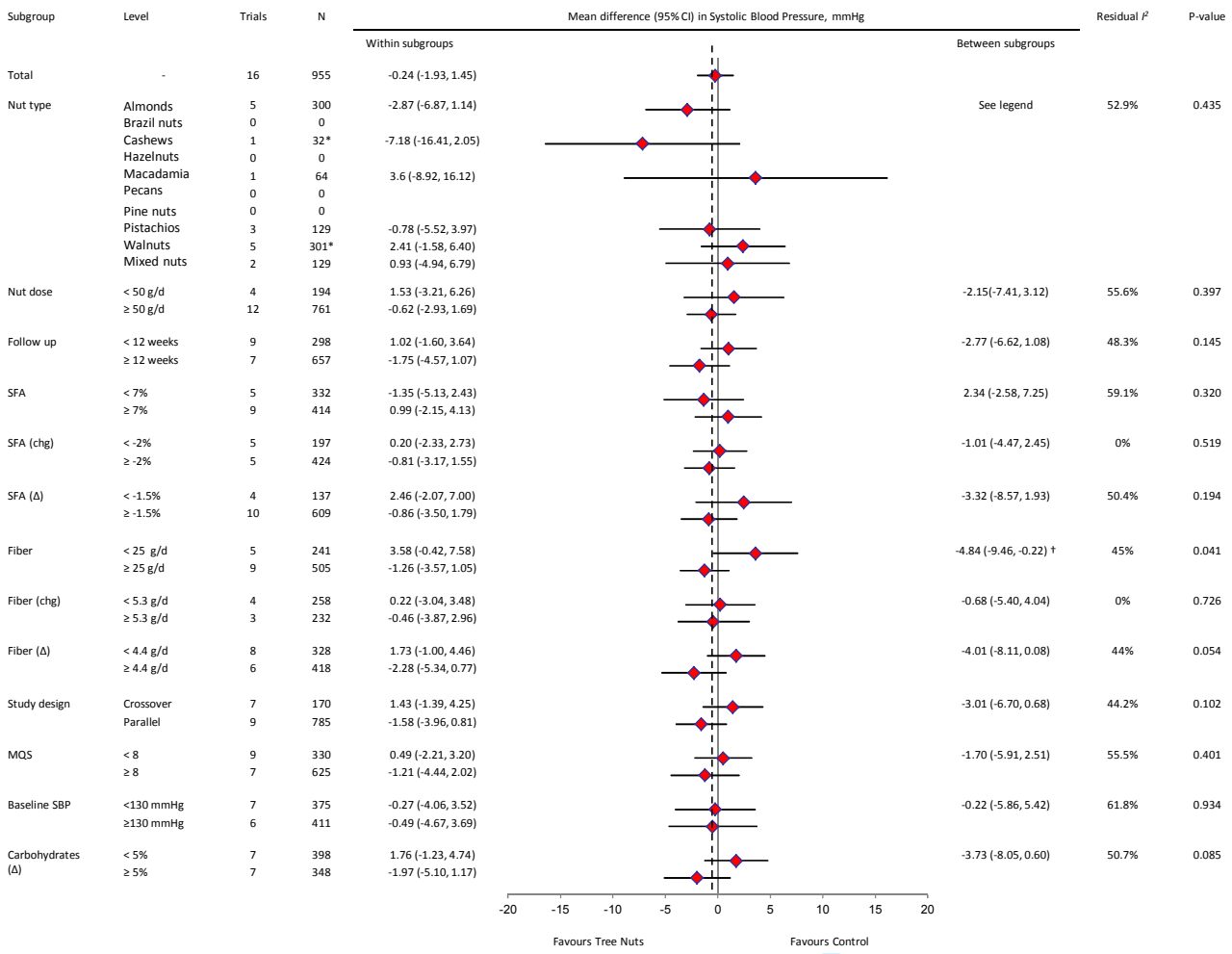
Appendix Figure 8A. Forest plot of subgroup analyses for categorical variables for Systolic Blood Pressure.

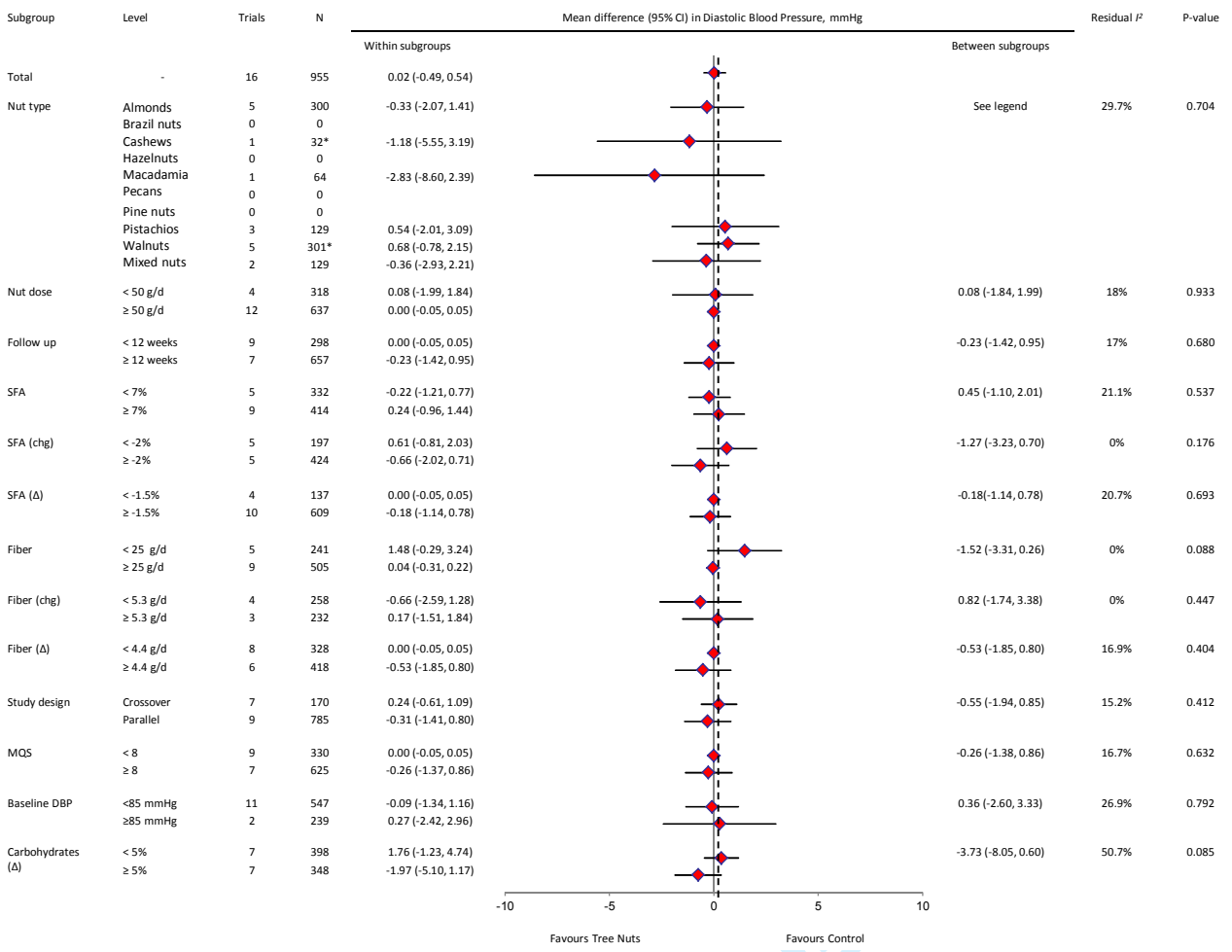


Point estimates for each subgroup level are the pooled effect estimates and are represented by diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value indicates the interstudy heterogeneity unexplained by the subgrouping. Pairwise between-subgroup mean differences (95% CIs) for nut type are not shown due to lack of statistical significance between groups. SFA = Saturated Fatty Acids, SFA (chg) = change within treatment diet for SFA, SFA (Δ) = difference between groups for SFA, Fiber (chg) = change within treatment diet for Fiber, Fiber (Δ) = difference between groups for SFA, MQS = Heyland Methodological Quality Score, SBP = systolic blood pressure.

* Both nut types were studied within the same trial, for the sole purposes of number of participants, the control group was divided in half.

† Statistically significant pairwise subgroup effect modification by meta-regression analysis ($p < 0.05$).

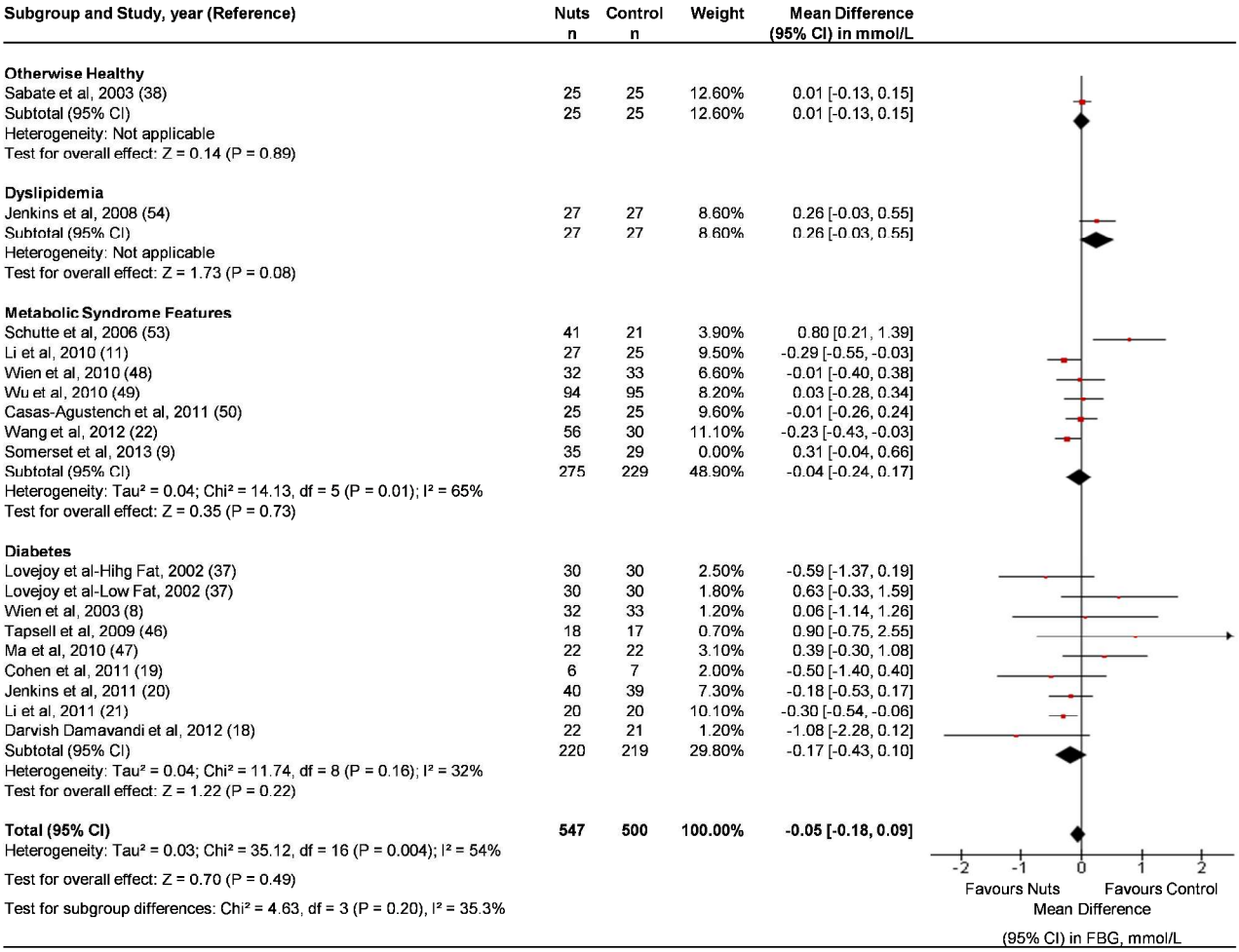
Appendix Figure 8B. Forest plot of subgroup analyses for categorical variables for Diastolic Blood Pressure.



Point estimates for each subgroup level are the pooled effect estimates and are represented by diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value indicates the interstudy heterogeneity unexplained by the subgrouping. Pairwise between-subgroup mean differences (95% CIs) for nut type are not shown due to lack of statistical significance between groups. SFA = Saturated Fatty Acids, SFA (chg) = change within treatment diet for SFA, SFA (Δ) = difference between groups for SFA, Fiber (chg) = change within treatment diet for Fiber, Fiber (Δ) = difference between groups for SFA, MQS = Heyland Methodological Quality Score, DBP = diastolic blood pressure.

* Both nut types were studied within the same trial, for the sole purposes of number of participants, the control group was divided in half.

Appendix Figure 9. Forest plot of the RCTs investigating the effect of Tree Nuts on Fasting Blood Glucose.



Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia, metabolic syndrome criteria, diabetes and their combination (total). Paired analyses were applied to all crossover trials (5) and one substudy. Data are expressed as mean differences (MD) with 95% CI, using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using the Cochrane's Q statistic (I^2) at a significance level of P<0.10 and quantified by I^2, levels ≥50 % represent considerable heterogeneity and ≥75%, substantial heterogeneity. FBG = Fasting Blood Glucose; mmol/L = mill moles per liter; HF = High Fat; LF = Low Fat.

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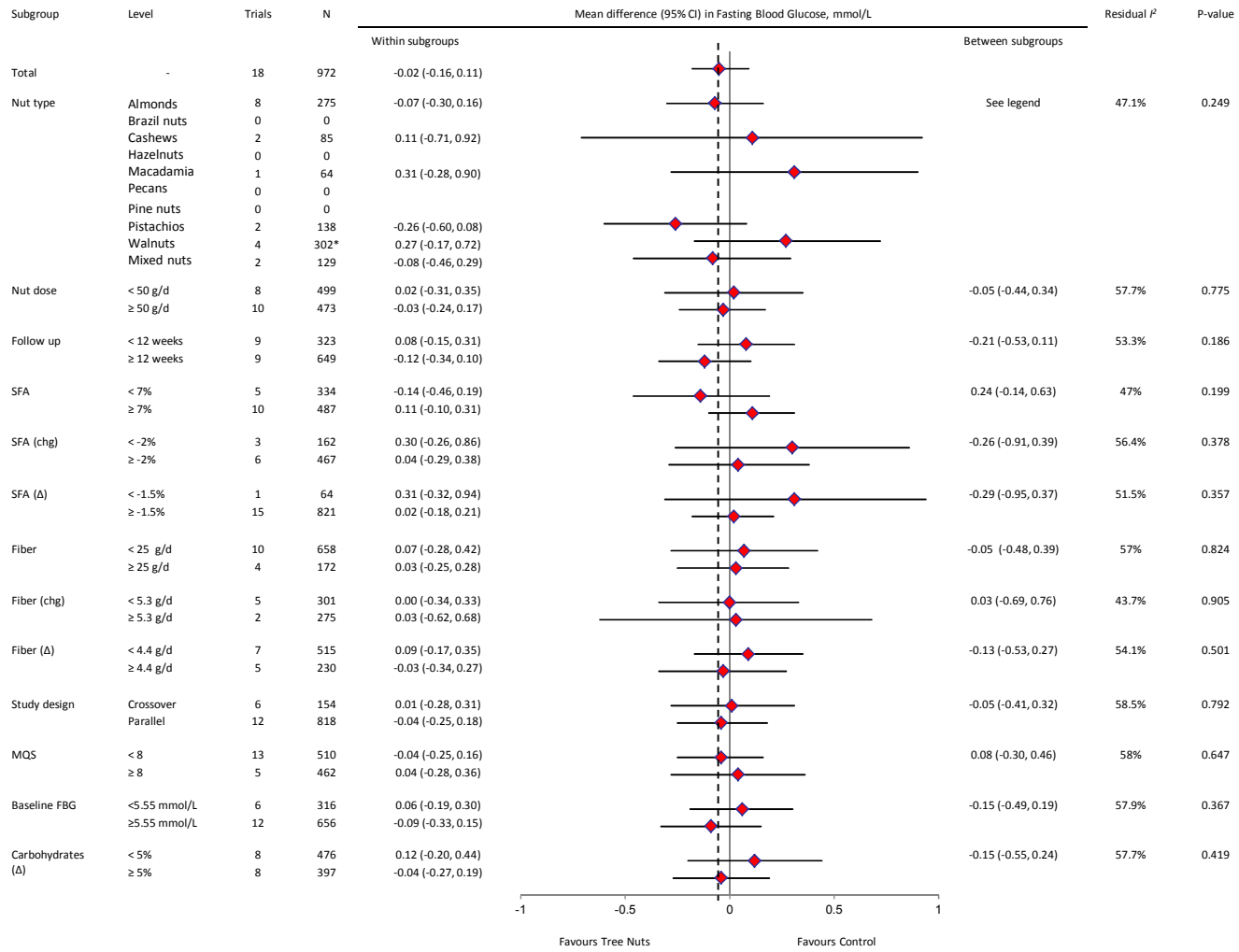
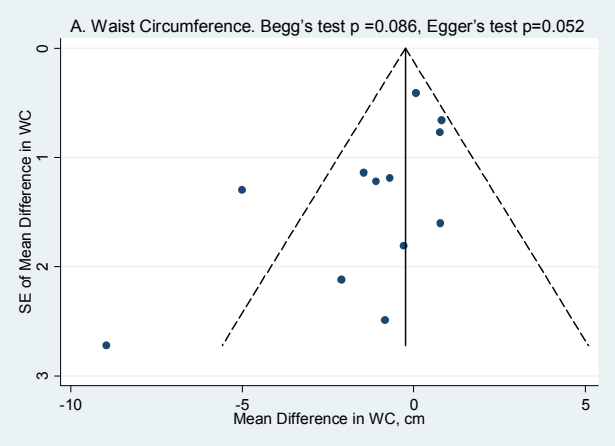
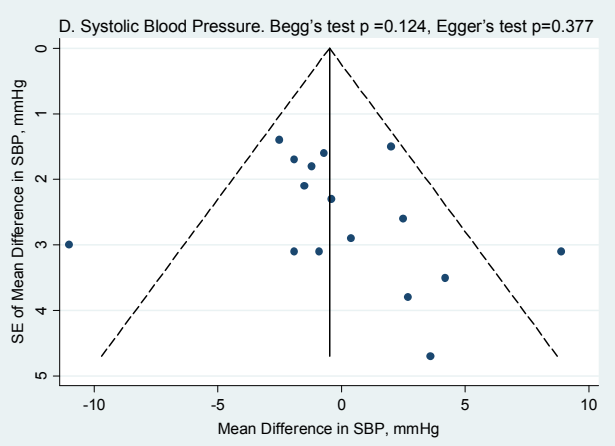
Appendix Figure 10. Forest plot of subgroup analyses for categorical variables.

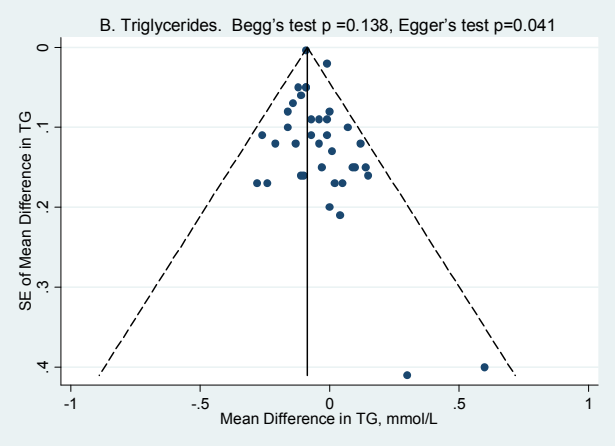


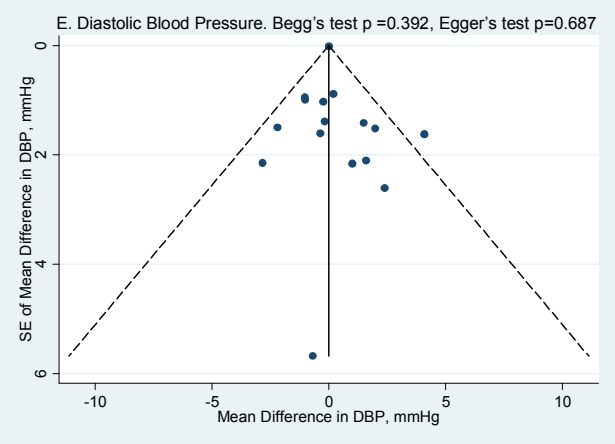
Point estimates for each subgroup level are the pooled effect estimates and are represented by diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value indicates the interstudy heterogeneity unexplained by the subgrouping. Pairwise between-subgroup mean differences (95% CIs) for nut are not shown due to lack of statistical significance. SFA = Saturated Fatty Acids, SFA (chg) = change within treatment diet for SFA, SFA (Δ) = difference between groups for SFA, Fiber (chg) = change within treatment diet for Fiber, Fiber (Δ) = difference between groups for SFA, MQS = Heyland Methodological Quality Score, FG = fasting glucose.
* Both nut types were studied within the same trial, for the sole purposes of number of participants, the control group was divided in half.

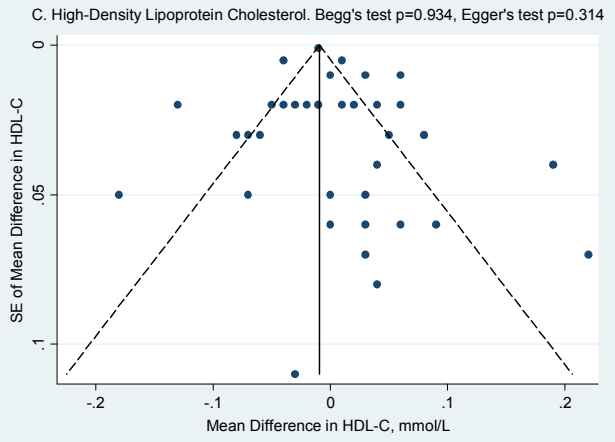
Appendix Figure 11. Funnel plots for evidence of publication bias.

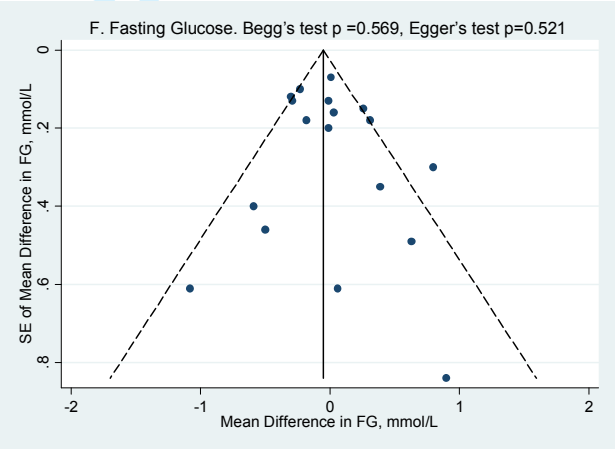












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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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EFFECT OF TREE NUTS ON METABOLIC SYNDROME CRITERIA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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EFFECT OF TREE NUTS ON METABOLIC SYNDROME CRITERIA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Running Title: Tree Nuts and Metabolic Syndrome

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ABSTRACT

Objective: To provide a broader evidence summary to inform dietary guidelines of the effect of tree nuts on criteria of the metabolic syndrome (MetS).

Design: We conducted a systematic review and meta-analysis of the effect of tree nuts on criteria of the MetS.

Data sources: We searched MEDLINE, EMBASE, CINAHL, and the Cochrane Library (through April 4, 2014).

Eligibility criteria for selecting studies: We included relevant randomized controlled trials (RCTs) of ≥ 3 weeks reporting at least one criterion of the MetS.

Data extraction: Two or more independent reviewers extracted all relevant data. Data were pooled using the generic inverse variance method using random effects models and expressed as mean differences (MD) with 95% confidence intervals (CI). Heterogeneity was assessed by the Cochran Q statistic and quantified by the I^2 statistic. Study quality and risk of bias were assessed.

Results: Eligibility criteria were met by 49 RCTs including 2,226 participants who were otherwise healthy or had dyslipidemia, MetS or diabetes mellitus. Tree nut interventions lowered triglycerides (MD = -0.06 mmol/L [95% CI, -0.09, -0.03 mmol/L]), and fasting blood glucose (MD = -0.08 mmol/L [95% CI, -0.16, -0.01 mmol/L]) compared with control diet interventions. There was no effect on waist circumference, HDL-C, or blood pressure with the direction of effect favouring tree nuts for waist circumference. There was evidence of significant unexplained heterogeneity in all analyses ($P < 0.05$).

Conclusion: Pooled analyses show a MetS benefit of tree nuts through modest decreases in triglycerides and fasting blood glucose with no adverse effects on other criteria across nut types. As our conclusions are limited by the short duration and poor quality of the majority of trials, as well as significant unexplained between-study heterogeneity, there remains a need for larger, longer, high quality trials.

Protocol Registration: ClinicalTrials.gov identifier, NCT01630980

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Strengths and limitations of this study

- This is the first systematic review and meta-analysis to look at the effect of tree nuts on metabolic syndrome criteria.
- This systematic review and meta-analysis involved a large number of trials (47 RCTs) in participants with a range of metabolic conditions.
- Most of the trials (74.4%) were of low quality (MQS < 8).
- Most of the trials (68.8%) were of short duration (< 12 weeks).
- Substantial inter-study heterogeneity remained unexplained.

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INTRODUCTION

Dietary patterns including tree nuts have received particular attention for their cardiovascular benefits, and the Food and Drug Administration (FDA) have granted a qualified health claim to tree nuts for cardiovascular risk reduction.[1] General dietary guidelines[2] and heart health guidelines[3 4] also continue to recommend tree nuts alone or as part of the Mediterranean, Portfolio, and Dietary Approaches to Stop Hypertension (DASH) dietary patterns for cardiovascular disease prevention and management.

Although these recommendations are based primarily on the LDL-C lowering benefits of tree nuts[4], the cardiovascular risk reduction seen with tree nuts is beyond that which would be predicted by this effect alone. The Prevención con Dieta Mediterránea (PREDIMED) trial showed that despite a non-significant effect on LDL-C early on in the trial[5] a Mediterranean diet supplemented with mixed nuts (30 g/day) compared with a low-fat control diet reduced major cardiovascular events by 30% in high cardiovascular risk participants.[6] Nut consumption of > 3 servings/week was also associated with other metabolic advantages such as a decreased risk of obesity, MetS, and diabetes.[7] Individual large trials of tree nuts have also shown that nuts improve criteria of the metabolic syndrome: waist circumference,[8 9] triglycerides,[5 10-12] HDL-C,[13-18] blood pressure[5 8] and glycemic control.[19-22]

The overall evidence for these additional metabolic benefits, however, remains uncertain. Guidelines have not recommended tree nuts directly for managing these risk factors. Although the Canadian Diabetes Association 2013 clinical practice guidelines for nutrition therapy[23] did acknowledge some of these metabolic benefits, the evidence was deemed insufficient for making a recommendation. Tree nut consumption was recommended only in so far as part of Mediterranean or DASH dietary patterns.[23] To synthesize the evidence on which recommendations are based for the metabolic benefits of tree nuts beyond LDL-C lowering, we conducted a systematic review and meta-analysis of randomized controlled dietary trials of the effect of tree nuts on criteria of the metabolic syndrome.

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METHODS

Protocol and Registration

We followed the guidelines of the Cochrane Handbook for Systematic Reviews of Intervention for the planning and conduct of this meta-analysis.[24] Reporting of results followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[25] The review protocol is available at ClinicalTrials.gov (registration number: NCT01630980).

Study Selection

We searched MEDLINE, EMBASE, CINAHL, and the Cochrane Library (through April 4, 2014) to identify randomized controlled dietary trials of tree nuts. Details of the search strategy are presented in **Appendix Table 1**. The electronic database searches were supplemented by manual searches of the reference list of included trials and reviews. No language restriction was used.

We included randomized dietary trials that reported the effect of diets rich in tree nuts (almonds, Brazil nuts, cashews, hazelnuts, macadamia nuts, pecans, pine nuts, pistachios, walnuts and mixed nuts)[1] as a whole compared to diets without tree nuts, but matched for energy, on at least one of the five criteria of the MetS: waist circumference, triglycerides, high-density lipoprotein cholesterol (HDL-C), blood pressure and fasting blood glucose. Included trials were ≥ 3 weeks duration, a duration that satisfies the minimum follow-up requirement for lipid-lowering health claims by the FDA used in the scientific evaluation of lipid-lowering health claims.[26] We excluded trials that incorporated tree nuts as paste, oil or skin nuts into the treatment diets and also those trials that added tree nuts as part of a dietary pattern and did not have a matched control group. The former exclusion was intended to eliminate contamination from the other nutritional aspects, and to isolate the effect of tree nuts. Where multiple intervention or control groups were presented, we only included those groups which allowed us to isolate the effect of tree nuts. When multiple

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publications existed for the same trial, data from the most recent report were included. Publications including additional relevant data were used as companion reports. The MetS endpoints were selected according to the 2009 harmonized definition for MetS.[27]

Data Extraction

Studies that met the inclusion criteria were extracted in full by two independent reviewers (SBM and one of EV, LSA, VH or AM) for study characteristics and data for endpoints. Study characteristics included: study design (crossover or parallel), participant characteristics, comparator, nut dose, nut type, duration of follow-up, dietary adherence measures, macronutrient profile, statistical analysis and funding sources. All disagreements amongst reviewers were resolved by consensus.

The Heyland Methological Quality Score (MQS) was used for assessment of study quality.[28] Scores from 0-2 points were given for each of the following evaluated criteria: methods (randomization, blinding and analysis), sample (selection, compatibility and follow-up), and intervention (protocol, co-intervention and crossovers). This scale gave a maximum MQS of 13 points. Studies with a score of ≥ 8 were considered of high quality.

The Cochrane Collaboration Risk of Bias Tool was used to assess the study risk of bias.[24] Trials were classified as “unclear risk of bias” when insufficient information was provided to permit judgment, “high risk of bias” when the methodological flaw was likely to have affected the true outcome and “low risk of bias” when a methodological flaw was deemed inconsequential to determine the true effect within a study. As blinding of participants in dietary trials is difficult to achieve, we scored the trials based on the intensity of the dietary advice given to the randomized groups. If treatment intensity was judged to be more intensive in one intervention over another, then trials were classified as “high risk”. If both interventions were emphasized equally, then trials were classified as “low risk of bias”. Trials reported in abstract format only were not included in assessments of MQS or of bias owing to a lack of information.

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Means (SD) for baseline values, end values, change-from baseline differences, end-differences, and mean differences were recorded for primary endpoints (waist circumference, triglycerides, HDL-C, blood pressure and fasting blood glucose). Reported *t*-values or *F*-statistics, and *P*-values for differences were also recorded. Missing information for any endpoint data or study details were requested directly from authors. Where SDs were not reported or given directly by authors, we attempted to calculate these missing SDs from the available statistics using methods recommended by the Cochrane Collaboration.[24] If this was not possible, then we imputed these missing SDs using a pooled correlation coefficient derived from a meta-analysis of correlation coefficients from those trials reporting sufficient data.[24] These correlation coefficients were then transformed into *z*-scores and meta-analyzed using inverse-variance weighing. The pooled effect estimate from the *z*-scores was then back transformed to impute the missing SDs. We used a derived pooled correlation coefficient of 0.635 for triglycerides, 0.856 for HDL-C, 0.327 for systolic blood pressure, 0.508 for diastolic blood pressure and 0.446 for fasting blood glucose.

Statistical Analyses

Data were analyzed using Review Manager (RevMan) 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) for primary analyses and Stata (version 12, College Station, USA) for subgroup analyses. Pooled analyses were conducted using the Generic Inverse Variance method with random effects models. Data were expressed as mean differences (MD) with 95% CI and considered significant at $P < 0.05$. Paired analyses were applied to all crossover trials.[29] In cases where there were multiple intervention or control groups, we combined either intervention or control groups to create single pairwise comparisons with the aim of diminishing the unit-of-analysis error.[24]

The presence of between-studies-heterogeneity was assessed by the Cochran Q statistic (significance set at $P < 0.10$) and quantified by the I^2 statistic. An $I^2 \leq 50\%$ indicated "moderate" heterogeneity, ≥ 50% indicated "substantial" heterogeneity and ≥ 75% indicated "considerable" heterogeneity.[24] Analyses were stratified by participant health status:

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otherwise healthy, dyslipidemia, MetS criteria and type 2 diabetes based on trial entry criteria. Sources of heterogeneity were explored using sensitivity and subgroup analyses. To determine if any single trial exerted an undue influence on the overall results, sensitivity analyses were preformed, in which each individual trial was removed from the meta-analysis, and the effect size re-calculated with the remaining trials. Sensitivity analyses were also undertaken using correlation coefficients of 0.25, 0.50 and 0.75 to determine whether the overall results were robust to the use of different derived correlation coefficients in paired analyses of crossover trials. A priori subgroup analyses were done for baseline values (according to MetS diagnostic criteria),[27] absolute fibre intake (treatment diet < 25 g/day vs. ≥ 25 g/day[23] and change in [within and between the diets]), absolute saturated fatty acid (SFA) intake (treatment diet < 7% vs. ≥ 7% of total energy[23] and change in [within and between the diets]), tree nut dose (< 50 g/day vs. ≥ 50 g/day), tree nut type (almonds, Brazil nuts, cashews, hazelnuts, macadamia nuts, pecans, pine nuts, pistachios, walnuts and mixed nuts),duration of follow-up (< 3 months vs. ≥ 3 months), study design (crossover vs. parallel), and study quality (MQS < 8 vs. ≥ 8). *Post-hoc* subgroup analyses were conducted for the difference in percent carbohydrate intake between the control and intervention arm (carbohydrate displacement). The significance of between-subgroup differences were assessed using meta-regression (P < 0.05). Publication bias was assessed by visual inspection of funnel plots and formally complemented by Begg's and Egger's tests.

RESULTS

Trial Selection

Figure 1 shows flow of studies through the search and selection process. We identified a total of 2,531 reports, from which 752 reports were duplicates and 1,631 reports were deemed irrelevant (determined by review of title and abstract). The remaining 146 reports were reviewed in full, of which 97 reports were excluded for not meeting inclusion criteria. A total of 49 reports on 47 trials[8-23 30-59] as well as four companion reports[60-63] that addressed at least one criterion of the metabolic syndrome (waist circumference [15 trials, *n*

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= 1050], triglycerides [44 trials, *n* = 1,690], HDL-C [45 trials, *n* = 2,142], blood pressure [20 trials, *n* = 1,267], and fasting blood glucose [26 trials, *n* = 1,360] were included).

Trial Characteristics

Table 1 presents characteristics of the included trials. There were 47 trials involving 49 comparisons in 2,211 participants. Twelve trials (26.7%)[10 12 14 16 30 32 34 39 43 49 59] were conducted in otherwise healthy participants. Two of these trials contained a minority of participants with dyslipidemia who had been classified as otherwise healthy.[36 43] Eleven trials (24.4%)[8 18-21 35 37 44 45 54 55] were conducted in participants with type 2 diabetes or a mix of patients with overweight and type 2 diabetes in one case[8]. The remaining trials were conducted in people with dyslipidemia (9 trials [20%][13 15 17 31 33 38 41 42 53]), MetS [5 trials[22 40 47 48 58]], some MetS criteria (13 trials [28.9%]: overweight 7 trials[9 11 50-52 56 57], or prediabetes [1 trial[46]]). Median age for participants was 50.2 years (IQR: 42.5 to 55.8 years). Median body weight for participants was 81.4 kg (IQR: 72.1 to 91.7 kg).

Trials tended to be of considerable size, with a median number of 40 participants (IQR: 25 to 61participants). The majority were conducted in the United States of America (24 trials [53.3%]) with the rest conducted in various other countries: 3 trials (6.7%) each in Australia, New Zealand, and Iran; 2 trials (4.4%) each in Canada, and Spain; and 1 trial (2.2%) each in Japan, Turkey, Italy, China, Taiwan, Germany, India and South Africa. A similar number of trials used parallel (24 trials [53.3%]) and crossover (21 trials [46.7%]) designs. All trials were conducted in an outpatient setting.

Control diets included usual diets (9 trials, 20%), a National Cholesterol Education Program step 1 diet (5 trials, 11.1%), an average American Diet (3 trials, 6.7%), a low fat diet (3 trials, 6.7%), among others. Twenty-seven trials (60%) provided test food supplements, 12 trials (26.7%) provided all study foods under metabolic feeding control conditions, and 4 trials provided dietary advice (8.9%). Five trials (11.1%) used a control diet in which a muffin or pretzel[11 15 20 53] or cheese sticks[19] were exchanged for nuts. The test and control diets were matched for energy in all cases; however 2 of the trials[11 50] featured a negative energy

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balance tree nut diet compared with a matched negative energy balance control diet. Tree nut types included almonds (13 trials, 28.3%), cashews (2 trials, 4.3%), hazelnuts (3 trials, 6.5%), macadamia nuts (3 trials, 6.5%), pecans (2 trials, 4.3%), pistachios (8 trials, 17.4%), walnuts (13 trials, 28.3%), and mixed nuts (2 trials, 4.3%). We were unable to find studies on Brazil nuts or pine nuts. Median nut dose intake was 49.3 g/day (IQR: 42 to 70.5 g/day). Median follow-up was 8 weeks (IQR: 4 to 12 weeks).

Macronutrient profiles varied across studies and between treatment and control groups, median values reported for carbohydrate intake were 48% (IQR: of 44 to 51%) for the treatment group and 50.5% (IQR: 46 to 57%) for the control group. Median values for fat intake were 35% (IQR: 31 to 39%) and 30% (IQR: 27.3 to 34%) for tree nut and control group respectively. Median values for protein intake were 16% (IQR: 15 to 17%) and 17% (IQR: 15 to 18.8%) for tree nut and control group correspondingly.

Appendix Table 2 and Appendix Figure 1 present the assessment and summary of the risk of bias by using The Heyland MQS and The Cochrane Risk of Bias Tool. The Heyland MQS ranged from 3 to 9. Thirty-two trials (74.4%) were considered to be low quality (MQS < 8) and 11 trials (25.6%) high quality (MQS ≥ 8). The main contributors of low scores were absence of double-blinding, loss of participants to follow up, and poor description of crossovers in the control group. The Cochrane Risk of Bias Tool showed that 34 trials (70.8%) were unclear risk and 14 trials (29.2%) were low risk for random sequence generation; 29 trials (60.4%) were unclear risk and 19 trials (39.6%) were low risk for allocation concealment; 26 trials (54.2%) were unclear risk and 22 trials (45.8%) were low risk for blinding of participants and personnel; 5 trials (10.4%) were unclear risk, 35 trials (72.9%) were low risk, and 8 trials (16.7%) were high risk for incomplete outcome data; and 28 trials (58.3%) were unclear risk, 19 trials (39.6%) were low risk, and 1 trial (2.1%) was high risk for selective reporting.

Most of the trials reported research funding from an agency 28/45 (62.2%), while others were funded from a combination of agency and industry 5/45 (11.1%) or industry

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alone 6/45 (13.3%). One trial (2.2%) reported no funding. Five trials[18 38 45 52 53] did not report their funding source (11.1%).

Waist Circumference

Appendix Figure 2 presents data on the effect of tree nuts on waist circumference**.** Tree nuts did not significantly decrease waist circumference (MD = -0.62 cm [95% CI, -1.54, 0.30 cm]) in the overall analyses with evidence of substantial heterogeneity (I^2 = 67%, P < 0.001). Stratification by health status failed to demonstrate a significant effect for any of the sub samples. Sensitivity analyses did not alter the results (data not shown).

Appendix Table 3-A and Appendix Figure 3 present the *a priori* continuous and categorical subgroup analyses, respectively, for waist circumference. There was evidence of statistically significant effect modification by the difference in carbohydrate intake in the continuous subgroup analyses (P < 0.05) between tree nut and control interventions. Trials with lower carbohydrate intakes in the tree nut intervention arms showed larger reductions in waist circumference. No other subgroup analyses were statistically significant.

Triglycerides

Figure 2 presents data on the effect of tree nuts on triglycerides. Tree nuts showed a significant triglyceride-lowering effect (MD = -0.06 mmol/L, [95% CI, -0.09, -0.03 mmol/L]) in the overall analysis with evidence of moderate heterogeneity (I^2 = 34%, P = 0.02). The same effect was seen with evidence of moderate heterogeneity (I^2 = 42%, P = 0.05) in the subsample of participants who were otherwise healthy (MD = -0.07 mmol/L [95% CI, -0.11, -0.04 mmol/L]). Although the reductions were not statistically significant in people with dyslipidemia MetS criteria or diabetes, they did not significantly differ from the reductions in participants who were otherwise healthy. Sensitivity analyses did not alter the results (data not shown).

Appendix Table 3-B and Appendix Figure 4 present data from the *a priori* continuous and categorical subgroup analyses, respectively, for triglycerides. There was

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significant effect modification by nut type in categorical analyses ($P < 0.05$). Pairwise comparisons showed that pecan, walnut, and pistachio interventions all significantly decreased triglycerides more than almond interventions ($P < 0.05$) and almond, macadamia, pecan, pistachio and walnut more than hazelnut ($P < 0.05$). No other subgroup analyses were statistically significant.

HDL-C

Appendix Figure 5 presents the effect of tree nuts on HDL-C**.** Tree nuts did not significantly affect HDL-C (MD = 0.00 mmol/L [95% CI, -0.01, 0.01 mmol/L]) in the overall analysis with evidence of considerable heterogeneity ($I^2 = 86\%$, $P < 0.001$). Stratification by health status failed to demonstrate a significant effect for any of the subsamples. Sensitivity analyses did not alter the results (data not shown).

Appendix Table 3-C and Appendix Figure 6 present the a priori continuous and categorical subgroup analyses, respectively, for HDL-C. None of the subgroup analyses were significant.

Blood Pressure

Appendix Figures 7-A and 7-B present the effect of tree nuts on systolic and diastolic blood pressure, respectively. Tree nuts did not significantly increase either systolic (MD = 0.07 mmHg [95% CI, -1.54, 1.69 mmHg]) or diastolic blood pressure (MD = 0.23 mmHg [95% CI, -0.38, 0.83 mmHg]) in the overall analysis with evidence of substantial heterogeneity in the systolic blood pressure analysis ($I^2 = 64\%$, $P < 0.001$) and evidence of moderate heterogeneity in the diastolic blood pressure analysis ($I^2 = 34\%$, $P = 0.07$). Stratification by health status failed to demonstrate an effect for any of the subsamples. Sensitivity analyses did not alter the results (data not shown).

Appendix Tables 3-D and 3-E present the *a priori* continuous subgroup analyses and **Appendix Figures 8-A and 8-B** present the *a priori* categorical subgroup analyses for systolic and diastolic blood pressure, respectively. There was evidence of statistically

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significant effect modification by difference in fibre intake and by the difference in carbohydrate intake in the continuous subgroup analyses, both for systolic blood pressure ($P < 0.05$ and $P < 0.01$ respectively) between tree nut and control interventions. Trials with higher fibre intakes in the tree nut intervention arms showed larger reductions in systolic blood pressure. Trials in which tree nuts displaced more carbohydrates or contained lower levels of SFA intake leading to larger differences between the tree nut and control interventions were more likely to favour the Tree nut diet in systolic blood pressure. Tree nut intervention arms with higher fibre intake showed reductions in diastolic blood pressure and also explained the heterogeneity in the overall analyses reducing the residual-I^2 to 1.6%. No other subgroup analyses were statistically significant for either systolic or diastolic blood pressure.

Fasting Blood Glucose

Figure 3 presents the effect of tree nuts on fasting blood glucose. Tree nuts showed a significant fasting blood glucose-lowering effect (MD = -0.08 mmol/L [95% CI, -0.16, -0.01 mmol/L]) in the overall analysis, with evidence of moderate heterogeneity (I^2 = 41%, P < 0.05). Stratification by health status failed to demonstrate an effect for any of the subsamples. Sensitivity analyses did not alter the results (data not shown).

Appendix Table 3-F and Appendix Figure 9 present *a priori* continuous and categorical subgroup analyses, respectively, for fasting blood glucose. None of the subgroup analyses were significant.

Publication Bias

Appendix Figure 10 presents the funnel plots for publication bias for each endpoint. Visual inspection of the funnel plots revealed some evidence of asymmetry in several of the endpoints. There was a small trial with larger effect estimate favoring tree nuts than control for waist circumference, which argues that the “small-study” effect was actually not a source of potential bias (i.e. smaller studies that favoured control were published). On the other

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hand, there were more small trials with larger effect estimates favouring control than tree nuts for triglycerides. Egger's test confirmed these small study effects for triglycerides ($P < 0.05$). No other evidence of small study effects was detected by Egger's test and Begg's tests.

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis to look at the effect of tree nuts on MetS criteria. Our systematic review and meta-analysis included 47 randomized trials in 2,211 participants who were otherwise healthy or had MetS criteria, dyslipidemia, or type 2 diabetes. Tree nut consumption at a median dose of ~50 g/day was found to decrease triglycerides significantly by ~0.06 mmol/L, and to decrease fasting blood glucose significantly by ~0.08 mmol/L over a median follow-up of 8-weeks. No adverse effects were seen on waist circumference, HDL-C, or blood, suggesting an overall net metabolic benefit of tree nuts.

Results in relation to other studies

Our findings of a reduction in triglycerides without the expected reciprocal increase in HDL-C are in accordance with previous evidence. Although Sabate et al[64] did not show a triglyceride lowering effect of nut interventions (nonspecific to tree nuts) in overall pooled analyses in an patient-level meta-analysis of controlled feeding trials, he did show that nut interventions lowered triglycerides when analyses were restricted to a subsample of participants with baseline triglycerides ≥ 1.7mmol/L, without an increase in HDL-C. A triglyceride benefit has also been seen in individual trials and meta-analyses of trials investigating the effect of a Mediterranean dietary pattern containing tree nuts in people with diabetes.[65 66] This triglyceride-lowering effect, however, was accompanied by an HDL-C increasing effect.[65 66] Our findings add to these data by showing a similar triglyceride-lowering effect, especially for walnuts, pistachios, macadamia and pecans, in the absence of an HDL-C increasing effect, across all subsamples of participants, without differences in

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triglycerides by baseline levels. The lipid benefits of tree nuts can be attributed to numerous cardioprotective nutrients such as unsaturated fatty acids, plant protein, fibre and phytochemicals.[67] The fibre content and high unsaturated fat content with its ability to displace high glycemic index carbohydrate from the diet and so effect a lower glycemic load diet are likely the main factors in lowering triglycerides.[20]

Our results of a reduction in fasting blood glucose are in accordance with an evidence-based review for the 2013 CDA guidelines that found evidence to support small improvements in overall glycemic control in people with diabetes.[23] Individual trials have shown evidence of improvements in other aspects of glycemic control.[19-22] A fasting blood glucose-decreasing effect has also been seen in long-term glycemic control as assessed by HbA1c for tree nuts as part of Mediterranean[65 66 68] and DASH[69] dietary patterns in people with diabetes.[70] The ability of tree nuts to decrease fasting blood glucose in our analyses may relate to the proposed displacement mechanism by which tree nuts reduce the glycemic load of the diet, as this mechanism would be expected to improve long-term glycemic control through a reduction in postprandial glycaemia,[71] and possibly decrease insulin resistance,[48] neither of which were assessed in our review.

The lack of effect we observed on waist circumference reinforces the view that tree nuts do not have an adverse effect on body weight. Dietary guidelines have raised concerns about the potential of tree nuts to contribute to weight gain,[2] owing to their high energy density; however prospective cohort studies and randomized trials have shown the opposite. A pooled analysis of Harvard cohorts showed an increase in one serving per day of nuts was associated with significant weight loss.[72] Controlled trials of tree nuts alone or as part of Mediterranean,[65 66 68] Portfolio,[73] or DASH[69] dietary patterns have shown neutral or weight loss effects, and no influence on body fat mass or body fat percentage.[74] Dietary patterns that incorporated nuts have reported weight loss under isocaloric conditions or no weight gain under hypercaloric feeding conditions,[75] perhaps because of the metabolically-available energy from nuts is less than the calculated value, as incomplete digestion of nuts leading to energy excretion in the feces.[76] Our findings further suggest that tree nuts do not have a

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significant effect on the most metabolically adverse weight gain involving an increase in waist circumference. We observed a tendency for a reduction in waist circumference, especially where nuts displaced high glycemic index carbohydrate to effect a lower-glycemic load diet (as opposed to where tree nuts were used to displace saturated fat). These data suggest that the inclusion of a greater number of long-term trials in which tree nuts are used to displace high-glycemic index carbohydrate to effect a low-glycemic load diet may yet demonstrate a waist circumference benefit in future meta-analyses.

We were surprised not to see an improvement in blood pressure. Individual trials have shown evidence of improvements in blood pressure[5 8] A blood pressure-decreasing effect of tree nuts has also been seen in the context of Portfolio[73] and DASH[69 77 78] dietary patterns across a range of participant types. As elevated blood pressure in the metabolic syndrome often relates to the underlying insulin resistance, the lack of effect on BP may also be explained by a lack of trials using tree nuts to displace high-glycemic index carbohydrate to decrease the low-glycemic load of the diet (trials taking advantage of this mechanism were more likely to show reductions than trials that did not in subgroup analyses). Alternatively, it may be explained by the need for tree nuts to be combined with the other aspects of a DASH dietary pattern, which collectively result in larger amounts of potassium, calcium, magnesium, dietary fibre, and protein.

Limitations

There are some limitations to our work. First, the majority of trials (74.4%) were of low quality (MQS < 8). Factors that contributed the most to low quality scores were incomplete outcome data and poor reporting. However, in our *a priori* subgroup analyses there was no effect modification by study quality. Second, the risk of bias remains uncertain for most of the available trials owing to poor reporting. This point is particularly concerning given that the majority of the trials were conducted after the Consolidated Standards of Reporting Trials (CONSORT) guidelines were first reported in 1993 and published in 1996.[79] Third, the majority of the available trials were < 3 months, which is perhaps, too short a time

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to observe an effect for some outcomes (waist circumference, blood pressure). This also made it difficult to assess the sustainability of the observed effects over the long term. We did not, however, observe significant effect modification by follow-up in categorical or continuous subgroup analyses for any of the endpoints. Finally, our analyses were complicated by significant unexplained heterogeneity for waist circumference and HDL-C, , which we attempted to accommodate using of random effects models, remains a source of uncertainty in the summary effect estimates for these endpoints.

Practical Implications

Tree nuts are a high-energy food that contain cardioprotective nutrients.[67] Even though the median fat intake (33.6%) of the tree nut containing diets was above that of the control (30.5%), but both within the recommended (20-35%) by dietary guidelines,[23] a beneficial effect was seen only in the tree nut containing diets. The median dose of ~50 g/day tree nuts can be easily integrated as a snack, into a dietary pattern or as a substitution for animal fats or carbohydrates. No increase in side effects compared with control diets were reported in any of the trials, suggesting diets which emphasize tree nuts are as safe as conventional diets (except in individuals with tree nut allergies).

Conclusion

In conclusion, our pooled analyses indicate that daily tree nut consumption has an overall metabolic benefit, through modest decreases in triglycerides and fasting blood glucose while preserving waist circumference, HDL-C, and blood pressure in people who are otherwise healthy or have dyslipidemia, MetS criteria, or type 2 diabetes. These data support recommendations to consume tree nuts alone or as part of heart healthy dietary patterns such as the Mediterranean, Portfolio, Vegetarian, and DASH dietary patterns as a means for improving metabolic control.[69 80-83] Careful interpretation of the results is advised, as our conclusions are limited by the short duration and poor quality of the majority of trials, as well as the presence of significant unexplained heterogeneity in our analyses. These limitations

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highlight the need for larger, longer, high quality trials. Trials in which tree nuts are used to displace high-glycemic index carbohydrate to decrease the glycemic load of the diet will be especially relevant to understand the role of tree nuts in reducing cardiometabolic risk associated with the metabolic syndrome.

Contributions

Conception and design: S Blanco Mejia, CWC Kendall, LS Augustin, JL Sievenpiper.

Analysis or interpretation of the data: S Blanco Mejia, CWC Kendall, E Viguiliouk, LS Augustin, V Ha, A Cozma, A Mirrahimi, A Maroleanu, L Chiavaroli, LA Leiter, RJ de Souza, DJA Jenkins, JL Sievenpiper.

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Administrative, technical, or logistic support: CWC Kendall, E Viguiliouk, LS Augustin, V Ha, A Cozma, A Mirrahimi, A Maroleanu, L Chiavaroli.

Collection and assembly of data: S Blanco Mejia, E Viguiliouk, LS Augustin, V Ha, A Cozma, A Maroleanu.

Guarantors: CWC Kendall and JL Sievenpiper.

Transparency declaration

The manuscript's guarantors affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have

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been omitted; and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Ethical Approval

Not required.

Potential Conflicts of Interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: **SBM, LSA, AM, AIC, EV, AM and LAL declare** no conflicts of interest related to this paper. **CWCK** has received research support from the Advanced Foods and Material Network, Agrifoods and Agriculture Canada, the Almond Board of California, the American Pistachio Growers, Barilla, the California Strawberry Commission, the Calorie Control Council, CIHR, the Canola Council of Canada, the Coca-Cola Company (investigator initiated, unrestricted grant), Hain Celestial, the International Tree Nut Council Nutrition Research and Education Foundation, Kellogg, Kraft, Loblaw Companies Ltd., Orafti, Pulse Canada, Saskatchewan Pulse Growers, Solae and Unilever. He has received travel funding, consultant fees and/or honoraria from Abbott Laboratories, the Almond Board of California, the American Peanut Council, the American Pistachio Growers, Barilla, Bayer, the Canola Council of Canada, the Coca-Cola Company, Danone, General Mills, the International Tree Nut Council Nutrition Research and Education Foundation, Kellogg, Loblaw Companies Ltd., the Nutrition Foundation of Italy, Oldways Preservation Trust, Orafti, Paramount Farms, the Peanut Institute, PepsiCo, Pulse Canada, Sabra Dipping Co., Saskatchewan Pulse Growers, Solae, Sun-Maid, Tate and Lyle, and Unilever. He is on the Dietary Guidelines Committee for the Diabetes Nutrition Study Group of the European Association for the Study of Diabetes and has served on the scientific advisory board for the Almond Board of California, the International Tree Nut Council, Oldways Preservation Trust, Paramount Farms and Pulse Canada. **VH** has received research support from the CIHR and the World Health Organization (WHO) for work on a systematic review and meta-analysis commissioned by WHO of the relation of saturated fatty acids with health outcomes. She received a travel award to attend a science day hosted by PepsiCo Inc. and the New York Academy of

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Sciences. **LC** has received research support from the CIHR and the Agricultural Bioproducts Innovation Program through the Pulse Research Network (PURENet), and Saskatchewan Pulse Growers. She is also a casual clinical research coordinator at Glycemic Index Laboratories. **RJdS** is funded by a CIHR Postdoctoral Fellowship Award and has received research support from the CIHR, the Calorie Control Council, the Canadian Foundation for Dietetic Research and the Coca-Cola Company (investigator initiated, unrestricted grant). He has served as an external resource person to WHO's Nutrition Guidelines Advisory Group and received travel support from WHO to attend group meetings. He is the lead author of 2 systematic reviews and meta-analyses commissioned by WHO of the relation of saturated fatty acids and trans fatty acids with health outcomes. **DJAJ** has received research grants from Saskatchewan Pulse Growers, the Agricultural Bioproducts Innovation Program through the Pulse Research Network, the Advanced Foods and Material Network, Loblaw Companies Ltd., Unilever, Barilla, the Almond Board of California, the Coca-Cola Company (investigator initiated, unrestricted grant), Solae, Haine Celestial, the Sanitarium Company, Orafti, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, the Canola and Flax Councils of Canada, the Calorie Control Council, the CIHR, the Canada Foundation for Innovation and the Ontario Research Fund. He has been on the speaker's panel, served on the scientific advisory board, and/or received travel support and/or honoraria from the Almond Board of California, Canadian Agriculture Policy Institute, Loblaw Companies Ltd, the Griffin Hospital (for the development of the NuVal scoring system), the Coca-Cola Company, Saskatchewan Pulse Growers, Sanitarium Company, Orafti, the Almond Board of California, the American Peanut Council, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, Herbalife International, Pacific Health Laboratories, Nutritional Fundamental for Health, Barilla, Metagenics, Bayer Consumer Care, Unilever Canada and Netherlands, Solae, Kellogg, Quaker Oats, Procter & Gamble, the Coca-Cola Company, the Griffin Hospital, Abbott Laboratories, the Canola Council of Canada, Dean Foods, the California Strawberry Commission, Haine Celestial, PepsiCo, the Alpro Foundation, Pioneer Hi- Bred

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Nutrition Therapy of both the Canadian Diabetes Association and the European Association for the Study of Diabetes, and he is on the American Society for Nutrition writing panel for a scientific statement on the metabolic and nutritional effects of fructose, sucrose and high-fructose corn syrup. He is a member of the Carbohydrate Quality Consortium and an unpaid scientific advisor for the Food, Nutrition and Safety Program of the International Life Science Institute North America. His wife is an employee of Unilever Canada.

Data Sharing

No additional data available.

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Table 1. Characteristics of RCTs Investigating the effect of Tree Nuts on Criteria of the MetS

MetS: metabolic syndrome; DM2: type 2 diabetes mellitus; OW: overweight; HLP: hyperlipidemic; NL-HLP: normal to mildly hyperlipidemic; HC: Hypercholesterolemic; NL-HC: normal to hypercholesterolemic; M: men; W: women; BMI: body mass index; OP: out-patient; IP: In-patient; USA: United States of America; SUPP: supplement; Met: metabolic; DA: dietary advice; N/A: not available; AHA: American Heart Association; AAD: Average American Diet; NCEP: National Cholesterol Education Program; CHO-LCD: Self-selected Complex Carbohydrate diet; WKS: weeks; MQS: Heyland Methodological Quality Score.

* Companion reports: Jenkins et al, 2008 for Jenkins et al, 2002; Schutte et al, 2006 for Mukuddem-Petersen et al, 2007; West et al, 2012 and Holligan et al, 2013 for Gebauer et al, 2008.

† Baseline characteristics were given based on the number of randomized participants for Li et al, 2010 *n* = 70; Ma et al, 2010 *n* = 24; Zambon et al, 2000 *n* = 55; Katz et al, 2012 *n* = 46; Sauder et al, 2013 *n* = 30; Gulati et al, 2014 *n* = 68 for recruited subjects for Tapsell et al. 2009 (*n* = 50), and for age for Darvish Damavandi et al, 2013 (*n* = 50).

‡ Mean age was given separately for men and women.

§ Body weight is reported in kg and BMI is reported in kg/m^2. BMI is reported only when no data on weight were available.

‖ Nut dose is given based on g/day, 1oz = 28 g.

¶ Median was taken from a range given. Iwamoto et al, 2010 range 50-54 g/day; Jenkins et al, 2011 range 50-75 g/day; Lovejoy et al, 2002 range 57-113 g/day; Mukuddem-Petersen et al, 2007 range 63-108 g/day; Torabian et al, 2010 range 28-64 g/day; Zambon et al, 2000 range 41-56 g/day.

** Based on 2100 kcal for Griel et al, 2008 and based on 1400 kcal (~60 kg) for Gulati et al, 2014.

†† Energy from carbohydrate:fat:protein.

‡‡ Values for carbohydrates are given in geometric means.

§§ Trials with scores ≥8 were considered to be of high quality.

‖‖ Agency funding is that from government, university, or not-for-profit health agency sources.

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FIGURE LEGENDS

Figure 1. Summary of evidence search and selection

Figure 2. Forest plot of the RCTs investigating the effect of Tree Nuts on Triglycerides. Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia, metabolic syndrome criteria, diabetes and their combination (total). Paired analyses were applied to all crossover trials (20) and one substudy. Data are expressed as mean differences (MD) with 95% CI, using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using the Cochrane's Q statistic (I^2) at a significance level of $P < 0.10$ and quantified by I^2, levels ≤ 50% represent moderate heterogeneity, ≥ 50 % represent substantial heterogeneity and ≥ 75%, considerable heterogeneity. TG = Triglycerides, mmol/L = mill moles per liter, A = Almond, AC = Almond + Chocolate, HF = High Fat, LF = Low Fat.

Figure 3. Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia, metabolic syndrome criteria, diabetes and their combination (total). Paired analyses were applied to all crossover trials (10) and one substudy. Data are expressed as mean differences (MD) with 95% CI, using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using the Cochrane's Q statistic (I^2) at a significance level of $P < 0.10$ and quantified by I^2, levels ≥ 50 % represent substantial heterogeneity and ≥ 75%, considerable heterogeneity. FBG = Fasting Blood Glucose; mmol/L = mill moles per liter; HF = High Fat; LF = Low Fat.

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Table 1.- Characteristics of RCTs Investigating the effect of Tree Nuts on Criteria of the MetS

Study, year (Reference)	Participants	Mean Age (SD or range), y	Mean Body Weight or BMI (SD or range)§	Setting	Design	Feeding Control	Nut type	Nuts Dose (g/day)‖
Sabate et al, 1993 (30)								
Walnut	18 (18 M)	30	73	OP, USA	Crossover	Met	Walnut	84
Control								
Chisholm et al, 1998 (13)								
Walnut	16 HLP	45 (6.8)	28.4 (4.3)	OP, New Zealand	Crossover	DA	Walnut	78
Control								
Spiller et al, 1998 (31)								
Almond	30 HLP	53 (10)	66 (13)	OP, Italy	Parallel	Supp	Almond	100
Control								
Curb et al, 2000 (10)								
Macadamia	30 (15 M, 15 W)	35.25 (18-53)	23 (19.1 - 28.3)	OP, USA	Crossover	Met	Macadamia	46
Control								
Control								
Morgan et al, 2000 (32)								
Pecan	19 (4 M, 15 W)	37 (12)	24 (5)	OP, USA	Parallel	Supp	Pecan	68
Control		45(10)	24 (4)					
Zambon et al, 2000 (33)								
Walnut	49 HC (26 M, 23 W)	56 (11)	70.6 (12.1)	OP, Spain	Crossover	Supp	Walnut	48.5
Control								
Rajaram et al, 2001 (14)								
Pecan	23 (14 M, 9 W)	25-55	74.4 (16.7)	OP, USA	Crossover	Met	Pecan	72
Control								
Iwamoto et al, 2002 (34)								
Walnut	40 (20 M, 20 W)	23.8 (3.1)‡	22.2 (0.5)	OP, Japan	Crossover	Met	Walnut	52¶
Control		23.6 (4.6)‡	20.7 (0.5)					
Jenkins et al, 2002 (15)								
Almond	27 HLP (15 M, 12 W)	64 (9)	71.2 (2.5)	OP, Canada	Crossover	Supp	Almond	73
Control			71.0 (2.4)					

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Lovejoy et al, 2002 (35)								
High Fat Almond	30 DM2 (13 M, 17 W)	53.8 (10.4)	33.0 (5.5)	OP, USA	Crossover	Met	Almond	85¶
Low Fat Almond							Almond	
High Fat Control								
Low Fat Control								
Sabate et al, 2003 (36)								
High-Almond	25 NL-HC (14 M, 11 W)	41 (13)	N/A	OP, USA	Crossover	Met	Almond	83
Low-Almond							Almond	42
Control								
Wien et al, 2003 (8)								
Almond	65 OW/DM2 (28 M, 37 W)	53 (2)	113 (5)	OP, USA	Parallel	Supp	Almond	84
Control		57 (2)	114 (5)					
Tapsell et al, 2004 (37)								
Walnut	37 DM2	57.7 (9)	87.6 (12.8)	OP, Australia	Parallel	Supp	Walnut	30
Control		59.3 (7.1)	81.9 (11.2)					
Tamizifar et al, 2005 (38)								
Almond	30 HC (17 M, 13 W)	56 (6.1)	63 (8.9)	OP, Iran	Crossover	Supp	Almond	25
Control								
Kocyigit et al, 2006 (16)								
Pistachio	44 (24 M, 20 W)	32.8 (6.7)	24.2 (6.1)	OP, Turkey	Parallel	DA	Pistachio	69
Control			24.6 (5.6)					
Kurlandsky et al, 2006 (39)								
Almond	47 (47 W)	41.8 (11.7)	25.3 (3.5)	OP, USA	Parallel	Supp	Almond	60
Almond + Dark Chocolate		46.2 (7.8)	27.2 (4.2)				Almond	
Dark chocolate		36.5 (11.9)	23.9 (3.3)					
Control		51.3 (6.3)	26.1 (4.1)					
Schutte et al, 2006 (60)*								
Walnut	62 MetS	45.5	35.9	OP, South Africa	Parallel	Met	Walnut	85.5
Cashew		45.7	34.7				Cashew	
Control		44.4	35.5					
Mukuddem-Petersen et al, 2007 (40)								
Walnut	64 MetS	45 (10)	107	OP, South Africa	Parallel	Met	Walnut	85.5¶

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Cashew			99				Cashew	
Control			106					
Sheridan et al, 2007 (17)								
Pistachio	15 HC	60 (11.2)	175 (26)	OP, USA	Crossover	Supp	Pistachio	35
Control								
Gebauer et al, 2008 (41)								
1 Pistachio							Pistachio	37
2 Pistachio	28 HLP (10 M, 18 W)	48 (7.9)	76.6 (13.2)	OP, USA	Crossover	Met	Pistachio	74
Control								
Griel et al, 2008 (42)								
Macadamia	25 HC	50.2 (8.4)	26.3 (3.3)	OP, USA	Crossover	Met	Macadamia	42.5**
Control								
Jenkins et al, 2008 (61)*								
Almond	27 HLP (15 M, 12 W)	64 (9)	71.2 (2.5)	OP, Canada	Crossover	Supp	Almond	73
Control			71.0 (2.4)					
Rajaram et al, 2009 (43)								
Walnut	25 NL-HLP (14 M, 11 W)	23-65	71.9 (15.5)	OP, USA	Crossover	Met	Walnut	42.5
Control			71.7 (15.5)					
Tapsell et al, 2009 (44)								
Walnut	35 DM2†	54 (8.7)	92.3 (15.7)	OP, Australia	Parallel	Supp	Walnut	30
Control			93.4 (3)					
Li et al, 2010 (11)								
Almond	52 OW†	45.4 (2.0)	86 (26.8)	OP, USA	Parallel	Supp	Pistachio	53
Control		47.3 (2.3)	85.5 (40.2)					
Ma et al, 2010 (45)								
Walnut	22 DM2†	58.1 (9.2)	89 (15.5)	OP, USA	Crossover	Supp	Walnut	56
Control								
Torabian et al, 2010 (12)								
Walnut	87 (38 M, 49 W)	54 (10.2)	75.6 (13.2)	OP, USA	Crossover	Supp	Walnut	46
Control								
Wien et al, 2010 (46)								
Almond	65 PD (17 M, 48 W)	53 (9)	82.9 (14.4)	OP, USA	Parallel	Supp	Almond	58
Control		54 (11)	80.5 (14.4)					

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Wu et al, 2010 (47)								
Walnut	189 MetS	48.2 (8.4)	72.2 (11.4)	OP, USA	Parallel	Supp	Walnut	30
Control		48.6 (8)	70.6 (10.9)					
Casas-Agustench et al, 2011 (48)								
Mixed Nuts	50 MetS (28 M, 22 W)	52.9 (8.4)	31.6 (2.8)	OP, Spain	Parallel	Supp	Mixed Nuts	30
Control		50.6 (8.4)	30.0 (3.3)					
Cohen et al, 2011 (19)								
Almond	13 DM2 (7 M, 6 W)	66 (11.9)	96.1 (40.4)	OP, USA	Parallel	Supp	Almond	28
Control			105.1 (32.1)					
Jenkins et al, 2011 (20)								
Mixed Nuts	79 DM2 (52 M, 27 W)	63 (9)	80 (15)	OP, Canada	Parallel	Supp	Mixed nuts	75¶
Control		61 (10)	83 (15)					
Li et al, 2011 (21)								
Almond	20 DM2 (9 M, 11 W)	58 (8.9)	26 (3.1)	OP, Taiwan	Crossover	Met	Almond	56
Control								
Tey et al, 2011 (49)								
Hazelnut	61	38.9 (14.3)	72 (11.1)	OP, New Zealand	Parallel	Supp	Hazelnut	42
Control		36.1 (15.2)	67.3 (9.5)					
Darvish Damavandi et al, 2012 (18)								
Cashew	43 DM2 (9 M, 34 W)	51 (7.9)	72.1 (13.1)	OP, Iran	Parallel	Supp	Cashew	30
Control		56 (5.7)	71.9 (9.7)					
Foster et al, 2012 (50)								
Almond	123 OW (11 M, 112 W)	47 (12)	94 (13.1)	OP, USA	Parallel	Supp	Almond	56
Control		46.7 (13)	91.5 (11.9)					
Katz et al, 2012 (51)								
Walnut	40 OW†	57.4 (11.9)	33.2 (4.4)	OP, USA	Crossover	Supp	Walnut	56
Control								
Wang et al, 2012 (22)								
Pistachios	86 MetS	51.9 (8.8)	28.1 (3.2)	OP, China		Supp	Pistachio	42
High pistachios		51.8 (9.4)	28 (4.5)				Pistachio	70
Control		50.7 (9.9)	28 (4.4)					
West et al, 2012 (62)*								
1 Pistachio	28 HLP (10 M, 18 W)	48 (7.9)	76.6 (13.2)	OP, USA	Crossover	Met	Pistachio	37

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2 Pistachio						Pistachio	74
Control							
Anderson et al, 2013 (52)							
Pistachio	22 OW	55 (2)	90 (3.6)	OP, USA	Parallel	N/A	Pistachio	35.4
Control							
Berryman et al, 2013 (53)							
Almond	53 HC	N/A	N/A	OP, USA	Crossover	N/A	Almond	42.5
Control							
Darvish Damavandi et al, 2013 (54)							
Hazelnut	48 DM2†	55.7 (7.7)	72.1 (10.3)	OP, Iran	Parallel	Supp	Hazelnut	29
Control			72 (9.6)				
Holligan et al, 2013 (63)*							
1 Pistachio							Pistachio	37
2 Pistachio	28 HLP (10 M, 18 W)	48 (7.9)	76.6 (13.2)	OP, USA	Crossover	Met	Pistachio	74
Control							
Sauder et al, 2013 (55)							
Pistachio	30 DM2 (15 M, 15 W)†	56.1 (1.4)	31.2 (1.1)	OP, USA	Crossover	Met	Pistachio	73.4
Control							
Somerset et al, 2013 (9)							
Macadamia	64 OW (10 M, 54 W)	43.7 (8.4)	95 (14.7)	OP, Australia	Parallel	DA	Macadamia	46
Control		43.2 (10.9)	99.6 (15.2)					
Tan et al, 2014 (56)								
Almond (Breakfast)	137 OW (48 M, 89 W)	32.9 (11.5)	80.5 (15)	OP, USA	Parallel	Supp	Almond	43
Almond (Morning snack)		27.8 (10.7)	83.2 (21.1)				Almond	43
Almond (Lunch)		29.3 (13.5)	84.8 (13.7)				Almond	43
Almond (Afternoon snack)		29 (11.9)	81.8 (14.6)				Almond	43
Control		28.7 (9.6)	77.2 (16.8)					
Tey et al, 2013 (57)								
Hazelnut 30 g	107 OW (46 M, 61W)	43.8 (13.5)	86.2 (11.8)	OP, New Zealand	Parallel	Supp	Hazelnut	30
Hazelnut 60 g		42.8 (10.6)	92 (19.6)				Hazelnut	60
Control		41.1 (13.1)	88.7 (16.7)					
Gulati et al, 2014 (58)								
Pistachio	68 MetS (37 M, 31 W)	41.6 (8.4)	81.6 (12.9)	OP, India	Parallel	DA	Pistachio	50**

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Control		43.3 (8.1)	80.3 (10.3)					
Wu et al, 2014 (59)								
Walnut	40 (10 M, 30 W)	60 (1)	24.9 (0.6)	OP, Germany	Crossover	Supp	Walnut	43
Control								

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EFFECT OF TREE NUTS ON METABOLIC SYNDROME CRITERIA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Running Title: Tree Nuts and Metabolic Syndrome

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ABSTRACT

Objective: To provide a broader evidence summary to inform dietary guidelines of the effect of tree nuts on criteria of the metabolic syndrome (MetS).

Design: We conducted a systematic review and meta-analysis of the effect of tree nuts on criteria of the MetS.

Data sources: We searched MEDLINE, EMBASE, CINAHL, and the Cochrane Library (through April 4, 2014).

Eligibility criteria for selecting studies: We included relevant randomized controlled trials (RCTs) of ≥ 3 weeks reporting at least one criterion of the MetS.

Data extraction: Two or more independent reviewers extracted all relevant data. Data were pooled using the generic inverse variance method using random effects models and expressed as mean differences (MD) with 95% confidence intervals (CI). Heterogeneity was assessed by the Cochran Q statistic ~~Chi~~^{2} and quantified by the I^2 statistic. Study quality and risk of bias were~~as~~ assessed.

~~**Background:** Chronic disease guidelines support tree nut consumption alone or as part of the Mediterranean, Dietary Approaches to Stop Hypertension (DASH), or Portfolio dietary patterns to reduce cardiovascular risk, based on their favourable LDL-C lowering effect. The effects of nuts on metabolic risk factors other than LDL-C, however, remain uncertain. We conducted a systematic review and meta-analysis of the effect of tree nuts on criteria metabolic syndrome (MetS) components to provide a broader evidence summary to inform dietary guidelines.~~

~~**Methods**: We searched MEDLINE, EMBASE, CINAHL, and the Cochrane Library (through March 19, 2013April 4, 2014). We included relevant randomized controlled trials (RCTs) of ≥ 3 weeks reporting at least 1 one criterion of metabolic syndromeMetS. Two or more independent reviewers extracted all relevant data. Data were pooled using the generic~~

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~~inverse-variance-method-using-random-effects-models-and-expressed-as-mean-differences (MD) with 95% confidence intervals (CI). Heterogeneity was assessed by Chi^2 and quantified by I^2. Study quality was assessed.~~

Results: Eligibility criteria were met by ~~39RCTsincluding~~149 RCTs including 2,226~~,676~~ participants who were otherwise healthy or had dyslipidemia, ~~metabolic syndrome~~MetS or diabetes mellitus. Tree nut interventions lowered triglycerides ~~and fasting blood glucose compared with control diet interventions~~ (~~triglycerides~~MD = -0.~~07~~ 06 mmol/L [95% CI, ~~-~~ -0.09~~11~~, -0.0~~3~~4 mmol/L]), and fasting blood glucose (MD = -0.08 mmol/L [95% CI, -0.16, -0.01 mmol/L]) compared with control diet interventions~~, but had~~. There was no effect ~~s~~ on waist circumference, HDL-C, or blood pressure~~, or fasting blood glucose~~ with the direction of effect favouring tree nuts for ~~all except HDL C~~waist circumference. There was evidence of significant unexplained heterogeneity in all analyses ($P < 0.05$).

~~**Limitations:** Most of the trials were of short duration (< 12 weeks) and of poor quality (MQS < 8). Substantial unexplained heterogeneity remained in most analyses.~~

Conclusion: Pooled analyses show a MetS ~~net~~ benefit of tree nuts ~~for metabolic syndrome MetS with~~ through modest decreases in triglycerides and fasting blood glucose ~~across nut types and~~ with no adverse effects on other criteria across nut types. As our conclusions are limited by the short duration and poor quality of the majority of trials, as well as significant unexplained between-study heterogeneity, there remains a need for larger, longer, high quality trials.~~Longer and higher quality trials are needed.~~

Protocol Registration: ClinicalTrials.gov identifier, NCT01630980

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Key words: systematic review, meta-analysis, randomized trials, tree nuts, metabolic syndrome.

Strengths and limitations of this study

- This is the first systematic review and meta-analysis to look at the effect of tree nuts on metabolic syndrome criteria.
- This systematic review and meta-analysis involved a large number of trials (36 47 RCTs) in participants with a range of metabolic conditions.
- Most of the trials (69.474.4%) were of low quality (MQS < 8).
- Most of the trials (66.78.8%) were of short duration (< 12 weeks).
- Substantial inter-study heterogeneity remained unexplained.
-

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INTRODUCTION

Dietary patterns including tree nuts have received particular attention for their cardiovascular benefits, and the Food and Drug Administration (FDA) have granted a qualified health claim to tree nuts for cardiovascular risk reduction.[1] General dietary guidelines[2] and heart health guidelines[3 4] also continue to recommend tree nuts alone or as part of the Mediterranean, Portfolio, and Dietary Approaches to Stop Hypertension (DASH) dietary patterns for cardiovascular disease prevention and management.

Although these recommendations are based primarily on the LDL-C lowering benefits of tree nuts[4], the cardiovascular risk reduction seen with tree nuts is beyond that which would be predicted by this effect alone. The Prevención con Dieta Mediterránea (PREDIMED) trial showed that despite a non-significant effect on LDL-C early on in the trial[5] a Mediterranean diet supplemented with mixed nuts (30 g/day) compared with a low-fat control diet reduced major cardiovascular events by 30% in high cardiovascular risk participants.[6] Nut consumption of > 3 servings/week was also associated with other metabolic advantages such as a decreased risk of obesity, MetS, and diabetes.[7] Individual large trials of tree nuts have also shown that nuts improve criteria of the metabolic syndrome: waist circumference,[8 9] triglycerides,[5 10-12] HDL-C,[13-18] blood pressure[5 8] and glycemic control.[19-22]

The overall evidence for these additional metabolic benefits, however, remains uncertain. Guidelines have not recommended tree nuts directly for managing these risk factors. Although the Canadian Diabetes Association 2013 clinical practice guidelines for nutrition therapy[23] did acknowledge some of these metabolic benefits, the evidence was deemed insufficient for making a recommendation. Tree nut consumption was recommended only in so far as part of Mediterranean or DASH dietary patterns.[23] To synthesize the evidence on which recommendations are based for the metabolic benefits of tree nuts beyond LDL-C lowering, we conducted a systematic review and meta-analysis of randomized controlled dietary trials of the effect of tree nuts on criteria of the metabolic syndrome.

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METHODS

Protocol and Registration

We followed the guidelines of the Cochrane Handbook for Systematic Reviews of Intervention for the planning and conduct of this meta-analysis.[24] Reporting of results followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[25] The review protocol is available at ClinicalTrials.gov (registration number: NCT01630980).

Study Selection

We searched MEDLINE, EMBASE, CINAHL, and the Cochrane Library (through ~~March 19, 2013~~April 4, 2014) to identify randomized controlled dietary trials of tree nuts. Details of the search strategy are presented in **Appendix Table 1**. The electronic database searches were supplemented by manual searches of the reference list of included trials and reviews. No language restriction was used.

We included randomized dietary trials that reported the effect of diets rich in tree nuts (almonds, Brazil nuts, cashews, hazelnuts, macadamia nuts, pecans, pine nuts, pistachios, walnuts and mixed nuts)[1] as a whole compared to diets without tree nuts, but matched for energy, on at least ~~1~~ one of the five~~5~~ criteria of the MetS: waist circumference, triglycerides, high-density lipoprotein cholesterol (HDL-C), blood pressure and fasting blood glucose. Included trials were ≥ 3 weeks duration, a duration that satisfies the minimum follow-up requirement for lipid-lowering health claims by the FDA used in the scientific evaluation of lipid-lowering health claims.[26] We excluded trials that incorporated tree nuts as paste, oil or skin nuts into the treatment diets and also those trials that added tree nuts as part of a dietary pattern and did not have a matched control group. The former exclusion was intended to eliminate contamination from the other nutritional aspects, and to isolate the effect of tree nuts. Where multiple intervention or control groups were presented, we only included those groups which allowed us to isolate the effect of tree nuts. When multiple

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publications existed for the same trial, data from the most recent report were included. Publications including additional relevant data were used as companion reports. The MetS endpoints were selected according to the 2009 harmonized definition for MetS.[27]

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Data Extraction

Studies that met the inclusion criteria were extracted in full by ~~2independent~~ two independent reviewers (SBM and one of EV, LSA, VH or AM) for study characteristics and data for endpoints. Study characteristics included: study design (crossover or parallel), participant characteristics, comparator, nut dose, nut type, duration of follow-up, dietary adherence measures, macronutrient profile, statistical analysis and funding sources. All disagreements amongst reviewers were resolved by consensus.

The Heyland Methological Quality Score (MQS) was used for assessment of study quality.[28] Scores from 0-2 points were given for each of the following evaluated criteria: methods (randomization, blinding and analysis), sample (selection, compatibility and follow-up), and intervention (protocol, co-intervention and crossovers). This scale gave a maximum MQS of 13 points. Studies with a score of ≥ 8 were considered of high quality.

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The Cochrane Collaboration Risk of Bias Tool was used to assess the study risk of bias.[24] Trials were classified as "unclear risk of bias" when insufficient information was provided to permit judgment, "high risk of bias" when the methodological flaw was likely to have affected the true outcome and "low risk of bias" when a methodological flaw was deemed inconsequential to determine the true effect within a study. As blinding of participants in dietary trials is difficult to achieve, we scored the trials based on the intensity of the dietary advice given to the randomized groups. If treatment intensity was judged to be more intensive in one intervention over another, then trials were classified as "high risk". If both interventions were emphasized equally, then trials were classified as "low risk of bias". Trials reported in ~~an~~ abstract format only ~~were~~ not included ~~for reporting~~in assessments of ~~study quality scores due~~MQS or of bias owing to a lack of ~~data~~information."~~.~~

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Means (SD) for baseline values, end values, change-from baseline differences, end-differences, and mean differences were recorded for primary endpoints (waist circumference, triglycerides, HDL-C, blood pressure and fasting blood glucose). Reported *t*-values or *F*-statistics, and ~~*p*~~*P*-values for differences were also recorded. Missing information for any endpoint data or study details were requested directly from authors. Where SDs were not reported or given directly by authors, we attempted to calculate these missing SDs from the available statistics using methods recommended by the Cochrane Collaboration.[24] If this was not possible, then we imputed these missing SDs using a pooled correlation coefficient derived from a meta-analysis of correlation coefficients from those trials reporting sufficient data.[24] These correlation coefficients were then transformed into *z*-scores ~~t~~ and meta-analyzed using inverse-variance weighing. The pooled effect estimate from the *z*-scores was then back transformed to impute the missing SDs. We used a derived pooled correlation coefficient of 0.~~664~~ 635 for triglycerides, 0.~~903~~ 856 for HDL-C, 0.~~282~~ 32~~7~~19 for systolic blood pressure, 0.~~604~~ 508 for diastolic blood pressure and 0.~~658~~ 446 for fasting blood glucose. ~~Sensitivity analyses were undertaken with correlation values of 0.25, 0.50 and 0.75 to determine whether the overall result of the analyses is robust to the use of a derived pooled correlation coefficient.~~

Statistical Analyses

Data were analyzed using Review Manager (RevMan) 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) for primary analyses and Stata (version 12, College Station, USA) for subgroup analyses. Pooled analyses were conducted using the Generic Inverse Variance method with random effects models. Data were expressed as mean differences (MD) with 95% CI and considered significant at $P <$ 0.05. Paired analyses were applied to all crossover trials.[29] In cases where there were multiple intervention or control groups, we combined either intervention or control groups to create single pairwise comparisons with the aim of diminishing the unit-of-analysis error.[24]

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The presence of between-studies-heterogeneity was assessed ~~(~~by the Cochran Q ~~-~~ statistic ~~(; significant~~ significance set at P < 0.10) and quantified by the ~~quantified (~~I^2 statistic~~)~~. An I^2 ≤ 50% ~~even though~~ indicated "moderate" heterogeneity~~, but it might not be important,~~ ≥ 50% indicated "substantial" heterogeneity and ≥ 75% indicated "considerable" heterogeneity.[24] Analyses were stratified by participant health status: otherwise healthy, dyslipidemia, MetS criteria and type 2 diabetes based on trial entry criteria. Sources of heterogeneity were explored using sensitivity ~~analyses~~ and ~~*a priori*~~ subgroup analyses. To determine if any single trial exerted an undue influence on the overall results, sensitivity analyses were preformed, in which each individual trial was removed from the meta-analysis, and the effect size re-calculated with the remaining trials. Sensitivity analyses were also undertaken using ~~different~~ correlation coefficients of 0.25, 0.50 and 0.75 to determine whether the overall results were robust to the use of different derived ~~pooled~~ correlation coefficients in paired analyses of crossover trials. ~~for~~ A priori subgroup analyses were done for baseline values (according to MetS diagnostic criteria)[27]~~,~~ absolute fibre~~r~~ intake (treatment diet < 25 g/day vs. ≥ 25 g/day[23] and change in [within and between the diets]), absolute saturated fatty acid (SFA) intake (treatment diet < 7% vs. ≥ 7% of total energy[23] and change in [within and between the diets]), tree nut dose (< 50 g/day vs. ≥ 50 g/day), tree nut type (almonds, Brazil nuts, cashews, hazelnuts, macadamia nuts, pecans, pine nuts, pistachios, walnuts and mixed nuts),duration of follow-up (< 3~~<~~ months vs. ≥ 3 months), study design (crossover vs. parallel), and study quality (MQS < 8 vs. ≥ 8). *Post-hoc* subgroup analyses were conducted for the difference in percent carbohydrate intake between the control and intervention arm (carbohydrate displacement). The significance of between-subgroup differences were assessed using meta-regression (P < 0.05). ~~To determine if any single trial exerted an undue influence on the overall results, sensitivity analyses were preformed, in which each individual trial was removed from the meta-analysis, and the effect size re-calculated with the remaining trials.~~ Publication bias was assessed by visual inspection of funnel plots and formally complemented by Begg's and Egger's tests.

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RESULTS

Trial Selection

Figure 1 shows flow of studies through the search and selection process. We identified a total of 2,~~190~~531 reports, from which ~~701~~752 reports were duplicates and 1,~~367~~631 reports were deemed irrelevant (determined by review of title and abstract). The remaining ~~120~~ 146 reports were reviewed in full, of which ~~81~~97 reports were excluded for not meeting inclusion criteria. A total of ~~39~~ 49 reports on ~~38~~47 trials[8-23 30-59] as well as ~~3~~ four companion reports[60-63] that addressed at least one criterion of the metabolic syndrome (waist circumference ~~([1~~25 trials, *n* = ~~1050~~813~~]~~), triglycerides [~~(44~~37 trials, *n* = 1,~~515~~690~~]~~), HDL-C [~~(45~~36 trials, *n* = ~~1,607~~2,142~~)~~], blood pressure [~~(20~~16 trials, *n* = 1,267~~955)~~], and fasting blood glucose ~~([18~~26 trials, *n* = ~~957~~1,360~~)~~] were included).

Trial Characteristics

Table 1 presents characteristics of the included trials. There were ~~38~~ 47 trials involving ~~38~~ 49 comparisons ~~in1706~~ in 2,211 participants. ~~Eleven~~ Twelve trials (~~30.6~~26.7%)[10 12 14 16 30 32 34 39 43 49 59] were conducted in~~reported~~ otherwise healthy participants. Two of these trials contained a minority of participants with dyslipidemia who had been classified as otherwise healthy.[36 43] ~~Nine~~ Eleven trials (~~25~~24.4%)[8 18-21 35 37 44 45 54 55] were conducted in participants with type 2 diabetes or a mix of patients with overweight and type 2 diabetes in one case[8]. The remaining trials were conducted in people with dyslipidemia (~~8~~ 9 trials [2~~2.2~~0%][13 15 17 31 33 38 41 42 53]), MetS [5 trials[22 40 47 48 58]], ~~or with criteria of~~ some MetS criteria (~~8~~ 13 trials [~~22.2~~28.9%]: overweight ~~3~~ 7 trials[9 11 50-52 56 57], ~~full MetS [4 5 trials[22, 42, 49, 50, 60]], and~~ or prediabetes [1 trial[46]]). Median age for participants was 50.2 years (IQR: 42.5~~3.7~~ to 55.~~5~~8 years). Median body weight for participants was 81.~~47~~ kg (IQR: 72.1 to 91.7~~5.3~~ kg).

~~Most t~~Trials tended to be of considerable size, with a ~~small (~~median number of ~~participants~~40 participants , ~~??~~ [~~(~~IQR: , 25 to 61~~??~~participants) ~~to ??]~~)(192~~4 [52.83.3%]) were~~ . The majority were conducted in the United States of America (24 trials [53.3%]). ~~The~~ with

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the rest ~~were~~ conducted in various other countries: 3 trials (~~8.3~~6.7%) each in Australia, New Zealand, and Iran; 2 trials (~~5~~4.4.~~6~~%) each in Canada, and Spain~~, Iran, and New Zealand~~; and 1 trial (2.2~~8~~%) each in Japan, Turkey, Italy, China, Taiwan, Germany, India and South Africa. A similar number of trials used parallel (~~19~~24 trials [53.3~~2.8~~%]) and crossover (~~17~~ 21 trials [46.7~~7.2~~%]) designs. All trials were conducted in an outpatient setting.

Control diets included usual diets~~,~~ (9~~8~~ trials, 2~~2.2~~0%), a National Cholesterol Education Program ~~(NCEP)~~ step 1 diet (5 trials, 1~~3.9~~1.1%), an average American Diet (3 trials, ~~8.3~~6.7%), a low fat diet (~~2~~ 3 trials, ~~5.~~6.7%), among others. Twenty~~-two~~ seven trials (~~61~~60%) provided test food supplements, 12~~1~~ trials (~~31~~26.7%) provided all study foods under metabolic feeding control conditions, and ~~3~~ 4 trials provided dietary advice (8.9%). ~~Four~~ Five trials (11.1%) used a control diet in which a muffin or pretzel[11 15 20 53] or cheese sticks[19] were exchanged for nuts. The test and control diets were matched for energy in all cases; however 2 of the trials[11 50] featured a negative energy balance tree nut diet compared with a matched negative energy balance control diet. Tree nut types included almonds (13~~1~~ trials, 28.3~~30.6~~%), cashews (2 trials, 4.3~~5.6~~%), hazelnuts (~~2~~3 trials, ~~5.6~~6.5%), macadamia nuts (3 trials, ~~8.3~~6.5%), pecans (2 trials, ~~5.6~~4.3%), pistachios (~~5~~ 8 trials, ~~12.8~~17.4%), walnuts (~~10~~ 13 trials, ~~27.8~~28.3%), and mixed nuts (2 trials, ~~5.6~~4.3%). We were unable to find studies on Brazil nuts or pine nuts. Median nut dose intake was ~~53~~ 49.3 g/day (IQR: 42 to ~~72.5~~70.5 g/day). Median follow-up was ~~7~~ 8 weeks (IQR: 4 to 12 weeks).

Macronutrient profiles varied across studies and between treatment and control groups, median values reported for carbohydrate intake were 48~~47~~% (IQR: of 44 to ~~52.3~~51%) for the treatment group and 50.5% (IQR: 46 to ~~56.8~~57%) for the control group. Median values for fat intake were ~~36.5~~35% (IQR: ~~31.8~~31 to 39%) and ~~30.5~~30% (IQR: ~~28~~27.3 to ~~34.8~~34%) for tree nut and control group respectively. Median values for protein intake were 16% (IQR: 15 to ~~18~~17%) and 17% (IQR: 15 to ~~19~~18.8%) for tree nut and control group correspondingly.

Appendix Table 2 and Appendix Figure 1 present the assessment and summary of the risk of bias by using The Heyland MQS and The Cochrane Risk of Bias Tool. The

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Heyland MQS ranged from 3 to 9. ~~Twenty~~Thirty-~~five~~two trials (~~69.4~~74.4%) were considered to be low quality (MQS < 8) and 11 trials (~~30.6~~25.6%) high quality (MQS ≥ 8). The main contributors of low scores were absence of double-blinding~~-blinding of participants, and crossovers between intervention treatments, followed by sample comparability and~~loss of participants to follow up, and poor description of crossovers in the control group. The Cochrane Risk of Bias Tool showed that ~~in our study, for allocation concealment,~~ 34 trials (70.8%) were unclear risk and 14 trials (29.2%) were low risk for random sequence generation; 29~~7~~/48 trials (60.4~~56.3~~%) were unclear risk and 19~~21~~/48 trials (39.6~~43.8~~%) were low risk for allocation concealment;~~, for blinding of participants and personnel,~~ 26~~8~~/48 trials (54.2~~8.3~~%) were unclear risk and 22~~0~~/48 trials (45.8~~1.7~~%) were low risk for blinding of participants and personnel; 5 trials (10.4%) were unclear risk, ~~, for incomplete outcome data,~~ 35/48 trials (72.9%) were low risk, and 8/48 trials (16.7%) were high risk ~~and 5/48 trials (10.4%) were unclear risk~~ for incomplete outcome data; ~~,~~ and ~~for selective reporting,~~ 28/47 trials (5~~9.6~~8.3%) were unclear risk, 1~~8~~9/47 trials (~~38.3~~39.6%) were low risk, and 1/47 trial~~s~~ (2.1%) were~~as~~ high risk for selective reporting. ~~was considered mainly "low risk of bias" (blinding of participants and crossovers in our included dietary trials are not feasible~~is very ~~difficult to achieve) and that a few studies~~ trials ~~were considered "high risk of bias" due to incomplete outcome data and selective reporting.~~

Most of the trials reported research funding from an agency ~~27/36~~28/45 (62.2~~75~~%), while others were funded from a combination of agency and industry 5/~~36~~45 (~~13.9~~11.1%) or industry alone 6/45 (13.3%). One trial (2.~~8~~2%) ~~was funded exclusively by industry~~reported no funding. ~~Three~~ Five trials[18 38 45 52 53] did not report their funding source (~~8.3~~11.1%).

Waist Circumference

Appendix Figure 2 presents data on the effect of tree nuts on waist circumference. Tree nuts did not significantly decrease waist circumference ~~in the overall analyses~~ (MD ~~=~~, -0.~~91~~ 62 cm [95% CI, -1.~~99~~54, 0.~~18~~ 30 cm]) in the overall analyses with evidence of ~~significant~~ substantial heterogeneity (I^2 = ~~65~~67%, P < 0.001). Stratification by health status

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failed to demonstrate a significant effect for any of the sub samples. Sensitivity analyses did not alter the results (data not shown).

Appendix Table 3-A and Appendix Figure 3 present the *a priori* continuous and categorical subgroup analyses, respectively, for waist circumference. There was evidence of statistically significant effect modification by the difference in ~~SFA intake in the categorical subgroup analyses (P<0.05) and by the difference in~~ carbohydrate intake in the continuous subgroup analyses ($P < 0.05$) between tree nut and control interventions. ~~Trials in which tree nuts displaced more SFA leading to larger differences between the tree nut and control interventions were more likely to favor the control diet.~~ Trials with lower carbohydrate intakes in the tree nut intervention arms showed larger reductions in waist circumference. No other subgroup analyses were statistically significant.

Triglycerides

Figure 2 presents data on the effect of tree nuts on triglycerides. Tree nuts showed a significant triglyceride-lowering effect (MD ~~=~~ -0.06 ~~7~~mmol/L, [95% CI, -0.09, -0.0~~4~~3 mmol/L]) in the overall analysis ~~without~~ with evidence of moderate ~~evidence of significant~~ heterogeneity (I^2= ~~24~~34%, P = 0.~~13~~02). ~~The same effect was seen with evidence of significant~~evidence of moderate heterogeneity (I^2= ~~48~~42%, P = 0.~~03~~05) in the subsample of participants who were otherwise healthy (MD ~~=~~ -0.07 mmol/L [95% CI, -0.11, -0.04 mmol/L]) ~~and without evidence of heterogeneity in the subsample of participants with MetScriteria(MD, -0.09 mmol/L [95% CI, -0.18, 0.00 mmol/L])~~. Although the reductions were not statistically significant in people with dyslipidemia MetS criteria or diabetes, they did not significantly differ from the reductions in participants who were otherwise healthy ~~or with MetS~~. Sensitivity analyses did not alter the results (data not shown).

Appendix Table 3-B and Appendix Figure 4 present data from the *a priori* continuous and categorical subgroup analyses, respectively, for triglycerides. There was significant effect modification by nut type in categorical analyses ($P < 0.05$). Pairwise comparisons showed that pecan, walnut, and pistachio interventions all significantly

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decreased triglycerides more than almond interventions ($P < 0.05$) and almond, macadamia, pecan, pistachio and walnut more than hazelnut ($P < 0.05$). No other subgroup analyses were statistically significant.

HDL-C

Appendix Figure 5 presents the effect of tree nuts on HDL-C**.** Tree nuts did not significantly affect HDL-C ~~in the overall analysis~~ (MD ~~=~~, 0.00 mmol/L [95% CI, -0.01, 0.01 mmol/L]) in the overall analysis with evidence of considerable heterogeneity (I^2 = 8~~6~~7%, P =< 0.001). Stratification by health status failed to demonstrate a significant effect for any of the subsamples. Sensitivity analyses did not alter the results (data not shown).

Appendix Table 3-C and Appendix Figure 6 present the a priori continuous and categorical subgroup analyses, respectively, for HDL-C. None of the subgroup analyses were significant.

Blood Pressure

Appendix Figures 7-A and 7-B present the effect of tree nuts on systolic and diastolic blood pressure, respectively. Tree nuts did not significantly ~~decrease~~ increase either systolic (MD ~~=~~, ~~-0.24~~0.07 mmHg [95% CI, -1.~~93~~54, 1.69~~45~~ mmHg]) or diastolic blood pressure (MD ~~=~~, 0.~~0~~23 mmHg [95% CI, -0.38~~49~~, 0.83~~54~~ mmHg]) in the overall analysis with evidence of substantial heterogeneity in the systolic blood pressure analysis (I^2 = 64~~53~~%, P < 0.001) and evidence of moderate heterogeneity in the diastolic blood pressure analysis (I^2 = 34%, P = 0.07). Stratification by health status failed to demonstrate an effect for any of the subsamples. Sensitivity analyses did not alter the results (data not shown).

Appendix Tables 3-D and 3-E present the *a priori* continuous subgroup analyses and **Appendix Figures 8-A and 8-B** present the *a priori* categorical subgroup analyses for systolic and diastolic blood pressure, respectively. There was evidence of statistically significant effect modification by difference in fibre intake ~~in both the continuous and categorical subgroup analyses~~ and by the difference in carbohydrate intake in the

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continuous subgroup analyses, both for systolic blood pressure (*P* < 0.05 and *P* < 0.01 respectively) between tree nut and control interventions. Trials with higher fibre intakes in the tree nut intervention arms showed larger reductions in systolic blood pressure. Trials in which tree nuts displaced more carbohydrates or contained lower levels of SFA intake leading to larger differences between the tree nut and control interventions were more likely to favour the Tree nut diet in systolic blood pressure. ~~Change in SFA or fibre intake in the tree nut intervention arms~~Tree nut intervention arms with higher fibre intake showed reductions in diastolic blood pressure and also explained the heterogeneity in the overall analyses reducing the residual-I^2 to ~~0~~1.6%. No other subgroup analyses were statistically significant for either systolic or diastolic blood pressure.

Fasting Blood Glucose

~~**Appendix**~~ **Figure ~~9~~ 3** presents the effect of tree nuts on fasting blood glucose. Tree nuts ~~did not~~showed a significant~~ly decrease~~ fasting blood glucose-lowering effect ~~in the overall analysis~~ (MD ~~,=~~ -0.0~~82~~ mmol/L [95% CI, -0.16, -0.0~~1~~1 mmol/L])~~,~~ in the overall analysis, with ~~evidence of significant~~~~no~~evidence of moderate heterogeneity (I^2 = ~~57~~41%, ~~p~~P < 0.~~01~~05). Stratification by health status failed to demonstrate an effect for any of the subsamples. Sensitivity analyses did not alter the results (data not shown).

Appendix Table 3-F and Appendix Figure ~~10~~ 9 present *a priori* continuous and categorical subgroup analyses, respectively, for fasting blood glucose. ~~There was evidence that the attained difference in SFA intake between tree nut and control interventions (in both continuous and categorical subgroup analyses (P<0.05)) influenced the effect of nuts on blood glucose. Trials in which tree nuts displaced less SFA leading to smaller differences in SFA between the tree nut and control interventions were more likely to favor the control diet~~None of the subgroup analyses were significant.

Publication Bias

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Appendix Figure 1~~0~~1 presents the funnel plots for publication bias for each endpoint. Visual inspection of the funnel plots revealed some evidence of asymmetry in several of the endpoints. There ~~were~~ was a ~~more~~ small trial~~s~~ with larger effect estimate~~s~~ favoring tree nuts than control for waist circumference, which argues that the "small-study" effect was actually not a source of potential bias (i.e. ~~2~~ smaller studies that favoured control were published). On the other hand, there were more small trials with larger effect estimates favouring control than tree nuts for triglycerides. Egger's test confirmed these small study effects for triglycerides ($P < 0.05$). No other evidence of small study effects was detected by Egger's test and Begg's tests.

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DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis to look at the effect of tree nuts on MetS criteria ~~of the MetS~~. Our systematic review and meta-analysis included ~~36~~ 47 randomized trials in ~~1691~~ 2,211 participants who were otherwise healthy or ~~met~~ had MetS criteria, dyslipidemia, or type 2 diabetes. Tree nut consumption at a median dose of ~50 g/day was found to decrease triglycerides significantly by ~0.~~07~~ 06 mmol/L, and to decrease fasting blood glucose significantly by ~0.08 mmol/L over a median follow-up of ~~7~~8-weeks. No adverse effects were seen on waist circumference, HDL-C, or blood ~~pressure or fasting blood glucose. However the direction of effect favoured tree nuts in the case of waist circumference, blood pressure, and fasting blood glucose.~~, suggesting an overall net metabolic benefit of tree nuts.

Results in relation to other studies

Our findings of a reduction in triglycerides without the expected reciprocal increase in HDL-C are in accordance with previous evidence. Although Sabate et al[64] did not show a triglyceride lowering effect of nut interventions (nonspecific to tree nuts) in overall pooled analyses in an patient-level meta-analysis of controlled feeding trials, he did show that nut interventions lowered triglycerides when analyses were restricted to a subsample of

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participants with baseline triglycerides ≥ 1.7mmol/L, without an increase in HDL-C. A triglyceride benefit has also been seen in individual trials and meta-analyses of trials investigating the effect of a Mediterranean dietary pattern containing tree nuts in people with diabetes.[65 66] This triglyceride-lowering effect, however, was accompanied by an HDL-C increasing effect.[65 66] Our findings add to these data by showing a similar triglyceride-lowering effect, especially for walnuts, pistachios, macadamia and pecans, in the absence of an HDL-C increasing effect, across all subsamples of participants, without differences in triglycerides by baseline levels. The lipid benefits of tree nuts can be attributed to numerous cardioprotective nutrients such as unsaturated fatty acids, plant protein, fibre and phytochemicals.[67] The fibre content and high unsaturated fat content with its ability to displace high glycemic index carbohydrate from the diet and so effect a lower glycemic load diet are likely the main factors in lowering triglycerides.[20]

Our results of a reduction in fasting blood glucose are in accordance with an evidence-based review for the 2013 CDA guidelines that found evidence to support small improvements in overall glycemic control in people with diabetes.[23] Individual trials have shown evidence of improvements in other aspects of glycemic control.[19-22] A fasting blood glucose-decreasing effect ~~of tree nuts~~ has also been seen in long-term glycemic control as assessed by HbA1c for tree nuts as part of Mediterranean[65 66 68] and DASH[69] dietary patterns in people with diabetes.[70] ~~However, the diabetes subgroup in our analyses did not show a statistical decrease in fasting blood glucose, this may relate to the statistical approach used for missing values in the crossover studies, where the constant correlation used to calculate CIs was derived from all health subgroups. Therefore, CIs were slightly wider than if the correlation value was derived only from trials on participants with diabetes (in press by Viguiliouk et al).~~ The ability of tree nuts to decrease fasting blood glucose in our analyses may relate to the proposed displacement mechanism by which tree nuts reduce the glycemic load of the diet, as this mechanism would be expected to improve long-term glycemic control

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through a reduction in postprandial glycaemia,[71] and possibly decrease insulin resistance,[48] neither of which were ~~not~~ assessed in our review.

The lack of effect we observed on waist circumference reinforces the view that tree nuts do not have an adverse effect on body weight. Dietary guidelines have raised concerns about the potential of tree nuts to contribute to weight gain,[2] owing to their high energy density; however prospective cohort studies and randomized trials have shown the opposite. A pooled analysis of Harvard cohorts showed an increase in one serving per day of nuts was associated with significant weight loss.[72] Controlled trials of tree nuts alone or as part of Mediterranean,[65 66 68] Portfolio,[73] or DASH[69] dietary patterns have shown neutral or weight loss effects, and no influence on body fat mass or body fat percentage.[74] Dietary patterns that incorporated nuts have reported weight loss under isocaloric conditions or no weight gain under hypercaloric feeding conditions,[75] perhaps because of the metabolically-available energy from nuts is less than the calculated value, as incomplete digestion of nuts leading to energy excretion in the feces.[76] Our findings further suggest that tree nuts do not have a significant effect on the most metabolically adverse weight gain involving an increase in waist circumference. We observed a tendency for a reduction in waist circumference, especially where nuts displaced high glycemic index carbohydrate to effect a lower-glycemic load diet (as opposed to where tree nuts were used to displace saturated fat). These data suggest that the inclusion of a greater number of long-term trials in which tree nuts are used to displace high-glycemic index carbohydrate to effect a low-glycemic load diet may yet demonstrate a waist circumference benefit in future meta-analyses.

We were surprised not to see an improvement in blood pressure ~~and fasting blood glucose~~. Individual trials have shown evidence of improvements in blood pressure[5 8] ~~and other aspects of glycemic control.[19-22] An evidence based review for the 2013 CDA guidelines also found evidence to support small improvements in overall glycemic control in people with diabetes.[79]~~ A blood pressure-decreasing effect of tree nuts has also been seen in the context of Portfolio[73] and DASH[69 77 78] dietary patterns across a range of participant types. ~~The same is true for improvements in long term glycemic control as assessed by~~

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~~HbA1c for tree nuts as part of Mediterranean[67, 68, 72] and DASH[74] dietary patterns in people with diabetes. The inability of tree nuts to decrease fasting blood glucose in our analyses may relate to the proposed displacement mechanism by which tree nuts reduce the glycemic load of the diet, as this mechanism would be expected to improve long-term glycemic control through a reduction in postprandial glycaemia, which was not assessed.~~ As elevated ~~the~~ blood pressure in the metabolic syndrome often relates to the underlying insulin resistance, the lack of effect on BP may also be explained by a lack of trials using tree nuts to displace high-glycemic index carbohydrate to decrease the low-glycemic load of the diet (trials taking advantage of this mechanism were more likely to show reductions than trials that did not in subgroup analyses). Alternatively, it may be explained by the need for tree nuts to be combined with the other aspects of a DASH ~~diet~~dietary pattern, which collectively result in larger amounts of potassium, calcium, magnesium, dietary fibre, and protein.

Limitations

There are some limitations to our work. First, the majority of trials (~~69.4~~74.4%) were of low quality (MQS < 8). Factors that contributed the most to low quality scores were incomplete outcome data and poor reporting. However, in our *a priori* subgroup analyses there was no effect modification by study quality. Second, the risk of bias remains uncertain for most of the available trials owing to poor reporting. This point is particularly concerning given that the majority of the trials were conducted after the Consolidated Standards of Reporting Trials (CONSORT) guidelines were first reported in 1993 and published in 1996.[79] Third, the majority of the available trials were < 3 months, which is perhaps, too short a time to observe an effect for some outcomes (waist circumference, ~~fasting glucose~~blood pressure). This also made it difficult to assess the sustainability of the observed effects over the long term. We did not, however, observe significant effect modification by follow-up in categorical or continuous subgroup analyses for any of the endpoints. Finally, our analyses were complicated by significant unexplained heterogeneity for waist circumference~~,~~ and HDL-C, ~~and fasting blood glucose~~, which we attempted to accommodate using of random

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effects models, remains a source of uncertainty in the summary effect estimates for these endpoints.

Practical Implications

Tree nuts are a high-energy food that contain cardioprotective nutrients,[67] Even though the median fat intake (~~36~~33.6%) of the tree nut containing diets was above that of the control (30.5%), but both within the recommended (20-35%) by dietary guidelines,[23] a beneficial effect was seen ~~when compared to a control diet that tended to meet macronutrient recommendations~~only in the tree nut containing diets. The median dose of ~50 g/day tree nuts can be easily integrated as a snack, into a dietary pattern or as a substitution for animal fats or carbohydrates. No increase in side effects compared with control diets were reported in any of the trials, suggesting diets which emphasize tree nuts are as safe as conventional diets (except in individuals with tree nut allergies).

Conclusion

In conclusion, our pooled analyses indicate that daily tree nut consumption has an overall ~~net modest~~ metabolic benefit, through modest decreases in~~ing~~ triglycerides and fasting blood glucose while preserving waist circumference, HDL-C, and blood pressure ~~and fasting blood glucose~~ in people who are otherwise healthy or have ~~-~~dyslipidemia, ~~criteria of the~~ MetS criteria, or ~~-~~type 2 diabetes. These data support recommendations to consume tree nuts alone or as part of heart healthy dietary patterns such as the Mediterranean, Portfolio, Vegetarian, and DASH dietary patterns as a means for improving metabolic control.[69 80-83] Careful interpretation of the results is advised, as ~~O~~our conclusions are limited by ~~the small sample sizes,~~the ~~-~~short duration~~,~~ and poor quality of the majority of trials, as well as~~nd~~ the presence of significant unexplained heterogeneity in our analyses. These limitations highlight the need for larger, longer, high quality trials. Trials in which tree nuts are used to displace high-glycemic index carbohydrate to decrease the glycemic load of the diet will be

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especially relevant to understand the role of tree nuts in reducing cardiometabolic risk associated with the metabolic syndrome.

Contributions

Conception and design: S Blanco Mejia, CWC Kendall, LS Augustin, JL Sievenpiper.

Analysis or interpretation of the data: S Blanco Mejia, CWC Kendall, E Viguiliouk, LS Augustin, V Ha, A Cozma, A Mirrahimi, A Maroleanu, L Chiavaroli, LA Leiter, RJ de Souza, DJA Jenkins, JL Sievenpiper.

Drafting of the article: S Blanco Mejia, JL Sievenpiper.

Critical revision of the article for important intellectual content: S Blanco Mejia, CWC Kendall, E Viguiliouk, LS Augustin, V Ha, A Cozma, A Mirrahimi, A Maroleanu, L Chiavaroli, LA Leiter, RJ de Souza, DJA Jenkins, JL Sievenpiper.

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Collection and assembly of data: S Blanco Mejia, E Viguiliouk, LS Augustin, V Ha, A Cozma, A Maroleanu.

Guarantors: CWC Kendall and JL Sievenpiper.

Transparency declaration

The manuscript's guarantors affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Ethical Approval

Not required.

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Potential Conflicts of Interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: **SBM, LSA, AM, AIC, EV, AM and LAL declare,** no conflicts of interest related to this paper. **CWCK** has received research support from the Advanced Foods and Material Network, Agrifoods and Agriculture Canada, the Almond Board of California, the American Pistachio Growers, Barilla, the California Strawberry Commission, the Calorie Control Council, CIHR, the Canola Council of Canada, the Coca-Cola Company (investigator initiated, unrestricted grant), Hain Celestial, the International Tree Nut Council Nutrition Research and Education Foundation, Kellogg, Kraft, Loblaw Companies Ltd., Orafti, Pulse Canada, Saskatchewan Pulse Growers, Solae and Unilever. He has received travel funding, consultant fees and/or honoraria from Abbott Laboratories, the Almond Board of California, the American Peanut Council, the American Pistachio Growers, Barilla, Bayer, the Canola Council of Canada, the Coca-Cola Company, Danone, General Mills, the International Tree Nut Council Nutrition Research and Education Foundation, Kellogg, Loblaw Companies Ltd., the Nutrition Foundation of Italy, Oldways Preservation Trust, Orafti, Paramount Farms, the Peanut Institute, PepsiCo, Pulse Canada, Sabra Dipping Co., Saskatchewan Pulse Growers, Solae, Sun-Maid, Tate and Lyle, and Unilever. He is on the Dietary Guidelines Committee for the Diabetes Nutrition Study Group of the European Association for the Study of Diabetes and has served on the scientific advisory board for the Almond Board of California, the International Tree Nut Council, Oldways Preservation Trust, Paramount Farms and Pulse Canada. **VH** has received research support from the CIHR and the World Health Organization (WHO) for work on a systematic review and meta-analysis commissioned by WHO of the relation of saturated fatty acids with health outcomes. She received a travel award to attend a science day hosted by PepsiCo Inc. and the New York Academy of Sciences. **LC** has received research support from the CIHR and the Agricultural Bioproducts Innovation Program through the Pulse Research Network (PURENet), and Saskatchewan

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Pulse Growers. She is also a casual clinical research coordinator at Glycemic Index Laboratories. **RJdS** is funded by a CIHR Postdoctoral Fellowship Award and has received research support from the CIHR, the Calorie Control Council, the Canadian Foundation for Dietetic Research and the Coca-Cola Company (investigator initiated, unrestricted grant). He has served as an external resource person to WHO's Nutrition Guidelines Advisory Group and received travel support from WHO to attend group meetings. He is the lead author of 2 systematic reviews and meta-analyses commissioned by WHO of the relation of saturated fatty acids and trans fatty acids with health outcomes. **DJAJ** has received research grants from Saskatchewan Pulse Growers, the Agricultural Bioproducts Innovation Program through the Pulse Research Network, the Advanced Foods and Material Network, Loblaw Companies Ltd., Unilever, Barilla, the Almond Board of California, the Coca-Cola Company (investigator initiated, unrestricted grant), Solae, Haine Celestial, the Sanitarium Company, Orafti, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, the Canola and Flax Councils of Canada, the Calorie Control Council, the CIHR, the Canada Foundation for Innovation and the Ontario Research Fund. He has been on the speaker's panel, served on the scientific advisory board, and/or received travel support and/or honoraria from the Almond Board of California, Canadian Agriculture Policy Institute, Loblaw Companies Ltd, the Griffin Hospital (for the development of the NuVal scoring system), the Coca-–Cola Company, Saskatchewan Pulse Growers, Sanitarium Company, Orafti, the Almond Board of California, the American Peanut Council, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, Herbalife International, Pacific Health Laboratories, Nutritional Fundamental for Health, Barilla, Metagenics, Bayer Consumer Care, Unilever Canada and Netherlands, Solae, Kellogg, Quaker Oats, Procter & Gamble, the Coca-Cola Company, the Griffin Hospital, Abbott Laboratories, the Canola Council of Canada, Dean Foods, the California Strawberry Commission, Haine Celestial, PepsiCo, the Alpro Foundation, Pioneer Hi- Bred International, DuPont Nutrition and Health, Spherix Consulting and WhiteWave Foods, the Advanced Foods and Material Network, the Canola and Flax Councils of Canada, the

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Nutritional Fundamentals for Health, Agri-Culture and Agri-Food Canada, the Canadian Agri-Food Policy Institute, Pulse Canada, the Saskatchewan Pulse Growers, the Soy Foods Association of North America, the Nutrition Foundation of Italy (NFI), Nutra- Source Diagnostics, the McDougall Program, the Toronto Knowledge Translation Group (St. Michael's Hospital), the Canadian College of Naturopathic Medicine, The Hospital for Sick Children, the Canadian Nutrition Society (CNS), the American Society of Nutrition (ASN), Arizona State University, Paolo Sorbini Foundation and the Institute of Nutrition, Metabolism and Diabetes. He received an honorarium from the US Department of Agriculture to present the 2013 W.O. Atwater Memorial Lecture. He received the 2013 Award for Excellence in Research from the International Nut and Dried Fruit Council. He received funding and travel support from the Canadian Society of Endocrinology and Metabolism to produce mini cases for the Canadian Diabetes Association. His wife is a director and partner of Glycemic Index Laboratories, and his sister received funding through a grant from the St. Michael's Hospital Foundation to develop a cookbook for one of his studies. **JLS** has received research support from the CIHR, Calorie Control Council, the Coca-Cola Company (investigator initiated, unrestricted grant), Pulse Canada, and the International Tree Nut Council Nutrition Research and Education Foundation. He has received travel funding, speaker fees, and/or honoraria from the American Heart Association, the American Society for Nutrition, the National Institute of Diabetes and Digestive and Kidney Diseases, the Canadian Diabetes Association, the Canadian Nutrition Society, the Calorie Control Council, the Diabetes and Nutrition Study Group of the European Association for the Study of Diabetes, the International Life Sciences Institute North America, the International Life Sciences Institute Brazil, the University of South Carolina, the University of Alabama at Birmingham, the Canadian Sugar Institute, Oldways Preservation Trust, the Nutrition Foundation of Italy, Abbott Laboratories, Pulse Canada, Dr. Pepper Snapple Group, Corn Refiners Association, and the Coca-Cola Company. He is on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of both the Canadian Diabetes Association and the European Association for the Study of Diabetes, and he is on the American Society for Nutrition writing panel for a

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scientific statement on the metabolic and nutritional effects of fructose, sucrose and high-fructose corn syrup. He is a member of the Carbohydrate Quality Consortium and an unpaid scientific advisor for the Food, Nutrition and Safety Program of the International Life Science Institute North America. His wife is an employee of Unilever Canada.~~has received consultant fees, honoraria, travel funding, or research support from or served on the scientific advisory board for the CIHR, Calorie Control Council, The Coca-Cola Company (investigator initiated, unrestricted), Abbott Laboratories, Advanced Food Materials Network, Almond Board of California, American Peanut Council, American Pistachio Growers, Barilla, California Strawberry Commission, Canola Council of Canada, Danone, General Mills, Hain Celestial, International Tree Nut Council, Kellogg, Loblaw Brands Ltd, Oldways, Orafti, Paramount Farms, Pulse Canada, Saskatchewan Pulse Growers, Solae and Unilever. **VH, AM, LC** have received research support from the Canadian Institutes of health Research (CIHR). **RJdS** has received research support from the Canadian Institutes of Health Research (CIHR), Calorie Control Council, and The Coca-Cola Company (investigator initiated, unrestricted). He has served as an external resource person to the World Health Organization's (WHO) Nutrition Guidelines Advisory Group (NUGAG), and was the lead author of systematic reviews and meta-analysis commissioned by the WHO of saturated and trans fatty acids and health outcomes. The WHO paid for his travel and accommodation to attend the 5th NUGAG Meeting in Hangzhou, China (4-7 Mar, 2013), and the 6th NUGAG Meeting in Copenhagen, Denmark (21-24 Oct, 2013). **DJAJ** has received consultant fees, honoraria, travel funding, or research support from or served on the scientific advisory board for the CIHR, Canadian Foundation for Innovation (CFI), Ontario Research Fund (ORF), and Advanced Foods and Material Network (AFMNet) Calorie Control Council, The Coca-Cola Company (investigator initiated, unrestricted), Barilla, Solae, Unilever, Hain Celestial, Loblaws Supermarkets, Inc., Sanitarium Company, Herbalife International, Pacific Health Laboratories, Inc., Metagenics/MetaProteomics, Bayer Consumer Care, Oldways Preservation Trust, The International Tree Nut Council Nutrition Research & Education, The Peanut Institute, Procter and Gamble Technical Centre Limited, Griffin Hospital for the

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Data Sharing

No additional data available.

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Table 1

Study, year (Reference)	Participants	Mean Age (SD or range), y	Mean Body Weight or BMI (SD or range)§	Setting	Design	Feeding Control	Nut type	Nuts Dose (g/day)‖	Comparator	Diet ††	En Bal			
Sabate et al, 1993 (30)														
Walnut	18 (18 M)	30	73	OP, USA	Crossover	Met	Walnut	84		55:31:14	Isocaloric	4 wks	6	Agency
Control									NCEP Step 1 diet	56:30:14				
Chisholm et al, 1998 (13)														
Walnut	16 HLP	45 (6.8)	28.4 (4.3)	OP, New Zealand	Crossover	DA	Walnut	78		40:38:17	Isocaloric	4 wks	4	Agency
Control									Low Fat Diet	46:30:19				
Spiller et al, 1998 (31)														
Almond	30 HLP	53 (10)	66 (13)	OP, Italy	Parallel	Supp	Almond	100		45:39:16	Isocaloric	4 wks	6	Agency
Control									Matched macronutrient diet	47:36:17				
Curb et al, 2000 (10)														
Macadamia							Macadamia	46		48:35:17				
Control	30 (15 M, 15 W)	35.25 (18-53)	23 (19.1 - 28.3)	OP, USA	Crossover	Met			AHA	54:30:16	Isocaloric	4 wks	4	Agency-Industry
Control									AAD	48:35:17				
Morgan et al, 2000 (32)														
Pecan	19 (4 M, 15 W)	37 (12)	24 (5)	OP, USA	Parallel	Supp	Pecan	68		45:43:12	Isocaloric	8 wks	6	Agency
Control		45(10)	24 (4)						Self-selected diet	46:36:18				
Zambon et al, 2000 (33)														
Walnut	49 HC (26 M, 23 W)	56 (11)	70.6 (12.1)	OP, Spain	Crossover	Supp	Walnut	48.5		48:34:18	Isocaloric	6 wks	6	Agency
Control									Mediterranean diet	50:31:19				
Rajaram et al, 2001 (14)														
Pecan	23 (14 M, 9 W)	25-55	74.4 (16.7)	OP, USA	Crossover	Met	Pecan	72		47:40:13	Isocaloric	4 wks	8	Agency
Control									NCEP Step 1 diet	57:28:15				
Iwamoto et al, 2002 (34)														
Walnut	40 (20 M, 20 W)	23.8 (3.1)‡	22.2 (0.5)	OP, Japan	Crossover	Met	Walnut	52¶		60:26:14	Isocaloric	4 wks	8	Agency
Control		23.6 (4.6)‡	20.7 (0.5)						Average Japanese Diet	62:24:14				
Jenkins et al, 2002 (15)														
Almond	27 HLP (15 M, 12 W)	64 (9)	71.2 (2.5)	OP, Canada	Crossover	Supp	Almond	73		47:36:17	Isocaloric	4 wks	6	Agency
Control			71.0 (2.4)						NCEP Step 2 diet + Muffin	57:26:18				
Lovejoy et al, 2002 (35)														
High Fat Almond							Almond			48:37:15				
Low Fat Almond	30 DM2 (13 M, 17 W)	53.8 (10.4)	33.0 (5.5)	OP, USA	Crossover	Met	Almond	85¶		60:25:15	Isocaloric	4 wks	5	Agency
High Fat Control									High Fat diet	48:37:15				
Low Fat Control									Low Fat diet	60:25:15				
Sabate et al, 2003 (36)														
High-Almond							Almond	83		46:39:14				
Low-Almond	25 NL-HC (14 M, 11 W)	41 (13)	N/A	OP, USA	Crossover	Met	Almond	42		35:51:14	Isocaloric	4 wks	5	Agency-Industry
Control									NCEP Step 1 diet	56:30:14				
Wien et al, 2003 (8)														
Almond	65 OW/DM2 (28 M, 37 W)	53 (2)	113 (5)	OP, USA	Parallel	Supp	Almond	84		53:18:29	Isocaloric	24 wks	8	Agency
Control		57 (2)	114 (5)						CHO-LCD	32:39:29				
Tapsell et al, 2004 (37)														
Walnut	37 DM2	57.7 (9)	87.6 (12.8)	OP, Australia	Parallel	Supp	Walnut	30		44:32:22	Isocaloric	6 months	6	Agency
Control		59.3 (7.1)	81.9 (11.2)						Modified Fat	41:33:23				
Tamizifar et al, 2005 (38)														
Almond	30 HC (17 M, 13 W)	56 (6.1)	63 (8.9)	OP, Iran	Crossover	Supp	Almond	25		47:37:17	Isocaloric	4 wks	5	N/A
Control									NCEP Step 1 diet	45:29:15				
Kocyigit et al, 2006 (16)														
Pistachio	44 (24 M, 20 W)	32.8 (6.7)	24.2 (6.1)	OP, Turkey	Parallel	DA	Pistachio	69		N/A	Isocaloric	3 wks	8	Agency
Control			24.6 (5.6)						Regular diet					
Kurlandsky et al, 2006 (39)														
Almond		41.8 (11.7)	25.3 (3.5)				Almond			51:34:15				
Almond + Dark Chocolate	47 (47 W)	46.2 (7.8)	27.2 (4.2)	OP, USA	Parallel	Supp	Almond	60		46:39:15	Isocaloric	6 wks	5	Agency-Industry
Dark chocolate		36.5 (11.9)	23.9 (3.3)						NCEP ATP III diet + Chocolate	55:30:15				
Control		51.3 (6.3)	26.1 (4.1)						NCEP ATP III diet	57:27:16				
Schutte et al, 2006 (60)*														
Walnut		45.5	35.9				Walnut			47:36:17				
Cashew	62 MetS	45.7	34.7	OP, South Africa	Parallel	Met	Cashew	85.5		47:36:17	Isocaloric	8 wks	7	Agency-Industry
Control		44.4	35.5						Control diet	50:33:18				
Mukuddem-Petersen et al, 2007 (40)														
Walnut			107				Walnut			49:35:16				
Cashew	64 MetS	45 (10)	99	OP, South Africa	Parallel	Met	Cashew	85.5¶		44:37:19	Isocaloric	8 wks	7	Agency-Industry
Control			106						Habitual diet	47:33:20				
Sheridan et al, 2007 (17)														
Pistachio	15 HC	60 (11.2)	175 (26)	OP, USA	Crossover	Supp	Pistachio	35		52:31:17	Isocaloric	4 wks	6	Agency
Control									Regular diet	53:31:16				

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Study, year (Reference)	Participants	Mean Age (SD or range), y	Mean Body Weight or BMI (SD or range)§	Setting	Design	Feeding Control	Nut type	Nuts Dose (g/d)‖	Comparator	Diet ††	Energy Balance	Follow-Up	MQS §§	Funding Sources ‖‖
Sabate et al, 1993 (32)														
Walnut	18 (18 M)	30	73	OP, USA	Crossover	Met	Walnut	84	NCEP Step 1 diet	55:31:14	Isocaloric	4 wks	6	Agency
Control										56:30:14				
Chisholm et al, 1998 (13)														
Walnut	16 HLP	45 (6.8)	28.4 (4.3)	OP, New Zealand	Crossover	DA	Walnut	78	Low Fat Diet	40:38:17	Isocaloric	4 wks	4	Agency
Control										46:30:19				
Spiller et al, 1998 (33)														
Almond	30 HLP	53 (10)	66 (13)	OP, Italy	Parallel	Supp	Almond	100	Matched macronutrient diet	45:39:16	Isocaloric	4 wks	6	Agency
Control										47:36:17				
Curb et al, 2000 (10)														
Macadamia							Macadamia	46		48:35:17				
Control	30 (15 M, 15 W)	35.25 (18-53)	23 (19.1 - 28.3)	OP, USA	Crossover	Met			AHA	54:30:16	Isocaloric	4 wks	4	Agency-Industry
Control									AAD	48:35:17				
Morgan et al, 2000 (34)														
Pecan	19 (4 M, 15 W)	37 (12)	24 (5)	OP, USA	Parallel	Supp	Pecan	68	Self-selected diet	45:43:12	Isocaloric	8 wks	6	Agency
Control		45(10)	24 (4)							46:36:18				
Zambon et al, 2000 (35)														
Walnut	49 HC (26 M, 23 W)	56 (11)	70.6 (12.1)	OP, Spain	Crossover	Supp	Walnut	48.5	Mediterranean diet	48:34:18	Isocaloric	6 wks	6	Agency
Control										50:31:19				
Rajaram et al, 2001 (14)														
Pecan	23 (14 M, 9 W)	25-55	74.4 (16.7)	OP, USA	Crossover	Met	Pecan	72	NCEP Step 1 diet	47:40:13	Isocaloric	4 wks	8	Agency
Control										57:28:15				
Iwamoto et al, 2002 (36)														
Walnut	40 (20 M, 20 W)	23.8 (3.1)‡	22.2 (0.5)	OP, Japan	Crossover	Met	Walnut	52¶	Average Japanese Diet	60:26:14	Isocaloric	4 wks	8	Agency
Control		23.6 (4.6)‡	20.7 (0.5)							62:24:14				
Jenkins et al, 2002 (15)														
Almond	27 HLP (15 M, 12 W)	64 (9)	71.2 (2.5)	OP, Canada	Crossover	Supp	Almond	73	NCEP Step 2 diet + Muffin	47:36:17	Isocaloric	4 wks	6	Agency
Control			71.0 (2.4)							57:26:18				
Lovejoy et al, 2002 (37)														
High Fat Almond							Almond	85¶		48:37:15				
Low Fat Almond	30 DM2 (13 M, 17 W)	53.8 (10.4)	33.0 (5.5)	OP, USA	Crossover	Met	Almond		High Fat diet	60:25:15	Isocaloric	4 wks	5	Agency
High Fat Control									Low Fat diet	48:37:15				
Low Fat Control										60:25:15				
Sabate et al, 2003 (38)														
High-Almond							Almond	83		46:39:14				
Low-Almond	25 NL-HC (14 M, 11 W)	41 (13)	N/A	OP, USA	Crossover	Met	Almond	42	NCEP Step 1 diet	35:51:14	Isocaloric	4 wks	5	Agency-Industry
Control										56:30:14				
Wien et al, 2003 (8)														
Almond	65 OW/DM2 (28 M, 37 W)	53 (2)	113 (5)	OP, USA	Parallel	Supp	Almond	84	CHO-LCD	53:18:29	Isocaloric	24 wks	8	Agency
Control		57 (2)	114 (5)							32:39:29				
Tapsell et al, 2004 (39)														
Walnut	37 DM2	57.7 (9)	87.6 (12.8)	OP, Australia	Parallel	Supp	Walnut	30	Modified Fat	44:32:22	Isocaloric	6 months	6	Agency
Control		59.3 (7.1)	81.9 (11.2)							41:33:23				
Tamizifar et al, 2005 (40)														
Almond	30 HC (17 M, 13 W)	56 (6.1)	63 (8.9)	OP, Iran	Crossover	Supp	Almond	25	NCEP Step 1 diet	47:37:17	Isocaloric	4 wks	5	N/A
Control										45:29:15				
Kocyigit et al, 2006 (16)														
Pistachio	44 (24 M, 20 W)	32.8 (6.7)	24.2 (6.1)	OP, Turkey	Parallel	DA	Pistachio	69	Regular diet	N/A	Isocaloric	3 wks	8	Agency
Control			24.6 (5.6)											
Kurlandsky et al, 2006 (41)														
Almond		41.8 (11.7)	25.3 (3.5)				Almond	60		51:34:15				
Almond + Dark Chocolate	47 (47 W)	46.2 (7.8)	27.2 (4.2)	OP, USA	Parallel	Supp	Almond		NCEP ATP III diet + Chocolate	46:39:15	Isocaloric	6 wks	5	Agency-Industry
Dark chocolate		36.5 (11.9)	23.9 (3.3)						NCEP ATP III diet	55:30:15				
Control		51.3 (6.3)	26.1 (4.1)							57:27:16				
Schutte et al, 2006 (53)*														
Walnut		45.5	35.9				Walnut	85.5		47:36:17				
Cashew	62 MetS	45.7	34.7	OP, South Africa	Parallel	Met	Cashew		Control diet	47:36:17	Isocaloric	8 wks	7	Agency-Industry
Control		44.4	35.5							50:33:18				
Mukuddem-Petersen et al, 2007 (42)														
Walnut			107				Walnut	85.5¶		49:35:16				
Cashew	64 MetS	45 (10)	99	OP, South Africa	Parallel	Met	Cashew		Habitual diet	44:37:19	Isocaloric	8 wks	7	Agency-Industry
Control			106							47:33:20				
Sheridan et al, 2007 (17)														
Pistachio	15 HC	60 (11.2)	175 (26)	OP, USA	Crossover	Supp	Pistachio	35	Regular diet	52:31:17	Isocaloric	4 wks	6	Agency
Control										53:31:16				

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Study, year (Reference)	Participants	Mean Age (SD or range), y	Mean Body Weight or BMI (SD or range)§	Setting	Design	Feeding Control	Nut type	Nuts Dose (g/day)‖	Comparator	Diet ††	Energy Balance	Follow-Up	MQS §§	Funding Sources ‖‖
Gebauer et al, 2008 (41)														
1 Pistachio	28 HLP (10 M, 18 W)	48 (7.9)	76.6 (13.2)	OP, USA	Crossover	Met	Pistachio	37	NCEP Step 1 diet	53:34:16	Isocaloric	4 wks	5	Agency
2 Pistachio							Pistachio	74		57:29:16				
Control										62:25:15				
Griel et al, 2008 (42)														
Macadamia	25 HC	50.2 (8.4)	26.3 (3.3)	OP, USA	Crossover	Met	Macadamia	42.5**	AAD	50:33:19	Isocaloric	5 wks	8	Agency-Industry
Control										52:33:17				
Jenkins et al, 2008 (61)*														
Almond	27 HLP (15 M, 12 W)	64 (9)	71.2 (2.5)	OP, Canada	Crossover	Supp	Almond	73	NCEP Step 2 diet + Muffin	47:36:17	Isocaloric	4 wks	6	Agency
Control			71.0 (2.4)							57:26:18				
Rajaram et al, 2009 (43)														
Walnut	25 NL-HLP (14 M, 11 W)	23-65	71.9 (15.5)	OP, USA	Crossover	Met	Walnut	42.5	AAD	60:31:15	Isocaloric	4 wks	5	Agency
Control			71.7 (15.5)							57:30:14				
Tapsell et al, 2009 (44)														
Walnut	35 DM2†	54 (8.7)	92.3 (15.7)	OP, Australia	Parallel	Supp	Walnut	30	Low Fat diet	42:29:24	Isocaloric	12 months	7	Agency
Control			93.4 (3)							41:34:20				
Li et al, 2010 (11)														
Almond	52 OW†	45.4 (2.0)	86 (26.8)	OP, USA	Parallel	Supp	Pistachio	53	Pretzel	55:30:15	Hypocaloric	12 wks	7	Agency
Control		47.3 (2.3)	85.5 (40.2)							65:20:15	Hypocaloric			
Ma et al, 2010 (45)														
Walnut	22 DM2†	58.1 (9.2)	89 (15.5)	OP, USA	Crossover	Supp	Walnut	56	Ad libitum diet	39:44:17	Isocaloric	8 wks	5	N/A
Control										43:38:19				
Torabian et al, 2010 (12)														
Walnut	87 (38 M, 49 W)	54 (10.2)	75.6 (13.2)	OP, USA	Crossover	Supp	Walnut	46	Habitual diet	N/A	Isocaloric	6 months	6	Agency
Control														
Wien et al, 2010 (46)														
Almond	65 PD (17 M, 48 W)	53 (9)	82.9 (14.4)	OP, USA	Parallel	Supp	Almond	58	AAD	42:39:19	Isocaloric	16 wks	9	Agency
Control		54 (11)	80.5 (14.4)							48:30:21				
Wu et al, 2010 (47)														
Walnut	189 MetS	48.2 (8.4)	72.2 (11.4)	OP, USA	Parallel	Supp	Walnut	30	AHA	48:37:15	Isocaloric	12 wks	9	Agency
Control		48.6 (8)	70.6 (10.9)							51:34:15				
Casas-Agustench et al, 2011 (48)														
Mixed Nuts	50 MetS (28 M, 22 W)	52.9 (8.4)	31.6 (2.8)	OP, Spain	Parallel	Supp	Mixed Nuts	30	Prudent diet	41:36:19	Isocaloric	12 wks	6	Agency
Control		50.6 (8.4)	30.0 (3.3)							42:36:19				
Cohen et al, 2011 (19)														
Almond	13 DM2 (7 M, 6 W)	66 (11.9)	96.1 (40.4)	OP, USA	Parallel	Supp	Almond	28	Cheese sticks	N/A	Isocaloric	12 wks	7	Agency
Control			105.1 (32.1)											
Jenkins et al, 2011 (20)														
Mixed Nuts	79 DM2 (52 M, 27 W)	63 (9)	80 (15)	OP, Canada	Parallel	Supp	Mixed nuts	75¶	NCEP Step 2 diet + Muffin	41:41:18	Isocaloric	12 wks	8	Agency
Control		61 (10)	83 (15)							46:35:19				
Li et al, 2011 (21)														
Almond	20 DM2 (9 M, 11 W)	58 (8.9)	26 (3.1)	OP, Taiwan	Crossover	Met	Almond	56	NCEP step 2 diet	47:37:17	Isocaloric	4 wks	5	Agency
Control										57:27:17				
Tey et al, 2011 (49)														
Hazelnut	61	38.9 (14.3)	72 (11.1)	OP, New Zealand	Parallel	Supp	Hazelnut	42	Regular diet	45:39:16‡‡	Isocaloric	12 wks	9	Agency
Control		36.1 (15.2)	67.3 (9.5)							50:33:17				
Darvish Damavandi et al, 2012 (18)														
Cashew	43 DM2 (9 M, 34 W)	51 (7.9)	72.1 (13.1)	OP, Iran	Parallel	Supp	Cashew	30	Regular diet	53:32:16	Isocaloric	8 wks	3	N/A
Control		56 (5.7)	71.9 (9.7)							57:27:16				
Foster et al, 2012 (50)														
Almond	123 OW (11 M, 112 W)	47 (12)	94 (13.1)	OP, USA	Parallel	Supp	Almond	56	Nut free diet	N/A	Hypocaloric	18 months	9	Agency
Control		46.7 (13)	91.5 (11.9)								Hypocaloric			
Katz et al, 2012 (51)														
Walnut	40 OW†	57.4 (11.9)	33.2 (4.4)	OP, USA	Crossover	Supp	Walnut	56	Ad libitum diet	41:41:17	Isocaloric	8 wks	7	Industry
Control										45:34:20				

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Study, year (Reference)	Participants	Mean Age (SD or range), y	Mean Body Weight or BMI (SD or range)§	Setting	Design	Feeding Control	Nut type	Nuts Dose (g/day)‖	Comparator	Diet ††	Energy Balance	Follow-Up	MQS §§	Funding Sources ‖‖
Gebauer et al, 2008 (43)														
1 Pistachio	28 HLP (10 M, 18 W)	48 (7.9)	76.6 (13.2)	OP, USA	Crossover	Met	Pistachio	37	NCEP Step 1 diet	53:34:16	Isocaloric	4 wks	5	Agency
2 Pistachio							Pistachio	74		57:29:16				
Control										62:25:15				
Griel et al, 2008 (44)														
Macadamia	25 HC	50.2 (8.4)	26.3 (3.3)	OP, USA	Crossover	Met	Macadamia	42.5**	AAD	50:33:19	Isocaloric	5 wks	8	Agency-Industry
Control										52:33:17				
Jenkins et al, 2008 (64)*														
Almond	27 HLP (15 M, 12 W)	64 (9)	71.2 (2.5)	OP, Canada	Crossover	Supp	Almond	73	NCEP Step 2 diet + Muffin	47:36:17	Isocaloric	4 wks	6	Agency
Control			71.0 (2.4)							57:26:18				
Rajaram et al, 2009 (45)														
Walnut	25 NL-HLP (14 M, 11 W)	23-65	71.9 (15.5)	OP, USA	Crossover	Met	Walnut	42.5	AAD	60:31:15	Isocaloric	4 wks	5	Agency
Control			71.7 (15.5)							57:30:14				
Tapsell et al, 2009 (46)														
Walnut	35 DM2†	54 (8.7)	92.3 (15.7)	OP, Australia	Parallel	Supp	Walnut	30	Low Fat diet	42:29:24	Isocaloric	12 months	7	Agency
Control			93.4 (3)							41:34:20				
Li et al, 2010 (11)														
Almond	52 OW†	45.4 (2.0)	86 (26.8)	OP, USA	Parallel	Supp	Pistachio	53	Pretzel	55:30:15	Hypocaloric	12 wks	7	Agency
Control		47.3 (2.3)	85.5 (40.2)							65:20:15	Hypocaloric			
Ma et al, 2010 (47)														
Walnut	22 DM2†	58.1 (9.2)	89 (15.5)	OP, USA	Crossover	Supp	Walnut	56	Ad libitum diet	39:44:17	Isocaloric	8 wks	5	N/A
Control										43:38:19				
Torabian et al, 2010 (12)														
Walnut	87 (38 M, 49 W)	54 (10.2)	75.6 (13.2)	OP, USA	Crossover	Supp	Walnut	46	Habitual diet	N/A	Isocaloric	6 months	6	Agency
Control														
Wien et al, 2010 (48)														
Almond	65 PD (17 M, 48 W)	53 (9)	82.9 (14.4)	OP, USA	Parallel	Supp	Almond	58	AAD	42:39:19	Isocaloric	16 wks	9	Agency
Control		54 (11)	80.5 (14.4)							48:30:21				
Wu et al, 2010 (49)														
Walnut	189 MetS	48.2 (8.4)	72.2 (11.4)	OP, USA	Parallel	Supp	Walnut	30	AHA	48:37:15	Isocaloric	12 wks	9	Agency
Control		48.6 (8)	70.6 (10.9)							51:34:15				
Casas-Agustench et al, 2011 (50)														
Mixed Nuts	50 MetS (28 M, 22 W)	52.9 (8.4)	31.6 (2.8)	OP, Spain	Parallel	Supp	Mixed Nuts	30	Prudent diet	41:36:19	Isocaloric	12 wks	6	Agency
Control		50.6 (8.4)	30.0 (3.3)							42:36:19				
Cohen et al, 2011 (19)														
Almond	13 DM2 (7 M, 6 W)	66 (11.9)	96.1 (40.4)	OP, USA	Parallel	Supp	Almond	28	Cheese sticks	N/A	Isocaloric	12 wks	7	Agency
Control			105.1 (32.1)											
Jenkins et al, 2011 (20)														
Mixed Nuts	79 DM2 (52 M, 27 W)	63 (9)	80 (15)	OP, Canada	Parallel	Supp	Mixed nuts	75¶	NCEP Step 2 diet + Muffin	41:41:18	Isocaloric	12 wks	8	Agency
Control		61 (10)	83 (15)							46:35:19				
Li et al, 2011 (21)														
Almond	20 DM2 (9 M, 11 W)	58 (8.9)	26 (3.1)	OP, Taiwan	Crossover	Met	Almond	56	NCEP step 2 diet	47:37:17	Isocaloric	4 wks	5	Agency
Control										57:27:17				
Tey et al, 2011 (51)														
Hazelnut	61	38.9 (14.3)	72 (11.1)	OP, New Zealand	Parallel	Supp	Hazelnut	42	Regular diet	45:39:16‡‡	Isocaloric	12 wks	9	Agency
Control		36.1 (15.2)	67.3 (9.5)							50:33:17				
Darvish Damavandi et al, 2012 (18)														
Cashew	43 DM2 (9 M, 34 W)	51 (7.9)	72.1 (13.1)	OP, Iran	Parallel	Supp	Cashew	30	Regular diet	53:32:16	Isocaloric	8 wks	3	N/A
Control		56 (5.7)	71.9 (9.7)							57:27:16				
Foster et al, 2012 (52)														
Almond	123 OW (11 M, 112 W)	47 (12)	94 (13.1)	OP, USA	Parallel	Supp	Almond	56	Nut free diet	N/A	Hypocaloric	18 months	9	Agency
Control		46.7 (13)	91.5 (11.9)								Hypocaloric			
Katz et al, 2012 (53)														
Walnut	40 OW†	57.4 (11.9)	33.2 (4.4)	OP, USA	Crossover	Supp	Walnut	56	Ad libitum diet	41:41:17	Isocaloric	8 wks	7	Industry
Control										45:34:20				

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Study, year (Reference)	Participants	Mean Age (SD or range), y	Mean Body Weight or BMI (SD or range)§	Setting	Design	Feeding Control	Nut type	Nuts Dose (g/d)ǁ	Comparator	Diet ††	Energy Balance	Follow-Up	MQS §§	Funding Sources ǁǁ
Gebauer et al, 2008 (43)														
1 PD	28 HLP (10 M, 18 W)	48 (7.9)	76.6 (13.2)	OP, USA	Crossover	Met	Pistachio	37	NCEP Step 1 diet	53:34:16	Isocaloric	4 wks	5	Agency
2 PD							Pistachio	74		57:29:16				
Control										62:25:15				
Griel et al, 2008 (44)														
Macadamia	25 HC	50.2 (8.4)	26.3 (3.3)	OP, USA	Crossover	Met	Macadamia	42.5**	AAD	50:33:19	Isocaloric	5 wks	8	Agency-Industry
Control										52:33:17				
Jenkins et al, 2008 (54)*														
Almond	27 HLP (15 M, 12 W)	64 (9)	71.2 (2.5)	OP, Canada	Crossover	Supp	Almond	73	NCEP Step 2 diet + Muffin	47:36:17	Isocaloric	4 wks	6	Agency
Control			71.0 (2.4)							57:26:18				
Rajaram et al, 2009 (45)														
Walnut	25 NL-HLP (14 M, 11 W)	23-65	71.9 (15.5)	OP, USA	Crossover	Met	Walnut	42.5	AAD	60:31:15	Isocaloric	4 wks	5	Agency
Control			71.7 (15.5)							57:30:14				
Tapsell et al, 2009 (46)														
Walnut	35 DM2†	54 (8.7)	92.3 (15.7)	OP, Australia	Parallel	Supp	Walnut	30	Low Fat diet	42:29:24	Isocaloric	12 months	7	Agency
Control			93.4 (3)							41:34:20				
Li et al, 2010 (11)														
Almond	52 OW†	45.4 (2.0)	86 (26.8)	OP, USA	Parallel	Supp	Pistachio	53	Pretzel	55:30:15	Hypocaloric	12 wks	7	Agency
Control		47.3 (2.3)	85.5 (40.2)							65:20:15	Hypocaloric			
Ma et al, 2010 (47)														
Walnut	22 DM2†	58.1 (9.2)	89 (15.5)	OP, USA	Crossover	Supp	Walnut	56	Ad libitum diet	39:44:17	Isocaloric	8 wks	5	N/A
Control										43:38:19				
Torabian et al, 2010 (12)														
Walnut	87 (38 M, 49 W)	54 (10.2)	75.6 (13.2)	OP, USA	Crossover	Supp	Walnut	46	Habitual diet	N/A	Isocaloric	6 months	6	Agency
Control														
Wien et al, 2010 (48)														
Almond	65 PD (17 M, 48 W)	53 (9)	82.9 (14.4)	OP, USA	Parallel	Supp	Almond	58	AAD	42:39:19	Isocaloric	16 wks	9	Agency
Control		54 (11)	80.5 (14.4)							48:30:21				
Wu et al, 2010 (49)														
Walnut	189 MetS	48.2 (8.4)	72.2 (11.4)	OP, USA	Parallel	Supp	Walnut	30	AHA	48:37:15	Isocaloric	12 wks	9	Agency
Control		48.6 (8)	70.6 (10.9)							51:34:15				
Casas-Agustench et al, 2011 (50)														
Mixed Nuts	50 MetS (28 M, 22 W)	52.9 (8.4)	31.6 (2.8)	OP, Spain	Parallel	Supp	Mixed Nuts	30	Prudent diet	41:36:19	Isocaloric	12 wks	6	Agency
Control		50.6 (8.4)	30.0 (3.3)							42:36:19				
Cohen et al, 2011 (19)														
Almond	13 DM2 (7 M, 6 W)	66 (11.9)	96.1 (40.4)	OP, USA	Parallel	Supp	Almond	28	Cheese sticks	N/A	Isocaloric	12 wks	7	Agency
Control			105.1 (32.1)											
Jenkins et al, 2011 (20)														
Mixed Nuts	79 DM2 (52 M, 27 W)	63 (9)	80 (15)	OP, Canada	Parallel	Supp	Mixed nuts	75¶	NCEP Step 2 diet + Muffin	41:41:18	Isocaloric	12 wks	8	Agency
Control		61 (10)	83 (15)							46:35:19				
Li et al, 2011 (21)														
Almond	20 DM2 (9 M, 11 W)	58 (8.9)	26 (3.1)	OP, Taiwan	Crossover	Met	Almond	56	NCEP step 2 diet	47:37:17	Isocaloric	4 wks	5	Agency
Control										57:27:17				
Tey et al, 2011 (51)														
Hazelnut	61	38.9 (14.3)	72 (11.1)	OP, New Zealand	Parallel	Supp	Hazelnut	42	Regular diet	45:39:16‡‡	Isocaloric	12 wks	9	Agency
Control		36.1 (15.2)	67.3 (9.5)							50:33:17				
Darvish Damavandi et al, 2012 (18)														
Cashew	43 DM2 (9 M, 34 W)	51 (7.9)	72.1 (13.1)	OP, Iran	Parallel	Supp	Cashew	30	Regular diet	53:32:16	Isocaloric	8 wks	3	N/A
Control		56 (5.7)	71.9 (9.7)							57:27:16				
Foster et al, 2012 (52)														
Almond	123 OW (11 M, 112 W)	47 (12)	94 (13.1)	OP, USA	Parallel	Supp	Almond	56	Nut free diet	N/A	Hypocaloric	18 months	9	Agency
Control		46.7 (13)	91.5 (11.9)								Hypocaloric			
Wang et al, 2012 (22)														
Pistachios	86 MetS	51.9 (8.8)	28.1 (3.2)	OP, China	Parallel	Supp	Pistachio	42	AHA Step 1 diet	N/A	Isocaloric	12 wks	5	Industry
High pistachios		51.8 (9.4)	28 (4.5)				Pistachio	70						
Control		50.7 (9.9)	28 (4.4)											
West et al, 2012 (55)*														
1 Pistachio	28 HLP (10 M, 18 W)	48 (7.9)	76.6 (13.2)	OP, USA	Crossover	Met	Pistachio	37	NCEP Step 1 diet	53:34:16	Isocaloric	4 wks	5	Agency
2 Pistachio							Pistachio	74		57:29:16				
Control										62:25:15				
Somerset et al, 2013 (9)														
Macadamia	64 OW (10 M, 54 W)	43.7 (8.4)	95 (14.7)	OP, Australia	Parallel	DA	Macadamia	46	Regular diet	36:38:21	Isocaloric	10 wks	9	Agency
Control		43.2 (10.9)	99.6 (15.2)							41:38:17				

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Study, year (Reference)	Participants	Mean Age (SD or range), y	Mean Body Weight or BMI (SD or range)§	Setting	Design	Feeding Control	Nut type	Nuts Dose (g/day)‖	Comparator	Diet ††	Energy Balance	Follow-Up	MQS §§	Funding Sources ‖‖
Wang et al, 2012 (22)														
Pistachios	86 MetS	51.9 (8.8)	28.1 (3.2)	OP, China		Supp	Pistachio	42	AHA Step 1 diet	N/A	Isocaloric	12 wks	5	Industry
High pistachios		51.8 (9.4)	28 (4.5)				Pistachio	70						
Control		50.7 (9.9)	28 (4.4)											
West et al, 2012 (62)*														
1 Pistachio	28 HLP (10 M, 18 W)	48 (7.9)	76.6 (13.2)	OP, USA	Crossover	Met	Pistachio	37	NCEP Step 1 diet	53:34:16	Isocaloric	4 wks	5	Agency
2 Pistachio							Pistachio	74		57:29:16				
Control										62:25:15				
Anderson et al, 2013 (52)														
Pistachio	22 OW	55 (2)	90 (3.6)	OP, USA	Parallel	N/A	Pistachio	35.4	N/A	N/A	N/A	6 wks	5	N/A
Control														
Berryman et al, 2013 (53)														
Almond	53 HC	N/A	N/A	OP, USA	Crossover	N/A	Almond	42.5	Muffin	51:33:16	Isocaloric	6 wks	N/A	N/A
Control										59:26:15				
Darvish Damavandi et al, 2013 (54)														
Hazelnut	48 DM2†	55.7 (7.7)	72.1 (10.3)	OP, Iran	Parallel	Supp	Hazelnut	29	Self-selected diet	55:31:16	Isocaloric	8 wks	6	None
Control			72 (9.6)							60:25:17				
Holligan et al, 2013 (63)*														
1 Pistachio	28 HLP (10 M, 18 W)	48 (7.9)	76.6 (13.2)	OP, USA	Crossover	Met	Pistachio	37	NCEP Step 1 diet	53:34:16	Isocaloric	4 wks	N/A	Agency
2 Pistachio							Pistachio	74		57:29:16				
Control										62:25:15				
Sauder et al, 2013 (55)														
Pistachio	30 DM2 (15 M, 15 W)†	56.1 (1.4)	31.2 (1.1)	OP, USA	Crossover	Met	Pistachio	73.4	Low fat diet	51:33:17	Isocaloric	4 wks	N/A	Industry
Control										55:27:18				
Somerset et al, 2013 (9)														
Macadamia	64 OW (10 M, 54 W)	43.7 (8.4)	95 (14.7)	OP, Australia	Parallel	DA	Macadamia	46	Regular diet	36:38:21	Isocaloric	10 wks	9	Agency
Control		43.2 (10.9)	99.6 (15.2)							41:38:17				
Tan et al, 2014 (56)														
Almond (Breakfast)	137 OW (48 M, 89 W)	32.9 (11.5)	80.5 (15)	OP, USA	Parallel	Supp	Almond	43	Regular diet	50:16:15	Isocaloric	4 wks	5	Industry
Almond (Morning snack)		27.8 (10.7)	83.2 (21.1)				Almond	43		51:15:14				
Almond (Lunch)		29.3 (13.5)	84.8 (13.7)				Almond	43		48:16:17				
Almond (Afternoon snack)		29 (11.9)	81.8 (14.6)				Almond	43		49:15:16				
Control		28.7 (9.6)	77.2 (16.8)							48:15:16				
Tey et al, 2013 (57)														
Hazelnut 30 g	107 OW (46 M, 61W)	43.8 (13.5)	86.2 (11.8)	OP, New Zealand	Parallel	Supp	Hazelnut	30	Usual diet	42:39:17	Isocaloric	12 wks	6	Agency
Hazelnut 60 g		42.8 (10.6)	92 (19.6)				Hazelnut	60		38:42:16				
Control		41.1 (13.1)	88.7 (16.7)							47:33:17				
Gulati et al, 2014 (58)														
Pistachio	68 MetS (37 M, 31 W)	41.6 (8.4)	81.6 (12.9)	OP, India	Parallel	DA	Pistachio	50**	Standard diabetic diet	51:29:20	Isocaloric	24 wks	4	Industry
Control		43.3 (8.1)	80.3 (10.3)							60:25:15				
Wu et al, 2014 (59)														
Walnut	40 (10 M, 30 W)	60 (1)	24.9 (0.6)	OP, Germany	Crossover	Supp	Walnut	43	Western-type diet	50:35:15	Isocaloric	8 wks	7	Industry
Control														

Table 1. Characteristics of RCTs Investigating the effect of Tree Nuts on Criteria of the MetS

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MetS: metabolic syndrome; DM2: type 2 diabetes mellitus; OW: overweight; HLP: hyperlipidemic; NL-HLP: normal to mildly hyperlipidemic; HC: Hypercholesterolemic; NL-HC: normal to hypercholesterolemic; M: men; W: women; BMI: body mass index; OP: out-patient; IP: In-patient; USA: United States of America; SUPP: supplement; Met: metabolic; DA: dietary advice; N/A: not available; AHA: American Heart Association; AAD: Average American Diet; NCEP: National Cholesterol Education Program; CHO-LCD: Self-selected Complex Carbohydrate diet; WKS: weeks; MQS: Heyland Methodological Quality Score.

* Companion reports: Jenkins et al, 2008 for Jenkins et al, 2002; Schutte et al, 2006 for Mukuddem-Petersen et al, 2007; ~~Wang~~ West et al, 2012 and Holligan et al, 2013 for Gebauer et al, 2008.

† Baseline characteristics were given based on the number of randomized participants for Li et al, 2010 *n* = 70; Ma et al, 2010 *n* = 24; Zambon et al, 2000 *n* = 55; Katz et al, 2012 *n* = 46; Sauder et al, 2013 *n* = 30; Gulati et al, 2014 *n* = 68 ~~and~~ for recruited subjects for Tapsell et al. 2009 (*n* = 50), and for age for Darvish Damavandi et al, 2013 (*n* = 50).

‡ Mean age was given ~~separetly~~separately for men and women.

§ Body weight is reported in kg and BMI is reported in kg/m^2. BMI is reported only when no data on weight were available.

‖ Nut dose is given based on ~~grams (g) per g~~/day, 1oz = 28 g.

¶ Median was taken from a range given. Iwamoto et al, 2010 range 50-54 g/day; Jenkins et al, 2011 range 50-75 g/day; Lovejoy et al, 2002 range 57-113 g/day; Mukuddem-Petersen et al, 2007 range 63-108 g/day; Torabian et al, 2010 range 28-64 g/day; Zambon et al, 2000 range 41-56 g/day.

** Based on 2100 kcal for Griel et al, 2008 and based on 1400 kcal (~60 kg) for Gulati et al, 2014.

†† Energy from carbohydrate:fat:protein.

‡‡ Values for carbohydrates are given in geometric means.

§§ Trials with scores ≥8 were considered to be of high quality.

‖‖ Agency funding is that from government, university, or not-for-profit health agency sources.

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FIGURE LEGENDS

Figure 1. Summary of evidence search and selection

Figure 2. Forest plot of the RCTs investigating the effect of Tree Nuts on Triglycerides. Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia, metabolic syndrome criteria, diabetes and their combination (total). Paired analyses were applied to all crossover trials (~~15~~20) and one substudy. Data are expressed as mean differences (MD) with 95% CI, using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using the Cochrane's Q statistic (I^2) at a significance level of $P < 0.10$ and quantified by I^2, levels ≤ 50% represent moderate heterogeneity, ≥ 50 % represent substantial ~~considerable~~ heterogeneity and ≥ 75%, considerable ~~substantial~~ heterogeneity. TG = Triglycerides, mmol/L = mill moles per liter, A = Almond, AC = Almond + Chocolate, HF = High Fat, LF = Low Fat.

Figure 3. Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia, metabolic syndrome criteria, diabetes and their combination (total). Paired analyses were applied to all crossover trials (10) and one substudy. Data are expressed as mean differences (MD) with 95% CI, using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using the Cochrane's Q statistic (I^2) at a significance level of $P < 0.10$ and quantified by I^2, levels ≥ 50 % represent substantial heterogeneity and ≥ 75%, considerable heterogeneity. FBG = Fasting Blood Glucose; mmol/L = mill moles per liter; HF = High Fat; LF = Low Fat.

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Figure 1. Summary of evidence search and selection

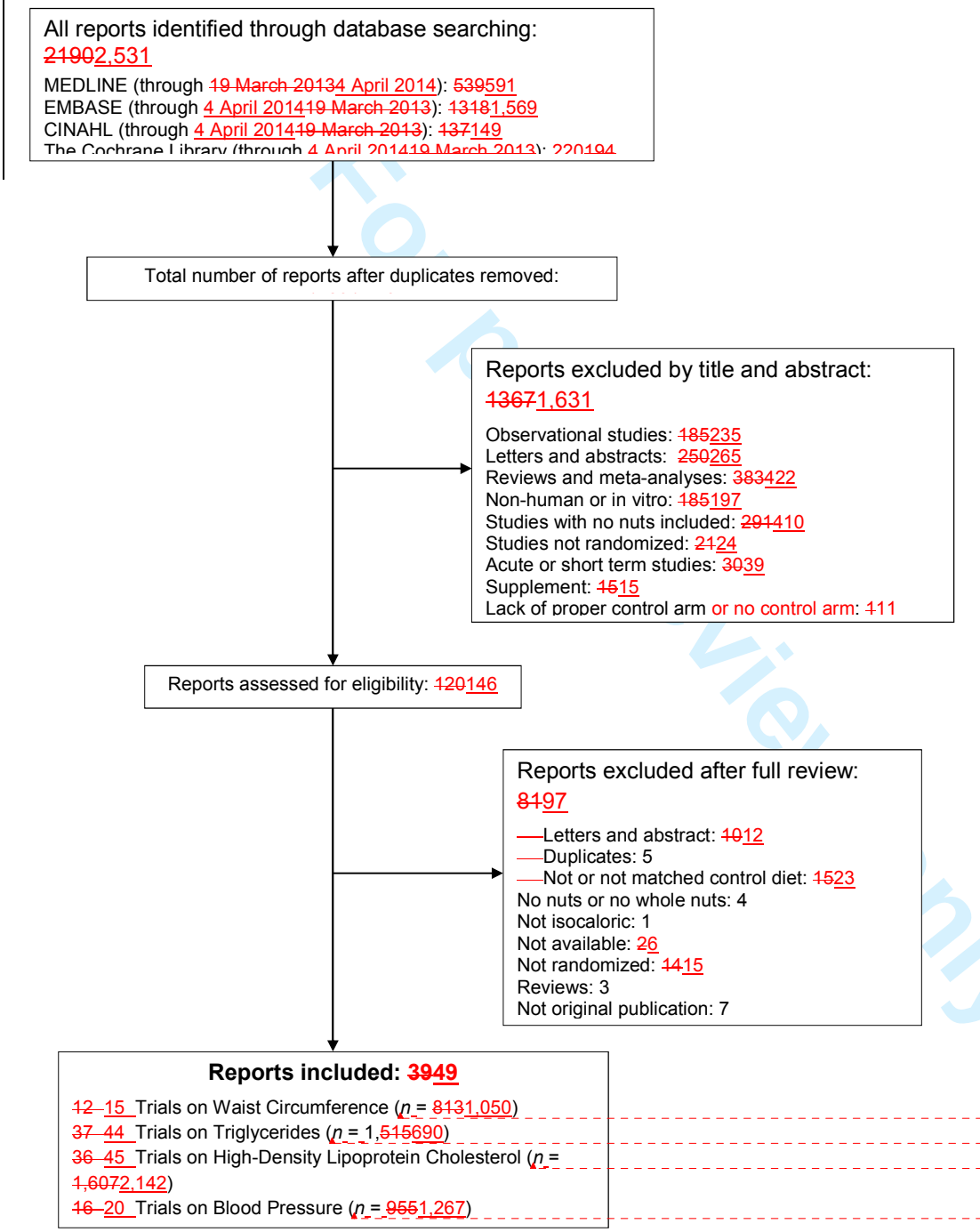

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Figure 2. Forest plot of the RCTs investigating the effect of Tree Nuts on Triglycerides

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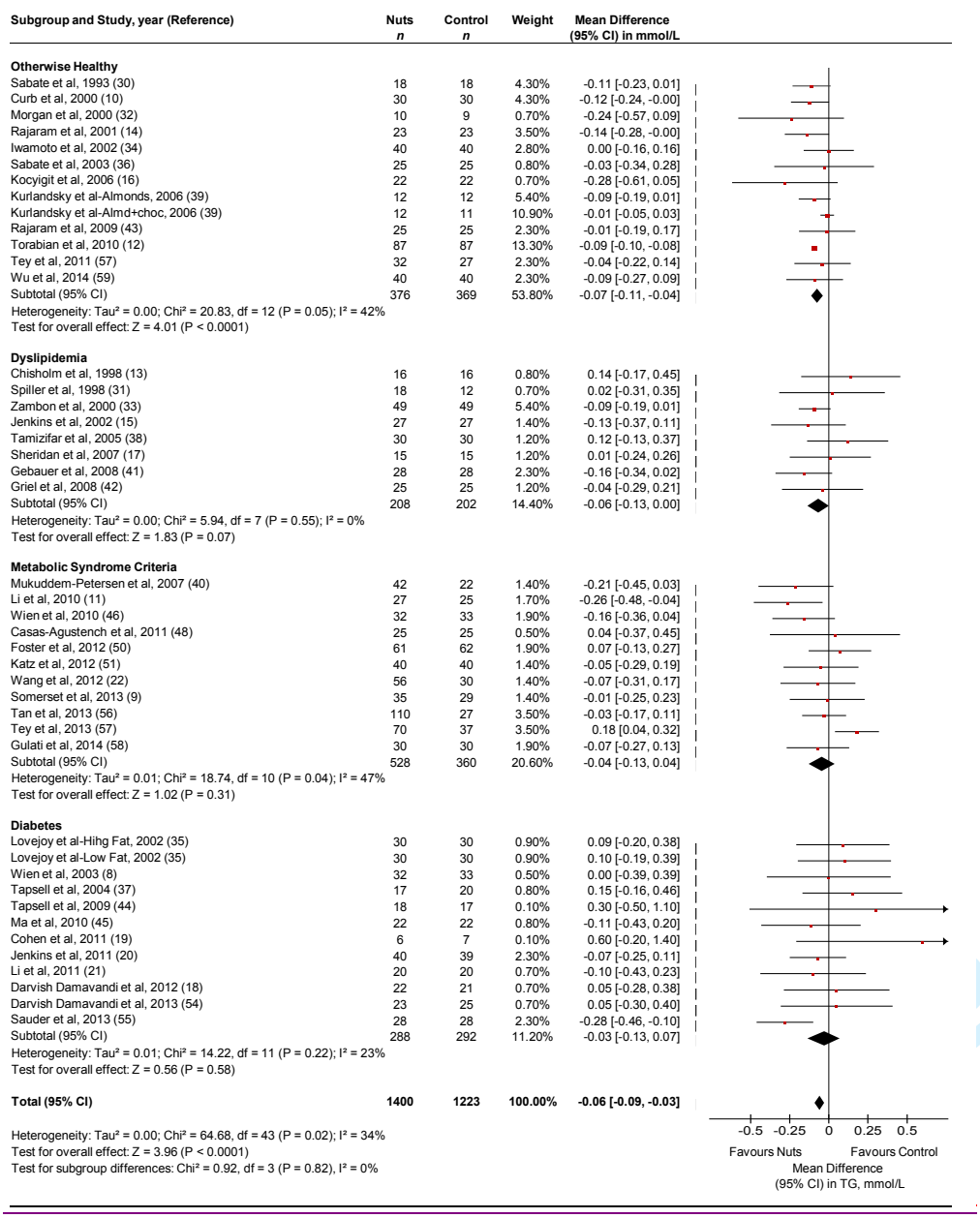

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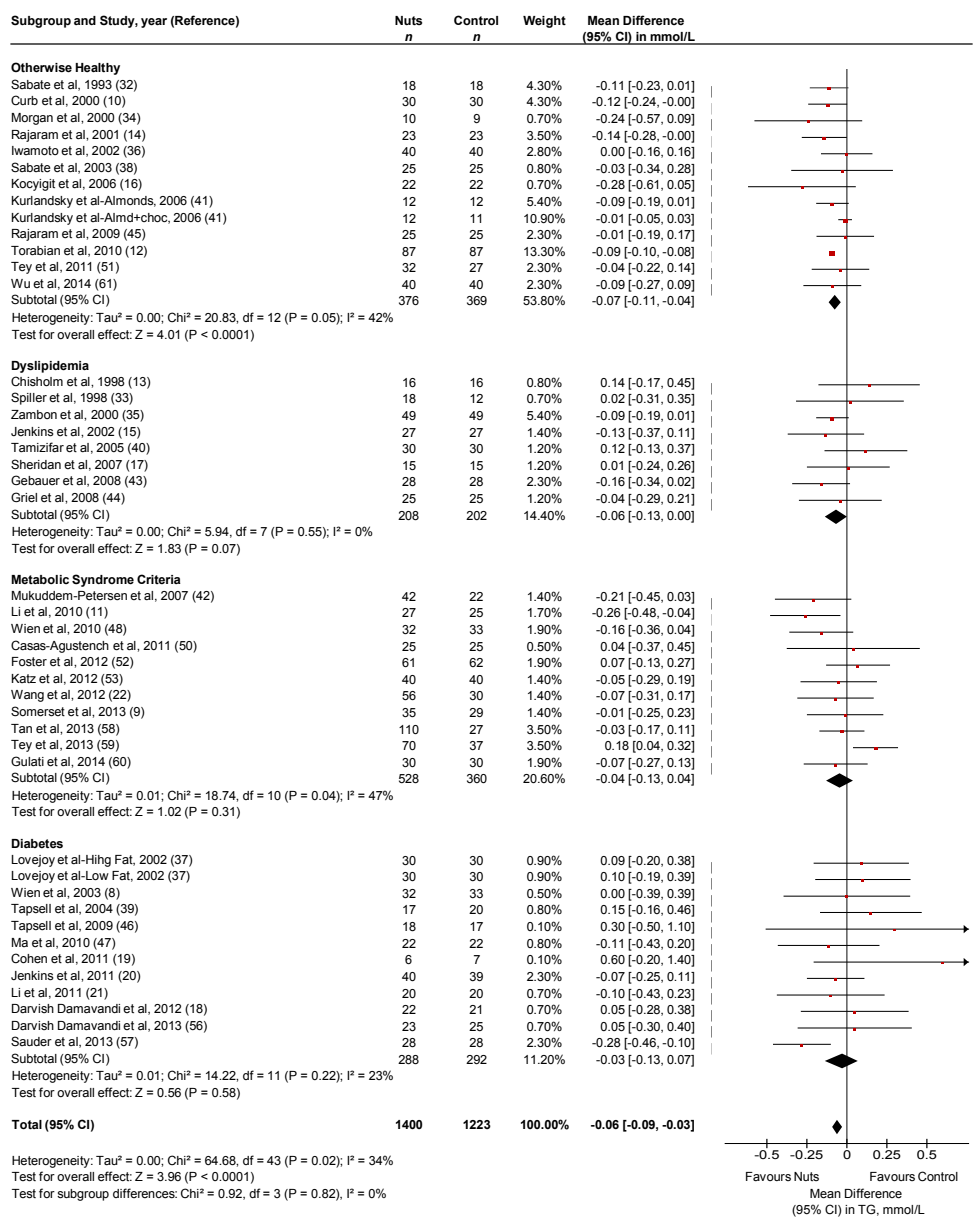

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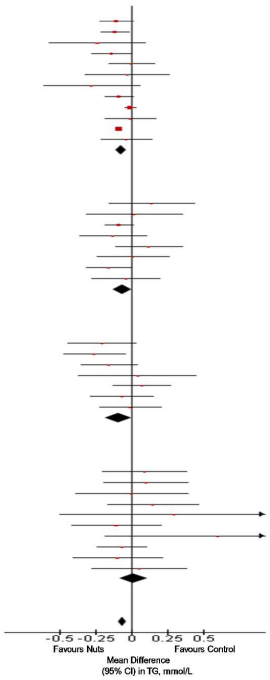
Subgroup and Study, year (Reference)	Nuts n	Control n n	Weight	Mean Difference (95% CI) in mmol/L
Otherwise Healthy				
Sabate et al, 1993 (32)	18	18	4.40%	-0.11 [-0.23, 0.01]
Curb et al, 2000 (10)	30	30	5.90%	-0.12 [-0.22, -0.02]
Morgan et al, 2000 (34)	10	9	0.70%	-0.24 [-0.57, 0.09]
Rajaram et al, 2001 (14)	23	23	3.40%	-0.14 [-0.28, -0.00]
Iwamoto et al, 2002 (36)	40	40	2.70%	0.00 [-0.16, 0.16]
Sabate et al, 2003 (38)	25	25	0.80%	-0.03 [-0.32, 0.26]
Kocyigit et al, 2006 (16)	22	22	0.70%	-0.28 [-0.61, 0.05]
Kurlandsky et al-Almonds, 2006 (41)	12	12	5.90%	-0.09 [-0.19, 0.01]
Kurlandsky et al-Almd+choc, 2006 (41)	12	11	15.90%	-0.01 [-0.05, 0.03]
Rajaram et al, 2009 (45)	25	25	2.20%	-0.01 [-0.19, 0.17]
Torabian et al, 2010 (12)	87	87	23.20%	-0.09 [-0.10, -0.08]
Tey et al, 2011 (51)	32	27	2.20%	-0.04 [-0.22, 0.14]
Subtotal (95% CI)	336	329	67.80%	-0.07 [-0.11, -0.04]
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 20.97$, df = 11 (P = 0.03); $I^2 = 48\%$				
Test for overall effect: Z = 3.89 (P = 0.0001)				
Dyslipidemia				
Chisholm et al, 1998 (13)	16	16	0.80%	0.14 [-0.15, 0.43]
Spiller et al, 1998 (33)	18	12	0.70%	0.02 [-0.31, 0.35]
Zambon et al, 2000 (35)	49	49	5.90%	-0.09 [-0.19, 0.01]
Jenkins et al, 2002 (15)	27	27	1.30%	-0.13 [-0.37, 0.11]
Tamizifar et al, 2005 (40)	30	30	1.30%	0.12 [-0.12, 0.36]
Sheridan et al, 2007 (17)	15	15	1.10%	0.01 [-0.24, 0.26]
Gebauer et al, 2008 (43)	28	28	2.70%	-0.16 [-0.32, -0.00]
Griel et al, 2008 (44)	25	25	1.30%	-0.04 [-0.28, 0.20]
Subtotal (95% CI)	208	202	15.00%	-0.06 [-0.13, 0.00]
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.82$, df = 7 (P = 0.45); $I^2 = 0\%$				
Test for overall effect: Z = 1.90 (P = 0.06)				
Metabolic Syndrome Features				
Mukuddem-Petersen et al, 2007 (42)	42	22	1.30%	-0.21 [-0.45, 0.03]
Li et al, 2010 (11)	27	25	1.50%	-0.26 [-0.48, -0.04]
Wien et al, 2010 (48)	32	33	1.80%	-0.16 [-0.36, 0.04]
Casas-Agustench et al, 2011 (50)	25	25	0.40%	0.04 [-0.37, 0.45]
Foster et al, 2012 (52)	61	62	1.80%	0.07 [-0.13, 0.27]
Wang et al, 2012 (22)	56	30	1.50%	-0.07 [-0.29, 0.15]
Somerset et al, 2013 (9)	35	29	1.50%	-0.01 [-0.23, 0.21]
Subtotal (95% CI)	278	226	9.80%	-0.09 [-0.19, 0.00]
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.37$, df = 6 (P = 0.29); $I^2 = 19\%$				
Test for overall effect: Z = 1.96 (P = 0.05)				
Diabetes				
Lovejoy et al-Hihg Fat, 2002 (37)	30	30	0.80%	0.09 [-0.20, 0.38]
Lovejoy et al-Low Fat, 2002 (37)	30	30	0.80%	0.19 [-0.19, 0.39]
Wien et al, 2003 (8)	32	33	0.50%	0.00 [-0.39, 0.39]
Tapsell et al, 2004 (39)	17	20	0.70%	0.15 [-0.16, 0.46]
Tapsell et al, 2009 (46)	18	17	0.10%	0.30 [-0.50, 1.10]
Ma et al, 2010 (47)	22	22	0.70%	-0.11 [-0.42, 0.20]
Cohen et al, 2011 (19)	6	7	0.10%	0.60 [-0.18, 1.38]
Jenkins et al, 2011 (20)	40	39	2.20%	-0.07 [-0.25, 0.11]
Li et al, 2011 (21)	20	20	0.70%	-0.10 [-0.41, 0.21]
Darvish Damavandi et al, 2012 (18)	22	21	0.70%	0.05 [-0.28, 0.38]
Subtotal (95% CI)	237	239	7.40%	0.01 [-0.09, 0.11]
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.97$, df = 9 (P = 0.74); $I^2 = 0\%$				
Test for overall effect: Z = 0.24 (P = 0.81)				
Total (95% CI)	**1059**	**996**	**100.00%**	**-0.07 [-0.09, -0.04]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 45.56$, df = 36 (P = 0.13); $I^2 = 21\%$				
Test for overall effect: Z = 4.74 (P < 0.00001)				
Test for subgroup differences: $Chi^2 = 2.94$, df = 3 ($I^2 = 0.40$), $I^2 = 0\%$				



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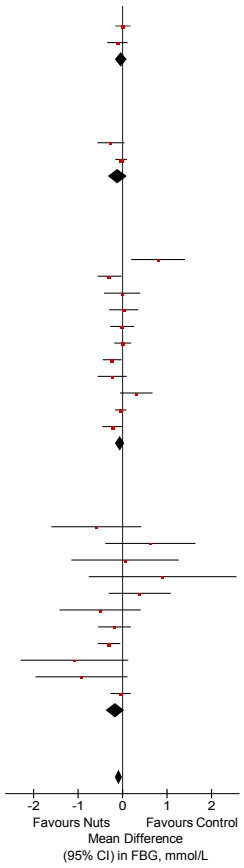
Subgroup and Study, year (Reference)	Nuts *n*	Control *n*	Weight	Mean Difference (95% CI) in mmol/L
Otherwise Healthy				
Sabate et al, 2003 (36)	25	25	7.80%	0.01 [-0.15, 0.17]
Wu et al, 2014 (59)	40	40	6.00%	-0.11 [-0.33, 0.11]
Subtotal (95% CI)	65	65	13.80%	-0.03 [-0.16, 0.10]
Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 1 (P = 0.38); I² = 0%				
Test for overall effect: Z = 0.49 (P = 0.63)				
Dyslipidemia				
Jenkins et al, 2008 (61)	27	27	4.20%	-0.26 [-0.55, 0.03]
Holligan et al, 2013 (63)	28	28	9.20%	-0.03 [-0.15, 0.09]
Subtotal (95% CI)	55	55	13.40%	-0.10 [-0.31, 0.11]
Heterogeneity: Tau² = 0.01; Chi² = 2.03 df = 1 (P = 0.15); I² = 51%				
Test for overall effect: Z = 0.97 (P = 0.33)				
Metabolic Syndrome Criteria				
Schutte et al, 2006 (60)	41	21	1.40%	0.80 [0.21, 1.39]
Li et al, 2010 (11)	27	25	5.00%	-0.29 [-0.54, -0.04]
Wien et al, 2010 (46)	32	33	2.80%	-0.01 [-0.40, 0.38]
Wu et al, 2010 (47)	94	95	3.80%	0.03 [-0.28, 0.34]
Casas-Agustench et al, 2011 (48)	25	25	5.00%	-0.01 [-0.26, 0.24]
Katz et al, 2012 (51)	40	40	7.20%	0.00 [-0.17, 0.18]
Wang et al, 2012 (22)	56	30	6.50%	-0.23 [-0.43, -0.03]
Anderson et al, 2013 (52)	11	11	3.80%	-0.23 [-0.54, 0.08]
Somerset et al, 2013 (9)	35	29	3.20%	0.31 [-0.04, 0.66]
Tan et al, 2013 (56)	110	27	9.30%	-0.04 [-0.16, 0.08]
Gulati et al, 2014 (58)	30	30	6.00%	-0.22 [-0.44, -0.00]
Subtotal (95% CI)	501	366	53.90%	-0.06 [-0.17, 0.06]
Heterogeneity: Tau² = 0.02; Chi² = 22.77, df = 10 (P = 0.01); I² = 56%				
Test for overall effect: Z = 0.97 (P = 0.33)				
Diabetes				
Lovejoy et al-Hihg Fat, 2002 (35)	30	30	0.50%	-0.59 [-1.59, 0.41]
Lovejoy et al-Low Fat, 2002 (35)	30	30	0.50%	0.63 [-0.37, 1.63]
Wien et al, 2003 (8)	32	33	0.40%	0.06 [-1.14, 1.26]
Tapsell et al, 2009 (44)	18	17	0.20%	0.90 [-0.75, 2.55]
Ma et al, 2010 (45)	22	22	1.10%	0.39 [-0.30, 1.08]
Cohen et al, 2011 (19)	6	7	0.60%	-0.50 [-1.40, 0.40]
Jenkins et al, 2011 (20)	40	39	3.20%	-0.18 [-0.53, 0.17]
Li et al, 2011 (21)	20	20	5.40%	-0.30 [-0.54, -0.06]
Darvish Damavandi et al, 2012 (18)	22	21	0.40%	-1.08 [-2.28, 0.12]
Darvish Damavandi et al, 2013 (54)	23	25	0.50%	-0.92 [-1.94, 0.10]
Sauder et al, 2013 (55)	28	28	6.00%	-0.04 [-0.26, 0.18]
Subtotal (95% CI)	271	272	18.80%	-0.16 [-0.37, 0.05]
Heterogeneity: Tau² = 0.03; Chi² = 14.82, df = 10 (P = 0.14); I² = 33%				
Test for overall effect: Z = 1.50 (P = 0.13)				
Total (95% CI)	**892**	**758**	**100.00%**	**-0.08 [-0.16, -0.01]**
Heterogeneity: Tau² = 0.01; Chi² = 42.36, df = 25 (P = 0.02); I² = 41%				
Test for overall effect: Z = 2.19 (P = 0.03)				
Test for subgroup differences: Chi² = 1.22, df = 3 (P = 0.75), I² = 0%				



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Subgroup and Study, year (Reference)	Nuts n	Control n	Weight	Mean Difference (95% CI) in mmol/L
Otherwise Healthy				
Sabate et al, 2003 (38)	25	25	7.80%	0.01 [-0.15, 0.17]
Wu et al, 2014 (61)	40	40	6.00%	-0.11 [-0.33, 0.11]
Subtotal (95% CI)	65	65	13.80%	-0.03 [-0.16, 0.10]
Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 1 (P = 0.38); I² = 0%				
Test for overall effect: Z = 0.49 (P = 0.63)				
Dyslipidemia				
Jenkins et al, 2008 (54)	27	27	4.20%	-0.26 [-0.03, 0.55]
Holligan et al, 2013 (65)	28	28	9.20%	-0.03 [-0.15, 0.09]
Subtotal (95% CI)	55	55	13.40%	0.08 [-0.19, 0.36]
Heterogeneity: Tau² = 0.01; Chi² = 32.03 df = 1 (P = 0.15); I² = 51%				
Test for overall effect: Z = 0.97 (P = 0.33)				
Metabolic Syndrome Criteria				
Schutte et al, 2006 (53)	41	21	1.40%	0.80 [0.21, 1.39]
Li et al, 2010 (11)	27	25	5.00%	-0.29 [-0.54, -0.04]
Wien et al, 2010 (48)	32	33	2.80%	-0.01 [-0.40, 0.38]
Wu et al, 2010 (49)	94	95	3.80%	0.03 [-0.28, 0.34]
Casas-Agustench et al, 2011 (50)	25	25	5.00%	-0.01 [-0.26, 0.24]
Katz et al, 2012 (53)	40	40	7.20%	0.00 [-0.17, 0.18]
Wang et al, 2012 (22)	56	30	6.50%	-0.23 [-0.43, -0.03]
Anderson et al, 2013 (54)	11	11	3.80%	-0.23 [-0.54, 0.08]
Somerset et al, 2013 (9)	35	29	3.20%	0.31 [-0.04, 0.66]
Tan et al, 2013 (58)	110	27	9.20%	-0.04 [-0.16, 0.08]
Gulati et al, 2014 (59)	30	30	6.00%	-0.22 [-0.44, -0.00]
Subtotal (95% CI)	501	366	53.90%	-0.06 [-0.17, 0.06]
Heterogeneity: Tau² = 0.02; Chi² = 22.77, df = 10 (P = 0.01); I² = 56%				
Test for overall effect: Z = 0.97 (P = 0.33)				
Diabetes				
Lovejoy et al-Hihg Fat, 2002 (37)	30	30	0.50%	-0.59 [-1.59, 0.41]
Lovejoy et al-Low Fat, 2002 (37)	30	30	0.60%	0.63 [-0.33, 1.59]
Wien et al, 2003 (8)	32	33	0.40%	0.06 [-1.14, 1.26]
Tapsell et al, 2009 (46)	18	17	0.20%	0.90 [-0.75, 2.55]
Ma et al, 2010 (47)	22	22	1.10%	0.39 [-0.30, 1.08]
Cohen et al, 2011 (19)	6	7	0.60%	-0.50 [-1.40, 0.40]
Jenkins et al, 2011 (20)	40	39	3.20%	-0.18 [-0.53, 0.17]
Li et al, 2011 (21)	20	20	5.40%	-0.30 [-0.54, -0.06]
Darvish Damavandi et al, 2012 (18)	22	21	0.40%	-1.08 [-2.28, 0.12]
Darvish Damavandi et al, 2013 (56)	23	25	0.50%	-0.92 [-1.94, 0.10]
Sauder et al, 2013 (57)	28	28	6.00%	-0.04 [-0.26, 0.18]
Subtotal (95% CI)	271	272	18.90%	-0.16 [-0.37, 0.05]
Heterogeneity: Tau² = 0.03; Chi² = 15.02, df = 10 (P = 0.13); I² = 33%				
Test for overall effect: Z = 1.47 (P = 0.14)				
Total (95% CI)	**892**	**758**	**100.00%**	**-0.08 [-0.16, -0.01]**
Heterogeneity: Tau² = 0.01; Chi² = 42.52, df = 25 (P = 0.02); I² = 41%				
Test for overall effect: Z = 2.182 (P = 0.03)				
Test for subgroup differences: Chi² = 1.17, df = 3 (P = 0.76), I² = 0%				

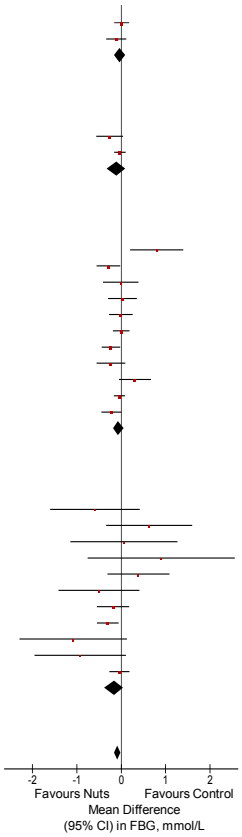

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Figure 1. Summary of evidence search and selection

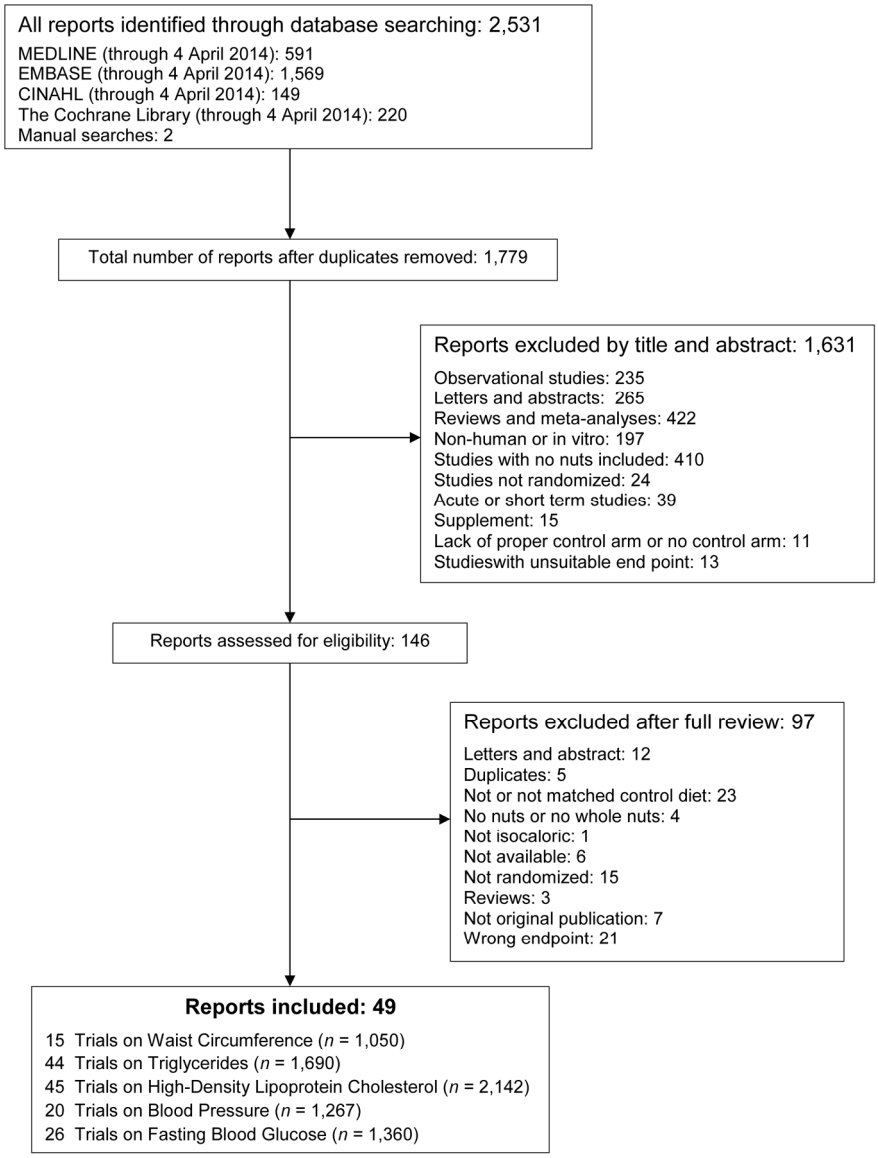

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Figure 2. Forest plot of the RCTs investigating the effect of Tree Nuts on Triglycerides

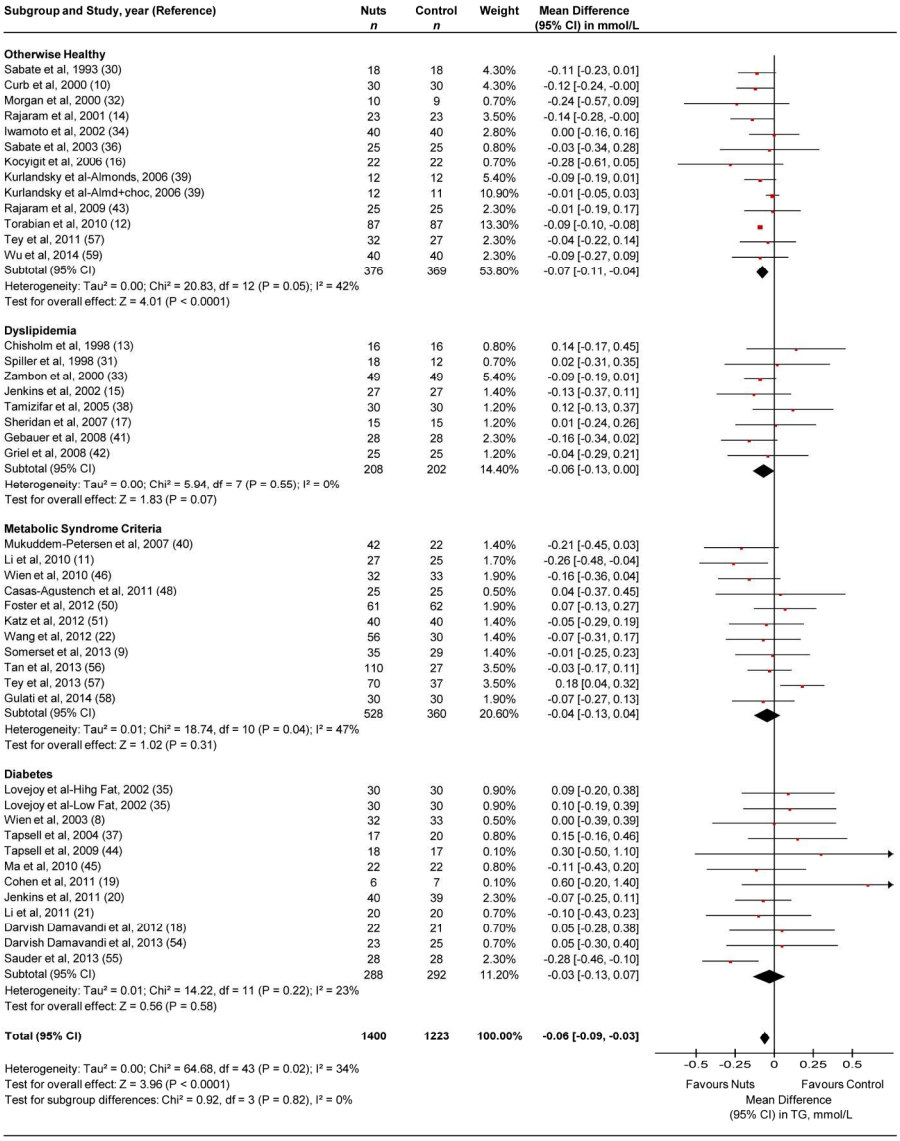

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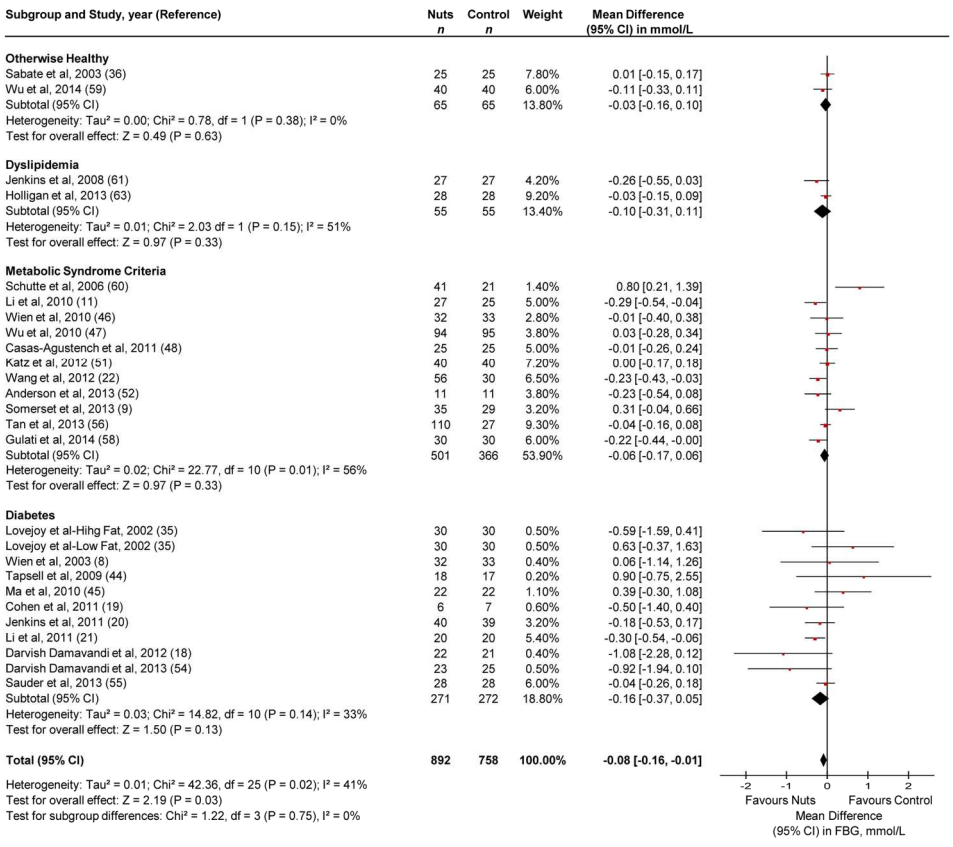
Figure 3. Forest plot of the RCTs investigating the effect of Tree Nuts on Fasting Blood Glucose



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Appendix Table 1. Search Strategy for Studies Assessing the Effect of Tree Nut consumption on Metabolic Syndrome Criteria in RCTs.

Database	SearchPeriod	Search
MEDLINE	1946 to March Week 4 2014	1. exp nut/ Or nuts.mp. Or nut.mp. Or expbertholletia/ Or walnut*.mp. Or expJuglans/ Or almond*.mp. Or expPrunus/ Or pecan*.mp. Or expCarya/ Or pistachio*.mp. Or expPistacia/ Or cashew*.mp. Or expAnacardium/ Or hazelnut*.mp. Or expCorylus/ Or macadamia*.mp. Or exp Macadamia/ 2. ogtt.mp. Or exp Glucose Tolerance Test/ Or "glucose tolerance test".mp. Or hba1c.mp. Or fructosamine*.mp. Or expFructosamine/ Or insulin*.mp. Or exp Insulin/ Or glycemia*.mp. Or glycaemia*.mp. Or hyperinsulin*.mp. Or expHyperinsulinism/ Or dysglycemia*.mp. Or dysglycaemia*.mp. Or gly* albumin.mp. Or expHemoglobin A, Glycosylated/ Or "blood glucose".mp. Or exp Blood Glucose/ Or hyperglycemia*.mp. Or 39. hyperglycaemia*.mp. Or expHyperglycemia/ Or "homeo* model assessment".mp. Or homa.mp. Or diabetes.mp. Or exp Diabetes Mellitus/ 3. exp Hypertension/ Or exp Blood Pressure/ Or "systolic blood pressure".mp. Or "diastolic blood pressure".mp. Or hypertension.mp. Or SBP.mp. Or DBP.mp. Or "mean arterial pressure".mp. 4. exp Triglycerides/ Or exp Hypertriglyceridemia/ Or hypertriglyceridemia*.mp. Or triglyceride*.mp. Or triacylglycerol*.mp. Or dyslipidemia*.mp. Or dyslipidaemia*.mp. Or exp Dyslipidemias/ 5. exp Cholesterol, HDL/ Or "high density lipoprotein cholesterol".mp. Or hdl.mp. 6. "abdominal obesity".mp. Or exp Obesity, Abdominal/ Or "waist circumference".mp. Or exp waist circumference/ Or "abdominal fat*".mp. Or exp Abdominal Fat/ 7. exp Insulin Resistance/ Or "metabolic syndrome".mp. 8. 1 and (2 or 3 or 4 or 5 or 6 or 7) 9. limit 8 to animals† 10. 8 not 9
EMBASE	1946 to 2014 Week 14	1. exp nut/ Or nuts.mp. Or nut.mp. Or expbertholletia/ Or walnut*.mp. Or expJuglans/ Or almond*.mp. Or expPrunus/ Or pecan*.mp. Or expCarya/ Or pistachio*.mp. Or expPistacia/ Or cashew*.mp. Or expAnacardium/ Or hazelnut*.mp. Or expCorylus/ Or macadamia*.mp. Or exp Macadamia/ 2. ogtt.mp. Or exp Glucose Tolerance Test/ Or "glucose tolerance test".mp. Or hba1c.mp. Or fructosamine*.mp. Or expFructosamine/ Or insulin*.mp. Or exp Insulin/ Or glycemia*.mp. Or glycaemia*.mp. Or hyperinsulin*.mp. Or expHyperinsulinism/ Or dysglycemia*.mp. Or dysglycaemia*.mp. Or gly* albumin.mp. Or expHemoglobin A, Glycosylated/ Or "blood glucose".mp. Or exp Blood Glucose/ Or hyperglycemia*.mp. Or 39. hyperglycaemia*.mp. Or expHyperglycemia/ Or "homeo* model assessment".mp. Or homa.mp. Or diabetes.mp. Or exp Diabetes Mellitus/ 3. exp Hypertension/ Or exp Blood Pressure/ Or "systolic blood pressure".mp. Or "diastolic blood pressure".mp. Or hypertension.mp. Or SBP.mp. Or DBP.mp. Or "mean arterial pressure".mp. 4. exp Triglycerides/ Or exp Hypertriglyceridemia/ Or hypertriglyceridemia*.mp. Or triglyceride*.mp. Or triacylglycerol*.mp. Or dyslipidemia*.mp. Or dyslipidaemia*.mp. Or exp Dyslipidemias/ 5. exp Cholesterol, HDL/ Or "high density lipoprotein cholesterol".mp. Or hdl.mp. 6. "abdominal obesity".mp. Or exp Obesity, Abdominal/ Or "waist circumference".mp. Or exp waist circumference/ Or "abdominal fat*".mp. Or exp Abdominal Fat/ 7. exp Insulin Resistance/ Or "metabolic syndrome".mp. 8. 1 and (2 or 3 or 4 or 5 or 6 or 7) 9. limit 8 to animals† 10. 8 not 9

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CINHAL	1982 to 4 April 2014	1. (MH "Nuts+) Or "pistachio" Or "hazelnut" Or "macadamia" Or "brazil nut" Or "brazil nuts" Or "pine nut" Or "pine nuts". 2. "ogtt" Or (MM "Hemoglobin A, Glycosylated") Or "HbA1c" Or "fructosamine" Or "Insulin" Or "glycemia" Or "hyperinsulin" Or "dysglycemia" Or "gly* albumin" Or "blood glucose" Or "hyperglycemia" Or "homa" Or (MH "Diabetes Mellitus") Or "diabetes mellitus". 3. (MH "Hypertension") Or "hypertension" Or "SBP" Or "DBP" Or "mean arterial pressure" Or "MAP". 4. "triglycerides" Or "hypertriglyceridemia" Or "TG" Or "TAG" Or "dyslipidemia". 5. "HDL" Or (MH "Lipoproteins, HDL Cholesterol") Or "hypercholesterolemia". 6. "abdominal obesity" Or "abdominal fat" Or "waist circumference". 7. "Insulin resistance" Or "metabolic syndrome". 8. 1 and (2 or 3 or 4 or 5 or 6 or 7).
The Cochrane Library	Through December 2013	1. nuts.mp. Or nut.mp. Or brazil nut.mp. Or brazil nuts.mp. Or pine nut.mp. Or walnut*.mp. Or almond*.mp. Or pecan*.mp. Or pistachio*.mp. Or cashew*.mp. Or hazelnut*.mp. Or macadamia.mp. 2. ogtt.mp. Or hba1c.mp. Or fuctosamine*.mp. Or Insulin*.mp. Or glycemia.mp. Hyperinsulin*.mp. Or dysglycemia.mp. Or gly* albumin.mp. Or exp Blood Glucose/ Or blood glucose.mp. Or expHyperglycemia/ Or homa.mp. Or exp Diabetes Mellitus/ Or diabetes mellitus.mp. 3. hypertension.mp. Or /blood pressure.mp. Or systolic blood pressure.mp. Or diastolic blood pressure.mp. Or hypertension.mp. Or SBP.mp. Or DBP.mp. Or mean arterial pressure.mp. Or MAP.mp. 4. triglycerides.mp. Or hypertriglyceridemia.mp. Or TG.mp. Or triacylglycerol*.mp. Or TAG.mp. Or dyslipidemia.mp. 5. HDL.mp. Or HDL cholesterol.mp. Or hypercholesterolemia.mp. 6. abdominal obesity.mp. Or abdominal fat.mp. 7. insulin resistance.mp. Or metabolic syndrome.mp. 8. 1 and (2 or 3 or 4 or 5 or 6 or 7)

* The symbol at the end of each search term is used in order to capture all possible endings with that word.
Original search date for all databases was May 25th 2012; update search dates for all databases were March 19th 2013 and April 4th 2014.
† Searches were limited to animals and then extracted from the general search.

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Appendix Table 2 – Study Quality Assessment by Using the Heyland MQS*

Study, Year (Reference)	Design†			Sample‡			Intervention§			MQS (n/13)
	Randomization (n/2)	Blinding (n/1)	Analysis (n/2)	Selection (n/1)	Comparability (n/1)	Follow-up (n/1)	Protocol (n/1)	Co-interventions (n/2)	Crossovers (n/2)	
Sabate et al, 1993 (32)	1	0	0	1	1	0	1	2	0	6
Chisholm et al, 1998 (13)	1	0	0	0	1	0	0	2	0	4
Spiller et al, 1998 (33)	1	0	0	1	1	0	1	2	0	6
Curb et al, 2000 (10)	1	0	0	0	1	0	0	2	0	4
Morgan et al, 2000 (34)	1	0	0	1	1	0	1	2	0	6
Zambon et al, 2000 (35)	2	0	0	0	1	0	1	2	0	6
Rajaram et al, 2001 (14)	2	0	0	1	1	1	1	2	0	8
Iwamoto et al, 2002 (36)	1	0	2	0	1	1	1	2	0	8
Jenkins et al, 2002 (15)	1	0	0	1	1	0	1	2	0	6
Lovejoy et al, 2002 (37)	1	1	0	0	1	0	0	2	0	5
Sabate et al, 2003 (38)	1	0	0	0	1	0	1	2	0	5
Wien et al, 2003 (8)	2	0	2	0	1	0	1	2	0	8
Tapsell et al, 2004 (39)	1	0	2	1	1	0	0	1	0	6
Tamizifar et al, 2005 (40)	1	0	0	0	1	0	1	2	0	5
Kocyigit et al, 2006 (16)	1	0	2	0	1	1	1	2	0	8
Kurlandsky et al, 2006 (41)	1	0	0	0	1	0	1	2	0	5
Schutte et al, 2006 (53)	2	0	0	1	1	0	1	2	0	7
Mukuddem-Petersen et al, 2007(42)	2	0	0	1	1	0	1	2	0	7
Sheridan et al, 2007 (17)	1	0	0	1	1	0	1	2	0	6
Gebauer et al, 2008 (43)	1	0	0	1	1	0	1	1	0	5
Griel et al, 2008 (44)	1	0	2	0	1	1	1	2	0	8
Jenkins et al, 2008 (54)	1	0	0	1	1	0	1	2	0	6
Rajaram et al, 2009 (45)	1	0	0	1	1	0	0	2	0	5
Tapsell et al, 2009 (46)	2	0	0	1	1	0	1	2	0	7
Li et al, 2010 (11)	2	0	0	1	1	0	1	2	0	7
Ma et al, 2010 (47)	1	0	0	1	1	0	1	1	0	5
Torabian et al, 2010 (12)	1	0	0	1	1	0	1	2	0	6
Wien et al, 2010 (48)	2	0	2	1	1	0	1	2	0	9
Wu et al, 2010 (49)	2	0	2	1	1	0	1	2	0	9
Casas-Agustench et al, 2011 (50)	1	0	0	1	1	0	1	2	0	6
Cohen et al, 2011 (19)	1	0	2	0	1	1	0	2	0	7
Jenkins et al, 2011 (20)	1	0	2	1	1	0	1	2	0	8
Li et al, 2011 (21)	1	0	0	0	1	0	1	2	0	5
Tey et al, 2011 (51)	2	0	2	1	1	0	1	2	0	9
DarvishDamavandi et al, 2012 (18)	1	0	0	0	0	0	1	1	0	3

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Foster et al, 2012 (52)	2	0	2	0	1	1	1	2	0	9
Katz et al, 2012 (53)	1	0	2	1	1	0	1	1	0	7
Wang et al, 2012 (22)	1	0	0	0	1	0	1	2	0	5
West et al, 2012 (55)	1	0	0	1	1	0	1	1	0	5
Anderson et al, 2013 (54)	1	0	2	0	1	1	0	0	0	5
Darvish Damavandi et al, 2013 (56)	2	0	0	0	1	0	1	2	0	6
Somerset et al, 2013 (9)	1	0	2	1	1	1	1	2	0	9
Tan et al, 2013 (58)	1	0	0	0	1	0	1	2	0	5
Tey et al, 2013 (59)	1	0	0	1	1	0	1	2	0	6
Gulati et al, 2014 (60)	1	0	0	0	1	0	0	2	0	4
Wu et al, 2014 (61)	2	0	0	1	1	0	1	2	0	7

MQS=Heyland Methodological Quality Score; n/ = total score per category and total MQS score.

* The Heyland MQS assigns a score of 0 or 1 or from 0 to 2 over 9 categories of quality related to study design, sampling procedures, and interventions, for a total of 13 points. Trials that scored ≥8 were considered to be of higher quality (11). Trials reported in abstract form were not included in the MQS scores (Berryman et al, 2013, Holligan et al, 2013 and Sauder et al, 2013).

† Randomization was scored 2 points for being randomized with the methods described, 1 point for being randomized without the methods described, or 0 points for being neither randomized nor having the methods described. Blinding was scored 1 point for being double-blind or 0 points for "other." Analysis was scored 2 points for being intention-to-treat; all other types of analyses scored 0 points.

‡ Sample selection was scored 1 point for being consecutive eligible or 0 points for being preselected or indeterminate. Sample comparability was scored 1 point for being comparable or 0 points for not being comparable at baseline. Follow-up was scored 1 point for being 100% or 0 points for <100%.

§ Treatment protocol was scored 1 point for being reproducibly described or 0 points for being poorly described. Co-interventions were scored 2 points for being described and equal, 1 point for being described but unequal or indeterminate, or 0 points for not being described. Treatment crossovers (where participants were switched from the control treatment to the experimental treatment) were scored 2 points for being <10%, 1 point for being >10%, and 0 points for not being described.

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Appendix Table 3. A priori subgroup analyses of continuous variables for criteria of the Metabolic Syndrome

A. Waist Circumference

Subgroups	No. of Trials	N	β [95% CI]	Residual I^2 (%)	*P* -value
Nuts Dose (g/day)	15	1050	-0.028 [-0.104, 0.048]	66.4	0.44
Duration (weeks)	15	1050	-0.152 [-0.347, 0.043]	60.4	0.12
Saturated Fat (%)	13	904	0.259 [-0.262, 0.781]	69.2	0.30
Change in Saturated Fat (%)	10	777	0.374 [-1.448, 2.195]	65	0.65
Difference in Saturated Fat (%)	13	904	0.662 [-1.011, 2.336]	71.4	0.40
Fibre Intake (g/day)	12	882	-0.059 [-0.357, 0.238]	73.4	0.67
Change in Fibre Intake (g/day)	8	688	0.020 [-0.430, 0.470]	71.6	0.92
Difference in Fibre Intake (g/day)	13	904	-0.124 [-0.394, 0.145]	70.8	0.33
Baseline (cm)	11	803	-0.014 [-0.082, 0.055]	73.7	0.66
Difference in Carbohydrate intake (%/day)	14	964	-0.874 [-0.377, 2.124]	49.7	0.01

B. Triglycerides

Subgroups	No. of Trials	N	β [95% CI]	Residual I^2 (%)	*P* -value
Nuts Dose (g/day)	44	1962	-0.002 [-0.004, 0.001]	39.9	0.05
Duration (weeks)	44	1962	0.002 [-0.001, 0.005]	35.5	0.11
Saturated Fat (%)	38	1541	0.012 [-0.001, 0.026]	11.9	0.08
Change in Saturated Fat (%)	21	1076	0.023 [-0.010, 0.005]	33.1	0.16
Difference in Saturated Fat (%)	38	1541	0.005 [-0.013, 0.022]	20.8	0.60
Fibre Intake (g/day)	33	1353	-0.005 [-0.012, 0.002]	19.7	0.14
Change in Fibre Intake (g/day)	17	865	-0.009 [-0.020, 0.002]	42.1	0.11
Difference in Fibre Intake (g/day)	34	1408	-0.001 [-0.010, 0.009]	24.9	0.94
Baseline (mmol/L)	35	1550	0.080 [-0.020, 0.180]	33.9	0.11
Difference in Carbohydrate intake (%/day)	39	1609	0.003 [-0.007, 0.012]	25.0	0.56

C. High-Density Lipoprotein Cholesterol

Subgroups	No. of Trials	N	β [95% CI]	Residual I^2 (%)	*P* -value
Nuts Dose (g/day)	45	2127	-0.001 [-0.002, 0.001]	85.8	0.42
Duration (weeks)	45	2127	0.000 [-0.002, 0.002]	85.8	0.93
Saturated Fat (%)	39	1730	0.000 [-0.010, 0.010]	84.6	0.99
Change in Saturated Fat (%)	22	1265	0.005 [-0.013, 0.022]	84.1	0.57
Difference in Saturated Fat (%)	39	1730	0.000 [-0.008, 0.008]	83.2	0.93
Fibre Intake (g/day)	34	1542	-0.001 [-0.005, 0.004]	88.4	0.76
Change in Fibre Intake (g/day)	18	1054	0.001 [-0.006, 0.007]	87.5	0.83
Difference in Fibre Intake (g/day)	35	1597	0.003 [-0.002, 0.007]	86.1	0.30
Baseline (mmol/L)	37	1692	0.022 [-0.093, 0.137]	87.1	0.70
Difference in Carbohydrate intake (%/day)	40	1798	0.000 [-0.005, 0.005]	82.2	0.89

D. Systolic Blood Pressure

Subgroups	No. of Trials	N	β [95% CI]	Residual I^2 (%)	*P* -value
Nuts Dose (g/day)	20	1267	-0.085 [-0.186, 0.017]	62.6	0.10
Duration (weeks)	20	1267	-0.043 [-0.166, 0.080]	64.4	0.47
Saturated Fat (%)	18	1058	0.505 [-0.177, 1.186]	64	0.14
Change in Saturated Fat (%)	13	803	-0.249 [-1.151, 0.653]	49.6	0.56
Difference in Saturated Fat (%)	18	1058	-1.307 [-2.681, 0.067]	59.8	0.06
Fibre Intake (g/day)	17	1036	-0.187 [-0.470, 0.097]	57	0.18
Change in Fibre Intake (g/day)	10	765	-0.071 [-0.382, 0.241]	55.1	0.62
Difference in Fibre Intake (g/day)	18	1058	-0.353 [-0.695, -0.011]	55.2	0.04
Baseline (mmHg)	16	1058	-0.112 [-0.398, 0.174]	69.6	0.42
Difference in Carbohydrate intake (%/day)	18	1058	0.564 [0.164, 0.963]	55.5	0.00

E. Diastolic Blood Pressure

Subgroups	No. of Trials	N	β [95% CI]	Residual I^2 (%)	*P* -value
Nuts Dose (g/day)	20	1267	-0.028 [-0.067, 0.011]	29.6	0.15
Duration (weeks)	20	1267	0.012 [-0.040, 0.064]	36.1	0.63
Saturated Fat (%)	18	1058	0.118 [-0.154, 0.390]	36.6	0.37
Change in Saturated Fat (%)	13	803	-0.152 [-0.595, 0.291]	27.4	0.47
Difference in Saturated Fat (%)	18	1058	-0.136 [-0.694, 0.423]	40.6	0.61
Fibre Intake (g/day)	17	1036	-0.067 [-0.173, 0.040]	21.3	0.20
Change in Fibre Intake (g/day)	10	765	0.021 [-0.147, 0.189]	46.4	0.78
Difference in Fibre Intake (g/day)	18	1058	-0.078 [-0.230, 0.074]	37.9	0.29
Baseline (mmHg)	16	1058	-0.009 [-0.220, 0.202]	45.3	0.93
Difference in Carbohydrate intake (%/day)	18	1058	0.088 [-0.071, 0.247]	39.5	0.26

F. Fasting Blood Glucose

Subgroups	No. of Trials	N	β [95% CI]	Residual I^2 (%)	*P* -value
Nuts Dose (g/day)	26	1319	0.004 [-0.002, 0.011]	44.5	0.19
Duration (weeks)	26	1319	-0.006 [-0.021, 0.008]	44.6	0.36
Saturated Fat (%)	21	1097	0.006 [-0.029, 0.042]	42.5	0.71
Change in Saturated Fat (%)	12	895	-0.003 [-0.068, 0.062]	48.3	0.92
Difference in Saturated Fat (%)	21	1097	-0.036 [-0.133, 0.062]	41.2	0.45
Fibre Intake (g/day)	19	1040	0.003 [-0.008, 0.014]	43.7	0.59
Change in Fibre Intake (g/day)	10	731	0.001 [-0.012, 0.015]	22.3	0.82
Difference in Fibre Intake (g/day)	20	1062	0.006 [-0.014, 0.026]	42.8	0.56
Baseline (mmol/L)	24	1251	-0.059 [-0.149, 0.031]	45.7	0.19
Difference in Carbohydrate intake (%/day)	23	1209	0.026 [-0.007, 0.058]	41.1	0.12

N: number of participants in each subgroup.

Residual I^2 was reported as a percent value, where $I^2 \leq 50\%$ indicated "moderate" heterogeneity, $I^2 \geq 50\%$ indicated "substantial" heterogeneity and $\geq 75\%$ indicated "considerable" heterogeneity. *P* -value significance for heterogeneity was set as $P < 0.10$.

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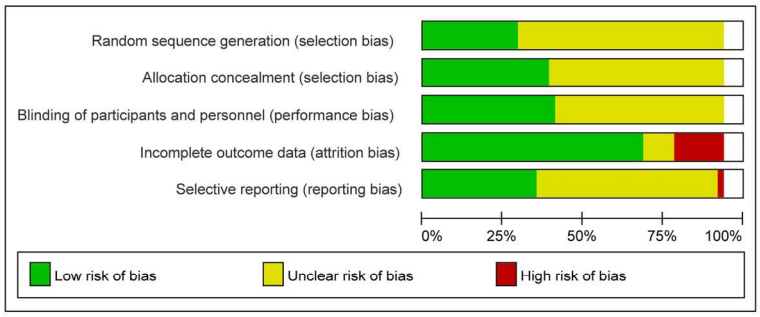
Appendix Figure 1. Cochrane risk of bias.



Review authors' judgements about each risk of bias item presented as percentages across all included studies.

194x82mm (300 x 300 DPI)

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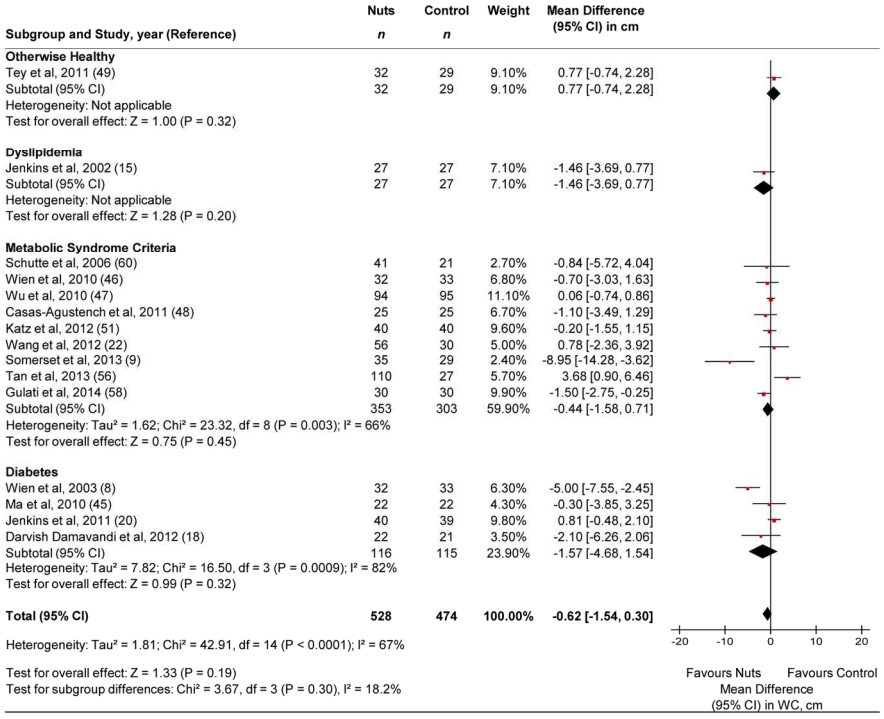
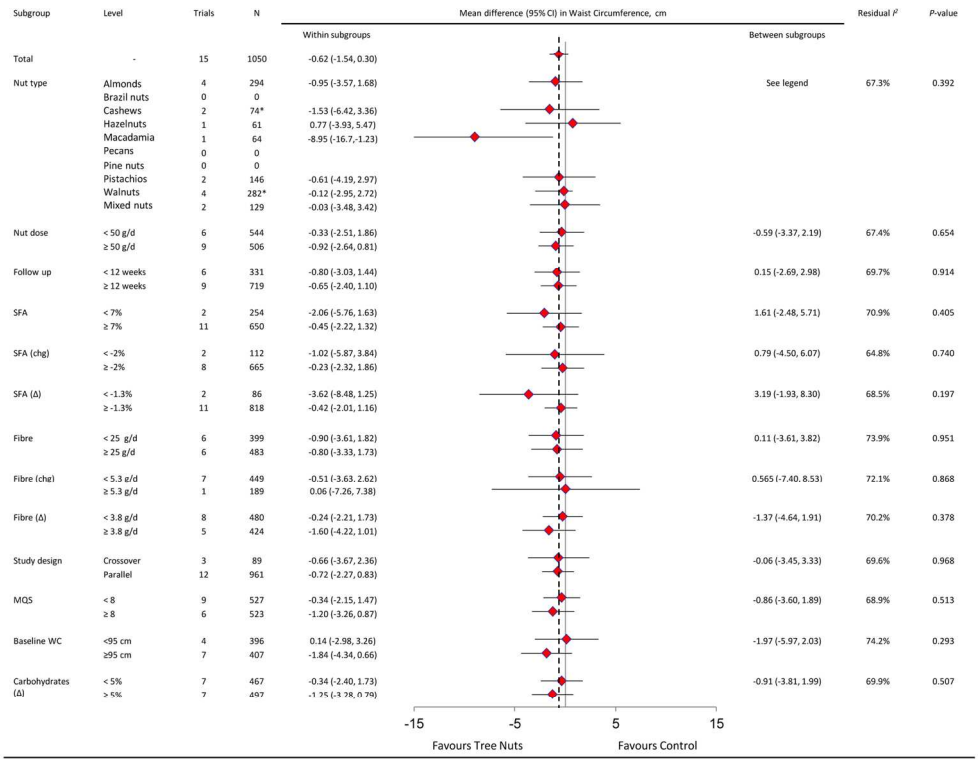
Appendix Figure 2. Forest plot of the RCTs of the effect of Tree Nuts on Waist Circumference



Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia, metabolic syndrome criteria, diabetes and their combination (total). Paired analyses were applied to all crossover trials (3). Data are expressed as mean differences (MD) with 95% CI, using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using the Cochrane's Q statistic (I^2) at a significance level of $P < 0.10$ and quantified by I^2, levels ≤ 50% represent moderate heterogeneity, ≥ 50 % represent substantial heterogeneity and ≥ 75%, considerable heterogeneity. WC = waist circumference, cm = centimeters.

173x176mm (300 x 300 DPI)

Appendix Figure 3. Forest plot of subgroup analyses for categorical variables for Waist Circumference



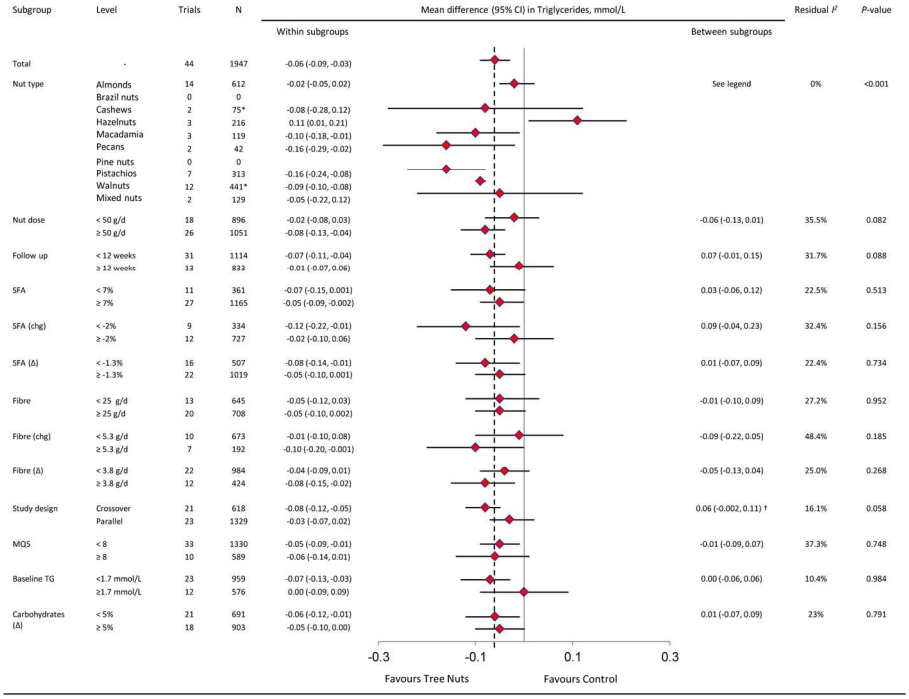
Point estimates for each subgroup level are the pooled effect estimates and are represented by diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value indicates the interstudy heterogeneity unexplained by the subgrouping. Pairwise between-subgroup mean differences (95% CIs) for nut type are not shown due to lack of statistical significance between groups. SFA = Saturated Fatty Acids, SFA (chg) = change within treatment diet for SFA, SFA (Δ) = difference between groups for SFA, Fibre (chg) = change within treatment diet for Fibre, Fibre (Δ) = difference between groups for SFA, MQS = Heyland Methodological Quality Score, WC = waist circumference, Carbohydrates (Δ)= difference between groups for carbohydrates.

* Both nut types were studied within the same trial, for the sole purposes of number of participants, the control group was divided in half.

† Statistically significant pairwise subgroup effect modification by meta-regression analysis ($P < 0.05$)

173x203mm (300 x 300 DPI)

Appendix Figure 4. Forest plot of subgroup analyses for categorical variables for Triglycerides.



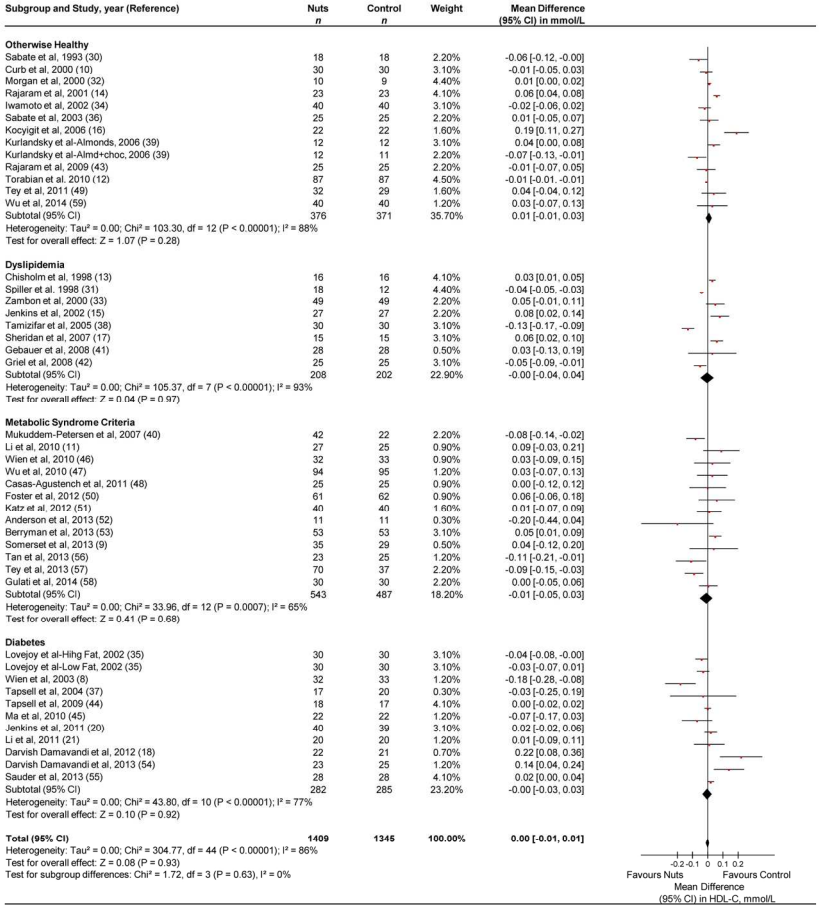
Point estimates within each subgroup level are the pooled effect estimates and are represented by diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value indicates the interstudy heterogeneity unexplained by the subgrouping. Significant pairwise between-subgroup mean differences (95% CIs) for nut types as follows: almonds vs. walnuts -0.07 mmol/L (-0.11, -0.04 mmol/L)†, almonds vs. pistachio -0.14 mmol/L (-0.23, -0.05 mmol/L)†, almonds vs. pecan -0.14 mmol/L (-0.27, -0.001 mmol/L)†, almonds vs. hazelnuts 0.13 mmol/L (0.02, 0.23 mmol/L)†, walnuts vs. hazelnuts -0.20 mmol/L (-0.30, -0.10 mmol/L)†, macadamia vs. hazelnuts -0.20 mmol/L (-0.33, -0.07 mmol/L)†, pistachio vs. hazelnuts -0.27 mmol/L (-0.40, -0.14 mmol/L)†, pecan vs. hazelnut -026 mmol/L (-0.43, -0.10 mmol/L)†, all others non-significant ($P > 0.05$),. SFA = Saturated Fatty Acids, SFA (chg) = change within treatment diet for SFA, SFA (Δ) = difference between groups for SFA, Fibre (chg) = change within treatment diet for Fibre, Fiber (Δ) = difference between groups for SFA, MQS = Heyland Methodological Quality Score, TG = Triglycerides.

* Both nut types were studied within the same trial, for the sole purposes of number of participants, the control group was divided in half.

† Statistically significant pairwise subgroup effect modification by meta-regression analysis ($P < 0.05$)

173x205mm (300 x 300 DPI)

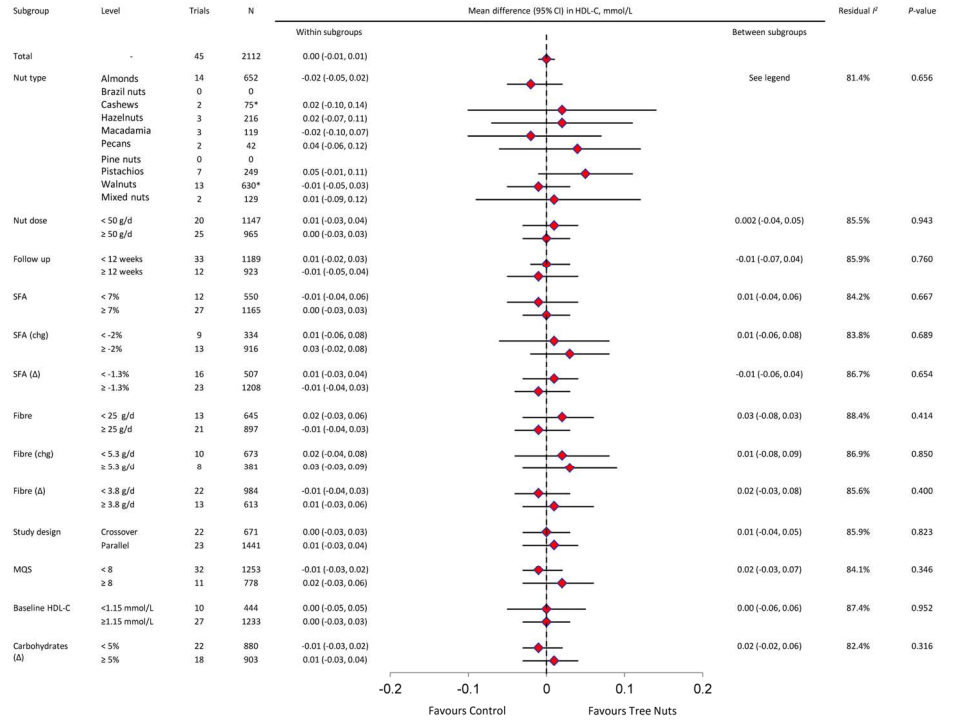
Appendix Figure 5. Forest plot of the RCTs investigating the effect of Tree Nuts on HDL-C.



Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia, metabolic syndrome criteria, diabetes and their combination (total). Paired analyses were applied to all crossover trials (21) and one substudy. Data are expressed as mean differences (MD) with 95% CI, using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using the Cochrane's Q statistic (I^2) at a significance level of $P < 0.10$ and quantified by I^2, levels ≤ 50% represent moderate heterogeneity, ≥ 50 % represent substantial heterogeneity and ≥ 75%, considerable heterogeneity. HDL-C = High-Density Lipoprotein Cholesterol, mmol/L = millimoles per liter, A = Almond, AC = Almond + Chocolate, HF = High Fat, LF = Low Fat.

173x222mm (300 x 300 DPI)

Appendix Figure 6. Forest plot of subgroup analyses for categorical variables for HDL-C.

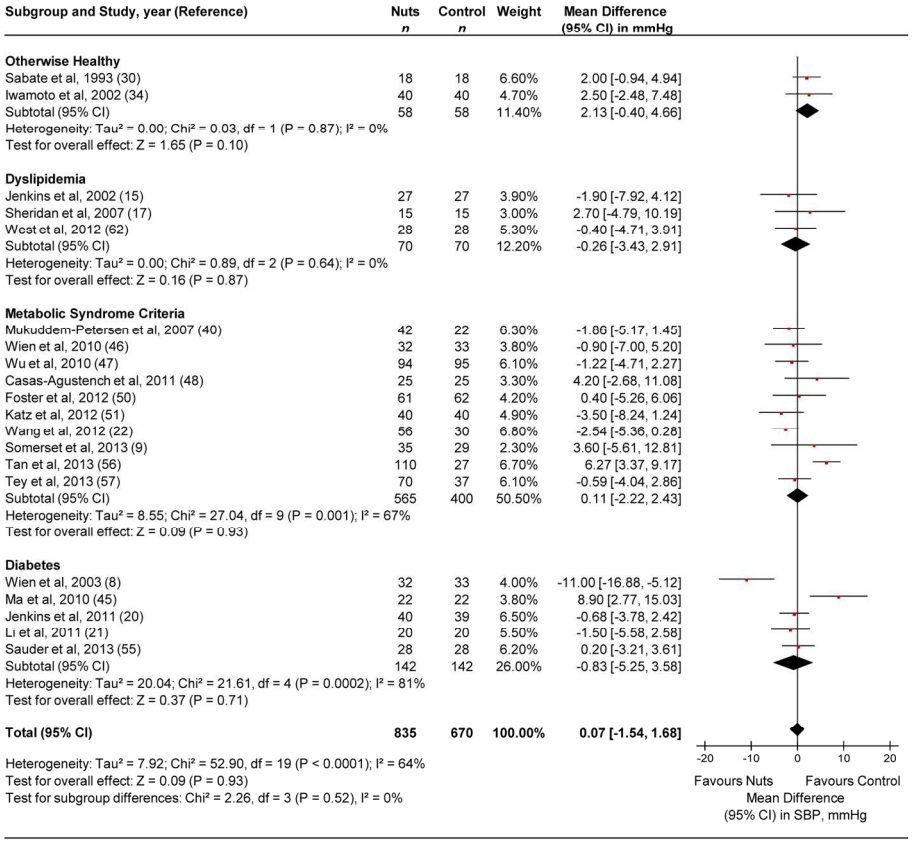


Point estimates for each subgroup level are the pooled effect estimates and are represented by diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value indicates the interstudy heterogeneity unexplained by the subgrouping. Pairwise between-subgroup mean differences (95% CIs) for nut type are not shown due to lack of statistical significance between groups. SFA = Saturated Fatty Acids, SFA (chg) = change within treatment diet for SFA, SFA (Δ) = difference between groups for SFA, Fibre (chg) = change within treatment diet for Fibre, Fibre (Δ) = difference between groups for SFA, MQS = Heyland Methodological Quality Score, HDL-C = high-density lipoprotein cholesterol.

* Both nut types were studied within the same trial, for the sole purposes of number of participants, the control group was divided in half.

173x190mm (300 x 300 DPI)

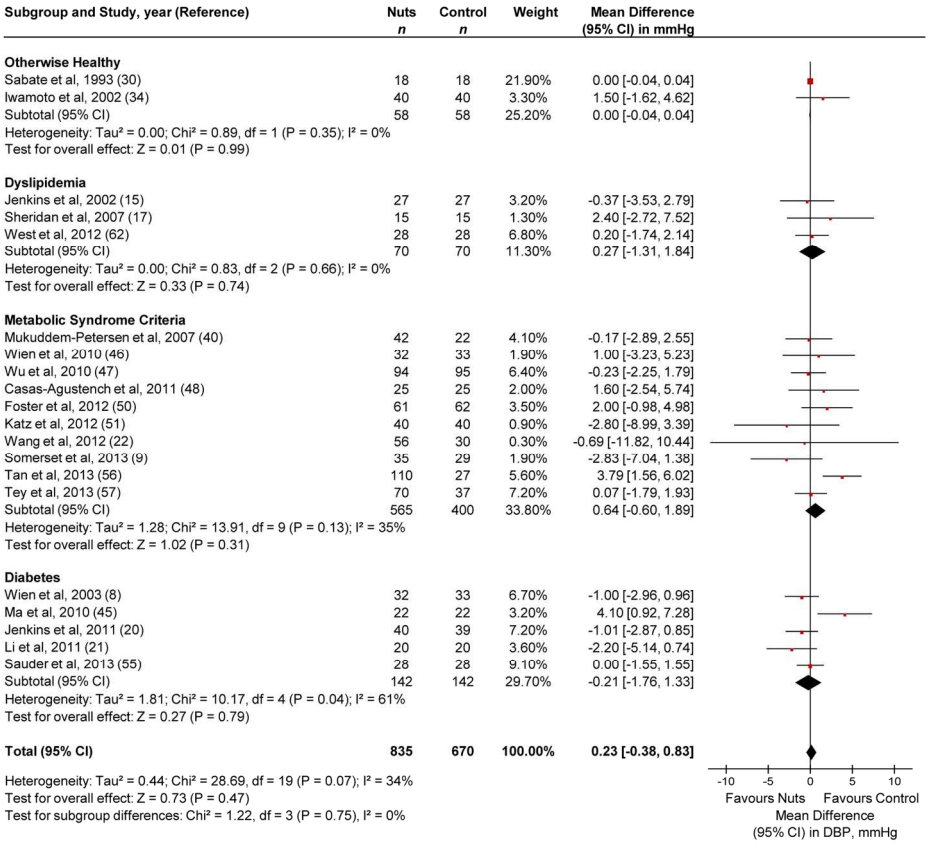
Appendix Figure 7A. Forest plot of the RCTs investigating the effect of Tree Nuts on Systolic Blood Pressure.



Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia, metabolic syndrome criteria, diabetes and their combination (total). Paired analyses were applied to all crossover trials (9). Pooled effects are mean differences (MD) with 95% CI, using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using the Cochrane's Q statistic (I^2) at a significance level of $P < 0.10$ and quantified by I^2, levels ≤ 50% represent moderate heterogeneity, ≥ 50 % represent substantial heterogeneity and ≥ 75%, considerable heterogeneity. SBP = Systolic Blood Pressure, mmHg = millimeters of mercury.

173x206mm (300 x 300 DPI)

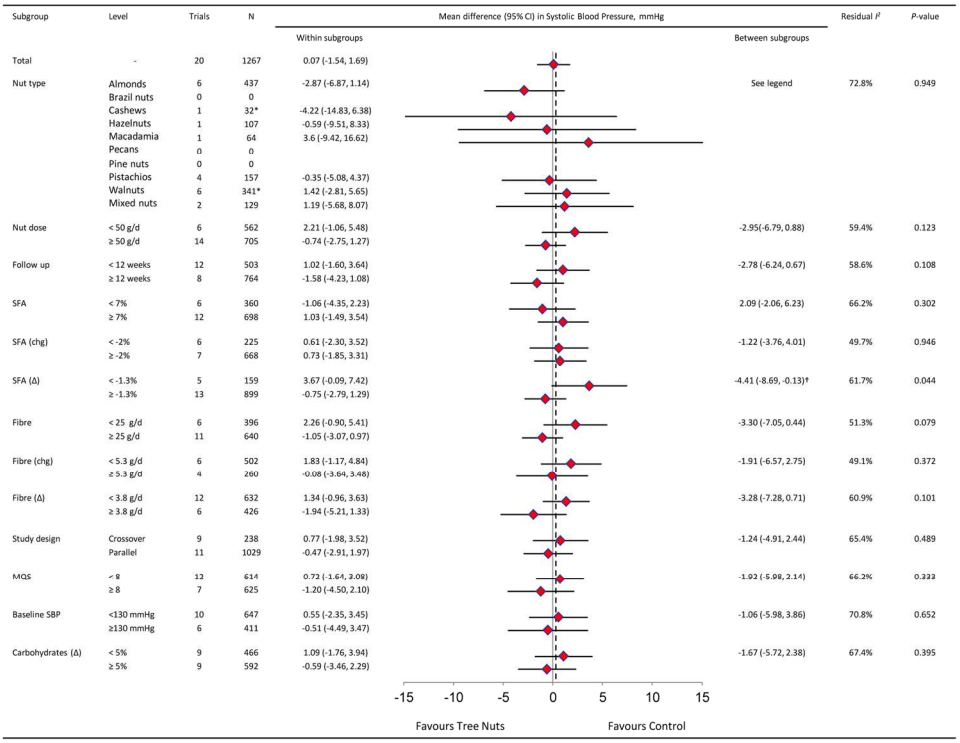
Appendix Figure 7B. Forest plot of the RCTs investigating the effect of Tree Nuts on Diastolic Blood Pressure.



Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia, metabolic syndrome criteria, diabetes and their combination (total). Paired analyses were applied to all crossover trials (9). Pooled effects are mean differences (MD) with 95% CI, using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using the Cochrane's Q statistic (I^2) at a significance level of $P < 0.10$ and quantified by I^2, levels ≤ 50% represent moderate heterogeneity, ≥ 50 % representing substantial heterogeneity and ≥ 75%, considerable heterogeneity. DBP = Diastolic Blood Pressure, mmHg = millimeters of mercury.

173x197mm (300 x 300 DPI)

Appendix Figure 8A. Forest plot of subgroup analyses for categorical variables for Systolic Blood Pressure.



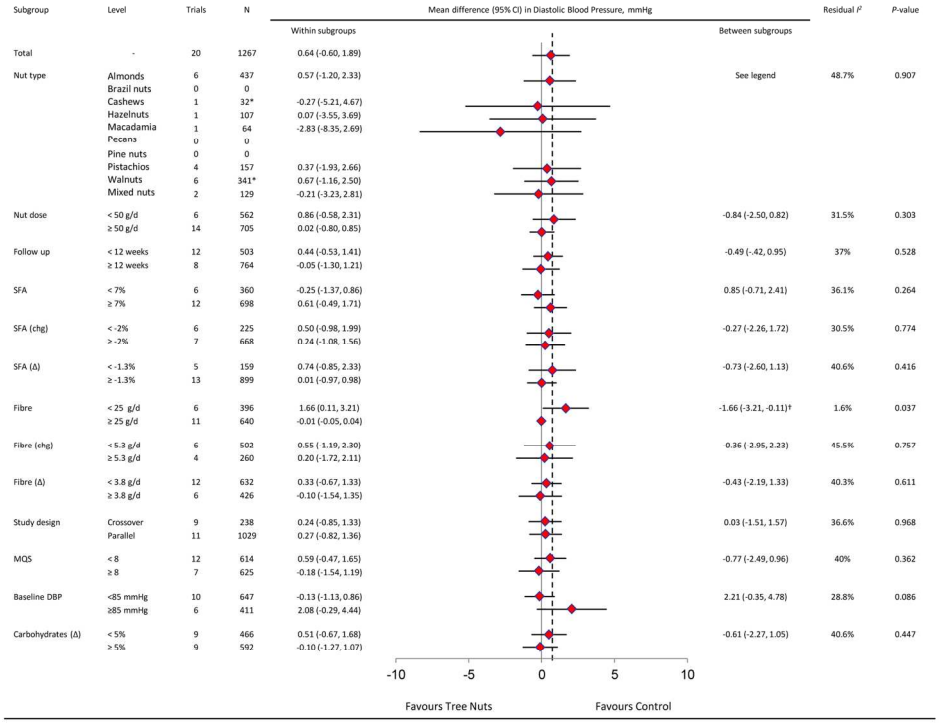
Point estimates for each subgroup level are the pooled effect estimates and are represented by diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value indicates the interstudy heterogeneity unexplained by the subgrouping. Pairwise between-subgroup mean differences (95% CIs) for nut type are not shown due to lack of statistical significance between groups. SFA = Saturated Fatty Acids, SFA (chg) = change within treatment diet for SFA, SFA (Δ) = difference between groups for SFA, Fibre (chg) = change within treatment diet for Fibre, Fibre (Δ) = difference between groups for SFA, MQS = Heyland Methodological Quality Score, SBP = systolic blood pressure.

* Both nut types were studied within the same trial, for the sole purposes of number of participants, the control group was divided in half.

† Statistically significant pairwise subgroup effect modification by meta-regression analysis ($P < 0.05$).

173x201mm (300 x 300 DPI)

Appendix Figure 8B. Forest plot of subgroup analyses for categorical variables for Diastolic Blood Pressure.



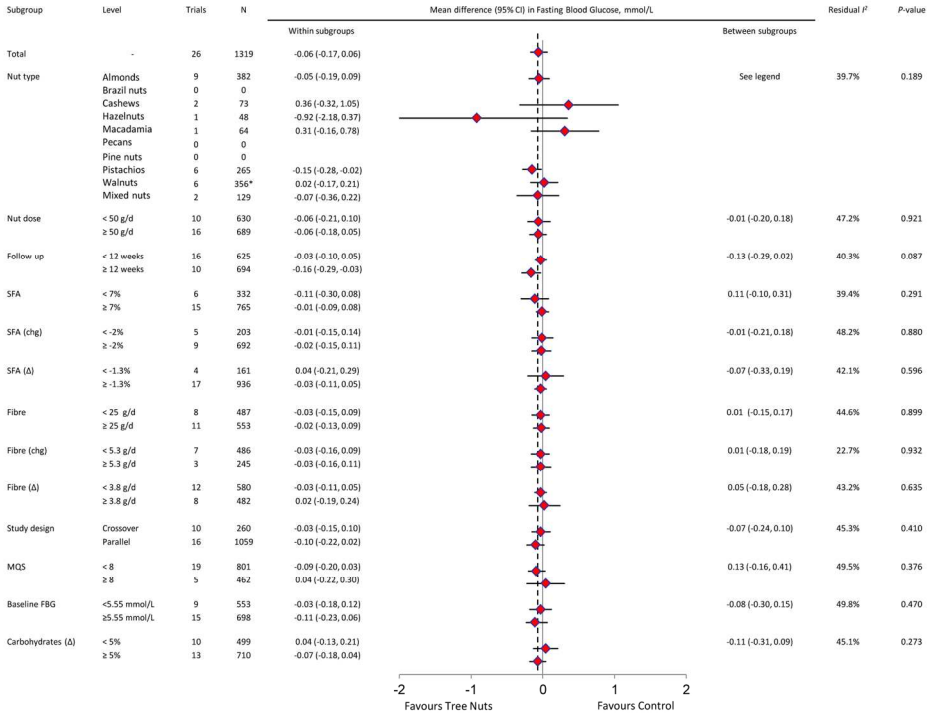
Point estimates for each subgroup level are the pooled effect estimates and are represented by diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value indicates the interstudy heterogeneity unexplained by the subgrouping. Pairwise between-subgroup mean differences (95% CIs) for nut type are not shown due to lack of statistical significance between groups. SFA = Saturated Fatty Acids, SFA (chg) = change within treatment diet for SFA, SFA (Δ) = difference between groups for SFA, Fibre (chg) = change within treatment diet for Fibre, Fibre (Δ) = difference between groups for SFA, MQS = Heyland Methodological Quality Score, DBP = diastolic blood pressure.

* Both nut types were studied within the same trial, for the sole purposes of number of participants, the control group was divided in half.

† Statistically significant pairwise subgroup effect modification by meta-regression analysis ($P < 0.05$).

173x194mm (300 x 300 DPI)

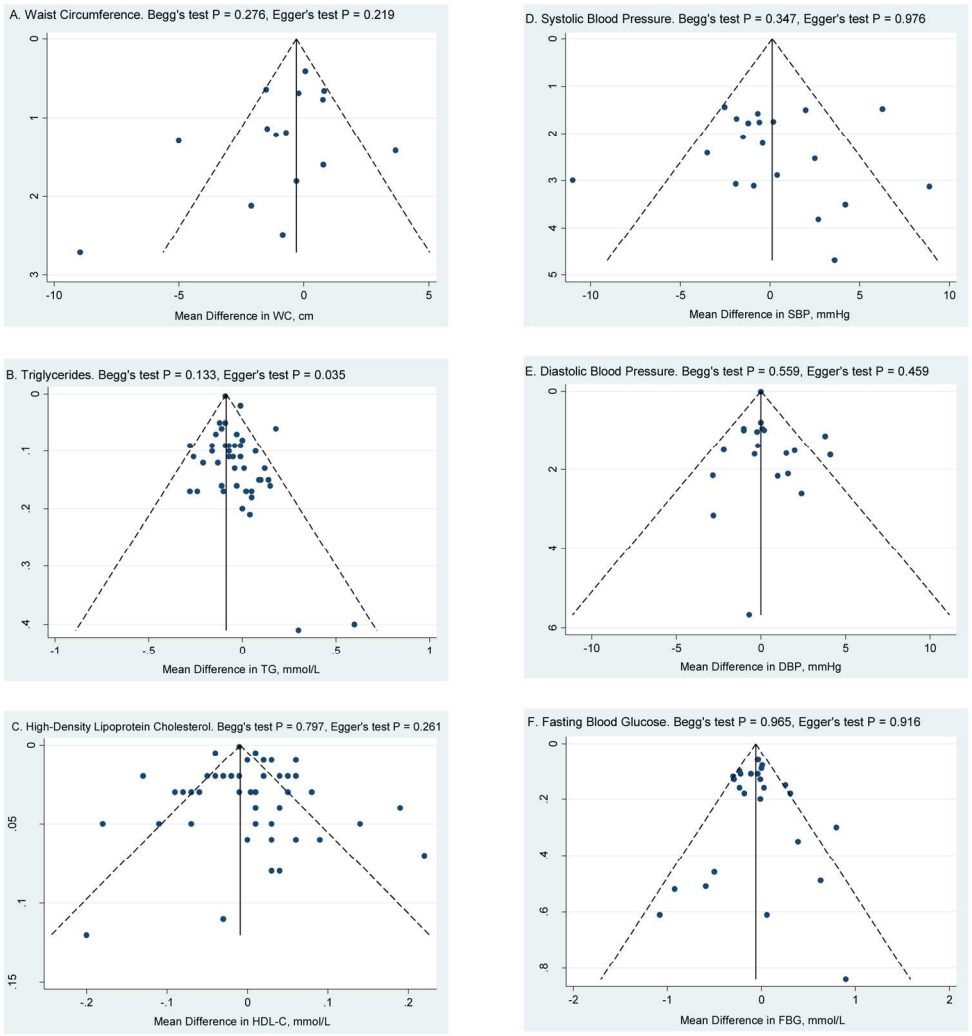
Appendix Figure 9. Forest plot of subgroup analyses for categorical variables for Fasting Blood Glucose.



Point estimates for each subgroup level are the pooled effect estimates and are represented by diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value indicates the interstudy heterogeneity unexplained by the subgrouping. Pairwise between-subgroup mean differences (95% CIs) for nut are not shown due to lack of statistical significance. SFA = Saturated Fatty Acids, SFA (chg) = change within treatment diet for SFA, SFA (Δ) = difference between groups for SFA, Fibre (chg) = change within treatment diet for Fibre, Fibre (Δ) = difference between groups for SFA, MQS = Heyland Methodological Quality Score, FG = fasting glucose.
* Both nut types were studied within the same trial, for the sole purposes of number of participants, the control group was divided in half.

173x184mm (300 x 300 DPI)

Appendix Figure 10. Funnel plots for evidence of publication bias.



173x197mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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