

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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2 3	37	ABSTRACT
4 5	38	Background: Chronic disease guidelines support tree nut consumption alone or as part of
6 7	39	the Mediterranean, Dietary Approaches to Stop Hypertension (DASH), or Portfolio dietary
8 9	40	patterns to reduce cardiovascular risk, based on their favourable LDL-C lowering effect. The
10 11	41	effects of nuts on metabolic risk factors other than LDL-C, however, remain uncertain. We
12 13	42	conducted a systematic review and meta-analysis of the effect of tree nuts on criteria
14 15	43	metabolic syndrome components to provide a broader evidence summary to inform dietary
16 17	44	guidelines.
18 19	45	Methods: We searched MEDLINE, EMBASE, CINAHL, and the Cochrane Library (through
20 21	46	March 19, 2013). We included relevant randomized controlled trials (RCTs) of \geq 3 weeks
22 23	47	reporting at least 1 criterion of metabolic syndrome. Two or more independent reviewers
24 25	48	extracted all relevant data. Data were pooled using the generic inverse variance method
26 27	49	using random effects models and expressed as mean differences (MD) with 95% confidence
28 29	50	intervals (CI). Heterogeneity was assessed by Chi ² and quantified by I ² . Study quality was
30 31	51	assessed.
32 33	52	Results: Eligibility criteria were met by 39RCTsincluding1,676 participants who were
34 35	53	otherwise healthy or had dyslipidemia, metabolic syndrome or diabetes mellitus. Tree nut
36 37	54	interventions lowered triglycerides compared with control diet interventions (MD=-0.07
38 39	55	mmol/L [95%CI, -0.11, -0.04 mmol/L]), but had no effects on waist circumference, HDL-C,
40 41	56	blood pressure, or fasting blood glucose with the direction of effect favouring tree nuts for all
42 43		
44 45	57	except HDL-C.
46 47	58	Limitations: Most of the trials were of short duration (<12 weeks) and of poor quality
48	59	(MQS<8). Substantial unexplained heterogeneity remained in most analyses.
49 50	60	Conclusion: Pooled analyses show a net benefit of tree nuts for metabolic syndrome with
51 52	61	decreases in triglycerides across nut types and no adverse effects on other criteria. Longer
53 54	62	and higher quality trials are needed.
55 56	63	Protocol Registration: ClinicalTrials.gov identifier, NCT01630980
57 58	64	
59 60		Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page 2
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65	Key words: systematic review, meta-analysis, randomized trials, tree nuts, metabolic
66	syndrome.
67	Strengths and limitations of this study
68	• This is the first systematic review and meta-analysis to look at the effect of tree nuts
69	on metabolic syndrome criteria.
70	• This systematic review and meta-analysis involved a large number of trials (36
71	RCTs) in participants with a range of metabolic conditions.
72	 Most of the trials (69.4%) were of low quality (MQS<8).
73	 Most of the trials (66.7%) were of short duration (<12 weeks).
74	 Substantial inter-study heterogeneity remained unexplained.
75	
76	
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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 guidelines² 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 trial⁵ 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 therapy²³ 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).

113 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)¹as 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 \geq 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

136 Data Extraction

137 Studies that met the inclusion criteria were extracted in full by 2independent 138 reviewers (SBM and one of EV, LSA, VH or AM) for study characteristics and data for 139 endpoints. Study characteristics included: study design (crossover or parallel), participant 140 characteristics, comparator, nut dose, nut type, duration of follow-up, dietary adherence 141 measures, macronutrient profile, statistical analysis and funding souces. All disagreements 142 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 followup), 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".

157 Means (SD) for baseline values, end values, change-from baseline differences, end-158 differences, and mean differences were recorded for primary endpoints (waist 159 circumference, triglycerides, HDL-C, blood pressure and fasting blood glucose). Reported t-160 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.

172 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 (I²). An I² ≥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 criteria²⁷). absolute fiber intake (treatment diet <25 g/d vs. \geq 25 g/d²³ 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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enerov²³ 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 guality (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

202 Trial Selection

Figure 1 shows flow of studies through the search and selection process. We identified a total of 2,190 reports, from which 701 reports were duplicates and 1,367 reports were deemed irrelevant (determined by review of title and abstract). The remaining 120 reports were reviewed in full, of which 81 reports were excluded for not meeting inclusion criteria. A total of 39 reports on 38trials^{8-22 32-52} as well as 3 companion reports⁵³⁻⁵⁵ 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).

212 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}
 ⁵¹reported 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 case⁸. 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 trial⁴⁸]).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 sticks¹⁹ 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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1		10
2 3	245	control group respectively. Median values for protein intake were 16% (IQR: 15 to 18%) and
4 5	246	17% (IQR: 15 to 19%) for tree nut and control group correspondingly.
6 7	247	Appendix Table 2 and Appendix Figure 1 present the assessment and summary of
8 9	248	the risk of bias by using The Heyland MQS and The Cochrane Risk of Bias Tool. The
10 11 12	249	Heyland MQS ranged from 3 to 9. Twenty-five trials (69.4%) were considered to be low
12 13 14	250	quality (MQS <8) and 11 trials (30.6%) high quality (MQS ≥8). The main contributors of low
14 15 16	251	scores were blinding of participants and crossovers between intervention treatments,
17 18	252	followed by sample comparability and follow up. The Cochrane Risk of Bias Tool showed
19 20	253	that in our study, blinding of participants and personnel was considered mainly "low risk of
20 21 22	254	bias" (blinding of participants and crossovers in our included dietary trials are not feasible)
23 24	255	and that a few studies were considered "high risk of bias" due to incomplete outcome data
25 26	256	and selective reporting.
27 28	257	Most of the trials reported research funding from an agency 27/36(75%), while others
29 30	258	were funded from a combination of agency and industry 5/36(13.9%).One trial (2.8%) was
31 32	259	funded exclusively by industry. Three trials ^{18 40 47} did not report their funding source (8.3%).
33 34	260	
35 36	261	Waist Circumference
37 38	262	Appendix Figure 2 presents data on the effect of tree nuts on waist circumference.
39 40	263	Tree nuts did not significantly decrease waist circumference in the overall analyses (MD, -
41 42	264	0.91 cm [95% Cl, -1.99, 0.18 cm]) with evidence of significant heterogeneity (I ² =65%,
43 44	265	P<0.001). Stratification by health status failed to demonstrate a significant effect for any of
45 46	266	the sub samples. Sensitivity analyses did not alter the results (data not shown).
47 48	267	Appendix Table 3-A and Appendix Figure 3 present the a priori continuous and
49 50	268	categorical subgroup analyses, respectively, for waist circumference. There was evidence
51 52	269	of statistically significant effect modification by the difference in SFA intake in the categorical
53 54	270	subgroup analyses (P<0.05) and by the difference in carbohydrate intake in the continuous
55 56	271	subgroup analyses (P<0.05) between tree nut and control interventions. Trials in which tree
57 58 50	272	nuts displaced more SFA leading to larger differences between the tree nut and control
59 60		Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page 10 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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

276 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 (1²=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.

294 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% Cl, -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 ($l^2=53\%$, 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-I² to 0%. No other subgroup analyses were statistically significant for either systolic or diastolic blood pressure. **Fasting Blood Glucose**

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327Appendix Figure 9 presents the effect of tree nuts on fasting blood glucose. Tree328nuts did not significantly decrease fasting blood glucose in the overall analysis (MD, -0.02329mmol/L [95% CI, -0.16, 0.11mmol/L]), with evidence of significant heterogeneity (I^2 =57%,330p<0.01). Stratification by health status failed to demonstrate an effect for any of the</td>331subsamples. 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.

339 Publication Bias

Appendix Figure 11 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 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 7weeks. 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 al⁵⁶ 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 Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page | 14

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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 DASH⁶³ 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 Portfolio⁶² 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 DASH⁶³ 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 Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page | 15

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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.

417 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 guality 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. 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. Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page | 17

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Sabate et al, 1993 (32) Walnut Control Chisholm et al, 1998 (13)			Weight or BMI	Setting	Design	Feeding Control	Nut type	Nuts Dose (g/d)II	Comparator	Diet ††	Energy	Follow-Up	MQS §§	Funding Sources II
Walnut Control		range), y	(SD or range)§			Control					Balance			
	18 (18 M)	30	73	OP, USA	Crossover	Met	Walnut	84		55:31:14	Isocaloric	4 wks	6	Agency
Chisholm et al, 1998 (13)	10 (10 M)	50	15	01,004	010330461	IVICL			NCEP Step 1 diet	56:30:14	1300410110	4 1113	0	Agency
Walnut					_		Walnut	78		40:38:17				
Control	16 HLP	45 (6.8)	28.4 (4.3)	OP, New Zealand	Crossover	DA			Low Fat Diet	46:30:19	Isocaloric	4 wks	4	Agency
Spiller et al, 1998 (33) Almond							Almond	100		45:39:16				
Control	30 HLP	53 (10)	66 (13)	OP, Italy	Parallel	Supp	Almond	100	Matched macronutrient diet	47:36:17	Isocaloric	4 wks	6	Agency
Curb et al, 2000 (10)								10						
Macadamia Control	30 (15 M, 15 W)	35.25 (18-53)	23 (19.1 - 28.3)	OP, USA	Crossover	Met	Macadamia	46	AHA	48:35:17 54:30:16	Isocaloric	4 wks	4	Agency-Industry
Control		,		- ,					AAD	48:35:17				<u> </u>
Morgan et al, 2000 (34) Pecan		37 (12)	24 (5)				Pecan	68		45:43:12				
Control	19 (4 M, 15 W)	45(10)	24 (5) 24 (4)	OP, USA	Parallel	Supp	recan	08	Self-selected diet	46:36:12	Isocaloric	8 wks	6	Agency
Zambon et al, 2000 (35)					0	0	14/-14	10.5		10.01.10				
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)										07.20.10				
Walnut	40 (20 M, 20 W)	23.8 (3.1)‡	22.2 (0.5)	OP, Japan	Crossover	Met	Walnut	52¶	Aurona lanana Dist	60:26:14	Isocaloric	4 wks	8	Agency
Control Jenkins et al, 2002 (15)		23.6 (4.6)‡	20.7 (0.5)						Average Japanese Diet	62:24:14				
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 Lovejoy et al, 2002 (37)	,		71.0 (2.4)						NCEP Step 2 diet + Muffin	57:26:18				,
High Fat Almond							Almond	85¶		48:37:15				
Low Fat Almond High Fat Control	30 DM2 (13 M, 17 W)	53.8 (10.4)	33.0 (5.5)	OP, USA	Crossover	Met	Almond	001	High Fat diet	60:25:15 48:37:15	Isocaloric	4 wks	5	Agency
Low Fat Control									Low Fat diet	40.37.15 60:25:15				
Sabate et al, 2003 (38)														
High-Almond Low-Almond	25 NL-HC (14 M, 11 W)	41 (13)	N/A	OP, USA	Crossover	Met	Almond Almond	83 42		46:39:14 35:51:14	Isocaloric	4 wks	5	Agency-Industry
Control									NCEP Step 1 diet	56:30:14				
Wien et al, 2003 (8) Almond		53 (2)	113 (5)				Almond	84		53:18:29				
Control	65 OW/DM2 (28 M, 37 W)	57 (2)	114 (5)	OP, USA	Parallel	Supp	, uniona	0.	CHO-LCD	32:39:29	Isocaloric	24 wks	8	Agency
Tapsell et al, 2004 (39) Walnut		57.7 (9)	87.6 (12.8)				Walnut	30		44:32:22				
Control	37 DM2	59.3 (7.1)	81.9 (11.2)	OP, Australia	Parallel	Supp	vvairiat	30	Modified Fat	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)									r togalar alot					
Almond Almond + Dark Chocolate		41.8 (11.7) 46.2 (7.8)	25.3 (3.5) 27.2 (4.2)				Almond Almond	60		51:34:15 46:39:15				
Dark chocolate	47 (47 W)	36.5 (11.9)	23.9 (3.3)	OP, USA	Parallel	Supp	Amona		NCEP ATP III diet + Chocolate	55:30:15	Isocaloric	6 wks	5	Agency-Industry
Control		51.3 (6.3)	26.1 (4.1)						NCEP ATP III diet	57:27:16				
Schutte et al, 2006 (53)* Walnut		45.5	35.9				Walnut	05.5		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 Mukuddem-Petersen et al, 2007 (42)		44.4	35.5						Control diet	50:33:18				
Walnut			107				Walnut	85.5¶		49:35:16				
Cashew Control	64 MetS	45 (10)	99 106	OP, South Africa	Parallel	Met	Cashew		Habitual diet	44:37:19 47:33:20	Isocaloric	8 wks	7	Agency-Industry
Sheridan et al, 2007 (17)			100							+1.00.20				
Pistachio	15 HC	60 (11.2)	175 (26)	OP, USA	Crossover	Supp	Pistachio	35	Regular dist	52:31:17 53:31:16	Isocaloric	4 wks	6	Agency
Control									Regular diet	53:31:16				

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Table 1 Cont'd

Study, year (Reference)	Participants	Mean Age (SD o 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 2 PD	28 HLP (10 M, 18 W)	48 (7.9)	76.6 (13.2)	OP, USA	Crossover	Met	Pistachio	37		53:34:16	Isocaloric	4 wks	5	Agonov
2 PD Control	20 HLP (10 W, 10 W)	40 (7.9)	70.0 (13.2)	0P, 05A	Clossover	IVIEL	Pistachio	74	NCEP Step 1 diet	57:29:16 62:25:15	ISOCAIONC	4 WKS	5	Agency
Griel et al, 2008 (44)									NCEF Step I diet	02.25.15				
Macadamia							Macadamia			50:33:19				
Control	25 HC	50.2 (8.4)	26.3 (3.3)	OP, USA	Crossover	Met	Macadaima	42.5**	AAD	52:33:17	Isocaloric	5 wks	8	Agency-Indust
Jenkins et al, 2008 (54)*									110	02.00.17				
Almond			71.2 (2.5)				Almond			47:36:17				
Control	27 HLP (15 M, 12 W)	64 (9)	71.0 (2.4)	OP, Canada	Crossover	Supp		73	NCEP Step 2 diet + Muffin	57:26:18	Isocaloric	4 wks	6	Agency
Rajaram et al, 2009 (45)			- ()											
Walnut			71.9 (15.5)	00.000			Walnut	42.5		60:31:15			-	
Control	25 NL-HLP (14 M, 11 W)	23-65	71.7 (15.5)	OP, USA	Crossover	Met			AAD	57:30:14	Isocaloric	4 wks	5	Agency
Tapsell et al, 2009 (46)			(/											
Walnut			92.3 (15.7)				Walnut	30		42:29:24				
Control	35 DM2†	54 (8.7)	93.4 (3)	OP, Australia	Parallel	Supp			Low Fat diet	41:34:20	Isocaloric	12 months	7	Agency
Li et al, 2010 (11)			50.4 (0)						Low Fut dict	41.04.20				
Almond		45.4 (2.0)	86 (26.8)				Pistachio	53		55:30:15	Hypocaloric			
Control	52 OW†	47.3 (2.3)	85.5 (40.2)	OP, USA	Parallel	Supp	1 lotaonio	00	Pretzel	65:20:15	Hypocaloric	12 wks	7	Agency
Ma et al, 2010 (47)			00.0 (10.2)						1101201	00.20.10	rijpodalorio			
Walnut					-	-	Walnut	56		39:44:17			_	
Control	22 DM2†	58.1 (9.2)	89 (15.5)	OP, USA	Crossover	Supp			Ad libitum diet	43:38:19	Isocaloric	8 wks	5	N/A
Torabian et al, 2010 (12)										10.00.10				
Walnut					-	-	Walnut	46		N/A			_	_
Control	87 (38 M, 49 W)	54 (10.2)	75.6 (13.2)	OP, USA	Crossover	Supp			Habitual diet		Isocaloric	6 months	6	Agency
Wien et al, 2010 (48)														
Almond		53 (9)	82.9 (14.4)				Almond	58		42:39:19				
Control	65 PD (17 M, 48 W)	54 (11)	80.5 (14.4)	OP, USA	Parallel	Supp	74110110	00	AAD	48:30:21	Isocaloric	16 wks	9	Agency
Wu et al, 2010 (49)		04(11)	00.0 (14.4)						110	40.00.21				
Walnut		48.2 (8.4)	72.2 (11.4)				Walnut	30		48:37:15				
Control	189 MetS	48.6 (8)	70.6 (10.9)	OP, USA	Parallel	Supp			AHA	51:34:15	Isocaloric	12 wks	9	Agency
Casas-Agustench et al, 2011 (50)		10.0 (0)	10.0 (10.0)							01.01.10				
Mixed Nuts	50 MetS (28 M, 22 W)	52.9 (8.4)	31.6 (2.8)	OP, Spain	Parallel	Supp	Mixed Nuts	30		41:36:19				
Control		50.6 (8.4)	30.0 (3.3)	, -p					Prudent diet	42:36:19	Isocaloric	12 wks	6	Agency
Cohen et al, 2011 (19)		00.0 (0.1)	00.0 (0.0)							12.00.10				
Almond			96.1 (40.4)				Almond	28						
Control	13 DM2 (7 M, 6 W)	66 (11.9)	105.1 (32.1)	OP, USA	Parallel	Supp	/ unond	20	Cheese sticks	N/A	Isocaloric	12 wks	7	Agency
Jenkins et al, 2011 (20)			100.1 (02.1)						0110000 010110					
Mixed Nuts		63 (9)	80 (15)				Mixed nuts			41:41:18				
Control	79 DM2 (52 M, 27 W)	61 (10)	83 (15)	OP, Canada	Parallel	Supp	minou nato	75¶	NCEP Step 2 diet + Muffin	46:35:19	Isocaloric	12 wks	8	Agency
Li et al, 2011 (21)		01(10)	00(10)							10.00.10				
Almond					_		Almond	56		47:37:17			_	
Control	20 DM2 (9 M, 11 W)	58 (8.9)	26 (3.1)	OP, Taiwan	Crossover	Met	74110110		NCEP step 2 diet	57:27:17	Isocaloric	4 wks	5	Agency
Tey et al, 2011 (51)										01.21.11				
Hazelnut		38.9 (14.3)	72 (11.1)			-	Hazelnut	42		45:39:16‡‡			_	
Control	61	36.1 (15.2)	67.3 (9.5)	OP, New Zealand	Parallel	Supp			Regular diet	50:33:17	Isocaloric	12 wks	9	Agency
Darvish Damavandi et al, 2012 (18)		/												
Cashew		51 (7.9)	72.1 (13.1)			-	Cashew	30		53:32:16			3	
Control	43 DM2 (9 M, 34 W)	56 (5.7)	71.9 (9.7)	OP, Iran	Parallel	Supp			Regular diet	57:27:16	Isocaloric	8 wks		N/A
Foster et al, 2012 (52)		()												
Almond		47 (12)	94 (13.1)	00.000			Almond	56		N/A	Hypocaloric			
Control	123 OW (11 M, 112 W)	46.7 (13)	91.5 (11.9)	OP, USA	Parallel	Supp			Nut free diet		Hypocaloric	18 months	9	Agency
Wang et al, 2012 (22)		. (. ,									,,			
Pistachios		51.9 (8.8)	28.1 (3.2)				Pistachio	42						
High pistachios	86 MetS	51.8 (9.4)	28 (4.5)	OP, China	Parallel	Supp	Pistachio	70		N/A	Isocaloric	12 wks	5	Industry
Control		50.7 (9.9)	28 (4.4)					-	AHA Step 1 diet					,
West et al, 2012 (55)*			/											
1 Pistachio							Pistachio	37		53:34:16				
2 Pistachio	28 HLP (10 M, 18 W)	48 (7.9)	76.6 (13.2)	OP, USA	Crossover	Met	Pistachio	74		57:29:16	Isocaloric	4 wks	5	Agency
Control	(, , , , , , , , , , , , , , , , , , ,	- (- /							NCEP Step 1 diet	62:25:15		-	-	5
Somerset et al, 2013 (9)										02.20.10				
Macadamia		43.7 (8.4)	95 (14.7)			DA	Macadamia	46		36:38:21				-
Control	64 OW (10 M, 54 W)	43.2 (10.9)	99.6 (15.2)	OP, Australia	Parallel				Regular diet	41:38:17	Isocaloric	10 wks	9	Agency
001100		TJ.2 (10.3)	00.0 (IU.Z)						INCYLICIT LICE	T1.30.17				

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$\begin{array}{c} 2\\ 3\\ 4\\ 5\\ 6\\ 7\\ 8\\ 9\\ 10\\ 11\\ 12\\ 13\\ 14\\ 15\\ 16\\ 17\\ 18\\ 19\\ 20\\ 21\\ 22\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 4\\ 35\\ 36\\ 37\\ 38\\ 9\\ 40\\ 41\\ \end{array}$	 Table 1. Characteristics of RCTs Investigating the effect of Tree Nuts on Criteriaof the MeIS MeIS: metabolic syndrome; DM2: type 2 diabetes mellitus, OW: overweight; HLP: hyperflipidemic; NL-HLP: normal to mildly hyperflipidemic; MC: Hyperflopidemic; NL-HC: momal to mild hyperflipidemic; MC: Hyperflopidemic; ML: Hyperflopidemic; ML: Hyperflopidemic; ML: MC: momal to hypercholesterolenic; MC: 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, 2009 me55 and for recruited subjects for Tapsell et al. 2009 (n=65). ‡ Meen 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. I Nut dose is given based on grams (g) per day, 10z = 28 g. ¶ Median was taken from a rang given. Iwamoto et al, 2017 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 Carbohydrate fat.protein. ‡* Values for carbohydrate fat.protein. ‡* Values for carbohydrate fat.protein. ‡* Values for carbohydrate fat.gover to means. §§ Triais with score 58 were considered to be of high quality. III Agency funding is that from gove

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 (I²) at a significance level of P<0.10 and quantified by I², levels \geq 50 % considerable heterogeneity and \geq 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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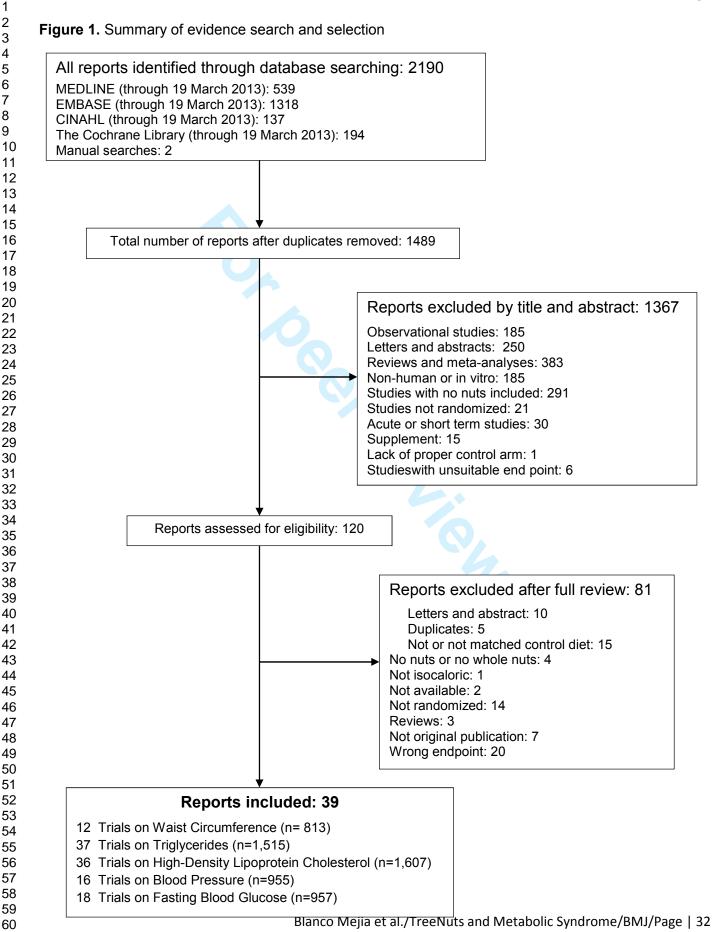


Figure 2. Forest plot of the RCTs investigating the effect of Tree Nuts on Triglycerides

Subgroup and Study, year (Reference)	Nuts	Control n	Weight	Mean Difference	
114 II 2007 0000	n	n		(95% CI) in mmol/L	
therwise Healthy abate 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) Rajaram et al, 2001 (14)	10 23	9 23	0.70%	-0.24 [-0.57, 0.09] -0.14 [-0.28, -0.00]	
Iwamoto et al, 2002 (36)	23 40	40	2.70%	0.00 [-0.16, 0.16]	
Sabate et al, 2003 (38) Kocyigit et al, 2006 (16)	25 22	25 22	0.80%	-0.03 [-0.32, 0.26] -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) Rajaram et al, 2009 (45)	12	11	15.90% 2.20%	-0.01 [-0.05, 0.03] -0.01 [-0.19, 0.17]	+
Torabian et al, 2010 (12)	25 87	25 87	23.20%	-0.09 [-0.10, -0.08]	
Tey et al, 2011 (51) Subtotal (95% Cl)	32 336	27 329	2.20% 67.80%	-0.04 [-0.22, 0.14] -0.07 [-0.11, -0.04]	
Heterogeneity: Tau ² = 0.00; Chi ² = 20.97, df = 11 (P = 0.03); l ² = 48%	550	525	01.0076	-0.07 [-0.11, -0.04]	•
Test for overall effect: Z = 3.89 (P = 0.0001)					
Dyslipidemia					
Chisholm et al, 1998 (13) Spiller et al, 1998 (33)	16 18	16 12	0.80% 0.70%	0.14 [-0.15, 0.43] 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) Tamizifar et al, 2005 (40)	27 30	27 30	1.30% 1.30%	-0.13 [-0.37, 0.11] 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) Subtotal (95% CI)	25 208	25 202	1.30% 15.00%	-0.04 [-0.28, 0.20] -0.06 [-0.13, 0.00]	
Heterogeneity: Tau ² = 0.00; Chi ² = 6.82, df = 7 (P = 0.45); l ² = 0%					•
Test for overall effect: Z = 1.90 (P = 0.06)					
Metabolic Syndrome Features			- 1999 (sec. d. 10)		
Mukuddem-Petersen et al, 2007 (42) Li et al, 2010 (11)	42 27	22 25	1.30% 1.50%	-0.21 [-0.45, 0.03] -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 61	25 62	0.40%	0.04 [-0.37, 0.45] 0.07 [-0.13, 0.27]	
Foster et al, 2012 (52) Wang et al, 2012 (22)	61 56	62 30	1.80% 1.50%	0.07 [-0.13, 0.27] -0.07 [-0.29, 0.15]	
Somerset et al, 2013 (9)	35	29	1.50%	-0.01 [-0.23, 0.21]	
Subtotal (95% Cl) Heterogeneity: Tau ² = 0.00; Chi ² = 7.37, df = 6 (P = 0.29); l ² = 19%	278	226	9.80%	-0.09 [-0.19, 0.00]	•
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) Wien et al, 2003 (8)	30 32	30 33	0.80%	0.10 [-0.19, 0.39] 0.00 [-0.39, 0.39]	
Tapsell et al, 2004 (39)	17 18	20	0.70%	0.15 [-0.16, 0.46] 0.30 [-0.50, 1.10]	
Tapsell et al, 2009 (46)	18 22	17	0.10% 0.70%	0.30 [-0.50, 1.10]	
Ma et al, 2010 (47) Cohen et al, 2011 (19)	6	22 7	0.10%	-0.11 [-0.42, 0.20] 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) Darvish Damavandi et al, 2012 (18)	20 22	20 21	0.70% 0.70%	-0.10 [-0.41, 0.21] 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); l ² = 0% Test for overall effect: Z = 0.24 (P = 0.81)					
Total (95% Cl) Heterogeneity: Tau² = 0.00; Chi² = 45.56, df = 36 (P = 0.13); l² = 21%	1059	996	100.00%	-0.07 [-0.09, -0.04]	•
First for overall effect: $Z = 4.74$ (P < 0.00001)					-0.5-0.25 0 0.25 0.5
est for subgroup differences: Chi ² = 2.94, df = 3 (P = 0.40), I ² = 0%					Favours Nuts Favours Control Mean Difference
					(95% CI) in TG, mmol/L

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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
Databaoo		1. exp nut/ Or nuts.mp. Or nut.mp. Or expbertholletia/ Or walnut*.mp. Or expJuglans/ Or almond*.mp. Or expPrunus/ Or
MEDLINE	1946 to March Week	pecan*.mp. Or expCarya/ Or pistachio*.mp. Or expPistacia/ Or cashew*.mp. Or expAnacardium/ Or hazelnut*.mp. Or
MEDEINE	1 2013	expCorylus/ Or macadamia*.mp. Or exp Macadamia/
	1 2013	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 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

CINHAL	1982 to 19 March 2013	 (MH "Nuts+) Or "pistachio" Or "hazelnut" Or "macadamia" Or "brazil nut" Or "brazil nuts" Or "pine nut" Or "pine nuts". "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". (MH "Hypertension") Or "hypertension" Or "SBP" Or "DBP" Or "mean arterial pressure" Or "MAP". "triglycerides" Or "hypertriglyceridemia" Or "TG" Or "TAG" Or "dyslipidemia". "HDL" Or (MH "Lipoproteins, HDL Cholesterol") Or "hypercholesterolemia". "abdominal obesity" Or "abdominal fat" Or "waist circumference". "Insulin resistance" Or "metabolic syndrome". 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 metabolic syndrome.mp. 8. 1 and (2 or 3 or 4 or 5 or 6 or 7) search term is used in order to capture all possible endings with that word.
Original sear	rch date for all data	bases was May 25th 2012; update search date for all databases was March 19th 2013. hals and then extracted from the general search.
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Appendix Table 2 – Study Quality Assessment by Using the Heyland MQS*

3 Study, Year (Reference)	De	sign†			Sample‡		Intervention§			MQS (n/13)
4 5 6	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)	Crossover s (n/2)	(
7										
8										
9 Sabate et al, 1993 (32)	1	0	0	1	1	0	1	2	0	6
10 Chisholm et al, 1998 (13)	1	0	0	0	1	0	0	2	0	4
11 Spiller et al, 1998 (33)		0	0	1	1	0	1	2	0	6
12 Curb et al, 2000 (10)		0	0	0	1	0	0	2	0	4
13 Morgan et al, 2000 (34)	1	0	0	1	1	0	1	2	0	6
14 Zambon et al, 2000 (35)	2	0	0	0	1	0	1	2	0	6
15 Rajaram et al, 2001 (14)	2	0	0	1	1	1	1	2	0	8
16 Iwamoto et al, 2002 (36)	1	0	2	0	1	1	1	2	0	8
17 Jenkins et al, 2002 (15)	1	0	0	1	1	0	1	2	0	6
18 Lovejoy et al, 2002 (37)	1	0	0	0	1	0	0	2	0	5 5
19 Sabate et al, 2003 (38)	1	0	0	0	1	0	1	2 2	0	-
¹⁹ Wien et al, 2003 (8)	2	0	2	0	1	0	1	2	0	8
21 Tapsell et al, 2004 (39)	1	•	2		1	0	0	1	0	6
²¹ Tamizifar et al, 2005 (40)	1	0	0	0		0	1	2 2	0	5
²² Kocyigit et al, 2006 (16)	1	0	2	0		1	1	2	0	8
²³ Kurlandsky et al, 2006 (41)	1	0 0	0	1		0	1	2	0	с 7
25 Schutte et al, 2006 (53) 25 Mukuddam Paterson et al. 2007(42)	2	0	0	1		0	1	2	0	7
26 Mukuddem-Petersen et al, 2007(42)	2		0	1		0	1	2	0	6
27 Sheridan et al, 2007 (17)	1	0	0	1		0	1	2	0	6
²⁷ Gebauer et al, 2008 (43)	1	0	0	1		1	1	2	0	5 8
20 Griel et al, 2008 (44) 29 Jonking et al, 2008 (54)	1	0	2	1	1		1	2	0	6 6
²⁹ Jenkins et al, 2008 (54) 30 Rajaram et al, 2009 (45)	1	0	0	1	1	0		2	0	5
31 Tapsell et al, 2009 (46)	1	0	0	1	1	0	1	2	0	5
32 Li et al, 2010 (11)	2	0	0	1	1	0		2	0	7
³³ Ma et al, 2010 (47)	<u>ک</u>	0	0	1	1	0	1	2	0	5
34 Torabian et al, 2010 (12)	1	0	0	1	1	0	1	2	0	6
35 Wien et al, 2010 (48)	1	0	0	1	1	0	1	2	0	9
36 Wu et al, 2010 (49)	2	0	2	1	1	0	1	2	0	9
³⁷ Casas-Agustench et al, 2011 (50)	1	0	2	1	1	0	1	2	0	6
38 Cohen et al, 2011 (19)	1	0	2	0	1	1	1	2	0	7
$\frac{39}{10}$ Jenkins et al, 2011 (20)	1	0	2	1	1	0	1	2	0	8
40 Li et al, 2011 (21)	1	0	<u>د</u>	0	1	0	1	2	0	о 5
⁴¹ Tey et al, 2011 (51)	2	0	2	1	1	0	1	2	0	9
⁴² DarvishDamavandi et al, 2012 (18)	<u>-</u> 1	0	0	0	0	0	1	2	0	3
43	,	U	U	U	0	0	I	I	U	0

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	Foster et al, 2012 (52)	2	0	2	0	1	1	1	2	0	9
1	Wang et al, 2012 (22)	1	0	0	0	1	0	1	2	0	5
2	West et al, 2012 (55)	1	0	0	1	1	0	1	1	0	5
3	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.

6 * 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 7 interventions, for a total of 13 points. Trials that scored ≥8 were considered to be of higher quality (11).

8 † Randomization was scored 2 points for being randomized with the methods described, 1 point for being randomized without the methods
 9 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
 10 for "other." Analysis was scored 2 points for being intention-to-treat; all other types of analyses scored 0 points.

¹¹ \ddagger Sample selection was scored 1 point for being consecutive eligible or 0 points for being preselected or indeterminate. Sample comparability was ¹² 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 ¹³ <100%. ¹⁴ § Treatment protocol was scored 1 point for being reproducibly described or 0 points for being poorly described. Co-interventions were scored 2

¹⁴ § Treatment protocol was scored 1 point for being reproducibly described or 0 points for being poorly described. Co-interventions were scored 2 16 points for being described and equal, 1 point for being described but unequal or indeterminate, or 0 points for not being described. Treatment 17 crossovers (where participants were switched from the control treatment to the experimental treatment) were scored 2 points for being <10%, 1 point 18 for being >10%, and 0 points for not being described.

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

Subgroups	No. of Trials	Ν	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

D. Systolic Blood Pressure

2.010101000011000010					
Subgroups	No. of Trials	Ν	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

B. Triglycerides

Subgroups	No. of Trials	Ν	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

E. Diastolic Blood Pressure					
Subgroups	No. of Trials	Ν	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

C. High-Density Lipoprotein Cholesterol

Subgroups	No. of Trials	Ν	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

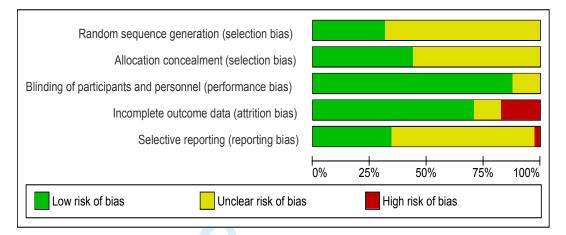
Subgroups	No. of Trials	Ν	β [95% CI]	Residual I ² (%)	P-value
Nuts Dose (g/d)	18	955	0.005 [-0.006, 0.015]	58.1	0.35
Duration (weeks)	18	955	0.004 [-0.027, 0.035]	59	0.78
Saturated Fat (%)	15	746	0.028 [-0.053, 0.109]	52.4	0.46
Change in Saturated Fat (%)	9	621	-0.145 [-0.353, 0.064]	48.1	0.15
Difference 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 1² was reported as a percent value, where 1² ≥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

Subgroup and Stu	udy, year (Reference)	Nuts	Control	Weight	Mean Difference		
		n	n		(95% Cl) in cm		
Otherwise Health	y .						1
Tey et al, 2011 (51 Subtotal (95% CI))	32 32	29 29	12.10% 12.10%	0.77 [-0.74, 2.28] 0.77 [-0.74, 2.28]		
Heterogeneity: Not	applicable ect: Z = 1.00 (P = 0.32)	52	25	12.10%	0.11 [-0.14, 2.20]		
Dyslipidemia						-	
Jenkins et al, 2002	(15)	27	27	9.50%	-1.46 [-3.69, 0.77]		
Subtotal (95% CI) Heterogeneity: Not	applicable	27	27	9.50%	-1.46 [-3.69, 0.77]		
	ect: Z = 1.28 (P = 0.20)						
Metabolic Syndro	me Features						
Schutte et al, 2006		41	21	3.80%	-0.84 [-5.72, 4.04]		-
Wien et al, 2010 (4		32	33	9.10%	-0.70 [-3.03, 1.63]	_	T
Wu et al, 2010 (49)		94	95	14.60%	0.06 [-0.74, 0.86]	_	Ī.
Casas-Agustench		25	25	8.90%	-1.10 [-3.49, 1.29]		
Wang et al, 2012 (56	30	6.80%	0.78 [-2.36, 3.92]		
Somerset et al, 20	13 (9)	35	29	3.30%	-8.95 [-14.28, -3.62]		
Subtotal (95% CI)	² = 2.00; Chi ² = 11.90, df = 5 (P = 0.04); l ² = 58%	283	233	46.50%	-0.92 [-2.53, 0.68]		1
	P = 2.00, $CHP = 11.90$, $H = 5$ ($P = 0.04$), $P = 58%ect: Z = 1.13 (P = 0.26)$						
Diabetes Wien et al, 2003 (8	,	32	33	8.40%	-5.00 [-7.55, -2.45]		
Ma et al, 2003 (47)		22	22	5.90%	-0.30 [-3.85, 3.25]		
Jenkins et al, 2010 (47)		40	39	12.90%	0.81 [-0.48, 2.10]		
Darvish Damavano		22	21	4.80%	-2.10 [-6.26, 2.06]	_	
Subtotal (95% CI)		116	115	32.00%	-1.57 [-4.68, 1.54]	-	
	² = 7.82; Chi ² = 16.50, df = 3 (P = 0.0009); ² = 82%						1
Test for overall effe	act: Z = 0.99 (P = 0.32)						
Total (95% CI)		458	404	100.00%	-0.91 [-1.99, 0.18]		
						-J. J.	1 1
	¹ ² = 1.93; Chi ² = 31.47, df = 11 (P = 0.0009); l ² = 65%					-20 -10	o 10 20
Test for overall effe	ect: Z = 1.64 (P = 0.10)					Favours Nuts	Favours Contr
Test for subgroup	differences: Chi² = 4.13, df = 3 (P = 0.25), l² = 27.3%					Mean [Difference
							in WC, cm

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 \geq 50 % represent considerable heterogeneity and ≥75%, substantial heterogeneity. WC = waist circumference, cm = centimeters.

Mean difference (95% Cl) in Waist Circumference, cm Subgroup Level Trials P-value Residual / Between subgroups Within subgroups Total 12 813 -0.91 (-1.99, 0.18) 157 -2.29 (-4.77, 0.18) See legend 42.7% 0.197 Nut type 3 Almonds Brazil nuts 0 Cashews 2 74* -1.55 (-6.21.3.10) Hazelnuts 61 0.77 (-2.77, 4.31) Macadamia 64 -8.95(-16.5,-1.37) 1 Pecans 0 0 Pine nuts a Pistachios 86 0.78 (-4.27, 5.83) Walnuts 242* -0.03 (-2.74, 2.68) Mixed nuts 2 129 0.08 (-2.58, 2.74) 12 Nut dose < 50 g/d 407 -1.16 (-3.63, 1.31) 0.22 (-3.04, 3.47) 67.6% 0.885 5 13 ≥ 50 g/d 406 7 -0.95 (-3.06, 1.17) 14 Follow up < 12 week 218 -2.18 (-4.93, 0.56) 1.71 (-1.54, 4.96) 62.3% 0.269 ≥ 12 weeks 595 -0.48 (-2.21, 1.26) 15 SFA < 7% 2 254 -2.04 (-5.63, 1.56) 1.09 (-3.00, 5.18) 70.8% 0.561 16 ≥ 7% 473 -0.94 (-2.90, 1.01) 57.1% SFA (chg) < -2% 2 112 -1.05 (-5.01, 2.91) 1.07 (-3.03, 5.16) 0 5 5 7 18 ≥ -2% 7 528 0.02 (-1.03, 1.07) 19 8.23 (1.29, 15,18) † SFA (Δ) < -1.5% 1 64 -8.95 (-15.78, -2.12) 56.7% 0.025 10 663 -0.72 (-1.99, 0.55) ≥ -1.5% 20 Fiber < 25 g/d 244 -1.92 (-4.68, 0.84) 1.19 (-2.29, -4.68) 67.4% 0.458 5 6 483 -0.73 (-2.86, 1.40) ≥ 25 g/d 22 Fiber (chg) < 5.3 g/d 362 -0.98 (-4.01, 2.05) 1.04 (-5.86, 7.94) 67.7% 0.715 ≥ 5.3 g/d 1 189 0.06 (-6.14, 6.26) 24 < 4.4 g/d 303 -0.85 (-3.15, 1.44) -0.75 (-4.21, 2.72) 70.3% 0.638 Fiber (Δ) ≥ 4.4 g/d 424 -1.60 (-4.19, 1.00) 26 Study design Crossover -0.98 (-4.99, 3.02) -0.05 (-4.42, 4.32) 67.3% 0.979 Parallel 10 764 -1.04 (-2.79, 0.72) MQS 290 -0.83 (-3.29, 1.62) -0.36 (-3.60, 2.88) 66.9% 0.810 < 8 6 28 ≥ 8 523 -1.19 (-3.32, 0.93) 29 <95 cm 259 -0.93 (-4.22, 2.37) -0.84 (-4.87, 3.20) Baseline WC 71.4% 0.645 30 ≥95 cm 407 -1.76 (-4.10.0.57) < 5% 434 -0.36 (-2.55, 1.84) -1.72 (-4.94, 1.50) 68.6% 0.257 Carbohydrates ≥ 5% 300 -2.08 (-4.43, 0.28) 32 33 -15 -10 -5 0 5 10 15 34 Favours Tree Nuts Favours Control 35

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

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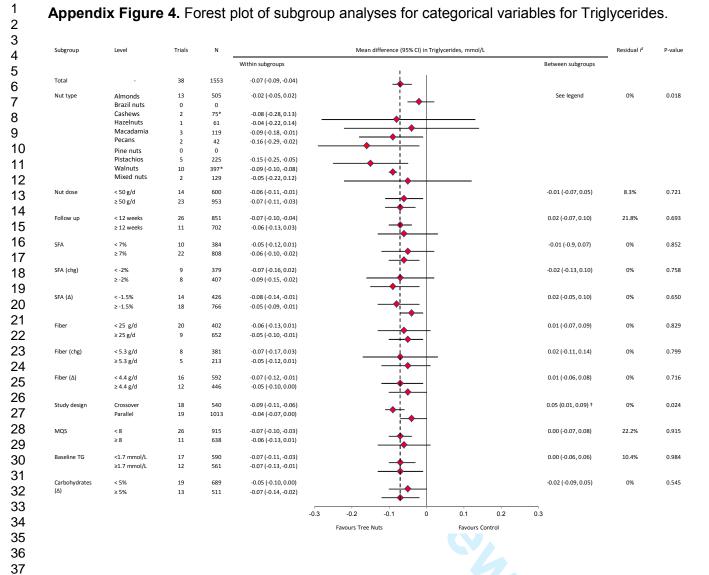
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36 Point estimates for each subgroup level are the pooled effect estimates and are represented by 37 diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual 38 I^2 value indicates the interstudy heterogeneity unexplained by the subgrouping. Pairwise between-39 40 subgroup mean differences (95% CIs) for nut type are not shown due to lack of statistical significance 41 between groups. SFA = Saturated Fatty Acids, SFA (chg) = change within treatment diet for SFA, SFA 42 (Δ) = difference between groups for SFA, Fiber (chg) = change within treatment diet for Fiber, Fiber (Δ) 43 = difference between groups for SFA, MQS = Heyland Methodological Quality Score, WC = waist 44 circumference, Carbohydrates (Δ)= difference between groups for carbohydrates. 45 46

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



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 I² 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) †II 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.

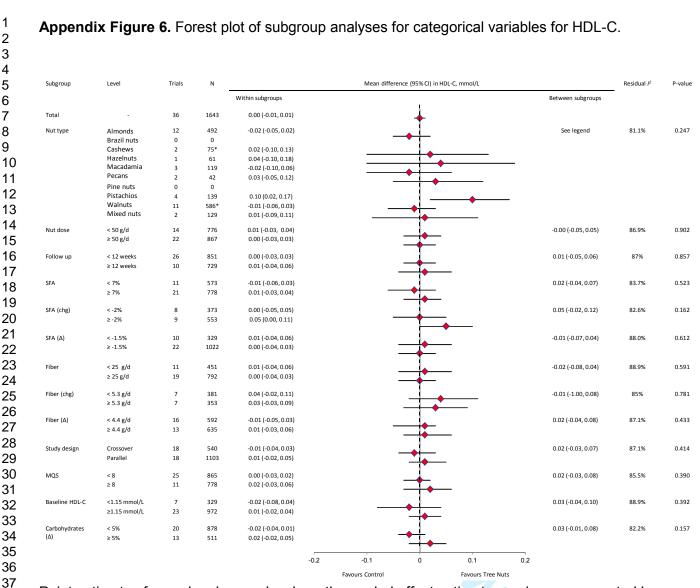
† Statistically significant pairwise subgroup effect modification by meta-regression analysis (p< 0.05)

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

Su	ubgroup and Study, year (Reference)	Nuts	Control	Weight	Mean Difference (95% CI) in mmol/L	
	12 8 30 88m		n		(95% CI) IN MINOR	
	therwise Healthy	10	40	0.00%	0.001.0.40.0.000	
	abate et al, 1993 (32) urb et al, 2000 (10)	18 30	18 30	2.60% 3.70%	-0.06 [-0.12, -0.00] -0.01 [-0.05, 0.03]	
	lorgan et al, 2000 (10)	10	9	5.30%	0.01 [0.00, 0.02]	-
	ajaram et al, 2000 (04)	23	23	4.90%	0.06 [0.04, 0.08]	-
	/amoto et al, 2002 (36)	40	40	3.70%	-0.02 [-0.06, 0.02]	
	abate et al, 2003 (38)	25	25	3.70%	0.01 [-0.03, 0.05]	
	ocyigit et al, 2006 (16)	22	22	1.90%	0.19 [0.11, 0.27]	· · · · ·
	urlandsky et al-Almonds, 2006 (41)	12	12	3.70%	0.04 [0.00, 0.08]	
	urlandsky et al-Almd+choc, 2006 (41)	12	11	2.60%	-0.07 [-0.13, -0.01]	
	ajaram et al. 2009 (45)	25 87	25 87	3.70% 5.40%	-0.01 [-0.05, 0.03]	
	orabian et al, 2010 (12) ev et al, 2011 (51)	32	29	1.90%	-0.01 [-0.01, -0.01] 0.04 [-0.04, 0.12]	
	ubtotal (95% CI)	336	331	42.90%	0.01 [-0.01, 0.03]	+
	eterogeneity: $Tau^2 = 0.00$; $Chi^2 = 103.18$, $df = 11$ (P < 0.00001); P = 89%	000	001	12.0070	0.01[0.01,0.00]	
	est for overall effect; Z = 0.98 (P = 0.33)					
	yslipidemia	40	40	4.00%	0.00 10.01 0.05	
	hisholm et al, 1998 (13) piller et al, 1998 (33)	16 18	16 12	4.90% 5.30%	0.03 [0.01, 0.05] -0.04 [-0.05, -0.03]	
	ambon et al, 1996 (35)	49	49	2.60%	0.05 [-0.01, 0.11]	
	enkins et al. 2002 (15)	27	43	2.60%	0.08 [0.02, 0.14]	
	amizifar et al, 2002 (40)	30	30	3.70%	-0.13 [-0.17, -0.09]	
SH	heridan et al, 2007 (17)	15	15	3.70%	0.06 [0.02, 0.10]	· · · · · · · · · · · · · · · · · · ·
	ebauer et al, 2008 (43)	28	28	0.80%	0.03 [-0.11, 0.17]	
	riel et al, 2008 (44)	25	25	3.70%	-0.05 [-0.09, -0.01]	
	ubtotal (95% CI)	208	202	27.20%	-0.00 [-0.04, 0.04]	
	eterogeneity: Tau² = 0.00; Chi² = 105.52, df = 7 (P < 0.00001); l² = 93% est for overall effect Z = 0.03 (P = 0.98)					
	etabolic Syndrome Features ukuddem-Petersen et al, 2007 (42)	42	22	2.60%	-0.08 [-0.14, -0.02]	
	etal, 2010 (11)	27	25	1.00%	0.09 [-0.03, 0.21]	
	(ien et al, 2010 (48)	32	33	1.00%	0.03 [-0.09, 0.15]	
	(u et al. 2010 (49)	94	95	1.40%	0.03 [-0.07, 0.13]	
C	asas-Agustench et al, 2011 (50)	25	25	1.00%	0.00 [-0.12, 0.12]	
	oster et al, 2012 (52)	61	62	1.00%	0.06 [-0.06, 0.18]	
	omerset et al, 2013 (9)	35	29	0.60%	0.04 [-0.12, 0.20]	
	ubtotal (95% CI)	316	291	8.70%	0.01 [-0.04, 0.07]	-
	eterogeneity: Tau ² = 0.00; Chi ² = 11.07, df = 6 (P = 0.09); P = 46% est for overall effect; Z = 0.45 (P = 0.65)					
15						
	iabetes					
	ovejoy et al-Hihg Fat, 2002 (37)	30	30	3.70%	-0.04 [-0.08, -0.00]	
	ovejov et al-Low Fat, 2002 (37)	30	30	3.70%	-0.03 [-0.07, 0.01]	+
	fien et al, 2003 (8) apsell et al, 2004 (39)	32	33	1.40%	-0.18 [-0.28, -0.08]	
	apsell et al, 2004 (39) apsell et al, 2009 (46)	17 18	20 17	0.40%	-0.03 [-0.25, 0.19] 0.00 [-0.02, 0.02]	
	a et al, 2010 (47)	22	22	1.40%	-0.07 [-0.17, 0.03]	
	enkins et al, 2011 (20)	40	39	3.70%	0.02 [-0.02, 0.06]	
Li	etal, 2011 (21)	20	20	1.40%	0.01 [-0.09, 0.11]	
	arvish Damavandi et al, 2012 (18)	22	21	0.80%	0.22 [0.08, 0.36]	
	ubtotal (95% CI)	231	232	21.10%	-0.02 [-0.05, 0.02]	•
He	eterogeneity: Tau² - 0.00; Chi² - 30.48, df - 8 (P - 0.0002); P - 74% est for overall effect: Z = 0.91 (P = 0.36)					
Т	otal (95% CI)	1091	1056	100.00%	-0.00 [-0.01, 0.01]	1
	eterogeneity; Tau ² = 0.00; Chi ² = 264.36, df = 35 (P < 0.00001); P = 87%	1001	1000	100.00 /4	-0.00 [-0.01, 0.01]	· · · • · ·
	est for overall effect Z = 0.05 (P = 0.96)				-	-0.2 -0.1 0 0.1 0.2
т,	est for subgroup differences: Chi ² = 1.72, df = 3 (P = 0.63), P = 0%					
	$\frac{1}{1} = \frac{1}{1} = \frac{1}$					Favours Nuts Favours Control Mean Difference
						(95% CI) in HDL-C, mmol/L

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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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 betweensubgroup 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 = highdensity 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.

Subgroup and Study, year (Reference)		Control	Weight	Mean Difference	
	n	n		(95% CI) in mmHg	
Otherwise Healthy					T
Sabate et al, 1993 (32)	18	18	9.30%	2.00 [-0.94, 4.94]	+
lwamoto et al, 2002 (36)	40	40	5.90%	2.50 [-2.60, 7.60]	+
Subtotal (95% CI)	58	58	15.20%	2.12 [-0.42, 4.67]	•
Heterogeneity: Tau ² = 0.00; Chi ² = 0.03, df = 1 (P = 0.87); l ² = 0% Test for overall effect: Z = 1.64 (P = 0.10)					
Test for overall effect. $Z = 1.04$ (F = 0.10)					
Dyslipidemia					
Jenkins et al, 2002 (15)	27	27	4.80%	-1.90 [-7.98, 4.18]	
Sheridan et al, 2007 (17)	15	15	3.70%	2.70 [-4.75, 10.15]	 -
West et al, 2012 (55)	28 70	28	6.70%	-0.40 [-4.91, 4.11]	
Subtotal (95% CI) Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 2 (P = 0.64); l² = 0%	70	70	15.30%	-0.24 [-3.49, 3.02]	—
Test for overall effect: $Z = 0.14$ (P = 0.89)					
Metabolic Syndrome Features					
Mukuddem-Petersen et al, 2007 (42)	42	22	8.60%	-1.90 [-5.23, 1.43]	
Wien et al, 2010 (48) Wu et al, 2010 (49)	32 94	33 95	4.80% 8.30%	-0.90 [-6.98, 5.18] -1.20 [-4.73, 2.33]	
Casas-Agustench et al, 2011 (50)	94 25	25	4.10%	4.20 [-2.66, 11.06]	
Foster et al, 2012 (52)	61	62	5.20%	0.40 [-5.28, 6.08]	
Wang et al, 2012 (22)	56	30	9.60%	-2.50 [-5.24, 0.24]	
Somerset et al, 2013 (9)	35	29	2.70%	3.60 [-5.61, 12.81]	
Subtotal (95% CI)	345	296	43.40%	-1.22 [-2.81, 0.38]	•
Heterogeneity: Tau ² = 0.00; Chi ² = 4.77, df = 6 (P = 0.57); l ² = 0%					
Test for overall effect: Z = 1.50 (P = 0.13)					
Diabetes					
Wien et al, 2003 (8)	32	33	5.00%	-11.00 [-16.88, -5.12]	.
Ma et al, 2010 (47)	22	22	4.80%	8.90 [2.82, 14.98]	
Jenkins et al, 2011 (20)	40	39	8.90%	-0.70 [-3.84, 2.44]	
Li et al, 2011 (21) Subtotal (95% CI)	20 114	20 114	7.30% 26.10%	-1.50 [-5.62, 2.62] -1.10 [-7.23, 5.02]	
Subtotal (95% CI) Heterogeneity: Tau ² = 32.87; Chi ² = 21.39, df = 3 (P < 0.0001); $ ^2$ = 86%		114	20.10%	-1.10[-1.20, 0.02]	
Test for overall effect: $Z = 0.35$ (P = 0.72)					
	1210				1
Total (95% CI)	587	538	100.00%	-0.24 [-1.93, 1.45]	
Heterogeneity: $Tau^2 = 5.76$; Chi ² = 32.26, df = 15 (P = 0.006); l ² = 53%					-20 -10 Ó 10 20
Test for overall effect: Z = 0.28 (P = 0.78)					Favours Nuts Favours Cont
Test for subgroup differences: Chi ² = 4.82, df = 3 (P = 0.19), I ² = 37.8%	1				Mean Difference
					(95% CI) in SBP, mmHg

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.

Subgroup and Study, year (Reference)	Nuts	Control	Weight	Mean Difference	
	n	n		(95% CI) in mmHg	
Otherwise Healthy					1
Sabate et al, 1993 (32)	18	18	51.30%	0.00 [-0.04, 0.04]	•
Iwamoto et al, 2002 (36)	40	40	3.20%	1.50 [-1.28, 4.28]	- •
Subtotal (95% CI)	58	58	54.50%	0.08 [-0.57, 0.73]	•
Heterogeneity: Tau ² = 0.12; Chi ² = 1.12, df = 1 (P = 0.29); l ² = 10% Test for overall effect: Z = 0.23 (P = 0.81)					
Dyslipidemia					
Jenkins et al, 2002 (15)	27	27	2.50%	-0.37 [-3.53, 2.79]	
Sheridan et al, 2007 (17)	15	15	1.00%	2.40 [-2.72, 7.52]	
West et al, 2012 (55)	28	28	7.40%	0.20 [-1.54, 1.94]	
Subtotal (95% CI)	70	70	10.90%	0.26 [-1.21, 1.72]	Ť
Heterogeneity: Tau ² = 0.00; Chi ² = 0.83, df = 2 (P = 0.66); l ² = 0%					
Test for overall effect. Z = 0.34 (P = 0.73)					
Metabolic Syndrome Features					
Mukuddem-Petersen et al, 2007 (42)	42	22	3.30%	-0.17 [-2.89, 2.55]	
Wien et al, 2010 (48)	32	33	1.40%	1.00 [-3.23, 5.23]	
Wu et al, 2010 (49)	94	95	5.80%	-0.23 [-2.25, 1.79]	
Casas-Agustench et al, 2011 (50)	25	25	1.50%	1.60 [-2.54, 5.74]	
Foster et al, 2012 (52)	61	62	2.80%	2.00 [-0.98, 4.98]	
Wang et al, 2012 (22)	56	30	0.20%	-0.69 [-11.82, 10.44]	
Somerset et al, 2013 (9)	35	29	1.40%	-2.83 [-7.04, 1.38]	
Subtotal (95% CI)	345	296	16.50%	0.19 [-1.03, 1.41]	Ť
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.24$, $df = 6$ (P = 0.64); $I^2 = 0\%$					
Test for overall effect: Z = 0.31 (P = 0.76)					
Diabetes					
Wien et al. 2003 (8)	32	33	6.10%	-1.00 [-2.96, 0.96]	-+
Maret al, 2000 (47)	22	22	2.50%	4.10 [0.92, 7.28]	
Jenkins et al, 2011 (20)	40	39	6.60%	-1.01 [-2.87, 0.85]	
Li et al, 2011 (21)	20	20	2.90%	-2.20 [-5.14, 0.74]	
Subtotal (95% CI)	114	114	18.10%	-0.21 [-2.39, 1.96]	+
Heterogeneity: Tau ² = 3.35; Chi ² = 9.88, df = 3 (P = 0.02); l ² = 70%		2.2.2	10.1070	5.2 T [2.00, 1.00]	
Test for overall effect: $Z = 0.19$ (P = 0.85)					
Total (95% CI)	587	538	100.00%	0.02 [-0.49, 0.54]	• • •
Heterogeneity: Tau ² = 0.13; Chi ² = 17.08, df = 15 (P = 0.31); $I^2 = 12\%$					-10 -5 0 5 10
Test for overall effect: $Z = 0.08$ (P = 0.93)					Favours Nuts Favours Cont
Test for subgroup differences: $Chi^2 = 0.35$, $df = 3$ (P = 0.98), $l^2 = 0\%$					Mean Difference
1001101000000000000000000000000000000					(95% CI) in DBP, mmHg

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.

5	Subgroup	Level	Trials	Ν		Mean difference (95% CI) in Systolic Blood Pressure, mmHg		Residual I ²	P-valu
6					Within subgroups	<u>!</u> .	Between subgroups		
7	Total	-	16	955	-0.24 (-1.93, 1.45)	_ _			
5	Nut type	Almonds	5	300	-2.87 (-6.87, 1.14)		See legend	52.9%	0.435
		Brazil nuts	0	0		i ji			
		Cashews	1	32*	-7.18 (-16.41, 2.05)	_			
0		Hazelnuts	0	0		<u>!</u>			
		Macadamia Pecans	1	64	3.6 (-8.92, 16.12)				
1			0	0					
2		Pine nuts Pistachios	0 3	0 129	0.70 (5.52, 2.07)				
		Walnuts	3	301*	-0.78 (-5.52, 3.97) 2.41 (-1.58, 6.40)				
3		Mixed nuts	2	129	0.93 (-4.94, 6.79)				
			2	125	0.55 (4.54, 0.75)				
4	Nut dose	< 50 g/d	4	194	1.53 (-3.21, 6.26)	i	-2.15(-7.41, 3.12)	55.6%	0.39
5		≥ 50 g/d	12	761	-0.62 (-2.93, 1.69)				
	Follow up	< 12 weeks	9	298	1.02 (-1.60, 3.64)		-2.77 (-6.62, 1.08)	48.3%	0.14
6	Follow up	< 12 weeks ≥ 12 weeks	9	657	-1.75 (-4.57, 1.07)		-2.77 (-0.02, 1.08)	48.3%	0.14
7		2 12 WEEKS	/	057	-1.75 (-4.57, 1.07)				
	SFA	< 7%	5	332	-1.35 (-5.13, 2.43)		2.34 (-2.58, 7.25)	59.1%	0.32
8		≥ 7%	9	414	0.99 (-2.15, 4.13)				
9									
	SFA (chg)	< -2%	5	197	0.20 (-2.33, 2.73)		-1.01 (-4.47, 2.45)	0%	0.51
0		≥ -2%	5	424	-0.81 (-3.17, 1.55)				
	CEA (A)	< -1.5%	4	137	2 46 (2 07 7 00)		2 22 (0 57 1 02)	50.4%	0.19
1	SFA (Δ)	< -1.5% ≥ -1.5%	4	609	2.46 (-2.07, 7.00) -0.86 (-3.50, 1.79)		-3.32 (-8.57, 1.93)	50.4%	0.19
2		2 -1.376	10	005	-0.80 (-5.50, 1.75)				
	Fiber	< 25 g/d	5	241	3.58 (-0.42, 7.58)		-4.84 (-9.46, -0.22) †	45%	0.04
3	1.001	≥ 25 g/d	9	505	-1.26 (-3.57, 1.05)		4.04 (3.40, 0.22)	4570	0.04
4						•			
	Fiber (chg)	< 5.3 g/d	4	258	0.22 (-3.04, 3.48)	i	-0.68 (-5.40, 4.04)	0%	0.72
5		≥ 5.3 g/d	3	232	-0.46 (-3.87, 2.96)				
3	Fiber (Δ)	< 4.4 g/d	8	328	1 72 (1 00 4 46)		4.01 / 0.11 0.00)	44%	0.00
	Fiber (Δ)	< 4.4 g/d ≥ 4.4 g/d	8	328 418	1.73 (-1.00, 4.46) -2.28 (-5.34, 0.77)	, • -	-4.01 (-8.11, 0.08)	44%	0.05
7		2 4.4 g/u	0	410	-2.28 (-3.34, 0.77)	• <u>i</u> †			
8	Study design	Crossover	7	170	1.43 (-1.39, 4.25)		-3.01 (-6.70, 0.68)	44.2%	0.10
	,8	Parallel	9	785	-1.58 (-3.96, 0.81)		(,,		
9									
	MQS	< 8	9	330	0.49 (-2.21, 3.20)		-1.70 (-5.91, 2.51)	55.5%	0.40
C		≥ 8	7	625	-1.21 (-4.44, 2.02)				
1	Deceline CDD	(120	-	275	0.27 (4.05 2.52)	1	0.22 (5.86 5.42)	C1 00/	0.07
	Baseline SBP	<130 mmHg ≥130 mmHg	7	375 411	-0.27 (-4.06, 3.52) -0.49 (-4.67, 3.69)		-0.22 (-5.86, 5.42)	61.8%	0.93
2		2120 IIIIIIng	o	411	-0.49 (-4.07, 5.09)				
3	Carbohydrates	< 5%	7	398	1.76 (-1.23, 4.74)	<u>!</u>	-3.73 (-8.05, 0.60)	50.7%	0.08
	(Δ)	≥ 5%	7	348	-1.97 (-5.10, 1.17)				
4						▼ I	_		
5					-20	-15 -10 -5 0 5 10 15	20		
6						Favours Tree Nuts Favours Control			

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 betweensubgroup 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).

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

4									
5	Subgroup	Level	Trials	N		Mean difference (95% CI) in Diastolic Blood	Pressure, mmHg	Residual I2	P-value
6					Within subgroups		Between subgroups	-	
7	Total	-	16	955	0.02 (-0.49, 0.54)	+			
-	Nut type	Almonds	5	300	-0.33 (-2.07, 1.41)	<u>i</u>	See legend	29.7%	0.704
8		Brazil nuts	0	0		•			
9		Cashews	1	32*	-1.18 (-5.55, 3.19)	 	-		
		Hazelnuts	0	0					
10		Macadamia	1	64	-2.83 (-8.60, 2.39)	!			
11		Pecans	0	0		i			
		Pine nuts	0	0		!			
12		Pistachios	3	129	0.54 (-2.01, 3.09)				
		Walnuts	5	301*	0.68 (-0.78, 2.15)				
13		Mixed nuts	2	129	-0.36 (-2.93, 2.21)				
14	Nut dose	< 50 g/d	4	318	0.08 (-1.99, 1.84)		0.08 (-1.84, 1.99)	18%	0.933
15		≥ 50 g/d	12	637	0.00 (-0.05, 0.05)	4			
	Follow up	< 12 weeks	9	298	0.00 (-0.05, 0.05)		-0.23 (-1.42, 0.95)	17%	0.680
16		≥ 12 weeks	7	657	-0.23 (-1.42, 0.95)				
17	SFA	< 7%	5	332	-0.22 (-1.21, 0.77)		0.45 (-1.10, 2.01)	21.1%	0.537
18	SFA	< 7% ≥ 7%	9	332 414	-0.22 (-1.21, 0.77) 0.24 (-0.96, 1.44)		0.45 (-1.10, 2.01)	21.1%	0.537
19	SFA (chg)	< -2%	5	197	0.61 (-0.81, 2.03)	! •	-1.27 (-3.23, 0.70)	0%	0.176
20		≥-2%	5	424	-0.66 (-2.02, 0.71)	+ <u>+</u> -			
21	SFA (Δ)	< -1.5%	4	137	0.00 (-0.05, 0.05)		-0.18(-1.14, 0.78)	20.7%	0.693
		≥ -1.5%	10	609	-0.18 (-1.14, 0.78)				
22	Fiber	< 25 g/d	5	241	1.48 (-0.29, 3.24)		-1.52 (-3.31, 0.26)	0%	0.088
23	TIDE!	≥ 25 g/d	9	505	0.04 (-0.31, 0.22)		-1.52 (-5.51, 0.20)	0,6	0.000
24									
	Fiber (chg)	< 5.3 g/d	4	258	-0.66 (-2.59, 1.28)		0.82 (-1.74, 3.38)	0%	0.447
25		≥ 5.3 g/d	3	232	0.17 (-1.51, 1.84)				
26	Fiber (Δ)	< 4.4 g/d	8	328	0.00 (-0.05, 0.05)		-0.53 (-1.85, 0.80)	16.9%	0.404
		≥ 4.4 g/d	6	418	-0.53 (-1.85, 0.80)				
27	Study design	Crossover	7	170	0.24 (-0.61, 1.09)	L .	-0.55 (-1.94, 0.85)	15.2%	0.412
28	Study design	Parallel	9	785	-0.31 (-1.41, 0.80)		-0.55 (-1.54, 0.05)	15.270	0.412
29									
	MQS	< 8	9	330	0.00 (-0.05, 0.05)	· · · · · · · · · · · · · · · · · · ·	-0.26 (-1.38, 0.86)	16.7%	0.632
30		≥8	7	625	-0.26 (-1.37, 0.86)	+			
31	Baseline DBP	<85 mmHg	11	547	-0.09 (-1.34, 1.16)		0.36 (-2.60, 3.33)	26.9%	0.792
		≥85 mmHg	2	239	0.27 (-2.42, 2.96)				
32	Carbohydrates	< 5%	7	398	1.76 (-1.23, 4.74)		-3.73 (-8.05, 0.60)	50.7%	0.085
33	(Δ)	≥ 5%	7	348	-1.97 (-5.10, 1.17)	_ ‡			
34									
						-10 -5 0	5 10		
35						Favours Tree Nuts	Favours Control		
36									

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 I² 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.

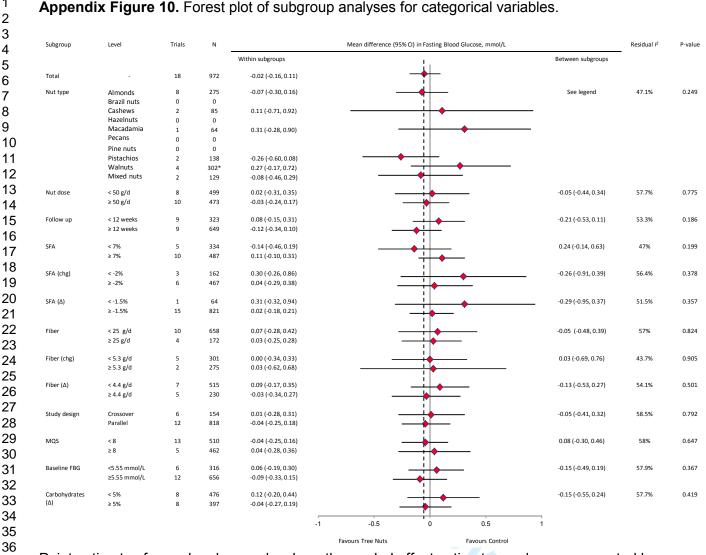
* Both nut types were studied within the same trial, for the sole purposes of number of participants, the control group was divided in half.

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

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	12.60%	0.01 [-0.13, 0.15]	
Subtotal (95% CI)	25	25	12.60%	0.01 [-0.13, 0.15]	Ť
Heterogeneity: Not applicable				anna a la mana na mana na	T
Test for overall effect: Z = 0.14 (P = 0.89)					
neresonarieros nos recemententes antenas en antenario en					
Dyslipidemia					
Jenkins et al, 2008 (54)	27	27	8.60%	0.26 [-0.03, 0.55]	L
Subtotal (95% CI)	27	27	8.60%	0.26 [-0.03, 0.55]	•
Heterogeneity: Not applicable					-
Test for overall effect: Z = 1.73 (P = 0.08)					
Metabolic Syndrome Features					
Schutte et al, 2006 (53)	41	21	3.90%	0.80 [0.21, 1.39]	
Li et al, 2010 (11)	27	25	9.50%	-0.29 [-0.55, -0.03]	
Wien et al, 2010 (48)	32	33	6.60%	-0.01 [-0.40, 0.38]	
Wu et al, 2010 (49)	94	95	8.20%	0.03 [-0.28, 0.34]	
Casas-Agustench et al, 2011 (50)	25	25	9.60%	-0.01 [-0.26, 0.24]	
Wang et al, 2012 (22)	56	30	11.10%	-0.23 [-0.43, -0.03]	_
Somerset et al, 2013 (9)	35	29	0.00%	0.31 [-0.04, 0.66]	
Subtotal (95% CI)	275	229	48.90%	-0.04 [-0.24, 0.17]	
Heterogeneity: Tau ² = 0.04; Chi ² = 14.13, df = 5 (P = 0.01); l ² = 65%					1
Test for overall effect: $Z = 0.35$ (P = 0.73)					
Diabetes					
Lovejoy et al-Hihg Fat, 2002 (37)	30	30	2.50%	-0.59 [-1.37, 0.19]	
Lovejoy et al-Low Fat, 2002 (37)	30	30	1.80%	0.63 [-0.33, 1.59]	
Wien et al, 2003 (8)	32	33	1.20%	0.06 [-1.14, 1.26]	
Tapsell et al, 2009 (46)	18	17	0.70%	0.90 [-0.75, 2.55]	
Ma et al, 2010 (47)	22	22	3.10%	0.39 [-0.30, 1.08]	
Cohen et al, 2011 (19)	6	7	2.00%	-0.50 [-1.40, 0.40]	
Jenkins et al, 2011 (20)	40	39	7.30%	-0.18 [-0.53, 0.17]	
Li et al, 2011 (21)	20	20	10.10%	-0.30 [-0.54, -0.06]	
Darvish Damavandi et al, 2012 (18)	22	21	1.20%	-1.08 [-2.28, 0.12]	
Subtotal (95% CI)	220	219	29.80%	-0.17 [-0.43, 0.10]	•
Heterogeneity: Tau ² = 0.04; Chi ² = 11.74, df = 8 (P = 0.16); l ² = 32% Test for overall effect: Z = 1.22 (P = 0.22)					
Total (95% CI)	547	500	100.00%	-0.05 [-0.18, 0.09]	_
Heterogeneity: Tau ² = 0.03; Chi ² = 35.12, df = 16 (P = 0.004); $ ^2 = 54\%$,	<u> </u>
Test for overall effect: Z = 0.70 (P = 0.49)					-2 -1 0 1 Favours Nuts Favours Cor
Test for subgroup differences: $Chi^2 = 4.63$, df = 3 (P = 0.20), $ ^2 = 35.3\%$					Mean Difference
					(95% CI) in FBG, mmol/L

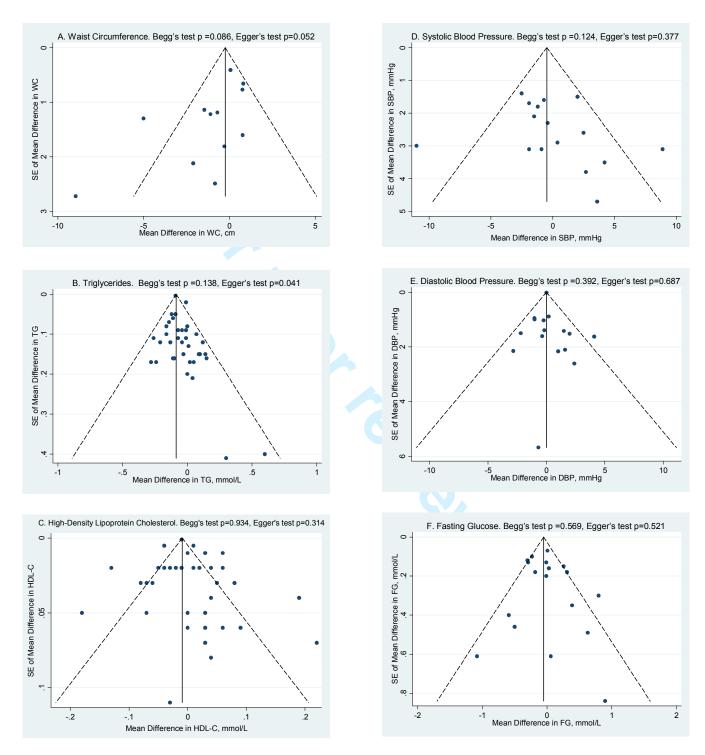
Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia, metabolic syndrome criteria, diabetes and their combination (total). Paired analyses were applied to all crossover trials (5) and one substudy. Data are expressed as mean differences (MD) 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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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 I² 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. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	6

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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	<u> </u>		
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. 43 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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Nutrition and metabolism
Nutrition and metabolism, Diabetes and endocrinology
Lipid disorders < DIABETES & ENDOCRINOLOGY, Diabetes & endocrinology < INTERNAL MEDICINE, NUTRITION & DIETETICS

SCHOLARONE Manuscripts

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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- **Figures:** 3
- **References:** 83
- 35 Appendices: 3 Tables & 10 Figures

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2 3	37	ABSTRACT
4 5	38	Objective: To provide a broader evidence summary to inform dietary guidelines of the effect
6 7	39	of tree nuts on criteria of the metabolic syndrome (MetS).
8 9	40	Design: We conducted a systematic review and meta-analysis of the effect of tree nuts on
10 11	41	criteria of the MetS.
12 13	42	Data sources: We searched MEDLINE, EMBASE, CINAHL, and the Cochrane Library
14 15	43	(through April 4, 2014).
16 17 18	44	Eligibility criteria for selecting studies: We included relevant randomized controlled trials
19	45	(RCTs) of \geq 3 weeks reporting at least one criterion of the MetS.
20 21 22	46	Data extraction: Two or more independent reviewers extracted all relevant data. Data were
23 24	47	pooled using the generic inverse variance method using random effects models and
25 26	48	expressed as mean differences (MD) with 95% confidence intervals (CI). Heterogeneity was
27 28	49	assessed by the Cochran Q statistic and quantified by the I ² statistic. Study quality and risk
29 30	50	of bias were assessed.
31 32	51	Results: Eligibility criteria were met by 49 RCTs including 2,226 participants who were
33 34	52	otherwise healthy or had dyslipidemia, MetS or diabetes mellitus. Tree nut interventions
35 36	53	lowered triglycerides (MD = -0.06 mmol/L [95% CI, -0.09, -0.03 mmol/L]), and fasting blood
37 38	54	glucose (MD = -0.08 mmol/L [95% CI, -0.16, -0.01 mmol/L]) compared with control diet
39 40	55	interventions. There was no effect on waist circumference, HDL-C, or blood pressure with
41 42	56	the direction of effect favouring tree nuts for waist circumference. There was evidence of
43 44	57	significant unexplained heterogeneity in all analyses (P < 0.05).
45 46	58	Conclusion: Pooled analyses show a MetS benefit of tree nuts through modest decreases
47 48	59	in triglycerides and fasting blood glucose with no adverse effects on other criteria across nut
49 50	60	types. As our conclusions are limited by the short duration and poor quality of the majority of
51 52	61	trials, as well as significant unexplained between-study heterogeneity, there remains a need
53 54	62	for larger, longer, high quality trials.
55 56	63	Protocol Registration: ClinicalTrials.gov identifier, NCT01630980
57 58 59	64	

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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 guidelines² 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 nuts⁴, 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^b 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 pressure⁵ 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 therapy²³ 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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103	
104	METHODS
105	Protocol and Registration
106	We followed the guidelines of the Cochrane Handbook for Systematic Reviews of
107	Intervention for the planning and conduct of this meta-analysis. ²⁴ Reporting of results
108	followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses
109	(PRISMA) guidelines. ²⁵ The review protocol is available at ClinicalTrials.gov (registration
110	number: NCT01630980).
111	
112	Study Selection
113	We searched MEDLINE, EMBASE, CINAHL, and the Cochrane Library (through April
114	4, 2014) to identify randomized controlled dietary trials of tree nuts. Details of the search
115	strategy are presented in Appendix Table 1. The electronic database searches were
116	supplemented by manual searches of the reference list of included trials and reviews. No
117	language restriction was used.
118	We included randomized dietary trials that reported the effect of diets rich in tree nuts
119	(almonds, Brazil nuts, cashews, hazelnuts, macadamia nuts, pecans, pine nuts, pistachios,
120	walnuts and mixed nuts) ¹ as a whole compared to diets without tree nuts, but matched for
121	energy, on at least one of the five criteria of the MetS: waist circumference, triglycerides,
122	high-density lipoprotein cholesterol (HDL-C), blood pressure and fasting blood glucose.
123	Included trials were \geq 3 weeks duration, a duration that satisfies the minimum follow-up
124	requirement for lipid-lowering health claims by the FDA used in the scientific evaluation of
125	lipid-lowering health claims. ²⁶ We excluded trials that incorporated tree nuts as paste, oil or
126	skin nuts into the treatment diets and also those trials that added tree nuts as part of a
127	dietary pattern and did not have a matched control group. The former exclusion was
128	intended to eliminate contamination from the other nutritional aspects, and to isolate the
129	effect of tree nuts. Where multiple intervention or control groups were presented, we only
130	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

135 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 followup), and intervention (protocol, co-intervention and crossovers). This scale gave a maximum MQS of 13 points. Studies with a score of \geq 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.

173 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 l² statistic. An l² \leq 50% indicated "moderate" heterogeneity, \geq 50% indicated "substantial" heterogeneity and \geq 75% indicated table "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 $q/day vs. \ge 25 q/day^{23}$ and change in [within and between the diets]), absolute saturated fatty acid (SFA) intake (treatment diet < 7% vs. \geq 7% of total energy²³ and change in [within and between the diets]), tree nut dose (< 50 g/day vs. \geq 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. \geq 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 reports⁶⁰⁻⁶³ that addressed at least one criterion of the metabolic syndrome (waist circumference [15 trials, *n* Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page | 8

214	= 1050], triglycerides [44 trials, $n = 1,690$], HDL-C [45 trials, $n = 2,142$], blood pressure [20
215	trials, $n = 1,267$], and fasting blood glucose [26 trials, $n = 1,360$] were included).
216	
217	Trial Characteristics
218	Table 1 presents characteristics of the included trials. There were 47 trials involving
219	49 comparisons in 2,211 participants. Twelve trials (26.7%) ^{10 12 14 16 30 32 34 39 43 49 59} were
220	conducted in otherwise healthy participants. Two of these trials contained a minority of
221	participants with dyslipidemia who had been classified as otherwise healthy. ^{36 43} Eleven trials
222	(24.4%) ^{8 18-21 35 37 44 45 54 55} were conducted in participants with type 2 diabetes or a mix of
223	patients with overweight and type 2 diabetes in one case ⁸ . The remaining trials were
224	conducted in people with dyslipidemia (9 trials [20%] ^{13 15 17 31 33 38 41 42 53}), MetS [5 trials ^{22 40 47}
225	^{48 58}], some MetS criteria (13 trials [28.9%]: overweight 7 trials ^{9 11 50-52 56 57} , or prediabetes [1
226	trial ⁴⁶]). Median age for participants was 50.2 years (IQR: 42.5 to 55.8 years). Median body
227	weight for participants was 81.4 kg (IQR: 72.1 to 91.7 kg).
228	Trials tended to be of considerable size, with a median number of 40 participants
229	(IQR: 25 to 61participants). The majority were conducted in the United States of America (24
230	trials [53.3%]) with the rest conducted in various other countries: 3 trials (6.7%) each in
231	Australia, New Zealand, and Iran; 2 trials (4.4%) each in Canada, and Spain; and 1 trial
232	(2.2%) each in Japan, Turkey, Italy, China, Taiwan, Germany, India and South Africa. A
233	similar number of trials used parallel (24 trials [53.3%]) and crossover (21 trials [46.7%])
234	designs. All trials were conducted in an outpatient setting.
235	Control diets included usual diets (9 trials, 20%), a National Cholesterol Education
236	Program step 1 diet (5 trials, 11.1%), an average American Diet (3 trials, 6.7%), a low fat diet
237	(3 trials, 6.7%), among others. Twenty-seven trials (60%) provided test food supplements,
238	12 trials (26.7%) provided all study foods under metabolic feeding control conditions, and 4
239	trials provided dietary advice (8.9%). Five trials (11.1%) used a control diet in which a muffin
240	or pretzel ^{11 15 20 53} or cheese sticks ¹⁹ were exchanged for nuts. The test and control diets
241	were matched for energy in all cases; however 2 of the trials ^{11 50} featured a negative energy
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242	balance tree nut diet compared with a matched negative energy balance control diet. Tree
243	nut types included almonds (13 trials, 28.3%), cashews (2 trials, 4.3%), hazelnuts (3 trials,
244	6.5%), macadamia nuts (3 trials, 6.5%), pecans (2 trials, 4.3%), pistachios (8 trials, 17.4%),
245	walnuts (13 trials, 28.3%), and mixed nuts (2 trials, 4.3%). We were unable to find studies on
246	Brazil nuts or pine nuts. Median nut dose intake was 49.3 g/day (IQR: 42 to 70.5 g/day).
247	Median follow-up was 8 weeks (IQR: 4 to 12 weeks).
248	Macronutrient profiles varied across studies and between treatment and control
249	groups, median values reported for carbohydrate intake were 48% (IQR: of 44 to 51%) for
250	the treatment group and 50.5% (IQR: 46 to 57%) for the control group. Median values for fat
251	intake were 35% (IQR: 31 to 39%) and 30% (IQR: 27.3 to 34%) for tree nut and control
252	group respectively. Median values for protein intake were 16% (IQR: 15 to 17%) and 17%
253	(IQR: 15 to 18.8%) for tree nut and control group correspondingly.
254	Appendix Table 2 and Appendix Figure 1 present the assessment and summary of
255	the risk of bias by using The Heyland MQS and The Cochrane Risk of Bias Tool. The
256	Heyland MQS ranged from 3 to 9. Thirty-two trials (74.4%) were considered to be low quality
257	(MQS < 8) and 11 trials (25.6%) high quality (MQS \ge 8). The main contributors of low scores
258	were absence of double-blinding, loss of participants to follow up, and poor description of
259	crossovers in the control group. The Cochrane Risk of Bias Tool showed that 34 trials
260	(70.8%) were unclear risk and 14 trials (29.2%) were low risk for random sequence
261	generation; 29 trials (60.4%) were unclear risk and 19 trials (39.6%) were low risk for
262	allocation concealment; 26 trials (54.2%) were unclear risk and 22 trials (45.8%) were low
263	risk for blinding of participants and personnel; 5 trials (10.4%) were unclear risk, 35 trials
264	(72.9%) were low risk, and 8 trials (16.7%) were high risk for incomplete outcome data; and
265	28 trials (58.3%) were unclear risk, 19 trials (39.6%) were low risk, and 1 trial (2.1%) was
266	high risk for selective reporting.
267	Most of the trials reported research funding from an agency 28/45 (62.2%), while
268	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%).

272 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% Cl, -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).

278Appendix Table 3-A and Appendix Figure 3 present the *a priori* continuous and279categorical subgroup analyses, respectively, for waist circumference. There was evidence280of statistically significant effect modification by the difference in carbohydrate intake in the281continuous subgroup analyses (P < 0.05) between tree nut and control interventions. Trials282with lower carbohydrate intakes in the tree nut intervention arms showed larger reductions in283waist circumference. No other subgroup analyses were statistically significant.

285 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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297 significant effect modification by nut type in categorical analyses (P < 0.05). Pairwise 298 comparisons showed that pecan, walnut, and pistachio interventions all significantly 299 decreased triglycerides more than almond interventions (P < 0.05) and almond, macadamia, 300 pecan, pistachio and walnut more than hazelnut (P < 0.05). No other subgroup analyses 301 were statistically significant.

303 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.

313 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 Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page | 12 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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-I² 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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1		14
2 3	353	hand, there were more small trials with larger effect estimates favouring control than tree
4 5	354	nuts for triglycerides. Egger's test confirmed these small study effects for triglycerides ($P <$
6 7	355	0.05). No other evidence of small study effects was detected by Egger's test and Begg's
8 9	356	tests.
10 11	357	
12 13	358	DISCUSSION
14 15	359	To our knowledge, this is the first systematic review and meta-analysis to look at the
16 17	360	effect of tree nuts on MetS criteria. Our systematic review and meta-analysis included 47
18 19 20	361	randomized trials in 2,211 participants who were otherwise healthy or had MetS criteria,
20 21 22	362	dyslipidemia, or type 2 diabetes. Tree nut consumption at a median dose of ~50 g/day was
23 24	363	found to decrease triglycerides significantly by ~0.06 mmol/L, and to decrease fasting blood
25 26	364	glucose significantly by ~0.08 mmol/L over a median follow-up of 8-weeks. No adverse
27 28	365	effects were seen on waist circumference, HDL-C, or blood, suggesting an overall net
29 30	366	metabolic benefit of tree nuts.
31 32	367	
33 34	368	Results in relation to other studies
35 36	369	Our findings of a reduction in triglycerides without the expected reciprocal increase in
37 38	370	HDL-C are in accordance with previous evidence. Although Sabate et al ⁶⁴ did not show a
39 40	371	triglyceride lowering effect of nut interventions (nonspecific to tree nuts) in overall pooled
41 42	372	analyses in an patient-level meta-analysis of controlled feeding trials, he did show that nut
43 44	373	interventions lowered triglycerides when analyses were restricted to a subsample of
45 46	374	participants with baseline triglycerides \geq 1.7mmol/L, without an increase in HDL-C. A
47 48	375	triglyceride benefit has also been seen in individual trials and meta-analyses of trials
49 50 51	376	investigating the effect of a Mediterranean dietary pattern containing tree nuts in people with
52 53	377	diabetes.65 66 This triglyceride-lowering effect, however, was accompanied by an HDL-C
54 55	378	increasing effect.65 66 Our findings add to these data by showing a similar triglyceride-
56 57	379	lowering effect, especially for walnuts, pistachios, macadamia and pecans, in the absence of
58 59	380	an HDL-C increasing effect, across all subsamples of participants, without differences in
60		Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page 14

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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 DASH⁶⁹ 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 DASH⁶⁹ 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 Portfolio⁷³ 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.

428 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 Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page | 16

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).

455 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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1		
2 3	465	highlight the need for larger, longer, high quality trials. Trials in which tree nuts are used to
4 5 6	466	displace high-glycemic index carbohydrate to decrease the glycemic load of the diet will be
6 7	467	especially relevant to understand the role of tree nuts in reducing cardiometabolic risk
8 9 10	468	associated with the metabolic syndrome.
10 11 12	469	
12 13 14	470	Contributions
14 15 16	471	Conception and design: S Blanco Mejia, CWC Kendall, LS Augustin, JL Sievenpiper.
17 18	472	Analysis or interpretation of the data: S Blanco Mejia, CWC Kendall, E Viguiliouk, LS
19 20	473	Augustin, V Ha, A Cozma, A Mirrahimi, A Maroleanu, L Chiavaroli, LA Leiter, RJ de Souza,
21 22	474	DJA Jenkins, JL Sievenpiper.
23 24	475	Drafting of the article: S Blanco Mejia, JL Sievenpiper.
25 26	476	Critical revision of the article for important intellectual content: S Blanco Mejia, CWC
27 28	477	Kendall, E Viguiliouk, LS Augustin, V Ha, A Cozma, A Mirrahimi, A Maroleanu, L Chiavaroli,
29 30	478	LA Leiter, RJ de Souza, DJA Jenkins, JL Sievenpiper.
31 32	479	Final approval of the article: S Blanco Mejia, CWC Kendall, E Viguiliouk, LS Augustin, V
33 34	480	Ha, A Cozma, A Mirrahimi, A Maroleanu, L Chiavaroli, LA Leiter, RJ de Souza, DJA
35 36	481	Jenkins, JL Sievenpiper.
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47 48	487	Cozma, A Maroleanu.
49 50	488	Guarantors: CWC Kendall and JL Sievenpiper.
51 52	489	
53 54	490	Transparency declaration
55 56	491	The manuscript's guarantors affirms that the manuscript is an honest, accurate, and
57 58	492	transparent account of the study being reported; no important aspects of the study have
59 60		Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page 18
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493 been omitted; and any discrepancies from the study as planned (and, if relevant, registered)494 have been explained.

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521 Ethical Approval

Not required.

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524 **Potential Conflicts of Interest**

525 All authors have completed the Unified Competing Interest form at 526 www.icmje.org/coi disclosure.pdf (available on request from the corresponding author) and 527 declare: SBM, LSA, AM, AIC, EV, AM and LAL declare no conflicts of interest related to 528 this paper. **CWCK** has received research support from the Advanced Foods and Material 529 Network, Agrifoods and Agriculture Canada, the Almond Board of California, the American 530 Pistachio Growers, Barilla, the California Strawberry Commission, the Calorie Control 531 Council, CIHR, the Canola Council of Canada, the Coca-Cola Company (investigator 532 initiated, unrestricted grant), Hain Celestial, the International Tree Nut Council Nutrition 533 Research and Education Foundation, Kellogg, Kraft, Loblaw Companies Ltd., Orafti, Pulse 534 Canada, Saskatchewan Pulse Growers, Solae and Unilever. He has received travel funding, 535 consultant fees and/or honoraria from Abbott Laboratories, the Almond Board of California, 536 the American Peanut Council, the American Pistachio Growers, Barilla, Bayer, the Canola 537 Council of Canada, the Coca-Cola Company, Danone, General Mills, the International Tree 538 Nut Council Nutrition Research and Education Foundation, Kellogg, Loblaw Companies Ltd., 539 the Nutrition Foundation of Italy, Oldways Preservation Trust, Orafti, Paramount Farms, the 540 Peanut Institute, PepsiCo, Pulse Canada, Sabra Dipping Co., Saskatchewan Pulse Growers, 541 Solae, Sun-Maid, Tate and Lyle, and Unilever. He is on the Dietary Guidelines Committee 542 for the Diabetes Nutrition Study Group of the European Association for the Study of Diabetes 543 and has served on the scientific advisory board for the Almond Board of California, the 544 International Tree Nut Council, Oldways Preservation Trust, Paramount Farms and Pulse 545 Canada. VH has received research support from the CIHR and the World Health 546 Organization (WHO) for work on a systematic review and meta-analysis commissioned by 547 WHO of the relation of saturated fatty acids with health outcomes. She received a travel 548 award to attend a science day hosted by PepsiCo Inc. and the New York Academy of

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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 highfructose 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.

612 Data Sharing

613 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
- 6 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
- Beducation 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.
- ¹³ † 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
- 15 = 30; Gulati et al, 2014 *n* = 68 for recruited subjects for Tapsell et al. 2009 (*n* = 50), and for age for
- ¹⁶ Darvish Damavandi et al, 2013 (n = 50).
- $\frac{1}{18}$ ‡ Mean age was given separately 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.
- 21 I Nut dose is given based on g/day, 1oz = 28 g.
- 122 ¶ 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-
- ²⁴ 108 g/day; Torabian et al, 2010 range 28-64 g/day; Zambon et al, 2000 range 41-56 g/day.
- ²⁵ ** Based on 2100 kcal for Griel et al, 2008 and based on 1400 kcal (~60 kg) for Gulati et al, 2014.
- 26 27 + Energy from carbohydrate:fat:protein.
- ²⁷ ‡‡ Values for carbohydrates are given in geometric means.
- $\frac{20}{29}$ §§ Trials with scores ≥8 were considered to be of high quality.
- $\frac{29}{30}$ III Agency funding is that from government, university, or not-for-profit health agency sources.

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 (I²) at a significance level of P < 0.10 and quantified by I², levels $\leq 50\%$ represent moderate heterogeneity, $\geq 50\%$ represent substantial heterogeneity and $\geq 75\%$, 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

Figure 3. Pooled effect estimates are shown as diamonds, one each for thats 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 (I²) at a significance level of *P* < 0.10 and quantified by I², 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 Control	18 (18 M)	30	73	OP, USA	Crossover	Met	Walnut	84
Chisholm et al, 1998 (13)								
Walnut Control	16 HLP	45 (6.8)	28.4 (4.3)	OP, New Zealand	Crossover	DA	Walnut	78
Spiller et al, 1998 (31)								
Almond Control	30 HLP	53 (10)	66 (13)	OP, Italy	Parallel	Supp	Almond	100
Curb et al, 2000 (10)								
Macadamia Control	30 (15 M, 15 W)	35.25 (18-53)	23 (19.1 - 28.3)	OP, USA	Crossover	Met	Macadamia	46
Control			- /					
Morgan et al, 2000 (32)		07 (10)	04 (5)				Decen	60
Pecan Control	19 (4 M, 15 W)	37 (12) 45(10)	24 (5) 24 (4)	OP, USA	Parallel	Supp	Pecan	68
Zambon et al, 2000 (33)								
Walnut Control	49 HC (26 M, 23 W)	56 (11)	70.6 (12.1)	OP, Spain	Crossover	Supp	Walnut	48.5
Rajaram et al, 2001 (14)								
Pecan Control	23 (14 M, 9 W)	25-55	74.4 (16.7)	OP, USA	Crossover	Met	Pecan	72
lwamoto et al, 2002 (34)								
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¶
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
				Blanco Mejia et al./Tre	eNuts and Me	tabolic Syndi	rome/BMJ/Page 3	32

Lovejoy et al, 2002 (35) High Fat Almond Low Fat Almond High Fat Control Low Fat Control Sabate et al, 2003 (36)	30 DM2 (13 M, 17 W)	53.8 (10.4)	33.0 (5.5)	OP, USA	Crossover	Met	Almond Almond	85¶
High-Almond Low-Almond Control	25 NL-HC (14 M, 11 W)	41 (13)	N/A	OP, USA	Crossover	Met	Almond Almond	83 42
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
Tapsell et al, 2004 (37)								
Walnut	37 DM2	57.7 (9)	87.6 (12.8)	OP, Australia	Parallel	Supp	Walnut	30
Control Tamizifar et al, 2005 (38)		59.3 (7.1)	81.9 (11.2)					
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 Control	44 (24 M, 20 W)	32.8 (6.7)	24.2 (6.1) 24.6 (5.6)	OP, Turkey	Parallel	DA	Pistachio	69
Kurlandsky et al, 2006 (39) Almond Almond + Dark Chocolate		41.8 (11.7) 46.2 (7.8)	25.3 (3.5) 27.2 (4.2)				Almond Almond	60
Dark chocolate	47 (47 W)	36.5 (11.9)	23.9 (3.3)	OP, USA	Parallel	Supp		
Control Schutte et al, 2006 (60)*		51.3 (6.3)	26.1 (4.1)					
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
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 Control			99 106				Cashew	
Sheridan et al, 2007 (17) Pistachio Control	15 HC	60 (11.2)	175 (26)	OP, USA	Crossover	Supp	Pistachio	35
Gebauer et al, 2008 (41) 1 Pistachio 2 Pistachio Control	28 HLP (10 M, 18 W)	48 (7.9)	76.6 (13.2)	OP, USA	Crossover	Met	Pistachio Pistachio	37 74
Griel et al, 2008 (42) Macadamia Control	25 HC	50.2 (8.4)	26.3 (3.3)	OP, USA	Crossover	Met	Macadamia	42.5**
Jenkins et al, 2008 (61)* Almond Control	27 HLP (15 M, 12 W)	64 (9)	71.2 (2.5) 71.0 (2.4)	OP, Canada	Crossover	Supp	Almond	73
Rajaram et al, 2009 (43) Walnut Control	25 NL-HLP (14 M, 11 W)	23-65	71.9 (15.5) 71.7 (15.5)	OP, USA	Crossover	Met	Walnut	42.5
Tapsell et al, 2009 (44) Walnut Control	35 DM2†	54 (8.7)	92.3 (15.7) 93.4 (3)	OP, Australia	Parallel	Supp	Walnut	30
Li et al, 2010 (11) Almond Control	52 OW†	45.4 (2.0) 47.3 (2.3)	86 (26.8) 85.5 (40.2)	OP, USA	Parallel	Supp	Pistachio	53
Ma et al, 2010 (45) Walnut Control	22 DM2†	58.1 (9.2)	89 (15.5)	OP, USA	Crossover	Supp	Walnut	56
Torabian et al, 2010 (12) Walnut Control	87 (38 M, 49 W)	54 (10.2)	75.6 (13.2)	OP, USA	Crossover	Supp	Walnut	46
Wien et al, 2010 (46) Almond Control	65 PD (17 M, 48 W)	53 (9) 54 (11)	82.9 (14.4) 80.5 (14.4)	OP, USA	Parallel	Supp	Almond	58
Control		0	55.5 (11.1)	Blanco Mejia et al./Ti	reeNuts and Met	abolic Sync	drome/BMJ/Page 34	Ļ

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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)		i aranci	oupp		
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)							A	
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)		62 (0)	90 (15)				Mixed nuts	
Mixed Nuts Control	79 DM2 (52 M, 27 W)	63 (9) 61 (10)	80 (15) 83 (15)	OP, Canada	Parallel	Supp	wixed huts	75¶
Li et al, 2011 (21)		01 (10)	03 (13)					
Almond							Almond	56
Control	20 DM2 (9 M, 11 W)	58 (8.9)	26 (3.1)	OP, Taiwan	Crossover	Met		00
Tey et al, 2011 (49)								
Hazelnut	61	38.9 (14.3)	72 (11.1)	OD New Zeeland	Derellel	Cumm	Hazelnut	42
Control	61	36.1 (15.2)	67.3 (9.5)	OP, New Zealand	Parallel	Supp		
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	40 DWZ (0 W, 04 W)	56 (5.7)	71.9 (9.7)	Or, nam	i aranci	Oupp		
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)	-)		1- 1-		
Katz et al, 2012 (51)								50
Walnut	40 OW†	57.4 (11.9)	33.2 (4.4)	OP, USA	Crossover	Supp	Walnut	56
Control								
Wang et al, 2012 (22)		E1 0 (0 0)	20.1(2.2)				Pistachio	40
Pistachios High pistachios	86 MetS	51.9 (8.8) 51.8 (9.4)	28.1 (3.2) 28 (4.5)	OP, China		Supp	Pistachio	42 70
Control	eo meto	50.7 (9.9)	28 (4.4)			Supp	T ISLACITIO	70
West et al, 2012 (62)*		00.7 (0.0)	20 (4.4)					
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 Control							Pistachio	74
Anderson et al, 2013 (52) Pistachio Control	22 OW	55 (2)	90 (3.6)	OP, USA	Parallel	N/A	Pistachio	35.4
Berryman et al, 2013 (53) Almond Control	53 HC	N/A	N/A	OP, USA	Crossover	N/A	Almond	42.5
Darvish Damavandi et al, 2013 (54) Hazelnut Control	48 DM2†	55.7 (7.7)	72.1 (10.3) 72 (9.6)	OP, Iran	Parallel	Supp	Hazelnut	29
Holligan et al, 2013 (63)* 1 Pistachio 2 Pistachio Control	28 HLP (10 M, 18 W)	48 (7.9)	76.6 (13.2)	OP, USA	Crossover	Met	Pistachio Pistachio	37 74
Sauder et al, 2013 (55) Pistachio Control	30 DM2 (15 M, 15 W)†	56.1 (1.4)	31.2 (1.1)	OP, USA	Crossover	Met	Pistachio	73.4
Somerset et al, 2013 (9) Macadamia Control	64 OW (10 M, 54 W)	43.7 (8.4) 43.2 (10.9)	95 (14.7) 99.6 (15.2)	OP, Australia	Parallel	DA	Macadamia	46
Tan et al, 2014 (56) Almond (Breakfast) Almond (Morning snack) Almond (Lunch) Almond (Afternoon snack) Control	137 OW (48 M, 89 W)	32.9 (11.5) 27.8 (10.7) 29.3 (13.5) 29 (11.9) 28.7 (9.6)	80.5 (15) 83.2 (21.1) 84.8 (13.7) 81.8 (14.6) 77.2 (16.8)	OP, USA	Parallel	Supp	Almond Almond Almond Almond	43 43 43 43
Tey et al, 2013 (57) Hazelnut 30 g Hazelnut 60 g Control	107 OW (46 M, 61W)	43.8 (13.5) 42.8 (10.6) 41.1 (13.1)	86.2 (11.8) 92 (19.6) 88.7 (16.7)	OP, New Zealand	Parallel	Supp	Hazelnut Hazelnut	30 60
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 Wu et al, 2014 (59)		43.3 (8.1)	80.3 (10.3)					
Walnut Control	40 (10 M, 30 W)	60 (1)	24.9 (0.6)	OP, Germany	Crossover	Supp	Walnut	43

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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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5 6			
7	37	References: 74 <u>835</u>	
8 9	38	Appendices: 3 Tables & 104 Figures	
10	39		Formatted: French (France)
11 12	40	ABSTRACT	
13	41	Objective: To provide a broader evidence summary to inform dietary guidelines of the effect	
14 15	42	of tree nuts on criteria of the metabolic syndrome (MetS).	
16	43	Design: We conducted a systematic review and meta-analysis of the effect of tree nuts on	
17 18	44	criteria of the MetS.	
19 20	45	Data sources: We searched MEDLINE, EMBASE, CINAHL, and the Cochrane Library	
21 22	46	(through April 4, 2014).	
23 24	47	Eligibility criteria for selecting studies: We included relevant randomized controlled trials	
25	48	(RCTs) of \geq 3 weeks reporting at least one criterion of the MetS.	
26 27	49	Data extraction: Two or more independent reviewers extracted all relevant data. Data were	
28 29	50	pooled using the generic inverse variance method using random effects models and	
30 31	51	expressed as mean differences (MD) with 95% confidence intervals (CI). Heterogeneity was	
32	52	assessed by the Cochran Q statistic Chi ² -and quantified by the 1 ² statistic. Study quality and	
33 34	53	risk of bias wereas assessed.	
35 36	54	Background: Chronic disease guidelines support tree nut consumption alone or as part of	
37 38	55	the Mediterranean, Dietary Approaches to Stop Hypertension (DASH), or Portfolio dietary	
39 40	56	patterns to reduce cardiovascular risk, based on their favourable LDL-C lowering effect. The	
41	57	effects of nuts on metabolic risk factors other than LDL C, however, remain uncertain. We	
42 43	58	conducted a systematic review and meta analysis of the effect of tree nuts on criteria	
44 45	59	metabolic syndrome (MetS) components to provide a broader evidence summary to inform	
46 47	60	dietary guidelines.	
48	61	Methods: We searched MEDLINE, EMBASE, CINAHL, and the Cochrane Library (through	
49 50	62	March 19, 2013 <u>April 4, 2014</u>). We included relevant randomized controlled trials (RCTs) of ≥	
51 52	63	3 weeks reporting at least 1 one criterion of metabolic syndromeMetS. Two or more	
53 54	64	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 Chi² and quantified by I². Study quality was assessed. Results: Eligibility criteria were met by 39RCTsincluding149 RCTs including 2,226,676 participants who were otherwise healthy or had dyslipidemia, metabolic syndromeMetS or diabetes mellitus. Tree nut interventions lowered triglycerides and fasting blood glucose compared with control diet interventions (triglyceridesMD_=_-0.07-06_mmol/L [95%_CI, -0.0911, -0.034 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-Cwaist 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 <<u>8). Substantial unexplained heterogeneity remained in most analyses.</u> 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 Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page | 3

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5 6 7	88	Key words: systematic review, meta analysis, randomized trials, tree nuts, metabolic	
8	89	syndrome.	
9			
10 11	90	Strengths and limitations of this study	
12 13	91	• This is the first systematic review and meta-analysis to look at the effect of tree nuts	
14	92	on metabolic syndrome criteria.	
15 16	93	• This systematic review and meta-analysis involved a large number of trials (36-47	
17 18	94	RCTs) in participants with a range of metabolic conditions.	
19 20	95	 Most of the trials (69.474.4%) were of low quality (MQS_<_8). 	
21	96	 Most of the trials (66.78.8%) were of short duration (<12 weeks). 	
22 23	97	Substantial inter-study heterogeneity remained unexplained.	Formatted: List Paragraph, Justified, Line
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6 7	102	INTRODUCTION	
8 9	103	Dietary patterns including tree nuts have received particular attention for their	
10 11	104	cardiovascular benefits, and_the Food and Drug Administration (FDA) have granted a	
12 13	105	qualified health claim to tree nuts for cardiovascular risk reductionGeneral_dietary	Field Code Changed
14	106	guidelines ² and heart health guidelines ^{3 4} also continue to recommend tree nuts alone or as	Field Code Changed
15 16	107	part of the Mediterranean, Portfolio, and Dietary Approaches to Stop Hypertension (DASH)	Field Code Changed Field Code Changed
17 18	108	dietary patterns for cardiovascular disease prevention and management.	Field Code Changed
19	109	Although these recommendations are based primarily on the LDL-C lowering benefits	
20 21	110	of tree nuts ⁴ , the cardiovascular risk reduction seen with tree nuts is beyond that which	Field Code Changed
22 23	111	would be predicted by this effect alone. The Prevención con Dieta Mediterránea	
24 25	112	(PREDIMED) trial showed that despite <u>a_non-significant</u> effect on LDL-C early on in the trial ⁵	Field Code Changed
26 27	113	a Mediterranean diet supplemented with mixed nuts (30_g/day) compared with a low-fat	
28	114	control diet reduced major cardiovascular events by 30% in high cardiovascular risk	
29 30	115	participants. ⁶ Nut consumption of >_3_servings/week was also associated with other	Field Code Changed
31 32	116	metabolic advantages such as a decreased risk of obesity, MetS, and diabetes, ⁷ Individual	Field Code Changed
33 34	117	large trials of tree nuts have also shown that nuts improve criteria of the metabolic	
35	118	syndrome: waist circumference ⁸ ⁹ triglycerides ⁵ ¹⁰⁻¹² HDL-C ¹³⁻¹⁸ blood pressure ⁵ ⁸ and	Field Code Changed
36 37	119	glycemic control,	Field Code Changed
38 39	120	The overall evidence for these additional metabolic benefits, however, remains	Field Code Changed
40 41	121	uncertain. Guidelines have not recommended tree nuts directly for managing these risk	Field Code Changed
42	122	factors. Although the Canadian Diabetes Association 2013 clinical practice guidelines for	Field Code Changed
43 44	123	nutrition therapy ²³ did acknowledge some of these metabolic benefits, the evidence was	Field Code Changed
45 46	124	deemed insufficient for making a recommendation. Tree nut consumption was	
47 48	125	recommended only in so far as part of Mediterranean or DASH dietary patterns $^{23}_{\star}$	Field Code Changed
49 50	126	synthesize the evidence on which recommendations are based for the metabolic benefits of	
51	127	tree nuts beyond LDL-C lowering, we conducted a systematic review and meta-analysis of	
52 53	128	randomized controlled dietary trials of the effect of tree nuts on criteria of the metabolic	
54 55	129	syndrome.	
56 57 58 59 60		Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page 5	

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6 7	130	
8 9	131	METHODS
10 11	132	Protocol and Registration
12	133	We followed the guidelines of the Cochrane Handbook for Systematic Reviews of
13 14	134	Intervention for the planning and conduct of this meta-analysis 24 Reporting of results
15 16	135	followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses
17 18	136	(PRISMA) guidelines, ²⁵ The review protocol is available at ClinicalTrials.gov (registration Field Code Changed
19 20	137	number: NCT01630980).
21	138	
22 23	139	Study Selection
24 25	140	We searched MEDLINE, EMBASE, CINAHL, and the Cochrane Library (through
26	141	March 19, 2013April 4, 2014) to identify randomized controlled dietary trials of tree nuts.
27 28 29	142	Details of the search strategy are presented in Appendix Table 1. The electronic database
29 30	143	searches were supplemented by manual searches of the reference list of included trials and
31 32	144	reviews. No language restriction was used.
33 34	145	We included randomized dietary trials that reported the effect of diets rich in tree nuts
35 36	146	(almonds, Brazil nuts, cashews, hazelnuts, macadamia nuts, pecans, pine nuts, pistachios,
37	147	walnuts and mixed nuts) ¹ as a whole compared to diets without tree nuts, but matched for Field Code Changed
38 39	148	energy, on at least 1-one of the five5 criteria of the MetS: waist circumference, triglycerides,
40 41	149	high-density lipoprotein cholesterol (HDL-C), blood pressure and fasting blood glucose.
42	150	Included trials were \geq 3 weeks duration, a duration that satisfies the minimum follow-up
43 44	151	requirement for lipid-lowering health claims by the FDA used in the scientific evaluation of
45 46	152	lipid-lowering health claims, ²⁶ We excluded trials that incorporated tree nuts as paste, oil or Field Code Changed
47 48	153	skin nuts into the treatment diets and also those trials that added tree nuts as part of a
49	154	dietary pattern and did not have a matched control group. The former exclusion was
50 51	155	intended to eliminate contamination from the other nutritional aspects, and to isolate the
52 53	156	effect of tree nuts. Where multiple intervention or control groups were presented, we only
54 55	157	included those groups which allowed us to isolate the effect of tree nutsWhen multiple
56 57 58 59 60	I	Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page 6

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 MetS²⁷

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162 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 followup), and intervention (protocol, co-intervention and crossovers)._-This scale gave a maximum MQS of 13 points. Studies with a score of \geq 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 an-abstract format only -were not included for reportingin assessments of study quality scores due MQS or of bias owing to a lack of datainformation."-

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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 tvalues 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 0.664-635 for triglycerides, 0.903-856 for HDL-C, 0.282-32749 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.

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203 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 < P0.05. Paired analyses were applied to all crossover trials²⁹ 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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212	The presence of between-studies-heterogeneity was assessed (by the Cochran Q	
213	statistic_(; significant_significance_set_ at <u>P_<_0.10)</u> and <u>quantified_by_the_quantified_(I</u> 2_	Formatted: Font: Italic
214	statistic). An I ² ≤ 50% even though indicated "moderate" heterogeneity, but it might not be	
215	$\frac{1}{1}$ $\frac{1}$	
216	heterogeneity. ²⁴ Analyses were stratified by participant health status: otherwise healthy,	Field Code Changed
217	dyslipidemia, MetS criteria and type 2 diabetes based on trial entry criteria. Sources of	
218	heterogeneity were explored using sensitivity analyses and a priori-subgroup analyses. To	
219	determine if any single trial exerted an undue influence on the overall results, sensitivity	
220	analyses were preformed, in which each individual trial was removed from the meta-	
221	analysis, and the effect size re-calculated with the remaining trials. Sensitivity analyses	
222	were also undertaken using <u>different</u> correlation coefficients of 0.25, 0.50 and 0.75 to	
223	determine whether the overall results were robust to the use of different derived-pooled	
224	correlation coefficients in paired analyses of crossover trials. for A priori subgroup analyses	
225	were done for baseline values (according to MetS diagnostic criteria), ²⁷), absolute fibrer	Field Code Changed
226	intake (treatment diet <_25 g/day vs. ≥_25 g/day ²³ and change in [within and between the	Field Code Changed
227	diets]), absolute saturated fatty acid (SFA) intake (treatment diet <_7% vs. \geq _7% of total	
228	energy ²³ and change in [within and between the diets]), tree nut dose (<_50_g/day vs. \geq _50	Field Code Changed
229	g/day), tree nut type (almonds, Brazil nuts, cashews, hazelnuts, macadamia nuts, pecans,	
230	pine nuts, pistachios, walnuts and mixed nuts),duration of follow-up (<_3< <u>months</u> vs. \geq _3	
231	months), study design (crossover vs. parallel), and study quality (MQS <_8 vs. ≥_8). <i>Post-hoc</i>	
232	subgroup analyses were conducted for the difference in percent carbohydrate intake	
233	between the control and intervention arm (carbohydrate displacement). The significance of	
234	between-subgroup differences were assessed using meta-regression ($P_<_0.05$). To	Formatted: Font: Italic
235	determine if any single trial exerted an undue influence on the overall results, sensitivity	
236	analyses were preformed, in which each individual trial was removed from the meta-	
237	analysis, and the effect size re-calculated with the remaining trials. Publication bias was	
238	assessed by visual inspection of funnel plots and formally complemented by Begg's and	
239	Egger's tests.	
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7	240		
8 9	241	RESULTS	
9 10 11	242	Trial Selection	
12	243	Figure 1_shows flow of studies through the search and selection process. We	
13 14	244	identified a total of 2, 190<u>531</u> reports, from which <u>701752</u> reports were duplicates and	
15 16	245	1,367631 reports were deemed irrelevant (determined by review of title and abstract). The	
17 18	246	remaining <u>120-146</u> reports were reviewed in full, of which <u>8197</u> reports were excluded for not	
19	247	meeting inclusion criteria. A total of 39 49 reports on 3847 trials ^{8-23 30-59} as well as 3-four Field Code Ch	anged [1]
20 21	248	companion reports, that addressed at least one criterion of the metabolic syndrome (waist	
22 23	249	circumference ([125 trials, $n = 1050813$]), triglycerides ((4437 trials, $n = 1,515690$), HDL-C Formatted	[2]
24 25	250	[<u>(45</u> 36 trials, $p_{=}$ <u>1,6072,142</u>], blood pressure [<u>(2016</u> trials, $p_{=}$ <u>1,267955</u>)], and fasting blood	
26 27	251	glucose <u>{[1826</u> trials, <u>n_=_9571,360}]</u> were included).	
28	252		
29 30	253	Trial Characteristics	
31 32	254	Table 1 presents characteristics of the included trials. There were 38 47 trials	
33 34	255	involving_38-49_comparisons in1706 in 2,211 participants. Eleven-Twelve trials (30.626.7%)10 Field Code Ch	anged [3]
35 36	256	12 14 16 30 32 34 39 43 49 59 were conducted inreported otherwise healthy participants. Two of these	
30 37	257	trials contained a minority of participants with dyslipidemia who had been classified as	
38 39	258	otherwise healthy. ^{36 43} - Nine-Eleven trials (2524.4 %) ^{8 18-21 35 37 44 45 54 55} were conducted in	
40 41	259	participants with type 2 diabetes or a mix of patients with overweight and type 2 diabetes in	
42	260	one case ⁸ . The remaining trials were conducted in people with dyslipidemia (8-9_trials	
43 44	261	[22.20%] ^{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	
45 46	262	<u>13</u> trials [22.2<u>28.9</u>%]:_overweight 3-7_trials^{9 11 50-52 56 57}, full MetS [4 <u>5</u>_trials^{22, 42, 49, 50, 60}], and <u>or</u>	
47 48	263	prediabetes [1 trial ⁴⁶])Median age for participants was 50.2 years (IQR: 42.53.7 to 55.58	
49	264	years). Median body weight for participants was 81. <u>4</u> 7 kg (IQR: 72.1 to 9 <u>1.7</u> 5.3 kg).	
50 51	265	Most tTrials tended to be of considerable size, with a small (median number of Formatted	[4]
52 53	266	participants40 participants , ?? [(IQR:, 25 to 61??participants) to ??])(1924 [52.83.3%]) were	
54 55	267	. The majority were conducted in the United States of America (24 trials [53.3%]). The with	
56 57	I	Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page 10	
57 58 59			

the rest were conducted in various other countries: 3 trials (8.36.7%) each in Australia, New Zealand, and Iran; 2 trials (54.4.6%) each in Canada, and Spain, Iran, and New Zealand; and 1 trial (2.28%) each in Japan, Turkey, Italy, China, Taiwan, Germany, India and South Africa. A similar number of trials used parallel (1924 trials [53.32.8%]) and crossover (17-21 trials [46.77.2%]) designs. All trials were conducted in an outpatient setting.

Control diets included usual diets, (<u>98</u> trials, 22.20%), a National Cholesterol Education Program (NCEP) step 1 diet (5 trials, 13.91.1%), an average American Diet (3 trials, 8.36.7%), a low fat diet (2-3 trials, 5.6.7%), among others. Twenty-two-seven trials (6160%) provided test food supplements, 124 trials (3126.7%) 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 sticks¹⁹ were exchanged for nuts. The test and control diets were matched for energy in all cases; however 2 of the trials¹¹⁵⁰ featured a negative energy balance tree nut diet compared with a matched negative energy balance control diet. Tree nut types included almonds (131 trials, 28.330.6%), cashews (2 trials, 4.35.6%), hazelnuts (23 trials, 5.66.5%), macadamia nuts (3 trials, 8-36.5%), pecans (2 trials, 5-64.3%), pistachios (5-8 trials, 12.817.4%), walnuts (10-13 trials, 27.828.3%), and mixed nuts (2 trials, 5.64.3%). 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 72.570.5 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 4847% (IQR: of 44 to 52.351%) for the treatment group and 50.5% (IQR: 46 to 56.857%) for the control group. Median values for fat intake were 36.535% (IQR: 31.831 to 39%) and 30.530% (IQR: 2827.3 to 34.834%) for tree nut and control group respectively. Median values for protein intake were 16% (IQR: 15 to <u>1817</u>%) and 17% (IQR: 15 to <u>1918.8</u>%) 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 Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page | 11

2 3 4 5		12	
6 7	296	Heyland MQS ranged from 3 to 9. TwentyThirty-fivetwo trials (69.474.4%) were considered	
8 9	297	to be low quality (MQS <_8) and 11 trials ($\frac{30.625.6}{\%}$) high quality (MQS ≥_8). The main	
10 11	298	contributors of low scores were absence of double-blinding-blinding of participants, -and	
12	299	crossovers between intervention treatments, followed by sample comparability and loss of	
13 14	300	participants to follow up, and poor description of crossovers in the control group. The	
15 16	301	Cochrane Risk of Bias Tool showed that in our study, for allocation concealment, 34 trials	
17 18	302	(70.8%) were unclear risk and 14 trials (29.2%) were low risk for random sequence	
19	303	generation; 297/48 trials (60.456.3%) were unclear risk and 1921/48 trials (39.643.8%) were	
20 21	304	low risk for allocation concealment;, for blinding of participants and personnel, 268/48 trials	
22 23	305	(54.28.3%) were unclear risk and 220/48 trials (45.81.7%) were low risk for blinding of	
24 25	306	participants and personnel; 5 trials (10.4%) were unclear risk, , for incomplete outcome data,	
26 27	307	35/48 trials (72.9%) were low risk, and 8/48 trials (16.7%) were high risk-and 5/48 trials	
28	308	(10.4%) were unclear risk-for incomplete outcome data; - and for selective reporting, 28/47	
29 30	309	trials (5 9.68.3%) were unclear risk, 189/47 trials (38.3 39.6%) were low risk, and 1 /47 trials	
31 32	310	(2.1%) wereas high risk for selective reporting. was considered mainly "low risk of bias"	
33 34	311	(blinding of participants and crossovers in our included dietary trials are not feasibleis very	
35	312	difficult to achieve) and that a few studies trials were considered "high risk of bias" due to	
36 37	313	incomplete outcome data and selective reporting.	
38 39	314	Most of the trials reported research funding from an agency 27/3628/45 (62.275%),	
40 41	315	while others were funded from a combination of agency and industry 5/3645 (13.911.1%) or	
42	316	industry alone 6/45 (13.3%). One trial (2.82%) was funded exclusively by industryreported	
43 44	317	no funding. Three Five trials ^{18 38 45 52 53} did not report their funding source (8-311.1%).	Field Code Changed
45 46	318		Field Code Changed Field Code Changed
47 48	319	Waist Circumference	Field Code Changed Field Code Changed
49 50	320	Appendix Figure 2 presents data on the effect of tree nuts on waist circumference.	
51	321	Tree nuts did not significantly decrease waist circumference in the overall analyses (MD_=, -	
52 53	322	0. 91-<u>62</u> cm [95% CI, -1.<u>9954</u>, 0.<u>18-30 cm]) in the overall analyses</u> with evidence of	
54 55	323	significant-substantial heterogeneity ($I^2 = 6567\%$, $P < 0.001$). Stratification by health status	Formatted: Font: Italic
56 57	I	Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page 12	

	13	
324	failed to demonstrate a significant effect for any of the sub samples. Sensitivity analyses did	
325	not alter the results (data not shown).	
326	Appendix Table 3-A and Appendix Figure 3 present the a priori continuous and	Formatted: Font: Italic
327	categorical subgroup analyses, respectively, for waist circumference. There was evidence	
328	of statistically significant effect modification by the difference in SFA intake in the categorical	
329	subgroup analyses (P<0.05) and by the difference in carbohydrate intake in the continuous	
330	subgroup analyses ($P < 0.05$) between tree nut and control interventions. Trials in which tree	Formatted: Font: Italic
331	nuts displaced more SFA leading to larger differences between the tree nut and control	
332	interventions were more likely to favor the control diet. Trials with lower carbohydrate intakes	
333	in the tree nut intervention arms showed larger reductions in waist circumference. <u>No other</u>	
334	subgroup analyses were statistically significant.	
335		
336	Triglycerides	
337	Figure 2 presents data on the effect of tree nuts on triglycerides. Tree nuts showed a	
338	significant triglyceride-lowering effect (MD <u>=</u> , -0.0 <u>6</u> ,7mmol/L, [95% CI, -0.09, -0.04 <u>3</u> mmol/L])	
339	in the overall analysis without with evidence of moderate evidence of significant	
340	heterogeneity ($I^2 = 2434\%$, $P = 0.4302$). The same effect was seen with evidence of	Formatted: Font: Italic
341	significantevidence of moderate heterogeneity ($I^2 = 4842\%$, $P = 0.0305$) in the subsample of	Formatted: Font: Italic
342	participants who were otherwise healthy (MD <u>=</u> , -0.07 mmol/L [95% Cl, -0.11, -0.04 mmol/L])	
343	and without evidence of heterogeneity in the subsample of participants with MetScriteria(MD,	
344	-0.09 mmol/L [95% Cl, 0.18, 0.00 mmol/L]). Although the reductions were not statistically	
345	significant in people with dyslipidemia MetS criteria or diabetes, they did not significantly	
346	differ from the reductions in participants who were otherwise healthy or with MetS	
347	Sensitivity analyses did not alter the results (data not shown).	
348	Appendix Table 3-B and Appendix Figure 4 present data from the a priori	Formatted: Font: Italic
349	continuous and categorical subgroup analyses, respectively, for triglycerides. There was	
350	significant effect modification by nut type in categorical analyses ($P < 0.05$). Pairwise	Formatted: Font: Italic
351	comparisons showed that pecan, walnut, and pistachio interventions all significantly	
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6 7	352	decreased triglycerides more than almond interventions (<i>P</i> < 0.05) and almond, macadamia. Formatted: Font: Italic
8 9	353	pecan, pistachio and walnut more than hazelnut (P < 0.05). No other subgroup analyses
10 11	354	were statistically significant.
12	355	
13 14	356	HDL-C
15 16	357	Appendix Figure 5 presents the effect of tree nuts on HDL-C. Tree nuts did not
17 18	358	significantly affect HDL-C in the overall analysis (MD <u>=</u> , 0.00 mmol/L [95% CI, -0.01, 0.01
19 20	359	mmol/L]) in the overall analysis with evidence of considerable heterogeneity ($l^2 = 867\%$, $P = <$ Formatted: Font: Italic
21	360	0.001). Stratification by health status failed to demonstrate a significant effect for any of the
22 23	361	subsamples. Sensitivity analyses did not alter the results (data not shown).
24 25	362	Appendix Table 3-C and Appendix Figure 6 present the a priori continuous and
26 27	363	categorical subgroup analyses, respectively, for HDL-C. None of the subgroup analyses
28	364	were significant.
29 30	365	
31 32	366	Blood Pressure
33 34	367	Appendix Figures 7-A and 7-B present the effect of tree nuts on systolic and
35 36	368	diastolic blood pressure, respectively. Tree nuts did not significantly decrease increase
37	369	either systolic (MD <u>=, 0.240.07</u> mmHg [95% CI, -1. 93<u>54</u> , 1. <u>69</u> 4 5 mmHg]) or diastolic blood
38 39	370	pressure (MD <u>=</u> , 0. 0 2 <u>3</u> mmHg [95% CI, -0. <u>38</u> 49, 0. <u>83</u> 54 mmHg]) in the overall analysis with
40 41	371	evidence of substantial heterogeneity in the systolic blood pressure analysis (I ² = <u>6453</u> %, P Formatted: Font: Italic
42 43	372	<_0.001) and evidence of moderate heterogeneity in the diastolic blood pressure analysis (12
44	373	= 34%, P = 0.07). Stratification by health status failed to demonstrate an effect for any of the
45 46	374	subsamples. Sensitivity analyses did not alter the results (data not shown).
47 48	375	Appendix Tables 3-D and 3-E present the <i>a priori</i> continuous subgroup analyses
49 50	376	and Appendix Figures_8-A and 8-B present the <i>a priori</i> categorical subgroup analyses for Formatted: Font: Italic
51	377	systolic and diastolic blood pressure, respectively. There was evidence of statistically
52 53	378	significant effect modification by <u>difference in fibre intake</u> in both the continuous and
54 55	379	categorical subgroup analyses and by the difference in carbohydrate intake in the
56 57	1	Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page 14
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380	continuous subgroup analyses, both for systolic blood pressure ($P < 0.05$ and $P < 0.01$	Formatted: Font: Italic
381	respectively) between tree nut and control interventions. Trials with higher fibre intakes in the	Formatted: Font: Italic
382	tree nut intervention arms showed larger reductions in systolic blood pressure. Trials in	
383	which tree nuts displaced more carbohydrates or contained lower levels of SFA intake	
384	leading to larger differences between the tree nut and control interventions were more likely	
385	to favo <u>u</u> r the Tree nut diet in systolic blood pressure. Change in SFA or fibre intake in the	
386	tree nut intervention armsTree nut intervention arms with higher fibre intake showed	
387	reductions in diastolic blood pressure and also explained the heterogeneity in the overall	
388	analyses reducing the residual-I ² to <u>Q1.6</u> %. No other subgroup analyses were statistically	
389	significant for either systolic or diastolic blood pressure.	
390		
391	Fasting Blood Glucose	
392	Appendix Figure 9-3 presents the effect of tree nuts on fasting blood glucose. Tree	
393	nuts did not<u>showed a</u> significantly decrease fasting blood glucose<u>-lowering effect</u> in the	
394	overall analysis (MD_ ,= -0.0 <u>8</u> 2 mmol/L [95% Cl, -0.16, <u>-</u> 0.011_mmol/L]) , in the overall	
395	analysis, with evidence of significant neevidence of moderate heterogeneity (I ² = <u>5741</u> %, pP	
396	<_0.0405). Stratification by health status failed to demonstrate an effect for any of the	
397	subsamples. Sensitivity analyses did not alter the results (data not shown).	
398	Appendix Table 3-F and Appendix Figure 10-9 present a priori continuous and	Formatted: Font: Italic
399	categorical subgroup analyses, respectively, for fasting blood glucose. There was evidence	
400	that the attained difference in SFA intake between tree nut and control interventions (in both	
401	continuous and categorical subgroup analyses (P<0.05)) influenced the effect of nuts on	
402	blood glucose. Trials in which tree nuts displaced less SFA leading to smaller differences in	
403	SFA between the tree nut and control interventions were more likely to favor the control	
404	dietNone of the subgroup analyses were significant.	
405		
406	Publication Bias	
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Appendix Figure 104_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 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 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 <u>MetS</u> criteria of the MetS. Our systematic review and meta-analysis included <u>36 47</u> randomized trials in <u>1691 2,211</u> participants who were otherwise healthy or <u>met_had</u> 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 78-weeks. No adverse effects were seen on waist circumference, HDL-C, <u>or</u> blood-pressure or fasting blood glucose. However the direction of effect favo<u>u</u>red tree nuts in the case of waist circumference, blood pressure, and fasting blood glucose_T 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 a_{h}^{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 Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page | 16

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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.⁶⁵⁶⁶ 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 DASH⁶⁹ 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 Cls was derived from all health subgroups. Therefore, Cls 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 glycaemia⁷¹ and possibly decrease insulin resistance⁴⁸ 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 $gain_{h}^{2}$ 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 DASH⁶⁹ 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 Portfolio⁷³ 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 Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page | 18

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HbA1c for tree nuts as part of Mediterranean^{67, 68, 72} and DASH⁷⁴ 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 dietdietary pattern, which collectively result in larger amounts of potassium, calcium, magnesium, dietary fibre, and protein.

503 Limitations

There are some limitations to our work. First, the majority of trials (69.474.4%) 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, facting glucoseblood 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, <u>and</u> HDL-C, and facting blood glucose, which we attempted to accommodate using of random Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page | 19

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6 7	518	effects models, remains a source of uncertainty in the summary effect estimates for these
8 9	519	endpoints.
10	520	
11 12	521	Practical Implications
13 14	522	Tree nuts are a high-energy food that contain cardioprotective nutrients, ⁶⁷ Even Field Code Changed
15 16	523	though the median fat intake (36<u>3</u>3.6 %) of the tree nut containing diets was above that of the
17 18	524	control (30.5%), but both within the recommended (20-35%) by dietary guidelines, ²³ a
19	525	beneficial effect was seen when compared to a control diet that tended to meet
20 21	526	macronutrient recommendationsonly in the tree nut containing diets. The median dose of
22 23	527	~50_g/day tree nuts can be easily integrated as a snack, into a dietary pattern or as a
24 25	528	substitution for animal fats or carbohydrates. No increase in side effects compared with
26 27	529	control diets were reported in any of the trials, suggesting diets which emphasize tree nuts
28	530	are as safe as conventional diets (except in individuals with tree nut allergies).
29 30	531	
31 32	532	Conclusion
33 34	533	In conclusion, our pooled analyses indicate that daily tree nut consumption has an
35 36	534	overall net <u>modest</u> metabolic benefit, through <u>modest</u> decreas<u>es ining triglycerides and</u>
37	535	fasting blood glucose while preserving waist circumference, HDL-C, and blood pressure and
38 39	536	fasting blood glucose in people who are otherwise healthy or have -dyslipidemia, criteria of
40 41	537	the-MetS <u>criteria</u> , or -type 2 diabetes. These data support recommendations to consume tree
42 43	538	nuts alone or as part of heart healthy dietary patterns such as the Mediterranean, Portfolio,
44	539	Vegetarian, and DASH dietary patterns as a means for improving metabolic control, 69.80-83 Field Code Changed
45 46	540	Careful interpretation of the results is advised, as Oour conclusions are limited by the small
47 48	541	sample sizes, the short duration, and poor quality of the majority of trials, as well as not the start the
49 50	542	presence of significant unexplained heterogeneity in our analyses. These limitations
51	543	highlight the need for larger, longer, high quality trials. Trials in which tree nuts are used to
52 53	544	displace high-glycemic index carbohydrate to decrease the glycemic load of the diet will be
54 55 56		
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60		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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5 6 7	545	especially relevant to understand the role of tree nuts in reducing cardiometabolic risk	
8	546	associated with the metabolic syndrome.	
9 10	547		
11 12	548	Contributions	
13 14	549	Conception and design: S Blanco Mejia, CWC Kendall, LS Augustin, JL Sievenpiper.	
15	550	Analysis or interpretation of the data: S Blanco Mejia, CWC Kendall, E Viguiliouk, LS	
16 17	551	Augustin, V Ha, A Cozma, A Mirrahimi, A Maroleanu, L Chiavaroli, LA Leiter, RJ de Souza,	
18 19	552	DJA Jenkins, JL Sievenpiper.	
20 21	553	Drafting of the article: S Blanco Mejia, JL Sievenpiper.	
22	554	Critical revision of the article for important intellectual content: S Blanco Mejia, CWC	
23 24	555	Kendall, E Viguiliouk, LS Augustin, V Ha, A Cozma, A Mirrahimi, A Maroleanu, L Chiavaroli,	
25 26	556	LA Leiter, RJ de Souza, DJA Jenkins, JL Sievenpiper.	
27 28	557	Final approval of the article: S Blanco Mejia, CWC Kendall, E Viguiliouk, LS Augustin, V	
29 30	558	Ha, A Cozma, A Mirrahimi, A Maroleanu, L Chiavaroli, LA Leiter, RJ de Souza, DJA	
31	559	Jenkins, JL Sievenpiper.	
32 33	560	Statistical expertise: RJ de Souza.	Formatted: French (France)
34 35	561	Obtaining of funding: CWC Kendall, DJA Jenkins, JL Sievenpiper.	
36 37	562	Administrative, technical, or logistic support: CWC Kendall, E Viguiliouk, LS Augustin, V	
38	563	Ha, A Cozma, A Mirrahimi, A Maroleanu, L Chiavaroli.	
39 40	564	Collection and assembly of data: S Blanco Mejia, E Viguiliouk, LS Augustin, V Ha, A	
41 42	565	Cozma, A Maroleanu.	
43 44	566	Guarantors: CWC Kendall and JL Sievenpiper.	
45	567		
46 47	568	Transparency declaration	
48 49	569	The manuscript's guarantors affirms that the manuscript is an honest, accurate, and	
50 51	570	transparent account of the study being reported; no important aspects of the study have	
52 53	571	been omitted; and any discrepancies from the study as planned (and, if relevant, registered)	
54	572	have been explained.	
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36 37	590	used.
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49	597	forms/licence-for-publication).
50 51	598	
52 53	599	Ethical Approval
54 55	600	Not required.
56		Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page 22
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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 Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page | 23

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scientific statement on the metabolic and nutritional effects of fructose, sucrose and highfructose 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 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, Abbott Laboratories, Advanced Food Materials Network, Almond Board of 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 Earms, Pulse Canada, Saskatchewan, Pulse Growers, Solae and Unilever, VH, AM, LC have received research support from the Canadian Institutes of health Research (CIHR). RJdS received research support from the Canadian Institutes of Health Research (CIHR), Calorie Control Council, and The Coca Cola Company (investigator initiated, unrestricted). 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 ews and meta analysis commissioned by the WHO of saturated and trans fatty acids and health The WHO paid for his travel and accommodation to attend the 5th China (4-7 Mar, NUGAG Meeting in Hangzhou. 2013). and the 6th NUGAG Meeting in (21-24-Oct. -2013). DJAJ -consultant fees scientific advisory board for research support from or served on the 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, Sanitarium Company, Herbalife International, Pacific Health Inc. Metagenics/MetaProteomics. Baver Consumer Care Oldwave <u>servation Trust. The International Tree Nut Council Nutrition Research & Education. The</u> Peanut Institute. Procter and Gamble Technical Centre Limited. Griffin Hospital for the Blanco Mejia et al./TreeNuts and Metabolic Syndrome/BMJ/Page | 26

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Cola Company. He is on the Clinical Practice Guidelines Expert Committee for Nutrition					
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writing panel for a scientific statement on the metabolic and nutritional effects of fructose,					
sucrose and high fructose corn syrup. He is an unpaid scientific advisor for the International					
Life Science Institute (ILSI) North America, Food, Nutrition, and Safety Program (FNSP).					
His wife is an employee of Unilever Canada.					

Data Sharing

No additional data available.

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			Table 1						*-				
Participants	Mean Age (SD o range), y	Weight or BMI	Setting	Design	Feeding Control	Nut type	Nuts Dose (g/day)ll	Comparator	Diet ††	Bal Hea	ader dista	ance fro	m edge: 0.49", F
10/1010			05.004			Walnut	84		55:31:14			2	
18 (18 M)	30	73	OP, USA	Crossover	Met			NCEP Step 1 diet	56:30:14	Isocaloric	4 WKS	6	Agency
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
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
30 (15 M, 15 W)	35.25 (18-53)	23 (19.1 - 28.3)	OP, USA	Crossover	Met	Macadamia	46	AHA	48:35:17 54:30:16 48:35:17	Isocaloric	4 wks	4	Agency-Industry
19 (4 M, 15 W)	37 (12) 45(10)	24 (5) 24 (4)	OP, USA	Parallel	Supp	Pecan	68		45:43:12	Isocaloric	8 wks	6	Agency
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
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
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
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
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
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
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
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
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
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
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
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
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
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
	18 (18 M) 18 (18 M) 16 HLP 30 (15 M, 15 W) 19 (4 M, 15 W) 49 HC (26 M, 23 W) 23 (14 M, 9 W) 40 (20 M, 20 W) 27 HLP (15 M, 12 W) 30 DM2 (13 M, 17 W) 25 NL-HC (14 M, 11 W) 65 OW/DM2 (28 M, 37 W) 37 DM2 30 HC (17 M, 13 W) 44 (24 M, 20 W) 47 (47 W) 62 MetS 64 MetS	Pallcipalits range), y 18 (18 M) 30 16 HLP 45 (6.8) 30 HLP 53 (10) 30 (15 M, 15 W) 3525 (18-53) 19 (4 M, 15 W) 37 (12) 49 HC (26 M, 23 W) 56 (11) 23 (14 M, 9W) 2555 40 (20 M, 20 W) 23.8 (3.1)‡ 27 HLP (15 M, 12 W) 64 (9) 30 DM2 (13 M, 17 W) 53.8 (10.4) 25 NL-HC (14 M, 11 W) 41 (13) 65 OW/DM2 (28 M, 37 W) 53.7 (2) 37 DM2 57.7 (9) 30 HC (17 M, 13 W) 56 (6.1) 44 (24 M, 20 W) 32.8 (6.7) 44 (24 M, 20 W) 32.8 (5.7) 30 5 C(113) 51.3 (6.3) 62 MeIS 45.7 64 MeIS 45 (10)	Integrity (BD or range)S 18 (18 M) 30 73 16 HLP 45 (6.8) 28.4 (4.3) 30 HLP 53 (10) 66 (13) 30 (15 M, 15 W) 35.25 (18-53) 23 (19.1 - 28.3) 19 (4 M, 15 W) 37 (12) 24 (4) 49 HC (26 M, 23 W) 66 (11) 70.6 (12.1) 23 (14 M, 9 W) 25-55 74.4 (16.7) 40 (20 M, 20 W) 23.8 (3.1)± 22.2 (0.5) 27 HLP (15 M, 12 W) 64 (9) 71.2 (2.5) 71 HLP (15 M, 12 W) 64 (9) 71.2 (2.5) 30 DM2 (13 M, 17 W) 53.8 (10.4) 33.0 (5.5) 25 NL-HC (14 M, 11 W) 41 (13) NA 65 OW/DAR (28 M, 37 W) 53 (2) 113 (5) 37 DM2 57.7 (9) 87.6 (12.8) 30 HC (17 M, 13 W) 56 (6.1) 63 (8.9) 44 (24 M, 20 W) 32.8 (6.7) 24.2 (6.1) 42.7 (8) 27.2 (4.2) 32.3 (5.1) 30 HC (17 M, 13 W) 56 (6.1) 63 (8.9) 44 (24 M, 20 W) 32.8 (6.7) 24.2 (6.1	Participants Mean Age (SD or range), y or (Weight of Bit (SD or range) (SD or range) Mean Body (SD or range) Setting 18 (18 M) 30 73 OP, USA 16 HLP 45 (6.8) 28.4 (4.3) OP, New Zealand 30 HLP 53 (10) 66 (13) OP, USA 19 (4 M, 15 W) 35.25 (18-53) 23 (19.1 - 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28.3) OP, USA Crossover Met 49 HC (26 M, 23 W) 56 (11) 70.6 (12.1) OP, Spain Crossover Met 40 (20 M, 20 W) 23.8 (3.1)‡ 22.2 (0.5) OP, USA Crossover Met 27 HLP (15 M, 12 W) 64 (9) 71.2 (2.5) OP, USA Crossover Met 30 DM2 (13 M, 17 W) 53.8 (10.4) 33.0 (5.5) OP, USA Crossover Met 25 NL-HC (14 M, 11 W) 41 (13) N/A OP, USA Crossover Met 65 OW/DM2 (28 M, 37 W) 55 (2) 113 (6) OP, USA Parallel Supp 30 HC (17 M,	Participants Mean Age (SD or range), y Mean Body (SD rrange) Setting Design Feeding Control Nut type 18 (18 M) 30 73 OP, USA Crossover Met Wainut 16 HLP 45 (6.8) 28.4 (4.3) OP, New Zealand Crossover DA Wainut 30 HLP 53 (10) 66 (13) OP, New Zealand Crossover DA Meacdamia 19 (4 M, 15 W) 35.25 (18-53) 23 (19.1 - 28.3) OP, USA Crossover Met Meacdamia 49 HC (26 M, 23 W) 56 (11) 70.8 (12.1) OP, Spain Crossover Met Pecan 40 (20 M, 20 W) 23.8 (3.1)‡ 22.2 (0.5) OP, USA Crossover Met Amond 30 DM2 (13 M, 17 W) 53.8 (10.4) 33.0 (5.5) OP, USA Crossover Met Amond 450 OM/2 (28 M, 37 W) 53.6 (2) 113 (5) OP, USA Crossover Met Amond 30 DM2 (13 M, 17 W) 53.8 (10.4) 33.0 (5.5) OP, USA Crossover Met	Participants Mean Age (SD or Instruct or (gddy)) Mean Body (SD or manppis) Setting Design Feeding Control Nut type Nut type Nut type 18 (18 M) 30 73 OP, USA Crossover Mat Wainut 84 16 HLP 45 (6.8) 28.4 (4.3) OP, New Zealand Crossover DA Wainut 78 30 HLP 53 (10) 66 (13) OP, Italy Parallel Supp Amond 100 30 (15 M, 15 W) 35 25 (18-53) 23 (19.1 - 28.3) OP, USA Crossover Met Mecadamia 48 19 (4 M, 15 W) 37 (12) 24 (6) OP, USA Parallel Supp Pecan 68 23 (14 M, 9 W) 25-65 74.4 (16.7) OP, USA Crossover Met Wainut 52% 24 (10) 22.3 (6.46)t 20.7 (0.5) OP, Japan Crossover Met Wainut 52% 24 (12 M, 20 W) 23.8 (10.4) 33.0 (5.5) OP, USA Crossover Met Amond	Participants Mean Age (SD or mage), Y Mean Body (BD or mage)s Setting Dasign Feeding Control Nut type Nut to Doe (graph)it Comparator 18 (18 M) 30 73 OP, USA Crossover Met Wainut 84 NCEP Step 1 diet 16 (18 M) 30 73 OP, USA Crossover DA Wainut 73 Low Fat Diet 30 HLP 53 (10) 66 (13) OP, Isaly Paratiel Supp Amond 100 Matched macronulrient diet 30 (15 M 15 W) 35.25 (18.53) 23 (16 1 - 28.3) OP, USA Paratiel Supp Pecan 68 Saft-selected diet 49 HC (26 M, 23 W) 56 (11) 70.6 (12.1) OP, USA Crossover Nut Pecan 72 NCEP Step 1 diet 40 (20 M, 20 W) 22.6 (6.8) 20.7 (0.5) OP, Lapan Crossover Met Amond 73 NCEP Step 1 diet 21 (14 M 9 W) 25.6 (3.1) 72.2 (0.5) OP, Canada Crossover Met Amond 65	Participants Mam. Reg. (SD) or March Lots Mam. Reg. (SD) or March Lots Same Res. Data (S) or March Lots Mathemarch Lots Comparator Data (SD) or March Lots 16 (16 M) 30 73 OP, USA Crossover Mat. Wannut 84 McEP Step 1 det 553:14 16 (16 M) 30 73 OP, USA Crossover MA Wannut 84 McEP Step 1 det 553:14 30 H_P 45 (6.8) 28 (4.3) OP, New Zawand Crossover Mat Wannut 84 McEP Step 1 det 553:17 30 (15 M, 15 W) 352 52 (16-53) 23 (181 - 23.3) OP, USA Crossover Mat Mat. 46.4 45.4 45.3 45.3 44.4 45.3 45.3 45.3 45.3 45.3 46.3 45.3 <t< td=""><td>Tebbe 1 Tebbe 1 Setting Setting Setting Nut type Comparator Deter fraction Nut type Setting Setting</td><td>Tebe 1 Tebe 1 Tebe 1 Tebe 1 Perincpare Mars Age (30) Ma</td><td>TENEL Contraction of the set of th</td></t<>	Tebbe 1 Tebbe 1 Setting Setting Setting Nut type Comparator Deter fraction Nut type Setting Setting	Tebe 1 Tebe 1 Tebe 1 Tebe 1 Perincpare Mars Age (30) Ma	TENEL Contraction of the set of th

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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)ll	Comparator	Diet ++	Energy Balance	Follow-Up	MQS §§	Funding Sources I
Sabate et al, 1993 (32)			(== =: :=::3=/3											
Walnut	18 (18 M)	30	73	OP, USA	Crossover	Met	Walnut	84		55:31:14	Isocaloric	4 wks	6	Agency
Control Chisholm et al, 1998 (13)									NCEP Step 1 diet	56:30:14				
Walnut					-		Walnut	78		40:38:17				
Control	16 HLP	45 (6.8)	28.4 (4.3)	OP, New Zealand	Crossover	DA	TT Can lot	10	Low Fat Diet	46:30:19	Isocaloric	4 wks	4	Agency
Spiller et al, 1998 (33)														
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				0,
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	madadamia	-10	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		45:43:12	Isocaloric	8 wks	6	Agency
Control Zambon et al, 2000 (35)		45(10)	24 (4)						Self-selected diet	46:36:18				0.1.7
Zambon et al, 2000 (35) Walnut					Crossover	Supp	Walnut	48.5		48:34:18				
Control	49 HC (26 M, 23 W)	56 (11)	70.6 (12.1)	OP, Spain	010330461	oupp	**dii lut	40.5	Mediterranean diet	50:31:19	Isocaloric	6 wks	6	Agency
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	20 (14 10, 5 11)	20-00	74.4 (10.7)	01,004	010330461	IVIGE			NCEP Step 1 diet	57:28:15	laocaloric	4 111.0	0	Agency
lwamoto et al, 2002 (36)			00.0 (0.5)					50-						
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 Jenkins et al, 2002 (15)		23.6 (4.6)‡	20.7 (0.5)						Average Japanese Diet	62:24:14				
Almond			71.2 (2.5)		-	-	Almond			47:36:17				
Control	27 HLP (15 M, 12 W)	64 (9)	71.0 (2.4)	OP, Canada	Crossover	Supp	/ uniona	73	NCEP Step 2 diet + Muffin	57:26:18	Isocaloric	4 wks	6	Agency
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			60:25:15	Isocaloric	4 wks	5	Agency
High Fat Control		,							High Fat diet Low Fat diet	48:37:15				0,
Low Fat Control Sabate et al, 2003 (38)									Low Fat diet	60:25:15				
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 Tapsell et al, 2004 (39)		57 (2)	114 (5)						CHO-LCD	32:39:29				0,
Walnut		57.7 (9)	87.6 (12.8)				Walnut	30		44:32:22				
Control	37 DM2	59.3 (7.1)	81.9 (11.2)	OP, Australia	Parallel	Supp	**dii lut	50	Modified Fat	41:33:23	Isocaloric	6 months	6	Agency
Tamizifar et al, 2005 (40)		00.0 (1.1)	01.0 (11.2)						mouniou i ut	11.00.20				
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	30 HG (17 W, 13 W)	50 (0.1)	03 (0.9)	OF, Itali	CIUSSOVEI	Supp			NCEP Step 1 diet	45:29:15	ISOCAIOTIC	4 WKS	5	IN/A
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	Decides dist	N/A	Isocaloric	3 wks	8	Agency
Control Kurlandsky et al, 2006 (41)			24.6 (5.6)						Regular diet					
Almond		41.8 (11.7)	25.3 (3.5)				Almond			51:34:15				
Almond + Dark Chocolate	17 (17 14)	46.2 (7.8)	27.2 (4.2)	OP, USA			Almond	60		46:39:15			5	
Dark chocolate	47 (47 W)	36.5 (11.9)	23.9 (3.3)	OP, USA	Parallel	Supp			NCEP ATP III diet + Chocolate	55:30:15	Isocaloric	6 wks	5	Agency-Industry
Control		51.3 (6.3)	26.1 (4.1)						NCEP ATP III diet	57:27:16				
Schutte et al, 2006 (53)*			05.0							17.00.17				
Walnut Cashew	62 MetS	45.5 45.7	35.9 34.7	OP. South Africa	Parallel	Met	Walnut Cashew	85.5		47:36:17 47:36:17	Isocaloric	8 wks	7	Agency-Industry
Casnew Control	UZ IVIGLO	45.7 44.4	34.7 35.5	or, ouur Airica	r ai aiidi	IVICI	Casnew		Control diet	47:36:17 50:33:18	SUCAIONC	O WAS	'	-gency-industry
Mukuddem-Petersen et al, 2007 (42)			30.5						Control dist	30.33.10				
Walnut			107				Walnut	95 E.C.		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)							B	05		50.04.45				
Pistachio Control	15 HC	60 (11.2)	175 (26)	OP, USA	Crossover	Supp	Pistachio	35	Bogular diat	52:31:17 53:31:16	Isocaloric	4 wks	6	Agency
Control									Regular diet	53:31:16				

Table 1 Cont'd

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

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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)ll	Comparator	Diet ††	Energy Balance	Follow-Up	MQS §§	Funding Sources
ebauer et al, 2008 (43) 1 Pistachio 2 Pistachio	28 HLP (10 M, 18 W)	48 (7.9)	76.6 (13.2)	OP, USA	Crossover	Met	Pistachio Pistachio	37 74		53:34:16 57:29:16	Isocaloric	4 wks	5	Agency
Control Griel et al, 2008 (44) Macadamia	25 HC	50.2 (8.4)	26.3 (3.3)	OP. USA	Crossover	Met	Macadamia	42.5**	NCEP Step 1 diet	62:25:15 50:33:19	Isocaloric	5 wks	8	Agency-Industr
Control enkins et al, 2008 (64)* Almond	27 HLP (15 M, 12 W)	64 (9)	71.2 (2.5)	OP, Canada	Crossover		Almond	73	AAD	52:33:17 47:36:17	Isocaloric	4 wks	6	• •
Control ajaram et al, 2009 (45) Walnut			71.0 (2.4) 71.9 (15.5)				Walnut	42.5	NCEP Step 2 diet + Muffin	57:26:18 60:31:15				Agency
Control apsell et al, 2009 (46)	25 NL-HLP (14 M, 11 W)	23-65	71.7 (15.5)	OP, USA	Crossover	Met			AAD	57:30:14	Isocaloric	4 wks	5	Agency
Walnut Control et al, 2010 (11)	35 DM2†	54 (8.7)	92.3 (15.7) 93.4 (3)	OP, Australia	Parallel	Supp	Walnut	30	Low Fat diet	42:29:24 41:34:20	Isocaloric	12 months	7	Agency
Almond Control a et al. 2010 (47)	52 OW†	45.4 (2.0) 47.3 (2.3)	86 (26.8) 85.5 (40.2)	OP, USA	Parallel	Supp	Pistachio	53	Pretzel	55:30:15 65:20:15	Hypocaloric Hypocaloric	12 wks	7	Agency
Walnut Control orabian et al, 2010 (12)	22 DM2†	58.1 (9.2)	89 (15.5)	OP, USA	Crossover	Supp	Walnut	56	Ad libitum diet	39:44:17 43:38:19	Isocaloric	8 wks	5	N/A
Walnut Control	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
ien et al, 2010 (48) Almond Control	65 PD (17 M, 48 W)	53 (9) 54 (11)	82.9 (14.4) 80.5 (14.4)	OP, USA	Parallel	Supp	Almond	58	AAD	42:39:19 48:30:21	Isocaloric	16 wks	9	Agency
u et al, 2010 (49) Walnut Control	189 MetS	48.2 (8.4) 48.6 (8)	72.2 (11.4) 70.6 (10.9)	OP, USA	Parallel	Supp	Walnut	30	AHA	48:37:15 51:34:15	Isocaloric	12 wks	9	Agency
asas-Agustench et al, 2011 (50) Mixed Nuts Control	50 MetS (28 M, 22 W)	52.9 (8.4) 50.6 (8.4)	31.6 (2.8) 30.0 (3.3)	OP, Spain	Parallel	Supp	Mixed Nuts	30	Prudent diet	41:36:19 42:36:19	Isocaloric	12 wks	6	Agency
ohen et al, 2011 (19) Almond Control	13 DM2 (7 M, 6 W)	66 (11.9)	96.1 (40.4) 105.1 (32.1)	OP, USA	Parallel	Supp	Almond	28	Cheese sticks	N/A	Isocaloric	12 wks	7	Agency
nkins et al, 2011 (20) Mixed Nuts Control	79 DM2 (52 M, 27 W)	63 (9) 61 (10)	80 (15) 83 (15)	OP, Canada	Parallel	Supp	Mixed nuts	75¶	NCEP Step 2 diet + Muffin	41:41:18 46:35:19	Isocaloric	12 wks	8	Agency
et al, 2011 (21) Almond Control	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 57:27:17	Isocaloric	4 wks	5	Agency
ey et al, 2011 (51) Hazelnut Control	61	38.9 (14.3) 36.1 (15.2)	72 (11.1) 67.3 (9.5)	OP, New Zealand	Parallel	Supp	Hazelnut	42	Regular diet	45:39:16## 50:33:17	Isocaloric	12 wks	9	Agency
arvish Damavandi et al, 2012 (18) Cashew Control	43 DM2 (9 M, 34 W)	51 (7.9) 56 (5.7)	72.1 (13.1) 71.9 (9.7)	OP, Iran	Parallel	Supp	Cashew	30	Regular diet	53:32:16 57:27:16	Isocaloric	8 wks	3	N/A
ster et al, 2012 (52) Almond Control	123 OW (11 M, 112 W)	47 (12) 46.7 (13)	94 (13.1) 91.5 (11.9)	OP, USA	Parallel	Supp	Almond	56	Nut free diet	N/A	Hypocaloric Hypocaloric	18 months	9	Agency
atz et al, 2012 (53) Walnut Control	40 OW†	57.4 (11.9)	33.2 (4.4)	OP, USA	Crossover	Supp	Walnut	56	Ad libitum diet	41:41:17 45:34:20	Isocaloric	8 wks	7	Industry
Control									Ad libitum diet	43.34.20				

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Study, year (Reference)	Participants	Mean Age (SD o 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 III
Gebauer et al, 2008 (43)							B. 1. 1.			50.04.40				
1 PD 2 PD Control	28 HLP (10 M, 18 W)	48 (7.9)	76.6 (13.2)	OP, USA	Crossover	Met	Pistachio Pistachio	37 74	NCEP Step 1 diet	53:34:16 57:29:16 62:25:15	Isocaloric	4 wks	5	Agency
Griel et al, 2008 (44) Macadamia Control	25 HC	50.2 (8.4)	26.3 (3.3)	OP, USA	Crossover	Met	Macadamia	42.5**	AAD	50:33:19 52:33:17	Isocaloric	5 wks	8	Agency-Industry
Jenkins et al, 2008 (54)* 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
Rajaram et al, 2009 (45) Walnut Control	25 NL-HLP (14 M, 11 W)	23-65	71.9 (15.5) 71.7 (15.5)	OP, USA	Crossover	Met	Walnut	42.5	AAD	60:31:15 57:30:14	Isocaloric	4 wks	5	Agency
Tapsell et al, 2009 (46) Walnut	35 DM2†	54 (8.7)	92.3 (15.7)	OP. Australia	Parallel	Supp	Walnut	30		42:29:24	Isocaloric	12 months	7	Agency
Control Li et al, 2010 (11) Almond		45.4 (2.0)	93.4 (3) 86 (26.8)	. ,			Pistachio	53	Low Fat diet	41:34:20 55:30:15	Hypocaloric			
Control Ma et al, 2010 (47)	52 OW†	47.3 (2.3)	85.5 (40.2)	OP, USA	Parallel	Supp			Pretzel	65:20:15	Hypocaloric	12 wks	7	Agency
Walnut Control Torabian et al, 2010 (12)	22 DM2†	58.1 (9.2)	89 (15.5)	OP, USA	Crossover	Supp	Walnut	56	Ad libitum diet	39:44:17 43:38:19	Isocaloric	8 wks	5	N/A
Walnut Control Wien et al, 2010 (48)	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
Almond Control	65 PD (17 M, 48 W)	53 (9) 54 (11)	82.9 (14.4) 80.5 (14.4)	OP, USA	Parallel	Supp	Almond	58	AAD	42:39:19 48:30:21	Isocaloric	16 wks	9	Agency
Wu et al, 2010 (49) Walnut Control	189 MetS	48.2 (8.4) 48.6 (8)	72.2 (11.4) 70.6 (10.9)	OP, USA	Parallel	Supp	Walnut	30	AHA	48:37:15 51:34:15	Isocaloric	12 wks	9	Agency
Casas-Agustench et al, 2011 (50) Mixed Nuts Control	50 MetS (28 M, 22 W)	52.9 (8.4) 50.6 (8.4)	31.6 (2.8) 30.0 (3.3)	OP, Spain	Parallel	Supp	Mixed Nuts	30	Prudent diet	41:36:19 42:36:19	Isocaloric	12 wks	6	Agency
Cohen et al, 2011 (19) Almond Control	13 DM2 (7 M, 6 W)	66 (11.9)	96.1 (40.4) 105.1 (32.1)	OP, USA	Parallel	Supp	Almond	28	Cheese sticks	N/A	Isocaloric	12 wks	7	Agency
Jenkins et al, 2011 (20) Mixed Nuts	79 DM2 (52 M, 27 W)	63 (9)	80 (15)	OP, Canada	Parallel	Supp	Mixed nuts	75¶		41:41:18	Isocaloric	12 wks	8	Agency
Control Li et al, 2011 (21) Almond	20 DM2 (9 M, 11 W)	61 (10) 58 (8.9)	83 (15) 26 (3.1)	OP, Taiwan	Crossover	Met	Almond	56	NCEP Step 2 diet + Muffin	46:35:19 47:37:17	Isocaloric	4 wks	5	Agency
Control Tey et al, 2011 (51) Hazelnut		38.9 (14.3)	72 (11.1)				Hazelnut	42	NCEP step 2 diet	57:27:17 45:39:16‡‡				
Control Darvish Damavandi et al, 2012 (18)	61	36.1 (15.2)	67.3 (9.5)	OP, New Zealand	Parallel	Supp			Regular diet	50:33:17	Isocaloric	12 wks	9	Agency
Cashew Control Foster et al, 2012 (52)	43 DM2 (9 M, 34 W)	51 (7.9) 56 (5.7)	72.1 (13.1) 71.9 (9.7)	OP, Iran	Parallel	Supp	Cashew	30	Regular diet	53:32:16 57:27:16	Isocaloric	8 wks	3	N/A
Almond Control Wang et al, 2012 (22)	123 OW (11 M, 112 W)	47 (12) 46.7 (13)	94 (13.1) 91.5 (11.9)	OP, USA	Parallel	Supp	Almond	56	Nut free diet	N/A	Hypocaloric Hypocaloric	18 months	9	Agency
Pistachios High pistachios Control West et al. 2012 (55)*	86 MetS	51.9 (8.8) 51.8 (9.4) 50.7 (9.9)	28.1 (3.2) 28 (4.5) 28 (4.4)	OP, China	Parallel	Supp	Pistachio Pistachio	42 70	AHA Step 1 diet	N/A	Isocaloric	12 wks	5	Industry
1 Pistachio 2 Pistachio Control	28 HLP (10 M, 18 W)	48 (7.9)	76.6 (13.2)	OP, USA	Crossover	Met	Pistachio Pistachio	37 74	NCEP Step 1 diet	53:34:16 57:29:16 62:25:15	Isocaloric	4 wks	5	Agency
Somerset et al, 2013 (9) Macadamia Control	64 OW (10 M, 54 W)	43.7 (8.4) 43.2 (10.9)	95 (14.7) 99.6 (15.2)	OP, Australia	Parallel	DA	Macadamia	46	Regular diet	36:38:21 41:38:17	Isocaloric	10 wks	9	Agency

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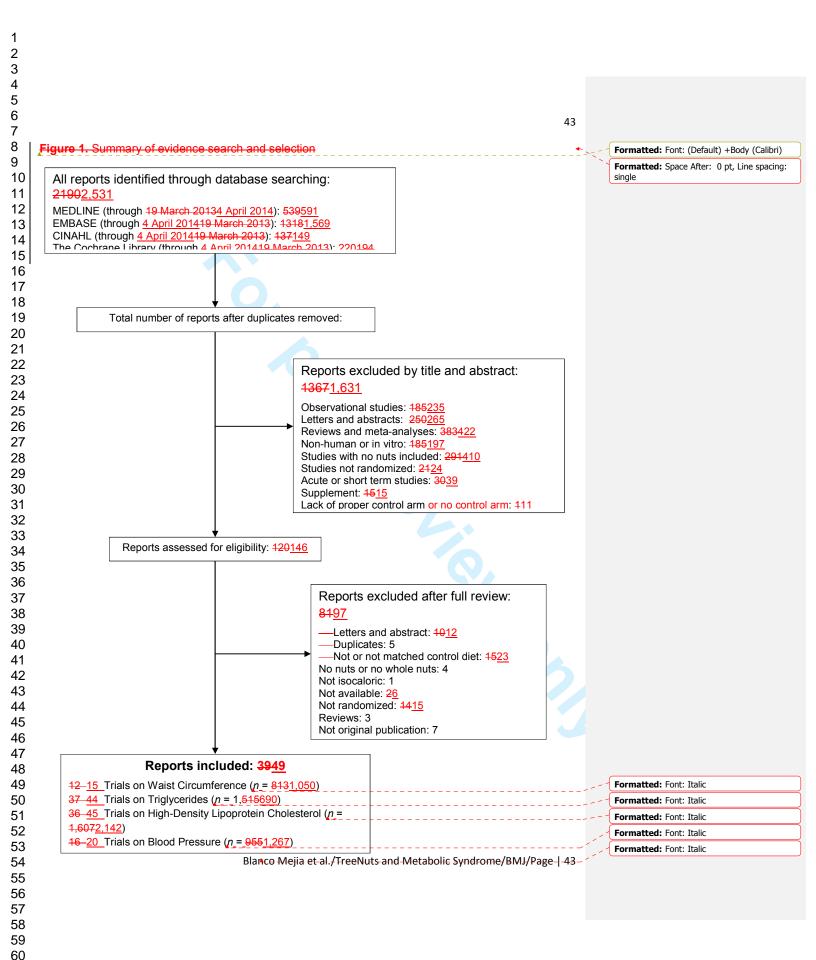
Study, year (Reference)	Participants	Mean Age (SD o range), y	Mean Body r Weight or BMI (SD or range)§	Setting	Design	Feeding Control	Nut type	Nuts Dose (g/day)I	Comparator	Diet ††	Form single		Space A	fter: 0 pt, Line
Wang et al, 2012 (22) Pistachios High pistachios Control	86 MetS	51.9 (8.8) 51.8 (9.4) 50.7 (9.9)	28.1 (3.2) 28 (4.5) 28 (4.4)	OP, China		Supp	Pistachio Pistachio	42 70	AHA Step 1 diet	N/A	Isocaloric	12 wks	5	Industry
West et al, 2012 (62)* 1 Pistachio	28 HLP (10 M, 18 W)		76.6 (13.2)	OP, USA	Crossover	Met	Pistachio	37 74	AHA Step 1 diet	53:34:16	l I Isocaloric	4 wks	5	Access/
2 Pistachio Control Anderson et al, 2013 (52)	26 HEP (10 W, 16 W)	48 (7.9)	70.0 (13.2)	UP, USA	Clossover	Wet	Pistachio		NCEP Step 1 diet	57:29:16 62:25:15	Isocaloric	4 WKS	5	Agency
Pistachio Control Berryman et al, 2013 (53)	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
Almond Control Darvish Damavandi et al, 2013 (54)	53 HC	N/A	N/A	OP, USA	Crossover	N/A	Almond	42.5	Muffin	51:33:16 59:26:15	Isocaloric	6 wks	N/A	N/A
Hazelnut Control Holligan et al, 2013 (63)*	48 DM2†	55.7 (7.7)	72.1 (10.3) 72 (9.6)	OP, Iran	Parallel	Supp	Hazelnut	29	Self-selected diet	55:31:16 60:25:17	Isocaloric	8 wks	6	None
1 Pistachio 2 Pistachio Control	28 HLP (10 M, 18 W)	48 (7.9)	76.6 (13.2)	OP, USA	Crossover	Met	Pistachio Pistachio	37 74	NCEP Step 1 diet	53:34:16 57:29:16 62:26:15	Isocaloric	4 wks	N/A	Agency
Sauder et al, 2013 (55) Pistachio Control	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 55:27:18	Isocaloric	4 wks	N/A	Industry
Somerset et al, 2013 (9) Macadamia Control	64 OW (10 M, 54 W)	43.7 (8.4) 43.2 (10.9)	95 (14.7) 99.6 (15.2)	OP, Australia	Parallel	DA	Macadamia	46	Regular diet	36:38:21 41:38:17	Isocaloric	10 wks	9	Agency
Tan et al, 2014 (56) Almond (Breakfast) Almond (Moming snack) Almond (Lunch) Almond (Afternoon snack) Control	137 OW (48 M, 89 W)	32.9 (11.5) 27.8 (10.7) 29.3 (13.5) 29 (11.9) 28.7 (9.6)	80.5 (15) 83.2 (21.1) 84.8 (13.7) 81.8 (14.6) 77.2 (16.8)	OP, USA	Parallel	Supp	Almond Almond Almond Almond	43 43 43 43	Regular diet	50:16:15 51:15:14 48:16:17 49:15:16 48:15:16	Isocaloric	4 wks	5	Industry
Tey et al, 2013 (57) Hazelnut 30 g Hazelnut 60 g Control Gulati et al, 2014 (58)	107 OW (46 M, 61W)	43.8 (13.5) 42.8 (10.6) 41.1 (13.1)	86.2 (11.8) 92 (19.6) 88.7 (16.7)	OP, New Zealand	Parallel	Supp	Hazelnut Hazelnut	30 60	Usual diet	42:39:17 38:42:16 47:33:17	Isocaloric	12 wks	6	Agency
Pistachio Control Wu et al, 2014 (59)	68 MetS (37 M, 31 W)	41.6 (8.4) 43.3 (8.1)	81.6 (12.9) 80.3 (10.3)	OP, India	Parallel	DA	Pistachio	50**	Standard diabetic diet	51:29:20 60:25:15	Isocaloric	24 wks	4	Industry
Walnut Control	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
Study, year (Reference)	Participants	Mean Age (SD o range), y	Mean Body or Weight or BMI (SD or range)§	Setting	Design	Feeding Control	Nut type	Nuts Dose (g/day)ll	Comparator	Diet ††	Energy Balance	Follow-Up	MQS §§	Funding Sources III
Wang et al, 2012 (22) Pistachios High pistachios Control	86 MetS	51.9 (8.8) 51.8 (9.4) 50.7 (9.9)	28.1 (3.2) 28 (4.5) 28 (4.4)	OP, China		Supp	Pistachio Pistachio	42 70	AHA Step 1 diet	N/A	Isocaloric	12 wks	5	Industry
West et al, 2012 (64)* 1 Pistachio 2 Pistachio Control	28 HLP (10 M, 18 W)	48 (7.9)	76.6 (13.2)	OP, USA	Crossover	Met	Pistachio Pistachio	37 74	NCEP Step 1 diet	53:34:16 57:29:16 62:25:15	Isocaloric	4 wks	5	Agency
Anderson et al, 2013 (54) Pistachio	22 OW	55 (2)	90 (3.6)	OP, USA	Parallel	N/A	Pistachio	35.4	N/A	02.25.15 N/A	N/A	6 wks	5	N/A
Control Berryman et al, 2013 (55) Almond	53 HC	N/A	N/A	OP, USA	Crossover	N/A	Almond	42.5		51:33:16	Isocaloric	6 wks	N/A	N/A
Control Darvish Damavandi et al, 2013 (56) Hazelnut	48 DM2†	55.7 (7.7)	72.1 (10.3)	OP, Iran	Parallel	Supp	Hazelnut	29	Muffin	59:26:15 55:31:16	Isocaloric	8 wks	6	None
Control Holligan et al, 2013 (65)* 1 Pistachio 2 Pistachio	28 HLP (10 M, 18 W)	48 (7.9)	72 (9.6) 76.6 (13.2)	OP, USA	Crossover	Met	Pistachio Pistachio	37 74	Self-selected diet	60:25:17 53:34:16 57:29:16	Isocaloric	4 wks	N/A	Agency
Control Sauder et al, 2013 (57) Pistachio					010330701		Pistachio	73.4	NCEP Step 1 diet	62:25:15 51:33:17	1300810110	4 10.0		Agency
Control Somerset et al, 2013 (9)	30 DM2 (15 M, 15 W)†		31.2 (1.1)	OP, USA	Crossover				Low fat diet	55:27:18	Isocaloric	4 wks	N/A	Industry
Macadamia Control Tan et al, 2014 (58)	64 OW (10 M, 54 W)	43.7 (8.4) 43.2 (10.9)	95 (14.7) 99.6 (15.2)	OP, Australia	Parallel	DA	Macadamia	46	Regular diet	36:38:21 41:38:17	Isocaloric	10 wks	9	Agency
Almond (Breakfast) Almond (Morning snack) Almond (Lunch) Almond (Afternoon snack) Control	137 OW (48 M, 89 W)	32.9 (11.5) 27.8 (10.7) 29.3 (13.5) 29 (11.9) 28.7 (9.6)	80.5 (15) 83.2 (21.1) 84.8 (13.7) 81.8 (14.6) 77.2 (16.8)	OP, USA	Parallel	Supp	Almond Almond Almond Almond	43 43 43 43	Regular diet	50:16:15 51:15:14 48:16:17 49:15:16 48:15:16	Isocaloric	4 wks	5	Industry
Tey et al, 2013 (59) Hazelnut 30 g Hazelnut 60 g Control Gulati et al, 2014 (60)	107 OW (46 M, 61W)	43.8 (13.5) 42.8 (10.6) 41.1 (13.1)	86.2 (11.8) 92 (19.6) 88.7 (16.7)	OP, New Zealand	Parallel	Supp	Hazelnut Hazelnut	30 60	Usual diet	42:39:17 38:42:16 47:33:17	Isocaloric	12 wks	6	Agency
	68 MetS (37 M, 31 W)	41.6 (8.4)	81.6 (12.9) 80.3 (10.3)	OP, India	Parallel	DA	Pistachio	50**	Standard diabetic diet	51:29:20 60:25:15	Isocaloric	24 wks	4	Industry
Pistachio Control Wu et al, 2014 (61)	00 11010 (07 11, 07 11)	43.3 (8.1)	00.0 (10.0)											

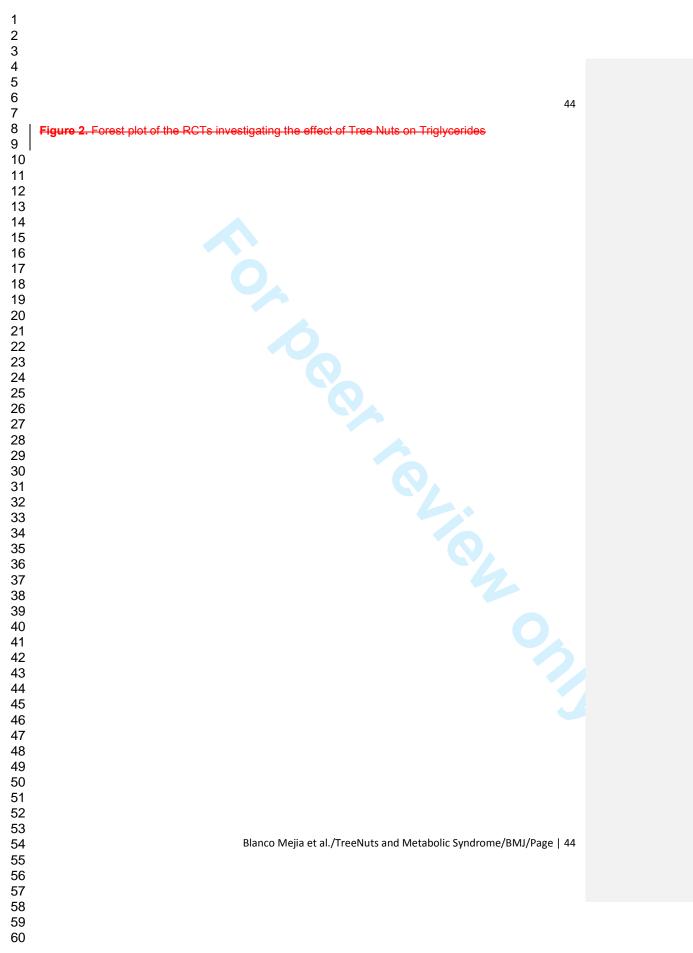
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8	MetS: metabolic syndrome; DM2: type 2 diabetes mellitus; OW: overweight; HLP: hyperlipidemic; NL-			
9	HLP: normal to mildly hyperlipidemic; HC: Hypercholesterolemic; NL-HC: normal to			
10	hypercholesterolemic; M: men; W: women; BMI: body mass index; OP: out-patient; IP: In-patient; USA:			
11	United States of America; SUPP: supplement; Met: metabolic; DA: dietary advice; N/A: not available;			
12	AHA: American Heart Association; AAD: Average American Diet; NCEP: National Cholesterol Education Program; CHO-LCD: Self-selected Complex Carbohydrate diet; WKS: weeks; MQS: Heyland			
13	Methodological Quality Score.			
14	* Companion reports: Jenkins et al, 2008 for Jenkins et al, 2002; Schutte et al, 2006 for Mukuddem-			
15	Petersen et al, 2007; Wang West et al, 2012 and Holligan et al, 2013 for Gebauer et al, 2008.			
16	† 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		ſ	Former Marcella Consta The Par
17	= 30; Gulati et al, 2010 n = 68 and for recruited subjects for Tapsell et al. 2009 $(n$ = 50), and for age for	\$2	. >	Formatted: Font: Italic Formatted: Font: Italic
18 19	Darvish Damavandi et al, 2013 ($n = 50$).	Ś	$\sim \geq$	
19 20	‡ Mean age was given separetly<u>separately</u> for men and women.		\searrow	Formatted: Font: Italic
20	§ Body weight is reported in kg and BMI is reported in kg/m ² . BMI is reported only when no data on		_ ≻	Formatted: Font: Italic Formatted: Superscript
22	weight were available. ∥ Nut dose is given based on grams (g) per g /day, 1oz = 28 g.		C	Formatted. Superscript
23	¶ Median was taken from a range given. Iwamoto et al, 2010 range 50-54 g/day; Jenkins et al, 2011		[]	Formatted: English (Canada)
24	range 50-75 g/day; Lovejoy et al, 2002 range 57-113 g/day; Mukuddem-Petersen et al, 2007 range 63-			
25	108 g/d <u>ay;</u> Torabian et al, 2010 range 28-64 g/d <u>ay</u> ; Zambon et al, 2000 range 41-56 g/d <u>ay</u> .			
26	** 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.			
27	t Values for carbohydrates are given in geometric means.			
28	§§ Trials with scores ≥8 were considered to be of high quality.			
29	III Agency funding is that from government, university, or not-for-profit health agency sources.			
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34 42 42 42 43 FIGURE LEGENDS 44 56 45 Figure 1. Summary of evidence search and selection 16 Figure 2. Forest plot of the RCTs investigating the effect of Tree Nuts on Triglycerides. Pooled effect 45 estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia, 46 metabolic syndrome_criteria, diabetes and their combination (total). Paired analyses were applied to all 47 crossover trials (4620) and one substudy. Data are expressed as mean differences (MD) with 95% Cl, 48 using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using 49 the Cochrane's Q statistic (l ²) at a significance level of P<0.0 and guantified by l ² , levels ≤ 50% 40 represent moderate heterogeneity. ≥50 % represent substantial eoneiderable heterogeneity and ≥ 475%, 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 420 420 420 421 420 420 420
67 42 78 FIGURE LEGENDS 79 Figure 1. Summary of evidence search and selection 71 Figure 2. Forest plot of the RCTs investigating the effect of Tree Nuts on Triglycerides. Pooled effect 71 estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia, 71 metabolic syndrome_criteria, diabetes and their combination (total). Paired analyses were applied to all 71 crossover trials (4520) and one substudy. Data are expressed as mean differences (MD) with 95% CI, 71 using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using 71 the Cochrane's Q statistic (l ²) at a significance level of <i>P</i> <0.010 and guantified by l ² , levels ≤ 50% 75%, considerable eubetantial- heterogeneity. ≥ 50 % represent substantial considerable- heterogeneity and ≥ 75%, considerable eubetantial- heterogeneity. TG = Triglycerides, mmol/L = mill moles per liter, A = 75%, considerable eubetantial- heterogeneity. TG = Triglycerides, mmol/L = mill moles per liter, A = 75% 75% 75% 75% 75% 75% 75% 75% 75% 75% 75% 75%
7 FIGURE LEGENDS 9 Figure 1. Summary of evidence search and selection 11 Figure 2. Forest plot of the RCTs investigating the effect of Tree Nuts on Triglycerides. Pooled effect 13 estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia, 14 metabolic syndrome_criteria, diabetes and their combination (total). Paired analyses were applied to all 17 crossover trials (1520) and one substudy. Data are expressed as mean differences (MD) with 95% CI, 18 using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using 19 the Cochrane's Q statistic (l ²) at a significance level of $P < 0.10$ and guantified by $ ^2$, levels $\leq 50\%$ 10 represent moderate heterogeneity. ≥ 50 % represent substantial considerable-heterogeneity and \geq 175%, considerable substantial-heterogeneity. TG = Triglycerides, mmol/L = mill moles per liter, A = 11 Almond, AC = Almond + Chocolate, HF = High Fat, LF = Low Fat. 12 Figure 3. Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise 128 Formatted: Font: Bold
9 Figure 1. Summary of evidence search and selection 11 Figure 2. Forest plot of the RCTs investigating the effect of Tree Nuts on Triglycerides. Pooled effect 13 estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia, 14 metabolic syndrome_criteria, diabetes and their combination (total). Paired analyses were applied to all 16 crossover trials (1520) and one substudy. Data are expressed as mean differences (MD) with 95% Cl, 19 using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using 10 the Cochrane's Q statistic (l ²) at a significance level of <i>P</i> < 0.10 and guantified by l ² , levels ≤ 50% 11 represent moderate heterogeneity. ≥ 50 % represent substantial considerable heterogeneity and ≥ 12 75%, considerable substantial heterogeneity. TG = Triglycerides, mmol/L = mill moles per liter, A = 11 Almond, AC = Almond + Chocolate, HF = High Fat, LF = Low Fat. 12 Figure 3. Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise
Figure 1. Summary of evidence search and selectionFigure 2. Forest plot of the RCTs investigating the effect of Tree Nuts on Triglycerides. Pooled effectestimates 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 allcrossover trials (1520) and one substudy. Data are expressed as mean differences (MD) with 95% Cl,using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by usingthe Cochrane's Q statistic (l ²) at a significance level of $P < 0.10$ and guantified by l^2 , levels $\leq 50\%$ represent moderate heterogeneity>50 % represent substantial considerable-heterogeneity and \geq 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 otherwiseFormatted: Font: Bold
12Figure 2. Forest plot of the RC1's investigating the effect of Tree Nuts on Triglycerides. Pooled effect13estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia,14metabolic syndrome_oriteria, diabetes and their combination (total). Paired analyses were applied to all16crossover trials (1520) and one substudy. Data are expressed as mean differences (MD) with 95% CI,18using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using20the Cochrane's Q statistic (l ²) at a significance level of <i>P</i> < 0.10 and guantified by l ² , levels ≤ 50%21represent moderate heterogeneity, ≥ 50 % represent substantial considerable heterogeneity and ≥2375%, considerable substantial heterogeneity. ≥ 50 % represent substantial considerable heterogeneity and ≥24Almond, AC = Almond + Chocolate, HF = High Fat, LF = Low Fat.25Figure 3. Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise28Formatted: Font: Bold
$\begin{array}{c} estimates are shown as dramons, one each for trials conducted in otherwise healthy, dyshpiderina, \\ \text{metabolic syndrome_criteria, diabetes and their combination (total). Paired analyses were applied to all \\ \text{crossover trials (1520) and one substudy. Data are expressed as mean differences (MD) with 95% CI, \\ \text{using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using \\ \text{the Cochrane's Q statistic (I2) at a significance level of P \leq 0.10 and guantified by I^2, levels \leq 50\%represent moderate heterogeneity. \geq 50\% represent substantial eonsiderable heterogeneity and \geq \\ 75\%, considerable substantial heterogeneity. TG = Triglycerides, mmol/L = mill moles per liter, A = \\ Almond, AC = Almond + Chocolate, HF = High Fat, LF = Low Fat. \\ \hline Figure 3. Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise \\ \hline Formatted: Font: Bold \\ \hline \end{array}$
15 16 17metabolic syndrome_criteria, diabetes and their combination (total). Paired analyses were applied to all crossover trials (1520) and one substudy. Data are expressed as mean differences (MD) with 95% CI,
17 crossover trials (1520) and one substudy. Data are expressed as mean differences (MD) with 95% CI, 18 using generic inverse-variance random-effects models. Interstudy heterogeneity was tested by using 20 the Cochrane's Q statistic (I ²) at a significance level of P < 0.10 and guantified by I ² , levels ≤ 50% 21 represent moderate heterogeneity. ≥ 50 % represent substantial considerable heterogeneity and ≥ 23 75%, considerable substantial heterogeneity. TG = Triglycerides, mmol/L = mill moles per liter, A = 25 Almond, AC = Almond + Chocolate, HF = High Fat, LF = Low Fat. 27 Figure 3. Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise
19 using generic inverse-variance random-effects models. Interstudy neterogeneity was tested by using 20 the Cochrane's Q statistic (l ²) at a significance level of <i>P</i> < 0.10 and guantified by l ² , levels ≤ 50% 21 represent moderate heterogeneity, ≥ 50 % represent substantial considerable heterogeneity and ≥ 23 75%, considerable substantial heterogeneity. TG = Triglycerides, mmol/L = mill moles per liter, A = 25 Almond, AC = Almond + Chocolate, HF = High Fat, LF = Low Fat. 27 Figure 3. Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise
20 the Cochrane's Q statistic (l²) at a significance level of P<0.10 and guantified by l², levels ≤ 50%
22 represent moderate heterogeneity, ≥ 50 % represent substantial considerable heterogeneity and ≥ 23 75%, considerable substantial heterogeneity. TG = Triglycerides, mmol/L = mill moles per liter, A = 24 Almond, AC = Almond + Chocolate, HF = High Fat, LF = Low Fat. 27 Figure 3. Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise Formatted: Font: Bold
 75%, <u>considerable substantial</u> 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
 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 Formatted: Font: Bold
 Figure 3. Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise Formatted: Font: Bold
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30 31 analyses were applied to all crossover trials (10) and one substudy. Data are expressed as mean
32 differences (MD) with 95% CL using generic inverse-variance random-effects models. Interstudy
$\frac{4}{100} = \frac{100}{100} = $
 35 36 quantified by l², levels ≥ 50 % represent substantial heterogeneity and ≥ 75%, considerable
37 38 <u>heterogeneity. FBG = Fasting Blood Glucose; mmol/L = mill moles per liter; HF = High Fat; LF = Low</u>
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ubgroup and Study, year (Reference)	Nuts n	Control	Weight	Mean Difference (95% CI) in mmol/L		
therwise Healthy					I	
abate et al, 1993 (30)	18	18	4.30%	-0.11 [-0.23, 0.01]		
curb et al, 2000 (10)	30	30	4.30%	-0.12 [-0.24, -0.00]		
forgan et al, 2000 (32)	10	9	0.70%	-0.24 [-0.57, 0.09]		
lajaram et al, 2001 (14) vamoto et al, 2002 (34)	23 40	23 40	3.50% 2.80%	-0.14 [-0.28, -0.00]		
abate et al, 2003 (36)	40 25	25	0.80%	0.00 [-0.16, 0.16] -0.03 [-0.34, 0.28]		
ocyigit et al, 2006 (16)	22	22	0.70%	-0.28 [-0.61, 0.05]		
urlandsky et al-Almonds, 2006 (39)	12	12	5.40%	-0.09 [-0.19, 0.01]		
urlandsky et al-Almd+choc, 2006 (39)	12	11	10.90%	-0.01 [-0.05, 0.03]	+	
tajaram et al, 2009 (43)	25	25	2.30%	-0.01 [-0.19, 0.17]		
orabian et al, 2010 (12)	87	87	13.30%	-0.09 [-0.10, -0.08]	•	
ey et al, 2011 (57)	32	27	2.30%	-0.04 [-0.22, 0.14]		
Vu et al, 2014 (59)	40	40	2.30%	-0.09 [-0.27, 0.09]		
ubtotal (95% CI) leterogeneity: Tau² = 0.00; Chi² = 20.83, df = 12 (P = 0.05); I²	376	369	53.80%	-0.07 [-0.11, -0.04]	•	
rest for overall effect: $Z = 4.01 (P < 0.001)$	- 42 70					
yslipidemia						
chisholm et al, 1998 (13)	16	16	0.80%	0.14 [-0.17, 0.45]		
piller et al, 1998 (31)	18	12	0.70%	0.02 [-0.31, 0.35]		
ambon et al, 2000 (33) enkins et al, 2002 (15)	49 27	49 27	5.40% 1.40%	-0.09 [-0.19, 0.01]		
amizifar et al, 2002 (15)	27	27	1.40%	-0.13 [-0.37, 0.11] 0.12 [-0.13, 0.37]		
heridan et al, 2007 (17)	15	15	1.20%	0.01 [-0.24, 0.26]		
Gebauer et al, 2008 (41)	28	28	2.30%	-0.16 [-0.34, 0.02]		
Griel et al, 2008 (42)	25	25	1.20%	-0.04 [-0.29, 0.21]		
ubtotal (95% CI)	208	202	14.40%	-0.06 [-0.13, 0.00]	•	
leterogeneity: Tau ² = 0.00; Chi ² = 5.94, df = 7 (P = 0.55); l ² = 0 est for overall effect: Z = 1.83 (P = 0.07)	%					
letabolic Syndrome Criteria						
lukuddem-Petersen et al, 2007 (40)	42	22	1.40%	-0.21 [-0.45, 0.03]		
i et al, 2010 (11)	27	25	1.70%	-0.26 [-0.48, -0.04]		
Vien et al, 2010 (46)	32	33	1.90%	-0.16 [-0.36, 0.04]		
asas-Agustench et al, 2011 (48)	25	25	0.50%	0.04 [-0.37, 0.45]		
oster et al, 2012 (50)	61	62	1.90%	0.07 [-0.13, 0.27]		
atz et al, 2012 (51)	40	40	1.40%	-0.05 [-0.29, 0.19]		
Vang et al, 2012 (22)	56	30	1.40%	-0.07 [-0.31, 0.17]		
omerset et al, 2013 (9)	35	29	1.40%	-0.01 [-0.25, 0.23]		
an et al, 2013 (56) ey et al, 2013 (57)	110 70	27 37	3.50% 3.50%	-0.03 [-0.17, 0.11]		
Sulati et al, 2014 (58)	30	30	1.90%	0.18 [0.04, 0.32] -0.07 [-0.27, 0.13]		
subtotal (95% CI)	528	360	20.60%	-0.04 [-0.13, 0.04]		
leterogeneity: Tau ² = 0.01; Chi ² = 18.74, df = 10 (P = 0.04); I ² iest for overall effect: Z = 1.02 (P = 0.31)						
liabetes						
ovejoy et al-Hihg Fat, 2002 (35)	30	30	0.90%	0.09 [-0.20, 0.38]		
ovejoy et al-Low Fat, 2002 (35)	30	30	0.90%	0.10 [-0.19, 0.39]		
Vien et al, 2003 (8)	32	33	0.50%	0.00 [-0.39, 0.39]		
apsell et al, 2004 (37)	17	20	0.80%	0.15 [-0.16, 0.46]		
apsell et al, 2009 (44)	18	17	0.10%	0.30 [-0.50, 1.10]		
la et al, 2010 (45)	22	22	0.80%	-0.11 [-0.43, 0.20]		
ohen et al, 2011 (19)	6	7	0.10%	0.60 [-0.20, 1.40]		
enkins et al, 2011 (20)	40	39	2.30%	-0.07 [-0.25, 0.11]		
i et al, 2011 (21)	20	20	0.70%	-0.10 [-0.43, 0.23]		
arvish Damavandi et al, 2012 (18)	22 23	21 25	0.70%	0.05 [-0.28, 0.38]		
arvish Damavandi et al, 2013 (54) auder et al, 2013 (55)	23 28	25 28	0.70% 2.30%	0.05 [-0.30, 0.40]		
ubtotal (95% CI)	28	28	2.30%	-0.28 [-0.46, -0.10] -0.03 [-0.13, 0.07]		
leterogeneity: Tau ² = 0.01; Chi ² = 14.22, df = 11 (P = 0.22); l ² iest for overall effect: Z = 0.56 (P = 0.58)		202	11.2070	0.00 [-0.10, 0.07]		
iotal (95% CI)	1400	1223	100.00%	-0.06 [-0.09, -0.03]	•	
					-0.5 -0.25 0 0.25 0.5	
leterogeneity: Tau ² = 0.00; Chi ² = 64.68, df = 43 (P = 0.02); I ²	= 34%					
iest for overall effect: $Z = 3.96 (P < 0.0001)$	- 0%				Favours Nuts Favours Control	
est for subgroup differences: Chi ² = 0.92, df = 3 (P = 0.82), I ²	= U%				Mean Difference (95% CI) in TG, mmol/L	

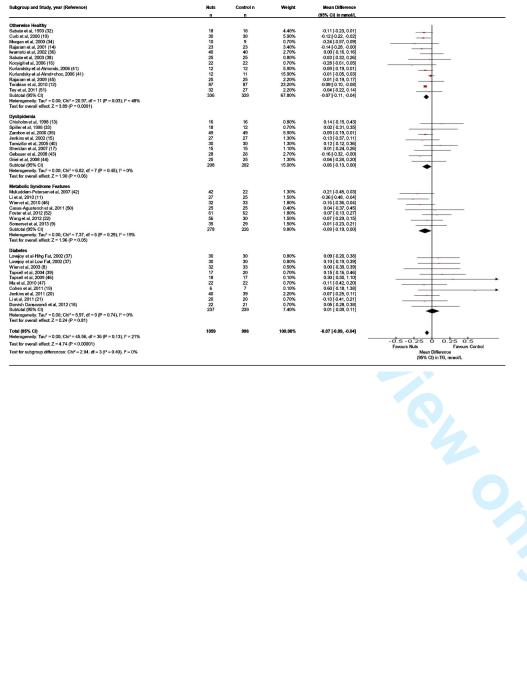
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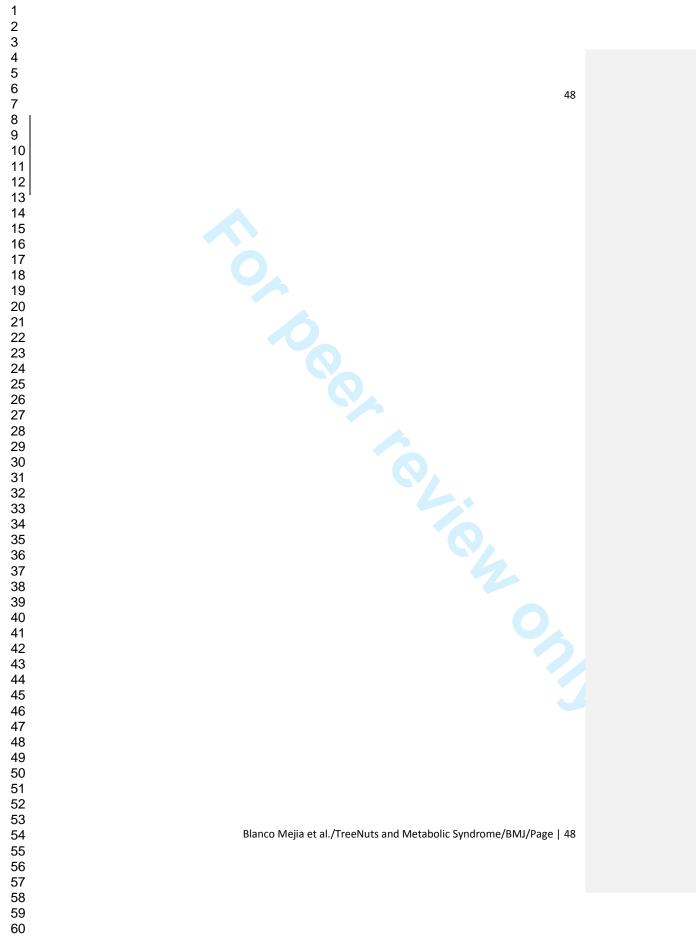
Subgroup and Study, year (Reference)	Nuts n	Control n	Weight	Mean Difference (95% CI) in mmol/L	
Otherwise Healthy					
Sabate et al, 1993 (32)	18	18	4.30%	-0.11 [-0.23, 0.01]	
Curb et al, 2000 (10)	30	30	4.30%	-0.12 [-0.24, -0.00]	
Morgan et al, 2000 (34) Rajaram et al, 2001 (14)	10 23	9 23	0.70% 3.50%	-0.24 [-0.57, 0.09] -0.14 [-0.28, -0.00]	
wamoto et al, 2002 (36)	40	40	2.80%	0.00 [-0.16, 0.16]	
Sabate et al, 2003 (38)	25	25	0.80%	-0.03 [-0.34, 0.28]	
Kocyigit et al, 2006 (16)	22	22	0.70%	-0.28 [-0.61, 0.05]	
Kurlandsky et al-Almonds, 2006 (41) Kurlandsky et al-Almd+choc, 2006 (41)	12 12	12 11	5.40% 10.90%	-0.09 [-0.19, 0.01]	
Rajaram et al, 2009 (45)	25	25	2.30%	-0.01 [-0.05, 0.03] -0.01 [-0.19, 0.17]	
Forabian et al, 2010 (12)	87	87	13.30%	-0.09 [-0.10, -0.08]	•]
Fey et al, 2011 (51)	32	27	2.30%	-0.04 [-0.22, 0.14]	
Vu et al, 2014 (61)	40	40	2.30%	-0.09 [-0.27, 0.09]	
Subtotal (95% CI) Heterogeneity: Tau² = 0.00; Chi² = 20.83, df = 12 (P = 0.05); l² = 42%	376	369	53.80%	-0.07 [-0.11, -0.04]	•
First for overall effect: $Z = 4.01 (P < 0.0001)$	0				
Dyslipidemia					
Chisholm et al, 1998 (13)	16	16	0.80%	0.14 [-0.17, 0.45]	
Spiller et al, 1998 (33) Zambon et al, 2000 (35)	18 49	12 49	0.70% 5.40%	0.02 [-0.31, 0.35] -0.09 [-0.19, 0.01]	
lenkins et al, 2000 (15)	49 27	49 27	5.40% 1.40%	-0.13 [-0.37, 0.11]	
Famizifar et al, 2005 (40)	30	30	1.20%	0.12 [-0.13, 0.37]	
Sheridan et al, 2007 (17)	15	15	1.20%	0.01 [-0.24, 0.26]	
Gebauer et al, 2008 (43)	28	28	2.30%	-0.16 [-0.34, 0.02]	
Griel et al, 2008 (44) Subtotal (95% CI)	25 208	25 202	1.20% 14.40%	-0.04 [-0.29, 0.21] -0.06 [-0.13, 0.00]	
Heterogeneity: Tau ² = 0.00; Chi ² = 5.94, df = 7 (P = 0.55); $l^2 = 0\%$	200	202	14.4070	-0.00 [-0.13, 0.00]	–
First for overall effect: Z = 1.83 (P = 0.07)					
Metabolic Syndrome Criteria					
Mukuddem-Petersen et al, 2007 (42) .i et al, 2010 (11)	42	22	1.40%	-0.21 [-0.45, 0.03]	
Vien et al, 2010 (48)	27 32	25 33	1.70% 1.90%	-0.26 [-0.48, -0.04] -0.16 [-0.36, 0.04]	
Casas-Agustench et al, 2011 (50)	25	25	0.50%	0.04 [-0.37, 0.45]	
oster et al, 2012 (52)	61	62	1.90%	0.07 [-0.13, 0.27]	
(atz et al, 2012 (53)	40	40	1.40%	-0.05 [-0.29, 0.19]	
Vang et al, 2012 (22)	56	30	1.40%	-0.07 [-0.31, 0.17]	
Somerset et al, 2013 (9) Fan et al, 2013 (58)	35 110	29 27	1.40% 3.50%	-0.01 [-0.25, 0.23] -0.03 [-0.17, 0.11]	
Fey et al, 2013 (59)	70	37	3.50%	0.18 [0.04, 0.32]]
Gulati et al, 2014 (60)	30	30	1.90%	-0.07 [-0.27, 0.13]	
Subtotal (95% CI)	528	360	20.60%	-0.04 [-0.13, 0.04]	◆
Heterogeneity: Tau ² = 0.01; Chi ² = 18.74, df = 10 (P = 0.04); l ² = 47% Fest for overall effect: Z = 1.02 (P = 0.31)	0				
Diabetes	20	20	0.000/	0.00.0.00.0.00.0	
.ovejoy et al-Hihg Fat, 2002 (37) .ovejoy et al-Low Fat, 2002 (37)	30 30	30 30	0.90% 0.90%	0.09 [-0.20, 0.38] 0.10 [-0.19, 0.39]	
Vien et al, 2003 (8)	32	33	0.50%	0.00 [-0.39, 0.39]	
Tapsell et al, 2004 (39)	17	20	0.80%	0.15 [-0.16, 0.46]	
Fapsell et al, 2009 (46)	18	17	0.10%	0.30 [-0.50, 1.10]	
/la et al, 2010 (47) Cohen et al, 2011 (19)	22 6	22 7	0.80%	-0.11 [-0.43, 0.20]	
lenkins et al, 2011 (20)	6 40	39	0.10% 2.30%	0.60 [-0.20, 1.40] -0.07 [-0.25, 0.11]	
i et al, 2011 (21)	20	20	0.70%	-0.10 [-0.43, 0.23]	`
Darvish Damavandi et al, 2012 (18)	22	21	0.70%	0.05 [-0.28, 0.38]	<u>+</u>
Darvish Damavandi et al, 2013 (56)	23	25	0.70%	0.05 [-0.30, 0.40]	_
Sauder et al, 2013 (57)	28	28	2.30%	-0.28 [-0.46, -0.10]	
Subtotal (95% CI) Heterogeneity: Tau² = 0.01; Chi² = 14.22, df = 11 (P = 0.22); l² = 23%	288	292	11.20%	-0.03 [-0.13, 0.07]	
First for overall effect: $Z = 0.56$ (P = 0.58)	-				
Fotal (95% CI)	1400	1223	100.00%	-0.06 [-0.09, -0.03]	, ♦
Heterogeneity: Tau ² = 0.00; Chi ² = 64.68, df = 43 (P = 0.02); l ² = 34% Fest for overall effect: Z = 3.96 (P < 0.0001)	6				-0.5 -0.25 0 0.25 0.5 Favours Nuts Favours Control
First for subgroup differences: $Chi^2 = 0.92$, $df = 3$ (P = 0.82), $I^2 = 0\%$					Mean Difference (95% CI) in TG, mmol/L

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Subgroup and Study, year (Reference)	Nuts n	Control n	Weight	Mean Difference (95% CI) in mmol/L	
Otherwise Healthy					I
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: Tau ² = 0.00; Chi ² = 0.78, df Test for overall effect: Z = 0.49 (P = 0.63)	= 1 (P = 0.38); I* = 0%				
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: Tau ² = 0.01; Chi ² = 2.03 df = Test for overall effect: Z = 0.97 (P = 0.33)	= 1 (P = 0.15); I ² = 51%				
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) Anderson et al, 2013 (52)	56 11	30 11	6.50% 3.80%	-0.23 [-0.43, -0.03] -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: Tau ² = 0.02; Chi ² = 22.77, di Test for overall effect: Z = 0.97 (P = 0.33)	f = 10 (P = 0.01); l ² = 56%				
Diabetes Lovejoy et al-Hihg Fat, 2002 (35)	30	30	0.50%	-0.59 [-1.59, 0.41]	
Lovejoy et al-Hing Fat, 2002 (35) Lovejoy et al-Low Fat, 2002 (35)	30 30	30 30	0.50%	-0.59 [-1.59, 0.41] 0.63 [-0.37, 1.63]	
Wien et al, 2003 (8)	30	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) Daprish Damayandi et al. 2012 (18)	20 22	20 21	5.40% 0.40%	-0.30 [-0.54, -0.06]	
Darvish Damavandi et al, 2012 (18) Darvish Damavandi et al, 2013 (54)	22 23	21	0.40%	-1.08 [-2.28, 0.12] -0.92 [-1.94, 0.10]	
Sauder et al, 2013 (55)	23	23	6.00%	-0.04 [-0.26, 0.18]	+
Subtotal (95% CI)	271	272	18.80%	-0.16 [-0.37, 0.05]	•
Heterogeneity: Tau ² = 0.03; Chi ² = 14.82, dt	f = 10 (P = 0.14); l ² = 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: Tau ² = 0.01; Chi ² = 42.36, dt	f = 25 (P = 0.02); l ² = 41%			-	-2 -1 0 1 2
Test for overall effect: Z = 2.19 (P = 0.03)					Favours Nuts Favours Control
Test for subgroup differences: Chi ² = 1.22, o	df = 3 (P = 0.75), I ² = 0%				Mean Difference
					(95% CI) in FBG, mmol/L

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Mean Difference (95% CI) in FBG, mmol/L

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Subgroup and Study, year (Reference) Nuts Control Weight Mean Difference n n (95% CI) in mmol/L Otherwise Healthy Sabate et al, 2003 (38) 0 25 40 65 25 7.80% 0.01 [-0.15, 0.17] Wu et al, 2014 (61) 40 6.00% -0.11 [-0.33, 0.11] 1 Subtotal (95% Cl) Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 1 (P = 0.38); l² = 0% Test for overall effect: Z = 0.49 (P = 0.63) 65 13.80% -0.03 [-0.16, 0.10] 2 3 Dyslipidemia Jenkins et al, 2008 (54) 4.20% -0.26 [-0.03, 0.55] 4 27 27 Holligan et al. 2013 (65) 28 55 28 55 9.20% -0.03[-0.15.0.09] Subtotal (95% CI) 13.40% 0.08 [-0.19, 0.36] 5 Test for overall effect: Z = 0.01; $Chi^2 = 32.03 \text{ df} = 1 (P = 0.15)$; $l^2 = 51\%$ Test for overall effect: Z = 0.97 (P = 0.33)6 Metabolic Syndrome Criteria Schutte et al, 2006 (53) Li et al, 2010 (11) 7 1.40% 5.00% 0.80 [0.21, 1.39] 41 27 21 25 8 -0.29 [-0.54, -0.04] 2.80% 3.80% 5.00% Wien et al, 2010 (48) Wu et al, 2010 (49) 33 95 25 -0.01 [-0.40, 0.38] 0.03 [-0.28, 0.34] 32 94 25 40 56 11 35 110 30 9 Casas-Agustench et al, 2011 (50) Katz et al, 2012 (53) -0.01 [-0.26, 0.24] 0 40 7 20% 0.00 [-0.17, 0.18] Wang et al, 2012 (33) Anderson et al, 2013 (54) -0.23 [-0.43, -0.03] -0.23 [-0.54, 0.08] 6.50% 30 11 29 27 30 1 3.80% 0.31 [-0.04, 0.66] -0.04 [-0.16, 0.08] Somerset et al, 2013 (9) 3.20% 2 Tan et al, 2013 (58) Gulati et al, 2014 (59) 9.20% 6.00% -0.22 [-0.44, -0.00] 3 501 Subtotal (95% CI) 366 53.90% -0.06 [-0.17, 0.06] Heterogeneity: Tau² = 0.02; Chi² = 22.77, df = 10 (P = 0.01); l² = 56% Test for overall effect: Z = 0.97 (P = 0.33) 4 5 Diabetes Lovejoy et al-Hihg Fat, 2002 (37) Lovejoy et al-Low Fat, 2002 (37) Wien et al, 2003 (8) 30 32 18 22 6 40 20 22 0.50% -0.59 [-1.59, 0.41] 6 30 30 33 17 22 0.60% 0.63 [-0.33, 1.59] 7 0.40% 0.06 [-1.14, 1.26] Tapsell et al, 2009 (46) Ma et al, 2010 (47) 0.20% 0.90 [-0.75, 2.55] 0.39 [-0.30, 1.08] 8 Cohen et al, 2011 (19) 7 0.60% -0.50 [-1.40, 0.40] 3.20% 5.40% 0.40% -0.30 [-1.40, 0.40] -0.18 [-0.53, 0.17] -0.30 [-0.54, -0.06] -1.08 [-2.28, 0.12] Jenkins et al, 2011 (20) Li et al, 2011 (21) 39 20 21 9 Li et al, 2011 (21) Darvish Damavandi et al, 2012 (18) Darvish Damavandi et al, 2013 (56) 0 23 28 271 25 28 272 0.50% 6.00% 18.90% -0.92 [-1.94, 0.10] -0.04 [-0.26, 0.18] -0.16 [-0.37, 0.05] 1 Sauder et al, 2013 (57) Subtotal (95% CI) 2 Heterogeneity: Tau² = 0.03; Chi² = 15.02, df = 10 (P = 0.13); l² = 33% Test for overall effect: Z = 1.47 (P = 0.14) 3 892 758 100.00% -0.08 [-0.16, -0.01]

4 Total (95% CI) Heterogeneity: Tau² = 0.01; Chi² = 42.52, df = 25 (P = 0.02); l² = 41%

Test for overall effect: Z = 2.182 (P = 0.03) Test for subgroup differences: Chi² = 1.17, df = 3 (P = 0.76), l² = 0%

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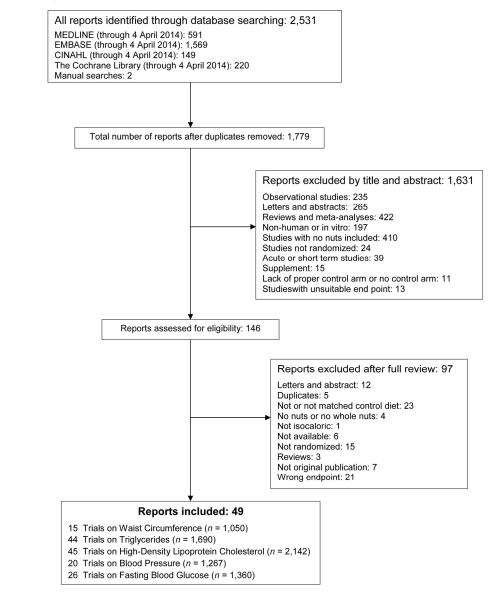
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piller et al, 1998 (31)					
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	18	12	0.70%	0.02 [-0.31, 0.35]	
	49	49	5.40%	-0.09 [-0.19, 0.01]	
enkins et al, 2002 (15)	27	27	1.40%	-0.13 [-0.37, 0.11]	
amizifar et al, 2005 (38)	30	30	1.20%	0.12 [-0.13, 0.37]	
heridan et al, 2007 (17)	15	15	1.20%	0.01 [-0.24, 0.26]	
ebauer et al, 2008 (41)	28	28	2.30%	-0.16 [-0.34, 0.02]	
iriel et al, 2008 (42)	25	25	1.20%	-0.04 [-0.29, 0.21]	
ubtotal (95% CI)	208	202	14.40%	-0.06 [-0.13, 0.00]	•
leterogeneity: Tau ² = 0.00; Chi ² = 5.94, df = 7 (P = 0.55); l ² = 0% est for overall effect: Z = 1.83 (P = 0.07)					•
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lukuddem-Petersen et al, 2007 (40)	42	22	1.40%	-0.21 [-0.45, 0.03]	
i et al, 2010 (11)	27	25	1.70%	-0.26 [-0.48, -0.04]	
Vien et al, 2010 (46)	32	33	1.90%	-0.16 [-0.36, 0.04]	
asas-Agustench et al, 2011 (48)	25	25	0.50%	0.04 [-0.37. 0.45]	
oster et al, 2012 (50)	61	62	1.90%	0.07 [-0.13, 0.27]	
atz et al, 2012 (51)	40	40	1.40%	-0.05 [-0.29, 0.19]	
Vang et al, 2012 (22)	56	30	1.40%	-0.07 [-0.31, 0.17]	
omerset et al, 2013 (9)	35	29	1.40%	-0.01 [-0.25, 0.23]	
an et al, 2013 (56)	110	27	3.50%	-0.03 [-0.17, 0.11]	
ey et al, 2013 (57)	70	37	3.50%	0.18 [0.04, 0.32]	
sulati et al, 2014 (58)	30	30	1.90%	-0.07 [-0.27, 0.13]	
ubtotal (95% CI)	528	360	20.60%	-0.04 [-0.13, 0.04]	
leterogeneity: Tau ² = 0.01; Chi ² = 18.74, df = 10 (P = 0.04); l ² = 4 est for overall effect: Z = 1.02 (P = 0.31)					
iabetes					
ovejoy et al-Hihg Fat, 2002 (35)	30	30	0.90%	0.09 [-0.20, 0.38]	
ovejoy et al-Low Fat, 2002 (35)	30	30	0.90%	0.10 [-0.19, 0.39]	
Vien et al, 2003 (8)	32	33	0.50%	0.00 [-0.39, 0.39]	
apsell et al. 2004 (37)	17	20	0.80%	0.15 [-0.16, 0.46]	
apsell et al, 2009 (44)	18	17	0.10%	0.30 [-0.50, 1.10]	
la et al, 2010 (45)	22	22	0.80%	-0.11 [-0.43, 0.20]	
ohen et al, 2011 (19)	6	7	0.10%	0.60 [-0.20, 1.40]	
enkins et al, 2011 (20)	40	39	2.30%	-0.07 [-0.25, 0.11]	
i et al, 2011 (21)	20	20	0.70%	-0.10 [-0.43, 0.23]	
arvish Damavandi et al, 2012 (18)	20	20	0.70%	0.05 [-0.28, 0.38]	
arvish Damavandi et al, 2013 (54)	23	25	0.70%	0.05 [-0.30, 0.40]	· · · · · · · · · · · · · · · · · · ·
auder et al, 2013 (55)	28	28	2.30%	-0.28 [-0.46, -0.10]	
ubtotal (95% CI)	288	292	11.20%	-0.28 [-0.48, -0.10] -0.03 [-0.13, 0.07]	
leterogeneity: Tau² = 0.01; Chi² = 14.22, df = 11 (P = 0.22); l² = 2 iest for overall effect: Z = 0.56 (P = 0.58)		292	11.20%	-0.03 [-0.13, 0.07]	•
otal (95% CI)	1400	1223	100.00%	-0.06 [-0.09, -0.03]	•
leterogeneity: Tau ² = 0.00; Chi ² = 64.68, df = 43 (P = 0.02); l ² = 3	34%			-	-0.5 -0.25 0 0.25 0.5
The end of					Favours Nuts Favours Control
est for subgroup differences: $Chi^2 = 0.92$, $df = 3$ (P = 0.82), $l^2 = 0.92$	0%				Mean Difference
(r = 0.02), r = 0.02, u = 0.02), r = 0.02)					(95% CI) in TG, mmol/L

163x212mm (300 x 300 DPI)

60

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

ubgroup and Study, year (Reference)	Nuts n	Control n	Weight	Mean Difference (95% CI) in mmol/L	
Otherwise Healthy					1
abate et al, 2003 (36)	25	25	7.80%	0.01 [-0.15, 0.17]	+
Vu et al, 2014 (59)	40	40	6.00%	-0.11 [-0.33, 0.11]	-
ubtotal (95% CI)	65	65	13.80%	-0.03 [-0.16, 0.10]	4
leterogeneity: Tau ² = 0.00; Chi ² = 0.78, df = 1 (P = 0.38); l ² = 0%	00	00	10.0070	0.00[0.10,0.10]	T
lest for overall effect: $Z = 0.49$ (P = 0.63)					
yslipidemia					
enkins et al, 2008 (61)	27	27	4.20%	-0.26 [-0.55, 0.03]	
Iolligan et al, 2013 (63)	28	28	9.20%	-0.03 [-0.15, 0.09]	+
ubtotal (95% CI)	55	55	13.40%	-0.10 [-0.31, 0.11]	•
leterogeneity: Tau ² = 0.01; Chi ² = 2.03 df = 1 (P = 0.15); I ² = 51%					
est for overall effect: Z = 0.97 (P = 0.33)					
letabolic Syndrome Criteria					
ichutte et al, 2006 (60)	41	21	1.40%	0.80 [0.21, 1.39]	
i et al, 2010 (11)	27	25	5.00%	-0.29 [-0.54, -0.04]	
Vien et al, 2010 (46)	32	33	2.80%	-0.01 [-0.40, 0.38]	
Vu et al, 2010 (47)	94	95	3.80%	0.03 [-0.28, 0.34]	
asas-Agustench et al, 2011 (48)	25	25	5.00%	-0.01 [-0.26, 0.24]	-
atz et al, 2012 (51)	40	40	7.20%	0.00 [-0.17, 0.18]	+
Vang et al, 2012 (22)	56	30	6.50%	-0.23 [-0.43, -0.03]	
nderson et al, 2013 (52)	11	11	3.80%	-0.23 [-0.54, 0.08]	
omerset et al, 2013 (9)	35	29	3.20%	0.31 [-0.04, 0.66]	
an et al. 2013 (56)	110	27	9.30%	-0.04 [-0.16, 0.08]	1
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]	
leterogeneity: Tau ² = 0.02; Chi ² = 22.77, df = 10 (P = 0.01); l ² = 56%	501	300	55.90%	-0.06[-0.17, 0.06]	•
The for overall effect: $Z = 0.97$ (P = 0.33)					
liabetes					
ovejoy et al-Hihg Fat, 2002 (35)	30	30	0.50%	-0.59 [-1.59, 0.41]	
ovejoy et al-Low Fat, 2002 (35)	30	30	0.50%	0.63 [-0.37, 1.63]	
Vien et al, 2003 (8)	32	33	0.40%	0.06 [-1.14, 1.26]	
apsell et al, 2009 (44)	18	17	0.20%	0.90 [-0.75, 2.55]	
fa et al, 2010 (45)	22	22	1.10%	0.39 [-0.30, 1.08]	
ohen et al, 2011 (19)	6	7	0.60%	-0.50 [-1.40, 0.40]	
enkins et al, 2011 (20)	40	39	3.20%	-0.18 [-0.53, 0.17]	
i et al, 2011 (21)	20	20	5.40%	-0.30 [-0.54, -0.06]	
arvish Damavandi et al, 2012 (18)	22	21	0.40%	-1.08 [-2.28, 0.12]	
arvish Damavandi et al, 2012 (10)	22	25	0.40%	-0.92 [-1.94, 0.10]	
auder et al, 2013 (55)	23	25	6.00%	-0.04 [-0.26, 0.18]	
ubtotal (95% CI)	271	272	18.80%		
leterogeneity: Tau ² = 0.03; Chi ² = 14.82, df = 10 (P = 0.14); l ² = 33%	211	212	10.0070	-0.16 [-0.37, 0.05]	
reterogeneity: $1at^2 = 0.03$; $Ch^2 = 14.02$; $dt = 10$ ($P = 0.14$); $t^2 = 33\%$ rest for overall effect: $Z = 1.50$ ($P = 0.13$)					
otal (95% CI)	892	758	100.00%	-0.08 [-0.16, -0.01]	•
leterogeneity: Tau ² = 0.01; Chi ² = 42.36, df = 25 (P = 0.02); l ² = 41%					-2 -1 0 1 2
est for overall effect: $Z = 2.19$ (P = 0.03)					Favours Nuts Favours Contro
est for subgroup differences: $Chi^2 = 1.22$, $df = 3$ (P = 0.75), $l^2 = 0.\%$					Mean Difference

173x163mm (300 x 300 DPI)

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

Database	SearchPeriod	Search
		1. exp nut/ Or nuts.mp. Or nut.mp. Or expbertholletia/ Or walnut*.mp. Or expJuglans/ Or almond*.mp. Or expPrunus/ Or
MEDLINE	1946 to March Week	pecan*.mp. Or expCarya/ Or pistachio*.mp. Or expPistacia/ Or cashew*.mp. Or expAnacardium/ Or hazelnut*.mp. Or
	4 2014	expCorylus/ Or macadamia*.mp. Or exp Macadamia/
	0	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 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 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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/	

1			
2 3 4 5 6 7 8 9 10	CINHAL	1982 to 4 April 2014	 (MH "Nuts+) Or "ogtt" Or (MM "I "dysglycemia" Or mellitus". (MH "Hypertens 4. "triglycerides" O "HDL" Or (MH " 6. "abdominal obe T. "Insulin resistar 1 and (2 or 3 or
$\begin{array}{c} 11\\ 12\\ 13\\ 14\\ 15\\ 16\\ 17\\ 18\\ 19\\ 20\\ 21\\ 22\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 536\\ 37\\ 38\\ 940\\ 41\\ 42\\ 43\\ 44\\ 45\\ 46\end{array}$	Original sear	Through December 2013	1. nuts.mp. Or nut pistachio*.mp. Or 2. ogtt.mp. Or hba albumin.mp. Or e diabetes mellitus. 3. hypertension.m Or SBP.mp. Or D 4. triglycerides.mp 5. HDL.mp. Or HE 6. abdominal obes 7. insulin resistand 8. 1 and (2 or 3 or search term is u pases was May 2
47 48			

L	1982 to 4 April 2014	 (MH "Nuts+) Or "pistachio" Or "hazelnut" Or "macadamia" Or "brazil nut" Or "brazil nuts" Or "pine nut" Or "pine nuts". "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).
		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
rane	Through December	pistachio*.mp. Or cashew*.mp. Or hazelnut*.mp. Or macadamia.mp.
/	2013	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)
ymbol	at the end of each	search term is used in order to capture all possible endings with that word.
l sear	ch date for all datab	bases was May 25 th 2012; update search dates for all databases were March 19 th 2013 and April 4 th 2014.
hes v	vere limited to anim	als and then extracted from the general search.

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

² ₃ Study, Year (Reference)	De	sign†			Sample‡			Intervention§		MQS (n/13)
4 5 6 7	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)	(
7 8 9 Sabate et al, 1993 (32)	1	0	0	1	1	0	1	2	0	6
10 Chisholm et al, 1998 (13)	1	0	0	0	1	0	0	2	0	4
11 Spiller et al, 1998 (33)		0	0	1	1	0 0	1	2	0	6
12 Curb et al, 2000 (10)		0	0	0	1	0	0	2 2	0	4 6
13 Morgan et al, 2000 (34) 14 Zambon et al, 2000 (35)		0	0	0	1	0	1	2	0	6
14 Zambon et al, 2000 (33) 15 Rajaram et al, 2001 (14)	$\frac{2}{2}$	0	0	1	1	1	1	2	0	8
$_{16}$ lwamoto et al, 2002 (36)	1	0	2	0	1	1	1	2	0	8
$_{17}^{16}$ Jenkins et al, 2002 (15)	1	Ő	Ō	1	1	Ö	1	2	0	6
17 comme of al, 2002 (10) 18 Lovejoy et al, 2002 (37)	1	1	Ů	0	1	Õ	0	2	0 0	5
19 Sabate et al, 2003 (38)	1	O	Ŏ	Õ	1	Õ	1	2	0 0	5
¹⁹ Wien et al, 2003 (8)	2	0	2	0	1	0	1	2	0	8
20 Tapsell et al, 2004 (39)	1	0	2	1	1	0	0	1	0	6
21 Tamizifar et al, 2005 (40)	1	0	0	0	1	0	1	2	0	5
55 Kocvigit et al. 2006 (16)	1	0	2	0	1	1	1	2	0	8
₂₄ Kurlandsky et al, 2006 (41)	1	0	0	0	1	0	1	2	0	5
$_{25}$ Schutte et al, 2006 (53)	2	0	0	1	1	0	1	2	0	7
26 Mukuddem-Petersen et al, 2007(42)	2	0	0	1	1	0	1	2	0	7
$_{27}$ Sheridan et al, 2007 (17)	1	0	0	1	1	0	1	2	0	6
$_{20}$ Gebauer et al, 2008 (43)	1	0	0	1	1	0	1	1	0	5
$_{20}$ Griel et al, 2008 (44)	1	0	2	0	1	1	1	2	0	8
$_{20}$ Jenkins et al, 2008 (54)	1	0	0	1	1	0	1	2	0	6
$_{21}$ Rajaram et al, 2009 (45)	1	0	0	1	1	0	0	2	0	5
20 Tapsell et al, 2009 (40)	2	0	0	1	1	0	1	2	0	/
$_{22}$ Li el al, 2010 (11)	2	0	0	1	1	0	1	2	0	/
2^{4} Ma et al, 2010 (47)	1	0	0	1	1	0 0	1	1 2	0	5
³⁴ Torabian et al, 2010 (12) 35 Wien et al, 2010 (48) 36 Wienet al, 2010 (40)	1	0	2	1	1	0	1	2	0	6 9
$^{36}_{27}$ Wu et al, 2010 (49)	2	0	2	1	1	0	1	2	0	9
$^{37}_{38}$ Casas-Agustench et al, 2011 (50)	2	0	0	1	1	0	1	2	0	9 6
38 Cohen et al, 2011 (19)	1	0	2	0	1	1	، ١	2	0	7
39 Jenkins et al, 2011 (20)	1	0	2	1	1	0	1	2	0	8
⁴⁰ Li et al, 2011 (21)	1	0	0	0	1	0	1	2	0 0	5
⁴¹ Tey et al, 2011 (51)	2	Ő	2	1	1	õ	1	2	0	9
⁴² DarvishDamavandi et al. 2012 (18)	1	Ő	0	0 0	0 0	õ	1	1	Ő	3
43			-	-	-	-			-	-

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

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

13 * 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 14 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 15 included in the MQS scores (Berryman et al, 2013, Holligan et al, 2013 and Sauder et al, 2013).

¹⁶ † Randomization was scored 2 points for being randomized with the methods described, 1 point for being randomized without the methods ¹⁷ 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 ¹⁸ for "other." Analysis was scored 2 points for being intention-to-treat; all other types of analyses scored 0 points.

¹⁹ \ddagger Sample selection was scored 1 point for being consecutive eligible or 0 points for being preselected or indeterminate. Sample comparability was ²⁰ 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 $\frac{21}{22} < 100\%$.

 $\frac{22}{23}$ § Treatment protocol was scored 1 point for being reproducibly described or 0 points for being poorly described. Co-interventions were scored 2 24 points for being described and equal, 1 point for being described but unequal or indeterminate, or 0 points for not being described. Treatment 25 crossovers (where participants were switched from the control treatment to the experimental treatment) were scored 2 points for being <10%, 1 point 26 for being >10%, and 0 points for not being described.

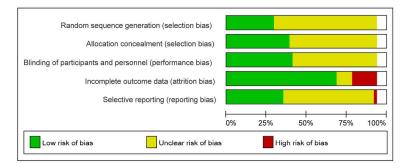
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A. Waist Circumference						D. Systolic Blood Pressure					
Subgroups	No. of Trials	N	β [95% CI]	Residual I ² (%)	P-value	Subgroups	No. of Trials	N	β [95% CI]	Residual I ² (%)	P-va
Nuts Dose (g/day)	15	1050	-0.028 [-0.104, 0.048]	66.4	0.44	Nuts Dose (g/day)	20	1267	-0.085 [-0.186, 0.017]	62.6	0.1
Duration (weeks)	15	1050	-0.152 [-0.347, 0.043]	60.4	0.12	Duration (weeks)	20	1267	-0.043 [-0.166, 0.080]	64.4	0.4
Saturated Fat (%)	13	904	0.259 [-0.262, 0.781]	69.2	0.30	Saturated Fat (%)	18	1058	0.505 [-0.177, 1.186]	64	0.1
Change in Saturated Fat (%)	10	777	0.374 [-1.448, 2.195]	65	0.65	Change in Saturated Fat (%)	13	803	-0.249 [-1.151, 0.653]	49.6	0.5
Difference in Saturated Fat (%)	13	904	0.662 [-1.011, 2.336]	71.4	0.40	Difference in Saturated Fat (%)	18	1058	-1.307 [-2.681, 0.067]	59.8	0.0
Fibre Intake (g/day)	12	882	-0.059 [-0.357, 0.238]	73.4	0.67	Fibre Intake (g/day)	17	1036	-0.187 [-0.470, 0.097]	57	0.:
Change in Fibre Intake (g/day)	8	688	0.020 [-0.430, 0.470]	71.6	0.92	Change in Fibre Intake (g/day)	10	765	-0.071 [-0.382, 0.241]	55.1	0.0
Difference in Fibre Intake (g/day)	13	904	-0.124 [-0.394, 0.145]	70.8	0.33	Difference in Fibre Intake (g/day)	18	1058	-0.353 [-0.695, -0.011]	55.2	0.
Baseline (cm)	11	803	-0.014 [-0.082, 0.055]	73.7	0.66	Baseline (mmHg)	16	1058	-0.112 [-0.398, 0.174]	69.6	0.
Difference in Carbohydrate intake (%/day)	14	964	-0.874 [-0.377, 2.124]	49.7	0.01	Difference in Carbohydrate intake (%/day)	18	1058	0.564 [0.164, 0.963]	55.5	0.0
B. Triglycerides						E. Diastolic Blood Pressure					
Subgroups	No. of Trials	Ν	β [95% CI]	Residual I ² (%)	P-value	Subgroups	No. of Trials	N	β [95% CI]	Residual I ² (%)	P-va
Nuts Dose (g/day)	44	1962	-0.002 [-0.004, 0.001]	39.9	0.05	Nuts Dose (g/day)	20	1267	-0.028 [-0.067, 0.011]	29.6	0.
Duration (weeks)	44	1962	0.002 [-0.001, 0.005]	35.5	0.11	Duration (weeks)	20	1267	0.012 [-0.040, 0.064]	36.1	0.
Saturated Fat (%)	38	1541	0.012 [-0.001, 0.026]	11.9	0.08	Saturated Fat (%)	18	1058	0.118 [-0.154, 0.390]	36.6	0.
Change in Saturated Fat (%)	21	1076	0.023 [-0.010, 0.005]	33.1	0.16	Change in Saturated Fat (%)	13	803	-0.152 [-0.595, 0.291]	27.4	0.
Difference in Saturated Fat (%)	38	1541	0.005 [-0.013, 0.022]	20.8	0.60	Difference in Saturated Fat (%)	18	1058	-0.136 [-0.694, 0.423]	40.6	0.
Fibre Intake (g/day)	33	1353	-0.005 [-0.012, 0.002]	19.7	0.14	Fibre Intake (g/day)	17	1036	-0.067 [-0.173, 0.040]	21.3	0.
Change in Fibre Intake (g/day)	17	865	-0.009 [-0.020, 0.002]	42.1	0.11	Change in Fibre Intake (g/day)	10	765	0.021 [-0.147, 0.189]	46.4	0.
Difference in Fibre Intake (g/day)	34	1408	-0.001 [-0.010, 0.009]	24.9	0.94	Difference in Fibre Intake (g/day)	18	1058	-0.078 [-0.230, 0.074]	37.9	0.
Baseline (mmol/L)	35	1550	0.080 [-0.020, 0.180]	33.9	0.11	Baseline (mmHg)	16	1058	-0.009 [-0.220, 0.202]	45.3	0
Difference in Carbohydrate intake (%/day)	39	1609	0.003 [-0.007, 0.012]	25.0	0.56	Difference in Carbohydrate intake (%/day)	18	1058	0.088 [-0.071, 0.247]	39.5	0
C. High-Density Lipoprotein Cholesterol						F. Fasting Blood Glucose					
Subgroups	No. of Trials	Ν	β [95% CI]	Residual I ² (%)	P-value	Subgroups	No. of Trials	N	β [95% CI]	Residual I ² (%)	P -v
Nuts Dose (g/day)	45	2127	-0.001 [-0.002, 0.001]	85.8	0.42	Nuts Dose (g/day)	26	1319	0.004 [-0.002, 0.011]	44.5	0.
Duration (weeks)	45	2127	0.000 [-0.002, 0.002]	85.8	0.93	Duration (weeks)	26	1319	-0.006 [-0.021, 0.008]	44.6	0
Saturated Fat (%)	39	1730	0.000 [-0.010, 0.010]	84.6	0.99	Saturated Fat (%)	21	1097	0.006 [-0.029, 0.042]	42.5	0
Change in Saturated Fat (%)	22	1265	0.005 [-0.013, 0.022]	84.1	0.57	Change in Saturated Fat (%)	12	895	-0.003 [-0.068, 0.062]	48.3	0
Difference in Saturated Fat (%)	39	1730	0.000 [-0.008, 0.008]	83.2	0.93	Difference in Saturated Fat (%)	21	1097	-0.036 [-0.133, 0.062]	41.2	0
Fibre Intake (g/day)	34	1542	-0.001 [-0.005, 0.004]	88.4	0.76	Fibre Intake (g/day)	19	1040	0.003 [-0.008, 0.014]	43.7	0
Change in Fibre Intake (g/day)	18	1054	0.001 [-0.006, 0.007]	87.5	0.83	Change in Fibre Intake (g/day)	10	731	0.001 [-0.012, 0.015]	22.3	0
Difference in Fibre Intake (g/day)	35	1597	0.003 [-0.002, 0.007]	86.1	0.30	Difference in Fibre Intake (g/day)	20	1062	0.006 [-0.014, 0.026]	42.8	(
Baseline (mmol/L)	37	1692	0.022 [-0.093, 0.137]	87.1	0.70	Baseline (mmol/L)	24	1251	-0.059 [-0.149, 0.031]	45.7	c
Difference in Carbohydrate intake (%/day)	40	1798	0.000 [-0.005, 0.005]	82.2	0.89	Difference in Carbohydrate intake (%/day)	23	1209	0.026 [-0.007, 0.058]	41.1	0

r of participants in each subgroup

Residual 1² was reported as a percent value, where 1² < 50% indicated "moderate" heterogeneity, 1² ≥ 50% indicated "substantial" heterogeneity and ≥ 75% indicated "considerable" heterogeneity. P-value significance for heterogeneity, response to a P < 0.10.

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)

	Nuts	Control	Weight	Mean Difference	
Subgroup and Study, year (Reference)	n	n		(95% CI) in cm	
Otherwise Healthy					
Tey et al, 2011 (49)	32	29	9.10%	0.77 [-0.74, 2.28]	L
Subtotal (95% CI)	32	29	9.10%	0.77 [-0.74, 2.28]	L
Heterogeneity: Not applicable					T
Test for overall effect: Z = 1.00 (P = 0.32)					
Dyslipidemia					
Jenkins et al, 2002 (15)	27	27	7.10%	-1.46 [-3.69, 0.77]	-
Subtotal (95% CI)	27	27	7.10%	-1.46 [-3.69, 0.77]	
Heterogeneity: Not applicable				1000000 • 00000000 000000000	
Test for overall effect: Z = 1.28 (P = 0.20)					
Metabolic Syndrome Criteria					
Schutte et al, 2006 (60)	41	21	2.70%	-0.84 [-5.72, 4.04]	
Wien et al, 2010 (46)	32	33	6.80%	-0.70 [-3.03, 1.63]	
Wu et al, 2010 (47)	94	95	11.10%	0.06 [-0.74, 0.86]	1
Casas-Agustench et al. 2011 (48)	25	25	6.70%	-1.10 [-3.49, 1.29]	
Katz et al, 2012 (51)	40	40	9.60%	-0.20 [-1.55, 1.15]	1
Wang et al. 2012 (22)	56	30	5.00%	0.78 [-2.36, 3.92]	
Somerset et al, 2013 (9)	35	29	2.40%	-8.95 [-14.28, -3.62]	
Tan et al, 2013 (56)	110	27	5.70%	3.68 [0.90, 6.46]	
Gulati et al, 2014 (58)	30	30	9.90%	-1.50 [-2.75, -0.25]	-
Subtotal (95% CI)	353	303	59.90%	-0.44 [-1.58, 0.71]	•
Heterogeneity: Tau ² = 1.62; Chi ² = 23.32, df = 8 (P = 0.003); l ² =	66%				1
Test for overall effect: $Z = 0.75$ (P = 0.45)					
Diabetes					
Wien et al. 2003 (8)	32	33	6.30%	-5.00 [-7.55, -2.45]	
Ma et al, 2010 (45)	22	22	4.30%	-0.30 [-3.85, 3.25]	
Jenkins et al, 2011 (20)	40	39	9.80%	0.81 [-0.48, 2.10]	+
Darvish Damavandi et al, 2012 (18)	22	21	3.50%	-2.10 [-6.26, 2.06]	
Subtotal (95% CI)	116	115	23.90%	-1.57 [-4.68, 1.54]	•
Heterogeneity: Tau ² = 7.82; Chi ² = 16.50, df = 3 (P = 0.0009); l ²	= 82%				
Test for overall effect: Z = 0.99 (P = 0.32)					
Total (95% CI)	528	474	100.00%	-0.62 [-1.54, 0.30]	
Heterogeneity: Tau ² = 1.81; Chi ² = 42.91, df = 14 (P < 0.0001); F	² = 67%				-20 -10 0 10 20
Test for overall effect: Z = 1.33 (P = 0.19)					Favours Nuts Favours Contro
Test for subgroup differences: Chi ² = 3.67, df = 3 (P = 0.30), I ² =	18.2%				Mean Difference (95% CI) in WC, cm

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 (l^2) at a significance level of P < 0.10 and quantified by l^2 , levels $\leq 50\%$ represent moderate heterogeneity, $\geq 50\%$ represent substantial heterogeneity and $\geq 75\%$, considerable heterogeneity. WC = waist circumference, cm = centimeters.

173x176mm (300 x 300 DPI)



Subgroup	Level	Trials	N		м	ean difference (95% CI) in	Waist Circumference, cm			Residual P	P-val
				Within subgroups		E,			Between subgroups		
Fotal		15	1050	-0.62 (-1.54, 0.30)		+					
Nut type	Almonds	4	294	-0.95 (-3.57, 1.68)			_		See legend	67.3%	0.39
	Brazil nuts	0	0			i					
	Cashews	2	74*	-1.53 (-6.42, 3.36)							
	Hazelnuts	1	61	0.77 (-3.93, 5.47)			•				
	Macadamia	1	64	-8.95 (-16.7,-1.23)		•i					
	Pecans	ō	0	0.55 (-10.7, 1125)		·**					
	Pine nuts	0	0								
	Pistachios	2	146	0 61 / 4 10 2 071							
				-0.61 (-4.19, 2.97)							
	Walnuts Mixed nuts	4	282*	-0.12 (-2.95, 2.72)							
	wixed huts	2	129	-0.03 (-3.48, 3.42)							
Nut dose	< 50 g/d	6	544	-0.33 (-2.51, 1.86)			-		-0.59 (-3.37, 2.19)	67.4%	0.65
	≥ 50 g/d	9	506	-0.92 (-2.64, 0.81)		-	-				
Follow up	< 12 weeks	6	331	-0.80 (-3.03, 1.44)					0.15 (-2.69, 2.98)	69.7%	0.91
	≥ 12 weeks	9	719	-0.65 (-2.40, 1.10)			_		,		
	. 764			0.05/15.75.4.50						70.00/	
SFA	< 7%	2	254	-2.06 (-5.76, 1.63)					1.61 (-2.48, 5.71)	70.9%	0.40
	≥ 7%	11	650	-0.45 (-2.22, 1.32)			-0				
FA (chg)	< -2%	2	112	-1.02 (-5.87, 3.84)		· · · · · · · · · · · · · · · · · · ·			0.79 (-4.50, 6.07)	64.8%	0.74
	≥ -2%	8	665	-0.23 (-2.32, 1.86)							
SFA (Δ)	< -1.3%	2	86	-3.62 (-8.48, 1.25)			_		3.19 (-1.93, 8.30)	68.5%	0.19
	≥ -1.3%	11	818	-0.42 (-2.01, 1.16)		· · · · · · · · · · · · · · · · · · ·	-				
Fibre	< 25 g/d	6	399	-0.90 (-3.61, 1.82)					0.11 (-3.61, 3.82)	73.9%	0.95
1016	≥ 25 g/d	6	483	-0.80 (-3.33, 1.73)					0.11 (-3.01, 3.02)	13.370	0.55
	C 23 8/0	0	405	-0.00 (-3.33, 1.73)		1					
ibre (chg)	< 5.3 g/d	7	449	-0.51 (-3.63. 2.62)					0.565 (-7.40. 8.53)	72.1%	0.8
	≥ 5.3 g/d	1	189	0.06 (-7.26, 7.38)			·				
ibre (Δ)	< 3.8 g/d	8	480	-0.24 (-2.21, 1.73)			-		-1.37 (-4.64, 1.91)	70.2%	0.3
	≥ 3.8 g/d	5	424	-1.60 (-4.22, 1.01)							
tudy design	Crossover	3	89	-0.66 (-3.67, 2.36)					-0.06 (-3.45, 3.33)	69.6%	0.9
read acaila	Parallel	12	961	-0.72 (-2.27, 0.83)					0.00 (0.40, 0.00)	051070	0.0
AQS	< 8	9	527	-0.34 (-2.15, 1.47)			_		-0.86 (-3.60, 1.89)	68.9%	0.5
1.45	< 8 ≥ 8	6	527						-0.00 (-3.00, 1.09)	00.370	0.5
	28	0	523	-1.20 (-3.26, 0.87)							
laseline WC	<95 cm	4	396	0.14 (-2.98, 3.26)					-1.97 (-5.97, 2.03)	74.2%	0.2
	≥95 cm	7	407	-1.84 (-4.34, 0.66)			-				
arbohydrates	< 5%	7	467	-0.34 (-2.40, 1.73)			<u>.</u>		-0.91 (-3.81, 1.99)	69.9%	0.5
2)	> 5%	7	497	-1 25 (-3 28, 0 79)			-				
					-15	-5	5	15			
					Favour	s Tree Nuts	Favours Co	ntrol			

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% Cls) 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)

Subgroup	Level	Trials	N		Me	an difference (95% C	1) in Triglycerides, mmol/L		Residual P	P-va
				Within subgroups				Between subgroups	-	
Total		44	1947	-0.06 (-0.09, -0.03)						
Nut type	Almonds	14	612	-0.02 (-0.05, 0.02)			<u> </u>	See legend	0%	<0.0
	Brazil nuts	0	0							
	Cashews	2	75*	-0.08 (-0.28, 0.12)	· · · · · · · · · · · · · · · · · · ·	•				
	Hazelnuts	3	216	0.11 (0.01, 0.21)						
	Macadamia	3	119	-0.10 (-0.18, -0.01)		-+				
	Pecans	2	42	-0.16 (-0.29, -0.02)		+ i				
	Pine nuts	0	0							
	Pistachios	7	313	-0.16 (-0.24, -0.08)		•				
	Walnuts	12	441*	-0.09 (-0.10, -0.08)		· · ·				
	Mixed nuts	2	129	-0.05 (-0.22, 0.12)						
Nut dose	< 50 g/d	18	896	-0.02 (-0.08, 0.03)				-0.06 (-0.13, 0.01)	35.5%	0.0
	≥ 50 g/d	26	1051	-0.08 (-0.13, -0.04)						
Follow up	< 12 weeks	31	1114	-0.07 (-0.11, -0.04)				0.07 (-0.01, 0.15)	31.7%	0.0
	a 12 weeks	13	833	-0.01 (-0.07, 0.06)		+-4				
SFA	< 7%	11	361	-0.07 (-0.15, 0.001)				0.03 (-0.06, 0.12)	22.5%	0.5
	≥ 7%	27	1165	-0.05 (-0.09, -0.002)			-			
SFA (chg)	< -2%	9	334	-0.12 (-0.22, -0.01)	_	i		0.09 (-0.04, 0.23)	32.4%	0.
	≥ -2%	12	727	-0.02 (-0.10, 0.06)		· · · + •				
SFA (Δ)	< -1.3%	16	507	-0.08 (-0.14, -0.01)				0.01 (-0.07, 0.09)	22.4%	0.3
	≥ -1.3%	22	1019	-0.05 (-0.10, 0.001)			-	,		
Fibre	< 25 g/d	13	645	-0.05 (-0.12, 0.03)				-0.01 (-0.10, 0.09)	27.2%	0.9
nore.	≥ 25 g/d	20	708	-0.05 (-0.10, 0.002)			-	0.01 (0.10, 0.00)	271270	0.
Fibre (chg)	< 5.3 g/d	10	673	-0.01 (-0.10, 0.08)				-0.09 (+0.22, 0.05)	48.4%	0.
10.01	≥ 5.3 g/d	7	192	-0.10 (-0.20, -0.001)	-	•	-			
ibre (Δ)	< 3.8 g/d	22	984	-0.04 (-0.09, 0.01)			_	-0.05 (-0.13, 0.04)	25.0%	0.
	≥ 3.8 g/d	12	424	-0.08 (-0.15, -0.02)						
itudy design	Crossover	21	618	-0.08 (-0.12, -0.05)				0.05 (-0.002, 0.11) †	16.1%	0.
	Parallel	23	1329	-0.03 (-0.07, 0.02)		· • •	-			
MQS	< 8	33	1330	-0.05 (-0.09, -0.01)				-0.01 (-0.09, 0.07)	37.3%	0.
	≥8	10	589	-0.06 (-0.14, 0.01)			+			
Baseline TG	<1.7 mmol/L	23	959	-0.07 (-0.13, -0.03)		_		0.00 (-0.06, 0.06)	10.4%	0.
	≥1.7 mmol/L	12	576	0.00 (-0.09, 0.09)			◆ ──			
Carbohydrates	< 5%	21	691	-0.06 (-0.12, -0.01)				0.01 (-0.07, 0.09)	23%	0.
(Δ)	≥ 5%	18	903	-0.05 (-0.10, 0.00)		i •	-			
					-0.3	-0.1	0.1	0.3		
					Favours Tr		Favours Control	0.05.00200		
					ravours fr	ee muts	ravours control			

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)

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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, 1993 (30)	18	18	2.20%	-0.06 [-0.12, -0.00]	
Curb et al, 2000 (10)	30	30	3.10%	-0.01 [-0.05, 0.03]	-
Morgan et al, 2000 (32)	10	9	4.40%	0.01 [0.00, 0.02]	
Rajaram et al, 2001 (14)	23	23	4.10%	0.06 [0.04, 0.08]	-
Iwamoto et al, 2002 (34)	40	40	3.10%	-0.02 [-0.06, 0.02]	
Sabate et al, 2003 (36) Kocylgit et al, 2006 (16)	25 22	25 22	2.20%	0.01 [-0.05, 0.07] 0.19 [0.11, 0.27]	
Kurlandsky et al-Almonds, 2006 (39)	12	12	3.10%	0.04 [0.00, 0.08]	
Kurlandsky et al-Almd+choc, 2006 (39)	12	11	2.20%	-0.07 [-0.13, -0.01]	-
Rajaram et al, 2009 (43)	25	25	2.20%	-0.01 [-0.07, 0.05]	
Torabian et al. 2010 (12)	87	87	4.50%	-0.01 [-0.010.01]	
Tey et al, 2011 (49)	32	29	1.60%	0.04 [-0.04, 0.12]	
Wu et al, 2014 (59)	40	40	1.20%	0.03 [-0.07, 0.13]	
Subtotal (95% CI)	376	371	35.70%	0.01 [-0.01, 0.03]	•
Heterogeneity: Tau ² = 0.00; Chi ² = 103.30, df = 12 (P < 0.00001); l ² = 8 Test for overall effect: Z = 1.07 (P = 0.28)	18%				
Dyslipidemia					
Chisholm et al, 1998 (13)	16	16	4.10%	0.03 [0.01, 0.05]	-
Spiller et al. 1998 (31)	18	12	4.40%	-0.04 [-0.05, -0.03]	-
Zambon et al, 2000 (33)	49	49	2.20%	0.05 [-0.01, 0.11]	
Jenkins et al, 2002 (15)	27	27	2.20%	0.08 [0.02, 0.14]	
Tamizifar et al, 2005 (38) Sheridan et al, 2007 (17)	30 15	30 15	3.10%	-0.13 [-0.17, -0.09] 0.06 [0.02, 0.10]	-
Gebauer et al, 2007 (17)	28	28	0.50%	0.03 [-0.13, 0.19]	
Griel et al, 2008 (42)	25	25	3.10%	-0.05 [-0.09, -0.01]	
Subtotal (95% CI)	208	202	22.90%	-0.00 [-0.04, 0.04]	
Heterogeneity: Tau ² = 0.00; Chi ² = 105.37, df = 7 (P < 0.00001); l ² = 93 Test for overall effect: Z = 0.04 (P = 0.97)	196				Ť
Metabolic Syndrome Criteria					
Mukuddem-Petersen et al, 2007 (40)	42	22	2.20%	-0.08 [-0.14, -0.02]	
Li et al, 2010 (11)	27	25	0.90%	0.09 [-0.03, 0.21]	
Wien et al, 2010 (46)	32	33	0.90%	0.03 [-0.09, 0.15]	
Wu et al, 2010 (47)	94	95	1.20%	0.03 [-0.07, 0.13]	
Casas-Agustench et al, 2011 (48)	25	25	0.90%	0.00 [-0.12, 0.12]	
Foster et al, 2012 (50) Katz et al, 2012 (51)	61 40	62	0.90%	0.06 [-0.06, 0.18] 0.01 [-0.07, 0.09]	
Anderson et al, 2013 (52)	11	11	0.30%	-0.20 [-0.44, 0.04]	
Berryman et al, 2013 (53)	53	53	3.10%	0.05 [0.01, 0.09]	
Somerset et al, 2013 (9)	35	29	0.50%	0.04 [-0.12, 0.20]	
Tan et al, 2013 (56)	23	25	1.20%	-0.11 [-0.21, -0.01]	
Tey et al, 2013 (57)	70	37	2.20%	-0.09 [-0.15, -0.03]	
Gulati et al, 2014 (58)	30	30	2.20%	0.00 [-0.05, 0.06]	
Subtotal (95% CI)	543	487	18.20%	-0.01 [-0.05, 0.03]	•
Heterogeneity: Tau ² = 0.00; Chi ² = 33.96, df = 12 (P = 0.0007); l ² = 65% Test for overall effect: Z = 0.41 (P = 0.68)	16				
Diabetes					
Lovejoy et al-Hing Fat, 2002 (35)	30	30	3.10%	-0.04 [-0.08, -0.00]	-
Lovejoy et al-Low Fat, 2002 (35)	30	30	3.10%	-0.03 [-0.07, 0.01]	-
Wien et al, 2003 (8) Tapsell et al, 2004 (37)	32 17	33 20	1.20%	-0.18 [-0.28, -0.08] -0.03 [-0.25, 0.19]	
Tapsell et al, 2004 (37)	18	17	4.10%	0.00 [-0.02, 0.02]	
Ma et al, 2010 (45)	22	22	1.20%	-0.07 [-0.17, 0.03]	+
Jenkins et al, 2011 (20)	40	39	3.10%	0.02 [-0.02, 0.06]	<u> </u>
Li et al, 2011 (21)	20	20	1.20%	0.01 [-0.09, 0.11]	
Darvish Damavandi et al, 2012 (18)	22	21	0.70%	0.22 [0.08, 0.36]	
Darvish Damavandi et al, 2013 (54)	23	25	1.20%	0.14 [0.04, 0.24]	
Sauder et al, 2013 (55)	28	28	4.10%	0.02 [0.00, 0.04]	-
Subtotal (95% CI)	282	285	23.20%	-0.00 [-0.03, 0.03]	•
Heterogeneity: Tau ² = 0.00; Chi ² = 43.80, df = 10 (P < 0.00001); l ² = 77 Test for overall effect: Z = 0.10 (P = 0.92)	70				
Total (95% CI)	1409	1345	100.00%	0.00 [-0.01, 0.01]	
Heterogeneity: Tau ² = 0.00; Chi ² = 304.77, df = 44 (P < 0.00001); l ² = 8	6%				
Test for overall effect: Z = 0.08 (P = 0.93) Test for substant differences (Chil = 1.72, df = 2.(D = 0.62) 12 = 00/					-0.2-0.1 0 0.1 0.2
Test for subgroup differences: Chi ² = 1.72, df = 3 (P = 0.63), I ² = 0%					Favours Nuts Favours Control Mean Difference
					(95% CI) in HDL-C, mmol/L

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)

Subgroup	Level	Trials	N			Mean differ	ence (95% CI) in H	DL-C, mmol/L			Residual I ²	P-va
				Within subgroups			Ľ.			Between subgroups		
Total		45	2112	0.00 (-0.01, 0.01)			-					
Nut type	Almonds	14	652	-0.02 (-0.05, 0.02)			-			See legend	81.4%	0.6
	Brazil nuts	0	0									
	Cashews	2	75*	0.02 (-0.10, 0.14)								
	Hazelnuts	3	216	0.02 (-0.07, 0.11)								
	Macadamia	3	119	-0.02 (-0.10, 0.07)								
	Pecans	2	42	0.04 (-0.06, 0.12)								
	Pine nuts	0	0									
	Pistachios	7	249	0.05 (-0.01, 0.11)								
	Walnuts	13	630*	-0.01 (-0.05, 0.03)		-	-					
	Mixed nuts	2	129	0.01 (-0.09, 0.12)								
lut dose	< 50 g/d	20	1147	0.01 (-0.03, 0.04)						0.002 (+0.04, 0.05)	85.5%	0.5
	≥ 50 g/d	25	965	0.00 (-0.03, 0.03)								
ollow up	< 12 weeks	33	1189	0.01 (-0.02, 0.03)						-0.01 (-0.07, 0.04)	85.9%	0.3
anna 1917 Ch	≥ 12 weeks	12	923	-0.01 (-0.05, 0.04)		-				and the second sec		
FA	< 7%	12	550	-0.01 (-0.04, 0.06)						0.01 (-0.04, 0.06)	84.2%	0.
	≥ 7%	27	1165	0.00 (-0.03, 0.03)		-						
FA (chg)	< -2%	9	334	0.01 (-0.06, 0.08)						0.01 (-0.06, 0.08)	83.8%	0.
	≥ -2%	13	916	0.03 (-0.02, 0.08)								
FA (Δ)	< -1.3%	16	507	0.01 (-0.03, 0.04)						-0.01 (-0.06, 0.04)	86.7%	0.
	≥ -1.3%	23	1208	-0.01 (-0.04, 0.03)								
ibre	< 25 g/d	13	645	0.02 (-0.03, 0.06)				_		0.03 (-0.08, 0.03)	88.4%	0.4
	≥ 25 g/d	21	897	-0.01 (-0.04, 0.03)			-					
ibre (chg)	< 5.3 g/d	10	673	0.02 (-0.04, 0.08)						0.01 (-0.08, 0.09)	86.9%	0.
	≥ 5.3 g/d	8	381	0.03 (-0.03, 0.09)								
ibre (Δ)	< 3.8 g/d	22	984	-0.01 (-0.04, 0.03)			_			0.02 (-0.03, 0.08)	85.6%	0.
	≥ 3.8 g/d	13	613	0.01 (-0.03, 0.06)			-++-					
tudy design	Crossover	22	671	0.00 (-0.03, 0.03)			_			0.01 (-0.04, 0.05)	85.9%	0.
	Parallel	23	1441	0.01 (-0.03, 0.04)						2000 Control (1977)		
1QS	< 8	32	1253	-0.01 (-0.03, 0.02)			-			0.02 (-0.03, 0.07)	84.1%	0.
	≥8	11	778	0.02 (-0.03, 0.06)			-++-	-				
aseline HDL-C	<1.15 mmol/L	10	444	0.00 (-0.05, 0.05)		-		-		0.00 (-0.06, 0.06)	87.4%	0.
	≥1.15 mmol/L	27	1233	0.00 (-0.03, 0.03)			-					
arbohydrates	< 5%	22	880	-0.01 (-0.03, 0.02)			-			0.02 (-0.02, 0.06)	82.4%	0.
Δ)	≥ 5%	18	903	0.01 (-0.03, 0.04)								
					-0.2	-0.1	0	0.1	0.2			
						Favours Control	,	Favours Tree Nu				
						ravours control		ravours Tree Nu	its			

Appendix Figure 6	Forest plot of subgrou	p analyses for categorica	I variables for HDL-C.
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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.

Subgroup and Study, year (Reference)	Nuts n	Control	Weight	Mean Difference (95% Cl) in mmHg	
Otherwise Healthy					1
Sabate et al, 1993 (30)	18	18	6.60%	2.00 [-0.94, 4.94]	+
wamoto et al, 2002 (34)	40	40	4.70%	2.50 [-2.48, 7.48]	
Subtotal (95% CI)	58	58	11.40%	2.13 [-0.40, 4.66]	•
Heterogeneity: Tau ² = 0.00; Chi ² = 0.03, df = 1 (P = 0.87); l ² = 0%					
est for overall effect: Z = 1.65 (P = 0.10)					
Dyslipidemia					
enkins et al, 2002 (15)	27	27	3.90%	-1.90 [-7.92, 4.12]	
Sheridan et al, 2007 (17)	15	15	3.00%	2.70 [-4.79, 10.19]	
Vest et al, 2012 (62)	28	28	5.30%	-0.40 [-4.71, 3.91]	
Subtotal (95% CI)	70	70	12.20%	-0.26 [-3.43, 2.91]	◆
Heterogeneity: Tau ² = 0.00; Chi ² = 0.89, df = 2 (P = 0.64); l ² = 0%					
est for overall effect: Z = 0.16 (P = 0.87)					
letabolic Syndrome Criteria					
/lukuddem-Petersen et al, 2007 (40)	42	22	6.30%	-1.86 [-5.17, 1.45]	
Vien et al, 2010 (46)	32	33	3.80%	-0.90 [-7.00, 5.20]	
Vu et al, 2010 (47)	94	95	6.10%	-1.22 [-4.71, 2.27]	
asas-Agustench et al, 2011 (48)	25	25	3.30%	4.20 [-2.68, 11.08]	
oster et al, 2012 (50)	61	62	4.20%	0.40 [-5.26, 6.06]	
Catz et al, 2012 (51)	40	40	4.90%	-3.50 [-8.24, 1.24]	
Vang et al, 2012 (22)	56	30	6.80%	-2.54 [-5.36, 0.28]	
Somerset et al, 2013 (9)	35	29	2.30%	3.60 [-5.61, 12.81]	
an et al, 2013 (56)	110	27	6.70%	6.27 [3.37, 9.17]	
ey et al, 2013 (57)	70	37	6.10%	-0.59 [-4.04, 2.86]	
Subtotal (95% CI)	565	400	50.50%	0.11 [-2.22, 2.43]	•
leterogeneity: Tau² = 8.55; Chi² = 27.04, df = 9 (P = 0.001); l² = € Fest for overall effect: Z = 0.09 (P = 0.93)	67%				
Diabetes					
Vien et al, 2003 (8)	32	33	4.00%	-11.00 [-16.88, -5.12]	
Aa et al, 2010 (45)	22	22	3.80%	8.90 [2.77, 15.03]	
enkins et al. 2011 (20)	40	39	6.50%	-0.68 [-3.78, 2.42]	
i et al, 2011 (21)	20	20	5.50%	-1.50 [-5.58, 2.58]	-+-
Sauder et al, 2013 (55)	28	28	6.20%	0.20 [-3.21, 3.61]	
subtotal (95% CI)	142	142	26.00%	-0.83 [-5.25, 3.58]	-
Heterogeneity: Tau ² = 20.04; Chi ² = 21.61, df = 4 (P = 0.0002); l ²			0	1.11 [0.20, 0.00]	
First for overall effect: $Z = 0.37$ (P = 0.71)	0170				
otal (95% CI)	835	670	100.00%	0.07 [-1.54, 1.68]	♦
Heterogeneity: Tau ² = 7.92; Chi ² = 52.90, df = 19 (P < 0.0001); I ²	= 64%				-20 -10 0 10 20
Test for overall effect: Z = 0.09 (P = 0.93)					Favours Nuts Favours Contr
est for subgroup differences: Chi ² = 2.26, df = 3 (P = 0.52), l ² = 0	0%				Mean Difference
					(95% CI) in SBP, mmHg

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 (12) at a significance level of P < 0.10 and quantified by 1^{2} , levels $\leq 50\%$ represent moderate heterogeneity, $\geq 50\%$ represent substantial heterogeneity and $\geq 75\%$, 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.

Subgroup and Study, year (Reference)	Nuts n	Control	Weight	Mean Difference (95% Cl) in mmHg	
Otherwise Healthy					1
Sabate et al, 1993 (30)	18	18	21.90%	0.00 [-0.04, 0.04]	+
wamoto et al, 2002 (34)	40	40	3.30%	1.50 [-1.62, 4.62]	
Subtotal (95% CI)	58	58	25.20%	0.00 [-0.04, 0.04]	
Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 1 (P = 0.35) Test for overall effect: Z = 0.01 (P = 0.99)	; ² = 0%				
Dyslipidemia					
Jenkins et al, 2002 (15)	27	27	3.20%	-0.37 [-3.53, 2.79]	
Sheridan et al, 2007 (17)	15	15	1.30%	2.40 [-2.72, 7.52]	
West et al, 2012 (62)	28	28	6.80%	0.20 [-1.74, 2.14]	-
Subtotal (95% CI)	70	70	11.30%	0.27 [-1.31, 1.84]	+
Heterogeneity: Tau ² = 0.00; Chi ² = 0.83, df = 2 (P = 0.66)	$ ^2 = 0\%$				T
Test for overall effect: Z = 0.33 (P = 0.74)					
Metabolic Syndrome Criteria					
Mukuddem-Petersen et al, 2007 (40)	42	22	4.10%	-0.17 [-2.89, 2.55]	
Wien et al, 2010 (46)	32	33	1.90%	1.00 [-3.23, 5.23]	
Wu et al, 2010 (47)	94	95	6.40%	-0.23 [-2.25, 1.79]	
Casas-Agustench et al, 2011 (48)	25	25	2.00%	1.60 [-2.54, 5.74]	
Foster et al, 2012 (50)	61	62	3.50%	2.00 [-0.98, 4.98]	
Katz et al, 2012 (51)	40	40	0.90%	-2.80 [-8.99, 3.39]	
Wang et al, 2012 (22)	56	30	0.30%	-0.69 [-11.82, 10.44]	
Somerset et al, 2013 (9)	35	29	1.90%	-2.83 [-7.04, 1.38]	
Tan et al, 2013 (56)	110	27	5.60%	3.79 [1.56, 6.02]	
Tey et al, 2013 (57)	70	37	7.20%	0.07 [-1.79, 1.93]	
Subtotal (95% CI)	565	400	33.80%	0.64 [-0.60, 1.89]	•
Heterogeneity: Tau ² = 1.28; Chi ² = 13.91, df = 9 (P = 0.13	3); I² = 35%				-
Test for overall effect: Z = 1.02 (P = 0.31)					
Diabetes					
Wien et al, 2003 (8)	32	33	6.70%	-1.00 [-2.96, 0.96]	
Vla et al, 2010 (45)	22	22	3.20%	4.10 [0.92, 7.28]	
Jenkins et al, 2011 (20)	40	39	7.20%	-1.01 [-2.87, 0.85]	
_i et al, 2011 (21)	20	20	3.60%	-2.20 [-5.14, 0.74]	
Sauder et al, 2013 (55)	28	28	9.10%	0.00 [-1.55, 1.55]	
Subtotal (95% CI)	142	142	29.70%	-0.21 [-1.76, 1.33]	•
Heterogeneity: Tau² = 1.81; Chi² = 10.17, df = 4 (P = 0.04 Test for overall effect: Z = 0.27 (P = 0.79)	4); I² = 61%				
Total (95% CI)	835	670	100.00%	0.23 [-0.38, 0.83]	•
Heterogeneity: Tau² = 0.44; Chi² = 28.69, df = 19 (P = 0.0	07); l² = 34%				-10 -5 0 5 10
Test for overall effect: Z = 0.73 (P = 0.47)					Favours Nuts Favours Cont
Test for subgroup differences: Chi ² = 1.22, df = 3 (P = 0.7	75), I² = 0%				Mean Difference
					(95% CI) in DBP, mmHg

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 (l^2) at a significance level of P < 0.10 and quantified by l^2 , levels $\leq 50\%$ represent moderate heterogeneity, $\geq 50\%$ representing substantial heterogeneity and $\geq 75\%$, considerable heterogeneity. DBP = Diastolic Blood Pressure, mmHg = millimeters of mercury.

173x197mm (300 x 300 DPI)

- 2 3 4 5 6 7 8 9 10 1 12 13 14 5 6 17 8 9 10 1 12 13 14 5 6 7 8 9 10 1 12 13 14 5 6 7 8 9 10 1 12 13 14 5 6 7 8 9 20 12 23 24 5 26 7 28 29 30 1 32 3 34 5 6 7 8 9 40 10 10 10 10 10 10 10 10 10 10 10 10 10	
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Nut dose follow up sFA sFA (chg)	Almonds Brazil nuts Cashews Hazelnuts Macadamia Piecans Pistachios Walnuts Mixed nuts Mixed nuts S0g/d ≥ 50g/d <12 weeks ≥ 12 weeks ≥ 12 weeks ≥ 12 weeks	20 6 0 1 1 0 0 4 6 2 6 14 12 8 5	1267 437 0 32* 107 64 0 157 341* 129 562 705 503 764	Within subgroups 0.07 (-1.54, 1.69) -2.87 (-6.87, 1.14) -4.22 (-1.48, 6.38) -0.59 (-5.15, 6.38) -0.59 (-5.15, 6.38) -0.59 (-5.15, 6.58) -0.55 (-5.08, 4.37) 1.42 (-2.81, 5.65) 1.19 (-5.68, 6.07) -2.21 (-1.06, 5.48) -0.74 (-2.75, 1.27) 1.02 (-1.60, 3.64) -1.58 (-4.23, 3.64)			+		• -	_		Between subgroups See legend -2.95(-6.79, 0.88)	- 72.8% 59.4%	0.949
lut type lut dose follow up iFA	Brazil nuts Cashews Hazelnuts Macadamia Pecans Pistachios Walnuts Mixed nuts < 50 g/d ≥ 50 g/d < 12 weeks ≥ 12 weeks < 7%	6 0 1 1 1 0 4 6 2 6 14 12 8 6	437 0 32* 107 64 0 157 341* 129 562 705 503	-2.87 (-6.87, 1.14) -4.22 (-14.83, 6.38) -0.59 (-5.1, 8.33) 3.6 (-9.42, 16.62) -0.35 (-5.08, 4.37) 1.42 (-2.81, 5.65) 1.19 (-5.68, 8.07) 2.21 (-1.06, 5.48) -0.74 (-2.75, 1.27) 1.02 (-1.60, 3.64)		-	-		• •	_				
Nut dose follow up sFA sFA (chg)	Brazil nuts Cashews Hazelnuts Macadamia Pecans Pistachios Walnuts Mixed nuts < 50 g/d ≥ 50 g/d < 12 weeks ≥ 12 weeks < 7%	0 1 1 0 0 4 6 2 6 14 12 8 6	0 32* 107 64 0 157 341* 129 562 705 503	-4.22 (-14.83, 6.38) -0.59 (-5.51, 8.33) 3.6 (-9.42, 16.62) -0.35 (-5.08, 4.37) 1.42 (-2.81, 5.65) 1.19 (-5.68, 8.07) 2.21 (-1.06, 5.48) -0.74 (-2.75, 1.27) 1.02 (-1.60, 3.64)		=			• =					
Nut dose follow up sFA sFA (chg)	Brazil nuts Cashews Hazelnuts Macadamia Pecans Pistachios Walnuts Mixed nuts < 50 g/d ≥ 50 g/d < 12 weeks ≥ 12 weeks < 7%	1 1 0 4 6 2 6 14 12 8 6	32* 107 64 0 157 341* 129 562 705 503	-0.59 (-9.51, 8.33) 3.6 (-9.42, 16.62) 1.42 (-2.81, 5.65) 1.19 (-5.68, 8.07) 2.21 (-1.06, 5.48) -0.74 (-2.75, 1.27) 1.02 (-1.60, 3.64)		=	-		• 	_		-2.95(-6.79, 0.88)	59.4%	0.123
tut dose follow up sFA sFA (chg)	HazeInuts Macadamia Pecans Pine nuts Pistachios Walnuts Mixed nuts <50 g/d <12 weeks ≥12 weeks <7%	1 0 4 6 2 6 14 12 8 6	107 64 0 157 341* 129 562 705 503	-0.59 (-9.51, 8.33) 3.6 (-9.42, 16.62) 1.42 (-2.81, 5.65) 1.19 (-5.68, 8.07) 2.21 (-1.06, 5.48) -0.74 (-2.75, 1.27) 1.02 (-1.60, 3.64)		=	• 	•	• 	_		-2.95(-6.79, 0.88)	59.4%	0.123
Nut dose Fállow up Fá A	Macadamia Pecans Pine nuts Pistachios Walnuts Mixed nuts < 50 g/d ≥ 50 g/d < 12 weeks ≥ 12 weeks < 7%	1 0 4 6 2 6 14 12 8 6	64 0 157 341* 129 562 705 503	3.6 (-9.42, 16.62) -0.35 (-5.08, 4.37) 1.42 (-2.81, 5.65) 1.19 (-5.68, 8.07) 2.21 (-1.06, 5.48) -0.74 (-2.75, 1.27) 1.02 (-1.60, 3.64)		_	_		• 	-		-2.95(-6.79, 0.88)	59.4%	0.123
Nut dose follow up IFA IFA (chg)	Pecans Pine nuts Pistachios Walnuts Mixed nuts < 50 g/d < 12 weeks ≥ 12 weeks < 7%	0 4 6 2 6 14 12 8 6	0 0 157 341* 129 562 705 503	-0.35 (-5.08, 4.37) 1.42 (-2.81, 5.65) 1.19 (-5.68, 8.07) 2.21 (-1.06, 5.48) -0.74 (-2.75, 1.27) 1.02 (-1.60, 3.64)					• 		_	-2.95(-6.79, 0.88)	59.4%	0.12
lut dose fallow up IFA FA (chg)	Pine nuts Pistachios Walnuts Mixed nuts < 50 g/d ≥ 50 g/d < 12 weeks ≥ 12 weeks < 7%	0 4 6 2 6 14 12 8 6	0 157 341* 129 562 705 503	1.42 (-2.81, 5.65) 1.19 (-5.68, 8.07) 2.21 (-1.06, 5.48) -0.74 (-2.75, 1.27) 1.02 (-1.60, 3.64)						-,		-2.95(-6.79, 0.88)	59.4%	0.12
Nut dose Follow up FA FA (chg)	Pistachios Walnuts Mixed nuts < 50 g/d ≥ 50 g/d < 12 weeks ≥ 12 weeks < 7%	4 6 14 12 8 6	157 341* 129 562 705 503	1.42 (-2.81, 5.65) 1.19 (-5.68, 8.07) 2.21 (-1.06, 5.48) -0.74 (-2.75, 1.27) 1.02 (-1.60, 3.64)						-		-2.95(-6.79, 0.88)	59.4%	0.12
Nut dose Follow up SFA SFA (chg)	Walnuts Mixed nuts < 50 g/d ≥ 50 g/d < 12 weeks ≥ 12 weeks < 7%	6 2 14 12 8 6	341* 129 562 705 503	1.42 (-2.81, 5.65) 1.19 (-5.68, 8.07) 2.21 (-1.06, 5.48) -0.74 (-2.75, 1.27) 1.02 (-1.60, 3.64)			_					-2.95(-6.79, 0.88)	59.4%	0.12
Nut dose Follow up FA FA (chg)	Mixed nuts < 50 g/d ≥ 50 g/d < 12 weeks ≥ 12 weeks < 7%	2 6 14 12 8 6	129 562 705 503	1.19 (-5.68, 8.07) 2.21 (-1.06, 5.48) -0.74 (-2.75, 1.27) 1.02 (-1.60, 3.64)				+				-2.95(-6.79, 0.88)	59.4%	0.12
Nut dose Follow up IFA IFA (chg)	< 50 g/d ≥ 50 g/d < 12 weeks ≥ 12 weeks < 7%	6 14 12 8 6	562 705 503	2.21 {-1.06, 5.48} -0.74 (-2.75, 1.27) 1.02 {-1.60, 3.64}						-		-2.95(-6.79, 0.88)	59.4%	0.12
Follow up FA FA (chg)	≥ 50 g/d < 12 weeks ≥ 12 weeks < 7%	14 12 8 6	705 503	-0.74 (-2.75, 1.27) 1.02 (-1.60, 3.64)				-				-2.95(-6.79, 0.88)	59.4%	0.123
Follow up FA FA (chg)	< 12 weeks ≥ 12 weeks < 7%	12 8 6	503	1.02 (-1.60, 3.64)										
iFA iFA (chg)	≥ 12 weeks < 7%	8												
FA FA (chg)	< 7%	6	764	-1.58 (-4.23, 1.08)								-2.78 (-6.24, 0.67)	58.6%	0.10
FA (chg)														
FA (chg)	≥ 7%		360	-1.06 (-4.35, 2.23)								2.09 (-2.06, 6.23)	66.2%	0.302
		12	698	1.03 (-1.49, 3.54)				-i+	-					
	< -2%	6	225	0.61 (-2.30, 3.52)								-1.22 (-3.76, 4.01)	49.7%	0.946
	≥ -2%	7	668	0.73 (-1.85, 3.31)				-	-					
iFA (Δ)	< -1.3%	5	159	3.67 (-0.09, 7.42)				į.				-4.41 (-8.69, -0.13)*	61.7%	0.044
	≥ -1.3%	13	899	-0.75 (-2.79, 1.29)				-++-						
ibre	< 25 g/d	6	396	2.26 (-0.90, 5.41)				1				-3.30 (-7.05, 0.44)	51.3%	0.075
	≥ 25 g/d	11	640	-1.05 (-3.07, 0.97)				++ `						
ibre (chg)	< 5.3 g/d	6	502	1.83 (-1.17, 4.84)				1.				-1.91 (-6.57, 2.75)	49.1%	0.372
	≥ 5.3 g/d	4	260	-0.08 (-3.64, 3.48)			-	•	-					
ibre (Δ)	< 3.8 g/d	12	632	1.34 (-0.96, 3.63)				1.				-3.28 (-7.28, 0.71)	60.9%	0.10
	≥ 3.8 g/d	6	426	-1.94 (-5.21, 1.33)			_	•						
itudy design	Crossover	9	238	0.77 (-1.98, 3.52)				i				-1.24 (-4.91, 2.44)	65.4%	0.48
	Parallel	11	1029	-0.47 (-2.91, 1.97)				-						
	~ 9	12	614	0.72 (-1.64, 3.08)				-	-			-1.92 (-5.98, 2.14)	66.2%	0.333
	≥8	7	625	-1.20 (-4.50, 2.10)			_	•						
Baseline SBP	<130 mmHg	10	647	0.55 (-2.35, 3.45)					_			-1.06 (-5.98, 3.86)	70.8%	0.65
	≥130 mmHg	6	411	-0.51 (-4.49, 3.47)			-		-					
Carbohydrates (Δ)	< 5%	9	466	1.09 (-1.76, 3.94)								-1.67 (-5.72, 2.38)	67.4%	0.39
	≥ 5%	9	592	-0.59 (-3.46, 2.29)			-	-						
					-15	-10	-5	0	5	10	15			

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)

Pressure	Э.								
Subgroup	Level	Trials	N		Mean difference	(95% CI) in Diastolic Blo	od Pressure, mmHg		Resid
				Within subgroups		. 1		Between subgroups	
Total		20	1267	0.64 (-0.60, 1.89)		-++			
Nut type	Almonds	6	437	0.57 (-1.20, 2.33)				See legend	48
	Brazil nuts	0	0			1			
	Cashews Hazelnuts	1	32* 107	-0.27 (-5.21, 4.67)					
	Macadamia	1	107	0.07 (-3.55, 3.69) -2.83 (-8.35, 2.69)			_		
	Pecana	0	04	-2.03 (-0.35, 2.09)	-	• i	-		
	Pine nuts	0	0						
	Pistachios	4	157	0.37 (-1.93, 2.66)		_	-		
	Walnuts	6	341*	0.67 (-1.16, 2.50)					
	Mixed nuts	2	129	-0.21 (-3.23, 2.81)			-		
Nut dose	< 50 g/d	6	562	0.86 (-0.58, 2.31)		1		-0.84 (-2.50, 0.82)	31
	≥ 50 g/d	14	705	0.02 (-0.80, 0.85)					
Follow up	< 12 weeks	12	503	0.44 (-0.53, 1.41)				-0.49 (42, 0.95)	3
ronow up	≥ 12 weeks	8	764	-0.05 (-1.30, 1.21)				-0.43 (42, 0.33)	
SFA	< 7%	6	360	-0.25 (-1.37, 0.86)		_ i		0.85 (-0.71, 2.41)	3
	≥ 7%	12	698	0.61 (-0.49, 1.71)		-			
SFA (chg)	< -2%	6	225	0.50 (-0.98, 1.99)				-0.27 (-2.26, 1.72)	30
	> -2%	7	668	0.24 (-1.08, 1.56)					
SFA (Δ)	< -1.3%	5	159	0.74 (-0.85, 2.33)				-0.73 (-2.60, 1.13)	40
5FA (6)	≥ -1.3%	13	899	0.01 (-0.97, 0.98)				-0.75 (-2.00, 1.15)	40
Fibre	<25 g/d	6	396	1.66 (0.11, 3.21)		++		-1.66 (-3.21, -0.11)†	1
	≥ 25 g/d	11	640	-0.01 (-0.05, 0.04)		+			
Fibre (chg)	< 5.3 g/d	6	502	0.55 (1.19, 2.30)				0.36 (-2.95, 2.23)	4
	≥ 5.3 g/d	4	260	0.20 (-1.72, 2.11)					
Fibre (Δ)	< 3.8 g/d	12	632	0.33 (-0.67, 1.33)				-0.43 (-2.19, 1.33)	4
ribic (d)	≥ 3.8 g/d	6	426	-0.10 (-1.54, 1.35)				0.45 (2.25, 2.55)	
						11			
Study design	Crossover	9	238	0.24 (-0.85, 1.33)				0.03 (-1.51, 1.57)	3
	Parallel	11	1029	0.27 (-0.82, 1.36)					
MQS	< 8	12	614	0.59 (-0.47, 1.65)		_ _		-0.77 (-2.49, 0.96)	4
	≥ 8	7	625	-0.18 (-1.54, 1.19)		-++			
Baseline DBP	<85 mmHg	10	647	-0.13 (-1.13, 0.86)				2.21 (-0.35, 4.78)	28
baseline DbP	<s5 mmhg<br="">≥85 mmHg</s5>	6	411	2.08 (-0.29, 4.44)				2.21 (-0.35, 4.78)	2
	_								
Carbohydrates (Δ)	< 5%	9	466	0.51 (-0.67, 1.68)				-0.61 (-2.27, 1.05)	40
	> 5%	9	592	-0.10 (-1.27, 1.07)					

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 I² value indicates the interstudy heterogeneity unexplained by the subgrouping. Pairwise betweensubgroup 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).

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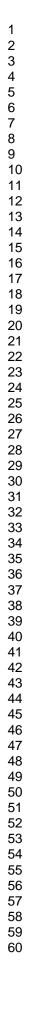
		Trials	N		Residual I ²	P-value		
				Within subgroups	Τ.	Between subgroups	-	
otal	141	26	1319	-0.06 (-0.17, 0.06)	+			
ut type	Almonds	9	382	-0.05 (-0.19, 0.09)		See legend	39.7%	0.18
	Brazil nuts	0	0					
	Cashews	2	73	0.36 (-0.32, 1.05)				
	Hazelnuts	1	48	-0.92 (-2.18, 0.37)	+			
	Macadamia	1	64	0.31 (-0.16, 0.78)	++++			
	Pecans	0	0					
	Pine nuts	0	0		i			
	Pistachios	6	265	-0.15 (-0.28, -0.02)	-+-			
	Walnuts	6	356*	0.02 (-0.17, 0.21)				
	Mixed nuts	2	129	-0.07 (-0.36, 0.22)				
ut dose	< 50 g/d	10	630	-0.06 (-0.21, 0.10)	<u> </u>	-0.01 (-0.20, 0.18)	47.2%	0.93
	≥ 50 g/d	16	689	-0.06 (-0.18, 0.05)	+			
sllow up	< 12 weeks	16	625	-0.03 (-0.10, 0.05)	4	-0.13 (-0.29, 0.02)	40.3%	0.08
	≥ 12 weeks	10	694	-0.16 (-0.29, -0.03)	- + i			
A	< 7%	6	332	-0.11 (-0.30, 0.08)		0.11 (-0.10, 0.31)	39.4%	0.2
	≥ 7%	15	765	-0.01 (-0.09, 0.08)				
A (chg)	< -2%	5	203	-0.01 (-0.15, 0.14)		-0.01 (-0.21, 0.18)	48.2%	0.8
	≥ -2%	9	692	-0.02 (-0.15, 0.11)				
Α (Δ)	< -1.3%	4	161	0.04 (-0.21, 0.29)		-0.07 (-0.33, 0.19)	42.1%	0.59
	≥ -1.3%	17	936	-0.03 (-0.11, 0.05)				
bre	< 25 g/d	8	487	-0.03 (-0.15, 0.09)		0.01 (-0.15, 0.17)	44.6%	0.89
	≥ 25 g/d	11	553	-0.02 (-0.13, 0.09)	T			
bre (chg)	< 5.3 g/d	7	486	-0.03 (-0.16, 0.09)		0.01 (-0.18, 0.19)	22.7%	0.9
ore (eng)	≥ 5.3 g/d	3	245	-0.03 (-0.16, 0.11)	—	0.01 (0.10) (0.10)	6.6.17.79	
bre (Δ)	< 3.8 g/d	12	580	-0.03 (-0.11, 0.05)		0.05 (-0.18, 0.28)	43.2%	0.6
	≥ 3.8 g/d	8	482	0.02 (-0.19, 0.24)				
udy design	Crossover	10	260	-0.03 (-0.15, 0.10)	i	-0.07 (-0.24, 0.10)	45.3%	0.4
	Parallel	16	1059	-0.10 (-0.22, 0.02)		0.0.1, 0.0.101		2.4
IQS	< 8	19	801	-0.09 (-0.20, 0.03)	3	0.13 (-0.16, 0.41)	49.5%	0.3
45	28	5	462	0.04 (-0.22, 0.30)	<u> </u>	5.15(-0.10, 0.41)	-2.376	0.5
seline FBG	<5.55 mmol/L	9	553	-0.03 (-0.18, 0.12)		-0.08 (-0.30, 0.15)	49.8%	0.4
	≥5.55 mmol/L	15	698	-0.11 (-0.23, 0.06)		0.00 (-0.50, 0.15)		0.4
		15						
arbohydrates (۵)	< 5%	10	499	0.04 (-0.13, 0.21)	ile .	-0.11 (-0.31, 0.09)	45.1%	0.2
	≥ 5%	13	710	-0.07 (-0.18, 0.04)				
					2 -1 0 1	2		

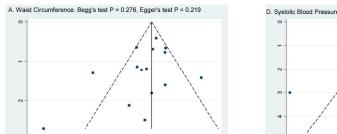
Appendix Figure 9. Forest plot of subgroup analyses for categorical variables for Fasting Blood

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.

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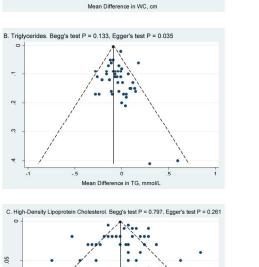






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Appendix Figure 10. Funnel plots for evidence of publication bias.



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Mean Difference in HDL-C, mmol/L

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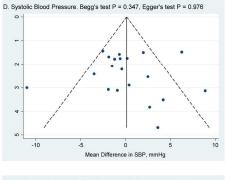
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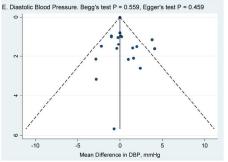
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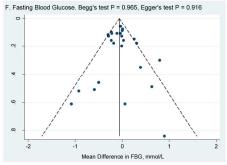
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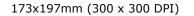
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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
2 Structured summary 3 1	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
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.	
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.	
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.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
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).	
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.	
) Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
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.	
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. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	6



PRISMA 2009 Checklist

Page 1 of 2 Reported							
Section/topic	#	# Checklist item					
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).					
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.					
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.					
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	24 Summarize the main findings including the strength of evidence for each main outcome; consider their relevance the key groups (e.g., healthcare providers, users, and policy makers).					
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. 43 doi:10.1371/journal.pmed1000097

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