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Effect of tree nuts on metabolic syndrome criteria: a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

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

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

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

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

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

Results: Eligibility criteria were met by 49 RCTs including 2226 participants who were otherwise healthy or had dyslipidaemia, MetS or type 2 diabetes mellitus. Tree nut interventions lowered triglycerides (MD=−0.06 mmol/L (95% CI −0.09 to −0.03 mmol/L)) and fasting blood glucose (MD=−0.08 mmol/L (95% CI −0.16 to −0.01 mmol/L)) compared with control diet interventions. There was no effect on waist circumference, high-density lipoprotein cholesterol or blood pressure with the direction of effect favouring tree nuts for waist circumference. There was evidence of significant unexplained heterogeneity in all analyses (p<0.05).

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

Trial registration number: NCT01630980.

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 (49 randomised controlled trials) in participants with a range of metabolic phenotypes.
- Most of the trials (74.4%) were of low quality (Methodological Quality Score (MQS) <8).
- Most of the trials (68.8%) were of short duration (<12 weeks).
- Substantial interstudy heterogeneity remained unexplained.

INTRODUCTION

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

Although these recommendations are based primarily on the low-density lipoprotein cholesterol (LDL-C)-lowering benefits of tree nuts,[4] the cardiovascular risk reduction seen with tree nuts is beyond that which would be predicted by this effect alone. The Prevención con Dieta Mediterránea (PREDIMED) trial showed that despite a non-significant effect on LDL-C early on in the trial,[5] a Mediterranean diet supplemented with mixed nuts (30 g/day) compared

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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, metabolic syndrome (MetS) and type 2 diabetes mellitus.[7] Individual large trials of tree nuts have also shown that nuts improve criteria of the MetS: waist circumference,[8 9] triglycerides,[5 10–12] high-density lipoprotein cholesterol (HDL-C),[13–18] blood pressure (BP)[5 8] and glycaemic 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 (CDA) 2013 clinical practice guidelines for nutrition therapy[23] did acknowledge some of these metabolic benefits, the evidence was deemed insufficient for making a recommendation. Tree nuts consumption was recommended only insofar as it was part of Mediterranean or DASH dietary patterns.[23] To synthesise 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 randomised controlled dietary trials of the effect of tree nuts on criteria of the MetS.

METHODS

Protocol and registration

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

Study selection

We searched MEDLINE, EMBASE, CINAHL and the Cochrane Library (through 4 April 2014) to identify randomised controlled dietary trials of tree nuts. Details of the search strategy are presented in online supplementary 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 randomised dietary trials that reported the effect of diets rich in tree nuts (almonds, Brazil nuts, cashews, hazelnuts, macadamia nuts, pecans, pine nuts, pistachios, walnuts and mixed nuts)[1] as a whole compared with diets without tree nuts, but matched for energy on at least one of the five criteria of the MetS: waist circumference, triglycerides, HDL-C, BP and fasting blood glucose. Included trials were ≥3 weeks' duration, a duration that satisfies the minimum follow-up requirement for lipid-lowering health claims by the FDA used in the scientific evaluation of lipid-lowering health claims.[26] We excluded trials that incorporated tree nuts as paste, oil or skin nuts into the treatment diets and also those trials that added tree nuts as part of a dietary pattern and did not have a matched control group. The former exclusion was intended to eliminate contamination from the other nutritional aspects, and to isolate the effect of tree nuts. Where multiple intervention or control groups were presented, we only included those groups which allowed us to isolate the effect of tree nuts. When multiple 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 end points were selected according to the 2009 harmonised definition for MetS.[27]

Data extraction

Studies that met the inclusion criteria were extracted in full by two independent reviewers (SBM and one of EV, LSA, VH or AM) for study characteristics and data for end points. Study characteristics included: study design (cross-over 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 among reviewers were resolved by consensus.

The Heyland Methodological Quality Score (MQS) was used for assessment of study quality.[28] Scores from 0 to 2 points were given for each of the following evaluated criteria: methods (randomisation, blinding and analysis), sample (selection, compatibility and follow-up) and intervention (protocol, cointervention and cross-overs). 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 judgement, '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 randomised 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 emphasised 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.

Means (SD) for baseline values, end values, change from baseline differences, end differences and mean differences (MD) were recorded for primary end points (waist circumference, triglycerides, HDL-C, BP and fasting blood glucose). Reported t values or F statistics and p values for differences were also recorded. Missing information for any end point data or study details was

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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-analysed 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 BP, 0.508 for diastolic BP and 0.446 for fasting blood glucose.

Statistical analyses

Data were analysed using Review Manager (RevMan) 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) for primary analyses and Stata (V.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 MD with 95% CI and considered significant at $p<0.05$. Paired analyses were applied to all cross-over trials.[29] In cases where there were multiple intervention or control groups, we combined either intervention or control groups to create single pairwise comparisons with the aim of diminishing the unit-of-analysis error.[24]

The presence of between-studies heterogeneity was assessed by the Cochran Q statistic (significance set at $p<0.10$) and quantified by the I^2 statistic. We interpreted the I^2 statistic as follows: <50% indicates 'moderate' heterogeneity; ≥50%, 'substantial' heterogeneity; and ≥75%, 'considerable' heterogeneity.[24] Analyses were stratified by participant health status: otherwise healthy, dyslipidaemia, MetS criteria and type 2 diabetes mellitus 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 recalculated with the remaining trials. Sensitivity analyses were also undertaken using correlation coefficients of 0.25, 0.5 and 0.75 to determine whether the overall results were robust to the use of different derived correlation coefficients in paired analyses of cross-over trials. A priori subgroup analyses were performed for baseline values (according to MetS diagnostic criteria),[27] absolute fibre intake on the tree nut diet (<25 vs ≥25 g/day[23]), change in fibre intake within the tree nut diet (<5.3 vs ≥5.3 g/day) and between the tree nut and control diets (<3.8 vs ≥3.8 g/day), absolute saturated fatty acid (SFA) intake on the tree nut diet (<7% vs ≥7% of total energy[23]), change in SFA intake within the tree nut diet (<−2% vs ≥−2% of total calories) and between the tree nut and control diets (<−2% vs ≥−2% of total calories), 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 (cross-over vs parallel) and study quality (MQS <8 vs ≥8). Post hoc subgroup analyses were conducted for the difference in per cent carbohydrate intake between the control and tree nut diets (carbohydrate displacement). The significance of between-subgroup differences was assessed using metaregression ($p<0.05$). 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 2531 reports, from which 752 reports were duplicates and 1631 reports were deemed irrelevant (determined by review of title and abstract). The remaining 146 reports were reviewed in full, of which 97 reports were excluded for not meeting inclusion criteria. A total of 49 reports on 47 trials[8–23 30–59] as well as four companion reports[60–63] that addressed at least one criterion of the MetS (waist circumference (15 trials, n=1050), triglycerides (44 trials, n=1690), HDL-C (45 trials, n=2142), BP (20 trials, n=1267) and fasting blood glucose (26 trials, n=1360)) were included.

Trial characteristics

Table 1 presents characteristics of the included trials. There were 47 trials involving 49 comparisons in 2211 participants. Twelve trials (26.7%)[10 12 14 16 30 32 34 36 39 43 49 59] were conducted in otherwise healthy participants. Two of these trials contained a minority of participants with dyslipidaemia who had been classified as otherwise healthy.[36 43] Eleven trials (24.4%)[8 18–21 35 37 44 45 54 55] were conducted in participants with type 2 diabetes mellitus or a mix of patients with overweight and type 2 diabetes mellitus in one case.[8] The remaining trials were conducted in people with dyslipidaemia (9 trials (20%)[13 15 17 31 33 38 41 42 53]), MetS (5 trials[22 40 47 48 58]), some MetS criteria (overweight (7 trials(15.6%)[9 11 50–52 56 57] and prediabetes (1 trial (2.2%)[46]). Median age for participants was 50.2 years (IQR 42.5–55.8 years). Median body weight for participants was 81.4 kg (IQR 72.1–91.7 kg).

Trials tended to be of considerable size, with a median number of 40 participants (IQR 25–61 participants). The majority were conducted in the USA (24 trials (53.3%)) with the rest conducted in various other countries: 3 trials (6.7%) each in Australia, New Zealand and Iran; 2 trials (4.4%) each in Canada and Spain and 1 trial (2.2%) each in Japan, Turkey, Italy, China, Taiwan, Germany, India and South Africa. A similar number of trials used parallel (24 trials (53.3%)) and cross-over (21

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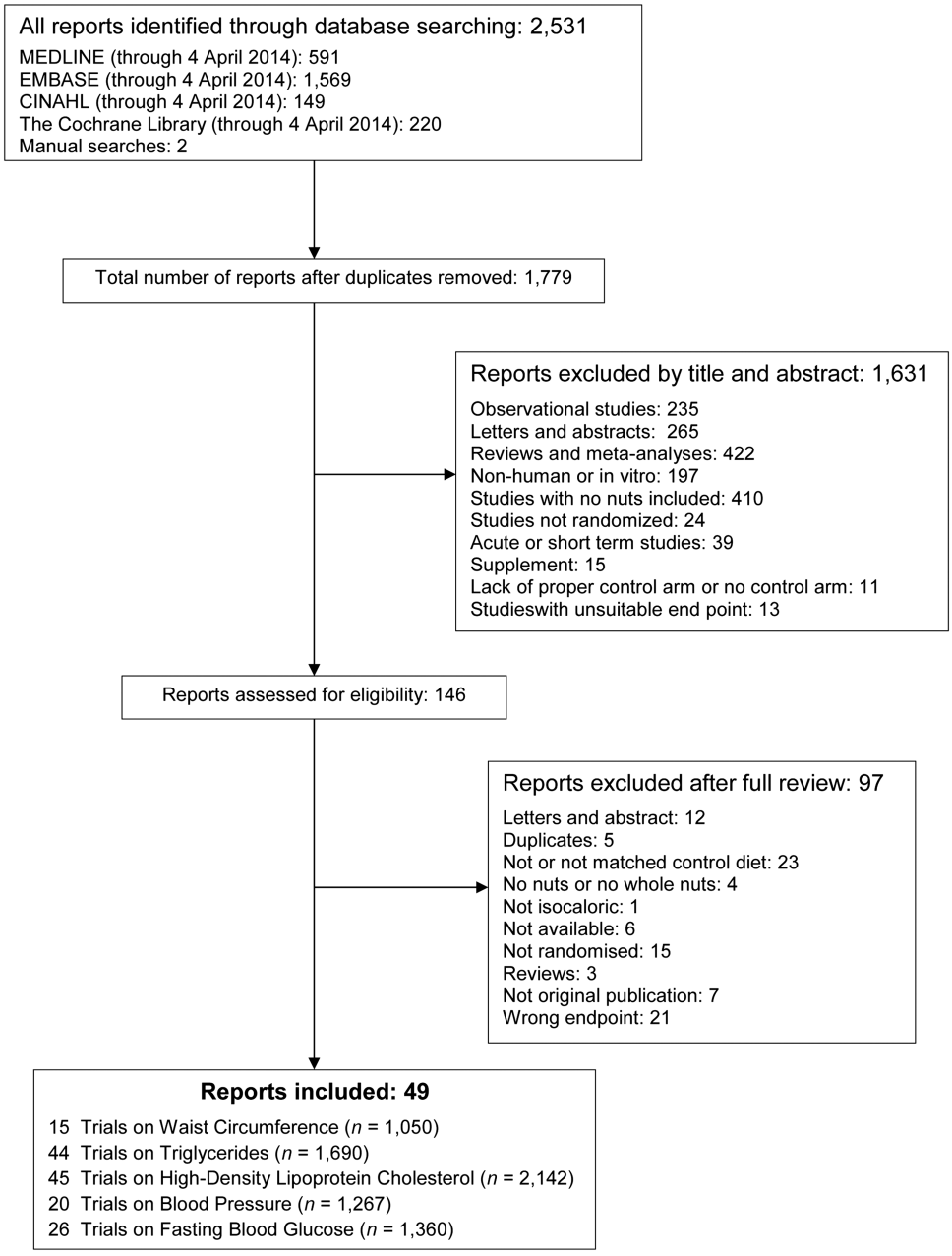

Figure 1 Summary of evidence search and selection.

trials (46.7%)) designs. All trials were conducted in an outpatient setting.

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

Macronutrient profiles varied across studies and between treatment and control groups; median values reported for carbohydrate intake were 48% (IQR 44–51%) for the treatment group and 50.5% (IQR 46–57%) for the control group. Median values for fat intake were 35% (IQR 31–39%) and 30% (IQR 27.3–34%) for tree

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), years	Mean body weight or BMI (SD or range)*	Setting	Design	Feeding control	Nut type	Nuts dose (g/day)†	Comparator	Diet‡	Energy balance	Follow-up	MQS§	Funding sources¶
Sabate *et al* (1993)[30]														
Walnut	18 (18 M)	30	73	OP, USA	Cross-over	Met	Walnut	84		55:31:14	Isocaloric	4 weeks	6	Agency
Control									NCEP step 1 diet	56:30:14				
Chisholm *et al* (1998)[13]														
Walnut	16 HLP	45 (6.8)	28.4 (4.3)	OP, New Zealand	Cross-over	DA	Walnut	78		40:38:17	Isocaloric	4 weeks	4	Agency
Control									Low-fat diet	46:30:19				
Spiller *et al* (1998)[31]														
Almond	30 HLP	53 (10)	66 (13)	OP, Italy	Parallel	Supp	Almond	100		45:39:16	Isocaloric	4 weeks	6	Agency
Control									Matched macronutrient diet	47:36:17				
Curb *et al* (2000)[10]														
Macadamia	30 (15 M, 15 W)	35.25 (18–53)	23 (19.1–28.3)	OP, USA	Cross-over	Met	Macadamia	46		48:35:17	Isocaloric	4 weeks	4	Agency–industry
Control									AHA	54:30:16				
Control									AAD	48:35:17				
Morgan and Clayshulte (2000)[32]														
Pecan	19 (4 M, 15 W)	37 (12)	24 (5)	OP, USA	Parallel	Supp	Pecan	68		45:43:12	Isocaloric	8 weeks	6	Agency
Control		45 (10)	24 (4)						Self-selected diet	46:36:18				
Zambon *et al* (2000)[33]														
Walnut	49 HC	56 (11)	70.6 (12.1)	OP, Spain	Cross-over	Supp	Walnut	48.5		48:34:18	Isocaloric	6 weeks	6	Agency
Control	(26 M, 23 W)								Mediterranean diet	50:31:19				
Rajaram *et al* (2001)[14]														
Pecan	23 (14 M, 9 W)	25–55	74.4 (16.7)	OP, USA	Cross-over	Met	Pecan	72		47:40:13	Isocaloric	4 weeks	8	Agency
Control									NCEP step 1 diet	57:28:15				
Iwamoto *et al* (2002)[34]														
Walnut	40 (20 M, 20 W)	23.8 (3.1)**	22.2 (0.5)	OP, Japan	Cross-over	Met	Walnut	52††		60:26:14	Isocaloric	4 weeks	8	Agency
Control		23.6 (4.6)**	20.7 (0.5)						Average Japanese diet	62:24:14				
Jenkins *et al* (2002)[15]														
Almond	27 HLP	64 (9)	71.2 (2.5)	OP, Canada	Cross-over	Supp	Almond	73		47:36:17	Isocaloric	4 weeks	6	Agency
Control	(15 M, 12 W)		71.0 (2.4)						NCEP step 2 diet + muffin	57:26:18				
Lovejoy *et al* (2002)[35]														
High-fat almond	30 DM2	53.8 (10.4)	33.0 (5.5)	OP, USA	Cross-over	Met	Almond	85††		48:37:15	Isocaloric	4 weeks	5	Agency
Low-fat almond	(13 M, 17 W)						Almond			60:25:15				
High-fat control									High-fat diet	48:37:15				
Low-fat control									Low-fat diet	60:25:15				
Sabate *et al* (2003)[36]														
High almond	25 NL-HC	41 (13)	NA	OP, USA	Cross-over	Met	Almond	83		46:39:14	Isocaloric	4 weeks	5	Agency–industry
Low almond	(14 M, 11 W)						Almond	42		35:51:14				
Control									NCEP step 1 diet	56:30:14				
Wien *et al* (2003)[8]														
Almond	65 OW/DM2	53 (2)	113 (5)	OP, USA	Parallel	Supp	Almond	84		53:18:29	Isocaloric	24 weeks	8	Agency
Control	(28 M, 37 W)	57 (2)	114 (5)						CHO-LCD	32:39:29				
Tapsell *et al* (2004)[37]														
Walnut	37 DM2	57.7 (9)	87.6 (12.8)	OP, Australia	Parallel	Supp	Walnut	30		44:32:22	Isocaloric	6 months	6	Agency
Control		59.3 (7.1)	81.9 (11.2)						Modified fat	41:33:23				
Tamizifar *et al* (2005)[38]														
Almond	30 HC	56 (6.1)	63 (8.9)	OP, Iran	Cross-over	Supp	Almond	25		47:37:17	Isocaloric	4 weeks	5	NA
Control	(17 M, 13 W)								NCEP step 1 diet	45:29:15				
Kocyigit *et al* (2006)[16]														
Pistachio	44 (24 M, 20 W)	32.8 (6.7)	24.2 (6.1)	OP, Turkey	Parallel	DA	Pistachio	69		NA	Isocaloric	3 weeks	8	Agency
Control			24.6 (5.6)						Regular diet					

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Table 1 Continued

Study (year) (reference)	Participants	Mean age (SD or range), years	Mean body weight or BMI (SD or range)*	Setting	Design	Feeding control	Nut type	Nuts dose (g/day)†	Comparator	Diet‡	Energy balance	Follow-up	MQS§	Funding sources¶
Kurlandsky and Stoke (2006)[39]														
Almond	47 (47 W)	41.8 (11.7)	25.3 (3.5)	OP, USA	Parallel	Supp	Almond	60		51:34:15	Isocaloric	6 weeks	5	Agency–industry
Almond + dark chocolate		46.2 (7.8)	27.2 (4.2)				Almond			46:39:15				
Dark chocolate		36.5 (11.9)	23.9 (3.3)						NCEP ATP III diet + chocolate	55:30:15				
Control		51.3 (6.3)	26.1 (4.1)						NCEP ATP III diet	57:27:16				
Schutte *et al* (2006)[60]‡‡														
Walnut	62 MetS	45.5	35.9	OP, South Africa	Parallel	Met	Walnut	85.5		47:36:17	Isocaloric	8 weeks	7	Agency–industry
Cashew		45.7	34.7				Cashew			47:36:17				
Control		44.4	35.5						Control diet	50:33:18				
Mukuddem-Petersen *et al* (2007)[40]														
Walnut	64 MetS	45 (10)	107	OP, South Africa	Parallel	Met	Walnut	85.5††		49:35:16	Isocaloric	8 weeks	7	Agency–industry
Cashew			99				Cashew			44:37:19				
Control			106						Habitual diet	47:33:20				
Sheridan *et al* (2007)[17]														
Pistachio	15 HC	60 (11.2)	175 (26)	OP, USA	Cross-over	Supp	Pistachio	35		52:31:17	Isocaloric	4 weeks	6	Agency
Control									Regular diet	53:31:16				
Gebauer *et al* (2008)[41]														
1 Pistachio	28 HLP	48 (7.9)	76.6 (13.2)	OP, USA	Cross-over	Met	Pistachio	37		53:34:16	Isocaloric	4 weeks	5	Agency
2 Pistachio	(10 M, 18 W)						Pistachio	74		57:29:16				
Control									NCEP step 1 diet	62:25:15				
Griel *et al* (2008)[42]														
Macadamia	25 HC	50.2 (8.4)	26.3 (3.3)	OP, USA	Cross-over	Met	Macadamia	42.5§§		50:33:19	Isocaloric	5 weeks	8	Agency–industry
Control									AAD	52:33:17				
Jenkins *et al* (2008)[61]‡‡														
Almond	27 HLP	64 (9)	71.2 (2.5)	OP, Canada	Cross-over	Supp	Almond	73		47:36:17	Isocaloric	4 weeks	6	Agency
Control	(15 M, 12 W)		71.0 (2.4)						NCEP step 2 diet + muffin	57:26:18				
Rajaram *et al* (2009)[43]														
Walnut	25 NL-HLP	23–65	71.9 (15.5)	OP, USA	Cross-over	Met	Walnut	42.5		60:31:15	Isocaloric	4 weeks	5	Agency
Control	(14 M, 11 W)		71.7 (15.5)						AAD	57:30:14				
Tapsell *et al* (2009)[44]														
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			93.4 (3)						Low-fat diet	41:34:20				
Li *et al* (2010)[11]														
Almond	52 OW¶¶	45.4 (2.0)	86 (26.8)	OP, USA	Parallel	Supp	Pistachio	53		55:30:15	Hypocaloric	12 weeks	7	Agency
Control		47.3 (2.3)	85.5 (40.2)						Pretzel	65:20:15	Hypocaloric			
Ma *et al* (2010)[45]														
Walnut	22 DM2¶¶	58.1 (9.2)	89 (15.5)	OP, USA	Cross-over	Supp	Walnut	56		39:44:17	Isocaloric	8 weeks	5	NA
Control									Ad libitum diet	43:38:19				
Torabian *et al* (2010)[12]														
Walnut	87 (38 M, 49 W)	54 (10.2)	75.6 (13.2)	OP, USA	Cross-over	Supp	Walnut	46		NA	Isocaloric	6 months	6	Agency
Control									Habitual diet					
Wien *et al* (2010)[46]														
Almond	65 PD	53 (9)	82.9 (14.4)	OP, USA	Parallel	Supp	Almond	58		42:39:19	Isocaloric	16 weeks	9	Agency
Control	(17 M, 48 W)	54 (11)	80.5 (14.4)						AAD	48:30:21				
Wu *et al* (2010)[47]														
Walnut	189 MetS	48.2 (8.4)	72.2 (11.4)	OP, USA	Parallel	Supp	Walnut	30		48:37:15	Isocaloric	12 weeks	9	Agency
Control		48.6 (8)	70.6 (10.9)						AHA	51:34:15				
Casas-Agustench *et al* (2011)[48]	50 MetS (28 M, 22 W)			OP, Spain	Parallel	Supp								
Mixed nuts		52.9 (8.4)	31.6 (2.8)				Mixed nuts	30		41:36:19	Isocaloric	12 weeks	6	Agency
Control		50.6 (8.4)	30.0 (3.3)						Prudent diet	42:36:19				

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Table 1 Continued

Study (year) (reference)	Participants	Mean age (SD or range), years	Mean body weight or BMI (SD or range)*	Setting	Design	Feeding control	Nut type	Nuts dose (g/day)†	Comparator	Diet‡	Energy balance	Follow-up	MQS§	Funding sources¶
Cohen and Johnston (2011)[19]														
Almond	13 DM2	66 (11.9)	96.1 (40.4)	OP, USA	Parallel	Supp	Almond	28		NA	Isocaloric	12 weeks	7	Agency
Control	(7 M, 6 W)		105.1 (32.1)						Cheese sticks					
Jenkins *et al* (2011)[20]														
Mixed nuts	79 DM2	63 (9)	80 (15)	OP, Canada	Parallel	Supp	Mixed nuts	75††		41:41:18	Isocaloric	12 weeks	8	Agency
Control	(52 M, 27 W)	61 (10)	83 (15)						NCEP step 2 diet + muffin	46:35:19				
Li *et al* (2011)[21]														
Almond	20 DM2	58 (8.9)	26 (3.1)	OP, Taiwan	Cross-over	Met	Almond	56		47:37:17	Isocaloric	4 weeks	5	Agency
Control	(9 M, 11 W)								NCEP step 2 diet	57:27:17				
Tey *et al* (2011)[49]														
Hazelnut	61	38.9 (14.3)	72 (11.1)	OP, New	Parallel	Supp	Hazelnut	42		45:39:16***	Isocaloric	12 weeks	9	Agency
Control		36.1 (15.2)	67.3 (9.5)	Zealand					Regular diet	50:33:17				
Damavandi (2012)[18]														
Cashew	43 DM2	51 (7.9)	72.1 (13.1)	OP, Iran	Parallel	Supp	Cashew	30		53:32:16	Isocaloric	8 weeks	3	NA
Control	(9 M, 34 W)	56 (5.7)	71.9 (9.7)						Regular diet	57:27:16				
Foster *et al* (2012)[50]														
Almond	123 OW	47 (12)	94 (13.1)	OP, USA	Parallel	Supp	Almond	56		NA	Hypocaloric	18 months	9	Agency
Control	(11 M, 112 W)	46.7 (13)	91.5 (11.9)						Nut-free diet		Hypocaloric			
Katz *et al* (2012)[51]														
Walnut	40 OW¶¶	57.4 (11.9)	33.2 (4.4)	OP, USA	Cross-over	Supp	Walnut	56		41:41:17	Isocaloric	8 weeks	7	Industry
Control									Ad libitum diet	45:34:20				
Wang *et al* (2012)[22]														
Pistachios	86 MetS	51.9 (8.8)	28.1 (3.2)	OP, China		Supp	Pistachio	42		NA	Isocaloric	12 weeks	5	Industry
High pistachios		51.8 (9.4)	28 (4.5)				Pistachio	70						
Control		50.7 (9.9)	28 (4.4)						AHA step 1 diet					
West *et al* (2012)[62]‡‡														
1 Pistachio	28 HLP	48 (7.9)	76.6 (13.2)	OP, USA	Cross-over	Met	Pistachio	37		53:34:16	Isocaloric	4 weeks	5	Agency
2 Pistachio	(10 M, 18 W)						Pistachio	74		57:29:16				
Control									NCEP step 1 diet	62:25:15				
Anderson *et al* (2013)[52]														
Pistachio	22 OW	55 (2)	90 (3.6)	OP, USA	Parallel	NA	Pistachio	35.4		NA	NA	6 weeks	5	NA
Control									NA					
Berryman *et al* (2013)[53]														
Almond	53 HC	NA	NA	OP, USA	Cross-over	NA	Almond	42.5		51:33:16	Isocaloric	6 weeks	NA	NA
Control									Muffin	59:26:15				
Damavandi *et al* (2013)[54]														
Hazelnut	48 DM2¶¶	55.7 (7.7)	72.1 (10.3)	OP, Iran	Parallel	Supp	Hazelnut	29		55:31:16	Isocaloric	8 weeks	6	None
Control			72 (9.6)						Self-selected diet	60:25:17				
Holligan *et al* (2013)[63]‡‡														
1 Pistachio	28 HLP	48 (7.9)	76.6 (13.2)	OP, USA	Cross-over	Met	Pistachio	37		53:34:16	Isocaloric	4 weeks	NA	Agency
2 Pistachio	(10 M, 18 W)						Pistachio	74		57:29:16				
Control									NCEP step 1 diet	62:25:15				
Sauder *et al* (2013)[55]														
Pistachio	30 DM2	56.1 (1.4)	31.2 (1.1)	OP, USA	Cross-over	Met	Pistachio	73.4		51:33:17	Isocaloric	4 weeks	NA	Industry
Control	(15 M, 15 W)¶¶								Low-fat diet	55:27:18				
Somerset *et al* (2013)[9]														
Macadamia	64 OW	43.7 (8.4)	95 (14.7)	OP, Australia	Parallel	DA	Macadamia	46		36:38:21	Isocaloric	10 weeks	9	Agency
Control	(10 M, 54 W)	43.2 (10.9)	99.6 (15.2)						Regular diet	41:38:17				
Tan and Mattes (2013)[56]														
Almond (breakfast)	137 OW	32.9 (11.5)	80.5 (15)	OP, USA	Parallel	Supp	Almond	43		50:16:15	Isocaloric	4 weeks	5	Industry
Almond (morning snack)	(48 M, 89 W)	27.8 (10.7)	83.2 (21.1)				Almond	43		51:15:14				

Continued

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Table 1 Continued

Study (year) (reference)	Participants	Mean age (SD or range), years	Mean body weight or BMI (SD or range)*	Setting	Design	Feeding control	Nut type	Nuts dose (g/day)†	Comparator	Diet‡	Energy balance	Follow-up	MQS§	Funding sources¶
Almond (lunch)		29.3 (13.5)	84.8 (13.7)				Almond	43		48:16:17				
Almond (afternoon snack)		29 (11.9)	81.8 (14.6)				Almond	43		49:15:16				
Control		28.7 (9.6)	77.2 (16.8)						Regular diet	48:15:16				
Tey *et al* (2013)[57]														
Hazelnut 30 g	107 OW	43.8 (13.5)	86.2 (11.8)	OP,	Parallel	Supp	Hazelnut	30		42:39:17	Isocaloric	12 weeks	6	Agency
Hazelnut 60 g	(46 M, 61W)	42.8 (10.6)	92 (19.6)	New Zealand			Hazelnut	60		38:42:16				
Control		41.1 (13.1)	88.7 (16.7)						Usual diet	47:33:17				
Gulati *et al* (2014)[58]														
Pistachio	68 MetS	41.6 (8.4)	81.6 (12.9)	OP, India	Parallel	DA	Pistachio	50§§		51:29:20	Isocaloric	24 weeks	4	Industry
Control	(37 M, 31 W)	43.3 (8.1)	80.3 (10.3)						Standard diabetic diet	60:25:15				
Wu *et al* (2014)[59]														
Walnut	40 (10 M, 30 W)	60 (1)	24.9 (0.6)	OP, Germany	Cross-over	Supp	Walnut	43		50:35:15	Isocaloric	8 weeks	7	Industry
Control									Western-type diet					

*Body weight is reported in kg and BMI is reported in kg/m^2. BMI is reported only when no data on weight were available.
†Nut dose is given based on g/day, 1 oz=28 g.
‡Energy from carbohydrate:fat:protein.
§Trials with scores ≥8 were considered to be of high quality.
¶Agency funding is that from government, university or not-for-profit health agency sources.
**Mean age was given separately for men and women.
††Medians were calculated from the ranges reported: Iwamoto *et al*[34] range 50–54 g/day; Jenkins *et al*[20] range 50–75 g/day; Lovejoy *et al*[35] range 57–113 g/day; Mukuddem-Petersen *et al*[40] range 63–108 g/day; Torabian *et al*[12] range 28–64 g/day; Zambon *et al*[33] range 41–56 g/day.
‡‡Companion reports: Jenkins *et al*[61] for Jenkins *et al*[15]; Schutte *et al*[60] for Mukuddem-Petersen *et al*[40]; West *et al*[62] and Holligan *et al*[63] for Gebauer *et al*[41].
¶¶Baseline characteristics were based on the number of randomised participants for Li *et al*[11] n=70; Ma *et al*[45] n=24; Zambon *et al*[33] n=55; Katz *et al*[51] n=46; Sauder *et al*[55] n=30; Gulati *et al*[58] n=68 for recruited participants for Tapsell *et al*[44] (n=50), and for age for Damavandi *et al*[54] (n=50).
§§Based on 2100 kcal for Griel *et al*[42] and based on 1400 kcal (~60 kg) for Gulati *et al*[58].
***Values for carbohydrates are reported as geometric means.
AAD, Average American Diet; AHA, American Heart Association; BMI, body mass index; CHO-LCD, self-selected complex carbohydrate diet; DA, dietary advice; DM2, type 2 diabetes mellitus; HC, hypercholesterolaemic; HLP, hyperlipidaemic; M, men; Met, metabolic; MetS, metabolic syndrome; MQS, Heyland Methodological Quality Score; NA, not available; NCEP, National Cholesterol Education Program; NL-HC, normal to hypercholesterolaemic; NL-HLP, normal to mildly hyperlipidaemic; PD, prediabetes; OP, out-patient; OW, overweight; RCT, randomised controlled trial; SUPP, supplement; W, women.

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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	4.30%	-0.11 [-0.23, 0.01]
Curb et al, 2000 (10)	30	30	4.30%	-0.12 [-0.24, -0.00]
Morgan and Clayshulte, 2000 (32)	10	9	0.70%	-0.24 [-0.57, 0.09]
Rajaram et al, 2001 (14)	23	23	3.50%	-0.14 [-0.28, -0.00]
Iwamoto et al, 2002 (34)	40	40	2.80%	0.00 [-0.16, 0.16]
Sabate et al, 2003 (36)	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 and Stoke, 2006 (39) - Almonds	12	12	5.40%	-0.09 [-0.19, 0.01]
Kurlandsky and Stoke, 2006 (39) - Almonds + dark chocolate	12	11	10.90%	-0.01 [-0.05, 0.03]
Rajaram et al, 2009 (43)	25	25	2.30%	-0.01 [-0.19, 0.17]
Torabian et al, 2010 (12)	87	87	13.30%	-0.09 [-0.10, -0.08]
Tey et al, 2011 (57)	32	27	2.30%	-0.04 [-0.22, 0.14]
Wu et al, 2014 (59)	40	40	2.30%	-0.09 [-0.27, 0.09]
Subtotal (95% CI)	376	369	53.80%	-0.07 [-0.11, -0.04]
Heterogeneity: Tau² = 0.00; Chi² = 20.83, df = 12 (P = 0.05); I² = 42%				
Test for overall effect: Z = 4.01 (P < 0.0001)				
Dyslipidemia				
Chisholm et al, 1998 (13)	16	16	0.80%	0.14 [-0.17, 0.45]
Spiller et al, 1998 (31)	18	12	0.70%	0.02 [-0.31, 0.35]
Zambon et al, 2000 (33)	49	49	5.40%	-0.09 [-0.19, 0.01]
Jenkins et al, 2002 (15)	27	27	1.40%	-0.13 [-0.37, 0.11]
Tamizifar et al, 2005 (38)	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 (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]
Subtotal (95% CI)	208	202	14.40%	-0.06 [-0.13, 0.00]
Heterogeneity: Tau² = 0.00; Chi² = 5.94, df = 7 (P = 0.55); I² = 0%				
Test for overall effect: Z = 1.83 (P = 0.07)				
Metabolic Syndrome Criteria				
Mukuddem-Petersen et al, 2007 (40)	42	22	1.40%	-0.21 [-0.45, 0.03]
Li et al, 2010 (11)	27	25	1.70%	-0.26 [-0.48, -0.04]
Wien et al, 2010 (46)	32	33	1.90%	-0.16 [-0.36, 0.04]
Casas-Agustench et al, 2011 (48)	25	25	0.50%	0.04 [-0.37, 0.45]
Foster et al, 2012 (50)	61	62	1.90%	0.07 [-0.13, 0.27]
Katz et al, 2012 (51)	40	40	1.40%	-0.05 [-0.29, 0.19]
Wang et al, 2012 (22)	56	30	1.40%	-0.07 [-0.31, 0.17]
Somerset et al, 2013 (9)	35	29	1.40%	-0.01 [-0.25, 0.23]
Tan and Mattes, 2013 (56)	110	27	3.50%	-0.03 [-0.17, 0.11]
Tey et al, 2013 (57)	70	37	3.50%	0.18 [0.04, 0.32]
Gulati et al, 2014 (58)	30	30	1.90%	-0.07 [-0.27, 0.13]
Subtotal (95% CI)	528	360	20.60%	-0.04 [-0.13, 0.04]
Heterogeneity: Tau² = 0.01; Chi² = 18.74, df = 10 (P = 0.04); I² = 47%				
Test for overall effect: Z = 1.02 (P = 0.31)				
Type 2 diabetes mellitus				
Lovejoy et al, 2002 (35) – High fat	30	30	0.90%	0.09 [-0.20, 0.38]
Lovejoy et al, 2002 (35) – Low fat	30	30	0.90%	0.10 [-0.19, 0.39]
Wien et al, 2003 (8)	32	33	0.50%	0.00 [-0.39, 0.39]
Tapsell et al, 2004 (37)	17	20	0.80%	0.15 [-0.16, 0.46]
Tapsell et al, 2009 (44)	18	17	0.10%	0.30 [-0.50, 1.10]
Ma et al, 2010 (45)	22	22	0.80%	-0.11 [-0.43, 0.20]
Cohen and Johnston, 2011 (19)	6	7	0.10%	0.60 [-0.20, 1.40]
Jenkins et al, 2011 (20)	40	39	2.30%	-0.07 [-0.25, 0.11]
Li et al, 2011 (21)	20	20	0.70%	-0.10 [-0.43, 0.23]
Damavandi, 2012 (18)	22	21	0.70%	0.05 [-0.28, 0.38]
Damavandi et al, 2013 (54)	23	25	0.70%	0.05 [-0.30, 0.40]
Sauder et al, 2013 (55)	28	28	2.30%	-0.28 [-0.46, -0.10]
Subtotal (95% CI)	288	292	11.20%	-0.03 [-0.13, 0.07]
Heterogeneity: Tau² = 0.01; Chi² = 14.22, df = 11 (P = 0.22); I² = 23%				
Test for overall effect: Z = 0.56 (P = 0.58)				
Total (95% CI)	**1400**	**1223**	**100.00%**	**-0.06 [-0.09, -0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 64.68, df = 43 (P = 0.02); I² = 34%				
Test for overall effect: Z = 3.96 (P < 0.0001)				
Test for subgroup differences: Chi² = 0.92, df = 3 (P = 0.82), I² = 0%				

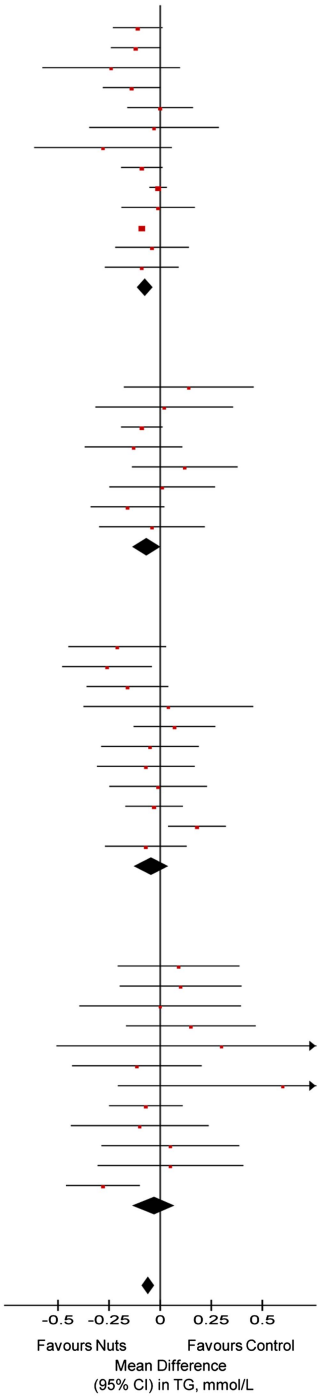

Figure 2 Forest plot of the randomised controlled trials (RCTs) investigating the effect of tree nuts on triglycerides (TG). Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidaemia, metabolic syndrome criteria, type 2 diabetes mellitus and their combination (total). Paired analyses were applied to all cross-over trials (20) and one substudy. Data are expressed as mean differences with 95% CI, using generic inverse-variance random effects models. Interstudy heterogeneity was tested by using the Cochran Q statistic (Chi^2) at a significance level of p<0.10 and quantified by the I^2 statistic.

nut and control groups, respectively. Median values for protein intake were 16% (IQR 15–17%) and 17% (IQR 15–18.8%) for tree nut and control groups, correspondingly.

Online supplementary appendix table 2 and appendix figure 1 present the assessment and summary of the risk of bias by using The Heyland MQS and The Cochrane Risk of Bias Tool. The Heyland MQS ranged

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Subgroup and Study, year (Reference)	Nuts n	Control n	Weight	Mean Difference (95% CI) in mmol/L
Otherwise Healthy				
Sabate et al, 2003 (36)	25	25	7.80%	0.01 [-0.15, 0.17]
Wu et al, 2014 (59)	40	40	6.00%	-0.11 [-0.33, 0.11]
Subtotal (95% CI)	65	65	13.80%	-0.03 [-0.16, 0.10]
Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 1 (P = 0.38); I² = 0%				
Test for overall effect: Z = 0.49 (P = 0.63)				
Dyslipidemia				
Jenkins et al, 2008 (61)	27	27	4.20%	-0.26 [-0.55, 0.03]
Holligan et al, 2013 (63)	28	28	9.20%	-0.03 [-0.15, 0.09]
Subtotal (95% CI)	55	55	13.40%	-0.10 [-0.31, 0.11]
Heterogeneity: Tau² = 0.01; Chi² = 2.03 df = 1 (P = 0.15); I² = 51%				
Test for overall effect: Z = 0.97 (P = 0.33)				
Metabolic Syndrome Criteria				
Schutte et al, 2006 (60)	41	21	1.40%	0.80 [0.21, 1.39]
Li et al, 2010 (11)	27	25	5.00%	-0.29 [-0.54, -0.04]
Wien et al, 2010 (46)	32	33	2.80%	-0.01 [-0.40, 0.38]
Wu et al, 2010 (47)	94	95	3.80%	0.03 [-0.28, 0.34]
Casas-Agustench et al, 2011 (48)	25	25	5.00%	-0.01 [-0.26, 0.24]
Katz et al, 2012 (51)	40	40	7.20%	0.00 [-0.17, 0.18]
Wang et al, 2012 (22)	56	30	6.50%	-0.23 [-0.43, -0.03]
Anderson et al, 2013 (52)	11	11	3.80%	-0.23 [-0.54, 0.08]
Somerset et al, 2013 (9)	35	29	3.20%	0.31 [-0.04, 0.66]
Tan and Mattes, 2013 (56)	110	27	9.30%	-0.04 [-0.16, 0.08]
Gulati et al, 2014 (58)	30	30	6.00%	-0.22 [-0.44, -0.00]
Subtotal (95% CI)	501	366	53.90%	-0.06 [-0.17, 0.06]
Heterogeneity: Tau² = 0.02; Chi² = 22.77, df = 10 (P = 0.01); I² = 56%				
Test for overall effect: Z = 0.97 (P = 0.33)				
Type 2 diabetes mellitus				
Lovejoy et al, 2002 (35) – High fat	30	30	0.50%	-0.59 [-1.59, 0.41]
Lovejoy et al, 2002 (35) – Low fat	30	30	0.50%	0.63 [-0.37, 1.63]
Wien et al, 2003 (8)	32	33	0.40%	0.06 [-1.14, 1.26]
Tapsell et al, 2009 (44)	18	17	0.20%	0.90 [-0.75, 2.55]
Ma et al, 2010 (45)	22	22	1.10%	0.39 [-0.30, 1.08]
Cohen and Johnston, 2011 (19)	6	7	0.60%	-0.50 [-1.40, 0.40]
Jenkins et al, 2011 (20)	40	39	3.20%	-0.18 [-0.53, 0.17]
Li et al, 2011 (21)	20	20	5.40%	-0.30 [-0.54, -0.06]
Damavandi, 2012 (18)	22	21	0.40%	-1.08 [-2.28, 0.12]
Damavandi et al, 2013 (54)	23	25	0.50%	-0.92 [-1.94, 0.10]
Sauder et al, 2013 (55)	28	28	6.00%	-0.04 [-0.26, 0.18]
Subtotal (95% CI)	271	272	18.80%	-0.16 [-0.37, 0.05]
Heterogeneity: Tau² = 0.03; Chi² = 14.82, df = 10 (P = 0.14); I² = 33%				
Test for overall effect: Z = 1.50 (P = 0.13)				
Total (95% CI)	**892**	**758**	**100.00%**	**-0.08 [-0.16, -0.01]**
Heterogeneity: Tau² = 0.01; Chi² = 42.36, df = 25 (P = 0.02); I² = 41%				
Test for overall effect: Z = 2.19 (P = 0.03)				
Test for subgroup differences: Chi² = 1.22, df = 3 (P = 0.75), I² = 0%				

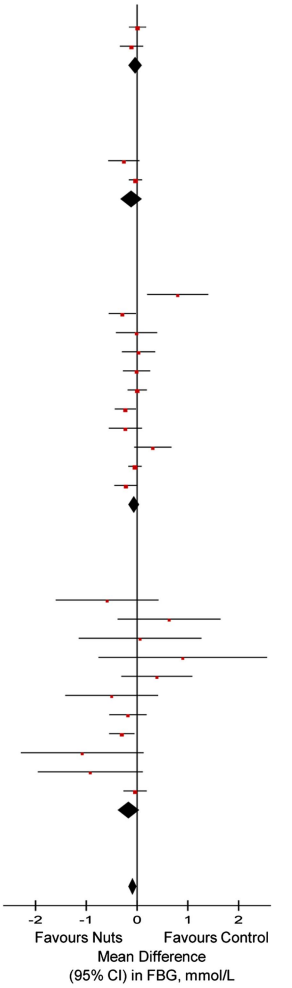

Figure 3 Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidaemia, metabolic syndrome criteria, type 2 diabetes mellitus and their combination (total). Paired analyses were applied to all cross-over trials (10) and one substudy. Data are expressed as mean differences with 95% CI, using generic inverse-variance random effects models. Interstudy heterogeneity was tested by using the Cochran Q statistic (Chi^2) at a significance level of p<0.10 and quantified by the I^2 statistic. FBG, fasting blood glucose; RCT, randomised controlled trial.

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

Most of the trials reported research funding from an agency (28 trials (62.2%)), while others were funded from a combination of agency and industry (5 trials (11.1%)) or industry alone (6 trials (13.3%)). One trial (2.2%) reported no funding. Five trials[18 38 45 52 53] did not report their funding source (11.1%).

Waist circumference

Online supplementary appendix figure 2 presents data on the effect of tree nuts on waist circumference. Tree nuts did not significantly decrease waist circumference (MD=−0.62 cm (95% CI −1.54 to 0.30 cm)) in the overall analyses with evidence of substantial heterogeneity

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(I^2=67%, 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).

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

Triglycerides

Figure 2 presents data on the effect of tree nuts on triglycerides. Tree nuts showed a significant triglyceride-lowering effect (MD=−0.06 mmol/L (95% CI −0.09 to −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 to −0.04 mmol/L)). Although the reductions were not statistically significant in people with dyslipidaemia, MetS criteria or type 2 diabetes mellitus, they did not significantly differ from the reductions in participants who were otherwise healthy. Sensitivity analyses did not alter the results (data not shown).

Online supplementary appendix table 3B 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) and almond, macadamia, pecan, pistachio and walnut more than hazelnut (p<0.05). No other subgroup analyses were statistically significant.

High-density lipoprotein cholesterol

Online supplementary 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 to 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).

Online supplementary appendix table 3C 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

Online supplementary appendix figures 7A and 7B present the effect of tree nuts on systolic and diastolic BP, respectively. Tree nuts did not significantly increase either systolic (MD=0.07 mm Hg (95% CI −1.54 to 1.69 mm Hg)) or diastolic BP (MD=0.23 mm Hg (95% CI −0.38 to 0.83 mm Hg)) in the overall analysis with evidence of substantial heterogeneity in the systolic BP analysis (I^2=64%, p<0.001) and evidence of moderate heterogeneity in the diastolic BP 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).

Online supplementary appendix tables 3D and 3E present the a priori continuous subgroup analyses and online supplementary appendix figures 8A and 8B present the a priori categorical subgroup analyses for systolic and diastolic BP, respectively. There was evidence of statistically significant effect modification by difference in fibre intake and by the difference in carbohydrate intake in the continuous subgroup analyses, for systolic BP (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 BP. 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 BP. Tree nut intervention arms with higher fibre intake showed reductions in diastolic BP and also explained the heterogeneity in the overall analyses reducing the residual I^2 to 1.6%. No other subgroup analyses were statistically significant for either systolic or diastolic BP.

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 to −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).

Online supplementary appendix table 3F and appendix figure 9 present the a priori continuous and categorical subgroup analyses, respectively, for fasting blood glucose. None of the subgroup analyses were significant.

Publication bias

Online supplementary appendix figure 10 presents the funnel plots for publication bias for each end point. Visual inspection of the funnel plots revealed some evidence of asymmetry in several of the end points. There was a small trial with larger effect estimate favouring tree nuts than control for waist circumference, which argues that the 'small-study' effect was actually not a source of potential bias (ie, smaller studies that favoured control

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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 and Begg's tests.

DISCUSSION

To the best of our knowledge, this is the first systematic review and meta-analysis to look at the effect of tree nuts on MetS criteria. Our systematic review and meta-analysis included 47 randomised trials in 2211 participants who were otherwise healthy or had MetS criteria, dyslipidaemia or type 2 diabetes mellitus. Tree nut consumption at a median dose of ~50 g/day was found to decrease triglycerides significantly by ~0.06 mmol/L, and decrease fasting blood glucose significantly by ~0.08 mmol/L over a median follow-up of 8 weeks. No adverse effects were seen on waist circumference, HDL-C or BP, suggesting an overall net metabolic benefit of tree nuts.

Results in relation to other studies

Our findings of a reduction in triglycerides without the expected reciprocal increase in HDL-C are in accordance with previous evidence. Although Sabate *et al*[64] did not show a triglyceride-lowering effect of nut interventions (non-specific to tree nuts) in overall pooled analyses in a patient-level meta-analysis of controlled feeding trials, they did show that nut interventions lowered triglycerides when analyses were restricted to a subsample of participants with baseline triglycerides ≥1.7 mmol/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 type 2 diabetes mellitus.[65 66] This triglyceride-lowering effect, however, was accompanied by an HDL-C increasing effect.[65 66] Our findings add to these data by showing a similar triglyceride-lowering effect, especially for walnuts, pistachios, macadamia and pecans, in the absence of an HDL-C increasing effect, across all subsamples of participants, without differences in triglycerides by baseline levels. The lipid benefits of tree nuts can be attributed to numerous cardioprotective nutrients such as unsaturated fatty acids, plant protein, fibre and phytochemicals.[67] The fibre content and high unsaturated fat content, with its ability to displace high-glycaemic index carbohydrate from the diet and so effect a lower glycaemic 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 glycaemic control in people with type 2 diabetes mellitus.[23] Individual trials have shown evidence of improvements in other aspects of glycaemic control.[19–22] A fasting blood glucose-decreasing effect has also been seen in long-term glycaemic control as assessed by glycated haemoglobin for tree nuts as part of Mediterranean[65 66 68] and DASH[69] dietary patterns in people with type 2 diabetes mellitus.[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 glycaemic load of the diet, as this mechanism would be expected to improve long-term glycaemic control through a reduction in postprandial glycaemia,[71] and possibly decrease insulin resistance,[48] neither of which was 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 randomised trials have shown the opposite. A pooled analysis of Harvard cohorts showed that an increase in one serving per day of nuts was associated with significant weight loss.[72] Controlled trials of tree nuts alone or as part of Mediterranean,[65 66 68] Portfolio[73] or DASH[69] dietary patterns have shown neutral or weight loss effects, and no influence on body fat mass or body fat percentage.[74] Dietary patterns that incorporated nuts have reported weight loss under isocaloric conditions or no weight gain under hypercaloric feeding conditions,[75] perhaps because the metabolically available energy from nuts is less than the calculated value, as incomplete digestion of nuts leads to energy excretion in the faeces.[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-glycaemic index carbohydrate to effect a lower glycaemic 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-glycaemic index carbohydrate to effect a low-glycaemic load diet may yet demonstrate a waist circumference benefit in future meta-analyses.

We were surprised not to see an improvement in BP. Individual trials have shown evidence of improvements in BP.[5 8] A BP-decreasing effect of tree nuts has also been seen in the context of Portfolio[73] and DASH[69 77 78] dietary patterns across a range of participant types. As elevated BP in the MetS 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-glycaemic index carbohydrate to decrease the low-glycaemic 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 results in larger amounts of potassium, calcium, magnesium, dietary fibre and protein.

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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 available trials were <3 months, which is perhaps, too short a time to observe an effect for some outcomes (waist circumference, BP). 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 end points. Finally, our analyses were complicated by significant unexplained heterogeneity for waist circumference, and HDL-C, which we attempted to accommodate using random effects models, but it remains a source of uncertainty in the summary effect estimates for these end points.

Practical implications

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

CONCLUSION

In conclusion, our pooled analyses indicate that daily tree nut consumption has an overall metabolic benefit, through modest decreases in triglycerides and fasting blood glucose while preserving waist circumference, HDL-C and BP in people who are otherwise healthy or have dyslipidaemia, MetS criteria or type 2 diabetes mellitus. 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 mean 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 highlight the need for larger, longer, high-quality trials. Trials in which tree nuts are used to displace high-glycaemic index carbohydrate to decrease the glycaemic load of the diet will be especially relevant to understand the role of tree nuts in reducing cardiometabolic risk associated with the MetS.

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Competing interests 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

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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 Pulse Growers. She is also a casual clinical research coordinator at Glycemic Index Laboratories. RJdS is funded by a CIHR Postdoctoral Fellowship Award and has received research support from the CIHR, the Calorie Control Council, the Canadian Foundation for Dietetic Research and the Coca-Cola Company (investigator initiated, unrestricted grant). He has served as an external resource person to WHO's Nutrition Guidelines Advisory Group and received travel support from WHO to attend group meetings. He is the lead author of two systematic reviews and meta-analyses commissioned by WHO of the relation of saturated fatty acids and trans fatty acids with health outcomes. DJAJ has received research grants from Saskatchewan Pulse Growers, the Agricultural Bioproducts Innovation Program through the Pulse Research Network, the Advanced Foods and Material Network, Loblaw Companies Ltd, Unilever, Barilla, the Almond Board of California, the Coca-Cola Company (investigator initiated, unrestricted grant), Solae, Haine Celestial, the Sanitarium Company, Orafti, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, the Canola and Flax Councils of Canada, the Calorie Control Council, the CIHR, the Canada Foundation for Innovation and the Ontario Research Fund. He has been on the speaker's panel, served on the scientific advisory board, and/or received travel support and/or honoraria from the Almond Board of California, Canadian Agriculture Policy Institute, Loblaw Companies Ltd, the Griffin Hospital (for the development of the NuVal scoring system), the Coca-Cola Company, Saskatchewan Pulse Growers, Sanitarium Company, Orafti, the Almond Board of California, the American Peanut Council, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, Herbalife International, Pacific Health Laboratories, Nutritional Fundamental for Health, Barilla, Metagenics, Bayer Consumer Care, Unilever Canada and Netherlands, Solae, Kellogg, Quaker Oats, Procter & Gamble, the Coca-Cola Company, the Griffin Hospital, Abbott Laboratories, the Canola Council of Canada, Dean Foods, the California Strawberry Commission, Haine Celestial, PepsiCo, the Alpro Foundation, Pioneer Hi-Bred International, DuPont Nutrition and Health, Spherix Consulting and WhiteWave Foods, the Advanced Foods and Material Network, the Canola and Flax Councils of Canada, the Nutritional Fundamentals for Health, Agri-Culture and Agri-Food Canada, the Canadian Agri-Food Policy Institute, Pulse Canada, the Saskatchewan Pulse Growers, the Soy Foods Association of North America, the NFI, Nutra-Source Diagnostics, the McDougall Program, the Toronto Knowledge Translation Group (St Michael's Hospital), the Canadian College of Naturopathic Medicine, The Hospital for Sick Children, the Canadian Nutrition Society (CNS), the American Society of Nutrition (ASN), Arizona State University, Paolo Sorbini Foundation and the Institute of Nutrition, Metabolism and Diabetes. 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Effect of tree nuts on metabolic syndrome criteria: a systematic review and meta-analysis of randomised controlled trials

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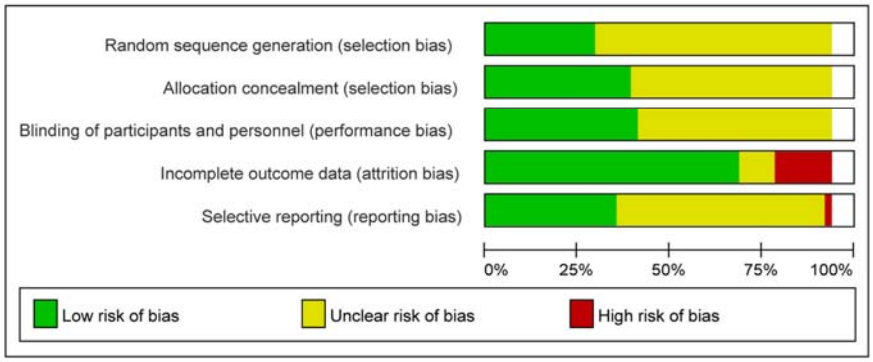
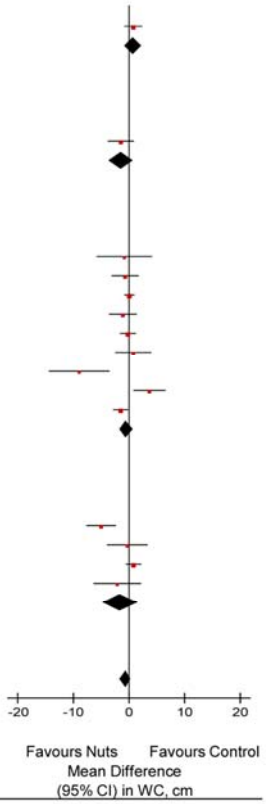
Appendix Figure 1. Cochrane risk of bias.



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

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

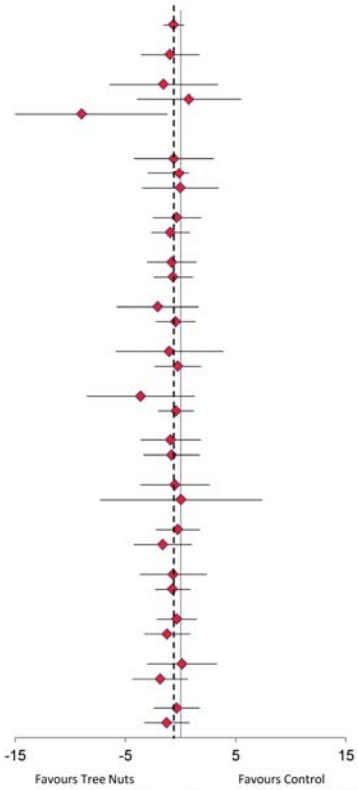
Subgroup and Study, year (Reference)	Nuts *n*	Control *n*	Weight	Mean Difference (95% CI) in cm
Otherwise Healthy				
Tey et al, 2011 (49)	32	29	9.10%	0.77 [-0.74, 2.28]
Subtotal (95% CI)	32	29	9.10%	0.77 [-0.74, 2.28]
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.00 (P = 0.32)				
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				
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]
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]
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 and Mattes, 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: Tau² = 1.62; Chi² = 23.32, df = 8 (P = 0.003); I² = 66%				
Test for overall effect: Z = 0.75 (P = 0.45)				
Type 2 diabetes mellitus				
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]
Damavandi, 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: Tau² = 7.82; Chi² = 16.50, df = 3 (P = 0.0009); I² = 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: Tau² = 1.81; Chi² = 42.91, df = 14 (P < 0.0001); I² = 67%				
Test for overall effect: Z = 1.33 (P = 0.19)				
Test for subgroup differences: Chi² = 3.67, df = 3 (P = 0.30), I² = 18.2%				



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

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

Subgroup	Level	Trials	N	Mean difference (95% CI) in Waist Circumference, cm: Within subgroups	Between subgroups	Residual I^2	*P*-value
Total	-	15	1050	-0.62 (-1.54, 0.30)			
Nut type	Almonds	4	294	-0.95 (-3.57, 1.68)	See legend	67.3%	0.392
	Brazil nuts	0	0				
	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)			
	Pecans	0	0				
	Pine nuts	0	0				
	Pistachios	2	146	-0.61 (-4.19, 2.97)			
	Walnuts	4	282*	-0.12 (-2.95, 2.72)			
	Mixed nuts	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%	0.654
	≥ 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%	0.914
	≥ 12 weeks	9	719	-0.65 (-2.40, 1.10)			
SFA	< 7%	2	254	-2.06 (-5.76, 1.63)	1.61 (-2.48, 5.71)	70.9%	0.405
	≥ 7%	11	650	-0.45 (-2.22, 1.32)			
SFA (within Δ)	< -2%	2	112	-1.02 (-5.87, 3.84)	0.79 (-4.50, 6.07)	64.8%	0.740
	≥ -2%	8	665	-0.23 (-2.32, 1.86)			
SFA (between Δ)	< -1.3%	2	86	-3.62 (-8.48, 1.25)	3.19 (-1.93, 8.30)	68.5%	0.197
	≥ -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%	0.951
	≥ 25 g/d	6	483	-0.80 (-3.33, 1.73)			
Fibre (within Δ)	< 5.3 g/d	7	449	-0.51 (-3.63, 2.62)	0.565 (-7.40, 8.53)	72.1%	0.868
	≥ 5.3 g/d	1	189	0.06 (-7.26, 7.38)			
Fibre (between Δ)	< 3.8 g/d	8	480	-0.24 (-2.21, 1.73)	-1.37 (-4.64, 1.91)	70.2%	0.378
	≥ 3.8 g/d	5	424	-1.60 (-4.22, 1.01)			
Study design	Crossover	3	89	-0.66 (-3.67, 2.36)	-0.06 (-3.45, 3.33)	69.6%	0.968
	Parallel	12	961	-0.72 (-2.27, 0.83)			
MQS	< 8	9	527	-0.34 (-2.15, 1.47)	-0.86 (-3.60, 1.89)	68.9%	0.513
	≥ 8	6	523	-1.20 (-3.26, 0.87)			
Baseline WC	<95 cm	4	396	0.14 (-2.98, 3.26)	-1.97 (-5.97, 2.03)	74.2%	0.293
	≥95 cm	7	407	-1.84 (-4.34, 0.66)			
Carbohydrates (between Δ)	< 5%	7	467	-0.34 (-2.40, 1.73)	-0.91 (-3.81, 1.99)	69.9%	0.507
	≥ 5%	7	497	-1.25 (-3.28, 0.79)			

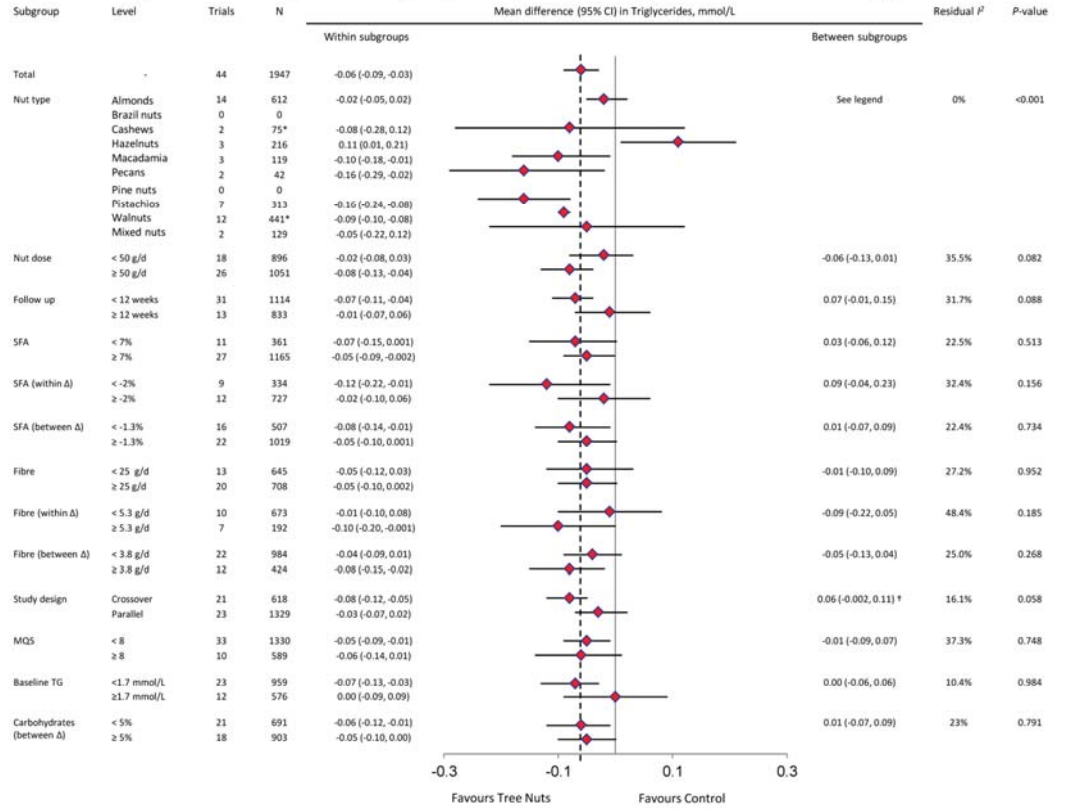


Point estimates for each subgroup level are the pooled effect estimates and are represented by diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value indicates the interstudy heterogeneity unexplained by the subgrouping. Pairwise between-subgroup mean differences (95% CIs) for nut type are not shown due to lack of statistical significance between groups. SFA = Saturated Fatty Acids, SFA (within Δ) = change within the tree nut diet for SFA, SFA (between Δ) = difference between the tree nut and control diets for SFA, Fibre (within Δ) = change within the tree nut diet for fibre, Fibre (between Δ) = difference between the tree nut and control diets for fibre, MQS = Heyland Methodological Quality Score, WC = waist circumference, Carbohydrates (between Δ)= difference between the tree nut and control diets 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 ($P < 0.05$)

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



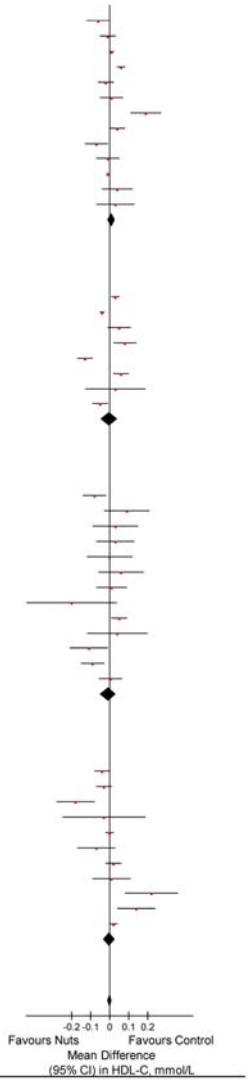
Point estimates within each subgroup level are the pooled effect estimates and are represented by diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value indicates the interstudy heterogeneity unexplained by the subgrouping. Significant pairwise 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 (within Δ) = change within the tree nut diet for SFA, SFA (between Δ) = difference between the tree nut and control diets for SFA, Fibre (within Δ) = change within the tree nut diet for fibre, Fibre (between Δ) = difference between the tree nut and control diets for fibre, MQS = Heyland Methodological Quality Score, TG = Triglycerides, Carbohydrates (between Δ)= difference between the tree nut and control diets 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 ($P < 0.05$)

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

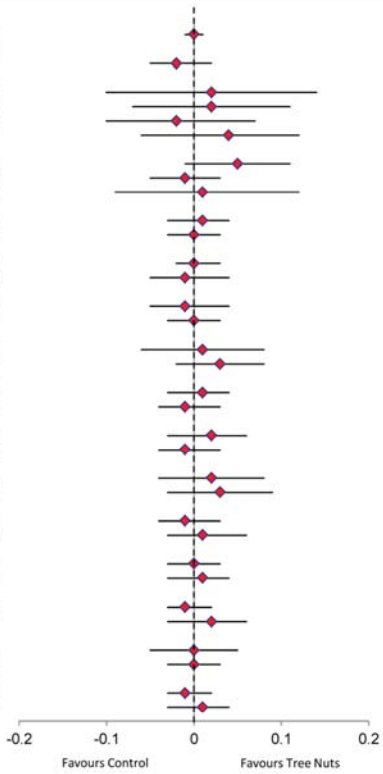
Subgroup and Study, year (Reference)	Nuts *n*	Control *n*	Weight	Mean Difference (95% CI) in mmol/L
Otherwise Healthy				
Sabate et al, 1993 (30)	18	18	2.20%	-0.06 [-0.12, -0.00]
Curb et al, 2000 (10)	30	30	3.10%	-0.01 [-0.05, 0.03]
Morgan and Clayshulte, 2000 (32)	10	9	4.40%	0.01 [0.00, 0.02]
Rajaram 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)	25	25	2.20%	0.01 [-0.05, 0.07]
Kocyigit et al, 2006 (16)	22	22	1.60%	0.19 [0.11, 0.27]
Kurlandsky and Stoke, 2006 (39) - Almonds	12	12	3.10%	0.04 [0.00, 0.08]
Kurlandsky and Stoke, 2006 (39) – Almonds + dark chocolate	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 [-0.01, -0.01]
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: Tau² = 0.00; Chi² = 103.30, df = 12 (P < 0.00001); I² = 88%				
Test for overall effect: Z = 1.07 (P = 0.28)				
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)	30	30	3.10%	-0.13 [-0.17, -0.09]
Sheridan et al, 2007 (17)	15	15	3.10%	0.06 [0.02, 0.10]
Gebauer et al, 2008 (41)	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: Tau² = 0.00; Chi² = 105.37, df = 7 (P < 0.00001); I² = 93%				
Test for overall effect: Z = 0.04 (P = 0.97)				
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)	61	62	0.90%	0.06 [-0.06, 0.18]
Katz et al, 2012 (51)	40	40	1.60%	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 and Mattes, 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: Tau² = 0.00; Chi² = 33.96, df = 12 (P = 0.0007); I² = 65%				
Test for overall effect: Z = 0.41 (P = 0.68)				
Type 2 diabetes mellitus				
Lovejoy et al, 2002 (35) – High fat	30	30	3.10%	-0.04 [-0.08, -0.00]
Lovejoy et al, 2002 (35) – High fat	30	30	3.10%	-0.03 [-0.07, 0.01]
Wien et al, 2003 (8)	32	33	1.20%	-0.18 [-0.28, -0.08]
Tapsell et al, 2004 (37)	17	20	0.30%	-0.03 [-0.25, 0.19]
Tapsell et al, 2009 (44)	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]
Li et al, 2011 (21)	20	20	1.20%	0.01 [-0.09, 0.11]
Damavandi, 2012 (18)	22	21	0.70%	0.22 [0.08, 0.36]
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: Tau² = 0.00; Chi² = 43.80, df = 10 (P < 0.00001); I² = 77%				
Test for overall effect: Z = 0.10 (P = 0.92)				
Total (95% CI)	**1409**	**1345**	**100.00%**	**0.00 [-0.01, 0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 304.77, df = 44 (P < 0.00001); I² = 86%				
Test for overall effect: Z = 0.08 (P = 0.93)				
Test for subgroup differences: Chi² = 1.72, df = 3 (P = 0.63), I² = 0%				



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.

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

Subgroup	Level	Trials	N	Mean difference (95% CI) in HDL-C, mmol/L: Within subgroups	Between subgroups	Residual I^2	P-value
Total	-	45	2112	0.00 (-0.01, 0.01)			
Nut type	Almonds	14	652	-0.02 (-0.05, 0.02)	See legend	81.4%	0.656
	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)			
Nut dose	< 50 g/d	20	1147	0.01 (-0.03, 0.04)	0.002 (-0.04, 0.05)	85.5%	0.943
	≥ 50 g/d	25	965	0.00 (-0.03, 0.03)			
Follow up	< 12 weeks	33	1189	0.01 (-0.02, 0.03)	-0.01 (-0.07, 0.04)	85.9%	0.760
	≥ 12 weeks	12	923	-0.01 (-0.05, 0.04)			
SFA	< 7%	12	550	-0.01 (-0.04, 0.06)	0.01 (-0.04, 0.06)	84.2%	0.667
	≥ 7%	27	1165	0.00 (-0.03, 0.03)			
SFA (within Δ)	< -2%	9	334	0.01 (-0.06, 0.08)	0.01 (-0.06, 0.08)	83.8%	0.689
	≥ -2%	13	916	0.03 (-0.02, 0.08)			
SFA (between Δ)	< -1.3%	16	507	0.01 (-0.03, 0.04)	-0.01 (-0.06, 0.04)	86.7%	0.654
	≥ -1.3%	23	1208	-0.01 (-0.04, 0.03)			
Fibre	< 25 g/d	13	645	0.02 (-0.03, 0.06)	0.03 (-0.08, 0.03)	88.4%	0.414
	≥ 25 g/d	21	897	-0.01 (-0.04, 0.03)			
Fibre (within Δ)	< 5.3 g/d	10	673	0.02 (-0.04, 0.08)	0.01 (-0.08, 0.09)	86.9%	0.850
	≥ 5.3 g/d	8	381	0.03 (-0.03, 0.09)			
Fibre (between Δ)	< 3.8 g/d	22	984	-0.01 (-0.04, 0.03)	0.02 (-0.03, 0.08)	85.6%	0.400
	≥ 3.8 g/d	13	613	0.01 (-0.03, 0.06)			
Study design	Crossover	22	671	0.00 (-0.03, 0.03)	0.01 (-0.04, 0.05)	85.9%	0.823
	Parallel	23	1441	0.01 (-0.03, 0.04)			
MQS	< 8	32	1253	-0.01 (-0.03, 0.02)	0.02 (-0.03, 0.07)	84.1%	0.346
	≥ 8	11	778	0.02 (-0.03, 0.06)			
Baseline HDL-C	<1.15 mmol/L	10	444	0.00 (-0.05, 0.05)	0.00 (-0.06, 0.06)	87.4%	0.952
	≥1.15 mmol/L	27	1233	0.00 (-0.03, 0.03)			
Carbohydrates (between Δ)	< 5%	22	880	-0.01 (-0.03, 0.02)	0.02 (-0.02, 0.06)	82.4%	0.316
	≥ 5%	18	903	0.01 (-0.03, 0.04)			

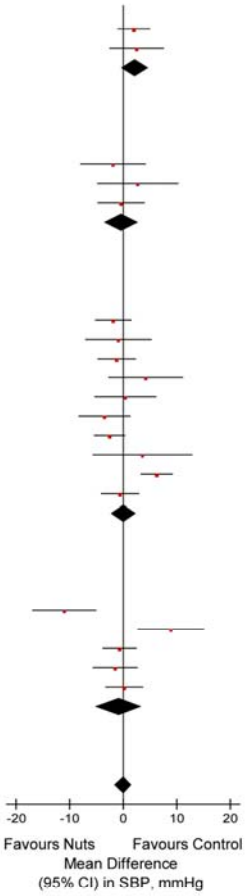


Point estimates for each subgroup level are the pooled effect estimates and are represented by diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value indicates the interstudy heterogeneity unexplained by the subgrouping. Pairwise between-subgroup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

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

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

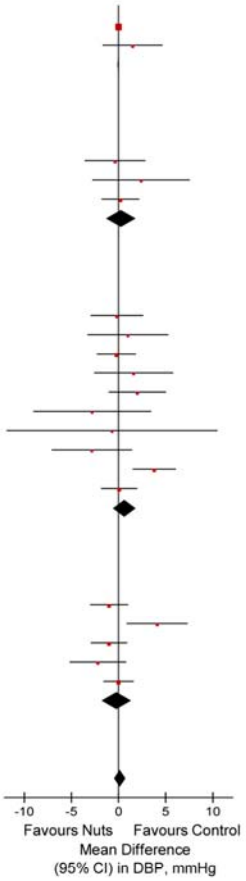
Subgroup and Study, year (Reference)	Nuts *n*	Control *n*	Weight	Mean Difference (95% CI) in mmHg
Otherwise Healthy				
Sabate et al, 1993 (30)	18	18	6.60%	2.00 [-0.94, 4.94]
Iwamoto et al, 2002 (34)	40	40	4.70%	2.50 [-2.48, 7.48]
Subtotal (95% CI)	58	58	11.40%	2.13 [-0.40, 4.66]
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%				
Test for overall effect: Z = 1.65 (P = 0.10)				
Dyslipidemia				
Jenkins 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]
West 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: Tau² = 0.00; Chi² = 0.89, df = 2 (P = 0.64); I² = 0%				
Test for overall effect: Z = 0.16 (P = 0.87)				
Metabolic Syndrome Criteria				
Mukuddem-Petersen et al, 2007 (40)	42	22	6.30%	-1.86 [-5.17, 1.45]
Wien et al, 2010 (46)	32	33	3.80%	-0.90 [-7.00, 5.20]
Wu et al, 2010 (47)	94	95	6.10%	-1.22 [-4.71, 2.27]
Casas-Agustench et al, 2011 (48)	25	25	3.30%	4.20 [-2.68, 11.08]
Foster et al, 2012 (50)	61	62	4.20%	0.40 [-5.26, 6.06]
Katz et al, 2012 (51)	40	40	4.90%	-3.50 [-8.24, 1.24]
Wang 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]
Tan and Mattes, 2013 (56)	110	27	6.70%	6.27 [3.37, 9.17]
Tey 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]
Heterogeneity: Tau² = 8.55; Chi² = 27.04, df = 9 (P = 0.001); I² = 67%				
Test for overall effect: Z = 0.09 (P = 0.93)				
Type 2 diabetes mellitus				
Wien et al, 2003 (8)	32	33	4.00%	-11.00 [-16.88, -5.12]
Ma et al, 2010 (45)	22	22	3.80%	8.90 [2.77, 15.03]
Jenkins et al, 2011 (20)	40	39	6.50%	-0.68 [-3.78, 2.42]
Li 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: Tau² = 20.04; Chi² = 21.61, df = 4 (P = 0.0002); I² = 81%				
Test for overall effect: Z = 0.37 (P = 0.71)				
Total (95% CI)	**835**	**670**	**100.00%**	**0.07 [-1.54, 1.68]**
Heterogeneity: Tau² = 7.92; Chi² = 52.90, df = 19 (P < 0.0001); I² = 64%				
Test for overall effect: Z = 0.09 (P = 0.93)				
Test for subgroup differences: Chi² = 2.26, df = 3 (P = 0.52), I² = 0%				



Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia, metabolic syndrome criteria, type 2 diabetes mellitus 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 (Chi^2) at a significance level of $P < 0.10$ and quantified by the I^2 statistic. SBP = Systolic Blood Pressure, mmHg = millimeters of mercury.

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

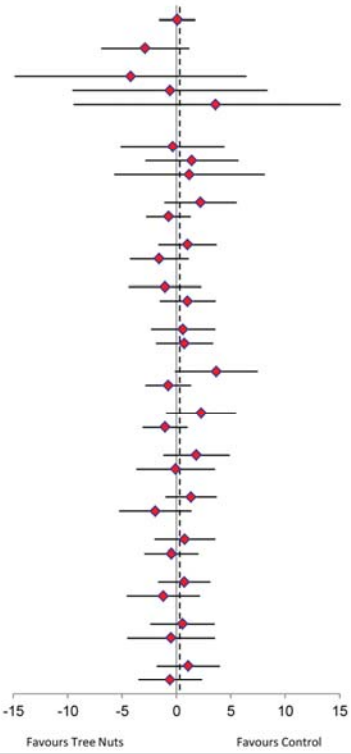
Subgroup and Study, year (Reference)	Nuts *n*	Control *n*	Weight	Mean Difference (95% CI) in mmHg
Otherwise Healthy				
Sabate et al, 1993 (30)	18	18	21.90%	0.00 [-0.04, 0.04]
Iwamoto et al, 2002 (34)	40	40	3.30%	1.50 [-1.62, 4.62]
Subtotal (95% CI)	58	58	25.20%	0.00 [-0.04, 0.04]
Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 1 (P = 0.35); I² = 0%				
Test for overall effect: Z = 0.01 (P = 0.99)				
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: Tau² = 0.00; Chi² = 0.83, df = 2 (P = 0.66); I² = 0%				
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 and Mattes, 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: Tau² = 1.28; Chi² = 13.91, df = 9 (P = 0.13); I² = 35%				
Test for overall effect: Z = 1.02 (P = 0.31)				
Type 2 diabetes mellitus				
Wien et al, 2003 (8)	32	33	6.70%	-1.00 [-2.96, 0.96]
Ma 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]
Li 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); I² = 61%				
Test for overall effect: Z = 0.27 (P = 0.79)				
Total (95% CI)	**835**	**670**	**100.00%**	**0.23 [-0.38, 0.83]**
Heterogeneity: Tau² = 0.44; Chi² = 28.69, df = 19 (P = 0.07); I² = 34%				
Test for overall effect: Z = 0.73 (P = 0.47)				
Test for subgroup differences: Chi² = 1.22, df = 3 (P = 0.75), I² = 0%				



Pooled effect estimates are shown as diamonds, one each for trials conducted in otherwise healthy, dyslipidemia, metabolic syndrome criteria, type 2 diabetes mellitus 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 (Chi^2) at a significance level of $P < 0.10$ and quantified by the I^2 statistic. DBP = Diastolic Blood Pressure, mmHg = millimeters of mercury.

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

Subgroup	Level	Trials	N	Mean difference (95% CI) in Systolic Blood Pressure, mmHg: Within subgroups	Between subgroups	Residual I^2	*P*-value
Total	-	20	1267	0.07 (-1.54, 1.69)			
Nut type	Almonds	6	437	-2.87 (-6.87, 1.14)	See legend	72.8%	0.949
	Brazil nuts	0	0				
	Cashews	1	32*	-4.22 (-14.83, 6.38)			
	Hazelnuts	1	107	-0.59 (-9.51, 8.33)			
	Macadamia	1	64	3.6 (-9.42, 16.62)			
	Pecans	0	0				
	Pine nuts	0	0				
	Pistachios	4	157	-0.35 (-5.08, 4.37)			
	Walnuts	6	341*	1.42 (-2.81, 5.65)			
	Mixed nuts	2	129	1.19 (-5.68, 8.07)			
Nut dose	< 50 g/d	6	562	2.21 (-1.06, 5.48)	-2.95(-6.79, 0.88)	59.4%	0.123
	≥ 50 g/d	14	705	-0.74 (-2.75, 1.27)			
Follow up	< 12 weeks	12	503	1.02 (-1.60, 3.64)	-2.78 (-6.24, 0.67)	58.6%	0.108
	≥ 12 weeks	8	764	-1.58 (-4.23, 1.08)			
SFA	< 7%	6	360	-1.06 (-4.35, 2.23)	2.09 (-2.06, 6.23)	66.2%	0.302
	≥ 7%	12	698	1.03 (-1.49, 3.54)			
SFA (within Δ)	< -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)			
SFA (between Δ)	< -1.3%	5	159	3.67 (-0.09, 7.42)	-4.41 (-8.69, -0.13)†	61.7%	0.044
	≥ -1.3%	13	899	-0.75 (-2.79, 1.29)			
Fibre	< 25 g/d	6	396	2.26 (-0.90, 5.41)	-3.30 (-7.05, 0.44)	51.3%	0.079
	≥ 25 g/d	11	640	-1.05 (-3.07, 0.97)			
Fibre (within Δ)	< 5.3 g/d	6	502	1.83 (-1.17, 4.84)	-1.91 (-6.57, 2.75)	49.1%	0.372
	≥ 5.3 g/d	4	260	-0.08 (-3.64, 3.48)			
Fibre (between Δ)	< 3.8 g/d	12	632	1.34 (-0.96, 3.63)	-3.28 (-7.28, 0.71)	60.9%	0.101
	≥ 3.8 g/d	6	426	-1.94 (-5.21, 1.33)			
Study design	Crossover	9	238	0.77 (-1.98, 3.52)	-1.24 (-4.91, 2.44)	65.4%	0.489
	Parallel	11	1029	-0.47 (-2.91, 1.97)			
MQS	< 8	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%	0.652
	≥130 mmHg	6	411	-0.51 (-4.49, 3.47)			
Carbohydrates (between Δ)	< 5%	9	466	1.09 (-1.76, 3.94)	-1.67 (-5.72, 2.38)	67.4%	0.395
	≥ 5%	9	592	-0.59 (-3.46, 2.29)			



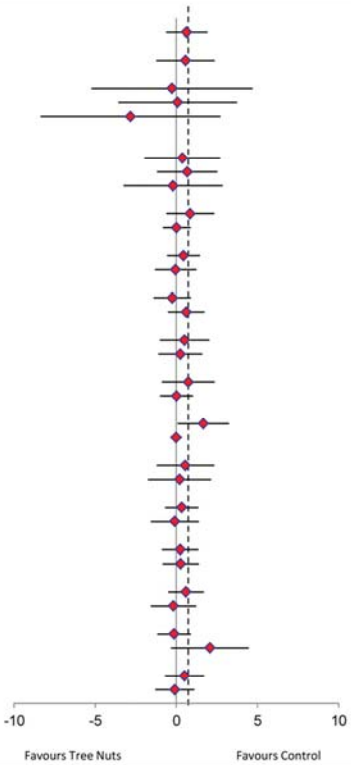
Point estimates for each subgroup level are the pooled effect estimates and are represented by diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value indicates the interstudy heterogeneity unexplained by the subgrouping. Pairwise between-subgroup mean differences (95% CIs) for nut type are not shown due to lack of statistical significance between groups. SFA = Saturated Fatty Acids, SFA (within Δ) = change within the tree nut diet for SFA, SFA (between Δ) = difference between the tree nut and control diets for SFA, Fibre (within Δ) = change within the tree nut diet for fibre, Fibre (between Δ) = difference between the tree nut and control diets for fibre, MQS = Heyland Methodological Quality Score, SBP = systolic blood pressure, Carbohydrates (between Δ)= difference between the tree nut and control diets 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 ($P < 0.05$).

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

Subgroup	Level	Trials	N	Mean difference (95% CI) in Diastolic Blood Pressure, mmHg: Within subgroups	Between subgroups	Residual I^2	*P*-value
Total	-	20	1267	0.64 (-0.60, 1.89)			
Nut type	Almonds	6	437	0.57 (-1.20, 2.33)	See legend	48.7%	0.907
	Brazil nuts	0	0				
	Cashews	1	32*	-0.27 (-5.21, 4.67)			
	Hazelnuts	1	107	0.07 (-3.55, 3.69)			
	Macadamia	1	64	-2.83 (-8.35, 2.69)			
	Pecans	0	0				
	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)	-0.84 (-2.50, 0.82)	31.5%	0.303
	≥ 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)	37%	0.528
	≥ 12 weeks	8	764	-0.05 (-1.30, 1.21)			
SFA	< 7%	6	360	-0.25 (-1.37, 0.86)	0.85 (-0.71, 2.41)	36.1%	0.264
	≥ 7%	12	698	0.61 (-0.49, 1.71)			
SFA (within Δ)	< -2%	6	225	0.50 (-0.98, 1.99)	-0.27 (-2.26, 1.72)	30.5%	0.774
	≥ -2%	7	668	0.24 (-1.08, 1.56)			
SFA (between Δ)	< -1.3%	5	159	0.74 (-0.85, 2.33)	-0.73 (-2.60, 1.13)	40.6%	0.416
	≥ -1.3%	13	899	0.01 (-0.97, 0.98)			
Fibre	< 25 g/d	6	396	1.66 (0.11, 3.21)	-1.66 (-3.21, -0.11)†	1.6%	0.037
	≥ 25 g/d	11	640	-0.01 (-0.05, 0.04)			
Fibre (within Δ)	< 5.3 g/d	6	502	0.55 (-1.19, 2.30)	-0.36 (-2.95, 2.23)	45.5%	0.757
	≥ 5.3 g/d	4	260	0.20 (-1.72, 2.11)			
Fibre (between Δ)	< 3.8 g/d	12	632	0.33 (-0.67, 1.33)	-0.43 (-2.19, 1.33)	40.3%	0.611
	≥ 3.8 g/d	6	426	-0.10 (-1.54, 1.35)			
Study design	Crossover	9	238	0.24 (-0.85, 1.33)	0.03 (-1.51, 1.57)	36.6%	0.968
	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)	40%	0.362
	≥ 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)	28.8%	0.086
	≥85 mmHg	6	411	2.08 (-0.29, 4.44)			
Carbohydrates (between Δ)	< 5%	9	466	0.51 (-0.67, 1.68)	-0.61 (-2.27, 1.05)	40.6%	0.447
	≥ 5%	9	592	-0.10 (-1.27, 1.07)			



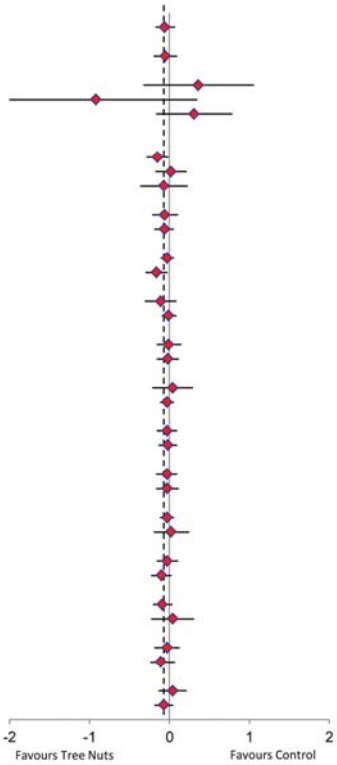
Point estimates for each subgroup level are the pooled effect estimates and are represented by diamonds. The dashed line represents the pooled effect estimate for the overall analysis. The residual I^2 value indicates the interstudy heterogeneity unexplained by the subgrouping. Pairwise between-subgroup mean differences (95% CIs) for nut type are not shown due to lack of statistical significance between groups. SFA = Saturated Fatty Acids, SFA (within Δ) = change within the tree nut diet for SFA, SFA (between Δ) = difference between the tree nut and control diets for SFA, Fibre (within Δ) = change within the tree nut diet for fibre, Fibre (between Δ) = difference between the tree nut and control diets for fibre, MQS = Heyland Methodological Quality Score, DBP = diastolic blood pressure, Carbohydrates (between Δ)= difference between the tree nut and control diets 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 ($P < 0.05$).

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

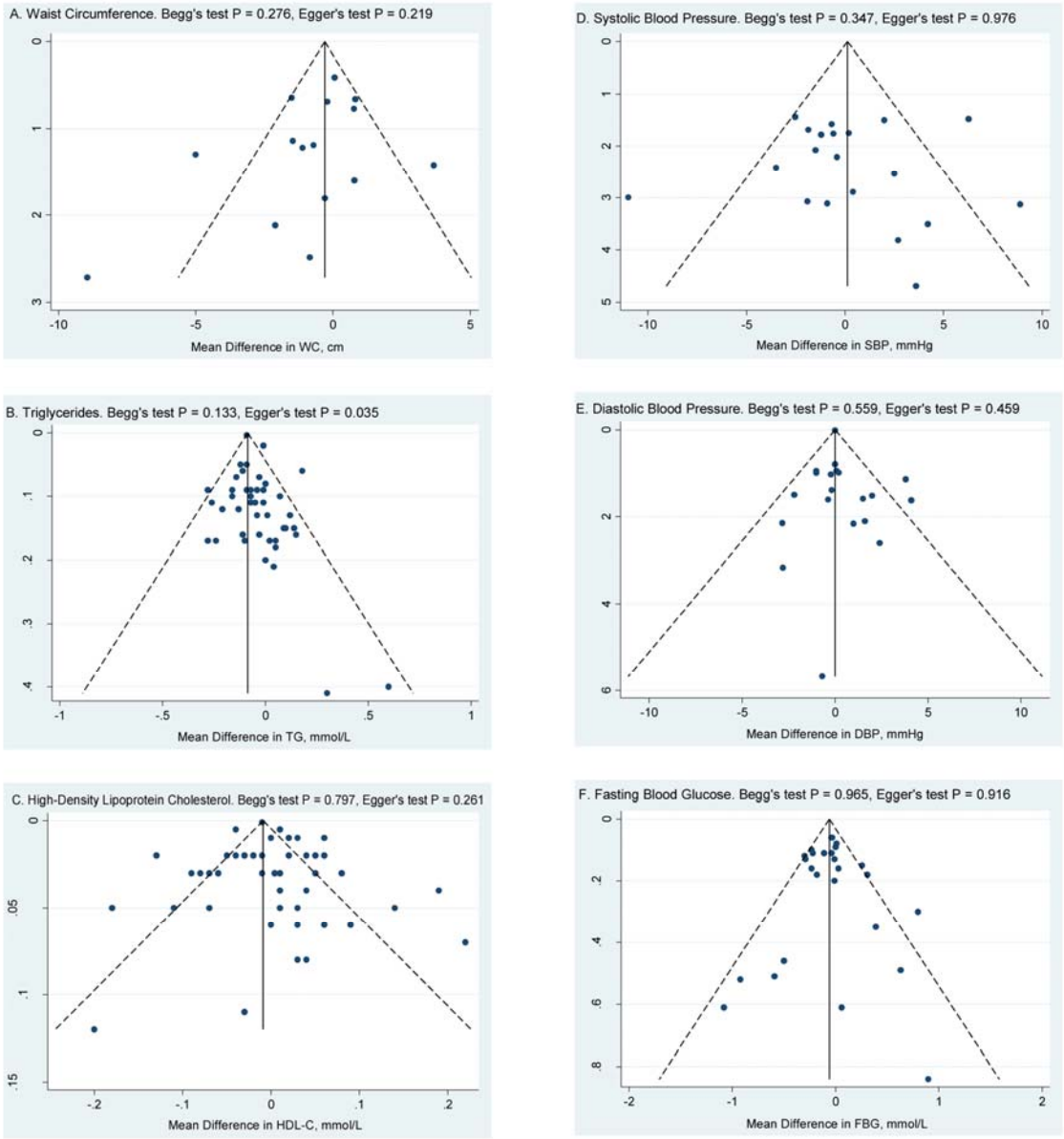
Subgroup	Level	Trials	N	Mean difference (95% CI) in Fasting Blood Glucose, mmol/L: Within subgroups	Between subgroups	Residual I^2	*P*-value
Total	-	26	1319	-0.06 (-0.17, 0.06)			
Nut type	Almonds	9	382	-0.05 (-0.19, 0.09)	See legend	39.7%	0.189
	Brazil nuts	0	0				
	Cashews	2	73	0.36 (-0.32, 1.05)			
	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				
	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)			
Nut dose	< 50 g/d	10	630	-0.06 (-0.21, 0.10)	-0.01 (-0.20, 0.18)	47.2%	0.921
	≥ 50 g/d	16	689	-0.06 (-0.18, 0.05)			
Follow up	< 12 weeks	16	625	-0.03 (-0.10, 0.05)	-0.13 (-0.29, 0.02)	40.3%	0.087
	≥ 12 weeks	10	694	-0.16 (-0.29, -0.03)			
SFA	< 7%	6	332	-0.11 (-0.30, 0.08)	0.11 (-0.10, 0.31)	39.4%	0.291
	≥ 7%	15	765	-0.01 (-0.09, 0.08)			
SFA (within Δ)	< -2%	5	203	-0.01 (-0.15, 0.14)	-0.01 (-0.21, 0.18)	48.2%	0.880
	≥ -2%	9	692	-0.02 (-0.15, 0.11)			
SFA (between Δ)	< -1.3%	4	161	0.04 (-0.21, 0.29)	-0.07 (-0.33, 0.19)	42.1%	0.596
	≥ -1.3%	17	936	-0.03 (-0.11, 0.05)			
Fibre	< 25 g/d	8	487	-0.03 (-0.15, 0.09)	0.01 (-0.15, 0.17)	44.6%	0.899
	≥ 25 g/d	11	553	-0.02 (-0.13, 0.09)			
Fibre (within Δ)	< 5.3 g/d	7	486	-0.03 (-0.16, 0.09)	0.01 (-0.18, 0.19)	22.7%	0.932
	≥ 5.3 g/d	3	245	-0.03 (-0.16, 0.11)			
Fibre (between Δ)	< 3.8 g/d	12	580	-0.03 (-0.11, 0.05)	0.05 (-0.18, 0.28)	43.2%	0.635
	≥ 3.8 g/d	8	482	0.02 (-0.19, 0.24)			
Study design	Crossover	10	260	-0.03 (-0.15, 0.10)	-0.07 (-0.24, 0.10)	45.3%	0.410
	Parallel	16	1059	-0.10 (-0.22, 0.02)			
MQS	< 8	19	801	-0.09 (-0.20, 0.03)	0.13 (-0.16, 0.41)	49.5%	0.376
	≥ 8	5	462	0.04 (-0.22, 0.30)			
Baseline FBG	<5.55 mmol/L	9	553	-0.03 (-0.18, 0.12)	-0.08 (-0.30, 0.15)	49.8%	0.470
	≥5.55 mmol/L	15	698	-0.11 (-0.23, 0.06)			
Carbohydrates (between Δ)	< 5%	10	499	0.04 (-0.13, 0.21)	-0.11 (-0.31, 0.09)	45.1%	0.273
	≥ 5%	13	710	-0.07 (-0.18, 0.04)			



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 (within Δ) = change within the tree nut diet for SFA, SFA (between Δ) = difference between the tree nut and control diets for SFA, Fibre (within Δ) = change within the tree nut diet for fibre, Fibre (between Δ) = difference between the tree nut and control diets for fibre, MQS = Heyland Methodological Quality Score, FG = fasting glucose, Carbohydrates (between Δ)= difference between the tree nut and control diets for carbohydrates.

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

A. Waist Circumference

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

B. Triglycerides

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

C. High-Density Lipoprotein Cholesterol

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

D. Systolic Blood Pressure

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

E. Diastolic Blood Pressure

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

F. Fasting Blood Glucose

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

N: number of participants in each subgroup.

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