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 I2 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.
with a low-fat control diet reduced major cardiovascular events by 30% in high cardiovascular risk participants. 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. Individual large trials of tree nuts have also shown that nuts improve criteria of the MetS: waist circumference, triglycerides, high-density lipoprotein cholesterol (HDL-C), blood pressure (BP), and glycaemic control.

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 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. 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. Reporting of results followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. 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) as a whole as 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. 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.

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 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. 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 crossovers). This scale gave a maximum MQS of 13 points. Studies with a score of ≥8 were considered of high quality.

The Cochrane Collaboration Risk of Bias Tool was used to assess the study risk of bias. 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...
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. 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. 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. 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. The presence of between-studies heterogeneity was assessed by the Cochran Q statistic (significance set at p<0.10) and quantified by the I² statistic. We interpreted the I² statistic as follows: ≤50% indicates ‘moderate’ heterogeneity; ≥50%, ‘substantial’ heterogeneity; and ≥75%, ‘considerable’ heterogeneity. 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 performed, 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), absolute fibre intake on the tree nut diet (<25 vs ≥25 g/day), 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), 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 trials8–23 30–35 as well as four companion reports40–43 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.42 43 Eleven trials (24.4%)8–23 30 33 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 53), MetS (5 trials22 40 47 48 58), some MetS criteria (overweight (7 trials(15.6%)9 11 50–52 56 57) and prediabetes (1 trial (2.2%)45), MetS (5 trials22 40 47 48 58), some MetS criteria (overweight (7 trials(15.6%)9 11 50–52 56 57) and prediabetes (1 trial (2.2%)45), 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 trials (46.7%)) designs. A number of trials used crossover designs, with a median intervention period of 12 weeks (IQR 12–26 weeks). A similar number of trials used single blind (30 trials (62.7%)) and double blind (18 trials (37.3%)) designs, with a median duration of 6 months (IQR 3–12 months). The type of control group varied, with a median dose of 53 g nuts/day (IQR 30–75 g nuts/day). A number of trials included a variety of control groups, with the median number of control groups per trial being 2 (IQR 1–3).
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 was exchanged for nuts. The test and control diets were matched for energy in all cases; however, two of the trials 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
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<th>Participants</th>
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<th>Design</th>
<th>Feeding control</th>
<th>Nut type</th>
<th>Nuts dose (g/day)†</th>
<th>Comparator</th>
<th>Diet‡</th>
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<th>Follow-up</th>
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<td>Katz et al (2012)</td>
<td>40 OW</td>
<td></td>
<td>OP, USA</td>
<td>Cross-over Supp</td>
<td>Walnut</td>
<td>56</td>
<td>Ad libitum</td>
<td>41:41:17</td>
<td>45:34:20</td>
<td>Isocaloric</td>
<td>8 weeks</td>
<td>7</td>
</tr>
<tr>
<td>Anderson et al (2013)</td>
<td>22 OW</td>
<td>OP, USA</td>
<td>Parallel</td>
<td>NA</td>
<td>Pistachio</td>
<td>35.4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>6 weeks</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>Berryman et al (2013)</td>
<td>53 HC</td>
<td>OP, USA</td>
<td>Cross-over</td>
<td>NA</td>
<td>Almond</td>
<td>42.5</td>
<td>Muffin</td>
<td>51:33:16</td>
<td>59:26:15</td>
<td>Isocaloric</td>
<td>6 weeks</td>
<td>NA</td>
</tr>
<tr>
<td>Tan and Mattes (2013)</td>
<td>137 OW (48 M, 89 W)</td>
<td>OP, USA</td>
<td>Parallel Supp</td>
<td>Almond</td>
<td>43</td>
<td></td>
<td>50:16:15</td>
<td>51:15:14</td>
<td>Isocaloric</td>
<td>4 weeks</td>
<td>5</td>
<td>Industry</td>
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Continued
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<thead>
<tr>
<th>Study (year) (reference)</th>
<th>Participants</th>
<th>Mean age (SD or range), years</th>
<th>Mean body weight or BMI (SD or range)*</th>
<th>Setting</th>
<th>Design</th>
<th>Feeding control</th>
<th>Nut type</th>
<th>Nuts dose (g/day)†</th>
<th>Comparator</th>
<th>Diet‡</th>
<th>Energy balance</th>
<th>Follow-up</th>
<th>MQS§</th>
<th>Funding sources¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almond (lunch)</td>
<td>29 (13.5)</td>
<td>29.3 (13.5)</td>
<td>84.8 (13.7)</td>
<td>Almond</td>
<td>Almond</td>
<td>43</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tey et al (2013)</td>
<td>57</td>
<td>107 OW (46 M, 61 W)</td>
<td>43.8 (13.5)</td>
<td>OP,</td>
<td>Parallel Supp</td>
<td>Hazelnut 30</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Agency</td>
</tr>
<tr>
<td>Hazelnut 60 g Control</td>
<td>41 (13.1)</td>
<td>42.8 (10.6)</td>
<td>82 (11.8)</td>
<td>New Zealand</td>
<td></td>
<td>Hazelnut 60</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gulati et al (2014)</td>
<td>58</td>
<td>68 MetS (37 M, 31 W)</td>
<td>41.6 (8.4)</td>
<td>OP,</td>
<td>Parallel DA</td>
<td>Pistachio 50§§</td>
<td>50§§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Industry</td>
</tr>
<tr>
<td>Pistachio Control</td>
<td>43.3 (6.1)</td>
<td>81.6 (12.9)</td>
<td>80.3 (10.3)</td>
<td>India</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wu et al (2014)</td>
<td>59</td>
<td>40 (10 M, 30 W)</td>
<td>24.9 (0.6)</td>
<td>OP,</td>
<td>Cross-over Supp</td>
<td>Walnut 43</td>
<td>43</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Industry</td>
</tr>
</tbody>
</table>

*Body weight is reported in kg and BMI is reported in kg/m². BMI is reported only when no data on weight were available.
†Nut dose is given based on 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 range 50–54 g/day; Jenkins et al range 50–75 g/day; Lovejoy et al range 57–113 g/day; Mukuddem-Petersen et al range 63–108 g/day; Torabian et al range 28–64 g/day; Zambon et al range 41–56 g/day.
‡‡Companion reports: Jenkins et al for Jenkins et al; Schutte et al for Mukuddem-Petersen et al; West et al and Holligan et al for Gebauer et al.
¶¶Baseline characteristics were based on the number of randomised participants for Li et al n=70; Ma et al n=24; Zambon et al n=55; Katz et al n=46; Sauder et al n=30; Gulati et al n=68 for recruited participants for Tapsell et al (n=50), and for age for Damavandi et al (n=50).
§§Based on 2100 kcal for Griel et al and based on 1400 kcal (~60 kg) for Gulati et al.
***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.
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...
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 (10.4%) did not report their funding source.

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.
were not statistically significant 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 (I²=34%, p=0.02). The same effect was seen with evidence of moderate heterogeneity (I²=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 (I²=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 (I²=64%, p<0.001) and evidence of moderate heterogeneity in the diastolic BP analysis (I²=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 interventions with higher fibre intake showed reductions in diastolic BP and also explained the heterogeneity in the overall analyses reducing the residual I² to 1.6%. No other subgroup analyses were statistically significant for either systolic or diastolic 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 (I²=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
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 2217 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 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. This triglyceride-lowering effect, however, was accompanied by an HDL-C increasing effect. 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. 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.

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. Individual trials have shown evidence of improvements in other aspects of glycaemic control. 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, Portfolio or DASH dietary patterns in people with type 2 diabetes mellitus. 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, and possibly decrease insulin resistance, 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, 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. Controlled trials of tree nuts alone or as part of Mediterranean, Portfolio or DASH dietary patterns have shown neutral or weight loss effects, and no influence on body fat mass or body fat percentage. Dietary patterns that incorporated nuts have reported weight loss under isocaloric conditions or no weight gain under hypercaloric feeding conditions, 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. 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. A BP-decreasing effect of tree nuts has also been seen in the context of Portfolio and DASH 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.
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. 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. Although the median fat intake of the tree nut containing diets (33.6%) was above that of the control diets (30.4%), but within the recommended limits of dietary guidelines (20–35%), 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. 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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Contributors SBM, CWCK, LSA and JLS were involved in conception and design. SBM, CWCK, EV, LSA, VH, AIC, AM, AM, LC, LAL, RJDs, DJAJ and JLS were involved in drafting of the article. SBM, CWCK, EV, LSA, VH, AIC, AM, AM, LC, LAL, RJDs, DJAJ and JLS were involved in critical revision of the article for important intellectual content. RJDs was involved in statistical expertise. CWCK, LSA, DJAJ and JLS were involved in obtaining funding. CWCK, EV, LSA, VH, AIC, AM, AM and LC were involved in administrative, technical or logistic support. SBM, EV, LSA, VH, AIC and AM were involved in collection and assembly of data. CWCK and JLS are the guarantors. All authors approved the final version of the article.

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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, Oratti, Pulse Canada, Saskatchewan Pulse Growers, Solae and Unilever. He has received travel funding, consultant fees and/or honoraria from Abbott.
Laboratories, the Almond Board of California, the American Peanut Council, the American Pistachio Growers, Barilla, Bayer, the Canola Council of Canada, the Coca-Cola Company, Danone, General Mills, the International Tree Nut Council Nutrition Research and Education Foundation, Kellogg, Loblaw Companies Ltd, the Nutrition Foundation of Italy (NFI), Oldways Preservation Trust, Orfali, Paramount Farms, the Peanut Institute, PepsiCo, Pulse Canada, Sabra Dipping Co, Saskatchewan Pulse Growers, Solae, Sun-Maid, Tate and Lyle, and Unilever. He is on the Dietary Guidelines Committee for the Diabetes Nutrition Study Group of the European Association for the Study of Diabetes and has served on the scientific advisory board for the Almond Board of California, the International Tree Nut Council, Oldways Preservation Trust, Paramount Farms and Pulse Canada. VH has received research support from the CIHR and the World Health Organization (WHO) for work on a systematic review and meta-analysis commissioned by WHO of the relation of saturated fatty acids with health outcomes. She received a travel award to attend a science day hosted by PepsiCo Inc and the New York Academy of Sciences. LC has received research support from the CIHR and the Agricultural Bioproducts Innovation Program through the Pulse Research Network (PURENet) and Saskatchewan 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 WHODietary 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 Celestal, the Sanitarium Company, Orfali, 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. 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He is on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of the CDA and the EASD, and he is on the ASN writing panel for a scientific statement on the metabolic and nutritional effects of fructose, sucrose and high-fructose corn syrup. He is a member of the Carbohydrate Quality Consortium and an unpaid scientific advisor for the Food, Nutrition and Safety Program of ILSI North America. His wife is an employee of Unilever Canada.

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