

# Nut consumption for the primary prevention of cardiovascular disease (Review)

Martin N, Germanò R, Hartley L, Adler AJ, Rees K



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[Intervention Review]

# Nut consumption for the primary prevention of cardiovascular disease

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## ABSTRACT

### Background

Nuts contain a number of nutritional attributes which may be cardioprotective. A number of epidemiological studies have shown that nut consumption may have a beneficial effect on people who have cardiovascular disease (CVD) risk factors. However, results from randomised controlled trials (RCTs) are less consistent.

### Objectives

To determine the effectiveness of nut consumption for the primary prevention of CVD.

### Search methods

We searched the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Web of Science Core Collection, CINAHL, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA) and Health Economics Evaluations Database (HEED) up to 30 July 2015. We searched trial registers and reference lists of reviews for further studies. We did not apply any language restrictions.

### Selection criteria

We included RCTs of dietary advice to increase nut consumption or provision of nuts to increase consumption lasting at least three months and including healthy adults or adults at moderate and high risk of CVD. The comparison group was no intervention or minimal intervention. The outcomes of interest were CVD clinical events and CVD risk factors.

### Data collection and analysis

Two review authors independently selected trials for inclusion, abstracted the data and assessed the risk of bias in included trials.

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## **Main results**

We included five trials (435 participants randomised) and one ongoing trial. One study is awaiting classification. All trials examined the provision of nuts to increase consumption rather than dietary advice. None of the included trials reported on the primary outcomes, CVD clinical events, but trials were small and short term. All five trials reported on CVD risk factors. Four of these trials provided data in a useable format for meta-analyses, but heterogeneity precluded meta-analysis for most of the analyses. Overall trials were judged to be at unclear risk of bias.

There were variable and inconsistent effects of nut consumption on CVD risk factors (lipid levels and blood pressure). Three trials monitored adverse events. One trial reported an allergic reaction to nuts and three trials reported no significant weight gain with increased nut consumption. None of the included trials reported on other secondary outcomes, occurrence of type 2 diabetes as a major risk factor for CVD, health-related quality of life and costs.

## **Authors' conclusions**

Currently there is a lack of evidence for the effects of nut consumption on CVD clinical events in primary prevention and very limited evidence for the effects on CVD risk factors. No conclusions can be drawn and further high quality longer term and adequately powered trials are needed to answer the review question.

## **PLAIN LANGUAGE SUMMARY**

### **Eating nuts to prevent cardiovascular disease**

#### **Review question**

This Cochrane review aims to answer the question whether or not eating nuts can prevent cardiovascular disease.

#### **Background**

Cardiovascular diseases are a group of conditions that affect the heart and blood vessels. They are a major cause of death worldwide. The food we eat may influence the risk of getting cardiovascular disease. Nuts, if consumed regularly and at relatively high doses (50 g to 100 g), are believed to reduce total cholesterol and low-density lipoprotein (LDL) cholesterol (bad cholesterol).

#### **Study characteristics**

This review includes randomised controlled trials, which lasted at least 12 weeks. Participants were between 37 to 54 years old on average. The evidence is current up to 30 July 2015.

#### **Key results**

We included five trials (435 participants), one of which had two treatment arms. All five trials investigated the effects of eating nuts. No studies were found which investigated the effect of giving advice to eat more nuts. None of the studies reported on deaths or cardiovascular events. None of the results show a clear effect on total cholesterol levels and blood pressure. One study reported one case of an allergic reaction to nuts. Three studies reported no significant weight gain with increased nut consumption. No other adverse events were reported.

#### **Quality of the evidence**

All included trials are small, with 60 to 100 participants, and have a high level of variation (heterogeneity). Therefore the results should be interpreted with caution. Overall we regarded the included trials as being at unclear risk of bias.

## BACKGROUND

### Description of the condition

Cardiovascular diseases (CVD), which include coronary heart disease (CHD) and cerebrovascular disease, are a variety of conditions that affect the heart and blood vessels (WHO 2013). They are the leading cause of death worldwide, with over 17 million deaths per year attributed to CVD (WHO 2013). In 2011, CVD accounted for nearly 160,000 deaths in the UK (BHF 2014). Around 74,000 of these deaths were caused by CHD (BHF 2014). Low- and middle-income countries (LMICs) are also affected by CVD. In 2001, three quarters of global deaths from CHD took place in LMICs (WHO 2013). According to Gaziano 2010, the rapid increase in CHD burden in LMICs is attributable to the acquisition of lifestyle-related risk factors, socio-economic changes and an increase in life span in these countries.

Dietary factors may play a vital role in the development of CVD and its risk factors, and may contribute to the geographic variability in CVD morbidity and mortality (Yusuf 2001; Scarborough 2011). These factors are important, not only because they have been linked to CVD development, but also because they can be modified. This makes them one of the main targets for interventions aimed at the primary prevention and management of CVD.

### Description of the intervention

Nuts have been in the human diet for thousands of years. Indeed, records show that people ate pistachio nuts as far back as 7000 BC (King 2008). This pattern has continued today with nuts eaten globally in a variety of ways, including as ingredients in recipes and as snacks (King 2008). However, the amount of nuts consumed around the world differs. For instance, nut consumption in countries with a Mediterranean style diet is twice that of those with an American diet (Dreher 1996; Sabaté 2006).

In botanical terms, nuts are considered as a dry fruit with one seed that has a hard shell or pericarp (Sabaté 2006). Nuts are an energy dense food containing around 44% to 76% total fat (Sabaté 2010). Their saturated fatty acid content is low, being 4% to 16%, with almost half of their total fat content consisting of unsaturated fatty acids (Ros 2006). They also contain protein (around 10% to 30%) (Blomhoff 2006) and a number of micronutrients and minerals, such as folic acid, selenium, zinc and niacin (Brufau 2006). Many nuts also contain antioxidants (Vinson 2012). Almonds, for instance, contain a number of flavonoids such as catechins, flavonols and flavonones, whilst walnuts contain a variety of polyphenols and tocopherols (Blomhoff 2006). Raw walnuts and toasted almonds in particular have shown a high antioxidant efficacy (Vinson 2012). This may explain why almonds and walnuts are the main types of nuts studied in trials (based on 25 nut consumption trials included in Sabaté 2010).

### How the intervention might work

A number of epidemiological studies show that nuts have a beneficial effect on CVD risk factors (Fraser 1992; Albert 2002). For example, in the Iowa Women's Health Study (IWHHS) CVD mortality was lower in people who ate nuts/peanut butter five or more times per week (hazard ratio (HR) 0.67 (95% confidence interval (CI) 0.56 to 0.81; Blomhoff 2006). Evidence also comes from systematic reviews of observational studies. Mukuddem-Petersen 2005 conducted a systematic review of observational studies looking at the effect of nuts on the lipid profile of normal and hyperlipidemic participants. They found that eating 1.5 to 3.5 servings of nuts five times or more per week along with a heart healthy diet significantly reduced low-density lipoprotein cholesterol (LDL-C) and total cholesterol. In particular, three studies of almond consumption showed that consuming 50 g to 100 g of almonds per day was associated with 4% to 17% lower total cholesterol and 7% to 19% lower LDL-C in both hypercholesterolemia and non-cholesterolemic participants. Randomised controlled trials (RCTs) also provide some evidence that nuts may be beneficial for people with CVD risk factors (Sabaté 1993; Jenkins 2002). One RCT comparing a recommended cholesterol-lowering diet with walnuts to one without found that incorporating 84 g of walnuts on a daily basis for four weeks decreased serum levels of total cholesterol by 12% (Sabaté 1993).

The mechanisms by which nuts reduce CVD risk are not exactly known. However, nuts contain a number of nutritional attributes that have been linked to cardioprotection (Sabaté 2010). For instance, walnuts contain high levels of n-3 fatty acids, which are known to be cardioprotective (Sabaté 2010). It is thought that the individual nutrients contained in nuts or the composite of cardioprotective nutrients that they contain, or both, may account for the beneficial effect of nuts on CVD and its risk factors (Kris-Etherton 2008). Furthermore, the beneficial ratio of unsaturated fatty acids to saturated fatty acids may be an important factor in the health benefits associated with frequent nut intake (Sabaté 2010).

### Why it is important to do this review

Despite the potential benefits from increased nut intake, there are few systematic reviews examining the effects of nut consumption on CVD prevention and, of those available, most include observational studies which are subject to bias and confounding (Mukuddem-Petersen 2005; Afshin 2014; Zhou 2014). One systematic review of the effects of walnut consumption on lipid levels included only short term trials (average six weeks duration) so the sustained effects could not be established (Banal 2009). To our knowledge, there are currently no systematic reviews examining RCT evidence on CVD risk factors or clinical outcomes over the longer term (three months or more). To address this, this Cochrane review will examine evidence from RCTs of three months or longer duration on nut consumption for the primary prevention of CVD

in the general population and in people at high risk of CVD.

## OBJECTIVES

To determine the effectiveness of nut consumption for the primary prevention of CVD.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included RCTs, reported as full-text articles, those published as abstract only, and unpublished data.

#### Types of participants

We included trials of adults (aged 18 years and older) from the worldwide population with and without CVD risk factors (e.g. hypertension, hyperlipidemia, overweight/obese). As this Cochrane review is interested in the primary prevention of CVD, we excluded people who experienced a myocardial infarction (MI), stroke, revascularization procedure (coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI)), and those with angina or angiographically defined CHD.

We excluded trials with > 25% of participants with diagnosed CVD or type 2 diabetes at baseline. Whilst type 2 diabetes is a major risk factor for CVD, interventions targeting specifically this patient group are covered by Cochrane reviews from the Cochrane Metabolic and Endocrine Disorders Group.

#### Types of interventions

We included trials comparing the provision of nuts or advice to increase nut consumption with no intervention or minimal intervention (e.g. leaflets with no face-to-face intervention or reinforcement). Trials were excluded in which the control group received an intervention which was not also given to the intervention group, e.g. particular foods other than nuts. We included trials of at least 12 weeks duration. Longer term studies are most informative in terms of behavioral change and sustained changes for public health interventions, with follow-up being seen as the time elapsed since the start of the intervention.

We did not include multifactorial intervention studies, such as those including exercise or lifestyle interventions, in this review in order to avoid confounding.

## Types of outcome measures

### Primary outcomes

1. Cardiovascular mortality.
2. All-cause mortality.
3. Non-fatal endpoints such as MI, CABG, PCI, angina or angiographically defined CHD, stroke, carotid endarterectomy and peripheral arterial disease (PAD).

### Secondary outcomes

1. Changes in blood pressure (systolic and diastolic) and blood lipids (total cholesterol, LDL-C, high-density lipoprotein (HDL) cholesterol and triglycerides).
2. Type 2 diabetes as a major CVD risk factor.
3. Health-related quality of life (using any validated scale).
4. Costs.
5. Adverse effects (as defined by the authors of the included trials, e.g. weight gain, anaphylaxis).

## Search methods for identification of studies

### Electronic searches

We systematically searched the following bibliographic databases on 30 July 2015:

- Cochrane Central Register of Controlled Trials (CENTRAL, Issue 6 of 12, 2015) on the Cochrane Library.
- MEDLINE (Ovid, 1946 to July week 4 2015).
- EMBASE Classic and EMBASE (Ovid, 1947 to 2015 July 29).
- CINAHL (EBSCO, 1937 to 17 July 2015).
- Web of Science Core Collection (Thomson Reuters, 1970 to 29 July 2015).
- Database of Abstracts of Reviews of Effects (DARE, Issue 2 of 4, 2015), Health Technology Assessment Database (HTA, Issue 2 of 4, 2015) and Health Economics Evaluations Database (HEED, Issue 2 of 4, 2015) on the Cochrane Library.

The search strategies are presented in [Appendix 1](#). We applied the Cochrane sensitivity-maximizing RCT filter ([Lefebvre 2011](#)) to MEDLINE (Ovid) and adaptations of it to the other databases, except the Cochrane Library.

We did not apply any restrictions on language of publication.

### Searching other resources

We searched ClinicalTrials.gov ([www.ClinicalTrials.gov](http://www.ClinicalTrials.gov)) and the WHO International Clinical Trials Registry Platform (WHO ICTRP) Search Portal ([apps.who.int/trialsearch/](http://apps.who.int/trialsearch/)) on 12 March 2015. Search terms used were 'cardiovascular and nuts'.

We contacted trial authors for additional information. We checked reference lists of included trials reports and review articles for additional references.

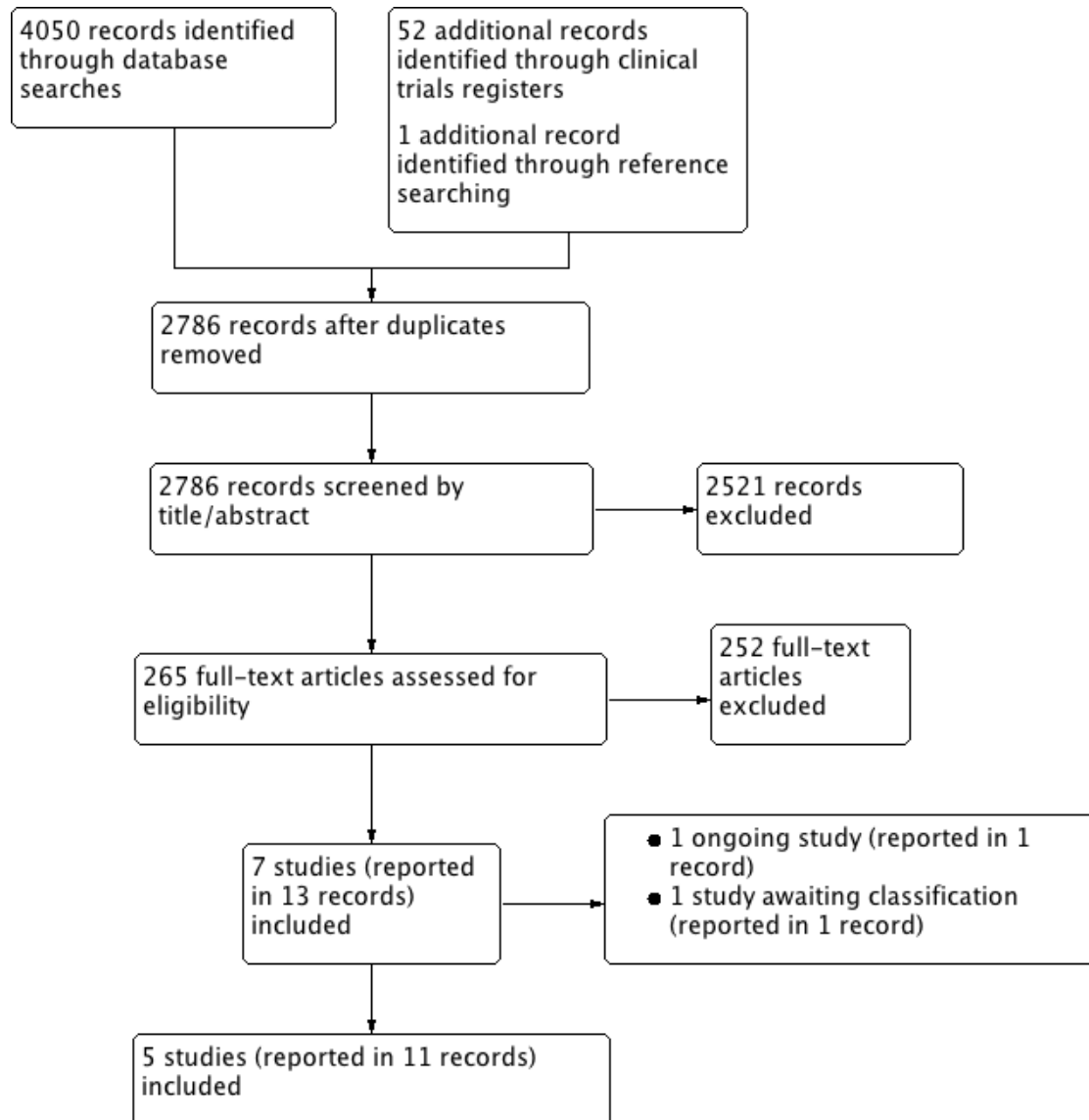
## **Data collection and analysis**

### **Selection of studies**

Two review authors (AA, RG, NM, KR) independently screened titles and abstracts for inclusion of all the potential studies identified by the searches and coded them as 'retrieve' (eligible or poten-

tially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports/publications. Two review authors (AA, RG, NM, KR) independently screened the full-text articles and identified trials for inclusion, and identified and recorded reasons for exclusion of the ineligible studies. We resolved any disagreements through discussion. We identified and excluded duplicates and collated multiple reports of the same trial so that each trial, rather than each report, is the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram ([Figure 1](#)) and [Characteristics of excluded studies](#) table.

**Figure 1. Study flow diagram.**



### **Data extraction and management**

We used a data collection form for trial characteristics and outcome data, which was piloted on at least one trial included in the review. Two review authors (AA, NM) extracted trial characteristics from included trials. We extracted the following trial characteristics:

1. Methods: trial design, total duration of trial, details of any 'run in' period, number of trial centres and location, trial setting,

withdrawals and date of trial.

2. Participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria and exclusion criteria.

3. Interventions: intervention, comparison, concomitant medications and excluded medications.

4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.



5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (AA, NM) independently extracted outcome data from included trials. We resolved disagreements by consensus or by involving a third review author (KR). One review author (NM) transferred data into the [RevMan 2014](#) file. We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (KR) spot-checked trial characteristics for accuracy against the trial report.

### Assessment of risk of bias in included studies

Two review authors (AA, NM) independently assessed risk of bias for each included trial using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by involving another review author (KR). We assessed the risk of bias according to the following domains:

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias (e.g. industry funding).

We graded each potential source of bias as either 'high', 'low' or 'unclear' and provided a quote from the study report together with a justification for our judgment in the 'Risk of bias' section of the [Characteristics of included studies](#) table. We summarised the 'Risk of bias' judgements across different trials for each of the domains listed. Where information on risk of bias related to unpublished data or correspondence with a trial author, we noted this in the 'Risk of bias' section of the [Characteristics of included studies](#) table.

When considering treatment effects, we took into account the risk of bias for the trials that contributed to that outcome.

### Assessment of bias in conducting the systematic review

We conducted this Cochrane review according to the published protocol (Martin 2015) and reported any deviations from it in the [Differences between protocol and review](#) section.

### Measures of treatment effect

We analysed continuous data as mean difference (MD) with 95% CIs. For continuous variables we present data for the change from baseline rather than end point data. We entered data presented as a scale with a consistent direction of effect, with the exception of HDL cholesterol where an increase in this outcome is a positive finding.

We planned to analyse dichotomous data as odds ratios or risk ratios with 95% CIs but that did not apply to any of our included analyses. Narratively describing skewed data reported as medians and interquartile ranges also did not apply to this review.

### Unit of analysis issues

#### Studies with multiple intervention groups

Data for the control group have been used for each intervention group comparison. We reduced the weight assigned to the control group by dividing the control group N by the number of intervention groups analysed.

#### Cluster RCTs

We planned to analyse cluster RCTs using the unit of randomisation (cluster) as the number of observations. However, none of the included trials are cluster RCTs.

#### Cross-over studies

For included cross-over studies we only used the first period.

### Dealing with missing data

We contacted trial authors or study sponsors in order to verify key trial characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where papers did not report results as change from baseline we calculated this. For the standard deviation differences we followed the methods presented in the *Cochrane Handbook for Systematic Reviews of Interventions* for imputing these (Section 16.1.3.2: Imputing standard deviations for changes from baseline; Higgins 2011), and assumed a correlation of 0.5 between baseline and follow-up measures as suggested by Follman 1992.

### Assessment of heterogeneity

We used the  $I^2$  statistic to measure heterogeneity among the trials in each analysis. If no heterogeneity was present, a fixed-effect meta-analysis was performed. If we identified substantial heterogeneity ( $I^2$  statistic > 50%) we reported it and explored possible causes by prespecified subgroup analysis if there were a sufficient number of trials. If the heterogeneity could not be explained, we either provided a narrative overview or used a random-effects model with appropriately cautious interpretation.

## Assessment of reporting biases

If we had been able to pool more than 10 trials, we would have created and examined a funnel plot to explore possible small study biases for the primary outcomes. However, this did not apply to this Cochrane review.

## Data synthesis

We performed statistical analysis using [RevMan 2014](#). None of the included trials reported dichotomous data, which we would have added as events and the number of participants. We entered continuous data as means and standard deviations. We performed meta-analysis if treatments and participants were similar enough. In the absence of substantial heterogeneity (> 50%) and provided that there are sufficient trials, we combined the results using a fixed-effect model.

## Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses:

1. Type of nut.
2. Dosage.
3. Duration of the intervention.
4. Type of intervention (provision or advice).
5. Risk level of participants (presence of CVD risk factors

versus no CVD risk factors).

We planned to use the formal test for subgroup interactions in [RevMan 2014](#).

There were an insufficient number of trials included in this Cochrane review to perform these analyses.

## Sensitivity analysis

We planned to carry out sensitivity analyses by only including trials at low risk of bias. However an insufficient number of trials met the inclusion criteria of the review to do this.

# RESULTS

## Description of studies

### Results of the search

The search of the main databases retrieved 4050 references, of which 1311 were duplicates, leaving 2739 to screen. The search of clinical trial registers retrieved 52 trial reports, of which 6 were duplicates, leaving 46 to screen. One reference was identified through reference checking. In total we screened 2786 references by title and abstract and excluded 2521. We retrieved and screened the full

text of 265 references, which led to the exclusion of 252. Eleven references were eligible for inclusion and reported on five studies. We identified one ongoing study and one study is awaiting classification. A PRISMA flow chart ([Figure 1](#)) illustrates this process.

## Included studies

This Cochrane review includes five trials (reported in 11 references) with a total of 435 participants (see [Characteristics of included studies](#)).

All studies were RCTs. Two studies were trials with two parallel treatment arms ([Balci 2012](#); [Abazarfard 2014](#)). One trial had two relevant treatment arms of different amounts of hazelnuts consumed and are denoted [Tey 2013 \(30 g\)](#) and [Tey 2013 \(60 g\)](#) as they are entered separately in the analysis. One study had four treatment arms ([Tey 2011](#)) of which we were only interested in the nut intervention and control arm. One study, [Sabaté 2005](#), was a cross-over trial and we only used the first period, as planned and described in the [Unit of analysis issues](#) section.

Two trials were conducted in New Zealand ([Tey 2011](#); [Tey 2013 \(30 g\)](#) and [Tey 2013 \(60 g\)](#)), one in USA ([Sabaté 2005](#)), one in Iran ([Abazarfard 2014](#)) and one does not provide the information ([Balci 2012](#)). None of the included RCTs investigated advice to increase nut consumption but instead they all provided nuts to the intervention groups. Almonds were studied in one trial ([Abazarfard 2014](#), 50 g per day), walnuts in two trials ([Balci 2012](#), 10 g per day; [Sabaté 2005](#), 28 g to 56 g per day) and hazelnuts in two trials ([Tey 2013 \(30 g\)](#), 30 g per day; [Tey 2013 \(60 g\)](#), 60 g per day; [Tey 2011](#), 42 g per day). Control groups were asked to follow their usual diet ([Sabaté 2005](#); [Tey 2011](#); [Tey 2013 \(30 g\)](#); [Tey 2013 \(60 g\)](#)) or to follow advice for a balanced diet ([Abazarfard 2014](#)) or healthy nutrition ([Balci 2012](#)). All participants, regardless of allocation to intervention or control group, were advised to maintain their usual activity habits ([Sabaté 2005](#); [Tey 2013 \(30 g\)](#); [Tey 2013 \(60 g\)](#); [Abazarfard 2014](#)) or had their physical activity measured at baseline and during the intervention ([Tey 2011](#)). One trial did not provide information on physical activity ([Balci 2012](#)).

In all studies, recruitment took place via public advertisements from the general population. The number of randomised participants per trial ranged from 60 to 110 (N = 60 in [Balci 2012](#); N = 110 in [Tey 2013 \(30 g\)](#) and [Tey 2013 \(60 g\)](#) combined; N = 108 in [Abazarfard 2014](#); N = 94 in [Sabaté 2005](#) and N = 63 in the two arms of interest in [Tey 2011](#)). The mean age of participants ranged from 37.4 to 54.3 years.

Studies varied in the types of participants recruited. One trial recruited only female participants ([Abazarfard 2014](#)) while the other trials included male and female participants with similar ratios ([Balci 2012](#), 45% male; [Tey 2011](#), 47% male; [Tey 2013 \(30 g\)](#) and [Tey 2013 \(60 g\)](#), 43% male; [Sabaté 2005](#), 44% male). [Abazarfard 2014](#) included pre-menopausal women aged 20 to 55 years with a BMI  $\geq 25$  kg/m<sup>2</sup>. [Balci 2012](#) included participants

with prediabetic metabolic syndrome. [Tey 2013 \(30 g\)](#) and [Tey 2013 \(60 g\)](#) included participants with BMI  $\geq 25$  kg/m<sup>2</sup>, aged between 18 and 65 years. [Tey 2011](#) also included participants aged 18 to 65 years with a BMI  $< 30$  kg/m<sup>2</sup>. Information for [Sabat  2005](#) differed between the two papers reporting this study regarding the inclusion of participants with BMI  $< 35$  kg/m<sup>2</sup>/BMI  $\leq 35$  kg/m<sup>2</sup>, aged between 30 and 72 years.

The duration of the intervention varied between the included trials. Two RCTs had a follow-up of 12 weeks ([Tey 2011](#); [Tey 2013 \(30 g\)](#) and [Tey 2013 \(60 g\)](#)), two RCTs of three months ([Balci 2012](#); [Abazarfard 2014](#)) and one RCT for six months ([Sabat  2005](#)).

We have provided details about one ongoing study, [NCT01950806](#), in the [Characteristics of ongoing studies](#) table. This study investigates whether pecans are effective in reducing the risk of CVD or diabetes.

One study awaiting classification ([Njike 2015](#)) is a published conference abstract. We have contacted the study authors for further details and are awaiting a response ([Characteristics of studies](#)

[awaiting classification](#)).

### Excluded studies

We have listed 116 references (reporting 112 studies) of the 252 excluded references with reasons for exclusion in the [Characteristics of excluded studies](#) table, because they most closely missed the inclusion criteria. The studies were excluded because they were not randomised (N = 12), the intervention was not of interest (N = 9), the intervention for the control group was inappropriate (N = 23), studying the wrong type of participants (N = 12) or the follow-up was less than 12 weeks (N = 56).

### Risk of bias in included studies

We have presented details of the risk of bias in included trials as part of the [Characteristics of included studies](#) table, and a 'Risk of bias' graph and summary in [Figure 2](#) and [Figure 3](#), respectively.

**Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.**

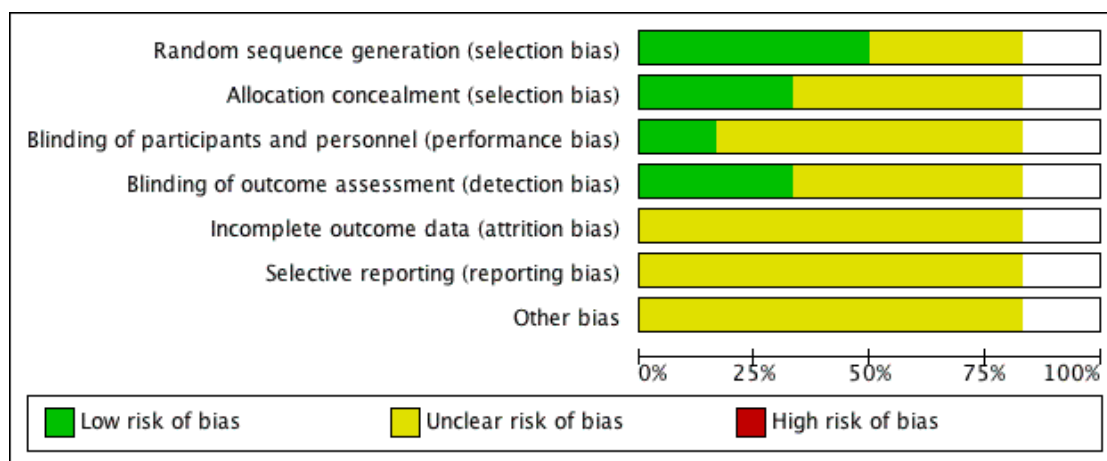


Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study. One study had two intervention arms (Tey 2013 (30 g) and Tey 2013 (60 g)), and whilst the two arms were treated separately in the analysis, we assessed the risk of bias for the total trial. The risk of bias for the second arm of Tey 2013 (60 g) is the same as Tey 2013 (30 g).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abazarfard 2014	+	?	?	?	?	?	?
Balci 2012	?	?	?	?	?	?	?
Sabaté 2005	?	?	?	?	?	?	?
Tey 2011	+	+	+	+	?	?	?
Tey 2013 (30 g)	+	+	?	+	?	?	?
Tey 2013 (60 g)							

Overall, the risk of selection bias was either at low risk of bias or unclear. Blinding of participants was judged to be of unclear risk of bias as participants cannot be blinded to the food they eat and it was unclear whether or not personnel were blinded. Blinding of the outcome assessors and incomplete outcome reporting were judged to be at low risk of bias in two studies and unclear risk of bias in the remaining three. Reporting bias and other sources of bias were judged to be unclear for all included studies. One trial had two intervention arms (Tey 2013 (30 g) and Tey 2013 (60 g)), and whilst the two arms were treated separately in the analysis, we assessed the risk of bias for the total trial.

### Allocation

The methods of random sequence generation were unclear in two studies (Sabaté 2005; Balci 2012). Three of the five studies which stated the method of random sequence generation were judged to have a low risk of bias in this domain (Tey 2011; Tey 2013 (30 g) and Tey 2013 (60 g); Abazarfard 2014). The methods of allocation concealment were unclear in three studies (Sabaté 2005; Balci 2012; Abazarfard 2014) and judged to be of low risk in two studies (Tey 2011; Tey 2013 (30 g) and Tey 2013 (60 g)).

### Blinding

Most trials were judged to be of unclear risk of bias in the domain blinding of participants and personnel as we consider it to be impossible to blind participants to the food they consume and it was unclear whether personnel were blinded or not. One trial's clinical trial registry entry stated it as double-blinded (Abazarfard 2014) but because participants are unable to be blinded to food they eat, it was judged to be at unclear risk of bias. One trial, Tey 2011, revealed from communication with the author that the personnel were blinded and this trial was considered to be at low risk of bias for this domain.

Outcome assessors were said to have been blinded in two trials (Tey 2011; Tey 2013 (30 g) and Tey 2013 (60 g)). They have therefore been judged to be of low risk of bias for this domain.

### Incomplete outcome data

One of the five included trials, Abazarfard 2014, reported losses to follow-up with similar numbers of losses in the intervention and control arm but without an intention-to-treat (ITT) analysis. We judged this study to be of unclear risk of bias. Two studies could not be judged on attrition bias as no information was provided (Sabaté 2005; Balci 2012). Two trials conducted an ITT analysis but did not report on how missing data were dealt with (Tey 2011; Tey 2013 (30 g) and Tey 2013 (60 g)). We therefore judged them to be of unclear risk of bias.

### Selective reporting

Selective reporting was judged to be an unclear risk of bias in all five studies (Sabaté 2005; Tey 2011; Balci 2012; Tey 2013 (30 g) and Tey 2013 (60 g); Abazarfard 2014) because of insufficient information to make this judgement.

### Other potential sources of bias

For all included RCTs there was insufficient information to judge the risk of bias from other potential sources.

### Effects of interventions

We found no studies investigating the effect of advice to increase nut consumption.

All five included RCTs investigated the effect of nut provision. None of the five trials reported on our primary outcomes: cardiovascular mortality, all-cause mortality and non-fatal endpoints such as MI, CABG, PCI, angina or angiographically defined CHD, stroke, carotid endarterectomy and PAD. Four of the five included trials provided usable data for analysis (Tey 2011; Balci 2012; Tey 2013 (30g) and Tey 2013 (60g); Abazarfard 2014). One trial did not provide any usable data and the trial author did not reply to our enquiry for the missing information (Sabaté 2005).

### Changes in blood pressure (systolic and diastolic)

Three trials (267 participants) measured mean change in systolic and diastolic blood pressure (mmHg) from baseline to last follow-up (Balci 2012; Tey 2013 (30g) and Tey 2013 (60g); Abazarfard 2014), which was three months for Abazarfard 2014 and Balci 2012 and 12 weeks for Tey 2013 (30 g) and Tey 2013 (60 g). For systolic blood pressure, heterogeneity was substantial between trials ( $I^2$  statistic = 55%) and we used a random-effects model. There was no statistically significant effect of nut consumption on systolic blood pressure (MD 3.22 mmHg, 95% CI -2.70 to 9.14;  $P = 0.29$ ; Analysis 1.1). However, one trial was a clear outlier with an extremely large reduction in systolic blood pressure in the control arm during the trial period of 14 mmHg (Abazarfard 2014). Excluding this trial from the sensitivity analysis gave a MD of -0.28 mmHg (95% CI -5.79 to 5.23;  $P = 0.92$ ).

For diastolic blood pressure, because of the substantial heterogeneity ( $I^2$  statistic = 87%) the pooled effect estimate was suppressed and results from individual trials are plotted (Analysis 1.2). One trial showed a statistically significant reduction (Abazarfard 2014), the two arms of the Tey 2013 trial showed a statistically significant increase in diastolic blood pressure with the intervention (Tey 2013 (30g); Tey 2013 (60g)) and the remaining trial showed no effect of the intervention (Balci 2012).

### Changes in blood lipids (total cholesterol, LDL-C, HDL cholesterol and triglycerides)

Three trials (266 participants) measured mean change in total cholesterol (mmol/L), HDL cholesterol (mmol/L), LDL cholesterol (mmol/L) and triglycerides (mmol/L) from baseline to last follow-up (Tey 2011; Tey 2013 (30g) and Tey 2013 (60g); Abazarfard 2014), which was three months for Abazarfard 2014 and 12 weeks for Tey 2011, Tey 2013 (30g) and Tey 2013 (60g). For total cholesterol, there was substantial heterogeneity between the trials ( $I^2$  statistic = 79%) which precluded meta-analysis. Results for individual trials are plotted and the pooled effect estimate is suppressed (Analysis 1.3). One trial showed large and statistically significant reduction in total cholesterol with nut consumption (Abazarfard 2014), one a small and borderline significant reduction (Tey 2011), and the remaining two arms of the Tey 2013 trial showed no effect of the intervention on total cholesterol levels (Tey 2013 (30g); Tey 2013 (60g)).

For LDL cholesterol, there was low to moderate heterogeneity between the trials ( $I^2$  statistic = 25%) and we used a fixed-effect model. There was no statistically significant effect of nut consumption in lowering LDL cholesterol (MD -0.02, 95% CI -0.1 to 0.06;  $P = 0.57$ ; Analysis 1.4).

For HDL cholesterol, there was no heterogeneity between the trials ( $I^2$  statistic = 0%), and we used a fixed-effect model for the analysis. There was no effect of nut consumption on HDL levels in the pooled analysis (MD -0.00, 95% CI -0.04 to 0.04;  $P = 0.82$ ; Analysis 1.5).

For triglycerides, there was substantial heterogeneity between trials ( $I^2$  statistic = 84%) and we did not perform a meta-analysis. We plotted individual trials and the pooled effect estimate is suppressed (Analysis 1.6). One trial showed a significant reduction in triglyceride levels with nut consumption (Abazarfard 2014), the remaining two trials showed no effect of the intervention on triglyceride levels (Tey 2011; Tey 2013 (30g); Tey 2013 (60g)).

### Occurrence of type 2 diabetes as a major CVD risk factor

None of the included trials reported on type 2 diabetes as a major CVD risk factor.

### Health-related quality of life (using any validated scale)

None of the included trials reported on quality of life.

### Costs

None of the included trials reported on costs.

### Adverse effects (as defined by the authors of the included trials, e.g. weight gain, anaphylaxis)

One trial, Tey 2011, reported one adverse event (1/32, allergic reaction to nuts) but also found that “nuts can be incorporated into the diet without adversely affecting body weight”. This was also found by two other trials. Sabaté 2005 reports a non-significant weight gain when consuming walnuts daily (mean daily consumption 35 g) for six months. Tey 2013 (30g) and Tey 2013 (60g) noted “no significant weight change” for both nut groups over the study period.

## DISCUSSION

### Summary of main results

We included five trials (435 participants randomised), one ongoing trial and one study is awaiting classification. All trials examined the provision of nuts to increase consumption rather than dietary advice. None of the included trials reported on our primary outcomes, CVD clinical events, but trials were small and short term. All five trials reported on CVD risk factors. Four of these trials provided data in a useable format for meta-analyses, but heterogeneity precluded meta-analysis for most of the analyses. Overall trials were judged to be at unclear risk of bias.

Heterogeneity was significant for most analyses of CVD risk factors with inconsistent effects seen for systolic blood pressure, diastolic blood pressure, total cholesterol and triglycerides. Heterogeneity was low for LDL and HDL cholesterol where there was no significant effect of nut consumption on these outcomes although the number of studies contributing to these analyses was small. Three trials monitored adverse events. One trial reported an allergic reaction to nuts and three trials no significant weight gain with increased nut consumption. None of the included trials reported on other secondary outcomes, occurrence of type 2 diabetes as a major risk factor for CVD, health-related quality of life and costs.

### Overall completeness and applicability of evidence

None of the included RCTs reported on our primary outcomes. Five trials reported on CVD risk factors (lipid levels and blood pressure) with inconsistent findings. There were limitations in the available data as only four trials provided data in a useable format for meta-analyses and for the remaining study we were unable to obtain additional information from the trial authors. The findings to date for these outcomes are inconclusive.

## Quality of the evidence

Overall, the included RCTs were at unclear risk of bias for most of the 'Risk of bias' domains. Provision of nuts is a behavioural intervention and as such participants cannot be blinded to group allocation although trial personnel were blinded in two studies (Tey 2011; Abazarfard 2014). Outcome assessors were blind to group allocation in three trials (Tey 2011; Tey 2013 (30 g) and Tey 2013 (60 g); Abazarfard 2014).

All studies recruited small numbers of participants and small study bias is of particular concern for this review (Sterne 2000; Sterne 2001; Nüesch 2010). Due to the relatively small number of included studies we were unable to examine the effects of publication bias in funnel plots.

## Potential biases in the review process

We performed a comprehensive search across major databases for interventions involving increased nut consumption for this Cochrane review. In addition, we screened the reference lists of systematic reviews and contacted study authors for information when needed. Two review authors independently performed all screening, inclusion and exclusion of articles, and extracted data from the included trials.

We only included trials with a minimum of 12 weeks duration as longer term studies are most informative in terms of behavioural change and sustained changes for public health interventions. However, this limited the number of trials eligible for inclusion and we excluded most studies because they were short term interventions.

## Agreements and disagreements with other studies or reviews

In terms of our primary outcome, CVD clinical events, none of the included trials reported this outcome. Previous evidence for an association between nut consumption and clinical endpoints comes from observational studies which are subject to bias and confounding (Blomhoff 2006).

We were unable to determine the effectiveness of nut consumption on major CVD risk factors (lipid levels and blood pressure) with the trials included in the current review due to missing information, heterogeneity between trials and the limited number of trials available. There are few systematic reviews examining the effects of nut consumption on CVD prevention and most include observational studies which are subject to bias and confounding (Mukuddem-Petersen 2005; Afshin 2014; Zhou 2014). One systematic review of the effects of walnut consumption on lipid levels

included only short term trials (average six weeks) so the sustained effects could not be established (Banal 2009).

A recent systematic review, Mohammadifard 2015, examined the effects of nut consumption on blood pressure and found beneficial effects on systolic blood pressure in participants at high risk of CVD. However, it is unclear if these effects are sustained as the review included very short term trials.

The global burden of disease (GBD) study suggests that 40% of the disability-adjusted life-years from ischemic heart disease are attributable to diets low in nuts and seeds (Lim 2012). This systematic review shows no RCT evidence on the effect of nuts on mortality or heart disease, bringing into question the validity of the evidence on the effect of diet on heart disease. The primary source of data for nuts in the GBD study is from non-randomised studies.

## AUTHORS' CONCLUSIONS

### Implications for practice

Currently there is insufficient evidence to determine the effects of increased nut consumption for reducing CVD risk in healthy participants and in people at increased risk of CVD, and no recommendations can be made.

### Implications for research

Currently there is no evidence for the effects of nut consumption on CVD clinical events in primary prevention and very limited evidence on the effects of CVD risk factors. No conclusions can be drawn and further high quality longer term and adequately powered trials are needed to answer the review question. We will add the results of the ongoing trial to the evidence base when they become available and will incorporate the data into an update of this Cochrane review.

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Abazarfard 2014

Methods	Individual randomisation, parallel group design 3 months duration	
Participants	<p>Participants were recruited via public advertisement in Shiraz, Iran</p> <p>Inclusion criteria: BMI <math>\geq 25</math> kg/m<sup>2</sup>, 20 to 55 years old, no exercise, premenopausal women</p> <p>Exclusion criteria: chronic illness, uncontrolled hypertension, on lipid-lowering medication, taking vitamin supplements, inflammatory condition, diabetes, use of antihyperglycemic drugs, working night shifts, pregnant, lactating, smoking, alcohol consumption, known allergy or sensitivity to nuts, on weight control diets or any other specific diets, use of medication known to affect body weight or a weight loss of <math>\geq 5</math> kg in preceding 6 months</p> <p>100% female</p> <p>Mean age of intervention group: <math>42.36 \pm 7.30</math></p> <p>Mean age of control group: <math>42.94 \pm 6.82</math></p> <p>Enrolment: N = 108</p> <p>Randomised to intervention group: N = 54</p> <p>Randomised to control group: N = 54</p> <p>Available at end of follow-up in intervention group: N = 50</p> <p>Available at end of follow-up in control group: N = 50</p>	
Interventions	<p>Intervention group: follow designed balanced low calorie diet. Provision of 50 g raw almond in form of two snacks per day</p> <p>Control group: follow designed balanced low calorie diet. No consumption of nuts</p> <p>Same for both groups: instructed to maintain their usual activity habits with recommendation to walk with medium speed 30 minutes every day. Training about diet, healthy nutrition and self-monitoring and stimulus control. Phone call every 15 days to ask about situations and diet compliance. Provision of suggestions to enhance compliance. Also 24 hr dietary recalls at baseline, end of study and at the end of each month</p>	
Outcomes	Systolic blood pressure, diastolic blood pressure, total cholesterol, total cholesterol/HDL cholesterol ratio, HDL cholesterol, LDL cholesterol, triglycerides at baseline and 3 months follow-up	
Notes	Contacted trial author for data on primary outcomes cardiovascular mortality, all-cause mortality, non-fatal endpoints and secondary outcomes (type 2 diabetes, quality of life, costs and adverse events) as well as selection bias and detection bias. We did not receive any reply	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement



**Abazarfard 2014** (Continued)

Random sequence generation (selection bias)	Low risk	“Participants were randomly assigned into almond and nut-free groups through the balanced block randomization method (block size of four).”
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote from IRCT entry: double blinded. However, participants cannot be blinded to food they eat and it is unclear whether this refers to personnel and outcome assessors
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	An equal number of participants (n = 4) were lost to follow-up in each group but no ITT analysis was performed
Selective reporting (reporting bias)	Unclear risk	Protocol not available, paper is an extract from a thesis.
Other bias	Unclear risk	No indications of further biases but information too limited to make judgement

**Balci 2012**

Methods	Individual randomisation, parallel group design. 3 months duration.
Participants	All participants had prediabetic metabolic syndrome diagnosed according to NCEP ATP III criteria 45% male, 55% female Mean age: unknown Enrolment: N = 60 Randomised to intervention group: N = 30 Randomised to control group: N = 30 Available at end of follow-up in intervention group: N = 30 Available at end of follow-up in control group: N = 30
Interventions	Intervention group: healthy nutrition with provision of 10 g walnuts per day Control group: healthy nutrition only
Outcomes	Systolic blood pressure, diastolic blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides at baseline and 3 months follow-up

**Balci 2012** (Continued)

Notes	Published conference abstract only. Could not identify trial author's email address to ask for missing data	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	"participants are randomly separated to two groups". Random sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants could not be blinded to food they eat and it is unclear whether or not personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described.
Selective reporting (reporting bias)	Unclear risk	Not described.
Other bias	Unclear risk	No indications of further biases but information too limited to make judgement

**Sabaté 2005**

Methods	Individual randomisation, cross-over design. 6 months duration.
Participants	Recruitment via advertisements in South-East California, USA Inclusion criteria: BMI > 25 kg/m <sup>2</sup> (=overweight), weight change < 1 kg during previous six months, BMI < 35 kg/m <sup>2</sup> , an habitual diet including nuts less than once a week Exclusion criteria: diagnosed metabolic disorder that can affect weight, i.e. diabetes, hypothyroidism, or aversion or known allergy to nuts 44.44% male, 55.56% female Mean age (range): 54.3 ± 10.6 (30 to 72 years) Enrolment: N = 94 Loss to follow-up: n = 4 (not stated from which group or at which stage of trial) Available at end of follow-up in intervention group: N = 49 Available at end of follow-up in control group: N = 41

Interventions	<p>Intervention group: provision of walnuts that corresponded to approximately 12% of their daily energy intake. Daily energy intake of 1800 to 2300 kcal = 28 g walnuts; 2300 to 2800 kcal = 46 g walnuts; &gt; 2800 kcal = 56 g walnuts. Walnut allotment was adjusted based on the daily energy intake reported in the 24 hr dietary recalls. Walnuts were distributed in portioned packs at each clinic visit every 2 months. They also got a large pack of walnuts for family members. They were requested to return any unconsumed portions</p> <p>Control group: participants were asked to refrain from eating walnuts and substantial amounts of any other nuts</p> <p>Same for both groups: participants were asked to follow their usual diet. Instructions to the change physical activity habits and not to attempt to lose weight while in the study. Seven 24h dietary recalls during 6 months intervention, unannounced and following a protocol, by phone</p>	
Outcomes	Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides	
Notes	We contacted the trial authors of <a href="#">Sabaté 2005</a> and Torabian 2010 for further information. We did not receive any reply	
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants cannot be blinded to food they eat and it is unclear whether personnel was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described.
Selective reporting (reporting bias)	Unclear risk	Not described.
Other bias	Unclear risk	No indications of further biases but information too limited to make judgement

Methods	Individual randomisation, parallel design with four arms (chocolate, crisps, nuts, control) 12 weeks duration.	
Participants	<p>Recruitment in New Zealand. Advertisement with flyers around University of Otago campus, supermarkets and university staff bulletin and papers. Interested people phoned/ emailed investigator</p> <p>Inclusion criteria: age between 18 and 65 years.</p> <p>Exclusion criteria: BMI <math>\geq</math> 30 kg/m<sup>2</sup>, asthma, pregnant or breastfeeding, chronic disease such as cancer, heart disease or diabetes, people with food allergies or food aversions</p> <p>47% male, 53% female</p> <p>Mean age (range): 37.4 <math>\pm</math> 14.0 (18 to 65)</p> <p>Enrolment to nuts and control group: N = 63</p> <p>Randomised to nut group: N = 32</p> <p>Randomised to control group: N = 31</p> <p>Available at end of follow-up in nut group: N = 27</p> <p>Available at end of follow-up in control group: N = 27</p>	
Interventions	<p>Intervention group(s): 42 g hazelnuts, 50 g chocolate or 50 g potato crisps. Snacks were individually portioned into daily serving sized bags and participants were asked to collect them every 3 weeks. Participants were asked to return any snacks that were not eaten</p> <p>Control group: no additional food.</p> <p>Same for all groups: all participants were asked to maintain their regular diet during a 2-week run-in period, then randomisation. Physical activity measured at baseline and during the intervention by wearing accelerometers for 7 days. Three-day diet records were collected</p>	
Outcomes	Total cholesterol, total cholesterol/HDL cholesterol ratio, HDL cholesterol, LDL cholesterol, triglycerides, adverse events	
Notes		
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Randomisation by minimisation, block size of four, 8 strata.
Allocation concealment (selection bias)	Low risk	"Allocation within each strata was conducted by an off-site statistician using blocks of size four"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants cannot be blinded to food they eat. Personnel blinded (from communication with author)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researchers assessing outcomes were blinded to treatment.

**Tey 2011** (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis conducted but unclear how missing data were dealt with
Selective reporting (reporting bias)	Unclear risk	Not described.
Other bias	Unclear risk	No indications of further biases but information too limited to make judgement

**Tey 2013 (30 g)**

Methods	Individual randomisation, 3-arm parallel group design - this comparison 30 g versus control 12 weeks duration.
Participants	Recruitment from general public in Dunedin, New Zealand. Inclusion criteria: aged between 18 and 65 years inclusive, with BMI $\geq$ 30 kg/m <sup>2</sup> Exclusion criteria: asthma, allergies or aversion to nuts, familial hyperlipidemia, major chronic disease or inflammatory disease such as Crohn or celiac disease, current smokers, pregnant or breastfeeding women, people who were participating in weight-loss programmes or taking medication known to affect inflammatory markers Mean age: 42.5 $\pm$ 12.4 43% male, 57% female Enrolment: N = 110 Randomised to nut group (30 g): N = 35 Randomised to control group: N = 38 Available at end of follow-up in nut group (30 g): N = 33 (excluded: n = 1 BMI < 25 kg/m <sup>2</sup> , n = 1 pregnant) Available at end of follow-up in control group: N = 37 (excluded: n = 1 BMI < 25 kg/m <sup>2</sup> ), for analysis: N = 18 as per methods planned in protocol
Interventions	Intervention group: hazelnuts were individually portioned into daily-serving sized bags (30 g). Participants were asked to collect their nuts every three weeks and to return any nuts not eaten. Compliance was assessed by weighing the bags returned, by nut diary and by three-day diet records Control group: received no additional food. Same for both groups: 2-week run in period with no nuts. Participants were encouraged to maintain their usual pattern of dietary habits and physical activity level and to maintain the same dosage of medications and supplements (if taken at baseline) throughout the study. All were asked to attend 6 clinic visits after a 12-hr overnight fast, twice each at baseline, after 6 weeks and at the end of the 12-week intervention. Physical activity was measured with accelerometers at baseline and at week 7. Participants were asked to wear the accelerometer for 7 days
Outcomes	Systolic blood pressure, diastolic blood pressure, total cholesterol, total cholesterol/HDL cholesterol ratio, HDL cholesterol, LDL cholesterol, triglycerides
Notes	

<i>Risk of bias</i>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Minimisation to balance groups by age, sex and BMI.
Allocation concealment (selection bias)	Low risk	"An off-site statistician conducted group allocation."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants cannot be blinded to food they eat and it is unclear whether personnel was blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Those researchers who assessed the outcomes were blinded to the treatments."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"All analyses were performed by using a modified intention-to-treat principle." Unclear how missing data were dealt with
Selective reporting (reporting bias)	Unclear risk	Not described.
Other bias	Unclear risk	No industry funding.

**Tey 2013 (60 g)**

Methods	Individual randomisation, 3-arm parallel group design - this comparison 60 g versus control 12 weeks duration.
Participants	Recruitment from general public in Dunedin, New Zealand. Inclusion criteria: aged between 18 and 65 years inclusive, with BMI $\geq 30$ kg/m <sup>2</sup> Exclusion criteria: asthma, allergies or aversion to nuts, familial hyperlipidemia, major chronic disease, or inflammatory disease such as Crohn or coeliac disease, current smokers, pregnant or breastfeeding women, people who were participating in weight-loss programmes or taking medication known to affect inflammatory markers Mean age: 42.5 $\pm$ 12.4 43% male, 57% female Enrolment: N = 110 Randomised to nut group (60 g): N = 37 Randomised to control group: N = 38 Available at end of follow-up in nut group (60 g): N = 37 Available at end of follow-up in control group: n = 37 (excluded: n = 1 BMI < 25 kg/m <sup>2</sup> ), for analysis: N = 19 as per methods planned in protocol
Interventions	Intervention group: hazelnuts were individually portioned into daily-serving sized bags (60 g). Participants were asked to collect their nuts every 3 weeks and to return any nuts not eaten. Compliance was assessed by weighing the bags returned, by nut diary and by 3-day diet records

	Control group: received no additional food. Same for both groups: 2-week run in period with no nuts. Participants were encouraged to maintain their usual pattern of dietary habits and physical activity level, and to maintain the same dosage of medications and supplements (if taken at baseline) throughout the study. All were asked to attend 6 clinic visits after a 12-hr overnight fast, twice each at baseline, after 6 weeks and at the end of the 12-week intervention. Physical activity was measured with accelerometers at baseline and at week 7. Participants were asked to wear the accelerometer for 7 days
Outcomes	Systolic blood pressure, diastolic blood pressure, total cholesterol, total cholesterol/HDL cholesterol ratio, HDL cholesterol, LDL cholesterol, triglycerides
Notes	

### Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Acharjee 2008	Follow-up was too short.
Acharya 2004	Intervention was not of interest.
ACTRN12615000176561	Inappropriate control.
Alper 2003	Not randomised.
Anderson 2013	Follow-up period was too short.
Baer 2012	Follow-up period was too short.
Bakhtiary 2011	Intervention was not of interest.
Bao 2013	Not randomised.
Barbour 2014	Not randomised.
Berryman 2010	Inappropriate control.
Berryman 2011	Inappropriate control.
Berryman 2013	Inappropriate control.
Blumberg 2011	Follow-up period was too short.
Bunner 2014	Intervention was not of interest.
Burns-Whitmore 2014	Follow-up period was too short.

(Continued)

Canales 2011	Follow-up period was too short.
Casas 2011	Intervention was not of interest.
Casas-Agustench 2011	Inappropriate control.
Chair 2003	Intervention was not of interest.
Chen 2014	Inappropriate control.
Cheng 2004	Intervention was not of interest.
Chisholm 1998	Follow-up was too short.
Chisholm 2010	Follow-up was too short.
Choudhury 2014	Not randomised.
Cohen 2011	Inappropriate control.
Colquhoun 1996	Follow-up was too short.
Cominetti 2012	Follow-up was too short.
Coppell 2010	Inappropriate participants - all diabetic.
Costa 2011	Follow-up was too short.
Curb 2000	Follow-up was too short.
Davis 2007	Follow-up was too short.
Din 2011	Follow-up was too short.
Edwards 1999	Follow-up was too short.
Esfahani 2010	Intervention was not of interest.
Foster 2012	Intervention was not of interest.
Garg 2007	Not randomised.
Gebauer 2008	Follow-up was too short.
Gebauer 2011	Follow-up was too short.
Ghadimi Nouran 2010	Follow-up was too short.



(Continued)

Gillen 2005	Inappropriate control.
Griel 2008	Follow-up was too short.
Gulati 2011	Inappropriate control.
Gulati 2014	Inappropriate control.
Hargrove 2001	Follow-up was too short.
Hernández-Alonso 2014	Inappropriate control.
Holligan 2011	Inappropriate control.
Holligan 2013	Follow-up was too short.
Holligan 2014	Follow-up was too short.
Hollis 2007	Follow-up was too short.
Hudthagosol 2011	Follow-up was too short.
Iwamoto 2002	Follow-up was too short.
Jaceldo-Siegl 2011	Not randomised.
Jambazian 2005	Follow-up was too short.
Jenkins 2008	Follow-up was too short.
Jenkins 2011	Inappropriate control.
Jones 2014	Inappropriate control.
Jonsson 2013	Intervention was not of interest.
Katz 2012	Follow-up was too short.
Kay 2010	Follow-up was too short.
Kendall 2002	Follow-up was too short.
Kendall 2003	Follow-up was too short.
Kendall 2009	Inappropriate control.

(Continued)

Kendall 2013	Inappropriate control.
Kochar 2010	Not randomised.
Kocyigit 2006	Follow-up was too short.
Li 2009	Inappropriate control.
Li 2010	Inappropriate control.
Li 2011	Follow-up was too short.
López-Uriarte 2010	Inappropriate control.
Maranhão 2011	Inappropriate participants - adolescents.
McKeown 2010	Not randomised.
Mercanligil 2007	Follow-up was too short.
Mohammadifard 2012	Not randomised.
Morgan 2000	Follow-up was too short.
Morgan 2002	Follow-up was too short.
Mukuddem-Petersen 2007	Follow-up was too short.
Munoz 2001	Follow-up was too short.
Nishi 2014	Inappropriate participants - all diabetics.
Núñez 2004	Follow-up was too short.
O'Byrne 1997	Not randomised.
Oliveira 2010	Inappropriate participants - adolescents.
Orem 2013	Not randomised.
Petersen 2013	Inappropriate participants - all diabetics.
Pieters 2005	Follow-up was too short.
Rajaram 2001	Follow-up was too short.
Rajaram 2010	Follow-up was too short.

(Continued)

Reinsma 2010	Inappropriate participants - all diabetics.
Ricklefs 2013	Inappropriate participants - all diabetics.
Rismankarzadeh 2005	Follow-up was too short.
Ros 2004	Follow-up was too short.
Sabate 1993	Follow-up was too short.
Sabaté 2003	Follow-up was too short.
Sari 2010	Not randomised.
Schutte 2006	Follow-up was too short.
Sheridan 2007	Follow-up was too short.
Somerset 2011	Follow-up was too short.
Somerset 2013	Follow-up was too short.
Storniolo 2013	Inappropriate control.
Sweazea 2014	Inappropriate participants - all diabetics.
Tan 2013	Follow-up was too short.
Tapsell 2004	Inappropriate participants - all diabetics.
Tapsell 2009	Inappropriate participants - all diabetics.
Tapsell 2010	Inappropriate participants - all diabetics.
Wang 2012	Inappropriate control.
West 2012	Follow-up was too short.
Wien 2010	Inappropriate control.
Wien 2014	Inappropriate participants - all diabetics.
Wu 2010	Inappropriate control.
Wu 2014	Follow-up was too short.
Zambón 1998	Follow-up was too short.

(Continued)

Zambón 2000	Follow-up was too short.
Zibaenezhad 2005	follow-up too short

### Characteristics of studies awaiting assessment [ordered by study ID]

#### Njike 2015

Methods	RCT, parallel design, 6 months duration.
Participants	112 participants.
Interventions	Participants randomised to ad libitum diet or calorie-controlled diet, then randomised again in each of these two groups to walnut-included and walnut-excluded diets
Outcomes	Diet quality, body mass index, percent body fat, percent body water, visceral fat, glucose, HbA1c, endothelial function, total cholesterol and LDL cholesterol
Notes	We contacted the trial author for more information and are awaiting a response

### Characteristics of ongoing studies [ordered by study ID]

#### NCT01950806

Trial name or title	The effect of pecans on biomarkers of risk for cardiovascular disease and diabetes
Methods	Randomised crossover double blind trial.
Participants	Adults at risk of CVD/type 2 diabetes; enrolment: 25.
Interventions	Pecan-containing diet versus nut-free diet.
Outcomes	Change in biomarkers of oxidative stress, inflammation, endothelial function, antioxidant activity, insulin resistance, blood pressure, plasma lipid profile compared with control diet
Starting date	23 September 2013.
Contact information	Diane L. McKay ( <a href="mailto:diane.mckay@tufts.edu">diane.mckay@tufts.edu</a> ), Jeffrey B. Blumberg ( <a href="mailto:jeffrey.blumberg@tufts.edu">jeffrey.blumberg@tufts.edu</a> ).
Notes	Expected completion date: November 2015.

## DATA AND ANALYSES

### Comparison 1. Secondary outcomes

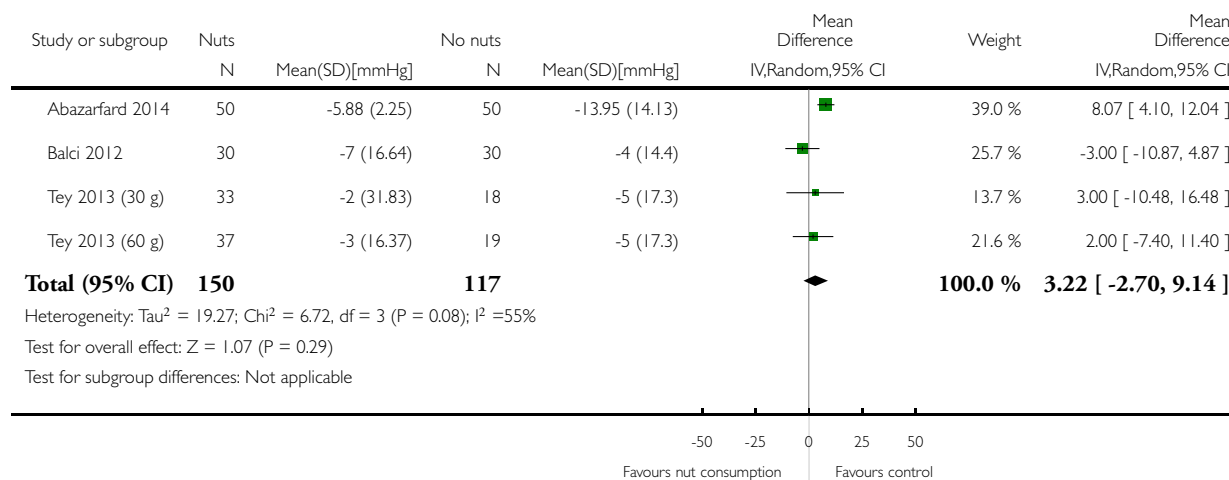
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Systolic blood pressure	4	267	Mean Difference (IV, Random, 95% CI)	3.22 [-2.70, 9.14]
2 Diastolic blood pressure	4		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Total cholesterol	4		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 LDL cholesterol	4	266	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.10, 0.06]
5 HDL cholesterol	4	266	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.04, 0.04]
6 Triglycerides	4		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

#### Analysis 1.1. Comparison 1 Secondary outcomes, Outcome 1 Systolic blood pressure.

Review: Nut consumption for the primary prevention of cardiovascular disease

Comparison: 1 Secondary outcomes

Outcome: 1 Systolic blood pressure

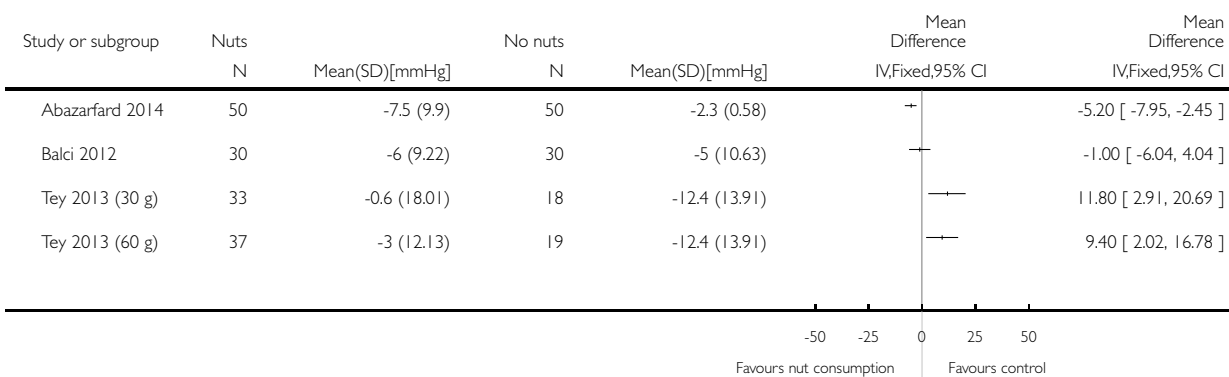


### Analysis 1.2. Comparison 1 Secondary outcomes, Outcome 2 Diastolic blood pressure.

Review: Nut consumption for the primary prevention of cardiovascular disease

Comparison: 1 Secondary outcomes

Outcome: 2 Diastolic blood pressure

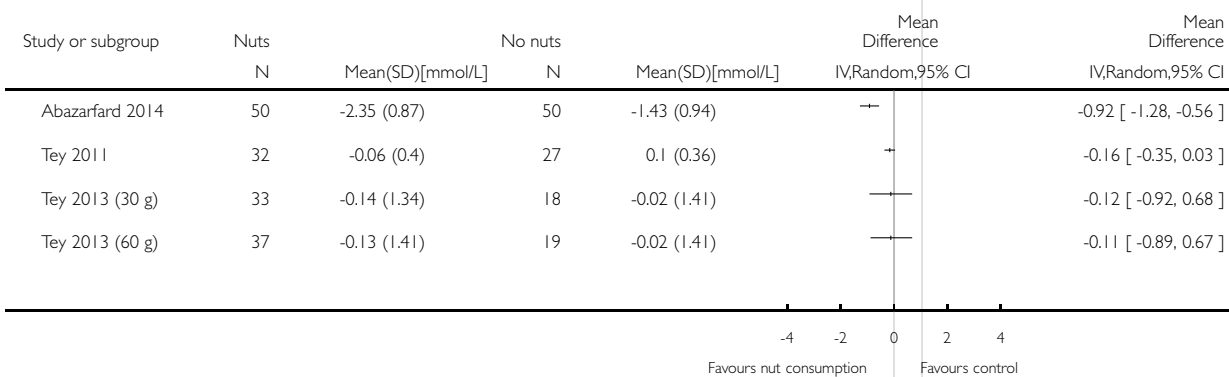


### Analysis 1.3. Comparison 1 Secondary outcomes, Outcome 3 Total cholesterol.

Review: Nut consumption for the primary prevention of cardiovascular disease

Comparison: 1 Secondary outcomes

Outcome: 3 Total cholesterol

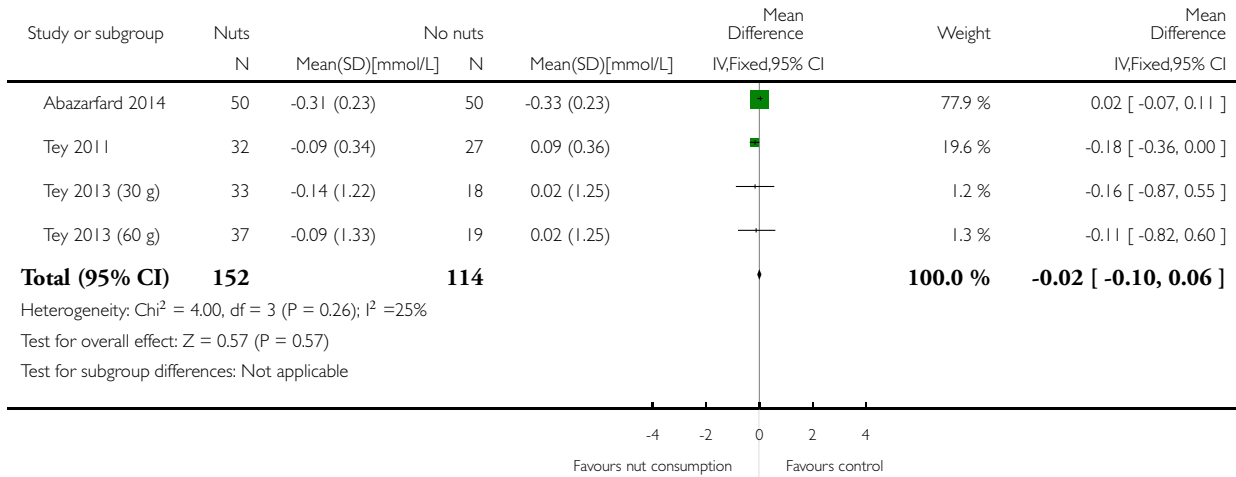


### Analysis 1.4. Comparison 1 Secondary outcomes, Outcome 4 LDL cholesterol.

Review: Nut consumption for the primary prevention of cardiovascular disease

Comparison: 1 Secondary outcomes

Outcome: 4 LDL cholesterol

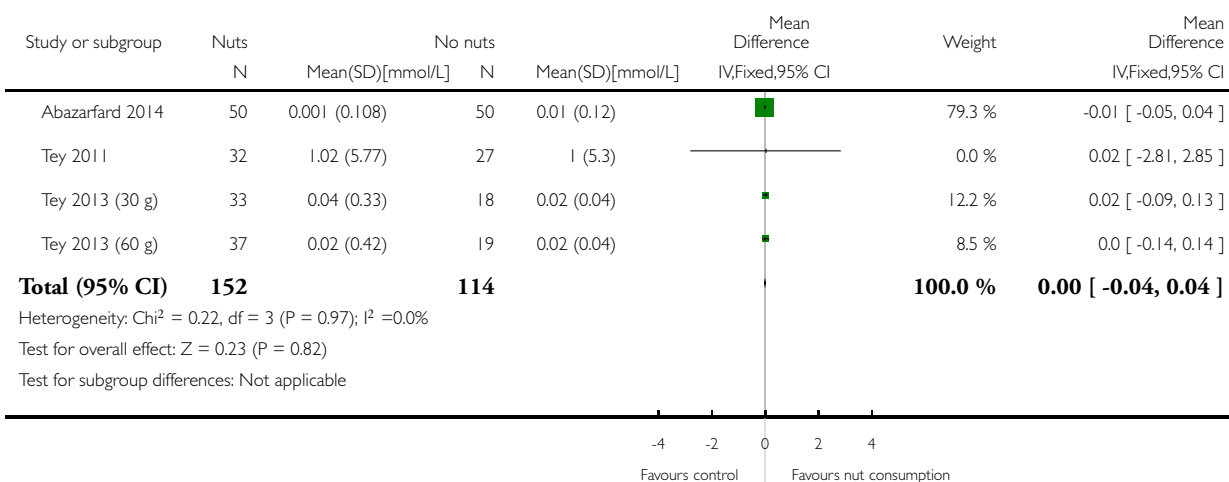


### Analysis 1.5. Comparison 1 Secondary outcomes, Outcome 5 HDL cholesterol.

Review: Nut consumption for the primary prevention of cardiovascular disease

Comparison: 1 Secondary outcomes

Outcome: 5 HDL cholesterol

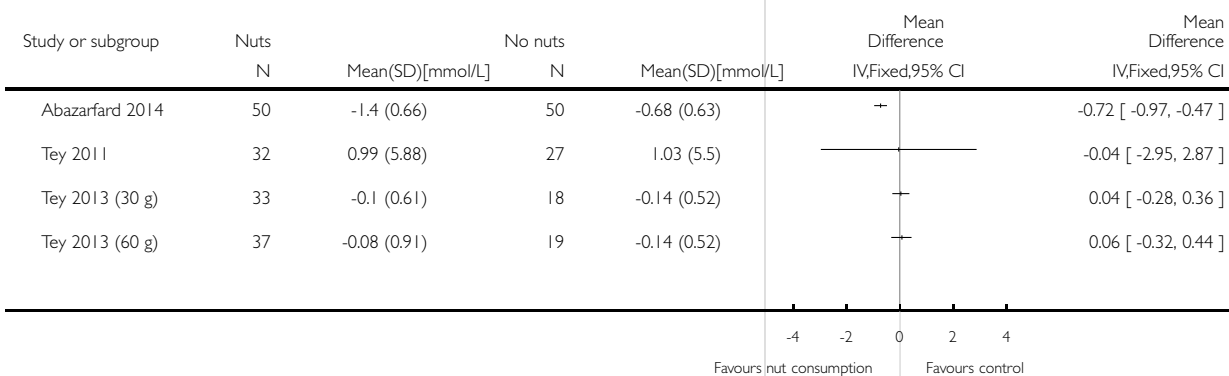


### Analysis 1.6. Comparison 1 Secondary outcomes, Outcome 6 Triglycerides.

Review: Nut consumption for the primary prevention of cardiovascular disease

Comparison: 1 Secondary outcomes

Outcome: 6 Triglycerides





## APPENDICES

### Appendix I. Search strategies

#### The Cochrane Library

#1 MeSH descriptor: [Nuts] this term only

#2 nut or nuts

#3 almond\* or walnut\* or peanut\* or pecan\* or hazelnut\* or chestnut\* or acorn\* or pistachio\* or cashew\* or macadamia\* or mongongo\* or buckwheat\* or coconut\*

#4 #1 or #2 or #3

#5 MeSH descriptor: [Cardiovascular Diseases] explode all trees

#6 cardio\*

#7 cardia\*

#8 heart\*

#9 coronary\*

#10 angina\*

#11 ventric\*

#12 myocard\*

#13 pericard\*

#14 isch?em\*

#15 emboli\*

#16 arrhythmi\*

#17 thrombo\*

#18 atrial next fibrillat\*

#19 tachycardi\*

#20 endocardi\*

#21 (sick next sinus)

#22 MeSH descriptor: [Stroke] explode all trees

#23 (stroke or strokes)

#24 cerebrovasc\*

#25 cerebral next vascular

#26 apoplexy

#27 (brain near/2 accident\*)

#28 ((brain\* or cerebral or lacunar) near/2 infarct\*)

#29 MeSH descriptor: [Hypertension] explode all trees

#30 hypertensi\*

#31 (peripheral next arter\* next disease\*)

#32 ((high or increased or elevated) near/2 blood pressure)

#33 MeSH descriptor: [Hyperlipidemias] explode all trees

#34 hyperlipid\*

#35 hyperlip?emia\*

#36 hypercholesterol\*

#37 hypercholester?emia\*

#38 hyperlipoproteinemia\*  
 #39 hypertriglyceridemia\*  
 #40 MeSH descriptor: [Arteriosclerosis] explode all trees  
 #41 MeSH descriptor: [Cholesterol] explode all trees  
 #42 cholesterol  
 #43 "coronary risk factor"  
 #44 MeSH descriptor: [Blood Pressure] this term only  
 #45 "blood pressure"  
 #46 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23  
 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or  
 #42 or #43 or #44 or #45  
 #47 #4 and #46

## MEDLINE

1. Nuts/
2. (nut or nuts).tw.
3. almond\*.tw.
4. walnut\*.tw.
5. peanut\*.tw.
6. pecan\*.tw.
7. hazelnut\*.tw.
8. chestnut\*.tw.
9. acorn\*.tw.
10. pistachio\*.tw.
11. cashew\*.tw.
12. macadamia\*.tw.
13. mongongo\*.tw.
14. buckwheat\*.tw.
15. coconut\*.tw.
16. (brazilnut\* or (brazil adj nut\*)).tw.
17. or/1-16
18. exp Cardiovascular Diseases/
19. cardio\*.tw.
20. cardia\*.tw.
21. heart\*.tw.
22. coronary\*.tw.
23. angina\*.tw.
24. ventric\*.tw.
25. myocard\*.tw.
26. pericard\*.tw.
27. isch?em\*.tw.
28. emboli\*.tw.
29. arrhythmi\*.tw.
30. thrombo\*.tw.
31. atrial fibrillat\*.tw.
32. tachycardi\*.tw.
33. endocardi\*.tw.
34. (sick adj sinus).tw.
35. exp Stroke/
36. (stroke or strokes).tw.
37. cerebrovasc\*.tw.
38. cerebral vascular.tw.

39. apoplexy.tw.
40. (brain adj2 accident\*).tw.
41. ((brain\* or cerebral or lacunar) adj2 infarct\*).tw.
42. exp Hypertension/
43. hypertensi\*.tw.
44. peripheral arter\* disease\*.tw.
45. ((high or increased or elevated) adj2 blood pressure).tw.
46. exp Hyperlipidemias/
47. hyperlipid\*.tw.
48. hyperlip?emia\*.tw.
49. hypercholesterol\*.tw.
50. hypercholester?emia\*.tw.
51. hyperlipoprotein?emia\*.tw.
52. hypertriglycerid?emia\*.tw.
53. exp Arteriosclerosis/
54. exp Cholesterol/
55. cholesterol.tw.
56. "coronary risk factor\* ".tw.
57. Blood Pressure/
58. blood pressure.tw.
59. or/18-58
60. 17 and 59
61. randomized controlled trial.pt.
62. controlled clinical trial.pt.
63. randomized.ab.
64. placebo.ab.
65. drug therapy.fs.
66. randomly.ab.
67. trial.ab.
68. groups.ab.
69. 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68
70. exp animals/ not humans.sh.
71. 69 not 70
72. 60 and 71

## EMBASE

1. exp nut/
2. (nut or nuts).tw.
3. almond\*.tw.
4. walnut\*.tw.
5. peanut\*.tw.
6. pecan\*.tw.
7. hazelnut\*.tw.
8. chestnut\*.tw.
9. acorn\*.tw.
10. pistachio\*.tw.
11. cashew\*.tw.
12. macadamia\*.tw.
13. mongongo\*.tw.
14. buckwheat\*.tw.
15. coconut\*.tw.
16. or/1-15

17. exp cardiovascular disease/
18. cardio\*.tw.
19. cardia\*.tw.
20. heart\*.tw.
21. coronary\*.tw.
22. angina\*.tw.
23. ventric\*.tw.
24. myocard\*.tw.
25. pericard\*.tw.
26. isch?em\*.tw.
27. emboli\*.tw.
28. arrhythmi\*.tw.
29. thrombo\*.tw.
30. atrial fibrillat\*.tw.
31. tachycardi\*.tw.
32. endocardi\*.tw.
33. (sick adj sinus).tw.
34. exp cerebrovascular disease/
35. (stroke or strokes).tw.
36. cerebrovasc\*.tw.
37. cerebral vascular.tw.
38. apoplexy.tw.
39. (brain adj2 accident\*).tw.
40. ((brain\* or cerebral or lacunar) adj2 infarct\*).tw.
41. exp hypertension/
42. hypertensi\*.tw.
43. peripheral arter\* disease\*.tw.
44. ((high or increased or elevated) adj2 blood pressure).tw.
45. exp hyperlipidemia/
46. hyperlipid\*.tw.
47. hyperlip?emia\*.tw.
48. hypercholesterol\*.tw.
49. hypercholester?emia\*.tw.
50. hyperlipoprotein?emia\*.tw.
51. hypertriglycerid?emia\*.tw.
52. exp Arteriosclerosis/
53. exp Cholesterol/
54. cholesterol.tw.
55. "coronary risk factor\*").tw.
56. Blood Pressure/
57. blood pressure.tw.
58. or/17-57
59. 16 and 58
60. random\$.tw.
61. factorial\$.tw.
62. crossover\$.tw.
63. cross over\$.tw.
64. cross-over\$.tw.
65. placebo\$.tw.
66. (doubl\$ adj blind\$).tw.
67. (singl\$ adj blind\$).tw.
68. assign\$.tw.
69. allocat\$.tw.

- 70. volunteer\$.tw.
- 71. crossover procedure/
- 72. double blind procedure/
- 73. randomized controlled trial/
- 74. single blind procedure/
- 75. 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74
- 76. (animal/ or nonhuman/) not human/
- 77. 75 not 76
- 78. 59 and 77

## CINAHL

- S49 S30 AND S48
- S48 S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47
- S47 TX cross-over\*
- S46 TX crossover\*
- S45 TX volunteer\*
- S44 (MH "Crossover Design")
- S43 TX allocat\*
- S42 TX control\*
- S41 TX assign\*
- S40 TX placebo\*
- S39 (MH "Placebos")
- S38 TX random\*
- S37 TX (doubl\* N1 mask\*)
- S36 TX (singl\* N1 mask\*)
- S35 TX (doubl\* N1 blind\*)
- S34 TX (singl\* N1 blind\*)
- S33 TX (clinic\* N1 trial?)
- S32 PT clinical trial
- S31 (MH "Clinical Trials+")
- S30 S4 AND S29
- S29 S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28
- S28 TI "Blood Pressure" OR AB "Blood Pressure"
- S27 (MH "Blood Pressure+")
- S26 TI "coronary risk factor\*" OR AB "coronary risk factor\*"
- S25 TI cholesterol OR AB cholesterol
- S24 (MH "Cholesterol+")
- S23 (MH "Arteriosclerosis+")
- S22 TI diabet\* OR AB diabet\*
- S21 (MH "Diabetes Mellitus+")
- S20 AB (hyperlipid\* OR hyperlip?emia\* OR hypercholesterol\* OR hypercholester?emia\* OR hyperlipoprotein?emia\* OR hypertriglycerid?emia\*)
- S19 TI (hyperlipid\* OR hyperlip?emia\* OR hypercholesterol\* OR hypercholester?emia\* OR hyperlipoprotein?emia\* OR hypertriglycerid?emia\*)
- S18 (MH "Hyperlipidemia+")
- S17 TI "high blood pressure" OR AB "high blood pressure"
- S16 AB (hypertensi\* OR "peripheral arter\* disease\*")
- S15 TI (hypertensi\* OR "peripheral arter\* disease\*")
- S14 (MH "Hypertension+")
- S13 TI (stroke OR strokes OR cerebrovasc\* OR cerebral N2 vascular OR apoplexy OR brain N2 accident\* OR brain N2 infarct\*)
- S12 (MH "Stroke")

S11 AB (“atrial fibrillat\*” OR tachycardi\* OR endocardi\* OR sick N2 sinus)  
 S10 TI (“atrial fibrillat\*” OR tachycardi\* OR endocardi\* OR sick N2 sinus)  
 S9 AB (pericard\* OR isch?em\* OR emboli\* OR arrhythmi\* OR thrombo\*)  
 S8 TI (pericard\* OR isch?em\* OR emboli\* OR arrhythmi\* OR thrombo\*)  
 S7 AB (cardio\* OR cardia\* OR heart\* OR coronary\* OR angina\* OR ventric\* OR myocard\*)  
 S6 TI (cardio\* OR cardia\* OR heart\* OR coronary\* OR angina\* OR ventric\* OR myocard\*)  
 S5 (MH “Cardiovascular Diseases+”)  
 S4 S1 OR S2 OR S3  
 S3 almond\* or walnut\* or peanut\* or pecan\* or hazelnut\* or chestnut\* or acorn\* or pistachio\* or cashew\* or macademia\* or mongongo\* or buckwheat\* or coconut\*  
 S2 nut or nuts  
 S1 (MH “Nuts+”)

### Web of Science

#10 #9 AND #8  
 9 TS=((random\* or blind\* or allocat\* or assign\* or trial\* or placebo\* or crossover\* or cross-over\*))  
 #8 #7 AND #3  
 #7 #6 OR #5 OR #4  
 #6 TS=(hypertensi\* or peripheral arter\* disease\* or ((high or increased or elevated) near/2 (“blood pressure”)) or hyperlipid\* or hyperlip?emia\* or hypercholesterol\* or hypercholester?emia\* or hyperlipoprotein?emia\* or hypertriglycerid?emia\*)  
 #5 TS=((stroke or strokes) or cerebrovasc\* or apoplexy or (brain near/2 accident\*) or ((brain\* or cerebral or lacunar) near/2 infarct\*))  
 #4 TS=(cardio\* or cardia\* or heart\* or coronary\* or angina\* or ventric\* or myocard\* or pericard\* or isch?em\*)  
 #3 #2 OR #1  
 #2 TS=(almond\* or walnut\* or peanut\* or pecan\* or hazelnut\* or chestnut\* or acorn\* or pistachio\* or cashew\* or macademia\* or mongongo\* or buckwheat\* or coconut\*)  
 #1 TS=(nut or nuts)

## CONTRIBUTIONS OF AUTHORS

Nicole Martin searched for and screened articles, performed data abstraction and analyses, drafted the review and approved the final review version.

Roberta Germano screened articles, drafted the review and approved the final review version.

Louisa Hartley drafted the review and approved the final review version.

Alma Adler screened articles, performed data abstraction, drafted the review and approved the final manuscript version.

Karen Rees screened articles, checked the data and analyses, drafted the review and approved the final review version.

## DECLARATIONS OF INTEREST

Nicole Martin: none known.

Roberta Germano: none known.

Louisa Hartley: none known.

Alma Adler: none known.

Karen Rees: none known.

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- Department of Non-communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine, UK.

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## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Due to limited resources, we did not search Google Scholar or conduct citation searching as planned in the protocol ([Martin 2015](#)).