# 'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease (Review)

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[Intervention Review]

# 'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease

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## ABSTRACT

### Background

The Seven Countries study in the 1960s showed that populations in the Mediterranean region experienced lower cardiovascular disease (CVD) mortality probably as a result of different dietary patterns. Later observational studies have confirmed the benefits of adherence to a Mediterranean dietary pattern on CVD risk factors. Clinical trial evidence is limited, and is mostly in secondary prevention.

### Objectives

To determine the effectiveness of a Mediterranean dietary pattern for the primary prevention of CVD.

### Search methods

We searched the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 9 of 12, September 2012); MEDLINE (Ovid, 1946 to October week 1 2012); EMBASE (Ovid, 1980 to 2012 week 41); ISI Web of Science (1970 to 16 October 2012); Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database and Health Economics Evaluations Database (Issue 3 of 12, September 2012). We searched trial registers and reference lists of reviews and applied no language restrictions.

### Selection criteria

We selected randomised controlled trials in healthy adults and adults at high risk of CVD. A Mediterranean dietary pattern was defined as comprising at least two of the following components: (1) high monounsaturated/saturated fat ratio, (2) low to moderate red wine consumption, (3) high consumption of legumes, (4) high consumption of grains and cereals, (5) high consumption of fruits and vegetables, (6) low consumption of meat and meat products and increased consumption of fish, and (7) moderate consumption of milk and dairy products. The comparison group received either no intervention or minimal intervention. Outcomes included clinical events and CVD risk factors.

### Data collection and analysis

Two review authors independently extracted data and contacted chief investigators to request additional relevant information.

**Main results**

We included 11 trials (15 papers) (52,044 participants randomised). Trials were heterogeneous in the participants recruited, in the number of dietary components and follow-up periods. Seven trials described the intervention as a Mediterranean diet. Clinical events were reported in only one trial (Women's Health Initiative 48,835 postmenopausal women, intervention not described as a Mediterranean diet but increased fruit and vegetable and cereal intake) where no statistically significant effects of the intervention were seen on fatal and non-fatal endpoints at eight years. Small reductions in total cholesterol (-0.16 mmol/L, 95% confidence interval (CI) -0.26 to -0.06; random-effects model) and low-density lipoprotein (LDL) cholesterol (-0.07 mmol/L, 95% CI -0.13 to -0.01) were seen with the intervention. Subgroup analyses revealed statistically significant greater reductions in total cholesterol in those trials describing the intervention as a Mediterranean diet (-0.23 mmol/L, 95% CI -0.27 to -0.2) compared with control (-0.06 mmol/L, 95% CI -0.13 to 0.01). Heterogeneity precluded meta-analyses for other outcomes. Reductions in blood pressure were seen in three of five trials reporting this outcome. None of the trials reported adverse events.

**Authors' conclusions**

The limited evidence to date suggests some favourable effects on cardiovascular risk factors. More comprehensive interventions describing themselves as the Mediterranean diet may produce more beneficial effects on lipid levels than those interventions with fewer dietary components. More trials are needed to examine the impact of heterogeneity of both participants and the intervention on outcomes.

## PLAIN LANGUAGE SUMMARY

**Mediterranean diet for the prevention of cardiovascular disease**

It is well established that diet plays a major role in cardiovascular disease risk. The traditional Mediterranean dietary pattern is of particular interest because of observations from the 1960s that populations in countries of the Mediterranean region, such as Greece and Italy, had lower mortality from cardiovascular disease compared with northern European populations or the US, probably as a result of different eating habits.

This review assessed the effects of providing dietary advice to follow a Mediterranean-style dietary pattern to healthy adults or people at increased risk of cardiovascular disease in order to prevent the occurrence of cardiovascular disease and reduce the risk factors associated with it. Definitions of a Mediterranean dietary pattern vary and we included only randomised controlled trials (RCTs) of interventions that reported at least two of the following components: (1) high monounsaturated/saturated fat ratio, (2) low to moderate red wine consumption, (3) high consumption of legumes, (4) high consumption of grains and cereals, (5) high consumption of fruits and vegetables, (6) low consumption of meat and meat products and increased consumption of fish, and (7) moderate consumption of milk and dairy products. The control group was no intervention or minimal intervention. We found 11 RCTs (15 papers) that met these criteria. The trials varied enormously in the participants recruited and the different dietary interventions. Four trials were conducted in women only, two trials were in men only and the remaining five were in both men and women. Five trials were conducted in healthy individuals and six trials were in people at increased risk of cardiovascular disease or cancer. The number of components relevant to a Mediterranean dietary pattern ranged from two to five and only seven trials described the intervention as a Mediterranean diet.

The largest trial, which recruited only postmenopausal women and was not described as a Mediterranean diet meeting only two of the criteria described above, reported no difference in the occurrence of cardiovascular disease between the dietary advice group and the control group. The other trials measured risk factors for cardiovascular disease. As the studies were so different, it was not possible to combine studies for most of the outcomes. Where it was possible to combine studies, we found small reductions in total cholesterol levels as well as in the harmful low-density lipoprotein (LDL) cholesterol concentrations. The reductions in total cholesterol were greater in the studies that described themselves as providing a Mediterranean diet. None of the trials reported side effects.

The review concludes that, from the limited evidence to date, a Mediterranean dietary pattern reduces some cardiovascular risk factors. However, more trials are needed to look at the effects of the different participants recruited and the different dietary interventions to see which interventions might work best in different populations.

# BACKGROUND

## Description of the condition

Cardiovascular disease (CVD) is one of the leading causes of death worldwide (WHO 2011a). In 2008, it accounted for 30% of total global deaths, including 6.2 million deaths due to stroke and 7.2 million due to coronary heart disease (CHD) (WHO 2011a). The burden of CVD also varies considerably between regions (Müller-Nordhorn 2008; Reddy 1998). Within Europe, there is a northeast to southwest gradient in mortality from ischaemic heart disease where mortality rates are higher in counties within Eastern Europe. The highest age-adjusted standardised mortality rates (SMR) are found in Latvia (SMR 461), Estonia (SMR 446), Slovakia (SMR 369) and Lithuania (SMR 357), while the lowest rates are found in France (SMR 65), Portugal (SMR 87), Italy (SMR 92) and Spain (SMR 92) (Müller-Nordhorn 2008). More globally, while reductions in CVD mortality have been observed in developed countries, there are increases in CVD mortality in developing countries (Reddy 1998). The World Health Organization state that over 80% of CVD deaths occur in low- and middle-income countries and the number of CVD deaths will increase to 23.3 million by 2030, with CVD remaining the single leading cause of death (Mathers 2006; WHO 2011b).

There is a longstanding recognition that diet plays a major role in the aetiology of many chronic diseases, thereby contributing to a significant geographical variability in morbidity and mortality rates from chronic disease across different countries and populations worldwide (WHO 2003). In particular, early data from the Seven Countries study in the 1960s showed that populations in countries of the Mediterranean region, such as Greece and Italy, experienced lower mortality from CVD compared with northern European populations such as Finland or the US, probably as a result of different dietary patterns (Keys 1986). Thereafter, the potential beneficial effects of the Mediterranean dietary pattern on longevity and health outcomes have become a source of much interest and investigation. Several observational studies have shown greater longevity and quality of life, as well as reduced mortality and morbidity from CVD, cancer and other nutrition-related diseases with greater adherence to a Mediterranean dietary pattern (Benetou 2008; Buckland 2009; Feart 2009; Fung 2009; Knoops 2004; Lagiou 2006; Mitrou 2007; Trichopoulou 1995; Trichopoulou 2003; Trichopoulou 2007). For example, findings from the Spanish European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study showed that a 1-unit increase in Mediterranean diet score (scale from 0 to 18 units) was associated with a 6% reduced risk of CHD, with similar risk estimates by sex (Buckland 2009). Systematic reviews of observational prospective studies have confirmed that greater adherence to a Mediterranean diet is associated with a significant improvement in health status and a significant reduction in overall mortality, as well as in morbidity and mortality from CVD and other major chronic diseases (Sofi 2008; Sofi 2010). Specifically, in the latest published meta-analysis of prospective cohort studies, a 2-point increase (scale from 0 to 7-9 points) in adherence to a Mediterranean dietary pattern was associated with an 8% reduction in all-cause mortality and a 10% reduction in CVD incidence or mortality (Sofi 2010).

Furthermore, the Mediterranean diet has been associated with favourable effects on major CVD risk factors. For example, studies have documented a decreased incidence of hypertension, diabetes mellitus and metabolic syndrome as a whole with a greater adherence to a Mediterranean dietary pattern (Martnez-Gonzalez 2008; Nunez-Cordoba 2009; Psaltopoulou 2004; Rumawas 2009; Sánchez-Taínta 2008). These findings have been corroborated by systematic reviews supporting beneficial effects of the Mediterranean diet on metabolic syndrome and its individual components (Buckland 2008; Kastorini 2011).

Against this large body of epidemiological observational studies, there is less evidence from well-conducted and adequately powered randomised controlled trials (RCTs), especially with regard to the potential efficacy of the Mediterranean diet in the primary prevention of CVD (Serra-Majem 2006). Most of the RCTs have addressed the effect of a Mediterranean type of diet on the occurrence of complications and recurrent events in people with existing CVD, showing favourable effects in CVD secondary prevention (Barzi 2003; de Lorgeril 1994; de Lorgeril 1996; de Lorgeril 1999). There is also considerable variability in the definition of, and duration of, the interventions evaluated.

## Description of the intervention

The Mediterranean diet has been defined (Helsing 1989; Nestle 1995; Serra-Majem 1993; Willett 1995), and includes the following dietary factors: a high intake of plant foods comprising mainly fruits and vegetables, cereals and whole-grain breads, beans, nuts and seeds; locally grown, fresh and seasonal, unprocessed foods; large quantities of fresh fruit consumed daily whereas concentrated sugars or honey are consumed a few times per week in smaller quantities; olive oil as a main cooking ingredient and source of fat; low to moderate amounts of cheese and yogurt; low quantities of red meat and higher quantities of fish; and low to moderate amounts of red wine often accompanying main meals. The original Mediterranean type of diet reflects the common dietary pattern of communities in countries of the Mediterranean region in the early 1960s (Keys 1986), which was an expression of common cultural and historical roots, and a shared set of lifestyle and eating habits rather than a mere assortment of specific micro- and macronutrients (Trichopoulou 1997).

The intervention under investigation for the current review was dietary advice to follow a Mediterranean-style diet or a provision of foods relevant to the Mediterranean diet. At least two components from the following list were required to reach our definition of a

Mediterranean-style dietary pattern (Helsing 1989; Nestle 1995; Serra-Majem 1993; Willett 1995):

1. high monounsaturated/saturated fat ratio (use of olive oil as main cooking ingredient);
2. low to moderate red wine consumption;
3. high consumption of legumes;
4. high consumption of grains and cereals;
5. high consumption of fruits and vegetables;
6. low consumption of meat and meat products and increased consumption of fish;
7. moderate consumption of milk and dairy products.

We chose at least two of the above components as our definition of a Mediterranean-style dietary pattern as one component does not constitute a dietary pattern.

### How the intervention might work

There is a large quantity of observational and experimental evidence supporting potential mechanisms to explain the beneficial effect of the Mediterranean diet on cardiovascular health (Serra-Majem 2006). For example, there is evidence of favourable effects of the Mediterranean diet on insulin resistance and endothelium-dependent vasoreactivity, as well as of the antioxidant and anti-inflammatory effects of the Mediterranean diet and its individual components such as fruits and vegetables, olive oil, whole grains, fish and red wine (Chrysohoou 2004; Dai 2008; Pitsavos 2005; Ryan 2000). In addition, the Mediterranean dietary pattern has been associated with beneficial effects on many cardiovascular risk factors, including lipoproteins, obesity, diabetes mellitus and hypertension (Buckland 2008; Kastorini 2011; Martnez-Gonzalez 2008; Nunez-Cordoba 2009; Psaltopoulou 2004; Rumawas 2009; Sánchez-Taínta 2008). There is additionally a large body of consistent epidemiological evidence supporting the notion that light to moderate red wine intake (one or two drinks/day), and moderate alcohol consumption in general, is associated with reduced all-cause and cardiovascular mortality and morbidity, and has beneficial effects on cardiovascular risk factors, when compared with both abstention and heavy drinking (Brien 2011; Corrao 2000; Di Castelnuovo 2002; Di Castelnuovo 2006; Ronksley 2011). In contrast, excess alcohol consumption is associated with an increased risk of cardiovascular mortality and morbidity, primarily through an increased risk of hypertension and stroke (Stranges 2004; Taylor 2009).

### Why it is important to do this review

Modification of dietary factors forms an integral part of the primary prevention of CVD disease. A Mediterranean-style dietary pattern is likely to produce a beneficial effect on the occurrence of several chronic diseases, primarily CVD, which are closely linked to lifestyle and eating habits. This notion is corroborated by dietary recommendations of several scientific associations for the prevention of major chronic disease (AHA 2006; WHO 2003). To our knowledge, there have been no systematic reviews conducted to examine the effectiveness of the Mediterranean dietary pattern in the primary prevention of CVD. Most of the randomised evidence has addressed the effect of a Mediterranean type of diet on the occurrence of complications and recurrent events in people with existing CVD, rather than in the primary prevention setting (Barzi 2003; de Lorgeril 1994; de Lorgeril 1999; Serra-Majem 2006). There is also a wide degree of heterogeneity in the definition and duration of the intervention.

## OBJECTIVES

To determine the effectiveness of dietary advice to follow a Mediterranean-style dietary pattern or the provision of foods relevant to the Mediterranean diet for the primary prevention of CVD.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

RCTs

#### Types of participants

Adults of all ages (18 years or more) from the general population and those at high risk of CVD. The review focused on the effects of a Mediterranean dietary pattern for the primary prevention of CVD. Therefore, we excluded studies where more than 25% of participants had CVD at baseline including people who had experienced a previous myocardial infarction (MI), stroke, revascularisation procedure (coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA)), people with angina, or angiographically defined CHD, cerebrovascular disease (stroke) and peripheral arterial disease. We also excluded studies where more than 25% of the participants had type 2 diabetes as while patients with type 2 diabetes are at increased risk of CVD, interventions for diabetes are covered specifically by the Cochrane Metabolic and Endocrine Disorders review group.

### Types of interventions

The intervention was specific dietary advice to follow a Mediterranean-style dietary pattern or provision of dietary factors relevant to the Mediterranean diet. At least two components from the following list were required to meet our definition of a Mediterranean-style diet (Helsing 1989; Nestle 1995; Serra-Majem 1993; Willett 1995).

1. High monounsaturated/saturated fat ratio (use of olive oil as main cooking ingredient).
2. Low to moderate red wine consumption.
3. High consumption of legumes.
4. High consumption of grains and cereals.
5. High consumption of fruits and vegetables.
6. Low consumption of meat and meat products and increased consumption of fish.
7. Moderate consumption of milk and dairy products.

We intended to consider studies examining dietary advice to follow a Mediterranean-style diet separately from studies examining the provision of foods, but, for all studies that met our inclusion criteria, the intervention was dietary advice. It was also our intention to stratify results according to the number of components constituting the Mediterranean dietary pattern, the intensity and duration of the intervention and follow-up period, and the effects of age and gender. However, there were insufficient trials that met the inclusion criteria to perform these analyses. We did consider interventions describing themselves as a Mediterranean diet or style of diet including the core components of increased fruit and vegetable consumption and exchange of saturated fat for monounsaturated fat, compared with other interventions that met our criteria, in subgroup analyses.

We focused on follow-up periods of three months or more. We only considered trials where the comparison group was no intervention or minimal intervention (e.g. leaflet to follow a dietary pattern with no person-to-person intervention or reinforcement). The rationale for this was to determine the effects of a Mediterranean dietary pattern more clearly rather than to include other dietary interventions as comparison groups. We did not exclude studies where loss to follow-up was greater than 20%, but we carried out sensitivity analyses to examine the effect of excluding these studies on the overall effect estimate.

### Types of outcome measures

Endpoints were measured using validated measures.

#### Primary outcomes

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

#### Secondary outcomes

1. Changes in blood lipids (total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides), and blood pressure (systolic and diastolic blood pressure).
2. Occurrence of type 2 diabetes as a major CVD risk factor.
3. Health-related quality of life.
4. Adverse effects (as defined by the authors of the included trials).
5. Costs.

## Search methods for identification of studies

### Electronic searches

We searched the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL, Issue 9 of 12, September 2012);
- MEDLINE (Ovid, 1946 to October week 1 2012);
- EMBASE (Ovid, 1980 to 2012 week 41);
- ISI Web of Science (1970 to 16 October 2012);
- Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database and Health Economic Evaluations Database (Issue 3 of 12, September 2012).

We used medical subject headings (MeSH) or equivalent and text word terms and the Cochrane sensitive-maximising RCT filter for MEDLINE (Lefebvre 2011), and adaptations of it for EMBASE and Web of Science. We applied no language restrictions. We tailored searches to individual databases (Appendix 1).

### Searching other resources

In addition, we checked reference lists of reviews for additional studies.

We searched the metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct), Clinicaltrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) for ongoing trials.

We contacted authors where necessary for additional information.

## Data collection and analysis

### Selection of studies

From the searches, two review authors (KR, LH or NF) reviewed the title and abstract of each paper and retrieved potentially relevant references. Following this initial screening, we obtained the

full-text reports of potentially relevant studies, and two review authors (KR, LH or NF) independently selected studies to be included in the review using predetermined inclusion criteria. In all cases, we resolved disagreements about any study inclusions by consensus and consulted a third review author (MT) if disagreement persisted.

### Data extraction and management

Two review authors (KR, LH or NF) independently extracted data using a proforma, and contacted chief investigators to request additional relevant information if necessary. We extracted details of the study design, participant characteristics, study setting, intervention (including number of components and duration), and outcome data including details of outcome assessment, adverse effects, and methodological quality (randomisation, blinding, attrition) from each of the included studies. We resolved disagreements about extracted data by consensus.

### Assessment of risk of bias in included studies

We assessed risk of bias by examining the quality of the random sequence generation and allocation concealment, description of dropouts and withdrawals (including analysis by intention to treat (ITT)), blinding (participants, personnel and outcome assessment) and selective outcome reporting (Higgins 2011). Two review authors (KR, LH or NF) independently assessed the risk of bias of included studies and rated each domain as having a 'low risk of bias', a 'high risk of bias' or an 'unclear risk of bias'.

### Measures of treatment effect

We processed data in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We expressed dichotomous outcomes (available for only one trial) as hazard ratios (HR) with 95% confidence intervals (CI). For continuous variables, we compared net changes (i.e. intervention group minus control group differences) and calculated mean differences (MD) and 95% CIs for each study.

### Assessment of heterogeneity

For each outcome, we carried out tests of heterogeneity (using the $Chi^2$ test of heterogeneity and the $I^2$ statistic). In the situation of no heterogeneity, we performed a fixed-effect meta-analysis. If we detected substantial heterogeneity, we looked for possible explanations for this (e.g. participants and intervention). If we could not explain the heterogeneity, the review authors considered the following options: provide a narrative overview and not aggregate the studies at all, or use a random-effects model with appropriate cautious interpretation.

### Subgroup analysis and investigation of heterogeneity

It was our intention to report the results separately for dietary advice to follow a Mediterranean dietary pattern and provision of foods relevant to a Mediterranean-style diet. However, to date we have found only trials of dietary advice to follow a Mediterranean dietary pattern. If there were sufficient trials that met the inclusion criteria it was also our intention to examine the impact of the number of components of the Mediterranean dietary pattern, the intensity and duration of the intervention, the follow-up period, and the effects of gender and age. We have performed subgroup analyses to examine the effect of interventions described as the Mediterranean diet or style of diet or those including both of the core components of increased fruit and vegetable consumption and exchange of saturated fat for monounsaturated fat, compared with other interventions meeting our criteria.

### Sensitivity analysis

If there had been sufficient trials that met the inclusion criteria, it was our intention to perform sensitivity analyses excluding studies of low methodological quality and undertake funnel plots and tests of asymmetry to assess possible publication bias (Egger 1997). We did perform sensitivity analyses excluding studies where loss to follow-up exceeded 20%.

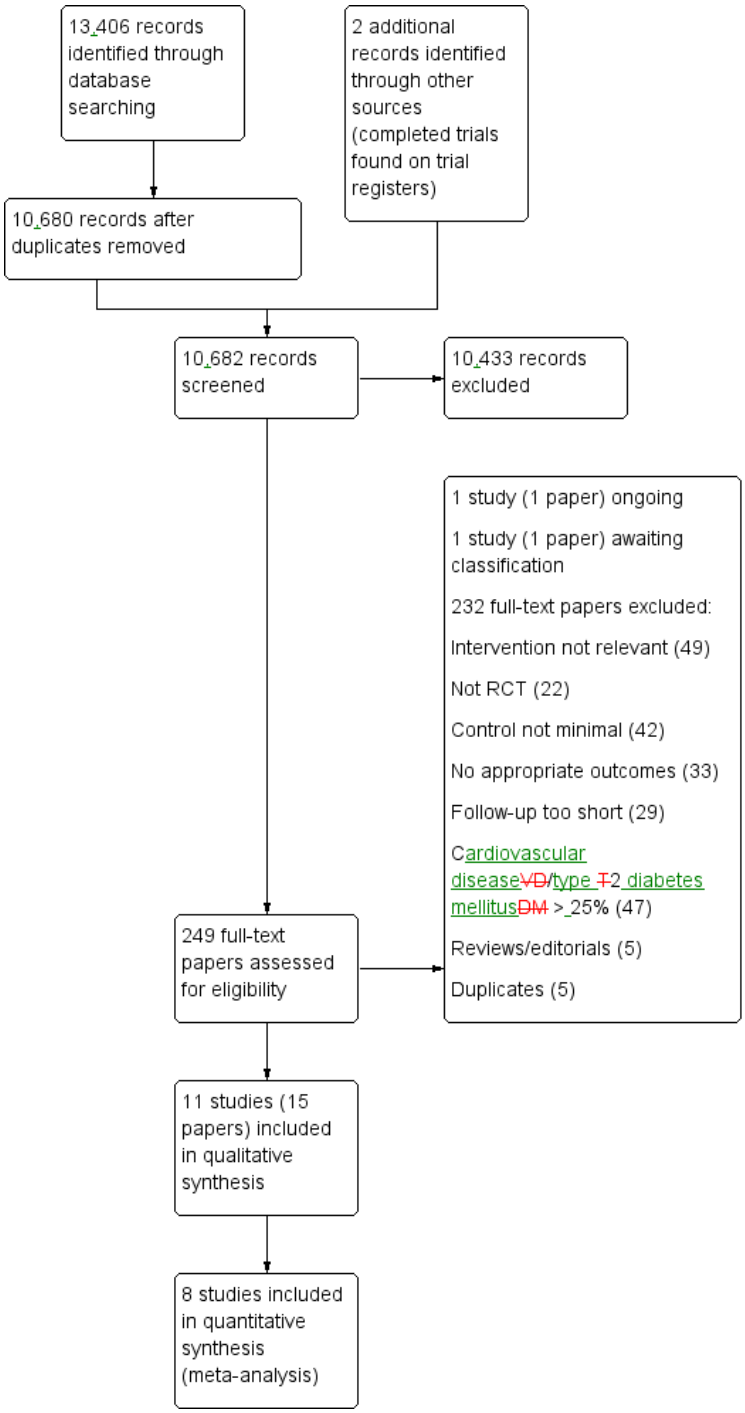
## RESULTS

### Description of studies

#### Results of the search

The database searches generated 13,406 hits and 10,680 after de-duplication. We identified two additional records by searching other resources. Screening the titles and abstracts of the 10,682 records identified 249 papers for formal inclusion or exclusion. Of these, 11 RCTs (15 papers) met the inclusion criteria. We identified one ongoing trial and one trial is awaiting classification. The flow of studies throughout the review is presented in the PRISMA diagram in Figure 1.

**Figure 1. Study flow diagram.**



### Included studies

Details of the methods, participants, intervention, comparison group and outcome measures for each of the studies included in the review are shown in the Characteristics of included studies table. Eleven trials (15 papers) were included with 52,044 participants randomised. The majority of participants were enrolled in one large multicentre trial (48,835 women; WHI)

The health status of participants varied between studies. The majority of participants (49,185 randomised) were classified as healthy and were recruited by five of the trials (Abedi 2010; Castagnetta 2002; Djuric 2009; Konstantinidou 2010; WHI). The remaining six trials recruited previously untreated hypercholesteraemic participants (Jula 2002; Wardle 2000), elderly participants with long-standing hypercholesterolaemia (Lindman 2004), overweight or obese participants with untreated hypertension (ENCORE), sedentary people with metabolic syndrome (Esposito 2004), and one trial recruited participants at high risk of colorectal cancer (Lanza 2001). Three trials including the largest trial recruited only women who were postmenopausal (Abedi 2010; Castagnetta 2002; WHI), and one trial recruited only women aged 25 to 65 years (Djuric 2009). In contrast, two trials recruited only men (Jula 2002; Lindman 2004), and the remaining five recruited both men and women (ENCORE; Esposito 2004; Konstantinidou 2010; Lanza 2001; Wardle 2000). The trials were conducted in the US (Djuric 2009; ENCORE; Lanza 2001; WHI), Italy (Castagnetta 2002; Esposito 2004), Finland (Jula 2002), Spain (Konstantinidou 2010), Norway (Lindman 2004), Iran ( Abedi 2010), and the UK (Wardle 2000), and the duration of the intervention and follow-up periods varied from three months (Jula 2002; Konstantinidou 2010; Wardle 2000 ), four months (ENCORE), six months (Abedi 2010; Castagnetta 2002; Djuric 2009; Lindman 2004), two years (Esposito 2004), four years (Lanza 2001), and up to eight years (WHI).

One trial had a dietary intervention that comprised five components that met our definition of a Mediterranean-style diet (see Types of interventions for list of components) (Castagnetta 2002), one trial had a dietary intervention that comprised four components (ENCORE), five trials had dietary interventions that comprised three components (Esposito 2004; Jula 2002; Konstantinidou 2010; Lindman 2004; Wardle 2000). The remaining four trials had a dietary intervention comprising two components (Abedi 2010; Djuric 2009; Lanza 2001; WHI). Seven trials described the intervention as a Mediterranean diet or Mediterranean-style diet (Castagnetta 2002; Djuric 2009; Esposito 2004; Jula 2002; Konstantinidou 2010; Lindman 2004; Wardle 2000). The remaining trials fulfilled our definition of two or more components of the Mediterranean diet but did not include both of the key components associated with the Mediterranean diet (increasing fruit and vegetable intake and exchanging saturated fat for monounsaturated fat) (Abedi 2010; ENCORE; Lanza 2001; WHI).

We identified one ongoing trial (Sanders 2012) (see Characteristics of ongoing studies table). Briefly, this trial examines the effects of a cardioprotective diet (decreased salt and saturated fatty acids intake, and increased whole grain cereals, fruit and vegetables and oily fish intake) with a control diet (average UK diet), in healthy men and women, for a period of three months. The outcomes measured include systolic blood pressure and lipid levels. The anticipated end date for this trial was December 2012.

One study is awaiting classification (Inguaggiato 2011) (see Characteristics of studies awaiting classification table).

### Excluded studies

Details and reasons for exclusion for the studies that most closely missed the inclusion criteria are presented in the Characteristics of excluded studies table. Reasons for exclusion for the majority of studies was due to the control group not being minimal (e.g. receiving face-to-face dietary advice) and studies not being RCTs.

## Risk of bias in included studies

Details are provided for each of the included studies in the 'Risk of bias' section of the Characteristics of included studies table. We assessed risk of bias as 'low', 'high' or 'unclear'.

### Allocation

The methods of random sequence generation were unclear in seven of the 11 included studies (Abedi 2010; Castagnetta 2002; Djuric 2009; Jula 2002; Lanza 2001; Lindman 2004; Wardle 2000). In the four studies where this was clear, we judged the methods used to be of low risk of bias (ENCORE; Esposito 2004; Konstantinidou 2010; WHI). The methods of allocation concealment were unclear in eight of the 11 included studies. Where this was clear, we judged the methods used to be at low risk of bias (ENCORE; Esposito 2004; Wardle 2000).

### Blinding

The blinding of participants and personnel was unclear in all 11 trials. However, the blinding of participants and personnel for behavioural interventions is difficult, if not impossible, in most cases. Blinding of outcome assessment was unclear in seven of the 11 trials (Abedi 2010; Castagnetta 2002; Djuric 2009; Konstantinidou 2010; Lanza 2001; Lindman 2004; Wardle 2000). In the remaining four trials, outcome assessments were made blind to the group

assignment and were judged to be at low risk of bias (ENCORE; Esposito 2004; Jula 2002; WHI).

### Incomplete outcome data

We judged four of the 11 trials to be of low risk of bias as reasons for exclusions and loss-to-follow-up were provided or ITT analyses were performed, or both (ENCORE; Esposito 2004; Konstantinidou 2010; WHI). We judged three studies to be at high risk of bias as no reasons were provided for excluded participants (Jula 2002), and there was differential loss to follow-up that exceeded 20% in the control group in one trial (Abedi 2010), and in the intervention group in another trial (Djuric 2009). We examined the exclusion of these two trials in sensitivity analyses. For the remaining trials, we judged the risk of bias as unclear.

### Selective reporting

For four of the studies, the risk of bias associated with selective reporting was unclear (Castagnetta 2002; Jula 2002; Konstantinidou 2010; Lindman 2004), the remaining seven studies clearly stated the primary and secondary outcomes and reported the results for these.

### Other potential sources of bias

There was insufficient information to judge the risk of bias in other sources of bias not covered above and we categorised all studies as unclear.

## Effects of interventions

### Clinical events

The largest trial had long-term follow-up of eight years and was the only trial reporting clinical events (WHI). In participants without a history of CVD (3.4% had CVD at baseline), there were no statistically significant effects of the dietary intervention on non-fatal MI (HR 0.91, 95% CI 0.8 to 1.04), CHD death (HR 1.01, 95% CI 0.81 to 1.27), revascularisation (HR 0.91, 95% CI 0.82 to 1.01), fatal stroke (HR 0.94, 95% CI 0.65 to 1.35), non-fatal stroke (HR 1.04, 95% CI 0.90 to 1.19) and total CVD events (clinical MI, silent MI, death due to CHD, CABG/percutaneous coronary intervention and stroke) (HR 0.96, 95% CI 0.89 to 1.03). The WHI trial was not described as a Mediterranean-style diet neither did it comprise of both an increase in fruit and vegetable consumption and exchanging saturated fat for monounsaturated fat. It met our inclusion criteria of two components that included increasing fruit and vegetable and cereal and grain intake. None of the studies describing their interventions as a Mediterranean diet reported clinical events.

### Cardiovascular risk factors

#### Lipid levels

##### Total cholesterol

Eight trials (4151 participants randomised) measured total cholesterol levels and reported data that could be used in meta-analyses (Abedi 2010; Djuric 2009; ENCORE; Esposito 2004; Konstantinidou 2010; Lanza 2001; Wardle 2000; WHI). Lipid levels were measured in only a subgroup (n = 2816) of the large WHI trial (WHI). There was significant heterogeneity between trials ($I^2$ = 74%). Pooling the studies resulted in similar estimates for both fixed-effect and random-effects models indicating that there was no strong evidence of small study effects, so we reported the random-effects model, with appropriate cautious interpretation. The dietary intervention reduced total cholesterol levels by 0.16 mmol/L (95% CI 0.06 to 0.26; random-effects model, P value = 0.003; Analysis 1.1). Two of the trials were at high risk of bias as there was differential loss to follow-up that just exceeded 20% in the control group (Abedi 2010), and intervention group (Djuric 2009), of each trial. Sensitivity analyses excluding these two trials produced a similar effect estimate (MD -0.18, 95% CI -0.28 to -0.07).

Two further trials measured total cholesterol but did not provide data in a useable format for meta-analyses despite our efforts to obtain these (Castagnetta 2002; Jula 2002). Both trials reported significant reductions in total cholesterol levels with the dietary intervention.

We performed subgroup analyses to examine the effect of interventions described as a Mediterranean or Mediterranean-style diet and those that comprised at least two components but did not comprise both of the core components of increasing fruit and vegetable intake and exchanging saturated fat for monounsaturated fat. The reduction in total cholesterol was statistically significantly greater for interventions describing themselves as a Mediterranean diet (MD 0.23, 95% CI -0.27 to -0.2) compared with those that did not (MD -0.06, 95% CI -0.13 to 0.01; Analysis 1.2).

##### Low-density lipoprotein cholesterol

Six trials (3227 participants randomised) measured LDL-cholesterol and provided data that could be pooled in a meta-analysis (Abedi 2010; Djuric 2009; ENCORE; Konstantinidou 2010; Wardle 2000; WHI). Heterogeneity was low to moderate ($I^2$ = 22%) and we performed a fixed-effect meta-analysis. There was a small but statistically significant reduction in LDL-cholesterol (MD -0.07 mmol/L, 95% CI -0.13 to -0.01) with the dietary intervention, and results were dominated by the largest trial (WHI) (Analysis 1.3). Two of the trials were at high risk of bias as there was differential loss to follow-up that just exceeded 20% in the control group (Abedi 2010) and intervention group (Djuric 2009) of

each trial. Sensitivity analyses excluding these two trials produced a similar effect estimate (MD -0.08, 95% CI -0.14 to -0.02).
A further trial reported LDL-cholesterol but did not report follow-up data and attempts to retrieve this were unsuccessful (Jula 2002). This trial reported a statistically significant reduction in LDL-cholesterol of 10.8% with the intervention.
We performed subgroup analyses to examine the effect of interventions describing themselves as a Mediterranean or Mediterranean-style diet and those that comprised at least two components but did not comprise both of the core components of increasing fruit and vegetable intake and exchanging saturated fat for monounsaturated fat. The reduction in LDL-cholesterol was greater for interventions describing themselves as a Mediterranean diet (MD -0.16, 95% CI -0.39 to 0.07; random-effects model) compared with those that did not (MD -0.06, 95% CI -0.12 to 0.00; random-effects model), but this did not reach statistical significance (Analysis 1.4).

### High-density lipoprotein cholesterol

Eight trials measured the effect of the diet on HDL-cholesterol (Abedi 2010; Djuric 2009; ENCORE; Esposito 2004; Jula 2002; Konstantinidou 2010; Wardle 2000; WHI, 3527 participants randomised) but we could not obtain follow-up data from one of the authors (Jula 2002). There was significant heterogeneity between the remaining seven trials ($I^2$ = 83%) and so we did not perform a meta-analysis. One trial reported a statistically significant increase in HDL-cholesterol levels with the intervention (MD 0.08 mmol/L, 95% CI 0.06 to 0.09) (Esposito 2004). The remaining six trials found no effect of the intervention on HDL-cholesterol levels (MD 0.01 mmol/L, 95% CI -0.08 to 0.1 (Abedi 2010); MD 0.03 mmol/L, 95% CI -0.15 to 0.2 (Djuric 2009); MD -0.04 mmol/L, 95% CI -0.17 to 0.09 (ENCORE); MD 0.00 mmol/L, 95% CI -0.08 to 0.08 (Konstantinidou 2010); MD -0.06 mmol/L, 95% CI -0.18 to 0.06 (Wardle 2000); MD -0.01 mmol/L, 95% CI -0.03 to 0.02 (WHI)). The study that did not provide follow-up data reported a statistically significant reduction in HDL-cholesterol of 4.9% (Jula 2002).

### Triglycerides

Nine trials measured triglyceride levels (Abedi 2010; Djuric 2009; ENCORE; Esposito 2004; Jula 2002; Konstantinidou 2010; Lindman 2004; Wardle 2000; WHI, 3626 participants randomised). Two of the trials provided postintervention values as medians (with 25th and 75th percentiles) and were not included in the analysis (Konstantinidou 2010; Lindman 2004) and one trial did not report follow-up data (Jula 2002). There was significant heterogeneity between the remaining six trials ($I^2$ = 94%) and so we did not perform a meta-analysis. There was a statistically significant reduction in triglyceride levels with the intervention in one trial (MD -0.21, 95% CI -0.23 to -0.19; Esposito 2004). In four trials, the dietary intervention showed no effect on triglyceride levels (MD -0.05 mmol/L, 95% CI -0.49 to 0.39 (Abedi 2010); MD 0.00 mmol/L, 95% CI -0.23 to 0.23 (Djuric 2009); MD -0.01 mmol/L, 95% CI -0.24 to 0.22 (ENCORE); MD 0.00, 95% CI -0.05 to 0.05 (WHI)). In the remaining trial, the dietary intervention produced a statistically significant increase in triglyceride levels (MD 0.36 mmol/L, 95% CI 0.15 to 0.57; Wardle 2000). In the two trials reporting medians, no effect of the diet on triglyceride levels was observed (Konstantinidou 2010; Lindman 2004). Similarly, in the study where no follow-up data were reported, no effect of the diet on triglyceride levels was seen (Jula 2002).

### Blood pressure

Five trials measured systolic and diastolic blood pressure (Abedi 2010; ENCORE; Esposito 2004; Konstantinidou 2010; WHI, 42,724 participants randomised). Substantial heterogeneity existed between the trials for both outcomes ($I^2$ = 94% and 93%, respectively), and differences were observed between fixed- and random-effects models suggesting small trial effects, so we did not perform meta-analyses. A statistically significant reduction in systolic blood pressure was observed in three of the trials (MD -7.8 mmHg, 95% CI -12.11 to -3.49 (ENCORE); MD -3.00 mmHg, 95% CI -3.46 to -2.54 (Esposito 2004); MD -0.70 mmHg, 95% CI -1.03 to -0.37 (WHI)). The remaining two trials did not show a statistically significant reduction in systolic blood pressure (Abedi 2010; Konstantinidou 2010). For diastolic blood pressure, a statistically significant reduction was observed in three of the trials (MD -3.7 mmHg, 95% CI -6.1 to -1.3 (ENCORE); MD -2.00 mmHg, 95% CI -2.29 to -1.71 (Esposito 2004); MD -0.70 mmHg, 95% CI -0.88 to -0.52 (WHI)). The remaining two trials did not show a statistically significant reduction in diastolic blood pressure (Abedi 2010; Konstantinidou 2010).

### Type 2 diabetes

Incident-treated diabetes was reported during the eight years of follow-up of the WHI trial (WHI). They found no statistically significant difference in the diabetes risk between the intervention and control group (HR 0.96, 95% CI 0.90 to 1.03).

### Health-related quality of life, adverse effects or costs

None of the trials reported health-related quality of life, adverse effects or costs.
There was significant heterogeneity in many of the outcomes and, in most cases, a narrative synthesis was performed. The heterogeneity is probably due to the varying interventions with different numbers of components relevant to the Mediterranean diet and also the participants, both healthy populations and those at high risk of CVD. It was our intention to explore this heterogeneity further in stratified analyses but, to date, there are insufficient studies

included in this review to do this. However, we will conduct this in an update of this review when more evidence accrues.

# DISCUSSION

The aim of this review was to evaluate the effectiveness of dietary advice to follow a Mediterranean-style diet or the provision of foods relevant to the Mediterranean diet for the primary prevention of CVD. We also examined the effects of a Mediterranean-style diet on major cardiovascular risk factors including blood lipids, blood pressure and occurrence of type 2 diabetes.

## Summary of main results

Relatively few trials were included in this review, 11 completed RCTs (15 papers) and one ongoing RCT met the inclusion criteria of our definition of a Mediterranean dietary pattern. All trials examined the effects of dietary advice to follow a Mediterranean-style dietary pattern; none of the trials examined the effects of provision of foods relevant to a Mediterranean diet. The number of components of the Mediterranean diet varied from two to five, and seven trials described the intervention as a Mediterranean diet. Only one trial, the largest with 48,835 postmenopausal women randomised, reported clinical events and showed no statistically significant effects of the intervention on both fatal and non-fatal endpoints at eight years' follow-up (WHI), and incident diabetes rates were also similar between the intervention and control group for this trial. The WHI trial was not described as Mediterranean diet and comprised only two of the components in our definition (WHI). None of the studies describing the intervention as a Mediterranean diet reported clinical events. Cardiovascular risk factors were measured in all trials but heterogeneity between trials precluded meta-analysis for some outcomes. Small reductions in total cholesterol and LDL-cholesterol occurred with the dietary interventions where pooling was appropriate (total cholesterol: MD -0.16 mmol/L, 95% CI -0.26 to -0.06, random-effects model; LDL-cholesterol: -0.07 mmol/L, 95% CI -0.13 to -0.01, respectively). Subgroup analyses revealed larger reductions in total cholesterol in those studies describing the intervention as a Mediterranean diet (MD -0.23 mmol/L, 95% CI -0.27 to -0.2 versus -0.06 mmol/L, 95% CI -0.13 to 0.01; P value < 0.001). Blood pressure was reduced in three of the five trials reporting this outcome. None of the trials reported health-related quality of life, adverse events or costs. There was significant heterogeneity in the different dietary interventions both in terms of the number of components relevant to a Mediterranean dietary pattern, intensity and duration, the participants recruited and the follow-up periods. To date there are an insufficient number of trials to perform stratified analyses to examine the effects of these further on outcomes.

## Overall completeness and applicability of evidence

We included 11 trials (15 papers) with 52,044 participants randomised. We also identified one ongoing trial (Sanders 2012). However, only the largest trial (WHI), which recruited postmenopausal women only (48,835 randomised), contributed data to our primary outcomes of major CVD clinical endpoints. Therefore, the applicability of these findings to the male population is uncertain, given the well-established differences in cardio-metabolic risk factor profiles between women and men (Mosca 2011). In addition, the intervention was not described as a Mediterranean diet and satisfied only two components of a Mediterranean dietary pattern.

There was also a large variation in the health status of participants between studies. The majority of participants (49,185 randomised) were classified as healthy and were recruited by five of the trials (Abedi 2010; Castagnetta 2002; Djuric 2009; Konstantinidou 2010; WHI); most of these were in women. The remaining six trials recruited high-risk individuals, that is hypercholesteraemic participants (Jula 2002, Lindman 2004; Wardle 2000), overweight or obese participants with untreated hypertension (ENCORE), and sedentary people with metabolic syndrome (Esposito 2004), and one trial recruited participants at high risk of colorectal cancer (Lanza 2001). Hence, the applicability of these findings to different population groups is uncertain. All trials were conducted in developed countries and most in Western populations; therefore, the generalisability of these findings to lower-income settings has to be confirmed.

The effectiveness of the provision of foods relevant to the Mediterranean diet could not be assessed, because all studies that met the inclusion criteria were based on dietary advice to follow a Mediterranean-style diet. It was also our intention to stratify results according to the number of components constituting the Mediterranean dietary pattern and the intensity and duration of the intervention. However, there was an insufficient number of trials that met the inclusion criteria to perform these analyses. However, we did perform subgroup analyses to examine the effect of interventions described as the Mediterranean diet with those that did not but met our criteria of two or more components. We found greater reductions in total cholesterol for interventions describing themselves as a Mediterranean diet that was statistically significant. A similar trend was seen for LDL-cholesterol but few studies were included in this analysis. Therefore, it seems that a more comprehensive intervention such as those described as a Mediterranean diet targeting several food groups simultaneously may be more effective at least in reducing lipid levels.

The duration of the intervention and follow-up periods varied widely across studies, ranging from short-term trials (three to six months, Abedi 2010; Castagnetta 2002; Djuric 2009; ENCORE; Jula 2002; Konstantinidou 2010; Lindman 2004; Wardle 2000) to long-term interventions (two to eight years, Esposito 2004; WHI). Both short- and long-term health effects of dietary in-

terventions are plausible in terms of cardiovascular health, given the relatively quick response of cardiovascular risk factors such as blood lipids and blood pressure to lifestyle and dietary modifications (AHA 2006; Appel 1997; Appel 2001; Appel 2006). However, it is likely that potential beneficial effects of dietary interventions for the prevention of major chronic disease endpoints, such as mortality, CVD and type 2 diabetes, should represent the outcome of a long-term process linked to the interplay of dietary patterns with genetic and environmental factors. In addition, the sustainability of long-term lifestyle and dietary modifications is challenging. Therefore, the public health relevance of trials with extremely short-term dietary interventions or follow-up periods in this context is questionable.

## Quality of the evidence

Overall, the studies included in this review, especially the smaller short-term trials, were at some risk of bias or there was insufficient information to judge the risk of bias; hence, results should be treated with some caution. The methods of random sequence generation were unclear in seven of the 11 included studies, in the four studies where this was clear, we judged the methods used to be of low risk of bias (ENCORE; Esposito 2004; Konstantinidou 2010; WHI). Similarly, the methods of allocation concealment were unclear in most of the included studies, and where this was clear, we judged the methods used to be at low risk of bias (ENCORE; Esposito 2004; Wardle 2000).

The blinding of participants and personnel was unclear in all 11 trials but the blinding of participants and personnel for behavioural interventions is difficult, if not impossible, in most cases. Blinding of outcome assessment was also unclear in most trials, outcome assessments were made blind to the group assignment in four trials and we judged them to be at low risk of bias (ENCORE; Esposito 2004; Jula 2002; WHI).

We judged four of the 11 trials to be of low risk of attrition bias as reasons for exclusions and loss-to-follow-up were provided or ITT analyses were performed, or both (ENCORE; Esposito 2004; Konstantinidou 2010; WHI). We judged three studies to be at high risk of bias as no reasons were provided for excluded participants (Jula 2002), and there was differential loss to follow-up that exceeded 20% in two trials (Abedi 2010; Djuric 2009). We examined the exclusion of these two trials in sensitivity analyses but they did not impact significantly on the effect estimates for either total cholesterol or LDL-cholesterol levels. For the remaining trials, we judged the risk of bias as unclear.

We judged selective reporting to be at low risk of bias for the majority of studies as the primary and secondary outcomes were stated and results were reported for these. For four of the studies, the risk of bias associated with selective reporting was unclear (Castagnetta 2002; Jula 2002; Konstantinidou 2010; Lindman 2004). For all trials, there was insufficient information provided to assess the risk of bias in other sources of bias not covered above.

## Potential biases in the review process

There was a high degree of heterogeneity between trials, from different sources (participants, nature and duration of intervention and follow-up, outcome data), which precluded statistical pooling for most outcomes.

The WHI was the largest trial included, the only study contributing data to our primary outcomes, and dominated findings of this review (WHI). However, this study was based on a highly selected group of participants (i.e. postmenopausal women aged 50 to 79 years), which makes the generalisability of these findings uncertain. In fact, the possibility of different or greater effects by dietary interventions of this nature among men or younger age groups cannot be ruled out. Furthermore, a good proportion of WHI participants were on cardiovascular medication at baseline (approximately 12% on lipid-lowering medication, 18% on aspirin and 43% had treated hypertension or blood pressure $\geq$140/90 mmHg), and some had prevalent CVD (3.4%). The distribution of cardiovascular medication was not different between intervention and comparison groups at baseline and did not change during the trial; however, this may have biased the results toward null findings if CVD risk factors such as blood pressure and lipid levels were optimally controlled prior to the intervention (bias against seeing no effect of the intervention). Indeed, after excluding participants with baseline CVD, there was an apparent trend toward small protective effects for CHD events in women without baseline disease (WHI), although this did not reach statistical significance. Finally, the WHI Dietary Modification Trial intervention comprised only two components that met our definition of a Mediterranean-style diet, and was not specifically tailored for CVD prevention. However, it is plausible that more aggressive and targeted dietary interventions are necessary to influence CVD risk factors and, therefore, achieve a significant public health impact on CVD events (AHA 2006; Appel 1997; Appel 2001; Appel 2006).

Our decision to restrict this review to interventions that only focused on the effectiveness of a Mediterranean dietary pattern per se avoided the potential confounding effects of other behavioural interventions on our outcomes, for example, those involving increased exercise or weight loss in the context of multifactorial trials. Also, our strict inclusion criteria, particularly with regard to the comparison group, excluded a number of well-known trials, such as the PREDIMED (Prevention with Mediterranean Diet) trial in Spain (Estruch 2006; Estruch 2013) or the DASH (Dietary Approaches to Stop Hypertension) trials (Appel 1997; Appel 2001; Appel 2006), where the control groups were not minimal. Our decision to exclude trials in people with diabetes who are at increased risk for CVD may also have missed relevant studies, but interventions for the management of diabetes are covered by the Cochrane Metabolic and Endocrine Disorders Group, and are not within the remit of the Cochrane Heart Group. Finally, the definition of the Mediterranean dietary pattern is not homogeneous, and may vary across different geographical and cultural contexts (Helsing 1989; Nestle 1995; Serra-Majem 1993;

Serra-Majem 2006; Willett 1995). The result of this potential misclassification would probably be to underestimate the true effect of the dietary intervention on the selected outcomes (Copeland 1977). Our choice to use a classification system rather than include only those studies describing the intervention as a Mediterranean diet attempted to address this heterogeneity, and given sufficient studies would allow further exploration of active components. The components required to meet our definition of a Mediterranean dietary pattern were based on previous definitions (Helsing 1989; Nestle 1995; Serra-Majem 1993; Serra-Majem 2006; Willett 1995), and two or more components were required to meet our inclusion criteria. However, this definition resulted in the inclusion of several trials whose interventions included advice to follow a low-fat diet (ENCORE; Lanza 2001; WHI), which does not constitute a Mediterranean dietary pattern, in addition to at least two other relevant components. Given the view that the original Mediterranean type of diet was an expression of common cultural and historical roots, and a shared set of lifestyle and eating habits rather than a mere assortment of specific micro- and macronutrients (Trichopoulou 1997), we have performed some further analyses to examine the effects of interventions describing themselves as the Mediterranean diet and those that do not. Where this was possible, more comprehensive interventions targeting a number of components simultaneously showed greater reductions in total cholesterol than less comprehensive interventions. Future updates of this review will explore this further when more evidence accrues.

### Agreements and disagreements with other studies or reviews

We are not aware of any previous systematic review involving only RCTs that has specifically examined the effectiveness of dietary advice to follow a Mediterranean-style diet or the provision of foods relevant to the Mediterranean diet, as the only dietary intervention compared with no or minimal intervention, for the primary prevention of CVD in the general population of healthy adults across all ages and among individuals at high risk of CVD.

For example, one systematic review and meta-analysis examined the effectiveness of a Mediterranean-style diet compared with a low-fat diet in RCTs among overweight/obese individuals with at least one additional cardiovascular risk factor or with established coronary artery disease (Nordmann 2011). Trials had to have a minimum follow-up of six months, and to report ITT data on cardiovascular risk factors (i.e. changes in body weight, blood pressure and lipid levels). In this review, Mediterranean diets were defined as diets with moderate-fat intake (where the main sources of added fat were olive oil and nuts), rich in vegetables and low in red meat (with poultry and fish replacing beef and lamb). Low-fat diets were defined as diets aiming at an energy intake with 30% or less of calories from fat, based on the American Heart Association (AHA) dietary guidelines (Krauss 2000). Six trials were identified, including one secondary prevention trial, with 2650 participants randomised (50% women). Results of this meta-analysis suggested favourable, though modest, effects of the Mediterranean diet, as compared with a low-fat diet, on a wide range of cardiovascular risk factors and inflammatory markers, such as body weight, systolic and diastolic blood pressure, fasting plasma glucose, total cholesterol and high-sensitivity C-reactive protein. These results are generally consistent with the favourable but relatively modest effects on total cholesterol and blood pressure levels reported by individual trials in our review. The main methodological differences between the two reviews were the inclusion or exclusion of secondary prevention trials and the different definitions of the dietary intervention (whole dietary pattern vs. individual components).

Other systematic reviews have pooled together the evidence from both observational studies and RCTs on the effects of the Mediterranean dietary pattern on metabolic syndrome and individual cardiovascular risk factors, supporting favourable effects of the Mediterranean diet on cardio-metabolic risk factors (Buckland 2008; Kastorini 2011).

The large primary prevention trial PREDIMED, which did not meet our strict inclusion criteria as the comparison group was not minimal, has reported beneficial effects of the Mediterranean diet on clinical endpoints (Estruch 2013). In this trial, 7447 participants were randomised to a dietary intervention that comprised five components of our definition of a Mediterranean-style dietary pattern in contrast to two components for the WHI trial included in our review that also reports clinical endpoints (WHI). After 4.8 years of follow-up, these authors showed a reduction of major CVD events of 30% (HR 0.7, 95% CI 0.54 to 0.92) with the Mediterranean dietary intervention and supplemented olive oil compared with a low-fat control group (Estruch 2013). The individuals recruited to this trial were all at high risk of CVD (type 2 diabetes or at least three CVD risk factors from smoking, hypertension, hypercholesterolaemia, overweight or obesity, or family history of CVD).

Likewise, systematic reviews and meta-analyses of observational prospective studies have confirmed that a greater adherence to a Mediterranean-style diet is associated with a significant improvement in health status and a significant reduction in overall mortality, as well as in morbidity and mortality from CVD and other major chronic diseases (Sofi 2008; Sofi 2010). Specifically, in the latest published meta-analysis of prospective cohort studies, a 2-point increase (scale from 0 to 7-9 points) in adherence to a Mediterranean dietary pattern was associated with an 8% reduction in all-cause mortality and a 10% reduction in CVD incidence or mortality (Sofi 2010).

## AUTHORS' CONCLUSIONS

## Implications for practice

Currently, there is limited trial evidence, especially on the effectiveness of dietary advice to follow a Mediterranean-style dietary pattern for the primary prevention of major cardiovascular clinical outcomes. Only one trial reported clinical endpoints and this trial was conducted in a selected group and the intervention was not described as a Mediterranean diet satisfying only two components of a possible seven in our classification. Therefore, more trial evidence is needed to establish the role of the Mediterranean dietary pattern as an effective lifestyle intervention to prevent cardiovascular events in the general population and high-risk individuals conclusively. Nevertheless, the available trial and observational evidence is promising and generally supportive of favourable effects of the Mediterranean-style diet on individual cardio-metabolic risk factors and potentially cardiovascular morbidity and mortality. This evidence is also corroborated by the biological plausibility of several mechanisms to explain the beneficial effect of the Mediterranean diet, as a whole, and of its individual components on cardiovascular health (Serra-Majem 2006).

Indeed, some aspects and components of a Mediterranean-style diet are already included in scientific and clinical guidelines for the prevention of cardiovascular disease (CVD), such as the DASH diet (AHA 2006; Appel 1997; Appel 2001; Appel 2006), and eating guidance on consumption of at least five portions of fruit and vegetables per day (Department of Health 2010).

## Implications for research

There are currently very few randomised controlled trials that meet our inclusion criteria to examine the effectiveness of dietary advice to follow a Mediterranean-style diet or the provision of foods relevant to the Mediterranean diet for the primary prevention of CVD. The limited trial evidence suggests some favourable effects on cardiovascular risk factors but more trials are needed to confirm this. In particular, there is a shortage of adequately powered clinical trials on the effectiveness of the Mediterranean dietary pattern in the primary prevention of major cardiovascular events both in the general population and among those at high risk of CVD. High-quality trials with long-term intervention and follow-up, measuring costs and adverse effects are also necessary to determine the sustainability of such dietary interventions across different population subgroups and various cultural settings. With the accrual of further evidence, the significant heterogeneity observed between trials in terms of both the nature and duration of the intervention and the range of participants recruited can be explored further and its impact on outcomes examined.

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* *Indicates the major publication for the study*

# CHARACTERISTICS OF STUDIES

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

**Abedi 2010**

| | |
|---|---|
| Methods | RCT of parallel group design. |
| Participants | Postmenopausal women recruited from a health clinic in Iran.<br>Inclusion criteria: women had at least primary education, were postmenopausal (no menstruation for at least 12 months) and CVD free (by self report)<br>76 women randomised, 38 in the intervention group (mean age (SD) 51.4 years (4.9)), and 38 to the control group (mean age 51.6 years (5.7)) |
| Interventions | Dietary education to increase consumption of fruits and vegetables and whole grains, to eat fish twice a week and limit saturated fat and salt. The intervention comprised 5 educational sessions (2 face-to-face and 3 lecture discussion classes with slide demonstrations) in the first month, a further face-to-face session at month 3 and telephone calls each month to remind women to remain on the diet. Information was also provided about CVD and the menopause as well as diet. The intervention period was 6 months, with follow-up at 6 months. The comparison group received no intervention |
| Outcomes | Total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, SBP and DBP |
| Notes | Differential loss to follow-up in the control group of greater than 20% so sensitivity analyses were performed to examine the effect of excluding this study on the overall effect estimates for lipid levels and blood pressure |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not stated. |
| Allocation concealment (selection bias) | Unclear risk | Not stated. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not stated. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not stated. |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Differential loss to follow-up of 7.9% in the intervention group compared with 23.7% in the control group. Participants in the intervention group did not attend education sessions, reasons were not given for losses to follow-up in the control group |

**Abedi 2010** (*Continued*)

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | Report all outcomes as stated. |
| Other bias | Unclear risk | Insufficient information to judge. |

**Castagnetta 2002**

| | |
|---|---|
| Methods | RCT of parallel group design. |
| Participants | Healthy postmenopausal female volunteers aged 44-71 years recruited by press campaign from Palermo (Southern Italy)<br>Inclusion criteria: postmenopausal for at least 2 years, no history of bilateral ovariectomy, no HRT within the previous year, no history of cancer, no adherence to a vegetarian or macrobiotic diet, no treatment for diabetes, thyroid disease or chronic bowel disease<br>230 fulfilled these eligibility criteria and 115 women were enrolled in the study based on serum testosterone levels equal to or greater than the median population level (0.14 $\mu$g/mL). 58 women were randomised to the intervention group, 55 women to the control group |
| Interventions | MEDIET project - the intervention group were invited to a weekly cooking course and to a social dinner with chefs addressing the principles of the traditional Mediterranean diet. The proposed recipes were based on a traditional Sicilian diet including whole cereals, legumes, seeds, fish, fruits, vegetables, olive oil and red wine. Women were asked to avoid refined carbohydrates, salt and additional animal fat. The intervention ran for 6 months from January to June 2000, then from 3 months from October to December 2000. Women were instructed to consume the same foods on a daily basis at home. The comparison group followed their usual diet. The follow-up period was at 6 and 12 months |
| Outcomes | Plasma cholesterol. |
| Notes | The primary publication (Castagnetta 2002) stated that the comparison group was advised to increase the consumption of fruits and vegetables as recommended by the WHO. However, other reports of the study stated that women in the control group followed their usual diets (Carruba 2006, secondary reference for this study)<br>No data were provided on cholesterol levels in the paper but simply a statement that they had reduced. We have contacted the authors several times to request the data to include in our analyses but, unfortunately, to date this has not been forthcoming |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Block randomisation stratified for baseline parameters. |
| Allocation concealment (selection bias) | Unclear risk | Not stated. |

**Castagnetta 2002** (*Continued*)

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not stated. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not stated. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | No ITT analysis, < 20% loss to follow-up in both groups but no reasons provided |
| Selective reporting (reporting bias) | Unclear risk | Insufficient information to judge. |
| Other bias | Unclear risk | Insufficient information to judge. |

**Djuric 2009**

| | |
|---|---|
| Methods | RCT of parallel group design. |
| Participants | Healthy non-obese women aged 25-65 years recruited from adverts in community newsletters, health fairs, flyers and employee newsletters in Michigan, US. Women completed 7-day food diaries<br>Eligibility criteria: fat intake was at least 23% of calories with no more than 48% from MUFA and fruit and vegetable intake was < 5.5 servings per day. This was to reflect a typical American intake. Women had to have good general health, be current non-smokers and be in the normal to overweight range (BMI 18-30)<br>Exclusion criteria: chronic diseases such as diabetes, autoimmune disease, hypertension, being on medically prescribed diets, taking dietary supplements > 150% RDA, pregnant or lactating and being treated with therapies or supplements that could obscure the results. 69 women were randomised, mean age 44 years (range 25-59) and mean BMI 24 (19-30) |
| Interventions | The intervention was a Greek Mediterranean exchange list diet with exchange goals determined by dieticians at baseline and focused on increasing fruit and vegetable intake and variety and increasing MUFA intake while maintaining the baseline energy intake and total fat intake. The fruit and vegetable goal was 7-9 servings/day depending on baseline calorie intake and maintaining baseline energy intake was achieved by substituting fruit and vegetables for other carbohydrates. Variety was achieved using exchange lists. The fat intake goal was PUFA:SFA:MUFA ratio of 1:2:5. This was achieved by reducing usual fat intakes by half using low-fat food and then adding in olive oil or other high MUFA to the diet to keep energy and total fat intake at baseline levels. Participants were given 3 L of extra-virgin olive oil at baseline and at 3 months. 7-day food records were taken at baseline, 3 months and 6 months. Counselling by the dieticians occurred weekly by telephone for the first 3 months and twice weekly thereafter. Face-to-face counselling occurred at baseline and 3 months. The intervention period was 6 months. Women were counselled on home eating patterns, restaurant eating, eating at work and special occasions<br>The comparison group followed their usual diets. They did not receive counselling, but |

| | |
|---|---|
| | were given the National Cancer Institutes Action guide to healthy eating and written materials on nutritional deficiencies if below 67% RDA. Follow-up was at 6 months after the end of the intervention period |
| Outcomes | Total cholesterol, LDL-cholesterol, HDL-cholesterol and triacylglycerol |
| Notes | Differential loss to follow-up in the intervention group of > 20% so sensitivity analyses were performed to examine the effect of excluding this study on the overall effect estimates for lipid levels<br>Body weight increased by 0.24 kg in the control group and decreased by 1.21 kg in the intervention group after the 6-month intervention period |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Method not stated. Subjects stratified by race and menopausal status prior to randomisation using a block design of 6 |
| Allocation concealment (selection bias) | Unclear risk | Not stated. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not stated. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not stated. |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Differential loss to follow-up of 23% in the intervention group compared with 3% in the control group. No reasons for loss to follow-up reported |
| Selective reporting (reporting bias) | Low risk | Report all outcomes as stated. |
| Other bias | Unclear risk | Insufficient information to judge. |

**ENCORE**

| | |
|---|---|
| Methods | RCT of parallel group design. |
| Participants | Participants were overweight or obese with untreated hypertension (SBP 130-159 mmHg, DBP 85-99 mmHg based on 4 screening visits) recruited from physician referrals, community screenings, mass media advertising in North Carolina, US. 144 participants randomised (46 to DASH alone, 49 to control), mean age was 52 years and 32. 6% were men |

**ENCORE** (*Continued*)

| | |
|---|---|
| Interventions | The DASH diet:<br>• was low in saturated fat, cholesterol and total fat;<br>• focused on fruits, vegetables, and fat-free or low-fat dairy products;<br>• was rich in whole grains, fish, poultry, beans, seeds and nuts;<br>• contained fewer sweets, added sugars and sugary beverages, and red meats than the typical American diet.<br>Participants in the intervention group received counselling on the DASH diet and provided feedback on their adherence in weekly group sessions. The goal of the sessions was to assist participants in learning how to buy and prepare appropriate foods, enhance their motivation to choose to eat these foods and to overcome any obstacles. A nutritionalist made the recommendations and small group sessions were held weekly (30-45 minutes each) at the research centre. Immediately after randomisation and before the counselling sessions participants entered a 2-week controlled isocalorific feeding period to improve compliance with the DASH diet. The comparison group were asked to maintain their usual dietary and exercise habits. Follow-up was at 4 months after the intervention period |
| Outcomes | Total, HDL-cholesterol, LDL-cholesterol, triglycerides, SBP, DBP |
| Notes | 2 intervention groups - DASH alone and DASH plus weight management. The review looked at only at the DASH alone arm |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomised in groups of 2-5 participants using a computer program |
| Allocation concealment (selection bias) | Low risk | Sealed envelopes used so allocation was concealed. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Participants were provided their treatment group assignments in sealed envelopes, which suggests they were unblinded. However, blinding of participants and personnel for behavioural interventions is difficult and often not possible so we have not judged this as at high risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Staff members performing the assessments were unaware of group assignment |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Only 1 participant lost to follow-up and ITT analysis used. |
| Selective reporting (reporting bias) | Low risk | All expected outcomes reported. |
| Other bias | Unclear risk | Insufficient information to judge. |

**Esposito 2004**

| | |
|---|---|
| Methods | RCT of parallel group design. |
| Participants | Men and women were recruited from June 2001 to January 2004 among those attending the outpatient department of the Division of Metabolic Diseases at the Second University of Naples, Naples, Italy. 180 adults (99 men and 81 women), mean age 44.3 years (intervention diet) and 43.5 years (control diet) with metabolic syndrome were enrolled in the study<br>Inclusion criteria: ≥ 3 of the following: (1) abdominal adiposity (defined as waist circumference 102 cm (men) or 88 cm (women)); (2) low levels of serum HDL-cholesterol (40 mg/dL (men) or 50 mg/dL (women)); (3) hypertriglyceridaemia (triglycerides level of ≥ 150 mg/dL); (4) elevated blood pressure (≥ 130/85 mmHg); and (5) impaired glucose homeostasis (fasting plasma glucose concentration ≥ 110 mg/dL)<br>Exclusion criteria: CVD, psychiatric problems, a history of alcohol abuse (alcohol consumption 500 g/week in the last year), if they smoked, or if they took any medication |
| Interventions | Intervention diet: 90 participants were given detailed advice about the usefulness of a Mediterranean-style diet. Through a series of monthly small-group sessions, participants received education in reducing dietary calories (if needed), personal goal-setting and self monitoring using food diaries. Behavioural and psychological counselling was also offered. Dietary advice was tailored to each participant on the basis of 3-day food records. The recommended composition of the dietary regimen was carbohydrates, 50-60%; proteins, 15-20%; total fat, < 30%; saturated fat, < 10%; and cholesterol consumption, < 300 mg/day. Participants were advised to consume at least 250-300 g of fruits, 125-150 g of vegetables, 25-50 g of walnuts, 400 g of whole grains (legumes, rice, maize and wheat) daily and to increase their consumption of olive oil. Participants were in the programme for 24 months and had monthly sessions with the nutritionist for the first year and twice monthly sessions for the second year. Compliance with the programme was assessed by attendance at the meetings and completion of diet diaries<br>Control diet: 90 participants were given general oral and written information about healthy food choices at baseline and at subsequent visits. The general recommendation for macro-nutrient composition of the diet was similar to that for the intervention group (carbohydrates, 50-60%; proteins, 15-20% and total fat, 30%). Participants had bimonthly sessions with study personnel<br>Participants in both groups also received guidance on increasing their level of physical activity, mainly by walking for a minimum of 30 minutes/day but also by swimming or playing aerobic ball games<br>Trial was conducted from June 2001 to January 2004. Follow-up period was 2 years |
| Outcomes | Total cholesterol, HDL-cholesterol, triglycerides, SBP, SBP. |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer-generated random number sequence. |

**Esposito 2004** (*Continued*)

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | Stored in sealed study folders and held in a central, secured location until informed consent obtained |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Staff members involved in the intervention had to be aware of the group assignment; thus, the study was only partly blinded. Blinding of participants and personnel for behavioural interventions is difficult and often not possible, so we have not judged this as at high risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Laboratory staff did not know to which group the participants were assigned |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | ITT analysis. |
| Selective reporting (reporting bias) | Low risk | All expected outcomes reported. |
| Other bias | Unclear risk | Insufficient information to judge. |

**Jula 2002**

| | |
|---|---|
| Methods | RCT cross-over design (analysed as a parallel group, 12-week intervention, 12-week follow-up) |
| Participants | Hypercholesterolaemic men, 35-64 years of age were screened from the clients of the occupational health service of 5 industrial plants and government offices in Turku in southwestern Finland. 120 men were enrolled<br>Inclusion criteria: a fasting serum cholesterol concentration 232-309 mg/dL (6.0-8.0 mmol/L) and fasting serum triglyceride concentration no higher than 266 mg/dL (3.0 mmol/L)<br>Exclusion criteria: BMI > 32 kg/$m^2$; coronary artery disease; cerebrovascular disease; claudication and pharmacologically treated hypertension, hyperlipidaemia, or diabetes |
| Interventions | Men included in the study entered first a 4- to 6-week open placebo run-in period, at the end of which they were randomly allocated to the intervention (60 men, mean age 48.0 years) or control group (60 men, mean age 48.4 years)<br>The intervention (a weight stable, modified, Mediterranean-type diet) consisted of no more than 10% energy from SFAa and transunsaturated fatty acids; cholesterol intake no more than 250 mg/day; omega-3 fatty acid intake of plant origin (linolenic acid) and marine origin of at least 4 g/day and the ratio of omega-6/omega-3 PUFAs < 4; and increased intakes of fruits, vegetables and soluble fibre. Men were advised to use leaner meat products, low-fat cheese, skimmed milk, fat-free sour milk and low-fat yogurt. Fish was recommended as a main meal once or twice a week. Rapeseed margarine was recommended as a replacement for butter, a mixture of butter and vegetable oils, and sunflower margarine. Rapeseed margarine and oil, oat bran (20 g/day), and frozen berries (blueberry, lingonberry or blackcurrant at 50 g/day) were supplied free to study |

**Jula 2002** (*Continued*)

| | |
|---|---|
| | subjects. The diet was supervised by a nutritionist in 1 individual session and in 2 group counselling sessions at the beginning of the treatment and in 5 subsequent monthly group brush-up sessions during the dietary treatment. The control group participants (habitual diet group) were advised to continue eating their usual diet during the study period<br>The trial was conducted between August 1997 and June 1998. |
| Outcomes | Total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides |
| Notes | Data were only used for the first 12 weeks of the trial (before the second randomisation and subsequent cross-over). Follow-up data (mean and SD) for each of the outcomes was missing. Authors were contacted 3 times for follow-up data for all outcomes but with no success |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not stated. |
| Allocation concealment (selection bias) | Unclear risk | Not stated. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Dietary treatment was performed single-blind. Blinding of participants and personnel for behavioural interventions is difficult and often not possible so we have not judged this as at high risk of bias |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | All measurements and analyses were done blinded to the treatment allocation of the subject |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | No reason given for attrition. |
| Selective reporting (reporting bias) | Unclear risk | Blood pressure not reported. |
| Other bias | Unclear risk | Insufficient information to judge. |

**Konstantinidou 2010**

| | |
|---|---|
| Methods | RCT of parallel group design. |
| Participants | From October 2007 to October 2008, 90 eligible community-dwelling adults (26 men and 64 women, aged 20-50 years) were recruited from primary care centres. They were considered healthy on the basis of a physical examination and routine biochemical and haematological laboratory determinations |

| | |
|---|---|
| | Exclusion criteria: intake of antioxidant supplements; intake of acetosalicylic acid or any other drug with established antioxidative properties; high levels of physical activity (3000 kcal/week in leisure-time physical activity); obesity (BMI 30 kg/$m^2$); hypercholesterolaemia (total cholesterol 8.0 mM or dyslipidaemia therapy); diabetes (glucose 126 mg/dL or diabetes treatment); hypertension (SBP $\geq$ 140 mmHg) or (DBP $\geq$ 90 mmHg) , or both or antihypertensive treatment; multiple allergies; coeliac or other intestinal diseases; any condition that could limit the mobility of the subject, making study visits impossible; life-threatening illnesses or other diseases or conditions that could worsen adherence to the measurements or treatments; vegetarianism or a need for other special diets; and alcoholism or other drug addiction |
| Interventions | Participants were assigned to 1 of 2 interventions or a control group as follows:<br>1. Traditional Mediterranean diet with virgin olive oil (30 participants);<br>2. Traditional Mediterranean diet with washed virgin olive oil (30 participants)<br>The dietician gave personalised advice during a 30-minute session to each participant following the traditional Mediterranean diets, with recommendations on the desired frequency of intake of specific foods. Participants were instructed to use olive oil for cooking and dressing; increase consumption of fruit, vegetables and fish; consume white meat instead of red or processed meat; prepare homemade sauce with tomato, garlic, onion, aromatic herbs and olive oil to dress vegetables, pasta, rice, and other dishes; and, for alcohol drinkers, moderate consumption of red wine<br>3. Control group (30 subjects): participants were advised by a dietician to maintain their habitual lifestyle<br>Intervention period and follow-up was 3 months. |
| Outcomes | Total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, SBP, DBP |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer generated random number sequence. |
| Allocation concealment (selection bias) | Unclear risk | Not stated. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not stated. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not stated. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Only 1 participant dropped out of the trial. |

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Unclear risk | Not stated. |
| Other bias | Unclear risk | Not stated. |

**Lanza 2001**

| | |
|---|---|
| Methods | RCT of parallel group design. |
| Participants | The Polyp Prevention Trial - a multicentre trial (8 US clinical centres) to examine the effect of diet on recurrence of adenomatous polyps in the large bowel. Participants were at high risk with ≥ 1 colorectal adenomas removed within 6 months before recruitment. Referrals were from endoscopists and recruitment took place between 1991 and 1994. 2079 participants were randomised, 64.5% men, mean age 61 years |
| Interventions | Intensive counselling to follow a low-fat (< 20% calories), high-fibre (18 g/1000 cal) diet and to increase fruit and vegetable consumption to 3.5 servings/1000 cal. Nutritional education and behavioural modification techniques used by a registered dietician. In the first year, counselling sessions were weekly for the first 6 weeks, biweekly for the next 6 weeks and monthly thereafter. In year 2, counselling sessions were in groups every 2 months and participants were also contacted by telephone at least once a month. In years 3 and 4, counselling sessions were held quarterly in groups. More than 50 hours of counselling sessions over 4 years. Comparison group were given a standard brochure on healthy eating. Follow-up at 4 years |
| Outcomes | Plasma cholesterol in mmoles/litre |
| Notes | Plasma cholesterol only measured in a subgroup of participants, n = 370 and n = 374 for the intervention and control groups, respectively |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not stated. |
| Allocation concealment (selection bias) | Unclear risk | Not stated. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not stated. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not stated. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | ITT analysis used and loses to follow-up reported. |

**Lanza 2001** (*Continued*)

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | All outcomes stated are reported. |
| Other bias | Unclear risk | Insufficient information to judge. |

**Lindman 2004**

| | |
|---|---|
| Methods | RCT of parallel group design (2 x 2 factorial design). |
| Participants | 219 older men with long-standing hypercholesterolaemia were recruited from the Diet and Omega-3 Intervention trial on atherosclerosis (DOIT) study, Norway. Mean age 69.7 years for both genotypes |
| Interventions | Men were randomised into 3 intervention groups or the control group as follows:<br>• usual care and placebo capsules (control group) (n = 51);<br>• dietary advice ('Mediterranean-type' diet) and placebo capsules (n = 47);<br>• usual care and VLC n-3 capsules (n = 51);<br>• dietary advice ('Mediterranean-type' diet) and VLC n-3 capsules (n = 52).<br>Diet counselling was given individually by a clinical nutritionist based on a food frequency questionnaire. The food frequency questionnaire was also answered by the participants at the end of the main study (36 months). Energy content and nutrient composition was of the diet were calculated from the questionnaires at baseline and 36 months. Dietary advice was given during 30-45 minutes at time of randomisation, and for 30 minutes after 3 months. Participants were supported with a margarine rich in PUFA and vegetable oils free of cost. Advice was given to increase intake of vegetables, fruit and fish, and decrease consumption of meat and target energy percents at 27-30% fat, 15-18% protein and 50-55% carbohydrate. To fulfil these goals participants were recommended to use rapeseed or olive oil for cooking; use leafy vegetables daily; include fruits, berries and nuts in the diet; eat fish 3 times per week; use wholemeal bread, skimmed milk and reduced-fat cheese. 2 capsules were taken twice daily corresponding to 2.4 g VLC n-3 capsules or 2.4 g corn oil (placebo capsules)<br>Follow-up period was 6 months. |
| Outcomes | Triglycerides. |
| Notes | Only data from the usual care and placebo capsules (control group) (n = 51) and dietary advice ('Mediterranean type' diet) and placebo capsules (n = 47). (The focus of the study was to investigate the effect of long-term diet and VLC n-3 fatty acids intervention on plasma coagulation factor VII (FVII), choline-containing phospholipids and triglycerides, especially relating to the R353Q polymorphism of the FVII gene) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not stated. |

**Lindman 2004** (*Continued*)

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | Not stated. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not stated. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not stated. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Insufficient reporting of attrition/exclusions. |
| Selective reporting (reporting bias) | Unclear risk | Insufficient information to judge. |
| Other bias | Unclear risk | Insufficient information to judge. |

**Wardle 2000**

| | |
|---|---|
| Methods | RCT of parallel group design. |
| Participants | Participants were adults with mild to moderate hypercholesterolaemia with serum cholesterol levels above 5.2 mmol/L, not current or previous (within 3 months) users of lipid-lowering medication and with no serious illness. Participants were recruited from dietetic clinics, hospital physicians and general practitioners in London and the South East, UK. 117 participants were randomised, mean age 53.5 years, 43.5% men |
| Interventions | The intervention (Mediterranean diet) was delivered in 8 sessions during the 12-week intervention period using a combination of individual and group sessions with a dietician and psychologist. Dietary advice was to increase intake of fruit and vegetables, and oily fish and to reduce fat to 30% of energy with substitution of predominantly monosaturated fat for saturated fat. All participants received individualised advice to implement dietary changes based on their lifestyle and food preferences and group support in maintaining changes. Intervention participants were also given free spreading fats and oils high in monosaturated fats. The comparison group was a wait-list control. Participants were told it was necessary to wait for treatment but that they would be seen at 6-week intervals. They were not given any specific dietary advice but were not discouraged from making changes and some participants did so. 12 weeks' follow-up |
| Outcomes | Total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|

**Wardle 2000** (*Continued*)

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not stated. |
| Allocation concealment (selection bias) | Low risk | Opaque sealed envelopes. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | No details provided but the control group was a wait-list control |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Outcome assessment done by a member of the research team who was blinded (in most cases) |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | No ITT but details of attrition provided and reasons. |
| Selective reporting (reporting bias) | Low risk | All of the outcomes stated were reported. |
| Other bias | Unclear risk | Insufficient information to judge. |

**WHI**

| | |
|---|---|
| Methods | RCT of parallel group design. |
| Participants | 48,835 postmenopausal women aged 50-79 years were recruited and enrolled between 1993 and 1998 at 40 clinical centres across the US<br>Eligibility criteria: being postmenopausal and consuming at baseline a diet with fat intake of 32% or more of total calories, as assessed by a food frequency questionnaire<br>Exclusion criteria: history of breast cancer or colorectal cancer, any cancer within the previous 10 years except non-melanoma skin cancer, medical conditions with a predicted survival of less than 3 years, adherence or retention concerns, current dietary intake of less than 32% of energy from fat, and type 1 diabetes mellitus |
| Interventions | Women were randomly assigned to a usual-diet comparison group (n = 29,294, 60.0%) or an intervention group with a 20% low-fat dietary pattern with increased vegetables, fruits and grains (n = 19,541, 40.0%)<br>The intervention was designed to promote dietary change with the goals of reducing intake of total fat to 20% of energy intake (in kilocalories) by increasing intake of vegetables and fruits to at least 5 servings daily and of grains to at least 6 servings daily. The intervention did not include total energy reduction or weight loss goals. Although not a separate focus of the intervention, it was presumed that by reducing total fat intake to 20% kcal, intake of saturated fat would also be reduced (7% energy intake) . The intensive behavioural modification programme involved 18 group sessions in the first year and quarterly maintenance sessions thereafter, led by specially trained and certified nutritionists. Participants self monitored total fat-gram intake and also servings of vegetables, fruits and grains<br>Women in the comparison group received a copy of the Dietary Guidelines for Americans as well as other health-related materials, but had no contact with the nutrition |

**WHI** (*Continued*)

| | |
|---|---|
| | interventionists<br>Mean follow-up time for the WHI DMT was 8.1 years. |
| Outcomes | CVD mortality, myocardial infarction and stroke (at 8.1 years); total cholesterol, HDL-cholesterol and LDL-cholesterol (at year 3); triglycerides (at year 3); SBP and DBP (at years 1 and 3); type 2 diabetes (at 8.1 years) |
| Notes | Blood measures (total, HDL-cholesterol, LDL-cholesterol and triglycerides) were performed on a 5.8% subsample at year 3 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Used a randomised permuted block algorithm. |
| Allocation concealment (selection bias) | Unclear risk | Not stated. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not stated. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Carried out by physician adjudicators not involved in trial. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | ITT analysis. |
| Selective reporting (reporting bias) | Low risk | All outcomes reported. |
| Other bias | Unclear risk | Insufficient information to judge. |

BMI: body mass index; CVD: cardiovascular disease; DASH: ; DBP: diastolic blood pressure; HDL: high-density lipoprotein; HRT: hormone replacement therapy; ITT: intention to treat; LDL: low-density lipoprotein; MUFA: monounsaturated fatty acid; PUFA: polyunsaturated fatty acid; RCT: randomised controlled trial; RDA: recommended daily allowance; SBP: systolic blood pressure; SD: standard deviation; SFA: saturated fatty acid; VLC: very-long-chain; WHO: World Health Organization.

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

| Study | Reason for exclusion |
|---|---|
| Azadbakht 2005 | Not an RCT - control group were a separate population. |
| Barcelo 2009 | PREDIMED study. Low-fat diet arm had face-to-face nutritional advice as well as leaflets, therefore, not a minimal control |
| Bullo 2009 | Substudy of PREDIMED. Control group received face-to-face nutritional advice, therefore, not a minimal control, and there were no relevant outcomes |
| Mezzano 2003 | Not all subjects were randomised. |
| Papadaki 2008 | Not an RCT. |
| Vincent-Baudry 2005 | Medi-RIVAGE study. Control group was given dietary advice to eat fruit and vegetables, therefore, not a minimal control |

RCT: randomised controlled trial.

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

**Inguaggiato 2011**

| | |
|---|---|
| Methods | RCT of parallel group design |
| Participants | 219 participants with metabolic syndrome (NCEP-ATPIII criteria) |
| Interventions | 4 intervention groups: to follow a Mediterranean diet, a low GI Mediterranean diet, low GI diet and a generic diet (comparison group). Follow-up after the 12-week intervention period |
| Outcomes | Lipid levels, blood pressure |
| Notes | Conference abstract. Contacted authors for further details of the trial and outcome data. Authors are currently trying to publish a paper and are unwilling at present to share their data with us |

GI: glycaemic index; NCEP-ATPIII: National Cholesterol Education Program- Adult Treatment Panel III; RCT: randomised controlled trial.

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

**Sanders 2012**

| | |
|---|---|
| Trial name or title | Cardiovascular risk REduction Study: Supported by an Integrated Dietary Approach |
| Methods | Randomised parallel design single-centre controlled trial |
| Participants | Inclusion criteria:<br>1. Healthy men and women, aged 40-70 years<br>Exclusion criteria:<br>1. a reported history of angina, myocardial infarction, peripheral vascular disease, congenital heart disease or stroke;<br>2. Asymptomatic atrial fibrillation;<br>3. type 1 or type 2 diabetes mellitus (fasting plasma glucose > 7 mmol/L);<br>4. seated blood pressure > 160/105 mmHg;<br>5. current use of medication for lowering blood cholesterol (statins) or blood pressure;<br>6. body mass index < 18.5 and > 35 kg/$m^2$;<br>7. an overall risk of cardiovascular disease over the next 10 years of > 20% assessed according to current NICE guidelines in combination with untreated hypertension or raised cholesterol;<br>8. clinical history of cancer (excluding basal cell carcinoma) in the past 5 years;<br>9. chronic renal, liver or inflammatory bowel disease;<br>10. current cigarette smoker (confirmed by urinary cotinine analysis);<br>11. history of substance abuse or alcoholism (previous weekly alcohol intake > 60 units/men or 50 units/women);<br>12. current self reported weekly alcohol intake not exceeding 21 units for women and 28 units for men;<br>13. currently pregnant, planning pregnancy or having had a baby in the last 12 months;<br>14. unwilling to follow the protocol or give informed consent, or both;<br>15. unwilling to refrain from use of dietary supplements;<br>16. unwilling to restrict consumption of oily fish;<br>17. weight change of > 3 kg in preceding 2 months |
| Interventions | This is a controlled dietary intervention trial comparing a cardioprotective diet (decreased salt and saturated fatty acid intake, and increased whole grain cereals, fruit and vegetables and oily fish intake) with a control diet (average UK diet) for 3 months |
| Outcomes | Primary outcome measures:<br>1. a change in systolic blood pressure measured by ambulatory blood pressure;<br>2. a change in endothelial function measured by flow-mediated dilation;<br>3. a change in total/high-density lipoprotein (HDL) cholesterol ratio measured at baseline and 3 months.<br>Secondary outcome measures:<br>1. a change in arterial stiffness (pulse wave velocity and digital volume pulse), measured at baseline and 3 months;<br>2. a change in insulin sensitivity (revised quantitative insulin sensitivity test (RQUICKI) and serum adiponectin), measured at baseline and 3 months;<br>3. a change in C-reactive protein concentrations, measured at baseline and 3 months. |
| Starting date | 16 July 2010 |

**Sanders 2012** (*Continued*)

| | |
|---|---|
| Contact information | Prof Thomas Sanders<br>Nutritional Science Division<br>4th Floor, Franklin-Wilkins Building<br>150 Stamford Street<br>London<br>SE1 9NH<br>UK<br>+44 (0)20 7848 4273<br>+44 (0)20 7848 4171<br>tom.sanders@kcl.ac.uk |
| Notes | Ongoing trial (ISRCTN92382106) that has been classified as 'completed' on www.controlled-trials.com<br>Trial website: www.medscinet.net/CRESSIDA/<br>Study duration: July 2010 to December 2012 |

NICE: national Institute for Health and Clinical Excellence.

## DATA AND ANALYSES

**Comparison 1. Mediterranean dietary intervention versus no intervention or minimal intervention (secondary outcomes - CVD risk factors)**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Total cholesterol (mmol/L), change from baseline | 8 | 4151 | Mean Difference (IV, Random, 95% CI) | -0.16 [-0.26, -0.06] |
| 2 Total cholesterol (mmol/L), change from baseline, subgroup analysis | 8 | 3815 | Mean Difference (IV, Fixed, 95% CI) | -0.20 [-0.23, -0.17] |
| 2.1 Interventions described as Mediterranean diet (or comprise both increased fruit and vegetables and monounsaturated fatty acids) | 4 | 436 | Mean Difference (IV, Fixed, 95% CI) | -0.23 [-0.27, -0.20] |
| 2.2 Interventions with 2 components but not described as Mediterranean diet or comprising both increased fruit and vegetables and monounsaturated fatty acids | 4 | 3379 | Mean Difference (IV, Fixed, 95% CI) | -0.06 [-0.13, 0.01] |
| 3 LDL-cholesterol (mmol/L), change from baseline | 6 | 3227 | Mean Difference (IV, Fixed, 95% CI) | -0.07 [-0.13, -0.01] |
| 4 LDL-cholesterol (mmol/L), change from baseline, subgroup analysis | 6 | 3227 | Mean Difference (IV, Random, 95% CI) | -0.07 [-0.17, 0.03] |
| 4.1 Interventions described as Mediterranean diet (or comprise both increased fruit and vegetables and monounsaturated fatty acids) | 3 | 252 | Mean Difference (IV, Random, 95% CI) | -0.16 [-0.39, 0.07] |
| 4.2 Interventions with 2 components but not described as the Mediterranean diet or comprising both increased F&V and MUFAs | 3 | 2975 | Mean Difference (IV, Random, 95% CI) | -0.06 [-0.12, 0.00] |
| 5 HDL-cholesterol (mmol/L), change from baseline | 7 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 6 Triglycerides (mmol/L), change from baseline | 6 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 7 Systolic blood pressure (mmHg), change from baseline | 5 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 8 Diastolic blood pressure (mmHg), change from baseline | 5 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |

## Analysis 1.1. Comparison 1 Mediterranean dietary intervention versus no intervention or minimal intervention (secondary outcomes - CVD risk factors), Outcome 1 Total cholesterol (mmol/L), change from baseline.

Review: 'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease

Comparison: 1 Mediterranean dietary intervention versus no intervention or minimal intervention (secondary outcomes - CVD risk factors)

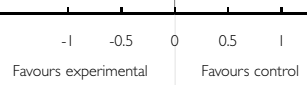
Outcome: 1 Total cholesterol (mmol/L), change from baseline

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| Abedi 2010 | 35 | 0.31 (0.67) | 29 | 0.31 (1) | | 4.7 % | 0.0 [ -0.43, 0.43 ] |
| Djuric 2009 | 27 | -0.026 (0.97) | 33 | -0.1 (0.86) | | 4.0 % | 0.08 [ -0.39, 0.55 ] |
| ENCORE | 46 | 0 (0.88) | 49 | -0.03 (0.88) | | 6.4 % | 0.03 [ -0.32, 0.38 ] |
| Esposito 2004 | 90 | -0.284 (0.155) | 90 | -0.05 (0.052) | | 25.7 % | -0.23 [ -0.27, -0.20 ] |
| Konstantinidou 2010 | 60 | -0.125 (0.6) | 29 | 0 (0.6) | | 9.5 % | -0.12 [ -0.39, 0.14 ] |
| Lanza 2001 | 370 | -0.14 (0.96) | 374 | 0.07 (0.88) | | 18.3 % | -0.21 [ -0.34, -0.08 ] |
| Wardle 2000 | 53 | -0.7 (0.91) | 50 | -0.2 (0.68) | | 7.8 % | -0.50 [ -0.81, -0.19 ] |
| WHI | 1408 | -0.26 (0.93) | 1408 | -0.2 (0.97) | | 23.5 % | -0.06 [ -0.13, 0.01 ] |
| **Total (95% CI)** | **2089** | | **2062** | | | **100.0 %** | **-0.16 [ -0.26, -0.06 ]** |

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 26.49$, df = 7 (P = 0.00041); $I^2 = 74\%$

Test for overall effect: Z = 3.01 (P = 0.0026)

Test for subgroup differences: Not applicable



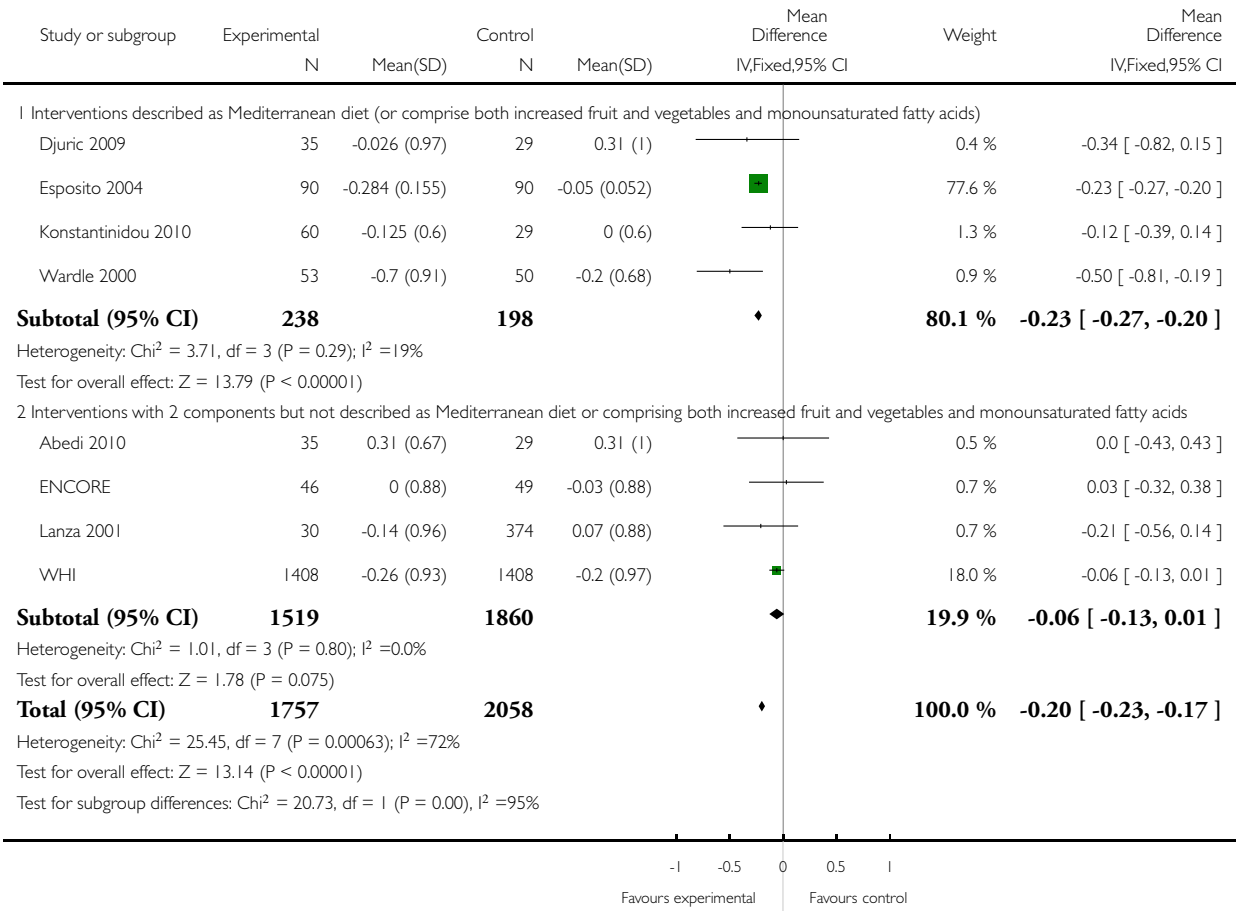
**Analysis 1.2. Comparison 1 Mediterranean dietary intervention versus no intervention or minimal intervention (secondary outcomes - CVD risk factors), Outcome 2 Total cholesterol (mmol/L), change from baseline, subgroup analysis.**

Review: 'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease

Comparison: 1 Mediterranean dietary intervention versus no intervention or minimal intervention (secondary outcomes - CVD risk factors)

Outcome: 2 Total cholesterol (mmol/L), change from baseline, subgroup analysis

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Interventions described as Mediterranean diet (or comprise both increased fruit and vegetables and monounsaturated fatty acids) | | | | | | | |
| Djuric 2009 | 35 | -0.026 (0.97) | 29 | 0.31 (1) | | 0.4 % | -0.34 [ -0.82, 0.15 ] |
| Esposito 2004 | 90 | -0.284 (0.155) | 90 | -0.05 (0.052) | | 77.6 % | -0.23 [ -0.27, -0.20 ] |
| Konstantinidou 2010 | 60 | -0.125 (0.6) | 29 | 0 (0.6) | | 1.3 % | -0.12 [ -0.39, 0.14 ] |
| Wardle 2000 | 53 | -0.7 (0.91) | 50 | -0.2 (0.68) | | 0.9 % | -0.50 [ -0.81, -0.19 ] |
| **Subtotal (95% CI)** | **238** | | **198** | | | **80.1 %** | **-0.23 [ -0.27, -0.20 ]** |
| Heterogeneity: $Chi^2$ = 3.71, df = 3 (P = 0.29); $I^2$ =19% | | | | | | | |
| Test for overall effect: Z = 13.79 (P < 0.00001) | | | | | | | |
| 2 Interventions with 2 components but not described as Mediterranean diet or comprising both increased fruit and vegetables and monounsaturated fatty acids | | | | | | | |
| Abedi 2010 | 35 | 0.31 (0.67) | 29 | 0.31 (1) | | 0.5 % | 0.0 [ -0.43, 0.43 ] |
| ENCORE | 46 | 0 (0.88) | 49 | -0.03 (0.88) | | 0.7 % | 0.03 [ -0.32, 0.38 ] |
| Lanza 2001 | 30 | -0.14 (0.96) | 374 | 0.07 (0.88) | | 0.7 % | -0.21 [ -0.56, 0.14 ] |
| WHI | 1408 | -0.26 (0.93) | 1408 | -0.2 (0.97) | | 18.0 % | -0.06 [ -0.13, 0.01 ] |
| **Subtotal (95% CI)** | **1519** | | **1860** | | | **19.9 %** | **-0.06 [ -0.13, 0.01 ]** |
| Heterogeneity: $Chi^2$ = 1.01, df = 3 (P = 0.80); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 1.78 (P = 0.075) | | | | | | | |
| **Total (95% CI)** | **1757** | | **2058** | | | **100.0 %** | **-0.20 [ -0.23, -0.17 ]** |
| Heterogeneity: $Chi^2$ = 25.45, df = 7 (P = 0.00063); $I^2$ =72% | | | | | | | |
| Test for overall effect: Z = 13.14 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 20.73, df = 1 (P = 0.00), $I^2$ =95% | | | | | | | |



### Analysis 1.3. Comparison 1 Mediterranean dietary intervention versus no intervention or minimal intervention (secondary outcomes - CVD risk factors), Outcome 3 LDL-cholesterol (mmol/L), change from baseline.

Review: 'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease

Comparison: 1 Mediterranean dietary intervention versus no intervention or minimal intervention (secondary outcomes - CVD risk factors)

Outcome: 3 LDL-cholesterol (mmol/L), change from baseline

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Abedi 2010 | 35 | -0.155 (0.7) | 29 | -0.33 (0.88) | | 2.2 % | 0.18 [ -0.22, 0.57 ] |
| Djuric 2009 | 27 | -0.052 (0.85) | 33 | -0.13 (0.69) | | 2.2 % | 0.08 [ -0.32, 0.48 ] |
| ENCORE | 46 | 0 (0.78) | 49 | -0.03 (0.8) | | 3.4 % | 0.03 [ -0.29, 0.35 ] |
| Konstantinidou 2010 | 60 | -0.07 (0.45) | 29 | 0.05 (0.46) | | 8.5 % | -0.12 [ -0.32, 0.08 ] |
| Wardle 2000 | 53 | -0.6 (0.91) | 50 | -0.2 (0.81) | | 3.2 % | -0.40 [ -0.73, -0.07 ] |
| WHI | 1408 | -0.26 (0.89) | 1408 | -0.19 (0.89) | | 80.5 % | -0.07 [ -0.14, 0.00 ] |
| **Total (95% CI)** | **1629** | | **1598** | | | **100.0 %** | **-0.07 [ -0.13, -0.01 ]** |

Heterogeneity: $Chi^2$ = 6.40, df = 5 (P = 0.27); $I^2$ =22%

Test for overall effect: Z = 2.41 (P = 0.016)

Test for subgroup differences: Not applicable

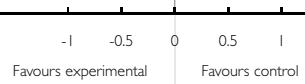
**Analysis 1.4. Comparison 1 Mediterranean dietary intervention versus no intervention or minimal intervention (secondary outcomes - CVD risk factors), Outcome 4 LDL-cholesterol (mmol/L), change from baseline, subgroup analysis.**

Review: 'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease

Comparison: 1 Mediterranean dietary intervention versus no intervention or minimal intervention (secondary outcomes - CVD risk factors)

Outcome: 4 LDL-cholesterol (mmol/L), change from baseline, subgroup analysis

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Interventions described as Mediterranean diet (or comprise both increased fruit and vegetables and monounsaturated fatty acids) | | | | | | | |
| Djuric 2009 | 27 | -0.052 (0.85) | 33 | -0.13 (0.69) | | 5.8 % | 0.08 [ -0.32, 0.48 ] |
| Konstantinidou 2010 | 60 | -0.07 (0.45) | 29 | 0.05 (0.46) | | 18.1 % | -0.12 [ -0.32, 0.08 ] |
| Wardle 2000 | 53 | -0.6 (0.91) | 50 | -0.2 (0.81) | | 8.0 % | -0.40 [ -0.73, -0.07 ] |
| **Subtotal (95% CI)** | **140** | | **112** | | | **31.8 %** | **-0.16 [ -0.39, 0.07 ]** |
| Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.52$, df = 2 (P = 0.17); $I^2 = 43\%$ | | | | | | | |
| Test for overall effect: Z = 1.33 (P = 0.18) | | | | | | | |
| 2 Interventions with 2 components but not described as the Mediterranean diet or comprising both increased F%V and MUFAs | | | | | | | |
| Abedi 2010 | 35 | -0.155 (0.7) | 29 | -0.33 (0.88) | | 5.8 % | 0.18 [ -0.22, 0.57 ] |
| ENCORE | 46 | 0 (0.78) | 49 | -0.03 (0.8) | | 8.7 % | 0.03 [ -0.29, 0.35 ] |
| WHI | 1408 | -0.26 (0.89) | 1408 | -0.19 (0.89) | | 53.6 % | -0.07 [ -0.14, 0.00 ] |
| **Subtotal (95% CI)** | **1489** | | **1486** | | | **68.2 %** | **-0.06 [ -0.12, 0.00 ]** |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.75$, df = 2 (P = 0.42); $I^2 = 0.0\%$ | | | | | | | |
| Test for overall effect: Z = 1.84 (P = 0.066) | | | | | | | |
| **Total (95% CI)** | **1629** | | **1598** | | | **100.0 %** | **-0.07 [ -0.17, 0.03 ]** |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.40$, df = 5 (P = 0.27); $I^2 = 22\%$ | | | | | | | |
| Test for overall effect: Z = 1.45 (P = 0.15) | | | | | | | |
| Test for subgroup differences: $Chi^2 = 0.63$, df = 1 (P = 0.43), $I^2 = 0.0\%$ | | | | | | | |



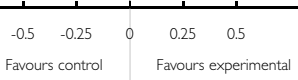
## Analysis 1.5. Comparison 1 Mediterranean dietary intervention versus no intervention or minimal intervention (secondary outcomes - CVD risk factors), Outcome 5 HDL-cholesterol (mmol/L), change from baseline.

Review: 'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease

Comparison: 1 Mediterranean dietary intervention versus no intervention or minimal intervention (secondary outcomes - CVD risk factors)

Outcome: 5 HDL-cholesterol (mmol/L), change from baseline

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Abedi 2010 | 35 | 0.01 (0.18) | 29 | 0 (0.18) | | 0.01 [ -0.08, 0.10 ] |
| Djuric 2009 | 27 | 0.026 (0.31) | 33 | 0 (0.37) | | 0.03 [ -0.15, 0.20 ] |
| ENCORE | 46 | -0.07 (0.3) | 49 | -0.03 (0.327) | | -0.04 [ -0.17, 0.09 ] |
| Esposito 2004 | 90 | 0.103 (0.052) | 90 | 0.03 (0.026) | | 0.08 [ 0.06, 0.09 ] |
| Konstantinidou 2010 | 60 | -0.05 (0.18) | 29 | -0.05 (0.18) | | 0.00 [ -0.08, 0.08 ] |
| Wardle 2000 | 53 | -0.1 (0.34) | 50 | -0.04 (0.28) | | -0.06 [ -0.18, 0.06 ] |
| WHI | 1408 | -0.01 (0.41) | 1408 | -0.01 (0.4) | | -0.01 [ -0.03, 0.02 ] |



### Analysis 1.6. Comparison 1 Mediterranean dietary intervention versus no intervention or minimal intervention (secondary outcomes - CVD risk factors), Outcome 6 Triglycerides (mmol/L), change from baseline.

Review: 'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease

Comparison: 1 Mediterranean dietary intervention versus no intervention or minimal intervention (secondary outcomes - CVD risk factors)

Outcome: 6 Triglycerides (mmol/L), change from baseline

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Abedi 2010 | 35 | -0.21 (0.78) | 29 | -0.16 (0.97) | | -0.05 [ -0.49, 0.39 ] |
| Djuric 2009 | 27 | 0.034 (0.47) | 33 | 0.03 (0.41) | | 0.0 [ -0.23, 0.23 ] |
| ENCORE | 46 | 0.08 (0.56) | 49 | 0.09 (0.57) | | -0.01 [ -0.24, 0.22 ] |
| Esposito 2004 | 90 | -0.203 (0.09) | 90 | 0.01 (0.034) | | -0.21 [ -0.23, -0.19 ] |
| Wardle 2000 | 53 | 0.3 (0.56) | 50 | -0.06 (0.53) | | 0.36 [ 0.15, 0.57 ] |
| WHI | 1408 | 0.04 (0.75) | 1408 | 0.04 (0.73) | | 0.0 [ -0.05, 0.05 ] |

### Analysis 1.7. Comparison 1 Mediterranean dietary intervention versus no intervention or minimal intervention (secondary outcomes - CVD risk factors), Outcome 7 Systolic blood pressure (mmHg), change from baseline.

Review: 'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease

Comparison: 1 Mediterranean dietary intervention versus no intervention or minimal intervention (secondary outcomes - CVD risk factors)

Outcome: 7 Systolic blood pressure (mmHg), change from baseline

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Abedi 2010 | 35 | 2.5 (16) | 29 | 3.6 (10) | | -1.10 [ -7.53, 5.33 ] |
| ENCORE | 46 | -11.2 (10.7) | 49 | -3.4 (10.7) | | -7.80 [ -12.11, -3.49 ] |
| Esposito 2004 | 90 | -4 (2) | 90 | -1 (1) | | -3.00 [ -3.46, -2.54 ] |
| Konstantinidou 2010 | 60 | -1.03 (10.79) | 29 | 1.4 (11) | | -2.43 [ -7.28, 2.42 ] |
| WHI | 17126 | -2.7 (17.15) | 25173 | -2 (16.9) | | -0.70 [ -1.03, -0.37 ] |

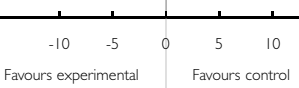
**Analysis 1.8. Comparison 1 Mediterranean dietary intervention versus no intervention or minimal intervention (secondary outcomes - CVD risk factors), Outcome 8 Diastolic blood pressure (mmHg), change from baseline.**

Review: 'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease

Comparison: 1 Mediterranean dietary intervention versus no intervention or minimal intervention (secondary outcomes - CVD risk factors)

Outcome: 8 Diastolic blood pressure (mmHg), change from baseline

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Abedi 2010 | 35 | -1 (11.2) | 29 | 0.7 (10.5) | | -1.70 [ -7.03, 3.63 ] |
| ENCORE | 46 | -7.5 (6.05) | 49 | -3.8 (5.89) | | -3.70 [ -6.10, -1.30 ] |
| Esposito 2004 | 90 | -3 (1) | 90 | -1 (1) | | -2.00 [ -2.29, -1.71 ] |
| Konstantinidou 2010 | 60 | 0.17 (7.8) | 29 | 1.67 (8) | | -1.50 [ -5.02, 2.02 ] |
| WHI | 17125 | -2 (9.15) | 25169 | -1.3 (9.05) | | -0.70 [ -0.88, -0.52 ] |




# APPENDICES

## Appendix 1. Search strategies

**Cochrane Central Register of Controlled Trials (CENTRAL), DARE, HTA, NHS EED (*The Cochrane Library) to September 2012***

#1 MeSH descriptor: [Fruit] explode all trees
#2 fruit*
#3 MeSH descriptor: [Vegetables] explode all trees
#4 MeSH descriptor: [Vegetable Proteins] this term only
#5 vegetable*
#6 MeSH descriptor: [Fabaceae] explode all trees
#7 fabaceae
#8 bean*
#9 legume*
#10 MeSH descriptor: [Lycopersicon esculentum] this term only
#11 lycopersicon next esculent*
#12 tomato*
#13 solanum next lycopersicum
#14 MeSH descriptor: [Nuts] this term only
#15 nut or nuts

#16 MeSH descriptor: [Bread] this term only
#17 bread*
#18 MeSH descriptor: [Cereals] explode all trees
#19 cereal*
#20 grain*
#21 MeSH descriptor: [Solanum tuberosum] this term only
#22 solanum next tuberosum
#23 potato*
#24 MeSH descriptor: [Seeds] this term only
#25 seed or seeds
#26 olive next oil
#27 MeSH descriptor: [Fatty Acids, Monounsaturated] this term only
#28 monounsaturated next fat*
#29 mono-unsaturated next fat*
#30 MeSH descriptor: [Seafood] explode all trees
#31 MeSH descriptor: [Fish Oils] explode all trees
#32 fish
#33 seafood*
#34 shellfish
#35 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#36 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
#37 #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
#38 #31 or #32 or #33 or #34
#39 #35 or #36 or #37 or #38
#40 (high or more or increase* or elevat* or much or rais*) near/6 (intake or consumption or consume or eat* or amount*)
#41 #39 and #40
#42 MeSH descriptor: [Dairy Products] explode all trees
#43 MeSH descriptor: [Milk Proteins] explode all trees
#44 milk*
#45 marg?rine*
#46 butter*
#47 dairy
#48 cheese*
#49 red next meat*
#50 processed next meat*
#51 yog?urt*
#52 red near/4 wine*
#53 #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52
#54 (low or little or medium or moderate or less or decrease* or reduc* or restrict*) near/6 (intake or consumption or consume or eat* or amount*)
#55 #53 and #54
#56 MeSH descriptor: [Diet, Mediterranean] this term only
#57 mediterranean near/3 diet*
#58 mediterranean near/6 food*
#59 mediterranean near/6 nutrition*
#60 mediterranean near/6 eat*
#61 (diet* or food* or nutrit* or eat*) near/2 (pattern* or habit*)
#62 MeSH descriptor: [Food Habits] this term only
#63 #56 or #57 or #58 or #59 or #60 or #61 or #62
#64 #41 or #55 or #63
#65 MeSH descriptor: [Cardiovascular Diseases] explode all trees
#66 cardio*
#67 cardia*

#68 heart*
#69 coronary*
#70 angina*
#71 ventric*
#72 myocard*
#73 pericard*
#74 isch?em*
#75 MeSH descriptor: [Stroke] explode all trees
#76 stroke or stokes
#77 cerebrovasc*
#78 apoplexy
#79 brain near/2 accident*
#80 (brain* or cerebral or lacunar) near/2 infarct*
#81 MeSH descriptor: [Hypertension] explode all trees
#82 hypertensi*
#83 peripheral next arter* next disease*
#84 (high or increased or elevated) near/2 (blood next pressure)
#85 MeSH descriptor: [Hyperlipidemias] explode all trees
#86 hyperlipid*
#87 hyperlip?emia*
#88 hypercholesterol*
#89 hypercholester?emia*
#90 hyperlipoprotein?emia*
#91 hypertriglycerid?emia*
#92 emboli*
#93 arrhythmi*
#94 thrombo*
#95 atrial next fibrillat*
#96 tachycardi*
#97 endocardi*
#98 sick next sinus
#99 MeSH descriptor: [Diabetes Mellitus] explode all trees
#100 diabet*
#101 MeSH descriptor: [Hyperglycemia] explode all trees
#102 hyperglycemi*
#103 glucose near/2 intoleran*
#104 MeSH descriptor: [Insulin Resistance] explode all trees
#105 metabolic near/3 syndrome near/3 x
#106 metabolic next cardiovascular next syndrome
#107 dysmetabolic next syndrome next x
#108 insulin next resistan*
#109 MeSH descriptor: [Arteriosclerosis] explode all trees
#110 MeSH descriptor: [Cholesterol] explode all trees
#111 cholesterol
#112 "coronary risk factor*"
#113 MeSH descriptor: [Blood Pressure] this term only
#114 "blood pressure"
#115 #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74
#116 #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84
#117 #85 or #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94
#118 #95 or #96 or #97 or #98 or #99 or #100
#119 #101 or #102 or #103 or #104 or #105 or #106 or #107 or #108 or #109 or #110 or #111 or #112 or #113 or #114
#120 #115 or #116 or #117 or #118 or #119

#121 #64 and #120

**MEDLINE Ovid (1946 to October week 1 2012)**

The Cochrane sensitive maximising RCT filter has been applied to the search (Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org).

1. exp Fruit/
2. fruit*.tw.
3. exp Vegetables/
4. Vegetable Proteins/
5. vegetable*.tw.
6. exp Fabaceae/
7. fabaceae.tw.
8. bean*.tw.
9. legume*.tw.
10. Lycopersicon esculentum/
11. lycopersicon esculent*.tw.
12. tomato*.tw.
13. solanum lycopersicum.tw.
14. Nuts/
15. (nut or nuts).tw.
16. Bread/
17. bread*.tw.
18. exp Cereals/
19. cereal*.tw.
20. grain*.tw.
21. Solanum tuberosum/
22. solanum tuberosum.tw.
23. potato*.tw.
24. Seeds/
25. (seed or seeds).tw.
26. olive oil.tw.
27. Fatty Acids, Monounsaturated/
28. monounsaturated fat*.tw.
29. mono-unsaturated fat*.tw.
30. exp Seafood/
31. exp Fish Oils/
32. fish.tw.
33. seafood*.tw.
34. shellfish.tw.
35. or/1-34
36. ((high or more or increase* or elevat* or much or rais*) adj6 (intake or consumption or consume or eat* or amount*)).tw.
37. 35 and 36
38. exp Dairy Products/
39. exp Milk Proteins/
40. milk*.tw.
41. marg?rine*.tw.
42. butter*.tw.
43. dairy.tw.
44. cheese*.tw.
45. red meat*.tw.
46. processed meat*.tw.
47. yog?urt*.tw.
48. red wine*.tw.

49. or/38-48
50. ((low or little or medium or moderate or less or decrease* or reduc* or restrict*) adj6 (intake or consumption or consume or eat* or amount*)).tw.
51. 49 and 50
52. Diet, Mediterranean/
53. (mediterranean adj3 diet*).tw.
54. (mediterranean adj6 food*).tw.
55. (mediterranean adj6 nutrition*).tw.
56. (mediterranean adj6 eat*).tw.
57. ((diet* or food* or nutrit* or eat*) adj2 (pattern* or habit*)).tw.
58. Food Habits/
59. or/52-58
60. 37 or 51 or 59
61. exp Cardiovascular Diseases/
62. cardio*.tw.
63. cardia*.tw.
64. heart*.tw.
65. coronary*.tw.
66. angina*.tw.
67. ventric*.tw.
68. myocard*.tw.
69. pericard*.tw.
70. isch?em*.tw.
71. exp Stroke/
72. (stroke or stokes).tw.
73. cerebrovasc*.tw.
74. apoplexy.tw.
75. (brain adj2 accident*).tw.
76. ((brain* or cerebral or lacunar) adj2 infarct*).tw.
77. exp Hypertension/
78. hypertensi*.tw.
79. peripheral arter* disease*.tw.
80. ((high or increased or elevated) adj2 blood pressure).tw.
81. exp Hyperlipidemias/
82. hyperlipid*.tw.
83. hyperlip?emia*.tw.
84. hypercholesterol*.tw.
85. hypercholester?emia*.tw.
86. hyperlipoprotein?emia*.tw.
87. hypertriglycerid?emia*.tw.
88. isch?emi*.tw.
89. emboli*.tw.
90. arrhythmi*.tw.
91. thrombo*.tw.
92. atrial fibrillat*.tw.
93. tachycardi*.tw.
94. endocardi*.tw.
95. (sick adj sinus).tw.
96. exp Diabetes Mellitus/
97. diabet*.tw.
98. exp Hyperglycemia/
99. hyperglycemi*.tw.
100. (glucose adj2 intoleran*).tw.

101. exp Insulin Resistance/
102. (metabolic adj3 syndrome adj3 x).tw.
103. metabolic cardiovascular syndrome.tw.
104. dysmetabolic syndrome x.tw.
105. insulin resistan*.tw.
106. exp Arteriosclerosis/
107. exp Cholesterol/
108. cholesterol.tw.
109. "coronary risk factor*".tw.
110. Blood Pressure/
111. blood pressure.tw.
112. or/61-111
113. 60 and 112
114. randomized controlled trial.pt.
115. controlled clinical trial.pt.
116. randomized.ab.
117. placebo.ab.
118. clinical trials as topic.sh.
119. randomly.ab.
120. trial.ti.
121. 114 or 115 or 116 or 117 or 118 or 119 or 120
122. exp animals/ not humans.sh.
123. 121 not 122
124. 113 and 123

**EMBASE Ovid (1980 to 2012 week 41)**

1. exp fruit/
2. fruit*.tw.
3. exp vegetable/
4. exp vegetable protein/
5. vegetable*.tw.
6. fabaceae.tw.
7. bean*.tw.
8. legume*.tw.
9. lycopersicon esculent*.tw.
10. tomato*.tw.
11. solanum lycopersicum.tw.
12. exp nut/
13. (nut or nuts).tw.
14. bread*.tw.
15. cereal*.tw.
16. grain*.tw.
17. exp grain/
18. solanum tuberosum.tw.
19. potato*.tw.
20. exp plant seed/
21. (seed or seeds).tw.
22. olive oil/
23. olive oil.tw.
24. monounsaturated fatty acid/
25. monounsaturated fat*.tw.
26. mono-unsaturated fat*.tw.
27. sea food/
28. fish oil/

29. fish meat/
30. fish.tw.
31. seafood*.tw.
32. sea food*.tw.
33. shellfish.tw.
34. or/1-33
35. ((high or more or increase* or elevat* or much or rais*) adj6 (intake or consumption or consume or eat* or amount*)).tw.
36. 34 and 35
37. exp dairy product/
38. milk*.tw.
39. marg?rine*.tw.
40. butter*.tw.
41. dairy.tw.
42. cheese*.tw.
43. red meat*.tw.
44. processed meat*.tw.
45. exp red meat/
46. yog?urt*.tw.
47. red wine*.tw.
48. or/37-47
49. ((low or little or medium or moderate or less or decrease* or reduc* or restrict*) adj6 (intake or consumption or consume or eat* or amount*)).tw.
50. 48 and 49
51. Mediterranean diet/
52. (mediterranean adj3 diet*).tw.
53. (mediterranean adj6 food*).tw.
54. (mediterranean adj6 nutrition*).tw.
55. (mediterranean adj6 eat*).tw.
56. ((diet* or food* or nutrit* or eat*) adj2 (pattern* or habit*)).tw.
57. eating habit/
58. or/51-57
59. 36 or 50 or 58
60. exp cardiovascular disease/
61. cardio*.tw.
62. cardia*.tw.
63. heart*.tw.
64. coronary*.tw.
65. angina*.tw.
66. ventric*.tw.
67. myocard*.tw.
68. pericard*.tw.
69. isch?em*.tw.
70. exp cerebrovascular disease/
71. (stroke or stokes).tw.
72. cerebrovasc*.tw.
73. apoplexy.tw.
74. (brain adj2 accident*).tw.
75. ((brain* or cerebral or lacunar) adj2 infarct*).tw.
76. exp hypertension/
77. hypertensi*.tw.
78. peripheral arter* disease*.tw.
79. ((high or increased or elevated) adj2 blood pressure).tw.
80. exp hyperlipidemia/

81. hyperlipid*.tw.
82. hyperlip?emia*.tw.
83. hypercholesterol*.tw.
84. hypercholester?emia*.tw.
85. hyperlipoprotein?emia*.tw.
86. hypertriglycerid?emia*.tw.
87. emboli*.tw.
88. arrhythmi*.tw.
89. thrombo*.tw.
90. atrial fibrillat*.tw.
91. tachycardi*.tw.
92. endocardi*.tw.
93. (sick adj sinus).tw.
94. exp diabetes mellitus/
95. diabet*.tw.
96. diabet*.tw.
97. diabet*.tw.
98. hyperglycemia/
99. hyperglycemi*.tw.
100. (glucose adj2 intoleran*).tw.
101. insulin resistance/
102. (metabolic adj3 syndrome adj3 x).tw.
103. metabolic cardiovascular syndrome.tw.
104. dysmetabolic syndrome x.tw.
105. insulin resistan*.tw.
106. exp Arteriosclerosis/
107. exp Cholesterol/
108. cholesterol.tw.
109. "coronary risk factor*".tw.
110. Blood Pressure/
111. blood pressure.tw.
112. or/60-111
113. random$.tw.
114. factorial$.tw.
115. crossover$.tw.
116. cross over$.tw.
117. cross-over$.tw.
118. placebo$.tw.
119. (doubl$ adj blind$).tw.
120. (singl$ adj blind$).tw.
121. assign$.tw.
122. allocat$.tw.
123. volunteer$.tw.
124. crossover procedure/
125. double blind procedure/
126. randomized controlled trial/
127. single blind procedure/
128. 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127
129. (animal/ or nonhuman/) not human/
130. 128 not 129
131. 59 and 112 and 130
132. limit 131 to embase

**Web of Science (1970 to 16 October 2012)**

#25 #24 AND #23
#24 TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)
#23 #22 AND #10
#22 #21 OR #18 OR #15
#21 #20 OR #19
#20 TS= ((diet* or food* or nutrit* or eat*) SAME (pattern* or habit*))
#19 TS=((mediterranean) SAME (diet* or food* or nutrition* or eat*))
#18 #17 AND #16
#17 TS=((low or little or medium or moderate or less or decrease* or reduc* or restrict*) SAME (intake or consumption or consume or eat* or amount*))
#16 TS=(milk* or marg?rine* or butter* or dairy or cheese* or "red meat*" or "processed meat*" or "red wine*")
#15 #14 AND #13
#14 TS=((high or more or increase* or elevat* or much or rais*) SAME (intake or consumption or consume or eat* or amount*))
#13 #12 OR #11
#12 TS=("solamun tuberosum" or potato* or seed or seeds or "olive oil" or "monounsaturated fat*" or "mono-unsaturated fat*" or fish or seafood* or shellfish)
#11 TS=(fruit* or vegetable* or fabaceae or bean* or legume* or "lycopersicon esculent*" or tomato* or "solanum lycopersicum" or nut or nuts or bread* or cereal* or grain*)
#10 #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#9 TS=(arteriosclerosis or cholesterol or "coronary risk factor*" or "blood pressure")
#8 TS=diabet*
#7 TS=(hyperlipid* or hyperlip?emia* or hypercholesterol* or hypercholester?emia* or hyperlipoprotein?emia* or hypertriglycerid?emia*)
#6 TS=("high blood pressure")
#5 TS=(hypertensi* or "peripheral arter* disease*")
#4 TS=(stroke or strokes or cerebrovasc* or cerebral or apoplexy or (brain SAME accident*) or (brain SAME infarct*))
#3 TS=("artrial fibrillat*" or tachycardi* or endocardi*)
#2 TS=(pericard* or isch?em* or emboli* or arrhythmi* or thrombo*)
#1 TS=(cardio* or cardia* or heart* or coronary* or angina* or ventric* or myocard*)

## CONTRIBUTIONS OF AUTHORS

All authors contributed to the protocol development. Karen Rees, Louise Hartley and Nadine Flowers screened titles and abstracts, assessed studies for formal inclusion and exclusion, abstracted data and assessed risk of bias of included studies. Karen Rees analysed data and drafted the methods and results sections, Saverio Stranges drafted the background and discussion. All authors commented on later drafts of the review.

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT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### External sources

- NIHR Cochrane Programme Grant, UK.


## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We intended to look at studies examining dietary advice to follow a Mediterranean-style diet separately from studies examining the provision of foods, but for all studies that met our inclusion criteria the intervention was dietary advice. It was also our intention to stratify results according to the number of components constituting the Mediterranean dietary pattern and the intensity and duration of the intervention. However, there were insufficient trials that met the inclusion criteria to perform these analyses. Similarly, we planned to stratify results by general population and high-risk participants, follow-up period, age and gender to determine their impact on effect estimates but there are insufficient trials to date to do this.

We also intended to examine the effect of alcohol consumption and other potential adverse effects of the Mediterranean diet in our analyses but this information was not reported in the few trials that met the inclusion criteria.

In the protocol, we stated that we would exclude studies where loss to follow-up exceeded 20%. We have relaxed this inclusion criterion and have instead performed sensitivity analyses excluding these studies to examine the impact on pooled effect estimates.

We also intended to focus on studies with follow-up of six months or more but studies with this length of follow-up were lacking and so studies with follow-up of three months or more were included.