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‘Mediterranean’ dietary pattern for the primary prevention of cardiovascular disease

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Abstract

This is the protocol for a review and there is no abstract. The objectives are as follows:

The primary objective is to determine 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.

BACKGROUND

Description of the condition

Cardiovascular disease (CVD) is one of the leading causes of death worldwide (WHO 2011). 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 2011). The burden of CVD also varies considerably between regions (Müller-Nordhorn 2008; Reddy 1998).

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 United States, 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;

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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 coronary heart disease, with similar risk estimates by sex (Buckland 2009). Recent 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, recent 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 recent 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 patients with existing CVD, showing favourable effects in cardiovascular disease 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 fruit 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 Mediterranean type of diet reflects the common dietary pattern of communities in countries of the Mediterranean region in the early 1960s (Keys 1986), which is 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 will be 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 will be required to reach 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

At least two of the above components were chosen as our definition of a Mediterranean style dietary pattern as one component does not constitute a dietary pattern. Studies examining dietary advice to follow a Mediterranean style diet will be examined separately from studies examining the provision of foods. We will examine the effects of studies reporting 2 components and 3 or more components, and if there are sufficient trials, results will be stratified further according to the number of components constituting the Mediterranean dietary pattern and the duration of the intervention.

How the intervention might work

There is a large body 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 vaso reactivity, 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 (1-2 drinks/day), and moderate alcohol consumption in general, is associated with reduced allcause and cardiovascular mortality and morbidity and has beneficial effects on cardiovascular risk factors, when compared to both abstention and heavy drinking (Corrao 2000; Di Castelnuovo 2002; Di Castelnuovo 2006; Ronksley 2011; Brien 2011). On the other hand, excess red wine and 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). We will examine the effect of alcohol consumption and other potential adverse effects of the Mediterranean diet in our analyses.

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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 diet 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 diet 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 patients 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

The primary objective is to determine 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.

METHODS

Criteria for considering studies for this review

Types of studies—Randomised controlled trials

Types of participants—Adults of all ages from the general population and those at high risk of CVD. The review will focus on the effects of a Mediterranean dietary pattern on the primary prevention of CVD. We will exclude those who have experienced a previous myocardial infarction (MI), stroke, revascularization procedure (coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA)), those with angina, or angiographically defined coronary heart disease CHD.

Types of interventions—The intervention will be specific dietary advice to follow a Mediterranean style diet or provision of dietary factors relevant to the Mediterranean diet. At least two components from the following list will be 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.

Studies examining dietary advice to follow a Mediterranean style diet will be examined separately from studies examining the provision of foods. We will examine the effects of studies reporting two components and three or more components, and if there are sufficient trials, results will be stratified further according to the number of components constituting the Mediterranean dietary pattern and the duration of the intervention.

We will focus on follow-up periods of six months or more as these are most relevant for public health interventions, there will be no minimal period for the duration of the intervention. Trials will only be considered where the comparison group is no intervention or minimal intervention (e.g. leaflet to follow a dietary pattern with no person to person intervention or reinforcement).

Types of outcome measures

Primary outcomes: Clinical outcomes such as mortality (cardiovascular and all-cause); non-fatal CVD endpoints such as myocardial infarction, CABG, PTCA, those with angina or angiographically defined CHD, stroke, carotid endarterectomy, peripheral arterial disease (PAD).

Secondary outcomes: Changes in major cardiovascular risk factors including blood pressure, blood lipids and occurrence of type 2 diabetes as a major risk factor for CVD, quality of life, adverse effects and costs.

Search methods for identification of studies

Electronic searches—The following electronic databases will be searched: the Cochrane Library (including the Cochrane Central Register of Controlled Trials (CENTRAL) and NHS Centre for Reviews and Dissemination (CRD) databases: Health Technology Assessment (HTA), Database of Abstracts of Reviews of Effects (DARE) and NHS Economic Evaluation Database (NEED)), MEDLINE, EMBASE, and the Web of Science (Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), Conference Proceedings Citation Index - Science (CPCI-S)). .

Medical subject headings (MeSH) or equivalent and text word terms will be used. Searches will be designed in accordance with the Cochrane Heart Group methods and guidance. There will be no language restrictions.

Searches will be tailored to individual databases. The search strategy for MEDLINE is shown in Appendix 1.

Searching other resources—In addition, reference lists of reviews and retrieved articles will be checked for additional studies and we will search OpenGrey for unpublished studies.

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

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Citation searches will be performed on key articles. Google Scholar will also be used to search for further studies. Experts in the field will be contacted for unpublished and ongoing trials. Authors will be contacted where necessary for additional information.

Data collection and analysis

Selection of studies—From the searches, the title and abstract of each paper will be reviewed by two reviewers (KR, LH) and potentially relevant references retrieved. Following this initial screening, the full text reports of potentially relevant studies will be obtained, and two reviewers (KR, LH) will independently select studies to be included in the review using predetermined inclusion criteria. In all cases disagreements about any study inclusions will be resolved by consensus and a third reviewer will be consulted if disagreement persists.

Data extraction and management—Data will be extracted independently by two reviewers (KR, LH) using a proforma, and chief investigators will be contacted to provide additional relevant information if necessary. 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) will be extracted from each of the included studies. Disagreements about extracted data will be resolved by consensus and a third reviewer will be consulted if disagreement persists.

Assessment of risk of bias in included studies—Risk of bias will be assessed by examining the quality of the random sequence generation and allocation concealment, description of drop-outs and withdrawals (including analysis by intention-totreat), blinding (participants, personnel and outcome assessment) and selective outcome reporting (Higgins 2011). The risk of bias in included studies will be assessed independently by two reviewers (KR, LH).

Measures of treatment effect—Data will be processed in accordance with the Cochrane Handbook for Systematic Reviews of interventions (Higgins 2011). Dichotomous outcomes will be expressed as odds ratios or relative risks, and 95% confidence intervals (CI) will be calculated for each study. For continuous variables net changes will be compared (i.e. intervention group minus control group differences) and a weighted mean difference (WMD) or standardised mean difference (SMD) and 95% CIs will be calculated for each study.

Assessment of heterogeneity—For each outcome tests of heterogeneity will be carried out (using the chi^2 test of heterogeneity and I^2 statistic). In the situation of no heterogeneity a fixed-effect meta-analysis will be performed. If substantial heterogeneity is detected the reviewers will look for possible explanations for this (e.g. participants and intervention). If the heterogeneity cannot be explained, the reviewers will consider 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—Results will be reported separately for dietary advise to follow a Meditteranean diet and provision of foods relevant to the Mediterranean diet. We will examine the effects of studies reporting two components and three or more components, and if there are sufficient trials, results will be stratified further according to the number of components constituting the Mediterranean dietary pattern and the duration of the intervention. Similarly, if there are sufficient trials and data are reported separately for men and women and by age group, we will examine the effects of gender and age.

Sensitivity analysis—Sensitivity analyses will be carried out excluding studies of low methodological quality. If there are sufficient trials, funnel plots and tests of asymmetry (Egger 1997) will be undertaken to assess possible publication bias.

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Internal sources

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External sources

- NIHR Cochrane Programme Grant, UK.

Appendix 1. MEDLINE search strategy

MEDLINE OVID

The Cochrane sensitive-precision maximising RCT filter has been applied to the search (Lefebvre 2011)

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.

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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.

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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. or/61-105

107. 60 and 106

108. randomized controlled trial.pt.

109. controlled clinical trial.pt.

110. randomized.ab.

111. placebo.ab.

112. clinical trials as topic.sh.

113. randomly.ab.

114. trial.ti.

115. 108 or 109 or 110 or 111 or 112 or 113 or 114

116. exp animals/ not humans.sh.

117. 115 not 116

118. 107 and 117

HISTORY

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