eTable. Characteristics of the Mediterranean diet adherence of included studies

Study	Dietary assessment	Components of adherence score	Adherence score scale	Mean MeDi score
Feart et al.[14]	236-item FFQ for dietary intake & composite score for adherence to MeDi	1.high fruit 2.high vegetable 3.high whole-grain products 4.high legume 5.high fish 6.high MUFA:SFA ratio 7.low meat 8.low dairy products 9.moderate alcohol consumption	0-9 points	4.36 (SD 1.66)
Psaltopoulou et al.[15]	150-item FFQ for dietary intake & composite score for adherence to MeDi	1.high fruit and nuts 2.high vegetable 3.high cereal 4.high legume 5.high fish 6.high MUFA:SFA ratio 7.low meat products 8.low dairy products 9.moderate alcohol consumption	0-9 points	4.3 (SD 1.65)
Cherbuin & Anstey[16]	215-item FFQ for dietary intake & composite score for adherence to MeDi	1.high fruit 2.high vegetable 3.cereal 4.high legume 5.high fish 6.high MUFA:SFA ratio 7.low meat 8.low dairy products 9.moderate alcohol consumption	0-9 points	4.89 (SD 1.64) (normal ppts)
Cherbuin, Kumar & Anstey[17]	215-item FFQ for dietary intake & composite score for adherence to MeDi	1.high fruit 2.high vegetable 3.cereal 4.high legume 5.high fish 6.high MUFA:SFA ratio 7.low meat 8.low dairy products 9.moderate alcohol consumption	0-9 points	4.80 (SD 1.59) (normal ppts)
Scarmeas et al.[19]	61-item SFFQ for dietary intake & composite score for adherence to MeDi	1.high fruit 2.high vegetable 3.high cereal 4.high legume 5.high fish 6.high MUFA:SFA ratio 7.low meat 8.low dairy products 9.moderate alcohol consumption	0-9 points	4.4 (non-demented)
Scarmeas et al.[20]	61-item SFFQ for dietary intake & composite score for adherence to MeDi	1.high fruit 2.high vegetable 3.high cereal 4.high legume 5.high fish 6.high MUFA:SFA ratio 7.low meat 8.low dairy products 9.moderate alcohol consumption	0-9 points	4.4 (non-demented)
Scarmeas et al.[21]	61-item SFFQ for dietary intake & composite score for adherence to MeDi	1.high fruit 2.high vegetable 3.high cereal 4.high legume 5.high fish 6.high MUFA:SFA ratio 7.low meat 8.low dairy products 9.moderate alcohol consumption	0-9 points	4.36 (SD 1.67)
Gu et al.[22]	61-item SFFQ for dietary intake & composite score for adherence to MeDi	1.high fruit 2.high vegetable 3.high cereal 4.high legume 5.high fish 6.high MUFA:SFA ratio 7.low meat 8.low dairy products 9.moderate alcohol consumption	0-9 points	4.37 (SD 1.7)
Roberts et al.[23]	128-item Health Habits and History Q. for dietary intake & composite score for adherence to MeDi	1.high fruit 2.high vegetable 3.high grain and cereal 4.high legume 5.high fish 6.high MUFA:SFA ratio 7.low red meat 8.low dairy products 9.moderate alcohol consumption	0-9 points	5[a]
Tangney et al.[18]	139-item FFQ for dietary intake & composite score for adherence to MedDiet	1.high fruit 2.high vegetable 3.high nonrefined cereals and breads 4.high legumes, nuts, beans 5.high potatoes 6.high fish 7.high olive oil 8.low red meats 9.low poultry 10.full-fat dairy 11.moderate alcohol consumption	0-45 points	28.2 (SD 0.1)
Scarmeas et al.[24]	61-item SFFQ for dietary intake & composite score for adherence to MeDi	1.high fruit 2.high vegetable 3.high cereal 4.high legume 5.high fish 6.high MUFA:SFA ratio 7.low meat 8.low dairy products 9.moderate alcohol consumption	0-9 points	4.4 (non-demented)
McMillan et al.[25]	Food diary: each meal/snack rated as being in accordance with the MeDi or not	Eating plan: increase intake of fruits, vegetables, fatty fish, nuts and seeds, low fat natural dairy, wholegrain cereals & exclude red meat, refined sugars and flour, processed foods, soft drinks, condiments	[if ≥ 80% of meals/snacks then in accordance with MeDi]	[93% of meals, 95% of snacks in DC group matched MeDi eating plan]

Abbreviations: MeDi, Mediterranean diet; FFQ, Food Frequency Questionnaire; SFFQ, Semi-quantitative Food Frequency Questionnaire; MUFA, monounsaturated fatty acids; SFA, saturated fatty acids; DC, dietary change group; MedDiet, Mediterranean diet; SD, standard deviation.
[a]: median

Review Protocol

Title

Is adherence to a Mediterranean diet associated with cognitive function and dementia?

Rationale

Diet plays an integral role in individuals' health status and it has been linked with the development of a range of chronic diseases [1, 2]. Specific nutrients and foods have drawn scientific attention for their potential beneficial effects on reducing the risk of chronic conditions. Thus, high consumption of fruits and vegetables has been found to be related with lowered risk for cardiovascular disease [3, 4] and cancer in different sites [5], while diets low in trans fatty acids and red meat and high in whole grain fibre and fish have been associated with lower rates of hypertension, coronary heart disease and type 2 diabetes [6-8].

The role of nutrition in cognitive function [9, 10] and dementia prevention [11] has been examined in epidemiological studies with conflicting results. Some studies have concluded to the beneficial role of specific nutrient intake in cognitive functions. Randomised controlled trials have showed improvements in cognitive tests after vitamins and trace elements [12], beta carotene [13] and folic acid supplementation [14], while cross-sectional studies have presented favourable findings for the role of unsaturated fats [15] and vitamin B-12 consumption in relation to cognitive performance [16]. Moreover, cohort studies have found associations between nutrients and foods and a decreased risk of dementia. These include antioxidants such as vitamin C and E [17, 18], flavonoids [19], moderate alcohol consumption and especially wine [20] and fish [21]. However, results from other observational studies do not support the protective effect of vitamins C and E [22], omega-3 and fish consumption on the risk of Alzheimer's disease [23] or an association between high intake of saturated fats and incident dementia [24].

Dietary patterns, as opposed to individual nutrients or foods, are an emerging area of research in recent years. It is believed that dietary patterns can reflect dietary behaviours of individuals more spherically, as they combine foods which in turn may have synergistic or antagonistic effects on health. The Mediterranean diet is a dietary pattern with promising findings associated with reduced risk of cardiovascular disease, some forms of cancer and all-cause mortality [2, 25]. The traditional Mediterranean diet refers to an eating behaviour characterised by 1) high intake of fruits, 2) vegetables, 3) cereals and 4) legumes, 5) low consumption of saturated fats with olive oil as the main source of fat, 6) moderate consumption of fish, 7) low to moderate intake of dairy products (in the form of yogurt and cheese), 8) low consumption of red meat and meat products and 9) moderate amount of alcohol , especially wine, usually consumed during meals [26]. Such a multi-nutrient approach includes most of the components studied in relation to cognitive decline and incident dementia. Thus, it is reasonable to believe that adherence to a Mediterranean diet may be protective against cognitive decline and dementia, while it may also prove useful in the management of malnutrition and vitamin deficiencies often observed in dementia patients and elderly people [27,28].

Purpose

Relationships between diet and physical health are well recognized as are the protective effects of the Mediterranean diet on the risk of various chronic diseases and longevity. The purpose of this systematic review is to investigate and determine the potential association between adherence to a Mediterranean diet and cognitive function and dementia.

Exposure

Adherence to a Mediterranean diet

Population

Adults (≥18yrs)

Comparators

Low adherence to a Mediterranean diet

Outcomes to be examined

If possible, outcome measures will include:

- Measures of cognitive function
- Prevalent and incident dementia (i.e. Alzheimer's disease, Vascular dementia, all-cause dementia and other dementia subtypes)

Methods of synthesis of evidence of association

The systematic review will synthesize evidence for the (strength of) association between adherence to a Mediterranean diet and cognitive function and dementia. The review will be undertaken following the general principles published by the NHS Centre for Reviews and Dissemination [29].

Search strategy

Refer to Appendix 1 for the draft search strategy for Medline.

The search strategy will comprise the following main elements:

- Searching the following databases: Medline, EMBASE and PsycINFO using the Ovid interface, HMCI, CINAHL, AMED, Cochrane Library and Web of Science.
- Scrutiny of reference lists of included studies
- Hand searching of relevant journals, e.g. Archives of Neurology, Journal of Alzheimer's Disease.
- Selected citation searching (searching for relevant studies from papers which have cited the studies that meet the inclusion criteria for the review)
- Contact with experts in the field
- Internet searching of the following relevant websites: Alzheimer's Society, Alzheimer's Disease Research, Alzheimer's Disease International, Alzheimer's Research UK and Alzheimer's Association.

Study selection criteria and procedures

Types of study to be included

- Studies that examine the association of a defined score used to measure adherence to a Mediterranean diet and include cognitive function and/or dementia as outcomes (with comparative data)
- Randomised clinical trials will be included, but it is anticipated their number will be limited if not minimal. All relevant observational studies and cross sectional studies will be included in the review. Although study design will not be used as an inclusion/exclusion criterion, methodology and reporting of each study will be assessed using a quality checklist developed for this review.

Types of study to be excluded

- Studies evaluating adherence to a non-specific dietary pattern or to a recommended dietary guideline but not to a Mediterranean diet
- Narrative reviews, letters, editorials, opinions
- Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality
- Animal models

Study selection

The titles and abstracts of references retrieved by the electronic searches will be screened for relevance by one reviewer and independently checked by a second using the pre-specified inclusion/exclusion criteria. Full-text copies of potentially relevant studies will be obtained. Using the same methods, the retrieved articles will be assessed for inclusion. Discrepancies will be resolved by discussion, with involvement of a third reviewer, where necessary. Duplicate papers will be double checked and excluded.

Quality assessment strategy

The quality of individual studies will be assessed by one reviewer, and checked by a second reviewer. Any disagreement will be resolved by consensus and if necessary a third reviewer will arbitrate. Appropriate quality assessment criteria will be used depending on the design and reporting of the included studies using a checklist adjusted for this review based on components from widely used scales and checklists [30-32].

Data extraction strategy

Data will be extracted from included studies by one reviewer into a piloted, standardised data extraction form and checked by another reviewer. Discrepancies will be resolved by discussion, with the involvement of a third reviewer if necessary.

Data synthesis

Data will be tabulated and discussed in a narrative review. Where appropriate, meta-analysis will be employed to estimate summary measures of effect on relevant outcomes (based on intention to treat analyses for analysis of trials).

If meta-analysis is conducted it will be carried out using fixed and random effects models, using STATA. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and I^2 statistic and, where appropriate, using meta-regression. Small- study effects (including publication bias) will be visually assessed using funnel plots and quantified using Egger's statistic.

Appendix 1

Database: Ovid MEDLINE(R) <1946 to January Week 1 2012>
Search Strategy:
---

1 exp Diet, Mediterranean/ (995)
2 (mediterranean adj2 diet*).ti,ab. (1425)
3 1 or 2 (1683)
4 cognit*.ti,ab. (151236)
5 dement*.ti,ab. (54727)
6 Alzheimer*.ti,ab. (68485)
7 Lewy bod*.ti,ab. (4513)
8 mental*.ti,ab. (179176)
9 memor*.ti,ab. (136639)
10 psychometric*.ti,ab. (19335)
11 neuropsycholog*.ti,ab. (27805)
12 frontotemporal lobar degenerat*.ti,ab. (846)
13 exp mental competency/ or exp mental processes/ or cognition/ (657102)
14 exp mild cognitive impairment/ or exp alzheimer disease/ or exp dementia, vascular/ (58540)
15 exp Memory/ (83666)
16 exp Neuropsychological Tests/ (55769)
17 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (1045087)
18 3 and 17 (102)

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References

1. Stampfer, M. J., Hu, F.B., Manson, J.E., Rimm, E.B. & Willett, W.C. (2000). Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med, 343*, 16-22.

2. Mitrou, P.N., Kipnis, V., Thiebaut, A.C.M., Reedy, J., Subar, A.F., Wirfalt, E., Flood, A., Mouw, T., Hollenbeck, A.R., Leitzmann, M.F. & Schatzkin, A. (2007). Mediterranean dietary pattern and prediction of all-cause mortality in a US population: Results from the NIH-AAPR Diet and Health Study. *Arch Inter Med, 167(22)*, 2461-2468.

3. Belin, R.J., Greenland, P., Allison, M., Martin, L., Shikany, J.M., Larson, J., Tinker, L., Howard, B.V., Lloyd-Jones, D. & Van Horn, L. (2011). Diet quality and the risk of cardiovascular disease: the Women's Health Initiative (WHI). *Am J Clin Nutr, 94*, 49–57.

4. Appel, L.J., Moore, T.J., Obarzanek, E., et al. (1997). A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med, 336,* 1117–24.

5. Ziegler, R.G. (1991). Vegetables, fruits, and carotenoids and the risk of cancer. *Am J Clin Nutr, 53*, 251S-9S.

6. Simopoulos, A.P. (1999). Essential fatty acids in health and chronic disease. *Am J Clin Nutr, 70(suppl),* 560S–9S.

7. McCullough, M.L., Feskanich, D., Stampfer, M.J., Giovannucci, E.L., Rimm, E.B., Hu, F.B., Spiegelman, D., Hunter, D.J., Colditz, G.A. & Willett, W.C. (2002). Diet quality and major chronic disease risk in men and women: moving toward improved dietary guidance. *Am J Clin Nutr, 76*, 1261–71.

8. Meyer, K.A., Kushi, L.H., Jacobs Jr, D.R., Slavin, J., Sellers, T.A. & Folsom, A.R. (2000). Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am J Clin Nutr, 71*, 921-930.

9. Requejo, A.M, Ortega, R.M., Robles, F., Navia, B., faci, M. & Aparicio, A. (2003). Influence of nutrition on cognitive function in a group of elderly, independently living people. *European Journal of Clinical Nutrition, 57 (Suppl.1),* S4-S7.

10. Solfrizzi, V., Panza, F. & Capurso, A. (2003). The role of diet in cognitive decline. *J Neural Transm, 110,* 95-110.

11. Morris, M.C. (2009). The role of nutrition in Alzheimer's disease: epidemiological evidence. *European Journal of Neurology, 16(Suppl.1),* 1-7.

12. Chandra, R.K. (2001). Effect of vitamin and trace element supplementation on cognitive function in elderly subjects. *Nutrition, 17*, 709-712.

13. Grodstein, F., Kang, J.H., Glynn, R.J., Cook, N.R. & Gaziano, J.M. (2007). A randomised trial of beta carotene supplementation and cognitive function in men: The physicians' health study II. *Arch Intern Med., 167(20),* 2184-2190.

14. Durga, J., van Boxtel, M.PJ., Schouten, E.G., Kok, F.J., Jolles, J., Katan, M.B. & Verhoef, P. (2007). Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double-blind, controlled trial. *Lancet, 369*, 208-216.

15. Kalmijn, S., van Boxtel, M.P.J., Ocke, M., Verschuren, W.M.M., Kromhout, D. & Lauren, L.J. (2004). Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. *Neurology, 62*, 275-280.

16. Riggs, K.M., Spiro, A., Tucker, K. & Rush, D. Relations of vitamin B-12, vitamin B-6, folate, and homocysteine to cognitive performance in the Normative Aging Study. *Am J Clin Nutr, 63*, 306–14.

17. Paleologos, M., Cumming, R.G. & Lazarus, R. (1998). Cohort study of vitamin C intake and cognitive impairment. *Am J Epidemiol, 148(1),* 45-50.

18. Morris, M.C., Evans, D.A., Bienias, J.L., Tangney, C.C., Bennett, D.A., Aggarwal, N., Wilson, R.S. & Scherr, P.A. (2002). Dietary intake of antioxidant nutrients and the risk of incident Alzheimer's disease in a biracial community study. *JAMA, 287,* 3230-3237.

19. Engelhart, m.J., Geerlings, M.I., Ruitenberg, A., Van Swieten, J.C., Hofman, A., Witteman, J.C.M. & Breteler, M.M.B. (2002). Dietary intake of antioxidants and risk of Alzheimer disease. *JAMA, 287,* 3223-3229.

20. Luchsinger, J.A., Tang, M-X., Shea, S. & Mayeux, R. (2004). Alcohol intake and risk of dementia. *Journal of the American Geriatrics Society, 52(4),* 540-546.

21. Morris, M.C., Evans, D.A., Bienias, J.L., Tangney, C.C., Bennett, D.A., Wilson, R.S., Aggarwal, N. & Schneider, J. (2003). Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. *Arch Neurol, 60,* 940-946.

22. Luchsinger, J.A., Tang, M-X., Shea, S. & Mayeux, R. (2003). Antioxidant vitamine intake and risk of Alzheimer disease. *Arch Neurol, 60,* 203-208.

23. Devore, E.E., Grodstein, F., van Rooij, F.J.A., Hofman, A., Rosner, B., Stampfer, M.J., Witteman, J.C.M. & Breteler, M.M.B. (2009). Dietary intake of fish and omega-3 fatty acids in relation to long-term dementia risk. *Am J Clin Nutr, 90,* 170-176.

24. Engelhart, M.J., Geerlings, M.I., Ruitenberg, A., Van Swieten, J.C., Hofman, A., Witteman, J.C.M. & Breteler, M.M.B. (2002). Diet and risk of dementia: Does fat matter? The Rotterdam study. *Neurology, 59,* 1915-1921.

25. Sofi, F., Abbate, R., Gensini, G.F. & Casini, A. (2010). Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. *Am J Clin Nutr, 92,* 1189-96.

26. Trichopoulou, A., Kouris-Blazos, A., Vassilakou, T., Gnardellis, Ch., Polychronopoulos, E., Venizelos, M., Lagiou, P., Wahlqvist, M. & Trichopoulos, D. (1995). The diet and survival of elderly Greeks: a link to the past. *Am J Clin Nutr, 61(suppl),* 1346S-1350S.

27. Scheltens, P. (2009). Moving forward with nutrition in Alzheimer's disease. *European Journal of Neurology, 16 (Suppl.1),* 19-22.

28. Selhub, J., Bagley, L.C., Miller, J. & Rosenberg, I. H. (2000). B vitamins, homocysteine, and neurocognitive function in the elderly. *Am J Clin Nutr, 71(suppl),* 614S-20S.

29. Centre for Reviews and Dissemination (2009). *Systematic reviews: CRD's guidance for undertaking reviews in health care*. University of York.

30. Tooth, L., Ware, R., Bain, C., Purdie, D.M. & Dobson, A. (2005). Quality of reporting of observational longitudinal research. *Am J Epidemiol, 161(3),* 280-288.

31. Wells, G.A., Shea, B., O'Connell, D., Peterson J., Welch, V., Losos, M. & Tugwell, P. (2000). The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis.

32. Downs, S.H. & Black, N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality of both randomized and non-randomised studies of health care interventions. *J Epidemiol Community Health, 52,* 377-384.

Quality Assessment Checklist

Study ID #: Date of extraction: Data extracted by:

Title:

Citation:

1. Are the participants' characteristics clearly described? RCT/ PC/CS*
   (Distribution of the population by age and sex, inclusion and/or exclusion criteria should be given)

Yes	
No	
Unclear	

2. Were the subjects asked to participate in the study representative of the population from which they were recruited? RCT/ PC/CS
   (Patients/participants would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or random sample)

Yes	
No	
Unclear	

3. Were the patients/participants in different intervention/exposure groups recruited from the same population? RCT/ PC/CS
   (The question should be answered 'No' for cohort and cross-sectional studies where participants are selected from a different source or where there is no description of the derivation of the non exposed group)

Yes	
No	
Unclear	

4. Was the method used for assessing adherence to Mediterranean diet appropriate? RCT/ PC/CS
   (the question should be answered 'Yes' if prior validation of the index used and/or estimates of reliability are mentioned in the paper or the reader is redirected to the relevant source)

Yes	
No	
Unclear	

5. Was adherence stability assessed during follow-up? RCT/ PC
   (For trials, the question should be answered 'Yes' where the compliance with the intervention was reliable)

Yes	
No	
Unclear	

6. Was there demonstration that outcome of interest was not present at the start of study? RCT/ PC/CS

Yes	
No	
Unclear	

7. Were confounders controlled for in the analyses? RCT/ PC/CS

   (Important confounders e.g. age, sex, apoE, cardiovascular risk factors)

Yes	
No	
Unclear	

8. Was the method used for the assessment of the outcome of interest appropriate? RCT/ PC/CS
   (The question should be answered 'Yes' if neuropsychological tests with proven validity and/or reliability were used or disease cases were confirmed according to relevant diagnostic criteria/guidelines)

Yes	
No	
Unclear	

9. Was the number of participants at each stage/wave specified? RCT/ PC

Yes	
No	
Unclear	

10. Was the follow-up sample adequate (number of participants lost to follow-up < 30%)? RCT/ PC

Yes	

No	
Unclear	

11. Were reasons for loss to follow-up quantified? RCT/ PC
(The question should be answered 'Yes' if the characteristics of participants were described and/or quantification of the major reasons was included)

Yes	
No	
Unclear	

12. Was loss to follow-up taken into account in the analyses? RCT/ PC

Yes	
No	
Unclear	

13. Were estimates of effect, including CIs and p-values, reported in the analysis? RCT/ PC/CS

Yes	
No	
Unclear	

14. Was the number of participants justified? RCT/ PC/CS
(The question should be answered 'Yes' if there is justification of the number of people needed to detect anticipated effects; evidence that power calculations were considered or included)

Yes	
No	
Unclear	

<u>Additional questions for RCTs only:</u>

15. Were study participants randomised to intervention groups?

Yes	

No	
Unclear	

16. Were the staff, places and facilities where the patients were treated, representative of the treatment the majority of patients receive?

Yes	
No	
Unclear	

17. Was an attempt made to blind study participants to the intervention they have received?

Yes	
No	
Unclear	

18. Was an attempt made to blind those measuring the main outcomes of the intervention?

Yes	
No	
Unclear	

* RCT: Randomised controlled trials; PC: prospective cohort studies; CS: cross-sectional studies