Effectiveness of the Mediterranean diet in the elderly

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Abstract: The Mediterranean diet is known to be one of the healthiest dietary patterns in the world due to its relation with a low morbidity and mortality for some chronic diseases. The purpose of this study was to review literature regarding the relationship between Mediterranean diet and healthy aging. A MEDLINE search was conducted looking for literature regarding the relationship between Mediterranean diet and cardiovascular disease (or risk factors for cardiovascular disease), cancer, mental health and longevity and quality of life in the elderly population (65 years or older). A selection of 36 articles met the criteria of selection. Twenty of the studies were about Mediterranean diets and cardiovascular disease, 2 about Mediterranean diets and cancer, 3 about Mediterranean diets and mental health and 11 about longevity (overall survival) or mental health. The results showed that Mediterranean diets had benefits on risks factors for cardiovascular disease such as lipoprotein levels, endothelium vasodilatation, insulin resistance, the prevalence of the metabolic syndrome, antioxidant capacity, the incidence of acute myocardial infarction, and cardiovascular mortality. Some positive associations with quality of life and inverse associations with the risk of certain cancers and with overall mortality were also reported.

Keywords: Mediterranean diet, elderly, health, review

Introduction

According to the 2002 World Health Organization (WHO) health report, a diet poor in fruits and vegetable is the third preventable risk factor for chronic diseases (specific types of cancers, cerebrovascular diseases and ischemia) which have replaced infectious disease as the leading cause of morbidity and mortality in the world. The same report showed that among the twenty countries with the highest life expectancy in the world, four of them are Mediterranean countries (France, Italy, Spain, and Greece) (WHO 2001).

Mediterranean countries share a common dietary pattern first defined by Ancel Keys (Keys et al 1986) when he observed important geographical differences in the incidence rates of cardiovascular disease, certain cancers and other nutrition-related diseases that were mostly attributable to supposedly unhealthy food patterns whereas the Mediterranean dietary pattern was considered as the responsible factor for health advantages. Such pattern was the main focus of study in 1993 at the International Conference on the Diets of the Mediterranean, although the Mediterranean dietary pattern had been previously defined in other meetings (Helsing et al 1989; Serra Majem et al 1993; Nestle et al 1995; Willett et al 1995). Mediterranean dietary patterns are comprised of: abundant plant foods (fruits, vegetables, breads, other forms of cereals, pulses, nuts and seeds); minimally processed, seasonally fresh and locally grown foods; fresh fruits as the typical daily dessert with sweets elaborated from nuts, olive oil and concentrated sugars or honey that are consumed during feast days; olive oil as the principal source of dietary lipids; dairy products (mainly cheese and yoghurt) consumed in low to moderate amounts; fewer than four eggs consumed per week;

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red meat consumed in low frequency and amounts; wine consumed in low to moderate amounts, and generally taken with meals. Such a dietary pattern assures a sufficient intake of certain nutrients that have been related in some way with a reduced risk of several chronic diseases. Various scores or indexes have been developed to assess the adherence to the Mediterranean diet pattern in the population and to link such patterns with several nutrient-related diseases (Bach et al 2006).

There is increasing available evidence that following a Mediterranean style diet correlates to higher longevity and delays the onset of the deterioration in health, not only in countries from the Mediterranean Basin but in other non-Mediterranean countries as well (Kouris-Blazos et al 1999; Havenam-Nies et al 2003). However, what ageing people aspire for is not only longer life but also optimal quality of life free of disability or disease that implies being dependent on others. As higher self-rating of health is associated to reduced mortality not only among elderly people but among the general population as well (Idler and Benyamini 1997), identifying which factors contribute to manage healthy aging is key for increasing the percentage of the population who enjoys their longevity. In this context, the relevant question should be: does the Mediterranean diet have any relationship to better self-rated health?

The purpose of this article is to review literature regarding the Mediterranean diet and its effects on healthy aging.

Material and methods

A search of the MEDLINE databases was performed. The keyword "Mediterranean diet" or related term (Mediterranean diet score, Mediterranean dietary pattern) were included as a criterion search. As a second search the following words were included: "cardiovascular disease", "coronary syndrome", "dislipaemia", "blood cholesterol", "hypertension", "diabetes", "obesity", "overweight", "waist circumference", "metabolic syndrome", "inflammatory markers", "endothelial function", "cancer", "neurodegenerative diseases", "dementia", "depression", "Alzheimer disease", "mental health", "health", "longevity", "quality of life".

Only those studies which evaluate the Mediterranean diet as a dietary pattern where taken into account, excluding those which evaluated single food items or nutrients, although they pertain to the Mediterranean dietary pattern. Only studies which included individuals of 65 years or older at the starting point of the study were analyzed. We excluded studies that evaluated the effect of a single Mediterranean Diet meal on the subjects under study and studies conducted in animals. Additional publications were identified from references published in the original papers.

Results

A total of 39 publications were selected, three of them were rejected because they did not accomplish the criterion of inclusion regarding the disorders they investigated. All results are summarized in Table 1. Publications were classified into four groups according to the main outcome they assessed: cardiovascular disease (including risk factors such as high blood pressure, hypercholesterolemia, diabetes, obesity, the metabolic syndrome and inflammatory markers of cardiovascular damage), cancer, mental health (including dementia, Alzheimer's disease and depression) and longevity and quality of life.

Twenty-one of the studies were about Mediterranean diets and cardiovascular disease, 8 of them being clinical trials. Two of the publications were about Mediterranean diets and cancer, three about Mediterranean diets and mental health and 11 about longevity or mental health. Twenty-two of the publications showed results from Mediterranean countries (Italy, Spain, France, and Greece), 10 from non Mediterranean countries (United Kingdom, Canada, Australia, USA, Denmark, Germany, and The Netherlands) and 4 from multicenter studies in Europe and the United States.

An overwhelming majority of them were beneficial, with very little evidence of null findings and no evidence of harm in any study (Table 1).

Discussion

Since the Seven Countries study publication, an increasing number of studies have supported the beneficial role of the Mediterranean diet on health prevention. There is a rapidly growing recent trend of good-quality observational studies and trials assessing the cardioprotective role of Mediterranean diets (Martínez-González et al 2004). The present review focused on existing evidence for the role of the Mediterranean dietary pattern on aging, or better stated, on successful aging. Modern medicine has managed to add years to life but not to delay the onset of chronic diseases, which implies a greater prevalence of disabilities and dependent people who suffer from any one of the most prevalent chronic diseases. In fact, much of the health-care costs associated to aging are attributed not to chronic disease per se but to activity limitations and all that this represents (Chan et al 2002). The research was restricted to the most prevalent non-communicable diseases leading to disability in older individuals from developed

Table 1 Characteristics of selected studies about the effectiveness of the Mediterranean diet in the elderly

Author/year publication	Country	Type study	Population	Methodology	Outcome	Results
CVD						
Panagiotakos et al 2002	Greece	multicenter restrospective case-control study (CARDIO2000)	848 hospitalized patients (695 M, 58 ± 10 y; 153 F, 65 ± 9 y) a with first event of CHD; 1,078 controls (830 M, 58 ± 10 y; 248 F, 64.8 ± 9 y)	FFQ; 526 patients and 765 controls adopted the Mediterranean-type of diet	BP, TC, blood glucose, BMI	> adherence to the MD = reduction of the coronary risk factors (in hypertensive patients)
Scali et al 2001	France	cross-sectional	989 subjects (473 M, 491 F; 3 age groups: 20–34 y, 35–54 y, 55–76 y)	FFQ, MDQI	BMI	in subjects aged 55–75y, > adherence MDQI associated to < % obesity
Martinez-Gonzalez et al 2002	Spain	case-control study	342 subjects (171 first acute myocardial infarction: 81 M, 90 F; mean age 61.7; controls: 171)	FFQ, MDscore	BP, TC, blood glucose, BMI	> adherence to the MD = reduction of myocardial infarction risk factors
Singh et al 2002	UK	RCT, single blind	56 subjects (26 M, 30 F; range 57–80 y, mean age 67 ± 1) with average sitting BP: 134/78 ± 3/1 mmHg	6 w healthy "M-type" diet, 6 w vitamin C supplements, or 6w placebo	plasma vitamin C, % dilatation by BK, % dilatation by GTN	Increase in plasma vitamin C similar with supplements compared with a "healthy diet". Healthy diet: significant increase in BK-dependent vasodilatation vs placebo (p < 0.011). Healthy diet: significant differences between the 3 study groups in GTN-dependent relaxation (p < 0.011). MD improved vasodilatator function in the forearm of healthy older subjects whereas supplementation of vitamin C as tablets had no major effect. Acute intra-arterial vitamin C did not alter dilatation to BK or GTN. Treatment with healthy diet (but not oral vitamin C) improved endothelium-dependent (p = 0.043) and endtothelium-independent dilatation (p = 0.011)
Barzi et al 2003	Italy	clinical trial (GISSI-Prevenzione trial)	11,323 subjects with MI (M and F; aged 19–90 y, mean age 59 ± 10)	advice to adhere to the MD; visit and dietary assessment 6th, 18th and 42nd months, clinical visit; dietary questionnaire; diet-score	Association of food intakes (fish, fruit, raw and cooked vegetables and olive oil), a combined dietary score and risk of death	Compared with people in the worst dietary score quartile, odds ratio for people in best score was 0.51. ↑ consumption of each food was associated with ↓ risk of death. MI patients can respond positively to simple dietary advice, and this can be expected to lead to a substantial reduction in the risk of early death. Regardless of any drug treatment prescribed, clinicians should routinely advise patients with myocardial infarction to increase their frequency of consumption of Mediterranean foods

(continued)

Table I Continued

Author/year publication	Country	Type study	Population	Methodology	Outcome	Results
Ciccarone et al 2003	Italy	case-control study	T2DM patients: 144 with PAD (103 M, 41 F; <60 y n:36, 60–69 y n:60, >70 y n:48); 288 without PAD (206 M, 82 F; <60 y n:72, 60–69 y n:120, >70 y n:96)	FFQ, diet-score	BMI, glycated hemoglobin (HbA1c)	> adherence to the MD = significant reduction in PAD risk, independently of diabetes duration and hypertension
Pitsavos et al 2003	Greece	multicenter case-control study (CARDIO2000)	848 hospitalized patients (695 M, 58±10 y; 153 F, 65±9 y) with a first event of ACS	FFQ, NCEP ATPIII	blood pressure, cholesterol level, blood glucose, BMI	> adherence to the MD = reduction of the coronary risk factors (in metabolic syndrome patients)
Sondergaard et al 2003	Denmark	intervention study (unblinded 1-to-1)	131 patients (70 M, 61 F; 18 to 80 y; mean age 62.5 ± 9.9) with documented IHD	n:68 intervention group (received MD advice), n:63 control group (no specific dietary advice); all patients started statin treatment with Fluvastatin at baseline; 24-hour recall	FMD, serum lipids, liver transaminases, blood glucose, TSH-samples every third month at regular clinical control session	improvement in FMD (p < 0.01) in the intervention group vs control (after 12 months); no differences in the arterial diameter or in the nitroglycerin response (NMD); LDL cholesterol levels p < 0.001 for the reduction in both of groups; triglyceride level p < 0.05 only in intervention group; unchanged in both of groups HDL-cholesterol
Fung et al 2005	USA	Nurse's Health Study	690 F, 43–69 y without cardiovascular disease, diabetes or cancer at the time blood was drawn	FFQ, HEI, AHEI, DQI-R, RFS, aMED, blood sample	BMI; CRP, IL-6, E-selectin, sICAM-I, sVCAM-I	> scores of HEI, AHEI, DQI-R = lower BMI. > AHEI and aMED scores = reduction in biomarker concentrations (CRP, IL-6, E-selectin)
Panagiotakos, Pitsavos, Matalas et al 2005	Greece	multicenter case-control study (CARDIO2000)	848 individuals (700 M, 59 ± 10 y; 148 F, 65 ± 9 y); 1078 controls	FFQ	BP, TC, blood glucose, BMI	inverse association between adherence to the MD and prevalence of hypertension, hypercholesterolemia (in both patients and controls)
Panagiotakos, Pitsavos, Chrysohoou et al 2005	Greece	cross-sectional study	3,042 subjects (1514 M, 1528 F; 18–89 y). Diabetes Mellitus: 118 M (7,8%), 92 F (6,0%); >65 y M 32 (25,4%), F40 (31,0%)	FFQ, MD score	fasting glucose, TC, LDL-C, HDL-C, TG, waist circumf.	> adherence to the MD = significantly lower odds of having diabetes. Age was associated to > diabetes; participants with diabetes: ↑obesity, ↑BMI, ↑WHR, ↑BP, ↑TC, ↑LDL-C, ↑TG, ↑hypercholesterolemia. A 10-unit increase in the diet score was associated with 21% lower odds of diabetes
Polychronopoulos et al 2005	Greece	cohort study	150 subjects, 65–100 y (53 M, 79 ± 8 y; 97 F, 75 ± 7 y)	FFQ, MD score	TCl, LDL, HDL, TG	inverse association between hypercholesterolemia, alcohol drinking and the adherence to MD

Serrano-Martinez M[49], 2005	Spain	case-control study	24 patients (14 M, 10 F; 61.4 ± 12.6 y) with unstable angina	FFQ, MD score, blood sample	TNF-alpha, VCAM-1	MED-diet score was inversely associated with the TNF-alpha and VCAM-1. MD may protect against coronary artery wall production of inflammatory mediators
Trichopoulou, Orfanos et al 2005	Greece	Cohort study (EPIC-Greece)	23,597 adults (M,F), aged 20–86 y	FFQ, MD score	BMI	adherence to MD was unrelated to BMI in both sexes and was weakly related to WHR only in women
Estruch et al 2006	Spain	Substudy of a multicenter, randomized, clinical trial of CVD (PREDIMED study)	772 asymptomatic subj. (M and F; 55–80 y)	3 groups: low-fat diet – group; 1 MD + 1 liter/week of olive oil; 2 MD + 30 g/d nuts + nutritional education	BP; CRP, IL–6, ICAM-1, VCAM-1	1MD and 2MD vs Low fat diet = < CRP (only 1MD), IL–6, ICAM-1, VCAM-1. MD have beneficial effects on cardiovascular risk factors
Álvarez Leon et al 2006	Spain	cross-sectional study	578 subjects (249 M, 329 F; aged >18 y)	NCEP ATPIII definition of MS, FFQ, anthropometric variables, BP	HOMA index, MD score	MD adherence was not related to MS prevalence, but subjects in the third tertile of adherence presented 70% lower prevalence of the blood pressure criteria and 2.5 times more prevalence of the glycaemia criteria with respect to the first tertile
Michaelsen et al 2006	Germany	clinical trial	101 patients (59.4 ± 8.6 y, 23% F) with established and treated CAD (80% statins)	48 subjects MD (1y programme of 100h of education); 53 subjects diet rich in ALA, PUFA, MUFA and low in SFA (written advice-only)	hs-CRP, fibrinogen, homocysteine, fasting insuline, HDL-C, LDL-C, TC, TG	MD has no effect on markers of inflammation and metabolic risk factors (hs-CRP, fibrinogen, homocysteine, fasting insulin, HDL-C, LDL-C, TC, TG)
Panagiotakos, Chrysohoou et al 2006	Greece	Greek Study of ACS (the GREECS)	2172 patients (1,649 M, 65 ± 13y; 523 F, 72 ± 11 y) with a discharge diagnosis of ACS	FFQ, MD score, blood sample	troponin I, creatine phosphokinase, creatine phosphokinase-MB, BP, TC, blood glucose, BMI	inverse correlation between Med-diet score with troponin I, creatine phosphokinase, creatine phosphokinase-MB. MD habits seems to be associated with lower severity of coronary heart disease
Fitó et al 2007	Spain	randomized controlled trial (cross-sectional analysis Substudy of PREDIMED Study)	372 subjects (162 M, 210 F; 55–80 y) with high cardiovascular risk	low fat diet (n: 121) or one of 2 TMDs (TMD + virgin olive oil, 1 L/wk or TMD + nuts, 30 g/d)	oxidative stress markers (oxidized LDL levels), MDA, serum glutathione peroxidase activity	decreased oxidized LDL levels in TMD with olive oil and in TMD with nuts, no change in Low-Fat diet; malondialdehyde changes in mononuclear cells paralleled those of oxidized LDL. No changes in serum glutathione peroxidase activity were observed
Salas-Salvadó et al 2007	Spain	cross-sectional analysis (Substudy of PREDIMED Study)	772 subjects, 55–80 y (339 M, 67.6 ± 6.5; 433 F, 69.8 ± 6.2) with T2DM and 3 or more CHD risk factors	FFQ, blood sample	CRP, IL-6, ICAM-1, VCAM-1	> adherence to the MD = did not show significantly lower concentrations of inflammatory markers (p < 0.1 for VCAM-I and ICAM-I). > consumption of fruits and cereals = lower concentrations of IL-6. > consumption of nuts and virgin olive oil = lowest concentrations of VCAM-I, ICAM-I, IL-6 and CRP; albeit only for ICAM-I was this difference statistically significant in the case of nuts (for trend 0.003) and for VCAM-I in the case of virgin olive oil (P for trend 0.02)

Table 1 *Continued*

Author/year publication	Country	Type study	Population	Methodology	Outcome	Results
Cancer						
Bosetti et al 2003	Italy	case-control studies (3)	1 = 598 patients with cancer of the oral cavity and pharynx, aged <78 y (512 M, 86 F), 1,491 hospital controls (1,008 M, 483 F); 2 = 304 patients with squamous cell carcinoma of the esophagus, aged <77 y (275 M, 29 F), 743 hospital controls (593 M, 150 F); 3 = 460 patients with squamous cell carcinoma of the larynx, aged <79 y (415 M, 45 F) 1,088 hospital controls (863 M, 225 F)	FFQ, MD score	OR	for all cancers considered: a reduced risk was found for increasing level of the MD score; > risk for cancers of the upper aerodigestive tract for no or high consumption of alcohol, high meat and meat products intake; < risk (estimates were not always significant) for high intake of monounsaturated/saturated fat ratio, vegetables
Nkondjock and Ghadirian 2007	Canada	case-control studies	280 subjects (30 M, 250 F; 56.2 ± 11.5 y) from 80 French-Canadian families. Each family had at least 3 cases of BC (diagnosed at <65 y), epithelial ovarian cancer or male BC. 100 subjects control, never had BC (F, 51 carriers, 49 non-carriers of a deleterious mutation in the BRCA gene)	FFQ, DQI-R, AHEI, aMED, CHEI	OR	no detected any association between the AHEI or aMED and BC. Strong and significant inverse relationship between DQI-R and CHEI and BRCA-associated risk

Mental Health

Reference	Country	Study design	Subjects	Methods	Outcome	Results
Scarmeas, Stern, Tang et al 2006	USA	Cohort study (participants of 2 related cohorts recruited in 1992 and 1999 WHICAP)	2,258 community-based nondemented individuals, (nondemented n = 1,964, 77.2 ± 6.6 y; during 4 y of follow-up incident AD n = 262)	FFQ, 7-day food records, MD score	DSM-III-R for the diagnosis of dementia; criteria of the NINCDS-ADRDA for diagnosis of probable or possible AD	> adherence to the MD = lower risk for AD (each additional unit of the MD score was associated with 9 to 10% less risk for development of AD)
Scarmeas, Stern, Mayeux et al 2006	USA	Cohort study (participants of 2 related cohorts recruited in 1992 and 1999 WHICAP)	1,984 subjects (non-demented n = 1,790, prevalent AD n = 194), 76.3 ± 6.6 y	FFQ, 7-day food records, MD score, BP, history hypertension, TC, HDL-C, TG, LDL-C	DSM-III-R for the diagnosis of dementia; criteria of the NINCDS-ADRDA for diagnosis of probable or possible AD	> adherence to the MD = lower risk for AD, this association does not seem to be mediated by vascular comorbidity
Solfrizzi et al 2006	Italy	Prospective study Italian Longitudinal Study on Aging (ILSA) (5,632 subjects 65–84 y, free-living or institutionalized)	278 free-living elderly subjects (154 M, 124 F; 65–84 y, 73.01 ± 5.52 y)	FFQ	intake MUFA, PUFA; MMSE	adherence to the MD (high MUFA and PUFA intakes) appeared to be protective against ARCD

Longevity

Reference	Country	Study design	Subjects	Methods	Outcome	Results
Trichopoulou et al 1995	Greece	Cohort study 2 y follow-up	182 subjects, (91 M, 91 F; >70 y, 53 died, survivors, mean age 75.4 y)	FFQ, 24h diet recall, MD score	overall mortality	> adherence to the MD: 17% reduction in overall mortality
Osler and Schroll 1997	Denmark	cohort study longitudinal study (part of the Euronut SENECA study)	202 subjects, (101 M and 101 F) (52 died); survivors 150 subjects (73 M, 53 F), mean age 72 y	3-day estimated record and a frequency checklist of foods; MD score; blood sample	TC, LDL-C, HDL-C	> adherence to the MD = reduction in overall mortality; > adherence to the MD = significantly higher plasma carotene levels. Low score and plasma carotene was negatively associated with mortality
Kouris-Blazos et al 1999	Australia	prospective cohort study	330 subjects (M, F), 189 greek-australians, 141 anglo-celts; >70 y, 70–85 + y	FFQ, MD score	Mortality rate ratio	A one unit increase in a diet score was associated with a 17% reduction in overall mortality. Mortality reduction with increasing diet score was evident in both greek-australians and anglo-celts
Lasheras et al 2000	Spain	Cohort study	161 volunteers (49 M, 112 F), 65–95 y	FFQ, MD score	BMI	adherence to the MD in elderly subjects aged <80 y: reduction in overall mortality (31%); but not in subjects aged >80 y (not have any available evidence)

Table 1 *Continued*

Author/year publication	Country	Type study	Population	Methodology	Outcome	Results
Trichopoulou et al 2003	Greece	population-based, prospective investigation (EPIC, Greece (1994–1999)	22,043 participants, 20–86 y, (5028, 55–64 y; 4369, >65 y)	FFQ, MD score	overall mortality	> adherence to the MD = significant reduction in total mortality among participants 55 y of age or older but not among participants younger than 55 y
Knoops et al 2004	multicenter study (11 European Countries)	Healthy Aging: a Longitudinal study in Europe population (HALE); SENECA and FINE	1,507 M, 832 F, 70–90 y; SENECA (M 781.73 ± 2.0 y; F 832.73 ± 1.8 y); FINE (M 726, 77 ± 4 y); (935 died)	FFQ, MD score	ten-year mortality from all causes, coronary heart disease, cardiovardiovascular diseases, and cancer	In individuals aged 70–90 y, > adherence to the MD and healthful lifestyle = 50% lower rate of all-causes and cause-specific mortality
Trichopoulou et al 2005	multicenter, prospective cohort study (9 European Countries)	European Prospective Investigation into Cancer and Nutrition-elderly	subjects 74,607 (M, F), > 60 y	FFQ, records of intake over 7 or 14 days, MD score modified (relying on plant foods and unsaturated lipids)	death from any cause	> adherence to the modified MD = reduced overall mortality
Waijers et al 2006	Netherlands	Cohort study, European Prospective Investigation into Cancer and Nutrition-elderly	5,427 F, 60–69 y	FFQ, 24 h diet recall	3 major principal components: a Mediterranean-like dietary pattern, traditional dutch dinner dietary pattern, healthy traditional dietary pattern	the healthy traditional dutch diet rather than a MD appears beneficial for longevity and feasible for health promotion in older Dutch women
Quality of life						
Haveman-Nies et al 2001	multicenter-study (USA and Europe)	Framingham Heart Study (USA) and European SENECA study	828 subjects (Framingham study) + 1,282 subjects (SENECA) 70–77 y	FFQ, MD score, HDI	Albumin, Haemoglobin, Waist circum., BMI	no association between HDI and Med diet score and albumin and haemoglobin. < score of HDI and MD score = > Waist circum., BMI
Haveman-Nies et al 2003	multicenter-study (Europe)	SENECA study (Survey in Europe on Nutrition and the Elderly: a Concerted Action)	1,091 M, 1,190 F; 70–75 y	FFQ, MD score	health staus measures and lifestyle indicators	high-quality diet (MD), physical activity, non-smoking were related to survival in elderly Europeans

| Stathakos et al 2005 | Greece | Nationwide study | 489 individuals (113 M, 376 F, 101.0 ± 2.0 y) | questionnaire for health disorders, anthropometric characteristics, activity of daily living, degree of autonomy, nutritional habits | health and functional assessment | most of greek centenarians adhere to the TMD. 19% dementia, 6% T2DM, 4% medical record of cancer |

Abbreviation: ACS, acute coronary syndrome; AD, Alzheimer Disease; AHEI, Alternate Healthy Eating Index; aMED, alternate Mediterranean Diet Index; ApoB, Apo lipoprotein B; ARCD, Age-Related Cognitive Decline; BC, Breast Cancer; BK, Bradykinin; BMI, Body Mass Index; BP, Blood Pressure; CAD, Coronary artery Disease; CHD, Coronary Heart Disease; CHEI, Canadian Healthy Eating Index; CRP, C-reactive protein; CVD, Cardiovascular Disease; DAS28, Disease Activity Score; DQI-R, Diet Quality Index-Revised; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition; EC50, 50% Effective Concentration; FFQ, Food Frequency Questionnaire; FMD, Flow Mediated Vasodilatation; GTN, Glyceryl-trinitrate; HAQ, Health Assessment Questionnaire; HbA1c, glycated haemoglobin; HDI, Healthy Diet Indicator; HDL-C, HDL Cholesterol; HEI, Healthy Eating Index; HOMA index, Homeostasis Model Assessment index; ICAM-1, Intracellular Adhesion Molecule-1; IHD, Ischemic Heart Disease; IL-6, Interleukin-6; LDL-C, LDL Cholesterol; MD, Mediterranean Diet; MDA, Malondialdehyde; MDQI, Mediterranean Diet Quality Index; MDscore, Mediterranean Diet score; MI, Myocardial Infarction; MMSE, Mini-Mental State Examination; MS, Metabolic Syndrome; MUFA, Monounsaturated Fatty Acids; NCEP ATPIII, National Cholesterol Education Program's Adult Treatment Panel III; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; NMD, Nitroglycerin-Mediated Dilatation; NSAID, Non-Steroidal Anti-Inflammatory Drugs; OR, Odds ratio; ORP, Outpatient based Rehabilitation Programme; PAD, Peripheral Arterial Disease; PUFA, Polyunsaturated Fatty Acids; RCT, Randomized Clinical Trial; RFS, Recommended Food Score; SFA, Saturated Fatty Acids; SF36, Short Form-36 Health Survey; sICAM-1, soluble Intercellular Cell Adhesion Molecule; sVCAM-1, soluble Vascular Cell Adhesion Molecule; TC, Total Cholesterol; TG, Tryglicerides; TNF-alpha, Tumor Necrosis Factor; TMD, Traditional Mediterranean Diet; T2DM, Type 2 Diabetes Mellitus; VCAM-1, Vascular Adhesion Molecule-1; VLDL-C, VLDL Cholesterol.

countries (cardiovascular diseases, certain types of cancer and neurodegenerative diseases) (Lopez et al 2006).

Referring to cardiovascular diseases, the review showed that the Mediterranean diet might exert some effect not only through its impact on the principal risk factors for such diseases but also on the severity of the disease once it appears. Several observational studies (Psaltopoulou et al 2004; Polychronopoulos et al 2005; Panagiotakos, Pitsavos, Chrysohoou, et al 2005; Panagiotakos, Pitsavos, Matalas, et al 2005; Fung et al 2005; Serrano Martinez et al 2005; Panagiotakos et al 2006) and intervention studies (Singh et al 2002; Sondergaard et al 2003; Fitó et al 2007; Salas-Salvadó et al 2007) have associated the Mediterranean diet pattern to lower levels of blood pressure, blood cholesterol, diabetes, inflammation and improved coagulation process and endothelial function, even in individuals with diabetes (Ciccarone et al 2003) or the metabolic syndrome (Pitsavos et al 2003; Álvarez León et al 2006). Recently, a cross sectional study conducted in Cyprus reported that individuals from 65 to 100 years with a higher adherence to the Mediterranean diet showed lower levels of blood cholesterol even among those treated with statins (Polychronopoulos et al 2005). Moreover, certain observational studies showed that the severity of acute coronary syndrome in hospital death and rehospitalization (the GREECS study, in males aged 65 and women aged 72 years) and the likelihood of having acute coronary syndromes (the CARDIO2000 study, in individuals from 61 ±10 years) were lower among individuals following a Mediterranean style diet (Martínez-González et al 2002; Panagiotakos et al 2005; Panagiotakos et al 2006). These results were in accordance with the findings reported by Lorgeril in the Lyon Heart study or by Barzi in the GISSI Prevezione trial (de Lorgeril et al 1999; Barzi et al 2003). The PREDIMED study, a primary prevention trial conducted in samples of elderly individuals showed that after three months of following a Mediterranean Diet, individuals improved their lipid profile and reduced blood concentrations of inflammatory molecules (Estruch et al 2006; Fitó et al 2007).

With respect to obesity, although some observational and prospective studies in younger individuals (Schroder et al 2004; Mendez et al 2006; Panagiotakos et al 2006) reported an inverse relationship with adherence to the Mediterranean diet and BMI and obesity, Trichopoulou's data of older individuals from the EPIC study (Trichopoulou et al 2005b) and the SUN prospective cohort (Sanchez-Villegas et al 2006) found lower BMI among subjects more adherent to the Mediterranean diet but they did not show any independent significant relationship. In a study comparing

individuals from the Framingham and the SENECA study, a lower waist circumference and BMI were reported in individuals representing high dietary quality not only for the Mediterranean diet but also for scores evaluating other types of dietary patterns (Havenam-Nies et al 2001). A cross sectional study conducted in France with a small sample showed that, especially among older individuals, a poor qualification of the Mediterranean Diet Quality index was associated to a higher prevalence of obesity (Scali et al 2001). These results were corroborated in the PREDIMED study, which demonstrated that the intervention did not imply an increase in body weight of participants (Estruch et al 2006). Recent clinical trials have reported benefits of the Mediterranean diet for several aspects of factors related to the incidence or prognosis of cardiovascular disease in individuals with given risk factors such as the diabetic population (Rodriguez Villar et al 2004; Antonopoulou et al 2006), even when relatively high dietary fat content and unrestricted salt intake were permitted.

The metabolic syndrome, a constellation of risk factors for cardiovascular disease, has also been related to the Mediterranean diet, but not without a certain degree of controversy. Data from a cross sectional study in the Canary Islands in Spain revealed that higher adherence to the Mediterranean diet was not related to a lower prevalence of metabolic syndrome (Álvarez et al 2006). Another cross-sectional study with data from five Mediterranean countries showed no relationship between the Mediterranean diet and the prevalence of the metabolic syndrome (Thanopoulou et al 2006), although a randomized clinical trial from Esposito (Esposito et al 2004) showed that after two years of intervention following a Mediterranean diet, a sample of middle age individuals had reduced the prevalence of metabolic syndrome, inflammatory markers and insulin resistance had declined and endothelial function had improved. On the contrary, another intervention study conducted in Germany showed no impact of adoption of the Mediterranean diet on inflammatory and metabolic risk markers in a sample of patients with coronary artery disease (Michaelsen et al 2006), results that some authors attribute to the study design or the effect the Mediterranean diet had on plasma fatty acid concentrations (Serrano-Martínez and Martínez-González 2007). Moreover, the PREDIMED study did not show a statistically significant relationship between a higher Mediterranean diet score and lower inflammatory biomarkers in the baseline cross-sectional assessment (Salas et al 2007). However, these markers of inflammation significantly improved with the Mediterranean diets after three

months of intervention (Estruch et al 2006). There are no cohort studies of Mediterranean diets assessing the incidence of the metabolic syndrome as the outcome.

Adiponectin, a beneficial adipose tissue–secreted cytokine, has been shown to improve insulin sensitivity, to regulate glucose and lipid metabolism, and to have pronounced antiatherosclerotic effects. The levels of circulating plasma adiponectin have been reported to be positively associated with the adherence to a Mediterranean-type dietary pattern among diabetic women (Mantzoros et al 2006).

The role that the Mediterranean diets may have on cancer prevalence has been studied for breast cancer and upper aerodigestive tract cancer. In a cohort of Canadian individuals with a family history of breast cancer or ovarian cancer, no significant association was found between adherence to a Mediterranean diet pattern and risk of BRCA mutation-related breast cancer (Nkondjock and Ghadirian 2007). As the authors stated, alcohol consumption linked to the Mediterranean dietary pattern may have had some effect on such results. On the contrary, data from three case-control studies in Italy showed a reduced risk of cancer of the oral cavity and pharynx, esophagus, and larynx for increasing levels of the Mediterranean diet score (Bosetti et al 2003). In addition, a four year follow-up of the Lyon Heart study showed a protective effect of the Mediterranean diet for certain cancers (de Lorgeril 1998).

Greater adherence to Mediterranean Diet has been related to improved mental depression, age related cognitive decline and Alzheimer's disease. Age related cognitive decline has recently been defined as an objective decline in cognitive functioning associated to aging but within the normal limits according to the person's age. Although defined as a normal process, its progression may be prevented. The Mediterranean dietary pattern may exert its effects on mental health through different mechanisms: ensuring an adequate intake of B vitamins, folate, and ω-3 fatty acids, which are all involved in the synthesis of certain central nervous system neurotransmitters and phospholipids. In addition, other favorable factors include its effect on vascular mechanisms (lowering certain risk factors such as hypertension, dyslipemia and diabetes or assuring lower homocysteine levels) through its antioxidant properties.

The relationship between Alzheimer's disease and nutrients are being widely explored (Solfrizzi et al 2003; Luchsinger and Mayeaux 2004) but little data on the relationship with the Mediterranean diet is available. Data from the Washington Heights-Inwood Columbia Aging Project in a non

Mediterranean population showed that higher adherence to the Mediterranean diet was associated with a reduction in the risk for Alzheimer's disease and a slower cognitive decline, in a dose-response manner, taking into account other confounding factors for Alzheimer's disease (Scarmeas, Stern, Mayeux, et al 2006; Scarmeas, Stern, Tang, et al 2006). After almost nine years of follow up, the Italian Longitudinal Study on Aging showed that a diet high in monounsaturated and poly-unsaturated fatty acids was associated with better cognitive performance in elderly individuals following a typical Mediterranean diet (Solfrizzi et al 2006).

Depression is known to be the leading cause of years of life lived with disability especially among females (López et al 2006). Few studies have related such disorders with Mediterranean diet adherence. The SUN (Seguimiento Universidad de Navarra) study, a prospective cohort study that analyzed the relationship between dietary intake and some chronic diseases reported an inverse association between vitamin B_{12} and ω-3 fatty acids intake and depression among women, and folate intake and depression among men (Sanchez Villegas 2006).

Studies developed in Mediterranean countries (Trichopoulou et al 1995; Lasheras et al 2000; Trichopoulou et al 2003) and non-Mediterranean countries (Osler and Schroll 1997, Kouris-Blazos et al 1999) have shown a decrease in overall mortality in relation to a high score evaluated by various types of Mediterranean diet indexes. Some of the studies had small samples (Trichopoulou et al 1995; Osler and Schroll 1997, Kouris-Blazos et al 1999; Lasheras et al 2000), whereas others had large samples of the population (Trichopoulou et al 2003). The studies showed that a one point increment in the diet score was associated with a percent reduction in total mortality that ranged from 17% (Trichopoulou et al 1995, Kouris Blazos et al 1999) to 31% (Lasheras et al 2000) and that a two point increase in such a score reduced overall mortality by 25% (Trichopoulou et al 2003). Although the protective effect has been shown to be stronger for individuals older than 55 years, some authors reported benefits in young women as well (Lagiou et al 2006). Data from the SENECA and FINE studies conducted in Europe also showed that a Mediterranean diet score of 4 or more was associated with a lower risk of all-cause mortality (Havenam-Nies et al 2003; Knoops et al 2004). Moreover, a modified Mediterranean diet score developed to take into account the different patterns in the use of added lipid in northern European countries showed that a two unit increment corresponded to an 8% reduction in overall mortality (Trichopoulou et al 2005). When evaluating the role the Mediterranean diet had on overall mortality in individuals suffering from a previous myocardial infarct, a higher adherence to Mediterranean diet was also associated to lower overall mortality (Trichopoulou et al 2005; Iestra et al 2006). In a recent nationwide study on Greek centenarians, the participants reported following a typical Mediterranean diet (Stathakos et al 2005). On the other hand studies conducted in non Mediterranean countries reported that their own healthy traditional diet was more accurate to predict longevity than a Mediterranean style diet (Waijers et al 2006).

The results found in this review support the role investigators have attributed to the Mediterranean diet. Unfortunately, although the number of publications about the Mediterranean diet and its health benefits is increasing (Serra-Majem et al 2006), the adherence to such dietary pattern is declining, even in the heart of the area where the Seven Countries study was conducted (Kafatos et al 1997). As Barzi et al (2003) remarks, when simple dietary advice adopted as therapeutic clinical intervention yields the type of results seen in the GIZZI study, such advice should be translated into dietary guidelines and should be addressed not only to coronary patients but to the entire population, especially when such an intervention is as cost-effective as demonstrated (Dalziel et al 2006). Otherwise, such efforts are naught as there will be no application of the findings in terms of what component/s of the Mediterranean diet is/are responsible for the health effects of such a dietary pattern.

Acknowledgments

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