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ORIGINAL COMMUNICATION

Mediterranean diet and all-causes mortality after myocardial infarction: results from the GISSI-Prevenzione trial

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Objective: To ascertain whether simple dietary advice to increase the consumption of Mediterranean foods, given in a clinical setting, leads to reduced mortality after a myocardial infarction.
Design: Data were used from the GISSI-Prevenzione clinical trial, analysed as a cohort study with adjustment for treatment allocation.
Setting: A total of 172 centres in Italy.
Subjects:A total of 11 323 men and women with myocardial infarction. All subjects received advice to increase their consumption of fish, fruit, raw and cooked vegetables and olive oil.
Measurements: The intakes of the five foods were assessed at baseline, 6, 18 and 42 months. Associations of food intakes, a combined dietary score, and the risk of death over 6.5 y were estimated adjusting for several non-dietary variables, using pooled logistic regression.
Results: Subjects generally improved their diet according to the advice given. All foods were associated with a significant reduction in risk of death. Compared with people in the worst dietary score quarter, the odds ratio for those in the best score quarter was 0.51 (95% CI 0.44–0.59). A good diet had a protective effect in sub-groups defined by age, sex, smoking, randomized treatment and concomitant drug therapy.
Conclusions: Myocardial infarction 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.
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Keywords: Mediterranean diet; antioxidants; mortality; repeated measurements

Introduction

In the Mediterranean region of Europe the incidence of coronary heart disease is much lower than in northern Europe, and it has been suggested that this may be due, in part, to dietary factors (Sans *et al*, 1997). Despite variations, the Mediterranean diet is characterized typically by the use of olive oil, as the principal source of fat, by an abundance of fruit and vegetables and by a moderate consumption of fish.

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A considerable number of large epidemiological studies have shown that specific nutrients in foods, such as dietary fats, antioxidants and fibre, are important determinants of cardiovascular disease risk (eg Rimm *et al*, 1993,1996; Stampfer *et al*, 1993; Khaw & Barrett-Connor 1987a,b; Knekt *et al*, 1994; Ness & Powles 1997; Hu *et al*, 1997; Todd *et al*, 1999). In these studies, diets that were low in saturated fat but rich in polyunsaturated fat, fruit and vegetables had significantly reduced risks of cardiovascular events.

Despite the extensive epidemiological evidence that the Mediterranean diet is healthy, there remains doubt, largely because of the lack of supporting evidence from clinical trials such as the HOPE Study (HOPE Study Investigators, 2000) and the Heart Protection Study (MRC/BHF Heart Protection Study Collaborative Group, 1999). Also, there remains doubt as to whether patients with existing cardiovascular disease can, and will, act on advice given by physicians to change to a more healthy diet that is rich in Mediterranean foods. In the GISSI-Prevenzione study, patients surviving a recent myocardial infarction were given simple dietary advice, in a clinic setting, aimed at strengthening and improving the positive characteristics of the Mediterranean diet (GISSI-Prevenzione Investigators, 1999). The large database of this study provides an excellent medium to assess response to dietary advice, the long-term maintainability of improved dietary habits and the impact of food items typical of the Mediterranean diet on the risk of all-cause mortality.

Methods

The GISSI-Prevenzione study was a clinical trial designed to test the benefits of vitamin E (300 mg daily) and n-3 polyunsaturated fatty acid supplementation (1 g daily) among patients surviving recent (3 months or less) myocardial infarction. The study was initiated in October 1993 and the last patient was recruited in September 1995. Altogether, the 172 participating centres across Italy recruited 11 323 men and women, aged between 19 and 90 y. The study design, eligibility criteria of participants, data collection and follow-up procedures have been described elsewhere (GISSI-Prevenzione Investigators, 1999). To be eligible for inclusion, subjects had to be without unfavourable short-term prognosis, allergy to fish oil, mental or physical disorders likely to affect compliance to treatment and known coagulation defects. In addition to allocation of treatment (according to an open-label, four-arm design), each patient received standard secondary prevention advice, including aspects of diet. Patients were followed up for 3.5 y, by means of clinical visits; vital status was ascertained up to 6.5 y from baseline, through contact with census offices.

Dietary intervention

A short leaflet describing, in simple language and pictures, the main tenets of correct lifestyle and dietary habits was given to GISSI-Prevenzione patients. The leaflet was designed to be easily understandable and practicable, and therefore was based on foods, rather than nutrients. In particular, suggestions as to the foods to be preferred (such as a variety of fruit and vegetables and grain products, including whole grains, and fat-free and low-fat dairy products, fish, legumes, poultry and lean meats) or limited (such as foods containing significant amount of animal fat) were given to all the patients. Emphasis was placed on the importance of increasing the use of olive oil, accompanied by as low an intake as possible of butter and of other vegetable oils.

Dieatary assessment

Dietary information was obtained at the randomization (baseline) visit and at the 6th, 18th and 42nd months of follow-up. A simple dietary questionnaire, which recorded frequency of consumption of fish, fruit, raw vegetables, cooked vegetables and olive oil, was administered at randomization to describe the long-term dietary exposure of individual patients before the index myocardial infarction. At the follow-up visits, frequencies of consumption at the current time were recorded. Each food was coded on a four-point ordinal scale from least to most frequent consumption: categories are shown in Figure 1.

Statistical methods

In this article the data are analysed using methods appropriate to cohort studies (Woodward, 1999), taking the treatment allocation during the trial as a confounding variable. The level of exposure to any one of the five foods was calculated by a cumulative average, weighted by the time period between follow-up visits, so as to take account of both former dietary habits (before the index myocardial infarction) and changing food consumption (subsequent to the myocardial infarction; Hu *et al*, 1999; Stampfer *et al*, 2000). This process is expressed mathematically in Appendix I.

Pooled logistic regression (Cupples *et al*, 1988; Allison, 1995) was used to estimate odds ratios for death, over the entire period of follow-up, for each individual food after adjustment for non-dietary potential confounding factors at baseline, and also after additional adjustment for all other food exposures. Based on previous analyses of the data (Marchioli *et al*, 2001), the non-dietary variables used were sex, smoking, hypertension, diabetes, claudication, electrical instability, left ventricular dysfunction, ischaemia, use of aspirin, angiotensin-converting enzyme inhibitors and β-blockers, the four-arm allocation of experimental drugs, HDL-cholesterol (grouped into four equal-sized categories) and age.

An overall dietary score, on a scale from 0 to 10, was derived from the regression coefficients of the full model with all food exposures and all non-dietary confounders. Odds ratios were calculated for a 1 unit increase, corresponding to a 10% rise, in this score. Individuals were classified for overall quality of diet (poor/moderate/good/very good)

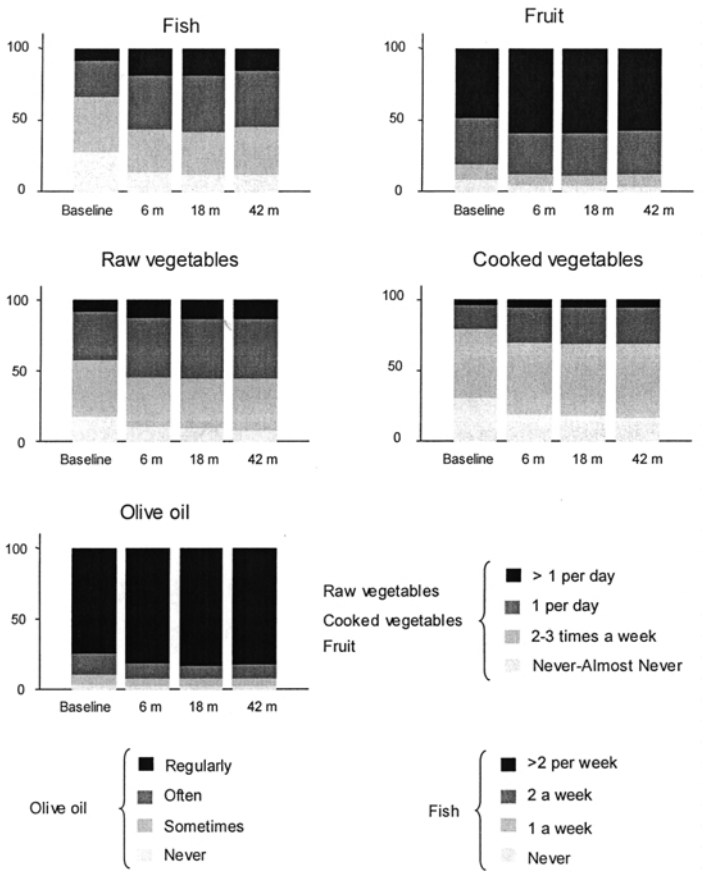

Figure 1 Percentage distribution of food frequencies, as recorded at baseline and 6, 18 and 42 months follow-up

according to increasing quarters of the score. Tests for heterogeneity were carried out by adding, to the regression model, interaction terms between the score and each of the non-dietary variables (Woodward, 1999).

Results

Of the 11 323 patients randomized to the clinical trial, 77 had missing dietary information at all visits and were excluded from this analysis. Of the remaining 11 246, 71.0% completed all five items on all four food frequency questionnaires. Those who failed to complete the questionnaires were similar to the rest except that they were more likely to be smokers and less likely to use aspirin, angiotensin-converting enzyme inhibitors and β-blockers. All the foods investigated here were fairly popular even before the index myocardial infarction, especially olive oil, which was consumed regularly by 75% of subjects. Dietary habits changed rapidly subsequent to myocardial infarction, with an increased consumption of all five foods (Figure 1). For example, whilst 31% declared that they never ate cooked vegetables prior to their myocardial infarct, only 20% made the same statement 6 months after baseline. For the remainder of the study, consumption of all five foods remained stable.

Table 1 shows the relationships between the average quality of diet over the study as a whole and a range of baseline variables. Subjects with better diets were less likely to be current smokers: 49% of those with the worst diets were smokers compared to 36% in the best diet group. People with better diets were more likely to be randomized more than 1 month after the index myocardial infarct and to be treated with aspirin and beta-blockers at baseline.

The subjects were followed up for 60 008 person-y, during which time there were 1660 deaths. Increasing frequency of consumption of each food, on average over the whole study, was associated with a decreased risk of death, after adjusting for the non-dietary variables considered to be potential confounders (Table 2). For example, for raw vegetables the odds ratios were 0.77 (95% CI 0.66–0.90), 0.60 (95% CI 0.51–0.70) and 0.54 (95% CI 0.43–0.69) for 2–3 times per week, once per day and more than once per day, compared with never eaten. Fish, fruit and cooked vegetables each had similar, very slightly less extreme, odds ratios. For olive oil there were too few in the category of 'never consumed' to make a meaningful analysis possible. Consequently the

Table 1 Characteristics of subjects at baseline, overall ($n = 11\,246$) and by average quality of diet[a] (in four equal-sized groups) over the entire course of the study

	Quality of diet				
Variable	*Poor*	*Moderate*	*Good*	*Very good*	*Total*
	Percentage of patients				
Male sex	84	86	87	86	85
Time since index MI $\geq$ 31 days	25	27	29	33	28
Arterial hypertension	35	35	34	37	35
Diabetes mellitus	14	15	14	15	15
Intermittent claudication	4	4	4	4	4
Smoking status					
Non-smokers	20	21	22	25	22
Ex-smokers	31	33	36	39	35
Current-smokers	49	45	42	36	43
Complication after MI					
Electrical instability	17	16	15	17	17
Left ventricular dysfunction	21	21	20	18	18
Residual myocardial ischemia	47	51	52	47	47
Pharmacological therapy					
Aspirin	79	80	80	80	80
Anti-platelet therapy	92	92	92	92	92
ACE-inhibitors	45	47	48	46	47
Beta-blockers	43	45	45	46	44
Experimental drugs					
n-3 PUFA	25	25	25	26	25
Vitamin E	25	26	25	25	25
n-3 PUFA plus vitamin E	25	24	26	25	25
Control	25	25	24	24	25
			Mean (s.d.)		
Age (y)	59.2 (11.1)	59.1 (10.6)	59.0 (10.2)	58.9 (10.0)	59.4 (10.6)
Body mass index (kg/M^2)	26.5 (4.1)	26.6 (3.5)	26.6 (3.5)	26.5 (3.4)	26.5 (3.7)
Ejection fraction	52.4 (10.2)	52.8 (10.4)	53.3 (10.5)	53.3 (10.7)	52.6 (10.6)
Total cholesterol (mg/dl)	209.9 (42.1)	210.1 (42.7)	211.5 (42.2)	212.5 (40.8)	210.8 (42.1)
HDL cholesterol (mg/dl)	41.3 (11.8)	41.4 (11.6)	41.5 (11.1)	41.9 (11.4)	41.5 (11.5)
Triglycerides (mg/dl)	164.8 (86.1)	162.9 (93.3)	161.7 (82.9)	159.8 (81.6)	162.0 (85.6)

[a]Quality of diet groups corresponds to quarters of the dietary score (see Methods). MI = myocardial infarction.

reference group was re-defined as 'never or sometimes'; odds ratios for 'often' and 'regularly' compared with this reference were 0.77 (95% CI 0.62–0.94) and 0.71 (95% CI 0.60–0.84), respectively. In all five cases there was a highly significant linear trend ($P < 0.002$). Further adjustment of each food for all the other foods increased the odds ratios slightly, without altering the basic inferences (Table 2).

The effect of the overall dietary score is shown by Figure 2; the log odds of death decreased, in a linear fashion, as the score increased. Weights used in the dietary score, by increasing frequency category (see Figure 1) were: fish 0, 0.8, 1.3, 1.7; fruit 0, 0.9, 0.9, 1.9; raw vegetables 0, 1.1, 2.5, 2.6; cooked vegetables 0, 0.8, 1.0, 2.1; olive oil (with the first two categories combined) 0, 1.6, 1.7. When the range of observed scores was split into equal quarters, the chance of death reduced by 31% (95% CI 21–39%), 34% (95% CI 24–42%) and 49% (95% CI 41–56%) for the second, third and fourth quarters, each compared with the first, after adjustment for non-dietary variables. Overall, a 10% (one unit) increase in the dietary score reduced the risk of mortality by 15% (95% CI 12–18%). Based on this score, the average risk reduction, across the entire study population, achieved by changing from the baseline to the follow-up diet was 14%. Only in the case of age and use of beta-blockers at baseline was there evidence of heterogeneity in the effect of diet. People aged greater than 60 y and non-beta-blocker users received more benefit from a healthier diet than did people less than 60 y old and beta-blocker users, respectively. Even then, there was still a strong protective effect in all subgroups (Figure 3).

Discussion

This study, of 11 246 survivors of a myocardial infarction, shows that simple dietary advice, based on the benefits of a Mediterranean diet, given routinely in a clinic setting, can be successfully acted upon and maintained. It confirms that, after a heart attack, people with a relatively high consumption of Mediterranean foods have relatively lower chance of premature death. Of the five foods considered, fish, fruit, raw and cooked vegetables and olive oil, there was no evidence that any one of the foods had a completely dominant effect

Table 2 All-causes mortality odds ratios by average frequency of consumption of five foods over the entire course

		OR (95% CI), adjusted for	
	Number of deaths	Non-dietary variables[a]	All variables[b]
Fish			
Never/almost never	270	1	1
1 per week	631	0.83 (0.71–0.96)	0.87 (0.75–1.02)
2 per week	596	0.73 (0.62–0.85)	0.81 (0.69–0.94)
>2 per week	163	0.66 (0.53–0.80)	0.76 (0.62–0.94)
P-value for trend		<0.001	0.0003
Fruit			
Never/almost never	55	1	1
2–3 times per week	160	0.80 (0.58–1.11)	0.86 (0.63–1.19)
1 per day	591	0.75 (0.56–0.99)	0.87 (0.65–1.17)
> 1 per week	852	0.58 (0.44–0.78)	0.73 (0.54–0.98)
P-value for trend		<0.0001	0.0002
Raw vegetables			
Never/almost never	219	1	1
2–3 times per week	749	0.77 (0.66–0.90)	0.83 (0.70–0.98)
1 per day	578	0.60 (0.51–0.70)	0.67 (0.56–0.79)
>1 per day	112	0.54 (0.43–0.69)	0.65 (0.51–0.84)
P-value for trend		<0.0001	<0.0001
Cooked vegetables			
Never/almost never	311	1	1
2–3 times per week	916	0.79 (0.69–0.90)	0.88 (0.76–1.01)
1 per day	386	0.69 (0.59–0.80)	0.84 (0.71–1.00)
>1 per day	46	0.55 (0.40–0.75)	0.70 (0.50–0.99)
P-value for trend		<0.0001	0.0177
Olive oil			
Never/sometimes	161	1	1
Often	263	0.77 (0.62–0.94)	0.77 (0.63–0.95)
Regularly	1236	0.71 (0.60–0.84)	0.76 (0.64–0.91)
P-value for trend		0.002	0.010

[a]Age, sex, hypertension, HDL-cholesterol, diabetes, smoking, claudication, electrical instability, left ventricular dysfunction, residual myocardial ischaemia, dietary supplementation (vitamin E, n-3 PUFA and the interaction), pharmacological therapies (aspirin, beta-blockers, angiotensin-converting enzyme inhibitors).
[b]As above plus all the other foods.
Note: due to four missing values for fruit, one for raw vegetables and five for cooked vegetables, the numbers of deaths for these foods do not add up to 1660.

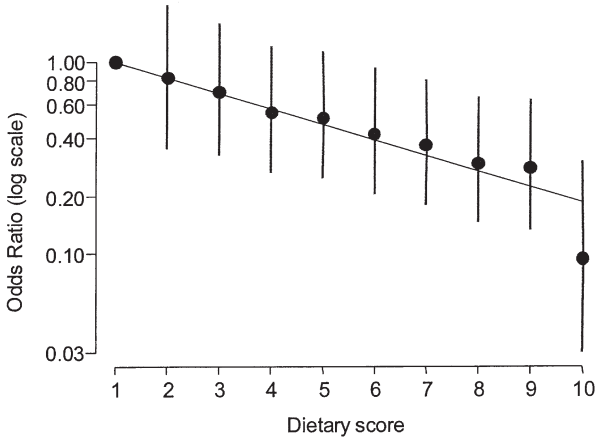

Figure 2 Odds ratios (on the log scale) for all-causes mortality, with 95% confidence intervals, against the dietary score. Results are given for each whole number of the score, taking the range 0–1 as the base level (odds ratio of unity). The line drawn is the linear regression line for the log odds ratio against the score treated as a continuous variable. Results adjusted for all non-dietary variables as in Table 2.

over the others; each of the foods seems to have an important protective effect even when the effects of the other four foods had been accounted for.

The five foods chosen here as macro indicators of healthy dietary habits after myocardial infarction have previously been shown to be associated with decreased risk, particularly for coronary heart disease. Most of the published evidence relates to the health benefits of fruit, vegetable and fibre intake. For instance, in a study of about 5000 Finnish men, Knekt *et al* (1994) reported a significant 34% reduction in risk of coronary heart disease for subjects above the top tertile of vegetables intake compared to subjects below the bottom tertile. In the Nurses' Health Study and the Health Professionals' Follow-Up Study, Joshipura *et al* (2001) found a significant 20% reduction in risk of coronary heart disease for people in the highest fifth of fruit intake compared with those in the lowest fifth, and a similar reduction for vegetable intake. In the Scottish Heart Health Study, fibre had a particularly strong effect on reducing the risk of both coronary and all-causes mortality (Todd *et al*, 1999). In a recent review (Ness & Powles, 1997) the effect of fruit and vegetables (or surrogate nutrients) on reducing coronary heart disease risk was significant in almost all of the ecological studies included, in two of the three case–control studies and in six of the 16 cohort studies; the results were stronger when stroke was considered. Although fewer studies are available, there is also evidence of the benefits of fruit and vegetables in secondary coronary prevention. The Lyon Diet Heart Study found that patients randomized to a Mediterranean-style diet, rich in fruit, vegetables and alpha-linolenic acid, experienced an extraordinary 72% decrease in the risk of a coronary event (de Lorgeril *et al*, 1999).

The importance of olive oil, and its monounsaturated fatty acids, as a major nutrient in the Mediterranean region's food supply has been underlined by the Nutrition Committee of the American Heart Association (Krauss *et al*, 2000). After the landmark paper by Ancel Keys (Keys, 1970), high intake of monounsaturated (MUFA) and polyunsaturated fatty acids (PUFA) has been repeatedly found associated with low coronary heart disease mortality in Mediterranean countries as well as in the USA (Serra-Majem *et al*, 1993; Hu *et al*, 1997; Artaud-Wild *et al*, 1993; Pietinen *et al*, 1997). A systematic review of dietary intervention studies has shown that reduction or modification of dietary fat intake leads to a significant reduction of all cardiovascular events (Hooper *et al*, 2001). Recently, a case–control study conducted in Spain (Fernandez-Jarne *et al*, 2002) reported on an 82% significant reduction in the risk of a first myocardial infarction for

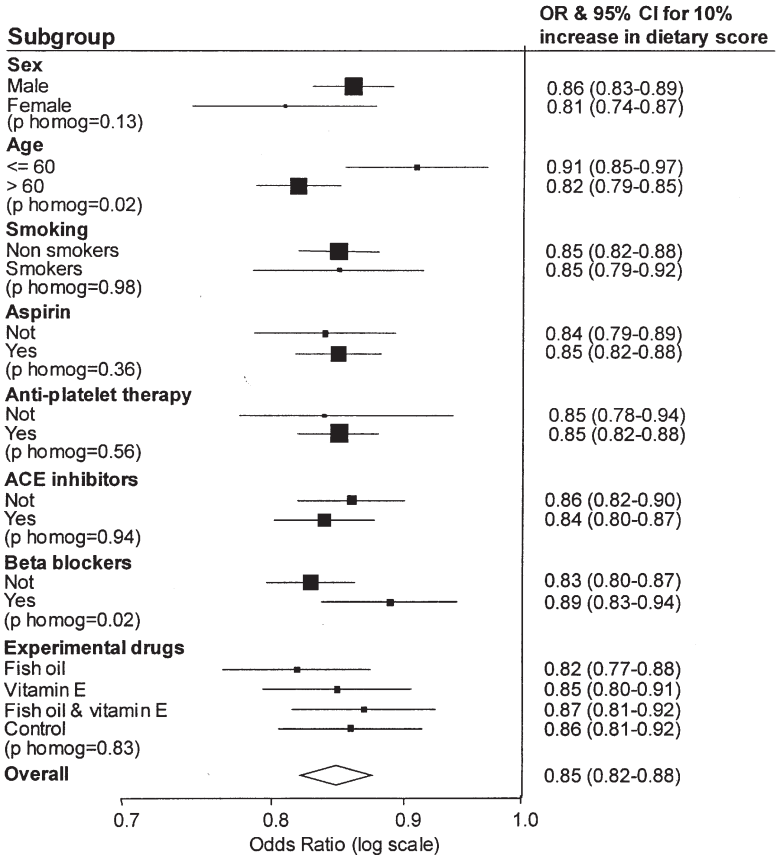

Figure 3 All-causes mortality odds ratios, adjusted for all non-dietary variables, for a 10% (one unit) increase in the dietary score. Horizontal lines and the width of the diamond represent 95% confidence intervals; boxes are drawn in proportion to number of deaths.

individuals with a median olive oil daily intake of 52.2 g as compared with those with a median daily intake of 6.1 g. Moreover, evidence from controlled clinical studies has shown that MUFAs favourably affect a number of risk factors for coronary heart disease, including plasma lipids and lipoproteins, factors related to thrombogenesis, *in vitro* LDL oxidative susceptibility (compared with PUFA), and insulin sensitivity. As to fish intake, the evidence on the protective effects of n-3 polyunsaturated fatty acids, as well as the results of the DART Trial (Burr *et al*, 1989) and the GISSI-Prevenzione trial itself (GISSI-Prevenzione Investigators, 1999), is now overwhelming, as the Nutrition Committee of the American Heart Association has recently recognized (Krauss *et al*, 2000).

Despite expectations, randomized trials have provided limited evidence for the role of isolated nutrients, such as are found in Mediterranean foods, in the prevention of cardiovascular disease or mortality. With the exception of n-3 and other polyunsaturated fatty acids, clinical trials testing the efficacy of antioxidants, such as beta-carotene and vitamin E, have reported no protective effects on cardiovascular disease (GISSI-Prevenzione Investigators, 1999; Marchioli, 1999, 2001; Dagenais *et al*, 2000; Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, 1994; Omenn, 1995; Hennekens *et al*, 1996; Omenn *et al*, 1996; HOPE Study Investigators, 2000, Collaborative Group of the Primary Prevention Project, 2001; Brown *et al*, 2001). For example, the recently completed Heart Prevention Study (MRC/BHF Heart Protection Study Collaborative Group, 1999) found that a cocktail of antioxidant vitamins had no benefit in patients at high risk of cardiovascular death, even with a sample size of over 20 000. These results suggest that the relationship between diet and cardiovascular disease is likely to be highly complex, involving a wide variety of dietary components, and is unlikely to be determined solely by individual nutrients.

The current study has the strengths of having a long duration and of using a large sample with detailed information on variables known to be related to future mortality, and strict quality assurance criteria. Unlike many longitudinal studies, there is no reliance here upon a single baseline measure of food frequency which may become dated as the study matures. The dietary advice given followed the American Heart Association dietary guidelines, namely 'dietary and other lifestyle practices that all individuals can safely follow throughout the life span as a foundation for achieving

and maintaining cardiovascular and overall health' and an 'overall pattern of food intake over an extended period of time and not on the intake of a single meal' (Krauss *et al*, 2000). In order to keep the dietary advice simple and the questionnaire short, and thus maintain compliance and accuracy, there was no attempt to measure the entire diet. The food items included in the short food frequency questionnaire were interpreted as macro indicators of dietary habits. However, since the entire diet was not recorded, it was not possible to estimate the total intake of individual nutrients, nor to take account of total energy consumption in the analyses. On the other hand, as recently discussed by Joshipura *et al* (2001), there is little evidence, to date, of the effects of foods, as opposed to nutrients, and this study redresses this imbalance.

As might be expected, in this study non-smokers had better diet than smokers. It is likely that other, unmeasured, aspects of lifestyle were also 'better' amongst those with high dietary scores in the current study. The independent protective effects of correct dietary habits in their own right have thus, almost certainly, been overestimated. This may partly account for discrepancies in the negative or null results of clinical trials and the positive results of epidemiological studies of, for example, beta carotene intake. In practice, it is unlikely that dietary choices would be made in isolation, nor that medical practitioners would choose to issue dietary advice without mentioning other aspects of maintaining a healthy lifestyle (quitting smoking, increasing exercise, moderate drinking, etc). The dietary variables measured here did, nevertheless, have beneficial effects independent of those non-dietary variables that were measured in the study and considered to be potential confounders.

The cumulative exposure variable used here attempts to capture the best available information on long-term dietary habits; a similar method was used in analyses of the Nurses' Health Study and the Health Professionals' Follow-Up Study (Stampfer *et al*, 2000; Joshipura *et al*, 2001). One alternative statistical approach is to use a time-dependent Cox model (Cupples *et al*, 1988; Allison, 1995); this was applied to the current data and produced very similar results. Further sensitivity analyses considered different measures of dietary exposure, such as not accumulating information over succeeding visits. Although foods lost or gained predictive power according to how the exposures were defined, the overall findings remained unchanged.

The current study confirms earlier epidemiological findings on the benefits of a Mediterranean diet, in this case in the context of delaying death after a heart attack. The anticipated advantages were achieved following simple dietary advice as a clinical intervention after a heart attack, regardless of other treatments received. Instead of treating this as merely a recommendation, guidelines for the treatment of coronary patients should include routine advice to increase frequency of consumption of fruit, vegetables, olive oil and fish, whilst also paying due attention to other key lifestyle factors, particularly smoking.

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Appendix

Let the food frequency recorded at the ith visit (i=1, 2, 3, 4) be Di. Let the time between the ith and the i+1th visit be Ti (i=1,2,3) and let T4 be the time from the last visit to the end of follow-up (death or censoring). The food consumption Cj (j=1,2,3,4) for the jth time interval was calculated as: Cj = j=1, 2, 3, 4.

$$C_j = \frac{\sum_{i=1}^{j}(D_i + D_{i+1})xT_i}{2x\sum_{i=1}^{j} T_i} \quad j = 1, 2, 3, 4$$

When Di was missing it was estimated by the most recent non-missing value of D (i.e. last information carried forward).