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Mediterranean dietary pattern and mortality among young women: a cohort study in Sweden

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Studies of diet and health focus increasingly on dietary patterns. Although the traditional Mediterranean diet is perceived as being healthy, there is little information on its possible benefit to young people. We studied whether closer adherence to the traditional Mediterranean dietary pattern was associated with overall and cancer mortality in a cohort of 42 237 young women, aged 30–49 years at enrolment, who were recruited in 1991–2 from the general population in the Uppsala Health Care Region, Sweden, and followed up, almost completely, for about 12 years. Adherence to the Mediterranean diet was assessed by a 10-point score incorporating the characteristics of this diet. Among women less than 40 years old at enrolment – whose causes of death are mainly cancer with probable genetic influences, injuries or suicide – there was no association of the Mediterranean diet score with total or cancer mortality. Among women 40–49 years old at enrolment, a 2-point increase in the score was associated with considerable reductions in overall mortality (13 %; 95 % CI 1 %, 23 %; $P\sim 0{\cdot}05$) and cancer mortality (16 %; 95 % CI −1 %, 29 %; $P\sim 0{\cdot}06$). Few cardiovascular deaths occurred in this cohort of young women. The findings of the present study in a northern European population of young women indicate that closer adherence to a Mediterranean dietary pattern reduces mortality even among young persons.

Mediterranean diet: Sweden: Women: Mortality: Cancer mortality: Diet: Cohort

Keys and his colleagues in the 1960s (Keys, 1980) advanced the hypothesis that the Mediterranean diet might protect against CHD, mainly on account of its low saturated lipid content. In the early 1990s, the emphasis was shifted from the low saturated lipid content of this diet towards its high content of vegetables and legumes and its heavy reliance on unsaturated lipids, largely derived, particularly in the Mediterranean countries, from olive oil (Sacks & Willett, 1991; Trichopoulou *et al.* 1995; Willett *et al.* 1995). Moreover, evidence has accumulated that the Mediterranean diet and its key components, including monounsaturated lipids, may have beneficial effects not only on CHD, but also on some forms of cancer and, eventually, on longevity itself (Wolk *et al.* 1998, Trichopoulou *et al.* 2000; Bosetti *et al.* 2003). The study of the association of the Mediterranean diet, as an integral dietary pattern, with various indicators of health and disease was facilitated by its operationalisation through a Mediterranean diet score (Trichopoulou *et al.* 1995), which assesses adherence to this dietary pattern and has been used extensively, in different variants, by several authors in many investigations in Mediterranean and non-Mediterranean countries (Osler & Schroll, 1997; Kouris-Blazos *et al.* 1999; Lasheras *et al.* 2000; Bosetti *et al.* 2003; Chrysohoou *et al.* 2004; Trichopoulou *et al.* 2005*b*).

There is now considerable evidence that a Mediterranean dietary pattern increases longevity among the elderly (Trichopoulou *et al.* 2003; Knoops *et al.* 2004). The effect of the Mediterranean diet on total mortality among younger persons, however, has not been extensively studied, because of obvious limitations in statistical power (few outcomes). In the study by Trichopoulou *et al.* (2003), no significant association of the Mediterranean diet score with overall mortality was evident among persons who were younger than 50 years at enrolment, possibly because there were fewer than fifty deaths in this group. There is therefore a genuine question over whether the Mediterranean diet is associated with reduced mortality among younger persons, because among this group mortality is dominated by cancer, as well as causes that are unlikely to be related to diet, that is, injuries, suicides and infections.

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We have investigated the association of the Mediterranean dietary pattern with overall and cancer mortality in a large cohort of Swedish women younger than 50 years at enrolment. These women were further distinguished into those who were 40 years or older and those who were less than 40 years at enrolment. In the latter group, very few deaths are of a cardiovascular nature, cancer has frequently strong genetic determinants (Loman *et al.* 2001; Hoedema *et al.* 2003; Li and Hemminki 2004), and many deaths are due to accidents and self-inflicted injuries, so that diet is unlikely to play an important role. Among women 40 years or older at enrolment, however, diet in general and the Mediterranean diet in particular could be an important determinant of mortality. Hence, the association of the Mediterranean dietary pattern with overall and cancer mortality was investigated separately for women who were 40 years or older, and younger than 40 years, at enrolment.

Methods

Recruitment

Women aged 30–49 years, residing in the Uppsala Health Care Region in Sweden in 1991–2, form the source population for this study. Of this source population, 96 000 women were randomly selected from four age strata (30–34, 35–39, 40–44 and 45–49 years) and were invited to participate in the Swedish component of the Scandinavian Women's Lifestyle and Health Cohort (Veierod *et al.* 2003). All women received a letter inviting them to participate in the study. The women were asked to fill in a questionnaire and return it in a pre-paid envelope. Of the women invited, over half decided to participate, and 49 261 returned the questionnaires and were enrolled in the study. The Swedish Data Inspection Board and the regional Ethical Committee approved the study.

Questionnaire and dietary assessment

The women filled in a self-administered questionnaire that included information on lifestyle variables (including a detailed smoking history and alcoholic drinking habits), anthropometry (height, weight, BMI), and medical history (previous diagnoses of major diseases). In this questionnaire, women also rated their overall level of physical activity (including activities in the house, occupational and recreational physical activity) on a 5-point scale with examples attached to levels 1, 3 and 5: 1 = sedentary (mainly sitting); 3 = moderate physical activity (a few walks a week); 5 = vigorous physical activity (sports/jogging several times a week). Dietary habits during the 6 months preceding the woman's enrolment in the study were ascertained through a validated food-frequency questionnaire that covered the frequency of consumption and quantity of about eighty food items and beverages (Wolk *et al.* 1998). Food consumption was translated into nutrient and energy intakes on the basis of the Swedish National Food Administration database (Bergstrom *et al.* 1991). A total of eleven food groups were constructed (all measured for each woman in g/d unless otherwise specified): vegetables, legumes, fruits and nuts, dairy products, cereals, meat and meat products, fish and seafood, potatoes, eggs, sugars and sweets, and non-alcoholic beverages (in ml/d). In addition, the intake of polyunsaturated, monounsaturated and saturated lipids (all in g/d), as well as the ratio between the latter two lipid types, the monounsaturated:saturated ratio, were calculated.

Mediterranean diet score

To assess adherence to the traditional Mediterranean diet, we used the scale developed by Trichopoulou and colleagues (Trichopoulou *et al.* 1995, 2003). The scale incorporates information on the consumption of seven food groups – vegetables, legumes, fruits and nuts, cereals, fish and seafood, meat and meat products, and milk and dairy products – as well as on alcohol consumption and the ratio of monounsaturated to saturated lipids in the diet. Using the median consumption as a cut-off, a value of 0 or 1 was assigned to each of the nine indicated components. For components presumed to be beneficial (vegetables, legumes, fruits, cereals, fish), persons whose consumption was below the median were assigned a value of 0, and persons whose consumption was at or above the median were assigned a value of 1. For components presumed to be detrimental (meat, dairy products), those whose consumption was below the median were assigned a value of 1, and those whose consumption was at or above the median were assigned a value of 0. For alcohol, a value of 1 was assigned to women who consumed between 5 and 25 g/d. Thus, the total Mediterranean diet score ranged from 0 (minimal adherence to the traditional Mediterranean diet) to 9 (maximal adherence).

Follow-up

Follow-up of the cohort was achieved through linkages with existing Swedish nationwide health registers. Because each resident in Sweden has a unique national registration number, one can link the data from the cohort with these registers for virtually complete follow-up with respect to death and emigration. From the Register of Total Population, we received information on dates of death for women who died during the follow-up period until 31 December 2003. Additional information on cause of death was derived from the Death Register and was updated till 31 December 2002. Dates of emigration for women who moved out of Sweden were provided by the Register of Total Population. The start of follow-up was defined as the date of return of the questionnaire during 1991–2. Observation time was calculated from the date of entry into the cohort until the occurrence of death, or censoring. For overall mortality, censoring was on account of emigration or the end of the observation period, whereas for cancer mortality, it was also on account of death from any other cause.

Statistical analysis

Of the original 49 261 Swedish women, the following were sequentially excluded: those who had emigrated without re-immigration prior to the start of the study (sixteen women), those who had not filled in the dietary questionnaire (583 women), those with prevalent cancer (excluding non-melanoma skin cancer), CHD or diabetes at enrolment (1418 women) and those with missing information on any of the covariates studied (4404 women), as well as those with energy intakes outside the first (1847 kJ/d) and 99th (12 474 kJ/d) centiles (603 women). Thus, a total of 42 237 women were available for the analysis.

The participating women, the person–time contributed and the deaths were initially grouped into categories of non-nutritional covariates including age, education, height, BMI, physical activity, smoking and alcohol intake. The associations between the individual covariates and overall mortality were examined with Cox's proportional hazards regression. The associations between these covariates and the Mediterranean diet score were examined by cross-tabulations and Spearman's rank correlation coefficients. The quartile values of food group and macronutrient intake were also determined, and Spearman's rank correlation coefficients relating the Mediterranean diet score to the food group and macronutrient intakes were calculated

Hazard ratios for overall mortality and mortality from cancer were estimated through Cox proportional hazards regression, using the Mediterranean diet score as the principal exposure. Mortality from CVD was not studied because, among these young women, very few deaths were due to these conditions. The models were adjusted for the following variables as reported at enrolment: age (years, continuously), height (cm, continuously), BMI (<25, 25–29·99, $\geq 30\,kg/m^2$, categorically), smoking status (never smokers, former smokers of four or fewer cigarettes/d former smokers of 5–9 cigarettes, former smokers of 10–14 cigarettes, former smokers of 15–19 cigaretted, former smokers of 20 or more cigarettes, current smokers of four or fewer cigarettes, current smokers of 5–9 cigarettes, current smokers of 10–14 cigarettes, current smokers of 15–19 cigarettes, current smokers of 20 or more cigarettes, categorically), physical activity (from 1:low to 5:high, categorically), education (0–10, 11–13, 14 or more years in school, categorically) and energy intake (continuously). They were also adjusted for the nutritional variables that were not part of the Mediterranean diet score, specifically potato intake (continuously), egg intake (continuously), polyunsaturated lipid intake (continuously), sweet and sugar intake (continuously) and non-alcoholic beverage intake (continuously). Fine control for tobacco smoking was necessary because of the powerful influence of smoking on mortality and the possibility that smoking might be associated with some dietary intakes. Moreover, control for foods that are not part of the Mediterranean diet score, which has minimal effect on statistical power, was deemed necessary to assure minimisation of possible conditional confounding.

All analyses were conducted for all women, as well as separately for women less than 40 years old at enrolment and for women 40 years or older at enrollment. This decision was made *a priori* because, among younger women, malignancies frequently have strong genetic determinants (Loman *et al.* 2001; Hoedema *et al.* 2003; Li and Hemminki, 2004) and many deaths are due to accidents and self-inflicted injuries, so that diet is unlikely to play an important role.

Statistical analyses were performed using the statistical software R version 2.0.1 (R Project for Statistical Computing, 2006). The Cox proportional hazards assumption was checked informally by graphs of scaled Schoenfeldt residuals *v.* time (Therneau & Grambsch, 2001). None of the model covariates showed a deviation from the proportional hazards assumption, and no evidence of co-linearity was detected.

Results

The 42 237 women were followed up for an average of 12·01 years, during which time 572 deaths were recorded. Table 1 shows the distribution of participating women, the contributed person-years and the recorded deaths, by sociodemographic, anthropometric and lifestyle variables. Age and mutually adjusted mortality ratios are also presented. The mortality patterns are in line with expectations by indicating that mortality increases with age and BMI, declines with years of schooling and physical activity, and is higher among smokers and heavy drinkers (although the results on alcohol drinking were based on only nine deaths among heavily drinking women).

In Table 2, the women are cross-classified by the previously indicated non-nutritional variables and three categories of the Mediterranean diet score. The score tends to be higher among older, more educated, physically more active, currently non-smoking and moderately drinking women. Thus, all these variables had the potential to confound the association of the Mediterranean diet score with mortality and were therefore controlled for in the analyses.

Table 3 presents the median values and quartiles of the nutritional variables studied and the association of these variables with the Mediterranean diet score. As expected, vegetables, legumes, fruits, cereals, fish and monounsaturated:saturated lipid ratio were positively associated with the Mediterranean diet score, whereas the intakes of dairy products and saturated lipids were inversely associated with this score. Energy intake was positively associated with the Mediterranean diet score, underlying the need to control for this variable in all analyses. Meat intake (a 'detrimental' component) was essentially unrelated to the score, probably because meat contributed about 30 % of the monounsaturated lipid intake in the diet of the study participants (Wolk *et al.* 1998) and intake of monounsaturated lipids is considered beneficial in the Mediterranean diet score.

Although deaths were recorded until the end of 2003, causes of death were available only for deaths that occurred up until the end of 2002. Table 4 shows the distribution of deaths by age and cause. Cancer was responsible for over 50 % of all deaths, whereas there were very few deaths from CHD, making it unrealistic to explore their relation with diet. About one third of all deaths and nearly 50 % of deaths among the very young women were due to infections, injuries, suicide or other causes that were unlikely to be related to diet. Thus, only total and cancer mortality could be investigated.

The distribution of the 280 cancer deaths by site were as follows: breast, sixty-one; lung, fifty-four; ovaries, twenty-nine; pancreas, nineteen; colorectal, nineteen; individually less common cancers, ninety-eight (brain, thirteen; various forms of leukaemia and lymphoma, thirteen; stomach, eleven; biliary tract, eleven; uterus, ten; urinary tract, ten; melanoma, seven; oral cavity, five; connective tissue, five; other, seven; unknown, primary seven). Moreover, because among very young women cancer frequently has a genetic basis and causes unrelated to diet dominate their mortality pattern, we particularly focused on women who were 40 years or older at enrolment. Among these women, there were forty-two

Table 1. Distribution of 42 237 Swedish women by non-nutritional characteristics and alcohol intake at enrolment, and corresponding mortality ratios (with 95 % CI)*

Variables	*n*	Woman-years	Number of deaths	Age-adjusted mortality ratios (95 % CI)	Multivariate† mortality ratios (95 % CI)
Age at enrolment (years)					
29–34	10 251	122 935	60	1·00	1·00
35–39	10 898	130 959	113	1·77 (1·29, 2·42)	1·78 (1·30, 2·43)
40–44	11 119	133 724	173	2·65 (1·98, 3·56)	2·53 (1·88, 3·40)
45–49	9969	119 706	226	3·87 (2·91, 5·14)	3·48 (2·59, 4·65)
P for trend				$<$0·001	$<$0·001
Education (years)					
0–10	12 537	150 997	265	1·00	1·00
11–13	16 418	197 547	183	0·67 (0·55, 0·82)	0·73 (0·61, 0·90)
$>$ 13	13 282	158 781	124	0·52 (0·42, 0·65)	0·63 (0·50, 0·78)
P for trend				$<$0·001	$<$0·001
Height (cm)					
$<$ 160	5239	62 675	90	1·00	1·00
160–164·9	11 920	143 212	159	0·78 (0·60, 1·00)	0·82 (0·63, 1·06)
165–169·9	13 538	162 756	186	0·82 (0·64, 1·05)	0·88 (0·68, 1·13)
$\geq$ 170	11 540	138 682	137	0·73 (0·56, 0·96)	0·81 (0·62, 1·06)
P for trend				0·07	0·29
BMI (kg/m^2)					
$<$ 25	30 663	368 257	366	1·00	1·00
25–29·9	9234	111 052	144	1·19 (0·98, 1·45)	1·08 (0·88, 1·31)
$\geq$ 30	2340	28 016	62	2·01 (1·53, 2·63)	1·66 (1·26, 2·19)
P for trend				$<$0·001	0·003
Physical activity					
1 (low)	1724	20 507	50	1·00	1·00
2	4496	53 843	81	0·63 (0·44, 0·89)	0·75 (0·52, 1·06)
3	25 183	302 909	338	0·46 (0·34, 0·62)	0·56 (0·41, 0·76)
4	7227	86 728	75	0·36 (0·25, 0·52)	0·51 (0·35, 0·73)
5 (high)	3607	43 338	28	0·29 (0·18, 0·45)	0·39 (0·25, 0·63)
P for trend				$<$0·001	$<$0·001
Smoking at enrolment					
Never smoker	17 427	209 536	160	1·00	1·00
Ex-smoker	12 476	149 948	158	1·35 (1·09, 1·69)	1·34 (1·08, 1·68)
Current smoker	12 334	147 840	254	2·32 (1·90, 2·82)	2·07 (1·69, 2·54)
P for trend				$<$0·001	$<$0·001
Alcohol intake (g/d)					
$<$ 5	31 453	378 110	415	1·00 (0·83–1·21)	1·01 (0·84, 1·23)
5–25	10 595	126 982	148	1·00	1·00
$>$ 25	189	2232	9	3·29 (1·68–6·38)	2·59 (1·32, 5·09)
P for trend				0·45	0·41

* Calculated by Cox proportional hazards regression.
† Adjusted for the variables in this table.

deaths from breast cancer, forty-five from lung cancer, twenty-five from ovarian cancer, fifteen from colorectal cancer, fifteen from pancreatic cancer and sixty-two from individually less common cancers.

Table 5 summarises the association of the Mediterranean diet with overall mortality and mortality from cancer in the total group of women, controlling for potential confounders. For total as well as for cancer mortality, results are presented for both the ordinal increase in the score (per 2 units) and for score categories (0–3 as reference, 4–5 and 6–9 units). An increasing Mediterranean diet score is associated with reduced overall mortality, and the reduction is largely accounted for by cancer mortality. In the fully adjusted models, however, neither of the two examined trends was statistically significant.

In Table 6, we evaluated separately the association of the score with overall and cancer mortality among very young women and women aged 40–49 years at enrolment. There was no association between the score and either total or cancer mortality among the very young women. Among women 40 years or older at enrolment, however, the Mediterranean diet score was associated with substantial reductions in both overall ($P<0{\cdot}05$) and cancer ($P\sim0{\cdot}06$) mortality. The interaction term assessing the difference in total mortality ratio among younger and older women (1·09 *v.* 0·87) is highly suggestive ($P\sim0{\cdot}056$). The interaction term assessing the difference in cancer mortality ratio among younger (1·07) and older (0·84) women is clearly not statistically significant ($P\sim0{\cdot}184$). The contrast of the ratios, however, is at least as striking for cancer as for total mortality, indicating that small numbers are possibly responsible for the lack of statistical significance.

Figure 1 shows Cox model-derived survival curves among women aged 40–49 years at enrolment by Mediterranean diet score category. It illustrates the substantial association of the Mediterranean diet score with overall mortality among women 40–49 years old at enrolment, largely accounted for by a reduction in mortality from cancer.

Table 2. Distribution of 42 237 Swedish women participants by Mediterranean diet score in conjunction with non-nutritional variables and alcohol intake

	Mediterranean diet score					
	0–3		4–5		6–9	
	n	%*	*n*	%*	*n*	%*
Age at enrolment (years)						
29–34	4049	39	4363	43	1839	18
35–39	3793	35	4817	44	2288	21
40–44	3510	32	4930	44	2679	24
45–49	2976	30	4346	43	2647	27
Spearman *r* (*P* value)†			+0·10 (<0·001)			
Education (years)						
0–10	4873	39	5269	42	2395	19
11–13	5805	35	7174	44	3439	21
> 13	3650	27	6013	45	3619	27
Spearman *r* (*P* value)†			+0·12 (<0·001)			
Height (cm)						
< 160	1896	36	2298	44	1045	20
160–164·9	4130	35	5137	43	2653	22
165–169·9	4491	33	5930	44	3117	23
≥ 170	3811	33	5091	44	2638	23
Spearman *r* (*P* value)†			+0·025 (<0·001)			
BMI (kg/m^2)						
< 25	10 418	34	13 269	43	6976	23
25–29·9	3053	33	4127	45	2054	22
≥ 30	857	37	1060	45	423	18
Spearman *r* (*P* value)†			+0·008 (0·12)			
Physical activity						
1 (low)	795	46	682	40	247	14
2	1700	38	1956	44	840	19
3	8797	35	10 998	44	5388	21
4	2051	28	3235	45	1941	27
5 (high)	985	27	1585	44	1037	29
Spearman *r* (*P* value)†			+0·10 (<0·001)			
Smoking at enrolment						
Never smoker	5495	32	7864	45	4068	23
Ex-smoker	3906	31	5432	44	3138	25
Current smoker	4927	40	5160	42	2247	18
Spearman *r* (*P* value)†			−0·07 (<0·001)			
Alcohol intake (g/day)						
< 5	12 187	39	13 669	43	5597	18
5–25	2063	19	4709	44	3823	36
> 25	78	41	78	41	33	17
Spearman *r* (*P* value)†			+0·23 (<0·001)			
Total	14 328	34	18 456	44	9453	22

* Percentage computed for each row.
† Non parametric correlation coefficient between the indicated non-nutritional variable (or alcohol) and the Mediterranean diet score. All covariates are used in actual values, except for the Mediterranean diet score (ordered 1–3), tobacco smoking (ordered 1–3) and alcohol intake (ordered 1–3).

Discussion

In a cohort study of 42 237 Swedish women, who were 30–49 years old at enrolment and were followed up for an average of 12·01 years, the association between adherence to the Mediterranean diet, operationalised through a 10-point score, and overall mortality or mortality from cancer was investigated. Too few of these young women died from CHD or stroke to allow meaningful investigation of a possible association of these conditions with diet. Among the 21 149 women who were less than 40 years old at enrolment, no association was found between the Mediterranean diet score and either overall mortality or mortality from cancer. In contrast, among the 21 088 women who were 40–49 years old at enrolment, the Mediterranean diet score was inversely associated with both overall mortality and mortality from cancer.

The lack of an association of the Mediterranean dietary pattern, or indeed any aspect of diet, with mortality among very young women is not surprising. Among the 153 deaths for which the cause was recorded, only thirteen were due to CVD, whereas sixty-four deaths were from causes that were unlikely to have nutritional aetiological components (injuries, suicide, infections, etc.). Cancer was responsible for seventy-six deaths, but it is well known that cancer in very young women is frequently under strong genetic influence (Loman *et al.* 2001; Hoedema *et al.* 2003; Li and Hemminki, 2004).

The inverse associations of the Mediterranean diet score with both overall mortality and mortality from cancer among women aged 40–49 years at enrolment, who were at their mid-fifties by the end of follow-up, are findings with

Table 3. Daily dietary intakes of food groups and selected macronutrients, and Spearman correlation coefficients with Mediterranean diet score

(Data from 42 237 Swedish women)

	25th centile	Median	75th centile	Spearman's *r**
Vegetables (g/d)	39·9	61·9	89·1	+0·54
Legumes (g/d)	4·0	17·5	26·2	+0·45
Fruits and nuts (g/d)	81·1	136·9	209·0	+0·45
Dairy products (g/d)	161·4	334·2	507·4	−0·29
Cereals (g/d)	136·1	183·3	241·0	+0·27
Meat (g/d)	62·0	84·4	109·8	+0·02
Fish (g/d)	14·1	22·7	31·6	+0·48
Monounsaturated to saturated lipid intake ratio	0·68	0·75	0·83	+0·37
Potatoes (g/d)	47·4	71·3	102·2	+0·06
Eggs (g/d)	6·6	14·1	14·1	+0·17
Sweets (g/d)	14·8	29·8	50·9	+0·09
Non-alcoholic beverages (ml/d)	499·0	695·7	905·9	+0·03
Monounsaturated lipids (g/d)	13·7	17·6	22·1	+0·04
Saturated lipids (g/d)	17·6	23·5	30·5	−0·09
Polyunsaturated lipids (g/d)	5·7	7·3	9·2	+0·19
Energy intake (kJ/d)	5213	6396	7710	+0·17

* All correlations rely on actual values of the respective covariates and are statistically significantly different from zero ($P<0·01$).

Table 4. Deaths by age and cause among Swedish women

Age at enrolment (years)	CHD *n* (%)	Stroke *n* (%)	Cancer *n* (%)	Infections, injuries, suicide and other *n* (%)	Total *n* (%)
<34	0 (0·0)	4 (8·2)	19 (38·8)	26 (53·1)	49 (100)
35–39	6 (5·8)	3 (2·9)	57 (54·8)	38 (36·5)	104 (100)
40–44	7 (4·5)	9 (5·7)	82 (52·2)	59 (37·6)	157 (100)
45–49	12 (6·2)	10 (5·1)	122 (62·6)	51 (26·2)	195 (100)
Total	25 (4·9)	26 (5·1)	280 (55·4)	174 (34·5)	505 (100)

Cause of death was available for women who died before 31 December 2002. For sixty-seven women who died during 2003, cause of death was not available.

Table 5. Overall and cancer mortality ratios (and 95 % CI)* among Swedish women by Mediterranean diet score

		Mortality ratio (95 % CI)	
	Deaths/participants	Age-adjusted	Fully adjusted†
Total mortality (trend per 2 point increase in score)	572/42 237	0·83 (0·75, 0·92)	0·93 (0·83, 1·03)
P for trend		0·001	0·180‡
Total mortality (per score category)			
Score 0–3	217/14 328	1 (reference)	1 (reference)
Score 4–5	245/18 456	0·82 (0·69, 0·99)	0·93 (0·78, 1·13)
Score 6–9	110/9 453	0·68 (0·54, 0·86)	0·85 (0·67, 1·08)
Cancer mortality (trend per 2 point increase in score)§	280/42 237	0·82 (0·71, 0·95)	0·89 (0·77, 1·04)
P for trend		0·015	0·200‡
Cancer mortality (per score category)§			
Score 0–3	106/14 328	1 (reference)	1 (reference)
Score 4–5	120/18 456	0·82 (0·63, 1·07)	0·91 (0·69, 1·18)
Score 6–9	54/9 453	0·67 (0·48, 0·93)	0·80 (0·57, 1·13)

* Calculated through Cox proportional hazards regression.

† Adjusted for: age at enrolment (years, continuously), height (cm, continuously), BMI (<25, 25–29·99 and ≥30 kg/m^2, categorically), smoking status (never smokers, former smokers of 4 or fewer cigarettes, former smokers of 5–9 cigarettes, former smokers of 10–14 cigarettes, former smokers of 15–19 cigarettes, former smokers of 20 or more cigarettes, current smokers of 4 or fewer cigarettes, current smokers of 5–9 cigarettes, current smokers of 10–14 cigarettes, current smokers of 15–19 cigarettes, current smokers of 20 or more cigarettes, categorically), physical activity (from 1:low to 5:high, categorically), education (0–10, 11–13 and 14 or more years in school, categorically), energy intake (continuously), potato intake (continuously), egg intake (continuously), polyunsaturated lipid intake (continuously), sweet intake (continuously) and non-alcoholic beverage intake (continuously).

‡ When potato, egg polyunsaturated lipid, sweet and non-alcoholic beverage intake were not adjusted for, the *P* for trend values for overall and cancer mortality were 0·22 and 0·19, respectively.

§ Deaths specified to be due to cancer were available only until December 2002.

Table 6. Total and cancer mortality ratio* among Swedish women associated with a 2-point increase in the Mediterranean diet score by age at enrolment

	Deaths/participants	Mortality ratio (95 % CI)	
		Age-adjusted	Fully adjusted†
Death from any cause			
Women <40 years	173/21 149	0·94 (0·78, 1·13)	1·09 (0·90, 1·32)
Women ≥40 years	399/21 088	0·79 (0·70, 0·89)	0·87 (0·76, 0·98)
P for interaction			0·056
Death from cancer‡			
Women <40 years	76/21 149	0·92 (0·70, 1·22)	1·07 (0·79, 1·43)
Women ≥40 years	204/21 088	0·78 (0·66, 0·93)	0·84 (0·71, 1·01)
P for interaction			0·184

* Calculated by Cox proportional hazards regression.
† Adjusted as indicated in the second footnote of Table 5. Due to lack of events for the analysis of cancer mortality, the smoking categories <4 and 5–9 cigarettes/d were collapsed to a combined category for both former and current smokers.
‡ Deaths specified to be due to cancer were available only until December 2002.

potentially important implications. The overall mortality ratio of 0·87 for these women in our study is close to the mortality ratio of 0·89 reported in an earlier Greek study (Trichopoulou *et al.* 2003) among men and women less than 55 years old at enrolment. It thus appears that the Mediterranean diet has beneficial effects on diseases with nutritional aetiological components, even among individuals in their forties.

In our study, the individual components of the Mediterranean diet score were generally weakly and non-significantly associated with overall mortality and mortality from cancer, even among women older than 40 years at enrolment. This was the case without mutual adjustment among nutritional factors, which was deemed inappropriate because of the underlying complex and co-linear associations between these factors – an important reason for using a score instead. A similar pattern of weak or no associations of mortality with the individual components of the Mediterranean diet score was also observed in an earlier Greek study (Trichopoulou *et al.* 2003) in which the score was a significant and important predictor of mortality. With respect to mortality from cancer, recent cohort studies have indicated that two crucial components of the Mediterranean diet – a high intake of vegetables and a high intake of fruits – are weakly associated with a reduced incidence of cancer (Hung *et al.* 2004) and that a third crucial component of this diet, a low intake of meat, is only weakly associated with reduced colorectal cancer risk (Chan *et al.* 2005).

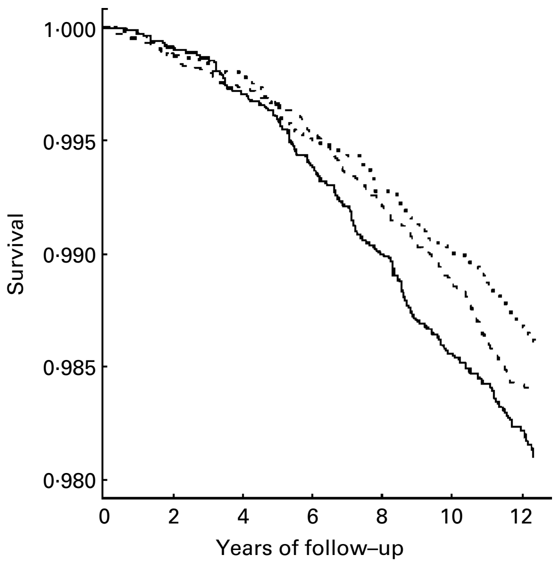

Fig. 1. Cox model-derived survival curves among Swedish women 40–49 years old at enrolment by Mediterranean diet (MD) score categories. ___ MD score 0–3; _ _ _ MD score 4–5; .... MD score 6–9.

Several explanations may apply (Jacques & Tucker, 2001; Trichopoulou *et al.* 2003) to the apparent contradiction between the strong associations of an overall dietary pattern and the weak associations of its individual constituents with overall and cancer mortality. First, individual components may have small effects that become apparent and statistically documentable only when the components are integrated into a unidimensional score. Second, there may be biological interactions between one or more components of the score that can only be detected in very large studies, but would still be discernible through a simple unidimensional score. Third, when individual components are evaluated, effects are examined against the background of average risk generated by the other nutritional components, whereas a dietary score accommodates the extremes of cumulative exposure in the absence of other major nutritional effects. In this study, as in earlier ones (Trichopoulou *et al.* 2005*b*), the Mediterranean diet score was found to be weakly positively associated with energy intake because more of the score components take a value of 1 with a higher intake of the corresponding food group. This necessitates adjustment for energy intake, but it has trivial consequences on long term BMI-associated conditions (Trichopoulou *et al.* 2005*a*).

Although the Mediterranean diet score was developed to assess adherence to the traditional Mediterranean diet (Trichopoulou *et al.* 1995), it should be recognised that the score incorporates current views about the essence of a healthy diet (Nube *et al.* 1987; Farchi *et al.* 1995; Michels & Wolk, 2002). Indeed, the traditional Mediterranean dietary pattern does not contradict the dietary recommendations of major bodies, except by allowing a higher consumption of lipids, provided they are unsaturated and preferably in the form of olive oil (in Greece, for example, the average consumption of olive oil being around 50 g/d (Psaltopoulou *et al.* 2004)). In this context, diets as different as those of Swedes and Greeks can be similarly operationalised, as has been done in this and other investigations (Trichopoulou *et al.* 2005*b*).

Strengths of our investigation are its large size, long follow-up time and minimal losses to follow-up assured by the Register linkage process. Comparability with non-responders is always difficult to assess, but women with missing values were generally similar to those included in the analysis, and, in cohort studies, selection of the study base does not compromise the validity of the results.

Limitations of the study are the unavoidable misclassification of dietary exposures, compounded by the customised classification of the dietary pattern studied and possible changes in dietary habits during the long follow-up period. Nevertheless, these misclassification errors can only attenuate any true association. Because the Mediterranean diet score, as originally introduced and subsequently used (Trichopoulou *et al.* 1995, 2003, 2005*b*; Osler & Schroll, 1997; Kouris-Blazos *et al.* 1999; Lasheras *et al.* 2000), did not grade in detail cereals and dairy products, cereals were not distinguished into whole-grain *v.* refined, nor were dairy products separated into high fat *v.* low fat. We have also not distinguished between types of alcoholic beverage because there was not a sufficient number of outcomes to allow the evaluation of different drinking patterns.

Confounding by most known powerful predictors of mortality has been controlled for, but minor or unidentifiable confounders may still operate, and some degree of residual confounding because of misclassification of the recorded confounders cannot be excluded. The residual confounding issue is, however, not specific to this study but haunts all observational investigations.

Using tertiles, quintiles or standardised quantities, instead of the median we employed, might have increased the discriminatory power of the Mediterranean diet score, but it would compromise the simplicity of the message, which is easily conveyed through the use of a median, under the implicit assumption of a monotonic relation. A more detailed quantitative score would have been necessary if one were attempting to explain the fraction of an outcome that could be attributed to various degrees of adherence to the Mediterranean diet, thus focusing, for example, on the components of variance of the outcome linked to a particular exposure. At this stage of research, however, emphasis is on assessment of the usefulness of the Mediterranean diet score in predicting mortality in populations outside the Mediterranean region. Moreover, a main objective of this study was to evaluate whether a dietary pattern approximating the Mediterranean one would be beneficial to young people, as it has been shown to be – through the use of similar instruments in different populations – among older people (Trichopoulou *et al.* 1995, 2003, 2005*b*; Osler & Schroll, 1997; Kouris-Blazos *et al.* 1999; Lasheras *et al.* 2000). Finally, the simple score we have used is applicable to most types of dietary questionnaire, including rudimentary ones, thus facilitating replication of the findings in more studies and population groups. We do not argue that a particular pattern in the Swedish diet (defined through the medians in the corresponding components) is Mediterranean. Our working hypothesis has been that the diet of Swedish women would be more conducive to longer survival if it tended to approximate towards the Mediterranean dietary pattern.

In conclusion, we have found evidence that, among women 40–49 years old at enrolment who were followed up for approximately 12 years, closer adherence to a Mediterranean dietary pattern was associated with reduced total mortality and probably mortality from cancer.

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