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The Mediterranean diet and risk of colorectal cancer in the UK Women's Cohort Study

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Version 3

Abstract

Background: Evidence from epidemiological studies investigating associations between adherence to the Mediterranean diet and colorectal cancer is inconsistent. The aim of this study is to assess whether adherence to the Mediterranean dietary pattern is associated with reduced incidence of cancers of the colon and rectum in the UK Women's Cohort Study.

Method: A total of 35 372 women were followed for a median of 17.4 years. A 10-component score indicating adherence to the Mediterranean diet was generated for each cohort participant using a 217-item food frequency questionnaire. The Mediterranean diet score ranged from 0 for minimal adherence to 10 for maximal adherence. Cox proportional hazards regression was used to provide adjusted hazard ratios (HR) and 95% confidence intervals (CI) for colon and rectal cancer risk.

Results: A total of 465 incident colorectal cancer cases were documented. In the multivariable-adjusted model, the test for trend was positive (HR=0.88, 95% CI: 0.78 to 0.99; P_{trend} = 0.03) for a 2-point increment in the Mediterranean diet score. For rectal cancer, a 2-point increment in the Mediterranean diet score resulted in an HR (95% CI) of 0.69 (0.56 to 0.86) whilst a 62% linear reduced risk (HR 0.38; 95% CI: 0.20 to 0.74; P_{trend} < 0.001) was observed for women within the highest vs. the lowest category of the MD score. Estimates for an association with colon cancer were weak (P_{trend} = 0.41).

Conclusion: Findings suggest women adhering to a Mediterranean dietary pattern may have a lower risk of colorectal cancer, especially rectal cancer.

Keywords: Mediterranean diet epidemiology colonic neoplasms rectal neoplasms

Version 3

Key Messages

- Primary data from the UK Women's Cohort study was used to investigate the associations between adherence to the Mediterranean diet score and colorectal, colon and rectal cancer risk.
- A moderate, inverse, non-linear association was observed between adherence to the Mediterranean diet score and risk of colorectal cancer.
- The estimates of the association were stronger for rectal than for colon cancer, though the confidence intervals were wide potentially implying no difference between the sites.

Introduction

Colorectal cancer (CRC) is the third most common cancer with 1.36 million cases diagnosed worldwide in 2012 (1). The Mediterranean diet (MD) has consistently been found to have a beneficial influence on total morbidity and mortality, as well as offering cardio protection and reduction in overall cancer incidence (2-4). It is traditionally characterised by a high intake of olive oil and nuts, cereals, fruit and vegetables, moderate intakes of fish, poultry and wine with meals, and low intakes of red and processed meats, dairy products and sweets (5).

However, studies exploring associations between the MD and risk of CRC are limited and have given inconsistent results. Fung and colleagues found no association between adherence to the MD and colorectal, colon or rectal cancers in a large cohort of middle-aged men and women (6). This was however inconsistent with findings from a large US cohort study (7) and form the large European cohort, European Prospective Investigation into Cancer and Nutrition (EPIC) (8), that both reported a reduced risk of CRC with adherence to the MD. Similar associations were reported for all CRC sites in the Italian section of EPIC (9). Notwithstanding, comparisons between studies should be made with caution in view of the variation in the derivation of the MD scores.

The aim of this study is to assess whether adherence to the Mediterranean dietary pattern is associated with reduced incidence of cancer of the colorectum, colon and rectum in a large UK cohort of women with a long follow up period.

Methods

Study design, study population and ethical approval

The UK Women's Cohort Study (UKWCS) of 35 372 middle-aged women was formed from participants of a WCRF 1995 direct mail survey, targeted towards women. 58% of the 61 000 women invited to participate completed a self-administered food frequency questionnaire (FFQ) between 1995 and 1998, providing data for the baseline dataset. Information on diet, lifestyle and health was also provided. The cohort participants are mainly white, middle-class and well-educated with 27% having a degree and 86% married with children. Details of recuitment and the cohort profile have been reported in detail elsewhere (10-11). The study carries with it ethical approval granted at its initiation in 1993 (Research Ethics Committee reference number is 15/YH/0027).

Baseline characteristics and dietary information

Anthropometrics, lifestyle factors and socio-demographic information were self-reported. Information on physical activity was collected whilst socio-economic status (SES) was based on occupation. The FFQ used at baseline was developed from one used in EPIC (12) and consisted of 217 food items and participants were asked to indicate average consumption frequency of food items over a 12 month period, with missing data assumed to be non-consumption. Standard portion weights were assigned and energy intake was derived using McCance & Widdowson's *The Composition of Foods* (5th Edition) (13).

Case definition

The cancer outcomes used in the analyses are incident malignant neoplasms of the colon (codes 153.0-153.9 or C18) and of the rectosigmoid junction and of the rectum (codes 154.0-

154.1 or C19 and C20) of the International Statistical Classification of Diseases (ICD), 9th and 10th editions (14-15). Registrations of cancer diagnosis for women in the UKWCS were made via record linkage of identification codes to the central register of NHS Digital. This data is available from baseline in 1995 until the 30th June 2015 for 98% of the cohort women.

Mediterranean diet score construction

A score indicating adherence to the MD was generated for each cohort participant. The definition used and the approach taken in constructing the score was as described by Trichopoulou and colleagues (16), though modified with respect to the lipid ratio as defined in a later study (17), in view of the non-Mediterranean British cohort under study. This resulted in 10 components, 9 of which had a binary score of 0 or 1 assigned, with the cohort median used as a cutoff. Thus, for components considered to have a beneficial effect – namely vegetables, legumes, fruit and nuts, cereal, fish and fatty acid ratio (sum of monounsaturated and polyunsaturated fats to saturated fat), women whose consumption was at or above the median were assigned a score of 1 whilst those whose intake was below the median were given a 0 value. Conversely, for components presumed to be detrimental – that is meat, poultry and dairy products, a score of 1 was assigned for intakes below the median and a score of 0 for intakes above the cutoff median respectively. For alcohol, the 10th component, daily intakes between 5 and 25g a value of 1 was assigned whilst women consuming intakes outside this range decreased their score by 1. The MD score was thus calculated as the sum of the 0s and 1s assigned to the different components respectively, with the total ranging from a minimal adherence score of 0 to a maximal adherence score of 10. Details are given in Table I.

(Table I here)

Statistical analysis

Statistical analysis were conducted using Stata version 13 statistical software (18). Descriptive statistics were used to describe lifestyle characteristics of participants. Survival analysis was conducted to explore the relationship between the Mediterranean diet score and colorectal, proximal colon, distal colon and rectal cancer risk. Cox proportional hazards regression was used to provide hazard ratios (HRs) and 95% confidence intervals (CI) for the estimation of relative risk of cancer. The proportional hazards assumption was tested graphically for all terms in the model. In order to account for the stratified sampling scheme at recruitment, over-sampling vegetarians and fish-eaters, statistical models used weights based on the inverse probability of being sampled to provide estimates more representative of the UK population. The time variable used in the models was time in the study, calculated from the date of questionnaire receipt until either death or censor date (30th June 2015).

Adherence to the MD score was modelled as categorical (0-2, 3, 4, 5-6 and 7-10), to create groups with similar numbers, with each category assigned a score 1, 2, 3, 4 & 5 respectively, and comparing each category to the lowest, reference category. Estimates per 2-point increment in the continuous MD score and tests for linear trend were also calculated. Analyses were carried out for colorectal cancer, and then for colon, proximal colon, distal colon and rectal cancer separately. The individual MD score components were split into thirds based on their tertiles, labelled as low, medium and high intakes and explored in association with incidence of colorectal, colon and rectal cancers, using the low intake as the reference category. Cox regression models were used to test for trend, using the continuous variable.

Risk factors for CRC previously identified in the literature were taken into consideration. Associations were estimated first as a simple age-adjusted model, and finally as a full model adjusting for age (years), body mass index (BMI) (kg/m^2), energy intake (kcal/day), physical activity (hr/day), ethanol intake (g/day), smoking status (never, current or former smoker), family history of CRC in a first degree relative and socio-economic status (professional/ managerial, intermediate or routine and manual). Participants with incomplete data on these variables were excluded. Education was included as an additional confounder in a third model, but several women were lost due to the missing data and no major differences were observed in the results (data not shown).

Restricted cubic splines based on three knots at 10, 50 and 90% through the distributions of the data were also used to explore potential deviation from linear associations in the continuous variables (29).

Results

Demographics

During a median follow-up time of 17.4 years (IQR=1.7), a total of 527 women in the UKWCS were diagnosed with incident CRC. Participants who did not provide sufficient data at baseline to allow flagging on NHS Digital (n=695), women self-reporting history of any previous malignant cancer at baseline, except for non-melanoma of the skin (n=2391), women who were diagnosed with CRC within one year of baseline (n=53) and women with energy intakes outside the plausible range of 500 to 6000kcal/day (n=79) were excluded. Following exclusions, 32 154 cohort participants were eligible for inclusion in the analysis with 465 CRC cases, of which 366 were located in the colon (173 in the proximal colon and 119 cases in the distal colon) and 154 cases were located in the rectum.

Baseline characteristics

The characteristics of study participants according to the 5 categories of the MD score are reported in Table II. Women in the highest category of the score were likely to be younger, had a lower BMI and engaged in more physical activity compared to those in the lower categories. High adherers to the MD score tended to have a higher energy intake but lower alcohol intake, were more likely to be vegetarians and fish eaters and to take supplements than women with lower adherence scores. Women with scores reflecting poor adherence tended to smoke and were less likely to have a degree or hold a managerial position.

(Table II here)

Survival analysis

The HRs and 95% CIs for incidence of colorectal, colon and rectal cancer across categories of adherence to the MD score are shown in Table III. In the multivariable-adjusted model, compared to the reference intake, all categories had a lower risk of CRC. The test for trend was statistically significant where the risk estimate per 2-point increment in the MD score was 0.88 (0.78 to 0.99; P_{trend} = 0.03). An inverse association for rectal cancer risk with adherence to the MD score was demonstrated, with a HR (95% CI) of 0.38 (0.20 to 0.74; P_{trend} < 0.001) for women within the highest category of the score in comparison to the reference category. In the continuous model, a 2-point increase in the MD score resulted in an HR (95% CI) of 0.69 (0.56 to 0.86) for rectal cancer. No strong association for risk of colon, proximal colon or distal colon cancer with adherence to a Mediterranean dietary pattern was found, although the risk estimates in both the categorical and continuous models for colon cancer suggest a possible protective association. Notwithstanding, although estimates for rectal cancer were stronger than for colon cancer, the confidence intervals were wide; hence the possibility of no difference in association between the two sites exists.

(Table III here)

The relationships portrayed in Table III were reflected in the restricted cubic spline models, depicted in Figure 1. A deviation from linearity was observed for the relationship between the MD score and CRC (Figure 1a) and colon cancer (Figure 1b) respectively, with adherence scores above 6 showing little risk reduction. The cubic spline model portraying the relationship between adherence to a MD and risk of rectal cancer showed no deviation from linearity (Figure 1c).

(Figure 1 here)

Analysis of the separate components of the MD score found no association with CRC or colon cancer, whilst an inverse association was seen only for the high intake of legumes on rectal cancer risk, with a 44% lower risk (95% CI: 0.35 to 0.91; P_{trend} = 0.02) when compared to the lowest reference intake. Estimated associations for legume intake and CRC risk, though weak, were in the expected direction.

(Table IV here)

Discussion

This study evaluated adherence to the Mediterranean dietary pattern in relation to risk of CRC in a UK cohort of middle-aged women, followed up for a median of 17.4 years. 465 cases of CRC were included in the analysis. The MD score chosen for this analysis was deemed most suitable for this British cohort. It gives a logical coverage of food types and its components were variables in the UKWCS database, allowing generation of the MD adherence score. The overall MD score was inversely associated with incidence of colorectal and rectal cancer; with the magnitude of the association being stronger for rectal cancer risk, whilst little association was seen for risk of colon cancer alone in multivariate adjusted analyses. Investigation of the separate score components showed that legume intake offered a degree of protection against risk of rectal cancer. No evidence of an association was found for the intake of any other individual component of the MD score with either site of the colorectum.

Several prospective studies have investigated the association between the MD and CRC risk (6-9), although results were not consistent. A meta-analysis of 21 cohort and 12 case-control studies reported a 14% reduced risk of CRC with high adherence to MD (20), which is comparable to the 18% decrease in risk reported for this cohort. The results of this study are in part in agreement with those of Agnoli and colleagues (9) who also reported a reduction in risk of developing colorectal and rectal cancer, but differed to the results of this cohort in finding evidence of an inverse association also for distal colon cancer, although our study may have been limited by small numbers for sub-site analysis. In contrast, no association for either cancer site in women was observed in the NIH-AARP Diet and Health Study (11). The cubic spline for MD score and CRC (Figure 1a) portrays a non-linear association above MD score 6, with a plateau being reached, potentially implying that the MD does not offer added benefit with respect to cancer risk reduction above this level of adherence. Conversely, for rectal cancer, the cubic spline shows no deviation from linearity across the MD score, reflecting the strong inverse association inferred in the results. If a true difference exists between different anatomic subsites of the colorectum, the heterogeneity in estimates could be attributed to the different microbial composition, molecular features and biochemical environment of the colonic lumen (21). Nevertheless, the apparent difference in associations may be due to the relatively small subsite numbers.

Whilst the magnitude of the association for CRC in this study is similar to that observed in the EPIC study (8), in the latter a strong inverse association was evident for colon cancer whilst that for rectal cancer was much weaker. Fung *et al.* (6) found no association between conformity to the MD and risk of CRC and colorectal adenomas, respectively, in women. This inconsistency in results from different studies may be due to different researchers' interpretation of what constitutes a Mediterranean dietary pattern, the variation in the scores used to assess adherence to it including cut-points for intake that may vary by sex, dietary measurement error resulting in the attenuation of modest associations as well as potential false reporting of interactions (22). Furthermore, a lower number of cases in studies that differentiate categories according to sex may result in weaker risk estimates for women.

The beneficial effect of the MD on risk of CRC may be due to the predominantly plant based nature of this dietary pattern, characterised by foods high in dietary fibre, including fruit, vegetables, nuts and legumes, and a low intake of red meat, specifically processed. The potential of an increased fibre (23-24) and fish consumption (25-26) to decrease CRC risk have been previously reported as has the association of high intakes of red and processed meat with increased risk of colorectal, colon and rectal cancers (27). Notwithstanding, a systematic review and meta-analysis by Magalhaes and colleagues (28) reported a higher risk of proximal and distal colon but not of rectal cancer in subjects with high consumption of red meat and low consumption of fruit and vegetables. In EPIC, inverse associations were observed for cereal fibre and colon and rectal cancer, whilst fibre from cereals but not from fruit and vegetables was associated with decreased rectal cancer (24). The estimated associations for vegetables, legumes, fish and red meat reported in Table IV, though not all strong, are in the expected directions and support the implication that such components are mediating the associations observed for adherence to the MD. Despite the standard MD adherence score (17) as used in this study attributing a detrimental effect to poultry and dairy products, recent evidence shows that poultry (29) and milk (30) moderately reduce CRC incidence, whilst the association with yoghurt warrants further investigation (21).

The exact mechanisms underlying the association between the MD and CRC remain unclear. In a review, Song *et al.* (21) states that diet affects CRC carcinogenesis directly through immune responsiveness and inflammation, indirectly through excess weight which is itself a risk factor and may result in insulin resistance and also attributes a role to the gut microbiota. Several relevant hypotheses have linked red meat consumption to CRC; it is a source of saturated fat and heme iron, the latter may induce the formation of the carcinogenic N-nitroso compounds, whilst the production of heterocyclic amines and polycyclic aromatic hydrocarbons during prolonged cooking at high temperatures may also be responsible for the association (21, 31). The anti-inflammatory and antineoplastic role of omega-3 polyunsaturated fatty acids (PUFAs) mainly through the reduction of prostaglandin E2 synthesis and/or synthesis of anti-inflammatory resolvins has been proposed as a mechanism (32) inversely relating PUFAs and thus fish consumption to CRC. Fibre from legume and vegetable intake in a MD may function in reducing CRC risk by diluting carcinogens from faeces and binding to carcinogenic bile acids, reducing colonic transit time and pH and may be fermented into beneficial short chain fatty acids (33-34).

Strengths of this study include the large size of this UK cohort, its design and the long follow up, cancer registry confirmed diagnosis and the ability to control for non-dietary potential confounding factors. Some limitations have also been identified. The single FFQ administered at baseline is the only method of assessment of dietary information, leaving potential changes in diet throughout follow-up unaccounted for. The use of a dietary score in itself has its limitations (35-36). In this study, the scoring system gave each component an equal weighting which may not equate to potential mechanisms of effect and limits the dietary advice that can be given. Furthermore, the small number of cases in the analyses by subsite results in limited power.

In conclusion, this study has given evidence of a non-linear relationship between the MD and CRC, and of a strong, linear risk reduction between the MD and rectal cancer. Women adhering to a MD pattern may have a lower risk of CRC.

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JC conceived and designed The UKWCS, which was at its conception funded by the World Cancer Research Fund. PJ conducted the analysis for this report, wrote the first version and contributed to all other versions. DG contributed to statistical methods. All authors contributed to the interpretation of the data and contributed to the manuscript. We also thank the women who took part in the UKWCS.

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Conflict of Interest

JC is the director of a University company, Dietary Assessment Ltd.

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Tables

Table I: Derivation of the Mediterranean dietary score

	Indicator Value	
MDS Component	1	0
Vegetables (g/day)	≥ 282	< 282
Legumes (g/day)	≥ 31	< 31
Fruit & nuts (g/day)	≥ 273	< 273
Cereals (g/day)	≥ 226	< 226
Fish (g/day)	≥ 24	< 24
MUFA + PUFA : SFA*	≥ 1.53	< 1.53
Meat (g/day)	< 40	≥ 40
Poultry (g/day)	< 13	≥ 13
Dairy (g/day)	< 97	≥ 97
Alcohol (g/day)	5-25	< 5 or > 25

* Ratio of the sum of monounsaturated fatty acids and polyunsaturated fatty acids to saturated fatty acids

Table II: Baseline characteristics of women in the UKWCS according to adherence to the Mediterranean dietary pattern.

		Mediterranean diet score				
	Total	1	2	3	4	5
MDS score range (median)	0 - 10	0-2 (2)	3	4	5-6 (5)	7-10 (7)
N (%)	32154 (100)	3631 (11.3)	4295 (13.4)	5610 (17.5)	11245 (35.0)	7373 (22.9)
Age (years)						
Mean	52.0	53.4	53.3	52.8	51.8	50.3
95% CI	(51.9, 52.1)	(53.1, 53.7)	(53.1, 53.6)	(52.6, 53.0)	(51.6, 52.0)	(50.1, 50.5)
BMI (kg/m^2)						
Mean	24.4	25.6	25.0	24.8	24.3	23.5
95% CI	(24.4, 24.5)	(25.5, 25.8)	(24.9, 25.1)	(24.6, 24.9)	(24.2, 24.4)	(23.4, 23.6)
Energy intake (kcal/day)						
Mean	2338	2104	2171	2236	2377	2575
95% CI	(2331, 2348)	(2085, 2123)	(2152, 2190)	(2216, 2252)	(2362, 2391)	(2560, 2591)
Physical activity (hr/day)						
Mean	0.24	0.18	0.20	0.21	0.25	0.30
95% CI	(0.23, 0.24)	(0.16, 0.19)	(0.18, 0.21)	(0.20, 0.22)	(0.24, 0.26)	(0.29, 0.31)
Ethanol (g/day)						
Median	5.5	1.9	3.6	4.8	6.1	8.0
IQR	11.8	6.8	10.8	11.8	12.1	11.6
Current smoker						
N (%)	3484 (11.2)	482 (13.7)	571 (13.7)	622 (11.4)	1124 (10.3)	685 (9.6)
Professional / Managerial SES						
N (%)	19956 (63.4)	1976 (55.9)	2401 (55.9)	3357 (61.4)	7145 (64.8)	5077 (70.2)
Degree level of education						
N (%)	8862 (27.4)	694 (18.9)	906 (21.0)	1421 (25.2)	3213 (28.4)	2605 (35.2)
Diet group						
Meat-eaters, N (%)	20663 (70.3)	3111 (98.1)	3440 (91.4)	4149 (82.7)	6989 (67.3)	2974 (42.2)
Fish-eaters, N (%)	4002 (13.6)	16 (0.5)	117 (3.1)	321 (6.4)	1388 (13.4)	2160 (30.7)
Vegetarians, N (%)	4712 (16.0)	45 (1.4)	207 (5.5)	547 (10.9)	2005 (19.3)	1908 (27.1)
Supplement users						
N (%)	16815 (57.5)	1542 (42.5)	2023 (47.1)	2810 (50.1)	6067 (54.0)	4373 (59.3)
Family history of colorectal cancer						
N (%)	1826 (6.0)	217 (6.0)	243 (5.7)	329 (5.9)	624 (5.5)	413 (5.6)

UKWCS UK Women's Cohort Study, MDS Mediterranean diet score, CI Confidence Interval, BMI Body mass index, SES Socioeconomic status

Table III: Hazard ratios and 95% confidence intervals for incidence of colorectal, colon and rectal cancer according to adherence to the Mediterranean diet score.

Cancer site	Mediterranean diet score categories	Cases[a]	Age-adjusted HR (95% CI)	Multivariable-adjusted[b] HR (95% CI)
Colorectal		465		
	1	74	1	1
	2	75	0.89 (0.65, 1.24)	0.91 (0.64, 1.30)
	3	88	0.80 (0.58, 1.10)	0.82 (0.58, 1.15)
	4	136	0.64 (0.48, 0.86)	0.63 (0.45, 0.87)
	5	92	0.76 (0.55, 1.06)	0.82 (0.57, 1.17)
	Per 2 unit increment		0.86 (0.77, 0.96)	0.88 (0.78, 0.99)
	P_{trend}		*0.007*	*0.030*
Colon		336		
	1	49	1	1
	2	54	0.98 (0.66, 1.44)	0.98 (0.64, 1.51)
	3	66	0.95 (0.65, 1.38)	0.92 (0.60, 1.39)
	4	100	0.72 (0.51, 1.02)	0.70 (0.47, 1.04)
	5	67	0.95 (0.65, 1.41)	1.03 (0.67, 1.57)
	Per 2 unit increment		0.92 (0.81, 1.04)	0.94 (0.82, 1.08)
	P_{trend}		*0.188*	*0.413*
Proximal colon		173		
	1	20	1	1
	2	35	1.55 (0.89, 2.70)	1.67 (0.90, 3.10)
	3	27	0.93 (0.52, 1.69)	0.92 (0.47, 1.80)
	4	53	0.97 (0.57, 1.64)	1.06 (0.59, 1.91)
	5	38	1.38 (0.78, 2.43)	1.66 (0.89, 3.10)
	Per 2 unit increment		0.99 (0.83, 1.18)	1.05 (0.87, 1.27)
	P_{trend}		*0.912*	*0.590*
Distal colon		119		
	1	18	1	1
	2	12	0.61 (0.29, 1.27)	0.60 (0.26, 1.34)
	3	35	1.39 (0.78, 2.48)	1.38 (0.72, 2.62)
	4	30	0.54 (0.29, 1.00)	0.48 (0.24, 0.97)
	5	24	0.89 (0.46, 1.72)	0.86 (0.41, 1.79)
	Per 2 unit increment		0.89 (0.71, 1.10)	0.87 (0.69, 1.11)
	P_{trend}		*0.272*	*0.255*
Rectal		154		
	1	30	1	1
	2	26	0.76 (0.45, 1.28)	0.77 (0.44, 1.35)
	3	26	0.52 (0.30, 0.90)	0.58 (0.32, 1.02)
	4	44	0.51 (0.32, 0.82)	0.50 (0.29, 0.83)
	5	28	0.41 (0.23, 0.72)	0.38 (0.20, 0.74)
	Per 2 unit increment		0.72 (0.60, 0.87)	0.69 (0.56, 0.86)
	P_{trend}		*0.001*	*0.001*

[a] Case numbers apply to multivariable adjusted models. [b]Adjusted for age, BMI, energy intake, physical activity, smoking status, socioeconomic status and family history of colorectal cancer.

Table IV: Multivariate adjusted HR of colorectal, colon and rectal cancer incidence according to intake of the MD score components

Mediterranean diet score components	Colorectal Cancer				Colon Cancer			Rectal Cancer		
	Median intake (g/day)	Cases[a]	Age-adjusted HR (95% CI)	Multivariate-adjusted[b] HR (95% CI)	Cases[a]	Age-adjusted HR (95% CI)	Multivariate-adjusted[b] HR (95% CI)	Cases[a]	Age-adjusted HR (95% CI)	Multivariate-adjusted[b] HR (95% CI)
Vegetables										
Low	164	174	1	1	129	1	1	52	1	1
Medium	281	145	0.82 (0.65, 1.03)	0.85 (0.66, 1.09)	106	0.80 (0.61, 1.05)	0.80 (0.60, 1.08)	50	0.98 (0.65, 1.46)	1.07 (0.69, 1.65)
High	452	146	0.82 (0.65, 1.03)	0.87 (0.68, 1.13)	101	0.79 (0.60, 1.04)	0.88 (0.65, 1.18)	52	0.90 (0.60, 1.36)	0.90 (0.57, 1.40)
P_{trend}			0.078	0.286		0.080	0.370		0.623	0.657
Legumes										
Low	12	194	1	1	138	1	1	65	1	1
Medium	31	151	0.84 (0.67, 1.05)	0.80 (0.63, 1.02)	111	0.89 (0.68, 1.15)	0.83 (0.62, 1.10)	49	0.78 (0.53, 1.15)	0.78 (0.51, 1.18)
High	73	120	0.83 (0.64, 1.06)	0.78 (0.60, 1.02)	87	0.91 (0.68, 1.21)	0.87 (0.64, 1.20)	40	0.72 (0.47, 1.11)	0.56 (0.35, 0.91)
P_{trend}			0.103	0.052		0.455	0.330		0.117	0.017
Fruit & nuts										
Low	134	148	1	1	105	1	1	50	1	1
Medium	271	166	0.98 (0.77, 1.23)	1.05 (0.81, 1.37)	123	1.00 (0.76, 1.31)	1.08 (0.79, 1.46)	55	0.99 (0.66, 1.47)	1.05 (0.67, 1.65)
High	485	151	0.86 (0.68, 1.09)	0.95 (0.73, 1.25)	108	0.86 (0.65, 1.14)	0.93 (0.67, 1.28)	49	0.81 (0.53, 1.23)	0.93 (0.57, 1.51)
P_{trend}			0.201	0.719		0.286	0.609		0.314	0.754
Cereals										
Low	132	172	1	1	125	1	1	56	1	1
Medium	227	158	0.99 (0.79, 1.24)	1.05 (0.81, 1.37)	108	0.94 (0.72, 1.22)	0.95 (0.69, 1.29)	61	1.15 (0.79, 1.68)	1.31 (0.83, 2.08)
High	354	135	0.90 (0.71, 1.14)	0.97 (0.72, 1.31)	103	0.99 (0.75, 1.30)	1.02 (0.72, 1.45)	37	0.67 (0.43, 1.05)	0.74 (0.42, 1.33)
P_{trend}			0.380	0.858		0.910	0.910		0.105	0.383
Fish										
Low	3	140	1	1	92	1	1	54	1	1
Medium	23	158	0.86 (0.67, 1.10)	0.89 (0.68, 1.17)	118	0.93 (0.69, 1.25)	0.98 (0.70, 1.36)	48	0.72 (0.47, 1.09)	0.75 (0.49, 1.17)
High	47	167	0.86 (0.67, 1.10)	0.87 (0.66, 1.14)	126	0.92 (0.69, 1.24)	1.03 (0.74, 1.43)	52	0.76 (0.51, 1.15)	0.68 (0.43, 1.07)
P_{trend}			0.265	0.360		0.620	0.804		0.273	0.112
MUFA & PUFA: SFA										
Low	1.20	159	1	1	114	1	1	55	1	1
Medium	1.53	166	1.16 (0.93, 1.46)	1.10 (0.87, 1.42)	117	1.15(0.88, 1.50)	1.04 (0.78, 1.40)	56	1.11 (0.76, 1.63)	1.12 (0.75, 1.68)
High	1.96	140	0.98 (0.77, 1.25)	0.99 (0.76, 1.29)	105	1.09(0.82, 1.44)	1.14 (0.84, 1.54)	43	0.76 (0.49, 1.17)	0.67 (0.42, 1.08)
P_{trend}			0.984	0.975		0.510	0.416		0.241	0.130
Meat										
Low	0	113	1	1	72	1	1	46	1	1
Medium	40	185	1.30 (1.00, 1.68)	1.35 (1.02, 1.80)	143	1.63 (1.20, 2.22)	1.61 (1.15, 2.27)	49	0.80 (0.51, 1.27)	0.99 (0.60, 1.61)
High	93	167	1.17 (0.89, 1.52)	1.17 (0.86, 1.58)	121	1.37 (1.00, 1.89)	1.29 (0.90, 1.85)	59	0.98 (0.63, 1.53)	1.13 (0.67, 1.90)
P_{trend}			0.699	0.795		0.474	0.752		0.747	0.566
Poultry										
Low	0	122	1	1	86	1	1	42	1	1
Medium	11	179	1.11 (0.86, 1.43)	1.13 (0.85, 1.50)	141	1.13 (0.84, 1.52)	1.15 (0.83, 1.60)	45	0.97 (0.61, 1.56)	1.06 (0.64, 1.76)
High	34	164	1.02 (0.79, 1.32)	1.04 (0.79, 1.38)	109	0.89 (0.65, 1.22)	0.95 (0.68, 1.33)	67	1.39 (0.91, 2.13)	1.38 (0.86, 2.22)
P_{trend}			0.848	0.968		0.200	0.450		0.057	0.141
Dairy										
Low	41	154	1	1	111	1	1	49	1	1
Medium	97	153	0.96 (0.76, 1.21)	1.09 (0.84, 1.43)	114	0.96 (0.73, 1.26)	1.08 (0.80, 1.46)	51	1.04 (0.69, 1.58)	1.14 (0.71, 1.83)
High	180	158	0.93 (0.73, 1.17)	1.00 (0.76, 1.31)	111	0.87 (0.66, 1.14)	0.89 (0.65, 1.22)	54	1.07 (0.71, 1.62)	1.18 (0.73, 1.92)
P_{trend}			0.515	0.954		0.307	0.433		0.739	0.505
Alcohol										
Low	0.40	161	1	1	110	1	1	59	1	1
Medium	5.51	157	1.06 (0.84, 1.34)	1.04 (0.81, 1.34)	120	1.17 (0.89, 1.54)	1.14 (0.84, 1.53)	50	0.96 (0.65, 1.44)	1.02 (0.66, 1.59)
High	16.96	147	1.09 (0.86, 1.37)	1.14 (0.88, 1.48)	106	1.15 (0.87, 1.53)	1.18 (0.87, 1.60)	45	0.90 (0.59, 1.37)	1.06 (0.66, 1.69)
P_{trend}			0.488	0.334		0.309	0.283		0.634	0.821

[a] Case numbers apply to multivariable adjusted models. [b]Adjusted for age, BMI, energy intake, physical activity, smoking status, socioeconomic status and family history of colorectal cancer.

Figures

Figure 1

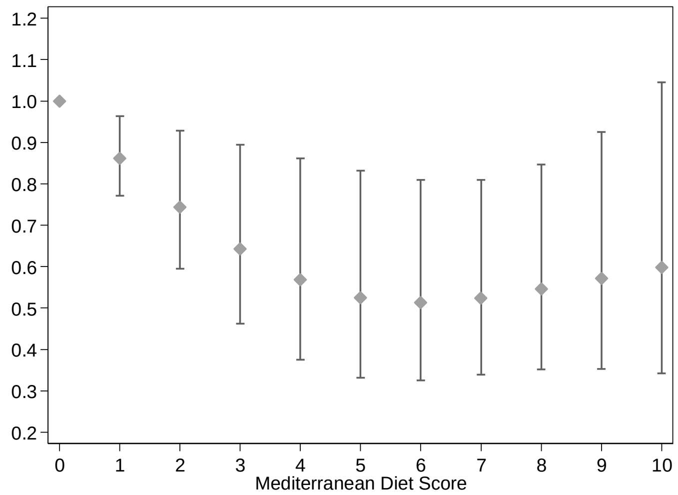

Figure 1a: MD score and colorectal cancer

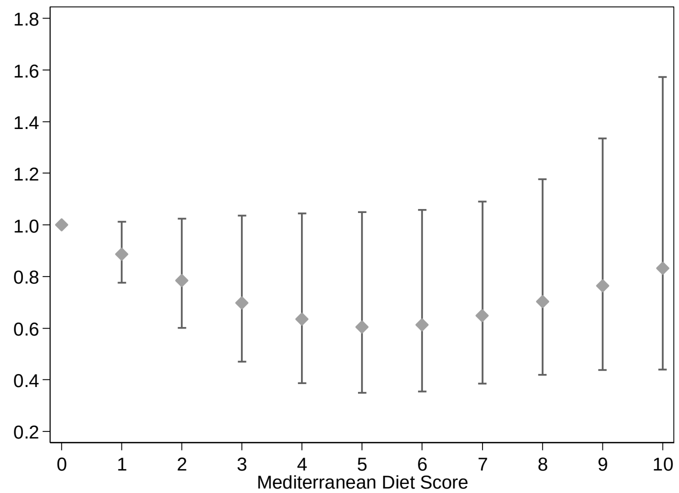

Figure 1b: MD score and colon cancer

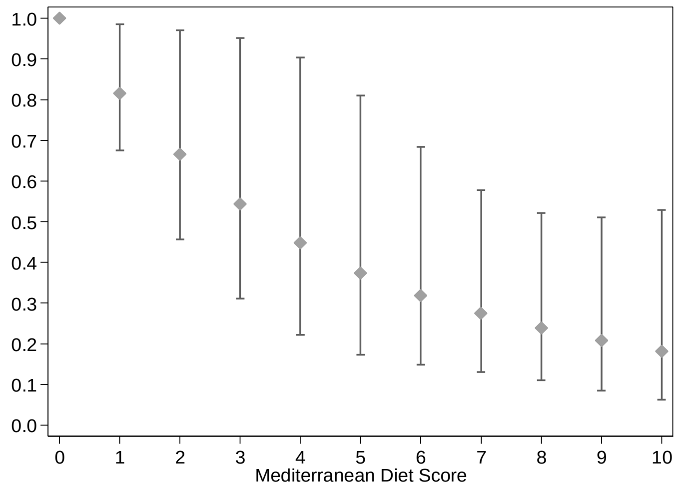

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Figure 1c: MD score and rectal cancer

Figure 1: Restricted cubic splines for the association between (a) colorectal, (b) colon and (c) rectal cancer and the Mediterranean diet (MD) score. Hazard ratios estimated using a Cox proportional hazards model, adjusted for age, body mass index, energy intake, smoking and socioeconomic status. Bars indicate 95% confidence intervals derived from 3-knot restricted cubic spline regression.