ORIGINAL RESEARCH

Adherence to a Mediterranean diet is associated with a lower risk of later-onset Crohn's disease: results from two large prospective cohort studies

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ABSTRACT

Objective To examine the relationship between Mediterranean diet and risk of later-onset Crohn's disease (CD) or ulcerative colitis (UC).

Design We conducted a prospective cohort study of 83 147 participants (age range: 45–79 years) enrolled in the Cohort of Swedish Men and Swedish Mammography Cohort. A validated food frequency questionnaire was used to calculate an adherence score to a modified Mediterranean diet (mMED) at baseline in 1997. Incident diagnoses of CD and UC were ascertained from the Swedish Patient Register. We used Cox proportional hazards modelling to calculate HRs and 95% CI.

Results Through December of 2017, we confirmed 164 incident cases of CD and 395 incident cases of UC with an average follow-up of 17 years. Higher mMED score was associated with a lower risk of CD (P_{trend}=0.03) but not UC (P_{trend}=0.61). Compared with participants in the lowest category of mMED score (0–2), there was a statistically significant lower risk of CD (HR=0.42, 95% CI 0.22 to 0.80) but not UC (HR=1.08, 95% CI 0.74 to 1.58). These associations were not modified by age, sex, education level, body mass index or smoking (all $P_{interaction}$ >0.30). The prevalence of poor adherence to a Mediterranean diet (mMED score=0–2) was 27% in our cohorts, conferring a population attributable risk of 12% for later-onset CD.

Conclusion In two prospective studies, greater adherence to a Mediterranean diet was associated with a significantly lower risk of later-onset CD.

Significance of this study

What is already known on this subject?

- Diet is widely thought to play an important role in the pathogenesis of inflammatory bowel disease.
- Several epidemiologic studies have identified fibre intake to be protective against Crohn's disease.

What are the new findings?

- Greater adherence to a Mediterranean diet is associated with a lower risk of later onset Crohn's disease.
- In two large prospective cohorts in Sweden, poor adherence to a Mediterranean diet conferred a population attributable risk of 12% for later-onset Crohn's disease.

How might it impact on clinical practice in the foreseeable future?

- Our findings further highlight the importance of continued research focusing on the benefits of the Mediterranean diet among individuals at risk of developing Crohn's disease.

INTRODUCTION

The pathogenesis of Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel disease (IBD), is thought to be related to an inappropriate immune response to the gut microbiota in a genetically susceptible host. Diet, through its interaction with the gut microbiome and host barrier function and immunity, plays an important role in the pathogenesis of IBD.[1] There are also accumulating data on the effectiveness of dietary strategies such as exclusive enteral nutrition (EEN) and the CD exclusion diet (CDED) in treatment of active CD,[1–4] further highlighting the critical role of diet in IBD. Nevertheless, prior epidemiologic studies of the relationship between diet and IBD have yielded very few plausible causal relationships.[5] The majority of these studies have focused on individual food groups and nutrients. In contrast, studies that focus on characterising the link between dietary patterns and risk of IBD can take into account overall eating patterns which represent the totality of all foods and beverages consumed, therefore preserving the complexities and potential for synergism between dietary components.

Recently, the Crohn's and Colitis Foundation has undertaken an initiative to study the therapeutic effectiveness of Mediterranean diet in patients with established IBD. However, the relationship between adherence to a Mediterranean diet, characterised by high intakes of fruit and vegetables, whole grains, polyunsaturated fat, and proteins from fish, legumes and nuts, and incident IBD has not been widely explored. Several lines of evidence suggest a role for Mediterranean diet in both prevention and treatment of IBD. First, ecologic studies have demonstrated lower incidence of IBD in Southern

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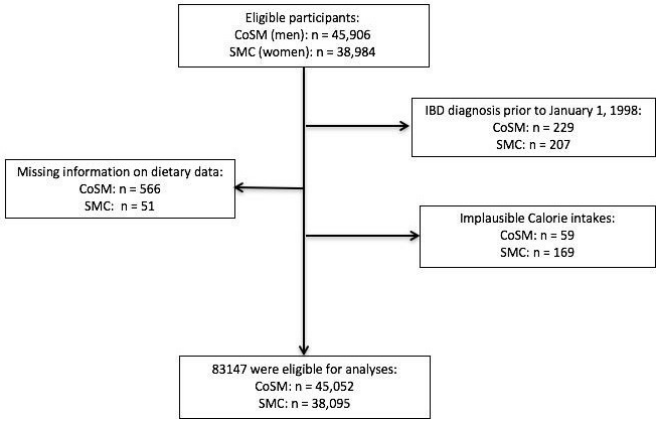

Figure 1 Flow chart of eligible participants in the study. CoSM, Cohort of Swedish Men; SMC, Swedish Mammography Cohort.

Europe where there is a higher consumption of a Mediterranean diet.[6] Second, previous studies have shown that a Mediterranean diet reduces plasma levels of inflammatory markers such as high sensitivity C-reactive protein and tumour necrosis factor alpha and the risk of development and progression of other immune-mediated disorders including psoriasis and rheumatoid arthritis.[7–10] Since IBD is characterised by a subclinical disease state marked by elevation in inflammatory and serological markers,[11 12] adherence to a Mediterranean diet may have a plausible benefit in preventing development of clinically significant disease. Third, at least one small pilot study (n=8) has demonstrated improvement in inflammatory markers, gene expression and the gut microbiome in CD patients who consume a Mediterranean diet for 6 weeks.[13] Finally, CDED has been shown to have therapeutic benefits in patients with CD,[1] and is comprised of components (ie, high intake of fruit and vegetables and low intake of red and processed meat) that overlap with Mediterranean diet.

We therefore sought to investigate the association between relative adherence to a Mediterranean diet and risk of incident CD and UC in two large prospective cohorts of men and women in Sweden. With detailed and validated data on dietary information on over 80 000 middle-aged men and women, these cohorts offered us a unique opportunity to examine the relationship between diet and later-onset IBD, where relative to younger-onset disease the overall contribution of environment is significantly greater.[14 15]

METHODS

Study population

Swedish Mammography Cohort (SMC) is a population-based prospective cohort study established between 1987 and 1990 in the Uppsala county of central Sweden. Briefly, all women who lived in Uppsala County and were born from 1914 and 1948 received an invitation by mail to participate in a mammography screening programme. A total of 66 651 women (74% response rate), age 40–74 years, returned completed questionnaires on diet, alcohol, weight, height and reproductive and menopausal factors. Additional data on other lifestyle factors (eg, smoking, physical activity), medications, and medical illnesses were collected in 1997, 2008 and 2009. Cohort of Swedish Men (CoSM) is a parallel prospective cohort of 45 906 men, age 45–79 years, established in Örebro and Västmanland Counties in Central Sweden in the autumn of 1997. Similar to SMC, all men born between 1918 and 1952 in these counties received an invitation to participate in this study. Similar to SMC, participants provided information on diet and lifestyle factors (eg, physical activity, smoking) at baseline in 1997. Follow-up questionnaires were administered in 2008 and 2009. Our study population included participants who had completed the 1997 questionnaires in both cohorts, which included all participants in CoSM and women in SMC who were still alive in 1997 and returned the dietary questionnaire (n=38 984, 70% response rate). We excluded participants with a diagnosis of IBD prior to baseline, who did not provide information on diet or had implausible total caloric intake defined by intakes not within three standard deviations of the log transformed mean (figure 1).

Primary exposure and other covariates

In both cohorts, dietary data were collected using a 96-item semiquantitative food frequency questionnaire (SFFQ) at baseline in 1997 (validation studies described below) as previously described.[16] Participants reported average frequency of consumption of each food item in the previous year. There were eight categories for frequency of intake ranging from zero servings per month to up to three times per day. Serving sizes for frequently consumed food groups (eg, bread, coffee, tea) were prespecified. For other food groups, serving frequency was converted to average daily intake based on age/sex-specific portion sizes and reference data from the Swedish National Food Agency database.[17]

We calculated a modified Mediterranean diet score (mMED score), ranging from 0 to 8, based on relative adherence to a traditional Mediterranean diet adapted from a diet scale originally reported by Trichopoulou and colleagues.[18 19] One point was given for intakes above the median for (1) fruit and vegetables (apple, banana, berry, orange/citrus and other fruit; carrot, beetroot, broccoli, cabbage, cauliflower, lettuce, onion, garlic, pepper, spinach, tomato and other vegetables); (2) legumes (beans, pea soup and lentils) and nuts; (3) non-refined or high-fibre grains (whole meal bread, crisp bread, oatmeal and wheat bran); (4) fermented dairy products (cultured milk, yoghurt and cheese); and (5) fish. In addition, one point was given for (6) intakes below the median of red and processed meat, for (7) use of olive or rapeseed oil for cooking or as dressing and for (8) moderate alcohol consumption with an average of 5–15 g of alcohol per day.

The SFFQ has been validated against fourteen 24-hour diet recall interviews conducted over a 1-year period in a subset of participants in CoSM (n=248). The Spearman coefficient correlations between SFFQ and fourteen 24-hour recall interview ranged between 0.70 to 0.81 for intakes of total carbohydrate, fat, fibre and alcohol.[20] In addition, the reproducibility of two SFFQ completed 1 year apart was good with intraclass correlation ranging from 0.65 to 0.85 for all macronutrients. In SMC, the SFFQ (version from 1987 similar to that used in CoSM and SMC in 1997) has been validated against four 1-week diet records done over a 1-year period in 129 women.[21] The Spearman correlation coefficient between SFFQ and diet records ranged from 0.63 to 0.73 comparing dietary patterns (ie, prudent vs western) and from 0.40 to 0.82 for main food groups in a Mediterranean diet. In addition, the reproducibility of these patterns between two SFFQ completed 1 year apart ranged from 0.41 to 0.73, consistent with other studies in Asia and the USA.[22–24] Validated data on weight, height and physical activity and detailed information on smoking and education level were also collected at baseline in both cohorts as previously described.[25–30] Finally, information on date of death and

emigration were collected from the Swedish Total Population Register.[31]

Outcome ascertainment

The Swedish Patient Register has collected nationwide data on hospital discharges since 1987.[32] Each entry represents an encounter and includes date of birth, sex, dates of hospital admission, hospital department and discharge diagnoses (including surgical procedures).[32] All encounters are organised according to individual's personal identify number. Starting in January of 2001, the Swedish Patient Register also included data on all non-primary care outpatient diagnoses and procedures.[33]

Incident cases of CD and UC were ascertained through linkage of SMC and CoSM participants to the Swedish Patient Register and were defined by at least two inpatient or outpatient encounters with a primary or secondary diagnosis (for UC ICD9: '556' or ICD10: 'K51'; for CD ICD9: 555 or ICD10: K50) following the return of baseline questionnaires in 1997 in both cohorts. Use ofInternational Classification of Diseases (ICD) coding for identifying a number of chronic diseases, including IBD, in the inpatient component of the Swedish Patient Register has a positive predictive value of 85%–95%.[34] In addition, in a recent validation study designed specifically for IBD, using both inpatient and outpatient components of the Swedish Patient Register, the positive predictive values using our definition for CD, UC and IBD cases were 81%, 90% and 93% respectively.[35]

Statistical analysis

Follow-up time was defined from 1 January 1998 to date of diagnosis, emigration, death or end of follow-up (31 December 2017), whichever came first. We assessed the mMED score as a quantitative exposure and categorised as 0–2, 3–4, 5 and 6–8. These categories were selected a priori to reflect extreme scores and to ensure an adequate number of participants in each group based on prior studies of mMED score in these cohorts.[36 37] The cutoffs for the lower and upper categories also correspond to the lower and upper quartiles of the mMED score distribution. In addition, we examined for non-linear associations between mMED score and risk of CD and UC using restricted cubic splines[38] and observed no evidence for such associations. We also used multiple imputations with chain equations to carry out 20 imputations of missing data on covariates. The proportion of missing data in our study was 9495 (11%) for physical activity, 2969 (3.5%) for body mass index (BMI), 1306 (1.5%) for smoking and 182 (0.2%) for education level.

We used Cox proportional hazards modelling to estimate the age/multivariable (MV)-adjusted HR and 95% CI. Our models were adjusted for age, BMI, education level, smoking, total caloric intake and physical activity (Met-hr/week). In addition, all models were stratified by sex (ie, cohort). Test for trend across categories was conducted by assigning the median value to each mMED category and modelling this as a continuous variable. We performed several sensitivity analyses. We restricted our follow-up to after January 2002 to account for the introduction of outpatient encounters in the Swedish Patient Register and to allow for 1-year gap for identifying prevalent cases of IBD previously not captured through inpatient register. In addition, this analysis allowed us to assess for the possibility of reverse causation related to participants' dietary changes as a result of symptoms related to undiagnosed subclinical or early disease. We also examined the possibility that the association between Mediterranean diet and risk of IBD may differ according to subgroups defined by age, sex, education level, BMI, physical activity and smoking. We tested for the significance of the interaction by entering mMED score and these covariates in our models as multiplicative interaction terms. Finally, we calculated the population attributable risk conferred by a relatively poor adherence to the Mediterranean diet (ie, mMED score=0–2), to estimate the percentage of IBD cases that might have been prevented if all participants had followed a Mediterranean diet, assuming a causal relationship.[39 40] We used SAS V.9.4 for these analyses. P values were 2-sided and values less than 0.05 were considered statistically significant. The study was approved by the regional ethics committee of Stockholm, Sweden. In both cohorts, consent to participate in the study was obtained through returned questionnaires.

RESULTS

After exclusions, 83 147 participants were eligible for our analyses. Through December of 2017, we confirmed 164 incident cases of CD and 395 incident cases of UC, yielding an incidence rate of 12 cases/100,000 person-years and 28 cases/100,000 person-years for CD and UC, respectively. The mean follow-up time of participants was 17 years (std=5). The age at diagnosis of CD and UC ranged from 47 to 83 years. Baseline characteristics of participants are reported in table 1. Compared with participants in the lowest category of mMED score, those in the highest category on average had a higher caloric intake and education level and were more likely to be female and have never smoked. There were no significant differences in age, BMI or physical activity.

In our age-adjusted model, we found that a higher mMED score was associated with a lower risk of CD (P_{trend}=0.02) (table 2). Specifically, compared with participants in the lowest category of mMED score, the age-adjusted HRs of CD were 0.70 (95% CI 0.49 to 0.99), 0.78 (95% CI 0.50 to 1.23) and 0.42 (95% CI 0.22 to 0.78) for participants with a mMED score of 3–4, 5 and 6–8, respectively. These associations were not altered after adjusting for potential confounders including education level, BMI, total caloric intake, smoking, physical activity and cohort (sex) (P_{trend}=0.03). The MV-adjusted HRs were 0.69 (95% CI 0.48 to 0.99), 0.78 (95% CI 0.49 to 1.24) and 0.42 (95% CI 0.22 to 0.80) for participants with a mMED score of 3–4, 5 and 6–8, respectively. We estimated that for every one-unit increase in mMED score, the MV-adjusted HR of CD was 0.87 (95% CI 0.78 to 0.96). Overall, the prevalence of relatively poor adherence to a Mediterranean diet (ie, mMED score=0–2) was 27% at baseline, conferring an adjusted population attributable risk of 12% (95% CI 3% to 26%) for later-onset CD, assuming a causal relationship between diet and CD. In contrast, we did not observe an association between mMED score and risk of UC (P_{trend}=0.61). Compared with participants in the lowest category of mMED score, the MV-adjusted HRs of UC were 1.35 (95% CI 1.04 to 1.76), 1.37 (95% CI 0.99 to 1.90) and 1.08 (95% CI 0.74 to 1.58) for participants with a mMED score of 3–4, 5 and 6–8, respectively.

In exploratory analyses, we examined the association between individual components of mMED score and risk of CD and UC (figure 2). Compared with participants with below the median consumption of nuts and legumes, the MV-adjusted HR of CD among participants with above the median consumption was 0.70 (95% CI 0.50 to 0.98). Higher consumption (above the median) of fruit and vegetable (MV-adjusted HR=0.83, 95% CI 0.60 to 1.15), fermented dairy (MV-adjusted HR=0.82, 95% CI 0.59 to 1.13), non-refined grains (MV-adjusted HR=0.78, 95% CI 0.55 to 1.10) and use of olive oil (MV-adjusted HR=0.70, 95% CI

Table 1 Baseline characteristics of participants in the SMC and CoSM according to mMED score*

	mMED score			
	(0–2) (n=22 237)	(3-4) (n=36 951)	(5) (n=13 630)	(6-8) (n=10 329)
Age (years)	62 (10)	61 (10)	61(9)	60 (9)
Sex (female), %	36	45	53	61
Education, %				
Primary school	80	73	65	57
High school	10	11	12	13
University	10	16	23	30
Body mass index (kg/m^2)	26 (4)	26 (4)	25 (3)	25 (3)
Ever smoking, %	60	55	52	49
Physical activity (Met-hours/week)	42(5)	42(5)	42(5)	42(5)
Total caloric intake	2038 (795)	2256(848)	2367 (847)	2411(783)
Components of mMED score				
Fruit and vegetables (g/day)	251 (156)	386 (223)	492 (231)	557 (225)
Legumes and nuts (g/day),	0.3 (1)	0.8 (2)	1 (3)	2 (4)
Non-refined/high fibre grains (g/day)	137 (115)	190 (131)	210 (128)	221 (121)
Fermented dairy (g/day)	151 (182)	253 (240)	325 (260)	376 (256)
Fish (g/day)	26 (29)	37 (37)	43 (33)	48 (30)
Red and processed meat (g/day)	83 (55)	78 (56)	73 (51)	62 (43)
Olive oil and/or rapeseed oil use, %	10	35	63	85
Moderate alcohol intake, %	14	29	42	61

*All characteristics were derived from the 1997 questionnaires. Unless notes, continuous variables are presented in mean (SD).
CoSM, Cohort of Swedish Men; mMED, modified Mediterranean diet; SMC, Swedish Mammography Cohort.

0.50 to 0.98) were also associated with decreased risk of CD, although most estimates did not reach statistical significance. In contrast, we did not observe an association between any of the components of mMED score and risk of UC. We explored whether the association between mMED score and risk of CD and UC was consistent across several subgroups defined by age, sex (cohort), education level, smoking, physical activity or BMI (tables 3 and 4) and observed no evidence for effect modification (all $P_{interaction}$ >0.35).

We conducted several sensitivity analyses. First, restricting our follow-up to after 1 January 2002 to account for dietary changes that might have resulted from subclinical or undiagnosed disease (ie, excluding cases of CD and UC that were diagnosed within 4 years of SFFQ administration) did not materially alter our effect estimates. Specifically, compared with participants in the lowest category of mMED score, the MV-adjusted HRs of CD and UC in the highest category of mMED score were 0.44 (95% CI 0.23 to 0.84) and 1.14 (95% CI 0.77 to 1.69), respectively. Second, because of the potential differential effect of fruit and vegetables on risk of IBD, we recalculated mMED score by separating these two food groups. Compared with participants in the lowest category of mMED score (0–2), the MV-adjusted HRs in the highest group of mMED group (7-9) were 0.57 (95% CI 0.32 to 0.99) for CD and 1.01 (95% CI 0.70 to 1.46) for UC. Third, as rapeseed oil was not included in the original definition of adherence to a Mediterranean diet, we conducted a sensitivity analysis excluding this from our calculation of mMED score. Compared with participants in the lowest category of mMED score (0–2), the MV-adjusted HRs in the highest group of mMED group (6-8) were 0.44 (95% CI 0.23 to 0.85) for CD and 1.07 (95% CI

Table 2 mMED score and risk of Crohn's disease and UC

	mMED score				
	(0–2) (n=22 237)	(3–4) (n=36 951)	(5) (n=13 630)	(6–8) (n=10 329)	P_{trend}*
Person-years of follow-up	361 082	624 597	238 698	185 790	
Crohn's disease					
Number of cases	56	67	29	12	
Age-adjusted, HR (95% CI)	1.0	0.70 (0.49–0.99)	0.78 (0.50–1.23)	0.42 (0.22–0.78)	0.02
MV-adjusted, HR (95% CI)†	1.0	0.69 (0.48–0.99)	0.78 (0.49–1.24)	0.42 (0.22–0.80)	0.03
UC					
Number of cases	84	193	74	44	
Age-adjusted, HR (95% CI)	1.0	1.34 (1.03–1.73)	1.33 (0.98–1.82)	1.02 (0.71–1.46)	0.81
MV-adjusted, HR (95% CI)†	1.0	1.35 (1.04–1.76)	1.37 (0.99–1.90)	1.08 (0.74–1.58)	0.61

*P_{trend} was calculated using the median value for each category.
†Models are adjusted for cohort (sex), age (years), education (primary school, high school and education), body mass index, smoking (never, past and current) and total caloric intake.
mMED, modified Mediterranean diet; MV, multivariable.

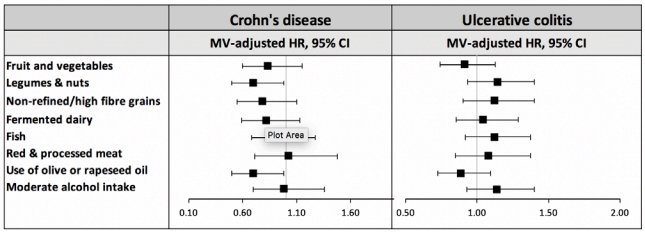

Figure 2 The association between adherence to individual components of modified Mediterranean diet (mMED) score and risk of CD and UC. For fruit and vegetables, legumes and nuts, non-refined/high fibre grains, fermented dairy and fish the estimates represent comparison of above the median consumption, representing a score=1 for mMED score to below the median consumption. For red and processed meat, the estimate represents comparison of below the median consumption, representing a score=1 for mMED score to above the median consumption. Moderate alcohol consumption is defined as 5–15 g of alcohol per day. MV, multivariable.

Table 3 mMED score and risk of Crohn's disease according to selected Strata

	Cases	Person-years	MV-adjusted HR, 95% CI*	$P_{interaction}$
Sex				
Male	99	749 531	0.32 (0.11 to 0.89)	0.78
Female	65	660 637	0.50 (0.21 to 1.21)	
Age at start of follow-up				
<60 years	101	773 622	0.45 (0.21 to 0.97)	0.84
≥60 years	63	636 546	0.31 (0.09 to 1.07)	
Body mass index†				
<25 kg/m^2	79	677 777	0.32 (0.13 to 0.79)	0.52
≥25 kg/m^2	85	732 391	0.56 (0.22 to 1.38)	
Education				
Primary school	120	979 353	0.45 (0.20 to 1.02)	0.99
High school	20	162 981	0.49 (0.09 to 2.57)	
University	24	267 834	0.46 (0.11 to 1.99)	
Physical activity†				
<median	77	547 956	0.33 (0.13 to 0.83)	0.82
≥median	56	558 895	0.61 (0.21 to 1.78)	
Smoking†				
Never smoker	60	623 266	0.83 (0.35 to 1.95)	0.55
Ever smoker	101	765 627	0.17 (0.05 to 0.57)	

*Comparing the extremes of mMED score quartiles. Models are adjusted for age (years), cohort (sex), body mass index, smoking (never, past and current) and total caloric intake.
†Missing data on these variables were not included or imputed for these analyses.
mMED, modified Mediterranean diet; MV, multivariable.

Table 4 mMED score and risk of UC according to selected Strata

	Cases	Person-years	MV-adjusted HR, 95% CI*	$P_{interaction}$
Sex				
Male	252	749 531	1.20 (0.74 to 1.96)	0.57
Female	143	660 637	0.98 (0.52 to 1.84)	
Age at start of follow-up				
< 60 years	247	773 622	0.96 (0.59 to 1.57)	0.85
≥ 60 years	148	636 546	1.32 (0.73 to 2.41)	
Body mass index†				
< 25 kg/m^2	173	677 777	1.10 (0.63 to 1.93)	0.97
≥ 25 kg/m^2	222	732 391	1.09 (0.65 to 1.84)	
Education				
Primary school	278	979 353	1.25 (0.79 to 1.99)	0.37
High school	42	162 981	1.71 (0.37 to 7.89)	
University	75	267 834	0.77 (0.35 to 1.71)	
Physical activity†				
< below the median	168	547 956	1.30 (0.76 to 2.21)	0.52
≥ below the median	157	558 895	0.99 (0.51 to 1.92)	
Smoking†				
Never smoker	104	623 266	1.03 (0.49 to 2.17)	0.91
Ever smoker	288	765 627	1.17 (0.75 to 1.83)	

*Comparing the extremes of mMED score quartiles. Models are adjusted for age (years), cohort (sex), body mass index, smoking (never, past and current) and total caloric intake.
†Missing data was not included or imputed for these analyses.
mMED, modified Mediterranean diet; MV, multivariable.

0.73 to 1.57) for UC. Finally, using a previously described array-based approach, we estimated that an unmeasured confounder would need to have a prevalence of 80% in the highest quartile of mMED score compared with 20% in the lowest quartile with a relative risk for CD of less than 0.17 to account for our observed association.[41]

DISCUSSION

In two large prospective cohorts of middle-aged men and women in Sweden, we demonstrate that greater adherence to a Mediterranean diet is inversely associated with risk of later-onset CD but not UC. These findings were consistent across multiple sensitivity and subgroup analyses.

To our knowledge, this is the first prospective cohort study that has examined the relationship between a Mediterranean diet and risk of incident CD and UC. Nevertheless, one prior study from the European Prospective Investigation into Cancer and Nutrition (EPIC) investigators did not show an association between a Mediterranean dietary pattern and risk of CD.[42] However, smaller numbers of CD cases and significant heterogeneity in methods used to collect dietary information across centres in EPIC-IBD's nested case-control design may have limited the

power of the study to find a significant association. In addition, the influence of a Mediterranean diet on risk of CD may not be as pronounced in populations that are largely adherent to such a diet. In contrast, several prior studies have shown a relationship between individual food groups and nutrients, found in high quantity in a Mediterranean diet and risk of IBD.[43 44] One prior study from the US prospective cohort studies of the Nurses' Health Study (NHS) and Nurses' Health Study (NHSII) found that higher intake of fibre particularly from cruciferous vegetables and cereals is associated with a decreased risk of incident CD.[43] Similarly, data from the EPIC have shown an inverse association between fibre derived from cereals and risk of CD among non-smokers.[44]

Our findings have plausible biologic mechanisms. Several dietary intervention studies have demonstrated significant changes in inflammatory markers, immune cell populations and response to oxidative stress with Mediterranean diet.[8 45] Specifically, in Healthy Lifestyle in Europe by Nutrition in Adolescence study, adherence to a Mediterranean diet was associated with an attenuation in oxidative stress response in adolescents.[45] Similarly, in the randomised controlled trial of European Project on Nutrition in Elderly People, adherence to a Mediterranean diet for 1 year was associated with significant changes in innate and adaptive immunity as measured by T cell degranulation, cytokine production and co-receptor expression.[8] These results are further supported by a number of cross-sectional analyses of patients with immune-mediated disorders including CD and psoriasis demonstrating an inverse relationship between adherence to a Mediterranean diet and disease activity.[9 46] In addition, adherence to a Mediterranean diet appears to have significant beneficial effect on the gut microbiome composition and function.[47 48] Finally, components of a Mediterranean diet such as fibre may also exert anti-inflammatory effect through modification of the barrier function and bacterial translocation.[49]

Our observation that the beneficial association of the Mediterranean diet appears to be exclusive to CD is in line with prior studies demonstrating that diet appears to be a stronger modifiable lifestyle factor for CD.[50] In addition, dietary intervention studies such as EEN and CDED have primarily been effective in CD.[1–4] Although the exact biologic rationale behind this unique relationship is unclear, it may be explained in part by the greater role of the gut microbiome in CD; specifically, CD is characterised by significant dysbiosis and further by improvement in disease activity with faecal diversion, as compared with UC.[51–53] Therefore, diet-induced changes in the gut microbiome may have a greater impact in preventing and treating CD.

We highlight several strengths of our study. First, the prospective nature minimised the risk of selection and recall biases that are commonly observed in cross-sectional studies of diet in IBD. Second, in our study we were able to account for other important lifestyle factors such as BMI, physical activity and smoking that are likely to confound the relationship between diet and IBD. Finally, we used a nationwide registry and a validated method to ascertain cases of CD and UC minimising the risk of outcome misclassification.

We acknowledge several limitations. First, our study population included mostly middle-aged men and women and therefore it is unclear whether our findings may be generalisable to younger individuals at risk of IBD. Nevertheless, environmental factors may play a greater role in development of later-onset IBD,[15] highlighting the importance of identifying modifiable risk factors in elderly onset disease. Further, many of the beneficial anti-inflammatory, immunologic and metabolic effects of Mediterranean diet have specifically been demonstrated in older adults.[8] Second, calculation of mMED score was based on the distribution of dietary intake in our cohorts, which may not be generalisable to other populations with a vastly different pattern of dietary intake. As an example, comparing the median intake of the components of mMED score to those published by Trichopoulou and colleagues[18] showed similar consumption of fruit and vegetables, red and processed meat, fish and alcohol but vastly different intakes of legumes, nuts and grains. Third, there are measurement errors associated with collection of dietary data. However, as demonstrated in our prior validation studies, when compared with other methods, SFFQ provides reasonably valid estimates of dietary intake. In addition, measurement error for diet is unlikely to be systematically associated with the outcome and therefore commonly results in a spurious underestimate of associations, rather than false overestimates.[54] Hence, the inverse association with CD may be greater than we detected. Fourth, we do not have updated dietary data. However, as has been shown in other studies, individuals' dietary intake remains relatively stable over time[55] and therefore it's less likely that their categorisation based on diet will significantly change over time . Finally, we acknowledge that our observed associations may be related to residual confounding related to our inability to adjust for other factors such as family history of IBD and early life exposures. However, adjusting for known confounders did not materially alter our estimates. In addition, in our sensitivity analysis, we demonstrated that it will be very unlikely for an unmeasured confounder to fully attenuate the observed association between mMED score and risk of CD.

CONCLUSION

In two large prospective cohort studies, we show that a greater adherence to a Mediterranean diet is associated with a lower risk of later onset CD. Our study further highlights the importance of continued research focusing on the benefits of the Mediterranean diet in patients with established CD. Such efforts including the ongoing clinical trial of specific carbohydrate and Mediterranean diets to induce remission of Crohn's disease will provide significant insight into the role of diet in IBD therapeutics.

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