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TITLE PAGE

Dietary patterns and risk of inflammatory bowel disease in Europe: results from the EPIC study

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Abbreviations:

aMED score: Adapted mediterranean score
BMI: Body mass index
CD: Crohn's disease
CI: Confidence intervall
EPIC: European Prospective Investigation Into Cancer
FFQs: Food frequency questionnaires
IBD: Inflammatory Bowel disease
IRR: Incident Rate Ratio
MDS: Mediterranean diet score
PUFAs: Polyunsaturated fatty acid
ROS: Reactive oxygen species
SCFA: Short chain fatty acid
SD: Standard deviation
UC: Ulcerative colitis

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ABSTRACT

Background:

Specific nutrients or foods have been inconsistently associated with ulcerative colitis (UC) or Crohn's disease (CD) risks. Thus we investigated associations between diet as a whole, as dietary patterns, and UC and CD risks.

Methods:

Within the prospective EPIC (European Prospective Investigation into Cancer) study, we set up a nested matched case-control study among 366 351 participants with IBD data, including 256 incident cases of UC and 117 of CD, and four matched controls per case. Dietary intake was recorded at baseline from validated food frequency questionnaires. Incident rate ratios (IRRs) of developing UC and CD were calculated for quintiles of the Mediterranean diet score and *a posteriori* dietary patterns produced by factor analysis.

Results:

No dietary pattern was associated with either UC or CD risks. However, when excluding cases occurring within the first two years after dietary assessment, there was a positive association between a "high sugar and soft drinks" pattern and UC risk (IRR for the fifth *vs.* first quintile 1.68 (1.00-2.82); p_{trend} = 0.02). When considering the foods most associated with the pattern, high consumers of sugar and soft drinks were at higher UC risk only if they had low vegetables intakes.

Conclusions:

A diet imbalance with high consumption of sugar and soft drinks and low consumption of vegetables was associated with UC risk. Further studies are needed to investigate if microbiota alterations or other mechanisms mediate this association.

Keywords: environmental factors, nutrition, dietary pattern, IBD

TEXT

Introduction

Diet is suspected to be an environmental factor involved in the etiology of inflammatory bowel disease (IBD).The rapid increase in the incidence of both Crohn's disease (CD) and ulcerative colitis (UC) over the past 50 years, the geographic distribution of patients with inflammatory bowel disease (IBD), and studies in migrants support the role of environmental factors in the etiology of IBD.[1,2] of which diet could be an important part. Experimental models show that diet contribute to gut inflammation through several mechanisms including antigen presentation, alteration of gut permeability, and changes in the composition of the gut microbiota.[3–5] Epidemiological studies performed in prospective cohorts of healthy volunteers reported associations between dietary components and the subsequent development of IBD. High intakes of linoleic acid,[6] animal proteins,[7] as well as low intakes of docosohexaenoic acid (DHA) have been associated with a higher risk of UC. High intakes of animal protein[7] as well as low intakes of fiber and fruit[8,9] and DHA[10] have been associated with a greater risk of CD. Recently, Chan et al, from our group did not find any association between total carbohydrate, mono and disaccharides or starch intakes with either UC or CD.[11] Nevertheless, all previous observational studies investigated specific foods and/or nutrients. However, diet is highly complex; therefore, the specific effect of an individual dietary constituent can be affected by that of others. To assess the impact of overall diet on the development of IBD, the correlations between groups of foods and nutrients that define different dietary patterns should be taken into account.[12] In several diseases, especially cancer[13–18], the beneficial effect of a "Mediterranean diet" as compared to a

"Western diet" has been hypothesized. The Mediterranean diet is characterized by high consumptions of vegetables, legumes, fruits and nuts, cereal products, fish and olive oil, a moderate consumption of wine and moderate-to-low consumptions of meat and dairy products. Interestingly, there is a well-known North-South gradient for IBD risk in Europe[19] that led us to investigate whether it could be due to diet. So far, dietary pattern approaches for IBD have been only investigated in retrospective case-control studies with inherent recall biases for diet.[20–22] Since no prospective studies are available in UC or CD, we conducted a study in a large European prospective cohort to examine the risk of developing UC and CD associated with adherence to Mediterranean diet score and with a posteriori dietary patterns produced by factor analysis.

Materials and Methods

Study population

The methodology of the European Prospective Investigation into Cancer and Nutrition (EPIC) study has been previously described.[23] The EPIC-IBD Study involves a sub-cohort that includes 366,351 healthy men and women aged 20–80 years recruited between the years 1992 and 2000 in Denmark, France, Germany, Italy, the Netherlands, Sweden, and the United Kingdom. In most EPIC study centers, participants were recruited from the general population except in France (women of a health insurance scheme for teachers); Utrecht (The Netherlands; women from a breast cancer screening program); and in Oxford (UK; where half of the cohort were vegans, lacto-ovo vegetarians, or fish eaters) (table 1).[23]

Case and control identification

After recruitment, the cohort was followed up until May 2004 to December 2010 (depending on centers). Participants who developed incident IBD during follow up were identified by several methods: self-report in follow-up questionnaires, population-based disease registries, hospital-based registries, pathology records, or health insurance schemes. For each case, local physicians ascertained the diagnosis of UC or CD by reviewing the medical, endoscopic, radiological and histological reports. Participants with prevalent IBD at baseline as well as participants who developed indeterminate colitis and microscopic colitis were excluded. Using incidence density sampling design, controls were randomly selected in a 4:1 ratio matched for center, sex, age (±6 months), and date of recruitment (±3 months). Controls were alive at the date the matched cases were diagnosed (incidence density matching), which ensured that duration of follow-up was similar for all case-control sets.

Dietary assessment

Usual diet was assessed at baseline, using country-specific validated[23] food frequency questionnaires (FFQs) which recorded average intakes of 200 food items over the past 12 months,[24,25] and enabled to compute individual mean consumptions of foods or food groups in grams per day. In all centers, the FFQs were validated against 24-h recall questionnaires.[26] : “As shown in the validation study[24-25] correlation between questionnaire measurements and individual average 24-hours recalls were acceptable and of similar magnitude in the different EPIC centers (estimated validity coefficients varying from 0.5 to 0.7 according to food compound and EPIC centers).Total energy intake (in Kcal per day) was calculated for each participant using national databases of

food composition.[27,28] Participants with implausible dietary intakes, namely within the lowest and highest 1% of the cohort distribution of the ratio of reported total energy intake over energy requirement, were excluded from the current study (*n* = 736).

Adherence to the Mediterranean diet Score (MDS)

Adherence to a Mediterranean diet score (MDS) was assessed using an adapted Mediterranean diet score (aMED) applied to the EPIC FFQs.[29,30] The score contained nine components, seven positively associated with MDS (vegetables, legumes, fruits and nuts, cereal products, fish and seafood, monounsaturated to saturated fatty acids ratio, and moderate alcohol consumption) and two negatively associated with MDS (meat and meat products, and dairy products). Dietary intakes of these food groups were categorized into low and high intakes according to the median value in controls specific to each country and sex. For assessment of the MDS, dietary intakes were assigned a value of 0 or 1 when below or above the median value respectively. The scoring was reversed for the two components inversely associated with the MDS. For alcohol, moderate alcohol consumption (ethanol intakes from 10 to <50 g/day in men and 5 to < 25 g/day in women) was assigned a value of 1, and all other consumptions were assigned a value of 0. Therefore, the aMED ranged from 0 (indicating the lowest adherence to the MDS) to 9 (the highest adherence to the MDS).

Principal component dietary patterns

Dietary patterns were also generated with no *a priori* hypothesis from the participant food intakes reported by controls at baseline. These *a posteriori* dietary patterns were produced by factor analysis using the procedure factor based on 25 major food groups.

The food groups were adapted from those used by Slimani et al. [31] by subdividing fats into mutually exclusive groups of deep frying fats, vegetable oils excluding those used for deep frying, margarine, butter, and other animal fats. A negative (respectively positive) factor loading meant that the food group was inversely (respectively positively) correlated with the factor. Factors were rotated by an orthogonal transformation, using the SAS "Varimax" option. For each subject, the factor score for each pattern was calculated by summing up the standardized consumption of food groups weighted by the factor loading. Labels were attributed to the dietary patterns according to the foods for which the loading coefficient was higher than 0.2 or lower than −0.2, as this value roughly corresponds to a statistical significance of $p = 0.05$.

Assessment of other covariates

Baseline standardized self-questionnaires recorded information on smoking. Body mass indexes (BMI) were calculated in kg/m² from the participants' weights and heights measured at baseline except in France and Oxford (UK), where anthropometric data were self-reported at baseline.[32]

Statistics

Baseline characteristics were compared between cases and controls using the Pearson's χ^2 test for categorical variables and the Wilcoxon test for continuous variables. We computed country- and sex-specific categories of food group intakes and dietary patterns. Associations between categories of dietary patterns and UC or CD risk were estimated by incidence rate ratios (IRR) with 95% confidence intervals (95% CI) using conditional logistic regression models adjusted for smoking (never, past, or current

smoker), BMI (continuous), and total daily dietary energy intake (continuous). To assess potential reverse causality due to delayed IBD diagnosis, we performed sensitivity analyses in which UC or CD cases diagnosed during the first 2 years after recruitment were excluded. For the tests for linear trend, we built-up semi-continuous variables considering the median value for each category of the studied variables, wich was entered in the logistic regression models. Potential interactions between dietary patterns and other covariates were tested by including interaction terms formed by the product of the potential effect modifier with the studied variable. Heterogeneity of effects according to sex and country were assessed by the X^2 statistic. For all potential confounders, values were missing in less than 5% of the subjects and were imputed to the modal or mean value in controls, considering sex and country. All tests were two-sided and statistical significance (p-value) was set at the 0.05 level. All analyses were performed using the SAS, version 9.3, software (SAS Institute, Inc., Cary, North Carolina).

Ethical considerations

Each EPIC center obtained individual written informed consent and local ethics approval.

Results

A total of 256 participants developed incident UC (median age at diagnosis 51.5 years, 61% female) and 117 incident CD (median age at diagnosis 50.3 years, 73% female) (table 2). The median time between entry into the cohort and diagnosis was 3.8 years for UC and 4.6 years for CD. Compared with controls, UC cases were more often ex-

smokers (p=0.01) and CD cases, current smokers (p=0.04). The wide variation in IBD incidence observed across centers, reflect different background characteristic of participants recruited in each center. For example, in UK, incidence rate of IBD was lower in Oxford which recruited health conscious subjects, mostly vegetarians as compared to Norfolk which recruited from general population.

Association between IBD and the aMED score

There were no associations between quintiles of the aMED score and either UC (p trend = 0.41) or CD (p trend = 0.67) (appendix 1). Because of the disputed place of alcohol in the MDS,[28] we also analyzed a Mediterranean score limited to eight food groups, excluding alcoholic beverages but adjusted on alcohol intake, and results were similar (data not tabulated, available on request).

Characteristics of the *a posteriori* dietary patterns

Based on the results of the correlation matrix, we identified three dietary patterns separately in UC and CD controls. The percent variance explained by these patterns was 26.8% (11.2, 8.5, and 7.1% for the first, second, and third pattern respectively) in UC and 29.0% (13.3, 8.1, and 7.6% respectively) in CD. Factor-loadings are tabulated in table 3 . In UC controls, pattern 1 was characterized by high consumptions of sugar and confectionery, and of soft drinks, and low consumptions of vegetables and non-processed seafood. It was labeled “sugar & soft drinks”. Pattern 2 was characterized by high consumptions of sugar and confectionery, and soft drinks, but also of vegetables, legumes, fruit, and sauces, and was labeled “sugar, soft drinks, vegetables & legumes”.

Pattern 3, was characterized by a high consumption of eggs, fresh and processed seafood, coffee, alcoholic drinks, and potatoes and labeled “eggs, seafood, potatoes, coffee and alcohol.” In CD controls, pattern 1 was characterized by a high consumption of vegetables, and was labeled “vegetables.” Pattern 2, was characterized by a high consumption of sugar and confectionery, and soft drinks, and was labeled “sugar & soft drinks”. Pattern 3, was characterized by a high consumption of alcoholic drinks, animal fats, non-processed and processed seafood, potatoes, and coffee and was labeled “animal fats, seafood, potatoes & alcohol”.

Association between dietary patterns and IBD risk

In UC (Table 4), the adjusted incidence rate ratio for the fifth *vs.* first quintile of the “sugar and soft drinks” pattern was 1.31 (95% CI: 0.85, 2.02; *p* trend = 0.05). The other patterns were not associated with UC risk. When restricting analyses to UC cases diagnosed 2 years or more after dietary assessment (table 4), the adjusted IRR for the fifth *vs.* first quintile of the “sugar and soft drinks” pattern was 1.68 (95% CI: 1.00, 2.82; *p* trend = 0.02). The association between UC risk and the “sugar and soft drinks” pattern was not modified by sex or country (test for interaction p=0.90 and 0.28 respectively). When considering the relationship between food groups that composed the dietary pattern and UC risk at least two years after the dietary assessment, a positive association between high consumptions of sugar and soft drinks, and UC onset was restricted to participants with intakes of vegetables the median population intake: IRR = 11.70; 95 % CI 3.65-37.51 in those over the median intake *vs.* 0.58; 95 % CI 0.29-1.16 in those under the median intake; p heterogeneity < 0.0001 (data not tabulated). This association was driven by high consumption of soft drinks rather than

sugar/confectionaries (IRR for the last versus first quintile: 2.44 (1.63-3.65) versus 0.61 (0.33-1.12) respectively (data not tabulated).

No food pattern was found to be associated with CD either overall (table 5), or when restricting analyses to case diagnosed at least two years after dietary assessment.

Sensitivity analyses stratified on median BMI were performed. No effect modification of BMI on UC risk (IRR= 1.78 (0.61-5.18) for BMI< 24.75: vs 1.65 (0.70-3.88) for BMI>24.75; p homogeneity =0.98) nor on CD risk (IRR=0.98 (0.27-3.55) for BMI<24.11: vs 0.88(0.22-3.44) for BMI >24.11; p homogeneity=0.82) was found.

DISCUSSION

In this large European study, we present for the first time the relationship between diet as a whole and IBD risk within a prospective design. A “sugar & soft drinks” pattern was associated with UC risk when diagnosed at least two years after diet recording. There was no association between a priori or a posteriori dietary patterns and CD risk.

Previous epidemiological studies reported conflicting results towards the association between sugar intake and UC. Indeed four publications[32–35] out of eight[7,33–39] reported a higher risk of UC associated with high intakes of mono-or disaccharides, but most of these studies were retrospective with inherent risk of recall bias and reverse causation. A recent prospective study performed by our group found no association between carbohydrates, sugar, or starch intakes and UC risk[11]. In the present analyses of dietary patterns, we aimed to explore diet as a whole, and addressed the complex relationships

between food groups associated with IBD onset. A previous study performed in children with IBD showed that a Western diet was associated with an increased risk for CD while a prudent diet was associated with a decreased risk of CD [21]. However, as a retrospective study it was prone to recall bias, and it did not investigate ulcerative colitis. In our study, a diet rich in sugar and soft drinks was associated with UC risk when diagnosed at least two years after diet recording with a dose-effect relationship, except when it was associated with high consumptions of vegetables. This suggests that the factor associated with UC could be an overall imbalance between consumptions of sugar and soft drinks on one hand, and of vegetables on the other hand. Regarding UC risk, earlier studies reported positive associations with sugar intake. Our results suggest that vegetable intake could modulate a deleterious effect of high soft drink consumption in UC. Vegetable intake seems to neutralize the harmful effects of soft drinks in UC. In our study we have found no association with CD. While previous studies reported an inverse association between fruit and vegetable intakes and CD risk, we failed to find such an association with pattern 1 that was typically rich in fruit and vegetables. Pattern 1 includes high amounts of vegetables, legumes and fruits; the IRR of the last quintile vs the first one is 1.00 (0.45-2.23) and the p trend for CD risk is 0.82. It is possible that dietary patterns exert a differential effect over the risk of UC and CD, such as that observed with tobacco. However the number of CD cases was limited, and could have been insufficient to detect dietary pattern associated with CD risk.

Soft drinks are characterized by high quantities of corn syrup (i.e. a glucose-fructose syrup) and of artificial sweeteners. Noticeably, the consumption of fructose and artificial sweeteners (mainly from soft drinks) has significantly increased worldwide, for the last decades[40,41] in North America and Western Europe, and more recently in Asia.[42,43] A

high consumption of sugar and soft drinks associated with a low consumption of vegetables, legumes, and fruit are major features of the Western diet. Interestingly, the Worldwide spread of the Western diet can be put in perspective with the geographic distribution[1] and time trends[44,45] of UC incidence rates across the World, i.e. a steady increase over the last three decades with recent stabilization[46] in the US and Europe compared with a strong increase in Asia in the most recent years.[47,48]

In vivo, fructose has been demonstrated to increase intestinal permeability,[49] stimulate the production of reactive oxygen species (ROS) and initiate pro-inflammatory processes.[50–52] Alterations in the microbiota composition associated with sugar intake have been described. Artificial sweeteners could induce compositional and functional alterations of the intestinal microbiota that promote glucose intolerance.[53] A high fat/high sugar diet is responsible for alterations of the gut microbiota composition and intestinal permeability, and promotes low grade inflammation and metabolic disorders in mice.[54] Lactic acid bacteria and gamma-Proteobacteria are the predominating organisms involved in sugar alcohol metabolism.[55] Sorbitol and mannitol fermentation are promoted by *Escherichia coli*, *Salmonella* spp., *Shigella* spp., as well as *Lactobacillus* spp. and *Streptococcus* spp.[56] On the other hand, interactions between dietary fiber and the gut microbiota are thought to play an important role in the regulation of the gut barrier integrity.[57] Dietary fiber largely provided by vegetables, fruit and legumes lead to the production of short chain fatty acids (SCFAs) and especially of butyrate by colonic bacterial fermentation. SCFAs enhance the integrity of the intestinal barrier[58,59] and could regulate the size and function of the colonic Treg pool that protects against experimental colitis in mice.[60,61] In addition, a diet rich in fruits and vegetables is associated with high gene counts, and therefore a more diverse intestinal microbiota. Of

relevance is that patients with UC exhibit an intestinal dysbiosis characterized by decreased bacterial diversity[62] and proportions of *Roseburia hominis* and *Faecalibacterium prausnitzii,* both butyrate-producing bacteria of the *Firmicutes* phylum.[58,63] The positive association observed in our study between UC risk and a diet high in sugar and soft drinks, and low in vegetables could be mediated by changes in the gut microbiota and increased intestinal barrier permeability. Further data are needed to explore the interactions between consumptions of sugar and soft drinks, and of vegetables on the gut microbiota composition and intestinal barrier function.

Our study has several strengths. For the first time in IBD, a pattern approach was prospectively used to explore relation between diet and IBD onset. This approach widely spread in nutritional epidemiology is useful to consider intercorrelations between various dietary compounds that can confound observed associations. It might be particularly advantageous to investigate whether diet in all its complex relationships and potential interactions contributes to the well-known North-South gradient for IBD risk in Europe[19]. Secondly, dietary assessments and other exposures were collected before diagnosis to avoid recall bias. Thirdly, the dietary questionnaires were validated,[24,25,64] and allowed assessing a wide diversity of diets and food groups.[31] Fourthly, the cohort design helped to minimize selection biases. We were able to consider important confounders such as smoking and country of residence.[19] We additionally adjusted for educational level (a proxy for socio economic status) and this did not modify the results (data not shown). Finally, IBD cases only included physician-confirmed CD or UC cases, thereby excluding participants with uncertain diagnoses. The strengthening of the association in the sensitivity analysis restricted to participants diagnosed at least two years after the dietary questionnaire is not in favor of a reverse causation mechanism.

Our study has some limitations. First, diet was measured once at baseline, which can introduce error if diet changes over time. This measurement error would result in underestimates of any potential associations and lock of sensitivity to detect weak associations. However, studies of repeated measures of longitudinal diet suggest that absolute dietary changes in adult are small.[65] Then, the identification of dietary patterns by factor analysis involves subjective decisions such as definition of food groups included in the factor analysis step, the number of components to extract, and the labeling of the identified patterns.[66] The main limitations are subjective definitions of food groups and labeling of identified patterns.[12,67,68] Nevertheless, in major chronic diseases, several studies have reported the stability over time of a posteriori dietary patterns derived from factor analysis,[27] as well as reproducibility across populations.[69,70] An essential point, is that dietary patterns were based on dietary intakes of participants included in the EPIC study (volunteers, among whom about 65% were women of middle age) and might not be representative of dietary habits of the overall European populations. It must be confirmed in other populations before pretending generalization of such results. The median age at recruitment into the cohorts was approximately 50 years, thus we mostly investigated late-onset IBD. In this class of age, incident UC is more frequent than incident CD (1), as observed in our study. In addition, as the number of cases was limited, we could have lacked the power to identify other specific dietary patterns with lower effect sizes, especially in CD. Also, as the number of controls was limited, they were randomly selected to insure their representativeness with participants of the entire cohort. Finally, as in all observational studies, we cannot rule out residual confounding from unmeasured factors.

In summary, this large European prospective study suggests that an imbalance between high consumptions of sugar and soft drinks on one hand, and low consumption of vegetables on the other hand, could be a factor associated with UC onset. These findings must be confirmed in other populations, and experimental data are needed to explore the effect of such a dietary pattern on the composition and activity of the gut microbiota and other pathways involved in the pathogenesis of IBD.

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Author's contributions to manuscript:

AR, FC and MCB designed and conducted research, analyzed data, and wrote paper . SSMC and ARH designed research, provided essential materials and had primary responsibility for final content. The remaining co-authors, HBM,BO, FvS, AT,AO, KO, FIC,TK,RL,KTK,ER,OG,SL,GH,PK,FCC,MB,HB,BB,DP and GM are principal investigators in their respective centers who contributed to the local design, development, and recruitment of participants into their cohorts.These authors generated the local IBD databases, and contributed to the analysis and writing of the manuscript.All authors read and approved the final manuscript.

Conflicts of interest: none

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TABLES

Table 1: Characteristics of the cohort

Country and center	Cohort size	Nature of cohort	Incident CD (N cases)	Incident UC (N cases)
United Kingdom				
Norfolk	25,639	Population based cohort of men and women aged 45-74 years. Recruited 1993-1997. Cases identified up to June 2004 from follow-up questionnaires, in-patient admission data and histopathology records.	12	31
Oxford	50,070	Members of UK vegetarian societies and readers of health food magazines (78% women), aged 20-80 years recruited 1994-1999. Cases identified up to May 2004 from follow up questionnaires	5	23
Germany				
Heidelberg	25,540	Population based cohort of men aged 45-65 years and women aged 35-65 years. Recruited 1994-1998. Cases identified up to June 2003 from follow-up questionnaires.	11	6
Potsdam	27,548	Population based cohort, men and women, aged 35-64 years. Recruited 1994-1998. Cases identified up to April 2007 from follow-up questionnaires.	5	17
Italy				
Florence	13,583	Population based cohort, men and women aged 34-64 years. Recruitment 1993-1998. Cases identified from a regional database of inflammatory bowel disease up to May 2004.	4	9
Sweden				
Umeå	25,732	Population based cohort, men and women aged 30-60 years. Recruited 1992-1996. Cases identified up to February 2007 from a regional database of inflammatory bowel disease.	9	20
Malmö	28,098	Population based cohort, men and women aged 45-69 years. Recruited between years 1991-1996. Cases identified up to October 2003 from a regional database of inflammatory bowel disease.	11	26
Denmark				
Aarhus and Copenhagen	57,053	Population based cohort of men and women aged 50-64 years. Recruited 1993-1997. Cases identified up to July 2007 from the national database of inflammatory bowel disease	16	48
France				
Regions throughout the country	72,996	Women aged 40-65 years recruited 1990-1993. Members of a health insurance scheme for school teachers and co-workers. Cases identified up to April 2008 by follow up questionnaires.	25	33

The Netherlands				
Amsterdam, Doetinchem, Masstricht and Utrecht	40,092	Men and women, aged 20-70 years, recruited 1993-1997 from the general population of 3 cities (Amsterdam, Doetinchem, Masstricht) and from the breast cancer screening programme in Utrecht. Cases identified up to December 2009 by regional inflammatory bowel disease databases.	16	43
Total	366,351		117	256

Table 2: Demographics of cases and controls

Baseline Characteristics	UC cases n=256	UC controls n=1,022	CD cases n=117	CD controls n=468
Female (%)	156 (61)	623 (61)	86 (73)	344 (72)
Age at recruitment (years, median, range)	51.5 (22.0-76.9)	51.6 (22.0-77.2)	50.3 (22.9-75.8)	50.1 (22.7-76.2)
Age at IBD diagnosis (years, median, range)	56.7 (24.5-80.8)	-	55.8 (27.0-78.7)	-
Time to IBD diagnosis (years, median, range)	3.8 (0.1-15.6)		4,6 (0.1-14.2)	
Smoking status (%) (no, past, current)	31.6/39.5/28.9	46.2/29.0/24.8	38.5/25.6/35.9	46.1/29.1/24.8
Body mass index (kg/m², mean, SD)	24.7 (4.0)	24.7 (4.1)	23.9 (3.9)	24.1 (3.9)
Total energy intake (Kcal/day, mean, SD)	2,083 (635)	2,033 (646)	2,078 (612)	2,051 (597)

Abbreviations:CD: Crohn's disease, IBD: Inflammatory bowel disease, SD: standard deviation UC: Ulcerative Colitis,

Table 3: Factor Loadings for the three rotated factors in ulcerative colitis & Crohn's disease controls.

Food Group	UC			CD		
	Pattern 1 Sugar & soft drinks	Pattern 2 Sugar, soft drinks vegetables & legumes	Pattern 3 Eggs, seafood, potatoes, coffee & alcohol	Pattern 1 Vegetables	Pattern 2 Sugar & soft drinks	Pattern 3, Animal fat, seafood, potatoes & alcohol
Sugar/confectionary	0.31	0.27	0.01	0.01	0.37	-0.12
Soft drinks	0.31	0.27	0.01	0.01	0.37	-0.12
Vegetables	-0.18	0.24	0.09	0.26	0.11	0.03
Legumes	-0.06	0.23	-0.03	0.19	0.12	0.02
Fruits	-0.09	0.20	-0.02	0.19	0.07	0.01
Potatoes	0.11	-0.03	0.22	-0.14	0.12	0.22
Fresh seafood	-0.20	0.10	0.28	0.14	0.06	0.25
Processed seafood	0.02	-0.05	0.26	-0.11	0.06	0.20
Eggs	-0.12	0.03	0.31	0.09	0.01	0.18
Red or processed meat	0.07	-0.07	-0.01	-0.15	-0.06	-0.01
White meat	-0.16	0.03	0.04	0.16	-0.03	0.02
Dairy products	-0.01	0.02	0.14	0.03	0.18	0.07
Deep frying vegetable fats	0.15	0.01	-0.06	-0.08	0.05	-0.13
Other vegetable fats	-0.15	0.08	-0.04	0.13	-0.06	0.07
Butter	0.01	0.03	-0.02	-0.03	-0.12	-0.04
Other animal fats	-0.02	0.01	0.16	0.03	0.01	0.25
Margarine	0.13	-0.03	0.17	-0.14	0.14	0.14
Sauces	-0.01	0.25	0.06	0.15	0.18	0.01
Cereals	-0.01	0.14	0.10	0.03	0.08	0.19
Nuts and seeds	-0.07	0.01	-0.03	-0.01	-0.03	0.09
Fruit & vegetable juices	0.01	0.06	-0.04	-0.03	-0.06	-0.12
Cakes & biscuits	0.01	0.09	-0.01	-0.03	-0.01	0.01
Coffee	0.02	-0.11	0.25	-0.11	0.01	0.20
Tea	0.02	0.12	-0.09	0.06	0.08	-0.14
Alcoholic beverages**	-0.03	-0.08	0.23	-0.05	-0.02	0.29

Abbreviations: UC: Ulcerative colitis CD: Crohn'sdisease.

*Dietary patterns were separately generated from a factor analysis using the procedure factor based on the individual food intakes reported by UC controls (n=1060) and CD controls (n=484) at baseline. ** As grams of alcohol

Table 4: Adherence to the a posteriori dietary patterns and risk of ulcerative colitis

UC (n=256)		Cases N (%)	Unadjusted IRR*(95% CI)	Adjusted IRR**(95% CI)	UC ≥ 2 years*** (n=196) N (%)	Adjusted IRR **(95% CI)
Sugar & soft drinks pattern	Quintile 1	53 (21)	Ref	Ref.	33 (17)	Ref.
	Quintile 2	38 (15)	0.72 (0.45-1.15)	0.75 (0.47-1.15)	32 (16)	1.00 (0.58-1.73)
	Quintile 3	45 (17)	0.86 (0.54-1.36)	0.87 (0.55-1.36)	39 (20)	1.10 (0.65-1.85)
	Quintile 4	53 (21)	1.09 (0.69-1.72)	1.06 (0.67-1.66)	40 (20)	1.24 (0.72-2.12)
	Quintile 5	67(26)	1.35 (0.88-2.08)	1.31 (0.85-2.02)	52 (27)	1.68 (1.00-2.84)
			P_{trend}=0.05	P_{trend}=0.05		P_{trend}=0.02
Sugar , soft drinks vegetables & legumes pattern	Quintile 1	43 (17)	Ref.	Ref.	34 (17)	Ref.
	Quintile 2	45 (18)	1.11 (0.69-1.78)	1.07 (0.67-1.72)	36 (18)	1.13 (0.66-1.93)
	Quintile 3	60 (23)	1.43 (0.91-2.24)	1.36 (0.87-2.13)	46 (24)	1.33 (0.80-2.22)
	Quintile 4	55 (21)	1.32 (0.83-2.08)	1.32 (0.83-2.12)	44 (23)	1.46 (0.86-2.48)
	Quintile 5	53 (21)	1.19 (0.74-1.92)	1.27 (0.77-2.10)	36 (18)	1.17 (0.65-2.09)
			P_{trend}=0.37	P_{trend}=0.38		P_{trend}=0.66
Potatoes & seafood pattern	Quintile 1	48 (18)	Ref.	Ref.	35 (18)	Ref.
	Quintile 2	53 (21)	1.12 (0.72-1.73)	1.07 (0.68-1.68)	44 (22)	1.20 (0.71-2.00)
	Quintile 3	53 (21)	1.09 (0.69-1.71)	1.00 (0.62-1.60)	39 (20)	0.92 (0.53-1.59)
	Quintile 4	52 (20)	1.11 (0.71-1.74)	0.93 (0.57-1.51)	43 (22)	0.95 (0.54-1.67)
	Quintile 5	52 (20)	1.04 (0.65-1.65)	0.83 (0.49-1.42)	35 (18)	0.77 (0.41-1.44)
			P_{trend}=0.87	P_{trend}=0.37		P_{trend}=0.62

Abbreviations: CI: confidence interval, IRR: Incidence rate ratio, UC: ulcerative colitis.
* Matched on age, sex, center and date of recruitment into EPIC.
** Matched on age, sex, center and date of recruitment into EPIC and adjusted for daily energy intake (kcal/day), body mass index (kg/m^2), smoking status (never/past/current smoker)
***Subgroup analyses restricting to UC cases diagnosed 2 years or more after dietary assessment.

Table 5: Adherence to the a posteriori dietary patterns and risk of Crohn's disease

CD (n=117)		Cases N (%)	Unadjusted IRR*(95% CI)	Adjusted IRR**(95% CI)	CD ≥ 2 years*** (n=82) N (%)	Adjusted IRR **(95% CI)
Vegetables pattern	Quintile 1	31 (26)	Ref	Ref.	19 (22)	Ref.
	Quintile 2	23 (19)	0.71 (0.39-1.31)	0.74 (0.40-1.36)	18 (21)	1.11 (0.54-2.29)
	Quintile 3	20 (17)	0.63 (0.33-1.19)	0.73 (0.39-1.37)	14 (16)	0.93 (0.43-2.03)
	Quintile 4	22 (19)	0.66 (0.36-1.23)	0.75 (0.40-1.38)	19 (22)	1.24 (0.60-2.55)
	Quintile 5	22 (19)	0.61 (0.32-1.18)	0.74 (0.39-1.43)	17 (19)	1.03 (0.48-2.20)
			P_{trend}=0.24	P_{trend}=0.46		P_{trend}=0.91
Sugar & soft drinks pattern	Quintile 1	15 (13)	Ref.	Ref.	9 (10)	Ref.
	Quintile 2	35 (30)	2.30 (1.17-4.54)	1.90 (0.97-3.72)	26 (30)	2.62 (1.13-6.10)
	Quintile 3	15 (13)	1.14 (0.52-2.50)	0.93 (0.42-2.04)	10 (12)	0.99 (0.37-2.70)
	Quintile 4	28 (24)	1.99 (0.96-4.10)	1.58 (0.76-3.30)	22 (25)	1.97 (0.80-4.85)
	Quintile 5	24 (20)	1.66 (0.80-1.60)	1.20 (0.56-2.56)	20 (23)	1.48 (0.60-3.61)
			P_{trend}=0.42	P_{trend}=0.98		P_{trend}=0.93
Animal fats, seafood, potatoes & alcohol pattern	Quintile 1	23 (20)	Ref.	Ref.	15 (17)	Ref.
	Quintile 2	25 (21)	1.03 (0.53-2.00)	1.00 (0.52-1.94)	18 (21)	1.20 (0.54-2.65)
	Quintile 3	25 (21)	1.19 (0.61-2.32)	0.94 (0.48-1.85)	20 (23)	1.08 (0.49-2.39)
	Quintile 4	20 (17)	0.81 (0.41-1.59)	0.72 (0.36-1.43)	16 (18)	0.97 (0.44-2.15)
	Quintile 5	24 (21)	1.00 (0.50-1.99)	0.65 (0.30-1.39)	18 (21)	0.71 (0.29-1.73)
			P_{trend}=0.83	P_{trend}=0.76		P_{trend}=0.32

Abbreviations: CI: confidence interval, IRR: Incidence rate ratio, UC: ulcerative colitis.
* Matched on age, sex, center and date of recruitment into EPIC.
** Matched on age, sex, center and date of recruitment into EPIC and adjusted for daily energy intake (kcal/day), body mass index (kg/m^2), smoking status (never/past/current smoker)
***Subgroup analyses restricting to CD cases diagnosed 2 years or more after dietary assessment.

TITLE PAGE

Dietary patterns and risk of inflammatory bowel disease in Europe: results from the EPIC study

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Abbreviations:

aMED score: Adapted mediterranean score
BMI: Body mass index
CD: Crohn's disease
CI: Confidence intervall
EPIC: European Prospective Investigation Into Cancer
FFQs: Food frequency questionnaires
IBD: Inflammatory Bowel disease
IRR: Incident Rate Ratio
MDS: Mediterranean diet score
PUFAs: Polyunsaturated fatty acid

ROS: Reactive oxygen species
SCFA: Short chain fatty acid
SD: Standard deviation
UC: Ulcerative colitis