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Original Article

Dietary Intake Pattern is Associated with Occurrence of Flares in IBD Patients

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Abstract

Background: Diet is associated with the onset of inflammatory bowel disease [IBD]. Up to half of IBD patients believe that diet contributes to flares. However, studies on this topic are sparse and merely focus on specific nutrients, food items or food groups. We aimed to analyse the association between dietary patterns and flare occurrence in two geographically distinct Dutch cohorts.

Methods: In this longitudinal study, 724 IBD patients [Northern cohort: $n = 486$, Southern cohort: $n = 238$] were included and followed for 2 years. Habitual dietary intake was obtained via semi-quantitative food frequency questionnaires at baseline. Principal component analysis [PCA] was conducted on 22 food groups to identify dietary patterns. Flare occurrence was analysed in 427 patients in remission at baseline, using multivariable Cox proportional hazards.

Results: Compared to the Southern cohort, patients in the Northern cohort were younger at diagnosis, comprised more females, and had lower overall energy intakes [all $p < 0.05$]. PCA revealed three dietary patterns explaining 28.8% of the total variance. The most pronounced pattern [explaining 11.6%] was characterized by intake of grain products, oils, potatoes, processed meat, red meat, condiments and sauces, and sugar, cakes and confectionery. Of the 427 patients, 106 [24.8%] developed an exacerbation during follow-up. The above dietary pattern was associated with flare occurrence (hazard ratio [HR]: 1.51, 95% confidence interval [CI]: 1.04–2.18, $p = 0.029$), as was female sex [HR: 1.63, 95% CI 1.04–2.55, $p = 0.032$].



Conclusions: A dietary pattern, which can be seen as a 'traditional [Dutch]' or 'Western' pattern was associated with flare occurrence. Confirmation in prospective studies is needed.

Key Words: Inflammatory bowel disease [IBD]; dietary patterns; disease course

1. Introduction

Inflammatory bowel disease [IBD], comprising Crohn's disease [CD] and ulcerative colitis [UC], is a chronic relapsing–remitting disorder of the gastrointestinal tract. The number of flares varies largely between patients and negatively affects health-related quality of life in IBD patients.¹ Furthermore, insufficient control of flares results in chronic irreversible bowel damage.² The aetiology of IBD has not been completely elucidated and the exact triggers of a flare are not clear. However, 33–57% of IBD patients believe that diet contributes to the development of a flare and often experiment with their food intake to avoid symptoms.^{3,4}

A longitudinal study in 183 UC patients found that meat [especially red and processed meat], protein, alcohol, sulphur and sulphate intake increase the likelihood of a flare.⁵ In CD a decreased *n-6/n-3* poly-unsaturated fatty acid ratio [$n = 76$] and avoidance of dietary fibres were reported to be associated with flare development in CD [$n = 1130$], but not in UC patients [$n = 489$].^{6,7} A more recent study in 135 IBD patients reported a positive association between dietary fibre and flare occurrence and an inverse association with high [saturated] fat intake.⁸ In currently available studies, study populations were small [between 76 and 183 patients],^{5,7,8} follow-up was limited [maximum of 1 year^{5,7}] and the definition of a flare is sometimes solely based on a clinical symptom score.⁵ The study by Brotherton et al.⁶ did include a large number [$n = 1613$] of IBD patients but had a relative short follow-up period of 6 months and focused on consumption of fibres. To gain better insight into dietary patterns and disease course, longitudinal follow-up in well-defined large IBD outpatient cohorts is important. It is of additional interest to take different geographical regions into account, because the habitual dietary intake and relative contribution of genetic and environmental factors in IBD phenotype may differ between regions.⁹ Furthermore, the focus of currently available studies is mainly on nutrients, food items or food groups.^{5–8} However, dietary patterns are of particular interest because nutrients are likely to act synergistically or antagonistically as part of a whole meal or daily dietary intake.¹⁰

Between 40 and 70% of the IBD patients have reported adjusting their diet in order to prevent symptoms.¹¹ To better support and advise patients in their search for symptom relief, research on the association between dietary patterns and flares is needed, especially because consistent scientific evidence is largely lacking.

The aim of this study was to identify dietary patterns in habitual dietary intake of IBD patients after diagnosis and subsequently to analyse the association between the identified dietary patterns and the occurrence of a flare in two geographically distinct, longitudinal IBD cohorts.

2. Materials and methods

2.1. Cohort description

For the present study, baseline data on habitual dietary intake and longitudinal data on disease course were collected for IBD patients from two geographically distinctive cohorts from the Northern and

Southern provinces of the Netherlands. Patients were included if they had a minimum age of 18 years and fulfilled the international diagnostic criteria for IBD.¹² Patients were excluded, **Figure 1**, when diagnosed with IBD unclassified or having an ileoanal pouch or ileorectal anastomosis, were on tube feeding or had missing data (i.e. disease course data could not be retrieved from medical records, patients participated in another intervention study whereby data from IBD-related visits could not be retrieved, or patients skipped multiple pages and therefore had incomplete food frequency questionnaire [FFQ] data). Furthermore, patients with implausible FFQ data [overall intake for males < 800 or > 4200 kcal/day and for females < 500 or > 3500 kcal/day]¹³ were excluded. All patients were followed prospectively with a maximum duration of 2 years, or until lost to follow-up. In both cohorts, information on demographic data, disease phenotype according to the Montreal classification,¹⁴ previous surgical procedures, disease activity (clinical symptoms, Harvey–Bradshaw Index [HBI],¹⁵ simple clinical colitis activity index [SCCAI],¹⁶ faecal calprotectin, C-reactive protein [CRP], endoscopy and radiological imaging) were retrieved retrospectively from medical records using standardized registration forms and similar definitions in both cohorts. The data underlying this article can be shared on reasonable request to the principal investigators of the respective cohorts and in line with European directives. The STROBE-Nut checklist, which is an extension of the STROBE statement for nutritional epidemiology, was used to report the results.¹⁷

2.2. Northern cohort

The 1000IBD project¹⁸ comprises a cohort to prospectively follow IBD patients in the Northern provinces of the Netherlands. This cohort is part of the 'Parelsnoer' Initiative [PSI],¹⁹ which is established by the Dutch Federation of University Medical Centers, to optimize clinical bio-banking within the eight Dutch university medical centres for research purposes. As part of PSI protocols [described elsewhere²⁰], IBD patients are monitored closely and followed prospectively in the University Medical Centre Groningen [UMCG]. The 1000IBD project was approved by the medical research ethics committee of the University Medical Centre Groningen [METC UMCG 1000IBD 2008.338]. All patients provided written informed consent.

2.3. Southern cohort

The IBD South-Limburg [IBDSL] cohort is a well-characterized population-based inception cohort in the South-Limburg area in the Netherlands.²¹ The IBDSL cohort has been used to study IBD epidemiology and disease course since 1991. IBDSL patients visiting the outpatient clinic of Maastricht University Medical Center+ [MUMC+] were checked for eligibility for participation in the current study and included after giving/providing written informed consent. This study was approved by the medical research ethics committee of the MUMC+ [NL42101.068.12] and registered in ClinicalTrial.gov [NCT01756963], the IBDSL cohort was also approved by the medical research ethics committee of MUMC+ [NL31636.068.10] and registered in ClinicalTrial.gov [NCT02130349]. The IBDSL

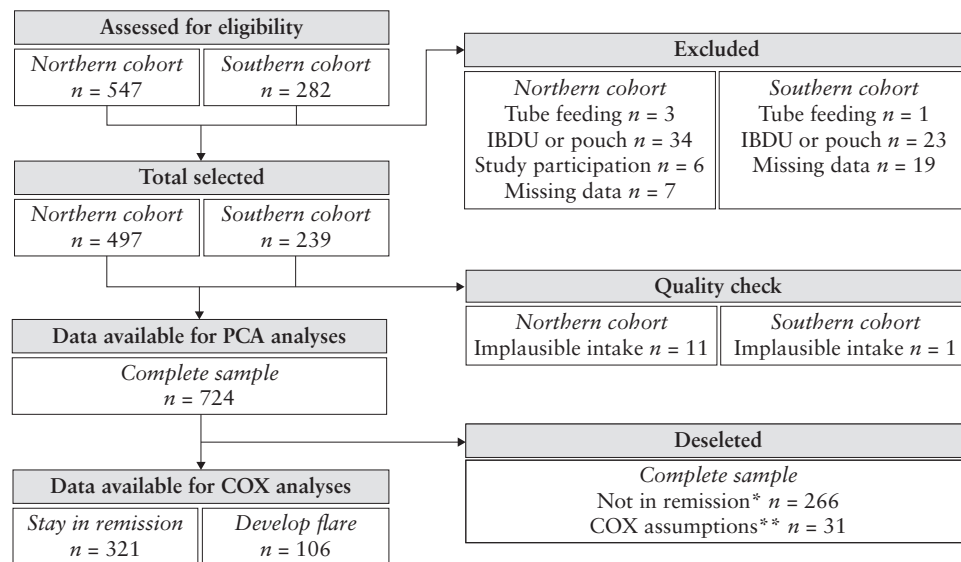


Figure 1. Flowchart of participant inclusion. Description: n = number. IBDU = IBD unclassified. Implausible intake = overall intake for males < 800 or > 4200 kcal/day and for females < 500 or > 3500 kcal/day. PCA = principal component analysis. *Patients are 'not in remission' if disease activity was detected at baseline and/or up to 3 months prior to inclusion. **COX assumptions = Cox proportional hazard regression analysis requires no missing data.

data warehouse was used to retrieve relevant clinical data for the present study.

2.4. Clinical data collection

Every visit to the outpatient clinic or hospitalization was registered in the medical record of a patient and was checked to assess if patients fulfilled the criteria of having a flare. Since data have been collected retrospectively from medical records, a flare was defined by the following criteria in line with clinical practice and previous studies^{22,23}: [i] presence of active disease confirmed by a physician availing endoscopy and/or radiological imaging [ultrasound, computed tomography or magnetic resonance imaging]; [ii] increased faecal calprotectin [≥ 250 $\mu\text{g/g}$]; [iii] faecal calprotectin ≥ 100 $\mu\text{g/g}$ with at least five-fold increase from previous visit; [iv] clinical symptoms indicative of disease activity or increased HBI or SCCAI accompanied by a dose escalation or initiation of a new drug; or [v] if the dose escalation or initiation of a new drug was accompanied by a CRP above the cut-off point of the relevant hospital [Northern cohort ≥ 5 mg/L, Southern cohort ≥ 10 mg/L]. Disease activity was determined according to the above-mentioned criteria over the course of 3 months prior to inclusion, at the time of inclusion and during the follow-up period with a maximum of 2 years. When data were incompletely registered in patients records in the period before inclusion, in addition to the above-mentioned criteria, IBD-related hospitalization due to disease activity and IBD-related surgery were examined to be able to evaluate disease activity. Furthermore, time since last flare and time to flare during a follow-up were calculated in months.

2.5. Dietary data collection

In both cohorts, habitual dietary intake was obtained via comparable FFQs developed [in collaboration with] and validated by the division of Human Nutrition of Wageningen University.²⁴⁻²⁶ In the Northern cohort, the FFQ was administered to patients between 2013 and 2016; in the Southern cohort, dietary data were collected between 2012 and 2017. The FFQ did not record intake of nutritional supplements. The intake over the previous month was used as a reference period. It was

assessed by scoring the frequencies of consumption on a seven- or ten-item scale: 'never' to '7 days per week', or a four-item scale: 'never', 'sometimes', 'often' and 'always' along with the usual amount taken in. Portion sizes were estimated using natural portions and commonly used household measures. In the Northern cohort, data on the frequency of food intake were linked to the Dutch food composition table [NEVO 2011, RIVM Bilthoven, the Netherlands], resulting in a calculated individual mean consumption of the reported macronutrients and 110 food items. In the Southern cohort, data on frequency were linked to the Dutch food composition table [NEVO 2010, RIVM Bilthoven, the Netherlands], resulting in a calculated individual mean intake of the reported macronutrients, and 148 food items. The food items of both cohorts were grouped into 22 food groups (Supplementary Table S1). For both cohorts, BMR% [total energy intake as percentage of basal metabolic rate]^{27,28} was calculated for men and women separately using the Harris Benedict Equation: $\text{BMR}_{\text{women}} = 655.0955 + [9.5634 * \text{Weight}] + [1.8496 * \text{Length}] - [4.6756 * \text{Age}]$ and $\text{BMR}_{\text{men}} = 66.4730 + [13.7516 * \text{Weight}] + [5.0033 * \text{Length}] - [6.7550 * \text{Age}]$.

2.6. Statistical analysis

2.6.1. General analysis

Baseline characteristics were presented as means with corresponding standard deviations [SD] for continuous variables and as the number of patients with corresponding percentages for categorical variables. Continuous data between the distinctive cohorts were compared by a Student's t -test and categorical data by Chi-square test or Fisher's exact test when appropriate. Although crude intake of food groups was reported, statistics were conducted on $\sqrt{\text{transformed}}$ variables when appropriate.

2.6.2. Principal component analysis [PCA]

PCA is a form of factor analysis, whereby patterns are identified based upon the correlation between food groups, explaining the maximum variance [i.e. complete diet of individuals]. For each 'factor' individual scores are generated, which then rank individuals based on the food group consumption by the weighting of those groups within the factor.²⁹

To extract *a-posteriori* dietary patterns, we conducted PCA with orthogonal [varimax] rotation to obtain optimal interpretability of the extracted components [dietary patterns] on the 22 food groups (which are standardized [Z-scores] per cohort) on all IBD patients.

Before analysis, suitability of the data was tested by using a correlation matrix, using Bartlett's Test of Sphericity and Kaiser-Meyer-Olkin test. Coefficients with absolute values above 0.3 were considered relevant for interpretability. Scree plots and interpretability of the components were used to determine the number of patterns to retain. Subsequently, for each patient, a factor score per dietary pattern was calculated as the sum of the food group weighted by the factor loadings.

As PCA is sensitive to outliers, an additional *robust* PCA with varimax rotation was performed to check whether the results could be confirmed,³⁰ using the same assumptions.

2.6.3. Cox proportional hazards regression analysis

To determine whether adherence to the identified dietary patterns is associated with development of a flare during follow-up, a multivariable Cox proportional hazards regression analysis was performed including all IBD patients being in remission at baseline, while correcting for clinical confounders [i.e. energy intake, study cohort, disease phenotype, gender, age at diagnosis, smoking behaviour and BMI]. Patients were excluded if a flare was detected at, or 3 months prior to, inclusion based on the above-mentioned criteria. In case of insufficient or missing data on disease status, patients were also regarded to be not in remission at baseline, and therefore not included for further analysis on flare development. Hazard ratios [HRs], with 95% confidence interval [95% CI], for the association between PCA-derived dietary patterns [as continuous variable] and flare development were calculated. Furthermore, again, *robust* PCA was used to check whether the regression analysis results could be confirmed. If patients were lost to follow-up, they were censored at time of their last clinical visit. Statistical analyses were performed using IBM SPSS statistics for Mac OS, Version 25 [IBM, Armonk, NY] and R 3.6.3 [R Core Team, 2014]. The PCA orthogonal [varimax] rotation was performed using the R package psych 1.9.12.31,³¹ the *robust* PCA was performed using the R package rrcov version 1.5.2,³² and the Cox proportional hazard regression analysis was estimated using the R package survival v3.1-12.^{33,34} A two-sided *p*-value of < 0.05 was considered significant.

3. Results

3.1. Baseline characteristics of the cohorts

A total of 724 patients were included (Figure 1, Table 1). In the Northern cohort, 486 patients participated consisting of 284 CD and 202 UC patients. Of all these patients, 60.7% were female, mean age at inclusion was 43.0 ± 14.4 years, disease duration was 12.6 ± 9.2 years, and body mass index [BMI] was 25.6 ± 5.1 kg/m². In the Southern cohort, 238 patients participated: 156 CD and 82 UC patients. Of these patients, 52.7% were female, their mean age at inclusion was 45.7 ± 14.8 years, disease duration was 11.5 ± 10.1 years and BMI was 25.5 ± 4.2 kg/m².

Comparing both cohorts revealed that patients in the Northern cohort were more probably female (295 [60.7%] vs 126 [52.9%], *p* = 0.047), were taller [174 ± 9.9 vs 172 ± 9.7 cm, *p* = 0.001], had a lower age [at diagnosis] [43.0 ± 14.4 vs 45.7 ± 14.8 years, *p* = 0.020] and a longer time to last flare at time of inclusion [20.5 ± 6.8 vs 18.6 ± 7.8 months, *p* = 0.013]. No differences were observed in

disease phenotype, BMI or smoking behaviour. The two cohorts showed differences in the Montreal classification [age at diagnosis: *p* = 0.002, location: *p* < 0.001, upper-gastrointestinal disease modifier: *p* = 0.045, behaviour: *p* < 0.001 and perianal disease modifier: *p* = 0.003, but not disease extent: *p* = 0.538] and IBD-medication use [*p* < 0.001]. Patients in the Northern cohort were more likely to have had bowel resection surgery prior to inclusion (156 [32.2%] vs 55 [23.1%], *p* = 0.012) than patients in the Southern cohort.

When comparing patients who remained in remission during follow-up [*n* = 321] with patients who developed a flare [*n* = 106], weight [77.5 ± 14.5 vs 74.1 ± 16.5 kg, *p* = 0.045] and duration of follow-up [22.6 ± 4.9 vs 23.5 ± 2.4 months, *p* = 0.009] were significant.

3.2. Habitual dietary intake

Compared to the Southern cohort, patients in the Northern cohort had a lower intake of all macronutrients: total energy intake [1930 ± 604 vs 2180 ± 634 kcal, *p* < 0.001], total protein [0.9 ± 0.3 vs 1.1 ± 0.3 g/kg, *p* < 0.001], plant protein [0.4 ± 0.2 vs 0.5 ± 0.2 g/kg, *p* < 0.001], animal protein [0.5 ± 0.2 vs 0.6 ± 0.2 g/kg, *p* < 0.001], fat (35.6 ± 5.6 vs 36.5 ± 5.2 energy [En]%, *p* = 0.038), carbohydrates [46.0 ± 6.5 vs 43.8 ± 6.2 En%, *p* < 0.001] and alcohol [1.5 ± 2.4 vs 2.8 ± 3.6 En%, *p* < 0.001; Table 2]. Moreover, they consumed less legumes [10.3 ± 20.5 vs 17.3 ± 37.0 g/day, *p* = 0.002], grain products [177 ± 85.3 vs 204 ± 86.8 g/day, *p* < 0.001], red meat [34.1 ± 19.9 vs 55.7 ± 36.1 g/day, *p* < 0.001], processed meat [27.8 ± 22.0 vs 44.3 ± 34.5 g/day, *p* < 0.001], fish [14.0 ± 15.1 vs 21.4 ± 22.3 g/day, *p* < 0.001], oils [22.9 ± 18.4 vs 30.1 ± 15.5 g/day, *p* < 0.001], confectionery [74.1 ± 50.7 vs 91.4 ± 61.9 g/day, *p* < 0.001], alcoholic beverages [55.9 ± 101 vs 134 ± 211 g/day, *p* < 0.001], and condiments and sauces [29.1 ± 22.5 vs 35.1 ± 31.5 g/day, *p* = 0.008], but more dairy [256 ± 190 vs 216 ± 177 g/day, *p* = 0.005], poultry [11.5 ± 11.4 vs 10.3 ± 16.9 g/day, *p* < 0.001], non-alcoholic beverages [286 ± 347 vs 219 ± 229 g/day, *p* = 0.009], tea [271 ± 261 vs 248 ± 318 g/day, *p* = 0.020] and prepared meals [31.0 ± 51.5 vs 17.6 ± 31.0 g/day, *p* < 0.001].

Compared to patients who had a flare during follow-up, patients who stayed in remission had a higher BMR% [1622 ± 249 vs 1559 ± 254, *p* = 0.025] but lower intakes of total protein [0.9 ± 0.3 vs 1.0 ± 0.3 g/kg, *p* = 0.035] and animal protein [0.5 ± 0.2 vs 0.6 ± 0.2 g/kg, *p* = 0.022]. Moreover, patients in remission had lower intakes of vegetables [100 ± 66.7 vs 117 ± 73.8 g/day, *p* = 0.027] and red meat [38.1 ± 23.7 vs 46.2 ± 34.8 g/day, *p* = 0.028].

3.3. Dietary patterns

The dietary data were found to be probably factorizable based upon the Bartlett's Test of Sphericity [*p* < 0.001] and Kaiser-Meyer-Olkin test [KMO = 0.655]. Subsequently, PCA was performed, identifying three dietary patterns explaining 11.6%, 8.9% and 8.3%, respectively [cumulative 28.8%] of the total variance in food group consumption for all patients [Table 3, Supplementary Figure S1]. The first dietary pattern is characterized by high intakes of potatoes, grain products, red meat, processed meat, oils, sugar, cakes and confectionery, and condiments and sauces. The second dietary pattern revealed high intakes of red meat, processed meat, coffee, alcoholic beverages, condiments and sauces, and snacks, and low consumption of fruits and tea. The third pattern is characterized by high intakes of vegetables, fruits, nuts, fish, eggs and alcoholic beverages, and low consumption of non-alcoholic beverages.

Table 1. Demographic and clinical characteristics of IBD patients at inclusion

	Complete sample [as used in PCA]		South	p-value [†]	Selection [‡] [as used in cox regression]		p-value ^{††}
	Complete	North			Remission ^{##}	Flare ^{###}	
	n = 724	n = 486	n = 238		n = 321	n = 106	
Demographic characteristics							
Sex [female]	421 [58.1]	295 [60.7]	126 [52.9]	0.047*	176 [54.8]	69 [65.1]	0.064
Age [years]	43.9 ± 14.6	43.0 ± 14.4	45.7 ± 14.8	0.020*	43.6 ± 15.0	43.3 ± 14.7	0.82
Height [cm]	174 ± 9.9	174 ± 9.9	172 ± 9.7	0.001*	174 ± 9.6	172 ± 10.0	0.057
Weight [kg]	77.1 ± 15.9	77.8 ± 16.4	75.5 ± 14.8	0.077	75.5 ± 14.5	74.1 ± 16.5	0.045*
BMI [kg/m ²]	25.6 ± 4.8	25.6 ± 5.1	25.5 ± 4.2	0.826	25.6 ± 4.4	25.0 ± 4.8	0.241
Smoking [active]	141 [19.8]	93 [19.5]	48 [20.4]	0.932	54 [16.8]	22 [20.8]	0.058
Clinical characteristics							
Disease duration [years]	12.2 ± 9.5	12.6 ± 9.2	11.5 ± 10.1	0.162	12.5 ± 10.0	12.1 ± 9.6	0.723
Duration follow up [months]	23.3 ± 4.0	23.2 ± 3.9	22.7 ± 4.4	0.208	22.6 ± 4.9	23.5 ± 2.4	0.009*
Time to flare [months during FU] [§]	19.8 ± 7.2	20.5 ± 6.8	18.6 ± 7.8	0.013*	22.6 ± 4.9	11.2 ± 6.6	<0.001*
Disease phenotype [UC]	284 [39.2]	202 [41.6]	82 [34.5]	0.066	138 [43.0]	37 [34.9]	0.142
Bowel resection prior inclusion [yes]	211 [29.2]	156 [32.2]	55 [23.1]	0.012*	87 [27.1]	30 [28.3]	0.810
Montreal classification[§]							
A1: ≤16 years	73 [10.2]	59 [12.3]	14 [5.9]		38 [11.8]	9 [8.5]	
A2: 17–40 years	472 [65.9]	321 [66.9]	151 [64.0]	0.002*	211 [65.7]	72 [67.9]	0.633
A3: >40 years	171 [23.9]	100 [20.8]	71 [30.1]		72 [22.4]	25 [23.6]	
L1: terminal ileum	138 [32.6]	101 [37.8]	37 [23.7]		59 [33.0]	19 [27.9]	
L2: colon	88 [20.8]	62 [23.2]	26 [16.7]	<0.001*	36 [20.1]	15 [22.1]	0.748
L3: ileocolonic	197 [46.6]	104 [39.0]	93 [59.6]		84 [46.9]	34 [50]	
L4: upper-GI modifier	42 [6.8]	26 [5.6]	16 [10.3]	0.045*	13 [4.6]	7 [8.1]	0.273
B1: non-stricturing, non-penetrating	234 [53.4]	145 [51.4]	89 [57.1]		103 [56.3]	35 [50.0]	
B2: stricturing	125 [28.5]	97 [34.4]	28 [17.9]	<0.001*	43 [23.5]	25 [35.7]	0.126
B3: penetrating	79 [18.0]	40 [14.2]	39 [25.0]		37 [20.2]	10 [14.3]	
P: perianal modifier	145 [22.8]	96 [20.0]	49 [31.4]	0.003*	59 [20.4]	21 [24.1]	0.457
E1: ulcerative colitis	37 [13.3]	28 [14.2]	9 [11.1]		16 [11.9]	4 [10.8]	
E2: left-sided	97 [34.9]	65 [33.0]	32 [39.5]	0.538	43 [31.9]	16 [43.2]	0.427
E3: extensive	144 [51.8]	104 [52.8]	40 [49.4]		76 [56.3]	17 [45.9]	
IBD medication at inclusion[¶]							
No medication	148 [20.5]	114 [23.6]	34 [14.3]		63 [19.6]	22 [20.8]	
5-ASA or topical steroids	146 [20.2]	104 [21.5]	42 [17.6]		70 [21.8]	18 [17.0]	
Systemic steroids	21 [2.9]	20 [4.1]	1 [0.4]	<0.001*	4 [1.2]	2 [1.9]	0.590
Immunomodulators	177 [24.5]	123 [25.5]	54 [22.7]		85 [26.5]	24 [22.6]	
Biologics	229 [31.8]	122 [25.3]	107 [45.0]		99 [30.8]	40 [37.7]	

Statistics are performed using a Student's *t*-test for continuous variables or Chi-squared test or Fisher's exact test for categorical variables. Values are reported as mean ± SD or number [%] when appropriate. [†]Comparison of Northern vs Southern cohort. ^{††}Comparison of patients in remission vs with active disease. [‡]Patients who are in remission at baseline and have shown no signs of disease activity 3 months prior to inclusion. ^{##}Patients who stay in remission during the follow-up period of a maximum 2 years. ^{###}Patients who have a flare up of their disease during the follow-up period of a maximum 2 years. [§]Significant *p*-value < 0.05. [¶]Only patients in remission [at baseline and/or up to 3 months prior to inclusion]. [§]Montreal classification: A = age, L = localization [CD only], B = behaviour [CD only], E = extent [UC only], 5-ASA = 5-aminosalicylic acid. [¶]Patients are categorized to the 'highest' category if they use multiple drugs; order [low to high]: no medication, 5-ASA/topical steroids, systemic steroids, immunomodulators, biologics. PCA = principal component analysis. BMI = body mass index. FU = follow-up period. GI = gastrointestinal. UC = ulcerative colitis.

Table 2. Habitual dietary intake of IBD patients

	Complete sample [as used in PCA]			Selection [as used in Cox regression]		
	Complete	North	South	Remission [#]	Flare [#]	<i>p</i> -value ^{††}
	<i>n</i> = 724	<i>n</i> = 486	<i>n</i> = 238	<i>n</i> = 321	<i>n</i> = 106	
Macronutrient intake						
Energy [kcal]	2012 ± 625	1930 ± 604	2180 ± 634	1987 ± 560	2044 ± 648	0.379
BMIR [%]	1609 ± 257	1616 ± 258	1591 ± 254	1622 ± 249	1559 ± 254	0.025*
Total protein [g/day]	71.7 ± 21.6	68.2 ± 19.7	78.7 ± 23.6	70.4 ± 19.6	72.9 ± 24.3	0.341
g/kg	1.0 ± 0.3	0.9 ± 0.3	1.1 ± 0.3	0.9 ± 0.3	1.0 ± 0.3	0.035*
Plant protein [g/day]	30.9 ± 11.4	29.1 ± 10.5	34.4 ± 12.2	30.8 ± 10.1	30.9 ± 12.7	0.910
g/kg	0.4 ± 0.2	0.4 ± 0.2	0.5 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	0.282
Animal protein [g/day]	40.9 ± 14.8	39.2 ± 13.4	44.3 ± 16.7	39.7 ± 14.3	42.1 ± 16.8	0.162
g/kg	0.5 ± 0.2	0.5 ± 0.2	0.6 ± 0.2	0.5 ± 0.2	0.6 ± 0.2	0.022*
Total fat [g/day]	81.1 ± 30.5	77.0 ± 29.0	89.5 ± 31.7	80.4 ± 28.4	82.4 ± 32.1	0.542
En [%]	35.9 ± 5.5	35.6 ± 5.6	36.5 ± 5.2	36.0 ± 5.5	35.7 ± 5.6	0.631
Carbohydrates [g/day]	227 ± 76.9	222 ± 78.3	237 ± 73.1	223 ± 68.8	231 ± 73.5	0.314
En [%]	45.3 ± 6.5	46.0 ± 6.5	43.8 ± 6.2	45.1 ± 6.3	45.6 ± 6.9	0.431
Alcohol ¹ [g/day]	5.6 ± 8.8	4.1 ± 6.5	8.7 ± 11.7	6.0 ± 8.8	5.5 ± 10.1	0.651
En [%] ¹	1.9 ± 2.9	1.5 ± 2.4	2.8 ± 3.6	2.1 ± 3.1	1.8 ± 2.9	0.326
Food group intake [g/day]¹						
Alcoholic beverages	81.5 ± 151	55.9 ± 101	134 ± 211	89.4 ± 151	78.8 ± 174	0.548
Coffee	318 ± 296	297 ± 263	359 ± 351	338 ± 308	288 ± 282	0.136
Condiments and sauces	31.1 ± 25.9	29.1 ± 22.5	35.1 ± 31.5	30.6 ± 27.2	31.8 ± 26.8	0.696
Cooking oils and fats	25.3 ± 17.8	22.9 ± 18.4	30.1 ± 15.5	23.8 ± 14.7	25.9 ± 18.7	0.295
Dairy	243 ± 187	256 ± 190	216 ± 177	247 ± 184	233 ± 170	0.489
Eggs	13.9 ± 13.8	13.8 ± 13.7	14.2 ± 14.0	14.3 ± 14.7	13.8 ± 15.1	0.747
Fish	16.5 ± 18.1	14.0 ± 15.1	21.4 ± 22.3	15.3 ± 16.9	19.5 ± 23.2	0.090
Fruits	133 ± 109	132 ± 107	134 ± 114	136 ± 107	131 ± 120	0.691
Grain products	186 ± 86.7	177 ± 85.3	204 ± 86.8	183 ± 77.8	191 ± 93.0	0.349
Legumes	12.6 ± 27.2	10.3 ± 20.5	17.3 ± 37.0	10.9 ± 16.9	17.2 ± 41.7	0.134
Non-alcoholic beverages	264 ± 315	286 ± 347	219 ± 229	255 ± 309	276 ± 361	0.561
Nuts	11.3 ± 17.6	10.8 ± 17.3	12.4 ± 18.2	13.3 ± 20.7	10.4 ± 15.6	0.177
Potatoes	82.7 ± 60.5	86.3 ± 64.9	75.4 ± 49.6	78.5 ± 54.2	83.8 ± 59.0	0.391
Poultry	11.1 ± 13.4	11.5 ± 11.4	10.3 ± 16.9	10.7 ± 13.7	12.4 ± 13.4	0.280
Prepared meals	26.6 ± 46.2	31.0 ± 51.5	17.6 ± 31.0	28.6 ± 50.4	29.0 ± 57.4	0.937
Processed meat	33.2 ± 27.8	27.8 ± 22.0	44.3 ± 34.5	31.9 ± 25.9	36.2 ± 32.3	0.166
Red meat	41.2 ± 28.2	34.1 ± 19.9	55.7 ± 36.1	38.1 ± 23.7	46.2 ± 34.8	0.028*
Soups	48.4 ± 58.7	46.5 ± 54.2	52.3 ± 66.9	43.5 ± 47.5	41.2 ± 50.6	0.671
Snacks	28.5 ± 25.2	27.3 ± 22.8	30.8 ± 29.4	30.0 ± 25.0	26.3 ± 24.0	0.185
Sugar, cakes and confectionery	79.8 ± 55.2	74.1 ± 50.7	91.4 ± 61.9	77.6 ± 50.2	77.9 ± 52.4	0.958
Tea	264 ± 281	271 ± 261	248 ± 318	268 ± 271	234 ± 245	0.250
Vegetables	105 ± 69.1	103 ± 69.4	109 ± 68.5	100 ± 66.7	117 ± 73.8	0.027*

Statistics are performed using a Student's *t*-test for continuous variables. Values are reported as mean ± SD. [†]Comparison of Northern vs Southern cohort. ^{††}Comparison of patients in remission vs with active disease. [#]Patients who stay in remission during the follow-up period of a maximum 2 years. ^{##}Patients who have a flare up during the follow-up period of a maximum 2 years. *Significant *p*-value < 0.05. ¹Crude intake reported, statistics conducted on $\sqrt{(\text{transformed variables})}$. BMIR[%] = total energy intake [kcal] as percentage of basal metabolic rate (calculated with Harris Benedict Equation); BMIR w/m en = 655.0955 + [9.5634 * Weight] + [1.8496 * Length] - [4.6756 * Age]; BMIR men = 66.4730 + [13.7516 * Weight] + [5.0033 * Length] - [6.7550 * Age]. En[%] = macronutrients as percentage of total energy intake (calculated as macronutrient/kcal * 100).

Furthermore, the additional *robust* PCA with varimax rotation retained the first two patterns, which were comparable to the PCA orthogonal [varimax] rotation analysis [Supplementary Table S2, Supplementary Figure S2]. Therefore, these two robust patterns were used for Cox proportional hazard regression analysis.

3.4. Cox proportional hazard regression analysis

Of the 724 patients included in the present study, 427 were in remission at baseline and eligible for multivariable Cox proportional hazard regression analysis. Of those patients, 106 [24.8%] developed a flare during follow-up. Adherence to the first and most pronounced dietary pattern [explaining 11.6% of the total variation]

Table 3. Factor loadings of PCA orthogonal [varimax] rotation derived dietary patterns

	Pattern 1	Pattern 2	Pattern 3
Alcoholic beverages	0.003	0.538	0.435
Coffee	0.081	0.445	0.202
Condiments and sauces	0.495	0.334	0.095
Cooking oils and fats	0.742	0.013	-0.001
Dairy	0.110	-0.014	0.048
Eggs	-0.003	0.078	0.566
Fish	-0.058	-0.134	0.611
Fruits	0.005	-0.462	0.371
Grain products	0.753	-0.064	0.019
Legumes	0.206	0.054	0.300
Non-alcoholic beverages	0.150	0.118	-0.391
Nuts	0.003	0.028	0.451
Potatoes	0.590	0.040	-0.052
Poultry	0.048	-0.175	0.014
Prepared meals	0.006	0.257	-0.043
Processed meat	0.504	0.382	0.032
Red meat	0.352	0.448	0.146
Soups	0.208	0.003	0.272
Snacks	0.188	0.407	-0.091
Sugar, cakes and confectionery	0.470	-0.021	-0.097
Tea	0.047	-0.636	0.152
Vegetables	0.276	-0.295	0.397
Explained variance	11.6%	8.9%	8.3%

Statistics are performed using principal component analysis [PCA]. Factor loadings > 0.3 and < -0.3 are indicated in bold type.

Table 4. Multivariable Cox proportional hazard analysis on flare during follow up

	Hazard ratio	95% CI	p-value
Dietary pattern 1 [†]	1.51	1.04–2.18	0.029*
Dietary pattern 2 [†]	1.08	0.87–1.35	0.469
Dietary pattern 3 [†]	1.14	0.92–1.41	0.229
Energy intake [kcal]	1.00	1.00–1.00	0.318
Cohort [Northern = ref]	1.23	0.80–1.89	0.336
Phenotype [CD = ref]	0.84	0.55–1.29	0.427
Sex [male = ref]	1.63	1.04–2.55	0.032*
Age at diagnosis	1.00	0.98–1.01	0.831
Active smoker [no = ref]	1.16	0.70–1.92	0.574
BMI	0.97	0.92–1.02	0.177

Statistics are performed using Cox proportional hazard analysis. CI = confidence interval. [†]Dietary pattern extracted from principal component analysis. *Significance = p-value < 0.05. Ref = reference category. CD = Crohn's disease. BMI = body mass index.

was found to be associated with an increased risk of flare development [HR: 1.51, 95% CI: 1.04–2.18, $p = 0.029$; Table 4]. In addition, women also had an increased hazard of flare development [HR 1.63, 95% CI 1.04–2.55, $p = 0.032$]. However, no interaction was observed between the dietary pattern and sex. Furthermore, no associations were found with other variables tested nor with the other two dietary patterns.

The first two dietary patterns [first pattern: HR 1.50, 95% CI 0.98–2.11, $p = 0.062$; second pattern: HR 0.99, 95% CI 0.82–1.20, $p = 0.917$] derived from the *robust* PCA showed comparable HRs for associations with flare development and female sex [HR: 1.59, 95% CI: 1.03–2.45, $p = 0.037$; Supplementary Table S3]. However, the first dietary pattern lost significance.

4. Discussion

In this prospective study in two distinctive cohorts we found, using PCA, three dietary patterns, cumulatively explaining 28.8% of the total dietary variance in 724 IBD patients after diagnosis. Adherence to the first, most prominent, dietary pattern, but not the second and third pattern, was prospectively associated with the occurrence of flares in 427 IBD patients. To our knowledge, this is the first study investigating the association between a-posteriori dietary patterns and longitudinal flare development in IBD patients during a 2-year follow-up period. The findings indicate the relevance of studying dietary patterns and flare occurrence and warrants future longitudinal studies.

The first dietary pattern we found is characterized by intake of grain products, cooking oils and fats, potatoes, processed meat, red meat, condiments and sauces, and sugar, cakes and confectionery, and can be regarded as a 'traditional [Dutch]' dietary pattern. A few other studies^{35–37} have also described a 'traditional' or 'traditional Dutch' dietary pattern. Overall, the patterns described in literature were largely comparable to our 'traditional [Dutch]' pattern. However, in contrast to dietary patterns established by Waijer et al.,³⁶ our first pattern did not include vegetables, which are typically consumed together with potatoes and meat in the Dutch cuisine.³⁸ Moreover, our pattern was characterized by high intakes of sugar, cakes and confectionery instead of the low intakes of sweets described by Vujkovic et al.³⁵ Using the Crohn's disease exclusion diet [CDED],³⁹ a whole-food diet coupled with partial enteral nutrition, promising results have been reported for the induction of remission in paediatric CD.⁴⁰ Interestingly, in the CDED trial, potatoes and oils [only olive oil and canola oil] are allowed, which is inconsistent with our findings, whereas processed meat, sauces, confectionery, wheat, breakfast cereals and breads are not allowed,⁴¹ reflecting the majority of the food groups of our first pattern. However, in a recent clinical trial in which participants were instructed to follow their usual diet and were assigned to either a high [minimum of two servings per week] or low [not more than one serving per month] red and/or processed meat consumption, no differences on symptomatic flare development in CD were found.⁴²

In the literature, analysing dietary patterns via PCA is increasingly used to study the combined effects of all foods consumed in an individual's diet.¹⁰ It is data-driven, which means no a-priori assumptions are made [except when food items are clustered into food groups], and challenging food interactions can be accounted for. However, the number of dietary patterns to retain is partly based on arbitrary choices [i.e. scree plot, interpretability criteria] and the naming and characterization of dietary patterns cannot be standardized and is therefore subjective.¹³ This can be

demonstrated as our first pattern is partly similar to the second dietary pattern, which is characterized by high intakes of red meat, processed meat, coffee, alcoholic beverages, condiments and sauces, and snacks and low intakes of fruits and tea. Red meat, processed meat, and condiments and sauces [parts of a 'Western' pattern] loaded positively on both patterns. However, an association between this second pattern and development of a flare was not established. However, the first pattern, which we classified as 'traditional [Dutch]' [especially due to the potato intake] also fits into the description of a 'Western' pattern because it is characterized by intakes of grain products, red meat and processed meat, cooking oils and fats, and sugar, cakes and confectionery. As the Netherlands is a Western country, it is not surprising that a 'traditional [Dutch]' dietary pattern is also nowadays [partly] a typical 'Western' diet or could be regarded as a variant of a 'Western' dietary pattern. Subsequently, this could explain why our finding that a 'traditional' pattern is associated with flare development is similar to the literature on a 'Western' dietary pattern in disease development.

Concerning the aetiology of IBD, a meta-analysis⁴³ showed that a 'Western' dietary pattern as defined by at least two of the following characteristics: high intake of refined grains, red or processed meat, animal protein, animal fats and high-fat dairy products, or low consumption of fruit and vegetables was associated with the incidence of IBD [Relative Risk 1.92, 95% CI 1.37–2.68]. Furthermore, a study by Vasseur et al.⁴⁴ found three dietary patterns and labelled these as 'healthy', 'traditional' and 'Western'. They reported an inverse association between a 'healthy' dietary pattern and incident IBD [p -trend = 0.02], whereas a 'Western' dietary pattern was associated with a higher risk on IBD [p -trend = 0.02]. After adjustment for covariates, those associations lost significance. Because a 'Western' dietary pattern seems to play a role in the aetiology of IBD, we did expect our second Western pattern to be associated with disease course as well. The lack of an association might refer to the complexity of dietary influences, which may also vary between individuals.

Our third dietary pattern resembles elements of a more 'Mediterranean'-type dietary pattern, or a 'prudent Dutch' dietary pattern⁴⁵ as it is characterized by high intakes of vegetables, legumes, fruits, nuts, fish, eggs and alcoholic beverages but low intake of non-alcoholic beverages.⁴⁶ Surprisingly, no inverse association was found between flare occurrence and this pattern, of which most of the food groups are in line with the recent dietary guidance recommendations by the International Organization of IBD [IOIBD].⁴⁷ The association of the Mediterranean diet and its health benefits has gained interest in recent years because of its anti-inflammatory potential in chronic diseases such as IBD, and its ability to improve diversity and richness of the gut microbiota and microbial metabolites (increase in faecal short-chain fatty acids [SCFAs]).^{48,49} Preliminary data of 38 patients with IBD in remission assigned and adhering to a Mediterranean diet for 6 months showed an increased quality of life and decrease of CRP.⁵⁰ Furthermore, in a cross-sectional analysis, patients with CD in remission [$n = 45$] had a higher Mediterranean diet score, compared to patients with active disease [$n = 41$, based on HBI].⁵¹

Although there is no consensus in the literature on how exactly to describe a 'Mediterranean' dietary pattern, it is often characterized by high intakes of vegetables, fruits, whole grains, legumes, nuts and seeds, and olive oil, and moderate consumption of fish, poultry and dairy foods, and little red meat. Although, over the years, this diet has changed and has been Westernized.⁵² Perhaps our patients

consumed a diet resembling a more 'Westernized Mediterranean' dietary pattern instead of a 'traditional Mediterranean' dietary pattern. This might be the reason why we could not confirm a beneficial association between adherence to this dietary pattern and flare development in the present study.

The importance of studying dietary patterns is supported by the rising incidence of IBD in Western and newly industrialized countries, which coincides with urbanization and adoption of a Western lifestyle, including a diet rich in fat, sugars, animal protein and processed foods, and low in fruit and vegetables.⁵³ Additionally, a higher IBD incidence among immigrants to Western countries and their successive generations^{54–56} as well as mechanistic animal and *in vitro* studies further support that a Western lifestyle is likely to play a role in the pathophysiology of IBD. For example, a high-fat diet is reported to affect the intestinal epithelial permeability in mice.⁵⁷ Others found that a high-fat, high-sugar diet in mice is characterized by microbial dysbiosis and decreased concentrations of SCFAs.⁵⁸ Dietary fibres, mainly from fruits and vegetables, are fermented in the colon into SCFAs, which serve as energy substrates for colonocytes and are important metabolites improving, amongst others, intestinal barrier disruption and inflammation.^{59,60} Meat, and especially red meat, is a source of dietary sulphur, which is fermented into hydrogen sulphide in the gut. Hydrogen sulphide is proposed to impair the intestinal barrier by degrading the mucus layer by reducing the disulphide bonds⁶¹ and in UC to inhibit butyrate production.⁶² Furthermore, several food additives are reported to affect intestinal permeability and/or immunity.^{63,64} Although the above-mentioned studies focus merely on elements of a Western diet, it nevertheless shows the importance of the role that nutrition could play in the pathophysiology of IBD.

As habitual dietary intake may differ between regions, it is of interest to take different geographical regions into account in dietary pattern analysis.⁹ When assessing the results of the FFQs, differences in the habitual dietary intake between our cohorts were found. A lower energy intake in the Northern cohort was observed, which could not be statistically explained by the fact that this cohort includes more females. Therefore, sex, energy and cohort were included in the regression models. Moreover, all macronutrients [total, plant and animal protein, fat, carbohydrates and alcohol] are higher in the Southern compared to the Northern cohort and intakes for the majority of food groups differed as well. Besides, differences in baseline characteristics were found between the two cohorts. This included, among others, known disease modifiers [L4: upper GI-disease; and P: perianal disease] indicating worse disease extent, as well as a more frequent use of biologicals in the Southern cohort. This may have contributed to the longer time to flare as observed in the Northern cohort. Moreover, in the Cox proportional hazard regression analysis, flare development was also positively associated with female sex, but an interaction between dietary pattern and gender was not found. This finding is in line with another prospective follow-up study in IBD patients.⁶⁵ However, data regarding the influence of sex on disease course are conflicting.⁶⁶ In explorative analyses, comparable dietary patterns were found in the two separate cohorts, pointing to the robustness of the findings. Because the sample sizes might be too small for Cox regression subanalysis and therefore warrants careful interpretation, we choose not to show these subanalyses but included, for example, study cohort as well as gender and disease phenotypes as confounders in the Cox regression analysis instead. A post-hoc power calculation was conducted after PCA,⁶⁷ using an alpha of 0.05 and a power of 80% [using the R package powerSurvEpi

version 0.1.0]. It demonstrated our sample size to be sufficient, but we acknowledge that the exact sample size that is needed can be different from the power analysis.⁶⁸

Some limitations of the present study should be acknowledged. Both FFQs were administered only at time of inclusion, representing the habitual dietary intake of the preceding month. Hence, changes in dietary habits during follow-up, which can be due to active disease, cannot be ruled out. Nevertheless, FFQs are an appropriate tool to assess longer-term habitual dietary intake,¹³ and patients were included throughout the year limiting seasonal influences. Furthermore, reliability between the FFQs was not checked because both were derived from the same FFQ, were developed by the same research group and have substantial overlap [Supplementary Table 1]. In addition, only four patients were classified as under-reporters and were excluded based on the lower energy cut-off. Two of these patients would have been excluded nonetheless for having active disease at baseline. Therefore, our approach is expected to have little impact on the outcome. Besides, in this study food groups were defined based on the corresponding categories as used in the Dutch Food table,⁶⁹ which sometimes leads to combining potentially healthy and unhealthy foods in the same category. It should be noted that more detailed food grouping could be relevant in future studies. Finally, an inevitable limitation in [nutritional] epidemiology is reverse causality; no causality between the found association on flare occurrence and dietary patterns can be claimed. These findings may also reflect a dietary change in intake made by patients due to symptoms and stress the need for repeated assessments in future longitudinal studies. As mentioned before, PCA results are always based on arbitrary choices of the defined food groups.

The strength of the present study is the combination of two large, geographically distinctive, IBD outpatient cohorts with 2-year longitudinal clinical follow-up. To our knowledge, there are no longitudinal studies analysing the association between dietary patterns [not habitual intake of food items or food groups] in combination with development of flares in IBD patients. Because endoscopic reviewing all flares is not feasible and expedient in daily clinical practice, this study utilizes the best possible robust alternatives to capture flares. Furthermore, two comparable semi-quantitative FFQs were used to assess dietary intake. The identification of similar patterns in each cohort separately further strengthens the robustness of our findings. In addition, the *robust* PCA, to reduce the influence of outliers,³⁰ strengthen our findings of the first two derived patterns and their HRs with flare occurrence, although the significance of the first dietary pattern with flare risk was lost. This study indicates the relevance of studying the association between dietary patterns and flare occurrence, even though classifying food items in groups is not always easy. Before recommendations for daily clinical practice can be provided, it is important that these findings are confirmed in larger, longitudinal studies, determining habitual dietary intake repeatedly. In the present study, none of the dietary patterns was found to be protective for flare occurrence. Mechanistic studies on the first dietary pattern can help us to understand the pathophysiology and form the basis for the development of a possible beneficial diet, which subsequently can be studied in intervention trials.

To conclude, a dietary pattern characterized by intake of grain products, cooking oils and fats, potatoes, processed meat, red meat, condiments and sauces, and sugar, cakes and confectionery, which can be regarded as a 'traditional [Dutch]' or variant of a 'Western'

dietary pattern, was associated with development of flares. These findings should be confirmed in larger studies and contribute to the evidence needed for the development of future prospective longitudinal studies, randomized controlled trials and dietary guidelines for patients in the future.

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Conflicts of Interest

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Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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