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Alimentary Tract

Diet and clinical remission in patients with inflammatory bowel disease: A multicenter cross-sectional study

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[1] All the members of the GETAID-Diet-in-IBD study group are listed in the Appendix.

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ABSTRACT

Background: Diet and risk of developing inflammatory bowel disease (IBD) has been extensively studied.
Aims: To investigate the association between diet and IBD activity.
Methods: Consecutive outpatients in 40 French and Belgian centers completed diet and IBD activity questionnaire between April and May 2023 in a cross-sectional study. Associations between diet and clinical remission were adjusted for gender, age, body mass index, education, smoking, and past CD-surgery.
Results: Among 2514 patients included, 1715 had Crohn's disease (CD) and 799 had ulcerative colitis (UC). Overall, the mean age was 42.4 years, 52.3 % were women, and 56.4 % were in clinical remission. Among CD patients, clinical remission was associated with a higher intake of fruits (aOR 1.60 [1.20–2.14]) and coffee (aOR 1.57 [1.17–2.11]). Among UC patients, clinical remission was associated with a higher intake of fruits (aOR 1.72 [1.15–2.56]) and salad (aOR 1.73 [1.12–2.66]). A higher adherence to a Mediterranean diet was associated with CD (aOR 1.39 [1.06–1.84]) but not UC remission. A higher adherence to a healthy diet was not associated with either CD nor UC remission.
Conclusions: CD remission was associated with higher intakes of fruits, coffee and a Mediterranean diet, while UC remission was associated with higher intakes of fruits and salad. As this was a cross-sectional study, the main limitation was the possibility of reverse causality.
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Bullet points.

What is already known?
- Diet and risk of developing inflammatory bowel disease has been extensively studied, but there is limited data for the association between diet and inflammatory bowel disease activity once diagnosed.

What is new here?
- Crohn's disease remission was associated with higher intakes of fruits and coffee and a Mediterranean diet; ulcerative colitis remission was associated with higher intakes of fruits and salad.

How can this study help patient care?
- To exclude reverse causality bias, further studies are needed to investigate the temporality between IBD activity and diet and give IBD patients further diet guidance.

1. Introduction

Incidence of Crohn's disease (CD) and ulcerative colitis (UC) have risen sharply in the second half of the 20th century in Western countries [1]. In low-income countries incidence tends to similarly increase upon industrialization. Multiple environmental factor have been identified including diet, smoking, antibiotics, a lack of physical activity, and psychological factors [2]. High intake of fruits, vegetables, fiber, unprocessed or minimally processed foods, and adherence to a Mediterranean diet are associated with a lower risk of CD [3–7] while ultra-processed foods, pro-inflammatory foods, and adherence to a healthy diet are associated with a higher risk of CD [4,5,8]. High intake of red meat and a sugar and soft drink pattern are associated with a higher risk of UC [6,7].

Apart from studies regarding the risk of developing IBD, there is fewer evidence on the association between diet and IBD activity, once diagnosed. Despite a lack of strong evidence to support dietary intervention in patients with IBD, the International Organization for the Study of IBD further recommends a diet rich in fruits and vegetables and low in saturated fats in CD, and a diet low in red meat and rich in omega-3 fatty acids from fish in UC. For both diseases, it recommends low exposure to artificial sweeteners, titanium dioxide and sulfites [9]. The European Society for Clinical Nutrition and Metabolism recommends increasing protein

consumption during flare-ups, a residue-free diet in case of diarrhea, and a low insoluble fiber diet for patients with intestinal stenosis [10,11].

Because there is little data available and the recommendations are not consistent, we aimed to investigate dietary patterns associated with clinical remission in patients with IBD in a prospective multicenter cross-sectional study.

2. Methods

2.1. Study population

We prospectively included consecutive outpatients presenting at the outpatient clinic or at the infusion unit in 40 French and Belgian IBD centres belonging to the Groupe d'Étude Thérapeutique des Affections Inflammatoires du tube Digestif (GETAID). Inclusion period includes two consecutive weeks in each center, between April and May 2023. Patients with UC patients that underwent subtotal/total colectomy were excluded. This study was conducted in accordance with French ethics and legal principles through reference methodology MR-004 (Institut National des Données de Sante registration number 2229845v0).

2.2. Auto questionnaire

Patients were asked to fill a 4-page anonymous questionnaire. Assistance of a trained nurse or Gastroenterologist was possible if needed. Questionnaire was retrieved by a nurse after full completion. Questionnaire included demographics, IBD characteristics, and diet (supplementary methods).

2.3. Food frequency questionnaire

We used a 22-item food frequency questionnaire (FFQ) developed and validated in the United Kingdom against a 217-item FFQ in the general population. This 22-item FFQ was translated into French [12]. The FFQ covered the previous 7 days and included: fruits, vegetables, salad, potatoes, legumes, wholemeal bread, refined grains, unprocessed red meat, processed red meat, unprocessed white meat, processed white meat, white fish, oily fish, batter fish, dairy products, ice cream, chips/salty snacks, sweet biscuits/cakes, fruit juices, soft drinks, coffee, tea. For each item, the frequency consumed was assessed in 8 categories: rarely or never, less than once a week, once a week, two to three times a week, four to six times a week, once or twice a day, three to four times a day, and more than five times a day. The amount consumed was then converted into grams per day using data from Irish and British dietary recommendations. Two dietary scores were computed from the food frequency questionnaire: the Mediterranean diet score and the Healthy diet score.

The alternative Mediterranean diet score is a score ranging from 0 to 7, and reflects adherence to a Mediterranean diet [13]. One point is awarded for each of the following foods consumed in quantities above the median evaluated in the study: vegetables, legumes, fruits, wholemeal bread, white/oily/batter fish. One point is awarded if the quantity is below the median evaluated for red meat and for moderate alcohol intake (5 to 25 g per day).

The Healthy diet score is a score of adherence to a healthy lifestyle ranging from 0 to 7 [2]. One point is awarded for each of the following dietary intakes: fruits ($\geq$3 times/day), vegetables ($\geq$3 times/day), white/oily/batter fish ($\geq$2 times/week), wholemeal bread ($\geq$3 times/day), refined grains ($\leq$1.5 times/day), processed red meat ($\leq$1 times/week), unprocessed red meats ($\leq$2.5 times/week).

2.4. Outcomes measures

The objective of the present study was to determine dietary patterns associated with clinical remission. Clinical remission was defined according to patient-reported outcome (PRO2) criteria presented in the STRIDE2 [14]. In patients with UC, clinical remission was defined by a stool frequency subscore of 0 and a rectal bleeding subscore of 0 while in patients with CD, clinical remission was defined by a stool frequency $\leq$3 and an abdominal pain subscore $\leq$1. Clinical remission according to patient-global assessment (yes or no) was used as sensitivity analysis.

2.5. Covariates

Patient characteristics, including patient demographics, body mass index, basic energy expenditure, smoking habits, and education level. IBD characteristics included IBD type, classification of IBD according to Montreal classification, history of IBD-related surgery, current and previous medical treatment.

2.6. Statistical analysis

Analyses were performed separately for CD and UC as they have different diet risk factors. Population was described by number (percentages), mean ($\pm$ standard deviation) or median (IQR) according to the distribution of the data. Intakes in grams per day were categorized into terciles. Chi2 tests were used to compare food consumption according to IBD activity status. The association between food intake and IBD clinical remission (PRO2) was assessed by multivariable logistic regression models to compute odds ratios (OR) and their 95 % confidence intervals (95 %CI). Models were adjusted for gender, age, body mass index, education and smoking (aOR). Age and body mass index were modeled as quartiles. Models for CD were also adjusted for a history of surgical resection. Linear trends were tested by using the mean value for each tercile category of the studied variables.

A sensitivity analysis was performed in which clinical remission was assessed by patient-global assessment (yes/no question). Subgroup analyses were performed according to CD location and UC extent among dietary items significant in the main analysis.

Considering missing data to be missing at random, simple imputation was performed by chain equation, due to an average missing data rate $<$5 % (R mice package). Analyses were performed with R® software. All tests were two-tailed, with a significance level of 0.05.

3. Results

3.1. Study population

Among the 2616 questionnaires collected from patients with IBD, we excluded 102 patients with UC and subtotal/total colectomy. Thus, 2514 patients were included in the analyses.

The initial characteristics of the study population are presented in Table 1. Of the 2514 patients studied, 1715 (68.2 %) had CD and 799 (31.8 %) had UC or indeterminate Colitis. Patients with CD were aged 41.8 $\pm$ 14.7 years, 52.2 % were women, 22.0 % were active smokers, mean CD duration was 14.5 $\pm$ 10.6 years, 44.6 % had isolated ileal disease, 28.5 % isolated colonic disease, 26.8 % ileocolonic disease, and 35.7 % had anoperineal involvement. Patients with CD were treated with advanced therapy in 1408 (84.6 %) of cases. Patients with UC were aged 43.6 $\pm$ 16.3 years, 52.3 % were women, 8.9 % were active smokers, mean UC duration was 11.3 $\pm$ 9.5 years, 30.9 % had proctitis, 33.7 % had left-sided UC, and 35.4 % an extensive colitis. Patients with UC were treated with advanced therapy in 610 (78.2 %) of cases.

Table 1
Description of analysis population (n = 2514).

	Crohn's disease n = 1 715	Ulcerative colitis / Indeterminate Colitis n = 799	p-value
Age (years), mean (std)	41.8 (14.7)	43.6 (16.3)	<0.01
Women, n (%)	896 (52.2)	418 (52.3)	1.00
Smoking status, n (%)			<0.001
Never	770 (44.9)	422 (52.8)	
Active	378 (22.0)	71 (8.9)	
Past	454 (26.5)	274 (34.3)	
Electronic cigarette	113 (6.6)	32 (4.0)	
Level of education, n (%)			<0.01
Middle school	174 (10.1)	84 (10.5)	
High school	621 (36.2)	234 (29.3)	
University	466 (27.2)	239 (29.9)	
Higher learning (>master)	454 (26.5)	242 (30.3)	
Body mass index (kg/m2), mean (std)	24.6 (5.0)	24.9 (5.1)	0.20
Basic energy expenditure (kcal), mean (std)	1558.1 (260.4)	1561.2 (272.7)	0.78
Duration of IBD progression (years), mean (std)	14.5 (10.6)	11.3 (9.5)	<0.001
Age at diagnostic >40years, n (%)	298 (17.4)	218 (27.3)	<0.001
Montreal Classification for Crohn's disease, n (%)			
Ileal	580 (44.6)		
Colonic	371 (28.5)		
Ileocolonic	349 (26.8)		
Upper disease, n (%)	112 (8.6)		
Ano-perineal lesions, n (%)	613 (35.7)		<0.001
Montreal Classification for UC, n (%)			
Proctitis			
Left-sided		216 (33.7)	
Extensive		227 (35.4)	
History of surgical resection, numbers (%)	698 (40.7)	0 (0.0)	<0.001
Treatment history, numbers (%)			
Azathioprine (Imuran)	683 (41.0)	246 (31.5)	<0.001
Methotrexate (Methotrexate)	230 (13.8)	52 (6.7)	<0.001
Anti-TNF			<0.001
0	973 (58.4)	539 (69.1)	
1	475 (28.5)	191 (24.5)	
2	209 (12.6)	47 (6.0)	
3 and more	8 (0.5)	3 (0.4)	
Vedolizumab	100 (6.0)	82 (10.5)	<0.001
Ustekinumab	178 (10.7)	34 (4.4)	<0.001
JAK inhibitor	10 (0.6)	23 (2.9)	<0.001
cyclosporine (Cyclosporine capsules)	4 (0.2)	7 (0.9)	0.05
Current treatment, numbers (%)			
None	97 (5.8)	19 (2.4)	<0.001
Salicylates	49 (2.9)	113 (14.5)	<0.001
Corticosteroids	101 (6.1)	69 (8.8)	0.02
Anti-TNF monotherapy	739 (44.4)	198 (25.4)	<0.001
Anti-TNF combination therapy	199 (12.0)	79 (10.1)	0.21
Thiopurine monotherapy	51 (3.1)	28 (3.6)	0.57
methotrexate (Methotrexate) monotherapy	73 (4.4)	26 (3.3)	0.26
Vedolizumab	147 (8.8)	218 (27.9)	<0.001
Ustekinumab	251 (15.1)	58 (7.4)	<0.001
JAK inhibitor	17 (1.0)	24 (3.1)	<0.001
Anti-IL23	26 (1.6)	5 (0.6)	0.09
Combination of biologics	47 (2.8)	5 (0.6)	<0.01
Any advanced therapy in current treatment, numbers (%)	1408 (84.6)	610 (78.2)	<0.001
Clinical remission, n (%)			
Patient-reported outcome (PRO2)	1090 (63.6)	329 (41.2)	<0.001
Patient-global assessment (yes/no)	1079 (62.9)	526 (65.8)	0.17

IBD: inflammatory bowel disease; UC: ulcerative colitis; TNF: tumor necrosis factor; std: standard deviation.

Among patients with CD, 1090 (63.6 %) were in clinical remission according to PRO2 (primary outcome) and 1079 (62.9 %) according to patient-global assessment, with moderate agreement (Kappa 0.49; 95 %CI: 0.45–0.54). Among patients with UC, the clinical remission rate was 329 (41.2 %) for PRO2 and 526 (65.8 %) for patient-global assessment, also with moderate agreement (Kappa 0.46; 95 %CI: 0.41–0.51).

Description of dietary exposure and association between dietary exposure and clinical remission.

The description of dietary exposure according to IBD activity is presented in Table 2 and supplementary Table 1 and the results of the association between food consumption and IBD activity in Tables 3 and 4. Results summary is presented in Fig. 1.

Among CD patients, as compared to patients with active disease, patient in clinical remission with both definitions (PRO2 and patient-global assessment) were associated with a high intake of fruits (tercile 1 active disease: 47.0 % vs tercile 1 clinical remission: 36.9 %; tercile 3 vs tercile 1: aOR 1.60 [1.20–2.14]; p-trend < 0.01) and coffee (36.8 % vs 31.9 %; aOR 1.57 [1.17–2.11]; p-trend < 0.01). For some food items, a p-trend was significant only for one of the two definitions of clinical remission: a higher intake of salad, legumes, and a lower intake of soft drinks. Other food items were not associated with clinical remission

Table 2
Description of dietary exposure according to disease activity assessed by patient-reported outcomes (PRO2).

	Crohn's disease			Ulcerative colitis / Indeterminate Colitis		
	No clinical remission	Clinical remission		No clinical remission	Clinical remission	
Food items	*n* = 625 N (%)	*n* = 1 090 N (%)	p (chi2)	*n* = 470 N (%)	*n* = 329 N (%)	p (chi2)
Healthy diet*			0.07			0.61
Tercile 1: 0–2	201 (32.2)	409 (37.5)		142 (30.2)	103 (31.3)	
Tercile 2: 3	349 (55.8)	552 (50.6)		258 (54.9)	170 (51.7)	
Tercile 3: 4–7	75 (12.0)	129 (11.8)		70 (14.9)	56 (17.0)	
Mediterranean diet*			<0.001			0.13
Tercile 1: 0–3	405 (64.8)	582 (53.4)		228 (48.5)	136 (41.3)	
Tercile 2: 4	116 (18.6)	268 (24.6)		111 (23.6)	86 (26.1)	
Tercile 3: 5–7	104 (16.6)	240 (22.0)		131 (27.9)	107 (32.5)	
Fruits			<0.001			<0.01
Tercile 1: 0–11.2	294 (47.0)	402 (36.9)		151 (32.1)	72 (21.9)	
Tercile 2: 28.8–56.8	220 (35.2)	413 (37.9)		178 (37.9)	133 (40.4)	
Tercile 3: 120.0–480.0	111 (17.8)	275 (25.2)		141 (30.0)	124 (37.7)	
Vegetables			<0.001			0.54
Tercile 1: 0–28.8	323 (51.7)	452 (41.5)		166 (35.3)	104 (31.6)	
Tercile 2: 56.8–120.0	242 (38.7)	535 (49.1)		247 (52.6)	181 (55.0)	
Tercile 3: 280–480.0	60 (9.6)	103 (9.4)		57 (12.1)	44 (13.4)	
Salad			<0.01			<0.01
Tercile 1: 0–4.0	308 (49.3)	452 (41.5)		196 (41.7)	102 (31.0)	
Tercile 2: 11.2–28.2	246 (39.4)	492 (45.1)		204 (43.4)	161 (48.9)	
Tercile 3: 56.8–480	71 (11.4)	146 (13.4)		70 (14.9)	66 (20.1)	
Potatoes			0.27			0.65
Tercile 1: 0–23.4	384 (61.4)	694 (63.7)		318 (67.7)	230 (69.9)	
Tercile 2: 60.1	175 (28.0)	306 (28.1)		121 (25.7)	82 (24.9)	
Tercile 3: 118.6–1002.0	66 (10.6)	90 (8.3)		31 (6.6)	17 (5.2)	
Legumes			<0.001			0.83
Tercile 1: 0–9.2	370 (59.2)	507 (46.5)		217 (46.2)	146 (44.4)	
Tercile 2: 25.8	124 (19.8)	315 (28.9)		137 (29.1)	96 (29.2)	
Tercile 3: 66.2–1104.0	131 (21.0)	268 (24.6)		116 (24.7)	87 (26.4)	
Wholemeal bread			0.61			0.56
Tercile 1: 0–2.2	275 (44.0)	460 (42.2)		170 (36.2)	130 (39.5)	
Tercile 2: 6.3–32.0	224 (35.8)	417 (38.3)		189 (40.2)	121 (36.8)	
Tercile 3: 67.5–270.0	126 (20.2)	213 (19.5)		111 (23.6)	78 (23.7)	
Refined grains			0.54			0.62
Tercile 1: 0–25.6	353 (56.5)	588 (53.9)		247 (52.6)	184 (55.9)	
Tercile 2: 50.4	127 (20.3)	243 (22.3)		103 (21.9)	65 (19.8)	
Tercile 3: 106.5–426.0	145 (23.2)	259 (23.8)		120 (25.5)	80 (24.3)	
Red meat, unprocessed			0.52			0.05
Tercile 1: 0–15.5	320 (51.2)	527 (48.3)		237 (50.4)	195 (59.3)	
Tercile 2: 40.0	236 (37.8)	434 (39.8)		184 (39.1)	107 (32.5)	
Tercile 3: 78.8–126.5	69 (11.0)	129 (11.8)		49 (10.4)	27 (8.2)	
Red meat, processed			0.15			0.62
Tercile 1: 0–4.0	271 (43.4)	433 (39.7)		217 (46.2)	141 (42.9)	
Tercile 2: 11.2	165 (26.4)	278 (25.5)		118 (25.1)	85 (25.8)	
Tercile 3: 28.8–91.2	189 (30.2)	379 (34.8)		135 (28.7)	103 (31.3)	
White meat, unprocessed			0.42			0.40
Tercile 1: 0–17.9	193 (30.9)	304 (27.9)		166 (35.3)	103 (31.3)	
Tercile 2: 46.1	324 (51.8)	586 (53.8)		232 (49.4)	178 (54.1)	
Tercile 3: 90.9–145.9	108 (17.3)	200 (18.3)		72 (15.3)	48 (14.6)	
White meat, processed			0.75			0.75
Tercile 1: 0	282 (45.1)	473 (43.4)		255 (54.3)	184 (55.9)	
Tercile 2: 8.5	136 (21.8)	251 (23.0)		88 (18.7)	64 (19.5)	
Tercile 3: 23.8–193.8	207 (33.1)	366 (33.6)		127 (27.0)	81 (24.6)	
White fish			0.48			0.39
Tercile 1: 0–6.0	314 (50.2)	542 (49.7)		196 (41.7)	147 (44.7)	
Tercile 2: 16.7	208 (33.3)	388 (35.6)		176 (37.4)	126 (38.3)	
Tercile 3: 42.8–135.7	103 (16.5)	160 (14.7)		98 (20.9)	56 (17.0)	
Oily fish			0.35			0.14
Tercile 1: 0–4.5	403 (64.5)	688 (63.1)		273 (58.1)	201 (61.1)	
Tercile 2: 12.6	135 (21.6)	266 (24.4)		111 (23.6)	85 (25.8)	
Tercile 3: 34.2–102.6	87 (13.9)	136 (12.5)		86 (18.3)	43 (13.1)	
Batter fish			0.08			0.64
Tercile 1: 0	272 (43.5)	455 (41.7)		240 (51.1)	159 (48.3)	
Tercile 2: 8.0	133 (21.3)	284 (26.1)		110 (23.4)	86 (26.1)	
Tercile 3: 22.4–182.4	220 (35.2)	351 (32.2)		120 (25.5)	84 (25.5)	
Dairy products			<0.01			0.01
Tercile 1: 0–35.6	295 (47.2)	428 (39.3)		187 (39.8)	109 (33.1)	
Tercile 2: 70.3–148.5	304 (48.6)	619 (56.8)		252 (53.6)	208 (63.2)	

(*continued on next page*)

Table 2 (*continued*)

	Crohn's disease			Ulcerative colitis / Indeterminate Colitis		
	No clinical remission	Clinical remission		No clinical remission	Clinical remission	
Tercile 3: 346.5–594.0	26 (4.2)	43 (3.9)		31 (6.6)	12 (3.6)	
Ice cream			0.09			0.26
Tercile 1: 0	403 (64.5)	644 (59.1)		306 (65.1)	217 (66.0)	
Tercile 2: 5.5	143 (22.9)	292 (26.8)		108 (23.0)	84 (25.5)	
Tercile 3: 15.4–660.0	79 (12.6)	154 (14.1)		56 (11.9)	28 (8.5)	
Chips / salty snacks						0.99
Tercile 1: 0	239 (38.2)	366 (33.6)		194 (41.3)	136 (41.3)	
Tercile 2: 1.2–3.5	253 (40.5)	495 (45.4)		193 (41.1)	134 (40.7)	
Tercile 3: 9.0–150.0	133 (21.3)	229 (21.0)		83 (17.7)	59 (17.9)	
Sweet biscuits / cakes			<0.001			0.96
Tercile 1: 0–12.7	266 (42.6)	358 (32.8)		189 (40.2)	129 (39.2)	
Tercile 2: 32.8–64.6	226 (36.2)	496 (45.5)		189 (40.2)	134 (40.7)	
Tercile 3: 136.5–546.5	133 (21.3)	236 (21.7)		92 (19.6)	66 (20.1)	
Fruit juice			1.00			0.24
Tercile 1: 0	215 (34.4)	373 (34.2)		185 (39.4)	119 (36.2)	
Tercile 2: 7.2–52.2	244 (39.0)	427 (39.2)		182 (38.7)	121 (36.8)	
Tercile 3: 102.9–870.0	166 (26.6)	290 (26.6)		103 (21.9)	89 (27.1)	
Soft drinks			0.01			0.91
Tercile 1: 0	243 (38.9)	370 (33.9)		226 (48.1)	153 (46.5)	
Tercile 2: 8.1–58.0	214 (34.2)	451 (41.4)		177 (37.7)	128 (38.9)	
Tercile 3: 114.3–966.0	168 (26.9)	269 (24.7)		67 (14.3)	48 (14.6)	
Coffee			0.12			0.96
Tercile 1: <1/week	230 (36.8)	348 (31.9)		164 (34.9)	112 (34.0)	
Tercile 2: 1–14/week	255 (40.8)	481 (44.1)		201 (42.8)	144 (43.8)	
Tercile 3: ≥21/ week	140 (22.4)	261 (23.9)		105 (22.3)	73 (22.2)	
Tea			0.75			0.24
Tercile 1: 0/ week	264 (42.2)	444 (40.7)		178 (37.9)	142 (43.2)	
Tercile 2: 1–14/ week	192 (30.7)	353 (32.4)		150 (31.9)	103 (31.3)	
Tercile 3: >7/ week	169 (27.0)	293 (26.9)		142 (30.2)	84 (25.5)	

*A Healthy Diet and a Mediterranean Diet with a higher score represent healthier diets.
Clinical remission was defined according to PRO-2 criteria. In patients with UC, clinical remission was defined by a stool frequency subscore of 0 and a rectal bleeding subscore of 0 while in patients with CD, clinical remission was defined by a stool frequency ≤3 and an abdominal pain scubscore of ≤1.

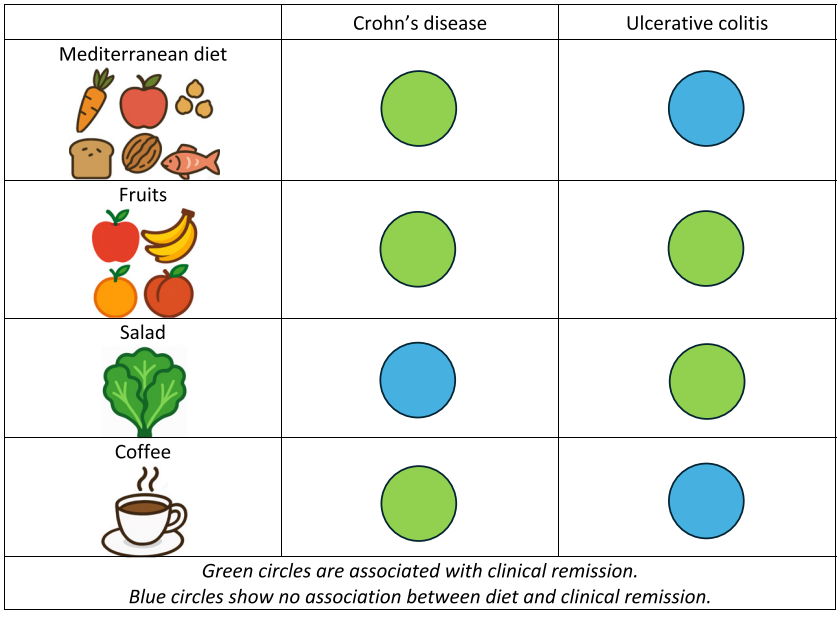


Fig. 1. Main results of the association between diet and clinical remission.

(Tables 3–4). Patients in clinical remission were associated with a higher adherence to a Mediterranean diet (aOR 1.39 [1.06–1.84]; p-trend < 0.01) but not to a healthier diet (aOR 0.80 [0.56–1.13]; p-trend = 0.06). The association between diet and CD clinical remission was particularly pronounced for ileal disease (supplementary Table 2).

Among UC patients, as compared to patients with active disease, patient in clinical remission with both definitions (PRO and patient-global assessment) were associated with a high intake of fruits (tercile 1 active disease: 32.1 % vs tercile 1 clinical remission: 21.9 %; tercile 3 vs tercile 1: aOR 1.72 [1.15–2.56]; p-trend = 0.02) and salad (41.7 % vs 31.0 %; aOR 1.73 [1.12–2.66]; p-trend = 0.02). For some food items, a p-trend was significant only for one of the two definitions of clinical remission: a higher intake of fruit juices, and a lower intake of unprocessed red meat. Other food items were not associated with clinical remission (Table 3). Patients in

Table 3
Multivariate models for an association between food consumption and clinical remission assessed by patient-reported outcomes (PRO2).

	Crohn's disease				Ulcerative colitis / Indeterminate Colitis			
	Tercile 1 (ref)	Tercile 2 aOR (95 %CI)	Tercile 3 aOR (95 %CI)	p-trend	Tercile 1 (ref)	Tercile 2 aOR (95 %CI)	Tercile 3 aOR (95 %CI)	p-trend
Healthy diet*	1	0.78 [0.62–0.97]	0.80 [0.56–1.13]	0.06	1	0.93 [0.66–1.29]	1.14 [0.72–1.80]	0.72
Mediterranean diet*	1	1.51 [1.16–1.96]	1.39 [1.06–1.84]	**<0.01**	1	1.18 [0.82–1.71]	1.22 [0.86–1.74]	0.23
Fruits	1	1.31 [1.04–1.66]	1.60 [1.20–2.14]	**<0.01**	1	1.38 [0.95–2.02]	1.72 [1.15–2.56]	**0.02**
Vegetables	1	1.51 [1.21–1.89]	1.10 [0.76–1.59]	0.42	1	1.00 [0.72–1.39]	1.22 [0.75–1.99]	0.40
Salad	1	1.36 [1.09–1.70]	1.38 [0.98–1.93]	0.08	1	1.36 [0.97–1.89]	1.73 [1.12–2.66]	**0.02**
Potatoes	1	0.94 [0.74–1.19]	0.77 [0.54–1.10]	0.14	1	0.91 [0.64–1.28]	0.72 [0.38–1.38]	0.29
Legumes	1	1.66 [1.28–2.14]	1.33 [1.02–1.72]	0.08	1	1.03 [0.73–1.46]	1.03 [0.72–1.48]	0.87
Wholemeal bread	1	1.11 [0.88–1.39]	1.04 [0.78–1.37]	0.88	1	0.83 [0.59–1.15]	0.95 [0.65–1.40]	0.99
Refined grains	1	1.05 [0.81–1.37]	0.98 [0.76–1.26]	0.85	1	0.80 [0.54–1.17]	0.83 [0.58–1.19]	0.34
Red meat, unprocessed	1	1.06 [0.85–1.32]	1.09 [0.78–1.54]	0.55	1	0.65 [0.47–0.90]	0.59 [0.34–1.01]	**<0.01**
Red meat, processed	1	1.05 [0.81–1.36]	1.28 [0.99–1.65]	0.06	1	1.12 [0.78–1.61]	1.21 [0.86–1.72]	0.29
White meat, unprocessed	1	1.15 [0.91–1.45]	1.10 [0.81–1.50]	0.52	1	1.17 [0.84–1.62]	1.03 [0.64–1.64]	0.83
White meat, processed	1	1.07 [0.81–1.41]	1.07 [0.84–1.38]	0.63	1	0.93 [0.63–1.39]	0.82 [0.56–1.20]	0.31
White fish	1	1.03 [0.82–1.30]	0.83 [0.61–1.12]	0.23	1	0.89 [0.64–1.25]	0.75 [0.50–1.14]	0.18
Oily fish	1	1.14 [0.89–1.46]	0.87 [0.64–1.19]	0.50	1	1.02 [0.71–1.45]	0.70 [0.46–1.07]	0.11
Batter fish	1	1.21 [0.93–1.58]	0.94 [0.74–1.20]	0.40	1	1.10 [0.76–1.59]	1.12 [0.77–1.63]	0.58
Dairy products	1	1.37 [1.11–1.69]	1.25 [0.74–2.13]	0.08	1	1.41 [1.03–1.93]	0.70 [0.34–1.46]	0.73
Ice cream	1	1.26 [0.98–1.61]	1.13 [0.83–1.54]	0.54	1	1.01 [0.72–1.43]	0.65 [0.39–1.08]	0.09
Chips / salty snacks	1	1.31 [1.03–1.65]	1.16 [0.87–1.55]	0.74	1	0.87 [0.62–1.21]	0.98 [0.64–1.50]	0.87
Sweet biscuits / cakes	1	1.64 [1.30–2.08]	1.33 [1.01–1.76]	0.19	1	1.04 [0.75–1.45]	1.08 [0.72–1.62]	0.73
Fruit juice	1	0.93 [0.73–1.18]	0.94 [0.72–1.22]	0.77	1	1.00 [0.71–1.42]	1.36 [0.92–2.00]	0.08
Soft drinks	1	1.42 [1.11–1.81]	1.16 [0.89–1.52]	0.95	1	0.98 [0.71–1.35]	1.01 [0.65–1.59]	0.92
Coffee	1	1.43 [1.11–1.83]	1.57 [1.17–2.11]	**<0.01**	1	1.03 [0.73–1.46]	0.94 [0.62–1.43]	0.90
Tea	1	1.03 [0.81–1.31]	1.03 [0.79–1.32]	0.84	1	0.82 [0.58–1.16]	0.69 [0.48–1.01]	0.05

*A Healthy Diet and a Mediterranean Diet with a higher score represent healthier diets.
aOR (95 %CI): adjusted odds ratio (95 % confidence interval)
Clinical remission was defined according to PRO-2 criteria. In patients with UC, clinical remission was defined by a stool frequency subscore of 0 and a rectal bleeding subscore of 0 while in patients with CD, clinical remission was defined by a stool frequency ≤3 and an abdominal pain subscore of ≤1.
Models were adjusted for gender, age, body mass index, education, smoking, and past CD-surgery.

clinical remission were neither associated with a higher adherence to a Mediterranean diet (aOR 1.22 [0.86–1.74]; p-trend = 0.23) nor to a healthier diet (aOR 1.14 [0.72–1.80]; p-trend = 0.72).

4. Discussion

This observational cross-sectional study included 2514 patients with IBD in France and Belgium. Patients with CD in clinical remission had higher intakes of fruits and coffee. Patients with UC in clinical remission had higher intakes of fruits and salad. CD remission was associated with a higher adherence to the Mediterranean diet.

We found that clinical remission was associated with higher intake of fruits, salad, coffee, and a higher adherence to a Mediterranean diet. Multiple hypotheses can be drawn from these results. First, clinical remission leads to increased fruits and salad intake as patients with active disease restrict themselves to a low-residue diet to reduce diarrhea. It was not possible to correct for this potential reverse causality bias in this study. Second, this association is the result of residual confounding as we would have failed to account for some confounding factors such as disease severity, exposure to pollutants, or other socio-economic characteristics. Nevertheless, our analyses were adjusted for gender, age, body mass index, education, smoking, and past CD-surgery. Third, intakes of these food items lead to clinical remission. As with any epidemiological study, it is not possible to establish causality in this study, but it might be plausible. Indeed, these foods (fruits, legumes) or food pattern (Mediterranean diet) have been associated with a lower risk for developing IBD, particularly CD [6–8,15]. It can be hypothesized that deleterious environmental factors for

Table 4
Multivariate models for an association between food consumption and clinical remission assessed by patient-global assessment (yes or no).

	Crohn's disease				Ulcerative colitis / Indeterminate Colitis			
	Tercile 1 (ref)	Tercile 2 aOR (95 %CI)	Tercile 3 aOR (95 %CI)	p-trend	Tercile 1 (ref)	Tercile 2 aOR (95 %CI)	Tercile 3 aOR (95 %CI)	p-trend
Healthy diet*	1	0.99 [0.80–1.23]	1.26 [0.89–1.79]	0.34	1	1.06 [0.76–1.49]	1.38 [0.86–2.22]	0.22
Mediterranean diet*	1	1.27 [0.99–1.64]	1.47 [1.12–1.94]	**<0.01**	1	0.98 [0.68–1.41]	1.78 [1.22–2.58]	**<0.01**
Fruits	1	1.24 [0.99–1.57]	1.30 [1.01–1.70]	**0.05**	1	1.68 [1.16–2.43]	2.02 [1.36–3.02]	**<0.01**
Vegetables	1	1.29 [1.04–1.60]	1.37 [0.94–1.99]	0.07	1	1.29 [0.93–1.81]	1.34 [0.81–2.20]	0.29
Salad	1	1.71 [1.37–2.12]	1.86 [1.33–2.61]	**<0.01**	1	1.69 [1.21–2.35]	1.84 [1.17–2.88]	**0.02**
Potatoes	1	1.05 [0.83–1.32]	1.03 [0.72–1.47]	0.83	1	1.03 [0.72–1.46]	1.12 [0.58–2.16]	0.72
Legumes	1	1.62 [1.26–2.08]	1.65 [1.27–2.14]	**<0.01**	1	0.98 [0.69–1.40]	1.34 [0.92–1.96]	0.11
Wholemeal bread	1	1.19 [0.95–1.50]	1.12 [0.85–1.48]	0.52	1	0.98 [0.70–1.38]	0.97 [0.65–1.44]	0.89
Refined grains	1	1.01 [0.78–1.31]	0.91 [0.71–1.16]	0.44	1	0.71 [0.49–1.05]	0.82 [0.57–1.19]	0.34
Red meat, unprocessed	1	1.09 [0.87–1.35]	0.85 [0.61–1.18]	0.54	1	0.82 [0.59–1.13]	0.68 [0.40–1.15]	0.10
Red meat, processed	1	1.08 [0.83–1.39]	1.01 [0.80–1.28]	0.98	1	0.93 [0.65–1.35]	1.14 [0.80–1.64]	0.41
White meat, unprocessed	1	0.98 [0.78–1.24]	0.82 [0.60–1.11]	0.20	1	1.23 [0.88–1.71]	1.41 [0.88–2.27]	0.14
White meat, processed	1	1.29 [0.98–1.69]	1.11 [0.87–1.41]	0.71	1	0.76 [0.51–1.13]	1.03 [0.70–1.52]	0.68
White fish	1	0.90 [0.72–1.13]	0.83 [0.62–1.11]	0.21	1	0.98 [0.70–1.38]	1.02 [0.67–1.56]	0.90
Oily fish	1	0.96 [0.75–1.22]	0.92 [0.68–1.25]	0.58	1	0.89 [0.62–1.28]	1.00 [0.66–1.53]	0.97
Batter fish	1	1.04 [0.80–1.35]	0.84 [0.66–1.06]	0.10	1	0.84 [0.58–1.22]	1.29 [0.88–1.90]	0.15
Dairy products	1	1.17 [0.95–1.44]	1.48 [0.86–2.54]	0.08	1	1.42 [1.03–1.95]	0.76 [0.39–1.47]	0.78
Ice cream	1	1.47 [1.15–1.88]	1.36 [1.00–1.85]	0.09	1	1.08 [0.75–1.54]	0.86 [0.53–1.42]	0.55
Chips / salty snacks	1	1.24 [0.98–1.56]	1.19 [0.90–1.59]	0.49	1	0.82 [0.58–1.15]	0.99 [0.64–1.54]	0.78
Sweet biscuits / cakes	1	1.30 [1.03–1.63]	1.08 [0.82–1.43]	0.87	1	1.08 [0.77–1.51]	1.03 [0.68–1.56]	0.92
Fruit juice	1	1.14 [0.90–1.45]	1.08 [0.83–1.40]	0.86	1	1.48 [1.05–2.10]	1.84 [1.22–2.76]	**0.01**
Soft drinks	1	1.27 [1.00–1.62]	0.86 [0.66–1.11]	**0.02**	1	1.08 [0.78–1.51]	0.87 [0.55–1.38]	0.46
Coffee	1	1.49 [1.17–1.91]	2.07 [1.54–2.78]	**<0.01**	1	1.49 [1.04–2.13]	1.22 [0.80–1.86]	0.11
Tea	1	1.01 [0.79–1.28]	1.08 [0.84–1.39]	0.58	1	0.94 [0.66–1.34]	1.12 [0.76–1.63]	0.61

*A Healthy Diet and a Mediterranean Diet with a higher score represent healthier diets.
aOR (95 %CI): adjusted odds ratio (95 % confidence interval)
Models were adjusted for gender, age, body mass index, education, smoking, and past CD-surgery.

development and worsening of IBD activity overlap. Indeed, smoking is similarly deleterious on the risk of development and worsening of CD [16–18]. It is also the case for other pathologies, such as cardiovascular disease, where improving risk factors for a first cardiovascular episode can reduce the risk of recurrence [19–21].

There are few data concerning the association between diet and IBD activity. A recent cross-sectional inception study within the UK biobank showed that patients with higher consumption of ultra-processed food had higher risk of IBD-related surgery [22]. Various diets, such as the specific carbohydrate diet, paleolithic diet, gluten-free diet, low-fermentable oligo-, di- and monosaccharides and polyols (FODMAPs), have been studied in the past but have failed to prove their efficacy due to the small numbers involved and their restrictive nature [10,23–25]. Only the Crohn's Disease Exclusion Diet has been shown to be effective in inducing and maintaining remission in children and adults (with or without enteral nutrition) [26,27]. In addition, exclusive enteral nutrition is effective in treating IBD flare-ups in the pediatric population, and to a lesser extend for adults. Unfortunately, none of these diets could be assessed in this study. As shown in other studies among CD patients, we also observed stronger associations between diet and clinical remission in ileal disease [28,29].

The Crohn's Disease Exclusion Diet (CDED) is a diet that reduces consumption of certain foods suspected of being involved in microbiota alteration. The daily foods required for initiation of this diet are chicken, eggs, bananas, apples and potatoes. Conversely, foods proscribed are dairy products, animal fats, alcoholic or sweetened beverages and ultra-processed foods. A study carried out in a pediatric population in 2021 compared the efficacy of the CDED combined with partial enteral nutrition versus exclusive enteral nutrition. At week 6, patients in the exclusive enteral nutrition group gradually returned to a conventional diet. The

efficacy of the different diets was similar in both groups up to week 6, then, on resumption of conventional feeding, the exclusive enteral nutrition group showed a resumption of disease activity, an increase of CRP (C-Reactive Protein) and an increase of fecal calprotectin. There was also a change in gut microbiota from week 6 onwards, with a return to the baseline microbiota present before the start of exclusive enteral nutrition [26,27]. Another dietary approach, known as the Tasty&Healthy diet, excludes ultra-processed food, gluten, red meat, and dairy (except for plain yogurt). In a recent randomized controlled trial, this diet demonstrated effectiveness in inducing clinical remission in patients with mild to moderate CD. The study found it to be non-inferior to exclusive enteral nutrition in achieving both clinical and biological remission [30].

The influence of diet on disease activity can be explained by its initial impact on the microbiota and the immune response of the digestive tract. A study published in 2019 showed the effect of fruit consumption on the composition of the microbiota, with a higher risk of developing pochitis in patients operated on for UC by total coloproctectomy who had a low fruit intake [31]. It is now known that changes in diet could explain up to 57 % of microbiota variations [32]. In addition to modulating the microbiota, diet represents a potential source of antigen for the epithelial barrier [33]. Fiber-rich diets, thanks to fermentation by the microbiota, allow a reduction in pH, leading to a decrease in enterobacteria and *Escherichia coli* in particular, in contrast to Western diets rich in sugars, fats and animal proteins, which are associated with an altered, pro-inflammatory microbiota [32,33]. Dietary fiber also enables overproduction of short-chain fatty acids, thanks to fiber degradation by the microbiota, with an immunomodulatory and anti-inflammatory effect [34]. This could explain the protective effect of dietary fiber consumption on the onset of IBD, but also on the activity of IBD when it is already present.

This study has several strengths. First, it is a large multicenter study carried out in France on 2514 consecutive and unselected patients and from over 40 centers, with a very low rate of missing data (<5 %), which improves the generalizability of this study. Second, the primary outcome, namely clinical remission, was assessed using patient reported outcomes using stool frequency, rectal bleeding, and abdominal pain subscores. Patient reported outcomes are recommended by the STRIDE-II consensus at the initiative of the Organization for the Study of IBD (IOIBD) [14] and are increasingly used in clinical trials [14]. However, biochemical remission (e.g. fecal calprotectin) and endoscopic remission were not available in this study.

This observational study also has limitations. First, as food intake over the last 7 days was assessed retrospectively, a memory bias can arise. However, this classification bias, if it exists, is non-differential and therefore tends to bias the results towards an absence of association and therefore did not create the observed associations. Second, no adjustment for multiple tests was carried out. However, as this is an evaluation and signal-seeking study and not a confirmatory study, multiple testing adjustment is not necessary [35]. Third, patients included were ambulatory followed in GETAID centers, most of which are IBD expert centers. Therefore, results may not be generalizable to all IBD populations.

In conclusion, CD remission was associated with a higher intake of fruits and coffee; and UC remission with a higher intake of fruits and salad. CD remission was associated with a higher adherence to the Mediterranean diet. The results of this study need to be supplemented to investigate the association between IBD activity and diet. A prospective study evaluating diet prior to IBD flare-ups should be carried out to obtain a good temporality between diet and IBD activity.

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Data

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics approval statement

This study was conducted in accordance with French ethics and legal principles through reference methodology MR-004 (Institut National des Données de Sante registration number 2229845v0).

Patient consent statement

Patients were informed that the completed questionnaires were not mandatory and were completed for research purposes. None of the patients included expressed opposition to participation in this study.

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Supplementary materials

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