Vegetarian or gluten-free diets in patients with inflammatory bowel disease are associated with lower psychological well-being and a different gut microbiota, but no beneficial effects on the course of the disease

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Abstract

Background: Many inflammatory bowel disease (IBD) patients follow a restrictive diet due to perceived positive effects on their symptoms. We assessed the prevalence of vegetarian (VD) and gluten-free diets (GFDs) in IBD patients, the reasons for following such a diet, and whether nutrition has an impact on disease activity and microbiota composition.

Methods: We included 1254 patients from the Swiss Inflammatory Bowel Disease Cohort Study with prospective acquisition of clinical data and psychosocial, disease-related and lifestyle factors between 2006 and 2015. Dietary habits were assessed through a self-report questionnaire. In 92 patients, we analysed intestinal mucosa-associated microbial composition using high-throughput sequencing.

Results: Overall, 4.1% ($n = 52$) of the patients reported following a VD and 4.7% ($n = 54$) a GFD. No differences regarding disease activity, fistula, hospitalization or surgery rates were observed. Patients on a VD or GFD had significantly higher levels of post-traumatic stress symptoms. Furthermore, GFD patients had significantly higher anxiety and depression symptom levels. The gut microbiota composition in IBD patients following a VD or GFD was significantly different compared to that of omnivores.

Conclusions: Although we did not identify a relevant impact of a specific diet on the course of the disease, there was a significant association with lower psychological well-being in VD and GFD patients.

Keywords

Crohn's disease, ulcerative colitis, vegetarian, inflammatory bowel disease, gluten-free, nutrition

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Study highlights

Summary of the established knowledge on this subject

- There exist no guidelines to favour or exclude any dietary habits in inflammatory bowel disease (IBD).
- Many patients with IBD follow specific diets in order to influence their disease.

What are the significant new findings of this study?

- Around 4% of IBD patients are vegetarian and nearly 5% follow a gluten-free diet.
- Despite the patients' belief of a favourable disease course, we could not objectify an impact on the disease course.
- Gluten-free and vegetarian diets in IBD patients appear to be associated with a lower psychological well-being.

Introduction

The incidence and prevalence of inflammatory bowel disease (IBD) has been globally increasing, with a more pronounced growth in developing countries.¹ Although the exact pathophysiological mechanisms underlying this increase are unknown, one potential explanation could be the Western diet, with high sugar, animal protein and fat intake, especially n-6 polyunsaturated fatty acids, but less consumption of vegetables.^{2–4} It is assumed that this 'Westernization' of dietary habits can trigger a pro-inflammatory environment⁵ in susceptible individuals.

Despite the lack of a general consensus^{6–8} or robust evidence^{9,10} on what diets modulate the course of disease in IBD, a multitude of dietary recommendations have been suggested, such as the specific carbohydrate diet, low fermentable oligosaccharides, disaccharides and monosaccharides, and the Palaeolithic diet.¹¹

These scarce data frequently result in unnecessarily restrictive diets in IBD patients.⁹

The prevalence of healthy subjects following a vegetarian diet (VD) is around 5% in the USA and in Switzerland.¹² Another important and growing population restricting intake of certain foods are healthy individuals who follow a gluten-free diet (GFD) without having coeliac disease (CeD). The prevalence of GFD without CeD in the USA in 2010 was around 0.5%¹³ and reached up to 1.7% in 2014.¹⁴

Regarding epidemiological data, a VD may have protective effects on the risk of IBD.¹⁵ However, only a few studies have investigated the beneficial or deleterious effects of specific diets on the course of the established disease. Higher intake of meat may increase the risk of a relapse in ulcerative colitis (UC)¹⁶ and a semi-VD could have a protective effect against relapse of Crohn's Disease (CD).¹⁷ Nevertheless, the data are currently insufficient to recommend any specific diet.

Amongst potential modulators of dietary intake and its effect on intestinal inflammation, the intestinal microbiome is certainly a key candidate.¹⁸ Many studies have shown a microbial dysbiosis in the gut of patients with IBD with lower diversity in their gut microbiota.^{19,20} Although it is still unclear if this dysbiosis contributes to the pathogenesis of IBD²¹ or rather represents a sequel of the disease itself (the hen and egg question), several studies indicate that the former applies.²²

Changes in IBD patients' diets might promote alterations in the microbial composition, which in turn might promote beneficial effects on the course of the disease. Importantly, microbial alterations induced by dietary changes might also induce an adverse effect in terms of the development of IBD and adversely impact the course of the disease, as widely suggested by various investigators attributing the increasing incidence of IBD in developing countries to a change in environmental factors, often considered to be the outcome of 'Westernization'.²³

In this study, we aimed to test for an association of dietary restriction with a VD and GFD (two distinctive globally highly prevalent restrictive dietary habits) in the Swiss Inflammatory Bowel Disease Cohort (SIBDC), a large, prospective and comprehensive cohort study. In addition, we investigated whether mucosa-associated intestinal microbial composition differs between IBD patients based on these daily dietary habits.

Materials and methods

Study design and characteristics

We used prospectively obtained data from the physicians' and patients' baselines, and annual follow-up questionnaires from adult patients included in the SIBDC Study (SIBDCS) between 2006 and 2015.²⁴ In addition, we developed an additional specific questionnaire relating to the patients' diet, which was sent to all patients participating in the SIBDCS (Supplemental Questionnaire). The SIBDCS is a nationwide cohort study enrolling IBD patients in Switzerland since 2006 and is supported by the Swiss National Science Foundation. Data are collected in multiple hospitals, including smaller regional hospitals and large tertiary referral centres, as well as private practices, throughout Switzerland. All patients in the SIBDCS who returned the self-reported and annual follow-up questionnaires were included in the study. The SIBDCS has been approved by the respective ethics committees in Switzerland and the lead ethics committee, the Cantonal Ethics Committee of Zurich. The presented study is part of the research plan of the SIBDCS

(number EK-1316, approved on 5 February 2007). Participants were enrolled only after they had provided written informed consent. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Outcome measures

Clinical and disease-related factors were obtained by a physician's questionnaire.

Every patient who answered 'never' in the questionnaire to the question 'How many times a week do you eat meat' was defined as a vegetarian. We considered all patients who answered 'yes' to the question 'Are you on a gluten-free diet?' to be GFD patients.

Independent variables were used to study potential associations with diet (see Supplementary file for variables (1)).

Data analysis

Categorical data were presented as raw numbers and percentages. Differences in categorical variables distribution between two or more groups were assessed using the Chi-square test, or Fisher's exact test in case of insufficient sample size. Continuous data distribution normality was assessed using normal QQ-plots and is summarized with their median, interquartile range (IQR) and range. Differences in continuous distributions between the two groups were assessed using the Mann-Whitney-Wilcoxon test.

Microbiota analysis of biopsies from IBD patients

A DNA extraction protocol was carried out for 213 human biopsies of 92 patients within the SIBDC using the manufacturer's instructions using an All Prep DNA/RNA Mini Kit (QIAGEN). Samples were taken alongside the lower gastrointestinal tract (within reach of standard ileocolonoscopy) starting from ileum, and incorporated three different locations in the colon and a sample from the rectum, as described in the study of Yilmaz et al.²⁵ There were some samples that were collected from the inflamed part based on clinician observation; however, when we analysed for microbiota differences between inflamed and non-inflamed tissue, we did not observe any substantial differences.²⁵

Briefly, 700 µl of buffer RLT plus β-mercaptoethanol with a metal bead were added into each sample, which were then homogenized using a Retsch Tissue Lyser (QIAGEN) at 30/revolution for 3 min, followed by 3 min centrifugation at maximum speed (Eppendorf). Supernatants were transferred to a spin column and centrifuged at 10,000 r/min for 1 min. Then, columns were washed/desalted using 500 µl of buffer AW1 and

buffer AW2, before elution with 30 µl EB buffer (QIAGEN) to elute DNA into 1.5 ml microfuge tubes. Afterwards, the V5/V6 regions of the 16S rRNA genes with barcoded forward primers were sequenced using the IonTorrent Personal Genome Machine™ (PGM) platform, according to the manufacturer's instructions (Thermo Fisher Scientific).

Samples with > 4000 reads were processed for further analysis and initially clustered using the QIIME 1.9.1 pipeline. Representative operational taxonomic units (OTUs) were picked after clustering UCLUST with a 97% sequence identity threshold and followed by taxonomy assignment using the Greengenes database. Then, species richness (alpha diversity analysis; observed OTUs, Simpson and Shannon index) and microbial differences (beta diversity analysis; Bray–Curtis dissimilarities) were calculated in the phyloseq library of R (v3.4). Non-parametric Mann–Whitney *U*-tests were used to check significant differences in alpha diversity analysis and Adonis (Permanova method on distances; 9999 permutations) was used to assess the statistical significance between groups in beta diversity. A $p < 0.05$ was considered significant. Taxonomy profiles associated with clinical metadata were analysed using the multivariate analysis by linear models (MaAsLin) R package and plotted later using the ggplot2 library in R. With a false discovery rate (FDR) using a Benjamini–Hochberg FDR correction of 0.05, taxa present $\leq 30\%$ of the samples with $> 0.001\%$ relative abundance were set as the cut-off value for significance. Significant taxa were plotted as arcsin-square root-transformed microbial relative abundances. To limit pre-analytical biases, our microbiota analysis between dietary groups were based on mucosa-associated and not faecal samples.

Results

VDs and GFDs in the SIBDCS

Of a total of 1993 patients currently enrolled in the SIBDCS, 1313 (66%) responded to the dietary questionnaire; 680 questionnaires were incomplete. We included a total of 1254 patients for the VD and 1223 for the GFD analysis. Overall, 4.1% ($n = 52$) of the IBD patients followed a VD and 4.7% ($n = 57$) a GFD, with median duration of 16.1 and 2.8 years, respectively (S-Figure 1A and B). Most of the gluten-avoiding IBD patients ($n = 50$, 4%) did not have a diagnosis of CeD. A vegan diet was reported by only 0.5% ($n = 6$) of patients. Differences in diet types are seen in Table 1 and Table 2 (text in supplementary file (2)).

Amongst GFD patients, we did not observe a gender difference. Differences in GFD versus regular diet (RD)

patients are demonstrated in Table 3 (text in supplementary file (3)).

Rationale for dietary restriction

In VD patients, the most frequently reported rationale underlying dietary restriction was ‘respect for animals’ (42.3%), while less than one in five patients reported ‘benefits for my IBD’ (17.3%) as the most important rationale. In contrast, the latter rationale (benefits for IBD) was the most frequently reported underlying rationale in GFD patients (40.4%; Figure 1).

Course of IBD

We did not find significant differences in either GFD or VD patient disease activities based on Crohn's Disease Activity Index (CDAI) and MTWAI (S-Figure 2A–D), hospitalization (S-Figure 3) or surgery (S-Figure 4) according to a dietary pattern. Likewise, the complication rate was similar in VD, GFD and RD patients (Figure 2(a)). However, in the subgroup of CD (but not UC) patients on a VD, we found a significantly lower complication rate (60.5 versus 42.4%, $p = 0.039$, Figure 2(b) and (c)).

Psychological variables

VD patients had higher scores on the post-traumatic stress diagnostic scale (PDS) (median 7.4 (IQR 3–11.9) versus 5.3 (IQR 2.5–9.9); $p = 0.042$) compared to their counterparts following an RD.

Moreover, VD patients had lower mental component levels of the SF-36 with lower levels indicating poorer mental health (median 45.6 (IQR 35.4–50.9) versus 48.5 (IQR 41.4–53.5); $p = 0.008$; Table 4(a)).

A GFD was associated with lower scores in the physical and mental component survey (SF-36) (median 48.6 (IQR 42.7–53.6) versus 51.6 (IQR 45.2–55.1), $p = 0.026$; respectively 42.1 (IQR 32.6–48.0) versus 48.7 (41.8–53.6), $p < 0.001$), and higher anxiety and depression scores (HADS); the higher the score in the HADS-A and HADS-D, the greater the level of distress from anxiety or depression (median 8.6 (IQR 5.3–10.9) versus 5 (IQR 2.9–7.7), $p < 0.001$; respectively 4.3 (IQR 2.9–6.6) versus 2.7 (IQR 1–5.3), $p < 0.001$), as well as higher PDS scores (median 8.7 (IQR 4–15) versus 5 (IQR 2.4–9.3), $p < 0.001$; Table 4(b)).

Mucosa-associated microbiota composition in VD and GFD versus RD patients

Overall, sequences of 213 mucosa-associated samples from 92 patients were available for microbial analysis, including 14 VD (26 samples) and 12 GFD (30 samples)

Table 1. Characteristics of patients following non-vegetarian and vegetarian diets.

	Not vegetarian	Vegetarian	<i>p</i> -value (Chi ² or Mann-Whitney-Wilcoxon)
Number of patients	1202 (95.85%)	52 (4.15%)	
Gender			
Male	582 (48.4%)	14 (26.9%)	0.002
Female	620 (51.6%)	38 (73.1%)	
Age at diagnosis			
Median, quartile 25–75, minimum–maximum	29.6, 21.7–39.6, 3.4–81.0	28.1, 20.6–35.8, 2.9–69.2	0.164
Disease duration			
Median, quartile 25–75, minimum–maximum	13.2, 7.7–21.9, 0.3–52.8	13.5, 7.9–25.4, 1.3–48.7	0.730
Diagnosis			
Crohn's disease	660 (54.9%)	33 (63.5%)	0.225
Ulcerative colitis/indeterminate colitis	542 (45.1%)	19 (36.5%)	
Weight (kg)			
Median, q25–75, minimum–maximum	71, 61–82, 37–145	63, 55.5–72, 47–100	< 0.001
Weight (stratified by sex; only men)			
Median, quartile 25–75	80, 72–87	75.5, 70–80	0.175
Minimum–maximum	50–145	67–90	
Weight (stratified by sex; only women)			
Median, quartile 25–75	63, 56–72	60, 52–66	0.038
Last location of Crohn's disease			
L1	195 (30.2%)	7 (23.3%)	0.725 (Fisher's exact test)
L2	239 (37.1%)	12 (40.0%)	
L3	191 (29.6%)	11 (36.7%)	
L4 only	20 (3.1%)	0 (0%)	
Unknown	15	3	
Maximal extent of Ulcerative colitis			
Proctitis	83 (15.6%)	1 (5.6%)	0.347 (Fisher's exact test)
Left-sided colitis	189 (35.4%)	5 (27.8%)	
Pancolitis	261 (49.0%)	12 (66.7%)	
Unknown	9	1	
Previous hospitalization related to inflammatory bowel disease			
No	872 (72.6%)	36 (69.2%)	0.601
Yes	330 (27.5%)	16 (30.8%)	
Intestinal surgery			
No	868 (72.2%)	38 (73.1%)	0.892
Yes	334 (27.8%)	14 (26.9%)	
Surgery for fistula			
No	1024 (85.2%)	41 (78.8%)	0.211
Yes	178 (14.8%)	11 (21.2%)	
Complications			
No	535 (44.5%)	26 (50.0%)	0.436
Yes	667 (55.5%)	26 (50.0%)	
Fistula or abscess			
No	856 (71.2%)	37 (71.2%)	0.992
Yes	346 (28.8%)	15 (28.8%)	

(continued)

Table 1. Continued

	Not vegetarian	Vegetarian	p-value (Chi ² or Mann-Whitney-Wilcoxon)
Stenosis			
No	879 (73.1%)	38 (73.1%)	0.993
Yes	323 (26.9%)	14 (26.9%)	
Last measure of C-reactive protein (mg/l)			
Median, quartile 25–75, minimum–maximum	2.9, 1–5.5, 0–200	1.15, 1–3, 0–39	0.069
Therapies and complements			
Therapies (at least once)			
5-aminosalicylic acid	935 (77.8%)	39 (75.0%)	0.637
Antibiotics	470 (39.1%)	21 (40.4%)	0.853
Immunomodulators	879 (73.1%)	41 (78.9%)	0.361
Biologicals	561 (46.7%)	32 (61.5%)	0.036
Steroids	990 (82.4%)	46 (88.5%)	0.256
Supplementation therapy (I.6.)			
No	421 (35.0%)	15 (28.8%)	0.360
Yes	781 (65.0%)	37 (71.2%)	
In particular:			
Calcium	314 (26.1%)	23 (44.2%)	0.004
Iron	114 (9.5%)	12 (23.1%)	0.001
Alternative medicine (I.7.)			
No	883 (73.5%)	26 (50.0%)	< 0.001
Yes	319 (26.5%)	26 (50.0%)	
In particular:			
Change in diet and lifestyle	76 (6.3%)	9 (17.3%)	0.002
Shiatsu	21 (1.7%)	3 (5.8%)	0.074 (Fisher's exact test)

Bold values are the statistically significant results.

patient samples. Age and body mass index, both of which are known microbial composition-modifying, and thus potential confounding, factors in these analyses were relatively evenly distributed across dietary groups (S-Figure 5). Within the majority of meat-eating patients (>95% of all SIBDCS patients), we further compared the microbiotas of the low- versus high-meat intake patients (i.e. ≤ 4 versus > 4 days per week) with regards to a potential dose-response.

Alpha diversity analysis tended to be higher in GFD CD patients versus RD CD patients ($p > 0.05$). Within CD patients, the lowest species richness was observed in those patients eating meat > 4 days per week. In UC patients, the GFD group tended to have the lowest species richness, with a trend for the highest species richness in patients eating meat on > 4 days (S-Figure 6).

Regarding beta diversity, we identified clustering of samples according to diet type in CD and UC patients. We calculated microbial feature differences using Bray–Curtis dissimilarities on principal component analysis (PCoA) plots and statistical tests performed using

Adonis (Permanova method on distances; 9999 permutations). When GFD, high-meat diets or VDs were compared, significant differences between diet types were observed in CD patients ($p=0.012$; R^2 : 0.02503; Supplementary Figure 7A) and in UC patients ($p < 0.001$; R^2 : 0.10771; Supplementary Figure 7B). It should be noted that beta dispersion of these PCoA plots was > 0.05 , indicating that we cannot reject the null hypothesis that our groups have the same dispersions.

Additionally, significant differences in the OTUs between diet types were seen ($p < 0.05$). In CD patients, several representatives of the phyla Bacteroidetes (unassigned OTUs within the genera *Bacteroidales*, *Bacteroides* and *Prevotella*) and Firmicutes (OTUs within the genera *Clostridiales* and *Faecalibacterium*) were significantly correlated with RD patients when compared to the GFD patients (Figure 3). In UC patients, we identified correlation with several OTUs from Firmicutes (unassigned OTUs within *Clostridiales* and *Ruminococcus* genera) in the

Table 2. Ordinal logistical regression (0 = no meat and 5 = meat consumption every day).

Univariate ordinal logistic regressions	Odds ratio (95% confidence interval; <i>p</i> -value)
Gender	
Male	1 (reference)
Female	0.494 (0.402–0.607; < 0.001)
Age at diagnosis (in years)	1.001 (0.994–1.009; 0.694)
Age (in years)	0.995 (0.988–1.002; 0.167)
Disease duration (in years)	0.988 (0.978–0.998; 0.015)
Diagnosis	
Crohn's	1 (reference)
Ulcerative colitis/indeterminate colitis	1.062 (0.867–1.300; 0.561)
Weight	1.021 (1.014–1.028; < 0.001)
Last location of Crohn's disease	
L1 (ileal)	1 (reference)
L2 (colic)	1.153 (0.823–1.615; 0.407)
L3 (ileocolic)	1.004 (0.705–1.430; 0.983)
L4 (upper gastrointestinal tract only)	1.365 (0.633–2.944; 0.428)
Last location of ulcerative colitis	
Proctitis	1 (reference)
Left-sided Colitis	1.307 (0.817–2.092; 0.265)
Pancolitis	1.310 (0.836–2.054; 0.239)
Previous hospitalization related to inflammatory bowel disease	
No	1 (reference)
Yes	0.909 (0.725–1.140; 0.410)
Intestinal surgery	
No	1 (reference)
Yes	0.922 (0.735–1.156; 0.482)
Surgery for fistula	
No	1 (reference)
Yes	0.880 (0.661–1.171; 0.380)
Complications	
No	1 (reference)
Yes	0.950 (0.775–1.164; 0.619)
Fistula or abscess	
No	1 (reference)
Yes	0.890 (0.711–1.115; 0.311)
Stenosis	
No	1 (reference)
Yes	0.889 (0.708–1.117; 0.313)
Last measure of C-reactive protein	1.003 (0.992–1.014; 0.601)
Therapies (at least once)	
5-aminosalicylic acid	0.950 (0.743–1.215; 0.684)
Antibiotics	0.944 (0.767–1.161; 0.584)
Immunomodulators	1.073 (0.856–1.345; 0.542)
Biologicals	0.906 (0.740–1.109; 0.338)

(continued)

Table 2. Continued

Univariate ordinal logistic regressions	Odds ratio (95% confidence interval; <i>p</i> -value)
Steroids	1.080 (0.830–1.406; 0.566)
Supplementation therapy	
No	1 (reference)
Yes	0.672 (0.543–0.830; < 0.001)
In particular:	
Vitamin D	0.726 (0.578–0.912; 0.006)
Calcium	0.770 (0.611–0.970; 0.026)
Iron	0.636 (0.451–0.896; 0.010)
Probiotics	0.610 (0.411–0.905; 0.014)
Magnesium	0.650 (0.482–0.878; 0.005)
Alternative medicine	
No	1 (reference)
Yes	0.730 (0.582–0.917; 0.007)*
In particular:	
Acupuncture	0.592 (0.376–0.931; 0.023)
Bach-flowers therapy	0.314 (0.155–0.638; 0.001)*
Anthroposophic medicine	0.196 (0.044–0.871; 0.032)*

*Proportional odds assumption has to be rejected in these cases.
Bold values are the statistically significant results.

meat-eating groups. Within the phylum Bacteroidetes, we observed a positive correlation with *Bacteroides* in the meat-eating and *Prevotella* in the GFD group (adjusted *p*-value < 0.01) (Figure 3). Analysing potential differences of specific OTUs between meat-eating and vegetarian UC patients, we found a higher abundance of representative strains from the genera *Bacteroides*, *Faecalibacterium* and *Sutterella* in meat-eating patients, and a higher abundance of most representatives from the Firmicutes phylum (*Blautia*, *Coprococcus*, *Ruminococcus* and *Dorea*) in the vegetarian group (Figure 4) (additional results in supplementary file (4)).

Discussion

We conducted a cross-sectional analysis in patients from the SIBDCS in order to investigate dietary restrictions, their influence on disease course and microbiota composition.

In this large investigation on the prevalence of specific diets, a total of 4.1% IBD patients followed a VD. This number of vegetarians is similar to the number in the general population of western countries and is analogous to a recently published study by Limdi et al.²⁶ concerning IBD patients. The main reported reason for following a VD was respect for animals, followed by an expected or perceived benefit on IBD and general health. The latter two motives appear to be

Table 3. Characteristics of patients following non-gluten-free and gluten-free diets.

	Non-gluten-free	Gluten-free	<i>p</i> -value (Chi ² or Mann-Whitney-Wilcoxon)
Number of patients	1166 (95.3%)	57 (4.7%)	
Gender			
Male	560 (48.0%)	21 (36.8%)	0.099
Female	606 (52.0%)	36 (63.2%)	
Age at diagnosis			
Median, quartile 25–75, minimum–maximum	29.6, 21.7–39.3, 2.9–78.1	26.4, 19.5–36.8, 10.1–81.0	0.085
Disease duration			
Median, quartile 25–75, minimum–maximum	13.1, 7.7–21.9, 0.3–52.8	13.7, 7.7–21.7, 0.3–35.1	0.862
Diagnosis			
Crohn's disease	642 (55.1%)	31 (54.4%)	0.920
Ulcerative colitis/indeterminate colitis	524 (44.9%)	26 (45.6%)	
Weight (kg)			
Median, quartile 25–75, minimum–maximum	71, 60–82, 37–145	69, 60–79, 46–100	0.302
Weight (stratified by sex; only men)			
Median, quartile 25–75, minimum–maximum	79.5, 72–87, 50–145	76, 69–81, 58–96	0.109
Weight (stratified by sex; only women)			
Median, quartile 25–75, minimum–maximum	62, 56–71, 37–135	64.5, 55–73.5, 46–100	0.477 0.477
Last location of Crohn's disease			
L1	183 (29.3%)	11 (35.5%)	0.679
L2	235 (37.7%)	9 (29.0%)	(Fisher's exact test)
L3	188 (30.1%)	10 (32.3%)	
L4 only	18 (2.9%)	1 (3.2%)	
Unknown	18	0	
Maximal extent of ulcerative colitis			
Proctitis	84 (16.3%)	3 (11.5%)	0.738
Left-sided colitis	180 (35.0%)	8 (30.8%)	(Fisher's exact test)
Pancolitis	10	0	
Previous hospitalization related to inflammatory bowel disease			
No	850 (72.9%)	41 (71.9%)	0.872
Yes	316 (27.1%)	16 (28.1%)	
Intestinal surgery			
No	847 (72.6%)	43 (75.4%)	0.643
Yes	319 (27.4%)	14 (24.6%)	
Surgery for fistula			
No	988 (84.7%)	53 (93.0%)	0.124
Yes	178 (15.3%)	4 (7.0%)	(Fisher's exact test)
Complications			
No	522 (44.8%)	26 (45.6%)	0.900
Yes	644 (55.2%)	31 (54.4%)	
Fistula or abscess			
No	828 (71.0%)	46 (80.7%)	0.114
Yes	338 (29.0%)	11 (19.3%)	

(continued)

Table 3. Continued

	Non-gluten-free	Gluten-free	p-value (Chi ² or Mann-Whitney-Wilcoxon)
Stenosis			
No	853 (73.2%)	46 (80.7%)	0.207
Yes	313 (26.8%)	11 (19.3%)	
Last measure of C-reactive protein (mg/l)			
Median, quartile 25-75, minimum-maximum	2.8, 1-5.1, 0-200	2.4, 1-8.5, 0.3-111	0.803
<i>Therapies and complements</i>			
Therapies (at least once)			
5-aminosalicylic acid	913 (78.3%)	46 (80.7%)	0.667
Antibiotics	456 (39.1%)	17 (29.8%)	0.160
Immunomodulators	852 (73.1%)	43 (75.4%)	0.694
Biologicals	540 (46.3%)	30 (52.6%)	0.350
Steroids	961 (82.4%)	50 (87.7%)	0.302
Supplementation therapy (I.6.)			
No	425 (36.4%)	12 (21.1%)	0.018
Yes	741 (63.6%)	45 (78.9%)	
In particular:			
Vitamin D	305 (26.2%)	22 (38.6%)	0.038
Iron	112 (9.6%)	10 (17.5%)	0.051
Probiotics	69 (5.9%)	11 (19.3%)	<0.001
Fish oil/omega 3	69 (5.9%)	10 (17.5%)	<0.001
Alternative medicine (I.7.)			
No	862 (73.9%)	23 (40.4%)	<0.001
Yes	304 (26.1%)	34 (59.6%)	
In particular:			
Homeopathy	68 (5.8%)	10 (17.5%)	<0.001
Change in diet and lifestyle	67 (5.7%)	17 (29.8%)	<0.001
H15	5 (0.4%)	2 (3.5%)	0.039 (Fisher's exact test)
Anthroposophic medicine	3 (0.3%)	2 (3.5%)	0.019 (Fisher's exact test)
Naturopathy	16 (1.4%)	8 (14.0%)	<0.001
Ayurvedic medicine	5 (0.4%)	2 (3.5%)	0.039 (Fisher's exact test)

Bold values are the statistically significant results.

considerably more pronounced in GFD-eating IBD patients. Our results draw an obvious conclusion that patients believe their VDs or GFDs positively influence their disease. However, despite rather strong beliefs of patients, there is little support for the benefits of a VD or GFD in IBD patients in the existing literature. Due to a lack of evidence, neither the European Society for Clinical Nutrition and Metabolism Guideline for clinical nutrition in IBD nor the European Crohn's and Colitis Organisation Guidelines support specific dietary habits.⁶⁻⁸

Overall, a total of 4.7% of our IBD patients followed a GFD, most of whom were without a diagnosis of CeD. The 4% of IBD patients who follow a GFD without suffering from CeD in our study is double the

prevalence in the general population, where the rate of GFD is approximately 2%.¹⁴ Our findings are supported by a cross-sectional study by Herfarth et al., in which a high prevalence of GFD (8%) in IBD patients without CeD could be seen.²⁷ Presumably, the higher percentage of IBD patients can be explained by the belief or expectation of a favourable effect on their disease course. This is also indicated by our results regarding the reasons why patients follow a GFD.

In contrast to the beliefs of the patients, our data could not objectify an association of restrictive dietary patterns with the course of IBD. However, as an exception, we identified lower rates of complications in vegetarian CD patients. Although this was only seen in a subgroup of patients, our findings support the

Figure 1. Rationale for dietary restriction.
IBD: inflammatory bowel disease.

Figure 2. Complication rates in all patients (a), Crohn's disease patients (b) and ulcerative colitis patients (c) regarding diet patterns.

Table 4. (a) Psychological scores in non-vegetarian versus vegetarian patients and (b) in non-gluten free versus gluten free patients (for each patient and each score, the mean value during follow-up is computed).

(a)	Non-vegetarian	Vegetarian	p-value (Mann-Whitney-Wilcoxon)
Physical component summary (SF-36)			
Median, quartile 25-75, minimum-maximum	51.4, 44.9-55.0, 22.2-64.3	50.7, 42.0-55.7, 28.4-64.1	0.511
Mental component summary (SF-36)			
Median, quartile 25-75, minimum-maximum	48.5, 41.4-53.5, 12.1-66.3	45.6, 35.4-50.9, 18.3-59.7	0.008
Anxiety score (HADS)			
Median, quartile 25-75, minimum-maximum	5.2, 3-8, 0-19.5	6.5,-9, 1-15	0.060
Depression score (HADS)			
Median, quartile 25-75, minimum-maximum	2.8, 1-5.5, 0-18.7	3.4, 1.3-6.2, 0-15.1	0.280
Post-traumatic stress Diagnostic scale: total score			
Median, quartile 25-75, minimum-maximum	5.3, 2.5-9.9, 0-45	7.4, 3-11.9, 0.8-50.3	0.042
(b)	Not gluten-free	Gluten-free	p-value (Mann-Whitney-Wilcoxon)
Physical component summary (SF-36)			
Median, quartile 25-75, minimum-maximum	51.6, 45.2-55.1, 22.2-64.3	48.6, 42.7-53.6, 25.4-63.9	0.026
Mental component summary (SF-36)			
Median, quartile 25-75, minimum-maximum	48.7, 41.8-53.6, 12.1-62.3	42.1, 32.6-48.0, 24.1-58.4	<0.001
Anxiety score (HADS)			
Median, quartile 25-75, minimum-maximum	5, 2.9-7.7, 0-19.5	8.6, 5.3-10.9, 1.5-16	<0.001
Depression score (HADS)			
Median, quartile 25-75, minimum-maximum	2.7, 1-5.3, 0-18.7	4.3, 2.9-6.6, 0.2-17.8	<0.001
Post-traumatic stress Diagnostic scale: total score			
Median, quartile 25-75, minimum-maximum	5, 2.4-9.3, 0-45	8.7, 4-15, 1-35	<0.001

HADS: higher anxiety and depression scores; SF-36: Short Form 36 Health Survey. A higher score indicates a better health status. Bold values are the statistically significant results.

assumption that dietary habits could potentially modulate the course of IBD, including a positive overall influence.

Interestingly, and in contrast to the results on the clinical course of IBD, psychological variables were significantly different between the dietary patterns. The VD IBD patients had lower mental SF-36 scores and a higher level of post-traumatic stress symptoms. We hypothesize that these psychological factors and patient

expectations are the main driving factors for the initiation and continuous following of dietary restriction. The alternative explanation, that refraining from meat would lead to stress and anxiety, seems much less likely. Although our cross-sectional data do not allow us to draw conclusions on causality, a study by Michalak et al.²⁸ supports our hypothesis that psychological factors and expectations affect subsequent dietary restriction.

Figure 3. Significant differences in the abundance of operational taxonomic units between Gluten-free versus regular diet in Crohn's disease and ulcerative colitis. All coloured dots without any distribution represent an operational taxonomic unit within the specified genera on the x-axes where no deeper classification is currently available.

CD: Crohn's disease; UC: ulcerative colitis.

The number of CeD-free individuals who follow a GFD is continuously increasing,¹⁴ but there are no data regarding mood disorders in this subgroup. Our results demonstrate an obvious association of reduced psychological well-being and quality of life with a GFD. All psychosocial variables differed significantly between non-GFD- and GFD-eating patients. It is probable that GFD-eating patients have an even stronger tendency to believing in the effects of their diet than vegetarian patients and thus try to positively influence their disease by modulating food intake. Our findings further support this suggestion, as GFD IBD patients in our study were more prone to try alternative medicine therapies. Greater psychological distress is also associated with more somatic symptoms,²⁹ which patients might attribute to IBD, prompting them to adjust their dietary habits in an attempt to exert control on their symptoms.

Another important aspect related to dietary restriction in general, and specifically the consumption of meat or gluten, is the alteration of microbiota

composition. The gut microbiota in vegetarians has been shown to be associated with higher bacterial diversity,³⁰ with a significantly lower counts of pathobionts Enterobacteriaceae³¹ and increased numbers of *Prevotella*,^{18,31} whereas the non-VD, especially the Western diet, has been associated with a greater abundance of *Bacteroides*^{18,21,31} and lower levels of Firmicutes.²¹ Furthermore, a GFD in healthy individuals can shift the gut microbiota to fewer bacterial strains that are considered to be more healthy, including *Bifidobacteria* and *Lactobacillus*, with lower counts of *Escherichia coli* and Enterobacteriaceae,³² which are often considered to be rather unhealthy bacteria.

On the other hand, previous studies have shown that patients with IBD have a lower diversity in their gut microbiota,^{19,20} with an increase invasive *E. coli*,³³ increased Enterobacteriaceae³⁴ and a reduced proportion of Firmicutes.²⁰

In our study, the gut microbiota composition in meat-eating IBD patients was significantly different

Figure 4. Significant differences in the abundance of operational taxonomic units between vegetarian versus meat-containing diets in ulcerative colitis patients.

compared to those following a VD or GFD. Our results demonstrated several bacterial changes in regularly meat-eating IBD compared to VD or GFD patients, specifically lower species richness with a dose-response effect in meat-eating CD patients. Interestingly, we could see the opposite finding in UC patients, with greater species richness in patients with a higher frequency of meat consumption.

Our study has several limitations. First, due to the cross-sectional analysis, we cannot draw any conclusion on cause and effect.

Dietary habits were self-reported, making them potentially unreliable, which is a limitation that is common to many studies investigating the role of diet in health and disease. Many different food frequency questionnaires exist³⁵ but, due to the specific nature of the questions that we wanted to ask, we created our own questionnaire. However, our dietary questions were distinctively targeted and easily comprehensible, in contrast to many other dietary interrogations that seek to obtain (semi-) quantitative information.

A further weakness relates to the non-available CeD serology; thus, we had to rely on patient reported-diagnosis of CeD, which may have led to over- or underestimation of the IBD patients following a GFD with genuine concomitant CeD. However, most of our IBD patients were well informed regarding their secondary diagnoses.

It must be considered that GFD represents a rather recent trend in subjects without CeD and the durations of GFDs in our patient population were considerably

shorter compared to the durations of VDs (S-Figure 1A and 1B). Therefore, any conclusions regarding the (long-term) impacts of a GFD on the course of the disease have to be drawn with caution.

In conclusion, our study demonstrates a similar prevalence of VDs and a higher percentage of GFDs in IBD patients compared to the general population. We could not observe an association between dietary patterns and the course of IBD, with the exception of lower complication rates in VD CD patients. In contrast, VDs and GFDs were both characterized by adverse psychological scores. Apparently, a significant fraction of IBD patients appear to restrict their diets due to underlying beliefs, expectations or perceptions of beneficial effects on disease course, rather than detectable objective benefits on the course of the disease. Furthermore, we found significant differences in mucosa-associated gut microbiota composition between VD and GFD IBD patients compared with counterparts not restricting their diets.

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Declaration of conflict interests

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Ethics approval

The SIBDCS has been approved by the respective ethics committees in Switzerland and the lead ethics committee, the Cantonal Ethics Committee of Zurich. The presented study is part of the research plan of the SIBDCS (number EK-1316, approved on 5 February 2007). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

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Informed consent

Participants were enrolled only after they had provided written informed consent.

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