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Trajectories of Fatigue in Inflammatory Bowel Disease

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Background: Fatigue is one of the most frequently reported symptoms by patients with inflammatory bowel disease (IBD), both during active disease phases as well as during clinical remission. This study addressed whether different trajectories of fatigue over time can be identified among patients with IBD. Subsequently, we compared the demographic and clinical characteristics between trajectories.

Methods: The current study included 849 patients with IBD diagnosed with either Crohn disease (CD; n = 511) or ulcerative colitis (UC; n = 338) who visited the University Medical Center in Groningen (the Netherlands) at least 3 times during a 9-year follow-up. We conducted latent class growth analyses to identify distinct trajectories.

Results: In all patients with IBD (and in the subgroup with CD), we found 5 trajectories for fatigue. In the UC subgroup, we found 4 fatigue trajectories. One trajectory present in both patients with CD (11.45%) and patients with UC (4.75%) was characterized by chronic elevated levels of fatigue across time. Women and parents were more prevalent in trajectories with higher fatigue severity. We also found significant associations among the fatigue trajectories with disease activity and psychological well-being.

Conclusions: The results clearly showed the existence of distinct fatigue paths over time in patients with IBD. Those reporting more chronic elevated levels of fatigue also reported greater disease activity and reduced well-being. Therefore, reducing disease activity may be important for the treatment of fatigue. In addition, given the significant association with well-being, it is possible that reducing fatigue may improve self-reported well-being.

Key Words: inflammatory bowel disease, Crohn disease, ulcerative colitis, fatigue, psychological well-being, disease activity, trajectories

INTRODUCTION

Inflammatory bowel diseases (IBD), primarily including Crohn's Disease (CD) and ulcerative colitis (UC), are chronic relapsing diseases of the gastrointestinal tract of unknown etiology.[1] Both CD and UC are characterized by inflammation and ulcerations that in UC are limited to the superficial mucosa of the colon and rectum and in CD are transmural and can affect the entire gastrointestinal tract but are predominant in the distal ileum and colon. Both UC and CD share clinical symptoms such as abdominal pain, diarrhea, constipation, anemia, and weight loss.[2]

One of the most frequently reported complaints by patients with CD or UC, in active disease phases and during clinical remission, is persistent fatigue.[3] Persistent fatigue can have a far-reaching impact on a person's life. Individuals who experience fatigue report lower stress tolerance, more hypersensitivity, longer periods to recover from overexhaustion, or an inability to multitask.[4] Chronic fatigue has been identified as interfering with work-related abilities, subsequently causing lower employment rates and increased health care costs.[5] Prevalence rates of fatigue range from 26% to 83% for patients with IBD in remission,[3] with 44% to 86% of patients with moderate to severely active IBD reporting fatigue.[6]

Approximately a decade ago, research on IBD fatigue was still scarce, as pointed out by van Langenberg and Gibson.[3] Their systematic review, which is still the most recent, showed that only 10 studies focused on fatigue in patients with IBD, with only 1 measuring fatigue as its primary outcome. However, during the past few years, several studies have been published assessing IBD fatigue, its experience, and management,[6] yet the majority of these studies have methodological weaknesses, such as using cross-sectional designs, small sample sizes, and

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assessment of fatigue in patients with CD or UC at the group level.[7] Only 3 studies so far have examined fatigue longitudinally among patients with IBD.[8-10] Graff et al[9] found a steady increase in fatigue in patients with a recent IBD disease onset over a span of 2 years. The other longitudinal study, by Banovic and colleagues[8] in 52 patients with CD, found stable levels of fatigue over a 1-year period. Conley and colleagues[10] clustered symptoms of IBD patients cross-sectionally[2] and longitudinally.[11] Their findings suggest a large group with several symptoms, including fatigue, that remain stable over a 1-year period. However, there is still a lack of a good understanding of the specific development of fatigue in patients with IBD and which patients' characteristics impact the severity and course of fatigue.

Specific demographics, such being younger or female, and clinical characteristics have been consistently linked to higher levels of fatigue in chronic diseases[12] but recently also in patients with IBD.[13] Even though fatigue occurs in patients of all ages and both sexes, a greater burden has consistently been suggested for women. Younger patients or those with a lower educational background have been found to report greater fatigue severity in previous studies among patients with IBD,[14] although not in all.[15] Among clinical factors, a shorter disease duration was related to greater fatigue by Vogelaar and colleagues[16] among patients with CD. Still, one of the most noted clinical factors associated with fatigue in IBD is disease activity. Previous research has shown that inflammation has been closely linked to fatigue in chronic conditions, such as rheumatic diseases, cancer, and systemic autoimmune disease,[17] but also in IBD.[6] Both CD and UC follow unpredictable courses, with alternating periods of active inflammatory processes and periods without any symptoms. Hence, one would hypothesize that in patients with IBD, higher disease activity is associated with fatigue severity. Several cross-sectional studies have found disease activity as a risk factor for greater fatigue severity[8, 18]. In a longitudinal study, Graff et al[9] showed that mean fatigue levels increased among patients with IBD even when patients were in remission. A study by Grimstad and colleagues[19] found that the severity of fatigue was independent of disease activity. However, their cohort consisted of only patients newly diagnosed with IBD.

The relationship between disease activity and fatigue is not yet completely understood. This circumstance is underlined by the observation of several scholars that a substantial group of patients in remission still report high levels of fatigue persistent over time.[9, 10] Research on how different trajectories of disease activity may relate to fatigue over time has not been conducted.

A close link between fatigue and the psychological well-being of patients has been suggested because of the restrictions on daily and work-related functioning in active disease.[20] In patients with IBD in remission, fatigue has also been associated with impaired psychological well-being.[9, 21, 22] Given the cross-sectional design of most of these studies, there is a lack of insight into how fatigue and well-being interact over time.

To overcome the methodological shortcomings in the study of fatigue in patients with IBD, the current longitudinal study examined the course of fatigue over a 9-year period in more than 800 patients with CD or UC. Rather than looking at average group levels of fatigue over time, the purpose of the current study was (1) to identify distinct subgroups of patients with different trajectories of fatigue, (2) to assess the association among demographic (age, sex, cultural background, education, having children) and clinical factors (eg, smoking status, disease, disease duration) and defined fatigue trajectories, and (3) to explore how trajectories of fatigue relate to disease activity and patients' psychological well-being. Such examinations have not yet been undertaken.

MATERIALS AND METHODS

The dataset analyzed during the current study is not publicly available because of patient confidentiality but is available from the authors upon reasonable request.

Design

The current study had a longitudinal design, using prospectively collected data from patient records collected during visits to an IBD outpatient clinic.

Cohort

Study participants were patients (N = 849) diagnosed with either UC (n = 338) or CD (n = 511) who received care at the IBD outpatient clinic at the University Medical Centrum Groningen (Groningen, the Netherlands) and were included within the Groningen 1000IBD project.[23] At each visit to the clinic, patients were examined and asked for demographic, clinical, and psychological information by the treating nurse or doctor. The staff documented all received information and electronically filed the data in the 1000IBD database.[23] Inclusion criteria of the current study were a documented diagnosis of either UC or CD (based on accepted clinical endoscopic outcomes); ≥3 recorded visits between January 1, 2009 and December 31, 2018 (with valid entries of all 3 outcome measures, ie, fatigue, disease activity, and well-being), and age >18 years. On average, patients with CD were assessed 7.2 times (maximum 38 consults; 5037 total consults), and patients with UC were assessed 6.3 times (maximum 51 consults; 2789 total consults). Power analysis methods have yet to be standardized for latent class analyses (LCA), but experts state that samples of 100 to 300 participants are recommended to run LCA.[24, 25] The total cohort included 849 patients, with subcohorts for UC and CD of 338 and 511 patients, respectively. It was therefore adequate to perform LCA.

Variables and Measures

Demographic and clinical factors

Demographic variables included age (at first consult to clinic), sex, educational level, cultural background, and having children (yes/no). Educational level was subdivided into 3 levels based on the Dutch educational system.[26] Clinical variables included smoking status (being a smoker at T0); type of IBD diagnosis; disease duration (at first consult to clinic); Montreal classification according to disease type: A (age at diagnosis), B (behavior), E (extent), L (location), and S (severity); fistulas; localization (ileum/colon); and having a stoma or pouch (in general, at baseline, type). If any information on the mentioned variables was missing at a patient's first visit, then data saved on a subsequent visit were included.

Fatigue

The primary outcome measure was fatigue, patient-rated and evaluated by a single item ("How fatigued has the patient been during the last 24 hours?"), based upon a visual analogue 10-point Likert scale at each consult (1 = not fatigued, 10 = very fatigued).

Disease activity

The modified Harvey-Bradshaw Index (HBI[27]) for CD (Supplementary Questionnaire 1) and the Simple Clinical Colitis Activity Index (SCCAI[28]) for UC (Supplementary Questionnaire 2) were used to measure self-reported disease activity. These clinical indices ask for the frequency of bowel movements, the presence of blood in the stool, extra-intestinal manifestations of IBD, and overall health. The following cutoff points were used to identify active disease: HBI >5 and SCCAI >2.5.[29]

Psychological well-being

Psychological well-being within the last 24 hours was rated by the patient and assessed by a single item ("How does the patient feel [during the last 24 hours]?"), based on a visual analogue 10-point Likert scale (1 = very bad, 10 = excellent).

Statistical Analysis

Data from the overall cohort, and from the CD and UC cohorts specifically, were described using distributions, means, medians and standard deviations, and frequencies, as appropriate (Table 1). Time was handled as a continuous variable as suggested by Singer and Willett.[30] The number of days since the start of the study (T0; January 1, 2009) to each visit at the clinic was divided by the total number of days of the study's timeframe (eg, May 19th 2011 => 868 days/3287 days = 0.264; number of days from January 1st 2009 to May 19th 2011 = 868 days). To classify the different trajectories of fatigue over time and to associate these with disease activity and psychological well-being, latent class growth analyses (LCGA) were performed in the statistical program LatentGold, version 5.1. The syntax used to run the analyses can be found in the Supplementary Syntax 1. Researchers have found LCGA to be a useful tool to find inherent differences in growth trajectories over time.

Dependent on the added value for model estimation calculated using means of deviance tests (see Supplementary Table 1), time was added as a predictor with different levels, ie, linear, quadratic, and/or cubic. To find the most representative models, we compared models with 1 to 8 classes for fatigue, disease activity levels, and psychological well-being separately. We fitted the models multiple times using random seed values to avoid convergence on local maxima. The best-fitting classification model was based on information criteria, including the Bayesian Information Criterion (BIC), which is a criterion calculated from the log-likelihood of the model and the number of parameters in the model, and the Akaike Information Criterion (AIC), which estimates out-of-sample prediction error. The AIC is used as an indicator for the relative quality of a statistical model.[31, 32] Lower values of the BIC and AIC suggest a better model fit.

Entropy was used to inspect latent class separation. Higher entropy levels (at least 0.6) reflect better separation between classes. An added class should also contain a substantial number of people (at least 5%).[33] In line with recommendations, we used a combination of the above-mentioned criteria and nonstatistical criteria for the final model classification.[32] These included the conceptual meaning and interpretability of a model when adding an extra class, because statistical criteria do not always correspond.[34, 35]

After the most suitable model had been selected, patients' class membership (based on most likely posterior probabilities) was exported to SPSS version 25.0 for further analyses. This procedure allowed us to assess the number of patients who fell within a particular subgroup. To determine whether demographic and clinical characteristics differed among identified subgroups, χ^2 tests and analyses of variance were performed to compare the trajectories for each variable. Nonparametric tests were used if the assumption of normality was not met. Cross-tabulations of the final models for fatigue, disease activity, and psychological well-being were created and tested for independence using χ^2 tests. Based on the assumption that disease activity scores, calculated by the indices of HBI and SCCAI, cannot be combined, no modeling of disease activity for the total IBD cohort was performed.

Ethical Considerations

Informed consents were obtained from all patients at their first recorded visit and documented in the database. This study received approval by the medical ethical committee of the University Medical Center Groningen (METc–nr MEC 08/279).

TABLE 1. Sociodemographic and Clinical Characteristics for Total IBD Cohort and per Disease Type

	Total Cohort (N = 849)	CD (n = 511)	UC (n = 338)	Significant Difference
Age, *M* (SD)	40.13 (14.87)	38.77 (14.47)	42.18 (15.25)	*
Female sex, n (%)	525 (61.8)	338 (66.1)	187 (55.3)	*
Education, n (%)				
No/lower	152 (17.9)	86 (17.8)	66 (19.5)	
Secondary	372 (43.8)	237 (46.4)	135 (39.9)	
Higher	253 (29.8)	141 (27.6)	112 (33.1)	
Other	33 (3.9)	19 (3.7)	14 (4.1)	
Ethnicity, n (%)				
Dutch Caucasian/White European	762 (89.8)	453 (88.6)	309 (91.4)	
Smoking status, n (%)				*
Yes	196 (23.1)	154 (30.1)	42 (12.4)	
Having children, n (%)				
Yes	415 (48.9)	227 (44.4)	188 (55.6)	
Disease duration, median (range)	7.00 (0-50)	8.00 (0-46)	7.00 (0-50)	*
Montreal classification A (age at diagnosis), n (%)				*
A1: <16 y	118 (13.9)	81 (15.9)	37 (10.9)	
A2: 17 y-40 y	530 (62.4)	333 (65.2)	197 (58.3)	
A3: >40 y	182 (21.4)	92 (18.0)	90 (26.6)	
Montreal classification B (behavior), n (%)				
B1: nonstricturing, nonpenetrating	—	208 (40.7)	—	
B2: stricturing	—	92 (18.0)	—	
B3: penetrating	—	53 (10.4)	—	
B1P: nonstricturing, nonpenetrating + perianal	—	56 (11.0)	—	
B2P: stricturing + perianal	—	61 (11.9)	—	
B3P: penetrating + perianal	—	39 (7.6)	—	
Montreal classification E (extent), n (%)				
E1: ulcerative proctitis	—	—	46 (13.6)	
E2: distal UC	—	—	113 (33.4)	
E3: extended UC (pancolitis)	—	—	169 (50.0)	
Montreal class L (location), n (%)				
L1: terminal ileum	—	180 (35.2)	—	
L2: colonic	—	97 (19.0)	—	
L3: ileocolonic	—	182 (35.6)	—	
L4: upper GI	—	10 (2.0)	—	
L1 + L4	—	16 (3.1)	—	
L2 + L4	—	9 (1.8)	—	
L3 + L4	—	12 (2.3)	—	
Montreal classification S (severity), n (%)				
S1: clinical remission	—	—	33 (9.8)	
S2: mild UC	—	—	91 (26.9)	
S3: moderate UC	—	—	115 (34.0)	
S4: severe UC	—	—	82 (24.3)	
Stoma/pouch, n (%)				
Ever	161 (19.0)	100 (19.6)	61 (18.0)	
Current	115 (13.5)	66 (12.9)	49 (14.5)	
Type stoma/pouch, n (%)				*
Colostoma	30 (3.5)	27 (5.3)	3 (0.9)	
Ileostoma	122 (14.4)	68 (13.3)	54 (16.0)	
Pouch	8 (0.9)	4 (0.8)	4 (1.2)	

TABLE 1. Continued

	Total Cohort (N = 849)	CD (n = 511)	UC (n = 338)	Significant Difference
Stoma because of perineal fistula	1 (0.1)	1 (0.2)	0 (0.0)	
Fistulas n (%)†	81 (9.5)	77 (15.1)	4 (1.2)	*

For CD, Montreal Classifications A, B, and L were collected; For UC, Montreal Classifications A, E, S were collected.
*$P < 0.05$ comparing CD and UC cohorts.
†150 out of 849 patients were missing.

RESULTS

Cohort Characteristics

The demographic and clinical data are presented in Table 1. Across the total cohort, approximately two-thirds were female, with a mean age of 40 years. The majority of patients were Dutch/Caucasian, with a median disease duration of 7 years. Significant differences between the cohorts were found for age, sex, smoking status, disease duration, Montreal classification A, type of stoma/pouch, and fistulas.

Fatigue Trajectories

Total cohort

Based on BIC, AIC, and entropy, a model with 8 classes could be considered. However, given a group size of <5% in models with 6 to 8 classes, we decided to use a 5-class model: FAT_total1 (M = 4.52; standard error [SE] = 0.033; 29.63% of patients), FAT_total2 (M = 5.42; SE = 0.058; 25.01%), FAT_total3 (M = 6.21; SE = 0.0518; 19.31%), FAT_total4 (M = 3.01; SE = 0.049; 16.65%), and FAT_total5 (M = 7.92; SE = 0.067; 9.39%). Four of the 5 fatigue trajectories depicted stable levels of fatigue over time (Fig. 1), with only 1 class (FAT_total2) steadily decreasing in fatigue over time.

CD

As in the total group, both BIC and AIC hinted toward a model with 8 classes in patients with CD. However, given a group size of <5% in models with 6 to 8 classes, the final model included 5 classes. The 5 classes were FAT_CD1 (M = 4.61; 25.09%), FAT_CD2 (M = 5.50; 24.34%), FAT_CD3 (M = 6.36; 22.30%), FAT_CD4 (M = 3.10; 16.82%), and FAT_CD5 (M = 7.97; 11.45%). Four of the 5 trajectories showed rather stable levels of fatigue (Fig. 2), with only 1 trajectory (FAT_CD2) representing 24.34% of patients with CD, decreasing in fatigue levels over time.

UC

In contrast to patients with CD, a model selection based on statistical indicators was less evident in patients with UC. With BIC and AIC decreasing and entropy levels still high, we looked into the model parsimony and clinical relevance of models with 4, 5, and 6 classes. We decided to use a model with 4 classes, even though the added class held less than 5% of patients. This model was clinically the most informative and in line with previous outcomes in the literature. It identified a class with high levels of fatigue severity (M = 8.12), which we also observed in the total and the CD groups. The following 4 classes for fatigue in patients with UC were distinguished: FAT_UC1 (M = 5.79; 38.68%), FAT_UC2 (M = 4.43; 34.25%), FAT_UC3 (M = 3.34; 22.83%), and FAT_UC4 (M = 8.12; 4.24%). As depicted in Fig. 3, the 4 subgroups of the final model for UC were comparable to the subgroups of the final model for CD, with the exception of an added class (FAT_CD3) that was not found for UC. All LCGA statistics for models of fatigue can be found in Supplementary Tables 2-4.

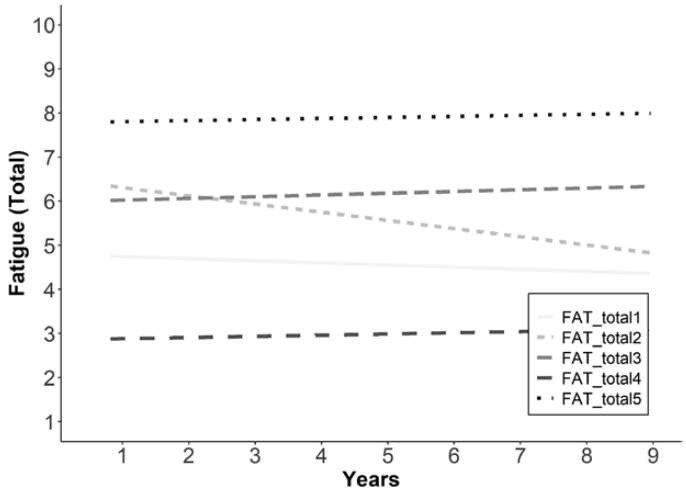

FIGURE 1. 5-class model for fatigue (FAT) in total cohort.

Demographic and Clinical Characteristics of Fatigue Trajectories

Total cohort

Significant associations between fatigue class and the following demographic variables were found: age (F [4,848] = 3.251; P = 0.021), female sex (χ^2 [4, n = 849] = 42.434; $P < 0.001$; V = 0.224), and being a parent (χ^2 [4, n = 624] = 10.200; P = 0.037; V = 0.128). The oldest patients were observed within FAT_total3 (mean age = 42.06, SD = 14.27), and the youngest

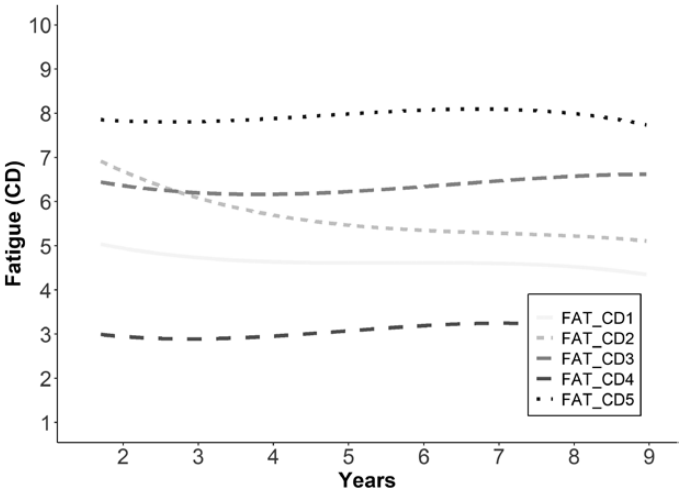

FIGURE 2. 5-class model for fatigue (FAT) in CD.

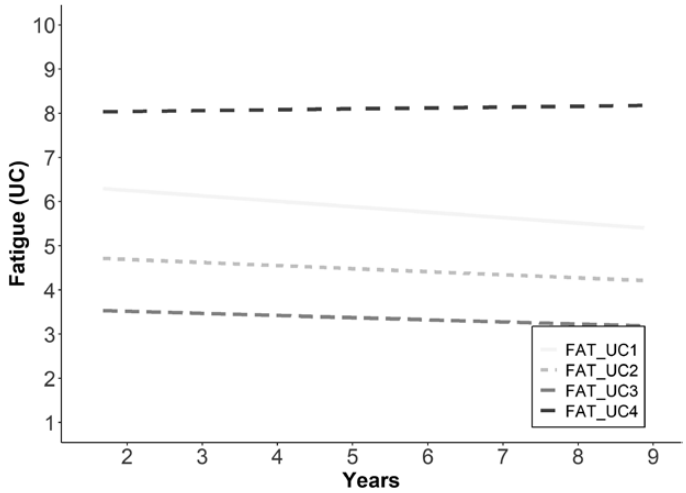

FIGURE 3. 4-class model for fatigue (FAT) in UC.

were observed in FAT_total5 (mean age = 37.91, SD = 14.93). Greater proportions of women fell within the class with highest fatigue scores (85.2%), and the lowest proportions of women were observed within the group with the lowest fatigue scores (FAT_total4). We found that 78.6% of patients classified with highest fatigue were parents.

For clinical variables, smoking status (χ^2 [4, n = 822] = 23.475; $P < 0.001$; $V = 0.169$) and disease duration differed across the groups with the highest mean rank score for FAT_total3 (χ^2 [4, n = 840] = 13.028; $P = 0.028$; $V = 0.013$), and disease duration based on Montreal classification A (disease onset; χ^2_{Total} [8, n = 830] = 19.883; $P = 0.011$; $V = 0.109$) was found to associate significantly with fatigue trajectories. For Montreal classification A, 74.4% patients in FAT_total5 were in the subgroup A2.

CD cohort

Within the CD cohort, female sex (χ^2 [4, n = 511] = 25.478; $P < 0.001$; $V = 0.228$), having children (χ^2 (4, n = 358) = 14.099; $P = 0.007$; $V = 0.198$), and smoking status were found to significantly differ in proportions among fatigue classes. Patients who smoked were more likely to be classified in fatigue classes with a higher mean score (smoking status: χ^2 [4, n = 494] = 17.826; $P = 0.001$; $V = 0.190$). The same accounted for patients with CD who were suffering from fistulas (at T0—first recorded visit; χ^2_{CD} [4, n = 435] = 11.552; $P = 0.021$; $V = 0.163$).

UC cohort

In line with the total cohort and the CD cohort, female sex (χ^2 [3, n = 338] = 8.540; $P = 0.036$; $V = 0.159$) and having children (χ^2 [3, n = 266] = 12.435; $P = 0.006$; $V = 0.216$) was found to significantly associate with the 4 fatigue classes found in patients with UC. Furthermore, disease onset (Montreal A classification) was found to have a significant association with fatigue classes (χ^2 [6, n = 324] = 13.249; $P = 0.011$; $V = 0.143$). 84.6% of patients classified within the trajectory FAT_UC4 had a disease onset between ages 17 and 40 years (subgroup A2). No additional significant associations with patient characteristics and fatigue class membership were found ($P > 0.05$).

Disease Activity Trajectories

Total sample

As mentioned above, we did not perform LCGA for disease activity across the total cohort because it cannot be assumed that the sum scores of the HBI and SCCAI are equally interpretable.

CD

Neither statistical indicators nor group size depicted a clear indicator for a suggested final model for disease activity. Considering the literature and the interpretability and clinical relevance, we decided on a final model of 5 classes for disease activity (Fig. 4): HBI_CD1 (M = 2.65; 34.77%), HBI_CD2 (M = 5.14; 24.29%), HBI_CD3 (M = 0.083; 20.48%), HBI_CD4 (M = 9.53; 10.46%), and HBI_CD5 (M = 0.0, 10.00%). Two of the 5 classes steadily remained under the cutoff score of 5, with 1 class characterized by no disease activity at all (HBI_CD5, 10.00%). The HBI_CD1, HBI_CD2, and HBI_CD4 classes showed great fluctuations in HBI scores over time, with HBI_CD2 oscillating around the cutoff score and HBI_CD4 fluctuating far above the cutoff score, with a slight decrease during the last 2 years.

UC

For disease activity based on SCCAI scores for patients with UC, a model with 8 classes could have been considered according to statistical measures of BIC, AIC, and entropy. We inspected models with 5 and 6 classes and decided that a final model with 5 classes seemed most parsimonious. The added

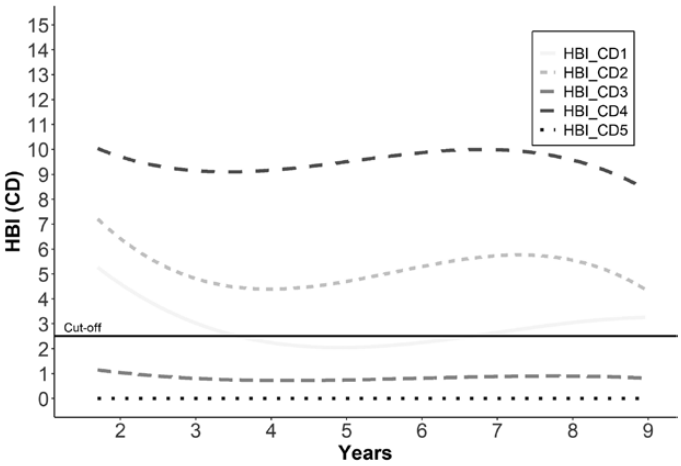

FIGURE 4. 5-class model for disease activity (based on HBI in CD.

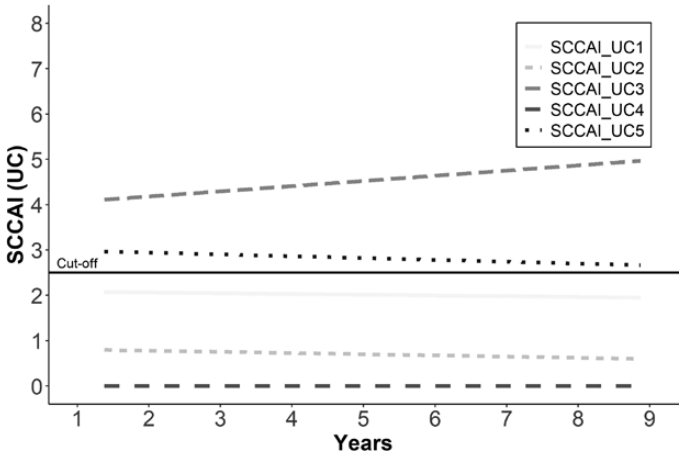

FIGURE 5. 5-class model for disease activity (based on SCCAI in UC.

class of the 6-class model did not pose a significant extension to the 5-class model. The following classes were observed: SCCAI_UC1 (M = 2.00; 35.27%), SCCAI_UC2 (M = 0.68; 25.20%), SCCAI_UC3 (M = 4.61; 18.93%), SCCAI_UC4 (M = 0.0; 14.51%), and SCCAI_UC5 (M = 2.79; 6.09%). As can be seen in Fig. 5, 3 trajectories of the 5 groups remained below the cutoff of 2.5 for the SCCAI scale. Overall, classes remained stable, with 1 class (SCCAI_UC3) steadily increasing over time.

Well-Being Trajectories

Total cohort

Statistical indicators of BIC, AIC, and entropy depicted no clear indication on a final model for psychological well-being in the total cohort. Based on clinical meaningfulness and the models' parsimony, we decided for a final model including 5 classes (Fig. 6): WB_total1 (M = 6.10; SE = 0.033; 39.45%), WB_total2 (M = 7.89; SE = 0.044; 26.79%), WB_total3 (M = 6.90; SE = 0.032; 21.76%), WB_total4 (M = 8.00; SE = 0.003; 6.85%), and WB_total5 (M = 4.13; SE = 0.070; 5.16%). Four classes showed a stable course of well-being over time, with a slight increase for class WB_total2. Some fluctuation within the class with the lowest mean score of psychological well-being (WB_total5) was observed.

CD

Similar to findings in the total group, statistical indicators, ie, BIC and AIC, continued to decrease the more classes a model held. Therefore, the selection of a fit model for psychological well-being in patients with CD patients was thus primarily based on its parsimony and clinical meaningfulness. As a result, we decided on a final model with 5 classes (see Fig. 2): WB_CD1 (M = 6.09; SE = 0.043; 41.08%), WB_CD2 (M = 7.01; SE = 0.038; 27.07%), WB_CD3 (M = 8.16; SE = 0.089; 17.53%), WB_CD4 (M = 4.17; SE = 0.077; 7.64%),

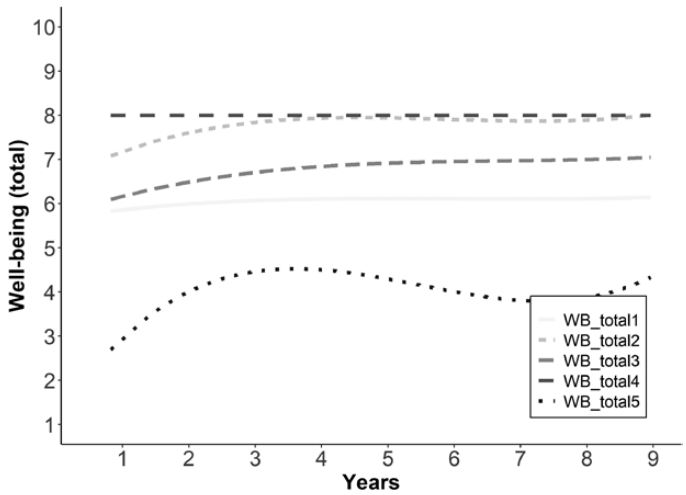

FIGURE 6. 5-class model for well-being (WB) in total cohort.

and WB_CD5 (M = 8.00; SE = 0.004; 6.68%). Four of the 5 classes followed a stable course of well-being over time, with WB_CD4, the class with the lowest mean well-being score, oscillating the most (Fig. 7).

UC

With BIC and AIC scores continuing to drop, we also considered model parsimony and clinical relevance. We thus decided on a final model of psychological well-being in patients with UC that included the following 5 classes (Fig. 8): WB_UC1 (M = 6.57; SE = 0.049; 39.87%), WB_UC2 (M = 7.91; SE = 0.073; 30.02%), WB_UC3 (M = 5.59; SE = 0.101; 15.83%), WB_UC4 (M = 8.0; SE = 0.006; 7.14%), and WB_UC5 (M = 7.00; SE = 0.005; 7.14%). All 5 classes followed a stable course over time. All LCGA statistics for disease activity and psychological well-being can be found in Supplementary Tables 5-9.

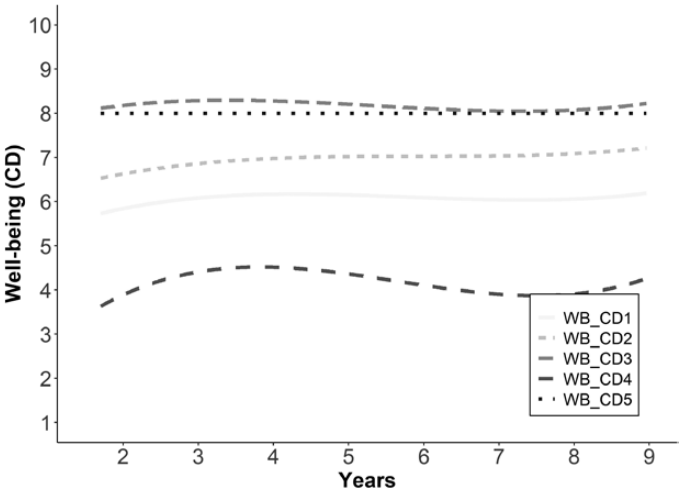

FIGURE 7. 5-class model for well-being (WB) in CD.

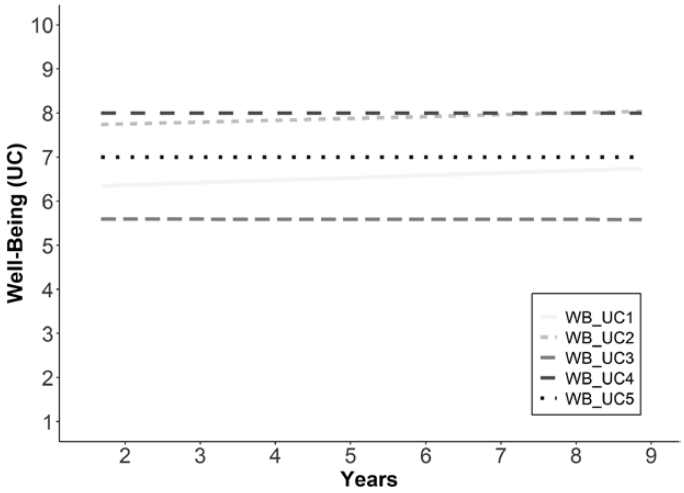

FIGURE 8. 5-class model for well-being (WB) in UC.

Associations of Fatigue Trajectories With Trajectories of Disease Activity and Well-Being

For both CD and UC, we found a significant association of fatigue classes with the course of disease activity (χ^2_{CD} [16, n = 511] = 197.579; $P < 0.001$; $V = 0.311$; χ^2_{UC} (12, n = 338] = 81.728; $P < 0.001$; $V = 0.284$), showing that patients with more severe fatigue courses were more likely to fall within classes of higher disease activity (Tables 2, 3). Moreover, for the total cohort and for both CD and UC, a significant relationship between classes of fatigue and classes of psychological well-being was observed, showing that patients with more severe fatigue courses were more likely to fall within classes with a lower well-being course ($\chi^2_{\text{Total sample}}$ [16, n = 849] = 632.62; $P < 0.001$; $V = 0.432$; χ^2_{CD} [16, n= 511] = 397.050; $P < 0.001$; $V = 0.441$; χ^2_{UC} [12, n = 338] = 148.700; $P < 0.001$; $V = 0.383$). Per Tables 2 and 3, we ordered classes according to average scores from lowest to highest. For the total cohort, the cross tabulations for classes of fatigue and disease activity as well as well-being can be found in Supplementary Table 10.

DISCUSSION

We performed a large longitudinal study with prospectively collected data that assessed fatigue trajectories in IBD over a course of 9 years. We found distinct classes of fatigue courses persisting in severity over time among patients with IBD with either CD or UC. Five classes were identified in patients with CD, of which 4 were comparable to those for patients with UC. Fatigue trajectories remained overall stable with distinctions in their level of severity. Notably, we observed 1 class of patients with persistently high levels of fatigue across time, more so in CD (11.45%) than in UC (4.75%). Across all 3 cohorts, being female or having children was identified as being associated with higher fatigue severity. Being a smoker or suffering from fistulas was associated within the CD cohort as a risk factor. Among patients with UC, the highest proportion of severe fatigue fell within the fatigue trajectories of the highest severity. Patients classified in fatigue trajectories with a higher severity were more likely to fall within the class of higher disease activity scores and lower well-being.

Four comparable stable fatigue trajectories were found in both CD and UC, which differed in their levels of fatigue severity. An additional subgroup with approximately 25% of patients was identified within the CD cohort. Overall, trajectories were characterized by their stability, which is in line with previous longitudinal research in chronic diseases, such as rheumatoid arthritis,[36] but also in IBD. Banovic et al[8] found stable fatigue courses over time across 1 year at the group level in 52 patients with CD. Our current cohort held more than 500 patients with CD and followed them across a longer time span, thereby extending Banovic and colleagues' findings by showing the distinct trajectories that fatigue may take in patients with IBD. A subgroup including 25% of patients with CD and 38.68% of patients with UC was characterized by a slight decrease over time in fatigue scores, although fatigue levels remained at approximately scores of 5 on a scale from 1 to 10. Such an observed decline is in contrast to findings by Graff et al,[9] who reported actual fatigue levels intensifying over a timespan of 2 years. This finding may stem from differences in cohorts in that Graff and colleagues only included patients with recent disease onset, with 2 assessments over a timespan of 2 years. In our cohort, patients had on average a disease duration of 7 years. Adjusting to the disease and receiving medication to alleviate symptoms may be a struggle for patients in the beginning but lessen with time. Conley, Jeon, and colleagues[10] also pointed out that fewer symptoms were observed in patients with IBD with a longer disease

TABLE 2. Coded by Shade of Cross-Tabulation Fatigue x Disease Activity/Psychological Well-Being of CD Cohort

		FAT_CD4 (*M* = 3.10)	FAT_CD1 (*M* = 4.61)	FAT_CD2 (*M* = 5.50)	FAT_CD3 (*M* = 6.36)	FAT_CD5 (*M* = 7.97)	Total
HBI_CD5 (*M* = 0.0)	n (%)	30 (34.5)	17 (12.7)	3 (2.7)	1 (0.8)	0 (0.0)	51
HBI_CD3 (*M* = 0.83)	n (%)	30 (34.5)	39 (29.1)	18 (16.1)	15 (12.6)	2 (3.4)	104
HBI_CD1 (*M* = 2.65)	n (%)	22 (25.3)	55 (41.0)	42 (37.5)	54 (45.4)	10 (16.9)	183
HBI_CD2 (*M* = 5.14)	n (%)	5 (5.7)	20 (14.9)	37 (33.0)	34 (28.6)	28 (47.5)	124
HBI_CD4 (*M* = 9.53)	n (%)	0 (0.0)	3 (2.2)	12 (10.7)	15 (12.6)	19 (32.2)	49
WB_CD4 (*M* = 4.16)	n (%)	0 (0.0)	0 (0.0)	2 (1.8)	7 (5.9)	26 (44.1)	35
WB_CD1 (*M* = 6.09)	n (%)	2 (2.3)	28 (20.9)	74 (66.1)	75 (63.0)	31 (52.5)	210
WB_CD2 (*M* = 7.01)	n (%)	22 (25.3)	71 (53.0)	17 (15.2)	35 (29.4)	1 (1.7)	146
WB_CD5 (*M* = 8.00)	n (%)	19 (21.8)	11 (8.2)	2 (1.8)	1 (0.8)	1 (1.7)	34
WB_CD3 (*M* = 8.16)	n (%)	44 (50.6)	24 (17.9)	17 (15.2)	1 (0.8)	0 (0.0)	86
Total		87	134	112	119	59	511

Darker shades of grey indicate higher frequency.
CD, based on Crohn's disease sub-cohort; FAT, Fatigue; HBI, Harvey-Bradshaw Index; SCCAI, Simple Clinical Colitis Activy Index; Total, based on total cohort; UC, based on ulcerative colitis sub-cohort; WB, Well-being. Example: WB_CD4 = 4th class/trajectory for well-being among CD patients.

TABLE 3. Coded by Shade Cross-Tabulation Fatigue x Disease Activity/Psychological Well-Being of UC Cohort

		FAT_UC3 (*M* = 3.34)	FAT_UC2 (*M* = 4.43)	FAT_UC1 (*M* = 5.79)	FAT_UC4 (*M* = 8.12)	Total
SCCAI_UC4 (*M* = 0.00)	n (%)	23 (31.9)	19 (15.1)	5 (4.0)	2 (14.3)	49
SCCAI_UC2 (*M* = 0.68)	n (%)	22 (30.6)	42 (33.3)	22 (17.5)	1 (7.1)	87
SCCAI_UC1 (*M* = 2.00)	n (%)	23 (31.9)	44 (34.9)	50 (39.7)	2 (14.3)	119
SCCAI_UC5 (*M* = 2.79)	n (%)	1 (1.4)	11 (8.7)	6 (4.8)	2 (14.3)	20
SCCAI_UC3 (*M* = 4.61)	n (%)	3 (4.2)	10 (7.9)	43 (34.1)	7 (50.0)	63
WB_UC3 (*M* = 5.59)	n (%)	4 (5.6)	4 (3.2)	36 (28.6)	6 (42.9)	14.8
WB_UC1 (*M* = 6.57)	n (%)	6 (8.3)	5 (46.0)	71 (56.3)	4 (28.6)	139
WB_UC5 (*M* = 7.00)	n (%)	2 (2.8)	15 (11.9)	4 (3.2)	3 (21.4)	24
WB_UC2 (*M* = 7.91)	n (%)	51 (70.8)	38 (30.2)	12 (9.5)	0 (0.0)	101
WB_UC4 (*M* = 8.00)	n (%)	9 (12.5)	11 (8.7)	3 (2.4)	7 (7.1)	24
		72	126	126	14	338

Darker shades of grey indicate higher frequencies.
CD, based on Crohn's disease sub-cohort; FAT, Fatigue; HBI, Harvey-Bradshaw Index; SCCAI, Simple Clinical Colitis Activy Index; Total, based on total cohort; UC, based on ulcerative colitis sub-cohort; WB, Well-being. Example: WB_CD4 = 4th class/trajectory for well-being among CD patients. Example: SCCAI_UC1 = 2nd class/trajectory for disease activity based on Simple Clinical Colitis Acitvity Index (SCCAI) among UC patients.

duration. In our study, patients may have had more time to adjust to their disease, including living with the challenges of IBD. However, significantly elevated fatigue levels across the patient subgroups for CD and UC remained.

For CD, approximately 58% of patients were classified in trajectories characterized by fatigue levels ≥5 on a 10-point scale, with 1 out of 10 patients with CD having persistently elevated fatigue levels of 8. For UC, approximately 43% of patients followed trajectories with fatigue levels ≥5. A smaller subgroup than in CD, 1 out of 20 patients with UC, experienced persistently high levels of fatigue over time. Our finding of subgroups including patients experiencing chronic high levels of fatigue is in line with previous studies showing that severe fatigue is more prevalent in CD than in UC, although with comparable levels in severity between the two conditions. These results are also in line with findings by Villoria and colleagues.[13]

Women and patients with children were at greater risk of a severe fatigue trajectory over time, accounting for both CD and UC. The finding that women are more at risk of fatigue was expected and in line with several other studies.[13, 18] However, higher proportions of parents were classified within the trajectory of greatest fatigue, in contrast with Norton et al,[37] who actually reported lowered fatigue at the group level for patients with IBD with children. One possible explanation may be the methodological setup of our study in contrast to the cross-sectional approach of Norton et al.[37] Unfortunately, we lacked more in-depth information on having children (eg, hours spent with children).

Smoking was only a risk factor for more severe fatigue levels in patients with CD but not with UC, in line with previous research.[22] Interestingly, smoking has been found to have a buffering effect on disease outcomes in patients with UC. In our cohort, however, only a very small number of patients with UC indicated that they were smokers (12.4%).

We found that patients suffering from fistulas were also more likely to report elevated but not the highest recorded levels of fatigue over time. Fistulas occur much more often in CD than in UC, with a risk of fistula appearance after 20 years of CD of approximately 50%. Treatment can be very difficult and carries a high risk of reoccurrence and failure. The available data on fistulas were limited, so the outcomes need to be treated with caution.

Within the UC cohort, disease onset was found to associate with different fatigue trajectories, but results were inconclusive in the subgroup with the highest fatigue levels over time. In contrast to previous cross-sectional and longitudinal studies, lower education did not have an impact on the severity of fatigue trajectories. Possible explanations may include the classification used for educational level, with 3 levels according to the Dutch standard. Many other studies have not described in detail in what way educational levels were considered.[11]

As hypothesized, a strong association between fatigue and disease activity was found. In detail, we observed a large proportion of patients, especially in CD, who experienced constant levels of disease activity. These patients were also the most likely to be classified within the subgroup with the highest fatigue severity. In contrast, patients with no disease activity at all across the entire time span were most likely to experience the lowest fatigue severity over time, with no one in this group classified in the group of patients with severely fatigue in the CD cohort and only a small group in the UC cohort. Our findings are in line with several other studies[8, 9, 38] but further extend the previous work by showing that (1) such a strong relationship holds over an extensive course of time, and (2) disease activity trajectories relate distinctively to different trajectories of fatigue. Furthermore, note that we also observed subgroups of patients reporting only very low levels of IBD symptomatology but who still experienced persistent fatigue over time. This finding is in accordance with findings of other scholars[3, 22, 38, 39] and underlines that disease activity cannot be seen as the only risk factor for IBD fatigue but is still a strong contributor.

In line with other research, we observed that on the one hand, patients with persistent severe fatigue over time reported the lowest levels of well-being, and on the other hand, a large proportion of patients with the lowest fatigue scores reported the highest well-being experience. This accounted for both CD and UC. Although we cannot draw causal conclusions, our findings further underline the far-reaching impact of fatigue on psychological well-being as noted by other scholars.[21] Such a strong relationship has also been found in other patient populations with chronic diseases; this impact stresses the need for suitable fatigue management options in patients with IBD.

Strengths and Limitations

The main strengths of this study are that we investigated trajectories of fatigue longitudinally and examined their relationship with disease activity and psychological well-being in a large cohort across a period of 9 years. This framework resulted in a more comprehensive understanding of the course of fatigue and correlates than any previous research. Advanced analyses (ie, LCGA) were used to capture the unobserved heterogeneity in the growth or development of fatigue courses over time, helping to classify patients with IBD into distinct subgroups. The advantage of this method is its person-centered approach. We were able to identify heterogeneous subgroups of individuals with different patterns of change.

However, when interpreting the results, several limitations need to be considered. First, there is no gold standard for model selection in LCGA. We considered different statistical indicators but foremost relied on a model's parsimony and clinical relevance based on knowledge extracted from previous literature. Second, fatigue and well-being were assessed with a single item. Although both items showed high content validity, it can be argued that we overlooked the importance of distinct aspects of fatigue (eg, affective, cognitive, physiological) and of psychological well-being. More comprehensive and validated measures should be considered in future research, such as the PROMIS measure used by Conley, Proctor, and colleagues.[2] Third, we only used self-reported clinical disease activity scores every time fatigue was assessed. Applying objective measures for inflammation, by means of fecal calprotectin or endoscopic assessment, could also have been considered for a more valid approach to measure disease activity. Fourth, even though we examined a wide range of correlates of fatigue in patients with IBD, we did not include factors such as anemia level, medication, diet, weight, and alcohol consumption. We suggest that future research examine these factors in relation to the development, levels, and course of fatigue in patients with IBD over time. Fifth, all data used in the current study were collected at 1 outpatient clinic in the northern part of the Netherlands, so our sample was mainly characterized by Caucasians. This limitation reduces the generalizability of our outcomes. We suggest that

these analyses should be replicated based on data from other clinics, in the Netherlands and internationally, and include a more diverse population with regard to sociodemographic characteristics, to further strengthen the validity of outcomes.

With this study, we took a first step and explored how different sociodemographic and clinical factors relate to the courses of fatigue. As a follow-up step, it would be highly valuable to address how psychological factors, such as coping strategies and personality traits, may be associated with the different identified trajectories of fatigue. Such an approach may help clinicians and physicians better understand whether a psychological intervention is necessary and at what point in time. In line with this suggestion, understanding the possible need for psychological care among patients with IBD cannot be disregarded in this context. Furthermore, we suggest that future research needs to shift toward a more frequent and detailed approach. Even though it is much more time-consuming, intensive longitudinal research including diary studies would allow for simultaneous monitoring of different factors, such as fatigue, disease activity, psychological well-being, medication intake and adherence, and day-to-day activities (eg, smoking behaviors, child care, working hours) in patients' daily life. Diary studies allow for an exploration of day-to-day fluctuations and on how different factors affect other factors, and they could provide more information on the development and persistence of fatigue in detail. In addition, monitoring may assist in the identification of or even predictive markers for future flare-ups and to provide treatment options to the patient as early as possible. Such a web-based application, which is filled in via smartphone by a patient, was recently introduced at the IBD Centrum in Groningen.[40]

The impact of fatigue in IBD cannot be disregarded in clinical practice because it may manifest within patients more persistently than so far acknowledged. Based on our finding that patients with active IBD or flare-ups were more likely to experience greater fatigue over time, we recommend that first-line treatment should still entail alleviating disease-related physical symptoms and disease activity,[41] complemented by simultaneous and frequent monitoring of fatigue. Practitioners need be aware of the proposed impact of fatigue, specifically on patients' psychological well-being, so that suitable management options can be recommended to patients.

For patients with chronic fatigue, cognitive-behavioral therapy[42] and mindfulness-based interventions (eg, mindfulness-based cognitive therapy [MBCT]) may be promising for alleviating fatigue symptoms, especially for patients in remission but with continually high rates of fatigue. Previous research has already proposed that MBCT can work effectively in patients with IBD, improving their quality of life.[43] We recently finished a multicenter MBCT trial in patients with severe chronic fatigue.

We emphasize that fatigue management options need to be offered in specific to individuals at greater risk, including women, parents, and patients with CD. In addition, smoking cessation needs to be considered within the subgroup of patients with CD. It is still an underused management strategy in primary and secondary care. However, promising programs are available (eg, counseling, nicotine replacement therapy[44]).

CONCLUSIONS

Distinct trajectories can be distinguished that report differing levels of fatigue over time. Because elevated, consistent fatigue is strongly related to greater disease activity, treatment should first be focused on reducing disease activity as much as possible, with an additional offering of psychological interventions to reduce fatigue and help patients learn to manage fatigue in daily life. It is important to identify elevated levels of fatigue early, given the strong association of elevated fatigue with reduced well-being. Future research is necessary to elucidate the complex and dynamic phenomenon of fatigue in IBD in detail, which will help researchers and physicians gain conclusive and important knowledge for clinical practice.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

REFERENCES

1. Mikocka-Walus A, Pittet V, Rossel JB, et al.; Swiss IBD Cohort Study Group. Symptoms of depression and anxiety are independently associated with clinical recurrence of inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2016;14:829–835.e1.
2. Conley S, Proctor DD, Jeon S, et al. Symptom clusters in adults with inflammatory bowel disease. *Res Nurs Health.* 2017;40:424–434.
3. van Langenberg DR, Gibson PR. Systematic review: fatigue in inflammatory bowel disease. *Aliment Pharmacol Ther.* 2010;32:131–143.
4. Jones DE, Gray JC, Newton J. Perceived fatigue is comparable between different disease groups. *Qjm.* 2009;102:617–624.
5. Bombardier CH, Buchwald D. Chronic fatigue, chronic fatigue syndrome, and fibromyalgia: disability and health-care use. *Med Care.* 1996;34:924–930.
6. Nocerino A, Nguyen A, Agrawal M, et al. Fatigue in inflammatory bowel diseases: etiologies and management. *Adv Ther.* 2020;37:97–112.
7. Cohen BL, Zoëga H, Shah SA, et al. Fatigue is highly associated with poor health-related quality of life, disability and depression in newly-diagnosed patients with inflammatory bowel disease, independent of disease activity. *Aliment Pharmacol Ther.* 2014;39:811–822.
8. Banovic I, Gilibert D, Cosnes J. Crohn's disease and fatigue: constancy and co-variations of activity of the disease, depression, anxiety and subjective quality of life. *Psychol Health Med.* 2010;15:394–405.
9. Graff LA, Clara I, Walker JR, et al. Changes in fatigue over 2 years are associated with activity of inflammatory bowel disease and psychological factors. *Clin Gastroenterol Hepatol.* 2013;11:1140–1146.
10. Conley S, Jeon S, Proctor DD, et al. Longitudinal changes in symptom cluster membership in inflammatory bowel disease. *J Nurs Scholarsh.* 2018;50:473–481.
11. Graff LA, Vincent N, Walker JR, et al. A population-based study of fatigue and sleep difficulties in inflammatory bowel disease. *Inflamm Bowel Dis.* 2011;17:1882–1889.
12. Miaskowski C. Gender differences in pain, fatigue, and depression in patients with cancer. *J Natl Cancer Inst Monogr.* 2004;32:139–143.
13. Villoria A, García V, Dosal A, et al. Fatigue in out-patients with inflammatory bowel disease: prevalence and predictive factors. *Plos One.* 2017;12:e0181435.

14. Bager P, Vestergaard C, Juul T, et al. Fatigue in IBD must be compared to the background population—generation of normative data for the IBD-F. *J Crohns Colitis.* 2017;11:S488–S489.
15. Jelsness-Jørgensen LP, Bernklev T, Henriksen M, et al. Chronic fatigue is associated with impaired health-related quality of life in inflammatory bowel disease. *Aliment Pharmacol Ther.* 2011;33:106–114.
16. Vogelaar L, van't Spijker A, van Tilburg AJP, et al. Determinants of fatigue in Crohn's disease patients. *Eur J Gastroent Hepatol.* 2013;25:246–251.
17. Louati K, Berenbaum F. Fatigue in chronic inflammation—a link to pain pathways. *Arthritis Res Ther.* 2015;17:254.
18. Romberg-Camps MJ, Bol Y, Dagnelie PC, et al. Fatigue and health-related quality of life in inflammatory bowel disease: results from a population-based study in the Netherlands: the IBD-South Limburg cohort. *Inflamm Bowel Dis.* 2010;16:2137–2147.
19. Grimstad T, Norheim KB, Isaksen K, et al. Fatigue in newly diagnosed inflammatory bowel disease. *J Crohns Colitis.* 2015;9:725–730.
20. Burkhalter H, Stucki-Thür P, David B, et al. Assessment of inflammatory bowel disease patient's needs and problems from a nursing perspective. *Digestion.* 2015;91:128–141.
21. Jackson H, MacLeod AK. Well-being in chronic fatigue syndrome: relationship to symptoms and psychological distress. *Clin Psychol Psychother.* 2017;24:859–869.
22. Jelsness-Jørgensen LP, Bernklev T, Henriksen M, et al. Chronic fatigue is associated with increased disease-related worries and concerns in inflammatory bowel disease. *World J Gastroenterol.* 2012;18:445–452.
23. Imhann F, Van der Velde KJ, Barbieri R, et al. The 1000IBD project: multi-omics data of 1000 inflammatory bowel disease patients; data release 1. *BMC Gastroenterol.* 2019;19:5.
24. Collins LM, Lanza ST. *Latent Class and Latent Transition Analysis: With Applications in the Social, Behavioral, and Health Sciences*. Hoboken, NJL Wiley; 2009.
25. Wurpts IC, Geiser C. Is adding more indicators to a latent class analysis beneficial or detrimental? Results of a Monte-Carlo study. *Front Psychol.* 2014;5:920.
26. Centraal Bureau voor Statistiek/Central Bureau of Statistics. *Standaard Onderwijsindeling/Standard Educational Classification* 2016; version 2019/2020. p.1-39. https://www.cbs.nl/nl-nl/onze-diensten/methoden/classificaties/onderwijs-en-beroepen/standaard-onderwijsindeling--soi--/standaard-onderwijsindeling-2016.
27. Best WR. Predicting the Crohn's disease activity index from the Harvey-Bradshaw Index. *Inflamm Bowel Dis.* 2006;12:304–310.
28. Walmsley RS, Ayres RC, Pounder RE, et al. A simple clinical colitis activity index. *Gut.* 1998;43:29–32.
29. Higgins PD, Schwartz M, Mapili J, et al. Patient defined dichotomous end points for remission and clinical improvement in ulcerative colitis. *Gut.* 2005;54:782–788.
30. Singer JD, Willett JB. *Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence*. New York: Oxford University Press; 2003.
31. Akaike H. Information theory and an extension of the maximum likelihood principle. In: Parzen E, Tanabe K, Kitagawa G, eds. *Selected Papers of Hirotugu Akaike*. Springer Series in Statistics. New York, NY: Springer; 1998:199–213.
32. Aho K, Derryberry D, Peterson T. Model selection for ecologists: the worldviews of AIC and BIC. *Ecology.* 2014;95:631–636.
33. Akaike H. Prediction and entropy. In: Atkinson AC, Fienberg SE, eds. *A Celebration of Statistics*. New York, NY: Springer; 1985:1-24.
34. Nylund KL, Asparouhov T, Muthén BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: a Monte Carlo simulation study. *Struct Equ Modeling.* 2007;14:535–569.
35. Porcu M, Giambona F. Introduction to latent class analysis with applications. *J Early Adolesc.* 2016;37:129–158.
36. Druce KL, Jones GT, Macfarlane GJ, et al. The longitudinal course of fatigue in rheumatoid arthritis: results from the Norfolk Arthritis Register. *J Rheumatol.* 2015;42:2059–2065.
37. Norton C, Czuber-Dochan W, Bassett P, et al. Assessing fatigue in inflammatory bowel disease: comparison of three fatigue scales. *Aliment Pharmacol Ther.* 2015;42:203–211.
38. Bager P, Befrits R, Wikman O, et al. Fatigue in out-patients with inflammatory bowel disease is common and multifactorial. *Aliment Pharmacol Ther.* 2012;35:133–141.
39. Piche T, Ducrotté P, Sabate JM, et al. Impact of functional bowel symptoms on quality of life and fatigue in quiescent Crohn disease and irritable bowel syndrome. *Neurogastroenterol Motil.* 2010;22:626–e174.
40. de Jong MJ, van der Meulen-de Jong AE, Romberg-Camps MJ, et al. Telemedicine for management of inflammatory bowel disease (myIBDcoach): a pragmatic, multicentre, randomised controlled trial. *Lancet.* 2017;390:959–968.
41. Houwert G, Nauta N. Diagnostiek en behandeling van inflammatoire darmziekten bij volwassenen. *Tijdschrift voor Bedrijfs-en Verzekeringsgeneeskunde [article in Dutch]*. 2010;18:307–310.
42. Artom M, Czuber-Dochan W, Sturt J, et al. Cognitive behavioural therapy for the management of inflammatory bowel disease—fatigue with a nested qualitative element: study protocol for a randomised controlled trial. *Trials.* 2017;18:213.
43. Schoultz M, Atherton I, Watson A. Mindfulness-based cognitive therapy for inflammatory bowel disease patients: findings from an exploratory pilot randomised controlled trial. *Trials.* 2015;16:379.
44. Wilson A. Smoking cessation strategies in Crohn's disease. *Frontline Gastroenterol.* 2011;2:10–12.