A longitudinal study of fatigue in a population-based inflammatory bowel disease cohort

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Abbreviations: IBD inflammatory bowel disease; CD Crohn's disease; UC ulcerative colitis; MIBDI Manitoba Inflammatory bowel disease index

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Abstract

Background & Aims: Cross-sectional studies have identified high levels of fatigue both when IBD is active and quiescent, but there has been very little attention to fatigue over time in IBD. We aimed to assess fatigue longitudinally in IBD and determine its course and contributors. *Methods*: Data were obtained from participants (n=312; 51% Crohn's disease) in the Manitoba IBD Cohort Study, a longitudinal population-based study. Symptomatic disease activity was measured every 6 months for 2 years to characterize long-term disease pattern as active, fluctuating, or inactive, using the validated Manitoba IBD Index. Fatigue (Multidimensional Fatigue Inventory), psychological functioning, and laboratory biomarkers were assessed concurrently at baseline, and 1 and 2 years later. *Results*: 26% had consistently inactive, 29% had fluctuating, and 45% had consistently active disease across the two years. Mean fatigue levels were strongly associated with disease activity, with the lowest fatigue at each time point for those with consistently inactive disease. Multivariate analyses indicated fatigue levels increased over time regardless of disease pattern ($p<0.001$). Adjusting for disease activity, disease type, age, and sex, the psychological variables of elevated distress ($p<0.001$), lower psychological well-being ($p=0.002$), and poor sleep quality ($p<0.001$) were independently associated with increases in fatigue over time. *Conclusion:* Fatigue may worsen over time in IBD, even when disease is in remission. Psychological factors are a useful target for intervention in order to impact fatigue.

Keywords: inflammatory bowel disease; fatigue; longitudinal; psychological functioning

Introduction

Fatigue is a common and distressing symptom of chronic disease, in particular for those with inflammatory conditions (1). Fatigue has been described as an overwhelming sense of tiredness and a distinct lack of energy resulting in difficulties with functioning spanning physical and mental domains (2). This systemic symptom has been associated with impaired quality of life in several diseases, including rheumatoid arthritis, Parkinson's disease, and inflammatory bowel disease (IBD) (3-5). For IBD, fatigue has been identified by patients as a greater concern than pain or bowel control (6,7). It is the second most common symptom after diarrhea that persons with active IBD complain of and the second most common symptom of concern after arthralgias for persons with inactive IBD (8).

Despite evident patient impact, fatigue is a poorly understood condition, and has received little research attention. A recent systematic review could only identify 10 studies that included data on fatigue and IBD in the previous 10 year period (9), and of those only one assessed fatigue as a primary outcome. Population-based and clinical studies have found that fatigue is highly prevalent, with almost three-quarters with active IBD and 30-40% with quiescent disease reporting significant fatigue (10-12).

As well, the experience of fatigue over time in the context of IBD is not clear. Certainly it is evident that fatigue is not solely linked to disease activity, given the high prevalence rates that persist even when the disease is in remission. A cross-sectional study by our group reported that problematic fatigue in IBD was strongly associated with disease and psychological factors (i.e., active disease, poor sleep quality, perceived stress), and was only modestly related to anemia,

general inflammatory markers (CRP), and amount of sleep (10), paralleling other findings in IBD (13) and rheumatoid arthritis (14).

The aim of this study was to build further on cross-sectional findings, by assessing fatigue longitudinally, using a population-based IBD sample, in order to determine the course of fatigue in IBD and the contributors to changes in fatigue. It is important to discern whether fatigue tracks with disease activity over time, and to identify other variables associated with fatigue, to provide direction for potential treatment targets that may impact this oft troubling symptom.

MATERIALS AND METHODS

Sample and Design

The Manitoba IBD Cohort Study is a prospective, longitudinal study that aims to identify determinants of IBD outcomes. This population-based sample of adults was recruited within seven years (median 4 years) of their diagnosis of IBD. They have been tracked prospectively through semi-annual surveys using standardized and validated self-report instruments, and annual clinical interviews and blood draws completed by research nurses. The participants were originally recruited from a validated population-based research registry that has been described elsewhere (15,16). Briefly, all adults with IBD in the province are included in a population-based database (the University of Manitoba IBD Epidemiology Database), drawn from the comprehensive provincial health administrative database using a validated definition of IBD. All those in the University of Manitoba IBD Epidemiology Database were invited to participate in a research registry. The University of Manitoba IBD Research Registry has subsequently been updated periodically with individuals identified from the administrative health database. Just

over half of all the provincial cases of IBD (n=3192) were enrolled in the Research Registry at the initiation of this study (15).

Of those enrolled in the Registry, 606 were eligible for this study, based on the criteria of adult age and recent disease onset. The final Cohort was comprised of 388 who completed the baseline survey and interview, after those who declined (14%) or could not be reached (17%) were excluded. The Cohort has been established as having excellent representativeness of the provincial IBD population, with comparative age distribution, sex distribution, and rural/urban residence (17). The Cohort Study was approved by the University of Manitoba Health Research Ethics Board and participants provided written informed consent.

All of the data for the variables of interest, including fatigue, sleep quality, psychological functioning, and biological indicators, were collected concurrently starting at 24 months after entry into the longitudinal Cohort study, at which time there were 318 individuals with confirmed diagnosis and subtype, and current disease activity information actively participating in the Cohort. Measures were obtained annually for the next two years, providing up to three measurements (baseline, 1 and 2 years) to track changes over time. Disease activity was assessed semi-annually, resulting in up to five measurements for this variable.

Measures

IBD diagnosis and disease activity

The IBD diagnosis and disease type of Crohn's disease (CD) or ulcerative colitis (UC) were verified through chart review, which was done by study staff at physician offices where the

clinical records were kept. Disease activity was assessed using the Manitoba IBD Index (MIBDI), a validated patient-report measure that characterizes symptomatic disease activity over a prior 6 month period, using a 6-level response format and symptom frequency anchors to facilitate more consistent reporting (18). The MIBDI has been validated with clinical indices for both CD (19) and UC (18,20). An advantage of the MIBDI is that it more readily characterizes extended disease experience than the 24 hour time frames which the clinical indices use.

Individuals were classified as having active disease in the recent six-month period if any of levels 1 to 4 were reported (e.g., daily to occasional symptoms that the respondent identified as active disease, over the previous six months), or classified as having inactive disease if symptoms were reported as occurring rarely or not at all (levels 5 to 6) in that time frame. Disease activity was measured semi-annually from baseline to two years (i.e., baseline, 6, 12, 18, 24 months). Participants were then assigned to one of three mutually exclusive groupings to characterize their disease activity pattern across the two-year period of this study using a previously published method (21): *consistently active* (active disease reported at 4 to 5 of the 5 time points), *consistently inactive* (inactive disease reported at 4 to 5 of the 5 time points) and *fluctuating disease* (all remaining individuals).

Fatigue & Sleep Quality

Fatigue and sleep quality were measured using the Multidimensional Fatigue Inventory (MFI) and Pittsburgh Sleep Quality Index (PSQI). The MFI is a standardized and validated self-report measure with 5 subscales to assess various domains of fatigue (22). However, the General Fatigue scale is typically used as the primary fatigue indicator, with a higher score reflecting higher fatigue (range 4-20). Problematic or high fatigue was defined as $\geq$ 13, a cutoff that has

been established in IBD studies based on the 95th percentile of the score in a healthy control group (23,24). Sleep quality was assessed using the global score of the validated PSQI (25). Scores can range from 0-21, and a score greater than 5 is indicative of poor sleep quality.

Psychological and Biological indicators

The Global Severity Index from the Brief Symptom Inventory (26) has well-established internal consistency and validity as a general distress indicator, with higher levels indicating greater psychological symptoms and distress. The Cohen Perceived Stress Scale is widely used to examine stress in disease (27). In addition, an interview-based measure of psychological wellbeing, the Psychological Wellbeing Scale (28) was obtained, as it reflects positive psychological functioning and not just the absence of negative emotionality.

Blood was drawn at 3 time points (baseline, 1 and 2 years) concurrently with the survey and clinical interview measures. Routine biochemical and hematological tests were performed to identify serum hemoglobin and CRP levels, and standard lab definitions of low hemoglobin (< 140 g/L for males; < 120 g/L for females) and high CRP (>8 mg/L) were used.

Statistical Analyses

The data were descriptively analyzed using frequencies and percentages. Univariate analyses of high fatigue, comparing the consistently active, consistently inactive, and fluctuating disease groups at baseline, 1 year, and 2 years were conducted using one-way analysis of variance (ANOVA), with multiple comparisons and Bonferroni correction (i.e., $\alpha/3$). Accordingly, a $p<0.02$ was considered statistically significant. Mixed-effects multiple regression models were

applied to the longitudinal fatigue data to assess the trajectory of change in fatigue (29, 30). The model included categorical covariates of disease activity, disease type, sex, and clinical biomarkers (CRP; hemoglobin), and continuous covariates of time, age, sleep quality, and the psychological factors. F statistics were used to assess the statistical significance of omnibus effects for each variable. Estimated regression coefficients (i.e., $\hat{b}$) and standard errors (SEs) are reported. Two-way interactions of time with disease activity and disease type were included to test for differences in the rate of change in fatigue over time related to these disease characteristics. The two-way interaction of disease activity and disease type was used to test for differences in fatigue between CD and UC respondents with different patterns of disease activity. The two-way interaction of sex and age was also tested. To ensure a parsimonious final model, interaction effects that were non-significant (p>0.05) were excluded. A random intercept and slope were used to account for subject-specific variation in fatigue over time. The intra-class correlation (ICC), which represents the proportion of total variation due to the random intercept, was computed. The ICC ranges from 0 to 1, with higher values indicating a greater proportion of total variance due to individual-specific variation. Model fit comparisons were evaluated using the Akaike Information Criterion (AIC). Descriptive profiles of the data and univariate analyses were used to identify any violations of the underlying model assumptions. All analyses were conducted using SAS version 9.2 (31).

Results

Six respondents were missing MIBDI disease activity data points and were excluded from further analysis (n=312). At baseline, the mean age of respondents was 43 years old (standard deviation [SD]=14.80), and they ranged from 19 to 85 years old. Sixty-one percent were female.

The Cohort was predominantly Caucasian (95%). Average disease duration was 6.4 years (SD=3.7). There were similar proportions of disease type (51% CD; 49% UC); Table 1 shows the demographic information for CD and UC separately. Over two-thirds were in a partnered relationship (married or common-law), and were employed full or part-time.

Considering disease activity patterns across the two year period, 26% met criteria for consistently inactive disease, 29% had fluctuating disease with intermittent symptoms, and 45% had consistently active disease. High fatigue (>95th percentile in a healthy sample) was very prevalent across the two years, particularly for those with fluctuating or consistently active disease patterns (see Figures 1a, 1b). Proportions with high fatigue ranged from 42% [i.e., at baseline, CD, fluctuating disease] to 76% [i.e., at year 2, CD, active disease]. In contrast, only 21% to 37% of those who had consistently inactive disease across the 2 year period reported problematic or high fatigue.

Mean fatigue levels mapped approximately to disease patterns, with the lowest average fatigue score at each time point reported for those with consistently inactive disease. Those with consistently active disease typically reported the highest mean levels of fatigue (Table 2).

The mixed-effects multiple regression model results to test for longitudinal change in fatigue are detailed in Table 3. The initial model showed minimal individual-specific variation in the rate of change over time in fatigue; retention of the random slope for time did not result in improved model fit as evaluated by the AIC, so the random slope was removed from the model. The resulting final model indicated moderate individual variation in fatigue levels at baseline

(ICC=0.36). There were no significant interactions among those tested. Overall, fatigue levels increased modestly over time regardless of disease activity pattern (F=17.79; $\hat{b}$ =0.03 p<0.001). Fatigue was associated with disease activity pattern as well (F=8.71, p=0.0002), and was higher over time for those with consistently active disease relative to those with consistently inactive disease ($\hat{b}$ =-1.40, p<0.001). Adjusting for disease activity and type, as well as each of the included psychological and biological factors, several variables were found to be independently associated with changes in fatigue across time including poor sleep quality (F= 139.40; $\hat{b}$ =0.30, p < 0.001), distress (F=297.15; $\hat{b}$ =0.16, p < 0.001), and lower psychological well-being (F=9.57; $\hat{b}$ =-0.03, p =0.002). Perceived stress was not statistically significant after the Bonferroni correction was applied, although it approached significance (F=4.94; $\hat{b}$ =-0.03, p = 0.026). Neither of the biological markers, CRP or hemoglobin, were independently associated with fatigue over time after controlling for other factors in the model. Since CRP in particular can present differently in CD compared to UC, the model was also run separately for each disease subtype to examine the role of CRP, with no change in results (data not shown). Women were more likely to report higher levels of fatigue (F=21.84; $\hat{b}$ =-1.26, p<0.001) as were those who were younger (F=5.71; $\hat{b}$ =-0.02, p=0.017).

Discussion

This population-based study is the largest to date and one of only two to assess fatigue in IBD over time. The results confirmed that fatigue was prevalent and persistent in IBD across some years. A relationship between disease activity and fatigue was evident, given that at any time point fatigue levels were higher for those with more active disease, and comparing longitudinally, disease activity was significantly associated with fatigue. However, disease activity does not

fully explain fatigue in IBD. Results indicated a significant proportion had pronounced fatigue even when disease was asymptomatic over a two year period. In addition, we found that emotional distress, psychological well-being, and sleep quality were independently associated with fatigue over time, after controlling for aspects such as disease activity level, CRP, and hemoglobin. Age and sex were also associated with fatigue presentation in IBD, with women reporting more fatigue, similar to the general population (32) and other IBD studies (24).

The one other study that evaluated fatigue in IBD longitudinally was a small study (n=52) which included CD patients in remission, all of whom reported fatigue at baseline and were assessed one year later (33). Their findings, consistent with ours, suggested that fatigue levels were associated with poorer sleep quality and depressive symptoms as well as higher disease activity (CDAI) scores. In that study, disease activity was only measured at the concurrent time point with fatigue and could not address disease experience over the prior year. The finding that psychological factors continue to be associated with fatigue in IBD over time, for both CD and UC patients, confirms prior cross-sectional findings in IBD describing an association between fatigue and psychological well-being, stress, and mood (13,34). Other research has examined the role of common pathways that contribute to mood changes, inflammation, and fatigue such as the role of pro-inflammatory cytokines, although no single cytokine has been identified as a mediator (35-37). Similarly, neuroendocrine pathways are implicated in the inter-relationship among stress, inflammation, and fatigue (38).

The one-year longitudinal study did not find any significant change in fatigue over time (33). Our study found a modest increase in fatigue over two years that was independent of the disease

and psychological factors. Disease duration was an average of six years, and considering time for adjustment to this chronic illness, fatigue was still problematic for many. A recent report examining mucosal healing and its relationship with quality of life in IBD found that those with established mucosal healing who did not return to a 'normal' quality of life (<20%) were more likely to experience fatigue (39). Fatigue may be a lasting systemic symptom of immune system challenge, and/or may be a manifestation of persisting comorbid psychological difficulties, given the higher prevalence of mood disorders in IBD (40). When fatigue has been examined longitudinally in other immune-mediated inflammatory conditions such as rheumatoid arthritis and psoriatic arthritis, factors such as psychological distress, pain, greater physical disability, and beliefs related to lack of control have been predictive of subsequent fatigue, with a smaller or minimal impact of disease severity (41-44).

Fatigue and its management have been perplexing in IBD and other inflammatory chronic diseases (1). Associations between fatigue and inflammatory markers or anemia often have been weak or nonsignificant (13,14,24,45,46), as was found in this study. These findings suggest that addressing iron levels or iron stores, for example, for IBD patients experiencing high fatigue may not be sufficient (47). Alternatively, this population-based sample had a lower proportion of anemia than is commonly reported in clinic-based samples, which may have affected the power to detect differences (48). As a further consideration, if anemia or iron deficiency was treated at the time it was observed, any effects on changes over time in fatigue may not have been as evident. Nevertheless, even if the multiple mechanisms cannot be clearly delineated, the association of psychological factors and sleep quality with fatigue in IBD over a longer term has implications for intervention, as these factors can be modifiable.

Cognitive behavioral therapy (CBT) targeting stress management and sleep quality to improve well being and reduce distress may be useful to address fatigue in IBD. A study of rheumatoid arthritis patients with early disease (< 8 years) and potential psychosocial risk found significant improvement in fatigue and depression following CBT, with effects sustained six months later (49). There has been limited evaluation of psychological interventions to support disease coping in IBD, despite growing recognition of the need for psychological care in conjunction with medical care (50). Studies that have assessed psychological interventions, including stress management, cognitive reframing, and relaxation training, have described favorable psychological outcomes (51-53), although impact on fatigue has rarely been assessed. The only study that evaluated fatigue outcomes was a controlled pilot study of psychological intervention aimed at enhancing coping using solution-focused therapy (54). They reported 60% to 86% had improved fatigue scores following treatment, although the changes were not significantly different from the control group, likely due to the small sample size (n=29).

There have been no studies to date in IBD assessing behavioral interventions for sleep, despite its efficacy as a first-line intervention for sleep disturbances (55). Other behavioral approaches, such as activity pacing or graded exercise may be of benefit, although they have not been tested for applicability to IBD-related fatigue. Higher levels of physical activity are associated with lower levels of fatigue and better general health related quality of life in the population in general and in a wide range of chronic diseases (56). A group exercise program has been shown to improve health in persons with inactive or mildly active CD (57) and supervised or unsupervised programs to increase physical activity have been associated with improved health in a wide range of medical conditions (56). While it remains to be determined if some type of exercise program

can improve fatigue in persons with IBD, this may be a fruitful area of investigation, especially since fatigue is so common, and exercise has other health benefits.

The strengths of this study are the prospective, population-based design, the monitoring of symptomatic disease activity across two years, and assessment of change in fatigue over time. Prior cross-sectional studies cannot readily address the direction of relationships between fatigue and other disease and psychological factors. However, optimally the study would also have included objective measurement of disease activity, as patient experience of disease does not fully correspond with inflammatory status. Patients can have subclinical inflammation without symptoms, or have symptoms without inflammation, which in turn may affect fatigue outcomes. While endoscopic investigation for inflammation may be impractical and costly in larger population-based studies to establish inflammation across several time points, noninvasive measurement such as fecal calprotectin shows promise as a tool for future use to assess inflammation concurrently with other disease activity indices (58-59). Fatigue was assessed by patient self-report, which is the current standard for measuring this symptom, and the validated measure that has been used in several IBD studies was incorporated here.

In conclusion, fatigue is indeed a persistent concern for patients with IBD, as problematic fatigue was prevalent over two years of follow up, with 20-30% of those with consistently inactive disease and up to75% of those with consistently active disease experiencing significant fatigue. This study examined disease, psychological, and biological factors concurrently and found that several were independently associated with fatigue, highlighting the complex and multifactorial nature of fatigue in chronic disease. Although we did not discern to what extent treating active

disease could lead to a reduction in fatigue, the association with modifiable psychological factors such as emotional distress provides direction for intervention in addition to medical management approaches. As fatigue is common in IBD and may persist even if disease is inactive, consideration of psychological well-being may also be relevant.

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Table 1 Baseline demographic characteristics of Crohn's disease and ulcerative colitis respondents

	CD (*n*=159)	UC (*n*=153)
Age Mean (SD)	41.4 (14.8)	45.4 (14.6)
Sex Male	38%	40%
Marital Status Married / Common-Law	65%	73%
Employment Full-time / Part-time	80%	75%
Education Greater than high school	25%	32%
Disease duration Mean (SD)	6.6 (4.7)	6.3 (2.1)

Table 2 Mean fatigue scores across 2 years for each disease activity pattern and IBD disease type

	Baseline Mean (SD)	Year 1 Mean (SD)	Year 2 Mean (SD)
CD consistently inactive	9.30 (3.79)	12.36 (4.69)	9.79 (3.68)
fluctuating	11.61 (4.23)	12.15 (4.34)	12.40 (4.45)
consistently active	14.53 (4.10)	12.82 (4.38)	14.74 (4.05)
UC consistently inactive	9.85 (3.76)	11.68 (4.09)	11.24 (4.36)
fluctuating	12.39 (4.31)	13.14 (3.93)	12.06 (4.07)
consistently active	13.18 (4.08)	13.40 (4.47)	14.59 (3.65)

Table 3 Mixed effects regression model results for fatigue.

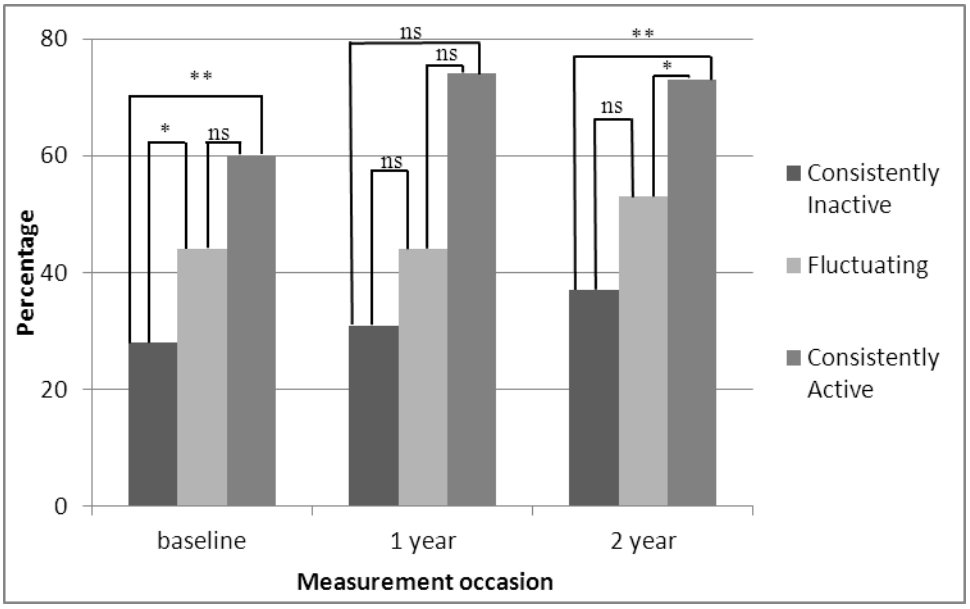
	$\hat{b}$	Standard error	*p*-value
Time	0.03	0.01	<0.001
2 year disease activity pattern			
Consistently inactive	-1.40	0.34	<0.0001
Fluctuating	-0.52	0.31	0.096
Consistently active	Reference		
Diagnosis CD UC	 -0.57 Reference	 0.27	 0.031
Sex: Male Female	-1.26 Reference	0.27	<0.0001
Age	-0.02	0.01	0.017
Sleep quality	0.30	0.03	<0.0001
Distress	0.16	0.01	<0.0001
Perceived Stress	-0.03	0.02	0.026
Psychological Wellbeing	-0.03	0.01	0.002
C-reactive protein: high normal	0.24 Reference	0.23	0.309
Hemoglobin: low normal	0.01 Reference	0.21	0.962

ICC (intraclass correlation) = 0.36

Note: Bolded *p*-values denote statistical significance (i.e., $p<0.02$) with the Bonferonni correction. A positive estimate value for the time effect indicates that fatigue increased over

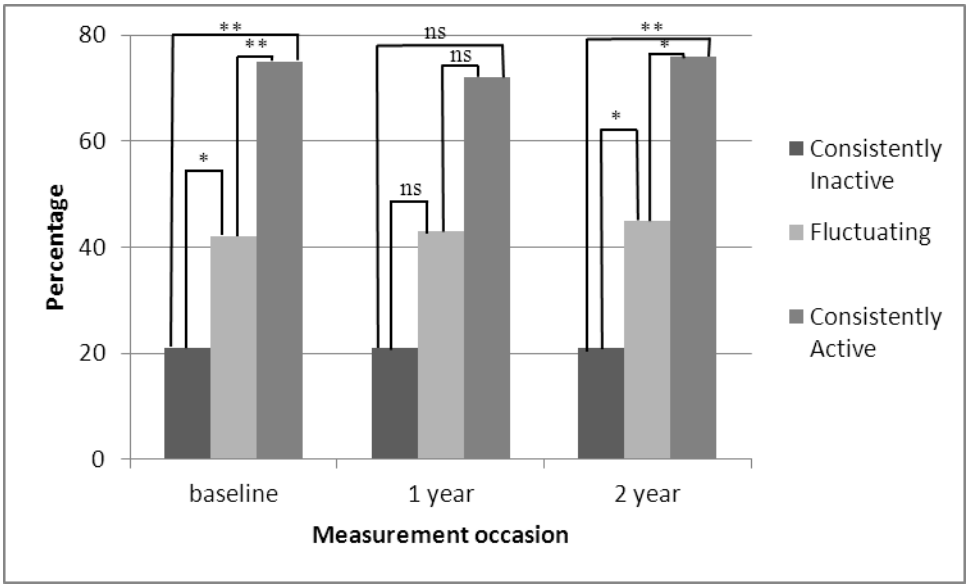
time; a positive value for the categorical variables indicates that the average fatigue score was higher than the reference group average score, while a negative value indicates that the average score was lower than the reference group average score.

Figure 1a. Percent with high fatigue for each disease activity pattern across time, in ulcerative colitis



*p<0.02; **p<0.001; ns = not significant

Figure 1b. Percent with high fatigue for each disease activity pattern across time, in Crohn's disease.



*p<0.02; **p<0.001; ns = not significant