A population-based study of fatigue and sleep difficulties in inflammatory bowel disease

Lesley A. Graff, PhD[1,2], Norah Vincent PhD[2] , John R. Walker, PhD, [1,2] , Ian Clara, PhD[1], Rachel Carr[1], Jason Ediger PhD[1,2], Norine Miller, RN[1], Linda Rogala, BN[1], Patricia Rawsthorne, RN[1], Lisa Lix, PhD[1,3], Charles N. Bernstein, MD[1,4]

[1]University of Manitoba Inflammatory Bowel Disease Clinical and Research Centre, Departments of [2]Clinical Health Psychology, [3]Community Health Sciences, [4] Internal Medicine, University of Manitoba, Winnipeg, Manitoba, Canada.

Conflicts of interest: Dr. Charles Bernstein has served in consultant and/or advisory board roles in the past year to Abbott Canada, has received educational grant support from Axcan Pharma. The other authors have no conflicts of interest to report.

Study funding: Canadian Institutes of Health Research (# 86482).

Address Correspondence to:
Lesley A. Graff, Ph.D.
University of Manitoba
PZ 350 – 771 Bannatyne Avenue
Winnipeg, MB CANADA R3E 3N4
Phone 204-787-7424
Fax 204-787-3755
Email: lgraff@hsc.mb.ca

Abstract

Background*:* There has been little investigation of fatigue, a common symptom in IBD. The aim of this study was to evaluate fatigue more comprehensively, considering relationships with psychological and biological factors simultaneously in a population-based IBD community sample. ***Methods***: Manitoba IBD Cohort Study participants (n=318; 51% Crohn's disease, CD) were assessed by survey, interview, and blood sample. Fatigue, sleep quality, daytime drowsiness, stress, psychological distress and quality of life were measured with validated scales. Hemoglobin (Hg) and C-reactive protein (CRP) levels were also obtained. Differences were tested across disease activity and disease subtype. ***Results***: Elevated CRP was found for 23% of the sample, and 12% were anemic. 46% had active disease. 72% of those with active and 30% with inactive disease reached clinical thresholds for fatigue (Multidimensional Fatigue Inventory; $p<0.001$); 77% and 49% of those with active or inactive disease respectively experienced poor sleep ($p<0.001$). There were few differences between those with CD and ulcerative colitis (UC) on the factors assessed, except for higher CRP levels in CD (mean 8.8 vs 5.3, $p<0.02$). Multiple logistic regression analyses found that elevated fatigue was associated with active disease (Odds Ratio [OR] 4.2, 95% CI 2.2-7.8), poor sleep quality (OR 4.0, 95% CI 1.9-8.6), and perceived stress (OR 4.2, 95% CI 2.2-8.1), but not with hours of sleep, Hg, or CRP. ***Conclusions***: Fatigue and poor sleep are not only highly prevalent in active disease, but both are still significant concerns for many with inactive disease. Psychological factors are associated with fatigue in IBD in addition to disease and sleep considerations.

INTRODUCTION

Fatigue that is persistent can have a debilitating effect on daily functioning and quality of life. It has been defined as an "overwhelming sense of tiredness, lack of energy and a feeling of exhaustion associated with impaired physical and/or cognitive functioning",[1] incorporating both the sense of physical depletion as well as interference. Sleepiness, or the propensity to doze, is classically a symptom of sleep disorders whereas fatigue is more commonly associated with many chronic diseases, including arthritis, cancer, stroke, and multiple sclerosis.[2] Fatigue is often described by patients as one of their most severe or troubling symptom. For patients with inflammatory bowel disease (IBD), a chronic inflammatory disorder of the gastrointestinal tract that has periods of symptom flares and remission, it is also a common concern and can be as problematic as diarrhea and abdominal pain.[3, 4]

Fatigue is a poorly-understood phenomenon that involves complex interactions of biological, behavioral and psychosocial processes. Inflammation, anemia, sleep difficulties and psychological comorbidities have all been linked to fatigue in chronic disease.[2] When it occurs in the context of active inflammatory disease, it is thought that fatigue may be the result of exposure to pro-inflammatory cytokines.[5] However, fatigue is a complaint even when disease is in remission.[6] Anemia has been found to be prevalent in IBD, with estimates that one-third may have anemia, many of whom have iron deficiency.[7,8] While treatment of anemia can result in improvements in disturbed sleep and quality of life, many patients still identify fatigue concerns.[4]

Restorative sleep has an important role in maintaining health, with disrupted or lower levels of sleep related to serious outcomes such as increased risk of coronary heart disease and all-cause mortality.[9,10] Among healthy adults, chronic partial sleep restriction increases sympathetic nervous system activity and reduces glucose tolerance, leptin and thyrotropin releasing hormones.[11,12] There are mixed findings regarding whether partial sleep restriction impacts on growth hormone concentration and inflammatory cytokines and adipokines. One study of healthy young adults found sleep restriction was significantly associated with increased levels of IL-17 and C-reactive protein (CRP), a marker of systemic inflammation.[13] Sleep disturbances have been associated with exacerbation of symptoms such as pain and fatigue in multiple chronic inflammatory conditions as well as worsening disease course.[14,15]

Studies on fatigue in IBD have primarily relied on smaller samples (n<100), tertiary clinic recruitment, and patients with IBD in remission,[6,16] thereby considering only part of the spectrum of IBD presentation. The aim of this study was to evaluate fatigue and its related parameters more comprehensively, considering sleep quality, psychological factors, and biological indicators of inflammation and serum hemoglobin (Hg) levels simultaneously, in order to clarify their presentation and relationships in IBD. Validated measures were used in a large population-based community sample of individuals with IBD that included both those with active and quiescent disease.

MATERIALS AND METHODS

Participants

The Manitoba IBD Cohort Study was initiated in 2002, with participating individuals in their 18th year or older and diagnosed with IBD within the previous 7 years. They were recruited from a validated population-based research registry that has been previously described.[17] The Registry identifies and recruits participants based on an administrative definition of IBD from the comprehensive health data base of Manitoba Health, the single insurer that provides health care to all residents in the province. Of those eligible, that is all those with IBD in the province, just over half participated in the Registry. The Cohort Study was approved by the University of Manitoba Health Research Ethics Board and participants provided written informed consent.

At the time of the Cohort study recruitment, there were 3192 participants in the Research Registry, of which 606 were eligible for this study, given the age and recent disease onset criteria. Approximately 17% could not be reached and 14% directly declined to take part. Complete data were obtained in the first contact from 388 of those enrolled, and they have subsequently served as the Cohort, described elsewhere in detail.[18] To assess representativeness, cohort participants were compared to all other IBD cases diagnosed in the same time period, using a comprehensive validated data set which includes all those in the province with IBD (the University of Manitoba IBD Epidemiology Database). There were no significant differences on standard demographic comparisons including mean age, age distribution, sex distribution, urban vs rural residence, and mean duration of disease, suggesting excellent representativeness.[19]

Data on fatigue and sleep quality were collected 24 months after entry into the longitudinal study, at which point there were 318 individuals with diagnostic and current disease activity

information actively participating in the Cohort. All the variables measured for this study were obtained through self-report survey, direct clinical interview, or blood samples.

Assessment of disease type and status

The diagnosis of IBD was verified through chart review, which was undertaken by study staff at physicians' offices. Disease activity was determined based on standardized clinical indices obtained during the clinical interview, using the Harvey-Bradshaw for Crohn's Disease (CD) and the Powell-Tuck for Ulcerative Colitis (UC).[20,21] Cut off levels of ≥ 5 were used to identify active IBD.[22,23]

Assessment of fatigue, sleep quality and daytime sleepiness

Fatigue and sleep parameters were assessed using standardized and validated measures in survey format. The Multidimensional Fatigue Inventory (MFI) is a 20-item self-report instrument designed to measure five aspects of current fatigue including physical and mental fatigue.[24] Each subscale can vary in scores from 4-20, with higher scores indicating greater fatigue. The General Fatigue subscale is commonly referenced as the primary fatigue descriptor, rather than a total MFI scale score. A cutoff of ≥ 13 for the General Fatigue subscale has been used in IBD studies to delineate significant fatigue, based on the 95th percentile of the score in a healthy control group.[6]

The Pittsburgh Sleep Quality Index (PSQI) is a widely used and well-validated self-report measure to assess sleep quality and sleep disturbance during the previous month.[25] It is comprised of seven sub-components derived from 19 items, including subjective sleep quality,

sleep latency, and sleep duration. The global PSQI score is the sum of all the sub-components (ranging from 0–21), with higher scores indicating poorer sleep. A score of greater than 5 indicates poor sleep quality. The measure also includes individual items that can flag potential sleep disturbance problems such as symptoms of restless leg syndrome. Objective polysomnography findings were well-correlated with the PSQI in an IBD sample.[26]

The Epworth Sleepiness Scale (ESS) has been found to be a reliable and valid measure of enduring daytime sleepiness, providing a practical assessment of interference during the day.[27,28] The likelihood of falling asleep in 8 common situations is rated. Total scores range from 0 to 24, with higher scores reflecting greater propensity to sleepiness. A score above 10 flags the likelihood of a sleep disorder.

Assessment of psychological distress and quality of life

Standardized and validated measures of perceived stress, psychological distress and disease-specific quality of life were used. These scales are based on self-report of functioning over the previous two to four weeks and are intended to provide dimensional measures of characteristics which vary over time. The 14-item Cohen Perceived Stress Scale (CPSS) is a widely-used instrument that was developed to examine the role of stress in disease. Each of the 14 items are rated from 1 (never) to 5 (very often), with a higher score indicating greater levels of stress.[29] The overall score can also be categorized as high versus low perceived stress, based on a median split.[30] The Brief Symptom Inventory assesses distress related to multiple psychological symptoms across nine dimensions including depression, interpersonal sensitivity, and anxiety. It has well-established internal consistency and validity, particularly for the global score (General Severity Index-GSI), a single indicator of distress.[31] The global distress score

(GSI) is typically reported as a T score, with a cutoff > 63 indicating clinically significant distress and elevated psychological symptoms or 'caseness'. The Inflammatory Bowel Disease Questionnaire (IBDQ) was used to measure disease-specific health-related quality of life. The 32-item scale has been found to be more sensitive in IBD than general health quality of life measures.[18]

Biological Indicators

A blood draw was done at the same time as the clinical interview, and routine biochemical and hematological tests were performed to identify serum Hg and CRP levels. Standard lab definitions of low Hg (<120 g/L) and high CRP (>8 mg/L) were used.

Statistical Methods

Descriptive analyses of the clinical measures were done comparing disease type (CD/UC) and disease status (inactive/active). Comparisons of disease subtypes and active/inactive subgroups were performed using two-tailed independent samples *t*-tests for continuous variables, and chi-squared tests of association for categorical variables. In order to control for error rates, a Bonferroni adjusted value of $p \leq 0.02$ was considered significant for these comparisons. Associations among the primary measures were assessed using Pearson correlations.

Bivariate and multiple logistic regression analyses were conducted to evaluate the relationship between fatigue and demographic characteristics, disease activity, sleep quality, psychological concerns, and biological indicators. For the logistic regression analyses, variables including the sleep, psychological and biological measures were categorized as high or low based on

established cutoffs or median split. Age was assessed using distributed categories (under 30, 30 -39, 40-49 and 50+) and disease duration and hours of sleep were assessed as continuous variables. Missing values were dealt with conservatively; in multi-item scales, an expectation maximization (EM) procedure was used in cases of a single missing item. The EM algorithm is a two-step iterative procedure whereby missing values are estimated, and a covariance matrix and mean vector are subsequently computed.[32] This process continues until there is a minimal difference between covariance matrices in adjacent maximization steps.

RESULTS

The IBD cohort participants had a mean age of 43 (SD =14.06), and ranged from 19 to 81 years old. The average duration of disease was 6.4 years (SD = 2.1) at the time of this study. The sample was 60% female and 95% Caucasian, with a minority having self-described backgrounds as East Indian, Hispanic, or Metis (of Aboriginal and European ancestry). One quarter of the sample reported a completed university degree. Most respondents were married or in a common-law relationship (67%) and employed full- or part-time (66%). Fifty-one percent (160) had Crohn's disease, and the remainder (158) had ulcerative colitis or ulcerative proctitis. Forty -six percent (n=147) had current active disease, based on the Harvey Bradshaw or Powell Tuck clinical indices. Lab values were not available for 18 individuals. Overall, in the IBD sample, 12% had low Hg levels (<120 g/L) and 23% had high CRP levels (>8 mg/L).

Comparisons across IBD subtypes

Table 1 shows the mean levels of the variables comparing CD and UC, broken down further based on disease activity, and Table 2 highlights the percentage reaching a clinically significant

threshold using the same subgroups. Comparisons assessing levels across IBD subtype (Table 1) indicated no significant differences between CD and UC in mean fatigue levels, sleep quality, or related sleep measures. Similarly there was no difference between CD and UC in the proportion of those who scored above the clinical threshold on these measures (Table 2). Mean hemoglobin levels were also similar; however CRP levels were higher for those with Crohn's compared to those with UC (mean 8.8 vs 5.3, $p < 0.02$), with 30% of Crohn's patients having an elevated CRP compared to only 16% of UC patients.

Comparisons across active and inactive disease

Those with current active disease scored significantly more poorly on almost all of the clinical variables compared to those with inactive disease as can be seen in Tables 1 and 2. From Table 2, considering all those with active disease regardless of IBD subtype, almost three quarters (72%) experienced high fatigue levels and 77% reported poor sleep. Surprisingly, almost one-third (30%) and one-half (49%) of those with inactive disease also reached clinical thresholds for fatigue and sleep difficulties, respectively.

Although participants with active IBD had significantly higher levels of daytime sleepiness than those with inactive disease (Table 1), the mean scores for both groups were within the normal alert range. Mean Hg levels were similar regardless of disease activity status, and were also within normal ranges. CRP levels were significantly higher for the active disease group, collapsing across CD and UC (mean =9.3 vs 5.3), although similar numbers had elevated CRP (Table 2) (i.e., > 8 mg/L: 24% vs 22%). When looking at a more conservative cutoff for elevated CRP (very high CRP > 20mg/L), while there were twice as many with active disease who had

very high levels (7.4% vs 3.8%), the difference was not significant. Overall, fewer than half of those with elevated CRP also scored in the active disease range on the clinical indices.

Relationship between fatigue and sleep, biological, psychological and quality of life variables

Table 3 shows the associations among these variables. General fatigue had strong correlations in the expected directions with sleep quality and daytime sleepiness. The number of hours of nightly sleep was very strongly related to sleep quality (i.e., the fewer hours of sleep the poorer the sleep quality), but only minimally related to general fatigue. Greater disease activity was associated with higher fatigue on most dimensions. There was a modest but significant relationship between fatigue and the hemoglobin and CRP levels, and between sleep quality and Hg levels. Fatigue was also clearly associated with greater distress and higher levels of perceived stress. Disease specific quality of life was inversely related to all aspects of fatigue, such that greater fatigue, both physically and mentally, as well as reduced activity were associated with poorer IBD-related quality of life.

Multivariate Analyses

Logistic regression analyses were used to examine the contributions of demographic, disease, sleep, psychological and biological variables to fatigue. Preliminary analyses suggested that variables including sex, age, marital status, work status, and education level as well as disease duration and disease subtype (CD/UC) were not related to fatigue levels. Consequently, these variables were not included in further analyses. In addition, quality of life was not included in the regression analyses as it was considered conceptually to be a 'downstream' variable more likely to reflect the impact of fatigue.

Table 4 shows both the bivariate and adjusted multivariate logistic regressions using the remaining variables in the analyses. Hg and CRP were retained in the analyses as they approached significance in the bivariate analyses. Poor sleep quality, active disease, high stress, significant distress, and lower total sleep time were individually associated with high levels of fatigue. In the multivariate analysis, when controlling for each of the other variables, active disease and poor sleep quality continued to be associated with a greater likelihood of significant fatigue. Stress also remained uniquely associated with fatigue, although CRP and Hg levels were not, when adjusting for these other factors.

A substantial number of those with inactive disease also reported problematic fatigue, so a secondary analysis was carried out on a subgroup of those with no current active disease, no evident anemia, and no elevated inflammatory marker. Of this group, 29% had significant fatigue. Poor sleep quality was strongly associated with high fatigue (adjusted OR 4.4, CI 1.5-13.3, p=0.008); hours of sleep were not contributory. Psychological factors were also strongly associated with fatigue, as those with high stress were more than four times as likely to experience high levels of fatigue, even when controlling for poor sleep quality (adjusted OR 4.4, CI 1.7-11.5, p=0.002). There were only 3% reporting high fatigue levels who had no apparent contributory factors; that is, they had inactive disease, no elevated biomarkers, stress, or distress, and no issues with sleep quality.

With recent reports querying the role of restless legs syndrome (RLS) in IBD,[33] possible RLS was assessed in the total IBD sample using a definition that involved significant daytime

sleepiness (ESS > 10) and prolonged sleep latency on the PSQI. Only 9% met this criteria, with the majority in the high fatigue group. When endorsement of leg movement/jerking during sleep and low Hg were added into the possible RLS definition, the prevalence dropped to 4% and 1% respectively.

DISCUSSION

This study is the largest to date to focus on fatigue and IBD. It evaluated the association of fatigue in IBD with multiple relevant parameters simultaneously, including sleep difficulties, psychological factors, and inflammatory and anemia markers, using validated measures. High rates of significant fatigue were evident in this IBD sample, and were found to be associated with disease activity, poor sleep quality, and perceived stress. While there was a modest association of fatigue with CRP and hemoglobin, those correlations were not strong compared to the relationships with other variables. Higher fatigue was strongly associated with lower quality of life. Further, an intriguing finding of the study was that almost one-third of those with inactive disease were also experiencing significant fatigue. Overall, only 3% of those with high fatigue did not have elevations in any of the factors considered, suggesting that these variables may be of primary importance in understanding and managing fatigue in IBD.

Despite the importance of fatigue to patients, there has been little systematic investigation in IBD. In one study of 70 IBD outpatients in remission attending a specialty GI clinic, 41% experienced significant fatigue.[6] Another tertiary clinic-based study comparing primarily patients with irritable bowel syndrome and IBD to a control sample concluded that fatigue impact was more severe for those with functional and organic GI disease.[16] Recently emerging studies on sleep disturbance using validated sleep quality measures have suggested that those

with quiescent IBD have greater sleep disturbance than healthy controls, and that poorer sleep was associated with lower IBD-related quality of life.[14,26]

In our sample of community-based IBD patients, fatigue was highly prevalent for those with active disease, with almost three-quarters reporting significantly elevated levels. This is in contrast to only 5% of a healthy sample who reached similar levels of fatigue.[6] General and physical fatigue mean scores were almost double those of normative samples.[34,35] Fatigue levels were similar to those with suspected chronic fatigue syndrome,[35] as well as rheumatoid arthritis and liver disease.[36,37]

Population-based studies of sleep quality, using the same measure that was used here, estimate that 32% of adults have poor sleep quality.[38] Results from our study showed that problematic sleep quality was considerably more common among those with active IBD (72-82%), but was also more common among those with inactive disease (47-51%). The strong correlations between fatigue and sleep suggest that these are related but separate experiences, paralleling findings in the general sleep literature.[39] Daytime sleepiness levels were similar, on average, to a population-based normative sample, although there were more with active disease scoring above the clinical cutoff (36% UC; 41% CD), relative to those in the general population (29%),[40] suggesting there may be a bimodal distribution. In contrast, the proportion with daytime sleepiness problems in the inactive IBD group were very similar (21% UC; 24% CD) to that of the general population.

Finally, specific sleep disturbances such as restless leg syndrome (RLS) were not contributory in this sample. Using estimates of the prevalence of RLS based on the sleep and sleepiness data, only 9% met the general criteria for probable RLS. This rate is similar to those in the general population,[41] and much lower than initial reports of RLS in an IBD sample.[33] More research on this problem may be warranted to establish a clearer estimate of the prevalence of RLS.

Fatigue is also a common symptom of depression, and that association has been previously identified in both IBD and other chronic diseases.[35,36,42] High distress levels were found to be associated with fatigue in our IBD community sample as well. However, even when controlling for sleep and these psychological symptoms, fatigue was still highly associated with perceived stress, with four times greater likelihood of significant fatigue with elevated stress. Stress can result in psychological strain as well as physiological changes involving the hypothalamus-pituitary-adrenal axis and the autonomic nervous system, interacting with both immune and inflammatory functions.

Anemia, which has been thought to be a primary contributor to fatigue in IBD,[4] was found in this study to have a minimal role when considered in the context of disease activity, sleep quality and stress. Rates of anemia were lower than has typically been reported in a clinical IBD sample, so it is possible there was insufficient power to detect a significant relationship. However, it may be that hemoglobin is not sensitive enough to detect relevant differences in iron levels in this population. There has been some exploration of the clinical relevance of nonanemia iron deficiency, looking at ferritin or serum transferrin receptor (T*f*R) levels, which have supported a relationship with fatigue and reduced energy.[43,44]

Similarly, the inflammatory marker, C-reactive protein, was only weakly associated with fatigue, paralleling findings by Simren and colleagues with both organic and functional gastrointestinal conditions.[16] This may reflect a smaller role for inflammatory processes in IBD-related fatigue, or that CRP is not sensitive enough to IBD inflammatory activity. Although CRP has been associated with clinical and endoscopic activity in IBD,[45] in our sample, CRP was not consistently elevated relative to active disease. Other markers, including fecal calprotectin and lactoferrin are being actively investigated and show some promise with regard to sensitivity and discriminative abilities for disease activity, and may in turn have more utility to flag fatigue.[46]

While active disease, distress or depression, sleep difficulties, and perceived stress cannot be established as causes of fatigue in a cross-sectional design, emerging work is pointing to plausible mechanisms for these relationships nevertheless. A recent experimental study using an animal model of colitis found that acute and intermittent sleep deprivation patterns aggravated inflammation and slowed recovery, with some evidence of a 'dose' response.[15] Stress has been found to alter the release of pro-inflammatory mediators, and increase intestinal permeability, which can contribute to intestinal inflammation.[47] Finally, a novel communication pathway between the immune system and the brain has been described,[48]suggesting that inflammation in chronic disease may cause fatigue through monocyte infiltration in the brain. These investigators found that liver inflammation in mice triggered microglia cells in the brain to produce CCL2, a chemical that attracts monocytes. When the CCL2 signalling was blocked, there was less monocyte infiltration, and behaviorally it was observed that lethargy and social interaction improved.

The high prevalence of significant fatigue in IBD, regardless of disease activity, has implications for the clinician. Even when disease was inactive, and hemoglobin was in the normal range, more than one in four (29%) were still reporting significant fatigue. Fatigue and its associated factors, including psychological distress, stress and sleep quality should be assessed, with consideration of targeted treatment. Adalimumab maintenance therapy has had some positive effects on fatigue.[49] Behavioral interventions for fatigue, including activity pacing and cognitive reframing used for conditions such as chronic fatigue syndrome may be of value to explore with IBD patients. There has already been some attention to stress management and treatment of depression or anxiety in IBD.[50,51] When sleep quality is a concern, cognitive behavioral therapy for sleep has been shown to be effective as a first-line intervention,[52] and may well have an important role in the care of the IBD patient.

This study has some limitations. The data are cross sectional and the findings cannot address the direction of associations. It is certainly probable that poorer sleep contributes to fatigue which in turn could increase distress, although conversely high stress could interfere with restorative sleep and contribute to ongoing autonomic arousal, affecting fatigue levels both directly and indirectly. Anemia and elevated CRP were less prevalent than expected, compared to levels reported in clinic samples, which may have resulted in less power to detect a contribution if one is relevant. However, other recent studies have found that CRP and hemoglobin levels are not highly related to fatigue and our findings provide further support in that direction. While there was no control group, the use of validated measures with comparison data available from community and clinical samples provides some context for the findings.

In conclusion, fatigue is common and problematic for those with active and inactive IBD. When screening for fatigue in IBD, it is highly likely the patient will report its presence, even when the disease is otherwise considered clinically inactive and there is no anemia. Assessment and intervention with other associated factors such as stress and sleep quality should also be considered.

ACKNOWLEDGMENT

This research was supported by an operating grant from the Canadian Institutes of Health Research (# 86482). Dr. Charles Bernstein is supported in part by a Research Scientist Award of the Crohn's and Colitis Foundation of Canada and holds the Bingham Chair in Gastroenterology. In the past year Dr Bernstein has served as a consultant to Abbott Canada, and has received an unrestricted educational grant from Axcan Pharma. The other authors have no conflicts of interest to declare.

References

1.Shen J, Barbera J, Shapiro C. Distinguishing sleepiness and fatigue: focus on definition and measurement. Sleep Med Rev. 2006;10:63-76.

2.Swain MG. Fatigue in chronic disease. Clin Sci. 2000;99:1-8.

3.Drossman DA, Patrick D, Mitchell CM *et al*. Health-related quality of life in inflammatory bowel disease: functional status and patient worries and concerns. Dig Dis Sci 1989;34:1379-86.

4.Gasche C, Lomer MC, Cavill I, et al. Iron, anaemia, and inflammatory bowel diseases. Gut. 2004;53:1190-1197.

5.Jager A, Sleijfer S, van der Rijt CC. The pathogenesis of cancer related fatigue: could increased activity of pro-inflammatory cytokines be the common denominator? Eur J Cancer. 2008;44:175-181.

6.Minderhoud IM, Oldenburg B, van Dam PS, et al. High prevalence of fatigue in quiescent inflammatory bowel disease is not related to adrenocortical insufficiency. Am J Gastro. 2003;98:1088-1093.

7.Vagianos K, Bector S, McConnell J, et al. Nutrition assessment of patients with inflammatory bowel disease. J Parenter Enteral Nutr. 2007;31:311-319.

8.Gasche C. Anemia in IBD: the overlooked villain. Inflamm Bowel Dis. 2000;6:142-150.

9.Ayas NT, White DP, Manson J, et al. A prospective study of sleep duration and coronary heart disease in women. Arch Int Med. 2003;163:205-209.

10.Hublin C, Partinen M, Koskenvuo M, et al. Sleep and mortality: a population-based 22-year follow-up study. Sleep. 2007;30:1245–1253.

11.Spiegel, K, Leproult, R, Van Cauter, E. Impact of sleep debt on metabolic and endocrine function. Lancet. 1999;354:1435-1439.

12.Stamatakis KA, Punjabi NM. Effects of sleep fragmentation on glucose metabolism in normal subjects. Chest. 2010;137:95-101.

13.van Leeuwen WM, Lehto M, Karisola P, et al. Sleep restriction increases the risk of developing cardiovascular diseases by augmenting proinflammatory responses through IL-17 and CRP. PLoS One. 2009;4:e4589.

14.Ranjbaran Z, Keefer L, Stepanski E, et al. The relevance of sleep abnormalities to chronic inflammatory conditions. Inflamm Res. 2007;56:51-57.

15.Tang Y, Preuss F, Turek FW, et al. Sleep deprivation worsens inflammation and delays recovery in a mouse model. Sleep Med. 2009;10:597-603.

16.Simren, M, Svedlund, J, Posserud, I, et al. Predictors of subjective fatigue in chronic gastrointestinal disease. Aliment Pharmacol Ther. 2008;28:638-647.

17.Bernstein CN, Blanchard JF, Rawsthorne P, et al. The epidemiology of Crohn's disease and ulcerative colitis in a central Canadian province: a population-based study. Am J Epidemiol. 1999;149:916-924.

18.Graff LA, Walker JR, Lix L, et al. The relationship of inflammatory bowel disease type and activity to psychological functioning and quality of life. Clin Gastro Hepatol. 2006;4:1491-1501.

19.Longobardi, T, Bernstein, CN. Hearsay: is patient self-report of health care utilization accurate? Gastroenterology. 2008;134(suppl 1):A-498.

20 Harvey RF, Bradshaw JM. A simple index of Crohn's disease activity. Lancet. 1980;1:514.

21.Powell-Tuck J, Brown RL, Lennard-Jones JE. A comparison of oral prednisolone given as single or multiple daily doses for active proctocolitis. Scand J Gastroenterol. 1978;13:833-837.

22.Vermeire S, Schreiber S, Sandborn WJ, et al. Correlations between the Crohn's Disease Activity and Harvey-Bradshaw indices in assessing Crohn's disease severity. Clin Gastro Hepatol. 2010;8:357-363.

23.Higgins PDR, Schwartz M, Mapili J, et al. Patient defined dichotomous end points for remission and clinical improvement in ulcerative colitis. Gut. 2005;54:782-788.

24.Smets EM, Garssen B, Bonke B, et al. The multidimensional fatigue inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res. 1995;39:315–325.

25.Buysse, DJ, Reynolds, CF, Monk, TH, et al. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28:193–213.

26.Keefer, L, Stepanski EJ, Ranjbaran, Z, et al. An initial report of sleep disturbance in inactive inflammatory bowel disease. J Clin Sleep Med. 2006;2:409-416.

27.Johns, MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14:540–545.

28.Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the Epworth sleepiness scale: failure of the MSLT as a gold standard. J Sleep Res. 2000;9:5-11.

29.Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24:385-396.

30.Cohen S. The Pittsburgh common cold studies: psychosocial predictors of susceptibility to respiratory infectious illness. Internat J Behav Med. 2005;12;123-131.

31.Derogatis LR, Savitz, KC. The SCL-90-R and Brief Symptom Inventory (BSI) in primary care. In : Maruish M, ed. Handbook of psychological assessment in primary care settings. New Jersey: Lawrence Erlbaum Associates, 2000:297-334.

32.Enders, CK. The impact of missing data on sample reliability estimates: implications for reliability reporting practices. Educ Psychol Meas. 2004;64:419-436.

33.Weinstock LB, Bosworth BP, Scherl EJ, et al. Crohn's disease is associated with restless legs syndrome. Inflamm Bow Dis. 2010;16:275-281.

34.Schwarz R, Krauss O, Hinz A. Fatigue in the general population. Onkologie. 2003;26:140-144.

35.Lin J, Brimmer D, Maloney E, et al. Further validation of the multidimensional fatigue inventory in a US adult population sample. Popul Health Metr. 2009;7:18.

36.Rupp I, Boshuizen H, Jacobi C, et al. Impact of fatigue on health-related quality of life in rheumatoid arthritis. Arthritis Rheum. 2004;51:578-585.

37.Unal G, de Boer JB, Borsboom GJ, et al. A psychometric comparison of health-related quality of life measures in chronic liver disease. J Clin Epidemiol. 2001;54:587-596.

38.Zeitlhofer J, Schmeiser-Reider A, Rosenberger TG, et al. Sleep and quality of life in the Austrian population. Acta Neurol Scand. 2000;102:249-257.

39.Ustinov Y, Lichstein KL, Taylor DJ, et al. Association between report of insomnia and daytime functioning. Sleep Med. 2010;11:65-68.

40.Sanford SD, Lichstein KL, Durrence HH, et al. The influence of age, gender, ethnicity, and insomnia on Epworth sleepiness scores: a normative US population. Sleep Med. 2006;7:319-326.

41.Berger K, Kurth T. RLS epidemiology, frequencies, risk factors and methods in population studies. Mov Disord. 2007;22(suppl 19):S420-423.

42.Bol Y, Duits AA, Vertommen-Mertens CER, et al. The contribution of disease severity, depression, and negative affectivity to fatigue in multiple sclerosis: a comparison with ulcerative colitis. J Psychosom Res. 2010;69:43-49.

43.Haas J, Brownlie T. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. J Nutr. 2001;131:676S-690S.

44.Verdon F, Burnand B, Stubi CL, et al. Iron supplementation for unexplained fatigue in non-anaemic women: double blind randomized placebo controlled trial. BMJ. 2003;326:1124.

45. Bitton A, Peppercorn M, Antonioli D, et al. Clinical, biological, and histological parameters as predictors of relapse in ulcerative colitis. Gastroenterology. 2001;120:13-20.

46.Schoepfer AM, Beglinger C, Straumann A, et al. Fecal calprotectin correlates more closely with the simple endoscopic score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. Am J Gastroenterol. 2010;105:162-169.

47.Collins SM. Stress and the gastrointestinal tract IV. Modulation of intestinal inflammation by stress: basic mechanisms and clinical relevance. Am J Physiol Gastrointest Liver Physiol 2001;280:G35-39.

48.D'Mello, Le T, Swain MG. Cerebral microglia recruit monocytes into the brain in response to tumor necrosis factor α signalling during peripheral organ inflammation. J Neuroscience. 2009;29:2089-2102.

49.Loftus, EV, Feagan, BG, Colombel, JF, et al. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial. Am J Gastroenterol. 2008;103:3132-3141.

50.Garcia-Vega E, Fernandez-Rodriguez C. A stress management programme for Crohn's disease. Behav Res Ther. 2004;42:367-383.

51.Graff LA, Walker, JR, Bernstein CN. Depression and anxiety in inflammatory bowel disease: a review of comorbidity and management. Inflamm Bow Dis. 2009;15:1105-1118.

52.Vincent N, Lewycky S. Logging on for better sleep: RCT of the effectiveness of online treatment for insomnia. Sleep. 2009;32:807-815.

Table 1: Fatigue, sleep, and laboratory measures in Crohn's disease (CD) and ulcerative colitis (UC) with active and inactive disease

	CD		UC		Statistical comparison	
	Active Mean (SD)	Inactive Mean (SD)	Active Mean (SD)	Inactive Mean (SD)	Disease type[a]	Disease Activity[b]
N	76	84	71	87		
Fatigue						
General Fatigue	14.8 (4.0)	10.4 (4.0)	14.3 (3.5)	10.2 (4.0)	p=0.42	**p<0.001**
Physical Fatigue	12.5 (4.0)	8.0 (3.0)	11.3 (3.7)	8.5 (3.9)	p=0.36	**p<0.001**
Mental Fatigue	9.3 (3.7)	7.7 (3.2)	9.6 (4.1)	8.4 (3.7)	p=0.30	**p<0.001**
Reduced Activity	11.0 (4.2)	7.6 (3.1)	10.1 (3.6)	8.2 (3.7)	p=0.71	**p<0.001**
Reduced Motivation	10.0 (3.8)	6.9 (2.6)	9.1 (3.3)	7.5 (3.4)	p=0.52	**p<0.001**
Global sleep quality	9.7 (4.1)	5.8 (3.5)	8.3 (4.4)	5.7 (3.3)	p=0.51	**p<0.001**
Sleep/night (hours)	6.4 (1.3)	7.1 (1.0)	6.5 (1.4)	7.1 (1.2)	p=0.48	**p<0.001**
Daytime sleepiness	8.1 (4.3)	6.4 (4.2)	8.7 (4.1)	6.5 (4.3)	p=0.66	**p<0.001**
Hemoglobin	135.7 (12.2)	135.9 (12.8)	132.7 (15.2)	139.7 (14.5)	p=0.61	p=0.03
C-reactive protein	12.3 (20.1)	5.6 (5.8)	5.7 (8.7)	5.0 (5.8)	**p=0.01**	**p=0.01**

[a]comparisons between CD and UC, collapsing across disease activity; [b]comparisons between active and inactive disease, collapsing across CD/UC; significant differences are indicate in bold type based on t-test and Bonferrroni correction ($p \leq 0.02$).

Table 2: Proportion of respondent with active and inactive Crohn's disease and ulcerative colitis with clinically elevated scores on fatigue, sleep, and laboratory measures.

	CD		UC		Statistical comparison	
	Active %	Inactive %	Active %	Inactive %	Disease type[a]	Disease activity[b]
High general fatigue	78	29	67	30	p=0.26	**p<0.001**
Poor sleep quality	82	51	72	47	p=0.53	**p<0.001**
High daytime sleepiness	41	24	36	21	p=0.27	**p<0.01**
Low hemoglobin	11	12	18	6	p=0.95	p=0.17
High C-reactive protein	31	29	17	15	**p<0.01**	p=0.62
Very high CRP (> 20 mg/L)	12	4	2	4	p=0.04	p=0.19

[a]comparisons between CD and UC, collapsing across disease activity; [b]comparisons between active and inactive disease, collapsing across CD/UC; significant differences are indicated in bold type, based on chi-squared test and Bonferrroni correction ($p \leq 0.02$).

Table 3: Correlations of fatigue subscales and sleep quality with sleep, disease activity, laboratory measures, psychological functioning, and quality of life

	General Fatigue	Physical Fatigue	Mental Fatigue	Reduced Activity	Reduced Motivation	Global sleep quality
Global sleep quality[a]	.51**	.47**	.31**	.40**	.35**	-------
Sleep hours/night	-.25**	-.18*	-.12	-.09	-.14	-.66**
Daytime sleepiness	.39**	.25**	.23**	.25**	.26**	.30**
Disease activity – CD	.48**	.56**	.18	.52**	.44**	.47**
UC	.50**	.44**	.22*	.31**	.33**	.30**
Hemoglobin	-.23**	-.18*	-.11	-.18*	-.12	-.17*
C-reactive protein	.15*	.18*	-.04	.18*	.11	.02
Perceived stress	.55**	.45**	.50**	.45**	.52**	.41**
Psychological distress	.57**	.51**	.43**	.48**	.53**	.50**
IBD-related quality of life	-.62**	-.62**	-.39**	-.59**	-.52**	-.56**

[a] higher scores indicate poorer sleep quality
* $p < 0.01$; ** $p < 0$ .001

Table 4: Bivariate and multivariate relationship between fatigue levels and sleep, disease activity, laboratory, and psychological variables

Variable	High Fatigue %	Low Fatigue %	Bivariate Logistic Regression Odds Ratio (95% CI)	Multiple Logistic Regression Adjusted Odds Ratio (95% CI)
Poor sleep quality	80	43	7.3** (3.8-14.0)	4.0** (1.9-8.6)
Mean (SD) hours sleep/night	6.6 (1.4)	7.0 (1.1)	0.7* (0.6-0.9)	1.2 (0.9-1.6)
Active disease	68	25	5.7** (3.4-9.6)	4.2** (2.2-7.8)
Low hemoglobin	16	8	2.3 (1.0-5.1)	2.2 (0.8-6.1)
High CRP	27	19	1.7 (0.9-2.9)	1.5 (0.7-3.1)
High perceived stress	68	25	7.4** (4.3-12.5)	4.2** (2.2-8.1)
High psychological distress	40	9	7.3** (3.8-14.2)	1.9 (0.8-4.4)

* $p \leq 0.02$ ** $p \leq 0.001$