# Quality of Life in Inflammatory Bowel Disease

## when IBD goes beyond the gut

Kwaliteit van leven bij inflammatoire darmziekten
wanneer IBD verder gaat dan de darmen

**Nynke Borren**

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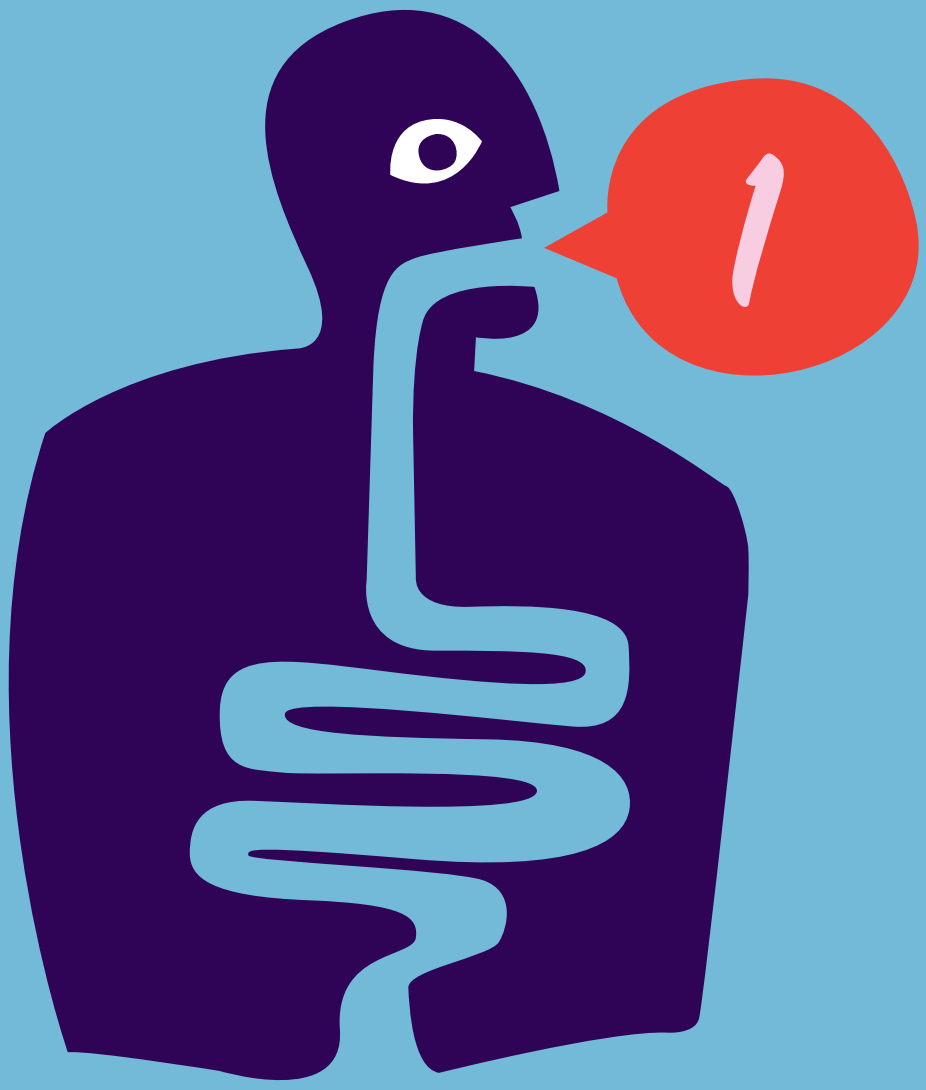
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# CHAPTER 1

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## General introduction, aims and outline of the thesis

## INTRODUCTION

Inflammatory Bowel Disease (IBD) comprising Crohn's disease (CD) and ulcerative colitis (UC) are chronic idiopathic immune-mediated diseases causing inflammation primarily located in the gastrointestinal tract. IBD is characterised by lifelong episodes of chronic (sometimes bloody) diarrhoea, urgency, abdominal discomfort and pain but symptom presentation differs widely between individuals. The heterogeneity of its clinical presentation and the relapsing-remitting character are challenging for both clinicians and patients and can have profound impact on the quality of life of the IBD patients[1]. The exact aetiology remains undefined but it is believed to result from a complex interaction between genetic, environmental and microbiota factors resulting in an abnormal immune response[2]. Patients are diagnosed relatively young as disease onset typically occurs between 20 and 40 years of age with a second peak onset between 50 to 60 years[3]. Diagnosis is generally established based on clinical symptoms, endoscopic and histologic findings and can be supported by laboratory findings.

While IBD was described for the first time in the 19th century[4] and the incidence increased during the early 1900s, the incidence of Crohn's disease and ulcerative colitis dramatically increased in Westernized countries during the second half of the 20th century[5-7]. The rapid increase in incidence is thought to be a result of the great industrialization with human civilization, economic welfare, increased food production and improved hygiene circumstances[8, 9]. This increased incidence in urban areas compared to rural areas is thought to be a sign of the influence of our 'Western' lifestyle. Where the peak incidence in Westernized countries is slowly stabilizing, a novel peak in increased incidence has been noted in newly developing countries in Asia, South America and the Middle East[10-12]. Interestingly, it confirms the hypothesis that our Westernized lifestyle is thought to be an important factor in causing IBD and the external environment has been noted to have strong effect on IBD aetiology.

In parallel to the increased incidence, our knowledge and understanding of the pathophysiology of IBD has been revolutionized. Initially, research studies were focused on genetic hereditary of IBD and despite large international collaborations and twin studies that identify over 200 disease variants that modify risk, genetics explained only 33% of the IBD appearance[13, 14]. Over the past two decades, many prospective cohort studies focused on environmental risk factors. This resulted in many associations, including low vitamin D levels, early life exposure to antibiotics, no breastfeeding and lower dietary fiber intake[15-19]. More recently, psychosocial factors such as stress, sleep and mood have been linked to IBD[20-22]. It is suggested that a bidirectional communication network between the gut and the central nervous system, better known as the gut-brain axis, might mediate psychological symptoms, and vice versa[23, 24]. Therefore IBD might not be restricted to the gut only, but goes even beyond the gut with significant effect on a patient's life.

Due to the early disease onset, IBD often affect individuals at a time they begin to pursue a career, expand their family and engage with society. Therefore, the limitations posed by IBD is related to psychological distress resulting in a negative impact on their quality of life[25]. Quality of life is a subjective term but has been defined by the World Health Organization as:

> *"Individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the persons' physical health, psychological state, level of independence, social relationships and their relationship to salient features of their environment[26]".*

Living with a chronic disease is challenging for many patients and impacts life significantly. In the United States, six percent of the patients with one or two known chronic conditions experienced limitations in their work, home and social life compared to 1% in the general population without a chronic condition[27]. A similar negative impact on the quality of life was observed in IBD patients. Large population studies have shown that IBD patients have a significant impaired Health Related Quality of Life (HRQOL) compared to the general population[28, 29]. Severe disease activity was a major driver of HRQOL with lower scores (IBDQ score: 156 for CD, 157 for UC) compared to the general population (IBDQ score: 183)[30]. This impairment of HRQOL is even seen during quiescent disease. Many daily activities are impaired in patients suffering from IBD that might affect interpersonal relationships, reduced social participation and impaired mental health[28, 30, 31]. For example, emotional health in CD and UC patients (SF-36 score: 68 and 74 respectively) was significantly lower compared to the general population (SF-36 score: 83)[28]. Therefore the highest disease burden for the patients are the "beyond the gut symptoms"[32].

Over the past decades, there is increasingly more recognition of the importance of patient-reported beyond the gut symptoms". One of the most frequently experienced complaint of IBD patients is fatigue which has a significant burden and impact on the quality of life[33]. An elegant cross-cultural study across eight different countries observed that fatigue was ranked fourth in major patient concerns associated to IBD[32]. While fatigue is more prevalent if the disease is active (~80%) fatigue persists in up to 40% of the patients in remission[34, 35]. In line with the previous described psychological distress and quality of life, fatigue has been poorly studied mainly due to the difficulty to assess the symptoms and typically relies on subjective reporting and therapeutic options are limited. Main reason for the absence of effective interventions to treat fatigue is the lack of knowledge about the pathogenesis of fatigue in IBD, particularly in quiescent disease. The few studies conducted in the past years suggest a potential role of the previously mentioned gut-brain-axis in mediating fatigue[36].

As recognition of subjective symptoms slowly evolve, IBD management strategies went through an evolution along. IBD therapy was initially focused on treating active inflammation and inducing disease remission. Whereas steroids and surgery were the main therapeutic options available, biologic therapies were introduced and therapeutic targets shifted to the aim for deep and long-lasting remission, including mucosal healing, with preventing complications and relapse of disease[37, 38]. Following the introduction of biologic therapies, namely anti-tumour necrosis factor (TNF) inhibitors, the IBD armamentarium expanded and improved clinical outcomes were noted with hospitalization and surgery rates drastically decreased[39]. The pharmaceutical clinical trials use well-known clinical and endoscopic indices to assess efficacy and safety of these new therapeutic agents but patient reported outcomes such as sleep disturbance, mood and fatigue symptoms are less frequently focused on. As these extra-intestinal manifestations have high impact on the quality of life in IBD patients and biologic agents might positively affects these "beyond the gut" symptoms.

Rapid advances in high-throughput technologies have revolutionized medical research. Mass spectrometry and next-generation sequencing have enabled scientists to collect large amounts of biological data from the same set of biological samples[40]. Integrating all the single type of data together is called a multi-'omics approach and encompasses genomics, transcriptomics, epigenomics, metabolomics, proteomics and microbiome data[41]. Each of these disciplines can quickly provide information of the processes within cells at multiple levels, allowing for new discoveries[42]. The first omics field to emerge, genomics, focuses on identification of genetic variations associated with IBD, response to therapy, or future prognosis[43]. A major concern of IBD patients is the genetic risk of IBD for their family members, which causes even more stress. This worry is not unjustified as between 8 and 20% of the IBD patients have an affected family member[44, 45]. However, genomics solely are not able to capture the IBD pathogenesis, therefore an integrative approach to combine multiple "omics" data is needed[40, 43]. A multi-'omics approach can not only be useful for unravelling the aetiology of IBD but also helps to identify environmental factors that contribute to IBD, to understand the gut-brain axis, to predict response to therapy and many more unsolved knowledge gaps. Multi-'omics profiling, with mostly biological samples obtained "beyond the gut", will leverage a more personalized medicine approach and will potentially ameliorate quality of life in IBD patients[46].

**Aims and outline of the thesis**

The aim of this thesis is to assess and understand clinical and biological factors influencing the quality of life of patients suffering from Inflammatory Bowel Disease.

One of the most frequent reported complaints in IBD patients with a major impact on their quality of life is fatigue. Current knowledge regarding the pathophysiology of fatigue is

lacking which limits physicians' ability to effectively treat this deliberating symptom. In **Chapter 2**, we review the current knowledge on the pathophysiology of fatigue, focusing on discoveries related to IBD. Also, the potential role of the gut microbiome in mediating fatigue and other psychological symptoms through the gut-brain axis is discussed. Finally, we explore the current evidence behind therapies and various psychological and pharmaceutical interventions on relieving fatigue and present a therapeutic strategy for the management of fatigue in IBD. Newly discovered biological therapies have shown to be effective to attain clinical and endoscopic remission in IBD but its effect on fatigue is less well established. In **Chapter 3** we aimed to define the longitudinal trajectory of fatigue over 1 year in patients initiating treatment with tumor necrosis factor α antagonist, vedolizumab, or ustekinumab. In parallel to this study, another understudied but important extra-intestinal manifestations are impairment of sleep and mood symptoms. These symptoms are associated with increased risk for relapsing disease, poor disease outcomes and impaired quality of life. The effect of biological therapies in improving sleep and mood symptoms is unclear. Therefore, in **Chapter 4**, we examine changes in sleep quality, depression, and anxiety after initiation of vedolizumab therapy. Those new advances in therapeutic options enable physicians to use more targeted biologics, but also resulted in IBD care becoming more complex and specialized. A delay in seeing a gastroenterologist specialized in IBD and receiving effective IBD therapy could result in disease complications such as hospitalization and need for surgery. One factor that could potentially be a barrier to access quality IBD care may be the physical distance to a specialized IBD facility. In **Chapter 5** we examine the impact of distance from area of residence to a referral IBD center on the need for surgery and biologic therapy in patients with IBD.

A major concern among IBD patients is the inheritance risk of IBD for their relatives, in particular their children. Multiple studies have identified the impact of family history on development of IBD, but little studies have studied if family history has impact on the disease course. Due to the higher genetic risk and common environmental factors, familial IBD may vary from sporadic IBD, which may result to similarities in gut microbial composition. In **Chapter 6** we define the impact of family history on the clinical characteristics and natural history of IBD and use new high-throughput technologies to compare the genetics and microbiome composition in a subset of patients with familial and sporadic IBD. These new emerging technologies have given us the opportunity to use a multi-'omics approach and to improve our understanding of IBD symptoms beyond the gut. We started this thesis to review current knowledge of the deliberating symptom fatigue and we will close this thesis with a chapter of fatigue symptoms in IBD. In **Chapter 7**, we integrate a multi-'omics approach to examine the role of alterations in the gut microbiome, serum metabolome, and proteome in causing fatigue in patients with quiescent IBD. Finally, in **Chapter 8**, we summarize and discuss the main findings and conclusions of our research studies and provide recommendations for future research.

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# CHAPTER 2

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## Fatigue in IBD: epidemiology, pathophysiology and management

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and Ashwin N Ananthakrishnan

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## ABSTRACT

Fatigue is an important clinical problem in patients with IBD, affecting nearly 50% of patients in clinical remission and > 80% of those with active disease. The resulting decrease in quality of life and impaired work productivity and functioning contribute markedly to the societal costs of fatigue. However, despite the burden and effects of fatigue, little is known about its aetiology and pathophysiology , which impairs our ability to effectively treat this symptom. Here, we review the theories behind the development of fatigue in IBD and the role of contributing factors, including nutritional deficiency , inflammation and altered metabolism. We also explore the potential role of the gut microbiome in mediating fatigue and other psychological symptoms through the gut–brain axis. We discuss the efficacy of nutrient repletion and various psychological and pharmacological interventions on relieving fatigue in patients with IBD and expand the discussion to non- IBD-related fatigue when evidence exists. Finally , we present a therapeutic strategy for the management of fatigue in IBD and call for further mechanistic and clinical research into this poorly studied symptom.

## KEYPOINTS:

- Fatigue is one of the most frequently reported concerns of patients with IBD and can result in a decrease in quality of life and impaired work productivity.
- Fatigue in IBD is multifactorial, with contributions from active inflammation, nutritional deficiency, altered metabolism and psychological comorbidity.
- Emerging evidence also suggest a possible role for bidirectional communication between the gut and central nervous system (the gut-brain axis) in mediating fatigue.
- The multidimensionality of contributing factors could imply that the mechanism of fatigue is not uniform in all patients and that there might be different subtypes of fatigue.
- The multidimensionality of fatigue suggests the existence of different subtypes that respond to different interventions.
- Studies conducted in the past few years suggest a potential role for psychological interventions, physical activity and microbiome-directed therapies for relief of fatigue.

## INTRODUCTION



Fatigue is one of the most prevalent and disabling symptoms in patients with IBD. Nearly 80% of those with active disease[1] and 50% of those with inactive IBD report substantial fatigue that impairs their health-related quality of life[2]. There are few estimates of the direct costs of fatigue in patients with IBD, but a survey among the general population in the United States published in 2007 estimated an excess annual direct and indirect cost of over $100 billion attributable to fatigue[3]. Fatigue in patients with IBD is probably multifactorial, consisting of several different components. Although some contributing factors such as nutritional deficiency or active inflammation might be modifiable by intervention, fatigue remains persistent in the absence of these factors in many individuals and its aetiology is unexplained. As many as 51% of patients with IBD state that fatigue and not having enough energy to get through the day is the most common reason for being absent from work due to the disease[4]. Mechanistic research into the basis of fatigue has so far been mostly conducted in patients with cancer or chronic fatigue syndrome (CFS). However, emerging research particularly in the realm of the brain–gut axis offers new hypotheses on the mechanisms underlying fatigue in chronic inflammatory diseases.

As definitions of health evolve, there is growing recognition of the importance of subjective symptoms that persist beyond resolution of inflammation. As described by the Global Burden of Disease Study 2010, "health is about more than avoiding death"[5], and if we extend it further "health in IBD may be more than just achieving clinical and endoscopic remission". Fatigue in IBD is an under-recognized and often sub-optimally treated symptom in clinical practice[6], resulting in reduced quality of life[7, 8] and high personal and societal costs[6, 9]. Therefore, it is important for both clinicians and researchers to gain a better understanding of this debilitating symptom to develop effective and targeted therapeutic interventions. In this Review, we summarize the current knowledge on the pathophysiology of fatigue, focusing on findings relevant to IBD. We also review the current evidence behind therapies and interventions for the management of fatigue.

## DEFINITION AND EPIDEMIOLOGY

A frequently used definition of fatigue is 'difficulty or inability to initiate or maintain activity'[10]. However, given its multidimensional nature, a simple definition might not capture the complexity of fatigue[11]. Markowitz *et al.* stated that fatigue consists of three components: the perception of generalized weakness, manifesting as inability or difficulty to initiate activities; quick fatigability and reduced capacity to maintain activities; and mental fatigue resulting in difficulty with concentration, emotional stability and memory[10].

**Fatigue in the general population**

Fatigue can affect as much as 8% of the general population at any given time[12]. The condition, one of the most common complaints seen in primary care, is the principal reason for seeking care in 5–7% of patients and is noted in up to 20% of all visits[13-15]. Fatigue is estimated to result in 7 million physician office visits per year in the USA according to data collected in the National Ambulatory Medical Care Survey published in 1992[16]. Fatigue not only lead to direct healthcare costs but also has a substantial indirect financial effect, through its effect on work productivity and functioning. Ricci *et al.* performed a national population-based random-digit-dial telephone survey of 28,902 adults and calculated health-related lost productive time in the USA[3]. They found that the total yearly costs attributable to fatigue amounted to US$136.4 billion per year compared with $35.4 billion per year for non-fatigued workers[3]. The effect of fatigue was even more striking from a large population study published in 2016, which reported that over a 20-year follow-up period, fatigue was associated with a 40% increase in mortality comparing the two extreme quartiles (hazard ratio (HR) 1.40, 95% CI 1.25–1.56)[17].

**Prevalence of fatigue in IBD**

Several studies have examined the burden of fatigue in patients with IBD. During active disease, the reported prevalence of fatigue ranges from 53% to 76%[18, 19], whereas in inactive disease the range varies from 15% to 54%[19, 20] (**Table 1**). Minderhoud *et al.* found that 41% of 80 patients with quiescent IBD suffered from fatigue, a prevalence comparable with that in patients with cancer[21]. A study from Spain found an even greater prevalence of fatigue, with 54% of 202 patients with IBD in remission having the condition20. An elegant population-based study compared aspects of fatigue in 440 patients with IBD over a 20-year follow-up with the Norwegian reference population, a sample of 2287 representative Norwegians in the age of 19-80 years randomly drawn by the Norwegian Government Computer Centre. Chronic fatigue was more common in patients with IBD (21% in patients with ulcerative colitis and 25% in patients with Crohn's disease) compared with the general population (11%), and the prevalence was greater in those with active disease (38% in those with ulcerative colitis and 38% in those with Crohn's disease) than in those in remission (16% in patients with ulcerative colitis and 20% in patients with Crohn's disease). Fatigue was also more common in women than in men (28% versus 17%)[22]. One of the most robust and generalizable estimates of fatigue in those with IBD is from a multicentre European survey of 631 patients[1]. Patients were asked about fatigue, although no formal definition was used to quantify this. Substantial fatigue was reported by 80% of patients overall, 73% of those with active disease[2] and by as many as 48% of those in remission. In those with IBD, fatigue is not merely a reflection of the cumulative effect of long-standing disease but is prevalent even in newly diagnosed individuals. Cohen *et al.* studied 220 patients within a median of 61 days after diagnosis of IBD. Even in this group with new-onset disease, 26.4% of patients had persistent fatigue according to

the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale[18]. In addition to its absolute prevalence, fatigue also ranks high among relative symptom concerns in patients with IBD. In a cross-cultural study from eight different countries, fatigue was ranked fourth in major patient concerns related to IBD[23]. Interestingly, fatigue was higher on the list of concerns than pain and bowel control. Additionally, the sum score exhibited a geographic trend within the European countries along a north–south gradient, with the highest scores in Italy and Portugal, the most southern countries, and the lowest scores in Sweden, the most northern country. Such differences might be attributable to differences in educational level, cultural differences, national prosperity and health expenditures in addition to the biology of disease.

**Table 1: Prevalence of fatigue in patients with IBD.**

| First Author | Population (*n*) | Method of assessment of fatigue | Prevalence of fatigue | | | Refs |
|---|---|---|---|---|---|---|
| | | | Overall | Active disease | Remission | |
| Minderhoud et al. (2003) | Adult outpatients with IBD, in remission (80) | MFI | – | – | 41% | 21 |
| Björnsson et al. (2004) | Adult outpatients with UC, in remission (77) | FIS | – | – | 48% UC | 2 |
| Minderhoud et al. (2007) | Adult outpatients with CD starting infliximab therapy or placebo (14) | MFI | – | 86% CD | – | 146 |
| Romberg-Camps et al. (2010) | Adult outpatients with IBD (707) | MFI | – | – | 40% | 7 |
| Jelsness-Jørgensen et al. (2011) | Adult outpatients with IBD (140) | FQ | 29% CD, 22% UC | – | – | 49 |
| Singh et al. (2011) | Adult outpatients with IBD (704) | Single question about fatigue | 54% CD, 33% UC | 76% | 15% | 19 |
| Graff et al. (2011) | Adult outpatients with IBD (318) | MFI | – | 72% | 30% | 64 |
| Römkens et al. (2011) | Adult outpatients with IBD (172) | PFS | 64% | 75% | 40% | 147 |
| Bager et al. (2012) | Adult outpatients with IBD (425) | MFI | 44% | 57% | 29% | 51 |
| Graff et al. (2013) | Adult outpatients with IBD, fatigue measured over 2 years (312) | MFI | – | 42%-76% | 21% - 37% | 43 |
| Cohen et al. (2014) | Newly diagnosed outpatients, adults and children with IBD (220) | FACIT-F scale | 26.4% | 53.3% CD, 33.3% UC | 23.5% CD, 18.8% UC | 18 |
| Danese et al. (2014) | Adult outpatients with IBD (631) | No formal questionnaire | 83.2% | 73% | 36% | 1 |
| Grimstad et al. (2015) | Newly diagnosed and untreated outpatients with IBD (81) | FSS and fVAS | 48-62% CD, 42-47% UC | – | – | 148 |
| Hashash et al. (2016) | Adult outpatients with IBD (685) | One item of SIBDQ | 58% (64% CD, 46% UC) | – | – | 149 |
| Villoria et al. (2017) | Adults outpatients with IBD receiving immunosuppressants or biologic therapy, in remission (202) | FACIT-F scale | – | – | 54% | 20 |
| Huppertz-Hauss et al. (2017) | Adult patients with IBD, 20 years after diagnosis (440) | FQ | 25.4% CD, 20.8% UC | 35.6% CD, 26.8% UC | 14.9% CD, 15.6% UC | 22 |
| Vogelaar et al. (2017) | Adult outpatients with IBD (84) | CIS-Fatigue | – | – | 65% | 44 |

CD, Crohn's disease; CIS-Fatigue, Checklist Individual Strength-fatigue; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FIS, Fatigue Impact Scale; FQ, Fatigue Questionnaire; FSS, Fatigue Severity Scale; fVAS, fatigue Visual Analogue Scale; MFI, Multidimensional Fatigue Inventory; PFS, Piper Fatigue Scale; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; UC, ulcerative colitis.

**Prevalence in other immune mediated diseases**

Fatigue is also prevalent in many other autoimmune diseases. Up to 81% of 120 patients with systemic lupus erythematosus report fatigue[24]. Seventy percent of individuals with rheumatoid arthritis[25] and 67% of those with Sjögren's syndrome suffer from fatigue[26]. Furthermore, up to 63% of patients with ankylosing spondylitis [27] reported substantial fatigue, and moderate fatigue occurred in 49% of patients with psoriatic arthritis according to the modified Fatigue Severity Scale[28].

## DIAGNOSIS OF FATIGUE

Given the subjective nature of fatigue, several patient-reported questionnaires have been developed to define and quantify fatigue (**Table 2**). Some assess general fatigue in a single dimension, whereas other questionnaires assess fatigue in multiple dimensions including physical, mental and social contexts. One of the most widely used scales is the Multidimensional Fatigue Inventory (MFI). The MFI is a 20-item self-reported instrument that covers the domains of general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity[29]. The scale has demonstrated robust construct validity and reliability, with higher scores representing greater levels of fatigue. The FACIT-F is a 13-item questionnaire initially developed in patients with cancer, but it is has been validated for use in IBD in a cohort of 209 patients[30]. The responses to the questions are each recorded on a 5-point Likert scale and total scores range from 0 to 52, with lower scores representing greater fatigue. In a study by Tinsley *et al.*, FACIT-F scores among a cohort of patients with IBD strongly correlated with those on repeated tests 180 days later and demonstrated external validity, correlating with disease activity, serum C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR) values. A difference of 3–4 points is considered as the minimal clinically important difference[31, 32]. The Inflammatory Bowel Disease Fatigue scale (IBD-F) is a disease-specific 40-item questionnaire developed in consultation with patients with IBD. The questionnaire has three sections: the first assessing frequency and severity of fatigue; the second assessing the experience of fatigue and its effects; and the third differs from the previously mentioned questionnaires because it contains an open text section asking for additional issues related to fatigue[33]. This questionnaire has not been tested in larger populations (n=567-605) and needs to be further examined for validity and stability in larger studies[34]. There is no clear consensus in the literature on which questionnaire is best to use in IBD, but multidimensional scales, such as the MFI, Fatigue Impact Scale (FIS), Fatigue Questionnaire (FQ) and Piper Fatigue Scale (PFS), have been widely used and been validated in several other chronic diseases and therefore might be preferable.

**Table 2: Overview of available fatigue measurement instruments in IBD.**

| Year | Instrument | Condition initially developed for | Main characteristics | Use in IBD clinical studies | Questionnaires used in other populations | Notes |
|---|---|---|---|---|---|---|
| 1989 | IBDQ[150] | IBD | • 20-item questionnaire<br>• Lower scores implicate lower quality of life | • Minderhoud et al. (2003[21], 2007[146])<br>• Jelsness-Jørgensen et al. (2011[49], 2012[151])<br>• Romberg-Camps et al. (2010)[7]<br>• Norton et al. (2015)[34] | None | Questions designed for patients with IBD |
| 1991 | MAF[152] | Rheumatoid arthritis | • 16 items on a numerical (1-10) rating scale<br>• Higher scores indicate higher fatigue. | • Norton et al. (2015)[34] | RA, HIV, Cancer, COPD, MS, coronary heart disease, breast-feeding women, postpartum women, AS, SLE, CFS and 13 more diseases | Four dimensions of fatigue (severity, distress, degree of interference in activities of daily living and timing) |
| 1993 | FQ[153] | General practice | • 11 items on a 4-point Likert scale<br>• Higher scores indicate higher fatigue | • Jelsness-Jørgensen et al. (2011[49], 2012[151])<br>• Huppertz-Hauss et al. (2017)[22] | CFS, postinfectious fatigue, MS, SLE, general population | • Brief and easy<br>• Two dimensions (physical and mental fatigue)<br>• Questions regarding the duration of fatigue |
| 1994 | CIS[154] | CFS | • 20 items on a 7-point Likert scale<br>• Higher scores indicate higher fatigue effect | • Vogelaar et al. (2011[121], 2015[94], 2017[44]) | CFS, MS, neurologic disorders, RA, CFS, general population | • Cut-off score available (fatigue >35)<br>• Four dimensions (subjective experience of fatigue, concentration, motivation and physical activity) |
| 1994 | FIS[155] | Chronic fatigue with multiple sclerosis or hypertension | • 40 items on a 5 point Likert scale<br>• Higher scores indicate higher fatigue | • Björnsson et al. (2004)[2]<br>• Kalaitzakis et al. (2008)[156]<br>• Piche et al. (2010)[157] | MS, liver disease, general population | • Physical, cognitive and psychosocial subscales available<br>• Recall period of 1 month |
| 1995 | MFI-20[29] | • Cancer<br>• CFS | • 20 items on a 5 point Likert scale<br>• Higher scores indicate higher fatigue | • Minderhoud et al. (2003[21], 2007[146])<br>• Banovic et al. (2010)[158]<br>• Bol et al. (2010)[159]<br>• Romberg-Camps et al. (2010)[7]<br>• Graff et al. (2011[64], 2013[43])<br>• Lesage et al. (2011)[160]<br>• Bager et al. (2012)[51]<br>• Norton et al. (2015)[34] | CFS, AS, RA, SLE, sarcoidosis, liver disease, cancer, pulmonary hypertension and general population. | • Good sensitivity to change<br>• Five dimensions of fatigue (general, physical activity, reduced activity, reduced motivation and mental fatigue) |

| | | | | | | |
|---|---|---|---|---|---|---|
| 1997 | FACIT-F[161] | Cancer with anaemia | • 13 items on a 5-point Likert scale<br>• Lower scores indicate higher fatigue | • Loftus et al. (2008)[101]<br>• Tinsley et al. (2011)[30]<br>• Cohen et al. (2014)[18]<br>• Villoria et al. (2017)[20] | PA, RA, SLE, iron deficiency anemia, general population and 15 other diseases | • Validated in IBD<br>• Brief and easy to understand. |
| 1998 | Revised PFS[162] | Cancer | • 22 items (originally 76 items) on a 0–10 numeric scale<br>• Higher scores indicate higher fatigue | • Römkens et al. (2011)[147] | Cancer, HIV, liver disease, coronary heart disease | Four dimensions (behavioral/ severity, emotional, physical and cognitive/mood) |
| 2014 | IBD-F scale [33] | IBD | • 35 items on a 5-point Likert scale and a free text section<br>• Higher scores indicate higher impact fatigue | • Norton et al. (2015)[34] | None | Validated and designed to assess fatigue in IBD |

AS, ankylosing spondylitis; CFS, chronic fatigue syndrome; CIS, Checklist Individual Strength; COPD, chronic obstructive pulmonary disease; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FIS, Fatigue Impact Scale; FQ, Fatigue Questionnaire; IBD-F, Inflammatory Bowel Disease Fatigue; IBDQ, Inflammatory Bowel Disease Questionnaire; MAF, Multidimensional Assessment of Fatigue; MFI, Multidimensional Fatigue Inventory; MS, multiple sclerosis; PA, psoriatic arthritis; PFS, Piper Fatigue Scale; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

## PATHOPHYSIOLOGY OF FATIGUE

The exact mechanisms of fatigue have not been robustly defined. The heterogeneity in its presentation, prevalence, and clinical course suggest that the aetiology could be multifactorial with several contributing factors (**Figure 1**). The leading theories that have been proposed to explain fatigue are summarized below.

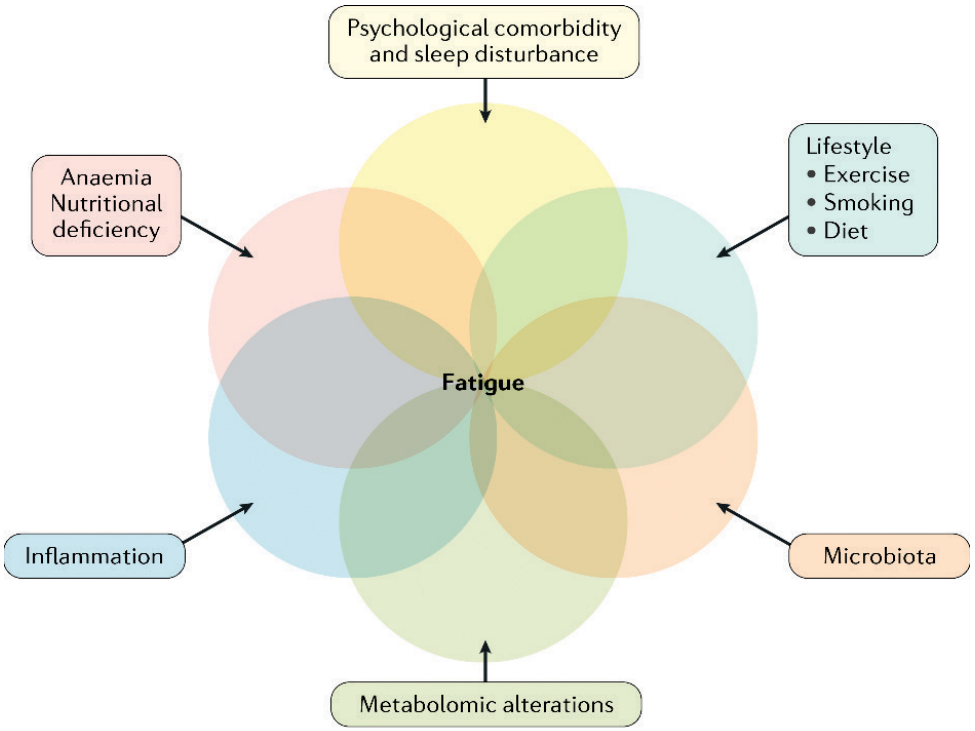


**Figure 1: Proposed multidimensional pathophysiology of fatigue in IBD.** The pathophysiology of fatigue in IBD is thought to be related to multiple contributing factors, including anaemia and nutritional deficiences, psychological comorbidity and sleep disturbance, lifestyle, microbiota and metabolomic alterations, and inflammation.

**Circulating pro-inflammatory state**

One proposed hypothesis is that fatigue, particularly that occurring in the setting of cancer and chronic disease, is due to a subclinical pro-inflammatory statecharacterized by elevated levels of circulating cytokines in the absence of overt symptoms of inflammation. For example, fatigued individuals who survive breast cancer have elevated levels of inflammatory cytokines, such as interleukin-1 receptor (IL-1RA) and soluble tumour necrosis α receptor Type II (sTNF-RII), compared with nonfatigued individuals who survive breast cancer[35]. Another experiment in 50 fatigued patients who survived breast cancer demonstrated that ex vivo monocyte production of soluble IL-6 (sIL-6) and TNF was higher than the production in non-fatigued controls, whereas levels of IL-6 receptor (IL-6R) on the monocyte cell surface were lower, consistent with inflammation-mediated shedding of IL-6R[36]. Soluble IL-6R is thought to stimulate IL-6 expression in a positive feedback loop, and this IL-6/sIL-6R-complex might mediate its effects on the central nervous system, including fatigue[37]. Single nucleotide polymorphisms (SNP) have been recognized in the promoter regions of multiple genes that encode inflammatory cytokines[38]. SNPs in IL-6, TNF and IL-1β were independently associated with higher fatigue scores[39] lending support to the 'cytokine-mediated sickness' hypothesis. These cytokines influence the hypothalamus–pituitary–adrenal axis, leading to increased corticotrophin-releasing hormone and adrenocorticotropic hormone levels and therefore higher cortisol secretion from the adrenal glands[40].

A few studies have examined whether this hypothesis is applicable to fatigue in IBD. Across studies, disease activity is consistently linked to fatigue and an increased prevalence of fatigue is found in those with active inflammation (**Table 1**)[41-43]. However, whether a pro-inflammatory state exists in fatigued patients with quiescent IBD have been examined by three studies that have yielded different results. Vogelaar *et al.* compared stimulated whole blood and serum cytokine profiles in 55 patients with IBD in clinical remission who were fatigued with 29 patients in clinical remission who were not fatigued[44]. They found that median serum levels of IL-12 and IL-10 were increased in those with fatigue, as were stimulated TNF and IFNγ levels. Serum IL-6 levels were lower in those with fatigue than in those who were not fatigued. By contrast, in a cohort of 202 outpatients with clinically inactive disease, Villoria *et al.* found no difference in serum levels of IL-5, IL-8, and IL-12 in patients with fatigue compared with those without fatigue[20]. In a study by Borren *et al.* of 45 patients with quiescent IBD and fatigue and 42 patients with quiescent IBD and no fatigue, those who were fatigued did not have elevated levels of pro-inflammatory cytokines.[45] However, patients with fatigue had lower serum levels of IL-2 (P=0.0160) and granulocyte-monocyte colony stimulating factor (GM-CSF) (p=0.003) when compared those without fatigue. Thus, although active disease is associated with an increased prevalence of fatigue in patients with IBD, it is less clear whether a subclinical circulating proinflammatory state leads to fatigue in patients with clinically quiescent disease.

**Nutritional deficiency and anaemia**

Anaemia is prevalent in patients with IBD: 14–19% of all patients with IBD are anaemic and 20–54% are deficient in iron[46, 47]. Several factors contribute to the anaemia, including intestinal blood loss (visible or microscopic), insufficient iron intake, reduced iron absorption, altered iron metabolism and storage, and suppression of erythropoiesis and iron binding by proinflammatory cytokines[48]. Anaemia has been associated with substantial fatigue in patients with IBD in many studies. In a prospective study of patients with IBD by Jelsness-Jørgensen *et al.*, anaemia was associated with chronic fatigue, measured with the FQ, of at least 6 months duration[49]. A Dutch study of 707 patients in which fatigue was quantified using the MFI-20 questionnaire reported that anaemia was associated with fatigue independently of disease activity in ulcerative colitis but not Crohn's disease[7]. Whether iron deficiency alone in the absence of anaemia can lead to fatigue is less clear. An interesting study of the Manitoba IBD cohort explored the relationship between iron deficiency and fatigue in 230 patients with IBD who were not anaemic[50]. This study found no difference in mean fatigue levels or the number of nonanemic patients with problematic fatigue between those who were iron deficient compared with those who were not iron deficient (ferritin <20mcg/l, 49% versus 45%, respectively). Similar results were reported from a large cross-sectional study of 425 outpatients with IBD in Denmark, Norway and Sweden, in which iron deficiency was not independently associated with fatigue in IBD[51].

Other micronutrient deficiencies are common in IBD, often due to decreased intake or malabsorption owing to luminal inflammation or altered post-surgical anatomy. One common nutritional deficiency is that of vitamin B12, which is absorbed in the distal ileum, the most common site of involvement of Crohn's disease. In a large prospective study of 250 patients with IBD, low serum vitamin B12 levels were noted in 16% of those with Crohn's disease compared with 4% in ulcerative colitis[52]. Vitamin B12 deficiency can lead to weakness and fatigue[53, 54]. Another vitamin deficiency more frequent in IBD than in the general population is that of vitamin D. Several studies suggest[55-58] that vitamin D deficiency is associated with worse disease activity and reduced health-related quality of life in patients with IBD. However, data that vitamin D deficiency is associated with fatigue are inconsistent. Among 405 Norwegian patients with IBD, of whom 48% reported substantial fatigue, mean serum 25-hydroxyvitamin D levels did not differ between those with and without fatigue[59]. By contrast, a small pilot study in 34 patients with quiescent Crohn's disease showed that supplementation with vitamin D improved depression and anxiety symptoms among 57% of those who had clinical depression and/or anxiety at baseline, suggesting an effect on psychological symptoms[60].

**Psychological comorbidity and sleep**

Depression and anxiety commonly accompany IBD, with a lifetime prevalence of 27% and 32% respectively[61]. Several studies have found psychological factors, independent of disease activity and inflammatory markers, to be important determinants of fatigue. A study by Norton *et al.* defined fatigue using the MFI, IBD-F scale and Multidimensional Assessment Fatigue (MAF) scale among 465 patients with IBD. Only depression and low quality of life were consistently associated with fatigue on all scales[34]. Similarly, a study of the population-based Inflammatory Bowel South-Eastern Norway (IBSEN) cohort compared 440 patients with IBD with the Norwegian reference population and identified anxiety, depression and poor sleep quality to be associated with fatigue at 20 years after IBD diagnosis[22]. As with other factors, not all studies have noted an association between mood disorders and fatigue[62]. Symptoms of depression and anxiety can manifest as fatigue and can be difficult to distinguish from IBD-associated fatigue, which confounds interpretation of the association between mood disorders and fatigue.

Sleep disturbance symptoms and their potential contributions to fatigue in IBD have gained increasing attention. Between 47% and 82% of patients with IBD report disrupted sleep, nighttime awakenings and nonrestorative sleep compared with one-third of the general population[63, 64]. In healthy individuals, sleep deprivation is associated with an increase in circulating pro-inflammatory cytokines such as sTNF-α and IL-6[65-67]. Poor sleep quality is also common in those with quiescent IBD (47-51%), and might increase risk of relapse[64, 68]. A positive feedback loop might exist whereby active disease leads to poor sleep that in turn worsens inflammation, with both factors leading to fatigue. In population-based studies from the IBSEN cohort and the Manitoba IBD cohort, sleep disturbance was associated with a four-fold increase in likelihood of fatigue[22, 43, 64]

**Functional changes in the brain**

Studies using MRI in patients with rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis showed that systemic inflammation might influence brain functioning through alterations in metabolic and cerebral perfusion[69-72]. A study using MRI found altered phospholipid metabolism in the occipital cortex in patients with chronic fatigue syndrome compared with healthy control individuals, suggesting that changes in intramembrane signalling might underlie fatigue (**Figure 2**)[73, 74]. A case-report of eicosapentaenoic acid supplementation in a patient with fatigue found that improvement in symptoms was associated with changes on MRI, suggesting that objective imaging-related parameters in the brain could be used to quantify fatigue[73]. The first MRI study in patients with IBD was performed by Van Erp *et al.* who imaged the brain using various magnetic resonance methods in fatigued patients with quiescent Crohn's disease. They found substantial changes in perfusion, neurochemistry and mental status (cognition, mood and quality of life) compared with healthy controls[75]. Patients with fatigue had reduced glutamate and

glutamine concentrations in the brain. Glutamate is an excitatory neurotransmitter that influences several brain functions including mood, whereas glutamine has an important role in energy metabolism. These results suggest that neurochemical and functional correlates in the brain might underlie fatigue in some individuals.

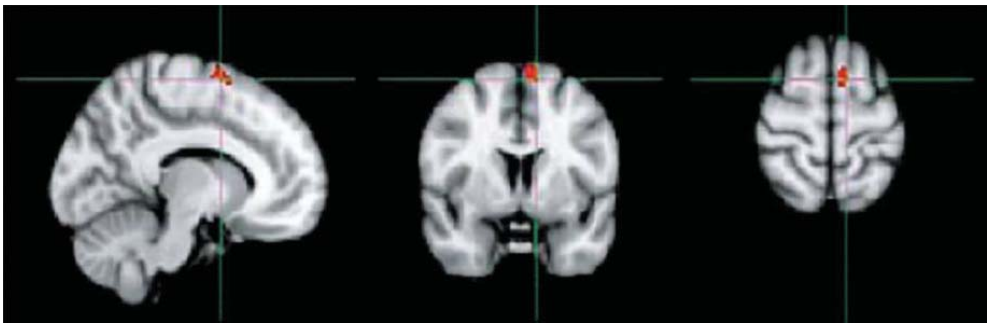

**Figure 2: MRI changes associated with fatigue in IBD.** Patients with quiescent Crohn's disease who are fatigued show changes in perfusion, neurochemistry and mental status compared with healthy control individuals[75]. Voxel-based morphomentry images were taken of patients with Crohn's disease and fatigue. The red colour shows significantly decreased grey matter volume in the left superior frontal gyrus in fatigued patients with Crohn's disease compared with healthy control patients ($P$<0.05). Adapted with permission from REF.[75], Baishideng Publishing Group.

**Altered metabolomic profile**

Mood and fatigue are mediated through central neurotransmitters, primarily serotonin (5-hydroxytryptamine), dopamine and noradrenaline, which require tryptophan and tyrosine for biosynthesis[76]. As branched-chain amino acids (BCAA) compete for the same transporters to pass the blood–brain barrier as tryptophan and tyrosine, altered circulating BCAA levels could potentially influence the synthesis of neurotransmitters in the brain, leading to fatigue. A study in nine ultra-triathletes that focused on metabolic alterations that occur during induced physical fatigue found that BCAA levels in the blood decreased to 22% of pre-exercise levels after exhaustive or sustained exercise, whereas tryptophan levels increased by 74%[77]. Similar results were found in experiments of mental fatigue[78]. Mizuno *et al.* evaluated changes in plasma amino acids in healthy volunteers subjected to fatigue-inducing mental tasks for 8 hours and showed a decrease in BCAA levels after the fatigue session compared with an 8-hour relaxation session[78]. In animal models, fatigued rats demonstrated changes in BCAA metabolism, urea cycle and proline metabolism compared with non-fatigued rats, and fatigued rats had increased levels of systemic oxidative stress[79, 80]. In human studies, administration of BCAA resulted in early recovery from muscle fatigue after exertion[81-83]. However, the applicability of these findings to IBD is uncertain as most studies were performed in athletes during prolonged exercise. A single study examined the contribution of metabolomic alterations in patients with quiescent IBD. In a prospective cohort of 87 patients with Crohn's disease or ulcerative

colitis in remission, our group found substantial differences in the levels of 15 circulating metabolites between fatigued and non-fatigued individuals; for example, those with fatigue had downregulated levels of glycerate and para-aminobenzoate levels, whereas levels of arginine, cytidine and deoxyadenosine were upregulated. Those with fatigue and those without fatigue had key differences in three pathways: pyrimidine metabolism, branched-chain amino acid biosynthesis (valine, leucine and isoleucine) and glyoxylate and dicarboxylate metabolism[45].

**Microbiota changes and the gut-brain axis**

Over the past decade, it has been well established that gut microbial dysbiosis has a central role in the propagation of intestinal inflammation in IBD[84]. The gut microbiota in IBD is characterized by reduced bacterial diversity, a reduction in the abundance of beneficial bacterial populations, such as *Bacteroides fragilis, Faecalibacterium prausnitzii* and *Roseburia*, and increased numbers of proinflammatory species, such as adhesive invasive Escherichia coli and other Enterobacteriaceae[85]. Emerging evidence suggests that there is a bidirectional communication system between the central nervous system and the gastrointestinal tract — the gut–brain axis — and that dysbiosis might be involved in the development of fatigue and other psychological symptoms[86]. The gut microbiota might mediate its effect through mechanisms including direct interaction with the immune system, altering the hypothalamus–pituitary–adrenal axis and altering the serum metabolomic profile via microbial mediators or through its effect on breakdown of dietary components (**Figure 3**). Support for this hypothesis comes from a study of 50 patients with CFS, in which those with CFS had reduced stool bacterial diversity compared with healthy control individuals[87]. In addition, those with CFS showed depletion of *Firmicutes* (27% of total phyla in CFS versus 30% in healthy control individuals) and increased abundance of *Alistipes* and *Bacteroides* (64.9% of total phyla in CFS versus 63.4% in healthy control individuals), which, intriguingly, are also observed in chronic IBD[87].

The intestinal epithelium functions as a barrier against lipopolysaccharide (LPS) translocation, which can stimulate innate immune responses. As such, increased serum concentrations of immunoglobulin A (IgA) and IgM against lipopolysaccharide from enterobacteria might suggest disruption of this mucosal barrier and increased gut permeability. These findings have been observed in patients with CFS compared with healthy individuals, and serum IgA levels in those with CFS were associated with fatigue severity[88]. Germ-free mice also have exaggerated hypothalamus–pituitary–adrenal axis responses to stress, an effect partially ameliorated in specific pathogen-free mice[89, 90]. Further support for the role of the gut-brain axis in mediating fatigue comes from interventional studies in animal models that demonstrate reduced anxiety and depressive behaviours with use of probiotics[91-93].

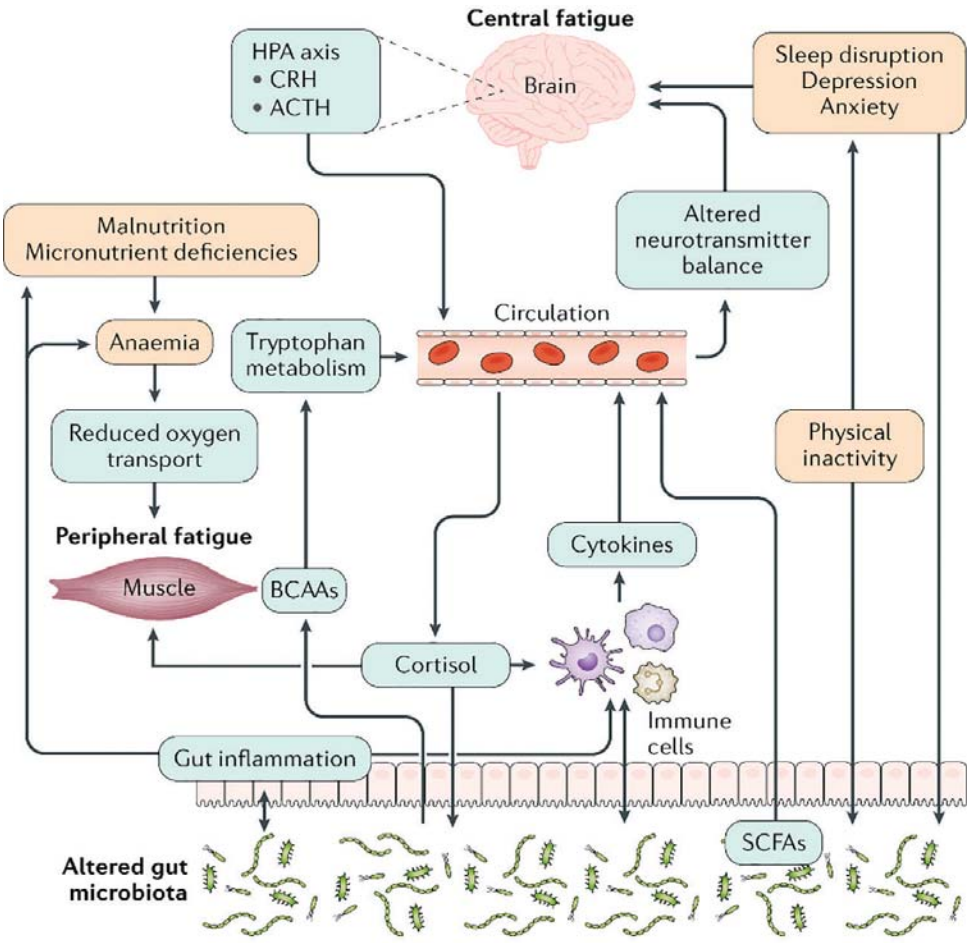


**Figure 3: Bidirectional communication between the gut microbiota and the brain.** Several direct and indirect pathways exist through which the gut microbiome can interact with the gut-brain axis and might alter fatigue in IBD. Key routes include immune pathways (cytokines), metabolomic pathways (tryptophan, branched-chain amino acids (BCAAs) and short-chain fatty acids (SCFAs)) and endocrine (cortisol) pathways. Conversely, the central nervous system might affect the microbiota through similar mechanisms as in mood disorders. Cytokines influence the hypothalamic-pituitary-adrenal (HPA) axis, leading to increased corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) levels and higher cortisol secretion from the adrenal glands, which in turn influences the microbiota.

### Muscle dysfunction and physical inactivity

Patients with quiescent Crohn's disease have reduced muscle mass compared with healthy control individuals[94]. Reduced muscle mass and muscle strength in healthy elderly individuals are associated with increased levels of circulating cytokines, especially IL-6 and TNF, which might mediate fatigue[95]. Reduced muscle mass in IBD might lead to reduced physical activity, which in turn has a negative effect on physical fitness, resulting

in fatigue[76, 94, 96, 97]. A study in 10 fatigued patients with quiescent IBD found that those with fatigue had impaired physical fitness and physical activity compared with those without fatigue[94]. Physical activity itself might also have an anti-inflammatory effect that could be explained by muscle-derived peptides known as myokines[98]. Myokines, such as IL-15, are released during contraction of skeletal muscles and can induce a direct anti-inflammatory effect[99]. Thus, through a potential pro-inflammatory role as well as an inverse association with muscle mass, physical inactivity might contribute to fatigue in patients with IBD.

## TREATMENT OF FATIGUE

The lack of clear understanding of the pathophysiologic basis of fatigue in IBD limits effective management. Patients frequently perceived that symptoms of fatigue are poorly addressed or managed in medical consultations[9]. Owing to its complex, multifactorial pathophysiology, effective treatment of IBD-related fatigue likely needs to be multidisciplinary (**Figure 4**). The initial assessment of the patient presenting with fatigue includes a comprehensive medical history and updated cancer screening to identify comorbidities that could suggest a specific underlying cause for fatigue. Secondly, key nutrient deficiencies such as Vitamin B12, Vitamin D and iron should be evaluated for and corrected by supplementation. Third, IBD with quiescent disease are in risk of relapse, especially if their IBD is not adequately treated or if they lost response to therapy. Therefore, clinical active symptoms and inflammatory markers such as CRP, ESR and fecal Calprotectin should be checked and if elevated, IBD therapy needs to be optimized. And last, psychologic comorbidities and sleep disorders can contribute to fatigue. Pharmacologic or behavioral interventions or consultation of an expert should be arranged if there is presence of depressive, anxious or sleep disturbance symptoms that could contribute to fatigue. Some patients present with persistent fatigue, but show no abnormalities on physical and mental examination or laboratory tests. In these cases, research studies suggest a potential role for psychologic interventions such as CBT and SFT, pharmacologic interventions such as psychostimulants and microbiome directed therapy and increased physical activity might alleviate fatigue symptoms in those with persistent fatigue symptoms. The evidence behind each of these interventions is discussed in detail below.

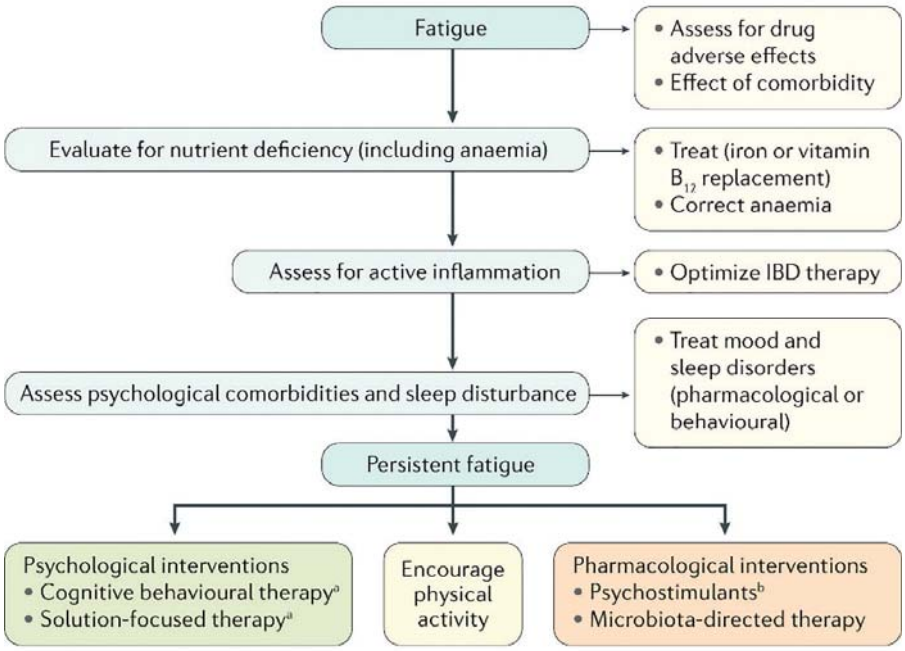


**Figure 4: Proposed algorithm for multidisciplinary management of fatigue in IBD.** The management of fatigue in patients with IBD is multidimensional, requiring sequential assessment for contributions from active inflammation and nutritional deficiency. If neither of these factors has a role, it is important to evaluate for psychological comorbidities such as depression, anxiety and sleep disorders. Finally, in the absence of any of the above parameters, research suggests a potential role for psychological interventions such as cognitive behavioural therapy and solution-focused therapy, pharmacological interventions such as psychostimulants and microbiome-directed therapy, and increased physical activity might alleviate fatigue symptoms in those with persistent fatigue symptoms. This algorithm is the opinion of the authors. [a]Greater than one study available in OBD. [b]No studies available in IBD.

### Therapy for IBD

Given the association between increased disease activity and fatigue, it is reasonable to surmise that immunomodulator or biological therapies that reduce systemic inflammation ameliorate fatigue in patients with IBD. In a placebo-controlled study of 83 patients with Crohn's disease, treatment with the anti-TNF agent infliximab was associated with reduced fatigue among those with moderate-to-severe active disease100. Infliximab reduced depression scores with 46% compared to 14% in the placebo group and improved the quality of life, with a 36-point Inflammatory Bowel Disease Questionnaire (IBDQ) score reduction in the infliximab group compared with a 5-point reduction in the placebo group after 4 weeks of treatment. Similar results for adalimumab, another anti-TNF drug, were demonstrated by Loftus *et al.*. In this study, fatigue scores as measured by the FACIT-F dramatically improved after adalimumab induction (23.0 versus 35.6) and continued to improve through week 56 (23.5 versus 36.8, $P<0.001$)[101]. No data exist on whether biologics improve fatigue symptoms in those who do not have clinically active bowel disease and

fatigue is the dominant symptom. In addition, many patients in remission on biological therapy also report persistent fatigue. A prospective cohort study in outpatients with IBD showed that patients receiving TNF-inhibitor therapy were more likely to experience fatigue than patients receiving immunosuppressant therapy (fatigue score 32 versus 38, $P$=0.003)[20].

**Other pharmacological treatments**

Most pharmacological treatments for fatigue are at investigational stages with evidence only from small studies. Psychostimulants such as methylphenidate and dexamethasone have shown promising results in patients with severe cancer-related fatigue[102-105]. Methylphenidate acts by increasing dopamine levels in the central nervous system[105]. Previous studies assessing the role of methylphenidate in cancer-related fatigue had small sample sizes ($n$ = 10-112) and short follow-up times (4-12 weeks). Two placebo-controlled trials failed to show any benefit of methylphenidate over placebo, whereas a small pilot study from Spain suggested that methylphenidate ameliorated the symptom of weakness in patients with breast cancer[106-108]. A meta-analysis by Gong et al that included 498 patients identified a therapeutic effect of methylphenidate on cancer-related fatigue, especially with longer treatment duration defined as ≥ 4 weeks[105]. There was no effect of methylphenidate on depression or cognition associated with cancer-related fatigue.

Dexamethasone is a steroid widely used for a variety of indications including treatment of chemotherapy-related emesis. A placebo-controlled trial randomly assigned 84 patients with advanced cancer and more than three cancer-related symptoms to receive either dexamethasone 4mg twice daily or placebo for 2 weeks. The researchers found an improvement in fatigue as measured by the FACIT-F scale (9 versus 3.1, $P$=0.008)[109, 110]. In addition, quality of life, physical well-being and physical distress improved. Similar to the methylphenidate study, the duration of treatment was short (14 days), and the applicability of either treatment in non-cancer-related fatigue and in IBD has not been established[109].

Several studies in treated patients with depression and residual fatigue[111], fatigued patients after stroke[112] and those with CFS[113] have assessed the role for antidepressants in the treatment of fatigue. A placebo-controlled trial conducted by Choi-Kwon *et al.*[114] found that antidepressants were not efficacious in patients with post-stroke fatigue, and the same conclusion was reached in a review by Marin *et al.* and in a systematic review of ten studies in fibromyalgia patients showed also no benefit of serotonin and noradrenaline reuptake inhibitors for reducing fatigue[111]. An earlier study that assessed the role of fluoxetine in patients with CFS found no beneficial effect of the drug on any characteristic of CFS[113]. Up to 30% of patients with IBD are prescribed antidepressants[115]. A small placebo-controlled study in 26 patients with quiescent Crohn's disease examined the addition of fluoxetine to standard therapy for Crohn's disease for 12 months and followed quality of

life and mental health[116]. No improvement in psychological, social, quality of life, anxiety or depressive symptoms was found in the treatment group compared with the placebo group. Interestingly, psychostimulants are a possible alternative to antidepressant therapy and reduce fatigue and promote alertness and wakefulness. Improved fatigue symptoms have been reported in 36 patients who survived stroke with non-resolving fatigue after daily modafinil therapy compared with patients receiving placebo ($P<0.001$)[117]. Thus, overall, no published data to support the efficacy of antidepressants on fatigue; in fact, the evidence suggests a lack of efficacy in this setting.

**Psychological interventions**

Various psychological interventions have been investigated in IBD, most with alleviation of depression and anxiety as the end point, although a few studies have specifically examined effects on fatigue. In CFS, CBT was more effective at alleviating fatigue than conventional treatment such as pharmacological treatment, supportive listening, relaxation and flexibility therapies[118, 119]. However, in IBD the effects are more mixed. In a systematic review of 18 studies by McCombie *et al.*, psychotherapy in IBD showed promising results in reducing fatigue, pain and disease relapse[120], but weaker effects were noted on depression, anxiety and quality of life. A small pilot study 29 patients with quiescent IBD studied the effect of two different psychological therapies designed to manage fatigue. Twenty-nine patients were randomly assigned to problem solving therapy (PST), solution focused therapy (SFT) or a control group that received standard medical care and no additional psychological interventions[121]. PST aims to improve the ability of the patient to handle daily stressful problems induced by their IBD, whereas SFT is a solution-based approach that focuses on the coping capabilities of patients, rather than concentrating on their problems. Those in the intervention groups had improved fatigue and quality of life scores compared with those in the control group. SFT had the greatest benefit, with 86% of patients reporting lower fatigue scores from baseline to follow up compared with 60% in the PST group and 46% with usual care. However, the greater number of sessions in PST than in SFT might have resulted in a higher dropout rate, thereby mitigating its benefits. The same group validated their results for SFT in a randomized controlled trial. Ninety-eight patients were randomly assigned to SFT or usual care for 3 months and were followed for a further 6 months[122]. Reductions in fatigue were greater in the SFT group than in the usual care group at 3 months (39% for SFT versus 18% for usual care), although at 9 months, there was no longer any statistically significant difference between the groups, suggesting a lack of long-term benefit.

**Diet and probiotics**

As described earlier, given the potential role for the microbiome in mediating fatigue and psychological symptoms in IBD, interventions aimed at modifying the gut microbial composition through either diet or probiotics might be beneficial in ameliorating fatigue.

Diets high in antioxidants and micronutrients might counter a pro-inflammatory state and improve fatigue. Under this hypothesis, a three-month randomized clinical pilot trial of a fatigue reduction diet (high in fruits, whole foods, vegetables and omega-3 rich foods) in individuals with fatigue who had survived breast cancer found that the intervention group had improved sleep quality and fatigue compared with the control group that continued normal diet and received eight general health attention sessions[123]. However, diet has not been examined in the context of fatigue in IBD. Although several elimination diets such as the specific carbohydrate diet, anti-inflammatory diet, and exclusive enteral nutrition, have been proposed for treatment of active IBD, none of these has been studied for their effects on fatigue.

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host[124]. In patients with CFS, probiotic therapy with strains of *Lactobacilli* and *Bifidobacteria* improves neurocognitive function and anxiety[125, 126]. In CFS-induced rats, probiotic supplementation with *Lactobacillus acidophilus* decreased post-swim fatigue time compared with nontreated rats. Reduced oxido-nitrosative stress in the brain and attenuated TNF levels in serum were also noted[127]. Rao *et al.* gave 19 patients with CFS *Lactobacillus casei* for two months to and compared the microbiome and anxiety symptoms with 12 patients receiving placebo. Treatment with the probiotic reduced anxiety and increased the abundance of *Lactobacillus* and *Bifidobacteria* species in the gut flora. *Lactobacillus* and *Bifidobacterium* produce inhibitory neurotransmitters such as acetylcholine and GABA[128, 129]. A benefit of short-term treatment was noted by Sullivan *et al.* in a cohort of patients with CFS; improved fatigue levels were found after only 2 weeks of probiotic supplementation with strains of *Lactobacillus, L. acidophilus* and *Bifidobacterium lactis* (Cultura Dofilus Natural Yogurt, Arla Foods, Stockholm, Sweden)[126]. Furthermore, beneficial effects of probiotic therapy have also been seen in depressive disorders. For instance, Steenbergen *et al.* observed a reduction of negative associated with sad mood (mean revised Leiden Index of Depression Sensitivity score 42.75 pre-intervention versus 33.35 post-intervention after intake of a probiotic mixture containing 9 bacterial strains (Ecologic® Barrier, Winclove, Amsterdam, The Netherlands) for 4 weeks compared with baseline)[130]. A meta-analysis of five randomized controlled trials calculated a reduced depression scale score (mean difference -0.30, 95% CI -0.51 to -0.09) after probiotic therapy, both in healthy individuals and in those with major depressive disorder[131]. These novel insights indicate that modification of the microbiome with probiotics can offer a promising approach to reduce fatigue symptoms.

**Micronutrient Supplementation**

Micronutrient deficiencies can induce fatigue symptoms, and various clinical trials have shown a beneficial effect of supplementation in ameliorating fatigue symptoms. A randomized placebo-controlled trial published in 2018 explored the effect of oral vitamin

B12 supplementation on fatigue in patients with IBD for 8 weeks[132] and found no beneficial clinical effect. Supplementation with vitamin D has been shown in some small studies of patients with IBD to decrease disease activity and improve quality of life scores[133-135]. However, overall only a few studies have assessed the role of vitamin D supplementation on fatigue in IBD. Promising results for vitamin D supplementation were seen in a small pilot study in 40 patients with juvenile-onset SLE, which showed improvement of fatigue scores ($P$<0.05) after 24 weeks of supplementation with oral cholecalciferol (vitamin D3) at a dose of 50,000 IU per week[136]. There are no studies published that examine the role of iron supplementation primarily for the treatment of fatigue in IBD. Iron supplementation with oral ferrous sulfate or intravenous iron sucrose in 21 patients with IBD who were anaemic improved quality of life after 6 months of treatment in 23% of patients compared with 29 anaemic patients with IBD without iron supplementation[137]. Interestingly, iron supplementation in non-anaemic women with unexplained fatigue in a primary care setting also resulted in a 29% reduction of fatigue compared with 13% in the placebo group ($P$=0.004)[138].

**Physical training**

Physical exercise can decrease inflammatory cytokine activity levels and, through these effects potentially ameliorate fatigue[95]. In an experimental study, rats with colitis induced by 2,4,6-trinitrobenzenesulfonic acid (TNBS) had accelerated healing of colitis when forced to run on a treadmill[139]. The benefits of physical activity on fatigue have been recognized in patients with cancer[139, 140] and CFS[141]. A 15 session multidimensional rehabilitation programme, consisted of individual exercise, sports, psychoeducation and information, in 72 patients who had survived cancer found that the programme reduced fatigue, and that changes in fatigue correlated with improvement in physical parameters140 . A similar 12-week exercise programme with counseling sessions was conducted in individuals who received a liver transplant 142 and substantially reduced (by 22-53%) severe fatigue symptoms. Even in healthy adults, 6 weeks of low-intensity exercise improved persistent fatigue symptoms[143] . Few studies have been performed to assess the effectiveness of exercise in patients with IBD. A small case series ($n$=11) by Nathan et al reported that physical activity had beneficial effects on mood, fatigue, weight maintenance and osteoporosis[144]. In a large survey among patients with IBD in the UK, 72% of 918 respondents reported that exercising made them feel better, and 12% reported boosted energy levels[145].

## CONCLUSIONS

Despite the prevalence and effect of fatigue in patients with IBD, much remains unknown. Fundamental basic research into the pathophysiological basis of fatigue in chronic inflammation is urgently needed. The multidimensionality of contributing factors could imply that the mechanism of fatigue is not uniform in all patients, and that there might

be different subtypes of fatigue in the population with IBD. Some patients with fatigue might respond well to microbiome-directed therapies, whereas others might respond to exercise-based interventions or behavioral modification. During the past decade, much of IBD research has focused on developing new therapies targeting immunological mechanisms of disease and evaluating their effects on disease activity; however, one of the most frequently reported concerns of patients with IBD is fatigue. Research on interventions for the treatment of fatigue in IBD is scarce, with the exception of behavioral modifications. There is an important need for prospective clinical trials of various pharmacological and non-pharmacological interventions in addition to comparative effectiveness studies. In parallel, education of both patients and healthcare providers about the prevalence and burden of fatigue is essential to ensure efforts to address this disabling and often underreported symptom.

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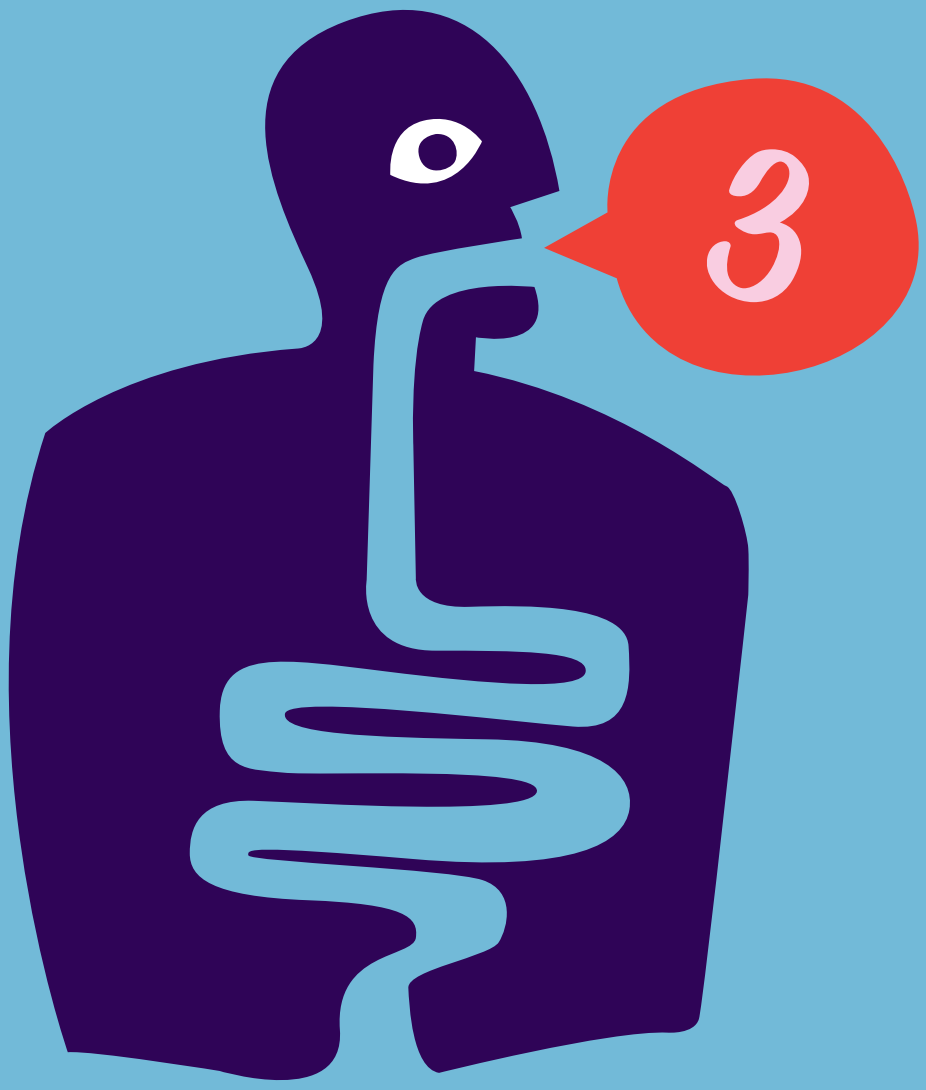
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# CHAPTER 3

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## Longitudinal trajectory of fatigue with initiation of biologic therapy in inflammatory bowel diseases: A prospective cohort study

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## ABSTRACT

**Backgrounds and aims:**

Fatigue is prevalent in patients with inflammatory bowel diseases (IBD). Biologic therapy is effective in achieving symptomatic and endoscopic remission, but its impact on fatigue is less well established. Our aim is to define the longitudinal trajectory of fatigue over 1 year in patients initiating biologic therapy.

**Methods:**

This prospective cohort enrolled patients diagnosed with Crohn's Disease (CD) or Ulcerative Colitis (UC) initiating biologic therapy with infliximab, adalimumab, ustekinumab, or vedolizumab. Fatigue was quantified using the 7-point fatigue question in the Short Inflammatory Bowel Disease Questionnaire (SIBDQ). A score of $\leq 4$ for this question was used to define fatigue. Multivariable regression models adjusting for relevant confounders examined the independent association between attaining clinical remission and resolution of fatigue.

**Results:**

Our study included 326 patients (206 CD, 120 UC) initiating biologic therapy (144 anti-TNF, 129 vedolizumab, 63 ustekinumab). A total of 61% of the included patients reported significant fatigue at baseline. This was associated with female gender, depressive symptoms, active disease and disturbed sleep ($p < 0.001$). Among the 198 patients who were fatigued at therapy initiation, 86 (70%), 55 (63%), and 44 (61%) remained fatigued at week 14, 30, and 54 respectively. At each of these time points, achieving clinical remission was associated with lower likelihood of persistent fatigue. However, despite achieving remission, 35%, 30%, and 28% of patients experienced persistent fatigue at weeks 14, 30, and 54 respectively.

**Conclusion:**

Fatigue is common in IBD. Though biologic therapy improves fatigue parallel symptomatic improvement, a significant proportion continue to experience persistent fatigue up to 1 year.

## INTRODUCTION

Fatigue is common in patients with inflammatory bowel disease (IBD: Crohn's disease (CD), ulcerative colitis (UC)). It has a significant negative impact on health-related quality of life and functioning[1, 2] and patients perceive it to be among the four most important symptoms with a burden comparable to that of having a stoma[3]. While it is likely multifactorial with contributions from inflammation, psychologic comorbidity, disturbed sleep, anemia, and nutritional deficiencies, much remains to be understood about its pathogenesis[4]. In cross-sectional surveys, up to 80% of patients with active disease report significant fatigue[5, 6].

Over the past two decades, biologic therapies targeting different immunologic pathways have improved the ability to achieve clinical and endoscopic remission, and reduced IBD-related surgery and hospitalization[7-10]. Apart from its effect on gut inflammation, evidence supports the efficacy of these therapies on extra-intestinal symptoms such as arthritis[11-13]. Analyses of clinical trials and observational cohorts also demonstrated that biologic therapies are effective in improving overall health-related quality of life[14, 15], mood, and sleep[16]. However, little is known about the impact of initiating biologic therapies on fatigue in patients with IBD. Specifically, given the multi-dimensional origin of fatigue, whether clinical response to therapy is associated with a simultaneous improvement in fatigue is unknown.

Using parallel prospective cohorts of patients with CD and UC, we aimed to define the longitudinal trajectory of fatigue over 1 year in patients initiating treatment with tumor necrosis factor α antagonist (anti-TNF), vedolizumab (VDZ), or ustekinumab (UST). We then compared the relative improvement in fatigue across the different therapeutic classes.

## METHODS

### Study Cohort

This prospective cohort included patients from the Prospective Registry for IBD Study[16, 17] at Massachusetts General Hospital (MGH) Crohn's and Colitis center. This is a tertiary referral IBD center serving over 4 million residents in Greater Boston and surrounding New England. Between December 2014 and June 2018, patients with moderate to severe CD or UC initiating therapy with infliximab (IFX), adalimumab (ADA), VDZ, or UST were approached for participation. Upon providing consent, patients completed an enrollment interview with a trained research coordinator where demographics, disease, and treatment history including current and past medications were noted and confirmed by medical record review.

All patients commenced outpatient biologic therapy at the standard induction dosing approved by the US Food and Drug Administration. Study assessments were obtained at weeks 0, 14, 30 and 54. At these time points, disease activity was assessed using the Harvey Bradshaw index (HBI)[18] in CD and simple clinical colitis activity index (SCCAI)[19] in UC, both validated and widely used in clinical practice[20, 21]. Laboratory inflammatory markers were noted if available (C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR)). Recruited patients additionally completed questionnaires assessing fatigue, sleep, and mood as outlined below. Fecal calprotectin was not used in routine clinical care during the study period.

**Assessment and validation of fatigue**

All patients enrolled in the cohort completed the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) at baseline and each of the above time points[22]. The SIBDQ is a 10-item questionnaire, where each response is scored on a Likert scale. The total score ranges from 10 to 70 with lower scores representing worse quality of life. Within the SIBDQ, presence of fatigue is ascertained through the question "How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks?" Patients have 7 options to answer, ranging from 1 "All the time" to 7 "None of the time".

We validated the accuracy of this question to discern fatigue in an independent cohort of patients with CD and UC[23, 24]. This validation cohort consisted of patients seeking care at the MGH Crohn's and Colitis center who were in clinical remission (HBI $\leq$ 4 or SCCAI $\leq$ 2) and had no evidence of inflammatory activity on colonoscopy and laboratory testing. Patients enrolled in this single visit cohort simultaneously completed, in addition to the SIBDQ, the multidimensional fatigue inventory (MFI) and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) for quantifying fatigue. The FACIT-F consists of 13 statements that are scored on a 5-point Likert scale. The total score ranges from 0 to 52, with low scores reflecting greater fatigue, whereas high scores indicate no fatigue symptoms. The FACIT-F was initially designed for patients with cancer[25], but has been validated[26] for use in IBD. A cut-off score of 43 or less on the FACIT-F has been shown to be the best in distinguishing anemia related fatigue in patients with cancer from those in the general population[27]. The MFI is a 20-item self-assessment instrument that covers the domains of general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity[28]. Each domain comprises four statements with scores ranging from 4 to 20 per domain. It is one of the most frequently used instruments for assessment of fatigue in patients with IBD.

**Covariates of Interest**

Disease related covariates of interest included disease extent (in UC), location and behavior (in CD) according to the Montreal classification[29]. We noted information on duration of

disease prior to initiation of biologic therapy and use of combination immunomodulator therapy with methotrexate or thiopurines (azathioprine, mercaptopurine). Information regarding sleep and mood symptoms were assessed by using the 8-item short-form questionnaires of the National Institute of Health Patient-Reported Outcome Measurement Information System for sleep disturbance, depression, and anxiety[30-32]. This yields a continuous score which is translated to a T-score. In our study, patients with a T-score above 50 were considered as having disturbed sleep, significant depressive, or anxiety symptoms.

**Statistical Analysis**

Statistical analysis was performed using Stata 13.1 (StataCorp, College Station, TX). First, we validated the ability of the question on fatigue in SIBDQ to accurately discern those with and without fatigue. To do so, we compared the Likert scale value for fatigue among those with FACIT-F scores > 43 (fatigue) to those with lower scores (no fatigue) using the Student's t test. The correlations between the SIBDQ and FACIT-F and MFI general domain scores were assessed using Spearman's correlation coefficients. We examined the performance of different Likert Scale cut-offs for fatigue in predicting FACIT-F $\leq$ 43 by comparing the area under receiver operating characteristics curves (AUC). AUC values $\geq$ 0.80 are considered good, and values $\geq$0.90 are considered excellent.

In the prospective biologic cohorts, continuous variables were summarized using means and standard deviations and compared using the *t* test if normally distributed or the Mann-Whitney-*U* test when appropriate. Categorical variables are shown as proportions and compared using the Chi-square test with the Fisher's exact test when needed. Variables impacting fatigue at baseline were defined by performing a univariate analysis with demographics, disease characteristics and sleep and mental health parameters. We compared the proportion of patients who were fatigued at baseline and at each of the following disease activity time points. Specifically, among those who were fatigued at baseline, we examined the resolution of fatigue at weeks 14, 30, and 54 by using the paired t-test. We compared changes in proportions of fatigue between baseline and week 14 among those who were in clinical remission (HBI $\leq$ 4 or SCCAI $\leq$ 2) at week 14 compared to those who had persistent disease activity. Multivariable regression models adjusting for variables significant in the univariate analysis at $p < 0.1$ examined the independent association between attaining clinical remission and resolution of fatigue. A two-sided p-value < 0.05 in the multivariable model indicated independent statistical significance. This study was approved by the Institutional Review Board of Partners Healthcare.

## RESULTS

### Validation of SIBDQ fatigue score

First, we validated the accuracy of the single question on fatigue in the SIBDQ in a cohort of 217 patients with IBD (127 CD, 90 UC) with a mean age of 41 years (**Supplemental Table 1)**. Just under half (47%) were women. The mean MFI general for the total cohort was 11 (± 4.2) and the mean SIBDQ was 56 (± 9.1). The mean Likert score for fatigue on the SIBDQ was 4 (±1.7). The mean FACIT-F score for the total cohort was 39 (± 10.8); 56% had FACIT-F scores $\leq$ 43, meeting our definition of fatigue. The SIBDQ fatigue question demonstrated strong correlation with FACIT-F (rho=0.85, p <0.001) and MFI general domains (rho=-0.81, p <0.001) (**Supplemental Table 2**). The magnitude of correlation between the SIBDQ fatigue question was similar to that between the two validated questionnaires (rho=-0.84, p <0.001) supporting the validity of its use for assessing fatigue in our prospective cohort. The AUC (**Supplemental Figure 1**) was 0.93 confirming that the SIBDQ fatigue question accurately identifies fatigue. The SIBDQ score cut-off $\leq$ 4 had good sensitivity (82.6%) and specificity (87.5%) for discriminating fatigue in our validation cohort and was used for further analysis.

### Prospective Biologic Cohort

The prospective study included 326 patients (206 CD, 120 UC) initiating biologic therapy with a mean age of 40.3 years. Just over half were women (52%). A total of 318 patients provided SIBDQ-scores at baseline (122 anti-TNF, 126 vedolizumab, 70 ustekinumab). Two-thirds of the patients (64%) reported fatigue at baseline (SIBDQ fatigue score $\leq$ 4) at baseline. Patients with fatigue at baseline were similar to those without fatigue in age, disease characteristics and medical history but were more likely to be women (**Table 1**). Those reporting significant fatigue also had higher clinical disease activity scores than those without fatigue (CD: HBI 8 vs 4; UC: SCCAI 6 vs 4) (p<0.001) and higher ESR (28.5 mm/h vs 16.6 mm/h respectively).

**Table 1: Baseline Characteristics of the Biologic therapy study cohort.**

| Characteristic | Fatigue at baseline (n=198) | No fatigue at baseline(n=110) | p-value |
|---|---|---|---|
| Female, n(%) | 115 (58.1) | 42 (38.2) | 0.001 |
| Age, mean (SD) | 39.9 + 14.7 | 40.3 + 14.6 | 0.851 |
| IBD type | | | 0.159 |
| Crohn's disease, n(%) | 119 (60.1) | 75 (68.2) | |
| Ulcerative colitis, n(%) | 79 (39.9) | 35 (31.8) | |
| Disease duration, mean (SD) | 11.3 + 9.5 | 12.5 + 11.7 | 0.340 |
| CD location | | | 0.156 |
| CD Ileitis, n(%) | 15 (15.0) | 20 (29.9) | |
| CD Ileocolitis, n(%) | 54 (54.0) | 33 (49.3) | |
| CD Colitis, n(%) | 31 (31.0) | 14 (20.9) | |
| UC extent | | | 0.685 |
| UC Proctitis, n(%) | 10 (13.7) | 3 (8.3) | |
| UC Left sided colitis, n(%) | 23 (31.5) | 11 (30.6) | |
| UC Pancolitis, n(%) | 40 (54.8) | 22 (61.1) | |
| Disease behavior | | | 0.180 |
| Inflammatory, n(%) | 57 (53.3) | 30 (40.5) | |
| Stricturing, n(%) | 15 (14.0) | 35 (32.7) | |
| Penetrating, n(%) | 35 (32.7) | 22 (31.9) | |
| Perianal disease | 38 (19.2) | 17 (15.5) | 0.412 |
| Disease activity, mean (SD) | | | |
| HBI* | 8.1 + 6.0 | 3.5 + 3.2 | <0.001 |
| SCCAI** | 6.1 + 3.1 | 3.8 + 2.4 | <0.001 |
| Clinical remission (HBI≤4 or SCCAI≤2), n(%) | 45 (23.9) | 55 (55.0) | <0.001 |
| Laboratory results, mean (SD) | | | |
| C-Reactive protein (mg/L) | 18.9 + 30.3 | 11.4 + 27.1 | 0.084 |
| Erythrocyte Sedimentation Rate (mm/h) | 28.5 + 29.6 | 16.6 + 18.4 | 0.003 |
| Past history | | | |
| Prior biologic therapy, n(%) | 130 (65.7) | 68 (61.8) | 0.543 |
| Prior surgery, n(%) | 32 (16.2) | 23 (20.9) | 0.297 |
| Immunomodulator, n(%) | 61 (30.8) | 38 (34.6) | 0.501 |
| Steroids, n(%) | 89 (45.2) | 45 (40.9) | 0.470 |
| Biologic therapy | | | 0.132 |
| Infliximab, n(%) | 28 (14.1) | 12 (10.9) | |
| Adalimumab, n(%) | 44 (22.2) | 38 (34.6) | |
| Ustekinumab, n(%) | 50 (20.2) | 20 (18.2) | |
| Vedolizumab, n(%) | 86 (43.4) | 40 (36.4) | |
| Sleep disturbance†, n(%) | 92 (72.4) | 22 (29.0) | <0.001 |
| Depressive symptoms†, n(%) | 85 (68.0) | 23 (30.3) | <0.001 |
| Anxiety symptoms†, n(%) | 93 (74.4) | 32 (41.6) | <0.001 |

* HBI: Harvey Bradshaw Index for Crohn's Disease
** SCCAI: Simple Clinical Colitis Activity Index for Ulcerative colitis
† Sleep disturbance, depressive and anxiety symptoms: patients with a T-score above 50 on the correlating NIH PROMIS questionnaire were considered as having disturbed sleep, significant depressive, or anxiety symptoms.

**Longitudinal follow-up of fatigue**

A total of 203, 150, and 122 patients provided data on fatigue at week 14, week 30 and week 54, respectively. Lower follow up at week 54 was not due to loss of follow up but rather due to drop off because patients stopped certain biologic therapy. Fatigue, defined as a SIBDQ fatigue score $\leq$ 4, was seen in 54%, 49% and 45% of the patients on week 14, 30 and 54 respectively (**Figure 1**). The mean SIBDQ fatigue score demonstrated an improvement in 193 patients who completed both fatigue SIBDQ scores at baseline and week 14, improving from 3.8 $\pm$ 1.8 to 4.2 $\pm$ 1.8, p<0.001). The mean fatigue SIBDQ score continued to improve at week 30 (4.6 $\pm$ 1.7, p<0.001) and week 54 (4.6 $\pm$ 1.7, p<0.001) suggesting benefit could be expected up to 1 year after treatment (**Figure 1**).

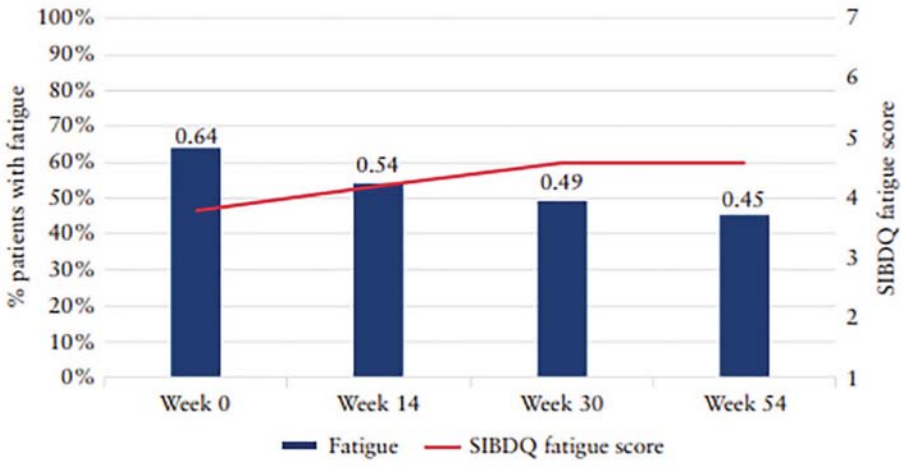


**Figure 1: Persistence of fatigue in patients with inflammatory bowel disease initiating therapy with biologic agents.** * Fatigue was defined as Short Inflammatory Bowel Disease Questionnaire (SIBDQ) fatigue score of ≤4.

Among the 198 patients reporting fatigue at baseline, 86 (70%), 55 (63%), and 44 (61%) remained fatigued at week 14, 30, and 54 respectively. Persistence of fatigue correlated with presence of continued symptoms and elevated inflammatory markers (comparing CRP of persistent fatigue to those with no fatigue: 11.0 vs 8.2 mg/L at week 14, 9.2 vs 7.5 mg/L at week 30 and 9.0 vs 7.1 mg/L at week 54). Over two-thirds of patients reporting fatigue reported active symptoms at each of those time points (68% at week 14, 69% at week 30 and 69% at week 54). Conversely, at each of these time points, achieving clinical remission was associated with a significant reduction in likelihood of fatigue (**Table 2**). Despite achieving clinical remission and normal CRP levels with biologic therapy initiation, 35%, 30%, and 28% of patients continued to be fatigued at weeks 14, 30, and 54 respectively (**Figure 2**). Age, gender, type of IBD or mood symptoms at baseline had

no influence on persistent fatigue symptoms after biologic therapy initiation. Sleep disturbance symptoms at baseline had almost a 10-fold risk to have persistent fatigue symptoms at week 14 (OR 9.7, 95% CI 2.10 – 45.09, p=0.004) but this effect diminished over time with a 7-fold increased risk at week 30 (OR 6.5, 95% CI 1.31 – 32.63, p=0.022) and no increased risk at week 54 (p=0.21). However, overall disease activity and sleep symptoms did not entirely explain fatigue in patients with IBD on biologic therapy. At each time-point, disease activity, sleep and mood symptoms together explained less than one-third of the variability in fatigue ($R^2$=0.31 week 14, $R^2$=0.21 week 30, $R^2$=0.19 week 54).

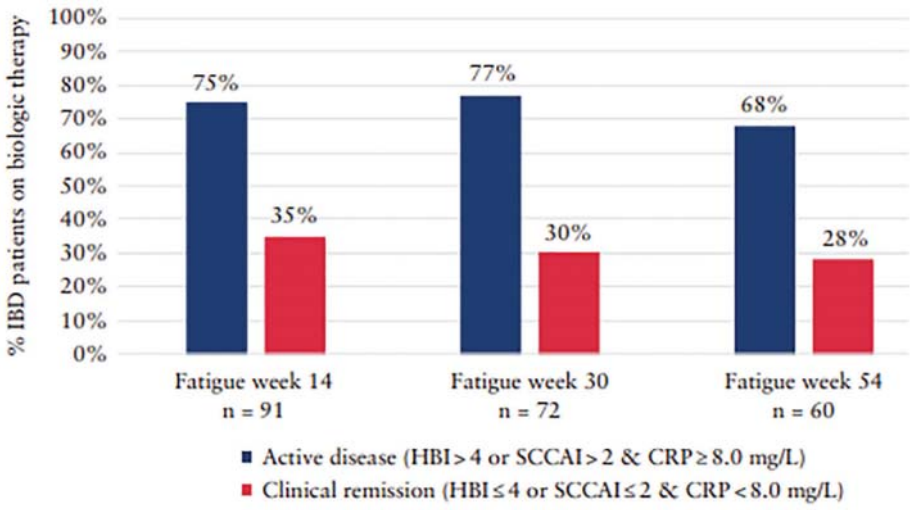


**Figure 2: Longitudinal trajectory of fatigue upon follow-up to 1 year, stratified by clinical remission status.** * Clinical remission defined as Harvey Bradshaw Index (HBI) score of ≤4 for Crohn's disease or Simple Clinical Colitis Activity Index (SCCAI) score ≤2 for ulcerative colitis and normal C-reactive protein level (<8.0 mg/L).

**Subgroup analysis**

We performed subgroup analysis by type of biologic therapy (anti-TNF / VDZ/ UST). A total of 72 (59%), 40 (67%) and 86 (68%) reported fatigue symptoms before biologic therapy initiation with anti-TNF therapy, vedolizumab or ustekinumab respectively. There were no significant differences between the different therapies in the proportion remaining fatigued at the various time-points (Wk 14: anti-TNF 67%, VDZ 82%%, UST 69%; Wk 30: anti-TNF 65%, VDZ 57%, UST 63%; Wk 54: anti-TNF 70%, VDZ 67%, UST 57%). Subgroup analysis was repeated by type of IBD (CD vs. UC). Again, no substantial differences in the proportion patients with persistent fatigue were found at the different time-points (**Supplemental Figure 2a**). Interestingly, when subgroup analysis was performed again by gender, we found a higher proportion persistent fatigue among the female gender

at week 14 (62% vs 47%, p=0.038) but this effect diminished after 30 weeks of biologic therapy (p=0.190) and at week 54 (p=0.094) (**Supplemental Figure 2b**).

## DISCUSSION

Inflammatory bowel diseases are complex immune-mediated diseases with a multifactorial etiology. However, IBD symptoms are not limited to physical disabilities alone but also encompass psychosocial health. Fatigue is one of these frequently reported psychosocial symptoms by IBD patients but often not recognized and understudied. In this prospective cohort study, we demonstrate that resolution of fatigue in part parallels improvements in symptom scores. However, many patients remain fatigued one year after initiating biologic therapy including one-third of patients who achieve clinical remission.

While fatigue is highly prevalent in patients with IBD, little is known about its trajectory with effective IBD treatment. In a placebo-controlled study by Lichtenstein *et al*.[33], among 108 CD patients initiating IFX, 20% of the infliximab group (n=82) reported no fatigue (score 6 or 7 on the IBDQ fatigue question) compared to 0% in the placebo group (n=23) and 17% versus 0% respectively reported to have lot of energy (p=0.019) by 4 weeks of treatment. Similar results were seen with ADA therapy by Loftus *et al*[34]. A significant improvement of the FACIT-F score (23.0 versus 35.6) was noted after ADA induction and there continued to be improvement till at least week 56 (23.5 versus 36.8). A few studies have studied the effect of biologic therapy on other psychosocial symptoms such as sleep, depression, anxiety and overall HRQoL. A large population-based study in Western and Eastern Europe showed that IBD patients needing biologic therapy had lower SIBDQ scores compared to biologic naïve IBD patients and biologic therapy improved SIBDQ scores only in CD patients (40.9 to 52.1, p<0.01)[34]. Our group had previously observed that both vedolizumab and anti-TNF biologic therapies were associated with improvement in sleep and mood quality in IBD after 6 weeks of treatment which lasted up to at least 1 year[16]. However, ongoing disease activity while on biologic therapy was a strong independent predictor of disturbed sleep. Similar results from the GEMINI trial reported long-term benefits in general well-being, sleep, fatigue and energy levels after VDZ initiation which had greater effect compared to placebo[35]. Ustekinumab (6mg/kg or 130mg) has also been shown to induce clinically meaningful IBDQ improvement compared to placebo (UNITI-1: 54.8%, 46.9% versus 36.5%, respectively; UNITI-2: 68.1%, 58.7% versus 41.1%, respectively; p <0.05). These results together are all in line with our findings that in addition to relieving inflammation, multiple classes of biologic therapies can improve psychosocial symptoms in patients with IBD.

An improvement in fatigue could be attributed to decrease in circulating inflammatory cytokines with effective treatment. Such cytokines may directly act on the central nervous

system, leading to fatigue. For example, increased serum levels of TNF-α, IFN-γ, IL-12 and IL-10 were seen in quiescent IBD patients with fatigue compared to those without fatigue[36]. However, while it is intuitive that this mechanism plays a role in the setting of active inflammation, the contribution of such circulating inflammatory markers to fatigue, particularly that which persists in quiescent disease is less clear. A prospective cohort study in quiescent IBD patients reported no elevation in serum levels of 23 pro-inflammatory cytokines in those who were fatigue compared to those without fatigue symptoms[23]. The contribution of other, as yet poorly defined factors, may explain both the time to resolution of fatigue in those with clinical improvement as well as its significant persistence in those in clinical remission. These factors may include alterations in the metabolomic profile, microbial changes with effect on the gut-brain axis or reduced muscle mass and strength in those patients with fatigue[4]. Reduced bacterial diversity is frequently reported in IBD[37] and emerging research studies have established that there is a bidirectional communication system between the gut and the gastrointestinal tract (the gut-brain axis)[38]. Dysbiosis of the gut might be involved in the pathophysiology of fatigue through altering the hypothalamus-pituitary-adrenal axis and changes in the metabolomic profile through microbial mediators.

The effect of biologic interventions on fatigue symptoms have been evaluated in studies of other immune-mediated diseases treated with biologic agents, primarily among patients with rheumatoid arthritis. A large British registry of Rheumatoid Arthritis patients (RA)[39] with clinically relevant fatigue commencing anti-TNF therapy demonstrated that 70% of severely fatigued patients had improvement of fatigue symptoms and two-third (66%) had no complaints of severe fatigue after 6 months. Limitation of the study was that most patients had high disease activity at baseline and analysis did not adjust for disease activity scores. However, the same group repeated analysis[40] and stratified their study cohort to those who achieved disease remission by 6 months. In total 10% (n=271) of the total cohort achieved disease remission by 6 months and the remainder continued to experience fatigue (63%) which is in line with our results. A systematic review of 32 studies in RA by Almeida et al.[41] had a similar conclusion that biologic therapies led to a small to moderate reductions in fatigue symptoms.

There are few implications to our findings. To our knowledge, our study is one of the first to evaluate the effects of biologic therapies on fatigue in patients with IBD in a real-world setting. While treatments goals of reducing clinical symptoms, achieving endoscopic remission and reducing inflammation are important in the management of IBD, psychosocial factors including fatigue are also key determinants of patient's general well-being and quality of life. The strong association between psychological comorbidities and fatigue has been reported by several studies[42-44], supporting a potential role for psychological therapies in the treatment of IBD. Therefore, it is important to both

systematically evaluate these factors within the context of clinical trials as well as for clinicians to consider these psychosocial symptoms during routine patient care. This, together with translational research into the mechanisms of fatigue, can offer new lines of intervention that can improve our patients' lives. Our findings also suggest that the single fatigue question in the SIBDQ can be a helpful and easy to use instrument in clinical practice to measure fatigue. Although biologic therapies are able to ameliorate fatigue symptoms together with reduction of disease activity, a significant proportion of IBD patients remain fatigued. Therefore, there is an unmet need for fundamental research studies into the etiology of fatigue in IBD. In parallel, prospective clinical trials of pharmacological and non-pharmacologic interventions are needed to develop an acceptable and long-term effective therapy for fatigue.

We readily acknowledge several limitations to our study. First, validation of the SIBDQ fatigue question was performed using a study cohort with quiescent IBD. However, Aniwan et al.[45] evaluated the correlation between SIBDQ and fatigue in inactive (23%) and active (77%) UC patients and showed a similarly strong correlation with the FACIT-F ($r = 0.86$), consistent with our findings. Secondly, not all patients had fatigue available at baseline and on follow-up though ours remains among the largest studies to examine this question. In line with that, patients who had discontinued biologic therapy (and thus were not included in the follow-up time point) due to inadequate response likelihood had greater disease activity and consequently higher fatigue. Thus, our estimates of persistence of fatigue are likely an underestimate. As in any observational study, there may be influence of unmeasured confounders. Sleep and mood are interconnected and overlapping with fatigue but not sufficient to explain it in a majority of patients. This may in part due to shared mechanisms as well as common risk factors such as active disease. Further work is needed to accurately define to what extent these are manifestations of a shared pathogenesis and the relative contribution of these to each other. We also did not have inflammation on objective markers of inflammation including endoscopic improvement and fecal calprotectin as these were not systematically obtained during this study. The same applies to objective markers of anemia and iron deficiency. And lastly, this study was performed at a tertiary referral center and therefore our population may have trended towards more severe disease though we would expect a similar effect of biologic therapy on fatigue irrespective of severity.

In conclusion, we demonstrate that fatigue improves with initiation of biologic therapy and paralleling resolution of clinical symptoms. However, over half the patients initiating such therapy remain fatigued at 1 year including one-third of those who are in clinical remission. It is important for clinicians to recognize fatigue symptoms in their patients and to address this burdensome and underreported symptom.

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**Supplemental Table 1: Baseline characteristics of the validation cohort.**

| Characteristic | Fatigue (n=121) | No fatigue (n=96) | p-value |
|---|---|---|---|
| Female, n(%) | 67 (55.4) | 35 (36.5) | 0.006 |
| Age, mean (SD) | 38.9 ±14.0 | 42.7 ± 14.2 | 0.049 |
| IBD type | | | 0.377 |
| Crohn's disease, n(%) | 74 (61.2) | 53 (55.2) | |
| Ulcerative colitis, n(%) | 47 (38.8) | 43 (44.5) | |
| SIBDQ*, mean (SD) | 51.2 ± 8.1 | 62.6 ± 5.7 | <0.001 |
| SIBDQ fatigue, mean (SD) | 3.2 ± 1.3 | 5.8 ± 1.1 | <0.001 |
| MFI** general, mean (SD) | 14.2 + 2.8 | 7.9 ± 3.1 | <0.001 |
| Sleep disturbance†, n(%) | 67 (55.8) | 17 (17.9) | <0.001 |
| Depressive symptoms†, n(%) | 68 (56.2) | 5 (16.0) | <0.001 |
| Anxiety symptoms†, n(%) | 78 (64.5) | 21 (22.6) | <0.001 |

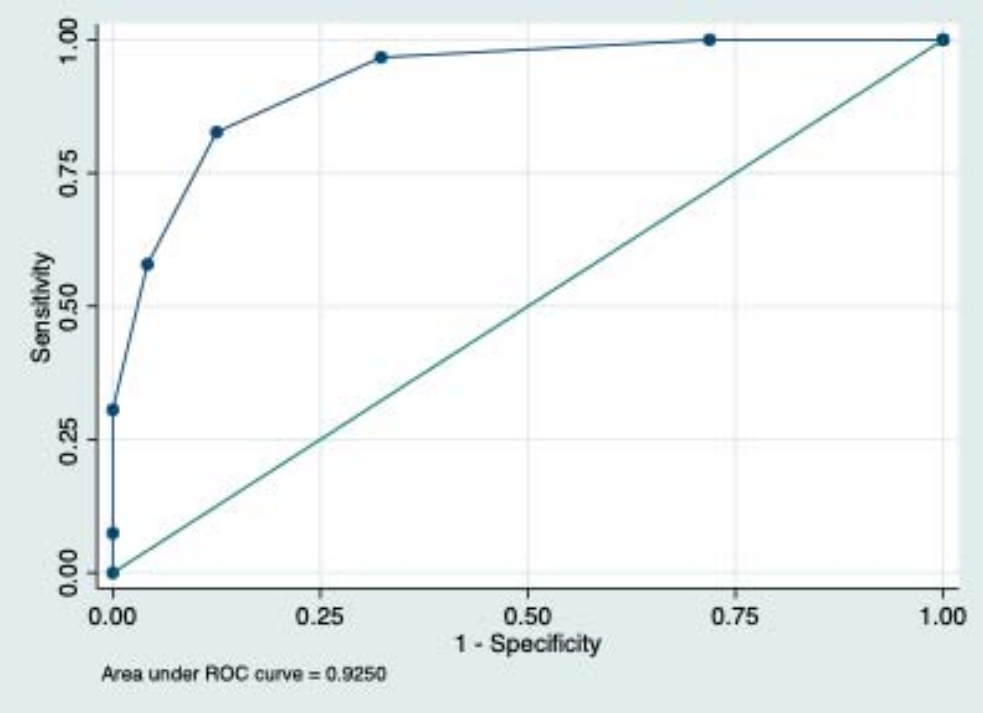
* SIBDQ: Short Inflammatory Bowel Disease Questionnaire
** MFI: Multidimensional Fatigue Index
† Sleep disturbance, depressive and anxiety symptoms: patients with a T-score above 50 on the correlating NIH PROMIS questionnaire were considered as having disturbed sleep, significant depressive, or anxiety symptoms.

**Supplemental Table 2: Correlations of one-item fatigue scale from SIBDQ with other measures for fatigue, sleep and mood symptoms.**

| | SIBDQ**** fatigue question | FACIT-F | MFI general | PROMIS sleep disturbance | PROMIS depressive symptoms |
|---|---|---|---|---|---|
| FACIT-F* | 0.85 | | | | |
| MFI general** | -0.81 | -0.83 | | | |
| PROMIS*** sleep disturbance | -0.49 | -0.52 | 0.53 | | |
| PROMIS depressive symptoms | -0.57 | -0.55 | 0.52 | 0.48 | |
| PROMIS anxiety symptoms | -0.56 | -0.58 | 0.57 | 0.44 | 0.74 |

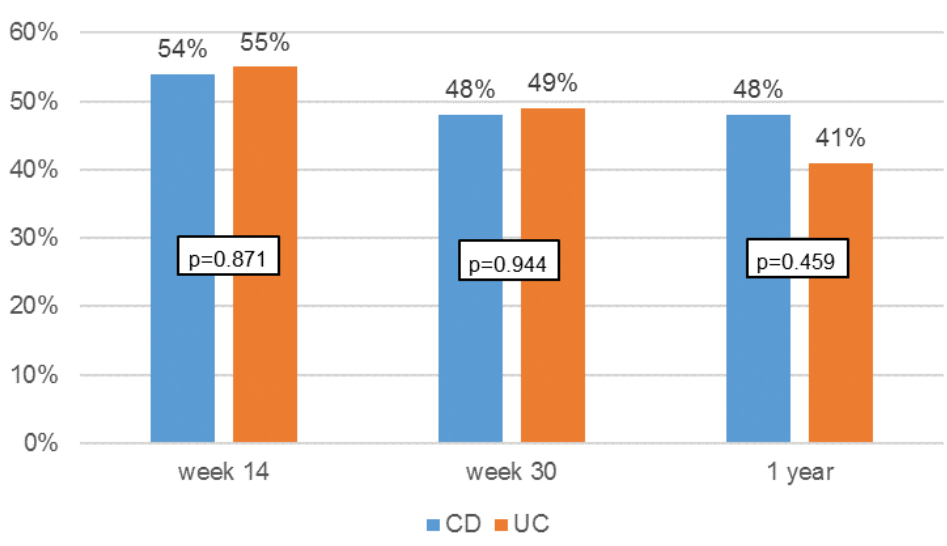
* FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue
** MFI: Multidimensional Fatigue Inventory
*** PROMIS: Patient-Reported Outcomes Measurement Information System
**** SIBDQ: Short Inflammatory Bowel Disease Questionnaire.

**Supplemental Figure 1: Area under the curve of the SIBDQ fatigue score compared with fatigued and non-fatigue subjects (against the reference standard of FACIT-F questionnaire).**
* Assessing the ability of the single fatigue question scores of the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) to discriminate between fatigued cases (FACIT-F ≤ 43) and non-fatigue cases (FACIT-F >43) by calculating the area under the curve.

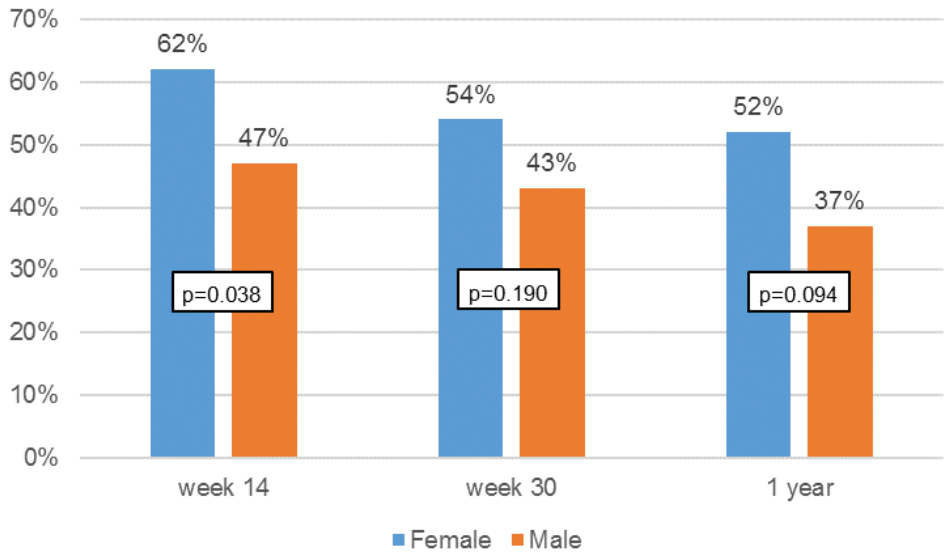


**Supplemental Figure 2: Change in fatigue symptoms stratified by IBD type (a) and gender (b) at week 14, week 30 and week 54.**

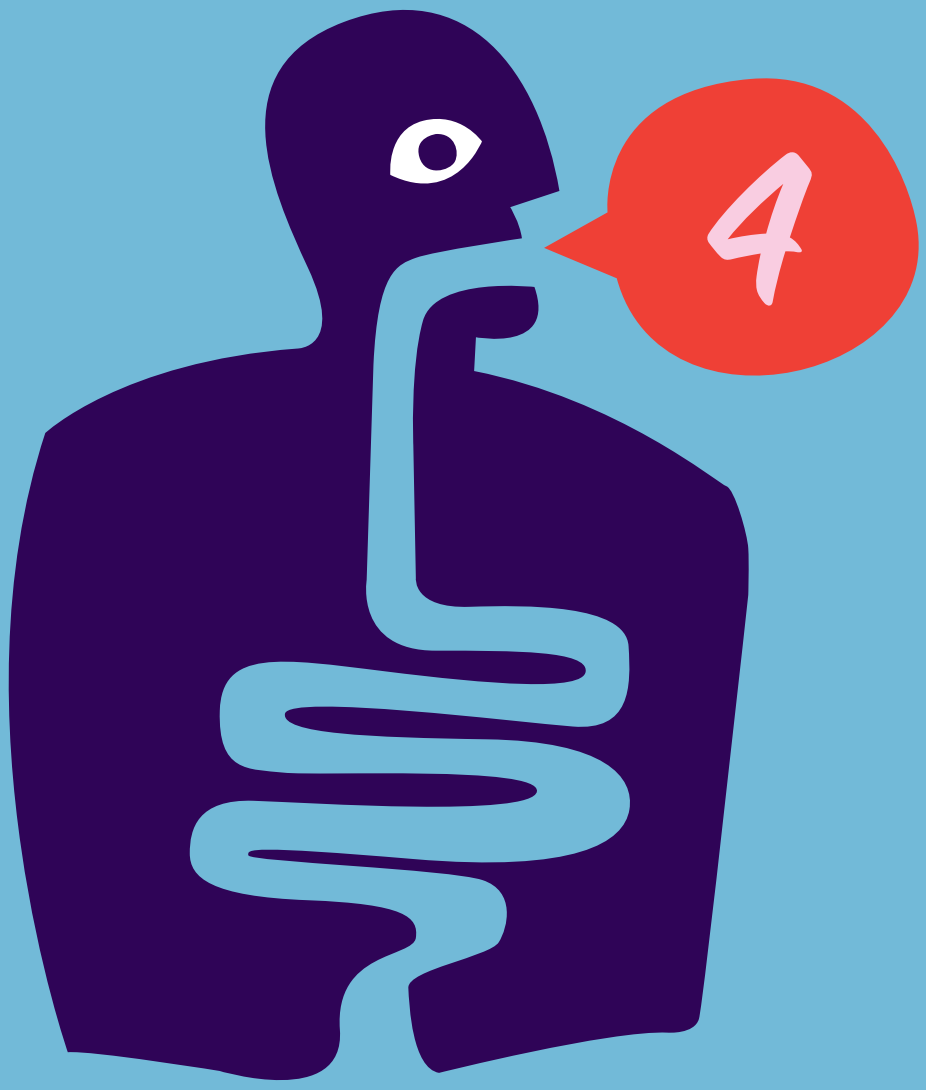
a. Proportion persistent fatigue by type of IBD




b. Proportion persistent fatigue by gender



3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# CHAPTER 4

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## Vedolizumab therapy is associated with an improvement in sleep quality and mood in inflammatory bowel diseases

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## ABSTRACT

**Backgrounds and aims:**

Poor sleep, depression, and anxiety are common in patients with inflammatory bowel diseases (IBD) and associated with increased risk of relapse and poor outcomes. The effectiveness of therapies in improving such psychosocial outcomes is unclear but is an important question to examine with increasing selectivity of therapeutic agents.

**Methods:**

This prospective cohort enrolled patients with moderate-to-severe CD or UC starting biologic therapy with vedolizumab or anti-tumor necrosis factor α agents (anti-TNF). Sleep quality, depression and anxiety were measured using validated short form NIH PROMIS questionnaires assessing sleep and mood quality over the past 7 days. Disease activity was assessed using validated indices. Improvement in sleep and mood scores from baseline was assessed and regression models were used to identify determinants of sleep quality.

**Results:**

Our study included160 patients with IBD (49 anti-TNF, 111 Vedolizumab) among whom half were women and the mean age was 40.2 years. In the combined cohort, we observed a statistically significant and meaningful decrease in mean scores from baseline (52.8) by week 6 (49.8), p=0.002). Among vedolizumab users, sleep T-score improved from baseline (53.6) by week 6 (50.7) and persisted through week 54 (46.5, p=0.009). Parallel reductions in depression and anxiety were also noted ($p < 0.05$ by week 6). We observed no difference in improvement in sleep, depression, and anxiety between vedolizumab and anti-TNF use at week 6.

**Conclusion:**

Both vedolizumab and anti-TNF biologic therapy were associated with improvement in sleep and mood quality in IBD.

## INTRODUCTION

With a growing incidence worldwide, inflammatory bowel diseases (IBD) affect an estimated 1.5 million people in the United States.[1, 2] Crohn's Disease (CD) and Ulcerative Colitis (UC), collectively comprising IBD, are chronic inflammatory conditions primarily involving the gastrointestinal tract but exerting a range of extra-intestinal influences. Characterized by periods of remission and relapse, the natural history of IBD is often complicated and frequently requires hospitalizations and surgeries.[3] In addition to physical manifestations, IBD has a major impact on health-related quality of life, impacting an individuals' career, relationships, and mental health.[4-6] Depression, anxiety, and stress are common in patients with IBD and their role as environmental influences on the pathogenesis and course of IBD is still being explored.[5, 7-10] Existing research shows that stress, coping, depression and anxiety may increase risk of CD and UC[11-13] and contribute to symptomatic relapses, hospitalizations, and surgeries.[14-18]

An important but understudied extra-intestinal symptom in patients with IBD is impairment of sleep. There likely exists a bidirectional association between sleep and inflammation such that active disease and elevations in inflammatory markers may contribute to poor sleep[19-22], while impaired sleep quality, in turn, may increase severity of clinical and histologic inflammation and risk of clinical relapse.[23, 24] Prior studies have shown that patients with IBD are more likely to have sleep deprivation when compared to healthy individuals, more commonly in those with clinically active disease but also in those in remission.[25, 26] Regardless of disease activity, sleep disturbance exerts a significant negative impact on patients' quality of life.[27]

Advances in therapeutics offer us increasingly effective medications to attain clinical and endoscopic remission.[28, 29] Immunosuppression, the cornerstone of long-term maintenance therapy in moderate-to-severe CD and UC, was initially achieved through broadly acting agents such as thiopurines or methotrexate[30-32], but evolved to more precise targets such as monoclonal antibodies targeting tumor necrosis factor α (anti-TNF; infliximab, adalimumab, certolizumab, golimumab)[33, 34] and more recently gut-selective anti-integrin therapy (vedolizumab).[35, 36] Systemic anti-TNF medications have demonstrated significant efficacy in treating extra-intestinal symptoms including improvement in sleep and depression.[37-40] Whether such effects are mediated through an improvement in disease activity alone or additionally by a direct central nervous system effect is unknown.[38] Consequently, it is important to examine if gut-selective therapy with vedolizumab can also similarly ameliorate sleep disturbances, depression and anxiety in patients with IBD.

## METHODS

### Study Cohort

This prospective cohort study was nested within the Prospective Registry for IBD Study at Massachusetts General Hospital (PRISM). Details of this cohort have been previously published.[41-43] For the purpose of this study, all patients receiving care at the Crohn's and Colitis center at Massachusetts General Hospital and commencing therapy with vedolizumab (vedolizumab cohort), or anti-TNF therapy (adalimumab, infliximab, certolizumab, or golimumab) (anti-TNF cohort) for CD and UC were approached for inclusion between May 2014 and March 2016. Eligible subjects were at least 18 years of age, had a confirmed diagnosis of CD or UC, and were initiating outpatient therapy with one of the above agents according to routine clinical care. Upon providing consent, all patients completed an enrolment interview with a trained research coordinator where demographics, disease, and treatment history including current and past medications were noted and confirmed by medical record review.

Consequently, we performed this study with the following aims: (1) To examine changes in sleep quality, depression, and anxiety after initiation of vedolizumab therapy for moderate-to-severe CD and UC; (2) To identify determinants of sleep quality at baseline, and improvement of sleep quality with therapy; and (3) To compare changes in sleep, depression and anxiety with vedolizumab to anti-TNF therapy.

### Study Protocol and Follow-up

All patients initiated therapy with an anti-TNF agent (infliximab or adalimumab) or vedolizumab according to standard induction and maintenance dosing. Study assessments were performed at weeks 0, 2, 6, 14, 22, 30 and 54. Data collected at each interval included sleep quality and mental health as outlined below and disease activity according to the Harvey Bradshaw Index (HBI) for CD and Simple Clinical Colitis Activity Index (SCCAI) for UC, and health-related quality of life assessed using the Short Inflammatory Bowel Disease Questionnaire (SIBDQ).[44-46] Clinical remission was defined as an HBI≤ 4 or a SCCAI ≤ 2. Whenever available (usually at every infusion), levels of serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were collected. Patients on self-administered adalimumab injection completed study questionnaires within a 4 week window of each of the above time points in addition to a week 14 evaluation.

### Study outcomes: Sleep, depression and anxiety

All enrolled patients were invited to complete questionnaires regarding sleep and mood quality using the short form National Institute of Health Patient-Reported Outcome Measurement Information System for sleep disturbance, depression and anxiety.[47, 48] Questionnaires from the PROMIS bank for sleep disturbance, depression and anxiety have

shown validity in multiple prior studies.[49, 50] Sleep quality was assessed using an 8-item NIH PROMIS questionnaire assessing sleep disturbance over the past 7 days. This yields a continuous score which is translated to a T-score ranging from 28.9 (best) to 76.5 (worst sleep quality). Depression and anxiety over the past 7 days were examined similarly with an 8-item questionnaire with T-scores ranging from 38.2 to 81.3 and 37.1 to 83.1 respectively. As a reference, a mean NIH PROMIS T-score corresponds to a value of 50; a deviation of 10 represents one standard deviation away from the mean. In our study, patients with a T-score above 50 were considered as having disturbed sleep, significant depressive or anxiety symptoms.

**Statistical analysis**

All statistical analysis was performed using Stata 13.1 (StataCorp, College Station, TX). Continuous variables were summarized using means and standard deviations and compared using the t-test if normally distributed or the Mann-Whitney-U test if skewed. Categorical variables were expressed as proportions and compared using the chi-square test with the Fisher's exact modification when appropriate. Week 0 estimates comprised the baseline values for all patients while the primary follow-up visit was at week 14. First, we defined factors impacting sleep quality at baseline by performing univariate linear regression analysis with demographic, disease-related, and psychosocial parameters. Multivariable models were then constructed including variables significant in the univariate analysis at $P < 0.05$. A forward-stepwise approach was used for the multivariable models, retaining variables as being independently significant at a two-sided P-value $< 0.05$. Next, we examined the change in sleep quality with initiation of therapy. Sleep, depression, and anxiety T-scores assessed at different study visits were compared with values at start of therapy at week 0, stratifying by whether the patients were on vedolizumab or anti-TNF therapy. In the cohort of individuals with no missing baseline or follow-up data, we compared the sleep, depression, and anxiety T-scores at each follow-up point (week 6, 14, 30, and 54) to baseline values using the paired t-test. Finally, we examined the association between sleep, depression, and anxiety and attainment of clinical response (defined as a 3 point improvement in HBI or SCCAI) or remission (SCCAI$< 2$ or HBI $< 4$) at week 14. Patients with a stoma or an ileal pouch anal anastomosis (IPAA) were not included in assessments of disease activity.

The study was approved by the Institutional Review Board of Massachusetts General Hospital.

## RESULTS

### Study cohort

Of the 183 patients with IBD (104 CD, 79 UC) included in the cohort, 52 patients (28%) were started on anti-TNF therapy (infliximab or adalimumab) and 131 patients (72%) started vedolizumab. After excluding patients who had missing sleep score both at baseline and week 14 follow up (n=23), we arrived at the final cohort of 160 patients (49 anti-TNF, 111 vedolizumab). Patients excluded were similar to the final cohort in age, sex, treatment type (anti-TNF or vedolizumab), type of IBD, disease activity, insomnia or depressive disorders but were slightly more likely to have anxiety and taking immunomodulators. A total of 117, 93 and 110 patients provided data on sleep quality at baseline, week 6 and week 14 respectively. Half the cohort was women (50%) with a mean age at enrolment of 40.2 years. Eight patients had an ileoanal pouch and 12 had a stoma. Patients receiving anti-TNF therapy were similar to those on vedolizumab in sex and type of IBD, a medical history of insomnia, depression and anxiety, current medication use, and CRP level (**Table 1**). Patients receiving vedolizumab were slightly older, had a longer duration of disease, had a higher HBI at baseline, and were more likely to have previously tried an anti-TNF therapy.

**Table 1: Baseline characteristics of the study cohort**

| | Anti-TNF (n=49) | Vedolizumab (n=111) | p-value |
|---|---|---|---|
| Mean age, yrs | 33 | 37 | 0.049 |
| Female sex, n (%) | 23 (46.9) | 58 (52.3) | 0.535 |
| Type of IBD | | | 0.069 |
| Crohn's disease, n(%) | 34 (69.4) | 60 (54.5) | |
| Ulcerative colitis, n(%) | 15 (30.6) | 51 (45.6) | |
| Mean duration of IBD, yrs | 5 | 11 | 0.001 |
| Smoking status | | | 0.421 |
| Never, n(%) | 38 (77.6) | 74 (67.3) | |
| Past, n(%) | 9 (18.4) | 30 (27.3) | |
| Current, n(%) | 2 (4.1) | 6 (5.5) | |
| MFI** general, mean (SD) | 14.2 + 2.8 | 7.9 ± 3.1 | <0.001 |
| Median SIBDQ score (95% CI) | 47 (31-67) | 46 (28-66) | 0.633 |
| Medical history | | | |
| Insomnia, n(%) | 7 (14.3) | 16 (14.4) | 0.983 |
| Depression, n(%) | 10 (20.4) | 19 (17.12) | 0.618 |
| Anxiety, n(%) | 5 (10.20) | 15 (13.5) | 0.560 |
| Median HBI score (95% CI) | 4 (0-16) | 6 (1-15) | 0.008 |
| Mean SCCAI score | 5.9 ± 4.2 | 5.9 ± 3.1 | 0.991 |
| Median CRP, mg/L (95% CI) | 2.6 (0.2-69.7) | 6.2 (0.3-53.5) | 0.530 |
| Median ESR, mm/h (95% CI) | 13 (2-55) | 15 (2-88) | 0.370 |
| Median WBC, K/uL (95% CI) | 7.8 (4.8-14.1) | 8.1 (4.3-15.4) | 0.924 |
| Median HGB, g/dL (95% CI) | 13.2 (10.8-15.6) | 12.9 (8.8-15.8) | 0.205 |
| Baseline sleep disturbance symptoms[1], n(%) | 27 (55.1) | 43 (38.7) | 0.840 |
| Baseline depressive symptoms[2], n(%) | 22 (44.9) | 41 (36.9) | 0.351 |
| Baseline anxiety symptoms[3], n (%) | 26 (53.1) | 48 (43.2) | 0.283 |
| Baseline medication use | | | |
| Steroids, n(%) | 25 (51.0) | 42 (37.8) | 0.119 |
| 5-aminosalicylates, n (%) | 10 (20.4) | 30 (27.0) | 0.373 |
| Immunomodulators, n (%) | 11 (22.5) | 41 (36.9) | 0.071 |
| Opioid, n (%) | 6 (12.2) | 17 (15.3) | 0.610 |
| Sleep aid, n (%) | 9 (18.4) | 20 (18.0) | 0.958 |
| Depression treatment[4], n(%) | 11 (22.5) | 28 (25.2) | 0.706 |
| Prior anti-TNF, n (%) | 7 (14.3) | 99 (89.2) | <0.001 |
| Ileal-pouch anal anastomosis, n (%) | 3 (6.1) | 5 (4.5) | 0.665 |
| Stoma, n (%) | 1 (2.0) | 9 (8.1) | 0.144 |

[1] Sleep disturbance symptoms were defined as having a PROMIS sleep disturbance T-score greater than 50
[2] Depressive symptoms were defined as having a PROMIS Depression T-score greater than 50
[3] Anxiety symptoms were defined as having a PROMIS Anxiety T-score greater than 50
[4] Depression treatment was defined as receiving a tricyclic antidepressant, selective serotonin reuptake inhibitor, or cognitive behavioral therapy.

### Factors associated with sleep disturbance at baseline

**Table 2** presents univariate comparisons of factors impacting sleep at baseline. Both depression (P=0.002) and anxiety (P<0.001) were associated with worse sleep quality at baseline. A baseline depression T-score > 50 and an anxiety T-score > 50 were associated with a 5- and 6-point worse sleep T-score compared to individuals without significant depression or anxiety symptoms. Higher disease activity was also associated with worse sleep with each 1 point increase in HBI or SCCAI worsening the sleep T-score by 0.53 (P=0.026). Other variables associated with sleep on univariate analysis were current smoking (P=0.036), use of opioids (P=0.046), and need for sleep aids (P=0.009). Use of corticosteroids, 5-aminosalicylates or immunomodulators did not demonstrate significant associations with the sleep T-score. There was no significant difference in sleep disturbance T-score at baseline between anti-TNF and vedolizumab users (P=0.136).

**Table 2: Factors associated with sleep quality at baseline**

| | Co-efficient | CI (95%) | P-value |
|---|---|---|---|
| Type of therapy (anti-TNF = reference) | 2.76 | -0.88 - 6.39 | 0.136 |
| Age | 0.09 | -0.30 - 0.21 | 0.142 |
| Sex (male = reference) | 0.36 | -3.24 - 3.96 | 0.844 |
| Type of IBD (CD = reference) | 0.33 | -3.30 - 3.97 | 0.857 |
| Duration of IBD | 0.05 | -0.11 - 0.22 | 0.522 |
| Smoking status (never = reference) | | | |
| Past | 0.44 | -3.92 - 4.81 | 0.842 |
| Current | 8.70 | 0.60 - 16.82 | 0.036 |
| Baseline activity | 0.53 | 0.07 - 1.00 | 0.026 |
| CRP, mg/L | -0.03 | -0.11 - 0.05 | 0.423 |
| ESR, mm/h | -0.002 | -0.08 - 0.08 | 0.957 |
| WBC, K/uL | 0.11 | -0.50 - 0.73 | 0.719 |
| HGB, g/dL | 0.04 | -0.94 - 1.02 | 0.932 |
| Baseline depressive symptoms[1] | 5.37 | 1.97 - 8.77 | 0.002 |
| Baseline anxiety symptoms[2] | 6.31 | 2.83 - 9.78 | 0.000 |
| Baseline medication use | | | |
| Steroids | 0.67 | -2.95 - 4.28 | 0.715 |
| 5-aminosalicylates | 0.36 | -3.70 - 4.43 | 0.860 |
| Immunomodulators | -0.27 | -4.10 - 3.56 | 0.888 |
| Opioids | 4.98 | 0.09 - 9.86 | 0.046 |
| Depression treatment | 4.93 | 0.92 - 8.94 | 0.016 |

[1] Depressive symptoms were defined as having a PROMIS Depression T-score greater than 50
[2] Anxiety symptoms were defined as having a PROMIS Anxiety T-score greater than 50

On multivariable analysis, the strongest factor independently associated with sleep T-score was presence of anxiety (Regress co-efficient (β) 7.14; 95% confidence interval (CI), 3.36-10.92) while opioid use showed a trend towards significance (β 5.02; 95% CI, -0.30 – 10.34). Disease characteristics and baseline disease activity were not associated with worse sleep quality at on adjusted analysis. Sensitivity analysis with the raw sleep score as the outcome, or dichotomizing at a sleep-t score of 50 yielded similar results (data not shown).



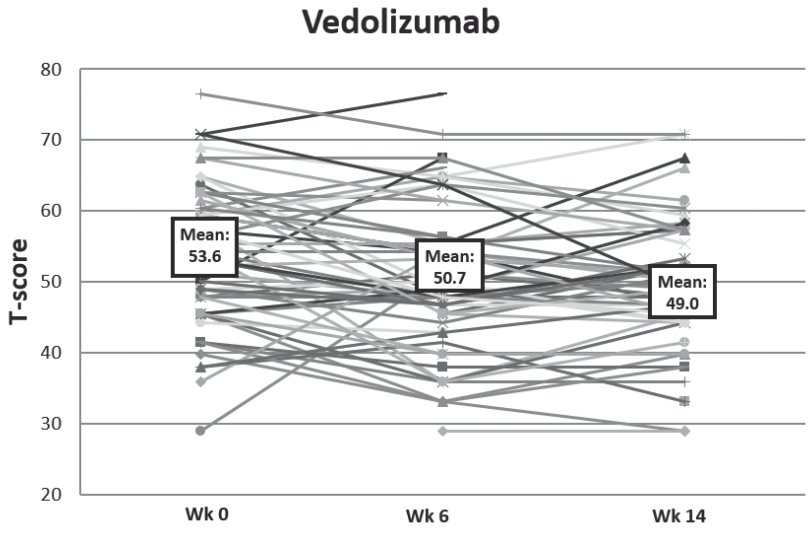
**Change in sleep and mood with biologic treatment**

In the combined cohort, the sleep disturbance T-score showed an early improvement in the 84 patients who had both sleep T-score at baseline and follow-up, showing a statistically significant and meaningful decrease in mean scores by week 6 (52.8 ± 9.7 (week 0) to 49.8 ± 9.4, P=0.002). At the week 14 analysis which included 67 patients, the sleep T score continued to show a significant improvement compared to baseline (52.6 ±10.1 (week 0) to 49.2 ± 8.8, P=0.002).

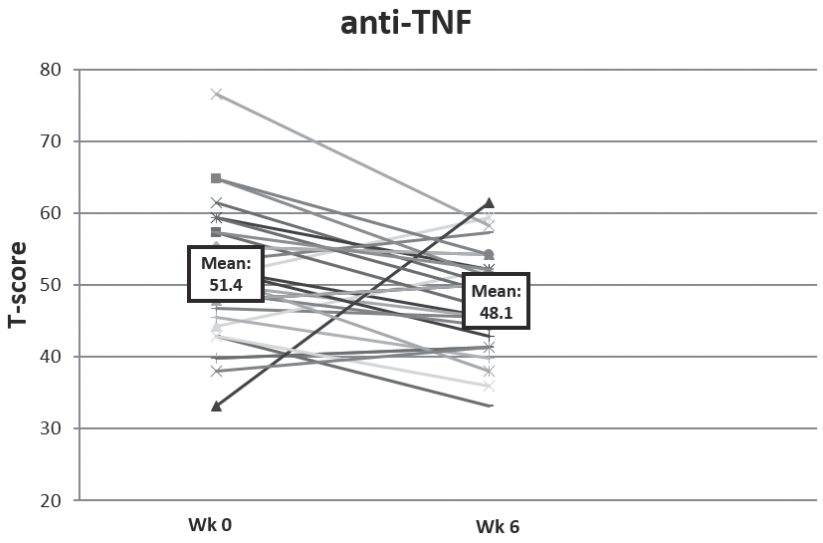
Analysis of vedolizumab users alone showed a similar early significant improvement of sleep disturbance T-score by week 6 (n = 56 patients) (50.7 ± 10.3, P=0.013), continuing to week 14 (n = 52 patients) (49.0 ± 8.4, P=0.003) (**Figure 1**). The mean sleep T-score continued to remain lower at week 30 (n=37) (49.6 ± 9.9, P=0.006) and at week 54 (n=13) (46.5 ±9.6, P=0.009) when compared to baseline. Analysis of anti-TNF users alone also showed a trend towards reduction in sleep score between baseline and week 6 (n=28) (51.4 ± 9.4 to 48.1 ± 7.3, P=0.069). That only a small number of patients had sleep measured at week 14 precluded meaningful statistical analysis but the estimates were numerically lower compared to baseline (n=15, 50.1 ± 10.1, P=0.447) (**Figure 1**). Among anti-TNF users, a statistically significant reduction in depression scores were noted from baseline (50.1) to week 6 (48.1) (p=0.02) and week 14 (49.4, p=0.058) though only 19 patients contributed to the week 14 time point (**Supplemental Figure 1**). The change in anxiety T-scores did not reach statistical significance at either of the two time points.

**Figure 1: Scatter plot demonstrating change in Sleep T-scores between baseline, week 6, and week 14 in vedolizumab and anti-TNF users.**

a. Vedolizumab

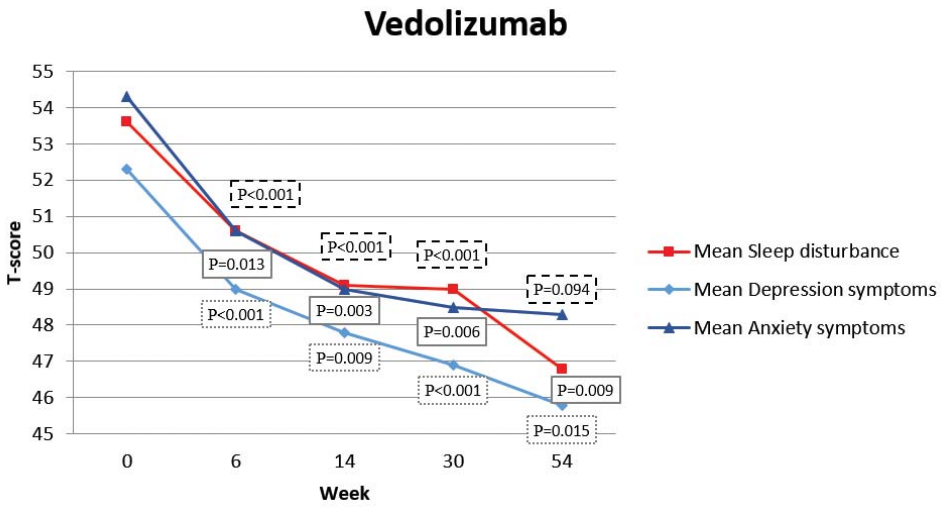



b. Anti-TNF biologics (infliximab, adalimumab)



In parallel with the improvement in sleep quality in vedolizumab, we noted a significant improvement in depression and anxiety T-scores as well (**Figure 2**). Depression T-score showed a 3-point decrease in mean by week 6 (52.3 ± 10.8 to 49 ± 10.6), a 4.5 point decrease at week 14 (47.8 ± 9.0) and an even greater long term improvement at week 30 (46.9 ± 8.9) and week 54 (45.8 ± 8.0). Although anxiety symptoms were more likely at baseline in comparison with depression symptoms, a similar result was noted with an early improvement by week 6 (54.3 ± 10.7 to 50.6 ± 10.9) and week 14 (49.0 ± 10.1). Long term improvement in anxiety was reported as well by week 30 (48.5 ± 10.5) and continued with a 6-point decrease at week 54 (48.3 ± 9.6)

**Figure 2: Temporal changes in sleep quality, depression, and anxiety with vedolizumab use through week 54.** *p-values represent comparison to baseline (week 0)




**Association between disease activity and sleep**

The clinical outcomes of patients in our cohort are provided in **Table 3**. Nearly half the patients attained clinical remission at week 14 (48%). Clinical status at week 14 was a strong determinant of sleep and mood. Patients with continued active disease were more likely to have disturbed sleep (T-score > 50) (56%) in comparison to patients who were in remission (30%) (P=0.01). They were also more likely to have depression (47%) and anxiety (56%) symptoms compared to those in remission (18% and 34% respectively) (P < 0.05 for both). On multivariable analysis, persistence of depressive symptoms (β6.85; 95% CI, 3.08 – 10.63, P=0.001) and ongoing disease activity (β 0.62; 95% CI, 0.11 – 1.14, P=0.019) were independent predictors of disturbed sleep on follow-up.

**Table 3: Comparison of disease activity and psychosocial outcomes based on remission status at week 14**

| | Active disease (n=60) | Disease in remission (n=55) | p-value |
|---|---|---|---|
| Median HBI score at follow up (95% CI) | 7 (5-20) | 2 (0-4) | <0.001 |
| Mean SCCAI score at follow up (SD) | 4.9 ± 1.8 | 1.2 ± 0.8 | <0.001 |
| Median CRP at follow up, mg/L (95% CI) | 3.8 (0.6-34) | 2.3 (0.2-56.6) | 0.047 |
| Sleep disturbance symptoms[1] at follow up, n(%) | 31 (56.4) | 13 (30.2) | 0.010 |
| Depressive symptoms at followup[2], n(%) | 26 (47.3) | 8 (18.2) | 0.002 |
| Anxiety symptoms at follow up[3], n (%) | 31 (56.4) | 15 (34.1) | 0.027 |

[1] Sleep disturbance symptoms were defined as having a PROMIS sleep disturbance T-score greater than 50
[2] Depressive symptoms were defined as having a PROMIS Depression T-score greater than 50
[3] Anxiety symptoms were defined as having a PROMIS Anxiety T-score greater than 50

## DISCUSSION

Crohn's disease and ulcerative colitis are complex, immunologically mediated diseases leading to considerable physical impairment, and need for hospitalizations and surgery. However, their impact extends beyond physical manifestations alone to psychosocial impairment and decrease in health-related quality of life that are influenced strongly but not exclusively by disease activity. Impairment of sleep and mood are important but understudied extra-intestinal complications of CD and UC, significantly affecting patients functioning. Therapies such as anti-TNF and anti-integrin biologic therapies have demonstrated significant efficacy in achieving clinical remission from symptoms, mucosal healing endoscopically, and reducing the need for surgery and hospitalizations. However, the effect of treatments on extra-intestinal and psychosocial outcomes is poorly studied but becomes increasingly important as therapies evolve to more gut-selective targeted immunosuppression. In a rigorously conducted prospective cohort study, we demonstrate that both vedolizumab and anti-TNF biologic therapy were associated with a significant improvement in sleep, depression, and anxiety within 6 weeks of initiation of therapy and that such improvements were sustained up to at least 1 year.

While disease activity is an important determinant of mood and sleep in patients with IBD, prior studies have shown significant sleep disturbance in patients with IBD even in the absence of clinically active disease. In a small study, Ranjbaran *et al.* demonstrated that even in the setting of inactive disease, overall subjective sleep quality was worse and sleep interruptions were frequent in patients with IBD compared to healthy controls.[25, 27] In other prospective cohorts, 48% of patients in remission had a sleep-T score greater than [50,24] and sleep disruption was independent of the presence of nocturnal symptoms.[22] One hypothesis proposed for this is that circulating inflammation markers themselves directly

may have a central effect, leading to disturbed sleep. Elevated CRP, IL-1, IL-6 and TNF-α levels have been found in patients with sleep disturbances. [19, 21, 22, 51] IL-6 has been reported to reduce REM sleep and increases wakefulness in patients, where IL-1 and TNF-α increase spontaneous sleep and the sleep rebound that occurs after sleep deprivation.[52, 53] Thus, hypothetically anti-inflammatory therapy could decrease the circulating inflammatory cytokines and improving the sleep quality in IBD patients. Few prior studies have examined the impact of such therapy in other auto-immune diseases and none in IBD. One study evaluated sleep deprivation and the effects of anti-TNF therapy on sleep deprivation in ankylosing spondylitis patients and noted a clear correlation between sleep disturbance and disease activity.[54] However no significant difference in sleep quality was found between patients using anti-TNF agents and controls. In contrast, Taylor-Gjevre *et al.* recognized an improved sleep efficiency and awakening after sleep onset time in rheumatoid arthritis patients treated with anti-TNF therapy.[55]

Similar to that observed for sleep quality, we also noted an improvement in both depression and anxiety with both vedolizumab and anti-TNF therapy. A bi-directional association between stress or depression and gut inflammation has been proposed in prior studies, explained by both the effect of depression on circulating inflammation as well as potentially through its influence on the gut microbiome. In a mouse model, depression was induced by mice in which colitis had been established and was in remission.[56] After induction, a reactivation of colitis was observed via the nicotinic receptor (α7nAchR) on macrophages. These macrophages also demonstrated increased pro-inflammatory cytokine secretion suggesting an association between depression and gut inflammation.[56] Supporting this relationship, Howren *et al.* found that depression was associated with increased levels of IL-1, IL-6 and CRP.[57] While several studies have demonstrated an improvement in overall health-related quality of life with anti-TNF biologic treatment, few have examined the effect of such therapies directly on depression and anxiety, and none with vedolizumab. Horst *et al.* showed in a small sample-size study that immunosuppressive therapy decreased depression scores significantly.[58] Another study found similar results after starting infliximab infusions but noted that patients with a current or past depressive disorder at baseline had a higher immune activation as well.[59] It is reassuring to both patients and providers that early and sustained improvement in sleep quality and mood were noted with both gut-selective anti-integrin therapy and systemic anti-TNF therapy in our cohort, leading to the hypothesis that a reduction in disease burden and circulating inflammation, rather than only a direct central effect, may be contributing to improvement in these parameters with treatment.

Multiple prior studies have assessed risk factors for poor sleep, depression, or anxiety in IBD. [5, 8, 11, 24, 27, 60] Predictors of sleep quality in our study were similar to those previously noted. Interestingly, we found that use of opioids showed a trend towards an association

with poor sleep quality which represents a novel association, potentially mediated through disease severity and chronic pain. Previous studies have demonstrated that health related quality of life was markedly lower in patient who used opioids for treatment of their IBD. [61,62] However, no other study have reported such a correlation between opioid use and sleep quality. This finding serves as an added incentive for patients to avoid long-term opioid use in patients with IBD.

There are a few implications to our findings. To our knowledge our study represents the first attempt to quantify the effects of biologic treatment, vedolizumab and anti-TNF agents, on sleep quality and mood in IBD patients. While resolution of physical symptoms, endoscopic healing, and prevention of bowel damage are key targets in the management of IBD, psychosocial symptoms are nevertheless important determinants of health-related quality of life and well being. It is important to include such assessments as structured endpoints in both observational cohorts and clinical trials to ensure that not only is resolution of the intestinal consequences of inflammation achieved but also a comparable improvement in the psychosocial consequences of disease. This attains particular importance with increasing selectivity of therapeutic targets as a significant proportion of patients with IBD experience such symptoms such as disrupted sleep, anxiety, depression, or fatigue. Such studies in conjunctional with translational research will aid in understanding the mechanisms behind such symptoms in patients with IBD, thus making it possible to have effective directed treatments that improve such outcomes.

We acknowledge several limitations with our study include the lack of objective measurement of sleep such as polysomnography and a relatively small sample size though it represents the largest observational cohort to date assessing such outcomes. As it was based at a referral center, our population may be skewed towards more severe disease. Third, while sleep and mood measurements were available in the vast majority of patients, not all patients had paired values both at baseline and week 14 (though the missing data was random). As in an observational study, there may be the effect of unmeasured confounders. We also did not have information on steroid dose and sleep aid use at each of the time points, and their impact on sleep quality.

In conclusion, we observed a significant improvement in sleep and mood quality in IBD patients after initiation of biologic therapy with vedolizumab or anti-TNF agents. Continued research is needed to understand the exact etiology of such symptoms in patients with IBD. Assessment of depression, anxiety, and sleep should become part of routine IBD clinical care owing to their impact on quality of life and interventional studies comparing effectiveness of different IBD-therapies in improving such parameters are important to ensure optimal patient outcomes.

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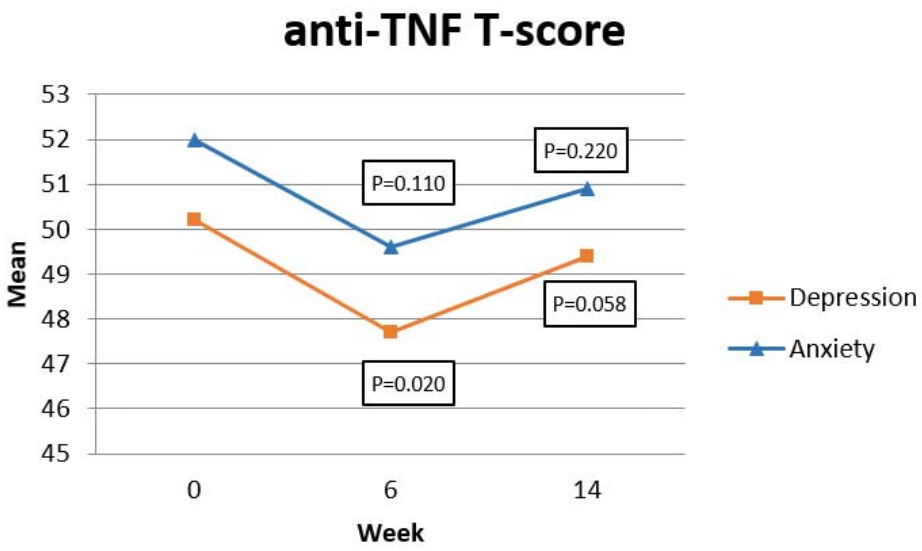
**Supplemental Figure 1: Change in depression and anxiety T-scores with use of anti-tumor necrosis factor α biologic therapy in inflammatory bowel diseases.**

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# CHAPTER 5

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## Distance to specialist care and disease outcomes in inflammatory bowel disease

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## ABSTRACT

**Introduction:**

Optimal treatment of inflammatory bowel disease requires specialized health care. Patients frequently travel long distances to obtain care for inflammatory bowel disease, which may hinder regular care and affect outcomes adversely.

**Methods:**

This study included patients with established CD or UC receiving care at a single referral center between January 2005 and August 2016. Distance to our healthcare center from the zipcode of residence was determined for each patient and classified into quartiles. Our primary outcome was need for IBD-related surgery with secondary outcomes being need for biologic and immunomodulator therapy. Logistic regression models adjusting for relevant covariates examined the independent association between travel distance and patient outcomes.

**Results:**

Our study included 2,136 patients with IBD (1,197 CD, 939 UC) among just over half were women (52%) and the mean age was 41 years. The mean distance from our hospital was 2.5 miles, 8.8 miles, 22.0 miles, and 50.8 miles for the first (most proximal) through fourth (most distant) respectively. We observed a statistically significant and meaningful higher risk among patients in the most distant quartile in the need for immunomodulator use (OR 1.69, 95% CI 1.29-2.22), biological therapy (OR 2.19, 95% CI 1.69-2.85) and surgery (OR 2.44, 95% CI 1.80 – 3.32). Differences remained significant on multivariable analysis and by type of IBD.

**Conclusion:**

Greater distance to referral healthcare center was associated with increased risk for needing IBD-related surgery in patients with Crohn's disease or ulcerative colitis.

## INTRODUCTION

Inflammatory bowel diseases (IBD) comprising Crohn's disease (CD) and Ulcerative Colitis (UC) affect an estimated 1.6 million individuals in the United States with as many as 70, 000 new patients diagnosed each year.[1] They are complex, relapsing-remitting diseases frequently leading to hospitalizations, surgery, and permanent bowel damage. Advances in therapeutics have increased the number of treatment options, expanding the armamentarium from broad conventional immunomodulator therapy to targeted biologics and small molecules including monoclonal antibodies to tumor necrosis factor α (anti-TNF) and gut-specific mucosal integrins.[2, 3] However, this has also resulted in care for IBD becoming increasingly complex and specialized with evolution towards therapeutic paradigms that suggest better outcomes with adoption of upfront biologic therapy early on in disease course and in combination with a conventional immunomodulators.[4, 5]



Several studies have examined the impact of specialist care on outcomes of patients with IBD.[6, 7] Care at a high IBD volume hospital is associated with lower post-operative mortality among patients undergoing surgery.[8, 9] Among hospitalized patients with UC, gastroenterologist care was associated with lower mortality for up to 1 year after the initial hospitalization compared to admissions under internists and general practitioners.[6] Even in a tertiary referral center, care by gastroenterologists specializing in IBD resulted in superior post-hospitalization outcomes and earlier access to IBD-related surgical interventions.[7] The impact of barrier to effective care may extend even prior to the diagnosis of IBD where a delay may reduce response to medical therapy, increase risk of fibrostenosis and need for surgery.[10, 11]

A delay in receiving effective therapy may not be solely due to patient behavior or physician expertise, but could also be determined by barriers to access quality IBD care. One such factor that may play hinder access to specialist IBD care may be the physical distance from such facilities. Prior studies examining the impact of distance from a hospital have focused on medical or surgical emergencies, demonstrating that in three-quarters of such studies, there existed a "distance decay" relationship with worse outcomes in patients living further away from the site of care.[12] One can envision that distance from care may also be relevant in diseases like IBD that are beset by unpredictable flares, requires periodic clinical and endoscopic evaluation to ensure remission, and rely on long-term adherence to therapy that requires a regular patient-provider relationship. Consequently, we performed this study with aim of examining the impact of distance from area of residence to a referral IBD center on the need for surgery and biologic therapy in patients with CD and UC.

## METHODS

### Study Population

The study cohort consisted of patients recruited for the Prospective Registry in IBD Study at Massachusetts General Hospital (PRISM). This prospective cohort is an ongoing registry of patients that is open to all adult patients with an established diagnosis of IBD who received longitudinal care at the Massachusetts General Hospital. Upon provision of informed consent, all patients completed an enrollment interview with a study research coordinator where demographics, disease characteristics, and history of medical and surgical treatments were obtained. All information was confirmed by medical record review.

### Covariates and Outcomes

Our main exposure of interest was distance from zip code of residence to our hospital (MGH). The zip code was obtained from the residential address field of the electronic medical record and distance calculated using a distance calculator (https://www.zip-codes.com/distance_calculator.asp). This distance was modeled in quartiles with the higher quartiles increasingly further away from the hospital. Other covariates obtained include gender, age at enrollment and at diagnosis, disease duration, and smoking status. Disease location and behavior in CD and extent in UC were classified according to the Montreal classification.[13] We also obtained information on education and employment status. Patients reporting a Bachelor's degree or higher were considered "highly educated". Engagement in employment was defined as performing paid work or being a student.

Our primary outcome was need for IBD-related surgery. Our secondary outcomes were need for biologic (infliximab, adalimumab, certolizumab, golimumab, natalizumab, or vedolizumab) therapy or immunomodulators (azathioprine, 6-mercaptopurine, methotrexate)

### Statistical analysis

All analysis was performed using Stata 13.0 (StataCorp, College Station, TX). Continuous variables were summarized using means and standard deviations while categorical variables were expressed as proportions and compared using the chi-square test. We first performed univariate analysis examining the association between distance quartiles and each of our study outcomes. Subsequently, multivariable models were constructed adjusting for disease-specific covariates including duration of disease, behavior and extent of involvement, education, and employment status. A p-value $<0.05$ in this analysis was considered to indicate independent statistical significance. Various sensitivity analyses were performed, excluding patients residing more than 25 miles and 50 miles away to minimize the potential for bias introduced by a referral population. Approval for this study was obtained from the Institutional Review Board of Massachusetts General Hospital.

## RESULTS

### Study cohort

Our cohort included 2,136 patients with IBD (1,197 CD, 939 UC) with a mean age of 41 years. Just over half (52%) were women. After excluding patients who lived more than 100 miles away from our hospital (likely representing a referral population) (n=112), we included 2,024 patients in our final analysis. The patients excluded from the study were similar to the final cohort in age and sex, type of IBD and paid work but were more likely to have CD and be highly education compared to included patients. Diving the cohort into quartiles based on proximity, the mean distance from zip code of residence to our hospital was 2.5 miles (±1.4), 8.8 miles (±2.6), 22.0 miles (±5.0), and 50.8 miles (±16.5) for the 1st, 2nd, 3rd, and 4th quartiles respectively. There were no differences in sex, type of IBD, location or behavior of CD, perianal involvement, and extent of UC between patients living near or far from our hospital (**Table 1**). Patients with a greater distance to the hospital were slightly older, were diagnosed with IBD at an older age, had a longer duration of disease, and were more likely to have a history of smoking. They were also less likely to be doing paid work or have a Bachelor's degree or higher.

**Table 1: Study characteristics**

| | Quartile 1 (n=469) | Quartile 2 (n=526) | Quartile 3 (n=563) | Quartile 4 (n=466) | p-value |
|---|---|---|---|---|---|
| Female, n(%) | 248 (52.9) | 278 (52.9) | 287 (51.0) | 241 (51.7) | 0.909 |
| Age, mean (SD) | 35.1 (±12.8) | 42.3 (±16.1) | 43.0 (±14.9) | 42.2 (±15.0) | 0.044 |
| Age at diagnosis, mean (SD) | 25.4 (±12.1) | 30.8 (±14.6) | 30.3 (14.3) | 30.0 (±14.3) | 0.023 |
| Duration disease, mean (SD) | 9.6 (±9.0) | 11.3 (±12.1) | 12.6 (±11.9) | 11.9 (±11.2) | <0.001 |
| Smoking, n(%) | | | | | 0.001 |
| Never | 341 (74.5) | 326 (63.8) | 353 (63.7) | 278 (61.1) | |
| Former | 96 (20.96) | 142 (27.8) | 164 (29.6) | 143 (31.4) | |
| Current | 21 (4.6) | 43 (8.4) | 37 (6.7) | 34 (7.5) | |
| High level education, n(%) | 394 (87.56) | 354 (69.01) | 345 (63.7) | 260 (58.2) | <0.001 |
| Working, n(%) | 409 (88.9) | 403 (77.7) | 418 (75.3) | 352 (77.9) | <0.001 |
| IBD type, n(%) | | | | | 0.157 |
| CD | 243 (51.8) | 285 (54.2) | 326 (57.9) | 269 (57.7) | |
| UC | 226 (48.2) | 241 (45.8) | 237 (42.1) | 197 (42.3) | |
| *CD location, n(%)* | | | | | 0.801 |
| TI (L1) | 57 (25.8) | 61 (24.0) | 75 (25.7) | 61 (26.0) | |
| Colon (L2) | 53 (24.0) | 70 (27.6) | 73 (25.0) | 55 (23.4) | |
| Ileocolon (L3) | 111 (50.23) | 122 (48.0) | 144 (49.3) | 117 (49.8) | |
| Upper GI (L4) | 0 (0) | 1 (0.4) | 0 (0) | 2 (0.9) | |
| CD *behavior*, n(%) | | | | | 0.060 |
| Inflammatory (B1) | 129 (57.6) | 135 (50.9) | 136 (45.6) | 108 (44.4) | |
| Stricturing (B2) | 39 (17.4) | 58 (21.9) | 62 (20.8) | 60 (24.7) | |
| Penetrating (B3) | 56 (25.0) | 72 (27.2) | 100 (33.6) | 75 (30.9) | |
| CD *perianal* disease, n(%) | 55 (24.6) | 70 (26.4) | 79 (26.5) | 65 (26.8) | 0.946 |
| *UC* extent, n(%) | | | | | 0.425 |
| Limited colitis | 88 (44.4) | 103 (47.9) | 104 (49.5) | 67 (41.6) | |
| Pancolitis | 110 (55.6) | 112 (52.1) | 106 (50.5) | 94 (58.4) | |

The mean distance from our hospital was 2.5 miles, 8.8 miles, 22.0 miles, and 50.8 miles for the first (most proximal) through fourth (most distant) respectively.

## Distance from hospital and disease outcomes

Patients living in the most distant quartile were significantly more likely to need IBD-related surgery than those living closer to the hospital (OR 2.44, 95% CI 1.80 – 3.32) (**Figure 1**) (**Table 2**). A dose-response relationship was seen with progressively greater likelihood for surgery in quartile 2 (OR 1.68, 95% CI 1.23 – 2.28) and 3 (OR 1.94, 95% CI 1.44 – 2.62). A similar relationship was also noted in biologic therapy where patients in the most distant quartile had a 2-fold increase in need in comparison with patients living near the hospital (OR 2.19, 95% CI 1.69-2.85). For immunomodulator use, a significantly elevated odds ratio

was noted only among patients in the most distant quartile compared to those living the closest (OR 1.69, 95% CI 1.29-2.22); no effect was noted in the 2nd and 3rd quartiles.

**Figure 1: Relationship between distance from hospital and need for surgery in patients with inflammatory bowel diseases.** The mean distance from our hospital was 2.5 miles, 8.8 miles, 22.0 miles, and 50.8 miles for the first (most proximal) through fourth (most distant) respectively.

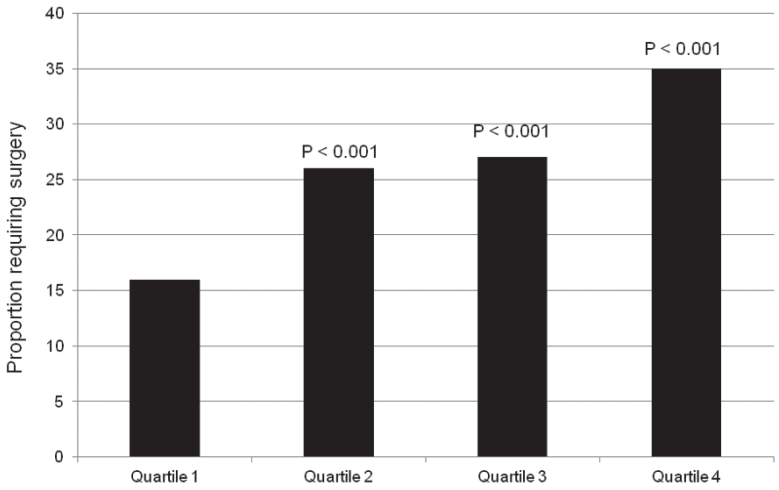




**Table 2: Univariate analysis of impact of travel distance on need for IBD-related surgery, biologic, and immunomodulator use**

| Outcome | OR | 95% CI | *P* |
|---|---|---|---|
| **Need for surgery (Q1=reference)** | | | |
| Quartile 1 | 1.00 | Reference | |
| Quartile 2 | 1.68 | 1.23 - 2.28 | 0.001 |
| Quartile 3 | 1.94 | 1.44 - 2.62 | <0.001 |
| Quartile 4 | 2.44 | 1.80 - 3.32 | <0.001 |
| **Need biologic therapy (Q1=reference)** | | | |
| Quartile 1 | 1.00 | Reference | |
| Quartile 2 | 1.10 | 0.85 - 1.41 | 0.486 |
| Quartile 3 | 1.51 | 1.18 - 1.94 | 0.001 |
| Quartile 4 | 2.19 | 1.69 - 2.85 | <0.001 |
| **Need immunomodulator therapy (Q1=reference)** | | | |
| Quartile 1 | 1.00 | Reference | |
| Quartile 2 | 0.82 | 0.64 - 1.06 | 0.130 |
| Quartile 3 | 1.20 | 0.93 - 1.54 | 0.158 |
| Quartile 4 | 1.69 | 1.29 - 2.22 | <0.001 |

These findings remained significant on our multivariable analysis. Each progressively further quartile was associated with a greater need for surgery in all IBD patients adjusting for age, type of IBD, duration of disease and engagement in paid employment. Patients residing in the most distant quartile were two-times as likely to need surgery as those residing closest to the hospital (OR 1.98, 95% CI 1.36-2.89). This relationship also persisted in the need for biologic therapy (Q4 vs. Q1: OR 2.18, 95% CI 1.60-2.97), and for the most distant quartile - the need for immunomodulator therapy (Q4 vs. Q1; OR 1.61, 95% CI 1.19-2.21). Similar results were obtained when distance from the hospital was modeled as a continuous variable with each 10 mile increase in distance being associated with an increased risk for surgery (OR 1.09, 95% CI 1.03 – 1.16, p=0.004) and biologic therapy (OR 1.14, 95% CI 1.08 – 1.20, p<0.001).

**Subgroup Analysis**

We performed subgroup analysis by type of IBD. In CD, additionally adjusting for the perianal involvement, disease location and behavior, higher quartiles of distance was associated with an increasing likelihood of surgery and biologic therapy (**Table 3**). For example, patients living in the most distant quartile had a two-fold increase in need for surgery (OR 1.75, 95% CI 1.04 – 2.97) and biologic therapy (OR 2.40, 95% CI 1.54 – 3.75). A similar effect was also noted in UC, additionally adjusting for disease extent. There was a three-fold greater need for surgery (OR 3.31, 95% CI 1.34 – 8.88) and two-fold increase in biologic therapy (OR 2.02, 95% CI 1.22 – 3.33) between the most distant and closest quartiles.

**Table 3: Multivariable analysis of impact of travel distance on need for IBD-related surgery, biologic, and immunomodulator use**

| | Quartile 2 | | Quartile 3 | | Quartile 4 | |
|---|---|---|---|---|---|---|
| **Crohn's disease*** | **OR (95%CI)** | **p-value** | **OR (95%CI)** | **p-value** | **OR (95%CI)** | **p-value** |
| Need surgery | 1.47 (0.88-2.48) | 0.143 | 1.31 (0.79-2.17) | 0.304 | 1.75 (1.04-2.97) | **0.036** |
| Need biologics | 1.29 (0.84-1.97) | 0.240 | 1.61 (1.05-2.46) | **0.029** | 2.40 (1.54-3.75) | **<0.001** |
| Need immunomodulator | 0.72 (0.47-1.12) | 0.144 | 0.84 (0.54-1.30) | 0.431 | 1.24 (0.78-1.97) | 0.367 |
| **Ulcerative colitis**** | **OR (95%CI)** | **p-value** | **OR (95%CI)** | **p-value** | **OR (95%CI)** | **p-value** |
| Need surgery | 2.75 (1.12-6.77) | **0.028** | 2.07 (0.82-5.26) | 0.122 | 3.31 (1.34-8.22) | **0.010** |
| Need biologics | 1.24 (0.76-2.03) | 0.380 | 2.02 (1.23-3.31) | **0.005** | 2.02 (1.22-3.33) | **0.006** |
| Need immunomodulator | 0.89 (0.57-1.38) | 0.596 | 1.54 (0.98-2.43) | 0.061 | 1.96 (1.22-3.16) | **0.005** |

Quartile 1 is the reference quartile.
* Adjusted for perianal disease, CD location and behavior
** Adjusted for UC extent

**Sensitivity Analysis**

To further minimize referral bias where patients with more aggressive disease are referred to us for specialized care, we performed sensitivity analysis excluding patients who lived 50 miles or more from our hospital. This showed a similar effect on multivariable analysis as with our primary analysis. All three outcomes remained statistically significant with an increasing likelihood of surgery (OR 1.82, 95% 1.20 - 2.79), biologic therapy (OR 2.55, 95% CI 1.78 - 3.65) and immunomodulator therapy (OR 1.76, 95% CI 1.22 – 2.54) between the most distant and closest quartiles.



## DISCUSSION

Treatment of IBD is complex and increasingly specialized. With expansion of the number of treatment options, therapeutic drug monitoring, and recognition of more robust treatment goals such as early attainment of mucosal healing, management of IBD increasingly requires close and frequent contact between the patient and the treatment team, with dynamic alterations of therapeutic strategies. However, physical access to specialized healthcare is not always easy and patients frequently have to travel long distances to receive such care, which in turn, may impact initiation and optimization of medical therapy. The impact of travel distance from a referral IBD hospital on patients' outcomes has not been examined previously. In a study from a single referral center, we demonstrated that greater distance from specialized care was associated with a higher risk for IBD-related surgery, and need for biologic or immunomodulator therapy. Our findings were robust to a range of assumptions of distances travelled excluding referral patients, and on adjustment for various disease related characteristics.

A few prior studies have examined the impact of specialized care on patients with IBD.[6,8,9,14] Murthy *et al.* assessed the impact of gastroenterologist care and observed a three to four-fold lower mortality among hospitalized UC patients when under the care of a gastroenterologist.[6] A similar result was seen in studies assessing the impact of hospital volume on outcomes of IBD-related hospitalizations. IBD patients undergoing surgery at high IBD volume admission centers had lower in-hospital and postoperative mortality.[8, 9, 15] Even within a single referral hospital, implementation of specialized IBD care pathway and dedicated care by a gastroenterologist specializing in IBD was associated with higher rates of remission at 3 months and facilitated early surgical intervention.[7] Equivalent results were observed in studies assessing the influence of specialized care in other diseases.[16-20] Thus overall, evidence suggests that the best outcomes in IBD may be obtained in specialized setting, particularly for patients at risk for more severe disease or requiring complex, multidisciplinary care.

The impact of travel distance on patient outcomes has been examined before for other indications and elegantly summarized in a systematic review by Kelly *et al.*[12] Over three-quarters of the examined studies demonstrated a distance-decay association with worse outcomes in individuals living further away from healthcare facilities. In our study, distance from the referral hospital was associated with greater need for surgery, immunomodulator, and biologic therapy. Greater travel distance may impact need for surgery in patients with IBD by impeding early initiation of effective treatment. Though in our study, the findings for biologic or immunomodulator therapy may be inverse to what one may expect, with patients residing close to the hospital more likely to be initiated on biologic therapy, this may not capture the effect of timing of initiating of such therapy. While there is robust data supporting the efficacy of biologic therapy in reducing surgery and hospitalizations in IBD, the timing of initiation of such therapy appears to be key. Prior studies have demonstrated that delayed initiation of biologic or immunomodulator therapy, particularly after chronic bowel damage and fibrostenosing complications has set in may not result in an optimal benefit.[21-25] Longer distance from the hospital may also affect patient adherence to treatment by impeding a robust patient-provider relationship which exerts an strong influence on adherence to recommendations.[26-28] Non-adherence in turn, has been associated with worse outcomes in IBD.[29] Longer distance may also interfere with ongoing monitoring using serologic markers, endoscopies and drug levels, thereby not allowing optimization of therapy.

We readily acknowledge a few sources of bias that may influence interpretation of our study results. First, it is possible that patients residing furthest away from hospital are referred to us for more severe disease. This is unlikely to be the sole explanation for our findings for a few reasons. First, our findings remained significant on restricting travel distances to within 25 or 50 miles, and it is unlikely that patients within this proximal vicinity are referral cases alone. Second, at our center, patients are recruited into our patient registry after the third visit (often later) to our offices, and are not one-time consultation referrals. A third limitation is that we did not have information on the duration of disease at immunomodulator or biologic initiation. It is important for future studies to be able to address for this and account for delay in initiation of effective treatment.

There are a few implications to our findings. Several studies have proposed centralization of health care services to improve outcomes, minimize regional differences in the quality of care, and reduce costs.[30, 31] However, often centralized high volume centers offering specialized care are necessarily located in large metropolitan centers, leading to increased travel distance (and consequently, reduced access) for patients residing in less populated areas further away.[32] As demonstrated in our study, this increased travel distance may result in worse patient outcomes or reduce the benefit of getting specialized care. While it may be logistically difficult for most of complex IBD care to be restricted to a few specialized

centers, it is of greater importance to define what components of specialized IBD care are associated with improved patient outcomes and to replicate such care in the community. The development of quality metrics by professional societies and organizations[33-35] is an important step in that regard.

In conclusion, we demonstrate that greater distance from a referral IBD hospital was associated with greater need for IBD-related surgery, immunomodulator, and biologic therapy. There is need for further studies to determine how specialized IBD care may be provided in a de-centralized way to optimize patient outcomes.

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6

# CHAPTER 6

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## Differences in clinical course, genetics, and the microbiome between familial and sporadic inflammatory bowel diseases.

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## ABSTRACT

**Objective:**

Family history is the strongest risk factor for developing Crohn's disease (CD) or ulcerative colitis (UC). We investigated whether the proximity of relationship with the affected relative and concordance for type of IBD modifies the effect of family history on phenotype and disease severity.

**Design:**

This cross-sectional study included patients with a confirmed diagnosis of IBD in a clinical registry. Family history of IBD was assessed by a questionnaire ascertaining presence of disease in a 1st degree, 2nd degree or a distant relative. Our primary outcomes were disease phenotype per the Montreal classification and severity measured by need for immunomodulator, biologic, or surgical therapy. Genotyping was performed on the Immunochip and fecal samples subjected to 16s rRNA microbiome sequencing.

**Results:**

Our study included 2,094 patients with IBD (1,173 CD, 921 UC). Just under one-third (32%) were familial IBD (17% 1st degree, 21% 2nd degree). Familial IBD was diagnosed at an earlier age, both in CD (26 vs. 28 years, p=0.0006) and UC (29 vs. 32 years, p=0.01). Among CD patients, a positive family history for CD was associated with an increased risk for complicated disease in the presence of an affected family member (OR 1.48, 95% CI 1.07 – 2.03). However, this effect was significant only for 1st degree relative (OR 1.82, 95% CI 1.19 – 2.78).

**Conclusion:**

A family history of CD in 1st degree relatives was associated with complicated CD. Family history discordant for type of IBD or in distant relatives did not influence disease phenotype or natural history.

## INTRODUCTION

Inflammatory bowel diseases (IBD) are complex immune-mediated diseases affecting over 1.6 million individuals in the United States, 2.2 million in Europe, and thousands more worldwide.[1, 2] Though the exact pathogenic mechanisms behind IBD are yet to be fully defined, the current hypothesis states that IBD develops at the interface of predisposing genetic variations, immunologic alterations, shifts in the gut microbiome, and external environmental influences.



Genetic predisposition is one of the strongest factors influencing the development of IBD. Genome-wide association studies have identified over 200 distinct single nucleotide polymorphisms (SNPs) predisposing to the development of Crohn's disease (CD) or ulcerative colitis (UC).[3] Between 8-20% of patients with CD or UC will have an affected close relative.[4-6] In the general population, a history of IBD in a first or second-degree family member increases risk of incident disease by eight-fold and two-fold respectively.[7] While many studies have examined the impact of family history on disease risk, fewer have examined if this history influences disease course in the index patient. Familial IBD may differ from sporadic IBD in having a stronger genetic predisposition and shared common environmental influences, which may, in turn, lead to similarities in gut microbial composition. Prior studies have demonstrated concordance in age at diagnosis, disease location, behavior, and need for IBD-related surgery in affected family members[4, 8, 9] but have been limited by small sample sizes, and lack of examination of the genetics or microbial composition underlying such phenotypes. In addition, prior studies often failed to examine the impact of proximity of the relationship of the affected family member or concordance for type of IBD.

Identifying the impact of family history on the natural history of IBD may also have prognostic implications, allowing for risk stratification and prediction of disease-related complications. Consequently, we performed this study using a large prospective cohort with the following aims – (1) To define the impact of family history on the clinical characteristics and natural history of IBD, stratifying by proximity of relationship and concordance for type of IBD; (2) to compare the genetics and microbiome composition in a subset of patients with familial and sporadic IBD.

## METHODS

### Study Cohort

This study included patients recruited in a prospective registry - the Prospective Registry for IBD Study at Massachusetts General Hospital (PRISM). All adult patients aged 18 years and older with a confirmed diagnosis of CD, UC, or IBD-unspecified (IBDU) seeking care

at the Massachusetts General Hospital (MGH) Crohn's and Colitis center were eligible for inclusion in the cohort as described in our previous publications.[10-12] After provision of informed consent, patients completed an enrollment interview with a trained research coordinator where information about demographics, disease characteristics including age at diagnosis, and phenotype according to the Montreal classification (location and behavior in CD, extent in UC) were obtained and confirmed by medical record review. Information was also obtained about current and past medical treatments and need for IBD-related surgery.

A family history of IBD was assessed by a detailed questionnaire ascertaining presence of either CD or UC in a 1st degree (parent, child, sibling), 2nd degree (grandparent, uncle, aunt), or a distant relative. Patients were considered to have *familial IBD* in the presence of CD or UC in any relative. Patients with no reported family history were considered to have *sporadic IBD*. Patients who had the same type of IBD as their affected family member were considered to have a concordant family history while those with the other type of IBD were labeled as having a discordant family history.

Our primary end point in both CD and UC was severe disease defined as needing IBD-related surgery. In CD, our co-primary outcome was complicated disease defined as the presence of stricturing (B2) or penetrating disease (B3) or perianal involvement.

**Genotyping**

All consented patients provided 10mL blood from which genomic DNA was extracted for genotyping. Patients were genotyped on the Illumina Immunochip, a custom-chip design to perform fine mapping of over 150,000 loci relevant to immune mediated diseases, at the Broad Institute.[13] We extracted data on 201 distinct IBD-risk single nucleotide polymorphisms (SNPs) reported and calculated a weighted genetic risk score (GRS) as described previously.[12, 14] For each of the risk alleles associated with either CD, UC or both, we determined each patient to have wild type (scored as 0), heterozygous (scored as 1), or homozygous (scored as 2) variants. Odds ratios for strength of association of each of the alleles with CD, UC or both were obtained from recent multicenter consortium publication[3]. A weighted genetic risk score was then constructed which was the cumulative sum of the natural logarithm of this odds ratio multiplied by the allele frequency[15]. This yielded three separate risk scores that quantified magnitude of genetic predisposition towards developing any IBD, CD, or UC respectively.

**Sequencing of the microbiome**

DNA was extracted from the fecal samples using the Qiagen AllPrep MiniKit (Qiagen, Inc, Valencia, CA, USA), incorporating bead-beating at several steps to improve homogenization as described previously.orgtan[16] Specimens were then sent to the

Broad Institute (Cambridge, MA) to generate a 16S DNA profile targeting the V4 region of the SSU rRNA gene via the Illumina HiSeq 2000 platform with 100bp paired-end reads, targeting ~2Gbp per sample. Raw sequence data (.fastq files) were demultiplexed and quality filtered using the computational pipeline QIIME[17]. Operational taxonomic unit (OTU) tables were built using the 'pick_closed_reference_otus.py' command in QIIME. The 'biome' output file was then imported into R using the 'Phyloseq' statistical package for further analysis[18]. Taxonomy was assigned using the 'Greengenes' reference database clustered at 97%[19].

**Statistical Analysis**



Institutional Review Board approval was obtained from the Partners Healthcare Human Subjects Research committee. Analysis of clinical covariates was performed using Stata 13.1 (StataCorp, College Station, Texas). Continuous variables were summarized using means and standard deviations while categorical variables were expressed as proportions and compared using the chi-square test. We first performed univariate analysis examining the association between family history and each of our study outcomes. Subsequently, multivariable models were constructed adjusting for disease-specific covariates including duration of disease, behavior and extent of involvement, education, and employment status. Adjusted regression models were used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI). A two-sided p-value <0.05 indicated independent statistical significance. Separate analysis was performed examining the association with history of IBD in a first degree relative alone, second degree relative or more distant relative, and by concordance for type of IBD.

Genetic analysis was performed using Plink v1.07.[20] A total of 185 (out of 201) SNPs passed our threshold of Hardy-Weinberg $p < 0.0001$ and a call rate > 95%. Individuals with genotyping success rates < 90% were excluded. First, we compared the weighted GRS between familial and sporadic IBD, by proximity to affected relative, and concordance for type of IBD. In an exploratory analysis, we then examined if specific SNPs were differentially distributed between familial and sporadic IBD adopting a p-value threshold of 0.01 for nominal significance, and 0.0003 adjusting for multiple comparisons.

Microbiome analysis was conducted using the 'Phyloseq' statistical package in R. Microbial alpha diversity was calculated on unfiltered data using the Shannon diversity index and stratified by relevant covariates. First, we compared the diversity of the microbiome in familial compared to sporadic IBD using the student t test. We then stratified by measures indicating proximity to the affected relative (for example, comparing those with IBD and an affected first degree relative to those with sporadic IBD) and degree of concordance (between those with a concordant family history compared to those with sporadic IBD). Differential abundance testing for each of these comparisons was done using the

MaAsLin pipeline[16]. Briefly, MaAsLin performs a per-feature differential abundance testing of all microbes (OTUS) by regressing the relative abundance of each feature in a linear model. The relative abundances were arcsin-square-root-transformed to approximate homoscedasticity when applying linear models. We limited our analysis to only those features that were both prevalent and abundant with mean abundance >0.01% in at least 40% of the samples. P-values of associations of each OTU were computed using ANOVA type III (tests of fixed effects), subjected to Benjamini–Hochberg false discovery rate (FDR) correction with a cutoff of 0.25[21]. All analyses adjusted for whether there was clinically active disease (Harvey Bradshaw index > 4 or simple clinical colitis activity index > 2) at the time of the stool sample collection.

## RESULTS

### Study Population

Our study included 2,094 patients with IBD (1,173 CD, 921 UC) with a mean age of 41 years. Just under half the cohort were women (48%). One-third of patients had a family history of IBD (32%); 17% had an effected 1$^{st}$ degree relative while 21% had an affected 2$^{nd}$ degree relative. In 69% of patients with a family history, there was concordance for type of IBD which was similar when the index diagnosis was CD or UC.

Patients with familial IBD were similar to those with sporadic IBD in age, type of IBD, and smoking status but were likely to have higher education status (**Table 1**). Patients with familial IBD had a younger age of diagnosis than those with sporadic IBD, both for CD (25.5 vs. 28.4 years, p=0.0006) and UC (29.4 vs. 31.8 years, p=0.01) . In CD, this association was noted irrespective of the concordance for type of IBD (concordant family history: 26 vs. 28 years, p=0.03; discordant family history 25 vs. 28 years, p=0.02). However, in UC, an earlier age of diagnosis was only noted when the affected family member had UC (29 vs. 32 years, p=0.01) but not CD (30 vs. 31 years, p=0.70).

**Table 1: Characteristics of the Study Population**

| Characteristic | Familial IBD* (n=677) | Sporadic IBD** (n=1,417) | p-value |
|---|---|---|---|
| Mean age (SD) (in yrs) | 39.8 (15.2) | 41.0 (15.1) | 0.070 |
| Female sex, n (%) | 294 (43.4) | 705 (49.8) | 0.006 |
| Mean age at diagnosis (SD) (in yrs) | 27.1 (12.5) | 29.9 (14.5) | <0.001 |
| Mean duration of IBD (SD) (in yrs) | 12.9 (11.8) | 11.0 (10.3) | <0.001 |
| Smoking status | | | 0.106 |
| Never, n(%) | 440 (66.2) | 901 (65.5) | |
| Past, n(%) | 171 (25.7) | 393 (28.6) | |
| Current, n(%) | 54 (8.1) | 82 (6.0) | |
| High level education, n(%) | 475 (72.1) | 907 (66.7) | **0.015** |
| Employment status, n(%) | 537 (80.6) | 1,104 (79.5) | 0.543 |
| Type of IBD | | | 0.125 |
| Crohn's disease, n (%) | 397 (58.6) | 776 (54.8) | |
| Ulcerative Colitis, n(%) | 280 (41.4) | 641 (45.2) | |
| CD location, n(%) | | | 0.100 |
| Ileal (L1) | 92 (25.6) | 171 (25.0) | |
| Colon (L2) | 75 (20.9) | 183 (26.8) | |
| Ileocolon (L3) | 192 (53.5) | 330 (48.3) | |
| CD behavior, n(%) | | | **0.019** |
| Inflammatory (B1) | 163 (44.3) | 365 (51.7) | |
| Stricturing (B2) | 76 (20.7) | 150 (21.3) | |
| Penetrating (B3) | 129 (35.1) | 191 (27.1) | |
| CD perianal disease, n(%) | 102 (27.7) | 183 (25.9) | 0.527 |
| UC extent, n(%) | | | 0.155 |
| Limited colitis | 37 (16.0) | 77 (13.5) | |
| Pancolitis | 194 (84.0) | 493 (86.5) | |
| Medical therapy | | | |
| Surgery, n(%) | 205 (30.3) | 364 (25.7) | **0.027** |
| Biologics, n(%) | 326 (48.2) | 653 (46.1) | 0.382 |
| Immunomodulators, n(%) | 416 (61.7) | 848 (60.7) | 0.642 |

CD – Crohn's disease; UC – ulcerative colitis; IBD – inflammatory bowel diseases; SD – standard deviation
* Patients in the presence of CD or UC in any relative.
** Patients with no reported family history of CD or UC

### Complicated Crohn's disease

On univariate analysis, CD patients with a family history were more likely to have complicated disease (56% vs. 48%, OR 1.35, 95% CI 1.05 – 1.73). However, differences were noted based on concordance for type of IBD. Upon adjustment for disease location, age at diagnosis, and duration of disease, CD patients with a concordant family history were more likely to have complicated disease (OR 1.48, 95% CI 1.07 – 2.03), particularly if the affected member was a 1st degree relative (OR 1.82, 95% CI 1.19 – 2.78) (**Table 2**). Among first degree relatives, the association was more striking in the presence of CD in a sibling (p=0.008) than parent (p=0.41) or child (p=0.42). The presence of CD in a second degree relative (OR 1.20, 95% CI 0.85 – 1.69), UC in a first (OR 0.64, 95% CI 0.37 – 1.10) or second degree relative (OR 0.88, 95% CI 0.56 – 1.37) did not modify risk of complicated CD.

**Table 2: Likelihood of complicated Crohn's disease, by proximity and concordance of affected family member**

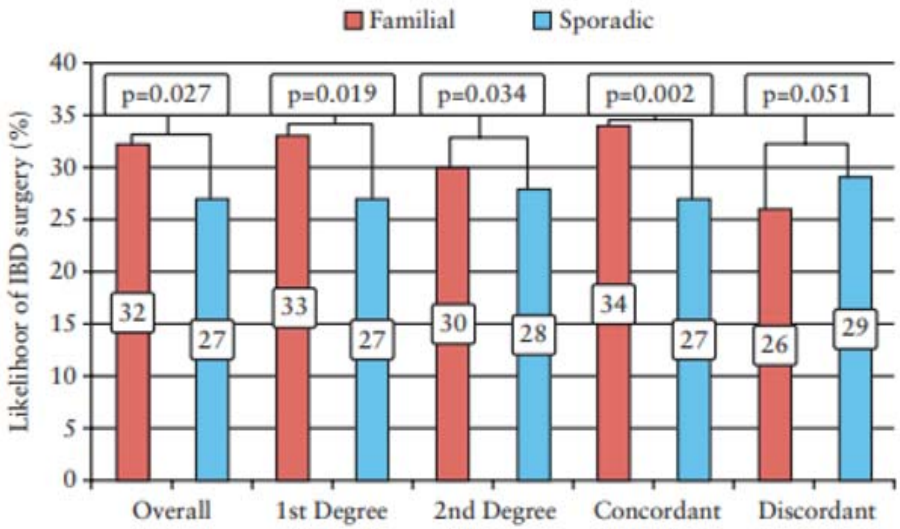
| Affected relative | Odds ratio (95% Confidence interval)* |
|---|---|
| Any family history (1st, 2nd, or distant) | 1.48 (1.07 – 2.03) |
| 1st degree relative with CD | 1.82 (1.19 – 2.78) |
| 2nd degree relative with CD | 1.17 (0.79 – 1.72) |
| Any relative with UC (Discordant) | 0.66 (0.42 – 1.02) |

CD, Crohn's disease; UC, ulcerative colitis.
* adjusted for disease location, age at diagnosis, and duration of disease

### IBD-related surgery

Patients with familial IBD were more likely to require IBD-related surgery than those with sporadic IBD (32% vs. 27% p=0.027) (**Figure 1**). This result was more striking when the affected family member was a first degree relative (33% vs. 27%, p=0.019) but not for a second degree relative (30% vs. 28%, p=0.34) (**Figure 1**). The association was also stronger when the family history was concordant for type of IBD (34% vs. 27%, p=0.002) than discordant (26% vs. 29%, p=0.51). In both CD and UC, multivariable analysis adjusting for disease behavior in addition to location, age at diagnosis and disease duration, yielded no statistically significant association between family history and need for IBD related surgery (CD: 1.04, 95% CI 0.75 – 1.43; UC: 1.10, 95% CI 0.67 – 1.79) suggesting that the influence of family history on IBD-surgery was mediated through effect on age of onset and disease behavior. We found no differences in need for biologic or immunosuppressive therapy based on the presence of family history of IBD or concordance for type of IBD (**Supplemental Table 1**). In stratifying by number of biologics, there was also no difference between the two groups on the number of patients receiving 0, 1, 2, 3, or 4 biologics for their IBD (data not shown).

**Figure 1: Likelihood of disease-related surgery among patients with Crohn's disease, stratified by concordance and proximity of affected family member.**

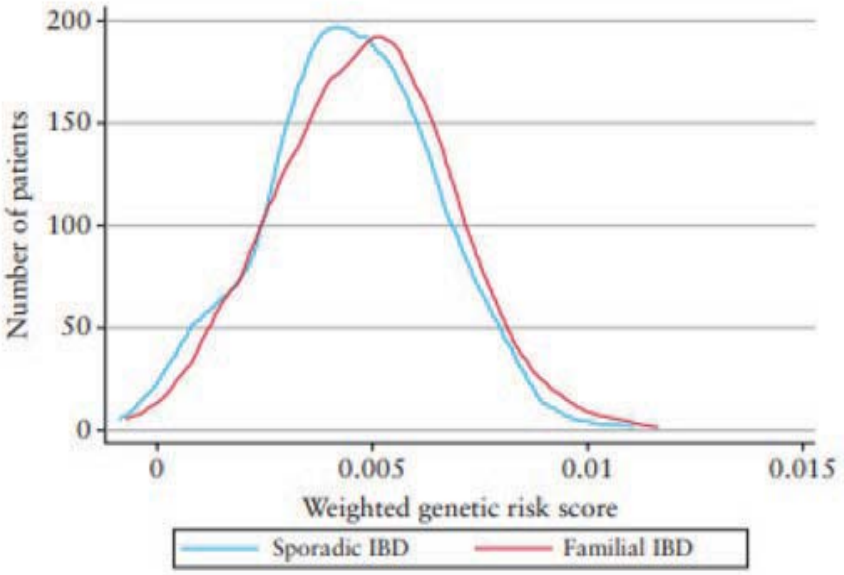





**Genetic analysis**

Genotype data for calculation of the weighted GRS was available in 1,277 patients (796 CD, 481 UC or IBD-U). Patients with familial IBD had a stronger genetic predisposition to develop IBD than those with sporadic IBD (p=0.006) (**Figure 2**). However, this difference was only in those with an affected first degree (p=0.004) but not second degree relative (p=0.35). The greater genetic predisposition was also noted only in those with a concordant family history (p=0.03) than when there was discordance for type of IBD (p=0.19). In CD, five SNPs were differently distributed between sporadic and familial CD with a p-value < 0.01 (**Supplemental Table 2**). One SNP (rs1569328), coding for FOS (FOS proto-oncogene, AP-1 transcription factor subunit), a regulator of TGF-β mediated signaling achieved significance above the false discovery threshold with a minor allele frequency of 18% in familial IBD compared to 10% in sporadic disease (OR 1.934, $p=1.27 \times 10^{-5}$). This achieved a p-value of 0.0012 in CD patients with a concordant (18% vs. 11%) but not discordant family member (17% vs. 12%, p=0.16). None of the SNPs met a p-value threshold of 0.01 for differential distribution between sporadic and familial disease among those with UC.

**Figure 2: Comparison of inflammatory bowel disease genetic risk score between familial and sporadic disease.**




**Microbiome analysis**

Stool was available for 16s rRNA microbiome analysis from 268 patients. IBD patients with a positive family history had a trend towards greater alpha-diversity than sporadic IBD (p=0.05, **Figure 3**). We noted some differences in the microbiome between sporadic and familial IBD, and by proximity to affected relative. Patients with familial IBD had greater abundance of *Ruminococcaceae* when compared to sporadic IBD (q=0.18) (**Supplemental Table 3**). Among those with an involved 1st degree relative, two families – *Lachnospiraeceae* and *Erysipelotrichaceae* (species *Eubacterum dolichum*) were more abundant in those with a family history while the genus streptococcus was less common than in those with sporadic IBD.

## DISCUSSION

Inflammatory bowel diseases are complex and heterogeneous in their natural history and are multi-factorial in origin with genetics, and consequently family history, being a strong risk factor for incident disease. Little is known about whether familial IBD differs from sporadic IBD in clinical characteristics, genetic architecture, or the gut microbiome. Using a large prospective cohort, we identified positive family history to be associated with earlier onset, complicated CD behavior, and need for IBD-related surgery. Also important in our findings is that the association with family history depends on proximity of relationship

to the index patient and concordance for type of IBD. We also describe a higher genetic burden in familial IBD and association with specific genetic polymorphisms in CD but not UC. In addition, certain microbial species were differentially abundant in the stool between familial and sporadic IBD.

It is widely accepted that the strongest risk factor for developing IBD is the presence of an affected first-degree relative with weaker influences of more distant relation.[4, 22, 23] The proportion with a positive family history in our study is similar to that noted in other studies[24-29], as is the concordance for type of IBD.[24] A key clinical observation from our study is that a positive family history was associated with stricturing or penetrating CD and an earlier age of diagnosis, and through these influences, greater need for IBD related surgery. This effect was notable primarily in those with an affected first degree relative and when the family member also had CD. Among first-degree relatives, the association was stronger when the affected family member was a sibling, consistent with prior studies demonstrating that siblings are at highest risk to develop IBD owing to being most genetically similar.[4, 25]



There is limited data on whether having an affected family member influences disease course in the index patient. Consistent with our study, Henriksen et al. found that familial disease had a younger age at diagnosis than sporadic disease among those with CD but not UC.[24] A meta-analysis by Childers et al. that included 71 studies with UC reported that a positive family history was more common in those with a younger age of diagnosis,[30] a finding also supported by a cohort from Korea.[31] The effect of family history on disease outcomes has yielded more conflicting results. A population-based cohort from Norway,[24] a small study of 181 Jewish CD patients[28] and a larger cohort of Finnish IBD patients[29], found no effect of family history on age at diagnosis, disease complications, and need for surgery. In contrast to these findings and consistent with our observations of the association between family history and disease severity, two larger studies from Korea noted more anti-TNF use[31, 32] and higher risk for CD-related surgery[31] in those with a positive family history compared to sporadic disease. A similarly large study using the national registry in Denmark by Trier Moller et al. also identified higher rates of major surgery in familial compared to sporadic CD and a shorter time to needing anti-TNF therapy in both familial CD and UC.[33] One reason for the differing results, in addition to the lack of statistical power in smaller studies, is that the effect of family history may be more nuanced and modified by proximity of relationship to the index patient and concordance for type of IBD, none of which have been examined in detail before.

Fewer studies have examined if familial IBD differs genetically from sporadic IBD and favors specific pathways. Prior studies have focused on either one or a few specific SNPs.[34-36] In a large Dutch study by Weersma et al., higher genetic burden defined as the number

of variants in 5 CD-specific SNPs was associated with diagnosis before the age of 40 years, and more complicated disease and need for IBD-related surgery.[35] Greater genetic predisposition has been linked to both early age at diagnosis15 and ileal involvement, the strongest predictor of disease behavior, which is supportive of our findings of a higher genetic risk score in familial compared to sporadic IBD.[27] There were no specific SNPs that were more commonly affected in familial UC; however in CD, variants at 5 SNPs including one at the FOS gene were nominally more common in familial disease. FOS plays a role in TGF-β signaling, which is important for the development of fibrosis in CD. Thus, the more common occurrence of FOS polymorphisms in familial CD may contribute to the higher risk of stricturing/penetrating phenotype in this cohort.

Gut microbial composition may predict progression of CD[37], and determine response to therapy.[38] While several studies have demonstrated that healthy relatives of patients with CD or UC demonstrate dysbiotic microbial profiles[39, 40], whether the microbiome of familial IBD differs from sporadic IBD has not been examined previously. Some of the differences in the microbiome between familial and sporadic IBD could contribute towards more complicated disease in the former. We found that a member of the *Ruminococcus* family was more common in individuals with a family history of CD. Interestingly, in a pediatric inception cohort the abundance of *Ruminococcus* was associated with the development of stricturing complications, consistent with our observation of the association of family history with complicated CD.[41] Other members belonging to *Ruminococcaceae*, in particular *R. gnavus*, was more abundant in patients with a discordant family history while *Dorea spp.* belonging to the family *lachnospiraeceae* was less common in those with an affected 2nd degree relative. In other cohorts, *R. gnavus* has been associated with CD disease activity while *Dorea spp.* have been inversely associated with active disease.[42] Thus, distinct microbial profiles of familial IBD influenced by shared genetic or environmental influences, may modify disease course in the index patient.

There are several limitations to this study. First, our study was at a tertiary referral centre which may be biased towards more severe disease when compared to a population-based cohort. Assessment of family history was done by a detailed questionnaire and we were unable to review records of family members to confirm diagnosis or ascertain IBD phenotype in relatives. However, the proportion with an affected family member in our cohort was similar to other studies supporting the generalizability of our findings. Third, information was also not available on time-varying covariates such as proximal extension of colitis or response to specific therapies. Our preliminary data suggesting some differences in disease phenotype lays the ground work for examining whether familial IBD differs from sporadic IBD in parameters such as response or lack thereof to specific therapies and for progression of disease. Fourth, information on genetics and the microbiome was available only in a small subset of patients, limiting our statistical

power. Larger cohorts are essential to more robustly define the similarities and differences between familial and sporadic IBD.

In conclusion, this large prospective cohort study provides evidence of earlier onset of disease in patients with familial IBD compared to sporadic cases of IBD. Furthermore, a family history of CD in 1st degree (but not 2nd degree) relatives was associated with complicated CD, strongest in those with an affected sibling and with concordance for type of IBD. This effect may be mediated through shared genetic risk factors and through differences in the microbiome. Our findings also provide useful data for risk stratification and determination of prognosis and disease course. Further studies in larger cohorts are essential to shed important light on the pathogenesis of these complex diseases.

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**Supplemental Table 1: Association between family history and need for IBD-related surgery, immunomodulator or biologic therapy in inflammatory bowel diseases**

| Type of family history | | Yes n(%) | No n(%) | p-value |
|---|---|---|---|---|
| **Any family member** | Biologics | 326 (48.1) | 653 (46.1) | 0.382 |
| | Immunomodulator | 416 (61.7) | 848 (60.7) | 0.642 |
| **1st Degree relative with IBD** | Biologics | 157 (43.7) | 822 (47.4) | 0.204 |
| | Immunomodulator | 215 (60.1) | 1,049 (61.2) | 0.686 |
| **2nd Degree relative with IBD** | Biologics | 218 (49.9) | 761 (46.0) | 0.143 |
| | Immunomodulator | 259 (59.5) | 1,005 (61.4) | 0.481 |
| **Concordant for type of IBD** | Biologics | 220 (47.3) | 759 (46.6) | 0.792 |
| | Immunomodulator | 285 (61.3) | 979 (60.9) | 0.886 |
| **Discordant for type of IBD** | Biologics | 106 (50.0) | 873 (46.4) | 0.321 |
| | Immunomodulator | 131 (62.7) | 1,133 (60.8) | 0.600 |

**Supplemental Table 2: Differentially distributed SNPs between familial and sporadic Crohn's disease**

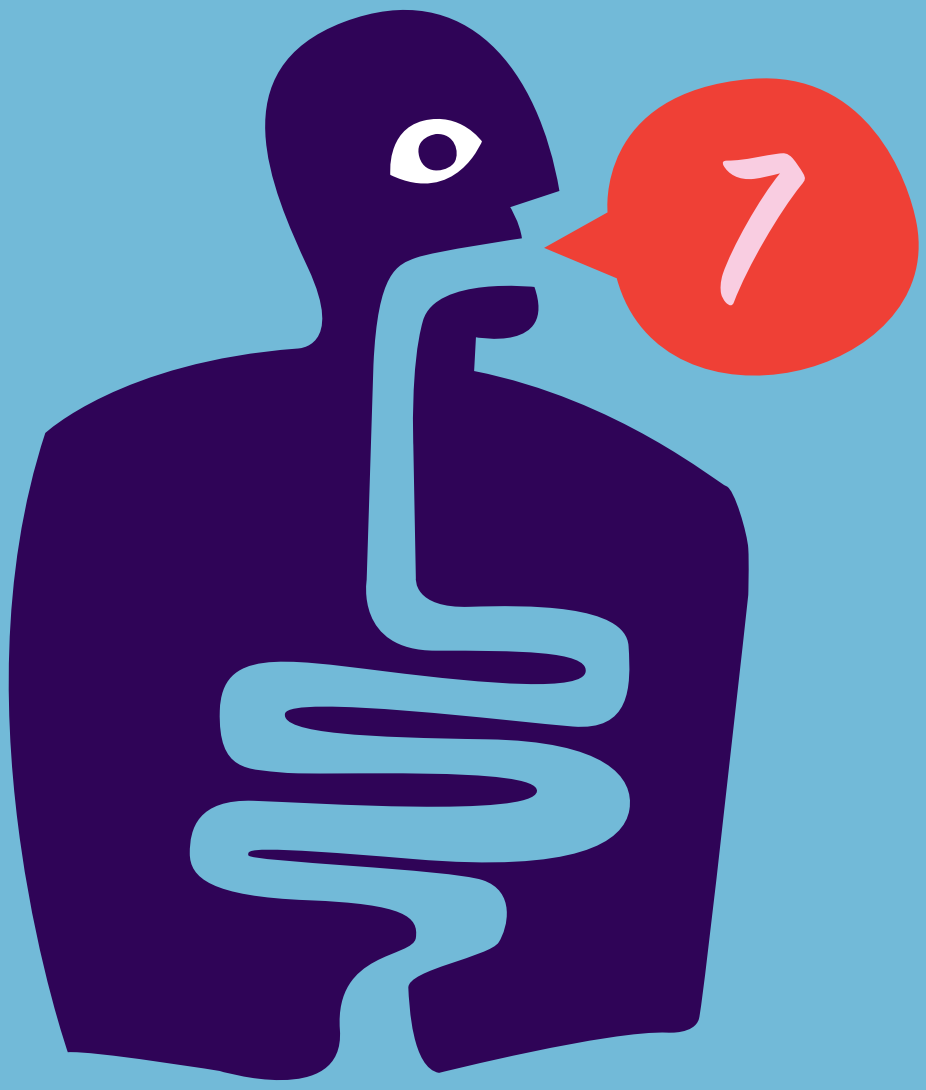
| Chr | SNP | Risk allele | Frequency | | p-value | Odds ratio | Putative genes at locus |
|---|---|---|---|---|---|---|---|
| | | | Familial IBD | Sporadic IBD | | | |
| 14 | rs1569328 | T | 0.18 | 0.10 | 1.27E-05 | 1.934 | FOS |
| 19 | rs11879191 | A | 0.14 | 0.21 | 0.000279 | 0.588 | **TYK2**,PPAN-P2RY11,ICAM1,(25) |
| 17 | rs1292053 | G | 0.40 | 0.48 | 0.003096 | 0.727 | TUBD1,RPS6KB1,(9) |
| 13 | rs3764147 | G | 0.33 | 0.27 | 0.006445 | 1.369 | LACC1,(3) |
| 7 | rs4728142 | A | 0.41 | 0.48 | 0.008312 | 0.753 | **IRF5**,TNPO3,TSPAN33,(11) |

Chr – chromosome; SNP – single nucleotide polymorphism

**Supplemental Table 3: Differences in the gut microbiome between sporadic and familial IBD on 16s rRNA analysis**

| Outcome (Yes vs. No) | Taxon | Coefficient | Number | P-value | Q-value |
|---|---|---|---|---|---|
| Familial IBD | k_Bacteria; p_Firmicutes; c_Clostridia; o_ Clostriales; f_Ruminococcaceae; g_; s_ | 0.008360817 | 172 | 0.00795607 | 0.184027271 |
| 1st Degree IBD | k_Bacteria; p_Firmicutes; c_Bacilli; o_Lacto-bacillales; f_Streptococcaceae; g_Strepto-coccus; s_ | -0.004379864 | 185 | 0.00489441 | 0.16475714 |
| 1st Degree IBD | k_Bacteria; p_Firmicutes; c_Erysipelptrichi; o_Erysipelotrichales; f_Erysipelotrichaceae; g_Eubacterium; s_dolichum | 0.01059649 | 204 | 0.00745847 | 0.180359419 |
| 1st Degree IBD | k_Bacteria; p_Firmicutes; c_Clostridia; o_ Clostridiales; f_Lachnospiraceae; g_; s_ | 0.01445223 | 208 | 0.00867696 | 0.192339184 |
| 2nd Degree IBD | k_Bacteria; p_Firmicutes; c_Clostridia; o_Clostridiales; f_Lachnospiraceae; g_Dorea; s_Formicigenerans | -0.017211321 | 148 | 0.00124616 | 0.09040314 |
| 2nd Degree IBD | k_Bacteria; p_Firmicutes; c_Clostridia; o_Clostridiales; f_Ruminococcaceae; g_Os-cillospira; s_ | 0.017105971 | 218 | 0.00177146 | 0.105295051 |
| Discordant IBD | k_Bacteria; p_Firmicutes; c_Clostridia; o_ Clostridiales; f_Lachnospiraceae; g_Blautia; s_Producta | 0.026787611 | 180 | 0.00000534 | 0.004762163 |
| Discordant IBD | k_Bacteria; p_Firmicutes; c_Clostridia; o_ Clostridiales; f_Lachnospiraceae; g_Rumino-coccus; s_Gnavus | 0.013396129 | 163 | 0.00586952 | 0.165106304 |
| Discordant IBD | k_Bacteria; p_Firmicutes;c_Erysipelotrichi; o_Erysipelotrichales; F_Erysipelotrichaceae; g_; s_ | 0.011994743 | 158 | 0.00780919 | 0.184027271 |

K – kingdom; p – phylum; c – Class; o – order; f – family; g – genus; s - species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# CHAPTER 7

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## Microbial and metabolomic alterations in fatigued patients with quiescent inflammatory bowel diseases: a prospective cohort study

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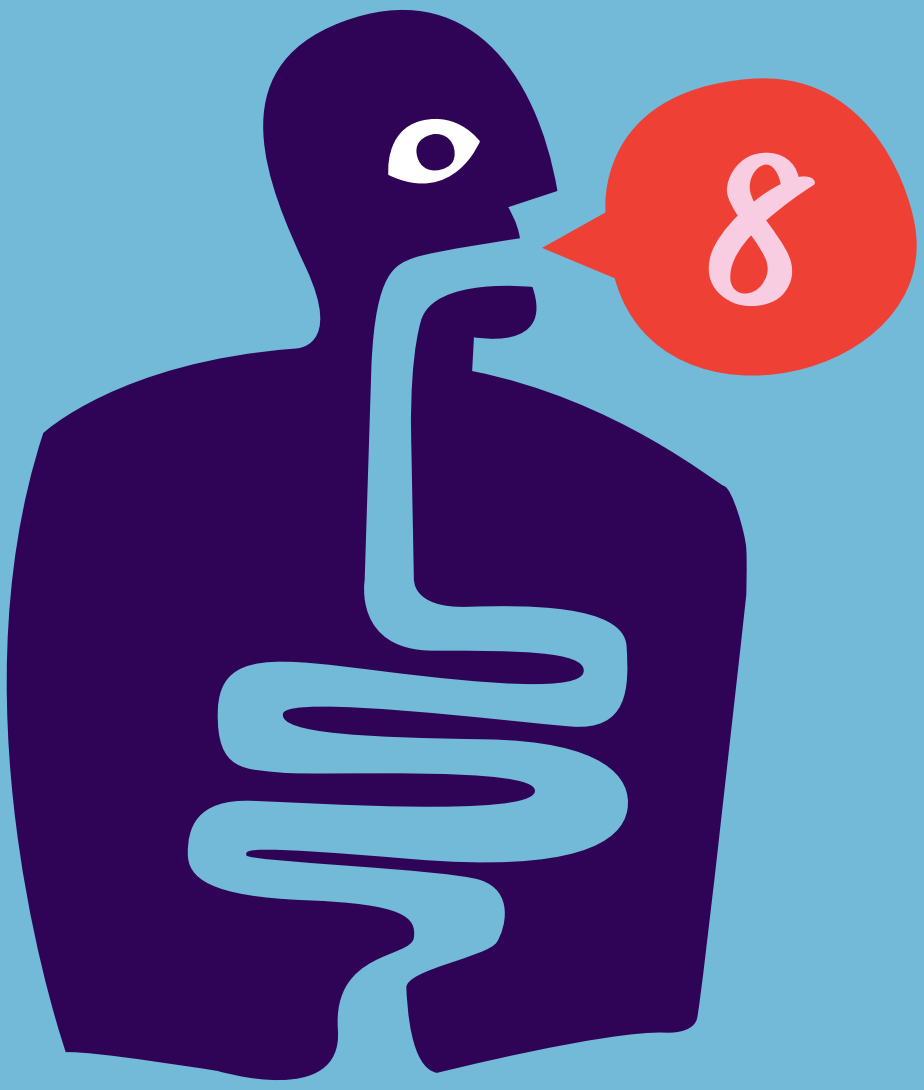
Nienke Z Borren, Damian Plichta, Amit D Joshi, Gracia Bonilla, Vincent Peng, Francis P Colizzo, Jay Luther, Hamed Khalili, John J Garber, C Janneke van der Woude, Ruslan Sadreyev, Hera Vlamakis, Ramnik J Xavier, Ashwin N Ananthakrishnan

*Submitted*



# CHAPTER 8

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## Summary & General Discussion

# SUMMARY & GENERAL DISCUSSION

This thesis aimed to provide more insight into clinical and biological factors influencing the quality of life of Inflammatory Bowel Disease patients. As clinicians and researchers, we tend to focus more on disease specific symptoms and objective disease markers and less on the quality of life which is one of the most important outcomes for patients. Therefore, little knowledge regarding determinants of quality of life are available and much remains unknown. In particular the pathophysiology of subjective symptoms such as fatigue, sleep and mood and their relation to IBD is unclear. This thesis started with exploring the current knowledge of the disabling symptom of fatigue in IBD patients followed by the assessment of the effect of new biological therapies on psychosocial symptoms such as fatigue, sleep and mood. The last part of this thesis used newly developed research technologies, known as 'omics research, to investigate the underlying mechanism of fatigue in IBD and to identify the impact of family history on the natural history of IBD.



## Quality of life & psychosocial symptoms

Living with a chronic disease can be a challenge for the patient and have a significant burden on the life of these patients. A large cohort study from Norway that followed newly diagnosed cases of IBD for five years, reported that 11.7% of the IBD patients were unemployed compared to 4.1% in the general Norwegian population[1]. Unemployment and sick leave were both negatively related to the patient's health related quality of life. Another important and high prevalent symptom in IBD patients with a profound negative effect on the quality of life is fatigue. Therefore, this thesis starts with a review (**Chapter 2**) that provided more insight in this disabling symptom and extensively discussed the current knowledge on the pathophysiology of fatigue. Although the exact aetiology of fatigue remains unknown, it's likely multifactorial with several contributing factors such as active inflammation, nutritional deficiencies and gut dysbiosis. Emerging evidence suggests a bi-directional communication system between gastrointestinal tract and the central nervous system, known as the gut-brain axis, and that disruption of the gut microbiome might contribute to the development of fatigue and other psychological symptoms[2, 3]. As stated in the review, several potential factors and underlying pathways that mediate fatigue have been identified and improved our understanding of fatigue in IBD but also highlight the urgent need for more fundamental research to unravel the exact pathophysiology of this frequented reported symptom. Due to the unclear pathophysiology and given the several challenges faced by clinicians treating these IBD patients – including the heterogeneity of symptom presentation and variety of therapeutic options with potential adverse effects – the assessment of fatigue and quality of life is often neglected, resulting in poorer disease outcomes. Indeed, quality of life was one of the main determinants of permanent work disability in patients with IBD[4]. Additionally, the research on therapies for fatigue is

scarce and limited to behavioural adjustments with short-term effect. Resulting in poor treatment of this disabling symptom.

## Biologic therapies & psychosocial symptoms

As stated in our previous review, fatigue is multifactorial and current therapy strategies might contribute to improvement of psychosocial symptoms but little evidence from research studies is available. Main focus of many research studies in IBD is to develop new therapeutic agents targeting specific parts of the immune system and evaluate their ability to reduce clinical symptoms and induce disease remission. However, IBD is not limited to the gut alone but also encompasses psychosocial disabilities but these psychosocial symptoms are rarely included as disease outcomes in pharmaceutical clinical trials. This motivated us to evaluate the effect of these new therapeutic biological agents on fatigue symptoms (**Chapter 3**). In parallel of improved disease activity symptoms, amelioration of fatigue symptoms after initiation of biologic therapy was observed in the first year. Although, it should be noted that the majority of the patients (61%) initiating one of these biologic agents remain fatigued at 1 year. Even if they achieved clinical remission, one third of these patients continued to experience significant fatigue symptoms. Although some patients were lost in follow up due to no effective response and consequently discontinuation of the therapy, it's likely that these patients had increased disease activity resulting in greater fatigue. Thus, our results could be an underestimation. Similar rates of residual fatigue while on biological therapy were observed in other autoimmune diseases treated with biologic agents. A large British registry for Rheumatoid Arthritis reported that 63% of the patients (n=271) continued to experience fatigue, despite achieving disease remission with anti-TNF therapy[5]. These results together show that amelioration of fatigue symptoms is only partially mediated through an improvement in disease activity and inflammation but there is likely another unknown pathway.

Another understudied extra-intestinal manifestation of IBD with profound impact on the quality of life is sleep impairment. Existing research suggest that there is a bidirectional interaction between active inflammation and sleep disturbance. Elevated inflammatory markers such as C-reactive protein, IL-1, IL-6 and TNF-α have shown strong association with poor sleep quality[6-9] and vice versa increased sleep disturbance may increase the risk of relapse of disease[10]. In parallel to sleep disturbance symptoms, similar associations have been observed for depressive and anxiety symptoms. While sleep and mood affect the patients functioning and decrease the quality of life, the symptoms are frequently poorly addressed and treated in IBD. Given the fact that new biological agents such as anti-TNF and anti-integrin demonstrated efficacy in achieving clinical, mucosal and endoscopic remission and reducing the need for surgical intervention and hospital admission, it is reasonable to presume that these agents may improve psychosocial

outcomes of IBD patients. Consequently, we performed a prospective cohort study in patients with moderate-to-severe IBD initiating biological therapy with vedolizumab or anti-tumour necrosis factor α (anti-TNF) (**Chapter 4**). Both vedolizumab and anti-TNF therapies showed significant reduction in disturbed sleep symptoms within 6 weeks of start of therapy (sleep T-score 52.8 vs 49.8 respectively, p=0.002) and continued at week 14 (49.2, p=0.002). Although available mood measurements at follow up was limited, improvement in both depression and anxiety was noted especially in the group that received vedolizumab therapy and a trend towards significance in the anti-TNF receiving group. Along with these positive results, disease activity improved with 48% of the enrolled patients achieving clinical remission at week 14. Those patients that achieved clinical remission at week 14 were less likely to experience disturbed sleep (13% vs 31%, p=0.010), depressive (18.2% vs 47.3%, p=0.002) and anxiety symptoms (34.1% vs 56.4%, p=0.027) compared to those that continued to have active disease. Thus, it is important to achieve disease remission which could decrease pro-inflammatory cytokines resulting in improved sleep symptoms in IBD patients. Whether amelioration of sleep and mood symptoms was mediated through improvement in gut inflammation only or by a direct communication system with the central nervous system remains unclear.



These advanced therapeutics offer physicians multiple effective treatment options to treat IBD patients but management of IBD also becomes more complex and increasingly specialized. A delay in optimal treatment of IBD can result in worsening disease outcomes followed by a decrease of quality of life. Thus, IBD patients would benefit from a gastroenterologist that is specialized in IBD care. Prior studies have shown that medical centers offering specialized IBD care had better disease outcomes and lower mortality for up to 1 year after hospital discharge[11] and earlier access to IBD-specific surgical treatment[12]. However, a center specialized in IBD is not naturally close to home and several patients have to travel a great distance to access such care, which potentially could delay initiation of optimal medical care. One can envision that patients living further away from specialized care might be at higher risk for worsening disease outcomes. Therefore, we assessed the impact of travel distance to a specialized IBD hospital (**Chapter 5**). The primary exposure of interest was the travel distance to Massachusetts General Hospital (MGH) which was divided in quartiles with the higher quartiles increasingly further distant to the hospital. Those patients with the greatest distance (most distant quartile) to the hospital were at higher risk to need IBD-related surgical intervention in comparison to those living in the closest quartile (OR 2.44, 95% CI 1.80-3.32). Additionally, we observed that those patients with the most distant travel distance had a two-fold increased risk to need biologic therapy (OR 2.19, 95% CI 1.69 – 2.85). Although MGH is known to welcome referred IBD patients with more complicated disease which could bias the results, we think the referral bias is not solely explaining our findings. As similar results were observed when analysis was restricted to travel distance within 40 or 80 kilometers and

the patients recruited for the study were not one-time consultation visits. Prior research studies have suggested to centralize specialized health care to share specific knowledge, improve quality of care and disease outcomes, and to reduce health care costs[13]. However, these specialized high volume healthcare centers are often located in large city centers, resulting in a greater physical distance and followed by limited access for patients living further away. As we observed in this study, this greater travel distance may lead in poorer disease outcomes or could negatively influence the benefit of receiving specialized care. A solution to minimize the impact of the travel distance could be the use of telemedicine to deliver specialized care and early results have shown promising results[14].

## Multi-'omics

The final part of this thesis made use of new advanced techniques that allow us to characterize complex biological processes in great detail. As a prior study demonstrated that disease activity contributed for 37% of health-related quality of life[15], we were looking for which factors influence the IBD disease course. Several factors have been identified to be associated with a complex disease course such as tobacco use[16], disease behavior and young age at diagnosis[17]. However, the impact of an IBD family history on disease course has never been assessed before. In a large prospective cohort study, we demonstrated that IBD patients with a known IBD relative are more likely to have an earlier disease onset and higher need for IBD-related surgery compared to those patients without (**Chapter 6**). Additionally, a family history of CD in first-degree relatives was associated with a more complicated CD behavior. Genotype data was available for over half of the cohort and demonstrated that patients with an affected first-degree IBD relative had a higher genetic predisposition to develop IBD than those with sporadic IBD ($p=0.004$) and only noted if the IBD relative was concordant for type of IBD ($p=0.03$). The distribution of five SNPs in CD patients was noted to be significantly different between familial CD and sporadic patients ($p<0.01$) but none of these SNPs was associated with familial UC. Additionally, metagenomic analysis was performed in a subset of the study population and observed higher abundance for *Ruminococcaceae* in familial IBD in comparison with sporadic IBD. Interestingly, prior research in a paediatric study population demonstrated a strong association between *Ruminococcaceae* abundance and more complicated stricturing disease[18], which is in line with our observation of the link between family history and complicated CD disease. Although the 'omics analysis was only done in a subset of the cohort, the results demonstrate that family history have effect on disease outcomes and this might be mediated through an underlying gut dysbiosis and through shared genetic predisposition.

As described previously, fatigue is prevalent in IBD patients despite quiescent inflammation and has a negative effect on their quality of life. The exact pathophysiology remains

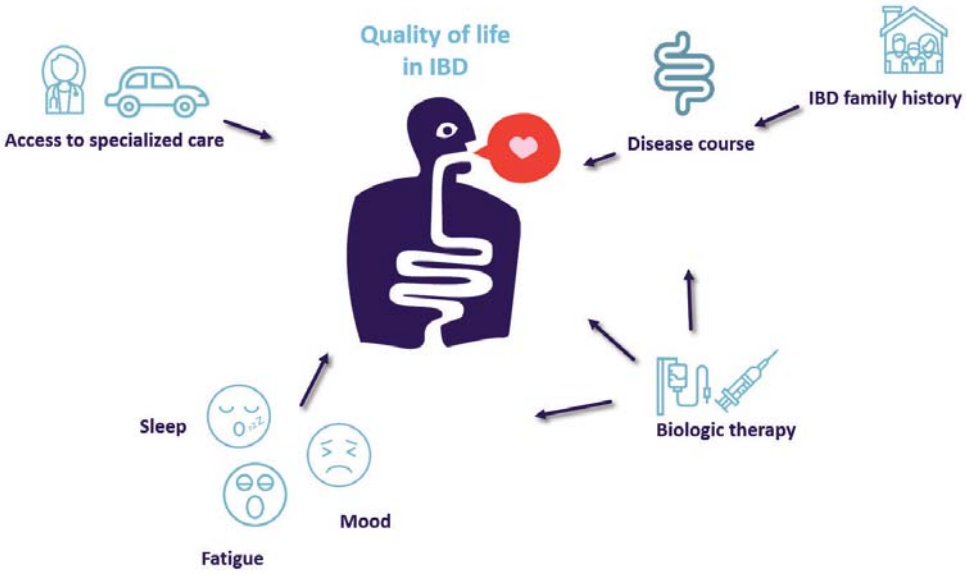
unclear and has not been previously explored despite the high impact. We leveraged a prospective observational cohort of IBD patients in clinical and endoscopic remission and compared those patients with fatigue to those without fatigue symptoms (**Chapter 7**). Using 'omics profiling, the serum proteome, metabolome and gut microbiome was analyzed to assess their role in mediating fatigue. Evidence was provided that fatigue is not likely a consequence of overt systemic inflammation but likely an underlying gut dysbiosis and metabolic alterations may play a role. Novel associations between metabolomic alterations such as depletion in tryptophan and other branched chain amino acids was observed in patients with fatigue and these findings were underpinned by underlying gut microbial perturbations including reduced butyrate-producing bacteria *Faecalibacterium Prausnitzii* and *Roseburia hominis*. Despite the limited available feces samples for metagenomic analysis, we were able to show a clear separation of microbial composition and function was seen between patient with and without fatigue. These data suggest that IBD goes beyond the gut suggesting a link between the gut and brain. The findings lay a foundation for a comprehensive study of fatigue and is a step forward to discovering specific biomarkers and novel treatments for this debilitating symptom.



## Conclusion

In this thesis, we were able to show an evident relationship between IBD and psychosocial factors from the close links and confirmed our title that IBD is not limited to the gut but goes beyond with great impact on the quality of life of these patients (**Figure**). Psychosocial symptoms and the gut are likely highly connected through several pathways and to our knowledge, we were the first to use comprehensive 'omics techniques to identify changes in the gut microbiome and metabolic alterations leading to fatigue symptoms. By publishing these results, we aim to improve the current knowledge of the patients and health-care providers about the prevalence and burden of psychosocial symptoms which may lead to better addressing of these frequently underreported IBD symptoms during routine patient care. Consequently, this might result in higher efforts to continue studying psychosocial symptoms in IBD (and beyond) into the underlying mechanism(s) and to translate the gained knowledge to effective therapeutic options with the ultimate goal to improve the quality of life of our patients.

**Figure: "Beyond the gut" determinants of quality of life in IBD patients shown in this thesis.**




## Future directions

Overall, this thesis gave more insight into psychosocial symptoms in IBD and their effect on the quality of life of IBD patients but also highlights the urgent need of further experimental and translational studies to identify the full mechanism of the interplay between the gut and psychosocial symptoms.

First, it is very valuable to include psychosocial assessments as constructive outcomes in future cohort studies and clinical trials to confirm that not only improvement in gut inflammation and the related consequences is achieved but also a similar beneficial result in the psychosocial outcomes of IBD. By routinely measuring these symptoms within clinical trials will offer new lines of intervention resulting in improved quality of care.

Further longitudinal studies for psychosocial symptoms in IBD like fatigue are necessary to evaluate potential underlying mechanisms that could take place antecedent to psychosocial symptoms and vice versa. The heterogeneity of its presentation and the multidimensionality of contributing factors suggest that the mechanism of psychosocial symptoms is not consistent in the entire population and implies that there might be several subtypes and grades of psychosocial symptoms within IBD patients. Additionally, these studies should include variables such as diet, physical activity and other lifestyle variables.

Our research group has initiated a study that combines clinical and translational research and follows quiescent IBD patients for two years with the aim to define subgroups of fatigue within the study population and identify the associated underlying mechanisms.

A key step towards unraveling the exact pathophysiology of these symptoms in IBD might be achieved by using a multi-'omics approach. These techniques are evolving and extremely valuable to extract a large amount of biological data with potentially clinical relevant information. Although we are just at the beginning of using multi-'omics approaches, it is promising that these techniques will provide us more insight into complex interactions between the gut and the brain and potentially identify biomarkers to objectively measure these symptoms. Ultimately, the gained knowledge may be translated into the development of novel therapeutics to effectively treat psychosocial symptoms.



Literature on effective therapies for psychosocial symptoms is sparse, some patients might benefit from microbiome-directed therapies while other patients benefit from physical exercise therapies or behavioural therapies. Interventions that attend to the bidirectional interplay between the gut and psychological factors could yield improved disease outcomes in patients with IBD and result in enhanced quality of life. One potential avenue may be microbiome-directed therapies such as fecal transplantations and probiotic therapy. Another initiative from our research group is an international multi-center randomized placebo controlled trial to examine the efficacy of a multi-strain probiotic mixture in relieving fatigue symptoms. Additionally, this study will provide us more information about probiotic therapy feasibility, side effects and if there is effect of probiotic therapy on the gut microbiome. These studies in combination with translational studies will likely help in understanding the underlying mechanism of psychosocial symptoms in IBD and may result in development of (long-term) effective therapies that ameliorate such symptoms.

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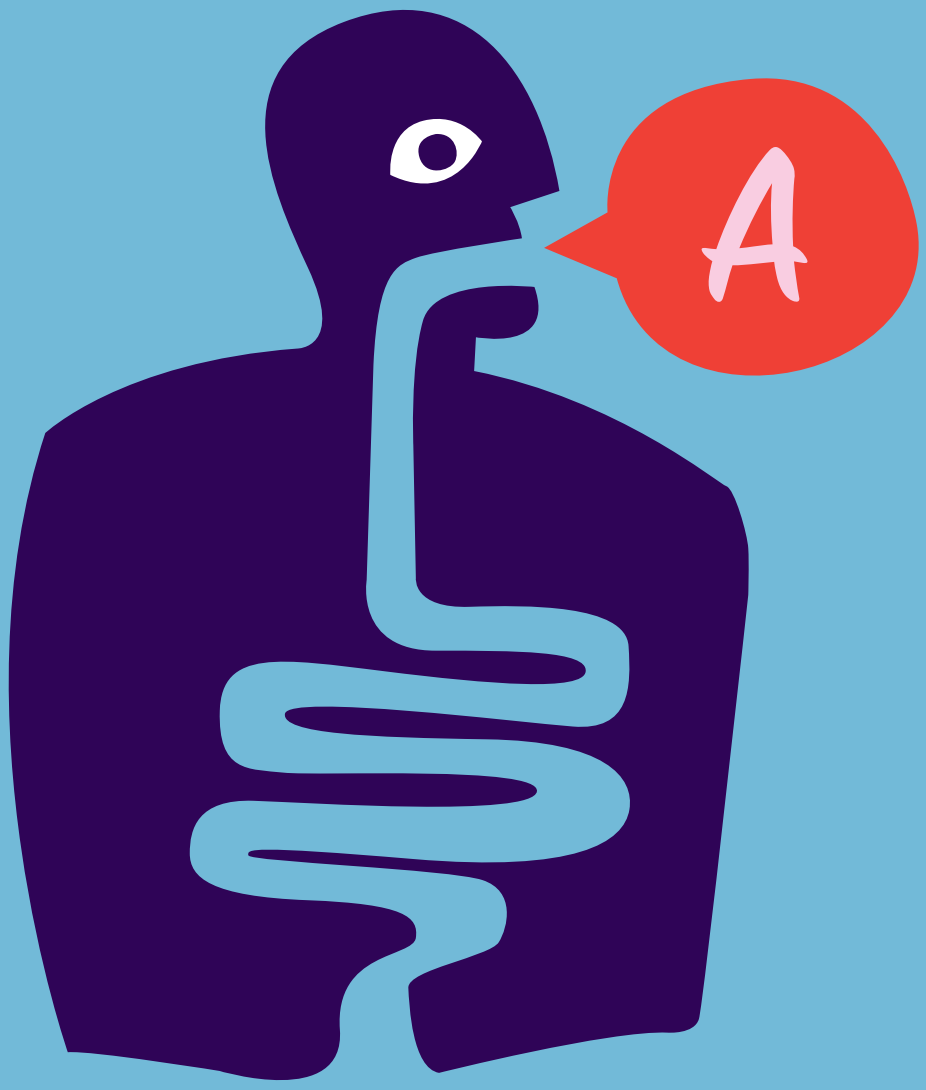
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# APPENDICES

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Nederlandse samenvatting
Contributing authors
List of publications
PhD portfolio
Dankwoord
About the author

## NEDERLANDSE SAMENVATTING

Het doel van dit proefschrift is om meer inzicht te geven in klinische en biologische factoren die de kwaliteit van leven van patiënten met een inflammatoire darmziekte (IBD) beïnvloeden. Als artsen en onderzoekers zijn we meestal meer gefocust op objectieve ziekte parameters terwijl de patiënt de kwaliteit van leven juist belangrijk vindt. Hierdoor schiet de huidige kennis ten aanzien van (behandelbare) factoren die de kwaliteit van leven beïnvloeden tekort. Dit proefschrift begint daarom met een uitgebreid overzicht van de huidige literatuur over één van de door IBD patiënten meest gerapporteerde symptomen: vermoeidheid. Vervolgens wordt onderzocht wat het effect is van de relatief nieuwe immunotherapieën op symptomen die de kwaliteit van leven negatief beïnvloeden, zoals vermoeidheid, slaap, depressie en angst maar ook wat de invloed is van de reisafstand naar het ziekenhuis voor patiënten hierop. In het laatste gedeelte van dit proefschrift wordt gebruik gemaakt van nieuwe ontwikkelingen in de wetenschap: de 'omics' technologieën. Met deze nieuwe technieken onderzochten we de onderliggende pathofysiologie van vermoeidheid in IBD en voorts welke impact een bekende IBD familiegeschiedenis heeft op het ziektebeloop.



### Kwaliteit van leven & psychosociale symptomen

Het leven met een chronische ziekte is een uitdaging voor de patiënt en is van grote invloed op het leven. Eerder onderzoek liet zien dat patiënten die recent gediagnosticeerd waren met IBD een hogere werkeloosheid meldden vijf jaar na diagnose in vergelijking met de algemene bevolking en dit was negatief gerelateerd aan kwaliteit van leven van de patient[1]. Een ander belangrijk en veelvoorkomend symptoom bij IBD patiënten met negatief effect op de kwaliteit van leven is vermoeidheid. Vandaar dat dit proefschrift begint met een overzicht van de huidige kennis van vermoeidheid (**Hoofdstuk 2**) In dit hoofdstuk geven wij meer inzicht over de mogelijke pathofysiologie van vermoeidheid. Hoewel de exacte etiologie van vermoeidheid niet bekend is, is het zeer waarschijnlijk multifactorieel bepaald met verschillende bijdragende factoren zoals actieve inflammatie, vitaminen deficiënties en een verstoorde samenstelling van de darmbacteriën. Er is een communicatiesysteem, dat in twee richtingen communiceert tussen het darmstelsel en het centrale zenuwstelsel, ook wel bekend als de "gut-brain axis". Verstoring van het microbioom in de darm zou kunnen bijdragen aan het ontwikkelen van vermoeidheid en andere psychologische symptomen[2, 3]. Het hoofdstuk laat echter ook zien dat er nog veel meer fundamenteel onderzoek gedaan moet worden naar de exacte pathofysiologie van moeheid. Hierdoor schiet de behandeling van deze symptomen bij IBD patiënten te kort met als gevolg slechtere ziekte uitkomsten en kwaliteit van leven. Dit werd bevestigd in een onderzoek waarbij vermoeidheid een bepalende factor bleek te zijn voor permanente arbeidsongeschiktheid bij IBD patiënten[4].

## Biologicals & psychosociale symptomen

Zoals beschreven in hoofdstuk 2, is vermoeidheid multifactorieel en mogelijk dragen huidige medicamenteuze behandelingen bij aan het verbeteren van psychosociale symptomen, echter is er maar beperkt bewijs beschikbaar van wetenschappelijke onderzoeken. De focus van de meeste wetenschappelijke studies in IBD is gericht op het ontwikkelen van nieuwe therapieën die aangrijpen op specifieke delen van het immuunsysteem en het effect van deze therapieën op het verminderen van symptomen en behalen van ziekte remissie. Echter, IBD beperkt zich niet tot de darm maar manifesteert zich ook buiten de darm waarbij ook psychosociale symptomen horen maar deze symptomen worden zelden meegenomen als uitkomstmaten in farmaceutische onderzoeken. Daarom hebben we het effect van biologicals op vermoeidheidsklachten onderzocht (**Hoofdstuk 3**). Naast een verbetering in ziekteactiviteit werd bij een deel van de patiënten ook een verbetering in vermoeidheid gezien na start van een biological. Helaas bleek een meerderheid van de patiënten (61%) nog steeds vermoeidheidsklachten hebben 1 jaar na start van therapie. Zelfs als ziekte remissie werd bereikt, bleef één derde van de patiënten last houden van moeheid. We vermoeden zelfs dat onze resultaten een onderschatting kunnen zijn. Enkele patiënten hadden geen vervolg resultaten doordat ze geen effectieve respons op de therapie hadden en daarom met de therapie stopten; daardoor is het zeer waarschijnlijk dat deze patiënten een actieve ziekte hadden met als gevolg meer last van vermoeidheid. Overigens is bij andere auto-immuunziekten zoals reumatoïde artritis ook gerapporteerd dat een vergelijkbaar percentage patiënten last blijft houden van vermoeidheid na start van biological therapie. Een groot Brits onderzoek voor reumatoïde artritis rapporteerde dat 63% van de patiënten (n=271) last bleef hebben van moeheid, ondanks het behalen van ziekte remissie met anti-TNF therapie[5]. Derhalve menen wij te mogen concluderen dat verbetering van vermoeidheidsklachten gedeeltelijk te wijten is aan de verbetering in ziekte activiteit en verlaging van de inflammatie maar zeer waarschijnlijk is er ook nog een ander onbekend mechanisme.

Slecht slapen is een ander onderbelicht IBD symptoom dat zich buiten de darm manifesteert en een negatieve impact heeft op de kwaliteit van leven. Eerder onderzoek suggereert dat er een interactie is tussen actieve inflammatie en slecht slapen. Verhoogde inflammatie markers zoals C-reactive protein, IL-1, IL-6 en TNF-α lieten een sterke associatie zien met slaap kwaliteit[6-9] en slecht slapen lijkt geassocieerd  met een opvlamming[10]. Soortgelijke associaties zijn ook geobserveerd voor angst- en depressieklachten waar zelfs meer ziekenhuisopnames en operaties werden beschreven. Omdat wij weinig geïnformeerd zijn over de slaap en gemoedstoestand van onze patiënten hebben we onderzoek verricht en gekeken of therapieën zoals anti-TNF therapie mogelijk deze symptomen kunnen verbeteren. In **Hoofdstuk 4** hebben we een prospectieve cohort studie uitgevoerd bij patiënten met matig-tot-ernstige IBD die startten met biological therapie vedolizumab

of anti-tumor necrosis factor α (anti-TNF). Zowel vedolizumab als anti-TNF therapie toonden een significante vermindering van slaapstoornissymptomen binnen 6 weken na het starten van de therapie (slaap T-score 52.8 vs 49.8 respectievelijk, p=0.002) en dit continueerde bij week 14 (49.2, p=0.002). Daarnaast werden er ook verbeteringen voor zowel depressie als angstklachten waargenomen, met name in de vedolizumab therapie groep en een trend richting significantie voor de anti-TNF therapie groep. De patiënten die klinische remissie behaalden op week 14 hadden minder last van slecht slapen (13% vs 31%, p=0.010), depressieve klachten (18.2% vs 47.3%, p=0.002) en angstklachten (34.1% vs 56.4%, p=0.027) vergeleken met de patiënten die geen ziekte remissie behaalden. Hieruit mogen we concluderen dat het belangrijk is om remissie van de ziekte te bereiken en dat mogelijk hierdoor bepaalde pro-inflammatie eiwitten afnemen met daarbij verbetering van de slaap kwaliteit van IBD patiënten. Of deze verbetering van slaap en gemoedstand wordt bewerkstelligd door verbetering van de darmontsteking alleen of door een direct communicatiesysteem met het centrale zenuwstelsel blijft onduidelijk.



Nieuwe behandelingen bieden artsen en patiënten met IBD meerdere opties om ziekte remissie te bereiken, maar het behandelen van IBD wordt hierdoor ook meer complex en zeer gespecialiseerd. Daarom zouden IBD patiënten baat kunnen hebben bij een Maag-, Darm en Leverarts gespecialiseerd in de behandeling van IBD. Eerdere studies hebben laten zien dat medische centra die gespecialiseerde IBD-zorg aanboden betere ziekte uitkomsten en lagere mortaliteit toonden na 1 jaar na ziekenhuisopname[11 12]. Echter een expert IBD centrum is niet vanzelfsprekend dichtbij huis; patiënten die verder weg wonen van gespecialiseerde zorg zouden een hoger risico kunnen hebben op slechtere ziekte uitkomsten. Daarom hebben we de impact van de reisafstand naar een gespecialiseerd IBD ziekenhuis onderzocht in **Hoofdstuk 5**. De reisafstand naar Massachusetts General Hospital (MGH) werd gedeeld in kwartielen waarbij de hogere kwartielen een grotere afstand naar het ziekenhuis betekenden. De patiënten met de grootste reisafstand (hoogste kwartiel) naar het ziekenhuis hadden een grotere kans dat een IBD-gerelateerde chirurgische interventie noodzakelijk was vergeleken met hen die in het dichtstbijzijnde kwartiel woonden (OR 2.44, 95% CI 1.80-3.32). Bovendien hadden de patiënten met de grootste reisafstand een tweevoudig hoger risico om een biological therapie te starten (OR 2.19, 95% CI 1.69 – 2.85). Weliswaar staat het MGH bekend om doorverwezen IBD patiënten met gecompliceerde ziekte te behandelen en dit zou onze resultaten beïnvloed kunnen hebben maar wij veronderstellen dat dit niet de enige uitleg kan zijn voor de resultaten. Reden hiertoe is dat vergelijkbare resultaten geobserveerd werden wanneer de analyse werd beperkt tot een reisafstand van 40km of 80km en daarnaast werden geen patiënten geïncludeerd die voor een eenmalige consultatie kwamen. Eerdere onderzoeken suggereren om gespecialiseerde zorg samen te brengen in één centrum om zo specifieke kennis te delen, zorgkosten te reduceren en verbeteren van de kwaliteit van de zorg en ziekte uitkomsten[13]. Echter, deze grote gespecialiseerde medische centra staan

vaak in grote steden, resulterend in een grotere reisafstand en verminderde toegang tot gespecialiseerd IBD-zorg voor patiënten die ver weg wonen. Zoals gezien in deze studie, kan een lange reisafstand leiden tot slechtere ziekte uitkomsten en kan het juist een negatieve invloed hebben op het goede effect van gespecialiseerde zorg. Een oplossing om de impact van de reisafstand te minimaliseren zou het gebruik van 'telemedicine' kunnen zijn om zo gespecialiseerde zorg te kunnen leveren en de eerste resultaten zijn veelbelovend[14].

## Multi-'omics

In het laatste deel van dit proefschrift wordt gebruik gemaakt van nieuwe laboratoriumtechnieken die het mogelijk maken om complexe biologische processen tot in detail te onderzoeken. Een eerdere studie toonde aan dat ziekte activiteit voor 37% bijdraagt aan de kwaliteit van leven[15] en om die reden hebben we gekeken naar factoren die invloed hebben op het ziektebeloop van IBD. Verscheidene factoren zijn bekend voor een complex ziektebeloop zoals roken[16], ziektegedrag en IBD diagnose op jonge leeftijd[17]. Maar de impact van een bekende familiegeschiedenis voor IBD op het ziektebeloop werd niet eerder onderzocht. In een grote prospectieve cohort studie hebben we aangetoond dat IBD patiënten die ook een familielid met IBD hebben vaak eerder worden gediagnosticeerd met IBD en eerder IBD-gerelateerde chirurgie nodig hebben in vergelijking tot patiënten zonder een familielid met IBD (**Hoofdstuk 6**). Daarnaast is een bekende familiegeschiedenis voor de ziekte van Crohn (CD) bij een eerstegraads familielid geassocieerd aan een gecompliceerd beloop van CD. Genetische data waren beschikbaar voor de meerderheid van de studiepopulatie en liet zien dat patiënten met een eerstegraads IBD familielid een grotere genetische aanleg hadden om IBD te ontwikkelen dan patiënten zonder IBD familiegeschiedenis ($p=0.004$) en als het familielid met IBD ook hetzelfde type IBD had ($p=0.03$). De distributie van vijf single nucleotide polymorphisms (SNPs) in CD patiënten was significant verschillend tussen patiënten met een familielid met CD diagnose en patiënten zonder ($p<0.01$). Geen van deze SNPs werd gelinkt aan familie-gerelateerde colitis ulcerosa (CU). Daarnaast werd een metagenomic analyse uitgevoerd bij een deel van de studiepopulatie waarbij een hogere aanwezigheid van de *Ruminococcaceae* werd gezien in familie gerelateerde IBD in vergelijking met patiënten zonder IBD familiegeschiedenis. Opvallend is dat eerder onderzoek bij kinderen met IBD een sterke correlatie toonde tussen *Ruminococcaceae* aanwezigheid en gecompliceerde CD met vernauwingen[18]. Dit is in overeenstemming met onze resultaten die een link toonden tussen IBD familiegeschiedenis en gecompliceerde CD. Weliswaar was de 'omics analyse enkel beschikbaar in een gedeelte van het studie cohort, toch laten onze resultaten zien dat een familiegeschiedenis voor IBD effect heeft op het ziektebeloop en dit mogelijk veroorzaakt wordt door een onderliggend verstoord microbioom en gezamenlijke genetische aanleg voor IBD.

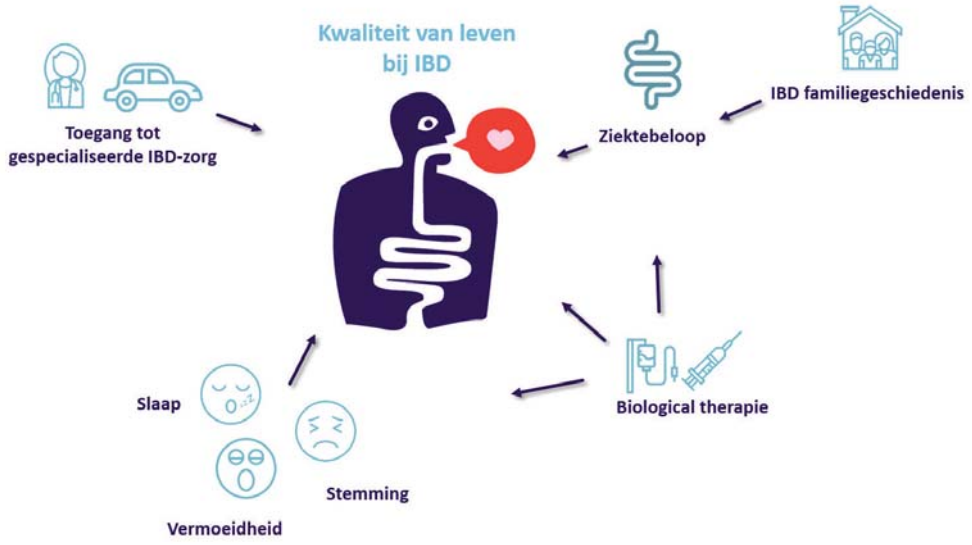
Zoals eerder beschreven, vermoeidheid is een groot probleem voor IBD patiënten ondanks dat de ziekte in remissie is. De exacte pathofysiologie blijft onduidelijk en werd niet eerder uitgebreid onderzocht ondanks de grote impact op de kwaliteit van leven. In het laatste hoofdstuk (**Hoofdstuk 7**) van dit proefschrift werden IBD patiënten met vermoeidheidsklachten vergeleken met IBD patiënten zonder vermoeidheidsklachten waarbij alle patiënten in klinische en endoscopische remissie verkeerden. Door gebruik te maken van 'omics technieken werd het serum voor het proteoom en metaboloom en ontlasting voor het microbioom geanalyseerd om na te gaan of verschillen hierin een rol spelen bij de ontwikkeling van vermoeidheidsklachten. De resultaten van de analyses lieten zien dat vermoeidheid waarschijnlijk niet een gevolg is van een systemische inflammatie maar dat mogelijk een onderliggend verstoord microbioom en veranderingen in het metaboloom een rol spelen. Nieuwe associaties tussen veranderingen in het metaboloom zoals verlaagd tryptofaan en andere 'branched chain' aminozuren werden geobserveerd in patiënten met moeheid en deze resultaten werden onderbouwd door verandering in het microbioom zoals verminderde aanwezigheid van butyraat producerende bacteriën *Faecalibacterium Prausnitzii* en *Roseburia hominis*. Ondanks de beperkte beschikbaarheid aan ontlastingmonsters werd er een duidelijk verschil in microbioom samenstelling én functie gezien tussen patiënten met en zonder vermoeidheid. Deze resultaten laten zien dat IBD verder gaat dan enkel het darmstelsel en dat er een verband is tussen het darmstelsel en de hersenen. De resultaten leggen de basis voor een uitgebreid vervolg onderzoek naar vermoeidheid en zet een eerste stap richting de ontwikkeling van specifieke biomarkers en nieuwe behandelingen voor dit veelvoorkomende symptoom.



## Conclusie

Dit proefschrift heeft laten zien dat er een duidelijke relatie is tussen IBD en psychosociale factoren en bevestigt de titel dat IBD zich niet beperkt tot de darmen maar zich ook manifesteert daar buiten, met als gevolg een grote impact op het leven van deze patiënten (**Figuur**). Psychosociale symptomen en het darmstelsel staan zeer waarschijnlijk met elkaar in verbinding via verschillende routes en, naar ons weten, zijn we de eerste die zodanig gebruik maakten van uitgebreide 'omics' technieken om veranderingen te identificeren in het microbioom en metaboloom, die mogelijk kunnen leiden tot vermoeidheid. Door het publiceren van deze resultaten hopen we de huidige kennis van de patiënten en zorgverleners over de prevalentie en de belasting van psychosociale symptomen te verbeteren en mogelijk leidt dit tot het beter bespreekbaar maken en behandelen van deze veelvuldig gerapporteerde IBD symptomen in de dagelijkse kliniek. Daarnaast hoopt dit proefschrift er toe aan te zetten dat er meer onderzoek wordt verricht naar psychosociale symptomen in IBD en te motiveren om de onderliggende mechanismen te ontrafelen en de daarbij verkregen kennis om te zetten naar effectieve behandelstrategieën met als uiteindelijke doel om de kwaliteit van leven te verbeteren van onze patiënten.

**Figuur: "Buiten de darm" factoren die bepalend kunnen zijn voor de kwaliteit van leven bij IBD patiënten, zoals beschreven in dit proefschrift.**



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16. Borren NZ, Plichta D, Joshi AD, Bonilla G, Sadreyev R, Vlamakis H, Xavier RJ, Ananthakrishnan AN. Multi-'omics profiling in patients with quiescent Inflammatory Bowel Disease identifies biomarkers predicting relapse. *Submitted*

17. Borren NZ, Tan W, Jess AT, Li PH, Garber JJ, Luther J, Colizzo FP, Khalili H, Ananthakrishnan AN. Assessment of body weight changes in patients with Inflammatory Bowel Diseases initiating biologic therapy: a prospective cohort study. *Submitted*

## PHD PORTFOLIO

| Courses | ECTs |
|---|---|
| CITI Program Good Clinical Practice and Human Research | 1.0 |
| Harvard Catalyst course: Certificate in Applied Biostatistics | 4.5 |
| Harvard Catalyst course: Introduction to Omics Research | 2.5 |
| Erasmus MC course: Scientific Integrity | 0.3 |
| MolMed course: Microbiomics | 0.6 |
| MolMed course: Introduction on R | 1.8 |
| MolMed course: Photoshop and Illustrator CC | 0.3 |

| Attended conferences | |
|---|---|
| European Crohn's and Colitis Organisation (ECCO) conference, Barcelona, Spain, 2017 | 1.0 |
| Digestive Disease Week (DDW), Chicago, IL, USA, 2017 | 1.0 |
| Digestive Disease Week (DDW), Washington DC, USA, 2018 | 1.0 |
| Crohn's and Colitis Conference, Las Vegas, NV, USA, 2019 | 1.0 |
| Digestive Disease Week (DDW), San Diego, CA, USA, 2019 | 1.0 |
| IBD Today & Tomorrow, Amsterdam, 2019 | 0.5 |
| Nederlandse Vereniging voor Gastro-enterologie congres, Veldhoven, 2019 | 0.5 |
| European Crohn's and Colitis Organisation (ECCO) conference, Vienna, Austria, 2020 | 1.0 |

| Oral presentations | ECTs |
|---|---|
| Fatigue in quiescent inflammatory bowel disease is associated with low GM-CSF levels and metabolomics alterations. Digestive Disease Week, Chicago, IL, USA. 2017 | 1.0 |
| Crohn's Disease patients with concordant family history are diagnosed earlier and are at increased risk for complicated disease. Digestive Disease Week, Chicago, IL, USA. 2017 | 1.0 |
| Gut microbial dysbiosis contributes to fatigue in patients with quiescent inflammatory bowel diseases. Digestive Disease Week, San Diego, CA, USA. 2019 | 1.0 |
| Multi-`omics analysis reveals gut microbial dysbiosis and metabolic alterations in fatigued patients with quiescent Inflammatory Bowel Diseases. Nederlandse Vereniging voor Gastro-enterologie congres, Veldhoven. 2019 | 1.0 |
| Multi-`omics analysis reveals gut microbial dysbiosis and metabolic alterations in fatigued patients with quiescent Inflammatory Bowel Diseases. Harvard TH Chan, Public School of Health. 2019 | 1.0 |

| | |
|---|---|
| Multi-`omics profiling in patients with quiescent Inflammatory Bowel Disease identifies biomarkers predicting relapse. European Crohn's and Colitis Organisation (ECCO) conference, Vienna, Austria, 2020 | 1.0 |

| **Poster presentations** | **ECTs** |
|---|---|
| Vedolizumab therapy is associated with an improvement in sleep quality and mood in inflammatory bowel diseases. ECCO, Barcelona, Spain & DDW, Chicago, IL, USA. 2017 | 0.5 |
| Fatigue in quiescent inflammatory bowel disease is associated with low GM-CSF levels and metabolomics alterations. ECCO, Barcelona, Spain. 2017 | 0.5 |
| Crohn's Disease patients with concordant family history are diagnosed earlier and are at increased risk for complicated disease. ECCO, Barcelona, Spain. 2017 | 0.5 |
| Distance to Specialist Care and Disease Outcomes in Inflammatory Bowel Disease. DDW, Washington DC, USA. 2018 | 0.5 |
| Second-Look Endoscopy in Hospitalized Severe Ulcerative Colitis: A Retrospective Cohort Study. DDW, Washington DC, USA. 2018 | 0.5 |
| Safety of biologic therapy in older patients with immune-mediated diseases: a systematic review and meta-analysis. CCFA conference, Las Vegas, NV, USA | 0.5 |
| Low-dose Methotrexate has Similar Outcomes to High-dose Methotrexate in Combination with Anti-TNF Therapy in Inflammatory Bowel Diseases. DDW, San Diego, CA, USA. 2019 | 0.5 |
| Impact of biologic therapy on resolution of fatigue symptoms in patients with active inflammatory bowel disease: a prospective cohort study. DDW, San Diego, CA, USA. 2019 | 0.5 |
| Infliximab trough levels are not predictive of relapse in IBD patients in endoscopic remission: a prospective cohort study. DDW, San Diego, CA, USA. 2019 | 0.5 |
| High infliximab trough levels have no impact on fatigue in IBD patients in endoscopic remission: a prospective cohort study. DDW, San Diego, CA, USA. 2019 | 0.5 |
| Weight gain European Crohn's and Colitis Organisation (ECCO) conference, Vienna, Austria, 2020 | 0.5 |

| **Other meetings** | **ECTs** |
|---|---|
| Attending Journal Clubs | 2.0 |
| Attending IDEA FAST 2F meeting, Kiel, Germany. 2019 | 0.5 |

| **Teaching** | **ECTs** |
|---|---|
| Co-supervising master thesis of N. Nalagathla. 2017 | 1.0 |

**Awards**

Certificate of recognition for the scientific accomplishment as an early career investigator. DDW, San Diego, CA, USA. 2019

Best poster abstract, DDW San Diego, CA, USA. 2019

Best basic science abstract, NVGE, Veldhoven. 2019

Best basic science abstract, ECCO, Vienna, Austria. 2020

## Dankwoord

En dan is het proefschrift ineens af. Tijdens mijn studie geneeskunde nooit gedacht dat fulltime onderzoek verrichten zoveel plezier en voldoening kon geven. Oké, het wegen van de ontvangen poepmonsters daar gelaten, maar hoe spannend het soms kon zijn wat er uit je analyses kwam en of er überhaupt wel iets uit kwam. Het heeft me enthousiast gemaakt om verder te gaan met onderzoek en het klinkt wellicht cliché maar dit enthousiasme en dit proefschrift waren er niet geweest zonder de mensen om mij heen. Daarom wil ik op deze laatste pagina's, het meest gelezen hoofdstuk van het proefschrift, iedereen bedanken die hieraan, in wat voor vorm dan ook, heeft bijgedragen. Allereerst zijn dat de, veelal Amerikaanse, patiënten die hebben deelgenomen aan de verschillende onderzoeken die in dit proefschrift beschreven staan. Omwille van de wetenschap waren ze bereid om aan deze Nederlandse onderzoeker hun poepmonsters op te sturen. Hoewel ik hen niet bij naam kan bedanken, ze zijn onmisbaar geweest.



Ashwin, you have been a tremendous mentor for me. You gave me the opportunity to start research in MGH by accepting me as an intern whilst I had no prior research experience. I couldn't have imagined a better place to first practice science. Luckily, it worked out well and you gave me the chance to come back after finishing medical school to continue our research. It is impressive and incredible to see how you are able to combine clinical work, scientific work, managing the Crohn's and Colitis center, guiding your residents and students and always be on time to pick up your daughter from daycare. And even then, you are always available for questions and guidance. Whether it be by e-mail (replies often come within seconds) or through a stop in your office, you are never too busy to tackle a burning question about research or to tell me the right Stata code to use, all whilst writing your clinical notes. Your interest went further than just my research projects, always asking about my weekend plans, Dutch habits and you even invited me for a goodbye dinner with your family. It meant a lot. I would like to thank you for encouraging my research and for allowing me to grow as a research scientist. Your advice, on both research as well as on my career, has been priceless. Fortunately, we still have few research studies to finish together and I'm very much looking forward to collaborating on future projects.

Janneke, tijdens ons kennismakingsgesprek, wat ineens een sollicitatiegesprek bleek te zijn, gaf jij me al gelijk vertrouwen en toonde jij meteen je scherpe blik door mij te wijzen op een typefout in mijn CV. Een promotietraject in het Erasmus MC mocht ik gaan doen waarop ik ja zei, om vervolgens na twee weken weer af te zeggen om terug te keren naar Boston. Gelukkig zag jij wel wat in mijn plan om terug naar Boston te keren, was jij nog steeds bereid om mijn promotor te worden en gaf jij mij zelfs een extra jaar in het EMC. Met name dat laatste jaar heb ik je enthousiasme voor onderzoek kunnen aanschouwen. Ik bewonder je vaardigheid om kritische vragen te stellen, de scherpe

correcties, de pragmatische feedback op presentaties en jouw efficiëntie om tot de kern van een probleem te komen. Het is mooi om te zien hoe het je, met al het komen en gaan van onderzoekers, toch steeds weer lukt om zo'n hecht team te vormen. Jouw humor en enthousiasme zorgen ervoor dat er altijd genoeg lol te beleven is in de groep, met als hoogtepunten het ECCO diner en kerstdiner. Tijdens mijn promotie was je er altijd om mee te denken, advies te geven over mijn toekomstige carrière en gaf je me blindelings vertrouwen om naar een internationale research meeting te gaan. Dank voor je kritische blik en voor alle vrijheid die jij mij gegeven hebt.

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The CRP research team, Mel, Liz, Thom, Grace, Will, Kelly, Ali and Mimi, without you all the research wouldn't have been as fun and probably none of my studies would have been approved by the IRB. Kathy, thank you for all your help in the lab and ordering me all the needed supplies. My windowless office buddies Keri, Christina and Pam, glad that we invested in our office beach view. The unlimited number of cookies and donuts, the dinosaur costume, Christina's dance moves, the Easter egg hunt made it never a normal office day at CRP. You all made me feel instantly at home and I hope to see you all soon!

The 'omics experts, Damian and Amit, thank you for all the incredible help with the analysis of all my samples. Both of you were able to make complicated science accessible to me and to help me answer my research questions.

IBD collega's, de inflammatoire bazen, het laatste jaar van mijn promotie haakte ik ineens aan bij de maandag research meetings. Veel heb ik van jullie mogen leren en het verbaast me altijd hoe scherp iedereen is op de maandagochtend, met de nodige dosis humor erbij. Rens, J9, Eline, Rogier, Jas en Sebas, onze gezamenlijke passie (poep onderzoek) konden we met elkaar delen, de nodige frustraties maar ook de successen op congressen. Blij dat

onze acteerkwaliteiten werden erkent met een heuse vermelding op het intranet. En in het bijzonder natuurlijk Ems, jouw enthousiasme en tomeloze inzet voor de Probiotica trial heeft mij zo onwijs veel geholpen. Zonder jou (en je OCD natuurlijk) was die studie nog steeds niet van start gegaan. Dank voor de tijd en energie die jij er in hebt gestoken, samenwerken met jou is een feest en we gaan er een mooi manuscript van maken!

Daklappers, maar voor mij toch echt Na-6, hoe fijn dat ik als mysterieuze PhD'er uit het buitenland gelijk mocht aansluiten bij de Rotterdamse borrels. Helaas waren het maar enkele maanden maar hoop hierna toch nog stiekem aan te sluiten.

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De siblings, alle vier zo anders maar des te leuker. Toon, als oudste broer heb jij mij vele fijne kneepjes bijgebracht. Letterlijk, in de pijnlijke zin, maar ook figuurlijk, als het aankomt op kritisch denken, het voorbereiden van sollicitaties en het fanatisme bij de spelletjes. Met Lotje aan je zijde en ook een beetje aan mijn zijde als er weer discussie is over een zorg gerelateerd politiek probleem. Lotje, heerlijk hoe jij lekker tegen hem in gaat en zo fijn om samen met je te kunnen sparren over de toekomst als arts. Daaf, de echte schrijver in de familie, jaloers om van te worden hoe snel jij de Afrikaanse ontwikkelingen weet om te zetten naar een boeiend verhaal. Je creativiteit en liefde voor het Afrikaanse continent zijn bewonderenswaardig en ik weet zeker dat jij in de toekomst daar gelukkig in gaat worden. Bollie, jij kreeg het soms zwaar te verduren met de drie boven je maar het is heerlijk om te zien hoe jij alles op je eigen manier doet en jouw eigen keuzes maakt. Die huisdieren hebben geluk met je! Wie weet in de toekomst toch nog samen een keer de relatie tussen de darmflora van de hond en zijn baasje onderzoeken?

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A

## About the author

Nynke Borren was born in Singapore on June 13th, 1991. She attended pre-university education at the Dr.-Knippenbergcollege in Helmond, from which she graduated in 2009. In that same year, she started medical school at the University of Groningen. After obtaining her bachelor's degree in 2012, she went abroad to volunteer in a community hospital and to teach English at a monastery school in Kathmandu, Nepal. Afterwards, she completed a minor in Entrepreneurship at the Faculty Economics & Business at the University of Groningen. Subsequently, she continued medical school and her enthusiasm for Gastroenterology and Hepatology evolved over her clinical rotations. She successfully applied for the Groningen International program of Science in Medicine. This program for medical students interested in science gave her the opportunity to perform medical research at the Crohn's and Colitis Center at Massachusetts General Hospital (Boston, MA, USA) under the supervision of Dr. A.N. Ananthakrishnan. After her final rotation at the department of Gastroenterology at the Onze Lieve Vrouwe Gasthuis in Amsterdam, she started working on the current PhD thesis under supervision of Dr. A.N. Ananthakrishnan and Professor C.J. van der Woude. As part of this she went back to Boston in May 2017 to work as a Research Fellow at Massachusetts General Hospital & Harvard Medical School for two years. She was given the opportunity to combine clinical and translational research, to initiate an international multi-center randomized controlled trial and to present her work at conferences around the world. In June 2019, she returned to the Netherlands to finish her PhD thesis at the department of Gastroenterology & Hepatology at Erasmus University Medical Center in Rotterdam. From February 2020 onwards she will work as a non-training resident at the department of Internal Medicine at Tergooi Ziekenhuis in Hilversum before applying for residency training in Gastroenterology & Hepatology. During the coming months and hopefully long into the future she will continue her research projects.