FATIGUE AND ASSOCIATED FACTORS IN ADULTS WITH INFLAMMATORY BOWEL DISEASE

by

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Inflammatory bowel disease (IBD) is an autoimmune disorder of the gastrointestinal tract and is characterized by chronic inflammation. Ulcerative colitis (UC) and Crohn's disease (CD) are the two major forms of IBD. Fatigue is one of the most common symptoms reported by those with IBD and about 22% to 77% of adults with IBD experience fatigue. The purposes of this study were to develop a parsimonious model that describes the influencing factors of fatigue in adults with IBD, adults with CD and adults with UC.

The study was a secondary analysis of cross sectional data obtained from IBD partners. The conceptual framework of the study was adapted from the middle range theory of unpleasant symptoms. The variables were organized as physiological, psychological and situational factors as influencing factors with fatigue as the symptom in the framework. The Patient Reported Outcomes Measurement Information System (PROMIS) short-form scales were used to measure fatigue, sleep disturbances, pain interference, anxiety, depression, and satisfaction with social roles (SSR). Additionally, physical activity, demographic and clinical variables were measured. The vast majority of the participants were White (92%) females (72%). The majority of the participants (85%) were < 60 years of age. Majority of the participants (63%) had CD in this

cohort. Three models were tested based on the conceptual framework to identify the direct and indirect effects of situational, physiological, and psychological factors on IBD-Fatigue. The data best fit with model with situational factors (physical activity and SSR) as the mediators for all adults with IBD, as well as in the stratified evaluation of adults with CD and UC. Significant direct effects were noted from disease activity, age, sleep disturbances, pain interference, anxiety and depression to fatigue in all adults with IBD as well as in adults with CD and UC ($p <. 001$). An additional direct effect was noted from narcotics to fatigue in adults with UC ($p <. 001$). Indirect effects were noted consistently from sleep disturbances, pain interference, and depression via physical activity and SSR in all final models in adults with IBD, adults with CD and adults with UC ($p <. 001$).

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CHAPTER I: BACKGROUND AND SIGNIFICANCE

Introduction

Inflammatory bowel disease (IBD) is an autoimmune disorder of the gastrointestinal tract (GI) and characterized by chronic inflammation (Ananthakrishnan, 2015). Ulcerative colitis (UC) and Crohn's disease (CD) are the two major forms of the disorder that comprise IBD (Pekow, 2015). The unpredictable disease trajectory of IBD, coupled with symptom burden, significantly lower the quality of life (QOL) of those with IBD (Knowles et al., 2018). Fatigue is one of the most common aggravating, challenging, and debilitating symptom reported by those with IBD (Chavarría et al., 2019; Cohen et al., 2014; Kreijne, Lie, Vogelaar, & van der Woude, 2016; Perler et al., 2019). Fatigue is a subcomponent of QOL and is inversely associated with poor QOL among adults with IBD (Cohen et al., 2014). Understanding IBD-Fatigue and the associated influencing factors are essential for developing specific interventions to manage fatigue among the IBD population. This chapter includes the background of IBD-Fatigue, the significance of IBD-Fatigue in research, research questions to answer the study, and a theory to guide the examination of IBD-Fatigue and influencing factors. Theoretical and operational definitions of the variables and assumptions are also addressed in this chapter.

Background

IBD-Fatigue

It is estimated that about 22% to 77% of adults with IBD experience fatigue affecting their QOL (Bazilchuk, 2016). An analysis of the subcategories of IBD, remission versus relapse and UC versus CD, found that 22% to 41% of adults with IBD in remission and 44% to 86% of adults with active disease experience fatigue (Czuber-Dochan, Ream, & Norton, 2013b; van

Langenberg & Gibson, 2010). Fatigue presentations between CD and UC are not clear. Some studies reported no difference or comparable results in fatigue between UC and CD participants (Chavarría et al., 2019; Grimstad et al., 2015). Other studies have reported a higher prevalence of fatigue among participants with CD (Bager et al., 2012; Jelsness-Jørgensen, Bernklev, Henriksen, Torp, & Moum, 2011b). More importantly, IBD-Fatigue was found to be more prevalent among adults with CD and UC compared to healthy controls (Grimstad et al., 2015; van Langenberg & Gibson, 2014). Comparison of prevalence rates of fatigue between IBD and other chronic conditions, such as cancer, multiple sclerosis, rheumatoid arthritis, fibromyalgia, systemic lupus erythematosus, psoriatic arthritis, Parkinson's disease, and primary biliary cirrhosis (Czuber-Dochan et al., 2013b; van Langenberg & Gibson, 2010), showed comparable results. However, IBD-Fatigue has not received similar attention in research and clinical practice compared to other chronic conditions (Czuber-Dochan et al., 2013b).

IBD-Fatigue is associated with the inflammation related to IBD (Grimstad et al., 2015; Vogelaar et al., 2015). The inflammation of IBD is a classic example of symptomology associated with a relapsing-remitting disorder, where those with IBD experience both remission as an inactive form of IBD and relapse or the active disease (Liverani, Scaioli, Digby, Bellanova, & Belluzzi, 2016). Several cascades of circulatory cytokines are associated with IBD-Fatigue. The inflammatory response to IBD leads to the upregulation of pro-inflammatory cytokines such as interleukins (IL-1, IL-6), and tumor necrosis factor alpha (TNF α) (Grimstad et al., 2015; Vogelaar et al., 2015). These mechanisms stimulate several immune systems and brain communication pathways, leading to fatigue, and considered a component of sickness behavior (Grimstad et al., 2015; Vogelaar et al., 2015). Sickness behavior is a term used to describe a coordinated set of behavioral changes due to inflammation (Dantzer & Kelley, 2007; Wohleb,

Franklin, Iwata, & Duman, 2016). Sickness behavior is manifested as symptoms of lethargy, fatigue, pain hypersensitivity, and reduced social interaction (Dantzer & Kelley, 2007; Wohleb et al., 2016).

The major contributors to fatigue in the IBD population are active inflammatory disease (Cohen et al., 2014; Kappelman et al., 2013; van Langenberg & Gibson, 2010; van Langenberg & Gibson, 2014); nutrition-related factors such as malabsorption and anemia (Bager et al., 2012; Jelsness-Jørgensen et al., 2011b; Romberg-Camps et al., 2010); and psychological stress (Artom, Czuber-Dochan, Sturt, & Norton, 2016; van Langenberg & Gibson, 2010). Besides these contributors, therapies for IBD can also contribute to fatigue. The medications used for IBD, such as azathioprine, methotrexate, thiopurine, and anti-TNF α, significantly correlate with fatigue experiences (Jelsness-Jørgensen, et al., 2011b; Kreijne, et al., 2016; Villoria et al., 2017). Further studies have highlighted an association between the use of corticosteroids and fatigue among adults with IBD (Chavarría et al., 2019; Kappelman et al., 2013; van Langenberg & Gibson, 2014). Thus, IBD-Fatigue is attributed to both the therapy and the pathological process of the disease.

The influence of fatigue on QOL in those with IBD is supported by several studies reporting an inverse relationship between IBD-Fatigue and QOL (Jelsness-Jørgensen et al., 2011b; Romberg-Camps et al., 2010). Fatigue negatively influenced the social and emotional well-being of those with IBD and limited their employment opportunities (Czuber-Dochan, Dibley, Terry, Ream, & Norton, 2013a). Additionally, IBD-Fatigue affected different domains of QOL, such as physical (reduced physical activity), cognitive (difficulty in concentrating), and affective (interferences with motivation and mood) domains (Aluzaite et al., 2018; van Langenberg & Gibson, 2010), indicating the multidimensional influence of IBD-Fatigue.

Adults with IBD consider fatigue as an expected norm (Czuber-Dochan et al., 2014). More concerning is that health care providers (HCPs) had a “don’t ask, don’t tell” approach for IBD-Fatigue (Czuber-Dochan et al., 2014). This was clearly articulated by those with IBD who disclosed their concerns that HCPs did not consider their fatigue presentations seriously, and they often felt that their fatigue symptoms were overlooked and unsupported (Czuber-Dochan et al., 2013a). Unfortunately, the symptom experience of fatigue in those with IBD is understudied with little research to support diagnosing and/or treating IBD-Fatigue (Bazilchuk, 2016). Understanding what factors contribute to IBD- Fatigue would assist in developing interventions to mitigate fatigue and improve QOL.

IBD-Fatigue and Other Symptoms

Fatigue often manifests with other symptoms as a cluster where two or more symptoms co-occur (Arnett & Clark, 2012). Because fatigue presentation due to inflammation is connected to the neurophysiology of cytokine-mediated sickness behavior, it is important to examine these symptoms when studying IBD-Fatigue. These symptoms include depressive behavior, sleep disturbances, increased sensitivity to pain, and psychomotor slowing (Arnett & Clark, 2012).

Psychological well-being negatively correlates with fatigue. Fatigued adults with IBD are more likely to have depressive symptoms compared to non-fatigued adults (Cohen et al., 2014). Due to the high prevalence of psychological comorbidities, such as anxiety (Goodhand et al., 2012; Nahone et al., 2012) and depression (Goodhand et al., 2012; Panara, Yarur, Reiders, Proksell, & Deshpande, 2014) among the IBD population, adults with IBD may perceive higher levels of somatization and fatigue severity (Nahon et al., 2012; Ratnakumaran et al., 2018). Multiple study results have indicated the association between anxiety and higher levels of IBD-Fatigue (Artom, Czuber-Dochan, Sturt, Murrells, & Norton, 2017; Chavarría et al., 2019;

Ratnakumaran et al., 2018). Both cross-sectional and longitudinal analyses revealed a significant association between reduced psychological well-being and increased depressive symptoms with increased fatigue levels among adults with IBD in general, as well as in adults with CD (Graff et al., 2013; van Langenberg & Gibson, 2014). Hence, measuring anxiety and depression is important when examining IBD-Fatigue.

Sleep disturbances and pain are some of the common physical presentations related to IBD-Fatigue. Sleep disturbances were observed in adults with both active and inactive forms of IBD (Kinnucan, Rubin, & Ali, 2013). Sleep disturbances can affect the immune system, leading to the release of pro-inflammatory cytokines (Kinnucan et al., 2013). The influence of sleep quality on fatigue among adults with IBD is previously established (Graff et al., 2011; Hashash et al., 2018). Results from both studies reported a negative association between sleep quality and fatigue (Graff et al., 2011; Hashash et al., 2018). In fact, sleep disturbances persisted 20 years after the diagnosis of IBD (Huppertz-Hauss et al., 2017). Thus, sleep disturbances are common among the IBD population irrespective of the disease activity, are concerning, and influence IBD-Fatigue.

Adults with IBD perceive higher pain intensity levels (Jelsness-Jørgensen et al., 2017). A study of adults with IBD found an association between pain perception and fatigue, and participants stated that increased pain further worsened their fatigue (Beck, Bager, Jensen, & Dahlerup, 2013). Researchers concluded several reasons for the association between fatigue and pain in adults with IBD, including prolonged pain exposure, the considerable amount of energy required to manage pain, and reduced capability to deal with pain due to fatigue symptoms (Jelsness-Jørgensen et al., 2017). Therefore, the measurement of pain in adults with IBD is important in the assessment and management of fatigue.

Other physiological factors related to IBD-Fatigue are age, disease duration, and surgical history. Higher levels of fatigue were reported by adults with IBD who are younger in age (Bager et al., 2012; Graff et al., 2013). Stratification with age revealed that adults with IBD < 60 were found to have higher scores of fatigue (Bager et al., 2012). Evidence supported the negative association between IBD-Fatigue and duration of the disease. Adults with IBD reported lower fatigue with longer duration of the disease (Aluzaite et al., 2018). Compared to age and disease duration, limited data are available regarding the association between IBD-Fatigue and surgical history. Based on the available literature, improvement in cognitive fatigue was reported among adults with CD who had a history of intestinal resection for the treatment of IBD (van Langenberg & Gibson, 2014). Examination of age, disease duration, and surgical history may be important variables in understanding IBD-Fatigue.

Besides psychological and physical correlates of fatigue, other factors have been strongly associated with fatigue presentation in adults with IBD, including physical activity and limited satisfaction with social roles due to the illness. Physical activity has a positive influence on the QOL of the IBD population. Previous research studies (Klare et al., 2015; Ng, Millard, Lebrun, & Howard, 2007) and reviews (Engels, Cross, & Long, 2017; Kreijne et al., 2016) supported the benefits of physical activity and exercise for improving intestinal inflammation as well as QOL in adults with IBD. In fact, the initiation of a regular physical activity program led to the improvement of fatigue symptoms among adults with CD (van Langenberg, & Gibson, 2014). Similar to psychological well-being, sleep disturbances, and pain, fatigue negatively influences the social life of adults with IBD. Adults with IBD and CD acknowledged their limitations in social relationships and their decreased satisfaction with social life due to the IBD-related symptoms (Kim et al., 2017; Sarid et al., 2017). Adults with IBD-Fatigue reported lack of energy

to continue their social life, pointing out that their fatigue experience led to a disconnection from society (Beck et al., 2013). Fatigue is associated with many of the psychological, physical, and social disruptions among adults with IBD and warrants further study.

Significance of the Problem

Fatigue was reported as the most (86.9%) experienced symptom in those with IBD (Vegni et al., 2019). Current evidence highlights the complex interplay between fatigue and different covariates such as anxiety, depression, sleep disturbances, pain, physical activity, and satisfaction with social roles. This complexity may be related to the multifactorial and multidimensional aspects of IBD-Fatigue (Artom et al., 2016). Yet, there are no studies dedicated to examining the combined influence of anxiety, depression, pain, sleep disturbances, physical activity, and satisfaction on social roles among adults with IBD. The European Crohn's and Colitis organization's nurses Delphi survey identified 'interventions to improve IBD-Fatigue' as one of the top five research priorities (Dibley et al., 2017). In addition to the negative influence of fatigue on psychological well-being, sleep disturbances, pain, and social life, the indirect influence of fatigue among adults with IBD led to disability related to work and activity impairment (Beck et al., 2013; Cohen et al., 2014) and limited employment opportunities (Czuber-Dochan et al., 2013a). Clearly, fatigue-related burden perceived by adults with IBD influences their physiological, psychological, and employment outcomes.

Fatigue management among IBD patients is essential considering the direct (inpatient care, outpatient care, medications, and procedures) and indirect costs (absenteeism from work, reduced income) associated with the symptom experiences of fatigue (Vogelaar et al., 2011). Fatigue contributed to $136.4 billion per year of health-related lost productive time compared to $35.4 billion per year for workers without fatigue among the United States (US) general public

(Borren, van der Woude, & Ananthakrishnan, 2019). Several studies' results noted the increased healthcare costs among the IBD population due to their lower QOL and symptom burden (Bähler, Vavricka, Schoepfer, Brüngger, & Reich, 2017; Ganz, Sugarman, Wang, Hansen, & Hakan-Bloch, 2015; Mehta, 2016). Understanding IBD-Fatigue and other associated factors would clarify targeted factors for intervention to increase QOL and reduce symptom burden resulting in reduced health care costs.

According to 2015 data, about 1.3% (3 million) of US adults are affected by IBD, and this number has increased from 0.9% or 2 million adults since 1999 (Centers for Disease Control and Prevention [CDC], 2019). Considering the physiological, psychological, and economic burden, understanding the complex interplay between fatigue and covariates of anxiety, depression, sleep disturbances, pain, physical activity, and satisfaction with the social roles are essential. Examining these associated factors is necessary in a biopsychosocial model of care, as supported by Artom and colleagues (2017), and to develop nursing interventions to reduce IBD-Fatigue.

Most studies of fatigue among IBD patients have been conducted outside the US where the culture, climate, food habits, and treatment modalities may differ from those in the US. Consequently, findings may not transfer to those who are living in the US. This lack of knowledge may contribute to health care providers' lack of understanding of the fatigue or the paucity of treatments for fatigue leading to avoiding the discussions of fatigue with adults with IBD (Czuber-Dochan et al., 2014). A biopsychosocial approach to IBD-Fatigue focuses on identifying relationships and multidimensional treatment (Borrell-Carrió, Suchman, & Epstein, 2004). Thus, a comprehensive holistic approach would prevent fragmenting treatments or addressing care related to one particular problem (Borrell-Carrió et al., 2004). This model or

approach purports that HCPs and IBD nurses combine biological (management of inflammation), psychological (management of anxiety and depression), and behavioral factors (improvement of sleep disturbances, pain, and physical activity) in IBD-Fatigue management. Understanding the complex interaction among these factors is essential in managing IBD-Fatigue (Artom et al., 2016; Borrell-Carrió et al., 2004).

Purposes of the Study

The purposes of this study were to comprehensively examine factors associated with IBD-Fatigue and use statistical modeling to determine the most effective and parsimonious model for identifying the influencing factors of fatigue among IBD patients.

Specific Aims and Research Questions

The specific aims and associated research questions (RQs) were:

Aim 1: To characterize fatigue, anxiety, depression, sleep disturbances, pain interference, physical activity, and satisfaction with social roles in adults who are 18 and older who have IBD, in adults with UC, and in adults with CD.

RQ1. What were the descriptives of physiological (age, disease duration, surgical history, disease activity, sleep disturbances, pain interference, and current medications), psychological (anxiety and depression), and situational (physical activity and satisfaction with social roles) factors in adults ages 18 and older who have IBD, in adults with UC, and in adults with CD?

Aim 2: To examine the relationships among fatigue and physiological (age, disease duration, surgical history, disease activity, sleep disturbances, pain interference, and current medications), psychological (anxiety and depression), and situational (physical activity and satisfaction with social roles) factors among adults with IBD, in adults with UC, and in adults with CD.

RQ2. What were the associations of fatigue, age, disease duration, surgical history, disease activity, sleep disturbances, pain interference, current medications, anxiety, depression, physical activity, and satisfaction with social roles in adults with IBD, in adults with UC, and in adults with CD?

Aim 3: To assess whether the relationships in the adapted version of the theory of unpleasant symptoms are reproducible in all adults with IBD, in adults with UC, and in adults with CD.

RQ3. Do physiological (age, disease duration, surgical history, disease activity, sleep disturbances, pain interference, and current medications), psychological (anxiety and depression), and situational (physical activity and satisfaction with social roles) factors predict clinically significant fatigue among adults with IBD, in adults with UC, and in adults with CD?

RQ4. What were the direct and indirect effects of physiological (age, disease duration, surgical history, disease activity, sleep disturbances, pain interference, and current medications), psychological (anxiety and depression), and situational (physical activity and satisfaction with the social roles) factors on fatigue among adults with IBD?

RQ5. Were there differences in direct and indirect effects of physiological (age, disease duration, surgical history, disease activity, sleep disturbances, pain interference, and current medications), psychological (anxiety and depression), and situational (physical activity and satisfaction with the social roles) factors on fatigue in adults with CD and those with UC?

Conceptual Framework

The middle range theory of unpleasant symptoms (MRTOUS) was the conceptual framework to guide the study and test the relationships. The MRTOUS was proposed as a framework to consolidate existing information about a variety of symptoms (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). The theory's underlying assumption is that identifying the commonalities among the symptoms will help to guide research and practice to develop interventions that may be effective in mitigating more symptoms (Lenz et al., 1997). Furthermore, the propositions of the MRTOUS acknowledge the multidimensionality of symptoms and the co-occurrence of many symptoms (Lenz & Pugh, 2014).

Influencing factors, symptoms, and performance outcomes are the three major concepts included in the MRTOUS. The preliminary description of the theory proposes the reciprocal relationship between influencing factors (physiological, psychological, and situational) and how these influencing factors determine the presence of a symptom or multiple symptoms and the nature of symptom experience. As a result, the symptom experience influences individual performance. The performance outcomes have a feedback connection to symptom experience itself as well as with the influencing factors (Lenz & Pugh, 2014).

Influencing Factors

The MRTOUS incorporates three groups of influencing factors: physiological, psychological, and situational factors (Lenz & Pugh, 2014). These three factors are interrelated to one another and influence the symptom experience as a single factor or a combination of factors (Lenz et al., 1997). Normally functioning body systems and the presence of any pathology are considered as physiological factors. Additionally, treatment-related variables are also included in physiological factors (Lenz & Pugh, 2014). The person's mental state or mood, affective reaction to illness, and mental states of anxiety and depression are included in the

psychological factor. The social and physical environments, which influence the experience of symptoms, are included in the situational factors of the theory. Examples of situational factors include support systems, access to health care, occupation, and lifestyle behaviors such as diet and physical activity (Lenz et al., 1997).

Symptoms

The conceptualization of MRTOUS started with symptoms and is addressed as the chief concept. The MRTOUS defines symptoms as subjectively perceived alterations in normal functioning, which are mostly experienced as unpleasant sensations. Because of this perception based definition, the symptom presentation can only be narrated by the individual who experiences it. In the MRTOUS, a symptom can manifest as a single concept or in conjunction with other symptoms (Lenz & Pugh, 2014).

Various measurable dimensions are attributed to the symptoms, which can vary based on the symptoms. These measurable dimensions include intensity or severity, degree of associated distress, timing, and quality of symptoms. Intensity is the most commonly measured and simplest characteristic of the symptom experience, which is comprised of the degree, strength, or severity of the symptom (Lenz & Pugh, 2014). The distress dimension focuses on affective characteristics or the emotional burden of the symptom experienced by an individual. The degree of distress is related to the intensity of a symptom, as well as the degree of focused attention given towards that symptom. For example, symptom management strategies can be directed toward distracting an individual's attention from the symptom. More importantly, the meaning attributed to a particular symptom significantly influences the degree of distress. For example, some individuals may consider the symptom as a positive outcome related to illness, whereas others may perceive it as distressing due to their negative experiences (Lenz & Pugh, 2014).

The difference in duration, frequency, and pattern of occurrence of the symptoms are associated with the time dimension. The time dimension takes into account the difference between acute and chronic symptoms as well as between intermittent and persistent symptoms while considering the duration, frequency, and pattern of occurrence of the symptoms. The quality of the symptom is the last dimension addressed in MRTOUS, and this dimension recognizes the unique characteristics of each symptom. These unique characteristics or descriptors of symptoms vary across diseases or progression of a particular disease (Lenz & Pugh, 2014).

Fatigue is the symptom examined in the proposed study. Fatigue is part of the symptom experience, which is the 'central focus' of the MRTOUS, where symptoms are measures of deviations from normal functioning as perceived by the individuals (Lenz et al., 1997).

Performance Outcomes

Performance is the outcome concept of the MRTOUS which denotes the consequence of the symptom experience (Lenz & Pugh, 2014). The MRTOUS states that the symptom experience influences the physical, cognitive, and socially defined roles of the individual. The performance outcomes are derived from the practice based observations and assist with the measurement of the theory. However, the MRTOUS does not consider QOL as a distinct outcome because of the overlap with functional status in many QOL measures (Lenz & Pugh, 2014).

Relationship Among Concepts

The revised version of the MRTOUS explains the complex and reciprocal relationship between symptoms, influencing factors, and performance outcomes. These three concepts can mediate or moderate a relationship between each. For example, depression may lead to fatigue which can interfere with satisfaction with social roles which can further increase depression and

vice versa. Additionally, physiological, psychological, and situational factors are related to each other. These three influencing factors can mediate or moderate their relationship with the symptom experience (Lenz & Pugh, 2014).

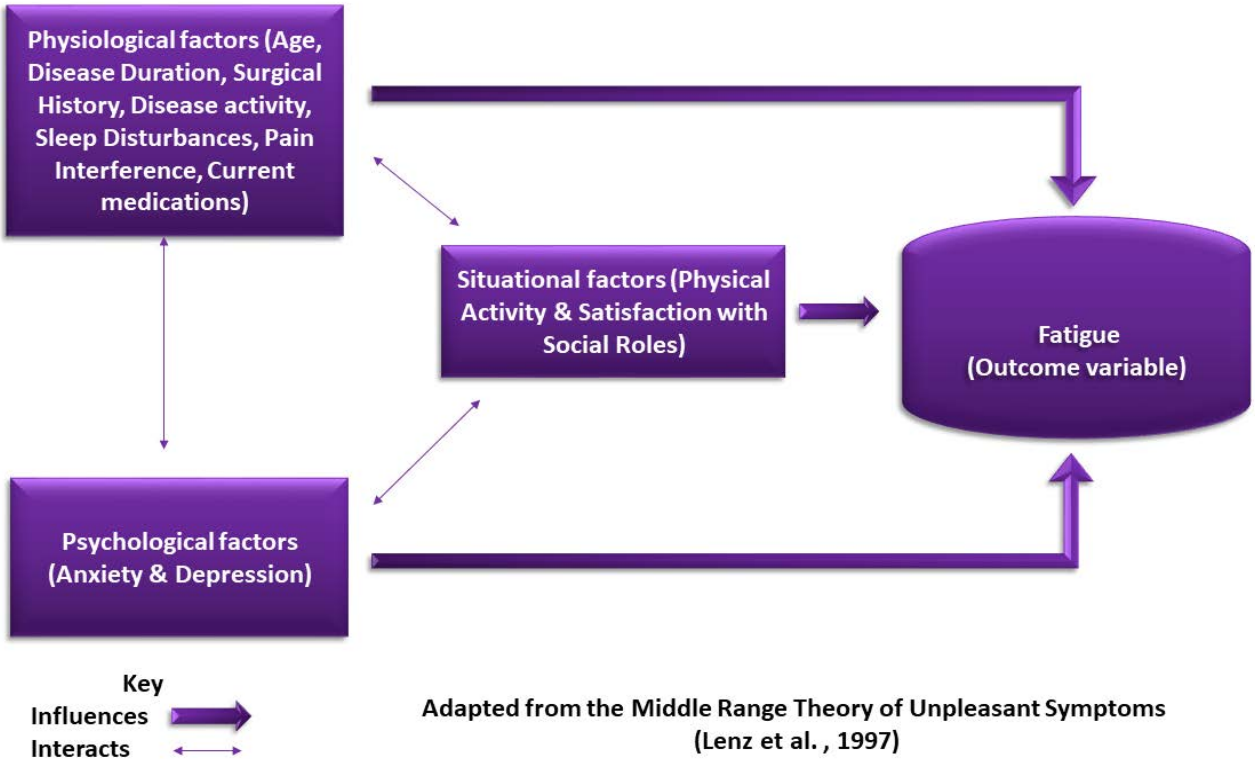
Application of Middle Range Theory of Unpleasant Symptoms in the Study

The study focused on examining the symptom of fatigue and the other influencing factors among adults with IBD. Fatigue was the outcome variable (symptom) of the study. As discussed previously, three groups of factors (physiological, psychological, and situational factors) influence the symptom experience in the MRTOUS. These factors may be pooled together based on the definition of each of the influencing factors. According to Lenz and Pugh (2014), physiological factors composed of normal body systems, any pathological changes, and treatment related factors. Therefore, sleep disturbances and pain interference, along with demographic factors such as age, disease duration, surgical history, disease activity, and current medications were included in physiological factors, whereas anxiety and depression were combined with psychological factors. Situational factors incorporate social and physical factors that influence a symptom experience. Therefore, satisfaction with social roles and physical activity were included as situational factors.

As addressed in MRTOUS, it is possible to test the relationship between physiological (age, disease duration, surgical history, disease activity, sleep disturbances, pain interference, and current medications), psychological (anxiety and depression), and situational (physical activity and satisfaction with social roles) factors in the proposed study. Additionally, the direct and indirect (mediating) effects of physiological (disease activity, age, sex, sleep disturbances, pain interference, and current medications), psychological (anxiety and depression), and situational (physical activity and satisfaction with social roles) factors on the symptom (fatigue) can be tested. The application of MRTOUS in the proposed study is included in Figure 1.

Figure 1

The application of MRTOUS in the study



Theoretical and Operational Definitions

A theoretical definition includes the theoretical meaning of a concept in a research study (Polit & Beck, 2017). The operational definition refers to the procedures employed to observe or measure a concept (Polit & Beck, 2017). Theoretical and operational definitions of each variable for this study are organized based on the MRTOUS and is defined based on the variables available in the data set.

Symptom of Fatigue

Fatigue is a chronic condition that is characterized by "persistent, overwhelming sense of tiredness, weakness or exhaustion resulting in a decreased capacity for physical or mental work" and is unrelieved by sleep or rest (van Langenberg & Gibson, 2010). Fatigue was operationalized

by using the patient reported outcome measurement information system (PROMIS) score for fatigue (Fatigue 4a – Adult v1.0), which assesses the frequency, duration, intensity, and interference characteristics of fatigue (National Institute of Health [NIH], 2019). The PROMIS fatigue scores are calibrated with a mean score of 50 for the US general population and the standard deviation is 10. The PROMIS fatigue scores were dichotomized into two categories: Clinically significant fatigue (score $\geq$ 55) and non-significant fatigue (score < 55).

Physiological Factors

For this study, physiological factors were operationalized to focus on the physiological data which include age, disease duration, surgical history, disease activity, sleep disturbances, pain interference, and current medications.

Age. According to the Merriam-Webster's online medical dictionary (2019), age refers to the development of an individual which is measured in terms of the years they lived. Age was operationalized as the chronological age in years.

Disease Duration. According to the Merriam-Webster online medical dictionary (2019), disease refers to the impairment of the normal body functioning of a living being which is manifested with specific signs and symptoms. According to the Merriam-Webster online dictionary (2019), duration refers to the length of time of existence of something. Disease duration was operationalized as the number of years the patient has had the diagnosis of IBD.

Surgical History. According to the Free Dictionary by Farlex online version (2019), surgical history refers to the history of any type of surgical procedures a person has had in the past. Surgical history was operationalized as the self-report of any surgical procedures for the treatment of IBD as "yes" (had surgery in the past), or "no" (did not have surgery in the past).

Disease Activity. Disease activity refers to the chronic nature of IBD which includes a stage of the disease-free period (remission), alternating with periods of active disease (relapse or

flare-ups) (Stein & Shaker, 2015). Disease activity was operationalized as identification of the current stage of IBD as inactive/remission (Yes) or active disease/relapse (No) based on the self-report of the adults with IBD for the total sample. Self-report of the continuous scores Simple Clinical Colitis Activity Index (SCCAI) was used for adults with UC. The SCCAI values were categorized into ≤ 2 for UC remission and > 2 for UC active. Additionally, the SCCAI values were categorized into inactive or UC remission (score ≤ 2), mild (score > 2 – ≤ 5), moderate (> 5 - ≤ 11) and severe (> 11) for further stratified analysis of categories of disease activity among adults with UC. Self-report of the continuous score of short Crohn's Disease Activity Index (sCDAI) was used for adults with CD. The sCDAI values were categorized into < 150 for CD remission and ≥ 150 for CD active. Additionally, the sCDAI values were categorized into inactive or CD remission (score < 150), mild (150- < 220), moderate (220- 450) and severe (> 450) for further stratified analysis of categories of disease activity among adults with CD.

Sleep Disturbance. Sleep disturbance refers to the symptoms related to prolonged sleep latency, frequent sleep fragmentation, a higher rate of using sleeping pills, and/or decreased daytime energy (Swanson, Burgess, & Keshavarzian, 2011). Sleep disturbance was operationalized using the scores on the PROMIS scale (PROMIS Short Form v1.0 – Sleep Disturbance 4a) for sleep disturbance which assesses the quality of sleep, refreshment gained after sleep, difficulty in falling asleep, and interruption during sleep (NIH, 2019). Higher scores indicate higher sleep disturbances associated with sleep.

Pain Interference. Pain interference refers to the extent to which pain interferes with the physical, physiological and social activities of an individual (Varni et al., 2010). Pain interference was operationalized by using the PROMIS scale scores (PROMIS Short Form v1.0 – Pain Interference 4a) for pain interference which assesses the degree to which pain impedes

social, recreational, and day to day activities of an individual (NIH, 2019). Higher scores indicate higher pain interference.

Current Medications. According to the Oxford Online Dictionary (2019), medication is a substance that is used to treat or prevent a disease. Current medication refers to the use of any forms of medications prescribed by a health care provider. Current medications were operationalized by categorizing the drugs taken by adults for IBD based on their self-reported use of aminosalicylates, steroids, immune modulators, and biologics, anti-TNF α medications, and narcotics. Each category of these medications will be reported individually as "yes" (taking the medication), or "no" (not taking the medication).

Psychological Factors

For this study, psychological factors were anxiety and depression.

Anxiety. According to the American Psychological Association (2019), anxiety refers to an abnormal emotion presented by feelings of tension, worried thoughts, and physical signs. Anxiety was operationalized by using the PROMIS scale scores (PROMIS Short Form v1.0 – Anxiety 4a) for anxiety which assesses the reaction to fear, inability to focus on other matters, worries, and uneasiness of adults with IBD (NIH, 2019). Higher scores indicate higher anxiety levels.

Depression. According to the American Psychiatric Association (2019), depression refers to the mood disorder characterized by sadness, reduced functional activity, and inability to think and concentrate. Depression was operationalized by using the PROMIS scale scores (PROMIS Short Form v1.0 – Depression 4a) for depression which assesses the extent of depression, helplessness, hopelessness, and worthlessness experienced by adults with IBD (NIH, 2019). The PROMIS depression scores were dichotomized into two categories: Presence of depression (score ≥ 55) or absence of depression (score < 55).

Situational Factors

For this study, situational factors were operationalized as the physical activity status and satisfaction with social roles.

Physical Activity. Physical activity is defined "as any bodily movement produced by skeletal muscles that results in energy expenditure" (Caspersen, Powell, & Christenson, 1985, p. 126). Different activities of daily life, such as occupational, sports, conditioning, household, or other activities, are considered as part of physical activity. Exercise is a subset of physical activity (Caspersen et al., 1985). Physical activity was operationalized by a single physical activity question: "How often did you participate in one or more physical activities of 20–30 minutes' duration per session during your leisure time within the past six months?" This physical activity question was measured on a 6-point Likert scale. The scores were dichotomized into two categories: Higher levels of physical activity (score ≥ 5) and lower levels of physical activity (score < 5).

Satisfaction with Social Roles. Satisfaction with social roles is defined as "satisfaction with one's usual roles in life's situations and activities" (Hahn et al., 2016, p.2). Satisfaction with social roles were operationalized using the PROMIS scale scores (PROMIS Short Form v1.0 – Satisfaction with Social Roles 4a) which assesses the degree to which adults with IBD are satisfied with their social roles, family responsibilities, and work responsibilities (NIH, 2019). Higher scores reflect more satisfaction with social roles.

Assumptions

Several assumptions were associated with the study. It was assumed that self-reported IBD status or disease activity is accurate and reliable, reflecting the true condition of participants. The second assumption was that all data entered in the data set are accurate. It was also assumed that variables are accurately extracted through the PROMIS tools of fatigue, sleep

disturbance, pain interference, anxiety, depression, satisfaction with social roles, and the one question related to physical activity through the honest responses of participants. The last assumption was that the proposed model will capture the influencing factors of fatigue among IBD patients.

Summary

This study aimed to identify a model that will inform the relationship between fatigue and other covariates to guide the development of interventions to manage IBD-Fatigue. The study has three distinct aims; (a) to characterize the nature of fatigue, anxiety, depression, sleep disturbances, pain interference, physical activity, and satisfaction with social roles in adults who are 18 and older who have IBD, in adults with UC, and in adults with CD; (b) to examine the relationships among fatigue and physiological (age, disease duration, surgical history, disease activity, sleep disturbances, pain interference, and current medications), psychological (anxiety and depression), and situational (physical activity and satisfaction with social roles) factors among adults with IBD, in adults with UC, and in adults with CD; and (c) to develop a model to predict fatigue in adults with IBD, in adults with UC, and in adults with CD?

Fatigue is a common symptom among adults with IBD because of the inflammatory, remitting, and relapsing course of IBD (Artom et al., 2017). Fatigue among adults with IBD is an emergent and understudied research area (Artom et al., 2017; Grimstad et al., 2015). Fatigue is a subjective and unpleasant phenomenon that disrupts the physical, emotional, and social well-being of an individual (Grimstad et al., 2015). Examining the associated factors of fatigue will assist in understanding IBD-Fatigue, and the findings will guide the development of appropriate interventions to manage IBD-Fatigue. Because of the multifactorial and multidimensional nature

of IBD- Fatigue, this study used a biopsychosocial model to determine if a single or group of variables best predict IBD- Fatigue.

CHAPTER II: REVIEW OF THE LITERATURE

Introduction

Almost 3 million of adults in the United States (US) are affected by inflammatory bowel disease (IBD) (Centers for Disease Control and Prevention, 2019). Characterized by chronic inflammation of the gastrointestinal tract with a disease trajectory of remission and relapse, IBD is comprised of two forms: Crohn's disease (CD) and Ulcerative Colitis (UC) (Ananthakrishnan, 2015). Fatigue is one of the most common symptoms reported by adults with IBD (Vegni et al., 2019). This chapter focused on the review of the literature of IBD-Fatigue and its associated factors. This chapter is organized based on the framework adapted from the middle range theory of unpleasant symptoms (MRTOUS). The MRTOUS postulates that physiological, psychological, and situational factors influence the symptom experience as a single factor or a combination of factors (Lenz et al., 1997; Lenz & Pugh, 2014). The symptom for this study was IBD-Fatigue. The independent variables affecting IBD-Fatigue were organized as physiological factors (age, disease duration, surgical history, disease activity, sleep disturbances, pain interference, and current medications); psychological factors (anxiety and depression); and situational factors (physical activity and satisfaction with social roles).

Fatigue

Fatigue is the physiological response to a certain activity in healthy individuals and is transient (Finsterer & Mahjoub, 2014). Fatigue is a common symptom experienced by many individuals with chronic illnesses (Davis & Walsh, 2010). Individuals with illness explain fatigue as an "overwhelming sense of tiredness at rest, exhaustion with activity, lack of endurance or as loss of vigor" (Finsterer & Mahjoub, 2014, p. 562). There are several definitions of fatigue,

including general, mental, central, and peripheral fatigue, with a perceived subjective and quantifiable objective focus (Davis & Walsh, 2010; Finsterer & Mahjoub, 2014). Additionally, fatigue may be further classified as acute (less than 6 months in duration) or chronic (greater than 6 months in duration) with multiple contributors attributed to a single symptom (Finsterer & Mahjoub, 2014).

Adults with autoimmune disorders report fatigue as their main concern (American Autoimmune and Related Disorders Association [AARDA], 2019). Evidence from the literature revealed fatigue as a common symptom in most of the autoimmune-related diseases and in adults with immune deficiency disorders (Chalah & Ayache, 2018; Chavarría et al., 2019; Dailey et al., 2016; del Pino-Sedeño et al., 2017; Hajjar et al., 2018; Katz, 2017). In fact, 98% of adults with autoimmune disease reported experiencing fatigue (AARDA, 2019).

The consequences of fatigue in autoimmune disorders include disruption of daily routines, limited physical activity and work, interference in social life, mood changes, impaired quality of life (QOL) and financial burden (Agarwal & Kumar, 2016; Allen & Naim, 2012; Sabes-Figuera et al., 2010; Ziellinski, Systrom, & Rose, 2019). Fatigue in autoimmune disease is multifaceted. One theory is that fatigue experienced in autoimmune disease is related to cytokine mediated inflammation. This inflammation is highly associated with anxiety, depression, pain, and sleep disturbances (Ziellinski et al., 2019).

Fatigue and Inflammatory Bowel Disease

Many of the earlier research studies on IBD did not define fatigue. However, definitions of fatigue in recent studies somewhat match the definition of fatigue in individuals with general illness. Overlapping and repetition of many terms were noted between the definitions. The common terms used in the definition of IBD-Fatigue include ‘overwhelming,’ ‘exhaustion,’ ‘lack

of energy,' and 'physical and cognitive impairment' (Artom et al., 2017; Bager et al., 2012; Graff et al., 2011; Jelsness-Jørgensen et al., 2011a). Research related to IBD-Fatigue is an emergent field, as there are few studies published prior to 2010 with fatigue as the primary outcome. Because of the lack of clear definitions and primitive stage of research in IBD-Fatigue, health care providers did not have defined guidelines to manage of IBD-Fatigue (Czuber-Dochan et al., 2014). Therefore, more research is required to explore IBD-Fatigue to identify its impact on adults with IBD as well as to look for interventions to manage it.

The multidimensional concept of IBD-Fatigue was first described by van Langenberg and Gibson (2010), who described the objective and subjective components of physical, cognitive, and affective levels of fatigue. Subsequent studies have consistently addressed the multidimensional nature of IBD-Fatigue (Artom et al., 2017; Bager et al., 2012; Banovic, Gilibert, Jebrane, & Cosnes, 2011; Borren et al., 2019; Czuber-Dochan, Dibley, Terry, Ream, & Norton, 2013a; Frigstad et al., 2018; Horta et al., 2019; Jelsness-Jørgensen et al., 2011b). Those with IBD described the burden of IBD-Fatigue in these studies as 'disabling' (Artom et al., 2017), 'debilitating' (Chavarría et al., 2017), 'distressing' and 'unpleasant' (Jelsness-Jørgensen, Bernklev, Henriksen, Torp, & Moum, 2011a), 'overwhelming' (Graff et al., 2013), and 'subjective' (Opheim, Fagermoen, Bernklev, Jelsness-Jørgensen, & Moum, 2014). The first comparison of IBD-Fatigue with fatigue in other autoimmune disorders was done by van Langenberg and Gibson (2010) who reported a comparable level of fatigue among adults with IBD and other autoimmune disorders.

Prevalence of IBD-Fatigue

Comparisons of the prevalence of fatigue among different studies have shown a higher rate of fatigue among adults with IBD. In an early study in the United States (US), adults with IBD reported worse fatigue scores compared to the general population (38.9 vs. 43.6, $p < .001$)

(Tinsley, Macklin, Korenik & Sands, 2011). Out of 220 participants, 26% reported fatigue in a second study in the US (Cohen et al., 2014). A 2018 study in the US reported the prevalence of fatigue as 57.5% (N = 685; Hashash et al., 2018). The prevalence of fatigue was found to be 41% (N = 544, 95% CI = 37–45%) in a multicenter Spanish study (Chavarría et al., 2019). Other cross-sectional studies also reported a higher prevalence of fatigue among adults with IBD. A study by Bager and colleagues (2012) reported the presence of fatigue in 44% (N = 425) of adults with IBD whereas 64% (N = 222) of IBD outpatients reported fatigue in a separate study (Romkens, Pinxteren, Nagengast, van Oijen, & de Jong, 2011). Additionally, a longitudinal assessment of fatigue in adults with IBD initiating biologic therapy confirmed the results of the cross-sectional analysis (Borren et al., 2019). Fatigue was consistently present among the study subjects at week 14 (70%, $n = 86$), week 30 (63%, $n = 55$), and week 54 (61%, $n = 44$) among the 198 participants who reported fatigue at biologic therapy initiation (Borren et al., 2019). Moreover, the prevalence of fatigue was significantly higher in participants with IBD compared to healthy controls (HC) (UC [28%] vs. HC [6%], $p < .001$; CD [13%] vs. HC [2%], $p = .002$; all IBD [41%] vs. HC [4%], $p < 0.001$) (Grimstad et al., 2015). Similar results were noted in three other studies where higher mean fatigue scores were found among adults with CD followed by UC and HC (Huppertz-Hauss et al., 2017, $p < .001$; Jelsness-Jørgensen et al., 2011a, $p < .001$; van Langenberg & Gibson, 2014, $p < .01$). Additionally, chronic fatigue scores (CF, defined as fatigue > 6 months) were found to be twice as common among the CD and UC group compared to the HC ($p < .001$ for both CD and UC) (Jelsness-Jørgensen et al., 2011a). More than 80% of adults with IBD described fatigue as the most frequently reported symptom (Perler et al., 2019; Vegni et al., 2019) and warrants concerns in considering treatment objectives for IBD (Casellas, Guise, Robies, Navarro, Borruel, 2016). A more recent study on IBD and chronic fatigue

syndrome(CFS) revealed a higher cumulative incidence of CFS in adults with IBD ($p < .001$) compared to the control group (Tsai et al., 2019). Overall, the prevalence rate of IBD-Fatigue ranged from 26% to 80% among the studies. Most studies reported fatigue prevalence to be higher in CD compared to UC. However, those with CD and UC had a higher prevalence of fatigue than HC.

Comparing IBD-Fatigue by CD and UC

Many study results reported no difference in fatigue between CD and UC (Bager et al., 2012; Chavarría et al., 2019; Cohen et al., 2014; Frigstad et al., 2018; Huppertz-Hauss et al., 2017; Romkens et al., 2011). On the contrary, other studies reported higher fatigue presentations among those with CD. Comparing the subtypes of IBD (CD vs. UC) and disease activity (active vs. inactive), fatigue scores were higher (53.3%) in those with active disease in CD compared to those in remission (23.5%, $p = .002$). However, no difference in fatigue was noted between active and inactive forms of UC (Cohen et al., 2014). Two of the study results reported significantly worse fatigue among adults with CD compared to adults with UC; $p = .003$ (Opheim et al., 2014) and $p < .005$ (Romberg-Camps et al., 2010). The results were similar for chronic fatigue presentations, where the chronic fatigue frequency was a little higher among the CD group (29%) compared to the UC group (22%) (Jelsness-Jørgensen et al., 2011a). Additionally, higher levels of mean chronic fatigue scores were noted among adults with CD (14.4) and UC (13.5) compared to the reference population (12.2) (Huppertz-Hauss et al., 2017). Adults with CD had a significantly higher risk of chronic fatigue syndrome compared to those without IBD (adjusted HR, 2.27; [CI, 1.70 – 3.03]) (Tsai et al., 2019). Those with CD had higher fatigue scores when compared to UC. Both groups had higher chronic fatigue than controls, and those with CD are at higher risk for chronic fatigue. Analyses of the results of fatigue between subtypes of IBD (CD vs. UC) are inconclusive. No difference in fatigue noted between CD and

UC in many study reports. However, some study reports highlighted a higher prevalence of fatigue among adults with active CD than UC. One limitation is comparison of fatigue in multiple studies and the variability in measuring fatigue between studies.

Fatigue Scales

A variety of fatigue scales were documented in the literature to assess IBD-Fatigue. The IBD-Fatigue scales were analyzed to determine the type of the scales used by the researchers. The Multidimensional Fatigue Inventory (MFI) (Bager et al., 2012; Banovic et al., 2012; Graff et al., 2013; Romberg-Camps et al., 2010) and the Fatigue Questionnaire (FQ) (Frigstad et al., 2018; Huppertz-Hauss et al., 2017; Jelsness-Jørgensen et al., 2011a; Jelsness-Jørgensen et al., 2011b) were the most commonly used scales. The Functional Assessment of Chronic Illness Therapy- Fatigue (FACIT-F) scale was also used to assess fatigue, with a cut-off score of ≤ 30 to indicate the symptom of fatigue (Cohen et al., 2014). Two studies assessed fatigue by using the Fatigue Impact Scale (FIS) (Pellino et al., 2014; van Langenberg & Gibson, 2014). Opheim and colleagues (2014) used the Fatigue Severity Scale (FSS) in their study. Another study (Ratnakumaran et al., 2018) used the IBD fatigue self-assessment (IBD-F) scale, which had two sections: The first section assessed the severity of fatigue, and the second section assessed the impact of fatigue. Fatigue was quantified by using the seven-point fatigue scale in the Short Inflammatory Bowel Disease Questionnaire (SIBDQ), where fatigue was defined as a score of ≤ 4 (Borren et al., 2019). Romkens and colleagues (2011) used the Revised Piper Fatigue Scale in their study. In summary, no pattern was observed between the researchers or the geographic location of the study related to the selection of fatigue scales. The number of questions and the domains of fatigue measured varied among the scales.

Only three studies used two different fatigue scales: Fatigue Severity Scale (FSS) and Fatigue Impact Scale (FIS) (Chavarría et al., 2019); Brief Fatigue Inventory (BFI) and MFI

(Aluzaite et al., 2018); and fatigue Visual Analogue Scale (fVAS) and FSS (Grimstad et al., 2015). The researchers' intentions were to assess the different dimensions of fatigue, as FSS and BFI are unidimensional instruments whereas FIS and MFI are multidimensional instruments.

Inflammation and IBD-Fatigue

In a systematic review, van Langenberg and Gibson (2010) addressed the intrinsic role of inflammation in fatigue pathology. Secretion of specific cells, cytokines, are the direct result of an inflammatory process (van Langenberg and Gibson, 2010). The authors presented the evidence from the cytokine research where higher levels of cytokines, interleukin 1 (IL-1), IL-6, and tumor necrosis factor alpha (TNF α) were correlated with the intensity of fatigue. Additionally, van Langenberg and Gibson (2010) discussed the central and peripheral aspects of IBD-Fatigue. The central origin of fatigue is related to the stress-induced changes in the hypothalamic-pituitary axis, changes in central neurotransmission, and central effects of circulatory cytokines. The inherent association between fatigue and mood disorders, including anxiety and depression, are explained based on the central origin of fatigue connecting the common neuroendocrine and neurotransmitter pathways between fatigue and mood disorders. The authors explained the peripheral aspects of fatigue, where centrally mediated fatigue results in reduced muscle mass and muscle strength in those with IBD. This impaired muscle performance thus led to peripheral or physical fatigue (van Langenberg & Gibson, 2010).

To understand fatigue and inflammation, Vogelaar and colleagues (2017) examined the relationship between fatigue and immune status. Adults with IBD were categorized as the fatigued group (FG, $n = 55$) and the non-fatigued group (NFG, $n = 29$). Subsets of leukocytes (lymphocytes, monocytes, and granulocytes) and cytokine analysis (IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, TNFα, IFN-ϒ) were conducted simultaneously. Comparison of monocytes between FG and NFG revealed a significantly lower percentage of monocytes in FG (median: FG [5.3], NFG

[7.2]; p = .011). Additionally, analysis of granulocytes denoted a higher percentage of neutrophils (median: FG [77], NFG [68.8]; p =. 033) in the FG compared to the NFG. Analysis of serum cytokines revealed the following results: The FG group had higher levels of IL-12 (median: FG [4.8], NFG [3.3], p < .001) and IL-10 (median: FG [2.2], NFG [2], p < .001) compared to the NFG. On the other hand, IL-6 levels were significantly lower (median: FG [2], NFG [2.3], p = .002) in the FG group compared to the NFG group. The authors concluded that the difference in immune parameters between FG and NFG is indicative of a link between the immune system and the brain in IBD-Fatigue (Vogelaar et al., 2017). However, contrasting results were noted in another study where approximately 30% to 63% of adults with IBD had no detectable interleukin (IL) levels (N = 177). Additionally, no statistical differences in IL levels were noted in those with detectable IL between fatigued and non-fatigued adults with IBD (Villora et al., 2017).

During the inflammatory process, there are additional early indicators and markers as the body responds. The most common biomarkers to evaluate the association of inflammation with IBD-Fatigue were C-reactive protein (CRP), fecal calprotectin, and ferritin (Artom et al., 2017; Bager et al., 2012; Cohen et al., 2014; Chavarría et al., 2019; Frigstad et al., 2018; Grimstad et al., 2016; Huppertz-Hauss et al., 2017; Villora et al., 2017); however, no association was found between these biomarkers and IBD-Fatigue. Calprotectin is a small calcium binding protein found in neutrophils; any disturbance to the intestinal mucosa due to inflammation results in leakage of calprotectin into the feces. A fecal calprotectin level of > 150µg/g is suggestive of IBD (Walsham & Sherwood, 2016). Only one study's results reported an association between higher erythrocyte sedimentation rate (ESR) levels and IBD-Fatigue (Chavarría et al., 2019). Vitamin D was measured in two studies, and no significant association was found between IBD-

Fatigue and vitamin D levels (Chavarría et al., 2019; Frigstad et al., 2018). A longitudinal assessment evaluated the association between CRP and hemoglobin over 12 months, but no significant association was found between these variables in relation to IBD-Fatigue over time (Graff et al., 2013). Two intervention studies (Vogelaar et al., 2011; Vogelaar et al., 2014), which tested the effectiveness of solution focused therapy on fatigue, also tested CRP, ferritin, and hemoglobin at both pre-intervention and post intervention stages, but no changes in blood parameters were noted. Even though the evidence strongly supported the association between IBD-Fatigue and inflammation, the reviewed studies did not confirm this association.

Fatigue and QOL

A strong association between IBD-Fatigue and health-related quality of life (HRQOL) was noted in all reviewed quantitative and qualitative studies (Beck, Bager, Jensen, & Dahlerup et al., 2013; Cohen et al., 2014; Czuber-Dochan et al., 2013a; Jelsness-Jørgensen et al., 2011b; Romberg-Camps et al., 2010; Villora et al., 2017). Quality of life scores were significantly lower in the fatigued CD (131 vs.180, $p < .001$) and UC (67.2 vs. 81.5, $p < .001$) participants compared to adults without fatigue in a US study (Cohen et al., 2014). Similar results were noted with CF and QOL in a different study in Norway. Chronic fatigue was associated with lower HRQOL scores in those in the CD ($p < .01$) and UC group ($p < .001$) (Jelsness-Jørgensen et al., 2011b). Additionally, the QOL scores were much lower in participants with CF compared to HC (Jelsness-Jørgensen et al., 2011b). A strong negative correlation was found between QOL and fatigue ($r = - 0.81$, $p < .001$) among adults with IBD in Spain (Villora et al., 2017). In a Netherlands study, disease activity and fatigue were independently associated with lower HRQOL in participants with UC and those with CD ($p < .05$) (Romberg-Camps et al., 2010). Moreover, 40% of adults with IBD (N = 117) reported that improving their QOL was the most

important treatment objective to support the importance of intervening on IBD-Fatigue (Casellas et al., 2016).

In a qualitative study conducted by Czuber-Dochan et al. (2013a) in the United Kingdom (UK), participants with IBD reported how fatigue affected specific aspects of their QOL, such as influencing their parenting and their decision not to have more kids, heavy dependence on their significant others to complete family tasks, and inability to think clearly. Moreover, adults with IBD reported irritability with worst fatigue symptoms and commented that it negatively influenced their relationships between family and friends (Beck et al., 2013).

Another important area of research to consider with IBD-Fatigue and QOL is the disease related worries of those with IBD. One study compared the disease-related worries of adults with IBD to their QOL (Jelsness-Jørgensen, Bernklev, Henriksen, Torp, & Moum, 2012). This study found that disease-related worries were associated with higher fatigue levels in both CD (r_s= 0.36) and UC (r_s= 0.49). Additionally, certain disease-related worries were significantly higher among adults with CD and UC with CF compared to those without CF ($p < .01$). An inverse relationship was noted between disease-related worries and disease-specific HRQOL in CD (r_s= -0. 53) and UC (r_s= -0. 51). More importantly, increased CF could lead to increased disease-related worries, which can reduce the QOL of adults with IBD (Jelsness-Jørgensen et al., 2012).

Some studies have addressed the impact of fatigue on work efficiency and employment (Beck et al., 2013; Cohen et al., 2014; Czuber-Dochan et al., 2013a). The Work Productivity and Activity Impairment (WPAI) scores of absenteeism, presenteeism, overall work impairment, and daily activity impairment demonstrated significant differences between fatigued and non-fatigued adults with CD ($p < .01$). However, only the WPAI scores of

presenteeism, overall work impairment, and daily activity impairment were different between fatigued and non-fatigued adults with UC ($p < .01$) (Cohen et al., 2014). Adults with IBD reported that fatigue interfered with their work quality and that they occasionally needed frequent rest periods to recharge themselves, which was often misunderstood by their employers. Participants reported that fatigue sometimes influenced their decision to stop working altogether (Czuber-Dochan et al., 2013a). The same concerns were reiterated in another qualitative study in Denmark where adults with IBD reported concentration problems at work due to mental fatigue, reduced work efficiency due to fatigue, and some were concerned about their colleagues' perceptions of their work qualities related to fatigue (Beck et al., 2013). Clearly, fatigue influences the QOL of those with IBD; however, the ways in which QOL is affected by fatigue varies among individuals. In general, the reviewed studies presented an inverse association between IBD-Fatigue and QOL of adults with IBD. Additionally, the results of the reviewed studies revealed a complex association between IBD-Fatigue and different dimensions of QOL, such as parenting styles, work efficiency and employment.

Interventions to Manage IBD-Fatigue

Very limited interventions are currently available to manage IBD-Fatigue. Different interventions documented in the literature regarding management of IBD-Fatigue include problem solving therapy (PST), solution focused therapy (SFT), psychoeducational intervention, AndoSan (medicinal Agaricus blazei Murill mushroom extract), electro acupuncture (EAc), Sham EAc (ShEAc), conventional non-biologic therapies and biologic therapies (Borren et al., 2019; Grimstad et al., 2016; Horta et al., 2019; O'Connor et al., 2019; Therkelsen, Hetland, Lyberg, Lygren, & Johnson, 2016; Vogelaar et al., 2011; Vogelaar et al., 2014). Except for two studies (Borren et al., 2019; Grimstad et al., 2016), all others were randomized controlled trials (RCTs).

The focus of SFT was to improve the existing coping abilities of adults in managing their fatigue (Vogelaar et al., 2011; Vogelaar et al., 2014). Besides SFT, Vogelaar and colleagues (2011) included PST to manage fatigue with structured steps. Strategies incorporated to improve participants' adherence to the intervention included adding a close relative of the participant in the fifth session of SFT and offering a booster session at six months (Vogelaar et al., 2014). Both psychological and physical interventions were included in the psychoeducational intervention to manage IBD-Fatigue (O'Connor et al., 2019). Relaxation techniques, which included diaphragmatic breathing PST and visualization and progressive muscular relaxation were adopted for the psychoeducational intervention. Conversely, Therkelsen and colleagues (2016) and Grimstad and colleagues (2016) tested the efficacy of administering a supplement and using conventional non-biologic therapy to manage IBD-Fatigue. AndoSan supplement 30 ml twice a day for 21 days was administered to test its anti-inflammatory properties in reducing IBF-Fatigue among adults with UC (Therkelsen et al., 2016). Conventional non-biologic therapy included topical or systemic 5-aminosalicylates in combination with corticosteroids and/or immunosuppressive drugs (azathioprine or mercaptopurine) (Grimstad et al., 2016). The effectiveness of biologic therapies, such as infliximab, adalimumab, ustekinumab, and vedolizumab, were assessed in adults with IBD by initiating these drugs to manage fatigue in a longitudinal assessment (Borren et al., 2019).

The three interventions (SFT, PST, and psychoeducational) that were focused on improving participants'coping skills demonstrated robust evidence for managing IBD-Fatigue, as fatigue scores reduced after the implementation of these interventions. Fatigue reduced to 85.7% at three months from baseline (Vogelaar et al., 2011), with significant reduction of fatigue among participants compared to controls (Vogelaar et al., 2014, $p = .001$) at six months, and

improvement in fatigue severity (9.7%) and impact (7.3%) among the participants of psychoeducational intervention (O'Connor et al., 2019) at six months. Vogelaar and colleagues (2011) reported other benefits of SFT, such as shorter duration of therapy, a lower dropout rate, and lower healthcare costs due to reduced outpatient visits and hospital admission.

The use of AndoSan, EAc, and Sham EAc were the other non-pharmacological complementary interventions that supported the management of IBD-Fatigue. Significant improvements in mean fatigue scores were found among adults with UC in the AndoSan group from baseline (16.6) to 21 days (15.1, $p = .018$) (Therkelsen et al., 2016). Similar results were noted among the acupuncture group where significant improvement in fatigue was found in both the EAc group (9.53 points, [6.75–12.3, 95% CI], $p < .001$) and the Sham EAc group (5.46 points, [2.7–9.7, 95% CI], $p = .015$) compared to controls after the completion of nine sessions (Horta et al., 2019).

Both the pharmacological interventions (non-biologic therapies and biologic therapies) revealed promising results for the management of IBD-Fatigue. The median fatigue score changed from 40 (at baseline) to 22 at three months after the use of conventional non-biologic therapies ($p < .001$). Moreover, lower fatigue scores were noted among adults with IBD in remission compared to those with active disease at three months after the intervention, but this was not statistically significant (Grimstad et al., 2016). However, the participants of the study (N = 82) were adults with newly diagnosed IBD; therefore, the application of the intervention for those with established IBD is unclear. The longitudinal assessment revealed significant improvement in fatigue from baseline to week 54 for those taking biologic therapies. The fatigue scores improved from baseline (3.8 ± 1.8) to week 14 (4.2 ± 1.8), $p < 0.001$), week 30 (4.6 ± 1.7, $p < 0.001$), and week 54 (4.6 ± 1.7, $p < 0.001$) (Borren et al., 2019).

Participants from two qualitative studies (Beck et al., 2013; Czuber-Dochan et al., 2013a) reported different strategies for managing IBD-Fatigue. Adults with IBD depended on careful planning and prioritization of daily tasks to use their energy wisely; they reported planning structured breaks and periods of relaxation to have a long nights' sleep to manage IBD-Fatigue (Beck et al., 2013; Czuber-Dochan et al., 2013a). Participants emphasized the need for rest in the afternoon and used books, television, music, or breathing techniques as relaxation strategies (Beck et al., 2013). However, some participants reported the persistence of fatigue despite adequate amounts of rest or sleep (Czuber-Dochan et al., 2013a). Moreover, few participants felt that being busy helped them to overcome the IBD-Fatigue (Czuber-Dochan et al., 2013a).

Although the interventional studies helped to manage IBD-Fatigue, none of them indicated how to manage daily living with IBD-Fatigue. This proposed study may assist in understanding the complex interplay of physiological, psychological, and situational factors contributing to IBD-Fatigue at a holistic level to develop more efficient interventions to prevent or mitigate IBD-Fatigue.

IBD-Fatigue and Physiological Factors

Age

The majority of the reviewed studies supported the fact that younger adults with IBD reported higher levels of fatigue compared to older adults**.** However, the categorization of adults with IBD as younger adults vs. older adults varied among the studies. Stratification with age revealed that adults with IBD who were < 60 years were found to have higher fatigue scores (Bager et al., 2012). Another study result reported a subgroup analyses based on age (< 65 years vs. > 65 years), where participants with mild disease activity who were < 65 years of age had higher fatigue scores compared to participants who were > 65 years of age (Pellino et al., 2014). Similar results were noted by Graff and colleagues (2013), where younger adults with IBD

reported higher levels of fatigue ($F = 5.71$, $\beta = -0.02$, $p < .001$). Comparable to these two studies, older adults with IBD reported significantly lower mental fatigue ($p < .006$) (Aluzaite et al., 2018). The study by Grimstad et al. (2015) measured fatigue using both fVAS and FSS, and age was negatively associated with fatigue scores in both scales (age, $p < .001$ for fVAS; age, $p < .001$ for FSS). Fatigue (72.1%, $n = 44$) was the most prevalent symptom reported by emerging adults (18–29) with IBD (Kemp, Dudley-Brown, Heitkemper, Wyatt, & Given, 2019). The reviewed studies consistently reported the fact that younger age is associated with higher levels of fatigue. Fatigue is related to inflammation, and older age is associated with altered inflammation (Kale & Yende, 2011). Other possible explanations are that older adults accommodate their lives resulting from the fatigue more readily than the younger ones. Moreover, older adults' work and home responsibilities may differ from those of younger adults. However, the literature is unclear as to the reason for these relationships, but recognizably age should be included as a variable when examining IBD-Fatigue.

Disease Duration

Adults with CD had a higher duration of disease (median 11 years, $p = .002$) compared to those with UC (median 7 years) (van Langenberg & Gibson, 2014). Three of the reviewed studies reported an inverse association between duration of the disease and fatigue (Aluzaite et al., 2018; Kappelman et al., 2014; Vogelaar et al., 2013). Adults with IBD reported lower fatigue with longer duration of the disease (Aluzaite et al., 2018). Similar results were noted with adults with CD, where a reduction of fatigue (-0.14 for each disease year) was associated with longer duration of the disease (Vogelaar et al., 2013). Adults who had been diagnosed with IBD less than one year reported worse Patient-Reported Outcomes Measurement Information System (PROMIS) domains of fatigue, anxiety, depression, pain interference, sleep disturbances, and satisfaction with social roles compared to those who had a longer disease duration (Kappelman et

al., 2014). However, a low positive correlation was found between disease duration and fatigue among adults with UC ($r = 0.23$, $p < .01$) (Bol et al., 2010).

The literature did not explain the reason behind the inverse association between disease duration and IBD-Fatigue. One possible explanation is that an individual adjusts to the disease trajectory of IBD as a norm. On the other hand, those who are newly diagnosed with IBD had to face several consequences of IBD-Fatigue and may take longer time to adapt to those consequences. Therefore, it is important to examine the association between disease duration and IBD-Fatigue in the proposed study.

Surgical History

Limited studies are available to assess surgical history with IBD-Fatigue. Based on the available study, improvement in cognitive fatigue was reported among adults with CD who had a history of intestinal resection for the treatment of IBD (van Langenberg & Gibson, 2014). Adults who had a previous surgical resection for UC reported better outcomes related to fatigue, anxiety, depression, pain interference, sleep disturbances, and satisfaction with social roles compared to those who did not have a surgical resection (Kappelman et al., 2014). This finding is consistent with a previous meta-analysis report stating that QOL is improved in adults with UC after colectomy (Heikens, de Vries, & van Laarhoven, 2012)**.** Therefore, examining the history of surgical intervention is important when determining physiological factors affecting IBD-Fatigue.

Disease Activity

Many studies have compared IBD-Fatigue based on IBD disease activity (active vs. remission), and a strong correlation has been found between fatigue and active disease among adults with IBD. When comparing active disease with remission, fatigue was found to be significantly higher among adults with active IBD than those in remission: $p < .001$ (Aluzaite et

al., 2018); $p < .05$ (Bager et al., 2012); $p < .03$ (Chavarría et al., 2019); UC 17.1 vs. 12.4, $p < .001$; CD 17.5 vs. 13.3, $p < .001$ (Huppertz-Hauss et al., 2017). Moreover, both fatigue severity ($p = .047$) and impact ($p = .01$) were higher among adults with active IBD compared to adults in remission (Ratnakumaran et al., 2018). A longitudinal assessment confirmed a similar conclusion, where higher levels of fatigue were noted among adults with active IBD ($n = 140$) and fluctuating disease ($n = 90$) over two years. However, a moderate increase in fatigue levels was noted over time regardless of the disease activity ($F = 17.79$, $\beta = 0.03$, $p < .001$) (Graff et al., 2013). Moreover, an association was noted between CF and disease activity indices. Simple Clinical Colitis Activity Index (SCCAI), a measure of UC disease activity, increased in participants with UC ($p = .044$), but no difference was noted in short Crohn's Disease Activity Index (sCDAI), a measure of disease activity of CD among those with CD (Jelsness-Jørgensen et al., 2011b). Conversely, a systematic review conducted by van Langenberg and Gibson (2010) reported fatigue prevalence of 86% in moderate to severely active Crohn's disease. More importantly, a comparison between adults with IBD and the control group revealed that participants with moderate to severe disease activity had worse fatigue compared to controls at any age ($p < .0001$) (Pellino et al., 2014).

Many studies have reported a higher prevalence of IBD-Fatigue irrespective of disease activity in those with IBD remission. For example, Aluzaite and colleagues (2018) reported the prevalence of fatigue as 39.5–44.2% ($n = 113$) among those in IBD remission; the prevalence of fatigue was approximately 40% in two studies in a subgroup of adults with IBD in remission, with $n = 161$ (Romberg-Camps et al., 2010) and $n = 124$ (Romkens et al., 2011). The systematic review by van Langenberg and Gibson (2010) reported prevalence of fatigue as 41–48% in adults with IBD remission. Moreover, a longitudinal assessment also noted the presence of

fatigue despite the status of clinical remission after biologic therapy in adults with IBD at weeks 14 (35%, *n* = 203), 30 (30%, *n* = 150), and 54 (28%, *n* = 122).

Sleep Disturbances

Sleep may be an important factor in IBD and IBD-Fatigue. Rapid eye movement (REM) sleep and non-REM (NREM) sleep are the two stages of human sleep (Kinnucan, Robin, & Ali, 2013). Almost 20% of adult sleep time includes REM sleep, and the remaining 80% is NREM sleep. The NREM sleep is further divided into four stages. Stages three and four are categorized as slow-wave sleep (SWS), which is considered the most restorative stage of sleep. Moreover, SWS is greatly influenced by the immune system's regulation; as a result, contractility of the colon is reduced, leading to 'rest periods' for the colon (Kinnucan et al., 2013). Therefore, any interference to the stages of SWS impedes gastrointestinal (GI) physiology and reduces mucosal integrity (Kinnucan et al., 2013; Tang, Preuss, Turek, Jakate, & Keshavarzian, 2009).

Evidence from the literature supports the association between sleep deprivation and activation of the immune system. This evidence has great implications for the IBD population, as the disorder is immune-mediated. Sleep deprivation can lead to increased pro-inflammatory cytokines, such as IL-1, IL-6, TNFα, and CRP (Irwin et al., 2006; Kinnucan et al., 2013). Both IL-1 and TNFα are considered sleep regulatory cytokines (Opp, 2005; Kinnucan et al., 2013). The cytokine IL-1 controls sleep through serotonin receptor pathways, and increased levels of IL-1 can cause NREM suppression and sleep fragmentation (Ranjbaran, Keefer, Stepanski, Farhadi, & Keshavarzian, 2007). Additionally, IL-6 leads to sleep deprivation by inhibiting REM sleep and increasing wakefulness in adults with IBD (Ranjbaran et al., 2007; Kinnucan et al., 2013).

Many nonimmune-mediated factors are also associated with sleep regulation. Among these, melatonin and cortisol (glucocorticoids) play a significant role in circadian rhythms and

altered sleep patterns (Terry, Villinger, Bubenik, & Sitaraman, 2009). Melatonin is found in the GI tract and controls GI motility. The use of exogenous glucocorticoids in the form of corticosteroids for chronic inflammation is associated with altered sleep patterns in adults with IBD (Ananthakrishnan et al., 2013).

The reviewed studies highlighted poor sleep quality among adults with IBD. Sleep disturbances were present in 60% of adults with IBD (N = 4366) in the US (Ananthakrishnan et al., 2013), 44.1% (N = 136) in Japan (Uemura et al., 2016), and 62% (N = 544) in Spain (Chavarría et al., 2019).

Sleep and IBD disease activity. Many studies connected poor sleep quality with the disease activity of adults with IBD. Adults with active disease (78% CD and 67% UC) were found to have higher levels of daytime sleepiness ($p < .001$) compared to those with inactive forms of the disease (29% CD and 30% UC) (Graff et al., 2011). Poor sleep quality was found in 23 (100%) adults with active IBD and in 13 (72%) adults with inactive IBD (OR = 2.8, $p = .007$) (Ali, Madhoun, Orr, & Rubin, 2013). The authors also identified a strong correlation between sleep quality and clinical disease activity in UC ($r = 0.7$, $p = .002$), but not in CD. The sleep disturbances were present in 48% of those in remission compared to 76% of adults with active IBD ($p < .001$) (Ali et al., 2013). Conversely, compromised sleep quality was also noted among adults with IBD in remission. A group of researchers objectively monitored sleep quality of adults with IBD in remission using polysomnography (N = 36) and compared it with HC (N = 27). Adults with IBD in remission had less REM sleep compared to HC ($p = .047$) and increased oxygen desaturation periods below 90% ($p = .07$) (Shitrit et al., 2018). Burgess, Swanson, and Keshavarzian (2010) objectively assessed the sleep quality of adults with inactive IBD using a wrist-worn actigraphy (N = 4). The study results revealed increased sleep onset latency and

decreased sleep efficiency compared to HC ($p < .05$ for both). However, results were not generalizable due to the small sample size of the study. A later study (Qazi et al., 2018) used the same method of measuring sleep disturbances by using actigraphy in adults with CD. Significant differences in sleep efficiency were noted, as individuals with moderate to severe CD had poorer sleep efficiency compared to those in remission (86% vs. 89%, $p = .03$). Additionally, participants with active CD had an increased amount of fragmented sleep compared to participants with CD remission (65.8 minutes vs. 44.3 minutes, $p < .05$) (Qazi et al., 2018). In summary, sleep disturbances were reported in adults with IBD irrespective of their disease activity.

Sleep disturbances and risks for active IBD. Sleep disturbances and risks for active IBD were reported in multiple research studies. Disturbed sleep doubles the risk of active disease at six months among the adults with CD in remission at baseline ($n = 1291$, OR = 2 [1.45–2.76], 95% CI, $p < .001$) compared to those with unimpaired sleep. However, no such difference was noted among adults with UC in remission (Ananthakrishnan et al., 2013). Similar findings were observed in a Japanese study, where 37.5% (N= 136) of adults experienced a disease flare at one year, and sleep disturbances were associated with higher odds for disease flare (OR = 3.09 [1.47–6.43], $p < .01$) (Uemura et al., 2016). A longitudinal assessment also confirmed the same results, but no risk for active disease with sleep disturbances was noted after one year (Borren et al., 2019). Those with sleep disturbances had a tenfold risk of experiencing fatigue at week 14 (OR = 9.7 [2.1–45.09], $p = .004$), but this risk reduced to sevenfold at week 30 (OR = 6.5 [1.31–32.63], $p = .022$), with no increased risk noted at week 54 ($p = .21$) among adults with IBD who were initiated on biologic therapies (Borren et al., 2019).

Other factors related to sleeping quality of adults with IBD included the duration of sleep and various clinical factors. A prospective study using Nurses' Health Study data revealed a higher incidence of UC ($p < .05$) in women who had sleep duration < 6 hours/day or > 9 hours/day compared to usual sleep duration of 7–8 hours/day. However, no such risk was observed in women in the CD group (Ananthakrishnan et al., 2014). Clinical factors, such as the use of systemic steroids, narcotics, anti-TNF medications, or previous surgical history, independently predicted sleep disturbances ($p < .001$) (Ananthakrishnan et al., 2013). Hence, it is important to assess sleep disturbances and clinical factors, such as IBD medications while examining IBD-Fatigue in the proposed study.

Sleep disturbances and IBD-Fatigue. All of the reviewed studies strongly supported the direct association between sleep disturbances and IBD-Fatigue. Poor sleep quality was more pronounced in adults with fatigue compared to those without fatigue (74% vs. 55%, $p < 0.01$) (Chavarría et al., 2019). Similar results were reported by another group of researchers where mean scores of day time sleepiness (8.67) were significantly higher ($p = .001$) in the higher fatigue group (MFI > 43) compared to the low fatigue group (5.78; MFI ≤ 43) (Banovic et al., 2012). Impaired sleep was positively correlated with both fatigue severity ($r = 0.47$, $p <. 10$) and impact ($r = 0.53$, $p < .10$) in another study (Artom et al., 2017). Altered sleep was correlated to fatigue in adults with UC in two studies (Huppertz-Hauss et al., 2017; Jelsness-Jørgensen et al., 2011a).

Poor sleep quality independently predicted fatigue in adults with IBD (Banovic et al., 2012, $\beta = 0.36$, $p = .009$; Huppertz-Hauss et al., 2017, $p < .05$). Altered sleep significantly predicted fatigue in adults with UC ($p < .001$) (Jelsness-Jørgensen et al., 2011a). Additionally, poor sleep quality was shown to increase the odds of elevated fatigue in adults with IBD (OR =

4, 95% CI [1.9–8.6], $p < .001$) (Graff et al., 2011), as well as increasing the odds for CF in adults with CD (OR = 3.65, 95% CI [1.61–8.27], $p < .01$) (Frigstad et al., 2018). Multivariate logistic regression analysis between fatigue and sleep quality yielded a higher likelihood of global, physical, and cognitive fatigue with impaired sleep quality (OR = > 1 for all types of fatigue, $p < .05$) among adults with IBD (van Langenberg & Gibson, 2014). However, the longitudinal assessment of the same study at 12 months among adults with CD revealed higher odds of improvement in cognitive fatigue (OR = 5.24, 95% CI [1.30–21.11], $p = .02$) with improvement in sleep quality between surveys (baseline to 12 months) (van Langenberg & Gibson, 2014). Another longitudinal assessment of fatigue undertaken every six months to two years revealed an independent association between sleep quality ($F = 139.4$, $\beta = 0.30$, $p < .001$) and an increase in fatigue across time (Graff et al., 2013).

Pain

One theory for abdominal pain in IBD is the inflammation mediated through cytokine pathways, and this inflammation increases the excitability of sensory nerves that relay information from the gut to the brain. The affective dimension of the pain (valence) increases the emotional responses impeding the descending inhibitory control mechanisms (Bielefeldt, Davis, & Binion, 2009; Coates et al., 2013), resulting in increased pain perception. However, the inflammation-based explanation does not sufficiently explain the pain, as individuals in IBD remission also experience significant pain; thus, the mechanism behind IBD associated pain is not clear (Bielefeldt, et al., 2009; Coates et al., 2013). One possible explanation behind IBD associated pain in adults with IBD remission is the higher rate of irritable bowel syndrome (IBS) symptoms, anxiety, and depression in this group which contribute to the functional symptoms of abdominal pain (Docherty, Jones, & Wallace, 2011; Farrokhyar, Marshall, Easterbrook, & Irwin, 2006; Graff, Walker, & Bernstein, 2009; Norton et al., 2016). The non-inflammatory sources of

pain include intestinal strictures, adhesions, small bowel obstruction, and narcotic bowel syndrome (Doherty et al., 2011; Norton et al., 2016).

Prevalence of pain in IBD. In a large Swiss cohort study of 1263 adults with IBD, 71% reported experiencing pain during the course of IBD. Pain was reported as a longstanding problem (> 5 years) in nearly half of adults with IBD (49% in UC and 55% in CD). Abdominal pain was the most commonly reported type of pain (59.5%) followed by back pain (38.3%) (Zeitz et al., 2016). More than half (59%, n = 158) of patients with spondyloarthritis also reported current arthralgia or back pain (Ossum et al., 2019) in a Norwegian study. Participants of a qualitative study emphasized the existence of pain in the joints, which limited their physical activity (Beck et al., 2013). The results of a retrospective analysis of adults with UC noted more than half of the participants (52.2%, N = 502) as experiencing abdominal pain; 21.5% of participants described having more frequent pain which was described as pain 'some of the time or more'; and 10% of adults with UC in remission (*n* = 33) complained of more frequent pain compared to those in remission (N = 326) (Coates et al., 2013). A group of researchers evaluated chronic pain among 120 adults with IBD, which was defined as pain occurring every day for three months within the past six month (Morrison, van Langenberg, Gibson, & Gibson, 2013). The participants of the study reported chronic pain in different body parts. Approximately 38% (N = 120) reported chronic pain; among these, chronic abdominal pain was present in 91% (n = 42), and 33% reported chronic joint and back pain (Morrison et al., 2013). Participants of a qualitative study reported that abdominal and joint pain are the two symptoms most difficult to live with, impairing their QOL (Norton, Thomas, Lomax, & Dudley-Brown, 2012). Pain was the third most frequent symptom (80%; N = 201) reported by adults with IBD, and the prevalence was higher in adults with CD compared to UC (88% vs. 74.5%, $p = .016$) (Vegni et al., 2019).

Other influencing factors of pain. In a follow-up assessment of a Swiss cohort study, researchers (Bon et al., 2019) computed the association between IBD-specific treatment and pain localizations around 10 different body parts, including abdominal pain. Those who were on anti-TNF therapy reported significantly less elbow pain ($p = .002$) compared to participants who were not on anti-TNF therapy. Additionally, those who were on steroids reported more elbow pain compared to those who were not on steroids ($p = .02$). No association was noted between IBD-specific therapy and the character, duration, and frequency of pain (Bon et al., 2019). A study of adults with UC (N = 502) revealed that opioid use was higher among those who rated their abdominal pain as being frequently or constantly present (8.3%) compared to those without abdominal pain (1.4%, $p < .01$) (Coates et al., 2013). Adults with UC with abdominal pain were found to be younger in age, female, experiencing concurrent mood disorders, and with a higher mean CRP and ESR compared to those without abdominal pain. Consistent with this analysis, factors that increased the odds of abdominal pain included opioid use (OR = 8.87 [1.77–45.58], $p < .01$), presence of a mood disorder (OR = 5.76 [1.39–23.89], $p = .02$), and presence of a pain syndrome (OR = 2.45 [1.01– 5.92], $p = .05$) (Coates, 2013). The worst scores of anxiety and depression, as well as a higher prevalence of opiate and paracetamol use were found among those who reported chronic pain (Morrison et al., 2013). Lastly, active disease ($p = .03$), maladaptive coping ($p = .003$), and depression ($p = .04$) increased the odds of chronic pain in adults with IBD (Morrison et al., 2013).

Pain and IBD- Fatigue. Analysis of results from a research study in Norway among adults with IBD (N = 408) showed higher pain intensity levels among those with both UC and CD, who reported substantial fatigue (SF) and CF. A higher impact of pain levels on fatigue was noted among adults with UC compared to those with CD (SF: Cohen's $d = -0.78$, $p < .001$; CF:

Cohen's d = -0.69, p < .001) and CD (SF: Cohen's d = -0.52, p < .001; CF: Cohen's d = -0.57, p < .001) (Jelsness-Jørgensen et al., 2017). In a qualitative study in Denmark, adults with IBD reported an association between pain and fatigue (Beck et al., 2016). Current arthralgia (OR = 2.68 [1.54–4.65], p < .01) and back pain (OR = 2.69 [1.46–4.96], p < .01) were independently associated with higher odds for experiencing chronic fatigue (Ossum et al., 2019).

Medications

Analysis of the reviewed studies strongly supports the role of IBD medications as a contributor to IBD-Fatigue. The use of immunomodulators, such as azathioprine and methotrexate were associated with IBD-Fatigue (p < .10) (Artom et al., 2017) and CF in adults with IBD (p = .024) (Jelsness-Jørgensen et al., 2011b). The associations between corticosteroids and IBD-Fatigue have been consistently documented in many studies (Artom et al., 2017; Chavarría et al., 2019; Kappelman et al., 2014; Romberg-Camps et al., 2010; van Langenberg & Gibson, 2014). The results of two studies reported the association between anti-TNF therapy and IBD-Fatigue as p < .10 (Artom et al., 2017) and p = .003 (Villora, 2017). The remaining studies reported the associations of IBD-Fatigue with immunosuppressants (p < .05) (Romberg-Camps et al., 2010) and thiopurine (p = .007) (Villora, 2017).

IBD-Fatigue and Psychological Factors

Anxiety and Depression

The link between depression and IBD is explained by using two biopsychosocial bidirectional pathways (Keefer & Kane, 2017). The first pathway was based on behavioral activation theory. Behavioral activation theory addresses depression on a continuum: A lack of environmental reinforcement (enjoyment of life) or excess of environmental punishment (severe illness). The diagnosis of IBD requires a shift in coping to adjust to the symptoms or changes in lifestyles. Poor adjustment or coping with IBD presents a higher chance of depression (Keefer &

Kane, 2017) The second pathway explains the relationships between depression and inflammation. The pro-inflammatory cytokines, such as IL-1, IL-6, IL-12, TNFα, and CRP, are elevated in depressed adults compared to HC (Keefer & Kane, 2017; Martin-Subero, Anderson, Kanchanatawan, Berk, & Maes, 2016; Valkanova, Ebmeier, & Allan, 2013). Evidence from the literature supports the premise that the immune system is activated in depressed individuals that is similar to an active infection, which may be the reason for increased risk of IBD flare in depressed individuals (Keefer & Kane, 2017; Martin-Subero et al., 2016).

Another bidirectional link between anxiety and depression has been shown to exist in the brain-gut axis. The brain-gut axis signals the activation of several mediators, resulting in inflammation. Stress leads to an imbalance of the hypothalamic-pituitary adrenal (HPA) axis, resulting in increased HPA axis activity and peripheral inflammation. Increased intestinal permeability occurs as a result of stress-induced pro-inflammatory effects on the gut. Increased intestinal permeability leads to the elevation of lipopolysaccharides, which have a dose-dependent effect on anxiety and depression symptoms (Bonaz & Bernstein, 2013; Grigoleit et al., 2011; Powell, Walker, & Talley, 2017). Thus, examining anxiety and depression as psychological factors associated with IBD-Fatigue is important.

Prevalence of anxiety and depression among adults with IBD. Reviewed studies indicated a higher prevalence of anxiety and depression among adults with IBD, suggesting a possible bidirectional link between anxiety, depression, and inflammation. Retrospective chart analysis of 327 adults with IBD revealed a prevalence of 25.8% depression and 21.2% anxiety in Canada (Byrne et al., 2017). Analysis of 103 adults with UC, 101 with CD, and 124 HC showed higher mean scores of anxiety (8.5 [UC] vs. 8.6 [CD] vs. 3.2 [HC], $p < .001$) and depression (4.1 [UC] vs. 4.7 [CD] vs. 1.4 [HC], $p < .001$) (Goodhand et al., 2012). In a German study, 422 adults

with IBD were compared to 140 age and sex-matched adults with chronic liver disease (CLD) and 422 age and sex-matched adults from the general population (GP) (Hauser, Janke, Kump, & Hinz, 2011). The anxiety and depression levels of adults with IBD were higher than the GP. The anxiety scores were similar among participants with IBD and CLD, but depression scores were higher among participants with CLD, followed by IBD when compared to controls (Hauser et al., 2011). In a mixed method analysis in Australia (N = 294), 21% of participants reported symptoms of depression, and 40% reported anxiety (Keeton, Mikocka-Walus, & Andrews, 2014). A recent systematic review by Mikocka-Walus and colleagues (2016a) reported a higher prevalence of anxiety and depression among adults with IBD in general, those with active IBD, and those with CD, as compared to HC, those with IBD remission, and those with UC. The prevalence rate of anxiety was 41%, whereas the depression rate was 11% among a sample of 1663 adults with IBD in France (Nahone et al., 2012). Among adults with IBD who had co-existing psychiatric comorbidity (major depressive disorder or generalized anxiety) from two tertiary referral hospitals (n = 5405 for CD and n = 5429 for UC), 18% of adults with CD and 19% of adults with UC had depression or anxiety prior to their first surgery. The diagnosis of anxiety was noted around 40% of adults with a diagnosis of depression (Ananthakrishnan, 2013b). In summary, the reviewed studies indicated a higher prevalence rate of anxiety and depression among adults with IBD in general, those with active IBD and among adults with CD.

Factors associated with anxiety and depression in IBD. Active disease, stress, female gender, body image dissatisfaction, adverse effects of IBD medications, unemployment, and socioeconomic deprivation are the major factors that led to anxiety and depression in IBD in the reviewed studies. Active disease was consistently documented in three of the reviewed studies (Byrne et al., 2017; Nahone et al., 2012; Panara, Yarur, Reiders, Proksell, & Deshpande, 2014)

as a contributing factor of anxiety and depression. Besides having active disease, the other contributors of anxiety and depression included the following: Female gender ($p = .01$) (Byrne et al., 2017); (HR = 1.3 [1.1–1.7], 95% CI, $p = .01$) (Panera et al., 2014); disabled or unemployed status, and socioeconomic deprivation ($p < .05$ for all) (Nahone et al., 2012); and perceived stress ($p < .0001$) (Goodhand et al., 2012). Abdominal pain was associated with anxiety in adults with CD ($p < .04$) (Goodhand et al., 2012). A positive association was noted between body image dissatisfaction and anxiety and depression ($p < .001$) in adults with IBD. The body image dissatisfaction scores were three times higher in participants with anxiety or depression scores above the median value compared to those with low scores (McDermott et al., 2015).

The use of certain IBD medications was found to be higher among those with anxiety and depression. Specifically, Ananthakrishnan and colleagues (2013b) reported higher use of corticosteroids among those who had anxiety and depression (50.5% vs. 36.7%, $p < .01$), and similar results were reported in another study (Navabi et al., 2018); treatment with corticosteroids also increased the odds of developing anxiety (OR = 1.5 [1.1–2.06], $p = .009$) (Nahone et al., 2012); and the use of biologic medications (62.5% vs. 51.3%, $p < .05$) were higher among those who had anxiety and depression (Navabi et al., 2018).

Analysis of longitudinal data (N = 170) from two large cohorts of the Nurses' Health Study revealed that depressive symptoms were associated with a two-fold increase in the risk of developing CD (multivariate-adjusted hazard ratio [HR], 2.39 [1.40–3.98], 95% CI, p trend = .001). No such risk was found in participants with UC. The authors excluded participants on antidepressant therapy to increase the effect size of the study. When comparing recent (within four years) and remote (baseline) assessment of depression to identify the disease risk, the recent

depressive symptoms have been found to be more detrimental in influencing risk of developing CD (Ananthakrishnan, 2013c).

The association between anxiety and depression, higher health care utilization, and worse health outcomes were documented in four of the reviewed studies (Ananthakrishnan, 2013b; Barnes et al., 2017; Limsrivilai et al., 2017; Navabi et al., 2018). Anxiety and depression were associated with higher requirement for colonoscopy ($p < .001$) and a higher number of outpatient visits compared to those without psychiatric comorbidity. Additionally, the presence of anxiety or depression as a psychiatric comorbidity prior to surgery was associated with a 28% increase in the risk of needing surgery (Adjusted OR = 1.28 [1.03–1.57], 95% CI) (Ananthakrishnan, 2013b). A 2013 nationwide readmission database (N = 52,498) was evaluated to determine factors associated with 90 days of hospital readmission. Anxiety (OR = 1.31 [1.21–1.43] for CD; OR = 1.28 [1.14–1.45] for UC) and depression (OR = 1.27 [1.07–1.50] for CD; OR = 1. 35 [1.07–1.70] for UC) significantly increased the odds of 90 days of readmission in both CD and UC, which led to an additional cost of $576 million (Barnes et al., 2017).

Another retrospective analysis using a sample of 1430 adults with IBD in the US showed that psychiatric illnesses, such as anxiety, depression, and bipolar disorders, were associated with high health care utilization and costs for adults with IBD: Specifically, IBD-related hospitalizations (OR = 1.60 [1.08–2.36], 95% CI), ED visits (OR = 1.61 [1.11–2.32], 95% CI), and high health care charges (> $30,000) (OR = 1.49 [0.97–2.24], 95% CI) (Limsrivilai et al., 2017). Similar results were noted in another retrospective analysis (N = 432) by Navabi and colleagues (2018), which showed that those who had IBD with anxiety and depression underwent more imaging studies (53.6% vs. 36.7%, $p < .05$), had more emergency department visits (30.7% vs. 20.8%, $p < .05$), and had more IBD-related hospitalizations (31.7% vs. 21.7%,

$p < .05$). Additionally, anxiety and depression increased the number of 'no shows' to the clinic over the study period (Navabi et al., 2018).

Evidence supports the relationship between anxiety and depression, certain personality traits, and dysfunctional coping (Bielinski et al., 2018; Jordan, Sin, Fear, & Chalder, 2016; Vigano et al., 2015). Affective temperament includes inherited personality traits, and the dysregulation of the temperament may lead to the development of affective disorders such as depression or bipolar disease (Bielinski et al., 2018). A group of researchers (Bielinski et al., 2018) evaluated the affective temperament among adults with IBD ($n = 68$ for CD and $n = 62$ for UC) and matched these with HC (N = 132). Results of the study revealed an increased prevalence of depressive ($p = .0004$, Cohen's $d = 0.43$), cyclothymic ($p = .0001$, Cohen's $d = 0.27$) and anxiety ($p = .001$, Cohen's $d = 0.52$) among adults with CD compared to HC. The authors concluded that the risk of anxiety and depression might be higher in adults with CD (Bielinski et al., 2018). Similarly, a systematic review (Jordan et al., 2016) evaluated the psychological correlates of adjustment outcomes in adults with IBD. This study highlighted the relationships between certain personality types, such as those who experienced neuroticism or negative perceptions of stress or illness, on the negative adjustment outcomes of adults with IBD (Jordan et al., 2016). Additionally, impaired coping strategies were noted in an observational study of depressed adults with CD in remission (Vigano et al., 2015).

A qualitative analysis by Jordan, Ohlsen, Hayee, and Chalder (2017) reported several concerns and worries related to the symptoms of anxiety/low mood. The participants reported the following concerns such as underperformance of work due to symptomatic disease activity and subsequent feelings of anxiety. Additionally, participants expressed their anxiety about toilet access. Participants with low mood reported a lack of understanding from others, and often

others underestimated their symptoms. Further, some participants connected symptoms of low mood to the stigma that others may consider them as unclean (Jordan et al., 2017). Similar to the qualitative analysis, a mixed method analysis by Keeton et al. (2014) addressed four major areas of concerns and worries of adults with IBD. The four major areas were; a) QOL – Participants reported their concerns about interference of IBD on their normal life and their worries about fear and isolation related to consequences of IBD; b) Unpredictability – Participants reported their worries related to their future and long-term health, with statements such as "Will I ever be better than I am now?"; c) Symptoms – Participants reported their concerns about symptoms such as pain, incontinence, low energy, and bleeding; and d) Treatments – 80% of participants were concerned about the side effects of medications (Keeton et al., 2014, p. 575). Additionally, disease duration was associated with symptoms; participants were more worried about symptoms if they had a longer disease duration (OR = 1.04 [1.01–1.06], 95% CI) (Keeton et al., 2014).

In a longitudinal assessment with 405 adults with IBD in the UK, 11.5% of those with normal anxiety and depression at baseline (n = 192) developed abnormal anxiety scores over six months (Gracie, Gutrrie, Hamlin, & Ford, 2018). Additionally, baseline CD or UC disease activity was associated with a six-fold increase in the likelihood of developing abnormal anxiety scores later (HR = 5.77 [1.89–17.7], 95% CI). Moreover, baseline abnormal anxiety scores significantly increased the later need for corticosteroids prescription or resulted in a flare of disease activity (HR = 2.08 [1.31–3.30], 95% CI, $p < .02$) in adults with IBD remission (Gracie et al., 2018). None of these associations were noted with depression scores. Another longitudinal assessment with 2007 adults with IBD in Switzerland showed a significant association between depression and clinical recurrence ($p = .000001$ for all with IBD; $p = .0007$ for CD; $p = .005$ for

UC) and anxiety and clinical recurrence (p = .0014 for all with IBD; p = .03 for CD). Anxiety was not related to the clinical recurrence of UC over time (Mikocka-Walus et al., 2016b).

Fatigue, anxiety, and depression. The majority of the reviewed studies on IBD-Fatigue consistently included anxiety and depression as an independent variable, and results of many studies pointed out the close connection between anxiety and depression and IBD-Fatigue. Depression scores were significantly higher among fatigued participants both in those with CD (10.4 vs. 3.1, $p < .001$) and those with UC (8.8 vs. 2.7, $p < .001$) (Cohen et al., 2014). Irrespective of the disease type, anxiety, not depression, was higher (p = .01) in those who also reported higher levels of fatigue (Banovic et al., 2012). Adults with higher anxiety scores presented with higher fatigue severity (p = .001) and impact ($p < .001$). However, higher depression scores were only associated with higher fatigue impact scores (p = .004) (Ratnakumaran et al., 2018).

Anxiety and depression either increased the likelihood of fatigue or independently predicted fatigue in many studies. Those with anxiety (OR = 2.5, [1.6–3.7], 95% CI, $p < .05$) and depression (OR = 2.4, [1.4–3.8], 95% CI, $p < .05$) had increased odds of fatigue (Chavarría, et al., 2019). Additionally, those with anxiety had increased odds of CF in adults with UC (OR = 7.5 [2.8–20.1], 95% CI, $p < .001$) (Huppertz-Hauss et al., 2017). Depression independently predicted fatigue (β = 4.5, $p < .001$) (Grimstad et al., 2015). Similarly, Huppertz-Hauss and colleagues (2017) found that both anxiety (β = 3, $p < .001$) and depression (β = 3.2, p = .001) independently predicted IBD-Fatigue in adults with UC, whereas only depression (β = 4.7, p = .001) predicted fatigue in adults with CD

In a longitudinal assessment over two years, psychological distress (F = 297.15, β = 0.16, $p < .001$) and lower psychological well-being (F = 9.57, β = -0.03, $p < .001$) were independently

associated with increased fatigue scores over two years (Graff et al., 2013). In another longitudinal study, improvement in depression rates significantly improved fatigue scores between the original and follow-up survey assessments ($p < .05$) (van Langenberg & Gibson, 2014) at 12 months. Disease-related worries were associated with higher fatigue levels in both CD ($r_s = 0.36$) and UC ($r_s = 0.49$) (Jelsness-Jørgensen et al., 2012). In a qualitative analysis, adults with IBD reported that the physical, mental, and work-related limitations due to fatigue which led to emotional consequences, such as feelings of anger, frustration, sadness, self-pity, worry, and grief (Beck et al., 2013).

IBD-Fatigue and Situational Variables

Physical Activity and Inflammatory Bowel Disease

Although exercise is a subset of physical activity (Caspersen, Powell, & Christenson, 1985), many of the reviewed studies used these terms interchangeably. Physical activity has been beneficial for many gastrointestinal (GI) illnesses and, specifically, for IBD. The benefits of physical activity have been recognized to assist cancer survivors and those suffering many chronic GI illnesses, including irritable bowel syndrome (IBS), as well as reducing the risk of colon cancer (Johannesson, Simren, Strid, Bajor, & Sadik, 2011; Schmitz et al., 2010; Sellar & Courneya, 2011). Physical activity has also been shown to reduce the risk of many gastrointestinal associated disorders, such as diverticular disease (Stallman, Smalley, & Hirano, 2015; Williams, 2009), constipation (Iovino et al., 2013; Tantawy, Kamel, Abdelbasset, & Elgohary, 2017), and cholilithiasis (Aune, Leitzmann, & Vatten, 2016; Banim, Luben, Wareham, Sharp, Khaw, & Hart, 2010). Adults with IBD have described the positive effects of exercise on their mood, fatigue, weight maintenance, bone health, as well as improvement to muscle mass

and function (Engels, Cross, & Long, 2017; Nathan, Norton, Czuber-Dochan, & Forbes, 2013; Schneider et al., 2008).

Types of physical activity. The majority of the research reviewed supported the benefits of systematic moderate intensity exercises on IBD in adults (Bilsky et al., 2015; Cronin et al., 2019; DeFippis et al., 2015; Lykouras, Karkoulias, & Triantos, 2017; Klare et al., 2015; DeFippis et al., 2015). However, results of two studies (Nathan et al., 2013; Ng, Millard, Lebrun, & Howard, 2007) mentioned benefits from low intensity physical activities. Walking was the most common type of physical activity reported (Chan, Robbins, Rogers, Clark, & Poullis 2014; Khalili et al., 2013; Mack, Wilson, Gilmore, & Gunnell, 2011; Nathan et al., 2013; Ng et al., 2007; Tew, Jones, & Mikocka-Walus, 2016), followed by running (Chan et al., 2014; Khalili et al., 2013; Klare et al., 2015; Tew et al., 2016). Adults with IBD participated in other forms of physical activities, such as swimming, cycling, yoga, gardening/yardwork, home-based exercises, jogging, tennis, and gym exercise classes (Khalili et al., 2013; Mack et al., 2011; Nathan et al., 2013; Tew et al., 2016). All but one study measured exercise based on the self-report of participants. Klare and colleagues (2015) supervised a running program among IBD participants to collect data on physical activity. In summary, the reviewed studies favored low to moderate intensity physical activities for those with IBD.

Besides self-reporting, several researchers directly supervised the exercise activities to measure the health outcomes of participants. The supervised exercise activities were as follows: combined effect of aerobic and resistance training of adults under the supervision of a gym instructor (Cronin et al., 2019); a supervised running program (Klare et al., 2015); progressive resistance training (PRT) which consisted of quadriceps training by leg extension on a weight machine (Tajiri, de Castro, & Zaltman, 2014); measurement of physical activity objectively by

accelerometers (van Langenberg, Papandony, & Gibson, 2014); cardiopulmonary exercise test (Lykouras, Karkoulias, & Triantos, 2017; Otto et al., 2012); evaluation of muscle strength (handgrip and quadriceps strength) using a dynamometer, sit up test (ability to rise from a chair), and gait speed (walking velocity with a trainer) by using a digital chronometer (Zaltman et al., 2014) ; and measurement of differences in physical activity between fatigued and non-fatigued adults with IBD using an activity monitor (Vogelaar et al., 2015). Additionally, high intensity interval training (HIIT) and moderate intensity continuous training (MICT) were provided to adults with IBD using a leg cycle ergometer (Tew et al., 2019).

Exercise advice with the help of a physical activity trainer is also documented in the literature. McNelly et al. (2016) focused on exercise advice as an intervention for adults with IBD. Each participant met with the researchers and a physical activity trainer for 15 minutes in week one. Advice was given to increase their physical activity > 30% based on their personalized goal and to track the physical activity goals and achievements in a diary (McNelly et al., 2016). Hence, besides self-report and supervised programs of physical activity/exercise, exercise advice needs to be considered when looking at the physical activity of those with IBD.

Anti-inflammatory benefits of physical activity. The anti-inflammatory benefits of exercise are well documented. Alternations in the intestinal immune system act as a triggering factor behind IBD inflammation. The anti-inflammatory benefits of exercise are related to the control of pro-inflammatory cytokines in the intestinal system. The immune system of the intestine is in a state of equilibrium between pro- and anti-inflammatory mechanisms in healthy individuals. However, when this equilibrium is disturbed, it leads to the activation of the intestinal immune system and subsequent inflammation in IBD (Saxena et al., 2012). Studies in animal models show that moderate exercise downregulates cytokines such as IL-1 and TNF α,

which reduces inflammation, suggesting the beneficial influence of exercise on IBD inflammation (Bilsky et al., 2015; Engels et al., 2017; Saxena et al., 2012). Additionally, anti-inflammatory effects of exercise are related to the release of myokines from the muscles. Muscles contract as a result of exercise, which leads to the release of myokines such as IL-6, IL-10, and IL-1ra. These myokines inhibit TNF α production, which reduces intestinal inflammation (Bilsky et al., 2015; Engels et al., 2017; Pedersen & Saltin, 2015).

There are mixed results regarding the type and intensity of exercise needed to affect inflammation (Engels et al., 2017). In a mouse model of colitis, worsened inflammation and increased mortality were observed with forced treadmill exercise. Conversely, reduced inflammatory responses in the distal colon and reduced diarrheal episodes were noted after 30 days of voluntary wheel training (Cook et al., 2013). Intense exercise increased systemic inflammation and increased the level of cytokines, resulting in worsened gastro-intestinal symptoms (Bilsky et al., 2015). A similar conclusion was documented in a previous research study where intensive exercise led to increased levels of pro-inflammatory cytokines in obese individuals with CD and worsening of symptoms (Narula & Fedorak, 2008). Therefore, a dose-effect approach should be considered with physical exercise in adults with IBD when considering the type of exercise, intensity, and duration (Bilsky et al., 2015).

Health outcomes after physical activity. Adults with IBD have reported many improvements in their health outcomes, including physical and mental, as well as better management of IBD symptoms after initiating exercise. A direct positive relationship between the quality of life (QOL) scores and exercise were reported in two studies: 79.4% of participants (N = 158, Gatt et al., 2019) reported an improvement in their QOL, and significant differences in QOL scores were noted between an exercise and non-exercise group ($p < .05$, Ng et al., 2007).

Similar results were reported after progressive resistance training in 148 women with IBD. The QOL scores significantly improved ($p = .0001$) after an 8-week training period (Tajiri et al., 2014). In a study by Klare et al. (2015), HRQOL scores did not differ between exercise and control groups. However, a significant improvement ($p = .023$) in the QOL social sub scores were noted, which suggested that exercise can promote QOL through improvements in social well-being. Similar results were also observed among adults with CD, where physically active adults with CD reported greater QOL ($p = .022$) (Crumbock, Loeb, & Fick, 2008).

The mental health outcomes of exercise were noted as improving mood in two studies (Nathan et al., 2013; Tew et al., 2019). Significant differences in stress scores were reported in one study between an exercise group and a control group ($p < .05$) (Ng et al., 2007). This was further supported by an evidence-based review by Pederson and Saltin (2015), which acknowledged the positive effect of regular exercise on anxiety, depression, and psychological well-being among the general population. These positive outcomes may be related to the influence of physical activity on hormonal changes, which affect mood. Further, anxiety symptoms improved in those who engaged in physical activity, as this helps to divert the anxiety symptoms of an individual (Pederson & Saltin, 2015). Other additional benefits of physical activity include improved energy and sleep quality, less gastrointestinal symptoms, and weight control, as a result of engaging in exercise and physical activities (Chan et al., 2014; Gatt et al., 2019; Nathan et al., 2013; Tew et al., 2019).

Besides the improvement of physical, mental, and IBD symptoms, physical activity helps to reduce fatigue among adults with IBD. A longitudinal assessment of 181 CD, 113 UC, and 85 controls identified regular exercise as a modifiable behavior to reduce physical and cognitive fatigue among participants (van Langenberg & Gibson, 2014). McNelly and colleagues (2016)

provided exercise advice as an intervention to measure the outcome of fatigue among adults with IBD (N = 52). Fatigue scores were significantly different between those receiving exercise advice and those receiving exercise placebo (p = .03). Another study evaluated the difference in physical fitness (physical activity, cardiorespiratory fitness, and muscle strength) between fatigued (N = 10) and non-fatigued (N = 10) adults with IBD (Vogelaar et al., 2015). As expected, the fatigued group engaged in lower levels of daily physical activity (Cohen's d = 1.02; p = .037) and reduced cardiovascular fitness as demonstrated via a 6-minute walk test (Cohen's d = 0.80; p = .030) compared to the non-fatigued group. Tew et al. (2019) tested two forms of exercises among adults with CD. Participants engaged in high intensity interval training (HIIT; N = 13) and moderate intensity continuous training (MICT; N = 12) using a leg cycle ergometer and compared the results with a control group (N = 11). Fatigue scores were reduced among the HIIT group, MICT group, and the control group compared to baseline, but this did not differ among the groups (Tew et al., 2019).

Two cross-sectional analyses supported the association between physical activity and fatigue, where higher levels of physical activity were associated with lower fatigue levels (Aluzaite et al., 2018; Artom et al., 2017). Specifically, participants who engaged in < 30 minutes of exercise per week had higher levels of fatigue (Artom et al., 2017). However, in a qualitative analysis, participants had different views about physical activity. Some of the participants were actively engaged in exercise, and they reported having more energy. Conversely, others reported a vicious circle between fatigue and exercise, where low energy prohibited them from engaging in exercise, which led to a more sedentary life (Beck et al., 2013).

Many studies highlighted the association between physical activity and the risk of developing IBD. The Nurse's Health Study II data were evaluated to identify the association between exercise and the risk of developing IBD (Khalili et al., 2013). The physical activity data were collected every two to four years longitudinally in this cohort. Physical activity was associated with a lower risk of developing CD. The risk of developing CD reduced by 44% in women who did nine hours per week of walking at an average pace. No association was noted between the risk of UC and physical activity (Khalili et al., 2013). The first population-based study of IBD risk factors in Asia-Pacific highlighted the protective effect of daily exercise in lowering the risk of developing CD in Asian adults with IBD (Ng et al., 2015). A Slovakian case-control study reported that infrequent physical activities in childhood increased the risk of IBD (Hlavety et al., 2013). Exercise reduced relapse in 41.3% (N = 158) of those who already had IBD (Gatt et al., 2019). Additionally, higher levels of exercise were significantly associated with reduced risk of active disease for CD among adults with CD in remission (p = .02) (Jones et al., 2015). Therefore, the importance of physical activity and exercise in IBD is clear.

Physical activity potentials and barriers among adults with IBD. Adults with IBD possess the potential to engage in exercise activities. The study of Lykouras, Karkoulias, and Triantos (2017) reported no significant differences in the cardiopulmonary exercise test (CPET) between active and inactive forms of IBD. The authors suggested motivating adults with IBD to perform moderate exercise on a regular basis to improve their health outcomes. Additionally, progressive resistance training significantly improved quadricep strength in adults with IBD (p = .001) (Tajiri et al., 2014). Another study (Cronin et al., 2019) explored the combined effect of aerobic and resistance training for eight weeks in adults with inactive forms of IBD. Results revealed significant changes in body composition parameters (decreased total body fat

percentage, $p = .022$ and increased lean tissue mass, $p = .003$) between the exercise and control groups. No differences in other outcomes (QOL, mood, anxiety, and pro-inflammatory cytokines) were noted due to exercise. These results did, however, support exercise as an inexpensive strategy for the prevention and treatment of IBD-related sarcopenia and obesity-related metabolic disorders (Cronin et al., 2019).

Contrary to the data supporting the exercise capacity of adults with IBD, a former study (Otto et al., 2012) showed a lower level of cardiorespiratory fitness in adults with IBD, as evidenced by lower anaerobic thresholds and peak oxygen uptake values. This may lead to other deficits, as noted by Zaltman et al. (2014), who described mild to moderate mobility limitations among adults with IBD when compared with age, gender, and body mass index (BMI) matched healthy cohorts. This discrepancy could be connected to the evidence associated with skeletal muscle changes associated with inflammation in adults with IBD. Increasing levels of pro-inflammatory markers increase the rate of muscle protein breakdown and reduce the rate of protein synthesis. Chronic inflammation also compromises endothelial integrity, which reduces oxygen delivery to muscles (Reboredo, Pinheiro, & Chebli, 2017; Shephard, 2016; Zaltman et al., 2014). In addition to muscular changes due to inflammation, the IBD medications, such as corticosteroids and cyclosporine, can have a negative effect on skeletal muscles (Otto et al., 2012; Reboredo et al., 2017). Based on this context of skeletal muscle dysfunction, adults with IBD should be encouraged to participate in exercise/physical activity to improve their muscle function, which can result in long-term health benefits.

Adults with IBD reported several barriers to engaging in physical activities. The common barriers associated with lower physical activity/exercise reported in studies were: Abdominal or joint pain ($n = 473$), fatigue ($n = 471$), disease flare up ($n = 430$), and increased toilet urgency (*n*

= 411) (Total N = 677) (Tew et al., 2016); fatigue (OR = 5.7, $p < .05$), longer duration of disease (OR = 1.2 per year, $p < .05$), elevated CRP (CRP < 3mg/dl; OR = 22.6, $p < .05$) and low vitamin D3 (OR = 13.1, $p < .05$) (van Langenberg, Papandony & Gibson, 2015); and fatigue (68%), lack of time (43%), lack of toilet access (35%), pain (32%), health concerns (34%), and financial constraints (21%) (N = 661) (Chan et al., 2014). Out of 227, 44% reported limitations in exercise due to IBD (DeFilippis et al., 2015). Common reasons include fatigue ($n = 81$), joint pain ($n = 37$), embarrassment ($n = 23$), weakness ($n = 21$), abdominal pain ($n = 13$), urgency ($n = 3$), and bowel incontinence ($n = 3$) (DeFilippis et al., 2015). Depression and disease activity were negatively associated with physical activity in adults with CD, whereas depression and age were negatively associated in adults with UC or indeterminate colitis ($p \leq .038$) (Tew et al., 2016). Out of 918 participants, 80% reported that they had to stop exercise at some point or permanently due to IBD diagnosis (Chan et al., 2014).

Analysis of data from research reports revealed mixed results regarding the engagement in physical activity by adults with IBD. Two study results noted a lack of participation in exercise based on the recommended guidelines (Mack et al., 2011; Tew, Jones, & Mikocka-Walus, 2016). Interestingly, the self-report of physical activity by participants matched with the objective measure of physical activity using accelerometers (van Langenberg et al., 2015). The accelerometer could capture the intensity, extent, and duration of movements in three planes. The results of the study highlighted impaired physical activity parameters among the CD group compared to HC ($p < 0.01$). Adults with CD preferred to spend their time carrying out light or sedentary activities as opposed to the recommended moderate to vigorous activity.

Three studies reported regular engagement in physical activity by the study participants. The proportions of participation were: 66% (N = 918; Chan et al., 2014), 57% (N = 17;

Crumbock et al., 2008), and 74% (N = 227; DeFippis et al., 2015). Gatt et al. (2019) evaluated the physical fitness of adults with IBD in remission before and after diagnosis. Adults diagnosed with IBD in the past 18 months were included in the study. The majority (69.5%, N = 158) of participants reported that IBD diagnosis affected their physical fitness whereas 30.5% did not report an effect. The diagnosis of IBD reduced participation in physical activities in those individuals who were involved with sports previously. However, 44.3% of participants who did not engage in sports prior to IBD diagnosis increased their level of physical activity after diagnosis.

Sustained effort and encouragement to participate in exercise/physical activity may result in long-term health benefits for adults with IBD. Recommendations for individually tailored physical activity are required for this group to maximize the benefits of exercise. In one study (Nathan et al., 2013), the participants reported that they determined the duration of exercise based on their energy levels and recommended the same strategy to others with IBD. However, the study participants reported a lack of discussion about the health benefits of exercise by their providers (Nathan et al., 2013). The same concern was raised by 46.1% (N = 158) of participants, who confirmed a lack of discussion regarding exercise by their medical professionals (Gatt et al., 2019).

The reviewed studies have highlighted that physical activity is not considered as a common adjunct to traditional therapies in adults with IBD. Moderate intensity physical activity has positive health outcomes in the course of IBD, including a protective role in maintaining remission. This study helps to understand how physical activity influences fatigue, which is a major barrier to participation in physical activity.

Satisfaction with Social Roles

Few quantitative studies have evaluated the association between satisfaction with social roles (SSR) in adults with IBD. One study (Kappelman et al., 2014) directly evaluated the SSR using the PROMIS scale. A second exploratory survey assessed the impact of UC on participants' social and professional lives (Calvet et al., 2018). Two other studies (Sarin et al., 2017; Kim et al., 2017) indirectly assessed the SSR by evaluating satisfaction with life (SWL) and difficulty engaging in relationships.

Kappelman and colleagues (2014) evaluated SSR among adults with IBD, along with many other PROMIS outcomes. Worse scores in participants' SSR were reported (M = 48 for overall IBD; M = 48 for CD; M = 49 for UC), indicating the disruption of social roles due to IBD. Additionally, duration of the disease and SSR were negatively associated, where the worst mean score (45) of SSR was found among participants with < 1-year disease duration (Kappelman et al., 2014). Out of 436 participants with UC, the majority (65.1%) reported the influence of the disease on their leisure activities and social or professional activities (57.6%) (Calvet et al., 2018). Adults with IBD were interviewed to assess their SWL in Israel (Sarin et al., 2017). A positive correlation was noted between SWL and sex, with higher scores reported by men ($r = 0.55$, $p < .01$). Emotion-focused coping strategies were positively correlated with SWL in females ($r = 0.25$, $p < .01$) whereas problem-focused coping strategies were negatively correlated with SWL in men ($r = -0.25$, $p < .01$). These results suggest different strategies are used between sexes to achieve life satisfaction (Sarin et al., 2017). In a Korean study, 61% of participants (N = 599) reported discontinuing their friendships due to IBD. Additionally, 41% had to end their intimate relationships due to IBD. The factors associated with negative impacts of IBD on relationships include young age ($p = .002$), previous surgeries ($p = .003$), and previous hospitalization ($p = .038$) (Kim et al., 2017).

All reviewed qualitative studies consistently addressed the disruption of social roles due to IBD symptoms and fatigue (Beck et al., 2013; Czuber-Dochan et al., 2013a; Devlen et al., 2014; Norton et al., 2012). Participants reported some of the consequences of fatigue, such as limited opportunities to socialize (Czuber-Dochan et al., 2013a). The same concern was reported by the qualitative study of Devlen et al. (2014), where participants reported difficulty in planning ahead and having to avoid certain activities, such as camping and travel, due to toilet access issues or dietary restrictions. Participants further elaborated that their social life was greatly restricted due to the avoidance of such activities (Devlen et al., 2014). In another qualitative study in those with CD, participants reported avoiding friends and colleagues because they could not have certain drinks or food. As a result, their social networks completely changed (Norton et al., 2012). Additionally, individuals with CD reported declining invitations or leaving events early due to fatigue. Participants also expressed their impaired parenting roles, as they missed their kids' sporting events or were unable to care for their kids due to fatigue (Norton et al., 2012).

Fatigue has been shown to negatively influence social life, and many participants reported cancellation of parties and family reunions (Beck et al., 2013). Participants expressed that they did not take initiatives to organize social gatherings as it required too much energy, which limited their social networks with close family and friends (Beck et al., 2013). Clearly, social engagement is associated with IBD-Fatigue and should be considered when examining IBD-Fatigue.

Summary

The reviewed studies presented the perceived challenges by adults with IBD due to IBD-Fatigue. Adults with IBD reported fatigue irrespective of their disease activity. The analyses

revealed the complex interplay between IBD-Fatigue and other associated factors such as physiological, psychological, and situational factors. One important point to note is that only four studies (Borren et al., 2019; Cohen et al., 2014; Hashash et al., 2018; Tinsley et al., 2011) were conducted in the US with IBD-Fatigue as the outcome variable. This is important because more studies are required in the US to examine the complex association between IBD- Fatigue and other associated factors. However, no studies have examined the combined influence of physiological (age, disease duration, surgical history, disease activity, sleep disturbances, pain interference, and current medications), psychological (anxiety and depression), and situational (physical activity and satisfaction with social roles) factors on IBD-Fatigue. Also, none of the studies have analyzed the direct and indirect (mediating) effects of physiological (age, disease duration, surgical history, disease activity, sleep disturbances, pain interference, and current medications), psychological (anxiety and depression), and situational (physical activity and satisfaction with social roles) factors on IBD-Fatigue nor examined these differences according to the type of IBD. Limited studies examined the influence of physical activity and satisfaction with social roles on IBD-Fatigue.

Based on the review of this literature, IBD-Fatigue is multifactorial. The review supported the interconnection between IBD-Fatigue and physiological (age, disease duration, surgical history, disease activity, sleep disturbances, pain interference, and current medications), psychological (anxiety and depression), and situational (physical activity and satisfaction with the social roles) factors. The review highlighted a lack of research in the US to support IBD-Fatigue. The independent variables were explored and organized in this review based on the conceptual framework adapted from the MRTOUS.

CHAPTER III: METHODS

Introduction

Inflammatory bowel disease (IBD) is a global disease, and the incidence of IBD is increasing (Ng et al., 2017; Stein & Shaker, 2015). Adults with IBD report fatigue as the most prominent (86.9%) symptom related to their illness (Vegni et al., 2019). Because of the multidimensional nature of IBD-Fatigue, understanding fatigue and its associated factors are important to develop holistic interventions to manage IBD-Fatigue. The purposes of this study were to comprehensively examine the factors associated with IBD-Fatigue and to use statistical modeling to determine the most effective and parsimonious model for identifying the influencing factors of fatigue among IBD patients. This chapter described the study methods, design, and analyses plan.

Design

The study was the secondary analysis of a non-experimental cross-sectional data. The data for this study had obtained from 'IBD Partners' (IBD Partners, n.d.). A secondary analysis of a cross-sectional design was appropriate, as the study was designed to examine IBD-Fatigue and the relationships among fatigue and other variables at a fixed point in time (Polit & Beck, 2017).

Setting

The secondary data were from *IBD Partners* which is an online research platform for adults with IBD initiated by the Crohn's and Colitis Foundation (CCF) and the University of North Carolina at Chapel Hill (UNC-CH). 'IBD Partners' began the enrollment of the online cohort in June 2011 under the name Crohn's and Colitis Foundation of America (CCFA)

Partners (Long et al., 2012), and later changed its name to IBD Partners. The online cohort includes participants from 50 states of the United States (US), and the enrollment is ongoing. The CCF and the Patient-Centered Outcomes Research Institute (PCORI) funded the parent study**.** The inclusion criteria include adults who are older than 18 years of age with a self-reported diagnosis of IBD and who have internet access (IBD Partners, n.d.). Participants were recruited through CCF email rosters, the CCF website, different social media sites, and educational and fundraising events (Kappelman et al., 2013). All participants completed a baseline survey using Patient Reported Outcomes Measurement Information System (PROMIS) questionnaires on anxiety, depression, fatigue, sleep disturbances, satisfaction with social roles, and pain interference. Additionally, the initial survey included the measurement of physical activity, demographic information, disease activity, and medication use. A follow-up was conducted every six months on the PROMIS questionnaires, physical activity, disease activity, and medication use (Kappelman et al., 2013).

Sample

Currently, as of June 2019, 16,452 participants were enrolled in IBD Partners. The sample for the study consisted of adults 18 years of age or older with a self-reported diagnosis of IBD, Crohn's disease (CD), or ulcerative colitis (UC) drawn from the internet-based cohort of IBD Partners. Randall and colleagues (2014) conducted a validation study among 184 CCFA partners (the previous name of IBD Partners) and confirmed the high validity between the participants' self-reported IBD statuses and the physician reports; the physician reports confirmed 97% of the participants' self-reported IBD statuses. Adults with IBD with ostomies or J pouches were excluded from the proposed study due to the lack of criteria to assess disease activity among IBD patients after these surgical procedures. The final sample was determined by

the date of the Institutional Review Board (IRB) approval (9-13-2019), at which point there was a total of 12,053 eligible participants.

Theoretically, a large sample size is needed for a stable path model estimation; however, how “large is large enough” is difficult to determine (Bauer & Curran, 2019). The primary data met the sampling guidelines for path analysis, as the final sample size includes 12,053 participants.

Human Subjects’ Protection

Institutional Review Board (IRB) approval was obtained from the parent organization (UNC-CH) and from East Carolina University (ECU). Non-human subject research certification approval was obtained from ECU, as the study was a secondary analysis of existing data and less than minimal harm was anticipated for study subjects. After receiving ECU IRB approval, a data use agreement form signed by the student researcher and the ECU research office was submitted to UNC-CH.

Instruments

The PROMIS short forms from the National Institute of Health (NIH) were used to measure fatigue, sleep disturbance, pain interference, anxiety, depression, and satisfaction with social roles. The PROMIS tools were developed based on item response theory (Fries, Bruce, & Cella, 2005). The PROMIS tools are reliable, precise, and have been consolidated to a unidimensional measure through the adoption of item response theory (Fries et al., 2005).

Assessment of fatigue, sleep disturbances, pain interference, anxiety, depression, and satisfaction with social roles was employed with the four-item PROMIS short form for each of these variables, and the occurrences of the symptom over the past seven days were measured. The PROMIS measures were rated on a 5-point Likert scale that ranged from *not at all* to *very*

much. The PROMIS scales were recomputed to a normalized *t-score*, where the mean of the US general population was 50 and the standard deviation (SD) was 10 (National Institute of Health, 2019). Higher scores indicate higher measurements or worse health outcomes in the domains of fatigue, sleep disturbances, pain interference, anxiety, and depression. However, higher scores indicate better health outcomes for positively worded concepts like satisfaction with social roles (National Institute of Health, 2019).

Based on patient input, the researchers at IBD Partners selected a single question to measure physical activity. Higher scores on the physical activity question denote better physical activity.

Fatigue

The PROMIS fatigue short form (Fatigue 4a – Adult v1.0) scale measures the frequency, duration, intensity, and interference of fatigue (National Institute of Health [NIH], 2019). The reliability of the PROMIS fatigue scale was more than 0.91 for scores with two SDs less than the mean to four SDs above the mean. Convergent validity of the PROMIS fatigue scale was established by computing the correlation coefficient between the PROMIS fatigue scale and the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale and the Short Form -36 (SF-36) vitality scale, which demonstrated correlation coefficient values of 0.95 and 0.89, respectively (Cella et al., 2010).

Sleep Disturbances

The PROMIS sleep disturbances short form (PROMIS Short Form v1.0 – Sleep Disturbance 4a) scale is designed to assess the quality, refreshment gained after sleep, difficulty in falling asleep, and interruptions in sleep (NIH, 2019). The reliability of the PROMIS sleep disturbances scale was greater than 0.88 across most of the score distributions. Convergent validity was established by computing the correlations between the PROMIS sleep disturbances

scale and the Pittsburgh Sleep Quality Index (PSQI), as both measure the same sleep constructs. The correlation coefficient was 0.85, which confirmed the convergent validity of the PROMIS sleep disturbances scale (Cella et al., 2010).

Pain Interference

The PROMIS pain interference short form (PROMIS Short Form v1.0 – Pain Interference 4a) scale assesses the degree to which pain impedes an individual's social, recreational, and day-to-day activities (NIH, 2019). The reliability of the PROMIS pain interference scale was 0.97 or higher for scores greater than or equal to the mean and 0.77 for scores one standard deviation (SD) below the mean. Convergent validity was established by computing the correlations between the PROMIS pain interference scale and the Brief Pain Inventory (BPI) interference subscale (r = 0.85) and the SF-36 bodily pain subscale (r = -0.86; Cella et al., 2010).

Anxiety

The PROMIS anxiety short form (PROMIS Short Form v1.0 – Anxiety 4a) scale assesses an individual's reaction to fear, inability to focus on other matters, worries, and uneasiness (NIH, 2019). The reliability of the PROMIS anxiety short-form scale was more than 0.89 for most of the score distributions. Convergent validity was established by computing the correlations between the PROMIS anxiety short-form scale and the general distress (anxiety) scale from the Mood and Anxiety Symptom Questionnaire (r = 0.80; Cella et al., 2010).

Depression

The PROMIS depression short form (PROMIS Short Form v1.0 – Depression 4a) scale measures the extent of depression, helplessness, hopelessness, and worthlessness experienced by adults (NIH, 2019). The reliability of the PROMIS depression scale was more than 0.92 for most of the score distributions. Convergent validity was established by computing the correlations

between the PROMIS depression scale and the Center for Epidemiological Studies Depression Scale (CES-D, $r = 0.83$; Cella et al., 2010).

Satisfaction with Social Roles

The PROMIS satisfaction with social role short form (PROMIS Short Form v1.0 – Satisfaction with Social Roles 4a) scale assesses the degree to which individuals are satisfied with their social roles, family responsibilities, and work responsibilities (NIH, 2019). The reliability of the PROMIS satisfaction with social role scale was 0.96 for scores that were two SDs less than the mean and one SD above the mean. The convergent validity of the PROMIS satisfaction with social roles was evaluated by examining correlations with corresponding legacy measures, such as the SF-36 Role Physical, Role Emotional, and Social Functioning Scale (r ranged from 0.57– 0.59) and the FACIT-Functional Well Being Scale ($r = 0.76$; Cella et al., 2010).

Physical Activity

A single question measured physical activity: "How often did you participate in one or more physical activities of 20–30 minutes' duration per session during your leisure time within the past 6 months?" This physical activity question was on a 6-point scale, and the scores ranged from 1 to 6. Adults with IBD reported that this one question best measured their physical activity. Therefore, the primary team decided to keep this question based on patient input. The student researcher conducted a preliminary analysis to compare the relationship between this one physical activity question and the Godin Leisure Time Activity (GLTA) index scale scores. A moderate correlation was found between the GLTA and the one physical activity question ($r_s = 0.686$, $p < .001$). Additionally, the polychoric correlation coefficient was computed, and a strong correlation was noted between the GLTA and the one physical activity question ($r = 0.74$, $p < .001$).

Procedures

After IRB approval was obtained, a signed data-use agreement form was submitted to UNC-CH. Next, a meeting was arranged with the statistician at UNC-CH to discuss the variables required for the study. The statistician retrieved the required data and saved it in the Statistical Package for the Social Sciences (SPSS) format. The data were transferred to a password-protected external memory device. Only the researcher has the access to this device, which will be kept in a locked compartment when not in use. The data will not be transmitted via email, email attachment, or file transfer protocol. Based on ECU policy, all research data should be stored on an approved secure drive. The information technology (IT) department of the ECU College of Nursing set up a "Nurse-research" pirate drive space for the student researcher, and access was granted to all dissertation committee members listed on the IRB. The Nurse-research pirate drive is approved for sensitive data, including the Health Insurance Portability and Accountability Act (HIPAA) data. The pirate drive is encrypted. No backup copies of the data were made.

Data Analyses

Checking for errors and finding and correcting any errors in the data file were the prerequisite steps performed before data analyses (Pallant, 2016; Tabachnick & Fidell, 2013). Minimum and maximum values and the number of missing and valid cases were assessed for each variable to check for errors and missing data. The "exclude case pairwise" option of SPSS was checked for missing data, as this option excludes a case (a participant) if it is missing the data required for a particular analysis. Those cases were included if they have sufficient data for any other analysis (Pallant, 2016; Tabachnick & Fidell, 2013). Outliers were checked by running a histogram and boxplot. If an outlier is found, the primary investigator (PI) of the parent study

was consulted to determine if the data is an error. If genuine, the score was retained (Pallant, 2016; Tabachnick & Fidell, 2013). Analyses were conducted with and without the outlier, and the results were compared. Frequencies, percentages, and means were computed to describe demographic variables, and frequency distribution were calculated for categorical data. Minimum and maximum values, means, standard deviations, skewness, and kurtosis will be examined for continuous variables (Pallant, 2016; Tabachnick & Fidell, 2013). Kolmogorov-Smirnov and Shapiro-Wilk statistical tests were used to evaluate the normality of the score distribution (Mertler & Reinhart, 2010, p. 33; Pallant, 2016). Normality is assumed if the Kolmogorov-Smirnov and Shapiro-Wilk statistical test results have a non-significant *p* value ($p > .05$). A *p* value $< .05$ indicates violating the assumption of normality, which is quite common with larger samples (Pallant, 2016). The statistical tests were performed using both the SPSS and Mplus software programs. Significance levels will be set at $p < .01$, which indicates a 1% chance that the results occurred at random.

Data Analyses for Specific Aims

The details of the data analyses that were used for each of the specific aims and the associated research questions are discussed below.

Aim 1: To characterize fatigue, anxiety, depression, sleep disturbances, pain interference, physical activity, and satisfaction with social roles in adults who are 18 and older who have IBD, in adults with UC, and in adults with CD.

RQ1. What were the descriptive of physiological (age, disease duration, surgical history, disease activity, sleep disturbances, pain interference, and current medications), psychological (anxiety and depression), and situational (physical activity and satisfaction with social roles) factors in adults ages 18 and older who have IBD, in adults with UC, and in adults with CD?

Minimum and maximum values and the number of missing and valid cases will be assessed for each variable to evaluate errors and missing data. The PROMIS scores were dichotomized into two categories: Clinically significant (score ≥ 55) and non-significant (score < 55), except for satisfaction with social roles. The PROMIS score for satisfaction with social roles were categorized in the reverse order, with a clinically significant score being ≤ 55 and a non-significant score being > 55. Proportions were calculated for the dichotomous scores of the PROMIS variables, such as fatigue, anxiety, depression, sleep disturbances, pain interference, and satisfaction with social roles, and physical activity. Proportions were calculated for demographic variables, such as surgical history, disease activity, and current medications. Minimum and maximum values, means, standard deviations, skewness, and kurtosis were examined for continuous variables, such as age and disease duration (Pallant, 2016; Tabachnick & Fidell, 2013). However, skewness and kurtosis values are sensitive to large samples; therefore, it is recommended to assess the shape of the distribution using a histogram (Pallant, 2016, p. 57; Tabachnick & Fidell, 2013, p. 80). If data are skewed, the median value is preferred, as it divides the distribution into half with a cut-off point. As recommended, the inter-quartile range will be reported with the median to indicate the spread of the scores (Mertler & Reinhart, 2010, p. 8; Pallant, 2016).

Aim 2: To examine the relationships among fatigue and physiological (age, disease duration, surgical history, disease activity, sleep disturbances, pain interference, and current medications), psychological (anxiety and depression), and situational (physical activity and satisfaction with social roles) factors among adults with IBD, in adults with UC, and in adults with CD?

RQ2. What were the associations of fatigue, age, disease duration, surgical history, disease activity, sleep disturbances, pain interference, current medications, anxiety, depression, physical activity, and satisfaction with social roles in adults with IBD, in adults with UC, and in adults with CD?

A chi-square analysis was used to identify the associations between the dichotomized scores of fatigue, anxiety, depression, sleep disturbances, pain interference, satisfaction with social roles, physical activity, age, disease duration, surgical history, disease activity, and current medications. The first step in chi-square analysis was to make sure that the assumption related to 'minimum expected cell frequency' is not violated. The 'minimum expected cell frequency' should be five or more, which means that at least 80% of the cells should meet the expected frequency of five. If this assumption is violated, the Fisher's exact probability test should be considered instead of the chi-square analysis (McDonald, 2014; Pallant, 2016). The significance level of the association was determined based on a p value < .01. The strength of the association was determined based on the *phi coefficient* value, which can range from 0 to 1. Higher values indicate a stronger association between variables (Pallant, 2016).

Aim 3: To assess whether the relationships in the adapted version of the theory of unpleasant symptoms are reproducible in all adults with IBD, in adults with UC, and in adults with CD.

RQ3. Can clinically significant fatigue be predicted by physiological (age, disease duration, surgical history, disease activity, sleep disturbances, pain interference, and current medications), psychological (anxiety and depression), and situational (physical activity and satisfaction with social roles) factors among adults with IBD, in adults with UC, and in adults with CD?

Logistic regression analysis was performed to answer research question three. Logistic regression is used to calculate the predictive ability of one or more dichotomous or continuous independent variables on a dichotomous dependent variable (Pallant, 2016; Tabachnick & Fidell, 2013). The following assumptions were checked prior to logistic regression.

First, the size and nature of the sample were examined to ensure an adequate ratio of cases to variables is included in the analysis. It is advised to run a descriptive statistic on each of the predictors and to collapse or delete categories if they have limited numbers (Mertler & Reinhart, 2010; Pallant, 2016). Therefore, descriptive statistics were computed for each of the physiological, psychological, and situational predictors of fatigue. Cases with missing data was excluded.

Second, logistic regression assesses the model's fit to the data. Assessment of goodness of fit includes checking the values for the expected frequencies for each cell. Discrete predictor variables were checked to make sure that all cells have a frequency of more than five (Mertler & Reinhart, 2010; Pallant, 2016). All the PROMIS scores were dichotomized. If any of the variables have more than two levels and have not met the minimum frequency, they were collapsed for the analyses.

Finally, because logistic regression is sensitive to higher correlations among predictor variables (multicollinearity) and outliers (Mertler & Reinhart, 2010; Pallant, 2016), collinearity statistics were performed. Collinearity statistics was assessed for low tolerance values (less than 0.1), which indicate highly correlating variables (Pallant, 2016; Tabachnick & Fidell, 2013). All highly inter correlating variables were removed. Additionally, the Mahalanobis distance was assessed to identify outliers. The cases with a Mahalanobis distance of more than the chi-square

criterion were deleted from the final analysis (Mertler & Reinhart, 2010). All these assumptions were checked prior to data analysis.

After all assumptions were met, the data analyses were conducted. All predictor variables were entered into the final model. The Hosmer-Lemeshow goodness of fit test was computed to assess the goodness of fit, which will result in a Chi-square value with degrees of freedom and a significance level. A significance level > .05 indicates non-significance and supports the model fit (Mertler & Reinhart, 2010; Pallant, 2016). Additionally, the Cox and Snell R-square and the Nagelkerke R-square values were examined to determine the amount of variation in the dependent variable explained by the model. These R-square values are expressed from a minimum value of 0 to a maximum value of 1 (Mertler & Reinhart, 2010). The model's sensitivity and specificity will also be evaluated. Sensitivity refers to the "percentage of the group with characteristics of interest that has been accurately identified by the model" (Pallant, 2016, p. 177). Specificity refers to "the percentage of the group without the characteristic of interest that is correctly identified" (Pallant, 2016, p. 177). Lastly, the odds ratios were examined to assess the chance or odds of influencing the outcome variable by one-unit increase in a predictor variable. An odds ratio > 1 denotes a higher likelihood of an influence on the outcome variable by the predictor variable (Mertler & Reinhart, 2010; Pallant, 2016).

RQ4. What were the direct and indirect effects of physiological (age, disease duration, surgical history, disease activity, sleep disturbances, pain interference, and current medications), psychological (anxiety and depression), and situational (physical activity and satisfaction with the social roles) factors on fatigue among adults with IBD?

RQ5. Were there differences in the direct and indirect effects of physiological (age, disease duration, surgical history, disease activity, sleep disturbances, pain

interference, and current medications), psychological (anxiety and depression), and situational (physical activity and satisfaction with the social roles) factors on fatigue between adults with CD and UC?

A path analysis using structural equation modeling (SEM) was used to answer research questions four and five. Path analysis is a causal modeling technique which helps the researcher to examine the causal effects among numerous variables (Mertler & Reinhart, 2010). The researcher is able to test a causal model illustrated in a path diagram based upon logic, theoretically based statements of relationships among variables, and/or experience (Kelloway, 2015; Mertler & Reinhart, 2010). Essentially, path diagrams are foundational models to SEM and act as a guide to clarify a researcher's idea about relationship between variables (Tabachnick & Fidell, 2013; Wang & Wang, 2012).

Path analysis is an extension of regression analysis. The regression analysis is aimed to assess the predictive ability of one or more independent variables on a single dependent variable which is a limitation of the regression analysis. Additionally, regression analysis does not support any further computations such as the direct and indirect effects between variables (Bauer & Curran, 2019; Mertler & Reinhart, 2010). Path analysis helps to overcome these limitations and permits analysis of multiple dependent variables and to test direct and indirect effects between variables (Bauer & Curran, 2019; Mertler & Reinhart, 2010).

Path analysis differs from SEM in many ways. First, path analysis accounts only for the relationships between the observed variables, whereas SEM includes both observed and latent variables. Thus, path analysis does not consider additional errors to the path coefficient (Barbeau, Boileau, Sarr, & Smith, 2019; Tabachnick & Fidell, 2013). Secondly, SEM is a confirmatory technique, which is often used to test a theory with a "prior knowledge of potential

relationships between variables" (Tabachnick & Fidell, 2013, p.687). On the other hand, path analysis is a causal modeling technique which allows to test a model based upon logic, theoretically based statements of relationships among variables, and/or experience (Kelloway, 2015; Mertler & Reinhart, 2010). The SEM consists of two models. First one is the measurement model that connects the observed variables to the underlying latent variables/factors, which is evaluated by confirmatory factor analysis (CFA). Second model is a structural model, which assess the potential relationships between latent variables after CFA confirms the latent variables or factors in the measurement model (Wang & Wang, 2012).

The path analysis was used to answer research questions four and five because the path diagram of the proposed study is based on the conceptual framework adapted from the middle range theory of unpleasant symptoms (MRTOUS), and not intended to test the MRTOUS. Additionally, data analysis of the study included the normalized *t-score*s of many of the variables (anxiety, depression, sleep disturbances, pain interference, and satisfaction with social roles) including the outcome variable (fatigue). Therefore, these variables were considered as observed variables without any latent factors. According to the literature, a structural model with observed variables are considered for path analysis, and not for SEM (Wang & Wang, 2012).

Path analysis requires a priori conceptual model or framework to determine the complex relationships between variables. Because researchers propose mechanisms that lead to many observable phenomena (by explaining the correlation between variables), path analysis can generate "many indices of best fit that can be used to compare multiple models for a single dataset" (Barbeau et al., 2019, p. 39). Additionally, path analysis makes it possible to test the direct (unmediated) and indirect (mediated) effects between variables. A mediator explains *why or how* one variable exerts an effect on another (Tabachnick & Fidell, 2013, p. 160). A straight

arrow denotes a unidirectional causal relationship between variables, and a curved arrow indicates an association between two or more variables; these relationships are permitted only between independent variables (Barbeau et al., 2019; Kline, 2016; Mertler & Reinhart, 2010; Wang & Wang, 2012).

The path analysis was performed with Mplus software and will use the dichotomized fatigue scores as the outcome variable. Weighted least square estimation is recommended for computing path analysis with a categorical dependent variable in Mplus (Muthén & Muthén, 2010). Many other authors (Beran & Violato, 2010; Wang & Wang, 2012) also supported weighted least square estimation; however, these authors strongly argued for sample sizes of 200 to 500 to achieve reliable estimates. Additionally, the bootstrapping method was used to infer mediation, in which the mean indirect effect is calculated utilizing a specified resampling method (Barbeau et al., 2019; Kelloway, 2015; Tabachnick & Fidell, 2013, p.143). Path analysis data was evaluated for multicollinearity and outliers, as path analysis is sensitive to these factors. Normality of the data was examined by checking the skewness and kurtosis values and examining the histogram of the distribution (Barbeau et al., 2019; Tabachnick & Fidell, 2013). The following three path diagrams (figure 2, figure 3, and figure 4) were developed from the study's conceptual framework, and they are adapted from MRTOUS. These path diagrams were used as a hypothesized model to perform the path analysis in the proposed research.

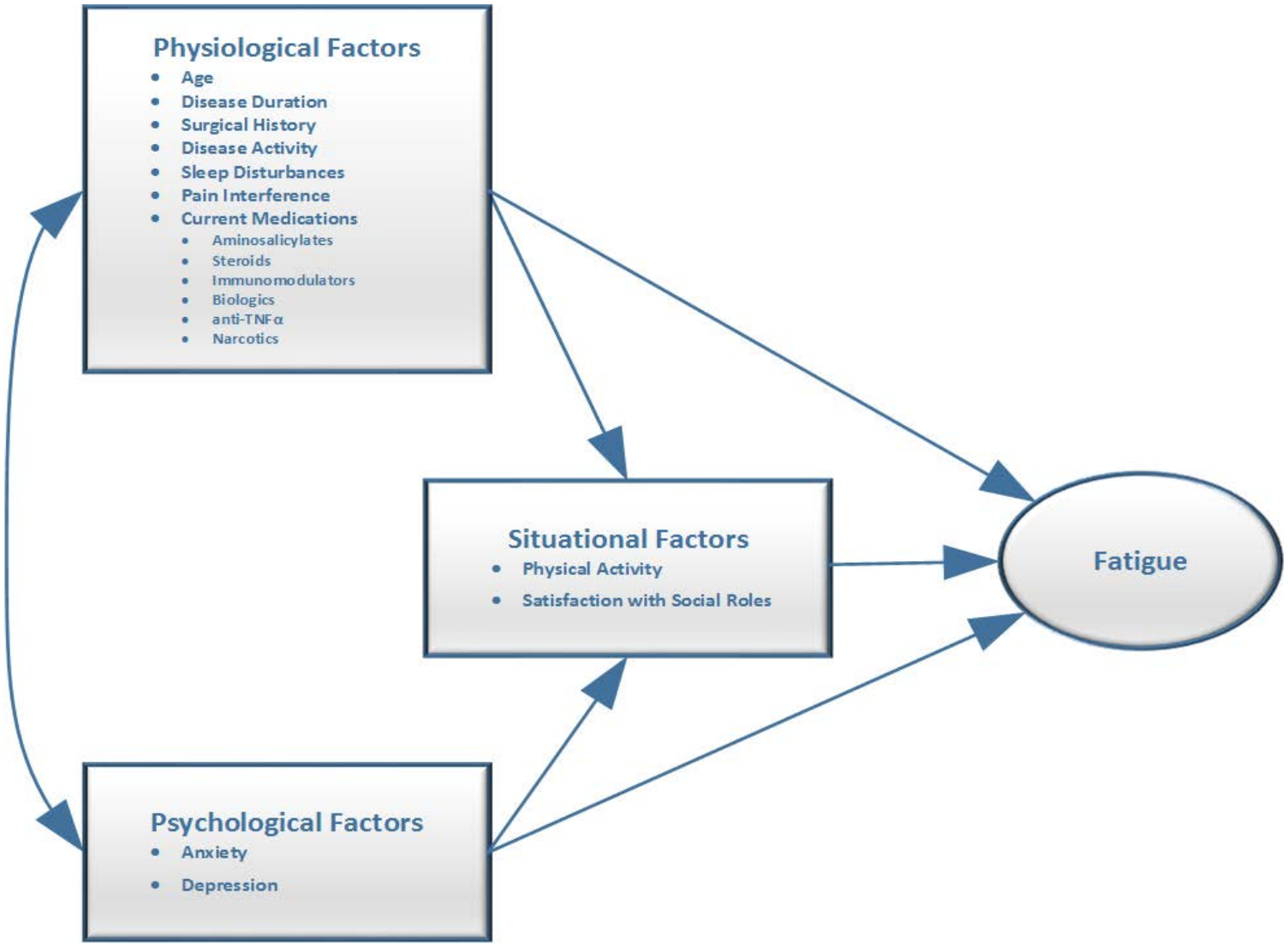


Figure 2

Proposed path diagram with situational factors as mediators

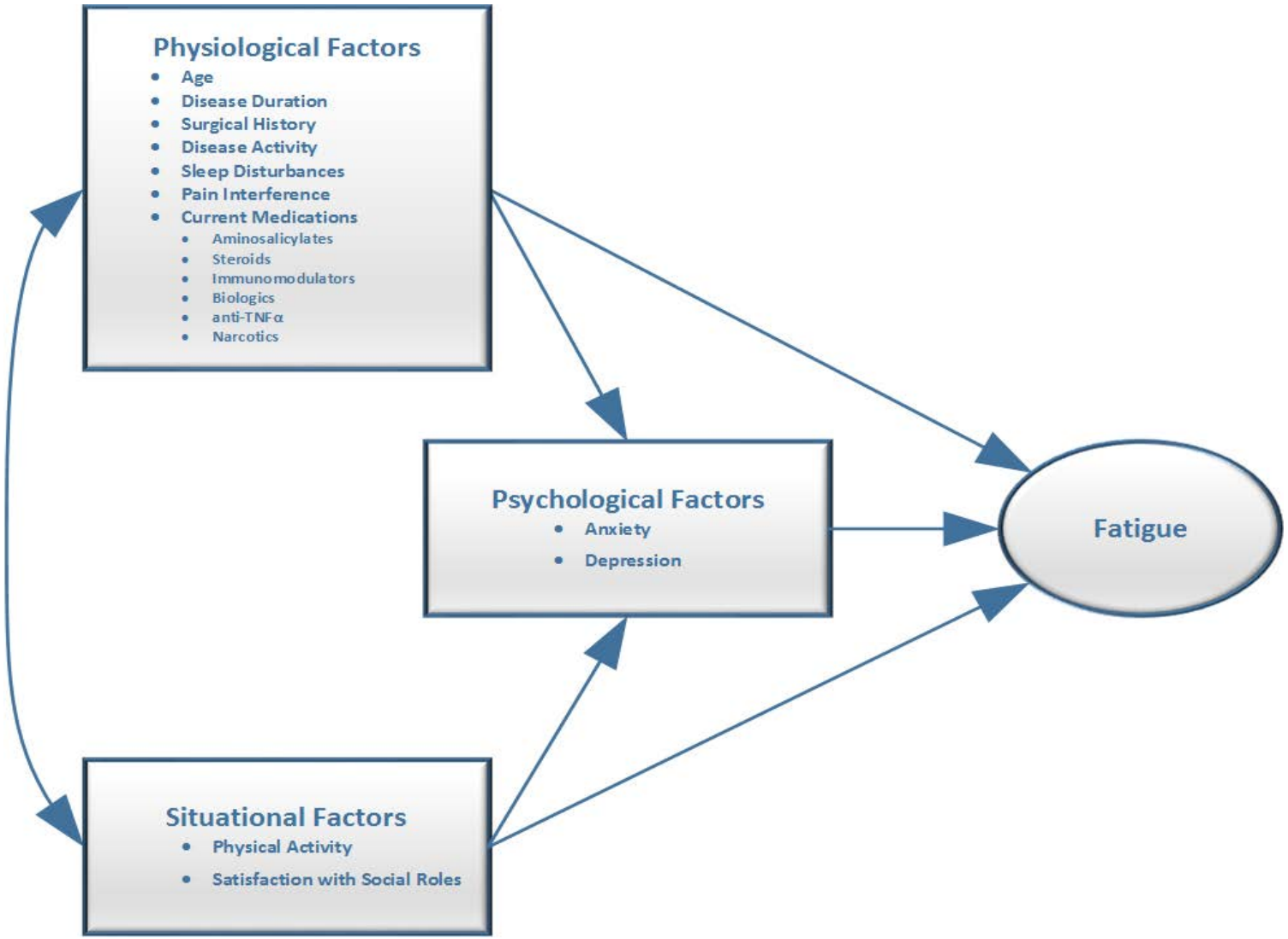


Figure 3

Proposed path diagram with psychological factors as mediators.

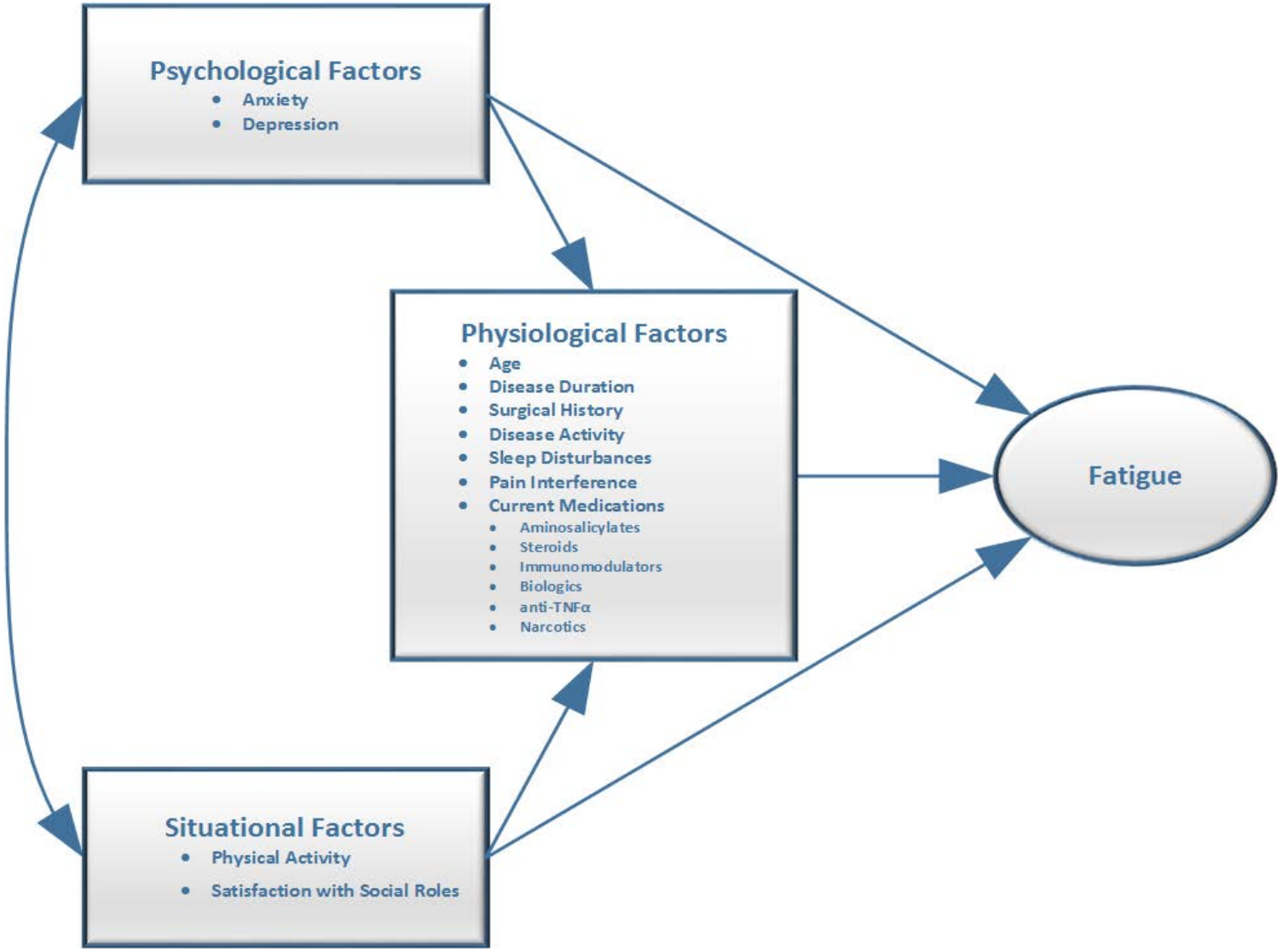


Figure 4

Proposed path diagram with physiological factors as mediators.

Testing the Model Fit in Path Analysis

Model fit includes the process that determines the extent to which the proposed model fits the data. The results of the path analysis are represented in the form of standardized path coefficients (β), which denote the strength (varying from -1.0 to +1.0) and direction (+ or -) of associations among the observed variables. The statistical significance of the path coefficients is determined using two-tailed α (α = .01). Non-significant paths are removed from the theory-driven hypothesized model to achieve model reduction, thereby obtaining the simplest model that can explain the maximum variance in the outcome variable with the smallest number of predictor variables (Bauer & Curran, 2019; Clayton & Pett, 2011; Kelloway, 2015; Tabachnick & Fidell, 2013). After model reduction, the next step is to assess for model fit to examine the match between the proposed model and the data. Several goodness of fit indices are included in the Mplus software package to test the model fit. The most important indices are: The Chi-square ($\chi 2$) goodness of fit test; the relative goodness of fit indices, such as Tucker-Lewis Index (TLI); the comparative fit index (CFI); and the absolute goodness of fit indices, such as the root mean squared error of approximation (RMSEA) and the standardized root mean square residual (SRMR). The $\chi 2$ statistics are used as a "badness of fit," where low $\chi 2$ values are considered good (the model fits the data well) and large $\chi 2$ values indicate that the model does not fit the data. A non-significant probability level of the $\chi 2$ test is expected for a model that fits the data well. The CFI and TLI values range from 0 to 1, and a value of 0.95 or higher denotes an acceptable model fit with the data. An RMSEA value < 0.05 indicates excellent fit, a value < 0.08 indicates a moderate fit, and a value > 0.10 indicates a poor fit of the model with the data. Generally, SRMR values < 0.08 are considered a good fit; however, there is no empirical evidence to support this value (Bauer & Curran, 2019; Clayton & Pett, 2011; Kelloway, 2015;

Tabachnick & Fidell, 2013). The researcher may have to alter the proposed models multiple times to identify the best fit model.

Limitations

The data from IBD Partners were collected online and, therefore, may not be sufficiently diversified in reflecting a sample that includes different socioeconomic backgrounds. The primary data did not include zip codes. Hence, it was not possible to divide the participants based on urban or rural status. Adults with IBD who are literate and who have internet access may be overrepresented in this online cohort. Therefore, a generalization of the results to unrepresented groups cannot be justified.

Summary

The study intended to explore IBD-Fatigue and its associated factors among adults with IBD. Each variable was examined for its ability to predict clinically significant fatigue among those with IBD. Finally, a priori conceptual model based on MRTOUS was tested to identify the direct and indirect effects of the associated factors on IBD-Fatigue among adults with IBD. Data from the online cohort of IBD Partners from UNC-CH were used to answer the research questions. The following procedures ensured the ethical guidelines: (a) IRB approval obtained from both UNC-CH and ECU and (b) a completed and signed data-use agreement form. The principal investigator of this study analyzed all the data with the help of the faculty advisor.

CHAPTER IV: INFLUENCING FACTORS OF IBD-FATIGUE: A PATH ANALYSIS MODEL MANUSCRIPT

Inflammatory bowel disease (IBD) is an autoimmune disorder of the gastrointestinal tract (GI) and is characterized by chronic inflammation. Ulcerative colitis (UC) and Crohn's disease (CD) are the two major forms of IBD (Ananthakrishnan, 2015). The inflammation of IBD is a classic example of symptomology associated with a relapsing-remitting disorder, in which those with IBD experience both remission as an inactive form of IBD, and relapse or the active disease (Liverani, Scaioli, Digby, Bellanova, & Belluzzi, 2016). The unpredictable disease trajectory of IBD, coupled with the symptom burden, significantly lowers the quality of life (QOL) of those with IBD (Knowles et al., 2018).

Fatigue is one of the most common aggravating, challenging, and debilitating symptoms reported by those with IBD (Chavarría et al., 2019; Cohen et al., 2014; Kreijne, Lie, Vogelaar, & van der Woude, 2016; Perler et al., 2019). Fatigue is a subcomponent of QOL and is inversely associated with poor QOL among adults with IBD (Cohen et al., 2014). It is estimated that about 22% to 77% of adults with IBD experience fatigue affecting their QOL (Bazilchuk, 2016). An analysis of the subcategories of IBD found that 22% to 41% of adults with IBD in remission and 44% to 86% of adults with the active disease experienced fatigue (Czuber-Dochan, Ream, & Norton, 2013a; van Langenberg & Gibson, 2010).

The major contributors to fatigue (hereinafter referred as IBD-Fatigue) in the IBD population are active inflammatory disease (Cohen et al., 2014; Kappelman et al., 2013; van Langenberg & Gibson, 2010; van Langenberg & Gibson, 2014); nutrition-related factors, such as malabsorption and anemia (Bager et al., 2012; Jelsness-Jørgensen et al., 2011b; Romberg-Camps et al., 2010); and psychological stress (Artom, Czuber-Dochan, Sturt, & Norton, 2016; van

Langenberg & Gibson, 2010). Besides these contributors, IBD therapies can also contribute to IBD-Fatigue. The use of medications for IBD, such as azathioprine, methotrexate, thiopurine, and anti-TNF α, also significantly correlate with fatigue experiences (Jelsness-Jørgensen et al., 2011b; Kreijne et al., 2016; Villoria et al., 2017). Further studies have highlighted an association between the use of corticosteroids and fatigue among adults with IBD (Artom, Czuber-Dochan, Sturt, Murrells, & Norton, 2017; Chavarría et al., 2019; Kappelman et al., 2013; van Langenberg & Gibson, 2014). Thus, IBD-Fatigue is connected to both the pathological process of the disease and the therapy used for treatment.

Fatigue often manifests with other symptoms as a cluster in which two or more symptoms co-occur (Arnett & Clark, 2012). Because fatigue presentation due to inflammation is connected to the neurophysiology of cytokine-mediated sickness behavior symptoms, it is important to examine these symptoms when studying IBD-Fatigue. These symptoms include anxiety, depressive behavior, sleep disturbances, increased sensitivity to pain, and psychomotor slowing (Arnett & Clark, 2012). Besides the physiological (sleep disturbances and increased sensitivity to pain) and psychological (anxiety and depression) symptoms associated with sickness behavior, other factors are strongly associated with fatigue presentation in adults with IBD. These include physical activity and limited satisfaction with social roles (SSR) due to the illness. Previous research studies (Klare et al., 2015; Ng, Millard, Lebrun, & Howard, 2007; van Langenberg & Gibson, 2014) and reviews (Engels, Cross, & Long, 2017; Kreijne et al., 2016) supported the benefits of physical activity and exercise for improving intestinal inflammation, as well as QOL and fatigue, in adults with IBD. Moreover, IBD-Fatigue negatively influences the social lives of adults with IBD. Adults with IBD-Fatigue reported lack of energy to continue their social lives,

pointing out that their fatigue experiences led to their disconnection from society (Beck, Bager, Jensen, Dahlerup & 2013).

According to 2015 data, about 1.3% (3 million) of US adults are affected by IBD, representing an increase from 0.9% (2 million adults) in 1999 (Centers for Disease Control and Prevention [CDC], 2019). Because of increase in the prevalence rate of IBD and considering the physiological, psychological, and social burdens, it is essential to understand the complex interplay between fatigue and covariates of anxiety, depression, sleep disturbances, pain, physical activity, and SSR. Examining these associated factors is necessary in a biopsychosocial model of care that integrates different factors, as supported by Artom colleagues (2017), and for developing nursing interventions to reduce IBD-Fatigue. Thus, the purposes of this study were to comprehensively examine factors associated with IBD-Fatigue and to develop a parsimonious model that describes the influencing factors of IBD-Fatigue.

Conceptual Framework

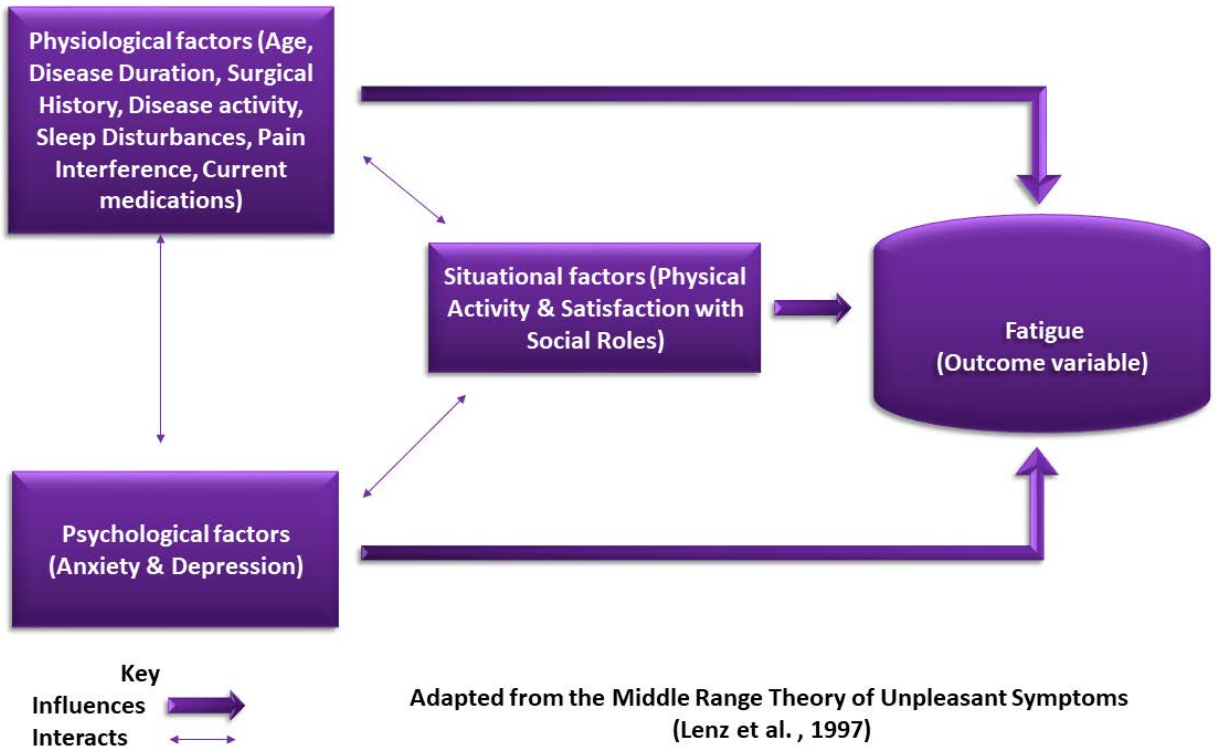
The middle range theory of unpleasant symptoms (MRTOUS) provided a framework to guide the study (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). Influencing factors, symptoms, and performance outcomes are the three major concepts included in the MRTOUS (Lenz et al., 1997). This study focused on the influencing factors and symptoms. The MRTOUS incorporates three groups of influencing factors: physiological, psychological, and situational factors (Lenz & Pugh, 2014). These three factors are interrelated to one another and influence the symptom experience individually or in combination (Lenz et al., 1997). Normally functioning body systems and the presence of any pathology were considered physiological factors, along with treatment-related variables (Lenz & Pugh, 2014). A person's mental state or mood, affective reaction to illness, and mental states of anxiety and depression were included as psychological factors. Meanwhile, social and physical environments, which influence the experience of

symptoms, were considered as the situational factors. Examples of situational factors include support systems; access to health care; occupations; and lifestyle behaviors, such as diet and physical activity (Lenz et al., 1997). Furthermore, physiological, psychological, and situational factors can mediate their relationships with the symptom experience as well (Lenz & Pugh, 2014).

As the MRTOUS proposes, fatigue is the symptom of the adapted conceptual framework. (see Figure 5).

Figure 5

Conceptual Framework



Sleep disturbances and pain interference, along with demographic and clinical factors, such as age, disease duration, surgical history, disease activity, and current medications, are considered physiological factors based on the definition of the MRTOUS. Anxiety and depression

are the psychological factors, with SSR and physical activity included as situational factors, according to the description of the MRTOUS. Therefore, we formulated the following research question to guide the study: What are the direct and indirect effects of physiological (age, disease duration, surgical history, disease activity, sleep disturbances, pain interference, and current medications), psychological (anxiety and depression), and situational (physical activity and satisfaction with the social roles) factors on fatigue in adults with IBD?

Methods

We conducted a secondary analysis of cross-sectional data obtained from *IBD Partners*, an online cohort of adults with IBD initiated by the Crohn's and Colitis Foundation (CCF) and the University of North Carolina at Chapel Hill (UNC-CH). IBD Partners began the enrollment of the online cohort in June 2011 under the name Crohn's and Colitis Foundation of America (CCFA) Partners (Long et al., 2012); the name was later changed to IBD Partners. The online cohort includes participants from the 50 states of the United States (US), and enrollment is ongoing. The inclusion criteria for IBD partners include adults who are older than 18 years of age with a self-reported diagnosis of IBD and who have internet access (IBD Partners, n.d.).

Sample

The inclusion criteria for the study included adults 18 years of age or older with a self-reported diagnosis of IBD, Crohn's disease (CD), or ulcerative colitis (UC) drawn from the internet-based cohort of IBD Partners. Adults with IBD with ostomies or J-pouches were excluded from the study due to the lack of criteria to assess disease activity among adults with IBD after these surgical procedures. Data were extracted on 09-13-2019, and the final sample size consisted of 12,053 eligible participants.

Human Subject Protection

The Institutional Review Boards (IRB) of the parent organization (UNC-CH) and East Carolina University (ECU) approved the study. After receiving approval, a data use agreement form was completed.

Variables and Measurements

The Patient Reported Outcomes Measurement Information System (PROMIS) short-form scales from the National Institute of Health (NIH) were used to measure fatigue, sleep disturbances, pain interference, anxiety, depression, and SSR. The PROMIS scales were recomputed to a normalized *t-score*, where the mean of the US general population was 50, and the standard deviation (SD) was 10 (NIH, 2019). To assess each variable, its corresponding four-item PROMIS short-form scale was used, and the occurrences of the symptom over the past seven days were measured. The PROMIS measures were rated on a 5-point Likert scale that ranged from *not at all* to *very much*. Higher scores indicated higher measurements or worse health outcomes in the domains of fatigue, sleep disturbances, pain interference, anxiety, and depression. However, higher scores indicated better health outcomes for positively-worded concepts, such as SSR (NIH, 2019). The PROMIS scores were dichotomized into two categories and for the purpose of this study, clinical significance on the PROMIS tools are set at: Clinically significant (score ≥ 55) and non-significant (score < 55), except for SSR based on the norms suggested by the developing team (Health Measures, 2020). The PROMIS scores for SSR were categorized in the reverse order, with a score ≤ 55 indicating clinical significance and a score > 55 indicating non-significance.

Fatigue. The PROMIS fatigue short-form scale (PROMIS Short Form v1.0 – Fatigue 4a) measures the frequency, duration, intensity, and interference of fatigue (NIH, 2019). The reliability of the PROMIS fatigue scale was more than 0.91 for scores with two SDs below the mean to four SDs above the mean. Convergent validity of the PROMIS fatigue scale was established by computing the correlation coefficient between the PROMIS fatigue scale and the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale and the SF-36 vitality scale, which demonstrated correlation coefficient values of 0.95 and 0.89, respectively (Cella et al., 2010).

Sleep Disturbances. The PROMIS sleep disturbances short-form scale (PROMIS Short Form v1.0 – Sleep Disturbance 4a) is designed to assess the quality of sleep, refreshment gained after sleep, difficulty in falling asleep, and interruptions in sleep (NIH, 2019). The reliability of the PROMIS sleep disturbances scale was greater than 0.88 across most of the score distributions. Convergent validity was established by computing the correlations between the PROMIS sleep disturbances scale and the Pittsburgh Sleep Quality Index (PSQI), as both measure the same sleep constructs. A correlation coefficient of 0.85 confirmed the convergent validity of the PROMIS sleep disturbances scale (Cella et al., 2010).

Pain Interference. The PROMIS pain interference short-form scale (PROMIS Short Form v1.0 – Pain Interference 4a) assesses the degree to which pain impedes an individual's social, recreational, and day-to-day activities (NIH, 2019). The reliability of the PROMIS pain interference scale was 0.97 or higher for scores greater than or equal to the mean and 0.77 for scores one SD below the mean. Convergent validity was established by computing the correlations between the PROMIS pain interference scale and the Brief Pain Inventory (BPI)

interference subscale (r = 0.85) and the Short Form -36 (SF-36) bodily pain subscale (r = -0.86; Cella et al., 2010).

Anxiety. The PROMIS anxiety short-form scale (PROMIS Short Form v1.0 – Anxiety 4a) assesses an individual's reaction to fear, inability to focus on other matters, worries, and uneasiness (NIH, 2019). The reliability of the PROMIS anxiety short-form scale was more than 0.89 for most of the score distributions. Convergent validity was established by computing the correlations between the PROMIS anxiety short-form scale and the general distress (anxiety) scale from the Mood and Anxiety Symptom Questionnaire (r = 0.80; Cella et al., 2010).

Depression. The PROMIS depression short-form scale (PROMIS Short Form v1.0 – Depression 4a) measures the extent of depression, helplessness, hopelessness, and worthlessness experienced by adults (NIH, 2019). The reliability of the PROMIS depression scale was more than 0.92 for most of the score distributions. Convergent validity was established by computing the correlations between the PROMIS depression scale and the Center for Epidemiological Studies Depression Scale (CES-D, r = 0.83; Cella et al., 2010).

Satisfaction with Social Roles. The PROMIS SSR short-form scale (PROMIS Short Form v1.0 – Satisfaction with Social Roles 4a) assesses the degree to which individuals are satisfied with their social roles, family responsibilities, and work responsibilities (National Institute of Health, 2019). The reliability of the PROMIS SSR scale was 0.96 for scores that were two SDs below the mean and one SD above the mean. The convergent validity of the PROMIS satisfaction with social roles was evaluated by examining correlations with corresponding legacy measures, such as the SF-36 Role Physical, Role Emotional, and Social Functioning Scale (r ranged from 0.57-0.59) and the FACIT-Functional Well Being Scale (r = 0.76; Cella et al., 2010).

Physical Activity. The following single question was used to measure physical activity: How often did you participate in one or more physical activities for 20-30 minutes' duration per session during your leisure time within the past 6 months? Adults with IBD reported that this one question best measured their physical activity. Therefore, the primary team of IBD Partners decided to keep this question based on patient input. This physical activity question was scored on a 6-point scale, and the scores ranged from 1 to 6. The scores were dichotomized into two categories: Higher levels of physical activity (score ≥ 5) and lower levels of physical activity (score < 5) as the scores from 1 to 4 reflected physical activities performed within a month and scores ≥ 5 reflected physical activities performed within a week. A preliminary analysis was conducted and this one question moderately correlated with the Godin Leisure Time Activity (GLTA) index scale scores of adults with IBD (r_s = 0.686, p < .001). Additionally, the polychoric correlation coefficient was computed, and a strong correlation was noted between the GLTA and the physical activity question (r = 0.74, p < .001) (Davis, Melendez, Crane, & Long, 2020).

Demographic and Clinical variables. The self-reported demographic and clinical variables included in the present study were age, IBD disease duration in years, history of surgical of treatment of IBD, current medications (aminosalicylates, steroids, immune modulators, biologics, anti-TNF α medications, and narcotics), and disease activity. Disease activity indices of both CD and UC are different and both were collected to assess the disease activity of the participants. Self-reporting of the Simple Clinical Colitis Activity Index (SCCAI) was used for adults with UC (Jowett et al., 2003). The SCCAI values were categorized into ≤ 2 for UC remission and > 2 for UC active. Self-reporting of the short Crohn's Disease Activity Index (sCDAI) was used for adults with CD (Thia et al., 2011). The sCDAI values were

categorized into < 150 for CD remission and ≥ 150 for CD active. The disease activity of all IBD sample were determined based on the results of SCCAI and sCDAI as active and inactive disease.

Data Analyses. We used SPSS version 24 software to analyze the descriptive statistics. Proportions were calculated for the dichotomous scores of the PROMIS measures (fatigue, anxiety, depression, sleep disturbances, pain interference, SSR), and physical activity. Proportions were calculated for the clinical variables, including surgical history, disease activity, and current medications. Minimum and maximum values, means, and SDs, were examined for continuous variables, such as age and disease duration. Chi-square analyses were computed to identify the associations between the dichotomized scores of fatigue, anxiety, depression, sleep disturbances, pain interference, SSR, physical activity, age, disease duration, surgical history, disease activity, and current medications. Furthermore, Mantel-Haenszel common odds ratios were calculated to identify the odds of predictor variables on IBD-Fatigue

Path analysis was used to examine relationships among numerous variables (Mertler & Reinhart, 2010) and to test a causal model illustrated in a path diagram based upon logic, theoretically-based statements of relationships among variables, and/or experience (Kelloway, 2015; Mertler & Reinhart, 2010). Path analysis was used because the path diagram of the study was based on the conceptual framework adapted from the MRTOUS and not intended to test the MRTOUS. Additionally, the data analysis of the study included the normalized *t-scores* of many of the variables (anxiety, depression, sleep disturbances, pain interference, and SSR), including the outcome variable (fatigue). Therefore, these variables were considered as observed variables. According to the literature, a structural model with observed variables is considered for path analysis (Wang & Wang, 2012).

The statistical software Mplus version 8 (Mplus) was used to compute the path analysis using the weighted least square mean and variance adjusted (WLSMV) estimation. This estimation is the default estimator for computing path analysis with a categorical dependent variable in Mplus (Muthén & Muthén, 2017). Two other authors (Beran & Violato, 2010; Wang & Wang, 2012) have supported using the weighted least square estimation with a categorical outcome variable. The primary data met the power and sampling guidelines for path analysis as the final sample size consisted of 12,053 participants. Significance levels were set at $p < .01$

Before conducting the path analysis, multicollinearity was assessed and patterns of missing data were examined. Multicollinearity of the variables were tested using tetrachoric correlation (see appendix A) as it is the preferred technique for binary variables using weighted least square estimation in Mplus (Muthén & Muthén, 2017). Over all, the data set had < 2% missing data for all the observed variables used in path analysis. The data were complete for seven of the variables included in the final model such as PROMIS scores of fatigue, anxiety, depression, sleep disturbances, pain interference, satisfaction with social roles and for physical activity scores. For the remaining two variables in the final model, the missing data were 0.1% for age and 0.6% for disease activity. Additionally, the weighted least square estimation of Mplus has a default setup of pairwise deletion to manage missing data (Wang & Wang, 2012).

Model fit was assessed using several goodness of fit indices including the Chi-square ($\chi 2$) goodness of fit test; the relative goodness of fit indices, such as the Tucker-Lewis index (TLI); the comparative fit index (CFI); and the absolute goodness of fit indices, such as the root mean squared error of approximation (RMSEA) and the standardized root mean square residual (SRMR). The χ^2 statistics were used as a "badness of fit," where low χ^2 values were considered good (the model fit the data well) and large χ^2 values indicated that the model did not fit the data.

A non-significant probability level of the χ^2 test is expected for a model that fits the data well (Clayton & Pett, 2011; Kelloway, 2015; Tabachnick & Fidell, 2013). However, one should be very cautious while looking at the nonsignificance level of a χ^2 test, as a significant χ^2 value is possible with a large sample (Tabachnick & Fidell, 2013). The CFI and TLI values ranged from 0 to 1; a value close to 0.95 or higher denotes an acceptable model fit with the data. An RMSEA value < 0.05 indicates excellent fit, a value < 0.08 indicates a moderate fit, and a value > 0.10 indicates a poor fit of the model with the data (Clayton & Pett, 2011; Kelloway, 2015; Tabachnick & Fidell, 2013). Generally, SRMR values < 0.08 are considered a good fit (Clayton & Pett, 2011; Kelloway, 2015; Tabachnick & Fidell, 2013).

Results

Sample Characteristics

The largest representation of the sample (N = 12,053) was White (92%), and more than two thirds (72%) were females. The mean age was 43 years old (SD = 15; range 18-91). Disease duration varied from < 1 year to 75 years with a mean of 13 years. The majority of the participants (85%) were < 60 years of age, and further age stratification showed closer proportions of age between 18-40 (48%) and 40-63 (41%) with 11% of participants > 63 years of age. Nearly equal proportions of disease activity were noted with 51% in remission and 49% having active disease. The majority (70%) had not undergone any surgical procedures to manage IBD. Of those who were taking medications, the majority were on aminosalicylates (46%), followed by biologics (37%) and anti-TNF-α (35%). This pattern was similar between those who are in remission and in active disease. See Table 1 for sample characteristics.

Table 1

Sample Characteristics (N = 12,053)

Description	n	%
Sex		
Female	8660	72
Male	3391	28
Age in years		
< 60	10187	85
≥ 60	1852	15
IBD Type		
CD	7546	63
UC	4501	37
Disease activity		
Remission	6158	51
Active Disease	5826	49
Disease Duration (years)		
<10	6291	52
10-20	2897	24
>20	2837	24
IBD Medications (Yes)		
Aminosalicylates	5583	46
Biologics	4483	37
Anti- TNF α	4204	35
Immunomodulators	3215	27
Corticosteroids	2449	20
Narcotics	1308	11

CD – Crohn's Disease; UC – Ulcerative Colitis; TNF – Tumor Necrosis Factor

Approximately half of the participants (56%) reported clinically significant fatigue ($t \geq 55$), followed by pain interference (51%) and anxiety (50%).Conversely, 78% reported not being satisfied with their social roles. The majority of the participants (62%) reported being physically active. Less than half of the participants reported sleep disturbances (34%) and being depressed (40%). See Table 2 for PROMIS and physical activity descriptions.

Table 2

Descriptives of PROMIS Scores and Physical Activity Scores (N = 12,053)

Description	*n*	%
PROMIS Fatigue		
< 55	5316	44
≥ 55	6737	56
PROMIS Anxiety		
< 55	6035	50
≥ 55	6018	50
PROMIS Depression		
< 55	7225	60
≥ 55	4828	40
PROMIS Pain Interference		
< 55	5907	49
≥ 55	6146	51
PROMIS Sleep Disturbances		
< 55	7936	66
≥ 55	4117	34
PROMIS Satisfaction with Social Roles		
> 55	2594	22
≤ 55	9459	78
Physical Activity		
< 5	4627	38
≥ 5	7426	62

Among the fatigued group ($t \geq 55$), 88% were < 60 years old; only 12% were above 60 years. Disease duration stratification among the fatigued group showed 55% had < 10 years of disease duration and nearly equal percentages had disease durations > 10-20 years (24%) and > 20 years (21%). Among the fatigued group, only 31% had a surgical procedure for IBD. Nearly one third of the participants who were fatigued (33.5%) were in remission. The majority of the adults in fatigued group were taking aminosalicylates (43.5%), followed by biologics (40%), anti-TNF-α (37%), immunomodulators (27%), steroids (25%), and narcotics (17%). Out of 6,737 participants in the fatigued group, 47% were engaged in low levels of physical activity. Higher prevalence rates in the PROMIS scores for anxiety (67%), depression (58%), and pain

interferences (72%) were noted among the fatigued adults with IBD. The sleep disturbances scores were equal for the fatigued (50%) and non-fatigued (50%) adults with IBD. However, the majority of the fatigued adults (93%) reported the worst scores in the domain of SSR indicating poor satisfaction with social roles.

Associations between IBD-Fatigue and other variables

A significant association was noted between fatigue and physiological factors (age, disease duration, disease activity, current medications [Aminosalicylates, corticosteroids, biologics, anti-TNF-α, and narcotics], sleep disturbances, and pain interference), psychological factors (anxiety and depression), and situational factors (physical activity and SSR). The presence of fatigue was significantly different by age category ($\chi^2 = 121.85$, $p < .001$) with 58% of those 18 to 40 years old, 57% of those 40 to 63 years old, and 42% of those over age 63 experiencing fatigue. Similarly, the presence of fatigue significantly differed by disease duration ($\chi^2 = 46.11$, $p < .001$) with 58% of those with < 10 years of disease duration, 57% of those with 10-20 years of disease duration, and 51% of those with > 20 years of disease duration experiencing fatigue. Based on the phi coefficient values (Pallant, 2016), a moderate effect was noted between fatigue and physiological factors of sleep disturbances and pain interference, as well as psychological factors of anxiety and depression. No significant associations were noted between fatigue and current use of immunomodulators. The Chi- square associations are presented in Table 3.

Table 3

Association Between Fatigue and Physiological, Psychological and Situational Factors

Variables	χ^2 (df, N)	*P* value	Phi coefficient
Physiological Factors			
Age (< 60 & ≥ 60)	133.92 (1, 12,039)	< .001	-0.11**
Age (18-40, > 40-63 & >63)	121.85 (2, 12,039)	< .001	0.10**
Disease duration (< 10, 10-20 & > 20)	46.11 (2, 12,025)	< .001	0.06**
Surgical history (Yes or No)	8.33(1, 12,053)	0.004	0.03*
Disease Activity (as remission Yes or No)	1935.68 (1, 11,984)	< .001	-0.40**
Aminosalicylates (Yes or No)	49.46 (1, 12,032)	< .001	-0.06**
Biologics (Yes or No)	40.69 (1, 11,974)	< .001	0.06**
Anti-TNF α (Yes or No)	26.34 (1, 11,974)	< .001	0.05**
Immunomodulators (Yes or No)	0.565(1, 11,993)	.452	0.007
Corticosteroids (Yes or No)	235.42 (1, 12,029)	< .001	0.14**
Narcotics (Yes or No)	491.29 (1, 10603)	< .001	0.203**
Psychological Factors			
Anxiety (> 55 vs. ≥ 55)	1913.55 (1, 12,053)	< .001	0.40**
Depression (> 55 vs. ≥ 55)	2039.9 (1, 12,053)	< .001	0.41**
Sleep Disturbances (> 55 vs. ≥ 55)	1646.06 (1, 12,053)	< .001	0.37**
Pain interference (> 55 vs. ≥ 55)	2702.92 (1, 12,053)	< .001	0.47**
Situational Factors			
Satisfaction with Social Roles (≤ 55 vs. > 55)	1932.92 (1, 12,053)	< .001	0.04**
Physical activity (< 5 vs ≥ 5)	468.41(1, 12,053)	< .001	-0.20**

***p* < .001 **p* < .01 TNF = Tumor Necrosis Factor

Significant associations were noted between current use of corticosteroid and narcotics consistently among PROMIS scores of sleep disturbances, pain interference, anxiety, depression, SSR, and physical activity. A similar result was observed where consistent significant

associations between age and disease activity were noted among PROMIS measures of sleep disturbances, pain interference, anxiety, depression, SSR and physical activity (See appendices B- G for details).

Odds Analysis

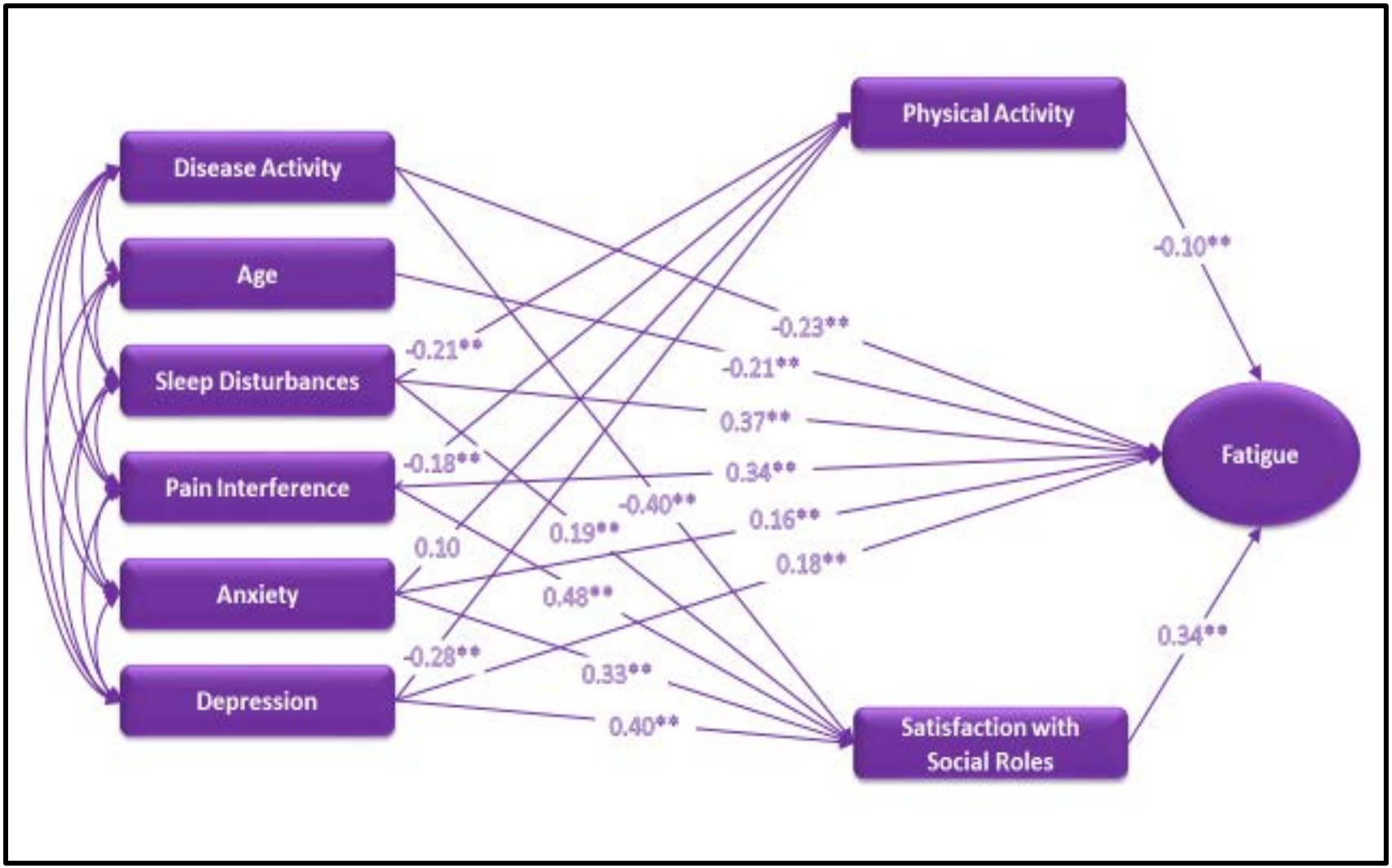
Odds ratios (OR) were computed to evaluate the factors that increased the risk of having IBD-Fatigue**.** All the PROMIS scores (anxiety, depression, sleep disturbances, pain interferences and satisfaction with social roles) consistently increased the odds of having IBD-Fatigue (see appendix H). Among them, higher odds were found to be with SSR (OR = 9.01, [8.08, 10.04], $p < .001$), pain interferences (OR = 8 [7.37, 8.69], $p < .001$), and depression (OR = 6.56, [6.02, 7.15], $p < .001$). Among the IBD medications, the odds of clinically significant fatigue symptoms are about 5.02 times greater for those currently taking narcotics, and 2.08 times higher for those who are currently on steroids than for those not taking such medications. Current use of biologics (OR = 1.28 [1.18, 1.38], $p < .001$) and current use of anti-TNF α (OR = 1.22 [1.13, 1.32], $p < .001$), significantly increased the odds of IBD-Fatigue.

Path Analysis Model

Three models were tested based on the conceptual framework adapted from the MRTOUS to identify the direct and indirect effects of situational, physiological, and psychological factors on IBD-Fatigue, as well as to evaluate the fit of the data to the proposed models. The results of the path analysis revealed the poor fit of all three models. We first trimmed the models based on significance levels and then modified each model by removing all non-significant paths and further re-specified them based the modification indices' results. The data best fit with model 1 with situational factors (physical activity and SSR) as the mediators: fit indices (χ^2 (4, 11,822) = 41.96, $p < 0.001$; RMSE = 0.028; CFI/TLI = 0.989/0.940; SRMR = 0.015). The final trimmed model with all direct effects are shown in Figure 2.

Figure 6

Final Trimmed Model with Direct Effects



**p < .001

Decomposition of the model: Direct effects. Path analysis results revealed that all direct paths from the physiological, psychological, and situational factors to IBD-Fatigue in the final model were significant. Refer to Table 4 for details. We observed the highest positive direct effect on IBD-Fatigue from sleep disturbances (β = 0.37, 99% CI [0.31, 0.43], $p < .001$) followed by SSR (β = 0.34, 99% CI [0.29, 0.38], $p < .001$) and by pain interference (β = 0.34, 99% CI [0.29, 0.41], $p < .001$). Depression (β = -0.28, 99% CI [-0.36, -0.19], $p < .001$), sleep disturbances (β = -0.21, 99% CI [-0.28, -0.17], $p < .001$) and pain interference had negative (β = -0.18, 95% CI [-0.30, -0.12], $p < .001$) direct effects on physical activity. Besides the direct effect from sleep disturbances, pain interferences, anxiety and depression, a significant negative direct path observed from disease activity to SSR (β = -0.40, 99% CI [-0.47, -0.34], $p < .001$). See Table 4 for details.

Decomposition of the model: Indirect effects. The indirect or mediating effects of physical activity on IBD-Fatigue were analyzed. We noticed three significant positive indirect effects on fatigue via physical activity; from sleep disturbances (β = 0.02, 99% CI [0.01, 0.03], $p < .001$); from pain interference (β = 0.02, 99% CI [0.01, 0.03], $p < .001$) and from depression (β = 0.03, 95% CI [0.02, 0.04], $p < .001$) through physical activity on fatigue. Similar results were noted where sleep disturbances, pain interference, and depression also had mediating effects on IBD-Fatigue via SSR. The indirect effects were from pain interference (β = 0.16, 99% CI [0.13, 0.19], $p < .001$), depression (β = 0.14, 99% CI [0.10, 0.16], $p < .001$), and sleep disturbances (β = 0.06, 99% CI [0.04, 0.08], $p < .001$) through SSR to IBD-Fatigue. Since the direct effects of sleep disturbances, pain interference, and depression on IBD-Fatigue were more than the indirect or mediating effects of these variables on IBD-Fatigue via physical activity and SSR, the mediation is considered as a partial mediation (Tabachnick & Fidell, 2013, p. 161).

Table 4

Decomposition of Effects of Final Path Model, (N = 12,053)

Variables	Direct effects on fatigue β & 99% CI	Direct effects on physical activity β & 99% CI	Direct effects on satisfaction with social roles β & 99% CI	Indirect effects on fatigue via physical activity β & 99% CI	Indirect effects on fatigue via SSR β & 99% CI
Physiological Factors					
Disease Activity	-0.23** [-0.28, -0.16]	-	-0.40** [-0.47, -0.34]	-	
Age	-0.21** [-0.27, -0.15]	-	-	-	
Sleep disturbances	0.37** [0.31, 0.43]	-0.21** [-0.28, -0.17]	0.19** [0.11, 0.24]	0.02** [0.01, 0.03]	0.06** CI [0.04, 0.08]
Pain interference	0.34** CI [0.29, 0.41]	-0.18** CI [-0.30, -0.12]	0.48** CI [0.40, 0.54]	0.02** CI [0.01, 0.03]	0.16** CI [0.13, 0.19]
Psychological Factors					
Anxiety	0.16** CI [0.10, 0.22]	0.10 CI [0, 0.09]	0.33** CI [0.26, 0.40]	-	-
Depression	0.18** CI [0.12, 0.25]	-0.28** CI [-0.36,- 0.19]	0.40** CI [0.32, 0.47]	0.03** CI [0.02, 0.04]	0.14** CI [0.10, 0.16]
Situational Factors					
Physical activity	-0.10** CI [-0.13, -0.08]	-	-	-	
Satisfaction with social roles	0.34** CI [0.29, 0.38]	-	-	-	

**$p < .001$ β = standardized coefficients CI = Confidence Interval SSR = Satisfaction with social roles

Discussion

To our knowledge this is the first study evaluating the direct and mediating effects of different factors on IBD-Fatigue using path analysis based on a model adapted from the MRTOUS in adults with IBD. This is also one of the few studies evaluating IBD-Fatigue as an outcome variable in the US (Borren et al., 2019; Cohen et al., 2014; Hashash et al., 2018; Tinsley, Macklin, Korenik, & Sands, 2011). Although many studies evaluated the factors that affect IBD-Fatigue, none of them evaluated the combination of physiological, psychological, and situational factors on IBD-Fatigue.

Consistent with previous findings (Chavarría et al., 2019; Tinsley et al., 2011), IBD-Fatigue was highly prevalent (56%, N = 12,053) in this study cohort. Among the fatigued group, 66.5% had the active disease, and a significant association was noted between disease activity and IBD-Fatigue. These findings are consistent with previous findings on the association between IBD-Fatigue and disease activity (Chavarría et al., 2019; Czuber-Dochan et al., 2013a). Furthermore, the results of the path analysis revealed a negative direct effect of disease activity on IBD-Fatigue and SSR. IBD-Fatigue was also present in 33.5% of those in remission similar to previous results noting adults with IBD reported fatigue even during remission (Aluzaite et al., 2018; Czuber-Dochan et al., 2013a).

We found a significant association between all IBD medications, except immunomodulators, and IBD-Fatigue. These findings are similar to other studies noting the influence of IBD medications on IBD-Fatigue (Artom et al., 2017; Chavarría et al., 2019). Additionally, the current use of anti- TNFα, and steroids significantly increased the odds of IBD-Fatigue in consistent with previous findings (Artom et al., 2017; Chavarría et al., 2019; Kappelman et al., 2014). We also noticed an increase in odds of IBD-Fatigue with current use of narcotics which are not explored in many studies. However, the final path model did not support

any IBD medications having an effect on IBD-Fatigue. One possible explanation is that variance in the number of participants who were currently taking medications (aminosalicylates [46%], biologics [37%], anti-TNFα [35%], immunomodulators [37%], corticosteroids [20%] and narcotics [11%]. Further studies are needed examining the varying effects of different medications and IBD-Fatigue.

Our study findings supported the fact that younger adults with IBD reported higher levels of fatigue compared to older adults, which is consistent with previously published data in which adults < 60 years of age with IBD were found to have higher fatigue scores (Bager et al., 2012). A direct negative effect was also observed from age to IBD-Fatigue in the path analysis, supporting that as age increases fatigue decreases. One possible explanation is that older adults adjust their lives based on their fatigue more readily than younger ones. Furthermore, older adults' work and home responsibilities may differ from those of younger adults. Moreover, individuals with chronic illness may adapt to the demands of the illness over the time and may eventually accept the illness (Aujoulat, Marcolongo, Bonadiman, & Deccache, 2008). Therefore, healthcare personnel need to understand age differences when developing strategies to manage IBD-Fatigue.

Our study findings supported the direct effects of sleep disturbances, pain interference, anxiety, and depression on IBD-Fatigue and on the mediating variables of physical activity and SSR. These findings support the cytokine-mediated sickness behavior related to IBD inflammation (Arnett & Clark, 2012). Previously published data supported the finding that poor sleep quality was more pronounced in adults with IBD-Fatigue (Chavarría et al., 2019), and an association noted between pain and IBD-Fatigue (Beck et al., 2013). Additionally, adults with higher anxiety and depression scores had higher fatigue impact scores (Ratnakumaran et al.,

2018). Therefore, it is recommended to add interventions to improve sleep habits and to manage or control pain, anxiety, and depression when managing IBD-Fatigue.

Our study highlighted the indirect or mediating effects of physical activity on IBD-Fatigue from sleep disturbances and pain interference, as well as from depression. The indirect effects showed the importance of considering physical activity as an intervening variable to manage IBD-Fatigue. Many research studies used the terms exercise and physical activity interchangeably and supported the benefit of physical activity/exercise to manage IBD-Fatigue (Tew et al., 2019; van Langenberg & Gibson, 2014). However, none of these intervention studies were conducted in the US. Additionally, physical activity helps manage other symptoms, such as sleep disturbances (Chan et al., 2014), improvements in mood (Nathan et al., 2013; Tew et al., 2019), and improvement in overall QOL (Gatt et al., 2019; Ng et al., 2007). Considering the multiple contributors to IBD-Fatigue and its close association with other symptoms, such as anxiety, depression, sleep disturbances, and pain interference, more studies are warranted among adults with IBD to demonstrate the effectiveness of physical activity on IBD-Fatigue and other symptoms.

Other important findings of the study were related to the association between IBD-Fatigue and SSR, which is an understudied area of IBD-Fatigue research. The results of the study pointed out the intervening or mediating effects of SSR on IBD-Fatigue from sleep disturbances, pain interference, and depression. About 78% of the participants reported not being satisfied in SSR, which matches previous data of low scores in satisfaction with social roles among adults with IBD (Kappelman et al., 2014). Furthermore, previous qualitative studies reported the disruption of social roles due to IBD symptoms and fatigue (Czuber-Dochan et al., 2013a;

Devlen et al., 2014). Therefore, the improvement of social roles and activities may help to improve IBD-Fatigue.

The majority (92%) of the participants in this study were Caucasians. Although the incidence of IBD is increasing in other ethnic groups, IBD is predominantly reported among Whites (Aniwan, Harmsen, Tremaine, & Loftus, 2019). Therefore, the sample from this study is similar to the IBD population.

In summary, this study demonstrated the direct effects of physiological factors such as disease activity, age, sleep disturbances, pain interference, psychological factors of anxiety and depression and situational factors of physical activity and satisfaction with social roles on IBD-Fatigue. Additionally, the study highlighted the intervening effects of physical activity and satisfaction with social roles on IBD-Fatigue.

Limitations

The data from IBD Partners were collected online and, therefore, may not sufficiently reflect the symptoms in those with various education levels or socioeconomic backgrounds. Because the primary data did not include zip codes, it was not possible to divide the participants based on urban or rural status. In addition, adults with IBD who are literate and who have internet access may be overrepresented in the online cohort. Therefore, a generalization of the results to unrepresented groups cannot be supported. Finally, we could not include any biomarkers of anemia, nutritional markers, or biomarkers of inflammation to evaluate their effects on fatigue as that information was not available in the IBD Partners dataset.

Conclusions

We have tested a path model, which was adapted from the MRTOUS, to evaluate factors associated with IBD-Fatigue. We identified two important mediating variables from this model,

which can be considered in potential interventions to manage IBD-Fatigue. Additionally, many associations between IBD-Fatigue and other physiological, psychological, and situational factors were explored in this study. Due to the multifactorial nature of IBD-Fatigue, the integration of all influencing factors should be considered in its management to provide a holistic approach in fatigue management.

CHAPTER V: A PATH ANALYSIS MODEL OF FATIGUE IN CROHN'S DISEASE AND ULCERATIVE COLITIS MANUSCRIPT

Almost three million adults in the United States (US) are affected by inflammatory bowel disease (IBD; Centers for Disease Control and Prevention, 2019). Crohn's disease (CD) and ulcerative colitis (UC) are the two major forms of IBD (Ananthakrishnan, 2015). The prevalence rate of UC is higher (238 per 100,000 population) than that of CD (201 per 100,000 populations; Molodecky, 2012). The classic pathophysiology of CD and UC is characterized by inflammation. The disease trajectory can alternate between remission or inactive disease and relapse or active form of the illness in both CD and UC. However, there are differences in the type of inflammation; CD involves inflammation of all layers of the intestine, whereas, in UC, inflammation only occurs in the peripheral layer of the intestine (Chandrasekhar & Venu, 2015). In addition, different structures are involved, as CD can affect any region of the gastrointestinal (GI) tract from the mouth to the anus, while UC is primarily limited to the colon and the rectum. Although inflammation is the key mechanism behind these two forms of IBD, the symptom presentations are quite different (Ananthakrishnan, Xavier, Podolsky, 2017).

The clinical presentations of CD include abdominal pain, diarrhea, bleeding, and malabsorption with a high rate of fistulas. The clinical presentations of UC include profound diarrhea and bowel urgency, diffuse abdominal pain, and rectal bleeding. Besides these intestinal symptoms, systemic symptoms, such as fever, weight loss, and fatigue, and extra intestinal manifestations such as joint pain, skin involvement and increased risk of clotting are commonly present in adults with UC and CD and can vary between both groups (Chandrasekhar & Venu, 2015). Therefore, the treatment pathways can be different in both groups based on the presentation of symptoms and severity of the disease.

In both CD and UC, inflammation is closely connected to cytokine-mediated sickness behavior, which includes classic symptoms of fatigue, anxiety, depression, sleep disturbances, and pain interference (Arnett & Clark, 2012). In more than 80% of adults with IBD, fatigue is the most frequently reported symptom (Perler et al., 2019; Vegni et al., 2019); therefore, fatigue warrants concern when considering treatment for IBD (Casellas, Guise, Robies, Navarro, & Borruel, 2016). The etiology of fatigue in adults with UC and CD is multifactorial. Active inflammation plays a key role in fatigue (Cohen et al., 2014; Kappelman et al., 2013; van Langenberg & Gibson, 2010), followed by psychological factors (Artom, Czuber-Dochan, Sturt, & Norton, 2016). Additionally, inadequate nutrition, such as deficiency of micronutrients and anemia, are commonly attributed to fatigue in those with UC and CD (Artom et al., 2016; Bager et al., 2012; Jelsness-Jørgensen, Bernklev, Henriksen, Torp, & Moum, 2011a). Additionally, fatigue has also been associated with several IBD medications, such as corticosteroids, anti-TNF α, and immunomodulators (Chavarría et al., 2019; Jelsness-Jørgensen, et al., 2011a). Thus, fatigue in adults with UC and CD has been linked to both IBD therapy and the pathology of inflammation.

Fatigue negatively affects the lives of adults with UC and CD. Previous studies (Cohen et al., 2014; Jelsness-Jørgensen, Bernklev, Henriksen, Torp, & Moum, 2011b), reported how fatigue affected the quality of life (QOL) of adults with UC and CD. Participants reported the negative influences of fatigue on their work efficiency, employment, and daily activities (Cohen et al..2014; Jelsness-Jørgensen et al., 2011b). Disturbed sleep was associated with higher levels of fatigue in adults with UC (Huppertz-Hauss et al., 2017; Jelsness-Jørgensen et al., 2011a), and CD (van Langenberg & Gibson, 2014). Additionally, fatigued adults with UC and CD reported higher pain intensity levels than non-fatigued adults (Jelsness-Jørgensen et al., 2017). In addition

to physiological manifestations of sleep disturbances and pain, psychological symptoms of anxiety and depression are higher among fatigued adults with UC and CD (Cohen et al., 2014; Ratnakumaran et al., 2018) and may be related to the bidirectional link between anxiety, depression, and inflammation through the brain-gut axis (Bonaz, & Bernstein, 2013; Keefer & Kane, 2017). Besides the physiological and psychological disturbances, interconnections between fatigue and external factors, such as physical activity and satisfaction with social roles (SSR), have been reported. Reports of the anti-inflammatory benefits of physical activity, suggest the beneficial influence of physical activity on IBD inflammation and thus may influence fatigue (Bilsky et al., 2015; Engels et al., 2017; Saxena et al., 2012). In fact, previous published data support the benefits of physical activity for reducing fatigue in adults with CD (van Langenberg & Gibson, 2014). Fatigue disrupts the activities and social roles of adults with UC and CD. In previous studies, participants reported some of the consequences of fatigue, including limited opportunities to socialize (Czuber-Dochan et al., 2013a), difficulty in planning ahead, and the need to avoid certain activities, such as travel (Devlen et al., 2014). Participants further elaborated that their social lives were greatly restricted due to the avoidance of such activities (Devlen et al., 2014), pointing out the association of fatigue and social roles of individuals with UC and CD.

Adults with IBD consider fatigue as an expected norm (Czuber-Dochan et al., 2014). The health care providers (HCPs) reported fatigue as a complex symptom and were hesitant to discuss it with adults with CD and UC. More concerning is that HCPs have a “don’t ask, don’t tell” approach for managing fatigue in adults with CD and UC (Czuber-Dochan et al., 2014). Unfortunately, the symptom experience of fatigue among those with IBD is understudied, with little research to support or treat fatigue (Bazilchuk, 2016). Analyses of the results of fatigue

between subtypes of IBD (CD vs. UC) are inconclusive. In fact, many studies found no differences in the presentations of fatigue between adults with CD and UC (Bager et al., 2012; Chavarría et al., 2019; Cohen et al., 2014; Frigstad et al., 2018; Huppertz-Hauss et al., 2017). However, some studies identified a higher prevalence of fatigue among adults with active CD than those with UC (Jelsness-Jørgensen et al., 2011a; Opheim et al., 2014; Romberg-Camps et al., 2010).

Fatigue management among individuals with UC and CD is essential given the direct (inpatient care, outpatient care, medications, and procedures) and indirect (absenteeism from work and reduced income) costs associated with fatigue symptoms (Vogelaar et al., 2011). An examination of the associated factors of fatigue in adults with UC and CD can assist in understanding fatigue, and the findings can guide the development of appropriate interventions to manage fatigue. A biopsychosocial approach to understanding fatigue is necessary due to the physiological, psychological, and social nature of fatigue; this type of approach would also prevent fragmented treatments or care that only addresses one area (Borrell-Carrió et al., 2004). Due to the varied differences in GI presentations and structural involvement of inflammation, treatment options, general symptom profiles between CD and UC, it is pivotal to examine the fatigue experiences in adults with CD and UC.

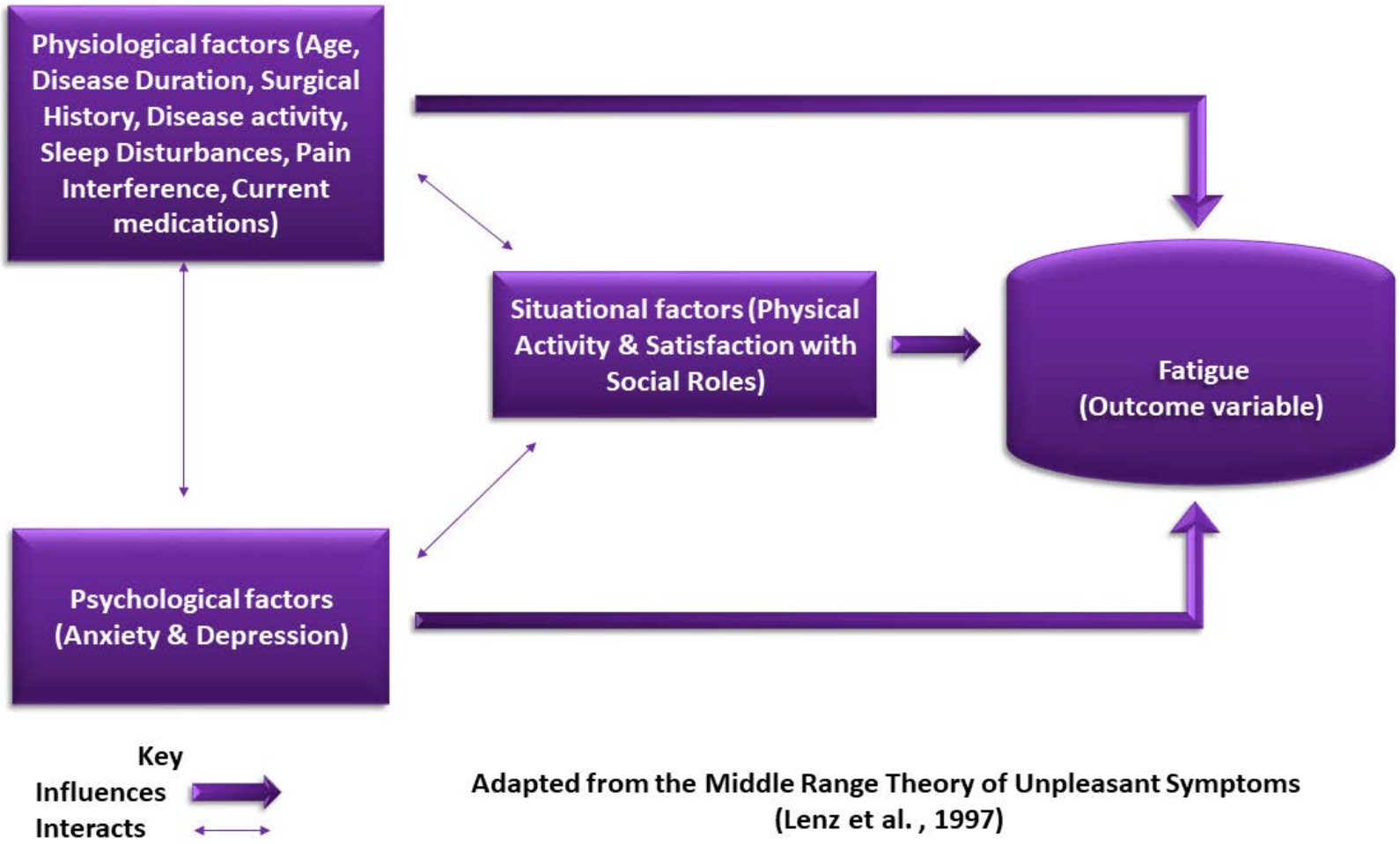
Conceptual Framework

We used the middle range theory of unpleasant symptoms (MRTOUS) to guide our study (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). The MRTOUS incorporates three major concepts: influencing factors, symptoms, and performance outcomes (Lenz et al., 1997). We examined the influencing factors and symptom of fatigue (See Figure 1). Physiological, psychological, and situational factors are the three types of influencing factors in the MRTOUS (Lenz & Pugh, 2014). Interrelationships are noted between these factors, and each of these factors can affect the

symptom experience alone or in combination with others (Lenz et al., 1997). Normal body systems, pathophysiology, and treatment-related factors are grouped under physiological factors. Psychological factors include the mental state of an individual, such as anxiety and depression. Situational factors incorporate social and physical factors, including diet and physical activity (Lenz et al., 1997). Additionally, physiological, psychological, and situational factors can act as mediators in their relationships with symptoms (Lenz & Pugh, 2014). **The following physiological factors were included in the conceptual framework of the study:** sleep disturbances; pain interference; demographic and clinical factors, including age, disease duration, surgical history, disease activity; and current medications. Anxiety and depression comprised the psychological factors, and physical activity and satisfaction with social roles (SSR) were grouped as the situational factors.

Figure 7

Conceptual Framework



Methods

We obtained cross sectional data from *IBD Partners*, an internet-based longitudinal cohort study of adults with IBD. A secondary analysis was conducted to answer the research question: Are there differences in the direct and indirect effects of physiological (age, disease duration, surgical history, disease activity, sleep disturbances, pain interference, and current medications [aminosalicylates, steroids, immunomodulators, biologics, anti-TNF α medications, and narcotics]), psychological (anxiety and depression), and situational (physical activity and satisfaction with the social roles) factors on fatigue in adults with CD and adults with UC? 'IBD Partners' was established by the Crohn's and Colitis Foundation (CCF) and the University of North Carolina at Chapel Hill (UNC-CH) and has participants from all 50 states in the United States (US). Adults with self-reported diagnoses of IBD, who were over 18 years of age and had internet access, were selected for IBD Partners (IBD Partners, n.d.).

Sample

Adults over 18 years of age with self-reported diagnoses of CD or UC were filtered from IBD Partners and included in the present study. Exclusion criteria included adults with ostomies or J pouches with IBD as there is no established criteria to assess disease activity after these surgical procedures. The data were extracted on 09-13-2019, and the final sample size included 7546 adults with CD and 4501 adults with UC.

Human Subject Protection

The study was approved by both the parent institution (UNC-CH) and East Carolina University (ECU). A data-use agreement form was completed after ECU institutional review board (IRB) approval.

Variables and Measurements

Fatigue, sleep disturbances, pain interference, anxiety, depression, and SSR were measured using the Patient Reported Outcomes Measurement Information System (PROMIS) short-form four- item scales and assessed the presence of each symptom over the past seven days (National Institute of Health [NIH], 2019). The scores of the PROMIS scales were recalibrated as a normalized *t-score* for the US general population with a mean of 50 and a standard deviation (SD) of 10 (NIH, 2019). The PROMIS responses were elicited using a 5-point Likert scale that ranged from *not at all* to *very much*. Higher scores reflected worse health outcomes in the measures of fatigue, sleep disturbances, pain interference, anxiety, and depression. For the positively worded domain of SSR, higher scores denoted better health outcomes (NIH, 2019). For the purpose of this study, we followed the recommendations of the developing team and PROMIS scores were categorized as clinically significant (score ≥ 55) and non-significant (score < 55), except for SSR (Health Measures, 2020). The SSR scores were categorized in the opposite order, with a score ≤ 55 denoting clinical significance and a score > 55 indicating non-significance.

Fatigue. The PROMIS Short Form v1.0 – Fatigue 4a was used to measure the frequency, duration, intensity, and interference of fatigue (NIH, 2019). The reliability and validity of the PROMIS fatigue scale was previously established with an acceptable value (Cella et al., 2010).

Sleep Disturbances. The PROMIS Short Form v1.0 – Sleep Disturbance 4a scale was used to assess the quality of sleep, refreshment gained after sleep, difficulty in falling asleep, and interruptions in sleep (NIH, 2019). The reliability and validity of the PROMIS sleep disturbances scale was reported previously (Cella et al., 2010).

Pain Interference. The PROMIS Short Form v1.0 – Pain Interference 4a was used to elicit the degree to which pain impeded individuals' social, recreational, and day-to-day activities

(NIH, 2019). The reliability and validity of the PROMIS pain interference scale was previously established with an acceptable score (Cella et al., 2010).

Anxiety. The PROMIS Short Form v1.0 – Anxiety 4a scale was used to assess an individual's reactions to fear, inability to focus on other matters, worries, and uneasiness (NIH, 2019). The reliability and validity of this scale was previously confirmed (Cella et al., 2010).

Depression. The PROMIS Short Form v1.0 – Depression 4a scale measured the extent of depression, helplessness, hopelessness, and worthlessness experienced by adults (NIH, 2019). The reliability and validity of this scale was confirmed previously (Cella et al., 2010).

Satisfaction with Social Roles. The PROMIS Short Form v1.0 – Satisfaction with Social Roles 4a measured the degree to which individuals were satisfied with their social roles, family responsibilities, and work responsibilities (NIH, 2019). The reliability and validity of the scale was confirmed previously Cella et al., 2010).

Physical Activity. A single question was used to measure the physical activity of the participant: How often did you participate in one or more physical activities for 20-30 minutes' duration per session during your leisure time within the past 6 months? This question was selected based on the input of participants of IBD Partners. A 6-point scale with a score range of 1 to 6 was used to measure physical activity. Because the scores from 1-4 reflected physical activities performed within a month and scores ≥ 5 reflected physical activities performed within a week, we dichotomized the scores to higher levels of physical activity (score ≥ 5) and lower levels of physical activity (score < 5). A preliminary analysis identified a moderate correlation (r_s = 0.686, p < .001) between this question and the Godin Leisure Time Activity (GLTA) index scale. We also computed a polychoric correlation, which revealed a strong correlation (r = 0.74, p < .001) between the GLTA and the physical activity question (Davis et al., 2020).

Demographic and clinical variables. The present study used the following self-reported clinical and demographic variables: age, IBD disease duration in years, history of surgical of treatment of IBD, current medications (aminosalicylates, steroids, immune modulators, biologics, anti-TNF α medications, and narcotics), and disease activity. Simple Clinical Colitis Activity Index (SCCAI) measures were used to calculate the disease activity of adults with UC (Jowett et al., 2003) and dichotomized to ≤ 2 for UC remission and > 2 for UC active. Additionally, we further stratified the SCCAI scores as remission (≤ 2), mild (3-5), moderate (6-11), and severe (≥ 12) UC disease activity per the recommendations of Walsh et al. (2014). The short Crohn's Disease Activity Index (sCDAI) scale was used to assess the disease activity of those with CD (Thia et al., 2011). The scores were dichotomized into < 150 for CD remission and ≥ 150 for CD active. We further stratified the sCDAI scores as remission (< 150), mild (150 to < 220), moderate (220-450), and severe (> 450) per the recommendations of Peyrin-Biroulet et al. (2014).

Data Analyses. Descriptive statistics were analyzed using SPSS version 24 software. We computed the proportions of PROMIS scores, physical activity, and clinical variables, including surgical history, disease activity, and current medications for the adults with CD and the adults with UC. Chi-square analyses were performed to examine the association between the dichotomized scores of the PROMIS measures and the physical activity, age, and clinical variables. Odds ratios of fatigue were analyzed using the Mantel-Haenszel common odds ratio test.

We computed the path analysis to test the conceptual framework adapted from the MRTOUS to identify the direct and indirect effects of the situational, psychological, and physiological factors on fatigue in the adults with UC and the adults with CD. All of the

PROMIS scores were normalized *t-scores* and considered as observed variables. A path analysis is appropriate for a structural model with observed variables (Wang & Wang, 2012).

The Mplus version 8 statistical software (Mplus) was used to conduct path analysis with the weighted least square mean and variance adjusted (WLSMV) estimation, which is the default estimator for computing path analysis with a categorical dependent variable in Mplus (Muthén & Muthén, 2017). The sample size met the sampling guidelines for path analysis. Significance levels were set at $p < .01$.

We conducted multicollinearity analysis using polychoric/tetrachoric correlation (see Appendix I and Appendix J) and examined the data for missing variables. All of the PROMIS measures and the physical activity variable had 100% complete data. We had less than 2% missing data of the other variables included in the path analysis. We followed several standard fit indices to compare the fit of the data with the model, including non-significant χ^2 statistics (Tabachnick & Fidell, 2013); relative goodness of fit indices, such as the Tucker-Lewis index (TLI) and the comparative fit index (CFI), in which a value close to 0.95 or higher is suggestive of adequate model fit with the data; a root mean squared error of approximation (RMSEA) in which a value < 0.05 denotes an excellent model fit; and, lastly, a standardized root mean square residual (SRMR) in which a value < 0.08 indicates adequate fit of the data to the model (Clayton & Pett, 2011; Kelloway, 2015; Tabachnick & Fidell, 2013).

Results

The majority (94%) of the participants with CD were White and nearly two thirds (73%) were female. Similar demographics were observed among the UC participants, 90% of whom were White and 70% were female (see Table 1). The mean age was 43 (SD = 15) for the participants of CD and the UC groups. The age ranges were almost identical (18-91 years for CD and 18-90 years for UC) for both groups. The average disease duration among those with CD was 14.7 years (SD = 12.65) with a range of < 1 year to 75 years. In contrast, participants with UC had a lower disease duration (M = 11.23; SD = 10.6) with a range of < 1 year to 58 years.

Table 5

Sample Characteristics

Description	CD (*n*)	CD (%)	UC(*n*)	UC(%)
Sex				
Female	5504	73	3150	70
Male	2042	27	1349	30
Age in years				
< 60	6415	85	3767	84
≥ 60	1125	15	726	16
Disease activity				
Remission	4359	58	1799	40
Active Disease	3159	42	2667	60
Disease Duration (years)				
< 10	3615	48	2673	60
≥ 10-20	1862	25	1033	23
> 20	2055	28	781	17
IBD Medications (Yes)				
Aminosalicylates	2501	33	3078	69
Biologics	3414	46	1029	23
Anti- TNF α	3247	43	957	21
Immunomodulators	2183	29	1032	23
Corticosteroids	1460	19	987	22
Narcotics	999	13	309	7

CD = Crohn's disease UC = Ulcerative Colitis TNF = Tumor Necrosis Factor

The majority of the adults with UC were taking aminosalicylates (ASA; 69%), whereas majority of the adults with CD were on biologics (46%) followed by anti-TNF α (43%). A slightly higher proportion (22%) of adults with UC were on corticosteroids than those with CD (19%). Meanwhile, 13% of the adults with CD were on narcotics compared to 7% of the adults with UC. Approximately 45% of the adults with CD had surgical procedures for IBD management, whereas only 5% of the adults with UC had surgical management for the disease. In addition, 60% of the adults with UC and 42% of the adults with CD had active disease status based on the dichotomized SCCAI and sCDAI scores, respectively. The disease activity scores of those with CD and UC greatly varied with a range of 44-628 for sCDAI and a range of 0-17

for SCCAI . We further stratified the disease activity and noted approximately 58% of the adults with UC had mild to moderate disease activity, whereas 40% of those with CD had mild to moderate disease activity (see Appendix K).

More than half of the CD (58%) and UC (52%) participants reported clinically significant fatigue ($t \geq 55$). The majority of those with CD (80%) and UC (78%) were not satisfied with their social roles (see Table 2). Equal proportions of the CD (50%) and UC (50%) participants had high anxiety scores. Over half of the CD (60%) and UC (64%) subjects were physically active.

Table 6

Descriptives of PROMIS Scores and Physical Activity Scores between UC and CD

Description	CD*(n)*	%	UC *(n)*	%
PROMIS Fatigue				
< 55	3137	42	2176	48
≥ 55	4409	58	2325	52
PROMIS Anxiety				
< 55	3797	50	2235	50
≥ 55	3749	50	2266	50
PROMIS Depression				
< 55	4508	60	2713	60
≥ 55	3038	40	1788	40
PROMIS Pain Interference				
< 55	3256	47	2377	53
≥ 55	4020	53	2124	47
PROMIS Sleep Disturbances				
< 55	4846	64	3085	68
≥ 55	2700	36	1416	32
PROMIS Satisfaction with Social Roles				
≤ 55	5966	80	3487	78
> 55	1580	21	1014	22
Physical Activity				
< 5	3021	40	1602	36
≥ 5	4525	60	2899	64

Among the adults with CD and UC who had clinically significant fatigue ($t \geq 55$), nearly equal proportions were < 60 years of old (88% of adults with CD and 87% adults with UC). The majority of the participants in the fatigued group had active disease, but the proportion was higher among adults with active UC (78%) than adults with active CD (60%). An examination of IBD medications revealed that 48% of the fatigued adults with CD were on biologics and 45% were on anti-TNF α; meanwhile, 66% of the fatigued adults with UC were on ASA. About 28% of the fatigued adults with UC were on steroids compared to 24% of the adults with CD. A comparison of the narcotics used among the fatigued participants indicated slightly higher levels of narcotic use among adults with CD (19%) than adults with UC (11%). The prevalence rates of PROMIS measures, such as anxiety, depression, pain interference, and SSR, were much higher in the fatigued group of adults with UC and CD than the non-fatigued group. The maximum burden was observed in the SSR category where 93% of the fatigued adults with CD or UC reported not being satisfied with their social roles (see Appendix L).

Associations between fatigue and other variables

Chi-square analyses revealed significant associations between physiological factors (age, disease duration, surgical history, disease activity, sleep disturbances, pain interference, and current medications [aminosalicylates, steroids, immunomodulators, biologics, anti-TNF α medications, and narcotics]), psychological factors (anxiety and depression), and situational factors (physical activity and SSR) and fatigue in adults with CD and UC except for the following physiological factors : surgical history and immunomodulators in adults with CD and surgical history, immunomodulators, biologics, and anti-TNF α in adults with UC. (see Table 3).

Table 7

Association Between Fatigue, and Physiological, Psychological and Situational Factors

Variable	χ^2 (df, N) for CD	Phi	χ^2 (df, N) for UC	Phi
Physiological Factors				
Age (< 60 & ≥ 60)	90.93** (1, 7540)	-0.11**	41.26**(1,4466)	-0.10**
Age (18-40, > 40-63 & >63)	100.94** (2, 7540)	0.12**	29.01**(1,4493)	0.08**
Disease duration (< 10, 10-20 & > 20)	32.75**(2,7532)	0.07**	29.24** (1, 4487)	0.08**
Surgical history (Yes or No)	0.001(1, 7546)	< 0.001	0.19(1,4501)	-0.007
Disease Activity (sCDAI & SCCAI Dichotomized)	1441.71**(1,7518)	0.44**	682.47** (1,4466)	0.39**
Disease Activity (remission, mild, moderate and severe categories of sCDAI & SCCAI)	1501.12**(3, 7518)	0.48**	843.95** (1,4466)	0.44**
Aminosalicylates (Yes or No)	10.59* (1,7531)	-0.04*	13.24** (1,4495)	-0.05**
Biologics (Yes or No)	19.57**(1,7502)	0.05**	4.69 (1,4466)	0.03
Anti-TNF α (Yes or No)	12.46**(1, 7502)	0.04**	1.48 (1, 4466)	0.02
Immunomodulators (Yes or No)	0.33 (1, 7506)	-0.007	1.55 (1, 4481)	0.02
Corticosteroids (Yes or No)	159.87**(1,7529)	0.15**	84.76** (1, 4494)	0.14**
Narcotics (Yes or No)	326.71** (1,7465)	0.21**	142.69**(1,4440)	0.18**
Sleep Disturbances (> 55 vs. ≥ 55)	1073.62**(1,7546)	0.38**	557.43**(1, 4501)	0.35**
Pain interference (> 55 vs. ≥ 55)	1760.27** (1, 7546)	0.48**	920.71**(1, 4501)	0.45**
Psychological Factors				
Anxiety (> 55 vs. ≥ 55)	1282.30** (1, 7546)	0.41**	647.34**(1,4501)	0.38**
Depression (> 55 vs. ≥ 55)	1337.79**(1, 7546)	0.42**	710.88**(1,4501)	0.40**
Situational Factors				
Satisfaction with Social Roles (≤ 55 vs. > 55)	1288.1**(1,7546)	0.41**	648.88**(1,4501)	0.38**
Physical activity (< 5 vs ≥ 5)	310.92** (1, 7546)	-0.20**	148.31** (1, 4501)	-0.18**

***p* < .001; **p* < .01; TNF = Tumor Necrosis Factor; sCDAI- short Crohn's Disease Activity Index; SCCAI - Simple Clinical Colitis Activity Index

The presence of fatigue significantly differed by age in both CD ($\chi^2 = 90.93$, $p < .001$) and UC ($\chi^2 = 41.26$, $p < .001$) subjects; specifically, 88% of adults < 60 years old and 46% of adults > 60 years in the CD group experienced fatigue, whereas 54% of adults < 60 years old and 41% of adults > 60 years in the UC group experienced fatigue. Additionally, the presence of fatigue differed significantly based on steroid and narcotic use in both groups; 55% of adults with CD who were not on steroids and 73% of those who were on steroids presented with fatigue ($\chi^2 = 159.87$, $p < .001$), and 48% of adults with UC who were not on steroids and 65% of those who were on steroids presented with fatigue ($\chi^2 = 84.76$, $p < .001$). A similar result was observed with narcotics; among adults with CD, 55% of those not on narcotics and 85% of those on narcotics presented with fatigue ($\chi^2 = 326.71$, $p < .001$), and, among adults with UC, 49% of those not on narcotics and 85% of those on narcotics presented with fatigue ($\chi^2 = 142.69$, $p < .001$).

Associations between physiological factors and PROMIS measures

Chi-square analyses revealed significant associations between age, disease activity, and PROMIS measures (anxiety, depression, sleep disturbances, pain interference, and SSR) and physical activity among adults with CD. A similar result was observed in the UC group except that no associations were noted between age or pain interference and physical activity. Further analysis demonstrated a consistent association between corticosteroids and narcotics and PROMIS measures (anxiety, depression, sleep disturbances, pain interference, and SSR) and physical activity in adults with CD and UC. (see Appendices M - R).

Odds analysis

We conducted the odds analyses to determine the increased risk of fatigue in adults with CD and UC. All the PROMIS scores (anxiety, depression, sleep disturbances, pain interference,

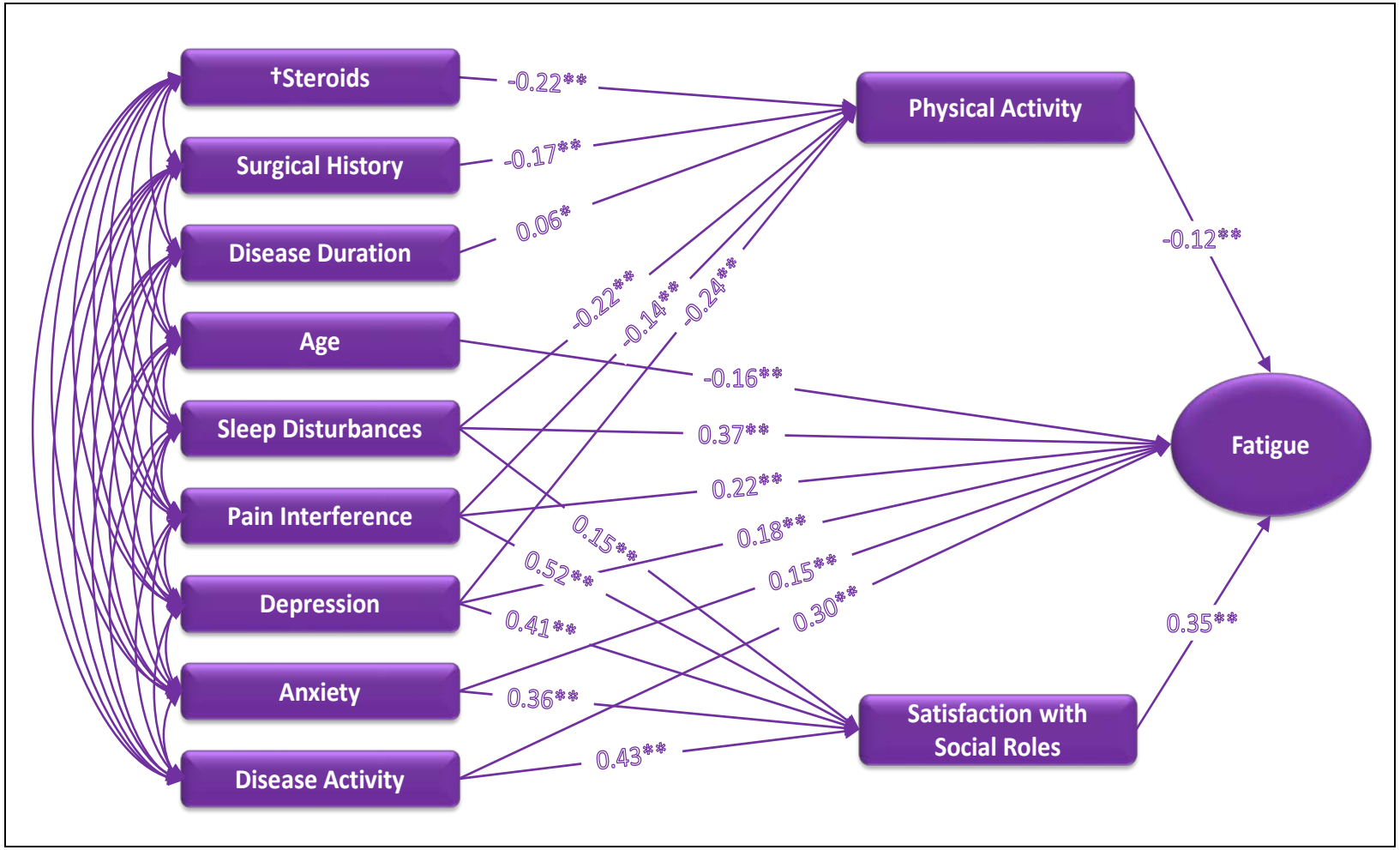
and SSR) consistently increased the likelihood of fatigue in adults with CD and UC (see Table 18 in Appendix S and Table 19 in Appendix T). Among the PROMIS measures, SSR (OR = 9.5 [8.3, 10.94], $p < .001$ for CD; OR = 8.24 [6.88, 9.86], $p < .001$ for UC) and pain interference (OR = 8.5 [7.65, 9.43], $p < .001$) for CD; OR = 7.12 [6.24, 8.12], $p < .001$ for UC) had consistently higher odds for fatigue in adults with CD and UC. Additionally, disease activity increased the odds of fatigue in adults with CD (OR = 7.73 [6.91, 8.65], $p < .001$) and adults with UC (OR = 5.43 [4.76, 6.19], $p < .001$). Among the IBD medications, the odds of clinically significant fatigue symptoms were greater for adults with CD and UC who were taking narcotics (OR = 4.65 [3.88, 5.56], $p < .001$ for CD; OR = 5.6 [4.09, 7.67], $p < .001$ for UC), steroids (OR = 2.23 [1.96, 2.53], $p < .001$ for CD; OR = 1.98 [1.71, 2.29], $p < .001$ for UC), and biologics (OR = 1.23 [1.2, 1.35], $p < .001$ for CD; OR = 1.17 [1.02, 1.34], $p < .001$ for UC).

Path Analysis Model

Three models were tested for CD and UC subjects with situational, psychological, and physiological factors as mediators. All of the initial models revealed a poor fit to the data. We trimmed the models by removing the non-significant paths and re-specified each based on the results of the modification indices. The model with situational factors as mediator best fit the data for both the CD (χ^2 (11, 7423) = 82.18, $p < 0.001$; RMSE = 0.03; CFI/TLI = 0.965/0.906; SRMR = 0.022) and UC (χ^2 (8, 4392) = 31.52, $p = .0001$; RMSE = 0.026; CFI/TLI = 0.979/0.923; SRMR = 0.019) samples. The final trimmed models with all direct effects are shown in Figure 2 and Figure 3.

Figure 8

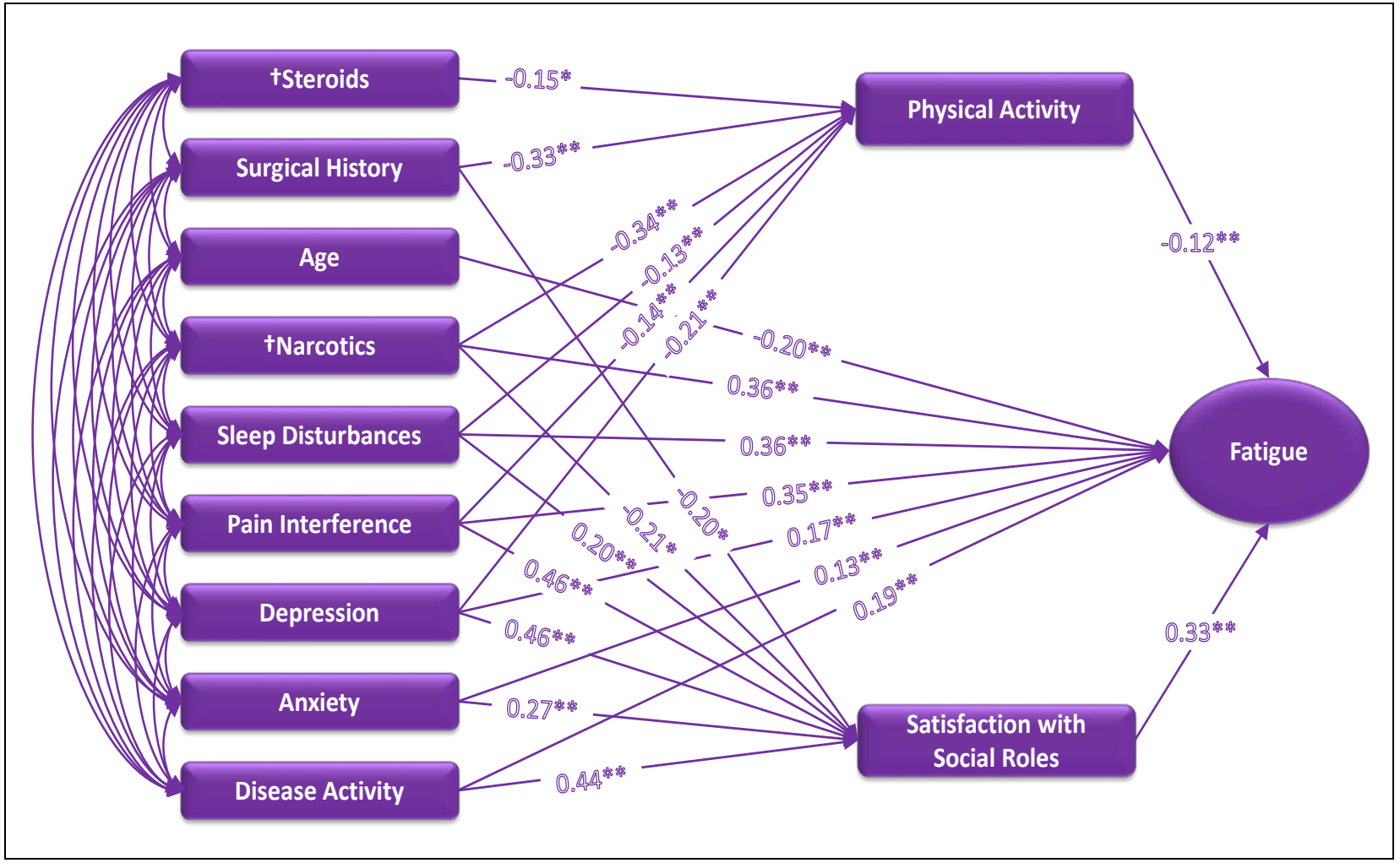
Final Trimmed Model for CD with Direct Effects



**p < .001 *p < .01 †Current Medication CD- Crohn's Disease

Figure 9

Final Trimmed Model for UC with Direct Effects



**p < .001 *p < .01 †Current Medications UC- Ulcerative Colitis

Decomposition of the models: Direct effects. All of the direct effects from the psychological factors (anxiety and depression) and the situational factors (physical activity and SSR) on fatigue in adults with CD were significant. Direct effects were only noticed from the physiological factors of disease activity, age, sleep disturbances, and pain interference on fatigue in adults with CD. The maximum direct effects on fatigue in adults with CD were from sleep disturbances (β = 0.37, 99% CI [0.29, 0.44], $p < .001$) followed by SSR (β = 0.35, 99% CI [0.30, 0.41], $p < .001$). A small direct effect noticed from disease duration to physical activity (β = 0.06, 99% CI [0.01, 0.12], $p < .01$) (see Table 4).

The direct effects of fatigue on adults with UC and those with CD were similar except that a direct effect was noticed from the current use of narcotics (β = 0.36, 99% CI [0.18, 0.56], $p < .001$) to fatigue in adults with UC. Unlike the samples with CD, an additional direct path was observed from the current use of narcotics (β = -0.34, 99% CI [-0.51, -0.14], $p < .001$) to physical activity in adults with UC. Compared to adults with CD, two additional direct paths were observed to SSR from the current use of narcotics (β = -0.21, 99% CI [-0.38, -0.02], $p < .01$) and surgical history of IBD (β = -0.20, 99% CI [-0.38, -0.03], $p < .001$) in adults with UC (see Table 5).

Table 8

Decomposition of Effects of Final CD Path Model, (N =7423)

Variables	Direct effects on fatigue β & 99% CI	Direct effects on physical activity β & 99% CI	Direct effects on satisfaction with social roles β & 99% CI	Indirect effects on fatigue via physical activity β & 99% CI	Indirect effects on fatigue via SSR β & 99% CI
Physiological Factors					
Disease Activity	0.30** [0.22, 0.38]	-	0.43** [0.33, 0.51]		0.15** [0.11, 0.18]
Age	-0.16** [-0.25, -0.08]	-	-	-	
Current use of Steroids	-	-0.22** [-0.31, -0.12]	-	0.03** [0.01, 0.05]	-
Surgical History	-	-0.17** [-0.25, -0.09]	-	0.02** [0.01, 0.03]	
Disease Duration	-	0.06* [0.01, 0.12]	-	-	
Sleep disturbances	0.37** [0.29, 0.44]	-0.22** [-0.30, -0.14]	0.15** [0.06, 0.24]	0.03** [0.01, 0.04]	0.05** [0.02, 0.09]
Pain interference	0.22** [0.19, 0.35]	-0.14** [-0.21, -0.04]	0.52** [0.43, 0.59]	0.02** [0.01, 0.03]	0.18** [0.14, 0.22]
Psychological Factors					
Anxiety	0.15** [0.06, 0.24]	-	0.36** [0.26, 0.47]	-	0.13** [0.09, 0.16]
Depression	0.18** [0.08, 0.26]	-0.24** [-0.34,- 0.15]	0.41** [0.31, 0.51]	0.03** [0.02, 0.05]	0.14** [0.10, 0.19]
Situational Factors					
Physical activity	-0.12** [-0.17, -0.09]	-	-	-	-
Satisfaction with social roles	0.35** [0.30, 0.41]	-	-	-	-

**$p < .001$; *$p < .01$; β = standardized coefficient; CI = Confidence Interval; SSR = Satisfaction with social roles; CD = Crohn's Disease

Table 9

Decomposition of Effects of Final UC Path Model (N = 4501)

Variables	Direct effects on fatigue β & 99% CI	Direct effects on physical activity β & 99% CI	Direct effects on satisfaction with social roles β & 99% CI	Indirect effects on fatigue via physical activity β & 99% CI	Indirect effects on fatigue via SSR β & 99% CI
Physiological Factors					
Disease Activity	0.19** [0.10, 0.27]	-	0.44** [0.33, 0.53]		0.15** [0.10, 0.19]
Age	-0.20** [-0.31, -0.08]	-	-	-	-
Current use of Steroids	-	-0.15* [-0.28, -0.04]	-	0.02* [0.004, 0.03]	-
Current use of Narcotics	0.36** [0.18, 0.56]	-0.34** [-0.51, -0.14]	-0.21* [-0.38, -0.02]	0.04** [0.02, 0.07]	-0.07* [-0.14, -0.005]
Surgical History	-	-0.33** [-0.51, -0.14]	-0.20* [-0.38, -0.03]	0.04** [0.01, 0.07]	-0.07* [-0.13, -0.008]
Sleep disturbances	0.36** [0.26, 0.45]	-0.13** [-0.24, -0.03]	0.20** [0.08, 0.32]	0.02* [0.003, 0.03]	0.07** [0.03, 0.11]
Pain interference	0.35** [0.24, 0.45]	-0.14** [-0.24, -0.02]	0.46** [0.35, 0.56]	0.02* [0.002, 0.04]	0.15** [0.10, 0.21]
Psychological Factors					
Anxiety	0.13** [0.03, 0.23]	-	0.27** [0.15, 0.38]	-	0.13** [0.05, 0.13]
Depression	0.17** [0.05, 0.29]	-0.21** [-0.34,- 0.08]	0.46** [0.34, 0.60]	0.03* [0.008, 0.05]	0.15** [0.11, 0.22]
Situational Factors					
Physical activity	-0.12** [-0.18, -0.06]	-	-	-	-
Satisfaction with social roles	0.33** [0.25, 0.41]	-	-	-	-

**$p < .001$; *$p < .01$; β = standardized coefficient; CI = Confidence Interval; SSR = Satisfaction with social roles; UC = Ulcerative Colitis

Decomposition of the models: Indirect effects. An indirect effect was noted on fatigue from the current use of steroids, surgical history of IBD, sleep disturbances, pain interference, and depression through physical activity in both adults with CD and UC (see Table 4 & Table 5). The evaluation of the indirect effects in the model for the adults with UC revealed an additional mediating effect from the current use of narcotics via both physical activity (β = 0.04, 95% CI [0.02, 0.06], $p < .001$) and SSR (β = -0.07, 95% CI [-0.12, -0.02], $p < .01$). Further, the mediating effect of surgical history of IBD (β = -0.07, 95% CI [-0.12, -0.02], $p < .01$) via SSR was noted (see Table 5).

Discussion

To our knowledge, our study is one of the first studies to comprehensively examine the effects of physiological, psychological, and situational factors on fatigue in adults with CD and adults with UC using a path analysis. The path model had a sound theoretical base as it was adapted from the MRTOUS. Although previously published data are available for the stratified evaluation of fatigue among adults with CD and those with UC (Opheim et al., 2014; Romberg-Camps et al., 2010), no studies have assessed the combination of physiological, psychological, and situational factors on fatigue. Furthermore, very few studies included the effects of pain interference (Jelsness-Jørgensen et al., 2017) or physical activity (Artom et al., 2017; van Langenberg & Gibson, 2014) on fatigue in their stratified evaluations of CD and UC. No studies were found that examined the effect of SSR on fatigue in adults with CD and UC.

The majority of participants (63%) in this study cohort had CD. The pooled incidence ratios of adults with CD and UC from 16 regions of North America, Europe, Australia and New Zealand revealed that the risk for CD is higher among females after 14 years of age (Shaw et al., 2018). No difference noticed in the incidence of UC between male and females till 45 years of

age. However, a statistically significant higher incidence rate of UC was noted among males after 45 years of age (Shaw et al., 2018). Our study results did not support these findings; among the male participants (n = 3391), 60% had CD and 40% had UC; among the female participants (n = 8654), 64% had CD and 36% had UC. Further stratification of age with IBD subtypes (CD vs. UC) did not reveal any distinct differences based on previously published data; majority of the male (59%) and female (64%) participants had CD in the age group of 18 to 45 years. Similar results were noted in both gender with participants who are > 45 years of age where majority of the males (60%) and females (62%) had CD. The proportion of fatigue in those with CD and UC was similar to findings by Opheim et al. (2014). Fatigue was higher ($t \geq 55$) in those with active disease (60% of the adults with CD and 78% of the adults with UC). Active disease not only had a direct effect on fatigue, but also on SSR and an indirect effect via SSR on fatigue in both groups. Although the direct effect of disease activity on SSR were similar in adults with CD and those with UC, the magnitude of the direct effect of disease activity on fatigue was higher in adults with CD ($\beta = 0.30$) than in adults with UC ($\beta = 0.19$). This finding may be due to the different pathophysiology of IBD progression in those with CD and UC. Despite the magnitude, clearly management of disease activity is paramount in affecting fatigue.

Disease flare was reported as a barrier to engaging in physical activities (Tew et al., 2016); however, our findings did not support this result as no direct effect was observed from disease activity to physical activity in subjects with both CD and UC. This finding may be related to assessing physical activity in the past month. Additionally, the nature of the treatment will be more aggressive in case of a flare to control the disease more rapidly and an individual may return to normal state of physical activity within a month after the flare. Further research is needed to examine the effect of disease activity and physical activity.

Our study results found significant associations between current IBD medications (ASA, corticosteroids, immunomodulators, biologics, anti-TNF α, and narcotics) and fatigue in adults with CD with the exception of immunomodulators. Conversely, significant associations were only noted between ASA, corticosteroids, and narcotics and fatigue in adults with UC. Additionally, biologics, corticosteroids, and narcotics significantly increased the odds of fatigue in CD and UC participants. Interestingly, anti-TNF α increased the odds of fatigue in only CD participants. These findings support previous studies indicating that IBD medication is a contributor to fatigue; specifically, previous published studies have shown that corticosteroids (Chavarría et al., 2019), anti-TNF α (Vogelaar et al., 2013), and biologics (van Langenberg & Gibson, 2014) led to fatigue in adults with CD. Additionally, the path model of adults with UC highlighted a direct path from the current use of narcotics on fatigue, physical activity, and SSR and an indirect effect on fatigue via both physical activity and SSR. This finding was supported by a previous study (Hashash et al., 2018), which found an association between narcotics and fatigue in adults with CD and adults with UC. In contrast, our study found no direct or indirect effects from narcotics to fatigue in adults with CD. This finding is interesting as only 47% adults with UC reported pain interference compared to 53% adults with CD and is consistent with another study noting the prevalence of pain is higher in adults with CD compared to adults with UC (Vegni et al., 2019). Data on the effect of narcotics on fatigue are scarce. In addition to the benefits of narcotics for pain management, more studies are recommended on the effects of narcotics on UC and CD symptoms, especially fatigue.

Contrary to previous findings (Artom et al., 2017; Chavarría et al., 2019; Long et al., 2014), we did not find a direct effect of corticosteroids on fatigue in adults with CD or UC. Corticosteroids were negatively associated with physical activity and had an indirect effect on

fatigue via physical activity in adults with CD and adults with UC. Although steroids are required to manage inflammation in both CD and UC, they can lead to side effects, such as reduced muscle mass and osteoporosis (Lee, Radford- Smith, & Taaffe, 2005; Mowat et al., 2011), which may alter physical activity levels.

Another important finding was related to the effect of surgical history of IBD on the fatigue of adults with CD and adults with UC, as supported by the final path model. Surgical history had both direct and indirect effects on physical activity among adults with CD, and in those with UC, surgical history had direct and indirect effects on both physical activity and SSR. The effect of surgical history on physical activity and SSR was negative, indicating that physical activity and SSR scores are better in the absence of surgical history. Brevinge et al. (1995) reported impaired exercise tolerance after bowel surgery and proctocolectomy in adults with CD; however, the study had a small sample size (N = 29). Additionally, the surgical procedures used at the time of Brevinge et al.'s (1995) study may not reflect current surgical practices. Conversely, another study reported no difference in exercise tolerance 12 months after surgical correction in adults with UC (Ohrstrom, Jansson, Wohlfart, Ekelund, 2004). Our findings may differ due to the lack of details on various surgical procedures. In total, only 45% of adults with CD and 5% of adults with UC had a history of surgery. Therefore, additional studies are required to explore the association between surgical history of IBD, physical activity, SSR and fatigue in adults with CD and adults with UC.

No differences were noted in the direct and indirect effects of sleep disturbances, pain interference, anxiety, and depression on SSR and fatigue in the stratified analysis between CD and UC. Sleep had the greatest direct effect on fatigue, and pain and depression had the greatest indirect effect on both those with CD and those with UC. These findings suggest the need to

consider these symptoms and their management when addressing fatigue in adults with CD and adults with UC. This holistic approach may work equally for clients with CD and UC.

The findings of the current study support the findings of Conley, Proctor, Jeon, Sandler, and Redeker (2017), who presented a high symptom burden in adults with IBD. The inflammation in CD and UC is linked to the cytokine-mediated sickness behavior with classic symptoms of fatigue, anxiety, depression, sleep disturbances and pain interference (Arnett & Clark, 2012). Because of the close association between fatigue and other symptoms, non-pharmacological or other alternative interventions may be beneficial in managing fatigue. Several non-pharmacological interventions are documented in the literature and piloted among adults with CD and UC including solution focused therapy (Vogelaar et al., 2014) and acupuncture (Horta et al., 2019) and should be explored further as an adjunct to pharmacological management. Considering the multifactorial nature of fatigue in adults with CD and adults with UC, the biopsychosocial approach recommended by Borrell-Carrió et al. (2004) is required to manage fatigue by addressing sleep disturbances, pain interference, anxiety, depression, physical activity, and SSR.

The developers of PROMIS defined SSR as how well an individual is satisfied with their social roles in life and activities (Cella et al., 2010). Previous published data which measured the SSR among adults with four chronic conditions highlighted significantly reduced levels of SSR in adults with four different chronic conditions (Multiple Sclerosis, Muscular Dystrophy, Post-Polio Syndrome, & Spinal Cord Injury) compared to US general population (Wilson, Bocell, Bamer, Salem, & Amtmann, 2019). The influence of SSR on fatigue in our study was noted in both groups. Assessing satisfaction with social roles may provide insight into fatigue in adults with UC and CD. Sleep disturbances, pain interference, depression, anxiety and disease activity

had a substantial direct effect on SSR and management of these factors may help to improve SSR and ultimately fatigue in adults with CD and UC.

Limitations

The data from IBD Partners are overrepresented with White females and may not be generalizable to other ethnic groups. Participants were recruited through Crohn's and Colitis Foundation (CCF) email rosters, the CCF website, different social media sites, and educational and fundraising events (Kappelman et al., 2013). Our results may not reflect those who were not aware of this study, without access to an internet, or those who chose not to participate as they may have reported different symptoms and experiences. The study analyzed cross-sectional data and lacked longitudinal evaluation. The lack of detail on type surgical procedures for both CD and UC is also a limitation. Finally, none of the biomarkers of inflammation were available to associate it with fatigue in adults with CD and adults with UC.

Conclusions

We evaluated the influencing factors of fatigue in adults with CD and adults with UC using a path model analysis. Although the mediating variables of the model were the same for CD and UC, we found differences in predictor variables, especially with the physiological factors. We conducted a stratified analysis of influencing factors of fatigue between CD and UC. We also explored many associations between fatigue and other physiological, psychological, and situational factors for CD and UC. Potential interventions to mitigate fatigue in adults with CD and adults with UC should consider different symptoms, physical activity, and SSR.

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APPENDIX A: NOTIFICATION OF UMCIRB APPROVAL

EAST CAROLINA UNIVERSITY
University & Medical Center Institutional Review Board
4N-64 Brody Medical Sciences Building· Mail Stop 682
600 Moye Boulevard · Greenville, NC 27834
Office **252-744-2914** · Fax **252-744-2284** ·
rede.ecu.edu/umcirb/

Not Human Subject Research Certification

From:
To: Suja Davis
CC:
Patricia Crane
Patricia Crane
Date: 9/13/2019
Re: UMCIRB 18-002456

On 9/13/2019, the IRB Chairperson (or designee) reviewed your proposed research and determined that it does not meet the federal definitions of research involving human participants, as applied by East Carolina University.

Therefore, it is with this determination that you may proceed with your research activity and no further action will be required. However, if you should want to modify your research activity, you must submit notification to the IRB before amending or altering this research activity to ensure that the proposed changes do not require additional UMCIRB review.

The UMCIRB appreciates your dedication to the ethical conduct of research. It is your responsibility to ensure that this research is being conducted in accordance with University policies and procedures, the ethical principles set forth in the Belmont Report, and the ethical standards of your profession. If you have questions or require additional information, please feel free to contact the UMCIRB office at 252-744-2914.

The Chairperson (or designee) does not have a potential for conflict of interest on this study.

IRB00000705 East Carolina U IRB #1 (Biomedical) IORG0000418
IRB00003781 East Carolina U IRB #2 (Behavioral/SS) IORG0000418

APPENDIX B: NOTIFICATION OF UNCIRB APPROVAL

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

OFFICE OF HUMAN RESEARCH ETHICS
720 Martin Luther King, Jr. Blvd.
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Federalwide Assurance (FWA) #4801

To: Robert Sandler
Department of Medicine

From: Biomedical IRB

Approval Date: 6/10/2019
Expiration Date of Approval: 6/09/2020
RE: Notice of IRB Approval by Expedited Review (under 45 CFR 46.110)
Submission Type: Renewal
Expedited Category: 7.Surveys/interviews/focus groups,5.Existing or non-research data
Study #: 10-0184

Study Title: IBD Partners: Patient Registry

This submission, Reference ID 247080, has been approved by the IRB for the period indicated.

Study Description:

The goal of this study is to create a large, diverse community of Inflammatory Bowel Disease (IBD) patients (~20,000) who can be studied to learn more about the natural history and disease course. Using Internet-based recruitment and data collection methods, the study will draw upon approximately 400,000 potential subjects from the member list maintained by the Crohn's & Colitis Foundation as well as those self selected from other Crohn's & Colitis Foundation outreach publications. Recruitment will also be done through other partner organizations such as health plans (HealthCore/Anthem and Humana) who will identify members to refer to IBD Partners.

Study Regulatory and other findings:

This research meets criteria for a waiver of written (signed) consent according to 45 CFR 46.117(c)(2).

This approval includes a limited waiver of HIPAA authorization to identify potential subjects for recruitment into this research study, as allowed under 45 CFR 164.512. This temporary waiver provides access to protected health information (PHI) to confirm eligibility and facilitate initial contact, after which consent and HIPAA authorization will be sought. Access and use is limited to the minimum amount of PHI necessary to review eligibility criteria and to contact potential subjects.

Investigator's Responsibilities:

Federal regulations require that all research be reviewed at least annually. It is the Principal Investigator's responsibility to submit for renewal and obtain approval before the expiration date. You may not continue any research activity beyond the expiration date without IRB approval. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.

If applicable, your approved consent forms and other documents are available online at http://apps.research.unc.edu/irb/index.cfm?event=home.dashboard.irbStudyManagement&irb_id=10-0184.

You are required to obtain IRB approval for any changes to any aspect of this study before they can be implemented. Any unanticipated problem involving risks to subjects or others (including adverse events reportable under UNC-Chapel Hill policy) should be reported to the IRB using the web portal at http://irbis.unc.edu.

The current data security level determination is Level III. Any changes in the data security level need to be discussed with the relevant IT official. If data security level II and III, consult with your IT official to develop a data security plan. Data security is ultimately the responsibility of the Principal Investigator.

This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), 21 CFR 50 & 56 (FDA), and 40CFR 26 (EPA), where applicable.

IRB Authorization Agreements have been executed for the UNC IRB to provide IRB review and continuing oversight for human subjects research performed for this study at the organizations identified below:

- Humana, Inc.
- Medical Outcomes Management Inc

A participating organization not included on this list may not proceed with human subjects research for this study until the UNC IRB approval for the organization is granted. Please note that approval for additional participating organizations requires a modification to the study.

CC:
Wenli Chen, Center for Gastrointestinal Biology and Disease
Joseph Galanko, Department of Medicine
Anna Hoffmeyer, Center for Gastrointestinal Biology and Disease
Michael Kappelman, Pediatrics
Alan Kaul, Center for Gastrointestinal Biology and Disease
Millie Long, Department of Medicine
Amber Robb, Center for Gastrointestinal Biology and Disease
Mano Selvan, Center for Gastrointestinal Biology and Disease
Laura Weisbein, Center for Gastrointestinal Biology and Disease

APPENDIX C: POLYCHORIC CORRELATION AMONG VARIABLES IN THE PATH MODEL

Table C1

Polychoric Correlation among Variables in the Path Model

	1	2	3	4	5	6	7	8
1.Disease Activity								
2. Age	0.10							
3. Physical Activity	0.12	0.04						
4. Anxiety	-0.45**	-0.17**	-0.13**					
5. Depression	-0.44**	-0.15**	-0.22**	0.85**				
6. Fatigue	-0.57**	-0.19**	-0.25**	0.58**	0.62**			
7. Sleep disturbances	-0.39**	-0.09**	-0.21**	0.44**	0.47**	0.58**		
8. Pain interference	-0.63**	-0.04*	-0.23**	0.52**	0.55**	0.67**	0.51**	
9. Satisfaction with Social Roles	-0.54**	-0.07**	-0.21**	0.57**	0.60**	0.65**	0.43**	0.61**

**$p < .001$; *$p < 0.01$

APPENDIX D: ASSOCIATION BETWEEN SLEEP DISTURBANCES AND PHYSIOLOGICAL, PSYCHOLOGICAL AND SITUATIONAL FACTORS

Table D1

Association Between Sleep Disturbances and Physiological, Psychological and Situational Factors

Variables	X^2 (df, N)	*P* value	Phi coefficient
Physiological Factors			
Age (< 60 & ≥ 60)	34.06 (1, 12,039)	< .001	-0.05**
Age (18-40, > 40-63 & >63)	38.26 (2, 12,039)	< .001	0.06**
Disease duration (< 10, 10-2 & > 20)	3.92 (2, 12,025)	0.141	0.02
Surgical history (Yes or No)	10.76 (1, 12,053)	0.001	0.03*
Disease Activity (Yes or No)	901.66 (1, 11,984)	< .001	-0.27**
Aminosalicylates (Yes or No)	28.37(1, 12,032)	< .001	-0.05**
Biologics (Yes or No)	26.75 (1, 11,974)	< .001	0.05**
Anti-TNF (Yes or No)	19.43 (1, 11,974)	< .001	0.04**
Immunomodulators (Yes or No)	4.43 (1, 11,993)	.035	-0.02
Corticosteroids (Yes or No)	178.58 (1, 12,029)	< .001	0.12**
Narcotics (Yes or No)	403.82 (1, 11911)	< .001	0.18**
Pain interference (> 55 vs. ≥ 55)	1267.66 (1, 12,053)	< .001	0.32**
Psychological Factors			
Anxiety (> 55 vs. ≥ 55)	978.70 (1, 12,053)	< .001	0.29**
Depression (> 55 vs. ≥ 55)	1107.10 (1, 12,053)	< .001	0.30**
Situational Factors			
Physical Activity (< 5 vs. ≥ 5)	237.88(1, 12,053)	< .001	-0.14**
Satisfaction with Social Roles (≤ 55 vs. > 55)	641.74 (1, 12,053)	< .001	0.23**

*$p < .001$ * $p < 0.01$

*

APPENDIX E: ASSOCIATION BETWEEN PAIN INTERFERENCE AND PHYSIOLOGICAL, PSYCHOLOGICAL AND SITUATIONAL FACTORS

Table E1

Association Between Pain Interference and Physiological, Psychological and Situational Factors

Variables	X^2 (df, N)	*P* value	Phi coefficient
Physiological Factors			
Age (< 60 & ≥ 60)	19.87 (1, 12,039)	< .001	-0.04**
Age (18-40, > 40-63 & >63)	39.96 (2, 12,039)	< .001	0.06**
Disease duration (< 10, 10-2 & > 20)	19.56 (2, 12,025)	< .001	0.04**
Surgical history (Yes or No)	17.17 (1, 12,053)	0.001	0.04*
Remission (Yes or No)	2779.99 (1, 11,984)	< .001	-0.49**
Aminosalicylates (Yes or No)	22.69 (1, 12,032)	< .001	-0.04**
Biologics (Yes or No)	18.92 (1, 11,974)	< .001	0.04**
Anti-TNF (Yes or No)	11.02 (1, 11,974)	.001	0.03*
Immunomodulators (Yes or No)	8.37 (1, 11,993)	.004	-0.03*
Corticosteroids (Yes or No)	472.66 (1, 12,029)	< .001	0.20**
Narcotics (Yes or No)	880.63 (1, 11911)	< .001	0.27**
Psychological Factors			
Anxiety (> 55 vs. ≥ 55)	1470.63 (1, 12,053)	< .001	0.35**
Depression (> 55 vs. ≥ 55)	1619.13 (1, 12,053)	< .001	0.37**
Situational Factors			
Physical Activity (< 5 vs. ≥ 5)	290.21(1, 12,053)	< .001	-0.16**
Satisfaction with Social Roles (≤ 55 vs. > 55)	1662.73(1, 12,053)	< .001	0.37**

**$p < .001$ *$p < .01$

APPENDIX F: ASSOCIATION BETWEEN DEPRESSION AND PHYSIOLOGICAL, PSYCHOLOGICAL AND SITUATIONAL FACTORS

Table F1

Association Between Depression and Physiological, Psychological and Situational Factors

Variables	X^2 (df, N)	*P* value	Phi coefficient
Physiological Factors			
Age (< 60 & ≥ 60)	76.75 (1, 12,039)	< .001	-0.08**
Age (18-40, > 40-63 & >63)	69.67 (2, 12,039)	< .001	0.08**
Disease duration (< 10, 10-2 & > 20)	38.54 (2, 12,025)	< .001	0.06**
Surgical history (Yes or No)	0.008 (1, 12,053)	0.930	0.001
Disease Activity (Yes or No)	1191.6 (1, 11,984)	< .001	-0.32**
Aminosalicylates (Yes or No)	8.81 (1, 12,032)	.003	-0.03*
Biologics (Yes or No)	7.39 (1, 11,974)	.007	0.03*
Anti-TNF (Yes or No)	4.61 (1, 11,974)	.032	0.02
Immunomodulators (Yes or No)	0.12 (1, 11,993)	0.729	0.003
Corticosteroids (Yes or No)	175.04 (1, 12,029)	< .001	0.12**
Narcotics (Yes or No)	354.12 (1, 11911)	< .001	0.17**
Psychological Factor			
Anxiety (> 55 vs. ≥ 55)	4907.94 (1, 12,053)	< .001	0.64**
Situational Factors			
Physical Activity (< 5 vs. ≥ 5)	268.36 (1, 12,053)	< .001	-0.15**
Satisfaction with Social Roles (≤ 55 vs. > 55)	1409.57(1, 12,053)	< .001	0.34**

*$p < .001$ * $p < .01$

APPENDIX G: ASSOCIATION BETWEEN ANXIETY AND PHYSIOLOGICAL, AND SITUATIONAL FACTORS

Table G1

Association Between Anxiety and Physiological, and Situational Factors

Variables	X^2 (df, N)	*P* value	Phi coefficient
Physiological Factors			
Age (< 60 & ≥ 60)	124.67 (1, 12,039)	< .001	-0.10**
Age (18-40, > 40-63 & >63)	140.64 (2, 12,039)	< .001	0.11**
Disease duration (< 10, 10-2 & > 20)	76.03 (2, 12,025)	< .001	0.08**
Surgical history (Yes or No)	3.87 (1, 12,053)	0.049	-0.018
Disease Activity (Yes or No)	1183.94 (1, 11,984)	< .001	-0.31**
Aminosalicylates (Yes or No)	2.4 (1, 12,032)	0.122	-0.014
Biologics (Yes or No)	0.44 (1, 11,974)	.509	0.006
Anti-TNF (Yes or No)	0.17 (1, 11,974)	.684	0.004
Immunomodulators (Yes or No)	4.06 (1, 11,993)	0.044	-0.018
Corticosteroids (Yes or No)	183.88 (1, 12,029)	< .001	0.12**
Narcotics (Yes or No)	243.33 (1, 11911)	< .001	0.14**
Situational Factors			
Physical Activity (< 5 vs. ≥ 5)	144.37 (1, 12,053)	< .001	-0.11**
Satisfaction with Social Roles (≤ 55 vs. > 55)	1440.33 (1, 12,053)	< .001	0.35**

**$p < .001$

APPENDIX H: ASSOCIATION BETWEEN SATISFACTION WITH SOCIAL ROLES AND PHYSIOLOGICAL, AND SITUATIONAL FACTORS

Table H1

Association Between Satisfaction with Social Roles and Physiological, and Situational Factors

Variables	X^2 (df, N)	*P* value	Phi coefficient
Physiological Factors			
Age (< 60 & ≥ 60)	38.1 (1, 12,039)	< .001	-0.056**
Age (18-40, > 40-63 & >63)	24.31 (2, 12,039)	< .001	0.05**
Disease duration (< 10, 10-2 & > 20)	12.63 (2, 12,025)	.002	0.03
Surgical history (Yes or No)	6.42 (1, 12,053)	.011	0.02
Disease Activity (Yes or No)	1203.01 (1, 11,984)	< .001	-0.32**
Aminosalicylates (Yes or No)	4.5 (1, 12,032)	.034	-0.02
Biologics (Yes or No)	7.7 (1, 11,974)	.006	0.025*
Anti-TNF (Yes or No)	3.1 (1, 11,974)	.078	0.016
Immunomodulators (Yes or No)	1.72 (1, 11,993)	.189	0.012
Corticosteroids (Yes or No)	189.87 (1, 12,029)	< .001	0.13**
Narcotics (Yes or No)	187.22 (1, 11911)	< .001	0.13**
Situational Factor			
Physical Activity (<5 & ≥ 5)	345.40 (1, 12,053)	< .001	-0.17**

**$p < .001$ *$p < .01$

APPENDIX I: ASSOCIATION BETWEEN PHYSICAL ACTIVITY AND PHYSIOLOGICAL FACTORS

Table II

Association Between Physical Activity and Physiological Factors

Variables	X^2 (df, N)	*P* value	Phi coefficient
Age (< 60 & ≥ 60)	8.72 (1, 12,039)	.003	0.03*
Age (18-40, > 40-63 & >63)	4.23 (2, 12,039)	0.121	0.02
Disease duration (< 10, 10-2 & > 20)	2.75 (2, 12,025)	.252	0.015
Surgical history (Yes or No)	27.99 (1, 12,053)	< .001	-0.048**
Disease Activity (Yes or No)	301.79 (1, 11,984)	< .001	0.16**
Aminosalicylates (Yes or No)	24.55 (1, 12,032)	< .001	0.045**
Biologics (Yes or No)	13.37 (1, 11,974)	< .001	-0.033**
Anti-TNF (Yes or No)	12.52 (1, 11,974)	< .001	0.03**
Immunomodulators (Yes or No)	0.62 (1, 11,993)	.432	-0.007
Corticosteroids (Yes or No)	63.41 (1, 12,029)	< .001	-0.073**
Narcotics (Yes or No)	129.29 (1, 11911)	< .001	-0.104**

APPENDIX J: ODDS ANALYSIS REPORT OF PREDICTORS OF FATIGUE

Table J1

Odds Analysis Report of Predictors of Fatigue

Variables	χ^2	Phi Coefficient	OR	99% CI for OR	P Value
Age (< 60 & ≥ 60)	133.92	-0.11	0.56	[0.50, 0.62]	< .001
Surgical History (Yes or No)	8.33	0.03	1.12	[1.04,1.22]	.004
Disease duration (≤ 20 & >20)	39.83	-0.06	0.76	[0.70, 0.83]	< .001
Disease Activity (active or inactive)	1935.68	-0.40	0.17	[0.16, 0.19]	< .001
Current use of Aminosalicylates (Yes or No)	49.46	-0.06	0.77	[0.72,0.83]	< .001
Current use of Biologics (Yes or No)	40.69	0.06	1.28	[1.18,1.38]	< .001
Current use of anti –TNF-α (Yes or No)	26.36	0.05	1.22	[1.13, 1.32]	< .001
Current use of Immunomodulators (Yes or No)	0.57	0.007	1.03	[0.95,1.12]	0.45
Current use of Steroids (Yes or No)	235.42	0.14	2.08	[1.9, 2.29]	< .001
Current use of Narcotics (Yes or No)	491.29	0.20	5.02	[4.23, 5.86]	< .001
Anxiety (> 55 vs. ≥ 55)	1913.55	0.40	5.51	[5.09, 5.96]	< .001
Depression (> 55 vs. ≥ 55)	2039.90	0.41	6.56	[6.02, 7.15]	< .001
Sleep Disturbances (> 55 vs. ≥ 55)	1646.06	0.37	5.87	[5.36, 6.42]	< .001
Pain Interference (> 55 vs. ≥ 55)	2702.92	0.47	8	[7.37, 8.69]	< .001
Satisfaction with Social Roles (≤ 55 vs. > 55)	1932.92	0.40	9.01	[8.08, 10.04]	< .001
Physical Activity (< 5 vs. ≥ 5)	468.41	-20	0.43	[0.40, 0.46]	< .001

OR = Odds Ratio CI = Confidence Interval TNF = Tumor Necrosis Factor

APPENDIX K: POLYCHORIC CORRELATION AMONG VARIABLES IN THE PATH MODEL OF ADULTS WITH CD

Table K1

Polychoric Correlation among Variables in the Path Model of Adults with CD

	1	2	3	4	5	6	7	8	9	10	11
1. Steroids											
2. Surgical History	0.02										
3. Age	-0.09*	0.21*									
4. Disease Duration	-0.10*	0.44*	0.45*								
5. Physical Activity	-0.20*	-0.10*	0.10*	0.07*							
6. Disease Activity	0.30*	0.01	-0.11*	0.03	-0.17*						
7. Anxiety	0.19*	-0.04	-0.20*	-0.12*	-0.17*	0.46*					
8. Depression	0.22*	-0.01	-0.15*	-0.08	-0.24*	0.46*	0.84*				
9. Fatigue	0.25*	-0.01	-0.19*	-0.08	-0.29*	0.63*	0.60*	0.63*			
10. Sleep Disturbances	0.21*	0.02	-0.10*	-0.04	-0.24*	0.41*	0.45*	0.48*	0.59*		
11. Pain Interferences	0.34*	0.02	-0.08	-0.07	-0.24*	0.68*	0.52*	0.56*	0.68*	0.52*	
12. Satisfaction with Social Roles	0.18*	0.01	-0.10	-0.006	-0.25*	0.58*	0.59*	0.62*	0.67*	0.42*	0.64*

*$p < .01$

APPENDIX L: POLYCHORIC CORRELATION AMONG VARIABLES IN THE PATH MODEL OF ADULTS WITH CD

Table L1

Polychoric Correlation among Variables in the Path Model of Adults with CD

	1	2	3	4	5	6	7	8	9	10	11
1. Steroids											
2. Narcotics	0.23*										
3. Surgical History	0.01	0.29*									
4. Age	-0.05	-0.02	0.14*								
5. Physical Activity	-0.14*	-0.18*	0.13*	0.01							
6. Disease Activity	0.17*	0.06	-0.10*	-0.06	-0.11*						
7. Anxiety	0.14*	0.11*	0.008	-0.08	-0.10*	0.30*					
8. Depression	0.14*	0.13*	0.04	-0.08	-0.16*	0.29*	0.64*				
9. Fatigue	0.17*	0.24*	-0.004	-0.12*	-0.27*	0.44*	0.47*	0.47*			
10. Sleep Disturbances	0.13*	0.17*	0.04	-0.04	-0.14*	0.24*	0.27*	0.29*	0.43*		
11. Pain Interferences	0.18*	0.18*	0.04	-0.006	-0.16*	0.44*	0.34*	0.36*	0.51*	0.30*	
12. Satisfaction with Social Roles	0.16*	0.04	0.06	-0.08	-0.19*	0.45*	0.45*	0.49*	0.62*	0.32*	0.47*

*$p < .01$

APPENDIX M: DISEASE ACTIVITY DETAILS

Table M1

Disease Activity Details

Disease Activity Description	*n*	%
Adults with CD		
Remission (sCDAI < 150)	4359	58
Mild (sCDAI 150 - < 220)	1609	21
Moderate (sCDAI 220-450)	1424	19
Severe (sCDAI > 450)	126	2
Adults with UC		
Remission (SCCAI ≤ 2)	1799	40
Mild (SCCAI 3-5)	1611	36
Moderate (SCCAI 6-11)	974	22
Severe (SCCAI ≥ 12)	82	2

CD – Crohn's Disease UC – Ulcerative Colitis

sCDAI- short Crohn's Disease Activity Index; SCCAI - Simple Clinical Colitis Activity Index

APPENDIX N: SAMPLE CHARACTERISTICS OF FATIGUED ADULTS (T ≥ 55) WITH CD AND UC

Table N1

Sample Characteristics of Fatigued Adults (t ≥ 55) with CD and UC

Description	CD (*n*)	CD (%)	UC(*n*)	UC(%)
Age in years				
< 60	3984	88	2026	87
≥ 60	512	12	296	13
Disease activity				
Remission	1745	40	501	22
Active Disease	2646	60	1805	78
Disease Duration (years)				
< 10	2211	50	1459	63
≥ 10-20	1094	25	515	22
> 20	1097	25	343	15
Surgical history of IBD				
Yes	1979	45	112	5
IBD Medications (Yes)				
Aminosalicylates	1396	32	1532	66
Biologics	2090	48	562	24
Anti- TNF α	1973	45	511	22
Immunomodulators	1265	29	550	24
Corticosteroids	1067	24	637	28
Narcotics	847	19	261	11
Anxiety *((t ≥ 55)*	2957	67	1597	69
Depression *(t ≥ 55)*	2543	58	1361	59
Sleep Disturbances *(t ≥ 55)*	2250	51	1099	47
Pain Interference *(t ≥ 55)*	3245	74	1605	69
Satisfaction with social roles *(t ≤ 55)*	4111	93	2158	93
Physical activity (<5)	2135	48	1023	44

CD = Crohn's disease UC = Ulcerative Colitis TNF = Tumor Necrosis Factor

APPENDIX O: ASSOCIATION BETWEEN SLEEP DISTURBANCES AND PHYSIOLOGICAL, PSYCHOLOGICAL AND SITUATIONAL FACTORS

Table O1

Association Between Sleep Disturbances and Physiological, Psychological and Situational Factors

Variable	χ^2 (df, N) for CD	Phi	χ^2 (df, N) for UC	Phi
Physiological Factors				
Age (< 60 & ≥ 60)	22.63** (1, 7540)	-0.06**	10.61*(1,4493)	-0.05*
Age (18-40, > 40-63 & >63)	30.71** (2, 7540)	0.07**	7.93(1,4493)	0.04
Disease duration (< 10, 10-20 & > 20)	3.53(2,7532)	0.02	4.97(1, 4487)	0.03
Surgical history (Yes or No)	1.004(1, 7546)	-0.02	1.71 (1,4501)	0.02
Disease Activity (sCDAI for CD & SCCAI for UC Dichotomized)	669.15**(1,7518)	0.30**	314.61** (1,4466)	0.27**
Disease Activity (remission, mild, moderate and severe categories of sCDAI for CD & SCCAI for UC)	820.43**(3, 7518)	0.33**	468.26** (1,4466)	0.32**
Aminosalicylates (Yes or No)	2.84 (1,7531)	-0.02	17.73** (1,4495)	-0.06**
Biologics (Yes or No)	12.98**(1,7502)	0.04**	4.34 (1,4466)	0.03
Anti-TNF α (Yes or No)	8.28*(1, 7502)	0.03*	3.20 (1, 4466)	0.03
Immunomodulators (Yes or No)	4.86 (1, 7506)	-0.03	1.24 (1, 4481)	-0.02
Corticosteroids (Yes or No)	103.86**(1,7529)	0.12**	80.92** (1, 4494)	0.13**
Narcotics (Yes or No)	266.79** (1,7465)	0.19**	122.19**(1,4440)	0.17**
Pain interference (> 55 vs. ≥ 55)	833.01** (1, 7546)	0.33**	422.84**(1, 4501)	0.31**
Psychological Factors				
Anxiety (> 55 vs. ≥ 55)	647.03** (1, 7546)	0.30**	335.07**(1,4501)	0.27**
Depression (> 55 vs. ≥ 55)	733.27**(1, 7546)	0.31**	373.22**(1,4501)	0.29**
Situational Factors				
Satisfaction with Social Roles (≤ 55 vs. > 55)	415.47**(1,7546)	-0.15**	224.49**(1,4501)	0.22**
Physical activity (< 5 vs ≥ 5)	171.35** (1, 7546)	-0.15**	63.67** (1, 4501)	-0.12**

**p < .001; *p < .01; TNF = Tumor Necrosis Factor; sCDAI- short Crohn's Disease Activity Index; SCCAI - Simple Clinical Colitis Activity Index

APPENDIX P: ASSOCIATION BETWEEN PAIN INTERFERENCES AND PHYSIOLOGICAL, PSYCHOLOGICAL AND SITUATIONAL FACTORS

Table P1

Association Between Pain Interferences and Physiological, Psychological and Situational Factors

Variable	χ^2 (df, N) for CD	Phi	χ^2 (df, N) for UC	Phi
Physiological Factors				
Age (< 60 & ≥ 60)	23.78** (1, 7540)	-0.06**	.74 (1,4493)	-0.01
Age (18-40, > 40-63 & >63)	50.88** (2, 7540)	0.08**	1.29(1,4493)	0.02
Disease duration (< 10, 10-20 & > 20)	21.42**(2,7532)	0.05**	6.66(1, 4487)	0.04
Surgical history (Yes or No)	0.43(1, 7546)	0.008	8.97* (1,4501)	0.05*
Disease Activity (sCDAI for CD & SCCAI for UC Dichotomized)	2028.6**(1,7518)	0.52**	975.2** (1,4466)	0.47**
Disease Activity (remission, mild, moderate and severe categories of sCDAI for CD & SCCAI for UC)	2114.99**(3, 7518)	0.53**	1138.42** (1,4466)	0.51**
Aminosalicylates (Yes or No)	0.84 (1,7531)	-0.01	8.97* (1,4495)	0.05*
Biologics (Yes or No)	7.14*(1,7502)	0.03*	1.63 (1,4466)	0.02
Anti-TNF α (Yes or No)	3.75*(1, 7502)	0.02*	0.25 (1, 4466)	0.007
Immunomodulators (Yes or No)	7.78* (1, 7506)	-0.03*	3.61 (1, 4481)	-0.03
Corticosteroids (Yes or No)	291.42**(1,7529)	0.20**	191.19** (1, 4494)	0.20**
Narcotics (Yes or No)	608.07** (1,7465)	0.29**	247.91**(1,4440)	0.17**
Psychological Factors				
Anxiety (> 55 vs. ≥ 55)	946.80** (1, 7546)	0.35**	533.23**(1,4501)	0.34**
Depression (> 55 vs. ≥ 55)	1031.22**(1, 7546)	0.37**	593.5**(1,4501)	0.36**
Situational Factors				
Satisfaction with Social Roles (≤ 55 vs. > 55)	1145.09**(1,7546)	0.39**	524.70**(1,4501)	0.34**
Physical activity (< 5 vs ≥ 5)	184.72** (1, 7546)	-0.16**	97.11** (1, 4501)	-0.15**

**p < .001; *p < .01; TNF = Tumor Necrosis Factor; sCDAI- short Crohn's Disease Activity Index; SCCAI - Simple Clinical Colitis Activity Index

APPENDIX Q: ASSOCIATION BETWEEN ANXIETY AND PHYSIOLOGICAL, PSYCHOLOGICAL AND SITUATIONAL FACTORS

Table Q1

Association Between Anxiety and Physiological, Psychological and Situational Factors

Variable	χ^2 (df, N) for CD	Phi	χ^2 (df, N) for UC	Phi
Physiological Factors				
Age (< 60 & ≥ 60)	101.8** (1, 7540)	-0.12**	27.48** (1,4493)	-0.08**
Age (18-40, > 40-63 & >63)	107.23** (2, 7540)	0.12**	37.82**(1,4493)	0.09**
Disease duration (< 10, 10-20 & > 20)	53.33**(2,7532)	0.08**	23.32**(1, 4487)	0.07**
Surgical history (Yes or No)	4.78(1, 7546)	-0.03	0.62 (1,4501)	0.01
Disease Activity (sCDAI for CD & SCCAI for UC Dichotomized)	777.97**(1,7518)	0.32**	433.32** (1,4466)	0.31**
Disease Activity (remission, mild, moderate and severe categories of sCDAI for CD & SCCAI for UC)	837.45**(3, 7518)	0.33**	531.93** (1,4466)	0.35**
Aminosalicylates (Yes or No)	0.27 (1,7531)	-0.006	5.62 (1,4495)	-0.04
Biologics (Yes or No)	0.03 (1,7502)	0.002	1.49 (1,4466)	0.02
Anti-TNF α (Yes or No)	0.10 (1, 7502)	0.004	0.29 (1, 4466)	0.008
Immunomodulators (Yes or No)	7.05* (1, 7506)	-0.03*	0.10 (1, 4481)	0.005
Corticosteroids (Yes or No)	90.91**(1,7529)	0.11**	93.85** (1, 4494)	0.15**
Narcotics (Yes or No)	184.50** (1,7465)	0.16**	62.09**(1,4440)	0.12**
Psychological Factors				
Depression (> 55 vs. ≥ 55)	3010.24**(1, 7546)	0.63**	1896.68**(1,4501)	0.65**
Situational Factors				
Satisfaction with Social Roles (≤ 55 vs. > 55)	940.61**(1,7546)	0.35**	503.64**(1,4501)	0.34**
Physical activity (< 5 vs ≥ 5)	105.04** (1, 7546)	-0.12**	41.52** (1, 4501)	-0.10**

**p < .001; *p < .01; TNF = Tumor Necrosis Factor; sCDAI- short Crohn's Disease Activity Index; SCCAI - Simple Clinical Colitis Activity Index

APPENDIX R: ASSOCIATION BETWEEN DEPRESSION AND PHYSIOLOGICAL, AND SITUATIONAL FACTORS

Table R1

Association Between Depression and Physiological, and Situational Factors

Variable	χ^2 (df, N) for CD	Phi	χ^2 (df, N) for UC	Phi
Physiological Factors				
Age (< 60 & ≥ 60)	43.42** (1, 7540)	-0.08**	33.07** (1,4493)	-0.09**
Age (18-40, > 40-63 & >63)	37.83** (2, 7540)	0.07**	35.34**(1,4493)	0.09**
Disease duration (< 10, 10-20 & > 20)	19.72**(2,7532)	0.05**	22.16**(1, 4487)	0.07**
Surgical history (Yes or No)	0.44(1, 7546)	-0.008	2.14 (1,4501)	0.02
Disease Activity (sCDAI for CD & SCCAI for UC Dichotomized)	791.85**(1,7518)	0.33**	443.77** (1,4466)	0.32**
Disease Activity (remission, mild, moderate and severe categories of sCDAI for CD & SCCAI for UC)	914.30**(3, 7518)	0.35**	592.34** (1,4466)	0.36**
Aminosalicylates (Yes or No)	2.75 (1,7531)	-0.019	6.99* (1,4495)	-0.04*
Biologics (Yes or No)	6.29 (1,7502)	0.03	0.95 (1,4466)	0.02
Anti-TNF α (Yes or No)	5.03 (1, 7502)	0.03	0.09 (1, 4466)	0.004
Immunomodulators (Yes or No)	0 (1, 7506)	0	0.24 (1, 4481)	0.007
Corticosteroids (Yes or No)	100.94**(1,7529)	0.12**	74.77** (1, 4494)	0.13**
Narcotics (Yes or No)	280.46** (1,7465)	0.19**	74.99**(1,4440)	0.13**
Situational Factors				
Satisfaction with Social Roles (≤ 55 vs. > 55)	876.29**(1,7546)	0.34**	533.59**(1,4501)	0.34**
Physical activity (< 5 vs ≥ 5)	188.72** (1, 7546)	-0.16**	81.17** (1, 4501)	-0.13**

**p < .001; *p < .01; TNF = Tumor Necrosis Factor; sCDAI- short Crohn's Disease Activity Index; SCCAI - Simple Clinical Colitis Activity Index

APPENDIX S: ASSOCIATION BETWEEN SATISFACTION WITH SOCIAL ROLES AND PHYSIOLOGICAL, AND SITUATIONAL FACTORS

Table S1

Association Between Satisfaction with Social Roles and Physiological, and Situational Factors

Variable	χ^2 (df, N) for CD	Phi	χ^2 (df, N) for UC	Phi
Physiological Factors				
Age (< 60 & ≥ 60)	26.18** (1, 7540)	-0.06**	11.85* (1,4493)	-0.05*
Age (18-40, > 40-63 & >63)	28.38** (2, 7540)	0.06**	2.32 (1,4493)	0.02
Disease duration (< 10, 10-20 & > 20)	4.07**(2,7532)	0.02**	18.04**(1, 4487)	0.06**
Surgical history (Yes or No)	3.39(1, 7546)	0.02	0.14 (1,4501)	0.005
Disease Activity (sCDAI for CD & SCCAI for UC Dichotomized)	716.46**(1,7518)	0.31**	553.75** (1,4466)	0.35**
Disease Activity (remission, mild, moderate and severe categories of sCDAI for CD & SCCAI for UC)	729.24**(3, 7518)	0.35**	589.74** (1,4466)	0.36**
Aminosalicylates (Yes or No)	0.25 (1,7531)	0.006	9.6* (1,4495)	-0.05*
Biologics (Yes or No)	2.08 (1,7502)	0.02	4.69 (1,4466)	0.03
Anti-TNF α (Yes or No)	0.33 (1, 7502)	0.007	2.52 (1, 4466)	0.02
Immunomodulators (Yes or No)	0.06 (1, 7506)	0.003	2.84 (1, 4481)	0.03
Corticosteroids (Yes or No)	97.23**(1,7529)	0.11**	97.76** (1, 4494)	0.15**
Narcotics (Yes or No)	137.55** (1,7465)	0.14**	47.38**(1,4440)	0.10**
Situational Factors				
Physical activity (< 5 vs ≥ 5)	244.07** (1, 7546)	-0.18**	101.05** (1, 4501)	-0.15**

**p < .001; *p < .01; TNF = Tumor Necrosis Factor; sCDAI- short Crohn's Disease Activity Index; SCCAI - Simple Clinical Colitis Activity Index

APPENDIX T: ASSOCIATION BETWEEN PHYSICAL ACTIVITY AND PHYSIOLOGICAL FACTORS

Table T1

Association Between Physical Activity and Physiological factors

Variable	χ^2 (df, N) for CD	Phi	χ^2 (df, N) for UC	Phi
Physiological Factors				
Age (< 60 & ≥ 60)	7.79* (1, 7540)	0.03*	1.1 (1,4493)	0.02
Age (18-40, > 40-63 & >63)	7.6 (2, 7540)	0.03	0.21 (1,4493)	0.007
Disease duration (< 10, 10-20 & > 20)	1.13(2,7532)	0.01	5.35(1, 4487)	0.04
Surgical history (Yes or No)	12.1*(1, 7546)	-0.04*	0.91 (1, 4501)	-0.01
Disease Activity (sCDAI for CD & SCCAI for UC Dichotomized)	229.30**(1,7518)	-0.18**	112.86** (1,4466)	-0.16**
Disease Activity (remission, mild, moderate and severe categories of sCDAI for CD & SCCAI for UC)	273.05**(3, 7518)	0.19**	143.51** (1, 4466)	0.18**
Aminosalicylates (Yes or No)	5.57 (1,7531)	0.03	7.53* (1, 4495)	0.04*
Biologics (Yes or No)	4.6 (1,7502)	-0.03	2.34 (1, 4466)	-0.02
Anti-TNF α (Yes or No)	4.2 (1, 7502)	-0.02	2.52 (1, 4466)	-0.02
Immunomodulators (Yes or No)	0.15 (1, 7506)	0.005	1.96 (1, 4481)	-0.02
Corticosteroids (Yes or No)	46.27**(1,7529)	-0.08**	19.75** (1, 4494)	-0.07**
Narcotics (Yes or No)	103.81** (1,7465)	-0.12**	18.08**(1,4440)	-0.06**

**$p < .001$; *$p < .01$; TNF = Tumor Necrosis Factor; sCDAI- short Crohn's Disease Activity Index; SCCAI - Simple Clinical Colitis Activity Index

APPENDIX U: ODDS ANALYSIS REPORT OF PREDICTORS OF FATIGUE IN ADULTS WITH CD

Table U1

Odds Analysis Report of Predictors of Fatigue in Adults with CD

Variables	χ^2	Phi Coefficient	OR	99% CI for OR	P Value
Age (< 60 & ≥ 60)	90.93	-0.11	0.54	[0.48, 0.61]	< .001
Surgical History (Yes or No)	0.001	< .001	1.0	[0.91,1.1]	.979
Disease duration (≤ 20 & >20)	29.81	-0.06	0.75	[0.68, 0.83]	< .001
Disease Activity (sCDAI <150 or sCDAI ≥150)	1441.71	0.44	7.73	[6.91, 8.65]	< .001
Current use of Aminosalicylates (Yes or No)	10.59	-0.04	0.85	[0.77,0.94]	< .01
Current use of Biologics (Yes or No)	19.57	0.05	1.23	[1.12,1.35]	< .001
Current use of anti –TNF-α (Yes or No)	12.46	0.04	1.18	[1.07, 1.30]	< .001
Current use of Immunomodulators (Yes or No)	0.33	-0.007	0.97	[0.88,1.07]	0.56
Current use of Steroids (Yes or No)	159.87	0.15	2.23	[1.96, 2.53]	< .001
Current use of Narcotics (Yes or No)	326.71	0.21	4.65	[3.88, 5.56]	< .001
Anxiety (> 55 vs. ≥ 55)	1282.30	0.41	6.03	[5.44, 6.68]	< .001
Depression (> 55 vs. ≥ 55)	1337.79	0.42	7.27	[6.50, 8.15]	< .001
Sleep Disturbances (> 55 vs. ≥ 55)	1073.62	0.38	6.22	[5.54, 6.98]	< .001
Pain Interference (> 55 vs. ≥ 55)	1760.27	0.48	8.5	[7.65, 9.43]	< .001
Satisfaction with Social Roles (≤ 55 vs. > 55)	1288.1	0.41	9.53	[8.3, 10.94]	< .001
Physical Activity (< 5 vs. ≥ 5)	310.92	-0.20	0.42	[0.38, 0.46]	< .001

OR = Odds Ratio CI = Confidence Interval TNF = Tumor Necrosis Factor

APPENDIX V: ODDS ANALYSIS REPORT OF PREDICTORS OF FATIGUE IN ADULTS WITH UC

Table V1

Odds Analysis Report of Predictors of Fatigue in Adults with UC

Variables	χ^2	Phi Coefficient	OR	99% CI for OR	P Value
Age (< 60 & ≥ 60)	41.27	-0.10	0.59	[0.50, 0.70]	< .001
Surgical History (Yes or No)	0.19	-0.007	0.94	[0.72,1.23]	.661
Disease duration (≤ 20 & >20)	22.57	-0.07	0.69	[0.59, 0.80]	< .001
Disease Activity (SCCAI ≤ 2or SCCAI > 2)	682.47	0.39	5.43	[4.76, 6.19]	< .001
Current use of Aminosalicylates (Yes or No)	13.24	-0.05	0.79	[0.70,0.90]	< .001
Current use of Biologics (Yes or No)	4.69	0.03	1.17	[1.02,1.34]	< .001
Current use of anti –TNF-α (Yes or No)	1.48	0.02	1.09	[0.95, 1.26]	0.225
Current use of Immunomodulators (Yes or No)	1.55	0.02	1.09	[0.95,1.26]	0.213
Current use of Steroids (Yes or No)	84.76	0.14	1.98	[1.71, 2.29]	< .001
Current use of Narcotics (Yes or No)	142.69	0.18	5.6	[4.09, 7.67]	< .001
Anxiety (> 55 vs. ≥ 55)	647.34	0.38	4.94	[4.36, 5.6]	< .001
Depression (> 55 vs. ≥ 55)	710.88	0.40	5.78	[5.06, 6.61]	< .001
Sleep Disturbances (> 55 vs. ≥ 55)	557.43	0.35	5.26	[4.55, 6.03]	< .001
Pain Interference (> 55 vs. ≥ 55)	920.71	0.45	7.12	[6.24, 8.12]	< .001
Satisfaction with Social Roles (≤ 55 vs. > 55)	648.88	0.38	8.24	[6.88, 9.86]	< .001
Physical Activity (< 5 vs. ≥ 5)	148.31	-0.18	0.46	[0.40, 0.52]	< .001

OR = Odds Ratio CI = Confidence Interval TNF = Tumor Necrosis Factor