Dissecting the complex interaction between inflammatory bowel disease and sleep

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Thesis

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Contents

List of Tables

List of Figures

Abbreviations

AMHC	Active mental health condition
BMI	Body Mass Index
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CI	Confidence interval
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
CS	Cohort study
ESS	Epworth Sleepiness Scale
DSS	Dextran sodium sulfate
FACIT	Functional Assessment of Chronic Illness Therapy
HBI	Harvey–Bradshaw Index
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IMID	Immune-mediated inflammatory diseases
ISI	Insomnia Severity Index
MET	Metabolic equivalent of task
MRI	Magnetic resonance imaging
NREM	Non-rapid eye movement
OR	Odds ratio
OSA	Obstructive sleep apnoea
PRISMA	Preferred Reporting Item for Systematic Reviews and Meta-analyses
PROMIS	Patient-reported Outcomes Measurement Information System
PSQI	Pittsburgh Sleep Quality Index
QoL	Quality of life
REM	Rapid eye movement
SCCAI	Simple Clinical Colitis Activity Index
SD	Standard deviation
SEM	Structural equation modelling
SF	Short form
UC	Ulcerative colitis
UK	United Kingdom

US	United States
WASO	Wake after sleep onset

Abstract

Introduction

Inflammatory bowel disease (IBD) is a group of chronic relapsing-remitting autoimmune condition(s) that involves a complex interplay of genetic and environmental factors. Sleep is likely to be impaired by symptoms of active IBD, and IBD-related pro-inflammatory cytokines may also influence sleep quality. Chronic sleep insufficiency, such as through sleep deprivation or obstructive sleep apnoea, has been linked to several adverse health outcomes including cardiovascular disease and worse all-cause mortality. Despite this, little is understood about the relationship between IBD activity and sleep quality, or the relationship between sleep quality and outcomes in IBD such as poor mental health, fatigue and quality of life (QoL).

Aims

The aims of this thesis were to:

1. Determine the presence and significance of the effect of IBD activity on sleep quality.

2. Determine whether there are relationships between sleep in IBD and mental health conditions and/or other patient-reported outcomes such as fatigue and QoL.

Methods

Systematic reviews and meta-analyses were conducted examining available data on IBD activity and sleep quality, prevalence of poor sleep in IBD and sleep quality in inactive IBD. A prospective observational study was conducted to determine the relationship between objective sleep quality—in the form of polysomnography—and objective IBD activity, assessed by endoscopy, magnetic resonance imaging or faecal calprotectin. A cross-sectional study explored the relationship between sleep, mental health conditions, fatigue and QoL in people with IBD. A structural equation modelling approach was used to understand the relationship between sleep and fatigue and other factors. A latent profile analysis was undertaken to identify latent profiles of fatigue.

Results

The pooled prevalence of poor sleep in people with IBD was 56%. Examination of objective sleep quality via polysomnography demonstrated shorter sleep duration in objectively active IBD than remission. A further meta-analysis found that sleep quality in people with IBD in

remission was worse than healthy controls. Use of opioids was associated with worse sleep quality—as was infliximab (a TNF-α inhibitor)—although the relationship with infliximab was confounded by weight. In people with IBD, insomnia was associated with abdominal pain, IBD activity and depression and anxiety.

Sleep quality was associated with worse QoL with this effect independent of the influence of mental health conditions or IBD activity. The magnitude of reduction in QoL seen with insomnia was similar to that seen with active IBD. Worse IBD-related disability was seen in people with concurrent insomnia.

A structural equation model of fatigue suggests that sleep is a mediating variable for other factors, and showed that depression was a high-value target for intervention. Latent profile analysis of fatigue identified four profiles of fatigue, with one profile defined by poor mental health and little to no significant depression or anxiety seen outside of this profile.

Conclusions

Objective sleep quality is worse in objectively active IBD than in remission. Sleep quality, typically not assessed in IBD clinics, is associated with reduced QoL and should be considered part of routine clinical care, especially in those in remission. Depression represents a high-value treatment target in fatigue and should be considered in any presentation of fatigue. Further research should consider determining the role of IBD-related pro-inflammatory cytokines in sleep quality and the longitudinal significance of objectively measured sleep quality.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of Flinders University.

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List of Publications

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List of Abstracts

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Barnes A, Mountifield R. Influence of inflammatory bowel disease activity on fatigue in Crohn's disease is mediated via sleep and depression. Australian Gastroenterology Week, Sept 2023, Brisbane, Australia.

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CHAPTER 1: INTRODUCTION

Inflammatory bowel disease

Definitions

Inflammatory bowel disease (IBD) is a term that encompasses two chronic inflammatory disorders known as Crohn's disease (CD) and ulcerative colitis (UC). UC is a disease characterised by chronic inflammation in the mucosa of the large bowel that involves the rectum; it spreads proximally and continuously through the large bowel and lacks the presence of granulomas on histology.[1] CD is differentiated from UC in that it may affect any portion of the gastrointestinal (GI) tract from the mouth to the anus, although it most commonly involves the terminal ileal region of the small bowel.[1] It is a chronic inflammatory condition that typically—although not exclusively—consists of granulomatous inflammation on histology specimens.[1] A third condition, IBD-unclassified, is used in reference to patients in whom it is not possible to definitively differentiate between CD and UC.[1] A further term, inflammatory bowel disease unclassified (IBD-U), is used to refer to a histology specimen from the large bowel in which differentiating between UC and CD is not possible.[1]

Pathogenesis

The pathogenesis of IBD remains poorly understood.[2,3] It is referred to as complex, multifactorial and involving genetics, immune dysregulation, the microbiome and the environment.[3,4] Some have gone so far as to create the term 'the interactome' to describe the association between all these factors.[5] There is also the concept the 'exposome', which includes environmental factors that may induce or exacerbate IBD,[6] including air pollution, stress, food additives and lifestyle. The use of these broad terms and the inclusion of factors from genetics to the environment indicates how poorly understood is the aetiology of this disorder.

Microbiome changes have been described in people with IBD yet this may be secondary to underlying immune dysfunction.[7-10] No single microbe has been consistently associated with IBD. Animal models of IBD have demonstrated that luminal bacteria are required for the development of colitis.[11] Many studies have suggested that IBD is due to a dysregulated immune response to the luminal microbiome. This dysregulation of the immune system has been described in a variety of forms including defects in epithelial barrier function[12,13];

recruitment, proliferation and activation of numerous different types of immune cells[14,15]; and elevated pro-inflammatory cytokines and chemokines.[16]

Epidemiology

IBD prevalence has been globally increasing over time with substantial variation among geographic regions.[17] The prevalence of IBD appears to be lower in less well-developed countries and it appears to increase with industrialisation.[18,19] As with other immune-mediated inflammatory diseases (IMID) there appears to be a higher rate of IBD as distance from the equator increases.[20]

IBD may develop at any age; however studies have shown a bimodal age distribution with typical age of onset between 15 and 30 years, with a second peak between 50 and 80 years of age.[21,22] Sex-related differences are slight with some studies suggesting a higher rate of UC in men[23] and a higher rate of adult onset CD in women.[24] There appear to be significant differences in ethnicity, with IBD much more common in ethnically Jewish populations[25] and a low incidence observed in black African populations.[26] Immigrant studies from Denmark are of some interest with the risk of IBD lower in first-generation immigrants in Denmark but no difference in IBD risk seen between second-generation immigrants to Denmark and natives.[27] These findings support a possible role for genetic differences as well as environmental factors in the development of IBD.

Epidemiological studies have highlighted several lifestyle factors that are associated with IBD. Smoking is known to be a risk factor for the development of CD[28] and increases the risk of complications from the condition.[29,30] Smoking may lower the risk of UC,[31] and people with UC who cease smoking have an increased risk of active disease and hospitalisation.[28] The differences in association between smoking and IBD subtypes are not well understood.[32]

The relationship between physical activity and IBD differs by IBD subtype. Physical activity appears to reduce both the risk of CD[33] and disease activity in people with CD;[34] however no such relationship is seen in UC.[33]

Dietary factors likely also play a significant role in IBD, with several associations identified. Dietary fibre from fruit and vegetables is associated with a decreased risk of CD but not UC.[35] Dietary fat—in particular animal fats—is associated with increased risk of both UC and CD.[36,37] Vitamin D is also significant, with deficiency associated with an increased risk of CD.[38]

Certain medications have been associated with the onset of IBD or exacerbation of IBD. These are as follows: antibiotic use associated with increased risk of CD but not UC[39], NSAIDs may exacerbate IBD[40], oral contraceptives may confer a small increased risk of developing IBD[41], isotretinoin has been associated with the development of IBD on a case report level[42], and more recently monoclonal antibodies to IL-17 have been associated with the development of IBD[43].

Findings are mixed on the association between appendicectomy and UC, with the weight of evidence now suggesting that appendicectomy may be associated with a decreased risk of UC.[44,45] Results also remain indeterminate regarding the relationship between appendicectomy and CD.[46]. Breast feeding has been associated with a decreased risk of developing CD and UC.[47] Sleep has been investigated as a potential causative and exacerbating factor in people with IBD. This is discussed in further detail in a later section.

Genetics

IBD is a polygenic disorder with particular genes being neither necessary nor sufficient to cause IBD. Its genetic basis remains poorly understood. IBD follows a non-Mendelian pattern of inheritance. In one study, the concordance rate for monozygotic twins was 50% in CD and 19% in UC.[48] Immediate relatives of a person with IBD are more likely to develop IBD (3–20-fold increased risk).[48] The risk increases further if both parents have IBD, although the child remains still likely to not develop IBD.[49] There is also some heritability in clinical features in CD with concordance between disease site and disease behaviour observed.[50,51] There is also some support for genetic anticipation in CD.[52]

Genome-wide association studies have identified over 300 genetic susceptibility loci for IBD, with most shared between CD and UC.[53,54] Some studies have related IBD disease location to polygenic risk score; for example.[55] Genetic variation also appears to influence prognosis, with certain genotypes associated with extensive disease.[56] The identified genetic loci contribute to several pathways, including intracellular innate immune pathways,[55] the autophagy pathway,[57] regulation of adaptive immunity[58] and regulation of epithelial function.[59]

Genetic syndromes have also been identified in association with IBD. Several specific genetic disorders have been identified that produce very early-onset IBD that presents in infancy.[60] Recognised genetic syndromes associated with an increased incidence of IBD

include Turner syndrome,[61] Hermansky–Pudlak syndrome[62] and glycogen storage disease type 1b.[63]

Clinical presentation

UC will typically present with symptoms that include bloody diarrhoea, urgency and pre-defecation colic. The presentation of CD varies according to disease location and severity; typically this involves diarrhoea, abdominal pain and weight loss. The numerous extra-intestinal manifestations of IBD include inflammatory arthropathy; ocular manifestations such as scleritis and iritis; skin manifestations such as pyoderma gangrenosum; hepatobiliary manifestations such as primary sclerosing cholangitis; increased venous and arterial thrombosis risk; autoimmune haemolytic anaemia; and pulmonary complications such as serositis and airway inflammation.

Assessing IBD activity

IBD activity can be defined in a number of ways. The assessment of IBD activity incorporates symptoms and signs, along with biochemical and stool-based markers and endoscopic, imaging and histological evidence of active inflammation.[1]

Subjective disease activity is based on patient-reported factors, now commonly referred to as 'PROs'. These include reported number of bowel actions, presence of blood, abdominal pain and extra-intestinal manifestations.[64] Various composite scores have been developed, the more common being the Crohn's Disease Activity Index(CDAI)[65] and the Partial Mayo Score.[66] Although CDAI does use some objective data, such as haematocrit and body weight, the score is largely driven by the PRO component, with the partial mayo score completely on PROs. The interpretation of this subjective disease activity is somewhat confounded by the high proportion of people with IBD who experience gut symptoms related to underlying irritable bowel syndrome (IBS).[67]

Objective disease activity refers to the presence of 'verifiable' evidence of inflammatory activity, with tissue damage or consequences thereof. This objective evidence includes biochemical markers such as C-reactive protein; stool markers such as faecal calprotectin; evidence of inflammation on endoscopic investigations and histology; and evidence of inflammation seen on imaging such as magnetic resonance imaging (MRI) enterography. IBD activity scores have been developed to describe the degree of IBD activity. For example, the severity of IBD activity on colonoscopy can be described using the Ulcerative Colitis Index

of Severity[68] and a simple endoscopic score for CD.[69] Histological activity scores do exist but are not widely used.

Fatigue in IBD

Fatigue is defined as 'subjective perception of lack of energy unrelieved by rest and unrelated to activity, impairing a person's function in life, often accompanied by emotional lability and decreased cognitive ability'.[70] Fatigue is common in IBD with a pooled prevalence of 47%.[71] Fatigue has been associated with IBD activity with estimates of fatigue in >80% of those with active IBD.[72] The prevalence of fatigue in IBD in remission is understandably lower, but remains substantial at 41%.[72] Fatigue in IBD has been shown to impact quality of life (QoL), psychosocial function and degree of work impairment.[73-76] Fatigue ranks highly among disease-related concerns of people with IBD.[77]

The aetiology of fatigue in IBD is complex and multifactorial. Various theories relate to inflammatory cytokines, micronutrient deficiencies, medications, microbiome dysregulation and anaemia.[78,79] More recently, studies in other inflammatory disease and CD have shown functional brain changes on MRI consistent with those seen in people with fatigue, suggesting perhaps a neurochemical basis to fatigue.[80-82]

Factors found to be associated with fatigue have been inconsistent across studies and include female gender, depression, anxiety, sleep disruption, pain, psychological distress and iron deficiency.[83-85] The trajectory of fatigue in IBD has also been investigated with IBD activity and psychosocial factors found to be important in the remission state.[86] Treatment algorithms have been proposed for fatigue that consider addressing IBD activity in the first instance and then other possible aetiologies in isolation.[78,79] The lack of consistent associations with fatigue across studies suggests that there may be different subtypes of fatigue.[79]

Quality of life in IBD

People with IBD often report impaired health-related QoL.[87] Determinants of health-related QoL include IBD activity, hospitalisation, corticosteroid treatment, anaemia, presence of extra-intestinal manifestations, pain, sleep quality and psychological illness.[88-90] Differences in QoL between CD and UC have not been consistently observed.[91] Meaning in life and body acceptance by others were associated with higher QoL.[92]

Treatment of IBD with medication or surgery has been shown to improve health-related QoL.[93-95] Of interest, entering remission may result in normalisation or near-normalisation of

QoL for the majority with UC.[96] However, in many studies, a proportion of people with IBD have continued to have poor QoL despite achieving remission.[93]

Quality of life is generally measured via questionnaire or survey. A disease-specific measure of health-related QoL—the Inflammatory Bowel Disease Questionnaire (IBDQ)—has been developed, with a short form subsequently released.[97,98] Other widely utilised instruments include the EQ-5D-5L[99]—which measures health-related QoL—which has been validated in IBD populations[100] and mapped to the IBDQ[101]. It has been used in a number of other disease states, making comparison possible. The 36-item short form survey (SF-36) has also been used in IBD cohorts.[102]

Sleep

The importance of sleep

Sleep is a phenomenon observed in all animals in some form, with humans spending around one-third of their life in this state.[103] The purpose of sleep is not well understood; however, the deleterious effects of sleep deprivation are well documented. Sleep deprivation has been associated with adverse health effects including cardiovascular morbidity[104] and metabolic syndrome,[105] car and occupational accidents[106,107], decreased quality of life and economic consequences such as lower productivity and greater health care utilisation.[108] Sleep may be important for learning and neuroplasticity[109]; an important part of brain metabolism; and has been observed to have a clearance function and an overall restorative function.[110]

Sleep is characterised by well-defined stages: rapid eye movement (REM) and non-REM (NREM) sleep. NREM stages are termed N1, N2 and slow-wave sleep, with a REM stage termed R.[111] Sleep follows a cyclical pattern and starts in NREM sleep; it proceeds through stage N1 to N2, to slow-wave sleep and then onto REM sleep.[111] Each cycle typically lasts around 90 minutes and continues through the night. The proportion of REM sleep in each cycle increases over the course of the night. [111] The NREM stages and REM sleep are characterised based on electromyography and electroencephalography findings.[111]

Sleep disorders

Sleep disorders are broadly classified into seven categories: insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep–wake disorders, parasomnias, sleep-related movement disorders and other sleep disorders.[112] Insomnia consists of chronic insomnia disorder—specifying a duration of symptoms of at least three months—short-term insomnia disorder and other insomnia disorders.[112] Sleep-related

breathing disorders are divided into central sleep apnoea syndromes, obstructive sleep apnoea (OSA) disorders, sleep-related hypoventilation disorders and sleep-related hypoxaemia disorders.[112] Central disorders of hypersomnolence include narcolepsy among other disorders of hypersomnolence.[112] Sleep-related movement disorders include restless leg syndrome among others.[112]

Measurement of sleep

Sleep can be measured in a variety of ways. Self or physician administered, validated questionnaires such as the Pittsburgh Sleep Quality Index (PSQI)[113] can be used to obtain a patient-reported measure of sleep. Actigraphy is a validated measure of sleep that utilises a device, typically an accelerometer, that is worn on the patient's wrist and measures sleep parameters and motor activity.[114] Actigraphy is more accurate than patient-reported sleep measures and can be performed in the patient's home; consequently it has greater external validity than laboratory sleep measurement.[115] Polysomnography can be laboratory or home based and consists of the recording of multiple variables during sleep, using tools such as electrocardiogram; electromyography to capture muscle movement; electroencephalography to capture brain activity; electrooculogram to capture eye movement; respiratory airflow channels to identify apnoeas or hypoapnoeas; pulse oximetry monitoring; respiratory effort channels to measure movement of chest and abdomen; and sometimes video monitoring.[111,116] Variables of interest in polysomnography are described in Table 1.1.

Table 1.1: Definition of objective sleep quality parameters from actigraphy and polysomnography.

Sleep quality variable	**Definition**
Sleep duration	Total number of minutes of sleep
Sleep latency	Time from going to bed to onset of sleep
Sleep efficiency	The portion of time asleep divided by time in bed
Time awake after sleep onset	Duration of any time awake after sleep onset
REM *	Duration of rapid eye movement sleep
N1*	Duration of stage 1 of sleep
N2*	Duration of stage 2 of sleep
Slow-wave sleep*	Duration of slow-wave sleep

*indicates only available from polysomnography.

CHAPTER 2: LITERATURE REVIEW

Sleep and inflammation

The interaction between sleep and the immune system is complex and incompletely understood.[117] Sleep deprivation has been demonstrated to lead to an increase in pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α ,[118] mediated through activation of the NF-kB pathway.[119] Administration of IL-1 and TNF results in increased time spent in NREM, and inhibition of these cytokines inhibits spontaneous sleep.[120] Administration of IL-6 results in increased subjective fatigue and suppression of REM sleep.[121] Many other cytokines have also been implicated in sleep regulation, including IL-2, IL-4, IL-10, IL-13, IL-15, IL-18 and interferon, although these are less well studied.[117] A meta-analysis of studies incorporating markers of inflammation and measurement of sleep showed an association between elevated markers of inflammation, sleep disturbance and long sleep duration.[122] Sleep deprivation has also been associated with a decreased antibody response to vaccination.[123,124] Infection with various pathogens has been associated with changes in sleep quality.[125-127] Sleep deprivation may confer susceptibility to viral infection.[128]

Sleep disruption has been observed in chronic inflammatory disorders such as rheumatoid arthritis,[129] systemic lupus erythematosus[130] and ankylosing spondylitis.[131] This association has been attributed to the increase in inflammatory cytokines seen with sleep deprivation. Improvement in sleep quality has been seen with the introduction of medications targeting TNF-α in these disease populations.[132-134]

Sleep and the gastrointestinal tract

The relationship between sleep disorders and the gastrointestinal (GI) tract has not been well studied. In gastro-oesophageal reflux disease, sleep disruption is common and associated with increased perception of acid reflux into the oesophagus.[135,136] Sleep apnoea has been associated with an increased risk of peptic ulcer-related bleeding and gastro-oesophageal reflux disease.[137,138]

Disordered gastric acid production suppression has been demonstrated in people with duodenal ulcers and disordered sleep.[139] Sleep disruption is common in functional GI disorders such as IBS[140] and functional dyspepsia.[141] Shorter sleep duration has been associated with the presence of adenomas on colonoscopy and colorectal cancer.[142,143]

Changes in the gut microbiome have been associated with OSA and circadian dysfunction.[144,145]

IBD and sleep

Studies investigating the significance of sleep in IBD can be classified in a variety of ways. Herein we choose to classify them as those related to animal models or those in humans. This is then further classified according to objectivity of sleep assessment. Sleep can be measured subjectively such as validated survey instruments or more objectively through forms such as actigraphy or polysomnography that will be discussed further. The literature so far has focussed on associations between subjective measurements of sleep and subjective IBD activity and has also considered longitudinal outcomes in a minority of studies.

Sleep in animal models of IBD

There has been exploration of the effect of sleep deprivation in animal models of IBD (see Table 2.1). These studies all used the dextran sodium sulfate (DSS) colitis mouse model of IBD. Sleep deprivation is induced through various effects including enforced movement and a water bath. The seminal work of Tang et al[146] considered both acute and chronic sleep deprivation in 36 mice with DSS colitis, divided into groups of 12 with a control group, acute sleep deprivation group and chronic sleep deprivation group. Severity was measured using a clinical index, histology, shortening of the colon and myeloperoxidase activity in colonic tissue as a marker of neutrophil activity. The acute sleep deprivation group had worse colonic inflammation and myeloperoxidase activity than did controls, but no clinical difference and no difference in colonic length. Amara et al[147] examined the effect of circadian disruption rather than sleep deprivation and found a similar result with worsening of DSS colitis.

Other studies in this area have focussed on melatonin as a potential therapeutic agent. Melatonin administration appears to result in clinical improvement and prolonged survival in mice with DSS colitis, with this result reproduced in three studies.[148-150] There have been efforts to understand how this is mediated, with colonic adiponectin mirroring melatonin and gut microbiome effects also apparent following melatonin administration.[151,152]

Studies in animal models have provided some indication that sleep may be important as an exacerbating factor in IBD and that treating this sleep disturbance may improve outcomes in IBD.

Table 2.1: Studies of animal models of IBD undergoing sleep deprivation.

First author	Year	Country	Population	Sample size	Comparator/Intervention	Main outcome
Tang[146]	2009	United States	Mice with DSS-induced colitis	36	Acute sleep deprivation and chronic intermittent sleep deprivation	Acute and chronic sleep deprivation exacerbates DSS colitis with worse clinical and histological findings.
Chung[148]	2013	South Korea	Mice with DSS-induced colitis	30	Sleep deprivation Melatonin injection	Sleep deprivation aggravates colitis in mice and melatonin improves colitis in mice.
Park[149]	2015	South Korea	Mice with DSS-induced colitis	24	Sleep deprivation Melatonin injection	Sleep deprivation aggravates colitis in mice. Melatonin reduced weight loss and prolonged survival in mice with colitis induced by sleep deprivation.
Kim[150]	2016	South Korea	Mice with DSS-induced colitis Control group	30	Sleep deprivation Melatonin injection Sleep deprivation and melatonin injection	Melatonin improved colitis, and improved sleep deprivation exacerbated colitis. Adiponectin expression in colonic tissue was correlated with melatonin effects.
Amara[147]	2019	Lebanon	Mice with DSS-induced colitis.	60	Circadian shifts for three months	Circadian disruption aggravates DSS-induced colitis, with corresponding faecal calprotectin.

Sleep quality in people with IBD

Sleep quality in people with IBD is commonly measured via subjective approaches. This approach utilises a survey-administered, validated measure of sleep quality—the most common being the Pittsburgh Sleep Quality Index.[113] The largest study comes from an internet-based survey from a large United States (US) IBD cohort that used Patient-reported Outcomes Measurement Information System (PROMIS-SD) scores.[153] Incorporating over 10,000 responses it reported a prevalence of sleep disturbance of 58% (based on a PROMIS-SD *t* score > 50). Sleep quality in IBD has also been inconsistently associated with psychosocial factors such as depression[154-161] and reduced physical activity.[162,163] The prevalence of poor sleep in IBD is considered further in a subsequent chapter with a systematic review and meta-analysis.

The association between IBD medications and sleep was investigated in two studies that reported an association with corticosteroids,[161,164] although this finding was not replicated in other studies.[154,165-168] No association between sleep quality and TNF-α inhibitors such as infliximab was observed. In those with active UC, treatment with vedolizumab demonstrated an improvement in sleep quality along with mood and disease activity.[158] The study also included an arm that received anti-TNF; unfortunately, because of the loss to follow-up rate (>70%) this study component did not provide any useful results.

Longitudinal studies in this area have suggested that sleep quality may be prognostic in CD with an association with risk of active IBD at six months[161]and risk of hospitalisation or surgery.[169] This was not observed in those with UC.

A retrospective analysis was conducted through the Nurses Health Study and suggested an increased risk of UC in those with fewer than six hours or more than nine hours of sleep per day. No association was seen with CD.[170] Night shift work was not associated with IBD.

Objectively measured sleep quality

Studies incorporating people with IBD have assessed sleep objectively using polysomnography and actigraphy (see Table 2.2). Control groups were included in several studies and sleep quality was worse in people with IBD than controls.[167,171-173] These studies were limited by their small sample sizes. Studies incorporating polysomnography have shown inconsistent differences relative to control populations, reporting at times decreased sleep efficiency; increased time awake after sleep; sleep fragmentation; longer REM latency; increased numbers of microarousal; and no objective difference in some.[171-175] This may in

part relate to differences in the choice of control populations and differences in aspects of IBD populations that may also influence sleep quality, such as depression, age or gender.

Table 2.2: Objective sleep studies involving IBD populations.

Study	**Study population**	**Sleep assessment**	**Summary**
Bar-gil Shitrit[171] et al 2018	IBD 36 Controls 27	Polysomnography	Light sleep and REM latency were longer in the IBD group.
Bazin[176] et al 2019	IBD 34	Actigraphy—7 days	Sleep efficiency is lower in active CD than in remission.
Beilman[174] et al 2020	IBD 15 Inactive disease	Polysomnography	Sleep fragmentation is present in IBD with inactive disease.
Conley[177] et al 2020	IBD 27	Actigraphy—10 days	Rest-associated activity rhythms are disrupted in IBD.
Iskandar[167] et al 2020	IBD 61 Controls 60	Actigraphy—7 days	Self-reported poor sleep was not confirmed by objective sleep measures.
Keefer[172] et al 2006	IBD 16 IBS 9 Controls 7	Polysomnography	The IBD and IBS groups were similar on most sleep parameters.
Qazi[178] et al 2019	IBD 50	Actigraphy—7 days	IBD activity was associated with objectively disturbed sleep.
Zhang[173] et al 2020	IBD 120 Controls 120	Polysomnography	Sleep quality of IBD patients was worse than control group.
Van Langenberg[163] et al 2015	CD 49 Controls 30	Actigraphy	People with CD exhibited poorer sleep quality and less sleep activity than controls.
Salwen-Deremer[175] 2023	IBD 15 Controls 8	Polysomnography	People with IBD exhibited a greater number of microarousals than healthy controls.

Small-scale actigraphy studies have suggested poorer sleep quality in people with IBD compared to controls; however no difference was seen in the largest actigraphy study conducted (n = 60) despite subjectively reporting worse sleep.[163,167,176,177,179] These studies incorporated wrist actigraphy rather than polysomnography, which has reduced accuracy in assessing wakefulness in bed compared with polysomnography, leading to potential underassessment of parameters such as sleep latency and sleep efficiency, which have been established as differing between IBD and controls in other polysomnography studies.[180]

It could be suggested that the cause of the differences seen in polysomnography may relate to symptoms experienced by people with IBD—such as pain—that may disrupt sleep. Studies incorporating objective sleep assessment uniformly incorporated subjective assessment of IBD activity, with none incorporating objective assessment of IBD activity.

Sleep disorders in IBD

Preliminary research has been undertaken to determine the prevalence of specific sleep disorders in people with IBD. Two studies have considered the distribution of sleep disorders in an IBD population, with insomnia and sleep apnoea most common.

Scott et al[181] utilised a web-based survey and included a control group using the Sleep-50 questionnaire[182]—a validated measure of symptoms of several sleep disorders. The IBD group reported higher symptom severity related to sleep apnoea, insomnia, narcolepsy and restless leg syndrome but not circadian dysfunction. This is of course not the same as a higher rate of diagnosis of any of these sleep disorders, and may well misattribute symptoms.

Salwen-Deremer et al[183] similarly used a web-based survey of an IBD cohort including separate validated questionnaires to assess for the risk or likelihood of a diagnosis of OSA, insomnia, circadian dysfunction—specifically evening chronotype and restless leg syndrome—as well as assessing overall sleep quality. Half of the cohort (50%) met criteria for insomnia order, with 22.9% at high risk for sleep apnoea. There was considerable cross-over between sleep disorders, with over a quarter of the cohort meeting criteria for two sleep disorders. These results were limited by a response rate of 15% that was predominantly female—typical for the method of survey administration.

OSA has been demonstrated to be more common in people with IBD, based on US-wide diagnostic coding[184] and similarly seen in a United Kingdom (UK) study using an online screening questionnaire.[185] Upper airway obstruction due to CD leading to OSA has been reported but is exceedingly uncommon.[186,187] Elevated pro-inflammatory cytokines, such as

TNF-α, are present in both IBD and OSA, at levels correlated with the severity of the obstruction.[188] Interestingly, anti-TNF-α therapy has been associated with improved sleepiness in obese patients with OSA.[189] We also note the microbiome changes seen in people with OSA and their potential relevance to the pathogenesis of IBD.[120]

Insomnia—perhaps the most common sleep disorder in IBD—may be due to the symptoms of active IBD—such as nocturnal diarrhoea and abdominal pain—that interfere with sleep. This sleep pattern persists following resolution of these symptoms, leading to conditioned insomnia.[190] Furthermore, insomnia is associated with depression and anxiety,[191] both of which are known to be prevalent in people with IBD.[192] Chronic pain may also be relevant; it is commonly seen in people with insomnia[193] and also in IBD.[194]

The prevalence of restless leg syndrome in IBD cohorts ranges from 8 to 20%; it is perhaps more common in CD.[195-197] Nutritional deficiencies such as iron deficiency are common in people with IBD and known to cause restless leg syndrome.[198] Restless leg syndrome has been associated with worse health-related QoL in people with IBD.[199]

Sleep quality and IBD activity

Two meta-analyses have considered the relationship between sleep quality and IBD activity in terms of objectivity of measurement of sleep quality or IBD activity. Ballesio et al demonstrated poorer sleep quality in remission than in active IBD, but did not find any significant difference in objective sleep quality in those with subjectively active IBD.[200] This was an extension of previous work performed by Hao et al that suggested an association between subjective IBD activity and objectively measured sleep efficiency.[201]

To investigate this further, our own systematic review and meta-analysis considered sleep quality and IBD activity.

This work has been submitted to the journal BMJ open, February 2024.

[Manuscript]A systematic review and meta-analysis of inflammatory bowel disease activity and sleep quality

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Data availability statement

The data underlying this article are available in the Harvard Dataverse Digital Repository at https://doi.org/10.7910/DVN/44KYPX

Abstract

Background

Poor sleep quality has been associated with active inflammatory bowel disease (IBD) in several studies. This review examines sleep quality in people with active IBD and in those in remission, via a meta-analysis that considers subjective and objective sleep quality and IBD activity.

Methods

Electronic databases were searched for publications from inception to 1 December 2020. Effect sizes were estimated to examine the association between sleep quality and IBD activity using a random effects model. Separate meta-analyses were performed for objective and subjective sleep and IBD activity, considering sleep quality in active and inactive IBD.

Results

Nineteen studies were included in the qualitative review, representing 4,972 IBD patients. Subjective IBD activity was associated with subjective poor sleep quality with pooled odds ratio (OR) of 3.04 (95% confidence interval [CI] 2.41–3.83). Sleep efficiency was lower in those self-reporting active IBD and time awake post sleep onset was higher in those with active disease with acceptable heterogeneity. Objective IBD activity was associated with subjective poor sleep, with pooled OR of 6.64 (95% CI 3.02–14.59). Insufficient data were available to consider objective IBD activity and objective sleep quality.

Conclusion

IBD activity is associated with poor sleep using subjective and objective measures of sleep quality. This manifests as decreased sleep efficiency and increased number of waking episodes post sleep onset. This may be due to IBD symptoms; however emerging data suggest sleep quality remains poor in those with sub-clinical inflammation. The relationship between objective IBD activity and sleep requires further investigation.

Keywords: sleep, inflammatory bowel disease, meta-analysis

Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing-remitting immune-mediated disorder that involves a complex interplay of genetic and environmental factors.[202] Epidemiological studies have shown an increasing incidence of IBD over the past several decades[203] with strong associations seen with environmental factors.[204] The aetiology and exacerbating factors are largely unknown, with known associations including active smoking, urban living, appendectomy and low vitamin D levels.[204] IBD can be associated with debilitating extra-intestinal manifestations including joint, eye and skin manifestations.[205] Sleep is likely to be deleteriously affected by the symptoms of active IBD but has also been examined as a potential extra-intestinal manifestation of IBD, and as an exacerbating or aetiological factor in IBD.

Sleep abnormalities (particularly short sleep duration) in the general population have been associated with increased all-cause mortality,[206] adverse health effects including cardiovascular disease[104] and metabolic syndrome,[105] and economic consequences such as lower productivity and greater health care utilisation.[108] Sleep also regulates a variety of G functions[207] including motility and secretion. Sleep disruption is associated with upregulation of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α,[208] which have also been implicated in the pathogenesis of IBD. Studies of other inflammatory disorders such as rheumatoid arthritis have suggested an association between disease activity and sleep abnormalities.[130,209]

Several studies have investigated the association between sleep and IBD[210-212] and postulated a bidirectional relationship.[213] Sleep can be assessed subjectively using a measure of perceived sleep via validated survey methods such as the Pittsburgh Sleep Quality Index (PSQI), using standardised cut-off values to define likely significant sleep disturbance referred to as 'poor sleep'.[113] Alternatively, objective measures of sleep can be obtained using actigraphy or polysomnography,[214] with output variables such as sleep efficiency and duration of time awake after onset of sleep (wake after sleep onset [WASO]) (see Table 1).

There is a paucity of longitudinal studies of sleep and IBD, with the literature using subjective measures of sleep producing inconsistent and somewhat contradictory outcomes. While some studies have demonstrated a relationship between subjective sleep disturbance and risk of disease flare in people with CD, this has not been seen for those with UC.[161] Consideration has also been given to whether sleep disturbance might precede or contribute

to disease onset, with a large cohort study finding subjective sleep disturbance was a risk factor for the development of UC, but not CD.[170] A recent (2020) meta-analysis of disease activity and sleep in IBD[201] suggested a significant relationship between sleep and disease activity; however there was significant heterogeneity in the study populations. This work was expanded on by Ballesio et al[200] who similarly found a significant relationship between subjective sleep quality and disease activity, and also that poor sleep was more common in IBD patients than controls. Since the publication of these meta-analyses there have been important publications[154-156,159,166,169,173] suggesting no significant relationship between IBD disease activity and disturbed sleep, with some suggesting that only perceived sleep may be different. Importantly, meta-analyses also have not considered—or have been unable to establish—a relationship between objective measurements of IBD disease activity and sleep quality.

The aim of this review was to examine the relationship between IBD activity and poor sleep. Moreover, to deepen our understanding of the potential relationships involving sleep and IBD, this review considers both subjective and objective measures of sleep and IBD activity to clarify the relationships among perceptions/symptoms and verifiable disturbances.

Methods

Protocol and registration

This systematic review and meta-analysis was prospectively registered with the International Prospective Register of Ongoing Systematic Reviews.[215] The systematic review and meta-analysis is reported according to the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) protocol guidelines.[216]

Search strategy

The following search string was used: (sleep OR circadian OR insomnia OR apnoea) AND (inflammatory bowel disease) OR (CD) OR (ulcerative colitis) OR IBD OR Crohn's OR colitis). Pubmed, MEDLINE and PsychINFO were searched from inception to December 2020, with the search restricted to articles published in the English language.

Eligibility criteria

Studies were considered eligible if they met the following inclusion criteria: (1) cross-sectional, observational, case control, cohort or randomised controlled trial available in English text; (2) included a distinct population of adults with IBD (age ≥ 18 years); (3) IBD

disease activity was assessed using either a validated subjective patient-reported measure of active IBD (e.g., Harvey–Bradshaw Index[217] [HBI] or Crohn's Disease Activity Index[65] [CDAI]), pathology or stool testing showing indirect evidence of active IBD (e.g., faecal calprotectin or C-reactive protein [CRP]) or direct evidence of active IBD (e.g., colonoscopy); (4) sleep quality assessment using either a validated subjective patient-reported measure of sleep (e.g., Pittsburgh Sleep Quality Index[113] [PSQI], SLEEP-50[182], Patient-Reported Outcome Measurement Information System Sleep Disturbance questionnaire (PROMIS-SD])[218] or an objective measure of sleep (e.g., wrist actigraphy or polysomnography).

Exclusion criteria were as follows: (1) inappropriate study population such as a paediatric or adolescent population; (2) case report or review; or (3) exclusively examining for specific sleep disorders such as sleep apnoea and restless leg syndrome.

Study selection

The first author (AB) performed the literature review and a second author (PS) independently screened full texts against eligibility criteria, with disagreement resolved by discussion with involvement of a third author (RM) when required.

Data collection

Data collection was performed by AB and reviewed by PS. A pre-defined spreadsheet was used for data collection. Items collected for each study population were type of IBD, age, gender, study design, sample size, IBD disease activity assessment, sleep assessment, effect size of poor sleep in active disease in IBD in reference to IBD in remission, other measures assessed and outcome of study

Study quality assessment

Risk of bias in individual studies was assessed according to study design. Cross-sectional or observational studies were assessed according to the modified Newcastle–Ottawa Scale. Cohort or case control studies were assessed according to the Newcastle–Ottawa Scale.[219]

Exposure and outcome measures

Exposure was considered to be active disease as defined by one of the following: (1) validated subjective measure of disease activity (e.g., HBI, CDAI); (2) objective biomarker disease activity (e.g., CRP, faecal calprotectin); or (3) direct evidence of inflammation (e.g., endoscopic appearance, histology). IBD activity was considered to be active or in remission.

Outcome was poor sleep defined as (1) subjective measure of poor sleep (e.g. PSQI > 5, PROMIS-SD > 50); or (2) objective measures of sleep quality as described in Table 1.

Statistical methods

Statistical analysis was performed using Stata SE 16 (StataCorp, College Station, TX, USA). IBD disease activity scores were used to define active disease and remission, and sleep quality assessment measures were used to calculate the OR for the odds of poor sleep in the setting of active disease. Heterogeneity among studies was assessed using the I2 statistic, with I2 >50% considered to indicate substantial heterogeneity. A random effects model was used. A forest plot was constructed to estimate individual and pooled effect sizes with associated 95% confidence interval (CI). Hedge's *g* was calculated as a standardised mean difference between two populations. Publication bias was assessed using funnel plots with significant visual asymmetry indicating publication bias. An Egger's test result with *p* value <0.05 was considered to indicate significant publication bias. Sensitivity analysis was performed to assess the robustness of the pooled estimates by systematically removing each study and recalculating the pooled results.

Separate meta-analyses were performed for (1) subjective sleep quality; (2) objective sleep quality; and (3) objective IBD disease activity using standardised mean difference as the effect measure in the latter. Subgroups considered included IBD subtype (CD and UC), objective measures of IBD activity and objective measures of sleep quality.

Results

The literature search (see Figure 2.1) identified 519 records following removal of duplicates, with 18 studies included in the qualitative synthesis, 11 in the meta-analysis for subjective sleep and disease activity, 5 in the meta-analysis for objective sleep and subjective disease activity and 4 in the meta-analysis for subjective sleep and objective disease activity.

Characteristics of the included studies are presented in Table 2. The pooled studies included 4,972 individuals with IBD, predominantly CD (3,040; 61% of subjects). Studies were published between 2011 and 2020. Quality assessment of the included studies was performed (Supplementary Table 1) with study quality considered to be at least fair and assessed as good in the majority.

Subjective sleep quality and subjective IBD activity

Effect sizes for poor sleep given subjective IBD disease activity were able to be calculated in 11 studies, with these subsequently included in the meta-analysis. Studies were excluded from the meta-analysis for the following reasons: not suitably defined or reported subjective disease activity[155,157,163,166]; or inadequate reporting of a definition of poor sleep based on subjective disease activity.[154,159,178] To obtain further data, email contact was attempted with authors of all excluded studies with no reply.

The forest plot (Figure 2.2) revealed a significant association between IBD activity and poor sleep with a pooled OR of 3.04 95% CI (2.41–3.83) and acceptable heterogeneity: I2 of 38.2%. A funnel plot (Supplementary Figure 1) showed no significant asymmetry. The Egger's test suggested no significant publication bias ($p = 0.32$). Sensitivity analysis (Supplementary Table 2) showed no results were significantly altered when individual studies were removed. Heterogeneity was due to Zhang et al[173] including only IBD patients with peripheral arthropathy whose arthropathy may lead to poor sleep irrespective of disease activity. Excluding those results gave a pooled OR of 3.43 95% CI (2.99–3.93) with no significant heterogeneity: I2 of 0%.

A subgroup analysis was performed that compared a group of studies including only patients with CD[167,169,176,220] with studies including UC in addition to CD. Pooled OR for studies including only CD was 2.99 (95% CI 1.22–7.34), which was not significantly different from the pooled OR for the remaining studies (3.46, 95% CI 3.00–4.00, $p = 0.75$).

Objective sleep quality and subjective IBD activity

Five studies ($n = 313$, 76% CD) were identified where an objective measure of sleep was obtained in addition to a measure of subjective IBD activity. Four of these studies used wrist actigraphy and the fifth, polysomnography. Significant differences within studies included lower sleep efficiency in those with active disease in three studies[173,176,178] and WASO longer with active disease in two studies. Van Langenberg et al did not report the duration of WASO.[163] A standardised mean difference was calculated for sleep efficiency and WASO duration between an IBD population with active disease and an IBD population in remission.

A forest plot (Figure 2.3) with effect size was calculated as standardised mean difference between two populations—pooled Hedge's g for sleep efficiency of –0.58 (95% CI –1.08 to –0.08, $p = 0.02$—however with significant heterogeneity (I2 = 75.6%), suggesting lower sleep efficiency in active disease compared to remission. The funnel plot (Supplementary Figure 2) was largely symmetric with Egger's test not significant ($p = 0.64$). The heterogeneity is

somewhat due to Zhang et al, who included an IBD population with peripheral arthropathy with significantly lower sleep efficiency than the other studies ($p = 0.02$). The forest plot for duration of WASO can be seen in Figure 2.4 with pooled Hedge's g of 0.34 (95% CI 0.09–0.59) favouring long duration in active disease and acceptable heterogeneity (I2 5.8%). A funnel plot (Supplementary Figure 3) was large symmetric and the Egger's test for small study effects was not significant ($p = 0.18$).

Objective IBD activity and subjective sleep quality

Seven studies [155-157,160,164,166,221] ($n = 903$, 48.5% CD) reported objective IBD disease activity along with survey-based assessment of sleep quality utilising PSQI or PROMIS-SD, with none using an objective measure of sleep. Four studies reported a significant association between objective markers of disease activity and higher PSQI, indicating poorer sleep. These objective markers of disease activity included endoscopic disease activity, histological inflammation, CRP and faecal calprotectin. Three studies[155,156,221] reported a correlation between biomarkers such as CRP or faecal calprotectin and PSQI scores, but did not define active IBD and did not define poor sleep. Unfortunately, insufficient data were available to derive these relationships.

A meta-analysis was performed to compare subjective sleep quality between those with active IBD and those in remission using objective measures of IBD disease activity. The forest plot can be seen in Supplementary Figure 4, with pool OR for poor sleep given active disease of 6.64 (95% CI 3.02–14.59, I2 93%). The substantial heterogeneity is likely a result of the different methods used to assess disease activity and differences in study populations, with Michalopoulos et al only including those in clinical remission.

Sub-clinical disease activity and subjective sleep quality

A population with sub-clinical disease activity was considered in 3 publications. Michalopoulus et al[166] ($n = 90$) examined the colonoscopy findings of 90 patients with IBD in clinical remission, along with subjective sleep quality using PSQI. They reported a significant association between sub-clinical disease activity and poor sleep quality. However this was only present in those with CD; there was no significant association in those with UC. Furthermore, a subgroup in a study by Ali et al[164] ($n = 41$) with clinically inactive but histological active disease all had an abnormal PSQI. Similarly, Wilson et al[160] ($n = 131$) found that elevated CRP as a marker of disease activity was associated with poor sleep quality irrespective of the presence of any nocturnal symptoms, consistent with above results.

Discussion and summary of evidence

Our meta-analysis suggests that sleep quality as measured by both subjective and objective measures (polysomnography and actigraphy) is significantly worse in those with active IBD than in those in remission. Objective measures of sleep quality showed lower sleep efficiency and higher duration of time awake post sleep onset in those with active IBD than in those in remission. There is also the suggestion that sleep quality is poor in those with sub-clinical active IBD.

One of the strengths of this meta-analysis is its consideration of objective and subjective measures of sleep quality and IBD activity. Previous meta-analyses[200,201] did not consider or were not able to elicit a relationship between objective measures of IBD activity and sleep quality. Fatigue, likely closely related to sleep, has also been investigated, with a recent meta-analysis[71] reporting a high prevalence of fatigue in people with IBD. Improved understanding of the role of sleep in IBD may lead to development of novel approaches to management of fatigue in this population.

These results raise the question of whether it is the nocturnal symptoms associated with active IBD that contribute to poor sleep or if poor sleep is a direct (systemic) consequence of active inflammation. Notably, irritable bowel syndrome (IBS) has also been associated with poorer sleep than in healthy controls,[140] despite there being little evidence of systemic inflammation in IBS. Consideration therefore needs to be given to the possibility that persistent GI symptoms—irrespective of disease activity such as so-called post-inflammatory syndrome or IBS—contribute to poor sleep in those with IBD. This is supported by Zargar et al[222] who showed that those with IBD in remission who met diagnostic criteria for IBS had poorer sleep than those not meeting criteria.

Emerging data suggest that the association with disease activity and poor sleep persists in those with sub-clinical disease activity defined by endoscopic activity,[166] biomarkers[160] or histological activity.[223] The complex relationship between the immune system and sleep leads to the possibility that IBD-related inflammation may lead to poor sleep irrespective of the symptoms experienced. Sleep deprivation has been shown to lead to a rise in pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α[118] that have also been implicated in the pathogenesis of IBD. Furthermore, abnormalities in circadian rhythm-associated clock genes[224] and sleeping duration[170] have been associated with the development of IBD and UC

respectively. The relationship between sleep and IBD has consequently been said to be bidirectional, with the prospect of feedback between each leading to deterioration of both.

There are also several possible established associations with IBD that may act as confounders for poor sleep. Depression is known to be prevalent in those with IBD, with several prevalence studies showing an association between depression and poor sleep, irrespective of IBD disease activity in a minority.[155,157,159,225] Extra-intestinal manifestations of IBD may also be significant contributors, with Zhang et al[173] reporting considerably lower sleep efficiency in the population of people with IBD and arthropathy compared to IBD without arthropathy and healthy controls. Other significant contributors include physical exercise, with two prevalence studies[157,163] showing positive associations with higher levels of physical exercise with sleep quality.

Limitations include the current lack of evidence to support the analysis of objective sleep quality and objective disease activity. A number of studies were excluded because of a lack of availability of sufficiently statistically formulated data to enable meta-analysis, which was not supplied despite attempts to contact the authors.

There have been no interventional studies to improve sleep in IBD, which may not only improve overall QoL but also IBD disease activity. Further work is required to ascertain the magnitude of the effect of sub-clinical disease activity on sleep. There is also a noticeable lack of high-quality studies with both objective sleep quality and objective IBD disease activity. There is similarly a paucity of longitudinal studies, with available evidence suggesting worse outcomes in those with poor sleep; however the confounding effects of mental health, physical activity, disease activity and disease severity are unclear. Furthermore, the directionality of the interaction between sleep and IBD activity needs to be determined.

Conclusions

Disease activity in IBD is associated with poorer sleep compared with remission. This manifests as lower sleep efficiency and longer duration of time awake post sleep onset. Sub-clinical disease activity is associated with lower quality sleep compared with that in remission. Further studies should consider objective measures of sleep and disease activity with longitudinal follow up, and consider a sleep-targeted intervention.

Figure 2.1: PRISMA flowchart—selection of studies and results of literature search for review and meta-analysis.

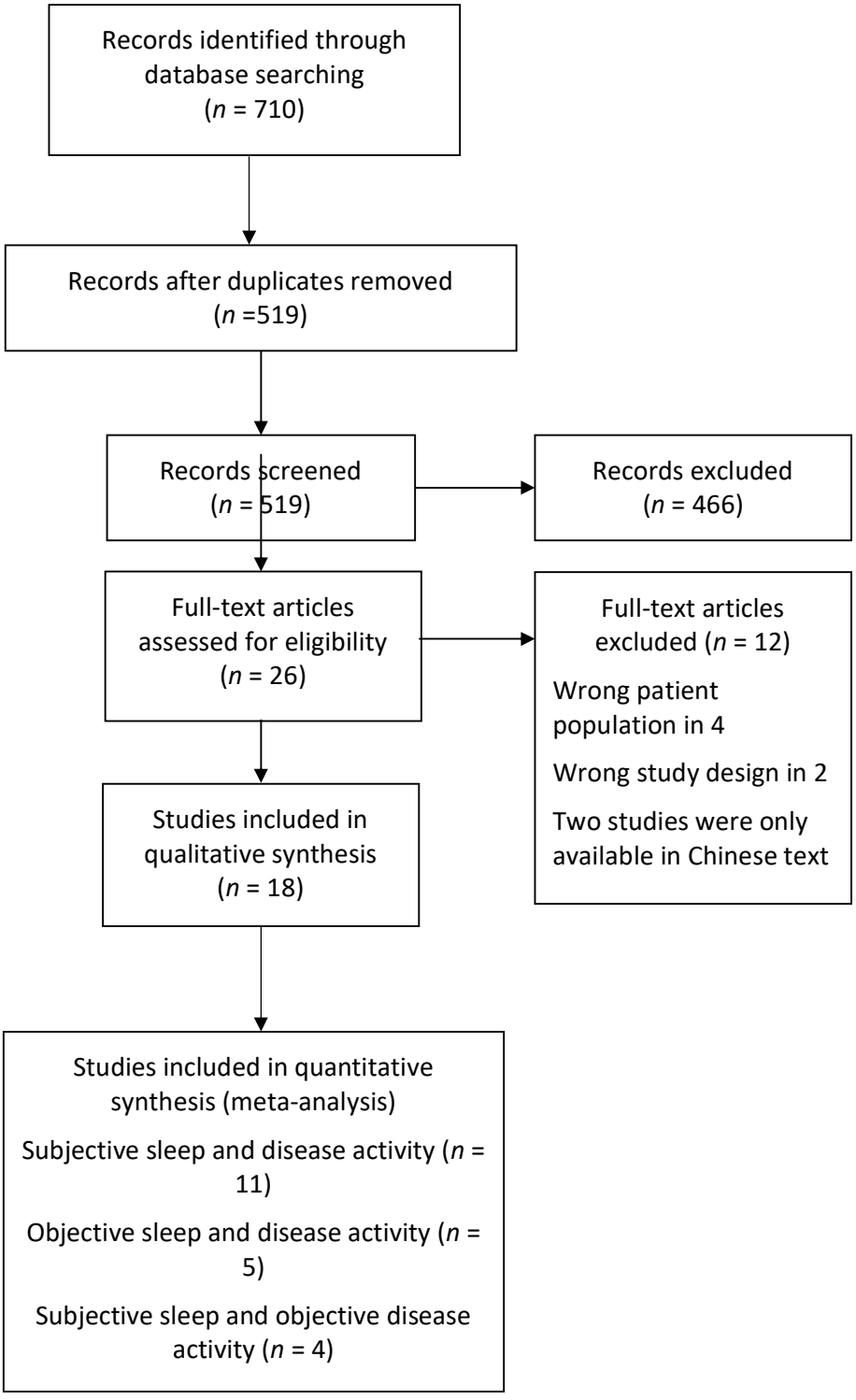

Figure 2.2: Forest plot of meta-analysis of odds of poor sleep in people with IBD with active disease compared to remission using subjective measures of sleep quality and subjective measures of IBD activity.

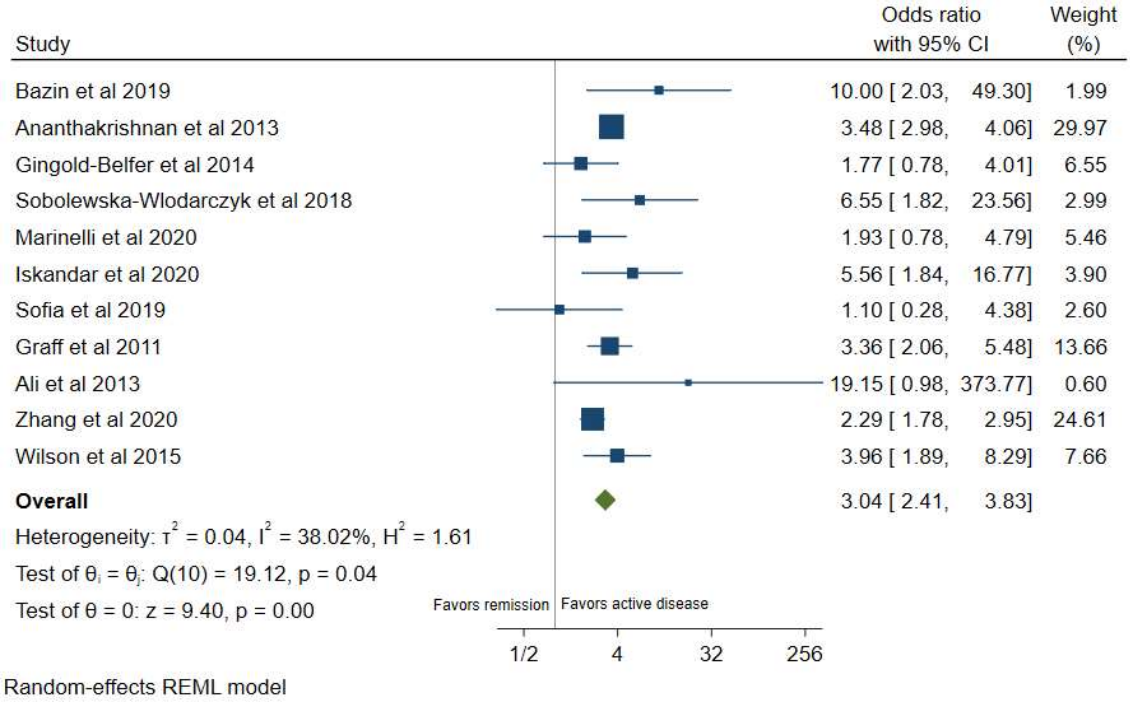

Figure 2.3: Meta-analysis of measures of objective sleep quality in active IBD and those in remission

via subjective disease activity assessment, with subgroups by type of sleep study performed, using Hedge's *g* as a measure of the standardised mean difference between two populations.

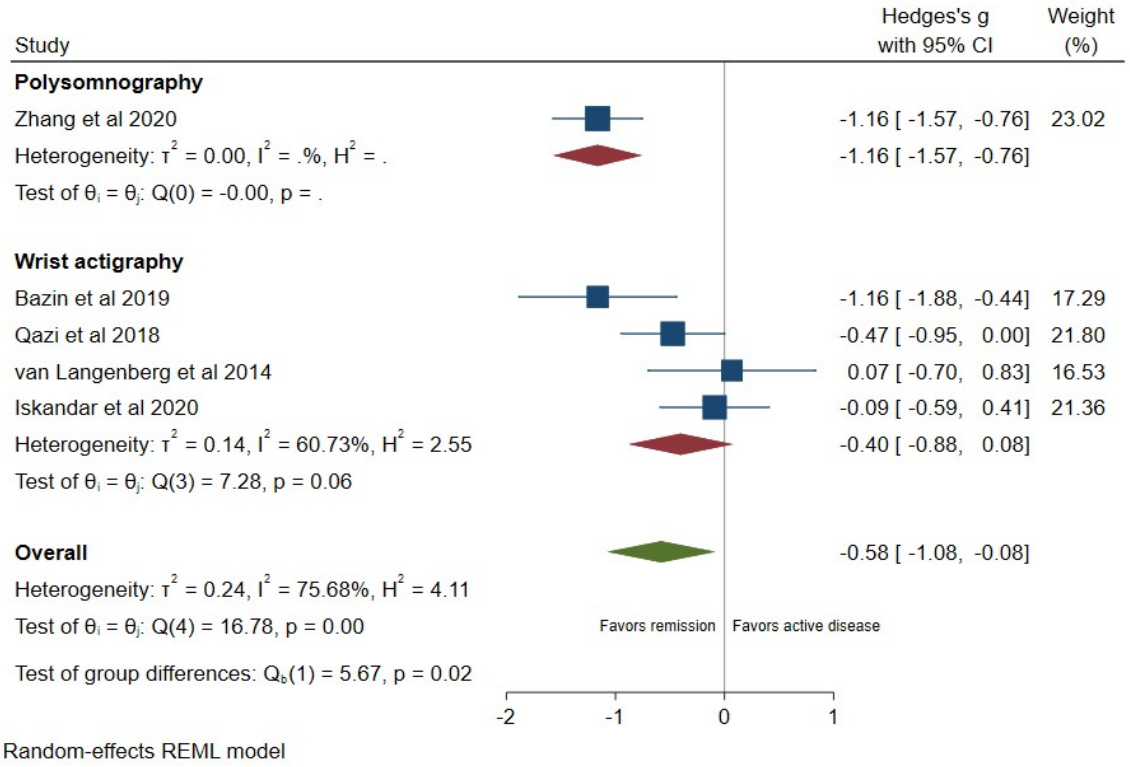

Figure 2.4: Meta-analysis of wake after sleep onset duration in those with active IBD and in remission, with subgroups by type of sleep study performed.

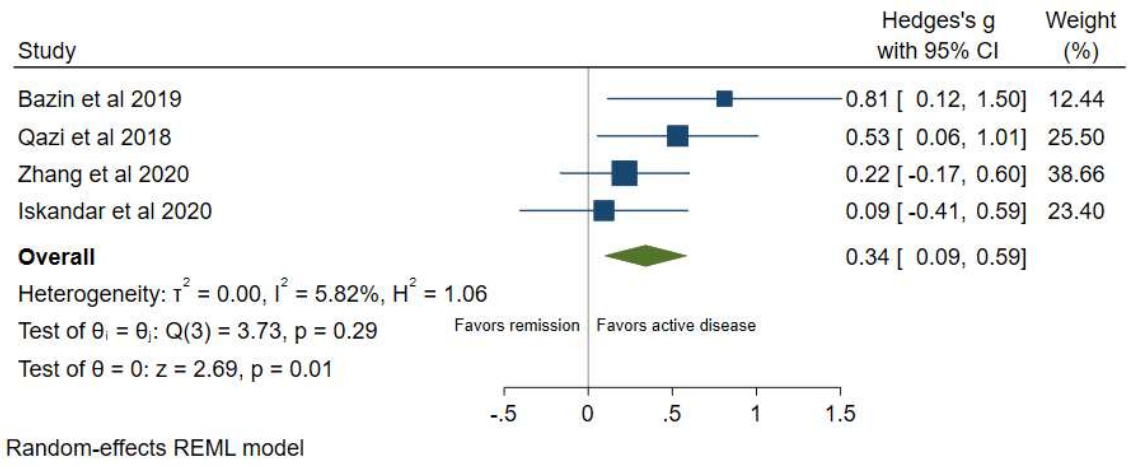

Table 1: Definition of objective sleep quality parameters from actigraphy and polysomnography.

Sleep quality variable	Definition
Sleep duration	Total number of minutes of sleep
Sleep latency	Time from going to bed to onset of sleep
Sleep efficiency	The portion of time asleep divided by time in bed
Time awake after sleep onset (WASO)	Duration of any time awake after sleep onset
REM*	Duration of rapid eye movement sleep
S1*	Duration of stage 1 of sleep
S2*	Duration of stage 2 of sleep
S3 + S4*	Duration of stage 3 and stage 4 of sleep

*indicates only available from polysomnography.

Table 2: Study characteristics including IBD disease activity measurement, sleep quality measurement, other measured quantities and overall outcome of the study.

First author	Year	Design	IBD population	Disease activity assessment—indicating active disease	Sleep quality assessment—indicating poor sleep	Main outcome of study
Bazin[176]	2019	CS	CD:34	HBI >4	PSQI >5 Wrist actigraphy	Lower sleep efficiency was seen in active CD.
Ananthakrishnan[161]	2013	CS	CD:2,079 UC:1,094	SCDAI ≥150 SCCAI >2	PROMIS-SD >50	Sleep disturbance was associated with risk of disease flare.
Gingold-Belfer[220]	2014	CS	CD:108 Control:66	CDAI ≥150	PSQI >5	CDAI and PSQI corresponded; however inactive disease group had similar PSQI to control group.
Sobolewska-Wlodarczyk[226]	2018	CS	CD:30 UC:35	CDAI ≥150 PMS > 0	PSQI >5	Sleep quality deteriorated with increasing severity of IBD disease activity.
Uemura[168]	2016	CS	CD:48 UC:88	HBI >4 PMS >3	PSQI >5.5	Sleep disturbance is a risk for factor for IBD flare.
Marinelli[156]	2020	CS	CD:87 UC:79	HBI >4 PMS >1 Faecal calprotectin > 250 ug/g	PSQI >5	No association with active disease and sleep, but sleep quality was correlated with mood, disability and QoL.

First author	Year	Design	IBD population	Disease activity assessment—indicating active disease	Sleep quality assessment—indicating poor sleep	Main outcome of study
Iskandar[167]	2020	CS	CD:61 Control:60	HBI >4	PSQI >5 Wrist actigraphy National foundation sleep log Urinary melatonin metabolite	CD patients reported worse sleep than controls and had worse sleep in active disease; however no difference was seen in sleep quality using objective sleep measures.
Ali[164]	2013	CS	CD:23 UC:18	HBI >4 PMS >0 CRP Histology	PSQI >5	Clinically active disease was associated with poor sleep quality. Clinical remission with abnormal sleep had high likelihood of inflammation on histology.
Sofia[169]	2019	CS	CD:92 Control:82	HBI >4	PSQI >5	High burden of poor sleep quality in CD, which is associated with risk for adverse outcomes.
Graff[221]	2011	C	CD:160 UC:158	HBI >4 PTI >4 CRP	PSQI >5 ESS	Poor sleep was associated with subjective IBD activity but did not correlate with CRP.
Sochal[154]	2020	C	CD: 68 UC: 65 Control:57	HBI >4 PMS >4	PSQI >5 AIS ESS	IBD patients had prolonged sleep latency and reduced sleep efficiency. IBD in flare had higher PSQI.

First author	Year	Design	IBD population	Disease activity assessment—indicating active disease	Sleep quality assessment—indicating poor sleep	Main outcome of study
Qazi[178]	2019	CS	CD:80	HBI >4	PROMIS-SD >50 ESS WHIR Wrist actigraphy	IBD patients with active disease had lower sleep efficiency and more fragmented sleep than those in remission.
Zhang[173]	2020	CS	UC:81 CD:39 UC-PA:87 CD-PA:33 Control:120	HBI >4 PMS >0	PSQI >5 Polysomnography	Sleep quality of those with IBD worse than control group and those with IBD-PA were worse than both groups.
van Langenberg[163]	2014	CS	CD:49 Control:30	HBI >4	PSQI >5 Wrist actigraphy	Patients with CD exhibited poorer sleep quality than well-matched healthy controls.
Michalopoulos[166]	2018	CS	UC:36 CD:54	Endoscopic disease activity on colonoscopy	PSQI >5	Absence of mucosal healing on colonoscopy was associated with poor sleep in sub-clinical CD but not sub-clinical UC.
Wilson[160]	2015	CS	UC:53 CD:78	PGA CRP ESR	PROMIS-SD >50	Elevated CRP was associated with poor sleep independent of nocturnal symptoms.

First author	Year	Design	IBD population	Disease activity assessment—indicating active disease	Sleep quality assessment—indicating poor sleep	Main outcome of study
Gîlc-Blanariu[159]	2020	CS	UC:76 CD:34 Control:66	PMS CDAI CRP Faecal calprotectin	PSQI >5	Sleep impairment was associated with psychological distress and several disease-related parameters.
Hood[155]	2018	CS	UC:47	CRP IL-6 Faecal calprotectin	PSQI >5	Poor sleep quality was not related to active disease but was related to depression.

CD: Crohn's disease, UC: ulcerative colitis, CS: cohort study, HBI: Harvey–Bradshaw Index, PSQI: Pittsburgh Sleep Quality Index, SCDAI: Simple Crohn's Disease Activity Index, SCCAI: Simple Clinical Colitis Activity Index, PMS: Partial Mayo Score, PTI: Powell–Tuck Index, AIS: Athens Insomnia Scale, WHIR: Women's Health Initiative Insomnia Rating Scale, PA: peripheral arthropathy, PGA: physician global assessment, ESS – Epworth sleepiness scale, CDAI Crohn's - disease activity index, CRP – C-reactive protein.

Supplementary Table 1: Study quality assessed by two authors (AB and PS) scored according to the Newcastle–Ottawa Scale with sub-scores and associated study quality detailed.

First author	Year	Selection	Comparability	Outcome	Study quality
Ali	2013	3	1	3	Good
Ananthakrishnan	2013	3	1	2	Good
Bazin	2019	3	1	3	Good
Gilc-Blanariu	2020	4	1	3	Good
Gingold-Belfer	2014	3	1	3	Good
Graff	2011	3	2	3	Good
Hood	2018	2	1	3	Fair
Iskandar	2020	2	2	3	Fair
Marinelli	2020	2	2	2	Fair
Michalopoulos	2018	2	2	3	Fair
Qazi	2018	2	1	3	Fair
Scott	2020	3	2	3	Good
Sobolewska-Włodarczyk	2018	3	1	3	Good
Sochal	2020	3	1	3	Good
Sofia	2019	3	1	2	Good
Uemura	2016	3	2	3	Good
Wilson	2015	3	2	2	Good
Zhang	2020	2	2	3	Fair

Supplementary Table 2: Sensitivity analysis of meta-analysis of subjective disease activity and subjective sleep quality

Study excluded	OR	UL	LL
Bazin et al 2019	2.97	2.36	3.74
Ananthakrishnan et al 2013	2.89	2.17	3.84
Gingold-Belfer et al 2014	3.16	2.48	4.02
Sobolewska-Włodarczyk et al 2018	2.97	2.35	3.75
Marinelli et al 2020	3.13	2.45	3.99
Iskandar et al 2020	2.97	2.34	3.76
Sofia et al 2019	3.12	2.47	3.95
Graff et al 2011	3.01	2.28	3.96
Ali et al 2013	3.01	2.38	3.79
Zhang et al 2020	3.43	2.99	3.93
Wilson et al 2015	2.98	2.32	3.82

Research question

Rationale: Sleep is currently not a consideration in the care of a person with IBD. The role of sleep in IBD has been investigated with cross-sectional and longitudinal studies, producing inconsistent results. The relationship between sleep and IBD activity is confounded by the presence of sub-clinical IBD activity that may not produce any visible symptoms, and the presence of IBS-like symptoms in inactive IBD that may be mistaken as symptoms of active IBD. The role of sub-clinical IBD in sleep quality may be significant.

Sleep may have an important role in QoL for people with IBD and may also influence the high prevalence of mental health conditions in this population.

Overarching aims of this thesis

The overarching aim of this thesis was to explore the relationship between sleep and IBD activity and its implications for QoL and fatigue.

Research objectives

1. To evaluate the prevalence of poor sleep in people with IBD.
2. To determine the influence of sleep on QoL in IBD.
3. To evaluate the relationship between objective sleep quality and objective disease activity.
4. To evaluate sleep quality in people with IBD in remission.
5. To evaluate the relationship between IBD medications and sleep quality
6. To determine the associations between common sleep disorders in people with IBD and IBD demographic and disease-related data, and mental health disorders.
7. To determine the influence of sleep on fatigue in IBD in the setting of IBD activity and mental health conditions.

Research process

Several studies were conducted to address the research objectives. The research was undertaken in Adelaide, Australia. As part of the research process two systematic reviews were undertaken.

Systematic review and meta-analysis 1: A systematic review and meta-analysis of the prevalence of poor sleep in IBD.

Systematic review and meta-analysis 2: A systematic review and meta-analysis of sleep quality in inactive IBD.

The research process then proceeded with two projects.

Project 1: To evaluate the relationship between objective IBD activity and objective sleep.

Project 2: To evaluate the relationship between sleep quality, mental health conditions, QoL and fatigue in IBD quality.

CHAPTER 3: A SYSTEMATIC REVIEW AND META-ANALYSIS OF THE PREVALENCE OF POOR SLEEP IN INFLAMMATORY BOWEL DISEASE

This chapter presents the manuscript 'A systematic review and meta-analysis of the prevalence of poor sleep in inflammatory bowel disease', unchanged from publication in *Sleep Advances*, Aug 2022, doi: 10.1093/sleepadvances/zpac025.

Author contributions

Alex Barnes: responsible for study concept and design, data acquisition, analysis and data interpretation, drafting of manuscript, critical revision of the manuscript.

Paul Spizzo: responsible for data acquisition, data interpretation, drafting of manuscript, critical revision of the manuscript.

Justin Baker: responsible for data acquisition and critical revision of the manuscript.

Peter Bampton: responsible for critical revision of the manuscript.

Jane Andrews: responsible for study conception

Robert J Fraser: responsible for study conception

Réme Mountifield: responsible for critical revision of the manuscript.

Sutapa Mukherjee: responsible for study concept and design, critical revision of the manuscript

Please see appendices for further authorship information.

[Manuscript] A systematic review and meta-analysis of the prevalence of poor sleep in inflammatory bowel disease

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Conflicts of interest include speakers fees, and Ad Boards from Abbott, AbbVie, Allergan, Anatara, AstraZeneca, Bayer, BMS 2020, Celegene, Celltrion, Falk, Ferring, Gilead, Hospira, Immuninc, ImmunsanT, Janssen, MSD, Nestle, Novartis, Progenity, Pfizer, Sandoz, Shire, Takeda, Vifor, RAH research Fund, The Hospital Research Fund 2020–2022 and The Helmsley Trust 2020–2023

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Data availability statement

The data underlying this article are available in the Harvard Dataverse Digital Repository at https://doi.org/10.7910/DVN/FVLPYA

Abstract

Background

Poor sleep in people with inflammatory bowel disease (IBD) has been reported with variable prevalence. Poor sleep in IBD has been associated with worse quality of life, along with comorbid anxiety, depression, and fatigue. This meta-analysis aimed to determine the pooled prevalence of poor sleep in IBD.

Methods

Electronic databases were searched for publications from inception to November 1st 2021. Poor sleep was defined according to subjective sleep measures. A random effects model was used to determine the pooled prevalence of poor sleep in people with IBD. Heterogeneity was investigated through subgroup analysis and meta-regression. Publication bias was assessed by funnel plot and Egger's test.

Results

519 studies were screened with 36 studies included in the meta-analysis incorporating a total of 24,209 people with IBD. Pooled prevalence of poor sleep in IBD was 56%, 95% CI (51 – 61%) with significant heterogeneity. The prevalence did not differ based on the definition of poor sleep. Meta-regression was significant for age, and objective IBD activity but not subjective IBD activity, depression, or disease duration.

Conclusion

Poor sleep is common in people with IBD. Further research is warranted to investigate if improving sleep quality in people with IBD will improve IBD activity and quality of life.

Introduction

Sleep is an important biologic function with increasing attention turning to its role in overall health. Abnormal sleep has been linked to poor health outcomes including cardiovascular disease,[104] metabolic syndrome[105] and increased all-cause mortality in some studies,[206] in addition to significant economic cost in the form of decreased productivity and increased health care utilisation.[108] Sleep has been shown to regulate a number of gastrointestinal functions including gastrointestinal motility and secretion.[207] Sleep disruption has been associated with increased levels of inflammatory cytokines, such as IL-6, and TNF-α, that have been implicated in the pathogenesis of inflammatory bowel disease.[227-229]

Inflammatory bowel disease (IBD) is a relapsing-remitting autoimmune disorder that results from a complex interaction between genetics and the environment.[202] The relationship between IBD activity and sleep quality has been investigated previously with mixed results. A recent meta-analysis on the subject reached the conclusion that subjective sleep quality is worse in those with active IBD.[200] IBD-related symptoms themselves, such as diarrhoea and abdominal pain, may well disruptive sleep,[201] however other studies suggest that endoscopically or histologically active IBD in the absence of any IBD symptoms may be sufficient to disrupt sleep.[164,166] Extra-intestinal manifestations may also be important with a study suggesting those with enteropathic arthropathy were more likely to have poor sleep than those without.[173] Others suggest that psychosocial factors may be important,[159] and in particular depression has been frequently associated with poor sleep[154-161] in an IBD population.

Sleep may also be relevant to the development of IBD with data from the Nurses' Health Study showing that sleep duration was associated with the risk of ulcerative colitis, but not Crohn's disease.[170] Sleep quality may also have prognostic value in Crohn's disease with sleep associations seen with increased likelihood of hospitalisation and risk of relapse. The effect of IBD therapeutic agents on sleep has been investigated with a prospective study showing improvement in sleep following introduction of biologic therapy[158]—this of course paralleled an improvement in IBD activity. Others have not been able to demonstrate a relationship between the different IBD therapies and sleep quality.[165]

In a recent meta-analysis subjective sleep quality was worse in those with IBD than controls.[200] This may be due to IBD associated symptoms, however there is some literature suggesting that those with inactive IBD also appear to have poor sleep,[161,172,221,230] although it

is unclear if sleep quality in inactive IBD is worse than those of controls. Much of this data relates to subjective sleep quality with few studies incorporating objective sleep quality. Results from studies incorporating objective sleep quality are so far inconsistent noting a recent meta-analysis unable to establish an associated between objective sleep quality and IBD activity.[200]

Fatigue has been associated with sleep quality[162,199,221,231-234] and is known to be highly prevalent in people with IBD.[71] Patient-reported outcomes are of increasing attention and interest in IBD with sleep warranting further attention. This meta-analysis aimed to establish the pooled prevalence of poor sleep in IBD. To the author's knowledge there has been no previously published estimate of the prevalence of poor sleep in IBD. An improved understanding of the burden of poor sleep in IBD may lead to further investigation and interventional studies in this area that may result in improved quality of life for this population.

Methods

This systematic review and meta-analysis was prospectively registered with the International Prospective Register of Ongoing Systematic Reviews.[215] It was performed according to the preferred reporting item for systematic reviews and meta-analyses (PRISMA) guidelines.[216]

Search strategy

Pubmed, MEDLINE, and PsychINFO were searched from inception to November 2021, including articles published in the English language using the following search string: (sleep OR circadian OR insomnia OR apnoea) AND [(inflammatory bowel disease) OR (crohn's disease) OR (ulcerative colitis) OR IBD OR crohn's OR colitis)].

Eligibility criteria

Studies were included if they met the following criteria: (1) Cross-sectional, observational, case control, cohort or randomised controlled trial available (2) Included a distinct population of people with inflammatory bowel disease (age ≥18 years old). Studies with control groups of a healthy population accepted. (3) Sleep quality assessment using a validated subjective patient-reported measures of sleep.

Exclusion criteria included: (1) Inappropriate study population such a paediatric or adolescent population. (2) Case report or review

Study selection

The first author (AB) performed the literature review and two other authors (PS&JB) independently screened full texts against eligibility criteria, with disagreement resolved by discussion with involvement of another author (RM) when required.

Data collection

Data collection was performed by AB. A pre-defined spreadsheet was used for data collection. Items collected for each study population included type of IBD, age, gender, study design, sample size, sleep assessment, outcome of study, disease activity, IBD disease duration, depression.

Study quality assessment

Risk of bias in individual studies was assessed according to study design. Cross-sectional or observational studies were assessed according to modified Newcastle–Ottawa Scale. Cohort or case control studies were assessed according to Newcastle–Ottawa Scale.[219]

Statistical analysis was performed using Stata SE 16 (StataCorp, College Station, TX, USA) and the 'metaprop' command to estimate the pooled prevalence of poor sleep in people with inflammatory bowel disease. Heterogeneity among studies was assessed using the I2 statistic with I2 >50% considered to indicate substantial heterogeneity. A random effects model was used. A forest plot was performed to estimate individual and pooled effect sizes with associated 95% CI. Publication bias was assessed using funnel plots with significant visual asymmetry used to indicate publication bias. Egger's test with p values less than 0.05 were considered to indicate significant publication bias. Trim-fill analysis was undertaken. In order to investigate sources of heterogeneity subgroup analysis and meta-regression were conducted.

Results

The literature search (see Figure 1) identified 519 records following removal of duplicates, which further reduced to 75 records following screening. Following exclusions 36 records were included in the meta-analysis incorporating 24,209 people with IBD.

Characteristics of included studies can be seen in Table 1 and further data in Supplementary Table 1. Publication dates ranged from 2011 to 2020. Most of the studies were single centre (n = 20), two were multicentre, three recruited from an existing IBD registry, two recruited from a longitudinal cohort study, three used internet survey data, and two used data from a

nationwide IBD cohort. The majority incorporated a cross-sectional design. No study included sample size calculations for prevalence estimates, and no study incorporated a population sampling regimen. Sample size ranged from 34 to 10,634 participants. The mean age of participants ranged from 25 to 45 years. The proportion of female participants ranged from 42 to 72%.

The Pittsburgh Sleep Quality Index (PSQI) was reported in the majority of included studies (n = 29) (see Table 1).The PSQI is a validated measure to assess perceived sleep quality.[113] The index consists of subscales on sleep duration, sleep disturbance, sleep latency, daytime dysfunction, sleep efficiency, overall sleep quality and medications for sleep. The score ranges from 0 to 21, with a PSQI > 5 considered to represent poor sleep quality. PSQI sub-scores were reported in seven studies and consequently this was not investigated further.

The Patient-Reported Outcomes Measurement Information Systems sleep disturbance (PROMIS-SD) questionnaire was used by six studies.[153,158,160,161,235,236] The PROMIS-SD questionnaire was developed by the National Institute of Health.[218] The PROMIS-SD has comparable performance to the PSQI in identifying poor sleep.[237] A single study[232] used the Basic Nordic Sleep Questionnaire.[238]

Prevalence of poor sleep in IBD

The prevalence of poor sleep varied from 32% to 99%, with random effects model derived pooled prevalence of 55%, 95% CI (51–59) with substantial heterogeneity (forest plot in Figure 2), outliers were removed[173,232]. Funnel plot was symmetric (Supplementary Figure 1) and Egger's test not significant (p = 0.49). Trim-fill method do not include any additional studies.

Subgroup analysis was performed for definition of poor sleep, study of origin and publication date. There was no difference in the prevalence of poor sleep by definition of poor sleep (PSQI or PROMIS-SD sleep, p = 0.75). Most studies were from the United States of America (n = 15), followed by Europe (n = 12), and others including Australia, Japan, Turkey and Iran. The pooled prevalence was similar between Europe (56% (49–63)), and the USA (58% (53–64), both of which were significantly different to other (Australia, Japan, Turkey, Iran) (44% (36–52)), (p = 0.01)(see Supplementary Figure 2). Publication date subgroups were considered from 2011 to 2016 (n = 10), and 2017 to 2020 (n = 23). The prevalence of poor sleep was higher in the 2017 to 2020 subgroup (p = 0.03, 58% (53–63) v 50% (44–55).

However, altering the publication date subgroups by a single year resulting in no effect seen, discounting the above result.

Meta-regression

Meta-regression was performed for demographics and IBD-related data (see Table 2). Age was significant (p = 0.005) with increasing proportion of poor sleep associated with increase in age. Meta-regression was not significant for gender (p = 0.28), IBD type (p = 0.88), and IBD disease duration (p = 0.54).

IBD activity

IBD activity was reported in 25 studies (n = 23,229) in the form of subjective disease activity scores such as the Harvey–Bradshaw Index[217] or the Crohn's Disease Activity Index.[65] Meta-regression was not significant (p = 0.95). Objective IBD activity was reported in 8 studies (n = 1,931), with objective measures including C-reactive protein, faecal calprotectin, endoscopic and histology. On meta-regression objective IBD activity was significant (p = 0.001), increasing proportion of poor sleep was associated with increase in objective disease activity.

Depression

Assessment of depression was performed in 15 studies (n = 10,744). Eight of these studies reported a significant association between poor sleep quality and depression.[154-161] Scoring systems included the Hospital Anxiety and Depression Scale[239] (n = 6), PROMIS[240] depression score (n = 4), Beck's Depression Inventory II[241] (n = 3), depressive symptoms (n = 1) and depression under treatment (n = 1). On meta-regression depression was not significant (p = 0.43).

Discussion

This is the largest and only meta-analysis to date providing prevalence estimates for poor sleep in IBD. The pooled prevalence for poor sleep in IBD was high (55%), eclipsing that reported in a recent meta-analysis of fatigue (47%),[71] and of symptoms of anxiety (32%) and depression (25%).[4] The prevalence of poor sleep reported here is of a higher magnitude than the prevalence of sleep disorder in IBS with a recent meta-analysis reporting a pooled prevalence of 37.6%.[140] This highlights the importance of poor sleep in IBD and suggests further resources should be allocated to investigate this area.

Sleep disturbances have also been demonstrated in a variety of other chronic inflammatory conditions.[242] Poor sleep has been associated with rheumatological conditions, such as rheumatoid arthritis where it has been reported to be present in up to 70%,[243] and more common than in controls.[244] Poor sleep is also prevalent in inflammatory neurological conditions, such as multiple sclerosis,[245] and once again more common than in controls.[246] A substantial proportion of those with multiple sclerosis have insomnia, which is also common in other chronic medical conditions.[247] Reported rates of insomnia in an IBD population range up to 58%.[181] The significance of insomnia in IBD has been investigated further with a small interventional study of cognitive behavioural therapy for insomnia demonstrating the feasibility and patient acceptance of this approach.[190]

Sources of heterogeneity in the prevalence estimate of poor sleep included age, geographic location, and objective disease activity. Age-related sleep changes have been well described with decreasing sleep quality accepted,[248] with a similar association between age and sleep quality seen in a rheumatoid arthritis population.[129,249] It was considered that the significance of age may also relate to IBD disease duration, however this was not significant on meta-regression.

Objective IBD activity did vary between studies and was a significant source of heterogeneity. A recent meta-analysis was unable to elicit a significant relationship between objective IBD activity and sleep.[200] It did however find that subjective IBD activity was associated with sleep quality—a finding not replicated here despite the variance between different studies. This suggests that the underlying inflammatory response may be more significant than the associated symptoms, consistent with studies associated histology activity and endoscopic activity in the absence of symptoms with poor sleep.[164,166] IBD activity may not be the only driver of poor sleep quality with a number of studies reporting frequent poor sleep in those with inactive disease.[161,172,221,230]

Depression was not a significant source of heterogeneity despite varying between studies and despite a number of positive findings in the literature.[154-161] Low physical activity[162,163] and the presence of extra-intestinal IBD manifestations[173] have also been associated with poor sleep, unfortunately these were reported a minority of studies making further investigation impractical.

Limitations

As a result of the paucity of studies incorporating objective sleep assessments, we used a definition of poor sleep based on self-reported sleep quality. There is a suggestion in some studies[156] that people with IBD will report significantly worse sleep than can be substantiated objectively, and consequently the true prevalence of poor sleep may be lower. This supports the need for objective sleep assessments in people with IBD. Other limitations include most studies being single centre, although results were similar to multicentre or nationwide studies. Although we note that prevalence from nationwide studies was similar to other single centre studies. No study incorporated sample size calculations or included a rigorous sampling approach.

Conclusion

This meta-analysis has demonstrated that the prevalence of poor sleep in IBD is significant, although there was substantial heterogeneity between studies. Further work should consider studies incorporating objective disease and sleep quality measurements to understand the relationship and type of sleep disorders in this population. There are few interventional studies in this area, with a need to establish if the potential benefit of improving sleep in people with IBD would extend beyond quality of life to incorporate IBD-related outcomes such as IBD activity, and surgery. There is also the lack of simple IBD-specific screening tool for use in IBD clinic to identify those with poor sleep who would benefit from referral onto a sleep physician.

Figure 3.1: PRISMA flowchart—selection of studies and results of literature search for review and meta-analysis.

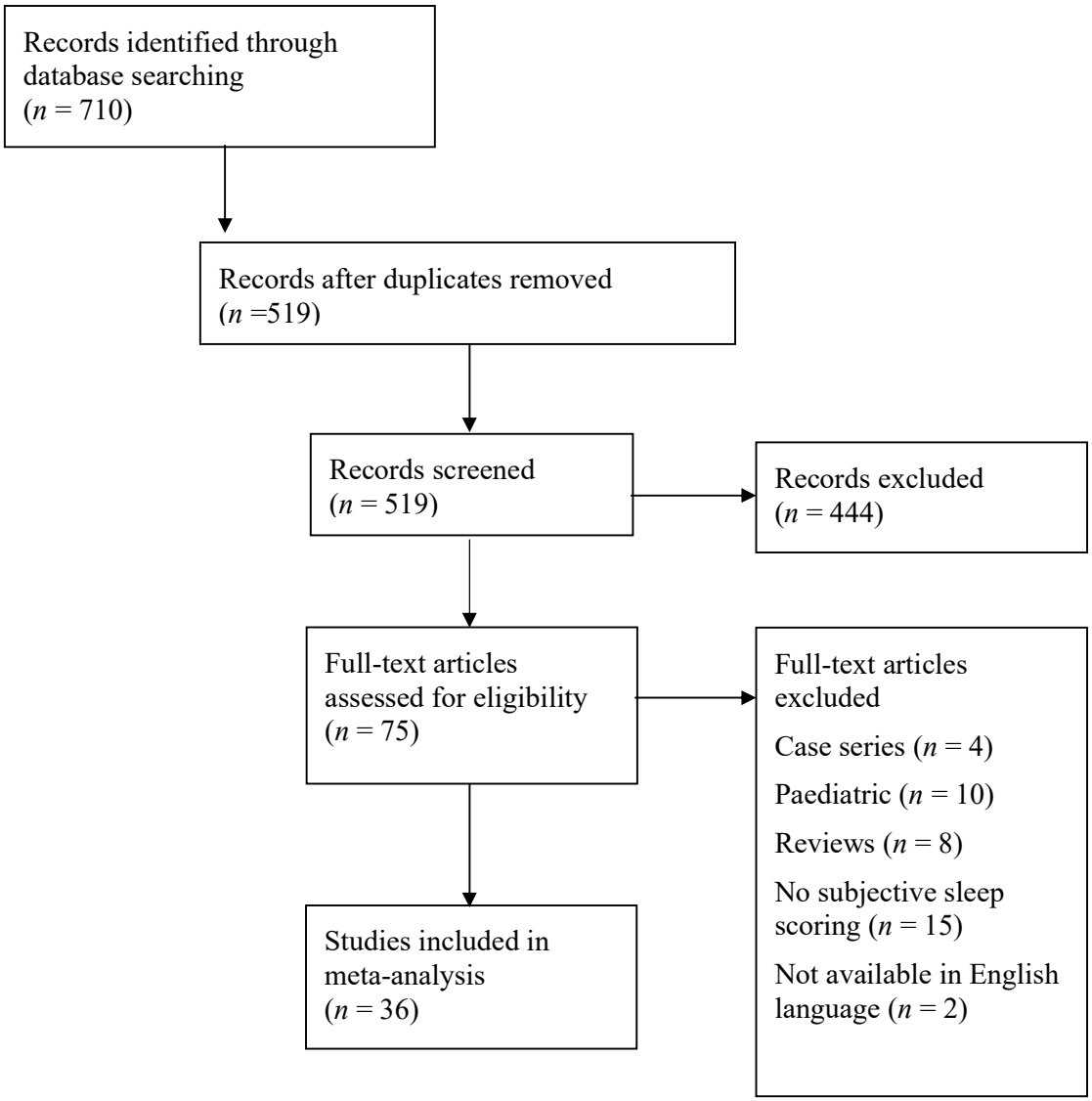


Figure 3.2: Forest plot of the prevalence of poor sleep in those with inflammatory bowel disease, using subjective sleep quality.

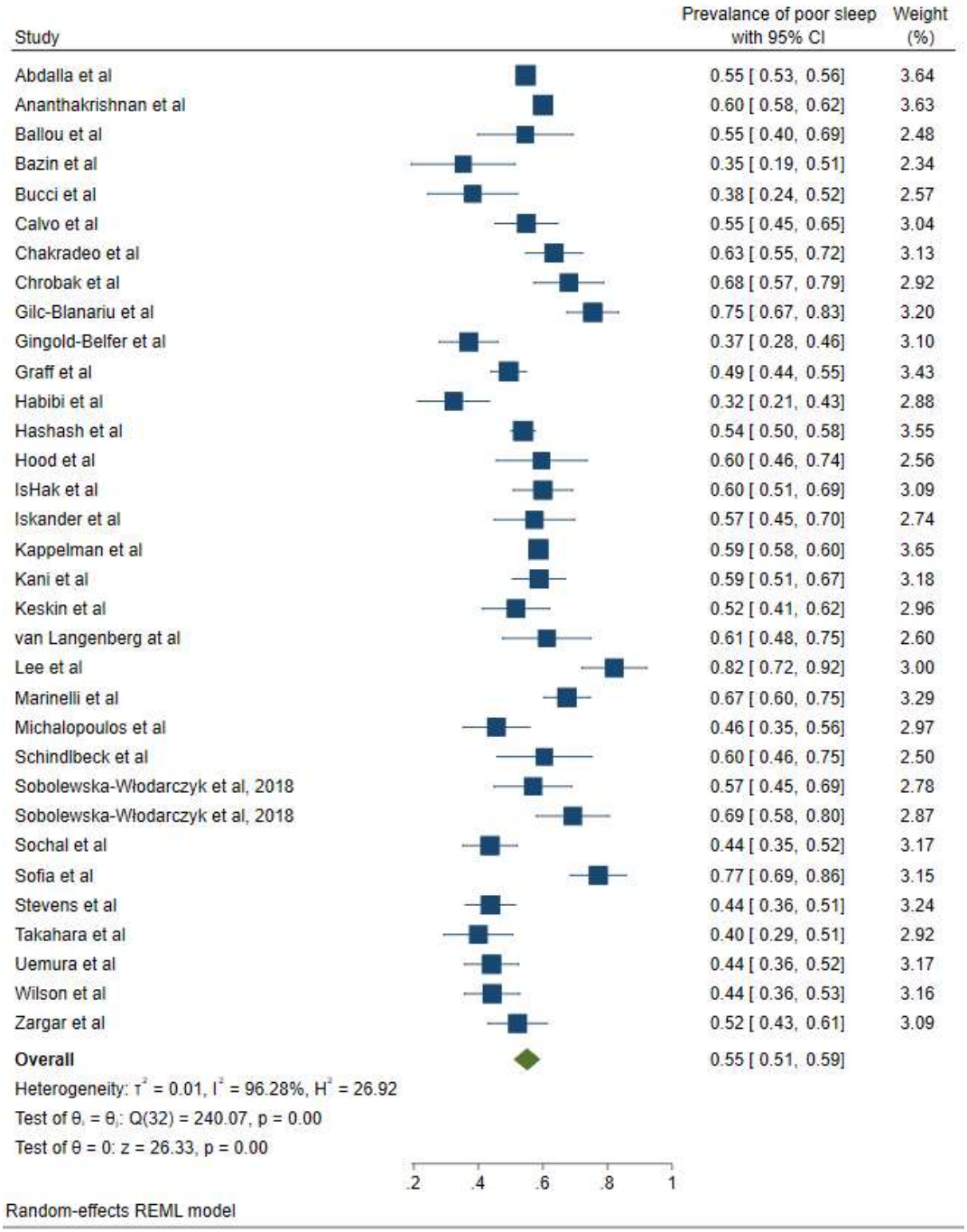


Table 3.1: Characteristics of studies included in the meta-analysis of poor sleep prevalence. See Supplementary Table 1 for further details.

Study	Year	Country	Poor sleep definition	Study population	Population	Sample size	Percentage female (%)	Age	Number with Crohn's disease	Proportion with poor sleep	Study summary
Abdalla et al[236]	2017	USA	PROMIS-SD *t* score >50	Patients within Crohn's colitis foundation of America Partners Cohort	IBD	6309	71	44	3947	0.54	IBD-IBS diagnosis was associated with increased narcotic usage and poor sleep.
Ali et al[164]	2013	USA	PSQI >5	Single centre–clinic	IBD	41	66	37	23	0.87	Clinically active IBD was associated with poor sleep.
Ananthakrishnan et al[161]	2013	USA	PROMIS-SD *t* score >50	CCFA partners cohort	IBD	3173	72	44	2079	0.6	Sleep disturbance was associated with an increased risk of disease flares in Crohn's disease but not ulcerative colitis.
Ballou et al[250]	2018	USA	PSQI >5	Single centre–clinic	IBD	44	71	42	22	0.54	IBD patients at a tertiary clinic have poorer sleep than healthy controls.
Bazin et al[176]	2019	France	PSQI >5	Single centre–clinic	Crohn's disease	34	44	40	34	0.35	Sleep efficiency is lower in those active Crohn's disease than in remission.

Study	Year	Country	Poor sleep definition	Study population	Population	Sample size	Percentage female (%)	Age	Number with Crohn's disease	Proportion with poor sleep	Study summary
Bucci et al[251]	2018	Italy	PSQI >5	Single centre–clinic	IBD	47	53	38	28	0.38	Bruxism was associated with pathological sleep.
Calvo et al[157]	2020	Spain	PSQI >5	Single centre–clinic	IBD	102	43	45	51	0.54	Poor sleep quality is present in more than half of people with IBD.
Chakradeo et al[252]	2018	USA	PSQI >5	Single centre–clinic	IBD	115	62	41		0.63	Later chronotype and markers of circadian misalignment were associated with IBD-specific complications and lower quality of life.
Chrobak et al[162]	2018	Poland	PSQI >5	Single centre–clinic	IBD	72	42	42	34	0.68	Chronotype preferences contribute to fatigue in IBD.
Frigstad et al[232]	2018	Norway	BSNQ	Multicentre	IBD	405	49	40	227	0.19	Sleep and depressive symptoms were associated with total fatigue scores.
Gîlc-Blanariu et[159] al	2020	Romania	PSQI >5	Single centre – clinic	IBD	110	47	44	34	0.75	Poor sleep is frequent in IBD and associated with psychological distress.
Gingold-Belfer et al[220]	2014	Israel	PSQI >5	Single centre – clinic	Crohn’s disease	108	47	40	108	0.37	Poor sleep is associated with active Crohn’s

Study	Year	Country	Poor sleep definition	Study population	Population	Sample size	Percentage female (%)	Age	Number with Crohn's disease	Proportion with poor sleep	Study summary
											disease but not inactive disease.
Graff et al[221]	2011	USA	PSQI >5	Manitoba IBD cohort	IBD	318	60	43	160	0.49	Poor sleep is prevalent in those with active IBD but also in those with inactive IBD.
Habibi et al[253]	2019	Iran	PSQI >5	Single centre – clinic	IBD	68	63	38	24	0.32	Poor sleep is prevalent in those with IBD including those in remission.
Hashash et al[233]	2016	USA	PSQI >5	Single centre – registry	IBD	685	53	44	418	0.54	Fatigue was associated wit poor sleep and psychopathology.
Hood et al[155]	2018	USA	PSQI >5	Multicentre – clinic	IBD	47			0	0.59	Poor sleep is prevalent in UC and related to depression.
IsHak et al[235]	2017	USA	PROMIS-SD *t* score >50	Single centre – clinic	IBD	110	43	42	62	0.6	Patient's with Crohn's disease demonstrated worse impairments in quality of life and function than those with ulcerative colitis.
Iskandar et al[167]	2020	USA	PSQI >5	Single centre – clinic	Crohn's disease	61		32	61	0.57	Crohn's disease patients reported more disturbed

Study	Year	Country	Poor sleep definition	Study population	Population	Sample size	Percentage female (%)	Age	Number with Crohn's disease	Proportion with poor sleep	Study summary
											sleep than controls but this was not confirmed with objective measures.
Kani et al[254]	2019	Turkey	PSQI >5	Single centre – clinic	IBD	136	58	39	72	0.59	Dream anxiety may lead to sleep disturbance in patients with IBD.
Kappelman et al[153]	2014	USA	PROMIS-SD *t* score >50	Internet cohort multicentre	IBD	10634	71	44	6689	0.58	Health outcomes measures differ between patients with IBD and the general population.
Keskin et al[255]	2020	Turkey	PSQI >5	Single centre – clinic	IBD	89	56	37	41	0.51	IBD risk factor for sleep disturbance with eveningness more common than in controls.
Lee et al[165]	2018	USA	PSQI >5	Single centre – clinic	IBD	56	66	45	39	0.82	Treatment with immunomodulators or biologics does not appear to improve sleep quality.
Marinelli et al[156]	2020	Italy	PSQI >5	Single centre – clinic	IBD	166	47	44	87	0.67	Sleep quality was not associated with IBD activity but with mood,

Study	Year	Country	Poor sleep definition	Study population	Population	Sample size	Percentage female (%)	Age	Number with Crohn's disease	Proportion with poor sleep	Study summary
											disability and quality of life.
Michalopoulos et al[166]	2018	Greece	PSQI >5	Single centre – clinic	IBD	90	46	40	54	0.45	In IBD in clinical remission endoscopic findings was associated with poor sleep.
Schindlbeck et al[199]	2016	Germany	PSQI >5	Single centre – clinic	IBD	43	72	47	30	0.61	Restless leg syndrome in inflammatory disease with associated with worse quality of life.
Sobolewska-Włodarczyk et al[226]	2018	Poland	PSQI >5	Single centre – clinic	IBD	65	43	40	30	0.69	Poor sleep in IBD related to IBD activity.
Sobolewska-Włodarczyk et al[256]	2020	Poland	PSQI >5	Single centre – clinic	IBD	65	47	40	30	0.57	Specific adipokine profiles are associated with circadian rhythms.
Sochal et al[154]	2020	Poland	PSQI >5	Single centre – clinic	IBD	133	55	37	68	0.43	Poor sleep in IBD is common and related to mood.
Sofia et al[169]	2019	USA	PSQI >5	Single centre – clinic	IBD	92	62	43	92	0.77	Poor sleep is common in Crohn’s disease and associated with adverse outcomes.

Study	Year	Country	Poor sleep definition	Study population	Population	Sample size	Percentage female (%)	Age	Number with Crohn's disease	Proportion with poor sleep	Study summary
Stevens et al[158]	2016	USA	PROMIS-SD *t* score >50	single centre – registry	IBD	160	48	35	94	0.44	Vedolizumab and anti-TNF biologics were associated with improvement in sleep quality.
Takahara et al[197]	2016	Japan	PSQI >5	Single centre – clinic	IBD	80	42	42	34	0.4	Restless leg syndrome occurs frequently in Japanese patients with IBD.
Uemura et al[168]	2016	Japan	PSQI >5.5	Single centre – clinic	IBD	136	44	42	48	0.44	Sleep disturbance common in Japanese IBD patients and associated with poor quality of life.
van Langenberg et al[257]	2017	Australia	PSQI >5	Single centre – clinic	IBD	49	58	44	49	0.63	Crohn's disease patients demonstrated subtle cognitive impairment.
Wilson et al[160]	2014	USA	PROMIS-SD *t* score >50	Single centre – registry	IBD	131	55	25	78	0.44	High CRP associated with poor sleep irrespective of night-time disruptions.
Zargar et al[258]	2019	Iran	PSQI >5	Single centre – clinic	IBD	115	49	38	30	0.51	IBS may worsen sleep disturbance in IBD.

Study	Year	Country	Poor sleep definition	Study population	Population	Sample size	Percentage female (%)	Age	Number with Crohn's disease	Proportion with poor sleep	Study summary
Zhang et al[173]	2020	China	PSQI >5	Single centre – clinic	IBD	120	50	36	39	0.99	Sleep quality in those with peripheral arthropathy and IBD was worse than those without.

USA – United States of America; IBD – inflammatory bowel disease; PSQI – Pittsburgh Sleep Quality Index; BSNQ – Basic Nordic Sleep Questionnaire – first question used.

Table 3.2: Meta-regression performed for prevalence of poor sleep. IBD – inflammatory bowel disease.

	Number of studies	**Coefficient**	**Standard error**	***P* value**
Crohn's disease	31	0.0147	0.10	0.88
Age	36	0.017	0.006	0.005
Female gender	33	0.002	0.002	0.28
IBD disease duration	18	0.005	0.007	0.54
Objective IBD activity	8	0.64	0.17	0.001
Subjective IBD activity	25	0.013	0.21	0.95
Depression	15	0.13	0.17	0.43

Supplementary Table 3.1: Study characteristics included in meta-analysis.

Study	Year	Country	Poor sleep definition	Study population	Population	Sample size	Percentage female (%)	Age	Number with Crohn's disease	Disease duration (mean, years)
Abdalla et al	2017	USA	PROMIS-SD *t* score >50	Crohn's Colitis Foundation of America Partners Cohort	IBD	6309	71	44	3947	
Ali et al	2013	USA	PSQI >5	Single centre–clinic	IBD	41	66	37	23	
Ananthakrishnan et al	2013	USA	PROMIS-SD *t* score >50	Crohn's Colitis Foundation of America Partners Cohort	IBD	3173	72	44	2079	7.6
Ballou et al	2018	USA	PSQI >5	Single centre–clinic	IBD	44	71	42	22	
Bazin et al	2019	France	PSQI >5	Single centre–clinic	Crohn’s disease	34	44	40	34	
Bucci et al	2018	Italy	PSQI >5	Single centre–clinic	IBD	47	53	38	28	7
Calvo et al	2020	Spain	PSQI >5	Single centre–clinic	IBD	102	43	45	51	8

Study	Year	Country	Poor sleep definition	Study population	Population	Sample size	Percentage female (%)	Age	Number with Crohn's disease	Disease duration (mean, years)
Chakradeo et al	2018	USA	PSQI >5	Single centre–clinic	IBD	115	62	41		7
Chrobak et al	2018	Poland	PSQI >5	Single centre–clinic	IBD	72	42	42	34	
Frigstad et al	2018	Norway	Basic Nordic Sleep Questionnaire	Multicentre	IBD	405	49	40	227	11.5
Gîlca-Blanariu et al	2020	Romania	PSQI >5	Single centre–clinic	IBD	110	47	44	34	
Gingold-Belfer et al	2014	Israel	PSQI >5	Single centre–clinic	Crohn's disease	108	47	40	108	15
Graff et al	2011	USA	PSQI >5	Manitoba IBD cohort	IBD	318	60	43	160	15
Habibi et al	2019	Iran	PSQI >5	Single centre–clinic	IBD	68	63	38	24	
Hashash et al	2016	USA	PSQI >5	Single centre–registry	IBD	685	53	44	418	
Hood et al	2018	USA	PSQI >5	Multicentre–clinic	IBD	47			0	

Study	Year	Country	Poor sleep definition	Study population	Population	Sample size	Percentage female (%)	Age	Number with Crohn's disease	Disease duration (mean, years)
IsHak et al	2017	USA	PROMIS-SD *t* score >50	Single centre–clinic	IBD	110	43	42	62	
Iskandar et al	2020	USA	PSQI >5	Single centre–clinic	Crohn's disease	61		32	61	
Kani et al	2019	Turkey	PSQI >5	Single centre–clinic	IBD	136	58	39	72	
Kappelman et al	2014	USA	PROMIS-SD *t* score >50	Internet cohort multicetnre	IBD	10634	71	44	6689	7.5
Keskin et al	2020	Turkey	PSQI >5	Single centre–clinic	IBD	89	56	37	41	8.7
van Langenberg at al	2017	Australia	PSQI >5	Single centre–clinic	IBD	49	58	44	49	10.1
Lee et al	2018	USA	PSQI >5	Single centre–clinic	IBD	56	66	45	39	6.4
Marinelli et al	2020	Italy	PSQI >5	Single centre–clinic	IBD	166	47	44	87	
Michalopoulos et al	2018	Greece	PSQI >5	Single centre–clinic	IBD	90	46	40	54	

Study	Year	Country	Poor sleep definition	Study population	Population	Sample size	Percentage female (%)	Age	Number with Crohn's disease	Disease duration (mean, years)
Schindlbeck et al	2016	Germany	PSQI >5	Single centre–clinic	IBD	43	72	47	30	5.7
Sobolewska-Włodarczyk et al	2018	Poland	PSQI >5	Single centre–clinic	IBD	65	43	40	30	14.9
Sobolewska-Włodarczyk et al	2020	Poland	PSQI >5	Single centre–clinic	IBD	65	47	40	30	3
Sochal et al	2020	Poland	PSQI >5	Single centre–clinic	IBD	133	55	37	68	
Sofia et al	2019	USA	PSQI >5	Single centre–clinic	IBD	92	62	43	92	5.5
Stevens et al	2016	USA	PROMIS-SD *t* score >50	Single centre–registry	IBD	160	48	35	94	5.8
Takahara et al	2016	Japan	PSQI >5	Single centre–clinic	IBD	80	42	42	34	13
Uemura et al	2016	Japan	PSQI >5.5	Single centre–clinic	IBD	136	44	42	48	
Wilson et al	2014	USA	PROMIS-SD *t* score >50	Single centre–registry	IBD	131	55	25	78	11.3

Study	Year	Country	Poor sleep definition	Study population	Population	Sample size	Percentage female (%)	Age	Number with Crohn's disease	Disease duration (mean, years)
Zargar et al	2019	Iran	PSQI >5	Single centre–clinic	IBD	115	49	38	30	
Zhang et al	2020	China	PSQI >5	Single centre–clinic	IBD	120	50	36	39	

HADS-D Hospital Anxiety and Depression Scale Depression sub-score; BDI-II Beck's Depression Inventory II; IBD – inflammatory bowel disease; PSQI – Pittsburgh Sleep Quality Index; CRP – C-reactive protein.

Supplementary table 1: continued

Study	Number of controls	Proportion with poor sleep	Proportion with active IBD	Proportion with objectively active IBD	Definition of objective IBD activity	Proportion with depression	Depression score	Study summary
Abdalla et al		0.54	0.42			0.01	BDI-II	IBD-IBS diagnosis was associated with increased narcotic usage and poor sleep.
Ali et al		0.87	0.49	0.71	histology	0.074	HADS-D	Clinically active IBD was associated with poor sleep.
Ananthakrishnan et al		0.6	0.43			0.089	Depression under treatment	Sleep disturbance was associated with an increased risk of disease flares in Crohn's disease but not ulcerative colitis.
Ballou et al		0.54				0.091	BDI-II	IBD patients at a tertiary clinic have poorer sleep than healthy controls.
Bazin et al		0.35	0.41			0.11	HADS-D	Sleep efficiency is lower in those active Crohn's disease than in remission.
Bucci et al	47	0.38				0.2	HADS-D	Bruxism was associated with pathological sleep.
Calvo et al		0.54				0.24	PROMIS-SD-depression	Poor sleep quality is present in more than half of people with IBD.

Study	Number of controls	Proportion with poor sleep	Proportion with active IBD	Proportion with objectively active IBD	Definition of objective IBD activity	Proportion with depression	Depression score	Study summary
Chakradeo et al	76	0.63				0.25	BDI-II	Later chronotype and markers of circadian misalignment were associated with IBD-specific complications and lower quality of life.
Chrobak et al	57	0.68				0.5	HADS-D	Chronotype preferences contribute to fatigue in IBD.
Frigstad et al		0.19	0.38	0.31	CRP >5	0.5	HADS-D	Sleep and depressive symptoms were associated with total fatigue scores.
Gîlca-Blanariu et al	66	0.75	0.49			0.5	PROMIS-SD-depression	Poor sleep is frequent in IBD and associated with psychological distress.
Gingold-Belfer et al		0.37	0.34			0.51	PROMIS-SD-depression	Poor sleep is associated with active Crohn's disease but not inactive disease.
Graff et al		0.49	0.46	0.23	CRP >8	0.51	Depressive symptoms	Poor sleep is prevalent in those with active IBD but also in those with inactive IBD.

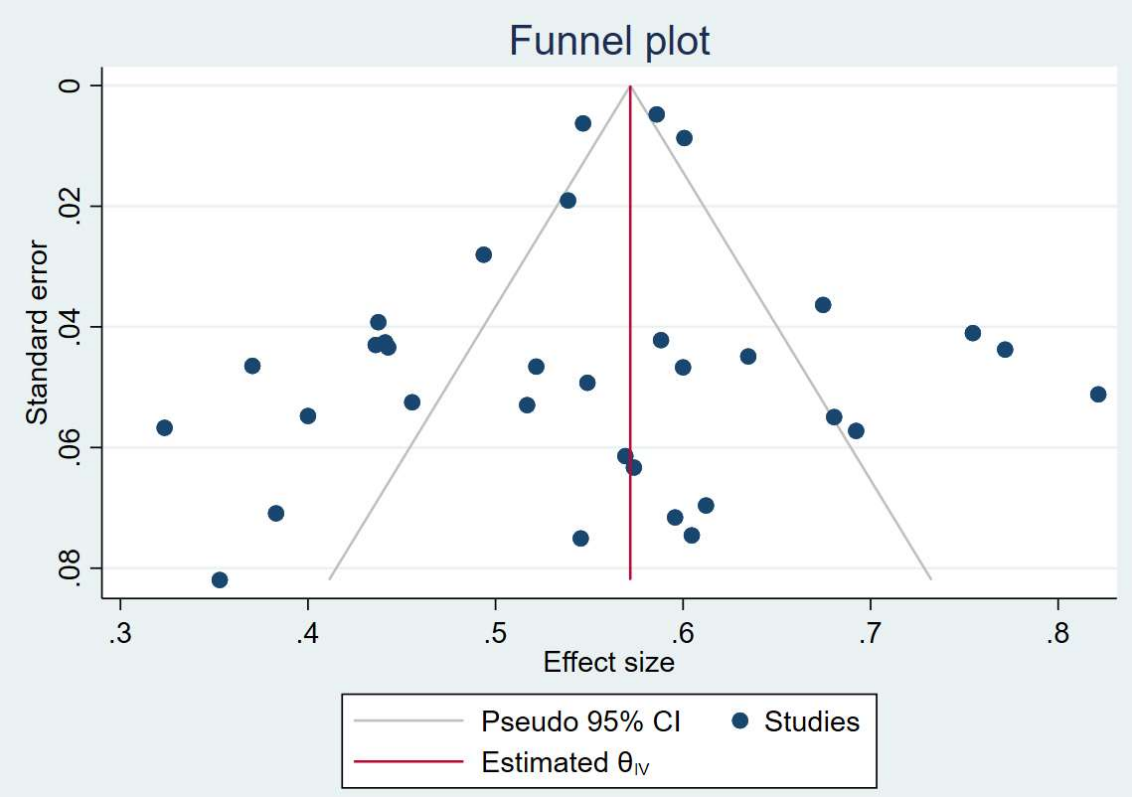
Study	Number of controls	Proportion with poor sleep	Proportion with active IBD	Proportion with objectively active IBD	Definition of objective IBD activity	Proportion with depression	Depression score	Study summary
Habibi et al		0.32	0.75			0.52	HADS-D	Poor sleep is prevalent in those with IBD including those in remission.
Hashash et al		0.54	0.21	0.216	CRP >7	0.55	PROMIS-SD-depression	Fatigue was associated with poor sleep and psycopathology.
Hood et al		0.59						Poor sleep is prevalent in ulcerative colitis and related to depression.
IsHak et al		0.6						Patient's with Crohn's disease demonstrated worse impairments in quality of life and function than those with ulcerative colitis.
Iskandar et al		0.57	0.55					Crohn's disease patients reported more disturbed sleep than controls but this was not confirmed with objective measures.
Kani et al	168	0.59	0.17	0.37	CRP >7			Dream anxiety may lead to sleep disturbance in patients with IBD.

Study	Number of controls	Proportion with poor sleep	Proportion with active IBD	Proportion with objectively active IBD	Definition of objective IBD activity	Proportion with depression	Depression score	Study summary
Kappelman et al		0.58	0.5					Health outcomes measures differ between patients with IBD and the general population.
Keskin et al	44	0.51						IBD risk factor for sleep disturbance with eveningness more common than in controls.
van Langenberg at al	31	0.63	0.42	0.27	CRP >5			Crohn's disease patients demonstrated subtle cognitive impairment.
Lee et al		0.82	0.46					Treatment with immunomodulators or biologics does not appear to improve sleep quality.
Marinelli et al		0.67	0.47	0.47	Calprotectin >250			Sleep quality was not associated with IBD activity but with mood, disability and quality of life.
Michalopoulos et al		0.45	0.43					In IBD in clinical remission endoscopic findings was associated with poor sleep.
Schindlbeck et al		0.61					BDI-II	Restless leg syndrome in inflammatory disease with

Study	Number of controls	Proportion with poor sleep	Proportion with active IBD	Proportion with objectively active IBD	Definition of objective IBD activity	Proportion with depression	Depression score	Study summary
								associated with worse quality of life.
Sobolewska-Włodarczyk et al		0.69	0.78					Poor sleep in IBD related to IBD activity.
Sobolewska-Włodarczyk et al		0.57	0.8					Specific adipokine profiles are associated with circadian rhythms.
Sochal et al		0.43	0.62					Poor sleep in IBD is common and related to mood.
Sofia et al		0.77	0.15					Poor sleep is common in Crohn's disease and associated with adverse outcomes.
Stevens et al		0.44						Vedolizumab and anti-TNF biologics were associated with improvement in sleep quality.
Takahara et al		0.4						Restless leg syndrome occurs frequently in Japanese patients with IBD.
Uemura et al		0.44	0.16					Sleep disturbance common in Japanese IBD patients and

Study	Number of controls	Proportion with poor sleep	Proportion with active IBD	Proportion with objectively active IBD	Definition of objective IBD activity	Proportion with depression	Depression score	Study summary
								associated with poor quality of life.
Wilson et al		0.44	0.42	0.19	CRP >8			High CRP associated with poor sleep irrespective of night-time disruptions.
Zargar et al		0.51						IBS may worsen sleep disturbance in IBD.
Zhang et al	120	0.99	0.35					Sleep quality in those with peripheral arthropathy and IBD was worse than those without.

Supplementary Figure 3.1: Funnel plot of meta-analysis for prevalence of poor sleep in those with inflammatory bowel disease.

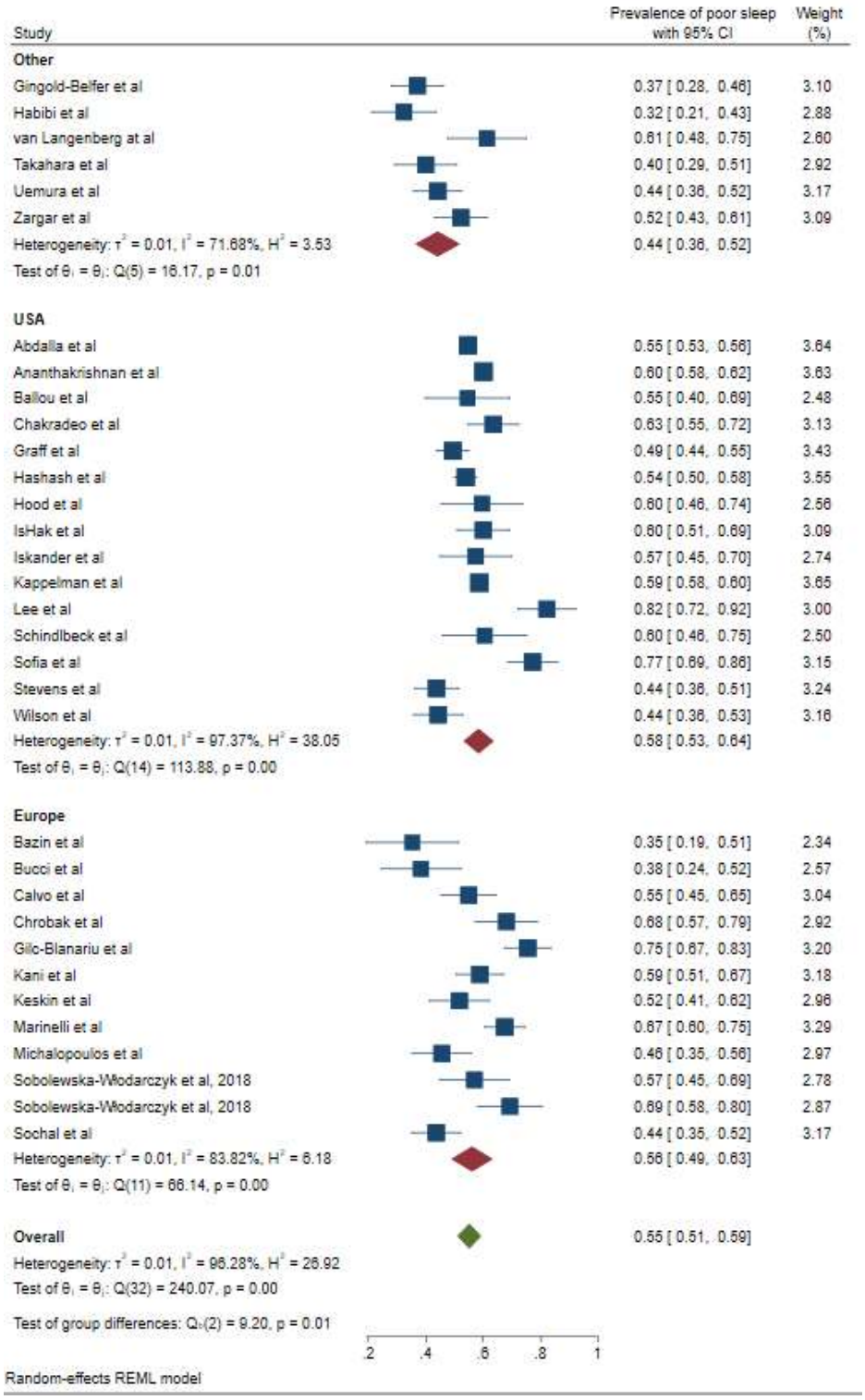


Supplementary Table 3.2: Study quality scored according to the Newcastle–Ottawa Scale with sub-scores and associated study quality detailed.

Study	Year	Selection	Comparability	Outcome	Study quality
Abdalla et al	2017	3	1	2	Good
Ali et al	2013	3	1	3	Good
Ananthakrishnan et al	2013	3	1	2	Good
Ballou et al	2018	2	1	2	Fair
Bazin et al	2019	3	1	3	Good
Bucci et al	2018	2	1	2	Fair
Calvo et al	2020	3	2	3	Good
Chakradeo et al	2018	4	2	2	Fair
Chrobak et al	2018	2	2	2	Fair
Frigstad et al	2018	3	2	2	Good
Gîlc-Blanariu et al	2020	4	1	3	Good
Gingold-Belfer et al	2014	3	1	3	Good
Graff et al	2011	3	2	3	Good
Habibi et al	2019	4	2	3	Good
Hashash et al	2016	2	2	3	Fair
Hood et al	2018	2	1	3	Fair
IsHak et al	2017	2	1	2	Fair
Iskandar et al	2020	2	2	3	Fair
Kani et al	2019	2	2	1	Fair
Kappelman et al	2014	3	2	2	Good
Keskin et al	2020	2	1	2	Fair
Lee et al	2018	3	2	2	Fair
Marinelli et al	2020	2	2	2	Fair
Michalopoulos et al	2018	2	2	3	Fair
Schindlbeck et al	2016	4	2	3	Good
Sobolewska-Włodarczyk et al	2018	3	1	3	Good
Sobolewska-Włodarczyk et al	2020	3	1	2	Fair
Sochal et al	2020	3	1	3	Good

Study	Year	Selection	Comparability	Outcome	Study quality
Sofia et al	2019	3	1	2	Good
Stevens et al	2016	4	2	3	Good
Takahara et al	2016	3	2	2	Good
Uemura et al	2016	3	2	3	Good
van Langenberg at al	2017	2	2	2	Fair
Wilson et al	2014	3	2	2	Good
Zargar et al	2019	4	2	2	Good
Zhang et al	2020	2	2	2	Fair

Supplementary Figure 3.2: Subgroup analysis of prevalence of poor sleep by geographic region.



CHAPTER 4: SLEEP AND QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE

This chapter presents the manuscript 'Sleep quality is associated with reduced quality of life in inflammatory bowel disease through its interaction with pain', that was under review at the journal JGH Open as of July 2024.

Author contributions

Alex Barnes: responsible for study concept and design, data acquisition, analysis, and data interpretation, drafting of manuscript, critical revision of the manuscript.

Robert V Bryant: responsible for critical revision of the manuscript.

Paul Spizzo: responsible for critical revision of the manuscript.

Sutapa Mukherjee: responsible for critical revision of the manuscript.

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Please see appendices for further authorship information.

[Manuscript] Sleep quality is associated with reduced quality of life in inflammatory bowel disease through its interaction with pain

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Réme Mountifield: responsible for critical revision of the manuscript.

Conflicts of interest include speakers fees, and Ad Boards from Abbott, AbbVie, Allergan, Anatara, AstraZeneca, Bayer, BMS 2020, Celegene, Celltrion, Falk, Ferring, Gilead, Hospira, Immuninc, ImmunsanT, Janssen, MSD, Nestle, Novartis, Progenity, Pfizer, Sandoz, Shire, Takeda, Vifor, RAH research Fund, The Hospital Research Fund 2020–2022 and The Helmsley Trust 2020–2023.

Ethics approval

Ethics approval for this study was obtained from the Southern Adelaide Human Research Ethics Committee (203.20).

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Data availability statement

The data underlying this article are available upon request to the author.

Abstract

Quality of life is reduced in people with inflammatory bowel disease (IBD) and poor sleep is prevalent in people with IBD. This study aimed to investigate the influence of sleep on quality of life (QoL) in people with inflammatory bowel disease.

Methods

An online questionnaire was administered through three tertiary IBD centres, social media and through Crohn's Colitis Australia. The questionnaire included the EQ-5D-5L measures of health-related QoL, the insomnia severity index, the Pittsburgh sleep quality index (PSQI) and validated IBD activity and mental health scores.

Results

There were 553 responses included with a diagnosis of Crohn's disease (62.2%), with over half on biologic therapy (53.1%). Poor sleep and clinically significant insomnia were associated with lower QoL (EQ-5D-5L scores: EQVAS, utility score, $p<0.001$ for all). Sleep quality scores correlated with the EQ-5D-5L domains of 'pain' (ρ 0.35,$p<0.001$), 'usual activities' (ρ 0.32,$p<0.001$), and 'depression-anxiety' (ρ 0.37,$p<0.001$). After adjusting for demographic variables, IBD activity, and depression and anxiety via multivariate regression the 'pain' domain continued to be associated with PSQI components 'sleep quality' ($p<0.001$), 'sleep disturbance' ($p<0.001$) and 'sleep duration' ($p<0.001$). Clinically significant insomnia was associated with a reduction in QoL (EQVAS, utility score) independent of IBD activity ($p<0.001$) and of a similar magnitude to that seen with IBD activity.

Conclusion

Health related QoL in IBD is influenced by aspects of sleep quality irrespective of IBD activity and mental health conditions. The presence of insomnia is associated with a reduction in health-related QoL. Consideration should be given to sleep targeting interventional studies in an IBD population.

Keywords: insomnia, inflammatory bowel disease, quality of life, pain interference

looking for sleep problems in people with IBD.

Introduction

Inflammatory bowel disease (IBD) is an immune-mediated condition with a chronic relapsing remitting course. The symptoms of active IBD are characterised by diarrhoea, abdominal pain and gastrointestinal bleeding and have a substantial impact on quality of life[259-261]. The impact of IBD disease activity on quality of life (QoL) is expectedly well-established, with evidence of an improvement in QoL following institution of medical treatment[94,262-264] and surgery[265-267]. However even in the absence of active disease, people with IBD have a poorer QoL than the general population[268-270]. Factors beyond disease activity are relevant to QoL, in particular psychosocial dysfunction [271] and the effect of IBD on relationships with food[272].

Poor sleep is common in people with IBD[273] and whilst worse in those with clinically active IBD[200], remains an issue for patients in remission[274]. In people with IBD disturbed sleep has also been linked to mental health conditions[159,167] fatigue[221], and opioid usage[275]Insomnia is the most common sleep disorder in people with IBD and has been associated with mental health conditions, IBD activity and worse IBD related disability[183,276].

Poor sleep quality has been associated with decreased health related quality of life[277]. A longitudinal study has explored sleep and QoL in IBD suggesting that sleep apnoea and insomnia symptoms were associated with worse health related QoL four weeks later[181]. Our study aimed to investigate sleep quality and insomnia severity and its associations with QoL, taking into account IBD activity and mental health conditions.

Methods

An online questionnaire was made available to people with IBD via tertiary hospital patient email lists, private gastroenterology practice email lists and social media associated with a patient support organisation. Individuals with a self-reported diagnosis of IBD over 18 years of age were invited to participate. Demographic data such as age and sex were recorded, along with IBD related data including disease duration and previous surgery. Ethics approval for this study was obtained from the Southern Adelaide Human Research Ethics Committee (203.20).

The Pittsburgh Sleep Quality Index (PSQI) is a validated tool which assesses perceived sleep quality[113]. The index consists of subscales on sleep duration, sleep disturbance, sleep latency, daytime dysfunction, sleep efficiency, overall sleep quality and medications for sleep. The score ranges from 0 to 21, with a PSQI > 5 considered to represent poor sleep quality.

The Insomnia Severity Index (ISI) is a self-reported questionnaire that been validated for assessment of insomnia, evaluating the response to treatment, and as an outcome measure for insomnia research[278-280]. The index consists of seven items with a 5-point Likert scale used to rate each item. A score between 0-7 is considered to indicate the absence of insomnia, 8-14 subthreshold insomnia, 15-21 moderate insomnia, and over 21 denotes severe insomnia. Clinically significant insomnia is defined as an ISI score greater or equal to 10 as is commonly used in screening[278].

IBD disease activity was assessed using the Harvey Bradshaw Index (HBI) in the case of Crohn's disease with HBI > 5 considered active disease[217]. The patient reported version of the HBI was utilised in the survey, although a decision was made to maintain the general well-being and abdominal pain score similar to the physician HBI rather than using a ten-point Likert scale[281]. The Simple Clinical Colitis Activity Index (SCCAI) was used in the case of ulcerative colitis, an SCCAI > 5 was considered active disease[282]. The patient reported form of the SCCAI was utilised[283] in the survey. The use of a self-reported SCCAI has been previously validated with good agreement with physician reported SCCAI[284].

Anxiety was assessed using the generalised anxiety disorder 7-item scale (GAD-7)[285] with a score over 10 used to indicate likely clinically significant anxiety. The Patient Health Questionnaire 9 (PHQ-9) was used to assess depression with a score over 15 used to indicate likely clinically significant depression[286].

QoL was assessed using the EQ-5D-5L[99] – which measures health related QoL and has been validated in IBD populations[100], with mapping available to the short inflammatory bowel disease questionnaire – an IBD specific measure of health related QoL[101]. The EQ-5D-5L was chosen due to its immediate comparability to other populations and its brevity. The EQ-5D-5L consists of five dimensions of health related QoL – these include – mobility, usual activities, self-care, pain and anxiety-depression. Each dimension has five levels ranging from no problem (1), slight problems (2), moderate problems (3), severe problems (4) and extreme problems (5). There is also a visual analogue scale of QoL referred to as EQVAS. The EQ-5D-5L produce a health state out of 3125 possible health states. The health states are then converted to a single utility index score – here we used the published value set for England[287]. These health states and utility index scores can then be compared to other populations. Here we used South Australian population norms[288].

The primary outcome of this study was the relationship between QoL (EQ-5D-5L domains) and sleep quality (PSQI components). Secondary outcomes included the relationship between PSQI score and EQ-5D-5L scores (utility score and EQVAS), insomnia scores and quality of life (EQ-5D-5L domains and scores) and examining the influence of IBD activity and depression and anxiety on these relationships.

Statistical analysis

Statistical analysis was performed using Stata SE 16 (StataCorp, College Station, TX, USA). Inadequate completion of score or index led to that result being discarded. For normally distributed variables mean and standard deviation (SD) were reported with comparisons made using the student t-test. For non-normally distributed variables median, and interquartile range (IQR) were reported, with comparisons made using the Mann- Whitney U test. Pearson's or Spearman's correlation was used as appropriate, with interpretation of coefficients as: very weak <0.19, weak 0.2-0.3, moderate 0.3-0.5, strong 0.5-0.79 and very strong >0.80.[289] One-way analysis of variance used with Tukey post-hoc test and adjusted for multiple comparisons as appropriate. Regression was undertaken to determine predictors of health-related QoL. Due to multicollinearity this was performed in a stepwise fashion with each PSQI component considered separately in univariate regression and then considering other factors such as IBD activity, depression and anxiety in multivariate regression. Regression was also performed for an outcome of EQVAS and the EQ-5D utility score to investigate the influence of ISI on these values.

Results

The cohort (n=553) was predominantly female (75.4%) with a diagnosis of Crohn's disease (62.2%), with over half on biologic therapy (53.1%) and over a third having had previous surgery for IBD (see Table 1). The completion rate for the questionnaire was 90.5%. Missing or incomplete responses resulted in exclusion of fifty-eight questionnaire responses. EQ-5D utility score for the cohort was (mean (SD)) 0.79 (0.15) (see Table 2), which was significantly lower than South Australian population norms, with similar results for the EQVAS (64.47 (19.9) v 78.55 (16.57), p <0.001)) The distribution of EQ-5D utility scores and EQVAS can be seen in Figures 1 and 2, and EQ-5D component scores and be seen in supplementary Figures 1-4. There was no significant difference in utility scores between Crohn's disease and ulcerative colitis (table 2), and no significant difference with EQVAS

and EQ-5D component scores, apart from a trend to worse scores for mobility component in Crohn's disease (supplementary table 1).

EQ-5D component scores

Sleep quality (PSQI) and insomnia severity scores both moderately correlated with utility score, EQVAS, 'usual activities', 'pain ' and 'anxiety-depression' scores, and weakly correlated with 'mobility ' scores (table 3). Neither score correlated with 'self-care'. This was further investigated with PSQI scores different between most scores in components 'anxiety-depression', 'pain ' and 'usual activities' (see supplementary figure 5) and little difference in scores in other EQ-5D components. Insomnia severity (see supplementary figure 6) had similar associations although less difference seen in ISI scores across the scores for EQ-5D component 'usual activities'.

IBD activity measures by HBI or SCCAI had a strong correlation with EQ-5D utility score and EQVAS, moderate correlation with 'usual activities', 'pain' and 'anxiety-depression' scores and weak correlation with 'mobility' scores. The general well-being component of SCCAI and HBI had the strongest correlation with EQVAS and the EQ-5D utility score, followed by the abdominal pain sub-score of the HBI (see supplementary table 4). Abdominal pain was more common in those with active disease in both Crohn's disease and ulcerative colitis($p<0.0001$), with differences seen between IBD subtypes in active disease ($p=0.014$) but not inactive disease ($p=0.21$) (see supplementary table 6). Extraintestinal manifestations were also considered with all manifestations associated with a decrease in the utility score with the largest decrease seen in oral involvement (see supplementary table 5).

Components of sleep quality

The EQ-5D utility score was worse with worse PSQI components sleep quality, daytime dysfunction, sleep disturbance and sleep duration (see supplementary figure 7). Sleep latency, sleep efficiency and sleep medications did not reach significance for worse 'utility' scores (supplementary figure 7). Similarly sleep efficiency, latency and medications did not reach above weak correlation with any EQ-5D component (see supplementary table 2). Further analysis of sleep quality, daytime dysfunction, sleep disturbance and sleep duration was undertaken.

Sleep duration

Sleep duration remained associated with domain scores 'anxiety-depression', 'pain' and 'usual activities' following adjustment by demographic variables (see table 5). Following

adjustment by IBD activity the association with sleep duration and domain scores was attenuated however remained for domains 'pain' (β 0.22 (0.15-0.30)) and 'anxiety-depression' (β 0.15 (0.06-0.25)). After inclusion of anxiety and depression only the 'pain' domain although further attenuated remained significant (β 0.17 (0.10-0.25))

Sleep disturbance

Sleep disturbance remained associated with domain scores 'anxiety-depression', 'pain' and 'usual activities' following adjustment by demographic variables. Following adjustment by IBD activity the association with sleep duration and domain scores was attenuated however remained relevant for all domains. After inclusion of anxiety and depression only the 'pain' domain although further attenuated remained significant (β 0.25 (0.12-0.37)).

Daytime dysfunction

Daytime dysfunction remained associated with domain scores 'anxiety-depression', 'pain' and 'usual activities' following adjustment by demographic variables (see supplementary table 4). Following adjustment by IBD activity the association with sleep duration and domain scores was attenuated however remained relevant for all domains. After inclusion of anxiety and depression the 'usual activities' domain remained significant but with a negligible coefficient (β 0.12 (0.0.006-0.22)).

Sleep quality

Sleep quality remained associated with domain scores 'anxiety-depression', 'pain' and 'usual activities' following adjustment by demographic variables (see table 5). Following adjustment by IBD activity the association with sleep duration and domain scores was attenuated however remained relevant for all domains. After inclusion of anxiety and depression only the 'pain' domain although further attenuated remained significant (β 0.18 (0.09-0.29)).

Insomnia

Clinically significant insomnia was present in 61.7% of the cohort with at least moderate insomnia in 36.3%. Health related QoL scores (utility score and EQVAS) were significantly worse in those with clinically significant insomnia and active IBD than with active IBD alone (see Table 4). This effect may be partially explained by the presence of higher IBD activity scores (SCCAI or HBI) in those with clinically significant insomnia and active IBD than active IBD alone (see table 4). Health related QoL scores were similar between those with

active IBD without insomnia and those with insomnia without active IBD (see table 4). There was no difference in the rate of clinically significant insomnia between ulcerative colitis and Crohn's disease (see supplementary table 3).

A change in insomnia severity score of 1 was associated with a reduction of 1.4 (1-17-1.6) (univariate regression see table 6) in the EQVAS, with clinically significant insomnia associated with a reduction of 13.6 (10.42-16.91) (univariate regression see table 6) in EQVAS. Following introduction of demographic and IBD activity the reduction in EQVAS for clinically significant insomnia remained significant (10.11 (6.96-13.27). However, after introduction of depression and anxiety scores there was no significant reduction in EQVAS. Similar results were obtained when considering the influence of insomnia on the utility score (table 6).

Discussion

This represents the largest study reporting on sleep quality and insomnia and its relationship to QoL in people with IBD. This study presents a detailed analysis of the relationship between health-related QoL and sleep quality, taking into account both IBD activity and co-existing mental health conditions. Of note sleep quality remained associated with the QoL pain domain after adjusting for IBD activity and depression and anxiety. Also of significance, insomnia in the absence of active IBD was associated with a reduction in QoL and this reduction was similar to magnitude to that seen with active IBD in the absence of insomnia.

Sleep quality, sleep duration, and disturbed sleep were associated with a poorer QoL, and the presence of insomnia was associated with worse QoL independent of IBD activity. Aspects of disrupted sleep such as sleep disturbance, daytime dysfunction and sleep quality were associated with worse QoL 'pain' scores following adjustment for demographic factors, IBD activity and depression and anxiety. Similarly sleep duration was associated with worse QoL 'usual activities' score.

Pain is commonly reported by people with IBD[194] and has been related to IBD symptoms. Chronic pain[290] that is more complex and influenced by many factors such as psychological factors[291], and maladaptive processes such as central sensitization are also recognised in patients with IBD[292,293]. Sleep quality has been associated with alterations in the perception of pain[294] that perhaps explains the association with the pain domain scores seen in this study. The relationship between the impact of pain on social and cognitive function, and sleep has

been explored in IBD with a conceptual model proposing important indirect effects from insomnia along with IBD activity, anxiety and depression[295].

Although these data suggest differences in QoL due to insomnia irrespective of IBD activity, it was not possible to establish a similar effect in relation to anxiety and depression. Insomnia is known to have a complicated and likely bidirectional relationship with anxiety and depression[276,296,297]. Depression and anxiety are prevalent in people with IBD[192] and in this study most of those with severe depression scores (79%) and two thirds of those with severe anxiety scores had clinically significant insomnia. A larger cohort with greater differentiation between those with insomnia and anxiety or depression may allow differences in QoL to be established.

Sleep represents a modifiable risk factor for impaired QoL. Treatment of insomnia, the most common sleep disorder in IBD[185], is readily available in the form for cognitive behavioural therapy in insomnia (CBTi)[298,299]. A pilot study of CBTi in an IBD population has demonstrated feasibility and suggested efficacy[190] although larger studies are required to determine this. Other causes of sleep disturbance such as obstructive sleep apnoea, noted to be more common in people with IBD than the general population[184], also have readily available treatment in the form of continuous positive airway pressure and other devices[300]. Screening for sleep disturbance in IBD clinic could be considered and may be possible with typical IBD clinic data[301].

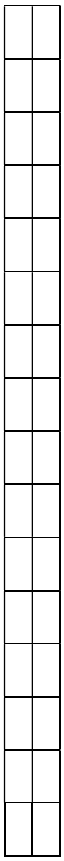
Limitations of this study include selection bias a result of the use of an online questionnaire and the predominantly female participants. Reporting bias is also relevant, noting a population of people with Crohn's disease self-reported worse sleep quality than that measured objectively[167]. The lack of an objective measure of sleep quality and IBD activity, such as endoscopic activity, is considered a limitation, as is the absence of a validated pain questionnaire.

Despite these limitations this study contributes to the IBD QoL literature highlighting the importance of sleep in this population. Further work should consider longitudinal data on the progression of QoL and its relationship to sleep, in particular its prognostic value in IBD outcomes and QoL. Consideration should also be given to implementing screening for sleep disorders in IBD clinic and intervention studies directed at sleep with a view to improving QoL.

Conclusions

Health related quality of life in IBD is influenced by aspects of sleep quality irrespective of IBD activity and mental health conditions. The presence of insomnia is associated with a significant reduction in health-related quality of life. Consideration should be given to sleep targeting interventional studies in an IBD population..

Table 4.1: Demographics of the inflammatory bowel disease population. *p<0.05



IBD and demographic data		Crohn's disease	Ulcerative colitis or indeterminate colitis
Cohort (n)	553	343	210
Age (median (IQR))	41 (32-52)	42 (32-53)	40 (32-50)
Female (%)	75.4	76.3	77.3
Weight (mean(SD))	78.3 (24.5)	81.1 (20.9)	79.1 (19.8)
Height	162.6 (31.9)	168.2 (9.3)	167.9 (8.8)
Crohn's disease (%)	62.2		
IBD disease duration (mean(SD))	12.8 (10.5)	14.1 (11.0)*	10.6 (8.9)*
Previous surgery for IBD (%)	34.0	49.5*	9.8*
Biologic usage (%)	53.1	64.3*	37.6*

Immunomodulator usage (%)	33.9	39.0	34.2
Aminosalicyate usage (%)	32.7	11.4*	63.2*
Corticosteroid usage (%)	7.5	7.4	11.5
Alcohol use (%)	35.4	36.7	45.5
Current smoker (%)	7.2	7.7	5.9
Opioid usage (%)	15.2	18.7*	8.9*

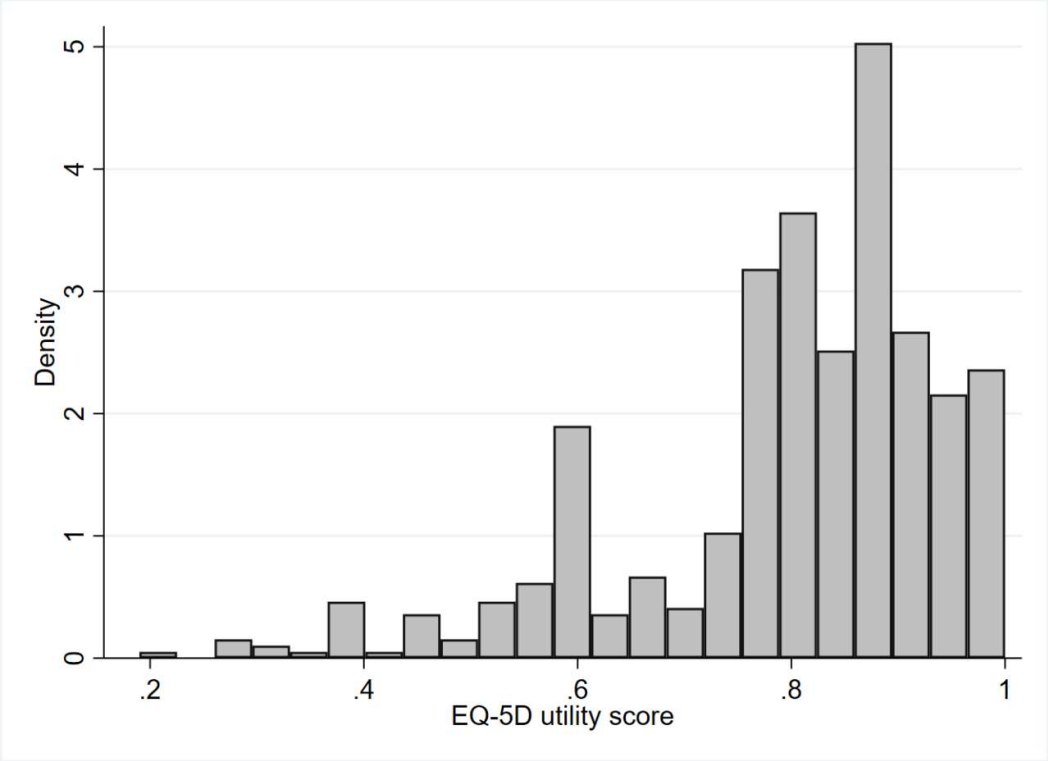


Figure 4.1: Distribution of EQ-5D utility scores.

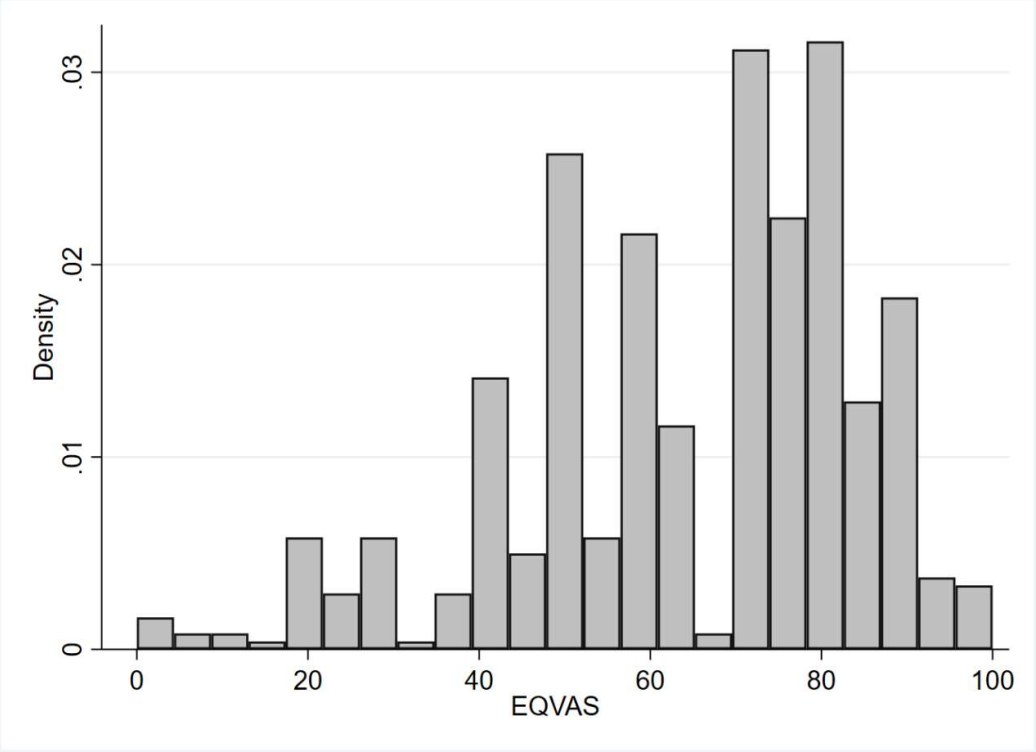


Figure 4.2: Distribution of EQ-5D EQVAS scores.

Table 4.2: EQ-5D weighted score (mean (standard deviation)) from South Australia (SA) population norms, and the study cohort.

Poor sleep quality (Pittsburgh Sleep Quality Index >5), good sleep quality (Pittsburgh Sleep Quality Index < 5), clinically active IBD (Harvey–Bradshaw Index >5 or Simple Clinical Colitis Activity Index > 5), clinically inactive IBD (Harvey–Bradshaw Index ≤5 or Simple Clinical Colitis Activity Index ≤5), clinically significant insomnia (Insomnia Severity Index >15), no significant insomnia (Insomnia Severity Index <7). Comparison between merged cells by Student's *t*-test.

	EQ-5D utility score (mean (standard deviation))	***p* value**
SA population norms	0.91 (0.14)	
Entire cohort	0.79 (0.15)	$p < 0.001$
Crohn's disease	0.80 (0.15)	
Ulcerative colitis	0.79 (0.15)	$p = 0.35$
Poor sleep quality	0.77 (0.15)	
Good sleep quality	0.87 (0.12)	$p < 0.001$
Clinically active IBD	0.77 (0.15)	
Clinically inactive IBD	0.88 (0.10)	$p < 0.001$
Clinically significant insomnia	0.71 (0.16)	
No significant insomnia	0.89 (0.11)	$p < 0.001$

Table 4.3: EQ-5D scores and Pearson's correlation with sleep quality, IBD activity and insomnia.

Sleep quality (Pittsburgh Sleep Quality Index (PSQI)), IBD activity as the Harvey–Bradshaw Index (HBI) for Crohn's disease and the Simple Clinical Colitis Activity Index (SCCAI) for ulcerative or indeterminate colitis, insomnia severity via the Insomnia Severity Index (ISI).

EQ-5D scores	**PSQI**	**HBI**	**SCCAI**	**ISI**
Utility score	-0.46*	-0.50*	-0.49*	-0.47*
EQVAS	-0.38*	-0.50*	0.51*	-0.43*
Mobility	0.22*	0.25*	0.24*	0.15*
Self-care	0.075	0.09	0.097	0.039
Activity	0.32*	0.37*	0.36*	0.31*
Pain	0.35*	0.42*	0.40*	0.31*
Depression and anxiety	0.37*	0.34*	0.33*	0.41*

* $p < 0.001$

	EQVAS (mean(SD))	Utility score (mean(SD))	IBD activity scores (mean(SD))
Inactive IBD	76.37 (14.64)	0.89 (0.095)	SCCAI 4.43 (1.43) HBI 3.91 (1.06)
Clinically significant insomnia without active IBD	68.72 (16.64)	0.83 (0.15)	SCCAI 4.83 (1.34) HBI 4.50 (0.78)
Active IBD without clinically significant insomnia	66.25 (19.31)	0.82 (0.11)	SCCAI 7.24 (2.47) HBI 7.20 (2.60)
Active IBD with clinically significant insomnia	54.67 (18.87)	0.70 (0.16)	SCCAI 8.98 (2.65) HBI 9.17 (2.95)

Table 4.4: Differences in EQ-5D utility score and EQVAS for groups active IBD, active IBD with clinically significant insomnia (insomnia severity index over 15), and inactive IBD.

Differences also assessed for IBD activity scores HBI (Harvey Bradshaw Index) for Crohn's disease and SCCAI (Simple Clinical Colitis Activity Index) for ulcerative or indeterminate colitis.

Oneway ANOVA for EQVAS (df=3, F=36.97, $p<0.0001$) , all comparisons significant ($p<0.001$), except 1v0 ($p=0.21$) and 2v1 ($p=0.94$)

Oneway ANOVA for utility score (df=3, F=76.64, $p<0.0001$) , all comparisons significant ($p<0.001$), except 1v0 ($p=0.21$) and 2v1 ($p=0.99$)

Oneway ANOVA for SCCAI (df=3, F=138.08, $p<0.0001$), all comparisons significant ($p<0.001$), except 1v0 ($p=0.83$)

Oneway ANOVA for HBI (df=3, F=159.34, $p<0.0001$), all comparisons significant ($p<0.001$), except 1v0 ($p=0.70$)

	Univariate	Multivariate[a]	Multivariate[a] with IBD activity	Multivariate[a] with IBD activity, depression and anxiety
	Coefficients (95% CI)	Coefficients (95% CI)	Coefficients (95% CI)	Coefficients (95% CI)
PSQI-sleep quality				
Depression-anxiety	0.44 (0.32-0.55)*	0.42 (0.31-0.53) *	0.38 (0.26-0.49) *	-0.03 (-0.12-0.06)
Pain	0.44 (0.34-0.54) *	0.36 (0.27-0.46) *	0.29 (0.19-0.38) *	0.18 (0.09-0.29)*
Activities	0.29 (0.19-0.38) *	0.23 (0.14-0.33) *	0.19 (0.09-0.28) *	-0.012 (-0.11-0.084)
PSQI-daytime dysfunction				
Depression-anxiety	0.57 (0.45-0.68) *	0.54 (0.42-0.65) *	0.50 (0.38-0.62) *	-0.04 (-0.15-0.06)*
Pain	0.43 (0.32-0.54) *	0.34 (0.24-0.44) *	0.24 (0.15-0.34) *	0.09 (-0.027-0.20)
Activities	0.46 (0.37-0.55)*	0.40 (0.31-0.49) *	0.36 (0.27-0.46) *	0.12 (0.006-0.22)[#]
PSQI-disturbance				
Depression-anxiety	0.55 (0.41-0.69) *	0.52 (0.38-0.66) *	0.46 (0.32-0.61) *	0.0073 (-0.11-0.12)
Pain	0.60 (0.48-0.72) *	0.47 (0.35-0.59) *	0.36 (0.24-0.48) *	0.25 (0.12-0.37)*
Activities	0.40 (0.29-0.52)*	0.32 (0.21-0.44) *	0.26 (0.14-0.38) *	0.068 (-0.050-0.19)
PSQI-duration				
Depression-anxiety	0.20 (0.11-0.30) *	0.18 (0.09-0.29) *	0.15 (0.06-0.25) *	-0.048 (-0.12-0.02)
Pain	0,32 (0.24-0.41) *	0.27 (0.20-0.36) *	0.22 (0.15-0.30) *	0.17 (0.10-0.25)*
Activities	0.15 (0.07-0.23)*	0.11 (0.03-0.19) *	0.08 (0.001-0.15)[#]	0.015 (-0.059-0.088)

Table 4.5: Pittsburgh sleep quality Index (PSQI) components and EQ-5D domains with univariate regression and multivariate regression for each PSQI component separately.

Multivariate regression was then conducted with demographic variables, and then sequentially with IBD activity (as a binary variable with active IBD defined by Harvey Bradshaw Index >= 5, Simple Clinical Colitis Activity Index over 5) as well and then finally including depression and anxiety scores (Patient Health Questionnaire-9, and Generalised Anxiety Disorder-7).

*p<0.0001, #p<0.05

a - Age, gender, IBD subtype, weight, biologic usage, smoker, alcohol, IBD surgery, opioid usage

	Univariate	Multivariate[a]	Multivariate[a] with IBD activity	Multivariate[a] with IBD activity, depression and anxiety
	Coefficients (95% CI)	Coefficients (95% CI)	Coefficients (95% CI)	Coefficients (95% CI)
EQVAS	-1.42 (-1.66- -1.17)*	-1.27 (-1.52 - -1.03)*	-1.09 (-1.34 - -0.84)*	-0.24 (-0.053 – 0.040)[#]
EQ-5D utility score	-0.011 (-0.013- -0.0098)*	-0.010 (-0.012- -0.0085)*	-0.0092 (-0.011 - -0.0073)*	-0.014 (-0.0033 – 0.00053)[#]

Table 4.6: Insomnia severity index score (ISI) and EQVAS with univariate regression, and multivariate regression including demographic factors, followed by inclusion of IBD activity

(as a binary variable with active IBD defined by Harvey Bradshaw Index >= 5, Simple Clinical Colitis Activity Index over 5) as well and then finally including depression and anxiety scores (Patient Health Questionnaire-9, and Generalised Anxiety Disorder-7).

Insomnia severity index score (ISI) and EQ-5D utility score with univariate linear regression and multivariate regression including demographic factors, followed by inclusion of IBD activity (as a binary variable with active IBD defined by Harvey Bradshaw Index >= 5, Simple Clinical Colitis Activity Index over 5) as well and then finally including depression and anxiety scores (Patient Health Questionnaire-9, and Generalised Anxiety Disorder-7).

*p<0.0001, #p>0.05

a - Age, gender, IBD subtype, weight, biologic usage, smoker, alcohol, IBD surgery, opioid usage

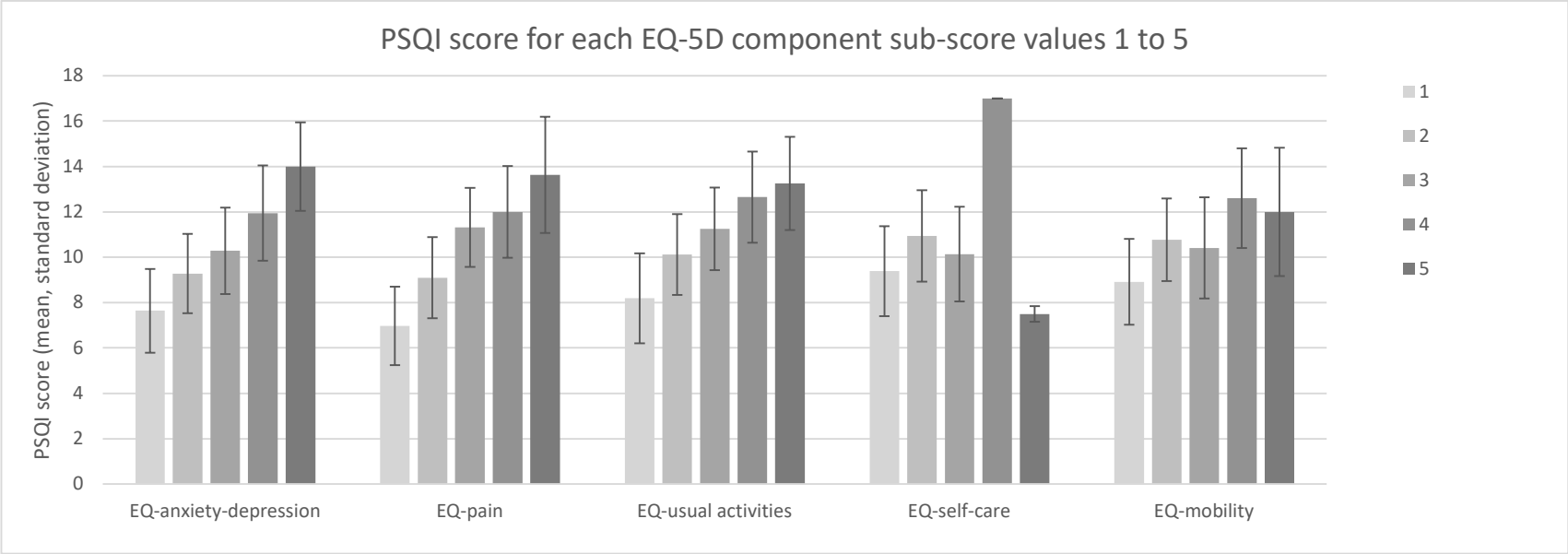


Figure 4.3: Pittsburgh Sleep Quality Index score (PSQI) (mean, standard deviation) for EQ-5D components scores.

EQ-anxiety–depression ANOVA (df = 4, F = 24.01, $p < 0.0001$) on post hoc Tukey's test all significant ($p < 0.001$) except 3v2, 4v3, 5v4. EQ-pain ANOVA (df = 4, F = 33.82, $p < 0.0001$) on post hoc Tukey's test all significant (<0.001) except 4v3, 5v3, 5v4. EQ-usual activities ANOVA (df = 4, F = 17.28, $p < 0.0001$) on post hoc Tukey's test significant results ($p < 0.04$) 2v1, 3v1, 4v1, 2v2 , otherwise no differences seen. EQ-self-care ANOVA (df = 4, F = 2.37, $p = 0.0519$) – no significant differences between groups. EQ-mobility ANOVA (df = 4, F = 8.19, $p < 0.0001$) on post hoc Tukey test significant result ($p < 0.03$) 2v1, 4v1; other comparisons not significantly different.

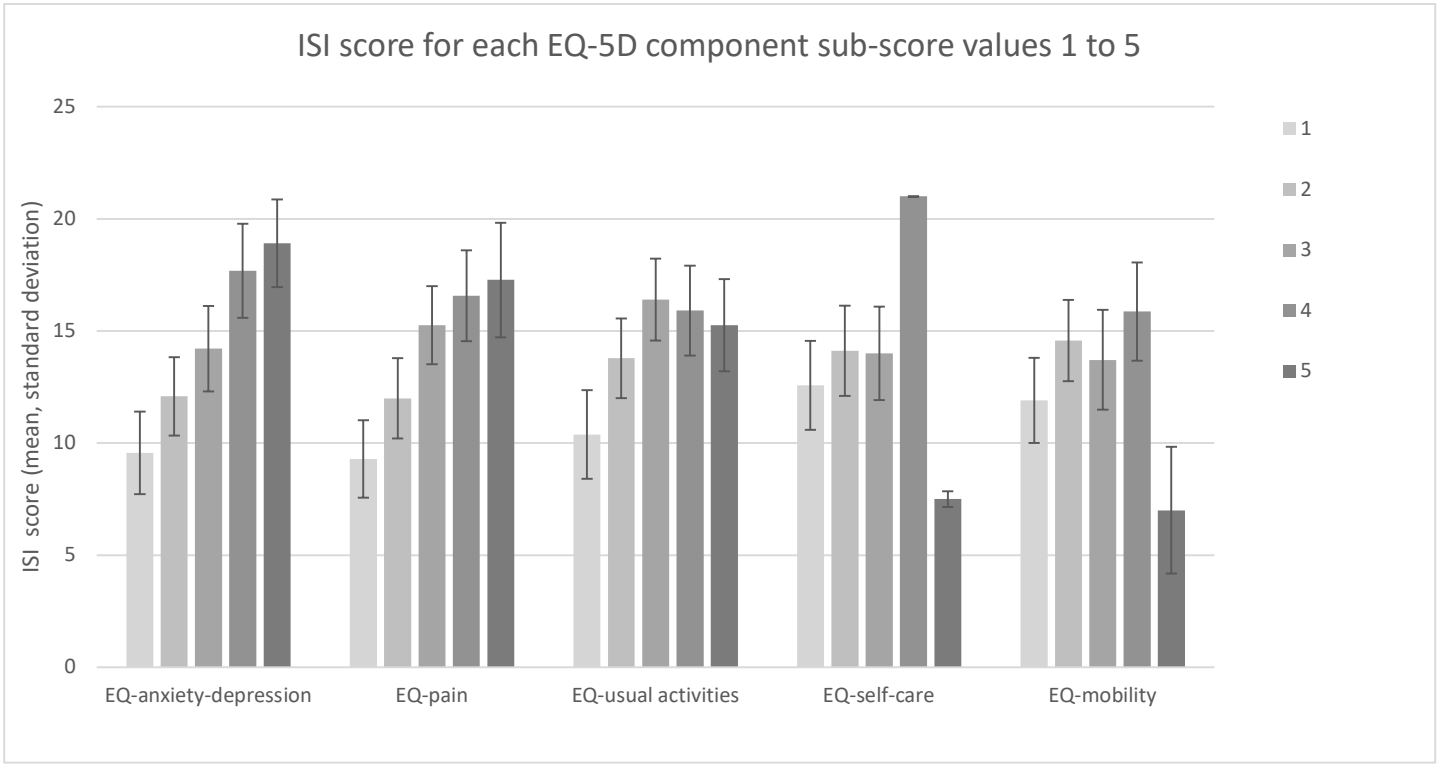
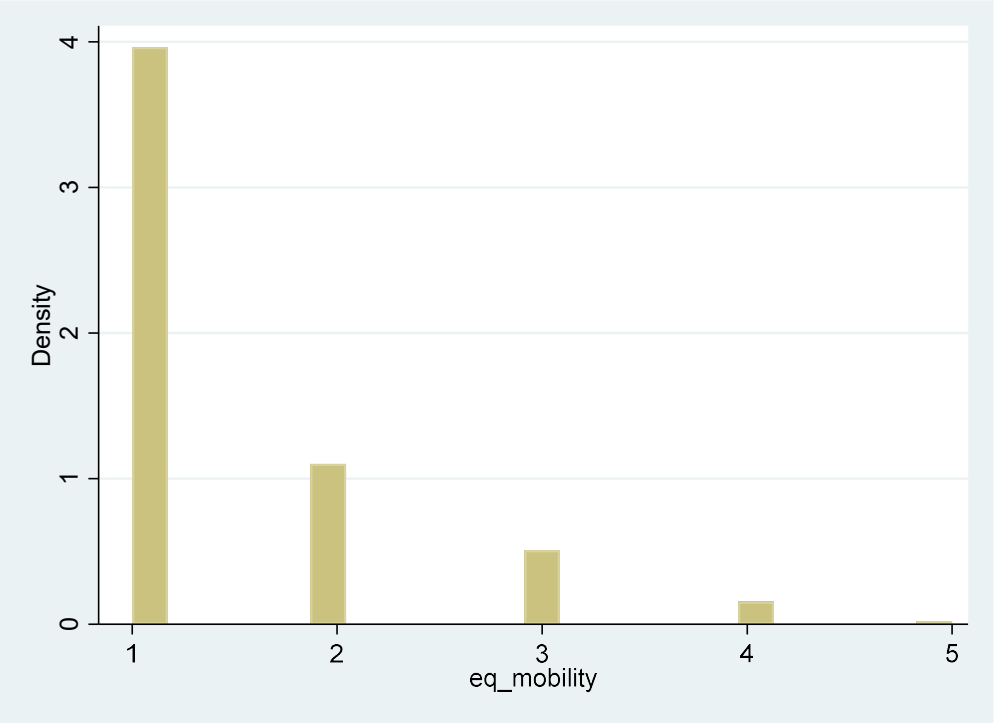


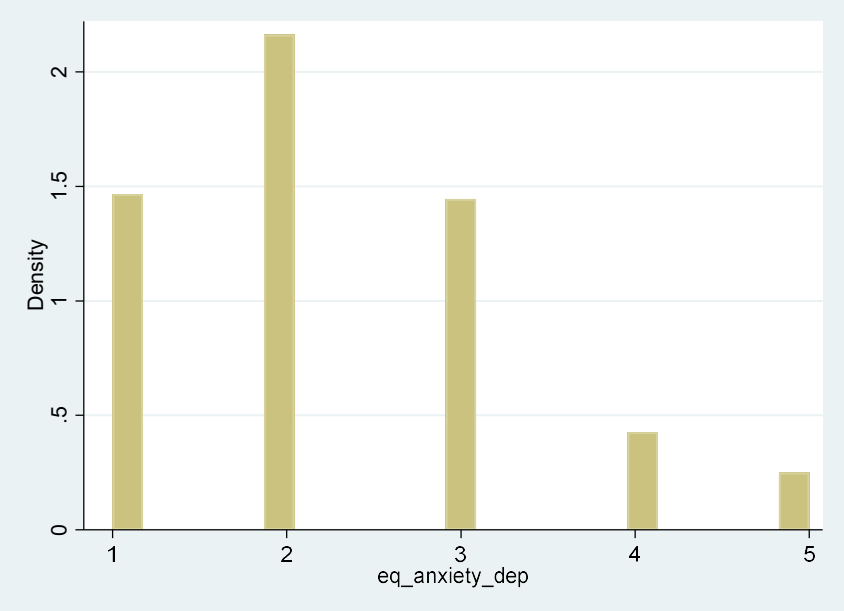
Figure 4.4: Insomnia Severity Index (ISI) (mean, standard deviation) for EQ-5D components scores.

EQ-anxiety–depression ANOVA (df = 4, F = 30.99, $p < 0.0001$) on post hoc Tukey's test all significant except ($p < 0.004$) except 5v4. EQ-pain ANOVA (df = 4, F = 26.88, $p < 0.0001$) on post hoc Tukey's test all significant ($p < 0.0001$) except 5v2, 4v3, 5v3, 5v4. EQ-usual activities ANOVA (df = 4, F = 22.39, $p < 0.0001$) on post hoc Tukey's test significant result ($p < 0.006$) 2v1, 3v1, 4v1 3v2, otherwise no differences seen. EQ-self-care ANOVA (df = 4, F = 1.48, $p = 0.21$) – no significant differences between groups. EQ-mobility ANOVA (df = 4, F = 6.09, $p < 0.001$) on post hoc Tukey's test significant result 2v1 ($p = 0.01$); otherwise no significant differences.

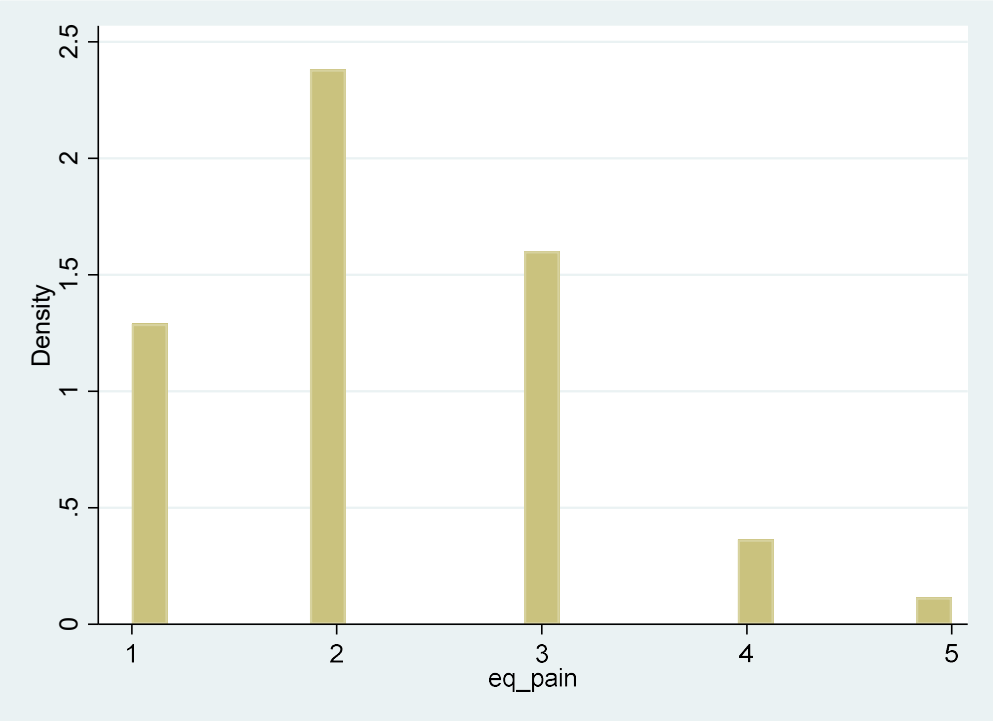
Supplementary Figure 4.1: Histogram of EQ-mobility score.



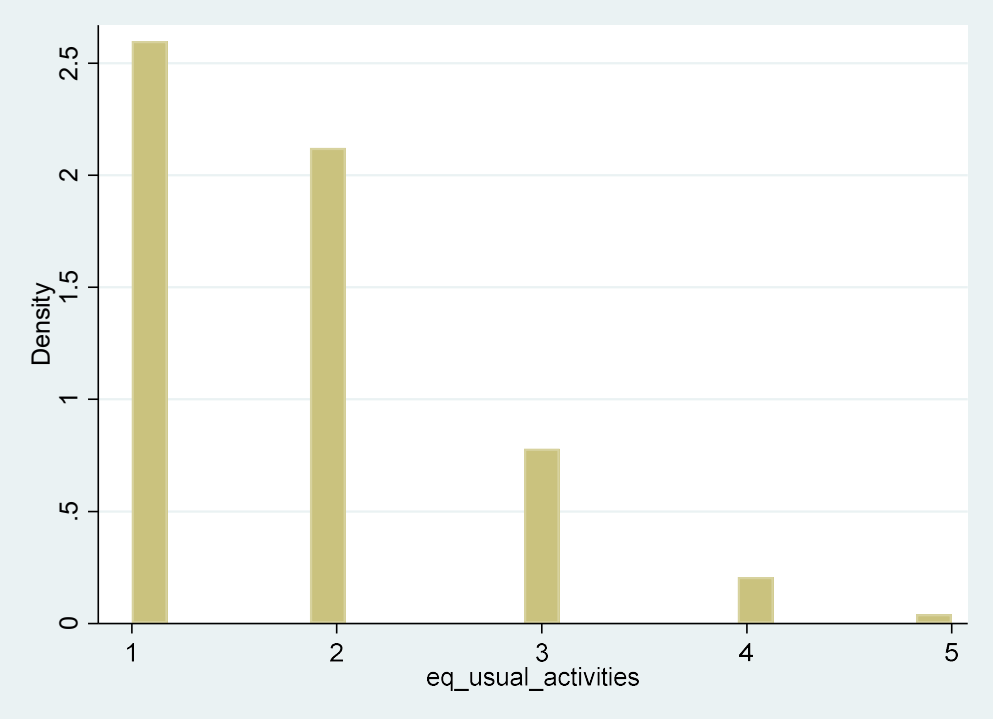
Supplementary Figure 4.2: Histogram of EQ-anxiety-depression score.



Supplementary Figure 4.3: Histogram of EQ-pain score.

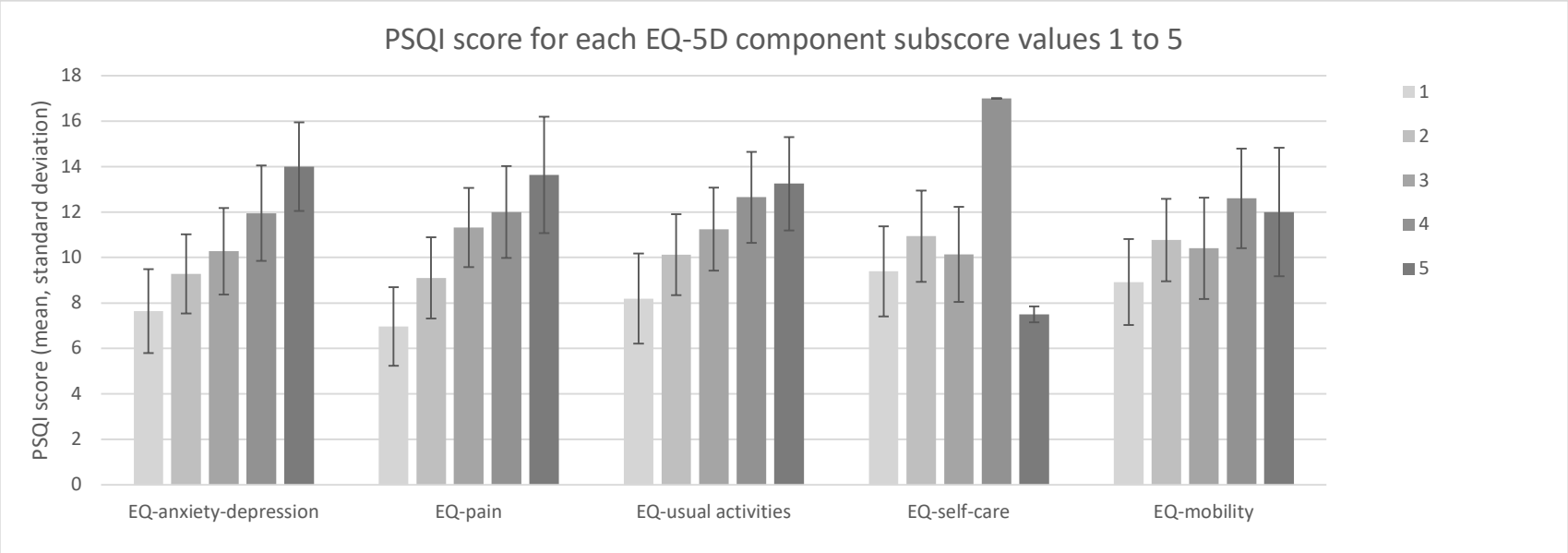


Supplementary Figure 4.4: Histogram of EQ-activities score.



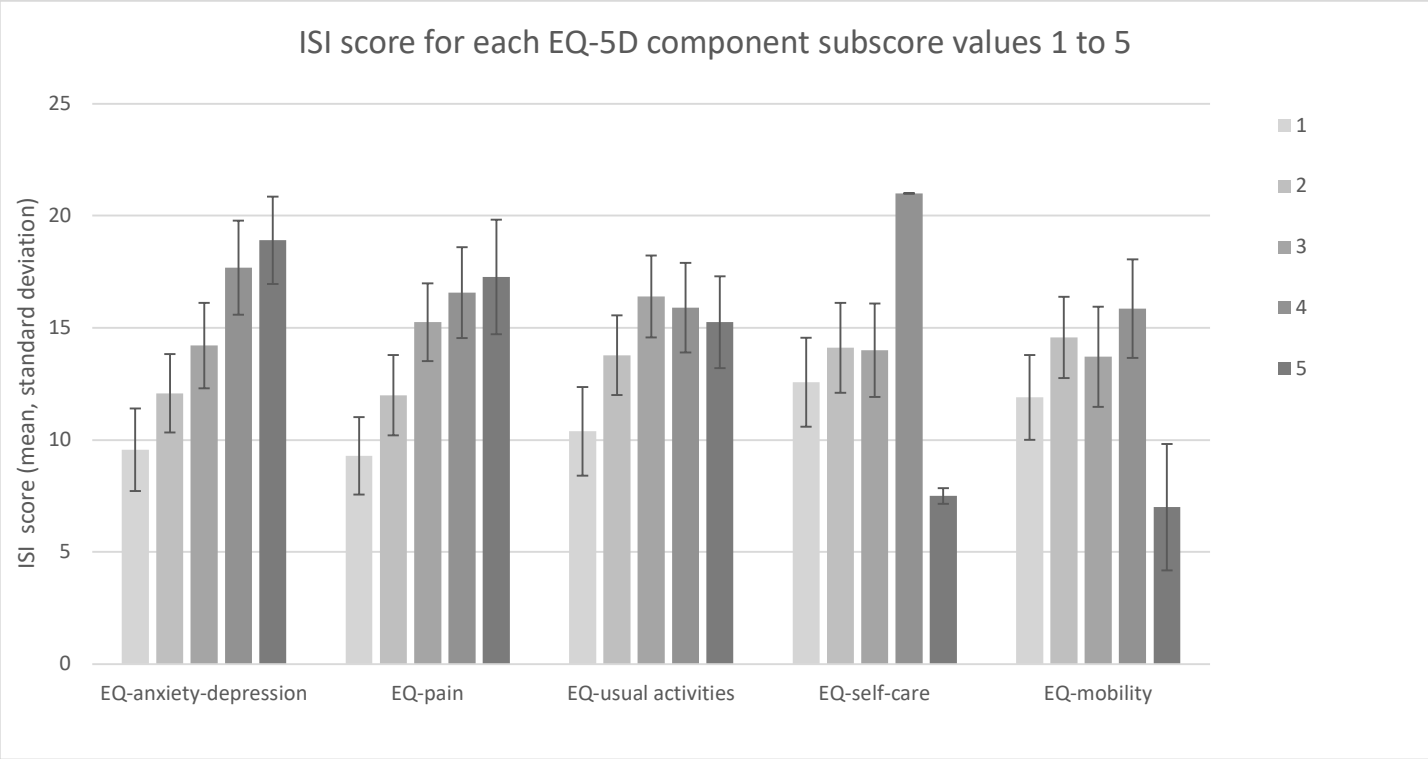
Supplementary Table 4.1: Inflammatory bowel disease subtypes Crohn's disease and ulcerative colitis and Q-5D utility score, EVQAS and EQ-5D component mean scores (Student's *t*-test).

EQ-5D scores	Crohn's disease	Ulcerative colitis	*p*
Utility score	0.79	0.80	0.35
EQVAS	64.09	65.10	0.56
Mobility	1.51 (0.82)	1.38 (0.75)	0.059
Self-care	1.13 (0.46)	1.08 (0.34)	0.12
Usual activity	1.81 (0.86)	1.71 (0.86)	0.20
Pain	2.27 (0. 19)	2.18 (0.96)	0.29
Depression and anxiety	2.27 (1.08)	2.27 (1.02)	0.96



Supplementary figure 4.5: Pittsburgh sleep quality index score (PSQI) (mean, standard deviation) for EQ-5D components scores. EQ-anxiety depression

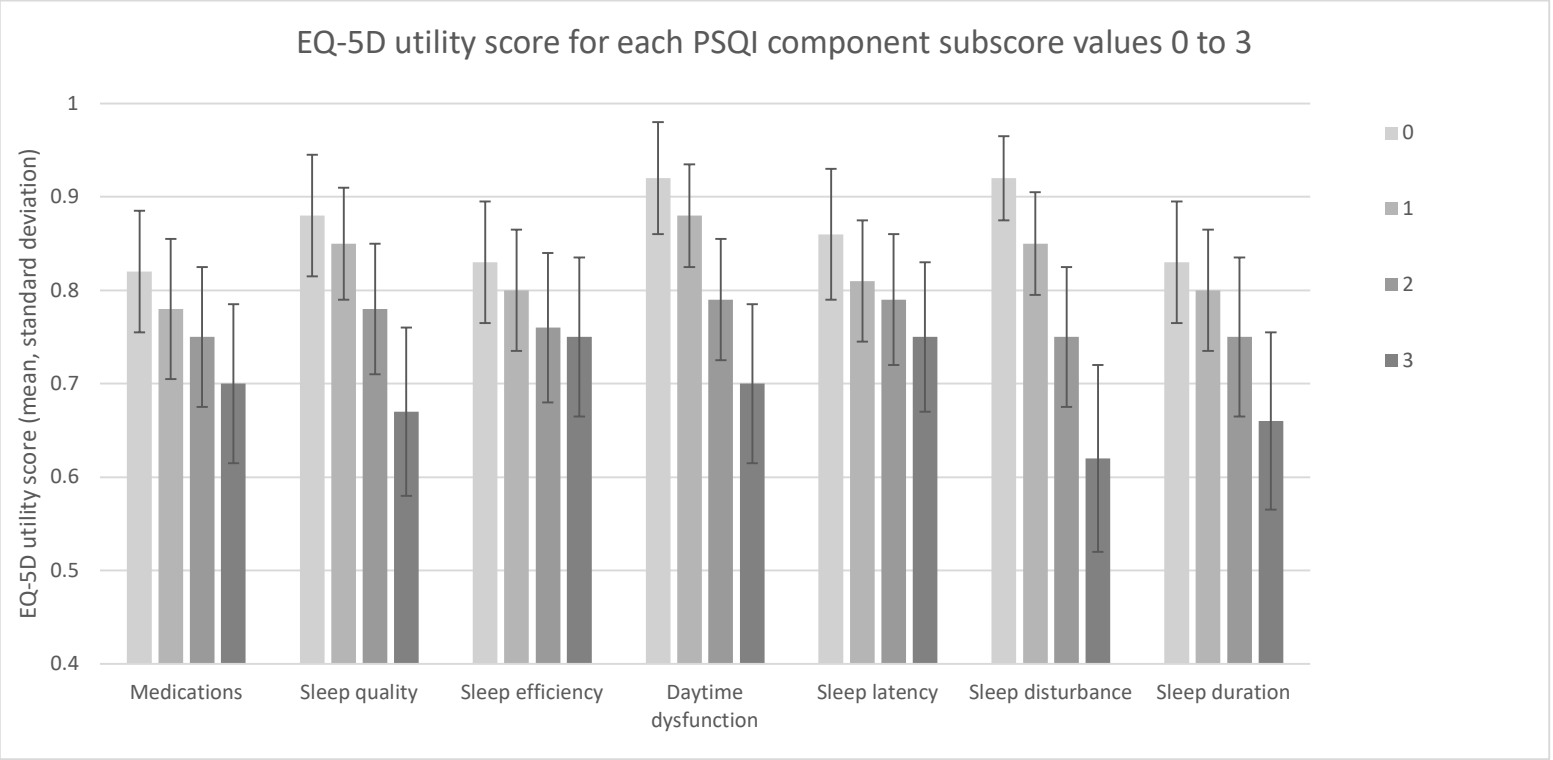
ANOVA (df=4, F=24.01, p<0.0001) on post hoc Tukey test all significant (p<0.001) except 3v2, 4v3, 5v4. EQ-pain ANOVA (df=4, F=33.82, p<0.0001) on post hoc Tukey test all significant (<0.001) except 4v3, 5v3, 5v4. EQ-usual activities ANOVA (df=4, F=17.28, p<0.0001) on post hoc Tukey test significant results (p<0.04) 2v1, 3v1, 4v1, 2v2 , otherwise no differences seen. EQ-self care ANOVA (df=4, F=2.37,p=0.0519) – no significant differences between groups. EQ-mobility ANOVA (df=4, F=8.19,p<0.0001) on post hoc Tukey test significant result (p<0.03) 2v1, 4v1, other comparisons not significantly different.



Supplementary figure 4.6: Insomnia Severity Index (ISI) (mean, standard deviation) for EQ-5D components scores. EQ-anxiety depression

ANOVA (df 4, F=30.99, p<0.0001) on post hoc Tukey test all significant except (p<0.004) except 5v4. EQ-pain ANOVA (df=4, F=26.88, p<0.0001) on post hoc Tukey test all significant (p<0.0001) except 5v2, 4v3, 5v3, 5v4. EQ-usual activities ANOVA (df=4, F=22.39, p<0.0001) on post hoc Tukey test significant result (p<0.006) 2v1, 3v1, 4v1 3v2, otherwise no differences seen. EQ-self care ANOVA (df=4, F=1.48,

p=0.21) – no significant differences between groups. EQ-mobility ANOVA (df=4, F=6.09, p<0.001) on post hoc Tukey test significant result 2v1 (p=0.01) otherwise no significant differences



Supplementary Figure 4.7: EQ-5D utility scores for each Pittsburgh Sleep Quality Index (PSQI) component.

PSQI-medications ANOVA (df=3, F=14.63, p < 0.001) on post hoc Tukey test significant results 3v0 p<0.001, 2v0 p=0.009, other comparisons not significant. PSQI-sleep quality ANOVA (df=3, F=30.94, p<0.001) on post hoc Tukey test all significant all (p< 0.002) except 1v0 (p=0.65).

PSQI-sleep efficiency ANOVA (df=3, F=10.29, p<0.001) on post hoc Tukey test significant result 3v0 p<0.001, 2v0 p=0.003, otherwise not significant. PSQI-daytime dysfunction ANOVA (df=3, F=42.2, p<0.0001) on post hoc Tukey test all significant (p < 0.0001) except 1v0, 2v0. PSQI-latency ANOVA (df=3, F=9.4, p<0.0001) on post hoc Tukey test significant results: p<0.0001, 3v0 p<0.001, 2v0 p=0.020, 3v1 p=0.002, otherwise not significant. PSQI-disturbance ANOVA (df=3, F=38.05, p<0.0001) on post hoc Tukey test all significant (p< 0.003), except 1v0 not significant. PSQI-duration ANOVA (df=3, F=17.2, p<0.0001) on post hoc Tukey test all significant (p<0.0014), except 1v0 not significant.

PSQI components	Mobility	Selfcare	Activity	Pain	Anxiety and depression
Duration	0.15*	0.018	0.16*	0.27*	0.17*
Disturbance	0.23*	0.068	0.27*	0.32*	0.31*
Latency	0.084	0.030	0.17*	0.12	0.19*
Daytime dysfunction	0.14*	0.080	0.36*	0.25*	0.36*
Efficiency	0.16*	0.047	0.18*	0.21*	0.13
Quality	0.10	-0.0019	0.23*	0.27*	0.31*
Medications	015*	0.094	0.13	0.18*	0.24*

Supplementary table 4.2: EQ-5D domains and Pearson's correlation with Pittsburgh Sleep quality index (PSQI) component scores. * p < 0.001

Supplementary table 4.3: Inflammatory bowel disease (IBD) subtypes and insomnia, depression, anxiety and disease activity.

No significant differences were seen between IBD subtypes. Clinically active IBD was present in 67.1% of those with Crohn's disease and 67.9% of those with ulcerative colitis or indeterminate colitis. Differences in insomnia, depression and anxiety were then considered within each IBD subtype by clinical IBD activity. ** $p<0.001$. * $p<0.05$

	Crohn's disease	Active IBD	Inactive IBD	Ulcerative colitis or indeterminate colitis	Active IBD	Inactive IBD
Clinically significant insomnia (%)	36.6	47.1	15.0**	38.3	42.6	13.1**
Clinically significant depression (%)	20.1	26.8	6.2**	18.9	25.5	4.8**
Clinically significant anxiety (%)	31.1	35.6	22.1*	30.7	38.0	15.5**

Supplementary table 4.4: Correlation between inflammatory bowel disease symptoms subscores and EQ-5D subscores.

General well-being as per Harvey Bradshaw Index and Simple clinical colitis activity index. Abdominal pain and number of liquid or soft stools scored as per the Harvey Bradshaw index. Urgency, nocturnal bowel motions and blood in stool as per the Simple clinical colitis activity index. *$p < 0.05$.

	Mobility	Selfcare	Activity	Pain	Anxiety and depression	EQVAS	Utility score
General well being	0.29*	0.14*	0.48*	0.44*	0.36*	-0.56*	-0.52*
Abdominal pain	0.19*	0.029	0.27*	0.42*	0.25*	-0.33*	-0.38*
Number of liquid or soft stools	0.035	0.020	0.11*	0.16*	0.12*	-0.18*	-0.17*
Urgency	0.094*	0.032	0.14*	0.17*	0.12*	-0.21*	-0.17*
Blood in stool	0.045	0.047	0.13*	0.19*	0.097*	-0.17*	-0.18*
Nocturnal bowel motions	-0.017	-0.076	0.053	0.055	0.084*	-0.10*	-0.093*

Supplementary table 4.5: Extraintestinal manifestations of inflammatory bowel disease and EQ-5D sub-scores.

Means and standard deviation reported of EQ-5D sub-scores for the presence of each extraintestinal manifestations (t-test performed). *** $p<0.0001$, ** $p<0.001$, * $p<0.05$

	Mobility	Selfcare	Usual activities	Pain	Anxiety and depression	EQVAS	Utility score
Population mean (SD)	1.5 (0.8)	1.1 (0.4)	1.7 (0.8)	2.2 (0.9)	2.3 (1.0)	64.5 (19.9)	0.79 (0.15)
Perianal disease	1.5 (0.8)	1.1 (0.3)	1.9 (0.9)*	2.5 (0.9)**	2.4 (1.1)	62.2 (20.1)	0.76 (0.16)*
Skin manifestation	1.6 (0.8)	1.1 (0.3)	1.9 (0.9)	2.4 (0.9)*	2.6 (1.0)***	59.7 (20.3)*	0.75 (0.16)*
Oral involvement	1.5 (0.7)	1.1 (0.4)	2.0 (0.9)**	2.5 (0.9)**	2.6 (1.2)***	57.8 (19.0)***	0.74 (0.16)***
Uveitis or other eye involvement	1.6 (0.8)**	1.1 (0.5)*	1.9 (0.9)**	2.4 (0.9)**	2.4 (1.1)***	60.8 (20.4) ***	0.76 (0.16)***
Active arthropathy	1.7 (0.9)**	1.1 (0.5)*	1.9 (0.9)**	2.5 (0.9)**	2.4 (1.1)***	60.0 (20.0) ***	0.75 (0.11)***

Supplementary table 4.6: Abdominal pain sub-score (mean (SD)) reported by Simple clinical colitis active index and Harvey Bradshaw Index

for ulcerative colitis or indeterminate colitis and Crohn's disease respectively. ** p<0.001, *p<0.05

	Abdominal pain sub-score	Active IBD	Inactive IBD	Comparison across active and inactive IBD
Crohn's disease	1.75 (0.86)	2.00 (0.89)	1.23 (0.48)	p< 0.0001
Ulcerative colitis or indeterminate colitis	1.73 (0.80)	1.80 (0.80)	1.27 (0.52)	p < 0.0001
Comparison between Crohn's disease and ulcerative colitis	p=0.54	p=0.014	p=0.21	

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CHAPTER 5: THE RELATIONSHIP BETWEEN INFLAMMATORY BOWEL DISEASE ACTIVITY AND SLEEP QUALITY ASSESSED WITH OBJECTIVE MEASURES

This chapter presents the manuscript 'Active inflammatory bowel disease is associated with short sleep duration.', which was published in Digestive Diseases and Sciences in June 2024 and is included here in its entirety.

Author contributions

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Sutapa Mukherjee: responsible for study concept and design, and responsible for critical revision of the manuscript

Jane Andrews: responsible for critical revision of the manuscript.

Paul Spizzo: responsible for critical revision of the manuscript

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[Manuscript] Active inflammatory bowel disease is associated with short sleep duration.

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Data availability statement

The data underlying this work is available upon a reasonable request to the corresponding author.

Keywords: *inflammatory bowel disease, sleep, sleep deprivation*

Abstract

Introduction

Poor sleep quality has been associated with inflammatory bowel disease (IBD) activity, although studies incorporating actigraphy suggest that the perception of sleep differs rather than objective difference in sleep quality. Short sleep duration has been associated with increased pro-inflammatory cytokines that have been implicated in the pathogenesis of IBD.

Methods

An observational study incorporated home based polysomnography that was conducted within twelve weeks of an objective assessment of IBD activity such as calprotectin, colonoscopy, or MRI. Participants completed a survey on subjective measures of sleep quality, clinical IBD activity, depression, and anxiety. Polysomnography results were normalised by standardised results for a healthy population matched by gender and age.

Results

Twenty participants were included in the final analysis. Those with objective evidence of active IBD had shorter stage 2 sleep duration, leading to shorter NREM sleep and total sleep time. Sleep latency was also longer in those with active IBD, leading to worse sleep efficiency– despite no difference in time available for sleep between the two groups. These changes persisted after normalisation of polysomnography results by health population age and gender matched norms. Depression scores correlated with sleep latency and stage 2 sleep duration and were associated with objectively active IBD.

Conclusions

Objectively confirmed active IBD was associated with shorter sleep duration. Observed sleep changes may, in part, relate to coexistent depression. Further research should consider the utility of changes in sleep duration and quality as a means of longitudinally assessing objective IBD activity.

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Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing remitting immune mediated disorder that involves a complex interplay of genetic and environmental factors[202]. Symptoms of active IBD, such as abdominal pain and diarrhoea, may influence sleep quality and duration. Irritable bowel syndrome like symptoms are common in people with inflammatory bowel disease and can be misinterpreted as active IBD[67].

Short sleep duration, in the general population has been associated with increased all-cause mortality[206], adverse health effects including cardiovascular disease[104] and metabolic syndrome[105], as well as economic consequences such as lower productivity and greater health care utilisation[108]. Upregulation of pro-inflammatory cytokines, such as IL-1β, IL-6 and TNFα, have been observed in short sleepers - with these same cytokines implicated in the pathogenesis of IBD[208]. Several previous studies have investigated the association between sleep and IBD[210-212] and postulated a bi-directional relationship between sleep and IBD activity[213].

Sleep can be assessed subjectively using a measure of perceived sleep via validated survey methods such as the Pittsburgh Sleep Quality Index (PSQI), with standardised cut off values to define likely significant sleep disturbance referred to as "poor sleep"[113]. Meta-analyses show that poor sleep is prevalent in people with IBD[273], worse in people with IBD than healthy controls[200], more common in those with subjectively active IBD[200] and worse in IBD in remission than in healthy controls[274].

However there have also been several publications[154-156,159,166,169,173] suggesting no significant relationship between IBD disease activity and disturbed sleep, with some suggesting that only perceived sleep may be different. Studies incorporating objective sleep measurement have suggested that sleep efficiency is worse in subjectively active IBD and wake after sleep onset is longer in subjectively active IBD[173]. The lack of objective IBD assessment in these studies leads to the possibility of irritable bowel syndrome like symptoms being mistaken for clinically active IBD. The authors aim to address this gap in the literature and compare the gold standard of sleep assessment – polysomnography with objective assessments of IBD activity.

Methods

Ethics approval for this study was obtained from the Southern Adelaide Human Research Ethics Committee (203.20). Informed consent was obtained from all participants. Participants

were recruited from a tertiary IBD unit and a private IBD service with the study advertised via email and flyer. Recruitment occurred from 2021 to the end of 2023. Participants were adults (age over 18) with a confirmed diagnosis of IBD from a gastroenterologist. Participants had a home sleep study (polysomnography) within 12 weeks of an objective assessment of IBD activity which was performed as per usual care. Accepted objective assessment(s) of IBD activity included magnetic resonance imaging enterography, colonoscopy, gastrointestinal ultrasound, and faecal calprotectin (>150ug/g). Current medications including corticosteroids were recorded during the interval between the sleep study and the IBD assessment. Participants were offered $100 AUD for completion of the sleep study. Participants also completed a survey including demographic data, subjective IBD activity, depression, anxiety, and subjective sleep quality. The study aimed to recruit a minimum of twenty participants based on reported differences in polysomnography (sleep efficiency and wake after sleep onset) reported in other studies that incorporated subjective IBD assessment[173], with a goal of forty participants.

Participants were excluded if they had an uncontrolled psychiatric disorder, substance abuse disorder, heavy vehicle licence or a known sleep disorder such as obstructive sleep apnoea.

Sleep quality assessment

Polysomnography consists of the recording of multiple variables during sleep and can be performed in sleep laboratory or home setting. Variables include – electrocardiogram, electromyography to capture muscle movement, electroencephalography to capture brain activity, electrooculogram to capture eye movement, respiratory airflow channels to capture apnoeas or hypopnoeas, pulse oximetry monitoring and respiratory effort channels to measure movement of chest and abdomen[111]. Sleep staging is divided into REM sleep (rapid eye movement) and NREM sleep – (non-rapid eye movement) which is further divided into stage 1, stage 2 and slow wave sleep (previously stage 3 and 4 sleep). Variables of interest in polysomnography can be seen in table 1. Given the well-established sleep differences due to age and gender[248,302] polysomnography results were normalised by published values based on age and gender[303].

Polysomnography was performed using the Compumedics Somte PSG and Somte PSG 2 devices (Compumedicas Limited, Victoria, Australia). All participants were manually setup by a trained technician. The device used does not show impedance values however all traces were visually checked via a staff member prior to leaving the sleep laboratory. All sleep

studies have electroencephalography, electrooculogram, electromyography, respiratory, ECG and limb recordings and are directly comparable to gold standard polysomnography. All of the data was manually scored with the exception of limb movements which was predominantly scored by auto analysis by Profusion software (Compumedicas Limited, Victoria, Australia). All the sleep studies were scored by a trained sleep technician with a minimum of 5 years' experience in sleep scoring. The sleep laboratory used regularly participates in QSleep quality assurance testing.

Questionnaire data

Clinical IBD activity was assessed using the Harvey Bradshaw Index (HBI) in participants with Crohn's disease; with HBI > 5 considered active disease[217]. The patient reported version of the HBI was used in the survey, although a decision was made to maintain the general well-being and abdominal pain score similar to the physician HBI rather than using a ten-point Likert scale[281]. The Simple Clinical Colitis Activity Index (SCCAI) was used in participants with ulcerative colitis; with an SCCAI > 5 considered active disease[282]. The patient reported form of the SCCAI was used. The use of a self-reported SCCAI has been previously validated with good agreement with physician reported SCCAI[284].

Anxiety was assessed using the generalised anxiety disorder 7-item scale (GAD-7)[285]. The Patient Health Questionnaire 9 (PHQ-9) was used to assess depression[286]. Subjective sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI), a validated tool to assess perceived sleep quality[113].

Statistical analysis

Statistical analysis was performed using Stata SE 16 (StataCorp, College Station, TX, USA). For normally distributed variables mean and standard deviation (SD) were reported with comparisons made using the student t-test or paired t-test when appropriate. For non-normally distributed variables median, and interquartile range (IQR) were reported, with comparisons made using the Mann- Whitney U test. For categorical data Pearsons $\chi 2$ test was used or Fisher's exact test when appropriate. No incomplete survey responses were included in the analysis. Pearson's or Spearman's correlation was used as appropriate, with interpretation of coefficients as: very weak <0.19, weak 0.2-0.3, moderate 0.3-0.5, strong 0.5-0.79 and very strong >0.80.[289] Any missing survey data result in exclusion of that instrument from analysis.

Individual polysomnography results were matched by age and gender to standardised health adult polysomnography results generated via an online calculator based on a meta-analysis of healthy population values from 169 studies[303] (https://omc.ohri.ca/psgnorms/). Individual polysomnography results were then normalised by matched age and gender polysomnography results. Polysomnography results were reported according to the American Academy of Sleep Medicine manual[111,304].

This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline[305].

Results

Twenty-nine participants were screened for inclusion. Two were excluded due to an unstable psychiatric disorder. Five were excluded due to a known sleep disorder (insomnia in one case and obstructive sleep apnoea in the others). Following screening 22 participants were included, however two participants did not undergo the sleep study within twelve weeks of objective IBD assessment and were subsequently excluded. The majority underwent polysomnography within a month of objective IBD activity measurement (65%) (for further details see supplementary figures). Polysomnography was performed prior to the objective IBD assessment in 60%. Objective IBD assessment took the form of calprotectin in 30%, magnetic resonance imaging in 40%, and colonoscopy in 50%. Evidence of active inflammation on any objective assessment was considered as objectively active IBD and was present in 40%.

The median age was 41 years (33-48), 55% male, and the majority had Crohn's disease (85%) (see table 2). Previous IBD surgery was reported by 40%, and over half were on advanced therapies such as biologics (65%) with none on small molecules. For all participants no medication changes, including no steroid use, occurred during the period between the sleep study and IBD assessment. No participant was admitted to hospital during the period between sleep study and IBD assessment. No participant had an ileostomy or colostomy.

Polysomnography

There was similar time available for sleep in both objectively inactive IBD and active IBD groups (see table 3, Figure 1). However total sleep time was less in those with active IBD ($p=0.049$) – primarily as decreased NREM sleep duration due to decreased stage 2 sleep time ($p=0.045$). No difference in the percentage of time in each sleep stage was seen. Sleep latency

was longer in the active IBD group (p=0.015); ie it took a longer time for them to fall asleep. As a result of this sleep efficiency was lower in the active IBD group (p=0.014). No difference in wake after sleep onset was seen (p=0.41). The polysomnography results were normalised by healthy population results matched by age and gender (see table 3) with similar differences between inactive and active IBD seen – that is those with active IBD had longer sleep latency, shorter total sleep time due to stage 2 sleep and worse sleep efficiency, although percentage of time in sleep stage was similar.

Questionnaire

Survey results were available for 75% of the cohort within one month of the sleep study. Subjective symptoms of active IBD were present in 45%, with mean HBI 5.6 (4.1) and mean SCCAI 3.3 (2.9). Objective evidence of active IBD was present in 40% of the cohort and was associated with higher depression scores (see supplementary table 1) but no difference in anxiety or subjective sleep quality scores. Depression scores moderately correlated with stage 2 sleep duration (ρ 0.53 p=0.046) and strongly correlated with sleep latency (ρ 0.75 p=0.0013) (see supplementary table 2). There were no significant correlations between other polysomnography measures and subjective IBD activity, depression scores, or anxiety scores. Subjective sleep quality (PSQI) moderately correlated with depression scores (PHQ9) (ρ 0.57, p=0.026). A modified PHQ9 score was considered excluding the PHQ9 question concerning sleep with correlations between this score and sleep latency (ρ 0.69, p=0.0059), and PSQI remaining significant (ρ 0.59, 0.025), with stage 2 sleep duration no longer significant (ρ 0.47, p=0.088).

Discussion

Herein we report novel evidence of associations between objective, but not subjective, IBD activity and objectively assessed sleep quality. Prolonged sleep latency in the active IBD group and shortened stage 2 sleep duration led to lower sleep efficiency and shorter total sleep time in the active IBD group. Unlikely previous actigraphy studies no difference in wake after sleep onset was seen[163,178]. This may be consistent - noting that actigraphy cannot accurately determine wakefulness whilst lying still compared to light sleep (unlike EEG measurement as with polysomnography) and therefore may misclassify wake after sleep onset among other parameters[180].

Subjective sleep quality in IBD has been previously associated with depression with similar results obtained in this study[155,159,160]. Aspects of polysomnography did correlate with

depression scores and not surprisingly depression scores were higher in those with objectively active IBD. Depression is associated with sleep abnormalities such as prolonged sleep latency that was observed in this study, but also other abnormalities such as decreased slow wave sleep and REM sleep abnormalities[306,307] – which were not seen in the objective active IBD group here. Consequently, we suggest that not all polysomnography differences demonstrated are explained by depression scores alone and may represent an additional influence from active IBD.

Objectively active IBD has been associated with elevated pro-inflammatory cytokines such as TNF-a and IL-6 – which are also produced via sleep restriction. In animal studies elevated pro-inflammatory cytokines drive the need to sleep and correlate with the duration of recovery sleep[308]. The understanding of inflammatory cytokines and sleep in human is less well understood[309]. In rheumatoid arthritis a small study demonstrated a reciprocal relationship between sleep efficiency and TNFa production[310]. Other studies in rheumatoid arthritis have not demonstrated any differences in polysomnography findings between active and inactive rheumatoid arthritis[311]. A meta-analysis of studies incorporating markers of inflammation and measurement of sleep showed an association between elevated markers of inflammation and sleep disturbance and long sleep duration[122]. Our findings are more consistent with sleep restriction rather than inflammatory cytokine mediated sleep recovery.

Limitations to this study include the limited sample size which is typically for studies incorporating polysomnography and limits the generalisability of these results. Whilst our use of objective IBD activity allowed a variety of different measures of IBD activity that likely introduces heterogeneity, it did allow for verification of active inflammatory disease. There was some difficulty in arranging sleep studies within an acceptable time of the IBD assessment with two participants not completing the sleep study within the allowed time. This was due to repeated cancellations or non-attendance by the participant. As a post hoc verification of date, we incorporated results from these two further participants and confirmed that it did not change the study outcomes. Also note that the study utilised a single night of polysomnography with others arguing for utilisation of multiple nights of polysomnography to increase validity of results and avoid a first night effect[175]. Recruitment for this study proved challenging as with other polysomnography studies because of the time needed for overnight polysomnography.

Future research should consider the prognostic value of objective measurement of sleep as a

marker of active IBD with less intrusive methods to measure sleep. Consideration should also be given to performing polysomnography in people with clinical remission but ongoing endoscopic activity in order to observe changes in sleep due to inflammatory cytokines and not IBD related symptoms.

Conclusion

Specific changes in sleep stages were demonstrated via polysomnography in active IBD compared to inactive IBD. Depression was associated with polysomnography differences along with IBD activity and may explain some but not all of the observed polysomnography changes. Further research should consider quantifying polysomnography differences associated with IBD related pro-inflammatory cytokines as well as considering the utility of changes in sleep quality as a means of longitudinally assessing objective IBD activity.

Table 5.1: Definition of objective sleep quality parameters from polysomnography.

Sleep quality variable	Definition
Total sleep time	Total number of minutes of sleep
Sleep latency	Time from going to bed to onset of sleep
Sleep efficiency	The portion of time asleep divided by time in bed
Time awake after sleep onset	Duration of any time awake after sleep onset
REM	Duration of REM sleep
REM latency	Time from onset of sleep to start of REM sleep
NREM	Duration of NREM sleep, consisting of stage 1 and 2 and slow-wave sleep
Stage 1	Duration of stage 1 of sleep
Stage 2	Duration of stage 2 of sleep
Slow-wave sleep	Duration of stage 3 and stage 4 of sleep

Table 5.2: Demographic and inflammatory bowel disease (IBD) data of study participants.

	Cohort
n	20
Age (years, median)	41 (33-48)
Female (%)	45
Crohn's disease (n)	17
Ileal (n)	7
Ileal and perianal (n)	2
Ileocolonic (n)	2
Ileal colonic and perianal (n)	1
Colonic (n)	1
Colonic and perianal (n)	4
Ulcerative colitis (n)	3
Extensive stage (n)	3
Disease duration (median, years)	7 (3-25)
Previous IBD surgery (%)	40
Current medications	
Mesalazine (n)	1
Sulfasalazine (n)	1
Immunomodulator (%)	30
Azathioprine (n)	3
Mercaptopurine (n)	1
Methotrexate (n)	2
Biologic (%)	65
Adalimumab (n)	2
Infliximab (n)	7
Ustekinumab (n)	4
Vitamin D (n)	4
Opioids (n)	1

	Active IBD (n-=8)	Inactive IBD (n=12)	P value	Normalised active IBD	Normalised inactive IBD	P value
Time available for sleep (minutes)	466.8 (411.9-521.7)	489.0 (456.7-541.4)	0.41			
Sleep efficiency	79.0 (73.1-84.9)	87.9 (83.2-92.5)	0.014	0.93 (0.87-0.99)	1.04 (0.98-1.10)	0.0081
Sleep latency (minutes)	32.6 (12.6-54.6)	12.4 (6.6-18.1)	0.015	2.21 (0.82-3.59)	0.84 (0.39-1.29)	0.019
Wake post sleep onset (minutes)	51.5 (20.2-82.8)	39.7 (23.9-55.5)	0.41	1.06 (0.42-1.69)	0.76 (0.43-1.11)	0.32
REM latency (minutes)	121.6 (83.3-154.9)	129.3 (83.7-174.9)	0.79	1.21 (0.86-1.57)	1.29 (0.85-1.71)	0.80
Total sleep time (minutes)	372.6 (307.2-438.1	435.7 (400.4-470.9)	0.049	0.99 (0.83-1.16)	1.17 (1.08-1.25)	0.028
NREM sleep (minutes)	293.8 (229.5-358.1)	354.8 (319.6-390.0)	0.053	0.97 (0.77-1.17)	1.18 (1.08-1.29)	0.028
REM sleep (minutes)	78.6 (64.4-92.8)	79.7 (69.7-89.8)	0.88	1.16 (0.92-1.41)	1.18 (1.03-1.32)	0.91
REM sleep (percent of total sleep time)	21.9 (16.6-27.2)	18.5 (15.9-21.2)	0.17	1.21 (0.93-1.50)	1.02 (0.86-1.17)	0.15
Stage 1 (minutes)	21.9 (7.5-36.4)	29.8 (17.9-41.7)	0.36	0.81 (0.29-1.35)	1.12 (0.65-1.59)	0.35
Stage 1 sleep (percent of total sleep time)	6.2 (2.2-10.3)	6.8 (4.1-9.5)	0.79	0.86 (0.28-1.45)	0.98 (0.58-1.37)	0.71
Stage 2 (minutes)	169.6 (115.5-223.6)	228.8 (192.3-265-3)	0.045	0.86 (0.58-1.14)	1.17 (0.98-1.36)	0.044

Stage 2 sleep (percent of total sleep time)	45.6 (34.1-57.0)	52.4 (45.2-59.6)	0.24	0.87 (0.65-1.09)	1.00 (0.86-1.14)	0.24
Slow wave sleep (minutes)	91.1 (37.1-145.1)	96.2 (68.4-123.9)	0.83	1.13 (0.54-1.72)	1.25 (0.89-1.60)	0.67
Slow wave sleep (percent of total sleep time)	23.6 (11.8-35.4)	21.9 (16.1-27.9)	0.76	1.13 (0.6-1.7)	1.06 (0.78-1.3)	0.78
Arousal (events/hour)	11.6 (5.5-17.6)	10.2 (4.9-15.5)	0.71	0.94 (0.39-1.49)	0.71 (0.36-1.09)	0.44
Periodic limb movements (events/hour)	14.7 (4.6-24.8)	13.2 (4.7-21.6)	0.79	5.53 (0.90-10.1)	4.04 (2.11-5.96)	0.44
Apnoea hypoxia index (events/hour)	7.6 (1.0 -16.3)	5.74 (2.6-8.8)	0.59	2.9 (1.5-4.4)	3.3 (2.2-4.5)	0.62

Table 5.3: Polysomnography results for active inflammatory bowel disease (IBD) and inactive IBD.

Normalised results are included that consistent of data that has been normalised by health population standard polysomnography results matched by gender and age. Arousal refers to total arousal - including limb, respiratory and spontaneous.

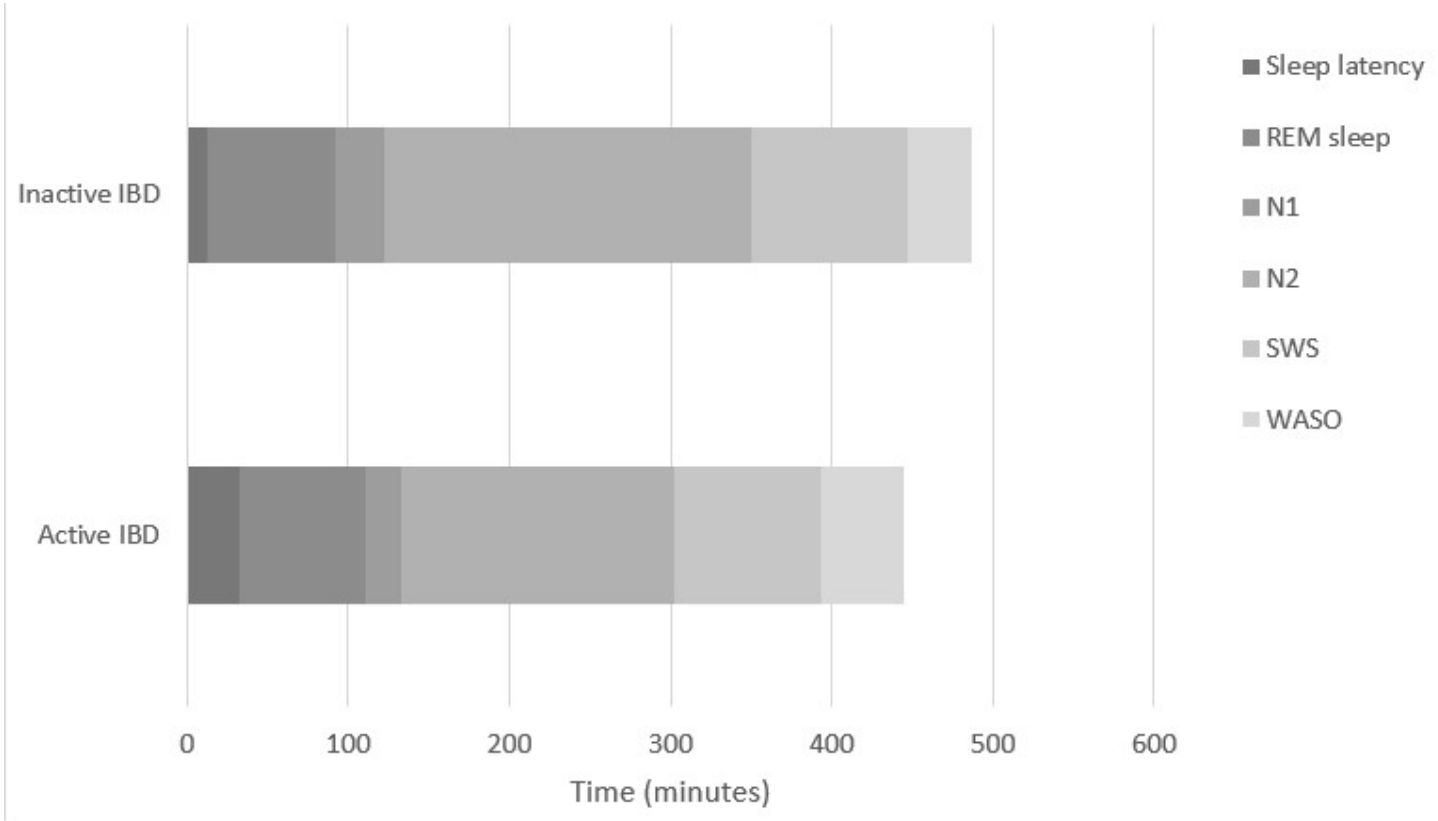


Figure 5.1: Sleep stage duration in minutes in those with objectively active inflammatory bowel disease (IBD) and inactive IBD. REM – rapid eye movement, S1 – stage 1 of sleep, S2 – stage 2 of sleep, SWS – slow-wave sleep, WASO – wake after sleep onset.

Supplementary data

Supplementary Table 5.1: Correlation between polysomnography parameters of interest and subjective IBD activity

(HBI – Harvey Bradshaw Index and SCCAI – Simple Clinical Colitis Activity Index), depression scores (PHQ9 – Patient Health Questionnaire 9), and anxiety scores (GAD7 – generalised anxiety disorder-7), subjective sleep quality (PSQI – Pittsburgh Sleep Quality Index). *P<0.050

	HBI	SCCAI	PHQ9	GAD7
Sleep efficiency	-0.25	-0.14	-0.39	-0.31
Sleep latency	0.27	0.23	0.75*	0.37
Total sleep time	0.036	0.22	-0.48	-0.46
NREM sleep	0.076	0.26	-0.40	-0.43
Stage 2	-0.42	-0.30	-0.53*	-0.49
PSQI	0.17	0.36	0.57*	0.35

Supplementary Table 5.2: Objective inflammatory bowel disease (IBD) activity by depression scores, anxiety scores and subjective sleep quality.

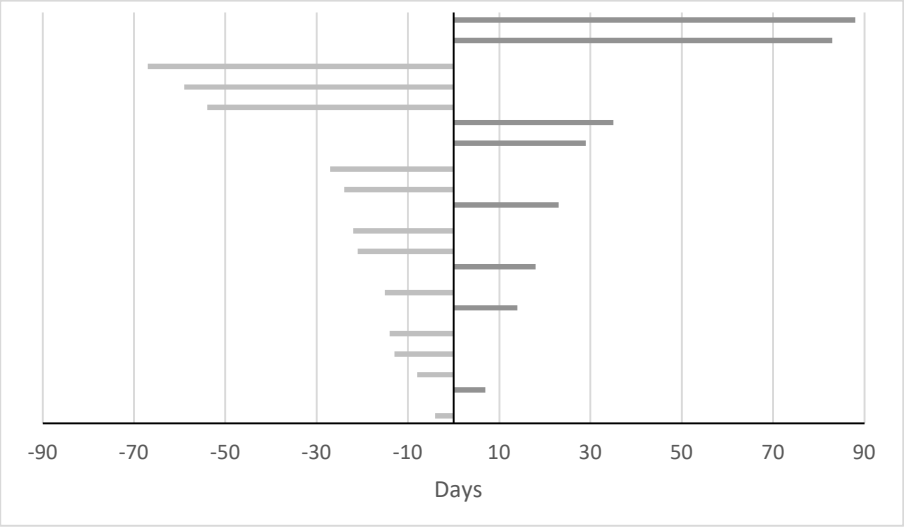
Depression score (Patient Health Questionnaire-9 – PHQ9), anxiety score (Generalised Anxiety Disorder-7 – GAD7) and subjective sleep quality (Pittsburgh Sleep Quality Index – PSQI).

	Active IBD	**Inactive IBD**	**P value**
PHQ9 (mean (SD))	12 (5.8)	6.1 (4.2)	0.038
GAD7 (mean (SD))	7.2 (2.9)	5.1 (4.8)	0.37
PSQI (mean (SD))	9.3 (6.8)	8.6 (6.3)	0.63

Supplementary Table 5.3: Paired t-test of polysomnography results for participants with inflammatory bowel disease (IBD) and health controls matched by age and gender from published normative data.

	IBD	Healthy controls	P value
Periodic limb movements	13.7 (12.5)	3.2 (1.4)	0.0011
Arousal	10.8(7.5)	13.4 (3.1)	0.16
AHI	3.2 (1.8)	6.5 (7.4)	0.055
Slow wave sleep	94.2 (51.5)	76.7 (6.1)	0.13
Stage 2 sleep	205.1 (65.8)	195.9 (5.8)	0.54
Stage 1 sleep	26.6 (18.1)	26.9 (1.8)	0.94
NREM sleep	399.8 (10.0)	330.4 (69.9)	0.052
Total sleep time	373.5 (10.7)	410.4 (71.0)	0.024
REM latency	126.2 (59.8)	100.4 (4.4)	0.065
Sleep latency	20.5 (18.9)	15.4 (1.7)	0.26
Sleep efficiency	84.3 (8.3)	84.6 (2.6)	0.90
REM sleep	79.3 (15.8)	67.8 (3.2)	0.0054
Time awake post sleep onset	44.4 (30.2)	51.8 (10.8)	0.29

Supplementary Figure 5.1: The number of days between the at-home sleep study and objective inflammatory bowel disease assessment.



CHAPTER 6: A SYSTEMATIC REVIEW AND META-ANALYSIS OF SLEEP QUALITY IN INACTIVE INFLAMMATORY BOWEL DISEASE

This chapter presents the manuscript 'A systematic review and meta-analysis of sleep quality in inactive inflammatory bowel disease', published in *JGH Open*, Sept 2022, doi:10.1002/jgh3.12817

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Alex Barnes: responsible for study concept and design, data acquisition, analysis and data interpretation, drafting of manuscript, critical revision of the manuscript.

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[Manuscript] A systematic review and meta-analysis of sleep quality in inactive inflammatory bowel disease

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Conflicts of interest include speakers fees, and Ad Boards from Abbott, AbbVie, Allergan, Anatara, AstraZeneca, Bayer, BMS 2020, Celegene, Celltrion, Falk, Ferring, Gilead, Hospira, Immuninc, ImmunsanT, Janssen, MSD, Nestle, Novartis, Progenity, Pfizer, Sandoz, Shire, Takeda, Vifor, RAH research Fund, The Hospital Research Fund 2020–2022 and The Helmsley Trust 2020–2023

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Data availability statement

The data underlying this article are available in the Harvard Dataverse Digital Repository at https://doi.org/10.7910/DVN/ZNF52C

Abstract

Background

Poor sleep in people with inflammatory bowel disease (IBD) has been demonstrated to be prevalent and has been associated with disease activity. This meta-analysis aimed to assess the prevalence of poor sleep in inactive inflammatory bowel disease and in controls by considering cohort and cross-sectional studies.

Methods

Electronic databases were searched for publications from inception to November 1st, 2021. Poor sleep and IBD activity were defined according to self-reported subjective sleep measures. A random effects model was used to determine the standardised mean difference between poor sleep in inactive IBD and healthy controls. Publication bias was assessed by funnel plot and Egger's test.

Results

519 studies were screened with 9 studies included in the meta-analysis incorporating a total of 729 people with IBD and 508 controls. A random effects model showed a standardised mean difference with poor sleep being more frequent in those with inactive IBD than controls with moderate effect size (Hedge's *g* 0.41, CI (0.22–0.59) and no significant heterogeneity. There was no publication bias evident.

Conclusion

Poor sleep is more common in individuals with inactive IBD than healthy controls. This finding suggests that IBD activity may not be the sole driver of the observed poor sleep in this population. Further studies should consider potential mechanisms to explain this result including the role of sub-clinical inflammation and psychosocial factors that may influence sleep quality in people with IBD.

Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing-remitting immune-mediated disorder that involves a complex interplay of genetic and environmental factors.[202] Epidemiological studies have shown increasing incidence of IBD over the past several decades[203] with strong associations with environmental factors.[204] The aetiology and exacerbating factors are largely unknown however there are known associations with active smoking, urban living, appendectomy, and low vitamin D levels. IBD can be associated with debilitating extra-intestinal manifestations including joint, eye, and skin manifestations.[205] Sleep is likely to be deleteriously affected by the symptoms of active IBD but has also been examined as a potential extra-intestinal manifestation of IBD, and as an exacerbating or aetiological factor in IBD.

There has been increasing interest in the relationship between sleep and IBD in recent times.[211] Firstly, sleep has a major role in as an important patient-reported outcome with its relationship to quality of life, and health-related outcomes such as cardiovascular disease.[206] Secondly, impaired sleep quality has been shown to be associated with IBD activity[200] with worse sleep quality in those with active rather than inactive IBD. One may see this as being related to IBD symptoms and in particular nocturnal symptoms; however, sleep disturbance may also be an indicator of sub-clinical inflammation with studies suggesting that endoscopic activity and histological activity in the setting of clinical remission had high rates of poor sleep.[164,166] Sleep quality in IBD has also been associated with psychosocial factors such as depression[154-161] and reduced physical activity.[162,163]

Two meta-analyses have explored the relationship between IBD activity and sleep quality with poor sleep being more common in those with IBD compared to controls, and more common in those with active IBD than inactive IBD.[200,201] In this study we aimed to extend their work by considering the relationship between sleep in clinically inactive IBD and controls. This may allow the introduction of sleep quality of an important patient-reported outcome and the usage of sleep quality as a way to monitor IBD and further reinforce the principle of achieving endoscopic rather than symptomatic remission.[312]

Methods

This systematic review and meta-analysis was prospectively registered with the International Prospective Register of Ongoing Systematic Reviews. It was performed according to the preferred reporting item for systematic reviews and meta-analyses (PRISMA) guidelines.

Search strategy

Pubmed, MEDLINE, and PsychINFO were searched from inception to November 2021, including articles published in the English language using the following search string: (sleep OR circadian OR insomnia OR apnoea) AND [(inflammatory bowel disease) OR (crohn's disease) OR (ulcerative colitis) OR IBD OR crohn's OR colitis)].

Eligibility criteria

Studies were included if they met the following criteria: (1) Cross-sectional, observational, case control, cohort or randomised controlled trial available (2) Included a distinct population of people with inflammatory bowel disease (age ≥18 years old) with a definition of inactive disease by subjective measures such as CDAI (Crohn's Disease Activity Index) or objective measures such as endoscopy. (3) Included a control population of suitably matched controls. (4) Sleep quality assessment using a validated subjective patient-reported measures of sleep questionnaire. Unfortunately there were insufficient number of studies incorporating objective measures of sleep quality or objective measures of IBD activity.

Exclusion criteria included: (1) Inappropriate study population such a paediatric or adolescent population. (2) Case report or review

Study selection

The first author (AB) performed the literature review and two other authors (PS&JB) independently screened full texts against eligibility criteria, with disagreement resolved by discussion with involvement of another author (RM) when required.

Data collection

Data collection was performed by AB. A pre-defined spreadsheet was used for data collection.

Study quality assessment

Risk of bias in individual studies was assessed according to study design. Cross-sectional or observational studies were assessed according to modified Newcastle–Ottawa Scale. Cohort or case control studies were assessed according to Newcastle–Ottawa Scale.

Statistical analysis was performed using Stata SE 16 (StataCorp, College Station, TX, USA). Heterogeneity among studies was assessed using the I2 statistic with I2 >50% considered to indicate substantial heterogeneity. A random effects model was used. A forest plot was performed to estimate individual and pooled effect sizes with associated 95% CI. Publication

bias was assessed using funnel plots with significant visual asymmetry used to indicate publication bias. The frim-fill method was used as required. Egger's test with *p* values less than 0.05 were considered to indicate significant publication bias.

Results

21 studies were initially identified for inclusion. 9 studies were included in the meta-analysis incorporating 729 people with IBD and 508 controls (see Figure 1, and Table 1). Publication date ranged from 2006 to 2020. Study quality scoring can be seen in Supplementary Table 1.

IBD disease activity was defined by clinical remission utilising subjective IBD activity scores such as the CDAI. A single study used physician assessment of disease activity and one study required stable therapy for six months in addition to physician assessment. Control groups consisted of relatives or friends of study participants, gastrointestinal clinic patients with normal endoscopic investigations, or volunteers identified via online or university recruitment without gastrointestinal disease. All studies required controls have no gastrointestinal disease with some requiring no autoimmune disease. Age matching was performed in one study,[255] and one study utilised age, sex and Body Mass Index matching.[154] No other matching was undertaken.

Effect sizes were calculated with standardised mean difference (pooled Hedge's *g* of 0.798) indicating moderate effect size of increased likelihood of poor sleep in those with inactive IBD compared to controls. Heterogeneity was significant with I2 99.6%. Outliers were removed[159,173] with moderate effect size again shown (Hedge's *g* 0.41, CI (0.22–0.59)), and with no significant heterogeneity (I2 0%), see forest plot in Figure 2 Funnel plot was symmetric (Supplementary Figure 1) and Egger's negative ($p = 0.37$).

Discussion

Herein we have shown that clinically inactive IBD patients demonstrate poorer subjective sleep quality than controls. This represents an important result in pursing the aetiology of poor sleep quality in people with IBD. There has been the presumption that nocturnal GI symptoms were the primary driver of poor sleep quality in this population. Whilst such symptoms are likely to impair sleep quality, inactive IBD may also impact sleep through a variety of mechanisms.

These mechanisms could include sub-clinically active IBD. Two studies, one utilising endoscopic[166] and the other histologic[164] measures, showed that sub-clinically active IBD is associated with poor sleep compared to IBD in remission. It may be that there are specific

sleep abnormalities that are associated with sub-clinically active IBD. There were insufficient studies incorporating objective measures of IBD activity or objective measures of sleep to pursue this further.

There is a complex relationship between the immune system and sleep which leads to the possibility that IBD-related inflammation may lead to poor sleep irrespective of the symptoms experienced. Sleep deprivation has been shown to lead to a rise in pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α[118] that have also been implicated in the pathogenesis of IBD. Furthermore abnormalities in circadian rhythm-associated clock genes[224] and sleeping duration[170] have been associated with the development of IBD and ulcerative colitis respectively. The relationship between sleep and IBD has consequently been said to be bidirectional with the prospect of feedback between each leading to deterioration of both.

Irritable bowel syndrome frequently coexists with IBD, and has also been associated with poor sleep compared to healthy controls,[140] despite there being little evidence of systemic inflammation in IBS. Consideration therefore needs to be given to the possibility that persistent GI symptoms irrespective of disease activity, such as so-called post-inflammatory syndrome or irritable bowel syndrome, contribute to poor sleep in those with inflammatory bowel disease. This is supported by Zargar et al[222] showing that those with IBD in remission who met diagnostic criteria for IBS had poorer sleep than those not meeting criteria.

Other contributors to poor sleep in inactive IBD may include differences in levels of physical activity or age, both known to be associated with poor sleep.[248] Mental health conditions such as anxiety and depression are prevalent in IBD and have been demonstrated to influence sleep.[154-161] It has also been hypothesized that this poor sleep may represent “learned insomnia” from previous active IBD and may respond well to targeted insomnia treatment such as specific cognitive behavioural therapy, with a recent feasibility study showing encouraging results.[190]

Limitations of this analysis including lack of matching which was performed in two studies only. Other factors known to impact sleep and are known to be prevalent in IBD, such as depression and anxiety, could have been considered for matching. Geographic origin of study and publication date were diverse. Unfortunately, there were insufficient studies to consider objective measures of sleep quality such as polysomnography or actigraphy. This should be pursued in future work.

Further research is required to investigate whether sleep abnormalities are associated with sub-clinical disease activity, defined by histological or endoscopic activity, or whether other non-inflammation related factors such as psychological symptoms account for this impairment of sleep in those with inactive disease.

Sleep assessment may become an important PRO and allow early identification of IBD activity before the onset of clinical symptoms. After further defining key contributors to this problem, further research should focus on sleep specific interventions in people with IBD, and the impact these interventions may have on both disease activity and quality of life and in people living with IBD.

Conclusion

This meta-analysis has shown that poor sleep assessed by subjective measures is more frequent in those with clinically inactive IBD than controls with moderate effect size. This suggests that sleep quality in people with IBD is not only due to IBD related symptoms and encourages investigation of those with poor sleep quality and consideration of sleep targeted interventions. Of much interest is the limited data that suggests that subclinical IBD related inflammation may be responsible for poor sleep[164,166]. Consequently, poor sleep in the absence of IBD related symptoms could prompt consideration of objective IBD assessment. Further research should consider what sleep interventions may be most efficacious and well tolerated in an IBD population.

Figure 6.1: PRISMA flowchart—selection of studies and results of literature search for review and meta-analysis.

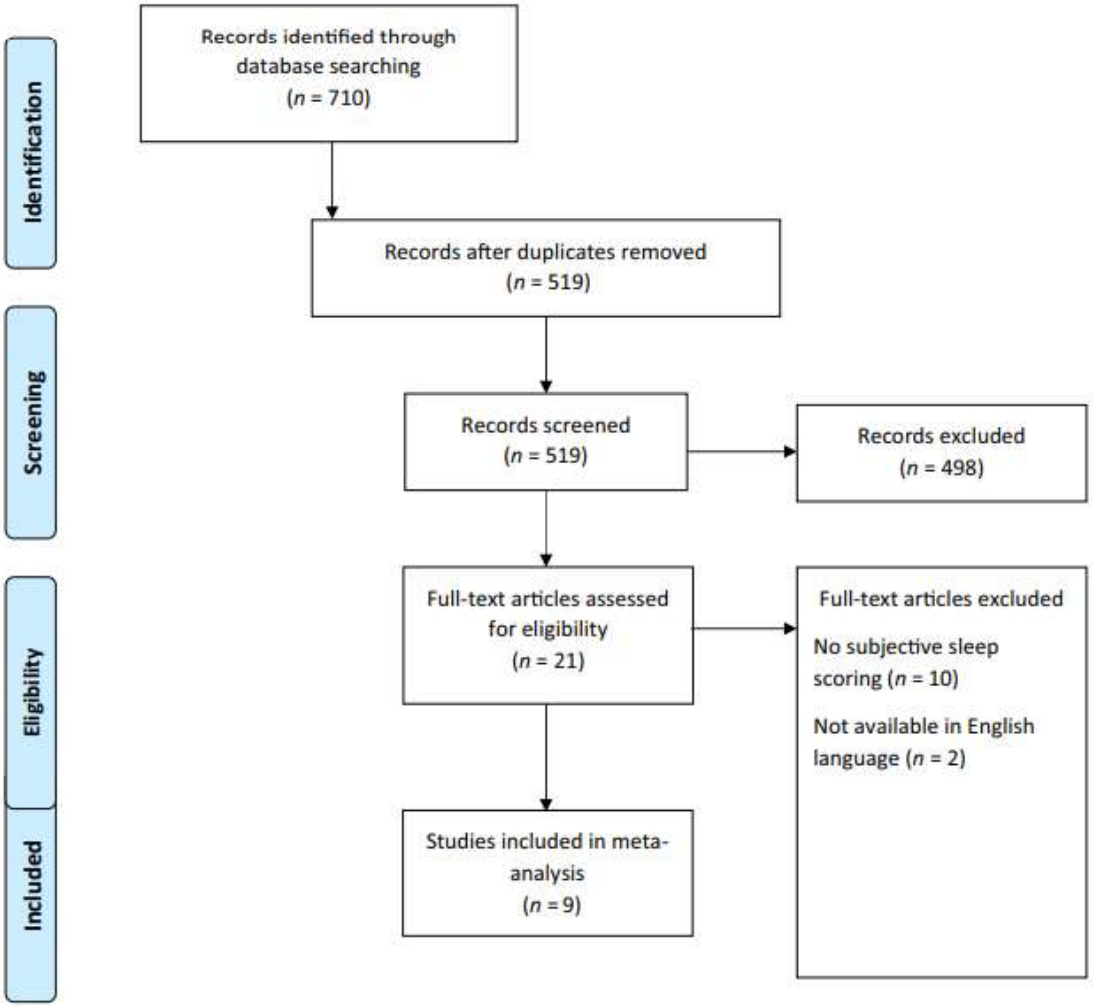


Figure 6.2: Forest plot of poor sleep in those with clinically inactive inflammatory bowel disease and controls. Standardised mean difference used as effect size. Outliers excluded.

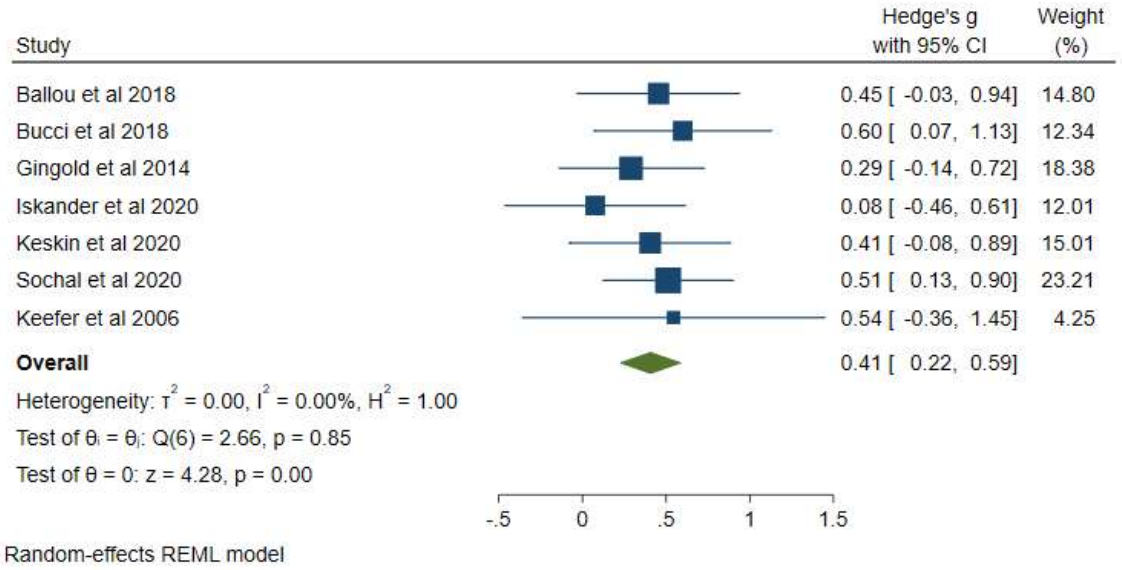


Table 6.1: Summary of studies included in meta-analysis of sleep quality in inflammatory bowel disease and controls.

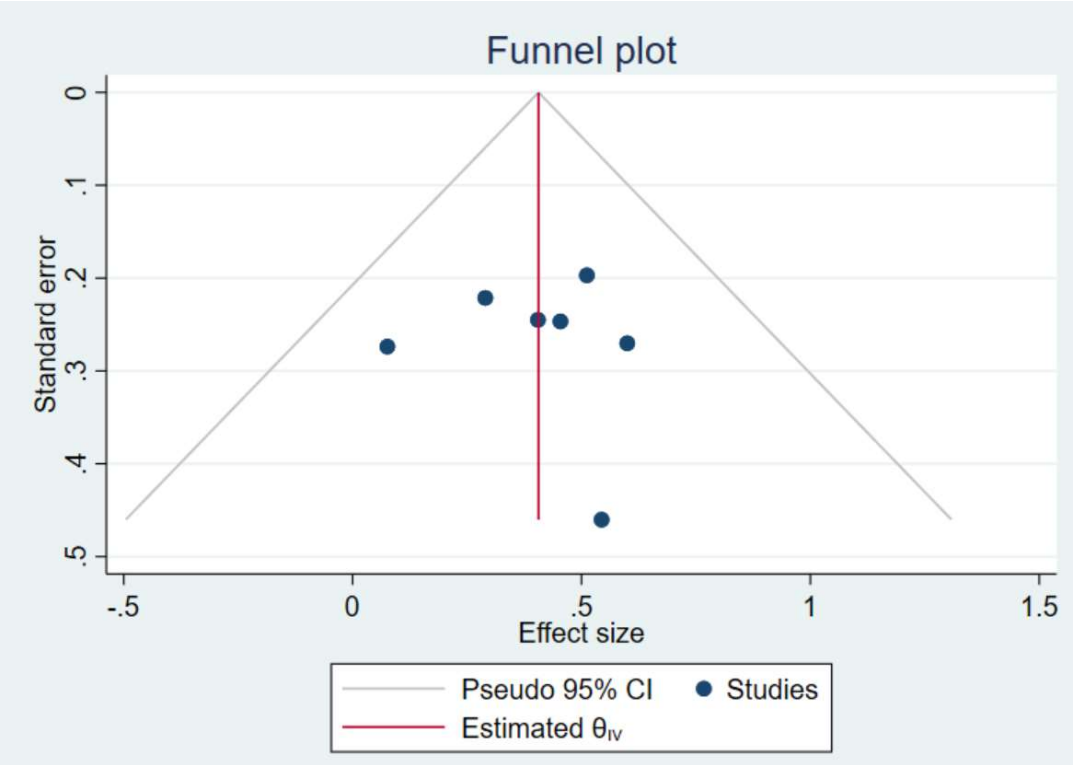
Study	Year	Country	Sample size	Age (mean)	Female (%)	Definition of inactive IBD	Definition of poor sleep	Type of controls	Study summary
Ballou et al[250]	2018	USA	IBD 44 Controls 41	IBD 44 Controls 42	IBD 70% Controls 56%	HBI ≤4 PMS ≤1	PSQI >5	Friends and family of study participants who do not have gastrointestinal diseases.	Tertiary gastrointestinal centre patients have poorer sleep than controls
Bucci et al[251]	2018	Italy	CD 28 UC 19 Controls 47	CD 38 UC 40 Controls 34		Stable therapy for six months physician assessment	PSQI >5	Volunteers with no gastroenterological disease, no infectious, immune-mediated or autoimmune diseases	Bruxism and enamel wear should be evaluated in people with Crohn's disease
Gîlc-Blanariu et al[159]	2020	Romania	IBD 110 Controls 66	IBD 42 Controls 44	IBD 47% Controls 60%	HBI ≤4 PMS ≤1	PSQI >5	Healthy volunteers with no digestive complaints and a normal colonoscopy	Sleep impairment is common in those with IBD and associated with psychological distress

Study	Year	Country	Sample size	Age (mean)	Female (%)	Definition of inactive IBD	Definition of poor sleep	Type of controls	Study summary
Gingold-Belfer et al[220]	2014	Israel	CD 71 controls 66	CD 40 controls 42	CD 38% Controls 54%	CDAI <150	PSQI >5	Healthy volunteers accompanying a relative having a screening colonoscopy	Poor sleep is associated with active Crohn's disease but not inactive disease.
Iskander et al[167]	2020	USA	CD 61 Controls 60	CD 32 Controls 31.5		HBI ≤4	PSQI >5	Health volunteers through university program to support research	Crohn's disease report poorer sleep than controls but no difference is seen based on objective measures
Keskin et al[255]	2020	Turkey	CD 41 UC 49 Controls 44	CD 33 UC 40 Controls 40	CD 56 UC 55 Controls 70	Physician assessment	PSQI >6	Age matched individuals without any chronic disease	IBD is a risk factor for sleep disturbance and eveningness is more common in IBD than controls
Keefer et al[172]	2006	USA	IBD 120 Controls 120	IBD 36 Controls 36	IBD 49 Controls 45	CDAI <150 UCAI <3	PSQI >5	Healthy volunteers from university	Sleep influences quality of life in those with IBD and controls

Study	Year	Country	Sample size	Age (mean)	Female (%)	Definition of inactive IBD	Definition of poor sleep	Type of controls	Study summary
								gastroenterology practice	
Sochal et al[154]	2020	Poland	IBD 133 Controls 57	IBD 37 Controls 38	IBD 55 Controls 58	HBI ≤4 PMS ≤2	PSQI >5	Healthy volunteers via snowball sampling matched by age, sex and BMI	Sleep impairment is common in IBD and associated with mood disturbance
Zhang et al[173]	2020	China	IBD 16 Controls 7	IBD 41 Controls 34	IBD 56% Controls 43%	HBI ≤4 PMS ≤ 1	PSQI >5	Healthy volunteers from online recruitment	Sleep in people with IBD was worse than the control group, and even worse in the IBD-PA group

IBD inflammatory bowel disease, CD Crohn's disease, UC ulcerative colitis, CDAI Crohn's Disease Activity Index, UCDAI Ulcerative Colitis Disease Activity Index, PMS Partial Mayo Score, HBI Harvey–Bradshaw Index, PSQI Pittsburgh Sleep Quality Index.

Supplementary Figure 6.1: Funnel plot of meta-analysis of poor sleep in those with clinically inactive inflammatory bowel disease and controls. Standardised mean difference used as effect size.



Supplementary Table 6.1: Study quality scored according to the Newcastle–Ottawa Scale with sub-scores and associated study quality detailed.

Study	Year	Selection	Comparability	Outcome	Study quality
Ballou et al	2018	2	1	2	Fair
Bucci et al	2018	2	1	2	Fair
Gîlc-Blanariu et al	2020	4	1	3	Good
Gingold-Belfer et al	2014	3	1	3	Good
Iskandar et al	2020	2	2	3	Fair
Keefer et al	2006	2	2	2	Fair
Keskin et al	2020	2	1	2	Fair
Sochal et al	2020	3	1	3	Good
Zhang et al	2020	2	2	2	Fair

CHAPTER 7: INFLAMMATORY BOWEL DISEASE MEDICATIONS AND SLEEP QUALITY

This chapter presents the manuscript 'Examining the influence of inflammatory bowel disease medications sleep quality', published in *JGH Open*, Feb 2023, doi: 10.1002/jgh3.12871.

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Alex Barnes: responsible for study concept and design, data acquisition, analysis and data interpretation, drafting of manuscript, critical revision of the manuscript.

Sutapa Mukherjee: critical revision of the manuscript

Paul Spizzo: critical revision of the manuscript.

Peter Bampton: responsible for critical revision of the manuscript.

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[Manuscript] Examining the influence of inflammatory bowel disease medications on sleep quality

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Robert J Fraser: responsible for critical revision of the manuscript.

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Data availability statement

The data underlying this article are available upon request to the author.

Keywords: inflammatory bowel disease, sleep, opioids, methotrexate, obesity

Abstract

Background and aims

Inflammatory bowel disease (IBD) can disrupt sleep leading to poor sleep quality. This may in part be due to the symptoms of IBD and the influence of pro-inflammatory cytokines on sleep. This study aimed to investigate the potential influence of IBD medications on sleep quality.

Methods

An online survey of adults with IBD was conducted which included measures of sleep quality, IBD activity, anxiety, depression, and physical activity. Logistic regression was used to investigate possible associations between IBD medications (corticosteroids, immunomodulators, biologics, Aminosalicyate) and outcome of poor sleep. A generalised linear model was built for outcome of sleep quality score.

Results

There were 544 participants included in the final analysis, median age 42, 61% with Crohn's disease. Increased odds of poor sleep were seen in those taking opioids, medications for anxiety or depression, corticosteroids, vitamin D, methotrexate, and infliximab. A multivariate model was built incorporating demographic and IBD variables with opioids present in the final model and associated with increased odds of poor sleep. This was in addition to medications for sleep, depression, anxiety, IBD activity and body weight. In a multivariate generalised linear model opioids and methotrexate were associated with worse sleep quality scores.

Conclusions

Opioids were associated with increased odds of poor sleep independent of other factors. This provides further support for avoiding these medications in people with IBD. Infliximab was associated with increased body weight and consequently increased odds of poor sleep.

Introduction

Sleep is an essential biologic function with an important role in overall health. Abnormal sleep has been linked to poor health outcomes including cardiovascular disease,[104] metabolic syndrome[105] and increased all-cause mortality in some studies,[206] in addition to significant economic cost in the form of decreased productivity and increased health care utilisation.[108] Sleep has been shown to regulate a number of gastrointestinal functions including gastrointestinal motility and secretion.[207] Sleep disruption has been associated with increased levels of inflammatory cytokines, such as IL-6, and TNF-α, that have been implicated in the pathogenesis of inflammatory bowel disease.[227-229]

Inflammatory bowel disease (IBD) is a relapsing-remitting autoimmune disorder that results from a complex interaction between genetics and the environment.[202] Poor sleep is prevalent in people with IBD with a recent meta-analysis suggesting a pooled prevalence of 56%.[273] IBD may impair sleep through its myriad of disabling symptoms, including abdominal pain and nocturnal diarrhoea.[201] Poor sleep is more common in those with IBD than controls,[11] more common in those with active IBD than inactive IBD,[200,201] and remains more common in those with inactive IBD than controls.[274] Endoscopically or histologically active IBD in the absence of any IBD symptoms may be sufficient to disrupt sleep.[164,166] There have been several association studies of sleep and IBD with comorbid depression[154-161] frequently associated with poor sleep, and low physical activity associated with poor sleep.[157,313]

The effect of IBD medications on sleep has been investigated with a prospective study following the introduction of a biologic medication with subsequent measurement of subjective sleep quality improving,[158] likely accompanied by an improvement in IBD activity. Others cross-sectional studies have been unable to demonstrate a relationship between biologics, immunomodulators and sleep quality,[154,165,166] although these studies may have been underpowered. Current use of corticosteroids was associated with worse sleep quality although confounded by IBD activity,[161,164] however this was not replicated in other studies.[154,167,168]

Sleep, being an immunologically active state, may be influenced by medications that alter the immune system such as TNF-α inhibitors.[314] In people with rheumatoid arthritis,[133] infliximab, a TNF-α inhibitor also commonly used in IBD,[315] was observed to improve some aspects of sleep quality and reduce daytime sleepiness.[316] Adalimumab, another TNF-α

inhibitor commonly used to treat IBD,[317] was associated with improved sleep quality in people with psoriasis,[318] and ankylosing spondylitis.[134]

This study aims to explore the relationship between medications used by people with IBD and sleep quality. It will also consider other influences of sleep quality such as IBD activity, physical activity, and mental health.

Methods

An online questionnaire was made available to people with IBD via tertiary hospital patient email lists, private gastroenterology practice email lists and social media. This study received ethics approval from the Southern Adelaide Human Research Ethics Committee (203.20). Individuals with a self-reported diagnosis of IBD over 18 years of age were invited to participate. Demographic data such as age and sex were recorded, along with data on IBD which included disease duration and previous surgery. Current medications were recorded including those specifically for IBD, sleep, mental health and pain control. Medications for sleep were sub-categorised as melatonin or, benzodiazepines and zolpidem.

Questionnaires

1. Sleep quality

The Pittsburgh Sleep Quality Index (PSQI) is a validated tool which assesses perceived sleep quality.[113] The index consists of subscales on sleep duration, sleep disturbance, sleep latency, daytime dysfunction, sleep efficiency, overall sleep quality and medications for sleep. The score ranges from 0 to 21, with a PSQI >5 considered to represent poor sleep quality.

2. IBD disease activity

IBD disease activity was assessed using the Harvey–Bradshaw Index in the case of Crohn's disease with HBI >5 considered active disease,[217] and the Simple Clinical Colitis Activity Index (SCCAI) in the case of ulcerative colitis. An SCCAI >2 was considered active disease.[282]

3. Physical activity

Physical activity was assessed using the international physical activity questionnaire short form (IPAQ-SF).[319] This allows the calculation of metabolic equivalent of task (MET) values over a one-week period of walking, moderate and vigorous activity, along with sitting time.

4. Anxiety and depression

Anxiety was assessed using the generalised anxiety disorder 7-item scale (GAD-7)[285] with a score over 10 used to indicate clinically significant anxiety. The Patient Health Questionnaire 9 (PHQ-9) was used to assess depression with a score over 15 used to indicate clinically significant depression.[286]

Statistical analysis

Statistical analysis was performed using Stata SE 16 (StataCorp, College Station, TX, USA). Inadequate completion of a score or index led to that result not being included. For normally distributed variables mean and standard deviation (SD) were reported with comparisons made using the Student's *t*-test. For non-normally distributed variables median, and interquartile range (IQR) were reported, with comparisons made using the Mann–Whitney U test. For categorical data Pearsons $\chi 2$ test was used or Fisher's exact test when appropriate. Logistic regression was performed for an outcome of poor sleep (PSQI >5). Logistic regression was used to calculate adjusted odds ratios for known IBD activity, anxiety, and depression. A multivariate logistic regression model was built for outcomes of poor sleep including demographic variables. This was model optimised by sequentially adding and removing variables to maximise the likelihood function. A generalised linear model was also constructed for outcome of raw PSQI score with univariate and multivariate regression performed with this optimised by the Bayesian information criterion.

Results

There were 544 participants who completed the questionnaire. Completion rate for the survey was 93%. Given the method of survey distribution we are unable to estimate the response rate. The mean age was 42 years (SD 13), 61% had Crohn's disease and median disease duration was 10 years (IQR 3–17). The mean HBI was 7.2 (3.1) and SCCAI was 7.2 (2.8), with clinically active IBD in 64%. IBD-related medications included biologics in 54.6% of the cohort, immunomodulators in 37.1%, 5ASA in 35.4%, corticosteroids in 10.1%, and immunomodulator in combination with a biologic in 20.5% (see Table 1).

Sleep quality

The mean (SD) PSQI for the cohort was 8.80 (4.56). In reference to different IBD medications (Table 2) the mean PSQI was higher in those on opioids, medication for anxiety or depression, benzodiazepines or zolpidem, melatonin, and corticosteroids ($p < 0.001$ for all). PSQI subscales for medications with a higher PSQI are detailed in Supplementary Table

1. Corticosteroids were associated with worse sleep efficiency, increased sleep duration, and worse sleep disturbance. Opioids impacted all PSQI subscales apart from need for medications for sleep.

Logistic regression was performed for outcome of poor sleep (PSQI > 5) (see Table 3) with increased odds of poor sleep seen in those on opioids, medications for sleep including zolpidem and benzodiazepines, medications for anxiety or depression, corticosteroids, vitamin D, methotrexate, and infliximab but not other biologics. No medication was associated with decreased odds of poor sleep. All those on melatonin had poor sleep. Considering PSQI subscales, Infliximab was associated with higher sleep disturbance scores and higher scores for needing medications for sleep (see Supplementary Table 1). Considering a subgroup of those not on any medications for sleep infliximab remained associated with poor sleep. Methotrexate had higher daytime dysfunction scores, worse sleep efficiency scores and worse sleep quality scores (see Supplementary Table 1).

Combinations of IBD medications were also considered (see Supplementary Table 2). All of the cohort on opioids and either methotrexate or infliximab had poor sleep. The combination of methotrexate and infliximab did not reach significance for an association with poor sleep (p = 0.094). There was no association with poor sleep seen for combinations of Aminosalicyate, biologics and immunomodulators.

Clinically active IBD

Clinically active IBD was defined as SCCAI >2 or HBI >5, mean SCCAI was 5.7 (4.1), and mean HBI was 5.7 (4.2). Clinically active IBD was associated with poor sleep (see Supplementary Table 3). Logistic regression was used to calculate adjusted odds ratios by IBD activity for outcomes of poor sleep (see Table 4). Adjusted odd ratios were no longer significant for corticosteroids and methotrexate. Opioids, infliximab, medications for sleep and vitamin D remained significantly associated with increased odds of poor sleep.

Depression

Clinically significant depression (PHQ-9 >15) was associated with poor sleep, (see Supplementary Table 3). Logistic regression was used to calculate adjusted odds ratios by depression (PHQ-9 >15) for outcomes of poor sleep (see Table 4). After adjustment corticosteroids were no longer significant (p = 0.054), other medications remained significantly associated with poor sleep.

Anxiety

Clinically significant anxiety (GAD-7 >10) was associated with poor sleep (see Supplementary Table 3). Logistic regression was used to calculate adjusted odds ratios by anxiety (GAD-7 >10) for outcomes of poor sleep (see Table 4). After adjustment corticosteroids were no longer significant ($p = 0.096$), other medications remained significantly associated with poor sleep.

Physical activity

Physical activity as measured by total METs, sitting time and vigorous METs was not associated with any sleep quality measure. Further analysis was consequently not undertaken.

Multivariate regression

A multivariate model was constructed for outcome of poor sleep that included medications—opioids, medications for sleep, infliximab, and vitamin D. The model also included demographic variables and IBD-related variables such as disease duration (for univariate logistic regression see Supplementary Table 4). In the final model (see Table 5) opioid usage and mediations for sleep remained associated with increased odds of poor sleep. Infliximab and vitamin D were not included in the final model. Other variables in the final model included body weight, IBD disease duration, clinically significant anxiety, clinically significant depression and clinically active IBD.

Infliximab was not significantly associated with poor sleep when adjusted for by body weight (see Supplementary Table 5). People on infliximab had a higher body weight than the remainder of the cohort (79.56. v 72.45 $p = 0.024$). Infliximab remained significantly associated with poor sleep when adjusted by other variables in the final model excluding body weight (Supplementary Table 5). This was similarly observed with vitamin D with those on vitamin D having a higher body weight than the remainder of the cohort (80.43 v 71.19, $p = 0.0005$). Vitamin D remained significantly associated with poor sleep when adjusted by the other variables in the final model excluding body weight (see Supplementary Table 5). Sub-scores from IBD clinical activity were considered for abdominal pain and nocturnal diarrhoea. Opioids were associated with abdominal pain ($p < 0.001$) but not nocturnal diarrhoea ($p = 0.19$). Adjusted odds ratio for poor sleep for those on opioids remained significant after adjustment for abdominal pain. Opioids were associated with longer IBD disease duration (14.6 (11.8–17.5) v 11.5 (10.6–12.4), $p = 0.014$), and higher SCCAI scores ($p < 0.012$) or HBI scores ($p < 0.0001$).

A generalised linear model was constructed for outcome of PSQI score with univariate (see Supplementary Table 6) and multivariate regression performed (see Supplementary Table 7). In respect to IBD medications the univariate regression was again significant for methotrexate and corticosteroids with increased odds of poor sleep but not infliximab and vitamin D. The final multivariate model included methotrexate in addition to opioids and medications for sleep including melatonin.

Discussion

Here we have described the results of an online questionnaire demonstrating a relationship between IBD medications and sleep quality in people with IBD. Opioids, commonly prescribed in IBD, were associated with increased odds of poor sleep as part of a multivariate model including clinically active IBD, body weight, depression, anxiety, IBD disease duration and medications for sleep. Infliximab and vitamin D were associated with poor sleep but this appeared to be confounded by body weight, with both medications not included in the final multivariate model. Methotrexate was associated with higher PSQI scores. This study builds on previous work that was did not show any significant relationship between sleep quality and biologics or immunomodulators.[165]

Chronic opioid usage in people with IBD has been associated with increased all-cause mortality,[320,321] worse IBD outcomes such as infection,[322] worse quality of life[323] and increased health care utilisation.[324] In our population opioids were associated with worse sleep quality. Opioids are known to alter sleep architecture[325] and are associated with sleep disordered breathing,[326] in particular central sleep apnoea.[327] We also note that opioids may be a marker of more severe IBD.[328] In our study opioids were associated with longer disease duration and higher clinical disease activity scores. Opioids remained associated with poor sleep following adjustment for abdominal pain however it is possible that other types of pain contributed to sleep quality that were not accounted for.

Infliximab has been associated with weight gain in people with IBD,[329-334] with the suggestion that infliximab may inhibit leptin production.[335] Infliximab-related weight gain has also been observed in cohorts of people with rheumatoid arthritis[336-338] and psoriasis.[339-341] Vitamin D deficiency has been associated with obesity,[342,343] although to the authors knowledge there is no known association between vitamin D replacement and weight gain.[344] Increased body weight is a risk factor for sleep apnoea[345] and perhaps the associated weight gain from infliximab or vitamin D deficiency increases the likelihood of sleep apnoea and

consequently more likely to have poor sleep. Vitamin D deficiency has been associated with increased risk of sleep disorders[346] and supplementation has been associated with improvement in sleep quality.[347]

Corticosteroids, known to cause sleep disturbances,[348] were associated with worse sleep quality scores and poor sleep. This replicates previous work showing worse sleep quality scores[161,164] in those on corticosteroids. The association with poor sleep was confounded by firstly IBD activity and also mental health scores, of which corticosteroids are well known to influence.[349]

Methotrexate was associated with higher PSQI scores on multivariate regression but not increased odds of poor sleep on multivariate regression. This may be due to the small number of participants on methotrexate (8%) and consequent vulnerability to some yet unidentified bias. Methotrexate is associated with fatigue[350,351] which commonly limit its use. Associations studies in a rheumatoid arthritis population have not demonstrated a relationship between sleep quality and methotrexate,[352] however in other prospective studies introduction of methotrexate did not lead to any improvement in sleep quality—unlike introduction of TNF-α inhibitors.[132,353]

Limitations of this study include selection bias a result of the use of an online questionnaire that may attract people with sleep problems. The rate of poor sleep in this cohort (75%) was higher than that reported in a recent meta-analysis on the prevalence of poor sleep in IBD[273] (56%), although a number of other studies have reported higher rates of poor sleep[159,164,165,169,173] than seen in our cohort. Similarly, the form of survey and method of recruitment is likely responsible for the predominantly female cohort. Reporting bias may also be significant, noting a study of people with Crohn's disease reported worse sleep quality than that observed by objective measures.[167] The absence of objective measures of sleep quality and objective IBD activity is also considered a limitation. Further studies should consider objective measures of IBD activity and sleep quality. Studies incorporating mental health interventions in those with poor sleep should be pursued. Consideration should also be given to examining the relationship between serum levels of vitamin D and sleep quality in an IBD population.

Conclusions

A large survey of people with IBD has shown that opioids are associated with increased odds of poor sleep. Infliximab and vitamin D usage was associated with poor sleep however this

was confounded by higher body weight and consequently perhaps increased rates of sleep apnoea. Further studies are required to confirm these results and should incorporate objective measures of sleep quality and IBD activity.

Table 7.1: Demographics, and IBD (inflammatory bowel disease) related data, and IBD medications.

n	**544**
Age, mean (SD)	42 (13)
Female gender, *n*	436
Weight (kg) , mean (SD)	78.9 (20.4)
Height (cm), mean (SD)	167.7 (8.9)
Crohn's disease, *n*	333
Ulcerative colitis, *n*	218
Indeterminate colitis, *n*	15
Disease duration (years, median (IQR))	10 (3-17)
Previous surgery for IBD, *n*	183
Corticosteroids	
Budesonide, *n* (%)	11 (2)
Prednisolone, *n* (%)	44 (8)
Biologics	
Adalimumab, *n* (%)	79 (14)
Infliximab, *n* (%)	95 (17)
Ustekinumab, *n* (%)	67 (12)
Vedolizumab, *n* (%)	50 (9)
Tofacitinib, *n* (%)	6 (1)
Immunomodulator	
Azathioprine, *n* (%)	105 (19)
Mercaptopurine, *n* (%)	53 (10)
Methotrexate, *n* (%)	44 (8)
Aminosalicyate	
Mesalazine, *n* (%)	172 (31)
Sulfasalazine, *n* (%)	21 (4)
Other IBD medication	
Bactrim, *n* (%)	1 (0.01)
Cyclosporine, *n* (%)	0

n	**544**
Tacrolimus, *n* (%)	2 (0.03)
Immunomodulator and biologic, *n* (%)	112 (20)
Aminosalicyate and biologic, *n* (%)	50 (9)
Aminosalicyate, immunomodulator and biologic, *n* (%)	28 (5)
Vitamin D, *n*	152 (28)
Medications for sleep Melatonin, *n* (%) Benzodiazepines or zolpidem, *n* (%)	 34 (6) 49 (9)
Medications for depression or anxiety, *n* (%)	128 (23)
Opioids, *n* (%)	78 (14)
Overnight shift work, *n* (%)	31 (6)

Table 7.2: Pittsburgh Sleep Quality Index (PSQI) scores for IBD medications.

Medication	**PSQI (mean, 95% CI)**	**P value**
Opioids	Yes: 11.92 (11.09-12.75) No: 9.05 (8.71-9.40)	$p < 0.0001$
Anti-anxiety or anti-depressant	Yes: 10.53 (9.79-11.27) No: 9.15 (8.78-9.51)	$p = 0.0005$
Medications for sleep	Yes: 11.82 (11.05-12.60) No: 9.09 (8.75-9.45)	$p < 0.001$
Benzodiazepines or zolpidem	Yes: 12.06 (11.03-13.09) No: 9.21 (8.87-9.56)	$p < 0.0001$
Melatonin	Yes: 11.23 (10.22-12.24) No: 9.35 (9.01-9.69)	$p = 0.0064$
Vitamin D	Yes: 9.77 (9.16-10.38) No: 9.35 (8.96-9.75)	$p = 0.26$
5ASA medication	Yes: 9.25 (8.70-9.80) No: 9.58 (9.17-9.99)	$p = 0.35$
Corticosteroids	Yes: 11.09 (9.97-12.21) No: 9.29 (8.95-9.64)	$p = 0.0014$
Immunomodulators	Yes: 9.47 (8.90-10.04) No: 9.47 (9.06-8.87)	$p = 0.99$
Thiopurine	Yes: 9.03 (8.39-9.66) No: 9.65 (9.26-10.04)	$p = 0.0942$
Methotrexate	Yes: 11.07 (9.84-12.29) No: 9.33 (8.99-9.68)	$p = 0.0051$
Biologics	Yes: 9.33 (8.89-9.78) No: 9.63 (9.13-10.13)	$p = 0.38$
Anti-TNF	Yes: 9.51 (8.92-10.09) No: 9.45 (9.05-9.86)	$p = 0.88$

Table 7.3: Table of medications and univariate logistic regression for outcome of poor sleep (Pittsburgh Sleep Quality Index score > 5) with odds ratio, 95% confidence interval and *p* value reported. All those on melatonin had poor sleep, consequently this was not included.

Medication	**Poor sleep**
Opioids	6.95 (2.49-19.37) $p < 0.001$
Anti-anxiety or anti-depressant	1.72 (1.03-2.85) $p = 0.035$
Medications for sleep	13.88 (3.36-57.31) $p < 0.001$
5ASA medication	1.16 (0.77-1.76) $p = 0.47$
Vitamin D	1.98 (1.22-3.23) $p = 0.006$
Corticosteroids	2.69 (1.13-6.45) $p = 0.026$
Immunomodulators	1.28 (0.85-1.92) $p = 0.23$
Methotrexate	3.34 (1.17-9.52) $p = 0.024$
Thiopurine	0.97 (0.63-1.49) $p = 0.89$
Biologics	1.43 (0.95-2.10) $p = 0.067$
Adalimumab	0.85 (0.49-1.46) $p = 0.56$
Infliximab	2.02 (1.11-3.69) $p = 0.022$
Vedolizumab	0.90 (.047-1.76) $p = 0.77$
Ustekinumab	1.54 (0.80-2.97) $p = 0.19$
Tofacitinib	0.64 (0.12-3.52) $p = 0.61$

Table 7.4: Logistic regression used to calculate odds ratio for poor sleep adjusted by IBD activity, or depression, or anxiety

Medication	Active IBD	Significant depression	Significant anxiety
Opioids	6.19 (2.19-17.53) $p = 0.001$	7.27 (2.58-20.41) $p < 0.001$	7.33 (2.60-20.63) $p < 0.001$
Infliximab	2.02 (1.08-3.77) $p = 0.028$	2.24 (1.21-4.12) $p = 0.010$	2.19 (1.18-4.06) $p = 0.013$
Methotrexate	2.68 (0.92-7.82) $p = 0.072$	3.21 (1.1-9.28) $p = 0.027$	3.48 (1.20-10.07) $p = 0.021$
Corticosteroids	2.39 (0.97-5.87) $p = 0.056$	2.39 (0.98-5.82) $p = 0.054$	2.14 (0.87-5.26) $p = 0.096$
Medications for sleep	12.13 (2.90-50.69) $p = 0.001$	14.7 (3.55-61.09) $p < 0.001$	13.40 (3.22-55.8) $p < 0.001$
Medications for anxiety or depression	1.29 (0.76-2.19) $p = 0.34$	1.35 (0.80-2.29) $p = 0.25$	1.37 (0.81-2.32) $p = 0.23$
Vitamin D	1.87 (1.13-3.10) $p = 0.015$	1.89 (1.15-3.10) $p = 0.012$	1.97 (1.19-3.24) $p = 0.008$

Table 7.5: Final multivariate logistic regression model for outcome of poor sleep including opioids, infliximab, vitamin D, medications for sleep and demographic variables.

Variable	Odds ratio	confidence interval	P value
Opioids	3.08	1.04-9.122	0.041
Benzodiazepines or zolpidem	9.21	2.08-40.86	0.003
Weight	1.02	1.01-1.03	<0.001
IBD disease duration	1.02	1.00-1.04	0.042
Clinically significant anxiety	3.82	1.88-7.78	<0.001
Clinically significant depression	3.67	1.21-11.08	0.021
Active IBD	2.56	1.64-4.00	<0.001

Supplementary Table 7.1: Pittsburgh Sleep Quality Index components for medications—opioids, corticosteroids, and vitamin D. Arrows to indicate significantly higher or lower score compared to remainder of cohort (*$p = 0.05$, ** indicates $p < 0.005$, * indicates $p < 0.0005$). Sleep efficiency is the time in bed that you are asleep divided by total time in bed. Sleep latency is the time taken to fall asleep.**

PSQI component	Opioids	Corticosteroids	Medication for anxiety or depression	Infliximab	Methotrexate	Vitamin D	Medications for sleep
Sleep duration	↑***	↑**	↔	↔	↔	↔	↔
Sleep disturbance	↑***	↑**	↑***	↑**	↑	↑***	↑**
Sleep latency	↑***	↑*	↑**	↔	↔	↔	↑***
Daytime dysfunction	↑***	↑*	↑**	↔	↑**	↑**	↑***
Sleep efficiency	↑***	↑***	↑***	↔	↑***	↔	↑**
Sleep quality	↑***	↑*	↑*	↔	↑**	↔	↔
Medications for sleep	↔	↔	↔	↑**	↔	↔	↑**

Supplementary Table 7.2: Univariate logistic regression for poor sleep (PSQI >5) for IBD maintenance medication combinations. All of the cohort on opioids in addition to either methotrexate or infliximab had poor sleep, and consequently these combination medication variables were not included in the table.

	Odds ratio, 95% confidence interval, *p* value
Opioids and biologics	1.50 (1.15-1.97) $p = 0.003$
Methotrexate and infliximab	5.64 (0.74-.42.76) $p = 0.094$
Immunomodulator and biologic	1.39 (0.83-2.32) $p = 0.20$
Aminosalicyate and Immunomodulator	0.89 (0.49-1.61) $p = 0.71$
Aminosalicyate and biologic	0.73 (0.38-1.37) $p = 0.33$
Aminosalicyate and immunomodulator and biologic	0.79 (0.34-1.84) $p = 0.59$
Biologic without any other IBD maintenance medication	1.27 (0.81-2.00) $p = 0.29$
Immunomodulator without any other IBD maintenance medication	0.98 (0.50-1.95) $p = 0.97$
Aminosalicyate without any other IBD maintenance medication	1.38 (0.78-2.44) $p = 0.26$

Supplementary Table 7.3: Sleep quality by poor sleep for clinically active IBD, clinically significant depression, anxiety

Clinically active IBD (SCCAI >2 or HBI >5), clinically significant depression (PHQ9 >15), clinically significant anxiety (GAD7 >10) with differences in sleep quality and odds ratios for poor sleep (PSQI >5) and clinically significant insomnia (ISI >14).

	Poor sleep (Odds ratio, 95% CI)
Clinically active IBD	4.16 (2.79-6.21) $p < 0.001$
Clinically significant depression	9.72 (3.51-26.97) $p < 0.001$
Clinically significant anxiety	6.53 (3.42-12.46) $p < 0.001$

Supplementary Table 7.4: Univariate logistic regression for poor sleep (PSQI >5) for demographic.

	Odds ratio, 95% confidence interval, *p* value
Crohn's disease	1.75 (1.19-2.57) $p = 0.004$
IBD disease duration	1.04 (1.01-1.06) $p < 0.001$
Previous surgery for IBD	1.54 (1.00-2.37) $p = 0.049$
Overnight shift work	1.28 (0.48-3.43) $p = 0.61$
Current smoker	1.71 (0.69-4.19) $p = 0.24$
Current alcohol usage	1.17 (0.77-1.77) $p = 0.47$
Body Mass Index	1.07 (1.03-1.11) $p < 0.001$
Weight	1.02 (1.02-1.03) $p < 0.001$
Height	1.01 (1.00-1.01) $p < 0.001$
Male gender	0.81 (0.50-1.30) $p = 0.38$
Age	1.02 (1.01-1.03) $p = 0.001$

Supplementary Table 7.5: Adjusted odds ratios for outcome of poor sleep for infliximab and vitamin D by variables included in the final multivariate model. Note—odds ratios adjusted by anxiety, depression and IBD activity have been described in Table 4.

Variable	**Opioids**	**Medications for sleep**	**Weight**	**IBD disease duration**
Infliximab	2.02 (1.09-3.71) $p = 0.024$	2.00 (1.09-3.70) $p = 0.025$	1.72 (0.93-3.18) $p = 0.085$	1.99 (1.08-3.66) $p = 0.026$
Vitamin D	1.82 (1.12-2.99) $p = 0.016$	1.88 (1.15-3.09) $p = 0.012$	1.62 (0.98-2.68) $p = 0.058$	1.85 (1.13-3.03) $p = 0.014$

Supplementary Table 7.6: Generalised univariate linear regression with outcome of Pittsburgh Sleep Quality Index score (PSQI score).

	Exponential of coefficient, 95% CI, *p* value
Crohn's disease	1.35 (0.68-2.65) $p = 0.39$
IBD disease duration	1.02 (0.99-1.05) $p = 0.25$
Previous surgery for IBD	1.51 (0.75-3.03) $p = 0.25$
Overnight shift work	0.85 (0.21-3.51) $p = 0.82$
Current smoker	2.46 (0.64-9.36) $p = 0.19$
Current alcohol usage	0.36 (0.18-0.72) $p = 0.004$
Obesity	0.26 (2.16-8.39) $p < 0.001$
Weight	1.03 (1.01-1.04) $p < 0.001$
Height	1.00 (0.99-1.01) $p = 0.80$
Male gender	0.48 (0.21-1.10) $p = 0.083$
Age	1.00 (0.99-1.00) $p = 0.51$
Opioids	17.54 (7.09-43.39) $p < 0.001$
Anti-anxiety or anti-depressant	3.98 (1.84-8.60) $p < 0.001$
Benzodiazepines or zolpidem	21.77 (6.35-74.58) $p < 0.001$
Melatonin	6.56 (1.70-25.24) $p = 0.006$
5ASA medication	0.72 (0.36-1.44) $p = 0.35$
Vitamin D	1.52 (0.73-3.17) $p = 0.26$
Corticosteroids	6.04 (2.01-18.09) $p = 0.001$
Immunomodulators	0.99 (0.50-1.97) $p = 0.99$
Methotrexate	5.67 (1.69-18.98) $p = 0.005$
Thiopurine	0.54 (0.26-1.11) $p = 0.094$
Biologics	0.74 (0.38-1.44) $p = 0.39$
Adalimumab	0.81 (0.32-2.09) $p = 0.67$
Infliximab	1.28 (0.54-3.07) $p = 0.57$
Vedolizumab	0.3 (0.12-1.14) $p = 0.082$
Ustekinumab	1.01 (.037-2.77) $p = 0.98$
Tofacitinib	2.82 (0.12-65.47) $p = 0.52$
Opioids and biologics	1.55 (1.06-2.28) $p = 0.025$
Methotrexate and infliximab	6.85 (1.10-42.67) $p = 0.039$

	Exponential of coefficient, 95% CI, *p* value
Immunomodulator and biologic	0.92 (0.41-2.07) $p = 0.84$
Aminosalicyate and Immunomodulator	0.57 (0.21-1.59) $p = 0.29$
Aminosalicyate and biologic	0.49 (0.16-1.51) $p = 0.21$

Supplementary Table 7.7: Generalised multivariate linear regression with outcome of Pittsburgh Sleep Quality Index score (PSQI score), optimised by Bayesian information criterion.

	Exponential of cofficient, 95% CI, *p* value
Opioids	6.83 (2.79-16.69) $p < 0.001$
Melatonin	5.52 (1.54-19.78) $p = 0.009$
Benzodiazepines or zolpidem	12.23 (4.02-37.16) $p < 0.001$
Methotrexate	5.99 (2.01-17.85) $p = 0.001$
Clinically significant depression	9.62 (4.10-22.54) $p < 0.001$
Clinically significant anxiety	4.53 (2.21-9.28) $p < 0.001$
Clinically active IBD	2.45 (1.29-4.62) $p = 0.006$

CHAPTER 8: INSOMNIA AND ITS RELATIONSHIP TO MENTAL HEALTH CONDITIONS IN INFLAMMATORY BOWEL DISEASE

This chapter presents the manuscript 'Insomnia is common in IBD and associated with mental health conditions as well as IBD activity', published in *Intestinal Research*, November 2023, doi: 10.5217/ir.2023.00028.

Author contributions

Alex Barnes: responsible for study concept and design, data acquisition, analysis, and data interpretation, drafting of manuscript, critical revision of the manuscript.

Jane Andrews: responsible for study concept¸ responsible for critical revision of the manuscript.

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[Manuscript] Insomnia is common in IBD and associated with mental health conditions as well as IBD activity

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Abstract

Insomnia is common in people with chronic medical conditions, such as inflammatory bowel disease (IBD), and is readily treatable through cognitive behavioural therapy for insomnia (CBTi). This study aimed to describe the associations with insomnia in people with IBD and its relationship to IBD-related disability.

Methods

An online questionnaire was administered through three tertiary IBD centres, social media and through Crohn's Colitis Australia. The questionnaire included the Insomnia Severity Index (ISI), a validated assessment of insomnia. Measures of anxiety, depression, physical activity, and disability were also included. IBD activity was assessed using validated patient-reported scores. A multivariate model was constructed for clinically significant insomnia and ISI score. Subpopulations of Crohn's disease and ulcerative colitis were considered.

Results

In a cohort of 670 respondents the median age was 41 years (32–70), with the majority female (78%), the majority had Crohn's disease (57%). Increasingly severe disability was associated with worse insomnia score. Clinically significant insomnia was associated with clinically active IBD, abdominal pain, anxiety, and depression, in a multivariate model. In an ulcerative colitis population SCCAI components general wellbeing and urgency were associated with worse ISI score in a model including depression and anxiety. In those with Crohn's disease the multivariate model included HBI score in addition to depression and anxiety.

Conclusion

Insomnia is common in people with IBD and was associated with increased disability. Abdominal pain and mental health conditions should prompt consideration for screening for insomnia and referral for CBTi.

Introduction

Sleep quality is of increased interest in inflammatory bowel disease. Abnormal sleep has been associated with several poor health incomes including cardiovascular disease[104] and all-cause mortality in some studies.[206] Meta-analyses have suggested that poor sleep is prevalent in those with IBD,[273] and more common in those with clinically active IBD,[200] worse than controls[201] and associated with mental health conditions[159,167] and worse quality of life.[87,181] Longitudinal studies have suggested that sleep disturbance is associated with fatigue,[221] disease activity[153,161,168] and, in Crohn's disease, the risk of hospitalisation.[170] Insomnia is likely the most common sleep disorder in an IBD population with studies suggesting a prevalence up to 58%.[181,183]

Chronic insomnia is common in those with chronic medical conditions.[247,354,355] This has been attributed to the effect of the symptoms associated with the disease and may exist as a symptom of the chronic medical condition itself.[356] Chronic pain is commonly seen in those with chronic insomnia with a prevalence of up to 40%.[193,357] Finally, chronic insomnia has been associated with an increased risk of cardiovascular disease[358,359] and poor outcomes such as increased hospitalisation[360] and work absenteeism.[361]

Others have postulated that the symptoms of active IBD, such as nocturnal diarrhoea and abdominal pain, may lead to sleep fragmentation and the development of conditioned insomnia.[190] This sleep pattern then persists following resolution of a flare and movement into an inactive IBD state. Irritable bowel syndrome-like symptoms in people with IBD may also be important with poor sleep prevalent in those with IBS.[140] Mental health conditions, such as depression and anxiety, commonly co-exist with IBD and are also associated with insomnia.[191]

The IBD and sleep literature has considered associations and predictors of poor sleep.[154,156,168,169,220,232,255] However there is only a single study considering IBD factors related to insomnia—noting the role of mental health conditions was not considered.[183]This study therefore aimed to explore whether there are specific disease or demographic factors associated with insomnia in an unselected IBD cohort in order to inform specific targets for an interventional study.

Methods

An online questionnaire was made available to people with IBD via tertiary hospital patient email lists, private gastroenterology practice email lists and social media associated with a

patient support organisation. Individuals with a self-reported diagnosis of IBD over 18 years of age were invited to participate. Demographic data such as age and sex were recorded, along with IBD-related data including disease duration and previous surgery. Ethics approval for this study was obtained from the Southern Adelaide Human Research Ethics Committee (203.20).

The Insomnia Severity Index (ISI) is a self-reported questionnaire that been validated for assessment of insomnia, evaluating the response to treatment, and as an outcome measure for insomnia research.[278-280] The index consists of seven items with a 5-point Likert scale used to rate each item. A score between 0–7 is considered to indicate the absence of insomnia, 8–14 subthreshold insomnia, 15–21 moderate insomnia, and over 21 denotes severe insomnia. Clinically significant insomnia is defined as an ISI score greater or equal to 10 as is commonly used in screening.[278]

IBD disease activity was assessed using the Harvey–Bradshaw Index (HBI) in the case of Crohn's disease with HBI >5 considered active disease.[217] The patient-reported version of the HBI was utilised in the survey, although a decision was made to maintain the general wellbeing and abdominal pain score similar to the physician HBI rather than using a ten-point Likert scale.[281] The Simple Clinical Colitis Activity Index (SCCAI) was used in the case of ulcerative colitis, an SCCAI >5 was considered active disease.[282] The patient-reported form of the SCCAI was utilised[283] in the survey. The use of a self-reported SCCAI has been previously validated with good agreement with physician-reported SCCAI.[284] The abdominal pain sub-score from HBI was utilised to form an abdominal pain dichotomous variable with an abdominal pain sub-score of mild used as the cut-off value, with values above mild encoded as one (present), and values mild or below encoded as a zero (absent). The nocturnal diarrhoea sub-score from SCCAI was utilised to form a nocturnal diarrhoea dichotomous variable with a nocturnal diarrhoea sub-score of above 1 encoded as a one (present), and scores 1 or less encoded as a zero (absent).

Physical activity was assessed using the international physical activity questionnaire short form (IPAQ-SF).[319] This allows the calculation of metabolic equivalent of task (MET) values over a one-week period of walking, moderate and vigorous activity, along with sitting time.

Anxiety was assessed using the generalised anxiety disorder 7-item scale (GAD-7)[285] with a score over 10 used to indicate likely clinically significant anxiety. The Patient Health

Questionnaire 9 (PHQ-9) was used to assess depression with a score over 15 used to indicate likely clinically significant depression.[286]

Disability was assessed using the IBD-Disability Index self-report (IBD-DI-SR) version.[362] The IBD-Disability Index self-report is a validated self-reported measure of disability in an IBD population. It was developed as a self-report form and a short form of the IBD-Disability Index.[363] The IBD-DI is considered an important endpoint for clinical trials and in clinical practice.

Statistical analysis

Statistical analysis was performed using Stata SE 16 (StataCorp, College Station, TX, USA). Inadequate completion of score or index led to that resultbeing discarded. For normally distributed variables mean and standard deviation (SD) were reported with comparisons made using the Student's *t*-test. For non-normally distributed variables median, and interquartile range (IQR) were reported, with comparisons made using the Mann–Whitney U test. For categorical data Pearsons $\chi 2$ test was used or Fisher's exact test when appropriate. One-way analysis of variance used with Tukey's post hoc test and adjusted for multiple comparisons as appropriate. A generalised linear model was also constructed for outcome of ISI score with univariate and multivariate regression performed with this optimised by the Bayesian information criterion. Logistic regression was performed for an outcome of clinically significant insomnia (ISI >15). A multivariate logistic regression model was built for outcomes of clinically significant insomnia including demographic variables. This was model optimised by sequentially adding and removing variables to maximise the likelihood function. The margins command used for post-estimation of probabilities. Regression was repeated for Crohn's disease and ulcerative colitis subpopulations. Disease active scores (HBI and SCCAI) and their relationship to insomnia were examined using one-way analysis of variance used with Tukey's post hoc test and adjusted for multiple comparisons as appropriate.

Results

There were 670 responses to the online questionnaire. Completion rate for the questionnaire was 90.5%. Median age was 41 years (32–70), with most being female (78%), the majority had Crohn's disease (57%). The mean disease duration was 11.9 years (10.4), 30% had undergone surgery for IBD and around half were on biologics (50.5%) (see Table 1).

Clinically significant depression (PHQ9 >15) was seen in 18%, and clinically significant anxiety (GAD-7 >10) seen in 29%.

The median ISI score was 13 (IQR 8–17). Clinically significant insomnia (ISI >10) was seen in 62% of the cohort and over a third of the cohort had at least moderate insomnia (see Table 2). A one-way ANOVA revealed differences in disability scores (IBD-DI-SR) (see Table 2) between insomnia severity groups ($F(3,619) = 20.99$, $p < 0.001$), with disability scores worsening with increasing severity of insomnia. Tukey's post hoc test showed significant differences between all groups except moderate and severe insomnia groups who had similar disability scores (see Supplementary Table 1).

Factors associated with an outcome of ISI score on univariate generalised linear regression included obesity, medications for sleep, opioids, current smoking status, clinically active IBD, abdominal pain, clinically significant anxiety, clinically significant depression, and methotrexate (see Table 3). The parameters maintained in the optimised multivariate model included opioids, clinically active IBD, abdominal pain, clinically significant anxiety, clinically significant depression, and methotrexate. The highest coefficient was seen with clinically significant depression (3.80 (2.68–4.93), $p < 0.001$).

Factors associated with an outcome of clinically significant insomnia on univariate logistic regression included clinically active IBD, abdominal pain, clinically significant anxiety, and clinically significant depression (see Table 4). The parameters retained in the optimised multivariate model included clinically active IBD, abdominal pain, clinically significant anxiety, and clinically significant depression. The highest odds ratio was seen with clinically significant depression (OR 3.32 (1.89–5.83), $p < 0.001$). The area under the receiver-operator curve for the logistic regression model was 0.72.

Clinically significant insomnia was seen in 62% of the cohort. Utilising the multivariate model for clinically significant insomnia post-estimation probabilities were calculated (see Table 5). Clinically significant depression resulted in the largest increase in the probability of clinically significant insomnia (23%).

A subpopulation of ulcerative colitis was considered with all SCCAI score components significantly associated with ISI score (generalised linear regression—Table 5). SCCAI general wellbeing and urgency score were included in an optimised multivariate model along with clinically significant anxiety, and clinically significant depression (Table 5). Despite abdominal pain not being part of the SCCAI this remained significantly associated with ISI

score. Significant differences in mean ISI score were seen within all SCCAI component scores (see Figure 1 and Supplementary Tables 2–7). Increasing SCCAI component score was generally associated with increasing mean ISI score (Figure 1), noting small patient numbers at the top end of SCCAI component scores. Frank blood was associated with a higher mean ISI score than no blood, with no further difference between the component scores seen.

A subpopulation of Crohn's disease was considered (see table 6). An outcome of ISI score was significant for all HBI components, except for perianal disease and oral Crohn's disease although this was limited by small numbers. HBI score was included in a final optimised multivariate model, along with clinically significant anxiety, and clinically significant depression. Significant differences in mean HBI were seen within all HBI component (Figure 2 and ANOVA see Supplementary Tables 7–11). Differences within HBI component score groups generally suggested higher HBI component score with higher mean ISI score (Figure 2 and Tukey's post hoc see Supplementary Tables 7–11), once again limited by small numbers at the top end of HBI component scores.

Discussion

In a large multicentre IBD cohort insomnia was associated with each of clinically active IBD, abdominal pain, depression, and anxiety. Insomnia was prevalent with clinically significant insomnia in over 60% of the cohort, with at least a third having moderate insomnia. The prevalence of insomnia reported in this cohort is similar to that reported in rheumatology populations[364] and similar to that reported in the other inflammatory bowel disease cohort in the literature.[183] In the general population chronic insomnia rates range from 6–20%.[365-367]

Insomnia has a well-established association with pain.[193] In our cohort, specifically, abdominal pain was associated with insomnia. The aetiology of the abdominal pain, whether related to active inflammation or irritable bowel syndrome-like symptoms, was beyond the scope of this study. It is well established that sleep deprivation is associated with hyperalgesia[368] suggesting that insomnia if present may worsen any abdominal pain. Sleep disturbances have also been linked to other gastrointestinal symptoms such as diarrhoea.[369] Nocturnal diarrhoea was associated with insomnia in ulcerative colitis but not in Crohn's disease. Data on other types of pain experienced by study participants was not available. Opioid usage, acting as an indicator of chronic pain, was associated with clinically significant insomnia and worse insomnia (higher ISI scores). SCCAI components urgency and general

health were included in the final multivariate model for ISI score over the inclusion of the overall SCCAI score. This may be a result of the lack of differentiation the blood SCCAI component score provided between ISI scores. SCCAI and HBI component score general wellbeing may in part relate to the presence of any depression, anxiety or disability.

Insomnia has been associated with mental health conditions.[296,297] Depression and anxiety were prevalent in this population and associated with insomnia. Sleep disruption is a common presentation of mood disorders.[370] Despite treatment of the underlying mood disorder residual symptoms persist which commonly will include insomnia.[191] Treatment for insomnia is widely available in the form of cognitive behavioural therapy targeted at insomnia (CBTi).[298,299] There has been a pilot trial of CBTi in an inflammatory bowel disease population where it was found to be feasible and acceptable.[190] The value of CBTi in those with mood disorders is unclear and treatment is typically first directed at the underlying mood disorder[371,372] Similarly, pain should be controlled as possible noting the relationship between sleep and hyperalgesia and acknowledging that CBTIi has shown some benefit in improving pain.[373]

Limitations of this study include selection bias a result of the use of an online questionnaire that may attract people with sleep problems. Similarly, the form of survey and method of recruitment is likely responsible for the predominantly female cohort. Reporting bias may also be significant, noting a study of people with Crohn's disease reported worse sleep quality than that observed by objective measures.[167] The absence of an objective measure of IBD activity is also considered a limitation. Further studies should consider objective measures of IBD activity and sleep quality. Studies incorporating mental health interventions in those with poor sleep should be pursued. The authors also acknowledge that there are many other factors the influence insomnia that were not measured in this study.

Conclusions

Insomnia is common in people with IBD with at least a third having moderate insomnia and almost two-thirds meeting criteria which warrant insomnia screening. Insomnia is associated with increased disability, clinically active IBD and depression and anxiety. Mood disorders and abdominal pain may represent insomnia treatment targets in individuals with IBD prior to consideration of CBTi.

Table 8.1: Demographics, and IBD (inflammatory bowel disease)-related data, and IBD medications. HBI – Harvey–Bradshaw Index, SCCAI – Simple Clinical Colitis Activity Index.

	Cohort
Age, median IQR	41 (32-70)
Female gender, *n* (%)	525 (78)
Crohn's disease, *n* (%)	384 (57)
Disease duration years, mean (SD)	11.9 (10.4)
Previous surgery for IBD, *n* (%)	201 (30.0)
Current steroid use, *n* (%)	58 (8.6)
Current biologic use, *n* (%)	339 (50.5)
Current immunomodulator use, *n* (%)	228 (34.0)
Obesity, *n* (%)	247 (36.9)
Smoking, *n* (%)	44 (6.6)
Alcohol usage, *n* (%)	213 (31.8)
Opioid usage, *n* (%)	93 (13.9)
Medications for sleep, *n* (%)	85 (12.7)
Clinically significant depression, *n* (%)	120 (17.9)
Clinically significant anxiety, *n* (%)	193 (28.8)
Clinically active IBD SCCAI, mean (SD) HBI, mean (SD)	 7.18 (2.86) 7.08 (3.29)
IBD-DI-SR, mean (SD)	-2.78 (6.01)

Table 8.2: Insomnia Severity Index (ISI) threshold scores with ANOVA used to demonstrate significant difference between disability scores between groups (IBD-DI-SR), $F(3,619) = 20.99$, $p < 0.001$).

ISI thresholds	***n* (%)**	**IBD-DI-SR scores, mean (SD)**
No significant insomnia	125 (20)	-0.56 (4.6)
Subthreshold insomnia	268 (43)	-2.6 (5.1)
Moderate insomnia	178 (29)	-5.1 (6.5)
Severe insomnia	52 (8)	-5.9 (7.4)

Table 8.3: Generalised linear univariate and multivariate regression for Insomnia Severity Index score, optimised by the Bayesian information criterion.

	Univariate regression, coefficient, 95% CI, *p* value	
Age	-0.034 (-0.071-0.002) $p = 0.062$	
Gender	-0.49 (-1.63-0.66) $p = 0.41$	
Obesity	1.1 (0.12-2.12) $p = 0.027$	
Crohn's disease	0.23 (-0.75-1.21) $p = 0.65$	
IBD disease duration	-0.003 (-.05-0.42) $p = 0.88$	
Previous surgery for IBD	-0.21 (-1.24-0.82) $p = 0.69$	
Mediations for sleep	2.41 (1.03-3.79) $p = 0.001$	
Corticosteroids	0.83 (-0.81-2.48) $p = 0.32$	
Opioids	2.52 (1.20-3.86) $p < 0.001$	1.68 (0.52-2.85) $p = 0.005$
Biologic	-0.21 (-1.17-0.75) $p = 0.66$	
Immunomodulators	-0.001 (-0.99-0.99) $p = 0.99$	
Current smoker	2.08 (0.20-3.97) $p = 0.030$	
Clinically active IBD	3.86 (2.68-5.03) $p < 0.001$	1.52 (0.42-2.64) $p = 0.007$
Abdominal pain	3.00 (2.07-3.93) $p < 0.001$	1.89 (1.01-2.76) $p < 0.001$
Nocturnal diarrhoea	0.77 (-0.54-2.08) $p = 0.25$	
Clinically significant anxiety	4.65 (3.74-5.58) $p < 0.001$	2.66 (1.65-3.67) $p < 0.001$
Clinically significant depression	5.46 (4.47-6.45) $p < 0.001$	3.80 (2.68-4.93) $p < 0.001$
Total METs	0.0000017 (-0.0009-0.0009) $p = 0.97$	
Vigorous METs	-0.0001 (-0.003-0.0001) $p = 0.38$	
Methotrexate	2.18 (0.43-3.94) $p = 0.015$	1.79 (.029-3.29) $p = 0.019$

Table 8.4: Univariate and multivariate regression for outcome of clinically significant insomnia. This was optimised by minimising the maximum likelihood ratio.

	Univariate regression, odds ratio, 95% CI, *p* value	**Multivariate regression, odds ratio 95% CI, *p* value**
Age	0.99 (0.97-1.00) $p = 0.16$	
Gender	0.84 (0.57-1.24) $p = 0.39$	
Obesity	1.31 (0.93-1.85) $p = 0.21$	
Crohn's disease	1.,12 (0.81-1.57) $p = 0.44$	
IBD disease duration	1.00 (0.99-1.02) $p = 0.69$	
Previous surgery for IBD	0.86 (0.60-1.22) $p = 0.40$	
Mediations for sleep	1.89 (1.12-3.16) $p = 0.015$	
Corticosteroids	1.39 (0.78-2.50) $p = 0.26$	
Opioids	1.92 (1.16-3.14) $p = 0.010$	
Biologic	0.95 (0.69-1.31) $p = 0.76$	
Immunomodulators	0.90 (0.64-1.26) $p = 0.54$	
Current smoker	2.11 (1.01-4.35) $p = 0.045$	
Clinically active IBD	3.04 (2.02-4.58) $p < 0.001$	1.87 (1.19-2.92) $p = 0.006$
Abdominal pain	2.28 (1.64-3.18) $p < 0.001$	1.84 (1.27-2.67) $p = 0.001$
Nocturnal diarrhoea	1.10 (0.71-1.72) $p = 0.65$	
Clinically significant anxiety	3.27 (2.26-4.73) $p < 0.001$	1.98 (1.28-3.08) $p = 0.002$
Clinically significant depression	4.62 (2.93-7.31) $p < 0.001$	3.32 (1.89-5.83) $p < 0.001$
Total METs	1.00 (0.99-1.00) $p = 0.87$	
Vigorous METs	0.99 (0.99-1.00) $p = 0.17$	
Methotrexate	3.78 (1.10-13.00) $p = 0.034$	

Table 8.5: Ulcerative colitis population: generalised linear regression for Insomnia Severity Index score reporting univariate regression and multivariate regression optimised by the Bayesian information criterion.

	Univariate regression, coefficient, 95% CI, *p* value	**Multivariate regression, odds ratio 95% CI, *p* value**
Age	-0.02 (-0.08 – 0.04) $p = 0.46$	
Gender	-.02 (-2.2 – 1.9) $p = 0.86$	
Obesity	0.25 (-1.5- -2.0) $p = 0.77$	
IBD disease duration	-0.06 (-0.15-0.032) $p = 0.20$	
Previous surgery for IBD	-1.5 (-4.5-1.5) $p = 0.33$	
Corticosteroids	0.7 (-1.8-3.3) $p = 0.57$	
Opioids	4.1 (1.2-7.1) $p = 0.005$	
Biologic	-0.5 (-2.3-1.2) $p = 0.55$	
Immunomodulators	0.5 (-1.2-2.3) $p = 0.54$	
5ASA	-1.1 (-2.8-0.67) $p = 0.22$	
Vitamin D	1.6 (-0.25-3.6) $p = 0.088$	
Current smoker	1.2 (-2.2 – 4.7) $p = 0.47$	
Clinically significant anxiety	4.9 (3.3-6.6) $p < 0.001$	2.8 (1.1-4.4) $p = 0.001$
Clinically significant depression	5.5 (3.6-7.3) $p < 0.001$	2.4 (0.58-4.3) $p = 0.010$
Any abdominal pain	3.3 (1.6-4.9) $p < 0.001$	
SCCAI	0.6 (0.42-0.81) $p < 0.001$	
SCCAI > 5	4.4 (2.4-6.4) $p < 0.001$	
SCCAI components		
Number of bowel actions during the day	1.4 (0.51-2.3) $p = 0.002$	
Number of bowel actions during the night	6.1 (1.1-11.0) $p = 0.016$	
Urgency	2.0 (0.92-3.1) $p < 0.001$	0.41 (-0.6-1.4) $p = 0.42$
Blood	1.2 (0.28-2.1) $p = 0.011$	

	Univariate regression, coefficient, 95% CI, *p* value	**Multivariate regression, odds ratio 95% CI, *p* value**
General wellbeing	3.1 (2.3-3.9) $p < 0.001$	2.1 (1.2-2.9) $p < 0.001$
Extra-intestinal manifestations	1.3 (0.6-2.0) $p < 0.001$	

SCCAI – Simple Clinical Colitis Activity Index. IBD – inflammatory bowel disease. 5ASA-5-aminosalicylate-based medication.

Table 8.6: Crohn's disease population—generalised linear regression for Insomnia Severity Index score reporting univariate regression and multivariate regression optimised by the Bayesian information criterion.

	Univariate regression, coefficient, 95% CI, *p* value	**Multivariate regression, odds ratio 95% CI, *p* value**
Age	-.004 (-0.09 – 0.66) $p = 0.27$	
Gender	-0.84 (-2.4 – 0.98) $p = 0.49$	
Obesity	1.7 (0.38-3.0) $p = 0.011$	
IBD disease duration	0.17 (-0.04-0.076) $p = 0.55$	
Previous surgery for IBD	0.01 (-0.49-0.069) $p = 0.74$	
Corticosteroids	1.6 (-0.95 – 4.2) $p = 0.21$	
Opioids	2.2 (0.45-3.7) $p = 0.012$	
Biologic	0.34 (-0.99-1.7) $p = 0.61$	
Immunomodulators	-0.42 (-1.7-0.89) $p = 0.53$	
5ASA	-.59 (-2.5-1.3) $p = 0.55$	
Current smoker	1.5 (-0.87 – 3.9) $p = 0.21$	
Clinically significant anxiety	5.4 (4.2-6.7) $p < 0.001$	2.3 (1.0-3.6) $p = 0.001$
Clinically significant depression	7.8 (6.5-9.2) $p < 0.001$	4.81 (3.2-6.4) $p < 0.001$
Methotrexate	2.7 (0.50 – 4.9) $p = 0.016$	
Azathioprine	-1.6 (-3.1 - -0.15) $p = 0.048$	
Any abdominal pain	3.9 (2.6-5.1) $p < 0.001$	
Any nocturnal bowel actions	5.8 (-1.0 – 12.6) $p = 0.096$	

	Univariate regression, coefficient, 95% CI, *p* value	**Multivariate regression, odds ratio 95% CI, *p* value**
HBI	0.54 (0.39-0.69) $p < 0.001$	0.58 (0.40-0.77) $p < 0.001$
HBI > 5	4.8 (3.6 – 6.1) $p < 0.001$	
HBI components		
General wellbeing	2.9 (2.3-3.6) $p < 0.001$	
Abdominal pain	2.5 (1.8-3.3) $p < 0.001$	
Number of liquid/soft stool	1.2 (0.5-1.9) $p < 0.001$	
Active arthropathy	3.3 (2.1-4.6) $p < 0.001$	
Ocular manifestations	3.0 (1.8-4.3) $p < 0.001$	
Skin manifestations	1.8 (0.16-3.5) $p = 0.031$	
Active perianal disease	1.0 (-0.52-2.6) $p = 0.19$	
Oral manifestations	1.4 (-0.049-2.9) $p = 0.058$	
Number of extra-intestinal manifestations	1.5 (0.99-2.0) $p < 0.001$	

HBI – Harvey–Bradshaw Index. IBD – inflammatory bowel disease. 5ASA- 5-aminosalicylate-based medication.

Figure 8.1: Simple Clinical Colitis Activity Index score component values and mean Insomnia Severity Index scores, with standard deviation as error bars. General wellbeing score varies from 0-very well, 1-slightly below par, 2-poor, 3-very poor, 5-terrible. Blood score varies from 0-none, 1-trace, 2-occassionally frank, 3-usually frank. Urgency score varies from 0-no urgency, 1-hurry, 2-immediately, 3-incontinence. Nocturnal bowel motions score varies from 0- 1-3 times, 1- 4-6 times. Daytime bowel motions score varies from 0- 1-3 times, 1 – 4-6 times, 3- 7-9 times, 4- >9 times. Extra-colonic features score is the number of active extra-colonic features.

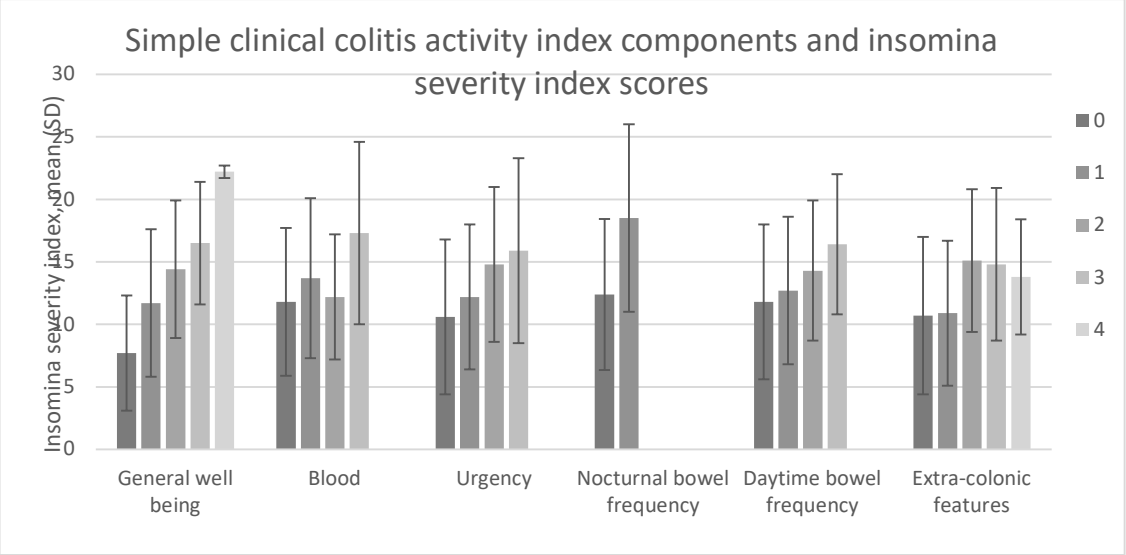
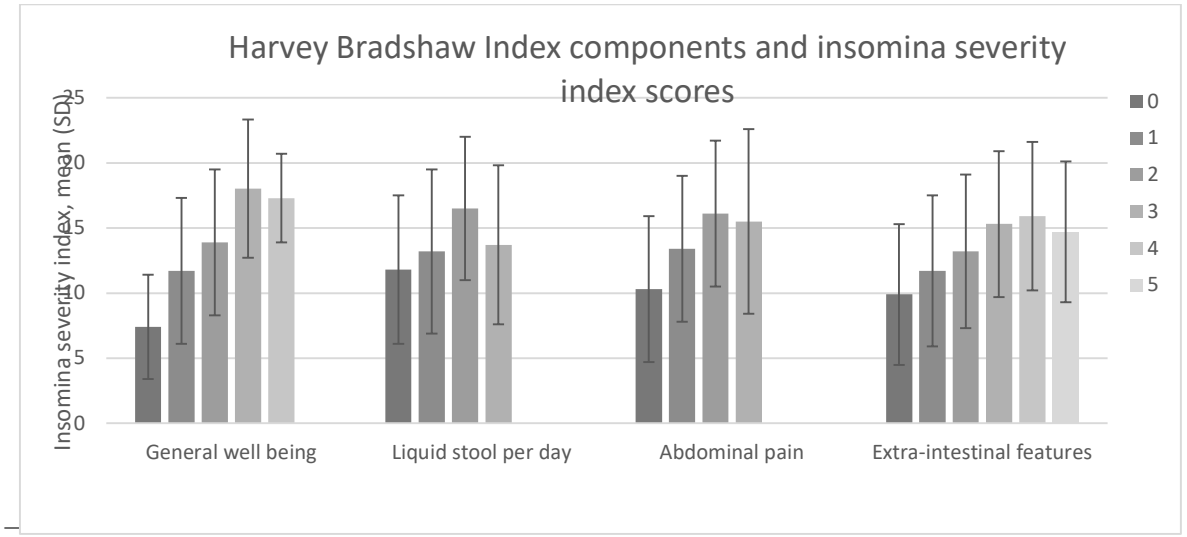


Figure 8.2: Harvey–Bradshaw Index score component values and mean Insomnia Severity Index scores, with standard deviation as error bars. General wellbeing score varies from 0-very well, 1-slightly below par, 2-poor, 3-very poor, 5-terrible. Liquid stool per day score varies from 0- none, 1- once, 2 – twice, 3 – three or more liquid bowel actions a day. Abdominal pain score varies from 0-none, 1-mild, 2-moderate, 3-severe. Extra-intestinal features score is the number of active extra-colonic features.



Supplementary Table 8.1: Tukey's post hoc test for insomnia severity groups defined by Insomnia Severity Index scores and disability scores.

Insomnia (0 – no insomnia, 1 – subthreshold insomnia, 2 – moderate insomnia, 3 – severe insomnia) defined by Insomnia Severity Index scores and disability scores (IBD-Disability Index Self-Report Questionnaire).

	Contrast	**Std. Err**	***P>|t|***	**95% Confidence interval**
1 vs 0	-2.051403	.6156848	0.005	-3.637421 -.4653847
2 vs 0	-4.589303	.6633471	0.000	-6.298101 -2.880506
3 vs 0	-5.393538	.9380252	0.000	-7.809913 -2.977164
2 vs 1	-2.5379	.5496352	0.000	-3.953774 -1.122027
3 vs 1	-3.342135	.8613714	0.001	-5.561048 -1.123223
3 vs 2	-.8042351	.8960594	0.806	-3.112505 1.504035

Supplementary Table 8.2: SCCAI – component – general wellbeing – results of ANOVA analysis of Insomnia Severity Index (ISI) and general wellbeing score from the SCCAI ($F(4,205) = 15.1$ $p < 0.0001$). Post hoc analysis via Tukey—significant results 2v1,3v1,4v1,5v1 3v2, 4v2, 5v2, 5v3. Otherwise no significant different seen.

General wellbeing	Summary of ISI scores	
	Mean	Std dev
1 – very well	7.7	4.6
2 – slightly below par	11.7	5.9
3 – poor	14.4	5.5
4 – very poor	16.5	4.9
5 - terrible	22.2	0.5

Supplementary Table 8.3: SCCAI – component – blood – results of ANOVA analysis of Insomnia Severity Index (ISI) and blood component score from the SCCAI ($F(3,206) = 3.62$ $p = 0.014$). Post hoc analysis via Tukey—significant results severe different to none ($p = 0.016$) otherwise no difference seen.

Blood	Summary of ISI scores	
	Mean	Std dev
None	11.8	5.9
Trace	13.7	6.4
Occasionally frank	12.2	5.0
Usually frank	17.3	7.3

Supplementary Table 8.4: SCCAI – component – urgency – results of ANOVA analysis of Insomnia Severity Index (ISI) and urgency score from the SCCAI ($F(3,208) = 4.45$ $p = 0.0047$). Post hoc analysis via Tukey—significant results immediately different to no urgency ($p = 0.006$); otherwise no difference between groups.

Urgency	**Summary of ISI scores**	
	Mean	**Std dev**
No urgency	10.6	6.2
Hurry	12.2	5.8
Immediately	14.8	6.2
Incontinence	15.9	7.4

Supplementary Table 8.5: SCCAI – component – nocturnal bowel motions – results of ANOVA analysis of Insomnia Severity Index (ISI) and nocturnal bowel motions score from the SCCAI ($F(1,208) = 5.83$ $p < 0.017$).

Nocturnal bowel motions	Summary of ISI scores	
	Mean	Std dev
1-3	12.4	6.04
4-6	18.5	7.5

Supplementary Table 8.6: SCCAI – component – daytime bowel motions – results of ANOVA analysis of Insomnia Severity Index (ISI) and daytime bowel motions score from the SCCAI ($F(3,206) = 3.27$ $p = 0.0223$). Post hoc analysis via Tukey—group with >9 times per day different to 1–3 times per day ($p = 0.025$), otherwise no difference.

Daytime bowel motions	**Summary of ISI scores**	
	Mean	**Std dev**
1-3 times	11.8	6.2
4-6 times	12.7	5.9
7-9 times	14.3	5.6
>9 times	16.4	5.6

Supplementary Table 8.7: SCCAI – component – extra-colonic manifestations – results of ANOVA analysis of Insomnia Severity Index (ISI) and extra-colonic manifestations score from the SCCAI ($F(4,205) = 5.9$ $p = 0.0001$). Post hoc analysis via Tukey significant differences between groups: 2 > 0, 3 > 0, 2 > 1, 3 > 1.

Number of extra-colonic manifestations	Summary of ISI scores	
	Mean	Std dev
0	10.7	6.3
1	10.9	5.8
2	15.1	5.7
3	14.8	6.1
4	13.8	4.6

Supplementary Table 8.8: HBI – component – number of liquid bowel motions– results of ANOVA analysis Of Insomnia Severity Index (ISI) and number of liquid bowel motions score from the HBI ($F(3,332) = 5.07$ $p = 0.0019$). Post hoc analysis via Tukey significant differences – 2v0 otherwise no differences seen.

Number of liquid bowel motions	Summary of ISI scores	
	Mean	Std dev
0	11.8	5.7
1	13.2	6.3
2	16.5	5.5
>3	13.7	6.1

Supplementary Table 8.9: HBI – component – abdominal pain– results of ANOVA analysis of Insomnia Severity Index (ISI) and abdominal pain score from the HBI ($F(3,332) = 15.61$ $p < 0.0001$). Post hoc analysis via Tukey significant differences – 4v1 $p = 0.04$, 3v1 $p < 0.001$, 2v1 $p < 0.001$, 3v2 $p = 0.022$

Abdominal pain score	Summary of ISI scores	
	Mean	Std dev
1-None	10.3	5.6
2-Mild	13.4	5.6
3-Moderate	16.1	5.6
4-Severe	15.5	7.1

Supplementary Table 8.10: HBI – component – general wellbeing– results of ANOVA analysis of Insomnia Severity Index (ISI) and general wellbeing score from the HBI ($F(4,331) = 19.72$ $p < 0.0001$). Post hoc analysis via Tukey significant differences between groups: 2v1, 3v1, 4v1, 5v1, 3v2, 4v2, 4v3, otherwise not significant.

General wellbeing	Summary of ISI scores	
	Mean	Std dev
1-Very well	7.4	4.01
2- Slightly below par	11.7	5.6
3-Poor	13.9	5.6
4-Very poor	18.02	5.3
5-Terrible	17.3	3.4

Supplementary Table 8.11: HBI – component – extra-intestinal manifestations – results of ANOVA analysis of Insomnia Severity Index (ISI) and extra-intestinal manifestations score from the HBI ($F(5,330) = 7.45$ $p < 0.0001$). Post hoc analysis via Tukey significant differences between groups: 2v0, 3v0, 4v0, 3v1, 4v1.

Number of extra-intestinal manifestations	Summary of ISI scores	
	Mean	Std dev
0	9.89	5.4
1	11.7	5.8
2	13.2	5.9
3	15.3	5.6
4	15.9	5.7
5	14.7	5.4

CHAPTER 9: OBSTRUCTIVE SLEEP APNOEA AND ASSOCIATIONS WITH INFLAMMATORY BOWEL DISEASE

This chapter presents the manuscript 'Simple novel screening tool for obstructive sleep apnea in inflammatory bowel disease', published in *Crohn's Colitis* 360, March 2023, doi: 10.1093/crocol/otad016.

Author contributions

Alex Barnes: responsible for study concept and design, data acquisition, analysis and data interpretation, drafting of manuscript, critical revision of the manuscript.

Sutapa Mukherjee: responsible for study concept, critical revision of the manuscript

Jane Andrews: responsible for study concept¸ responsible for critical revision of the manuscript.

Robert V Bryant: responsible for critical revision of the manuscript.

Peter Bampton: responsible for critical revision of the manuscript.

Paul Spizzo: responsible for critical revision of the manuscript.

Robert J Fraser: responsible for critical revision of the manuscript.

Réme Mountifield: responsible for study concept and design, responsible for critical revision of the manuscript.

Please see appendices for further authorship information.

[Manuscript] Simple novel screening tool for obstructive sleep apnoea in inflammatory bowel disease

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Data availability statement

The data underlying this article are available upon request to the author.

Keywords: inflammatory bowel disease, obstructive sleep apnoea, disability, psychology

Abstract

Introduction

Inflammatory bowel disease (IBD) has been associated with increased risk of obstructive sleep apnoea (OSA). We aimed to examine the associations of obstructive sleep apnoea, sleepiness and IBD-related data and comorbidities, with the aim of developing a screening tool for sleep apnoea in this population.

Methods

An online survey of adults with IBD was administered which included measures of assessment of risk of OSA, and measures of IBD activity, IBD-related disability, anxiety, and depression. Logistic regression was performed to investigate the associations between risk of OSA and IBD data, medications, demographics, and mental health conditions. Further models were built for an outcome of severe daytime sleepiness and a combined outcome of risk of OSA and at least mild daytime sleepiness. A simple score was constructed for the purpose of screening for OSA.

Results

There were 670 responses to the online questionnaire. The median age was 41 years, the majority had Crohn's disease (57%), median disease duration was 11.9 years and approximately half were on biologics (50.5%). Moderate–high risk of OSA was demonstrated in 22.6% of the cohort. A multivariate regression model for moderate–high risk of OSA included increasing age, obesity, smoking and abdominal pain sub-score. For a combined outcome of moderate–high risk of OSA and at least mild daytime sleepiness a multivariate model included abdominal pain, age, smoking, obesity, and clinically significant depression. A simple score was constructed for screening for OSA utilising age, obesity, IBD activity and smoking status with an area under the receiver operation curve of 0.77. A score above 2 had a sensitivity of 89% and a specificity of 56% for moderate–high risk of OSA and could be utilised for screening for OSA in IBD clinic.

Conclusion

Over one-fifth of an IBD cohort met significantly high-risk criteria for OSA to warrant referral for a diagnostic sleep study. The risk of OSA was associated with abdominal pain, along with more traditional risk factors such as smoking, increasing age, and obesity.

Consideration should be given for screening for OSA in IBD patients utilising a novel screening tool that utilises parameters typically available in IBD clinic.

Lay summary

This study investigated the relationship between inflammatory bowel disease (IBD) and the risk of obstructive sleep apnoea (OSA). A screening tool for OSA that can be used in IBD clinic was developed.

Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing-remitting inflammatory condition which is increasing in frequency worldwide.[17] The associated gastrointestinal symptoms may disrupt sleep leading to poor sleep quality. The prevalence of poor sleep in this population has been reported in a recent meta-analysis to be 56%.[273] Poor sleep is more common in those with IBD than controls,[200] more common in those with active IBD than inactive IBD,[200,201] and more common in those with inactive IBD than controls.[274] Mental health conditions such as anxiety and depression have been associated with poor sleep in an IBD population.[154-161]

Whilst IBD associated upper airway obstruction is rare,[186,187] obstructive sleep apnoea (OSA) was shown to be more common in people with IBD in a study utilising US-wide diagnostic coding data.[184] This finding was supported by a previous study that utilised an online screening questionnaire in a UK population.[185]

OSA is associated with a variety of medical conditions including obesity, cardiovascular disease,[374,375] Parkinson's disease,[376] and gastro-oesophageal reflux disease.[377,378] Relevant to IBD, OSA has been associated with an increase in circulating TNF-α levels, with higher levels associated with more severe obstruction and hypoxia.[188] Anti- TNF-α therapy has been associated with improved sleepiness in obese patients with OSA[189] and a lower frequency of OSA spondyloarthropathy population.[379] Active inflammatory bowel disease is associated with elevated TNF-α levels and consequently may influence the course or development of OSA. Furthermore, obesity is prevalent in people with IBD[380-382] and may somewhat explain the observed increased rates of sleep apnoea. However, in a nationwide study in a US population IBD remained associated with OSA after controlling for known risk factors such as obesity.[184] This suggests that risk factors for OSA in an IBD population may be different to known traditional risk factors.

Our study aimed to examine the rates of OSA and sleepiness in an IBD population as well as examine factors associated with OSA and sleepiness. The study also aimed to construct a simple score for screening for OSA using typical IBD clinic parameters.

Methods

Ethics approval for this study was obtained from the Southern Adelaide Human Research Ethics Committee (203.20). An online questionnaire was distributed to individuals with IBD through tertiary hospital IBD clinic patient email lists, a private gastroenterology practice patient email list and through Crohn's Colitis Australia, a charity organisation, via email

advertising and social media. Tertiary hospital IBD units and private gastroenterology groups routinely collect patient email addresses to allow communication between the IBD unit and the IBD cohort under care. Individuals with a self-reported diagnosis of IBD over 18 years of age were asked to participate. Demographic data such as age and sex were recorded, along with data on IBD which included disease duration, previous surgery, and current medications.

The OSA-50 is a validated screening tool for OSA in primary care.[383,384] It contains four components with scores for waist circumference, age, snoring and observed cessation of breathing during sleep. An OSA-50 score over 5 has been associated with moderate–severe OSA and is sufficient to justify direct referral for a sleep study in Australia (sensitivity 94%).[383] The Epworth Sleepiness Scale (ESS) is a validated measure of daytime sleepiness.[385] A score below 6 is considered below normal sleepiness, 6–10 normal, 11–12 mild sleepiness, 13–15 moderate sleepiness and a score over 15 considered to represent severe daytime sleepiness. The ESS in combination with the OSA-50 has been shown to provide high specificity for OSA (94%), however with reduced sensitivity (51%).[386]

IBD disease activity was assessed using the modified Harvey–Bradshaw Index (HBI) in the case of Crohn's disease with HBI >5 considered active disease,[217] excluding the physical exam question. The Simple Clinical Colitis Activity Index (SCCAI) was utilised to assess disease activity in those with ulcerative colitis, with a SCCAI >2 considered active disease.[282] The abdominal pain sub-score from HBI was utilised to form an abdominal pain dichotomous variable with an abdominal pain sub-score of mild used as the cut-off value, with values above mild encoded as one, and values mild or below encoded as a zero. The nocturnal diarrhoea sub-score from SCCAI was utilised to form a nocturnal diarrhoea dichotomous variable with a nocturnal diarrhoea sub-score of above 1 encoded as a one, and scores 1 or less encoded as a zero.

Anxiety was assessed using the generalised anxiety disorder 7-item scale (GAD-7)[285] with a score over 10 used to indicate likely clinically significant anxiety. The Patient Health Questionnaire 9 (PHQ-9) was used to assess depression with a score over 15 used to indicate likely clinically significant depression.[286]

Disability is defined as any inability to perform an activity considered normal for a human.[387] Disability was assessed using the IBD-Disability Index self-report (IBD-DI-SR).[362] The IBD-Disability Index self-report is a validated self-reported measure of disability in an IBD

population. It was developed as a self-report form and a short form of the IBD-Disability Index.[363]

Statistical analysis was performed using Stata SE 16 (StataCorp, College Station, TX, USA). For normally distributed variables mean, and standard deviation (SD) were reported with comparisons made using the Student's *t*-test. For non-normally distributed variables median, and interquartile range (IQR) were reported, with comparisons made using the Mann–Whitney U test. For categorical data Pearsons $\chi 2$ test was used, or Fisher's exact test when appropriate. Univariate logistic regression was performed, and a multivariate logistic regression model was built for moderate–high risk of OSA (OSA-50 > 5) incorporating all variables from univariate analysis with $p < 0.10$. The multivariate model was optimised by sequentially adding and removing variables to maximise the likelihood function. Separate models were constructed for an outcome of severe daytime sleepiness (ESS >15) and for a combined outcome of moderate–high risk of OSA (OSA-50 >5) and at least mild daytime sleepiness (ESS >10). Variables common to the multivariate models and considered to be typically available in IBD clinic were then further analysed to create a score for screening for OSA.

Results

There were 670 responses to the online questionnaire. Median age was 41 years (32–70), with most being female (78%). The majority had Crohn's disease (57%). The mean disease duration was 11.9 years (10.4), 30% had undergone surgery for IBD and around half were on biologics (50.5%) (see Table 1). Clinically significant depression (PHQ9 >15) was seen in 18%, and clinically significant anxiety (GAD-7 >10) seen in 29%. The mean IBD-DI-SR was −2.78 (6.01).

The median OSA-50 score was 3, with 22.6% having an OSA-50 score over 5 (see Table 1). Those who had an OSA-50 score over 5 were older ($p < 0.001$), smokers ($p = 0.004$), obese ($p < 0.001$), and had higher IBD activity scores ($p = 0.001$, and $p = 0.013$). Worse disability scores were seen in those with an OSA-50 scores over 5 ($p = 0.0008$).

Univariate and multivariate logistic regression for an outcome of moderate–high risk of OSA was performed including demographics, IBD data, IBD medications and IBD clinical activity (see Table 2). Univariate regression was significant for increasing age, obesity, clinically significant depression, abdominal pain sub-score, nocturnal diarrhoea sub-score, and clinically active IBD. A multivariate model was optimised with the final model including

increasing age, obesity, smoking and abdominal pain sub-score (see Table 2). Male gender was not significant. Male gender was associated with lower rates of obesity ($p = 0.002$), lower rates of clinically significant depression ($p = 0.004$), and lower rates of clinically active IBD ($p < 0.001$) but was also associated with higher rates of smoking ($p = 0.049$), and males were on average older (45.8 years (43.3–48.4) v 41.8 (40.7–42.9) $p = 0.0013$).

The mean ESS score was 7.9 (4.75), with 13.4% describing severe daytime sleepiness. Severe daytime sleepiness was associated with worse disability scores ($p = 0.0001$). Univariate and multivariate logistic regression was performed including demographics, IBD data, IBD medications and IBD clinical activity (see Table 3). Univariate regression was significant for smoking, clinically significant depression, clinically significant anxiety, and abdominal pain sub-score. Multivariate regression was significant for clinically significant depression, clinically significant anxiety, and abdominal pain sub-score (see Table 3).

A combined outcome of moderate–high risk of OSA (OSA >5) and at least mild daytime sleepiness (ESS >11) was considered. Univariate regression was significant for age, current corticosteroid use, obesity, current smoking, clinically significant depression, abdominal pain and clinically active IBD (see Table 4). Multivariate regression was significant for age, obesity, smoking, clinically significant depression, and abdominal pain (see Table 4).

A simple score was constructed (see Table 5) for risk of OSA utilising variables typically available in IBD clinic. The area under the receiver-operator curve for moderate–high risk of OSA (OSA50 >5) was 0.77 (0.73–0.81), with Youden's index of 1.46. A score above 2 had a sensitivity of 89% and a specificity of 56%. The area under the receiver-operator curve for moderate–high risk of OSA (OSA50 >5) and at mild daytime sleepiness (ESS >10) was 0.77 (0.71–0.82), with Youden's index of 1.41. A score above 2 had a sensitivity of 89% and a specificity of 56% for moderate–high risk of OSA.

Discussion

In a large IBD cohort the rate of and novel associations with OSA have been described. Over one-fifth of the cohort met criteria for high risk of OSA and could on this basis be referred for diagnostic polysomnography. Risk of OSA was associated with increased age, obesity, smoking and abdominal pain in a cohort of people with IBD. We also explored sleepiness, a common symptoms of sleep apnoea, with this associated in our cohort with mental health conditions and abdominal pain. We also proposed a novel simple score incorporating parameters typically used in IBD clinic to identify those at risk of OSA. The score

incorporated parameters typically available in IBD clinic and could consequently be readily applied.

Well-established risk factors for OSA include older age,[388-390] smoking[391] and obesity[392] – were apparent in our data, however no association with male gender,[388,393,394] as previously well described with OSA, was seen. This may be a result of the female predominance of the cohort (78% female), noting that a previous study did note an association between male gender and OSA in an IBD cohort.[184] We also note the perhaps confounding relationship between gender and other risk factors for OSA in our dataset such as IBD activity and depression.

Abdominal pain was associated with OSA and sleepiness. Poor sleep has been associated with increased perception of pain that may partly explain these results.[395,396] Furthermore OSA has been associated with irritable bowel syndrome[397]—known to be common in those with IBD.[67,236,398] In addition, OSA related nocturnal hypoxia may contribute to localised intestinal ischemia that has been previously postulated to play a role in the pathogenesis of IBD.[399]

OSA has been associated with cardiovascular disease[400] and in particular stroke,[401-403] which has been attributed to systemic inflammation and as well apnoea induced nocturnal ischaemia.[404-406] Identification of those with OSA will allow screening for associated cardiovascular complications and commencement of treatment such as continuous positive airway pressure (CPAP).[300] Treatment of those with OSA is associated with improved daytime sleepiness, along with improved quality of life.[407] Treatment of OSA has been shown to reduce blood pressure in those with hypertension[408] and additionally, long-term observational data also suggests a reduction in ischaemic heart disease and fatal cardiac events with usage of CPAP,[409] although no overall mortality benefit has been demonstrated and randomised controlled trial results have been mixed.[410] IBD has been associated with increased risk of cardiovascular disease[411,412] and consequently consideration should be given to identifying and treating those with OSA in order to reduce cardiovascular risk. The OSA-50 is commonly used to screen for OSA in Australia however this incorporates parameters typically not available in IBD clinic such as apnoeic events, waist circumference and snoring. We proposed a simple score incorporating parameters available in IBD clinic that could be used to screen for OSA and is consequently perhaps much more attractive to gastroenterologists. Further validation of this score in other IBD cohorts is required.

Limitations of this study include selection bias due to the use of an online questionnaire and the predominantly female cohort. The rates of anxiety and depression seen in our cohort were similar to that described elsewhere.[192] Our cohort likely represents a moderate–severe IBD cohort with biologic usage in around half and previous surgery in almost a third. Given that OSA is more common in males, the prevalence of moderate–high risk of OSA seen here is likely lower than in the broader IBD population.[413] Reporting bias may also be significant, noting a study of people with Crohn's disease reported worse sleep quality than that observed by objective measures.[167] The absence of objective measures of sleep quality and objective IBD activity is also considered a limitation. Further studies should consider objective measures of IBD activity and sleep quality.

Conclusion

Over one-fifth of an IBD cohort met high-risk criteria for OSA to warrant referral for a diagnostic sleep study. Risk of OSA was associated with abdominal pain, along with more traditional risk factors such as smoking, increasing age, and obesity. Those at risk of OSA have worse disability scores. A simple score using typical IBD clinic data could be used to screen for OSA.

No funding was received for this work.

Data availability statement

The data underlying this article are available upon request to the author.

Table 9.1: Demographic, IBD-related data, medications, clinical IBD activity, mental health conditions and disability scores of the cohort. Results reported for OSA-50 score over 5, with *p* value using Student's *t*-test or Pearson's χ^2 as appropriate. OSA-50: screening test for obstructive sleep apnoea.

	Cohort	**OSA-50 >5**	**OSA-50 ≤5**	***p* value**
Age, median IQR	41 (32-70)	49.9 (47.8-52.1)	40.3 (39.1-41.5)	<0.001
Female gender, *n* (%)	525 (78)	73%	78%	0.266
Crohn's disease, *n* (%)	384 (57)	59%	61%	0.59
Disease duration years, mean (SD)	11.9 (10.4)	13.8 (11.9-15.7)	12.2 (11.2-13.1)	0.095
Previous surgery for IBD, *n* (%)	201 (30.0)	72%	67%	0.24
Current steroid use, *n* (%)	58 (8.6)	11%	9%	0.30
Current biologic use, *n* (%)	339 (50.5)	56%	52%	0.41
Current immunomodulator use, *n* (%)	228 (34.0)	39%	36%	0.41
Obesity, *n* (%)	247 (36.9)	66%	26%	<0.001
Smoking, *n* (%)	44 (6.6)	12%	5%	0.004
Alcohol usage, *n* (%)	213 (31.8)	36%	33%	0.13
Opioid usage, *n* (%)	93 (13.9)	20%	14%	0.081
Medications for sleep, *n* (%)	85 (12.7)	14%	14%	0.95
Clinically significant depression, *n* (%)	120 (17.9)	31%	23%	0.069
Clinically significant anxiety, *n* (%)	193 (28.8)	32%	36%	0.37
Clinically active IBD SCCAI, mean (SD) HBI, mean (SD)	 7.18 (2.86) 7.08 (3.29)	 7.90 (7.42-8.39) 7.70 (7.13-8.28)	 6.95 (6.68-7.23) 6.89 (6.58-7.20)	 0.0010 0.013
IBD-DI-SR, mean (SD)	-2.78 (6.01)	-4.91 (-5.56- -3.94)	-3.04 (-3.65- -2.51)	0.0008

HBI – Harvey–Bradshaw Index measures clinical activity of Crohn's disease. SCCAI – Simple Clinical Colitis Activity Index measures clinical activity of ulcerative colitis. IBD-DI-SR is a self-reported questionnaire that measures disability in an IBD population. Clinically significant anxiety based on a Generalised Anxiety Scale-7 score greater than 10. Clinically significant depression based on a Patient Health Questionnaire 9 score over 15.

Table 9.2: Univariate and multivariate regression for moderate–high risk of sleep apnoea (OSA-50 > 5) considering demographic data, IBD medications, depression, anxiety and IBD data.

	Univariate regression (odds ratio, confidence interval, *p* value)	**Multivariate regression (odds ratio, confidence interval, *p* value)**
Age	1.05 (1.04-1.07) $p < 0.001$	1.06 (1.04-1.08) $p < 0.001$
Male gender	1.28 (0.83-1.99) $p = 0.27$	
Crohn's disease	0.90 (0.61-1.33) $p = 0.60$	
Disease duration	1.01 (0.99-1.03) $p = 0.096$	
Previous surgery for IBD	1.28 (0.84-1.96) $p = 0.24$	
Current steroid use	1.38 (0.75-2.54) $p = 0.302$	
Current biologic use	1.17 (0.80-1.72) $p = 0.41$	
Current immunomodulator use	1.18 (0.79-1.74) $p = 0.42$	
Obesity	5.39 (3.58-8.10) $p < 0.001$	6.42 (4.08-10.10) $p < 0.001$
Smoking	2.52 (1.31-4.81) $p = 0.005$	2.60 (1.26-5.39) $p = 0.010$
Alcohol usage	1.16 (0.78-1.73) $p = 0.45$	
Opioid usage	1.55 (0.94-2.55) $p = 0.082$	
Medications for sleep	0.98 (0.57-1.70) $p = 0.95$	
Clinically significant depression	1.76 (1.13-2.75) $p = 0.013$	
Clinically significant anxiety	0.92 (0.61-.139) $p = 0.69$	
Abdominal pain sub-score	1.33 (1.09-1.62) $p = 0.004$	1.32 (1.05-1.65) $p = 0.017$
Nocturnal diarrhoea sub-score	2.11 (1.11-3.99) $p = 0.022$	
Clinically active IBD	1.73 (1.01-2.93) $p = 0.044$	

Table 9.3: Univariate and multivariate regression for significant sleepiness (Epworth Sleepiness Score >14) considering demographic data, IBD medications, depression, anxiety and IBD data.

	Univariate regression (odds ratio, confidence interval, *p* value)	**Multivariate regression (odds ratio, confidence interval, *p* value)**
Age	0.99 (0.97-1.01) $p = 0.23$	
Male gender	0.87 (0.49-1.54) $p = 0.64$	
Crohn's disease	1.03 (0.64-1.67) $p = 0.88$	
Disease duration	0.99 (0.97-1.01) $p = 0.46$	
Previous surgery for IBD	0.95 (0.58-1.56) $p = 0.84$	
Current steroid use	1.66 (0.82-3.36) $p = 0.16$	
Current biologic use	0.92 (0.58-1.47) $p = 0.75$	
Current immunomodulator use	0.96 (0.59-1.56) $p = 0.87$	
Obesity	1.41 (0.88-2.26) $p = 0.15$	
Smoking	2.48 (1.20-5.16) $p = 0.015$	
Alcohol usage	0.88 (0.54-1.45) $p = 0.63$	
Opioid usage	1.17 (0.63-2.18) $p = 0.62$	
Medications for sleep	0.84 (0.41-1.70) $p = 0.63$	
Clinically significant depression	3.94 (2.38-6.53) $p < 0.001$	2.65 (1.46-4.80) $p = 0.001$
Clinically significant anxiety	2.99 (1.86-4,84) $p < 0.001$	1.66 (0.94-2.96) $p = 0.082$
Abdominal pain sub-score	1.42 (1.13-1.78) $p = 0.002$	1.33 (1.04-1.69) $p = 0.021$
Nocturnal diarrhoea sub-score	1.66 (0.82-3.36) $p = 0.16$	
Clinically active IBD	1.69 (0.87-3.30) $p = 0.12$	

Table 9.4: Univariate and multivariate regression for combined outcome of moderate–high risk of sleep apnoea (OSA-50 >5) and at least mild sleepiness (ESS >11) considering demographic data, IBD medications, depression, anxiety and IBD data.

	Univariate regression (odds ratio, confidence interval, *p* value)	**Multivariate regression (odds ratio, confidence interval, *p* value)**
Age	1.03 (1.01-1.05) $p = 0.001$	1.03(1.01-1.06) $p = 0.002$
Male gender	1.25 (0.68-2.29) $p = 0.47$	
Crohn's disease	0.86 (0.50-1.47) $p = 0.59$	
Disease duration	0.99 (0.97-1.02) $p = 0.60$	
Previous surgery for IBD	1.44 (0.78-2.64) $p = 0.24$	
Current steroid use	2.12 (1.01-4.45) $p = 0.046$	
Current biologic use	1.12 (0.70-2.04) $p = 0.50$	
Current immunomodulator use	1.47 (0.86-2.51) $p = 0.16$	
Obesity	5.29 (2.96-9.43) $p < 0.001$	5.25 (2.86-9.64) $p < 0.001$
Smoking	3.21 (1.49-6.91) $p = 0.003$	3.33 (1.44-7.67) $p = 0.005$
Alcohol usage	0.82 (0.46-1.47) $p = 0.52$	
Opioid usage	1.46 (0.74-2.86) $p = 0.27$	
Medications for sleep	1.26 (0.61-2.58) $p = 0.53$	
Clinically significant depression	2.14 (1.24-3.70) $p = 0.006$	1.91 (1.04-3.48) $p = 0.036$
Clinically significant anxiety	1.55 (0.90-2.63) $p = 0.11$	
Abdominal pain sub-score	1.44 (1.12-1.84) $p = 0.004$	1.37 (1.07-1.76) $p = 0.011$
Nocturnal diarrhoea sub-score	2.26 (0.96-5.33) $p = 0.061$	
Clinically active IBD	3.89 (1.38-10.96) $p = 0.010$	

Table 9.5: Simple score for screening for obstructive sleep apnoea utilising variables commonly available in inflammatory bowel disease (IBD) clinic – obesity (2 points), current smoking (1 point), age over 45 (1 point), and clinically active IBD (1 point). The area under the receiver-operator curve for moderate–high risk of obstructive sleep apnoea (OSA50 >5) was 0.77 (0.73–0.81), with Youden's index of 1.46. A score above 2 had a sensitivity of 89% and a specificity of 56%. Obesity is defined as Body Mass Index greater than 30, clinically active IBD refers to a Harvey–Bradshaw Index greater than 5 or a Simple Clinical Colitis Activity Index greater than 2.

Variables	**Score if present**
Obesity	2
Currently smoking	1
Age over 45	1
Clinically active IBD	1

CHAPTER 10: A STRUCTURAL MODELLING APPROACH TO FATIGUE AND SLEEP IN INFLAMMATORY BOWEL DISEASE

This chapter presents the manuscript 'Depression influences fatigue in inflammatory bowel disease amongst other factors: a structural modelling approach', that was accepted for publication in the journal Therapeutic Advances in Gastroenterology, July 2024.

Authorship

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[Manuscript] Depression influences fatigue in inflammatory bowel disease amongst other factors: a structural modelling approach

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Data availability statement

The data underlying this article are available upon request to the author.

Abstract

Objectives: Fatigue is common in people with inflammatory bowel disease (IBD) and has been shown to be associated with IBD activity, sleep disturbance, anxiety and depression. The relative contribution of these factors to fatigue is unclear. This study aimed to investigate the relationship between fatigue and these factors through a novel approach using structural equation modelling.

Design: Online questionnaire circulated via three tertiary IBD centers and Crohn's Colitis Australia.

Methods: Fatigue was assessed using the Functional assessment of chronic illness measurement system fatigue subscale. Validated measures of sleep, anxiety, depression and IBD activity were included. Following correlation analyses a structural equation model was developed for an outcome of fatigue score. Direct and indirect effects were calculated.

Results: There were 630 complete responses to the online questionnaire. The median age of respondents was 41 with the majority female, and over half (52%) on biologic medication. Structural equation models for Crohn's disease and ulcerative colitis demonstrated good fit. In Crohn's disease the relationship between IBD activity and fatigue was mostly mediated indirectly through the influence of IBD activity on sleep, anxiety, and primarily depression. Sleep quality mediated the influence of IBD activity and the indirect effects of depression on fatigue, but not anxiety. Unlike in Crohn's disease the direct influence of IBD activity on fatigue in ulcerative colitis was non-negligible, although remained of lesser magnitude than the indirect effect of IBD activity on fatigue. Depression was the primary indirect mediator of the influence of IBD activity on fatigue in ulcerative colitis.

Conclusion: In Crohn's disease IBD activity leads to fatigue through its influence on sleep quality and mental health. The data suggest treatment of clinically significant depression. in both ulcerative colitis and Crohn's disease, may result in the largest decline in fatigue score compared to other variables. Treatment algorithms for fatigue should consider depression a priority.

Keywords: depression, fatigue, poor sleep

Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing remitting immune disorder that can affect any part of the gastrointestinal tract and may also lead to extra-intestinal manifestations such as joint and skin disease. Fatigue is common in IBD patients with a prevalence of 48%[71]. The pathophysiology of fatigue in IBD is poorly understood[72,79] although frequently reported associations include IBD activity, sleep disturbance, anxiety and, depression[232,233,414-416]. Whether these factors directly cause fatigue or act via secondary mechanisms is currently unclear.

There has been increasing interest in a potential bidirectional relationship between sleep and IBD. Abnormal sleep patterns have been associated with poor health incomes including cardiovascular disease[104] and all-cause mortality[206]. Meta-analyses indicate that poor sleep is prevalent in patients with IBD[273], more common than in controls[201] and worse in those with clinically active disease [200]. It is also associated with mental health conditions[159,167] and poorer quality of life[87,181]. Longitudinal studies suggest that sleep disturbance is associated with fatigue[221] and disease activity[153,161,168]. Furthermore in Crohn's disease sleep disturbance increases the risk of hospitalisation[170]. Whilst anxiety and depression are prevalent in people with IBD[192], it is depression but not anxiety that is associated with poor sleep [156].

The aetiology of fatigue is complex and likely multifactorial. The frequently seen associations with fatigue in IBD (IBD activity, sleep, depression, and anxiety) have the potential to influence each other along with their influence on fatigue. This leads to a complex inter-connected web of cause and effect between these different factors. It is consequently unclear what the value of targeting a single cause of fatigue would be and what potential flow on effects it may have on other factors that also influence fatigue.

Structural equation modelling (SEM) is a technique that allows testing of hypotheses about relationship between variables and is increasingly used to understand multivariate relationships. Path analysis is a subset of SEM that involves the development of a model incorporating causal paths between variables based on the relevant literature. The model is then evaluated based on observational data and modified in an iterative process with paths or variables added or removed in order to improve model fit. Direct and indirect effects of variables on other variables can then be calculated based on the paths in the model. Amongst other applications SEM has been used in IBD to examine the influence of social support on disease activity and distress[417], investigate the relationship between depression and Crohn's

disease[418], evaluate patient satisfaction in IBD[419], and examine the factors influencing pain interference in IBD[295].

This study aimed to investigate the relationship between fatigue, sleep and IBD activity through SEM. We hypothesised that the effects of IBD activity and depression on fatigue are predominantly mediated via sleep quality.

Materials and Methods

An online questionnaire was circulated to patients with IBD using tertiary hospital patient email lists, private gastroenterology practice email lists and social media with individuals, with a self-reported diagnosis of IBD and over 18 years of age, invited to participate. Demographic data such as age and sex were captured, along with IBD related data including current treatment, disease duration and previous surgery. The study was approved by Southern Adelaide Human Research Ethics Committee (203.20). The study has been reported according to the Checklist for reporting results of internet E-surveys[420]. Two consumer advocates (people with IBD) were asked to provide feedback on the proposed research.

Potential participants received on-line information regarding the study, including expected duration and completion of the questionnaire was accepted as consent. No incentive was offered to complete the questionnaire. The questionnaire was available from January 2022 to December 2022. The questionnaire included seven screens with an average of fifteen items per screen. Participants were able to review as change their answers prior to survey completion. Neither cookies nor IP address tracking was used to identify duplicate entries. The data was examined by age, height and weight – with matching entries examined for duplicates.

Fatigue was measured using the FACIT-F scale which is a subscale of the Functional assessment of chronic illness measurement system (FACIT). The FACIT-F subscale has been validated as a measure of fatigue in an IBD population[421]. This comprises 13 questions with responses recorded on a 5-point Likert scale, with a score ranging from 0 to 52, with lower scores indicating worse fatigue and a score less than 30 indicating severe fatigue[422]. Of the many fatigue scores previously used in IBD populations FACIT-F was included due to its use in a variety of different diseases and its brevity[79].

Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI). The PSQI is a validated tool which assesses perceived sleep quality[113]. The index consists of subscales on sleep duration, sleep disturbance, sleep latency, daytime dysfunction, sleep efficiency, overall

sleep quality and medications for sleep. The PSQI score ranges from 0 to 21, with a value > 5 representing poor sleep quality.

IBD disease activity was assessed using the Harvey Bradshaw Index (HBI) in the case of Crohn's disease with HBI > 5 considered active disease[217]. The patient reported version of the HBI was utilised in the survey, although a decision was made to maintain the general well-being and abdominal pain score similar to the physician HBI rather than using a ten-point Likert scale[281]. The Simple Clinical Colitis Activity Index (SCCAI) was used in the case of ulcerative colitis, an SCCAI > 5 was considered active disease[282]. The patient reported form of the SCCAI was utilised[283] in the survey. The use of a self-reported SCCAI has been previously validated with good agreement with physician reported SCCAI[284].

Anxiety was assessed using the generalised anxiety disorder 7-item scale (GAD-7)[285] with a score > 10 indicating likely clinically significant anxiety. Depression was assessed by the Patient Health Questionnaire 9 (PHQ-9) with a score over 15 considered to show likely clinically significant depression[286].

Statistical analysis

Statistical analysis was performed using Stata SE 16 (StataCorp, College Station, TX, USA). Submissions with inadequate completion of score or index were excluded. Mean and standard deviation (SD) were reported for normally distributed variables, with comparisons made by the student t-test. Median, and interquartile range (IQR) were reported for non-normally distributed variables, with comparisons made using the Mann- Whitney U test. For categorical data Pearsons $\chi 2$ test or Fisher's exact test were used as appropriate. Pearson's or Spearman's correlation was used as appropriate, with interpretation of coefficients as: very weak <0.19, weak 0.2-0.3, moderate 0.3-0.5, strong 0.5-0.79 and very strong >0.80.[289]

To further investigate the relationship between sleep and fatigue and to test the hypothesis that sleep mediates the influence of IBD activity on fatigue SEM was performed using multivariate linear regression for path analysis[423]. Based on correlational analysis a general model was constructed using sleep quality, mental health and IBD activity (PSQI, GAD-7, PHQ-9, SCCAI, HBI) as inputs and fatigue (FACIT-F) as output. The model was optimised through an iterative process that involved sequential removal and addition of variables and pathways in order to improve model performance[424]. Separate models were constructed for Crohn's disease and ulcerative colitis (including indeterminate colitis). The model

performance was assessed considering the following multiple fit criteria – root mean square error of approximation (RMSEA) < 0.05, comparative fit index (CFI) > 0.95, Tucker-Lewis Index (TLI) > 0.95, standardised root mean residual (SRMR) < 0.09, Chi-squared goodness of fit statistic (X2P) > 0.05, Chi-squared to degrees of freedom value (X2/N) =1-4[425]. Direct and indirect effects were then calculated based on this model. A direct or indirect effect was considered negligible if it was less than ten percent of the associated direct or indirect effect. A direct or indirect effect was considered significant if it was statistically significant and non-negligible. For the purposes of improving interpretability the fatigue score has been inverted so that a numerically higher fatigue score indicates higher fatigue.

Results

There were 670 responses to the online questionnaire with 630 complete responses. The median age of the participants was 41 years (32-70), with majority being female (78%), 61% with Crohn's disease and 3% with indeterminate colitis. The mean disease duration was 12.6 years (+/-10.2), 32% had undergone surgery for IBD and approximately half were on biologic disease modifying therapy (52.8%) (see table 1).

The mean FACIT-F score was 27 (+/-11.9) with severe fatigue (FACIT-F < 30) seen in 62% of respondents, The mean sleep quality (PSQI) score was 9.49 (+/-3.99) with 75% of patients reporting a poor sleep quality (PSQI>5). Clinically significant depression (PHQ-9>15) was reported by 21%, and clinically significant anxiety (GAD-7 > 10) seen in 33%.

Pearson correlation coefficients were calculated for fatigue (FACIT-F), sleep quality (PSQI), anxiety (GAD-7), depression (PHQ-9), IBD data, demographic and IBD medication (table 2 and 3). There was a strong correlation between fatigue and depression, anxiety and sleep quality in those with Crohn's disease. In addition to this, sleep quality showed a strong correlation with depression and anxiety and moderate correlation with IBD activity. In those with ulcerative colitis there was a strong correlation between fatigue and depression and anxiety and moderate correlation between fatigue and IBD activity and sleep quality. In addition to this there was a moderate correlation with anxiety, depression and IBD activity.

Depression showed strong correlation with anxiety, and moderate correlation with IBD activity for both Crohn's disease and ulcerative colitis. Anxiety showed weak correlation with age and moderate correlation with IBD activity both Crohn's disease and ulcerative colitis. Previous IBD related surgery showed moderate correlation with IBD disease duration.

There was a very weak correlation between age and fatigue in ulcerative colitis but not Crohn's disease.

Crohn's disease

SEM was undertaken for the outcome of fatigue score (FACIT-F) including variables based on previous correlation analysis (see Figure 1). The model was optimised for fit with the final model demonstrating good fit (RMSEA 0.016, SRMR 0.013, CFI 1.00, TLI 0.99, X2(N)=3.46, X2p=0.32). The final model included IBD activity, depression, anxiety, sleep quality and weight. Consideration was given to including body mass index instead of weight however this resulted in overall worse fit. The model accounted for 91.2% of the variance of fatigue. Fatigue had a direct relationship with IBD activity, depression, anxiety, and sleep quality. Fatigue was indirectly influenced by depression, anxiety and IBD activity via sleep quality. Fatigue and sleep were indirectly influenced via body weight through depression.

Direct and indirect effects on fatigue scores were calculated from the SEM and were used to determine the direct effect on the fatigue score (see table 4) as well as the indirect effects via other intermediate variables. The effect of IBD activity on fatigue was primarily mediated through indirect effects (effect size 1.35) with its direct effect significantly smaller but not negligible (effect size 0.35). Depression influenced fatigue directly (effect size 1.55) with negligible indirect effects mediated via sleep (effect size 0.06). The direct effect of anxiety on fatigue was negligible with indirect effects predominantly via depression and to a lesser extent, sleep quality. Anxiety influenced fatigue indirectly via its influence on depression and sleep quality. Considering the various values of the scores for clinically significant depression (PHQ-9 >15), clinically significant anxiety (GAD-7 > 10), clinically active IBD (HBI>5) and poor sleep (PSQI > 5) – clinically significant depression had the largest overall total effect on fatigue scores.

Ulcerative colitis and indeterminate colitis

SEM was undertaken for outcome of fatigue score (FACIT-F) including variables with at least weak correlation with fatigue and sleep quality (see Figure 2). The model was optimised for fit with the final model demonstrating good fit (RMSEA 0.000, SRMR 0.016, CFI 1.00, TLI 1.00, X2(N)=2.997, X2p=0.39.). The final model accounted for 94.4% of the variance in fatigue scores and included IBD activity, depression, anxiety, age and sleep quality. Fatigue had a direct relationship with IBD activity, depression, anxiety, and sleep quality and was

indirectly influenced by depression, anxiety and IBD activity via sleep quality. Fatigue was indirectly influenced via age through anxiety.

Direct and indirect effects were calculated from this model and reported for fatigue scores (see table 4). The effect of IBD activity on fatigue score was primarily mediated through indirect effects but the direct effect, although smaller, remained relevant. Depression influenced fatigue directly with negligible indirect effects mediated through sleep quality. Anxiety influenced fatigue indirectly via its influence on depression and sleep quality with its direct effect on fatigue negligible. IBD activity had significant direct and indirect effects on fatigue. The influence of age on fatigue scores was mediated through anxiety. Considering the various values of the scores for clinically significant depression (PHQ-9 >15), clinically significant anxiety (GAD-7 > 10) and poor sleep (PSQI > 5) – clinically significant depression had the largest overall all total effect on fatigue scores.

Further analysis of indirect effects

Further analysis of indirect effects in terms of mediating variables yielded similar results for ulcerative colitis and Crohn's disease (see table 5). Sleep quality mediated the indirect effects of depression and IBD activity but did not mediate a significant proportion of the indirect effects of anxiety.

Discussion

This work describes a novel approach to understanding the causation of fatigue in patients with IBD using SEM to determine direct and indirect effects. Separate SEM models were developed for Crohn's disease and ulcerative colitis with good model fit. In both models, sleep was a mediating variable for IBD activity, anxiety, and depression with similar results for both Crohn's disease and ulcerative colitis. However, the effect size mediated by sleep was comparatively small. Rather, it was depression that primarily influenced fatigue in the IBD population and mediated most of the effect of IBD activity on fatigue. Noting the prevalence of depression in the IBD population it is likely that treating depression may lead to the largest overall improvement in fatigue. The methods to treat depression may include decreasing IBD activity.

These data are consistent with earlier findings which have suggested a treatment approach for fatigue in IBD patients that includes attention to optimising mental health issues, improving sleep quality and controlling IBD activity if present, all factors used in this model[79]. However, although our model provides some support for this approach, in that overall fatigue

scores were influenced by all of these factors, the new finding of the magnitude of effect from depression warrants that it receives a higher priority for assessment and treatment. It should be considered that clinically active IBD may also have a significant role in the severity of depression in this context.

Although fatigue in IBD is often considered as a single entity there were significant differences in the influence of disease activity on fatigue in patients with Crohn's disease, which was primarily mediated via indirect effects, compared to those with ulcerative colitis where direct magnitude was non-negligible. This may in part reflect the more systemic nature of inflammation in Crohn's disease or possibly to the influence of symptoms such as abdominal pain, more frequently seen in Crohn's disease, on sleep and mental health. Weight was included in the model of Crohn's disease with its effect mediated via depression rather than an influence on IBD activity. Inclusion of weight in the ulcerative colitis model resulted in worse overall fit and it was consequently not incorporated. Obesity is common in those with IBD with studies suggesting 15-40% are overweight[380,426], with a hypothesized negative influence of obesity on the course of Crohn's disease[380,427]. Age was included in the ulcerative colitis model and influenced fatigue via anxiety, with increasing age associated with less fatigue – an association that has been previously documented although not consistently seen[428]. There was no significant correlation between age and fatigue in the Crohn's disease population.

Limitations to this study include the possibility of selection bias due to use of an online questionnaire. This may attract patients with fatigue or sleep problems. Similarly, the form of survey and method of recruitment is likely responsible for the predominantly female cohort. Crohn's disease may be over-represented in this study population compared to the Australian IBD population[429]. However, we note that rates of anxiety, depression, fatigue and poor sleep quality were similar to other cohorts and consequently the results appear to be generalisable. Reporting bias may also be significant, noting a study of people with Crohn's disease reported worse sleep quality than that observed by objective measures[167]. Unfortunately implementing objective sleep measurement over such a large cohort is impractical. The absence of an objective measure of IBD activity is also a limitation.

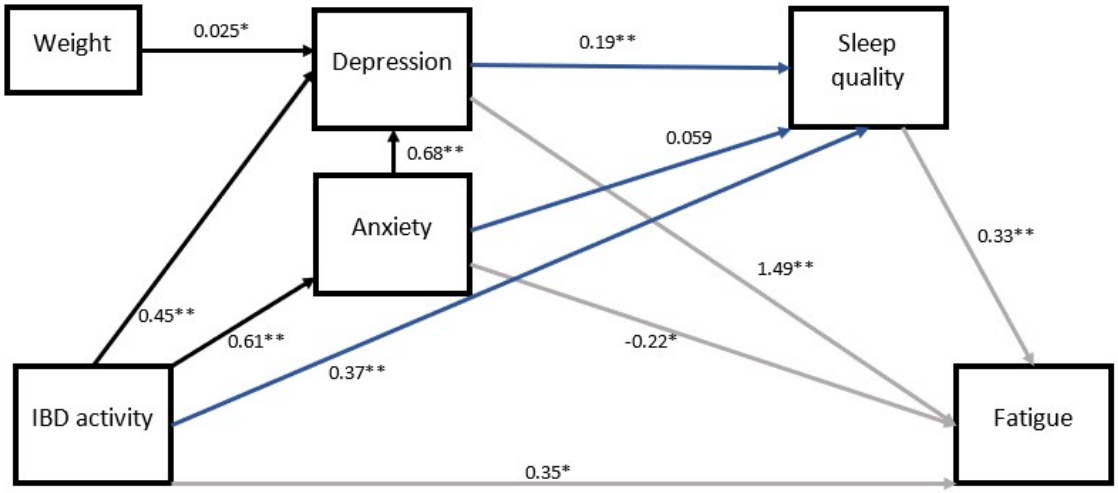
Using the above method of data collection there was no opportunity to assess for factors such as anaemia that been associated with fatigue[233]. However,[71] anaemia has not been associated with fatigue in numerous cross-sectional studies, and hence its lack of inclusion in the current model is not considered a significant limitation[83,430,431]. It is acknowledged that path analysis

is unable to determine the direction of effects. The causes of fatigue in IBD are complex and likely numerous. Acknowledging the complexity of this area and the stigma surrounding mental health the clinical implications of this study are limited and require further validation. Future work should consider a validation cohort incorporating other possible influences on fatigue and incorporate objective measures IBD activity such as calprotectin and biochemical parameters such as C-reaction protein and albumin. Consideration should be given to screening and treating for depression as part of routine IBD clinic, noting that further work is required in this area.

Conclusion

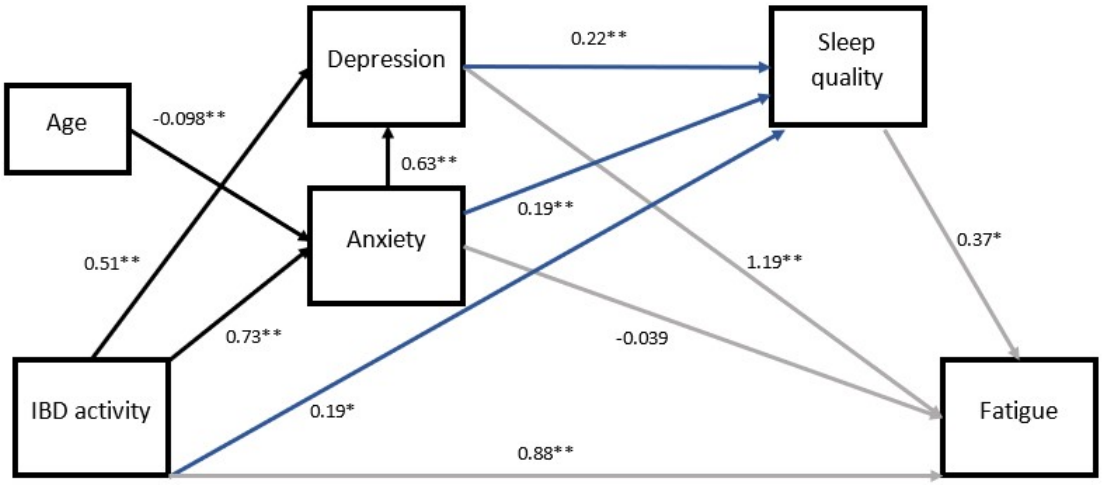
A new model was developed to examine the mediation of factors influencing fatigue in people with IBD. Using this we have shown that although sleep quality mediates the effects of clinically active IBD, and depression on fatigue, the mediated effect size is comparatively small. In Crohn's disease, unlike ulcerative colitis, the influence of IBD activity on fatigue was largely mediated indirectly through its influence on other factors. The data suggest treatment of clinically significant depression may result in the largest decline in fatigue score compared to other variables. Treating depression if present in people with IBD and fatigue should be considered a priority.

Figure 10.1: Structural equation modelling using multivariate linear regression for Crohn's disease and incorporating all significant variables from correlational analysis.



RMSEA 0.024, SRMR 0.019, CFI 0.999, TLI 0.996, X2(N)=3.57, X2p=0.31, AIC 12562.03, BIC 12634.21. Coefficients included on paths. Error terms not shown. Greater fatigue seen with higher scores as measured by inverted FACIT-FS scores. Anxiety indicated by anxiety scores Generalised anxiety disorder 7-item, higher scores indicate worse anxiety. Depression indicated by depression scores Patient Health Questionnaire 9-item, higher scores indicate worse depression. Sleep quality as per the Pittsburgh Sleep Quality Index, higher scores seen in worse sleep quality. IBD activity described by the Harvey Bradshaw Index. ** $p<0.001$, *$p<0.05$.

Figure 10.2: Structural equation modelling using multivariate linear regression for ulcerative colitis and indeterminate colitis, with all significant variables incorporated from correlational analysis.



RMSEA 0.000, SRMR 0.016, CFI 1.00, TLI 1.00, X2(N)=2.997, X2p=0.39, AIC 7517.046, BIC 7578.99. Coefficients included on paths. Error terms not shown. Greater fatigue seen with higher scores as measured by inverted FACIT-FS scores. Anxiety indicated by anxiety scores Generalised anxiety disorder 7-item, higher scores indicate worse anxiety. Depression indicated by depression scores Patient Health Questionnaire 9-item, higher scores indicate worse depression. Sleep quality as per the Pittsburgh Sleep Quality Index, higher scores seen in worse sleep quality. IBD activity described by the Simple Clinical Colitis Activity Index. ** $p<0.001$, *$p<0.05$.

Table 10.1: Cohort demographics and inflammatory bowel disease (IBD) data, SCCAI (Simple Clinical Colitis Activity Index), HBI (Harvey–Bradshaw Index), FACIT-FS (Functional Assessment of Chronic Illness Treatment measurement system—fatigue score).

	Cohort
Age, median IQR	41 (32-70)
Female gender, *n* (%)	445 (78)
Crohn's disease, *n* (%)	352 (61)
Disease duration years, mean (SD)	12.6 (10.2)
Previous surgery for IBD, *n* (%)	187 (32.5)
Current steroid use, *n* (%)	52 (9.0)
Current biologic use, *n* (%)	304 (52.8)
Current immunomodulator use, *n* (%)	213 (37.0)
Obesity, *n* (%)	208 (36.1)
Smoking, *n* (%)	39 (6.7)
Alcohol usage, *n* (%)	199 (34.6)
Opioid usage, *n* (%)	85 (14.7)
Medications for sleep, *n* (%)	78 (13.6)
Clinically significant depression, *n* (%)	120 (20.8)
Clinically significant anxiety, *n* (%)	189 (32.8)
Clinically active IBD SCCAI, mean (SD) HBI, mean (SD)	 7.2 (2.8) 7.1 (3.2)
FACIT-FS	27.0 (11.9)

Table 10.2: Pearson's correlation coefficients with significance levels for Crohn's disease population.

	Fatigue	Age	Weight	IBD years diagnosed	IBD activity	Anxiety	Depression	Sleep quality
Age	-0.047	1						
Weight	0.015*	0.19**	1					
IBD years diagnosed	-0.086	0.33***	0.024	1				
IBD activity	0.56***	0.12	0.20**	0.0052	1			
Anxiety	0.55***	-0.20**	0.04	-0.064	0.38***	1		
Depression	0.76***	-0.16*	0.18*	-0.11	0.47***	0.698***	1	

Sleep quality	0.52***	-0.0037	0.086	0.024	0.41***	0.50***	0.548***	1

*p<0.05, **p<0.005, ***p<0.0005

Greater fatigue seen with higher scores as measured by inverted FACIT-FS. Anxiety indicated by anxiety scores Generalised anxiety disorder 7-item, higher scores indicate worse anxiety. Depression indicated by depression scores Patient Health Questionnaire 9-item, higher scores indicate worse depression. Sleep quality as per the Pittsburgh Sleep Quality Index, higher scores seen in worse sleep quality. *P<0.05. ** p<0.005, ***p<0.0005. Bonferroni adjusted.

Table 10.3: Pearson's correlation coefficients with significance levels for ulcerative colitis and indeterminate colitis population.

	Fatigue	Age	Weight	IBD years diagnosed	IBD activity	Anxiety	Depression	Sleep quality
Age	-0.18***	1						
Weight	0.12*	0.19***	1					
IBD years diagnosed	-0.12*	0.48***	-0.029	1				
IBD activity	0.43***	-0.008	0.11*	0.00	1			
Anxiety	0.51***	-0.25***	-0.020	-0.10	0.32***	1		
Depression	0.78***	-0.18**	0.11*	-0.15-	0.44***	0.70***	1	
Sleep quality	0.49***	0.048	0.14*	0.068	0.44***	0.39***	0.49***	1

*p<0.05, **p<0.005, ***p<0.0005

Greater fatigue seen with higher scores as measured by inverted FACIT-FS. Anxiety indicated by anxiety scores Generalised anxiety disorder 7-item, higher scores indicate worse anxiety. Depression indicated by depression scores Patient Health Questionnaire 9-item, higher scores indicate worse depression. Sleep quality as per the Pittsburgh Sleep Quality Index, higher scores seen in worse sleep quality. *P<0.05. ** p<0.005 ***p<0.0005. Bonferroni adjusted.

Table 10.4: Direct and indirect effects for fatigue score (FACIT-F) incorporating depression (PHQ9), anxiety (GAD7), sleep quality (PSQI) and irritable bowel disease (IBD) activity (Harvey–Bradshaw Index) for structural equation models for Crohn's disease and ulcerative colitis or indeterminate colitis.

Variable	Total effect (mean, 95% CI)	Indirect effect (mean, 95% CI)	Direct effect (mean, 95% CI)
Crohn's disease			
Depression	1.55 (1.36 - 1.74)**	0.06 (0.009 - 0.12)*	1.49 (1.30 - 1.69)**
Sleep quality	0.33(0.08 - 0.56)**	No path	0.33 (0.088 - 0.56) **
IBD activity	1.70 (1.32 - 2.09)**	1.35 (1.03 - 1.67)**	0.35 (0.050 - 0.65)*
Anxiety	0.85 (0.66 - 1.04)**	1.07 (0.89 - 1.26)**	-0.22 (-0.42 - -0.032)*
Weight	0.039 (0.004 - 0.07)*	0.039 (0.0077 - 0.07)*	No path
Ulcerative colitis or indeterminate colitis			
Depression	1.27 (1.03-1.51)**	0.081 (0.0038 - 0.16)*	1.27 (0.95 - 1.44)**
Sleep quality	0.37 (0.066 - 0.67)*	No path	0.37 (0.06 - 0.67)*
IBD activity	2.22 (1.79 - 2.66)**	1.34 (0.98 - 1.70)**	0.88 (0.52 - 1.24)**
Anxiety	0.84 (0.60 - 1.07)**	0.87 (0.66 - 1.09)**	-0.039 (-0.28 - 0.21)
Age	-0.082 (-0.013 - -0.034)**	-0.11 (-0.45 - -0.18)*	No path

** $p < 0.001$, * $p < 0.05$.

Table 10.5: Indirect effects on fatigue score (FACIT-F) by mediating variables—sleep quality, depression (PHQ9), anxiety (GAD7)—from structural equation models for ulcerative colitis and Crohn's disease.

	Total indirect effect	Via sleep quality	Via depression	Via anxiety
Crohn's disease				
IBD activity	1.35	0.18	1.29	-0.12
Depression	0.06	0.06	No path	No path
Anxiety	1.07	0.06	1.01	No path
Ulcerative colitis				
IBD activity	1.34	0.2	1.15	-0.03
Depression	0.081	0.081	No path	No path
Anxiety	0.87	0.12	0.75	No path

Supplementary data 10.1: Crohn's disease model

Structural equation model — Number of obs = 330
Estimation method = ml
Log likelihood = -6262.0154

	OIM Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Structural						
sfs						
gad7	-.2264907	.0987359	-2.29	0.022	-.4200096	-.0329719
phq9	1.491272	.0997184	14.95	0.000	1.295827	1.686716
psqi	.3262078	.1206101	2.70	0.007	.0898164	.5625992
hbi_use	.3526881	.1542925	2.29	0.022	.0502804	.6550958
_cons	6.670029	1.197356	5.57	0.000	4.323256	9.016803
gad7						
hbi_use	.6156638	.0992446	6.20	0.000	.4211481	.8101796
_cons	3.234373	.7682207	4.21	0.000	1.728688	4.740058
phq9						
gad7	.6815305	.0414891	16.43	0.000	.6002133	.7628476
hbi_use	.4551046	.0795647	5.72	0.000	.2991605	.6110486
weight	.02553	.0103663	2.46	0.014	.0052123	.0458476
_cons	-.8518094	.9872051	-0.86	0.388	-2.786696	1.083077
psqi						
gad7	.0593678	.0449458	1.32	0.187	-.0287244	.14746
phq9	.1959103	.0442167	4.43	0.000	.1092471	.2825735
hbi_use	.3708743	.067397	5.50	0.000	.2387787	.5029699
_cons	4.630332	.4834068	9.58	0.000	3.682872	5.577792
var(e.sfs)	52.69033	4.101937			45.234	61.37576
var(e.gad7)	29.50311	2.296814			25.32805	34.36637
var(e.phq9)	16.70525	1.300502			14.34125	19.45893
var(e.psqi)	10.97614	.8544916			9.422883	12.78544

LR test of model vs. saturated: chi2(3) = 3.57, Prob > chi2 = 0.3118

Fit statistic	Value	Description
Likelihood ratio		
chi2_ms(3)	3.570	model vs. saturated
p > chi2	0.312	
chi2_bs(14)	759.999	baseline vs. saturated
p > chi2	0.000	
Population error		
RMSEA	0.024	Root mean squared error of approximation
90% CI, lower bound	0.000	
upper bound	0.099	
pclose	0.616	Probability RMSEA <= 0.05
Information criteria		
AIC	12562.031	Akaike's information criterion
BIC	12634.213	Bayesian information criterion
Baseline comparison		
CFI	0.999	Comparative fit index
TLI	0.996	Tucker-Lewis index
Size of residuals		
SRMR	0.019	Standardized root mean squared residual
CD	0.285	Coefficient of determination

Equation-level goodness of fit

depvars	fitted	Variance predicted	residual	R-squared	mc	mc2
observed						
sfs	143.9379	91.24752	52.69033	.6339369	.7962016	.6339369
gad7	32.94365	3.440549	29.50311	.1044374	.3231677	.1044374
phq9	38.00661	21.30135	16.70525	.5604645	.7486418	.5604645
psqi	15.81186	4.835713	10.97614	.3058283	.5530174	.3058283
overall				.2848338		

mc = correlation between depvar and its prediction
mc2 = mc^2 is the Bentler-Raykov squared multiple correlation coefficient

Residuals of observed variables

Mean residuals

	sfs	gad7	phq9	psqi	hbi_use	weight
raw	-0.000	0.000	-0.000	-0.000	0.000	0.000

Covariance residuals

	sfs	gad7	phq9	psqi	hbi_use	weight
sfs	-0.453					
gad7	-0.266	-0.000				
phq9	-0.327	-0.171	-0.233			
psqi	-0.080	-0.033	-0.056	-0.013		
hbi_use	-0.000	0.000	-0.000	0.000	0.000	
weight	-4.721	-6.692	-4.561	4.892	0.000	0.000

Direct effects

	OIM Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Structural						
sfs						
gad7	-.2264907	.0987359	-2.29	0.022	-.4200096	-.0329719
phq9	1.491272	.0997184	14.95	0.000	1.295827	1.686716
psqi	.3262078	.1206101	2.70	0.007	.0898164	.5625992
hbi_use	.3526881	.1542925	2.29	0.022	.0502804	.6550958
weight	0	(no path)				
gad7						
hbi_use	.6156638	.0992446	6.20	0.000	.4211481	.8101796
phq9						
gad7	.6815305	.0414891	16.43	0.000	.6002133	.7628476
hbi_use	.4551046	.0795647	5.72	0.000	.2991605	.6110486
weight	.02553	.0103663	2.46	0.014	.0052123	.0458476
psqi						
gad7	.0593678	.0449458	1.32	0.187	-.0287244	.14746
phq9	.1959103	.0442167	4.43	0.000	.1092471	.2825735
hbi_use	.3708743	.067397	5.50	0.000	.2387787	.5029699
weight	0	(no path)				

Indirect effects

	OIM Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Structural						
sfs						
gad7	1.079268	.0932408	11.58	0.000	.8965195	1.262017
phq9	.0639075	.0276833	2.31	0.021	.0096492	.1181657
psqi	0	(no path)				
hbi_use	1.353775	.1650802	8.20	0.000	1.030224	1.677327
weight	.0397037	.0163143	2.43	0.015	.0077283	.0716791
gad7						
hbi_use	0	(no path)				
phq9						
gad7	0	(no path)				
hbi_use	.4195937	.0723007	5.80	0.000	.2778869	.5613004
weight	0	(no path)				
psqi						
gad7	.1335188	.031212	4.28	0.000	.0723445	.1946932
phq9	0	(no path)				
hbi_use	.207913	.0377101	5.51	0.000	.1340026	.2818234
weight	.0050016	.0023235	2.15	0.031	.0004476	.0095556

Total effects

	OIM Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Structural						
sfs						
gad7	.8527774	.0984652	8.66	0.000	.6597891	1.045766
phq9	1.555179	.0979463	15.88	0.000	1.363208	1.74715
psqi	.3262078	.1206101	2.70	0.007	.0898164	.5625992
hbi_use	1.706463	.1970267	8.66	0.000	1.320298	2.092629
weight	.0397037	.0163143	2.43	0.015	.0077283	.0716791
gad7						
hbi_use	.6156638	.0992446	6.20	0.000	.4211481	.8101796
phq9						
gad7	.6815305	.0414891	16.43	0.000	.6002133	.7628476
hbi_use	.8746982	.1011325	8.65	0.000	.6764821	1.072914
weight	.02553	.0103663	2.46	0.014	.0052123	.0458476
psqi						
gad7	.1928866	.0345472	5.58	0.000	.1251754	.2605978
phq9	.1959103	.0442167	4.43	0.000	.1092471	.2825735
hbi_use	.5787873	.0651817	8.88	0.000	.4510336	.706541
weight	.0050016	.0023235	2.15	0.031	.0004476	.0095556

```
.
. estat stable

Stability analysis of simultaneous equation systems

   Eigenvalue stability condition
```

Eigenvalue	Modulus
-1.546e-09	1.5e-09
1.080e-09	1.1e-09
4.657e-10	4.7e-10
0	0

```
   stability index =  1.55e-09
   All the eigenvalues lie inside the unit circle.
   SEM satisfies stability condition.

.
. estat eqtest

Wald tests for equations
```

	chi2	df	p
observed			
sfs	568.65	4	0.0000
gad7	38.48	1	0.0000
phq9	416.19	3	0.0000
psqi	145.00	3	0.0000

Supplementary data 10.2: Ulcerative colitis and indeterminate colitis model

	OIM Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Structural						
sfs						
phq9	1.196117	.1251208	9.56	0.000	.9508845	1.441349
gad7	-.0394991	.1264765	-0.31	0.755	-.2873885	.2083903
psqi	.3670674	.1533824	2.39	0.017	.0664435	.6676913
sccai_use	.882102	.1855251	4.75	0.000	.5184794	1.245725
_cons	3.667487	1.454611	2.52	0.012	.8165029	6.518472
phq9						
gad7	.6327181	.0563274	11.23	0.000	.5223184	.7431179
sccai_use	.5125913	.1004622	5.10	0.000	.3156891	.7094936
_cons	.8248283	.7603418	1.08	0.278	-.6654142	2.315071
gad7						
sccai_use	.7352158	.1124073	6.54	0.000	.5149015	.9555301
pt_age	-.0981565	.025648	-3.83	0.000	-.1484257	-.0478872
_cons	6.580204	1.332782	4.94	0.000	3.968	9.192407
psqi						
phq9	.2217379	.0550983	4.02	0.000	.1137473	.3297285
gad7	.1905239	.0563083	3.38	0.001	.0801616	.3008862
sccai_use	.1961839	.0837703	2.34	0.019	.0319971	.3603708
_cons	4.146574	.5986183	6.93	0.000	2.973304	5.319844
var(e.sfs)	50.19783	4.982553			41.32341	60.97809
var(e.phq9)	17.05557	1.692907			14.04033	20.71834
var(e.gad7)	24.69873	2.451555			20.33227	30.00292
var(e.psqi)	10.51086	1.04329			8.652651	12.76812

LR test of model vs. saturated: chi2(3) = 3.00, Prob > chi2 = 0.3921

```
. estat gof, stats(all)
```

Fit statistic	Value	Description
Likelihood ratio		
chi2_ms(3)	2.997	model vs. saturated
p > chi2	0.392	
chi2_bs(14)	516.427	baseline vs. saturated
p > chi2	0.000	
Population error		
RMSEA	0.000	Root mean squared error of approximation
90% CI, lower bound	0.000	
upper bound	0.119	
pclose	0.592	Probability RMSEA <= 0.05
Information criteria		
AIC	7516.046	Akaike's information criterion
BIC	7578.997	Bayesian information criterion
Baseline comparison		
CFI	1.000	Comparative fit index
TLI	1.000	Tucker-Lewis index
Size of residuals		
SRMR	0.016	Standardized root mean squared residual
CD	0.382	Coefficient of determination

```
.
. estat eqgof

Equation-level goodness of fit
```

depvars	fitted	Variance predicted	residual	R-squared	mc	mc2
observed						
sfs	144.6179	94.42004	50.19783	.6528933	.8080181	.6528933
phq9	36.39118	19.33561	17.05557	.5313268	.7289217	.5313268
gad7	31.05841	6.359677	24.69873	.204765	.4525097	.204765
psqi	17.05647	6.545613	10.51086	.3837613	.6194847	.3837613
overall				.3824693		

```
mc  = correlation between depvar and its prediction
mc2 = mc^2 is the Bentler-Raykov squared multiple correlation coefficient
```

. estat residuals

Residuals of observed variables

Mean residuals

	sfs	phq9	gad7	psqi	sccai_use	pt_age
raw	-0.000	-0.000	-0.000	0.000	0.000	0.000

Covariance residuals

	sfs	phq9	gad7	psqi	sccai_use	pt_age
sfs	-0.000					
phq9	-0.000	-0.000				
gad7	-0.000	-0.000	-0.000			
psqi	-0.000	-0.000	0.000	0.000		
sccai_use	0.000	-0.000	-0.000	0.000	0.000	
pt_age	-3.061	-4.763	0.000	2.400	0.000	0.000

Direct effects

	Coef.	OIM Std. Err.	z	P>|z|	[95% Conf.	Interval]
Structural						
sfs						
phq9	1.196117	.1251208	9.56	0.000	.9508845	1.441349
gad7	-.0394991	.1264765	-0.31	0.755	-.2873885	.2083903
psqi	.3670674	.1533824	2.39	0.017	.0664435	.6676913
sccai_use	.882102	.1855251	4.75	0.000	.5184794	1.245725
pt_age	0	(no path)				
phq9						
gad7	.6327181	.0563274	11.23	0.000	.5223184	.7431179
sccai_use	.5125913	.1004622	5.10	0.000	.3156891	.7094936
pt_age	0	(no path)				
gad7						
sccai_use	.7352158	.1124073	6.54	0.000	.5149015	.9555301
pt_age	-.0981565	.025648	-3.83	0.000	-.1484257	-.0478872
psqi						
phq9	.2217379	.0550983	4.02	0.000	.1137473	.3297285
gad7	.1905239	.0563083	3.38	0.001	.0801616	.3008862
sccai_use	.1961839	.0837703	2.34	0.019	.0319971	.3603708
pt_age	0	(no path)				

Indirect effects

	Coef.	OIM Std. Err.	z	P>|z|	[95% Conf.	Interval]
Structural						
sfs						
phq9	.0813927	.0395698	2.06	0.040	.0038374	.1589481
gad7	.8782385	.1099988	7.98	0.000	.662645	1.093832
psqi	0	(no path)				
sccai_use	1.343508	.1828212	7.35	0.000	.9851846	1.70183
pt_age	-.0823277	.0246001	-3.35	0.001	-.130543	-.0341124
phq9						
gad7	0	(no path)				
sccai_use	.4651844	.0823006	5.65	0.000	.3038783	.6264905
pt_age	-.0621054	.017144	-3.62	0.000	-.095707	-.0285038
gad7						
sccai_use	0	(no path)				
pt_age	0	(no path)				
psqi						
phq9	0	(no path)				
gad7	.1402976	.0370315	3.79	0.000	.0677171	.212878
sccai_use	.3568861	.0605056	5.90	0.000	.2382973	.4754748
pt_age	-.0324723	.0096091	-3.38	0.001	-.0513058	-.0136387

Total effects

	OIM Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Structural						
sfs						
phq9	1.27751	.1220964	10.46	0.000	1.038205	1.516814
gad7	.8387395	.1215715	6.90	0.000	.6004636	1.077015
psqi	.3670674	.1533824	2.39	0.017	.0664435	.6676913
sccai_use	2.22561	.2213849	10.05	0.000	1.791703	2.659516
pt_age	-.0823277	.0246001	-3.35	0.001	-.130543	-.0341124
phq9						
gad7	.6327181	.0563274	11.23	0.000	.5223184	.7431179
sccai_use	.9777757	.1169254	8.36	0.000	.7486061	1.206945
pt_age	-.0621054	.017144	-3.62	0.000	-.095707	-.0285038
gad7						
sccai_use	.7352158	.1124073	6.54	0.000	.5149015	.9555301
pt_age	-.0981565	.025648	-3.83	0.000	-.1484257	-.0478872
psqi						
phq9	.2217379	.0550983	4.02	0.000	.1137473	.3297285
gad7	.3308215	.0459488	7.20	0.000	.2407635	.4208794
sccai_use	.55307	.0843469	6.56	0.000	.387753	.718387
pt_age	-.0324723	.0096091	-3.38	0.001	-.0513058	-.0136387

CHAPTER 11: A LATENT PROFILE APPROACH TO FATIGUE IN INFLAMMATORY BOWEL DISEASE

This chapter presents the manuscript 'Latent profiles of fatigue in inflammatory bowel disease', was published in the journal BMC Gastroenterology, in April 2024.

Author contributions

Alex Barnes: responsible for study concept and design, data acquisition, analysis, and data interpretation, drafting of manuscript, critical revision of the manuscript.

Barbara Toson: responsible for data analysis

RV Bryant: responsible for data interpretation, and critical revision of the manuscript.

Sutapa Mukherjee: responsible for critical revision of the manuscript

Jane Andrews: responsible for critical revision of the manuscript.

Paul Spizzo: responsible for critical revision of the manuscript

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Please see appendices for further authorship information.

[Manuscript] Latent profiles of fatigue in inflammatory bowel disease

Latent profiles of fatigue in inflammatory bowel disease

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Abstract

Introduction: Fatigue is prevalent in people with inflammatory bowel disease (IBD) and has been associated with IBD activity, sleep quality, depression, and anxiety. This study aimed to identify fatigue profiles or clusters through latent profile analysis.

Methods: An online questionnaire was administered through three tertiary IBD centres, social media and through Crohn's Colitis Australia. Fatigue was assessed via the Functional assessment of chronic illness measurement system fatigue subscale (FACIT-F), a validated assessment of fatigue and its severity. Validated measures of anxiety, depression, IBD activity and sleep quality were also included. Latent profile analysis was performed including fatigue, sleep quality, active IBD, and depression and anxiety. The relationships between profiles and IBD and demographic data were investigated.

Results: In a cohort of 535 respondents, 77% were female, the median age was 41 years (range 32-52 years), and the majority had Crohn's disease (62%). Severe fatigue was seen in 62%. Latent profile analysis identified four distinct profiles differing by fatigue score - low fatigue, at-risk profile, active IBD, and a poor mental health profile. Female gender, obesity and opioid usage were associated with higher risk of being in the active IBD and poor mental

health profile. Age over 40 was associated with lower risk of being in the poor mental health profile.

Conclusion: Latent profile analysis identifies four classes of fatigue in an IBD cohort with associations with specific risk factors for fatigue along with specific IBD and demographic attributes. This has implications for the classification of fatigue in IBD and treatment algorithms.

Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing remitting immune disorder that can affect any area of the gastrointestinal tract with extra-intestinal manifestations that includes joint and skin disease. Fatigue is a common symptom in people with IBD with a systemic review and meta-analysis reporting a prevalence of 48%[71]. The pathophysiology of fatigue in IBD is poorly understood[72,79]. Frequently reported associations with fatigue in IBD include disease activity, sleep disturbance, anxiety and, depression[232,233,414-416].

In people with fatigue, symptom clusters have been proposed[432]. For example, in patients with advanced cancer, fatigue symptom clusters have been observed including 'sleep, drowsiness and fatigue'[433] and 'sleep, depression, and fatigue'[434]. Proposed treatment algorithms for fatigue in IBD contain flow charts that consider separate causes of fatigue in isolation[78]. Other have previously sought to identify classes of fatigue trajectories in IBD populations considering fatigue, IBD activity and psychological well-being[435]. More generally, symptom clusters in IBD have been explored in a single study considering gastrointestinal and psychological symptoms[436] producing a model similar to that reported in populations with irritable bowel syndrome[437,438]. Others have identified that there are differences in healthcare utilisation between such symptom-defined clusters[439].

This study aimed to identify fatigue profiles or clusters in people in IBD considering known associations with fatigue using latent profile analysis incorporating fatigue, IBD activity, depression, anxiety and sleep quality. It was hypothesised that similar fatigue clusters with sleep, depression and fatigue will be seen and that there may exist a fatigue cluster that is independent of IBD activity. The authors then aimed to determine associations between demographic and IBD data and latent profile membership.

Methods

An online questionnaire was made available to people with IBD via tertiary hospital patient email lists, private gastroenterology practice email lists and social media. Individuals with a self-reported diagnosis of IBD over 18 years of age were invited to participate. Demographic data such as age and sex were recorded, along with IBD related data including disease duration and previous surgery. Ethics approval for this study was obtained from the Southern Adelaide Human Research Ethics Committee (203.20) and informed consent was obtained from all participants.

Fatigue was measured using the FACIT-F scale which is a subscale of the Functional assessment of chronic illness measurement system (FACIT). The FACIT-F subscale has been validated as a measure of fatigue in an IBD population[421]. The FACIT-F scale includes 13 questions with responses recorded on a 5-point Likert scale, with a score ranging from 0 to 52, with a lower score indicating worse fatigue. A score less than 32 indicates severe fatigue[422].

Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI). The PSQI is a validated tool which assesses perceived sleep quality[113]. The index consists of subscales on sleep duration, sleep disturbance, sleep latency, daytime dysfunction, sleep efficiency, overall sleep quality and medications for sleep. The score ranges from 0 to 21, with a PSQI > 5 considered to represent poor sleep quality.

IBD disease activity was assessed using the Harvey Bradshaw Index (HBI) in the case of Crohn's disease with HBI > 5 considered active disease[217]. The patient-reported version of the HBI was used in the survey, although a decision was made to maintain the general well-being and abdominal pain score similar to the physician HBI rather than using a ten-point Likert scale[281]. The Simple Clinical Colitis Activity Index (SCCAI) was used for ulcerative colitis, with an SCCAI > 5 considered active disease[282]. The patient reported form of the SCCAI was used[283] in the survey, which has been previously validated and shown to be closely concordant with physician reported SCCAI[284].

Anxiety was assessed using the generalised anxiety disorder 7-item scale (GAD-7)[285] with a score over 5 considered mild anxiety, 10-14 moderate and greater than 15 severe anxiety. The Patient Health Questionnaire 9 (PHQ-9) was used to assess depression with a score over 5 indicating mild depression, over 10 moderate depression, and over 20 severe depression[286].

Statistical analysis

Statistical analysis was performed using Stata SE 16 (StataCorp, College Station, TX, USA). Inadequate completion of score or index led to that result not being included. For normally distributed variables mean and standard deviation (SD) were reported with comparisons made using the student t-test. For non-normally distributed variables median, and interquartile range (IQR) were reported, with comparisons made using the Mann- Whitney U test. For categorical data Pearsons $\chi 2$ test was used or Fisher's exact test when appropriate. If any incomplete data were present the participant was excluded.

Latent profile analysis was used to determine if respondents could be divided into groups or profiles based on responses to the questionnaire used to determine fatigue scores (FACIT-F), depression (PHQ9), anxiety (GAD7), IBD activity (SCCAI > 5 or HBI > 5), and sleep quality (PSQI). Stata latent profile analysis was used to determine the latent profile models[440]. To identify profiles of fatigue a one class model was first estimated with further classes added until the model with best fit was identified. Class size from 1 to 8 was considered. Model fit was assessed on model interpretability in addition to model performance criteria such as the Bayesian information criteria and the Akaike information criterion, and the minimum class size[441]. Entropy was calculated following determination of class size. Covariates were included based on model performance and interpretability. Posterior class membership probabilities were calculated for each survey response. Each survey response was assigned to a profile based on the posterior class membership probabilities. Multinomial regression was undertaken to assess for predictors of class membership.

Results

There were 670 responses to the online questionnaire, following exclusions for any incomplete data there were 535 responses (79.8%) included in the analysis (see table 1). Median age was 41 years (32-52), with most being female (77%), the majority had Crohn's disease (61%). The mean disease duration was 10 years (5-19), 32% had undergone surgery for IBD and around half were on biologics (53%) (see table 1).

Latent profile analysis was undertaken including fatigue scores (FACIT-F score inverted), depression scores (PHQ9), anxiety scores (GAD7), sleep quality (PSQI) and IBD activity (SCCAI > 5, HBI > 5). Covariates were included in the model such as age, IBD subtype and BMI over 25. A four-profile solution based was chosen (see supplementary table 1, entropy was adequate at 0.82).

The latent profiles (See figure 1 and table 2) were named as follows: the low fatigue profile (23%) – encompassing mild levels of fatigue and low levels of depression and anxiety; the poor mental health profile representing the smallest group (14%) characterised by severe anxiety and depression; the active IBD profile (31%) with high levels of IBD activity and associated poor sleep quality, but only mild-moderate mental health impairment. Finally, there was the at-risk profile (33%), being the largest profile, with mild levels of depression and anxiety, and moderate levels of fatigue.

As age increased there was a decreased probability of measurement of the higher fatigue and mental health profiles and decreased probability of membership in the lower fatigue profiles (see covariate plotting in figure 2). No significant change in profile membership was seen with IBD subtype (see supplementary figure 1).

Female gender, opioid usage and obesity were associated with membership of higher fatigue profiles (multinomial regression with low fatigue profile as base see table 3). Age over 40 was associated with decreased likelihood of membership in the poor mental health profile. Current smoking status was associated with increased likelihood of being in the poor mental health profile and the at-risk profile but not in the active IBD profile. Corticosteroid usage was associated with increased likelihood of membership in the poor mental health class. No differences were seen with IBD subtype, IBD duration, or any biologic or immunomodulator usage.

Discussion

For the first time in the IBD literature this study used latent profile analysis to distinguish four fatigue profiles, differing by sleep quality, IBD activity, depression, and anxiety. The higher fatigue profiles were associated with opioid usage, younger age, female gender, corticosteroid usage and obesity. Depression and anxiety were closed related across the different profiles, similarly IBD activity and sleep quality remained related across the different profiles. The profile with the highest fatigue scores saw poor sleep, IBD activity and depression present in at least moderate severity.

The importance of mental conditions was highlighted by this data with moderate-high levels of depression and anxiety seen in the class with a high probability of severe fatigue. This may in part be a physiological consequence of the neurological effects of active IBD associated inflammatory cytokines[442,443]. There are likely bidirectional relationships between fatigue and mental health conditions, and mental conditions and IBD activity[418,444] making causation difficult to assess. Sleep disturbance has also been associated with worse depression or anxiety.

There was a profile referred to as ‘active IBD’ that had high proportion of active IBD and poor sleep quality with low-moderate anxiety/depression scores. Clinically active IBD certainly influences sleep quality and perhaps addressing IBD activity in those in this profile will lead to improvement in both aspects and reduce the likelihood of severe fatigue. Our initial hypothesis was incorrect – there was no profile with significant levels of fatigue and

low IBD activity. IBD activity in a way mirrored fatigue scores. It is important to note here that this is clinical IBD activity rather than objective IBD activity (calprotectin/endoscopy based), and consequently may relate to IBS related symptoms that are common in people with inactive IBD[398]. These IBS-like symptoms can often be influenced by other factors such as depression or anxiety.

Females were more likely to be in the higher fatigue and mental health profiles. Fatigue is more commonly seen in females[445] although in IBD populations gender differences in fatigue have been mixed[71]. Similarly, depression and anxiety are more common in females[446-448] which perhaps explains the observed associations with the profiles seen here. Variance in profile membership was seen with age but not with IBD duration.

Corticosteroid usage was more common in the poor mental health class. This may relate to the medications influence on mental health and to its usage – generally in those with clinically active IBD. The association between corticosteroids and high levels of fatigue may be due to its association with clinically active IBD. Opioid usage, and in particular opioid misuse, has been related to fatigued, perhaps due to associated sedation and have also been associated with more severe IBD[321,323,328].

The reported causes of fatigue in IBD are many and varied with current approaches suggesting considering causes in isolation with approaches varying from considering causes sequentially or in parallel[78,79]. The data here suggests that the common causes of fatigue frequently coexist – for example IBD activity and sleep were closely related. The authors would suggest that those presenting to IBD clinic with severe fatigue be screened for depression and evaluated for active IBD before pursuing other possible aetiologies.

Limitations of this study include selection bias a result of the use of an online questionnaire that may attract people with fatigue or sleep problems. Similarly, the form of survey and method of recruitment is likely responsible for the predominantly female cohort. The proportion of participants with Crohn's disease was above that present in Australian prevalence data[429]. Reporting bias may also be significant, noting a study of people with Crohn's disease reported worse sleep quality than that observed by objective measures[167]. Data on other medical conditions study participants may have that may influence fatigue, such as heart failure, was not available. There is no gold standard measure for choosing a latent profile measure – here we used statistical measures of model performance along with model interpretability and relevance to the previous literature.

The absence of an objective measure of IBD activity is also considered a limitation. A more valid approach would be to incorporate measures such as faecal calprotectin or endoscopic activity to define objective disease activity in addition to patient reported disease activity. Understanding the associations between fatigue profile membership and objective and subjective IBD activity would be valuable. Similarly, the inclusion of socioeconomic data in the model or subsequent analysis may also be valuable. Given the nature of data collection there was no opportunity to assess for anaemia that been associated with fatigue[233]. However, as others have noted[71] anaemia was not associated with fatigue in numerous cross-sectional studies, and hence its lack of inclusion in the model here is not considered a significant limitation[83,430,431].

Reviewing the plot of the latent profiles (see Figure 2) one may see that the 'low fatigue' and 'at risk' profiles are in some areas parallel – suggest that this may represent different severities of the same profile referred to as the Salsa effect[449]. However, the authors would note that the 'at risk' profile has a sharper rise in IBD activity and fatigue – suggesting that perhaps the increase in IBD activity leads to greater fatigue and a comparatively smaller increase in anxiety, depression, and sleep quality scores – and would argue that this does not represent simply the 'low fatigue' profile at a greater severity.

It would be valuable to assess how fatigue profiles change over time, alongside influencing factors and the prognostic relevance of fatigue on IBD outcomes. Current evidence suggests that fatigue remains stable in the majority of IBD patients over time[435]. The latent profiles of fatigue defined in this study add granularity to factors associated with fatigue in IBD patients, adding further opportunities to address these debilitating and prevalent symptoms.

Conclusions

Latent profile analysis identified four profiles differentiated by levels of fatigue. The observed profiles suggest that the common risk factors for fatigue in IBD will typically co-exist. The association between depression and fatigue underlines the importance of screening for depression during IBD clinic. Attention should also be given to other factors associated with higher fatigue profiles such as obesity, opioid usage and corticosteroid usage. Further research should consider changes in fatigue profiles over time.

Table 11.1: Cohort demographics and inflammatory bowel disease (IBD) data, Severe fatigue defined by FACIT-F < 32, clinically significant anxiety defined by GAD-7 > 10, clinically significant depression defined by PHQ-9 > 15

IBD and demographic data	
n	535
Gender (% female)	77.4
Age (median (IQR))	41 (32-52)
Crohn's disease (%)	61.3
IBD years diagnosed (median (IQR))	10 (5-19)
IBD-related surgery (%)	32.5
Obesity (%)	36.2
Active smoking (%)	6.8
Corticosteroids (%)	9.04
Aminosalicyate (%)	33.2
Biologics (%)	52.8
Immunomodulators (%)	37.04
Opioids (%)	14.8
Medications for sleep (%)	13.6
Colecalciferol (%)	28.0
Harvey–Bradshaw Index (mean(SD))	7.1 (3.2)
Simple Clinical Colitis Activity Index (mean(SD))	7.2 (2.8)
Clinically significant anxiety (%)	32.8
Clinically significant depression (%)	20.8
Severe fatigue (%)	57

Severe fatigue defined by FACIT-F <32, clinically significant anxiety defined by GAD-7 >10, clinically significant depression defined by PHQ-9 >15. IQR, interquartile range.

Table 11.2: Mean values in each latent profile – with interpretation based on established cut offs.

IBD (inflammatory bowel disease) activity refers to the proportion with clinically active IBD. Sleep quality via the Pittsburgh Sleep Quality Index. Depression via Patient Health Questionnaire 9 scoring. Anxiety via the Generalised anxiety disorder -7 score. Fatigue by the Functional assessment of chronic illness measurement system fatigue score.

Profile	Low fatigue	At-risk	Active IBD	Poor mental health
IBD activity	0.41	0.74	0.87	0.96
Sleep quality	6.07	8.76	11	13.2
Depression	Nil	Mild	Moderate	Severe
Anxiety	Nil	Mild	Moderate	Severe
Fatigue	Mild	Moderate	Severe	Severe

Table 11.3: Multinomial regression analyses with relative risk ratio reported relative to low fatigue profile. IBD (inflammatory bowel disease).

Profile	At-risk	Active IBD	Poor mental health
Age over 40	1.00 (0.63-1.60) p=0.99	0.63 (0.39-1.00) p=0.051	**0.49 (0.27-0.88) p=0.017**
Age over 60	1.19 (0.64-2.24) p=0.57	0.84 (0.43-1.63) p=0.60	0.39 (0.14-1.2) p=0.08
Female gender	**2.16 (1.30-3.61) p=0.003**	**2.84 (1.65-4.87) p<0.001**	**2.72 (1.38-5.39) p=0.004**
Obesity	**1.80 (1.04-3.13) p=0.037**	**3.32 (1.93-5.71) p<0.001**	**2.65 (1.39-5.05) p=0.003**
Ulcerative colitis	1.04 (0.65-1.67) p=0.86	1.03 (0.64-1.67) p=0.90	1.01 (0.56-1.82) p=0.97
Crohn's disease	0.78 (0.49-1.26) p=0.32	0.87 (0.54-1.41) p=0.58	0.88 (0.49-1.59) p=0.68
Corticosteroids	2.49 (0.88-6.99) p=0.083	2.65 (0.94-7.3) p=0.065	**4.12 (1.37-12.39) p=0.012**
Opioids	**2.77 (1.15-6.66) p=0.023**	**4.18 (1.78-9.83) p=0.001**	**4.21 (1.63-10.89) p=0.003**
Aminosalicyate	1.49 (0.90-2.48) p=0.12	1.24 (0.74-2.01) p=0.41	1.34 (0.72-2.49) p=0.36
Immunomodulators	0.88 (0.54-1.43) p=0.61	1.34 (0.83-2.18) p=0.23	0.97 (0.53-1.78) p=0.94
Biologics	0.91 (0.57-1.45) p=0.70	0.98 (0.61-1.56) p=0.93	0.83 (0.47-1.48) p=0.53
Vitamin D	1.35 (0.80-2.29) p=0.26	1.08 (0.63-1.86) p=0.78	1.78 (0.95-3.33) p=0.070
Previous IBD surgery	1.09 (0.67-1.77) p=0.71	0.86 (0.52-1.41) p=0.55	0.79 (0.43-1.47) p=0.46

IBD over 10 years since diagnosis	1.57 (0.98-2.50) p=0.056	0.80 (0.50-1.29) p=0.36	0.96 (0.54-1.70) p=0.88
Current smoking	**3.65 (1.02-12.98) p=0.046**	2.98 (0.81-10.92) p=0.099	**4.86 (1.25-18.91) p=0.023**

			1.01

Figure 11.1: Latent profiles of determinants of fatigue.

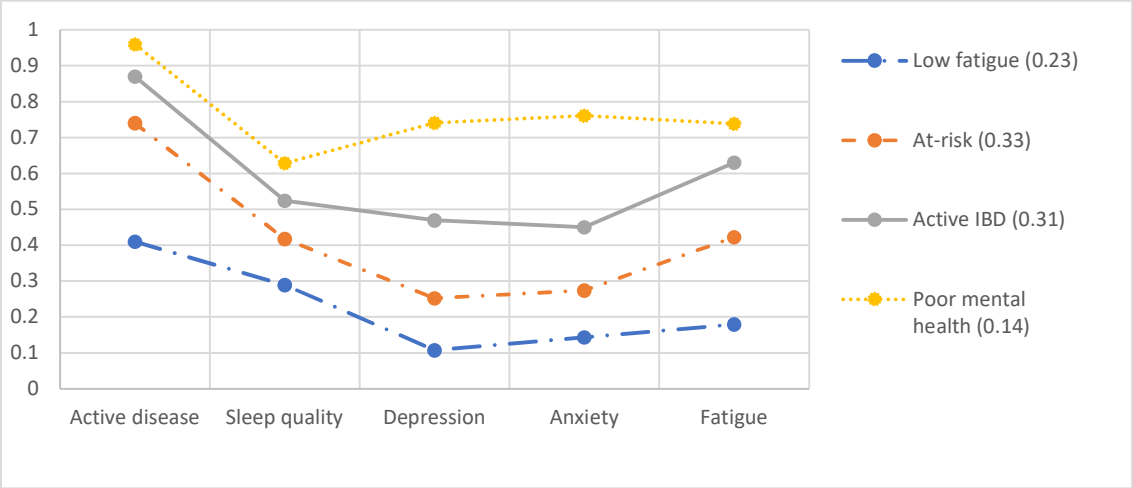
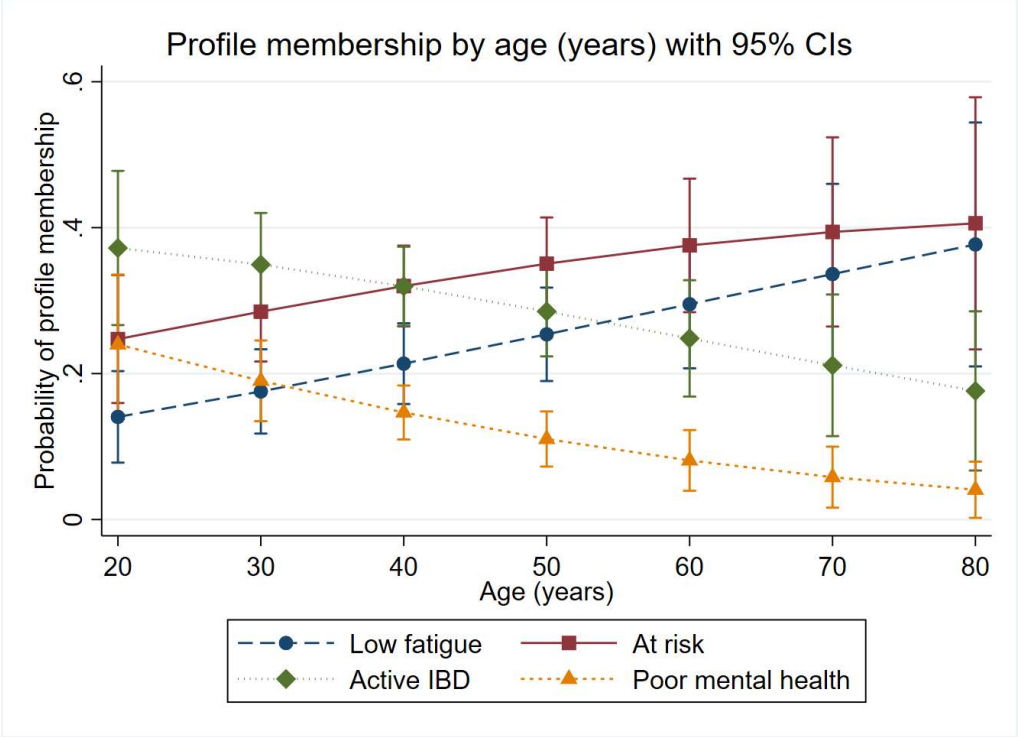


Figure illustrates the characteristics of each profile based on reported anxiety, depression, IBD activity, sleep quality and fatigue levels. A minority were in the poor mental health profile (14%), with the majority in the at-risk or active IBD profiles (33%). Scores have been normalised by highest possible response for each score.

Figure 11.2: Latent profiles of determinants of fatigue.



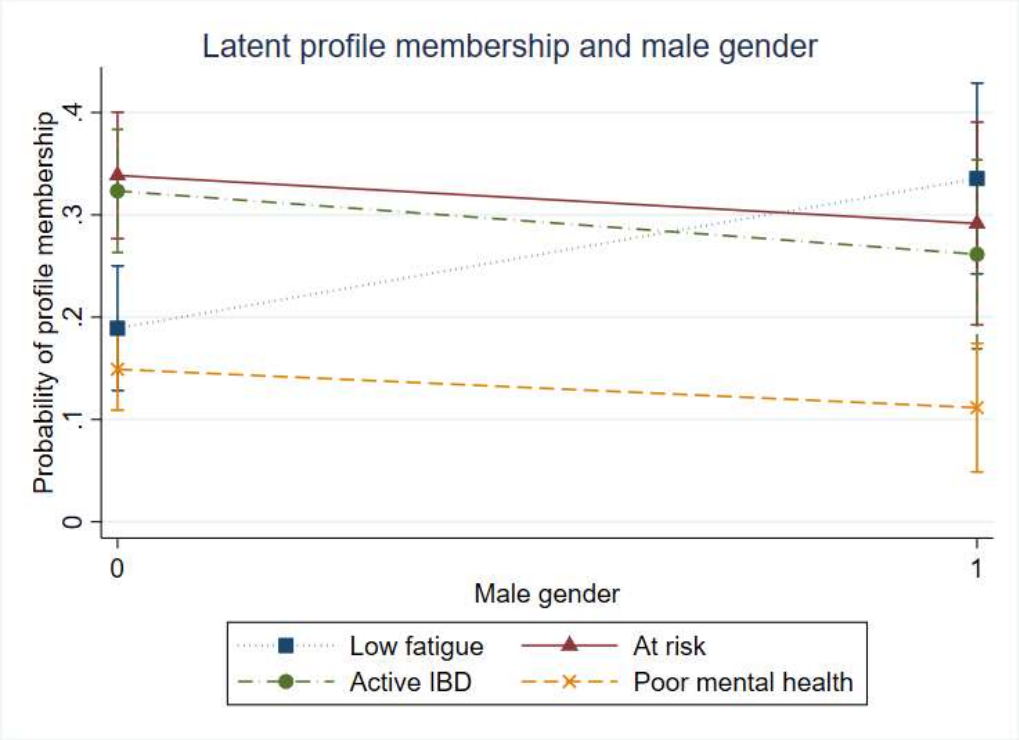
Age (covariate in latent model) plotted against each latent profile: low fatigue, at risk, active IBD, poor mental health.

Supplementary Table 11.1: Latent class profile model statistics for each profile.

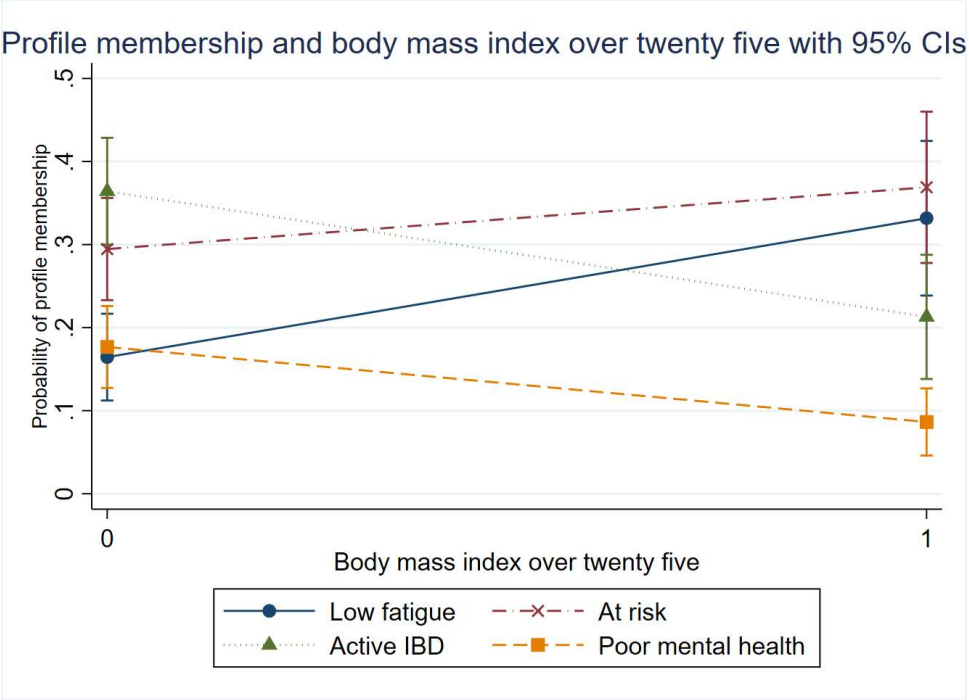
Profile	LL	df	AIC	BIC
1	-7291.11	9	14540.21	14578.69
2	-6836.24	19	13710.18	13791.7
3	-6700.46	29	13458.91	13582.88
4	-6641.87	39	13361.73	13528.45
5	-6613.66	49	13325.32	13534.78
6	-6596.68	59	13311.36	13563.58
7	-6580.26	67	13298.52	13593.48
8	-6551.06	79	13260.11	13597.82

AIC – Akaike information criterion, BIC – Bayesian information criterion, LL – log-likelihood, df – degrees of freedom.

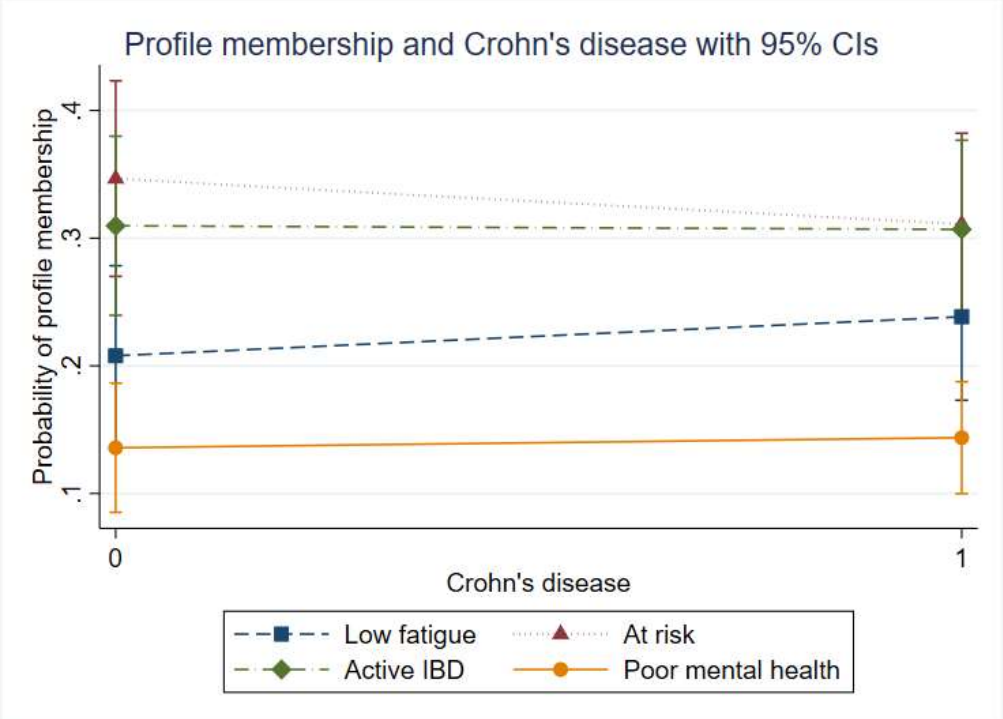
Supplementary figure 11.1: Latent profiles of determinants of fatigue. Male gender (covariate in latent model) plotted against each latent profile – low fatigue, at risk, active IBD, poor mental health.



Supplementary figure 11.2: Latent profiles of determinants of fatigue. Body mass index over twenty five (covariate in latent model) plotted against each latent profile – low fatigue, at risk, active IBD, poor mental health.



Supplementary figure 11.3: Latent profiles of determinants of fatigue. Crohn's disease (covariate in latent model) plotted against each latent profile – low fatigue, at risk, active IBD, poor mental health.



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CHAPTER 12: DISCUSSION

The body of research presented in this thesis describes the interplay among sleep quality, IBD activity and other important factors including fatigue, mental health and QoL.

Routine IBD care is focussed on reducing inflammation and maintaining remission while preventing harm from IBD-related medications or IBD-related complications. Current, holistic guidelines call for QoL and disability to be considered integral treatment goals for optimal management of IBD.[312] Improving QoL and disability for people with IBD will necessarily involve more than a focus on IBD activity alone and requires consideration of other areas such as mental health and sleep.

The novel work presented in this thesis indicates that sleep—although differing according to IBD activity—is also related to fatigue, mental health and some specific therapies. Moreover, sleep on its own has been demonstrated to be a suitable target to improve QoL in people with IBD. The work presented here derives from a prospective observation study incorporating objective measures of IBD activity and sleep quality and an online survey that allowed multiple aspects of the relationship between sleep quality and IBD activity to be addressed.

Key outcomes and significance

Key outcomes are summarised in Figure 12.1.

Poor sleep is prevalent in people with IBD. Sleep disruption has been reported in IBD and is a concern for many people with IBD. The systematic review and meta-analysis presented quantify the extent of this problem; producing a pooled prevalence of poor sleep of 56%, meaning that over half those living with IBD have poor sleep using validated measures.

Sleep quality influences QoL in IBD. The findings presented in this thesis demonstrate that sleep quality influences QoL in people with IBD. This was additionally demonstrated to be in excess of that due to the effect of depression, anxiety or IBD activity on QoL. This may be through sleep deprivation's negative influence on the perception of pain and its subsequent deleterious impact on QoL. Consequently, one may argue that sleep should be of interest to IBD clinicians because of its influence on QoL. Insomnia was associated with reduced QoL in the absence of active IBD and of similar magnitude to that seen in active IBD.

Objective sleep quality is worse in people with objectively active IBD than remission. Sleep has been associated with IBD in the subjective sense, relying on self-reported sleep and

IBD activity. This was improved on somewhat with a number of more recent studies including an objective measure of sleep quality—actigraphy. However, these studies produced widely varying results, including no difference in sleep quality between active and inactive IBD. Actigraphy has its limitations because of inability to definitively identify sleep and its tendency to over or underestimate parameters such as sleep latency and time awake after sleep onset, among others. Assessing IBD activity has primarily relied on patient-reported symptoms that may be confounded by IBS-like symptoms masquerading as active IBD and sub-clinically active IBD that does not produce any obvious symptoms.

An important strength of the evidence in this thesis is the use of polysomnography and objective IBD assessments to provide non-subjective evidence of differences in sleep quality between active and inactive IBD. The differences in sleep quality were significant despite there being similar time in bed in each group. Differences in polysomnography included longer sleep latency in active IBD and shorter stage 2 sleep in active IBD, resulting in poor sleep efficiency. The observed differences in sleep quality, rather than being related to pro-inflammatory cytokines, were more in keeping with IBD-related symptom-driven sleep disturbance or mental health-related sleep disturbance. This thesis provides objective evidence of differences between inactive and active IBD in sleep quality.

Sleep in people with IBD in remission is worse than population controls. The current research demonstrated through a further meta-analysis that sleep quality was worse in inactive IBD than population controls, highlighting the existence of factors over and above IBD activity that are negatively influencing sleep quality. These factors may include sub-clinical inflammation, IBS-like symptoms that are prevalent in people with IBD,[236] mental health conditions like depression that are also prevalent,[192] IBD-related disability and IBD medications.

Opioids are associated with poor sleep quality in people with IBD. Sleep can be influenced by a variety of factors that may include IBD medications. In a large cohort of people with IBD, opioids were associated with poor sleep irrespective of IBD activity, depression and other IBD and demographic factors. TNF-α medications in rheumatology studies have shown some improvement in sleep quality scores. In the population in the current study, infliximab was associated with higher sleep disturbance scores but this effect disappeared when adjusted by body weight. Corticosteroids were associated with worse sleep but this was cofounded by IBD activity and mental health conditions.

Insomnia and its associations with IBD. Insomnia was associated with clinically active IBD, abdominal pain, depression and anxiety. The role of different IBD-related symptoms was considered, with urgency important in UC, and overall general wellbeing more relevant in people with CD. Insomnia was associated with increased IBD-related disability. This may be a result of the influence of insomnia on overall disability but could be similarly explained by the development of insomnia as a result of cumulative IBD-related disability.

Screening for obstructive sleep apnoea in IBD. Obstructive sleep apnoea may be relevant to IBD because of its influence on cardiovascular disease and mortality, given that people with IBD also experience higher levels of cardiovascular disease than population controls. Screening tools such as the OSA-50 can be readily applied and have sufficient qualities to justify polysomnography. In the study cohort here, over one-fifth met high-risk criteria for OSA. The risk of OSA was associated with abdominal pain, as were more traditional risk factors such as smoking, increasing age and obesity. A screening tool for OSA specific to IBD was developed.

Sleep plays a mediating role in fatigue. Fatigue is common in people with IBD and is typically presumed to be multifactorial. Several authors have examined factors associated with fatigue with varying results, although consistently showing that IBD activity, sleep and mental conditions are associated with fatigue.

SEM was used to investigate and map the influence of sleep on fatigue. This demonstrated sleep as a mediating variable in the influence of IBD activity and mental health conditions on fatigue. Of interest, the influence of IBD activity on fatigue was largely indirect, mediated via its influence on other parameters such as sleep and depression. Depression appeared to have the largest reduction in fatigue score and is thus an important future target to improve fatigue among those with IBD.

A latent profile approach was used to define profiles of fatigue in IBD with sleep a differentiating factor between profiles. Clinically significant depression defined a profile of severe fatigue, poor sleep and IBD activity. Other profiles likely represented differences in IBD activity and associated poor sleep quality with associated gradient of fatigue severity. Latent profiles or classes of fatigue have not been previously described in this population.

Limitations

Limitations to this work include the limited cohort who underwent polysomnography, as is typical for studies incorporating such investigations. The use of objective IBD activity

incorporated a variety of measures of IBD activity that as a result likely introduced heterogeneity, although this is undoubtedly a superior approach to that used in many other studies that did not objectively assess IBD activity.

Limitations to this work include selection bias because of the use of an online questionnaire and the predominantly female cohort. The rates of anxiety and depression seen in the study cohort were similar to that described elsewhere.[192] The cohort likely represents a moderate–severe IBD cohort with biologic usage in around half and previous surgery in almost a third. Given that OSA is more common in males, the moderate–high risk of OSA seen here is likely lower than in the broader IBD population.[413] Reporting bias may also be significant, noting a study of people with CD reported worse sleep quality than that observed by objective measures.[167] The absence of objective measures of sleep quality and objective IBD activity is also considered a limitation. Further studies should consider objective measures of IBD activity and sleep quality.

Limitations to this work also include the lack of opportunity to assess factors such as anaemia, which been associated with fatigue.[233] However,[71] anaemia has not been associated with fatigue in numerous cross-sectional studies; hence its lack of inclusion in the current model is not considered a significant limitation.[83,430,431]

There are also limitations to the form of analysis used here. It is acknowledged that path analysis is unable to identify the direction of effects. There is no gold standard measure for choosing a latent profile measure; here statistical measures of model performance were used along with model interpretability and relevance to the literature.

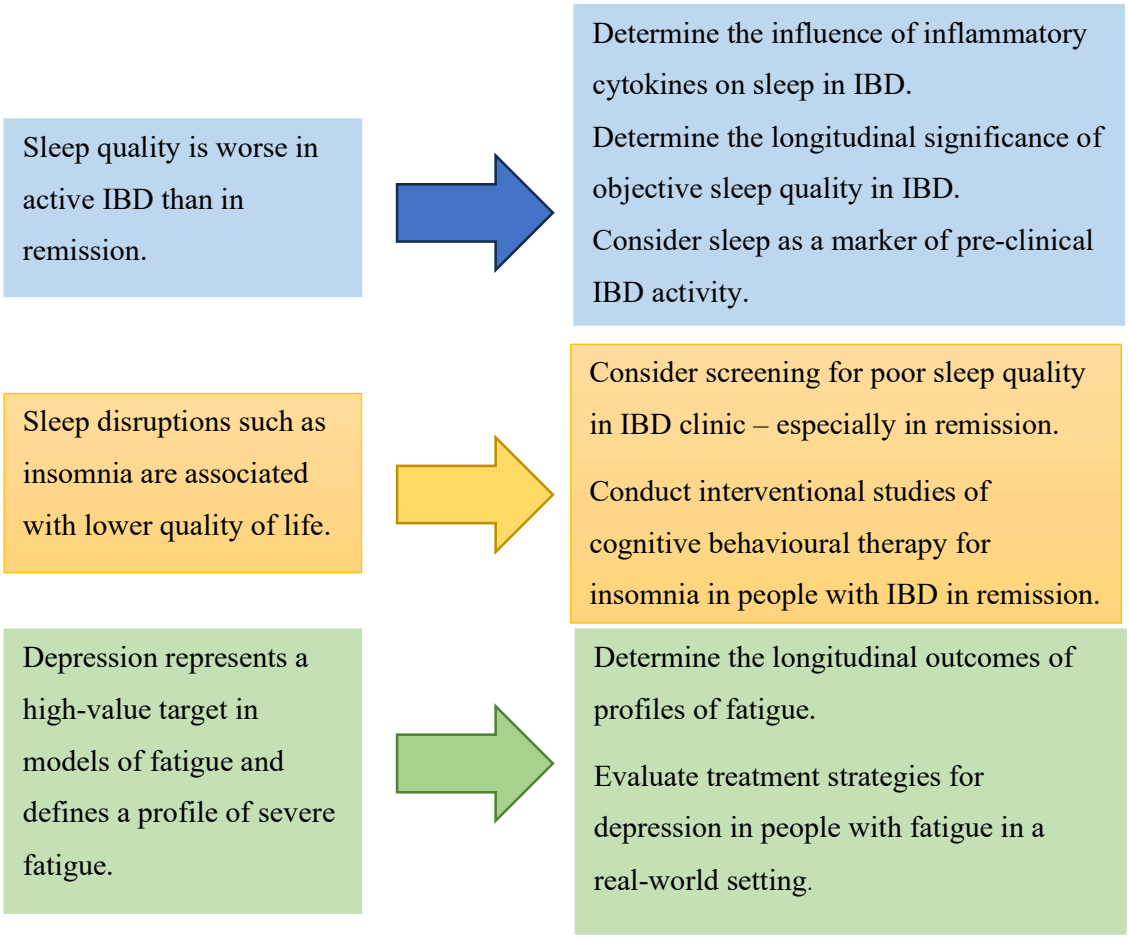

Figure 12.1: Key outcomes of the thesis and areas for future research

Implications for practice

Sleep is important in QoL in IBD. The work in this thesis has demonstrated lower QoL in people with poor sleep quality that is beyond that due to depression or IBD activity. Reduced QoL was also seen in people with insomnia, with a reduction of similar magnitude to that due to IBD activity. IBD-related disability was also seen to be worse in those with insomnia and those at risk of obstructive sleep apnoea. Consideration should be given to assessing sleep quality as a means of improving QoL in IBD, particularly in those in remission.

Depression is an important treatment target in fatigue in IBD. The work presented here on fatigue included the development of a structural equation model demonstrating sleep as a mediating variable in fatigue. The model also demonstrated the importance of depression in fatigue, suggesting that treating depression would have a valuable effect on improving fatigue. The latent profile analysis identified that the profile with the highest rates of severe fatigue had high rates of depression, with the other profiles having low rates of depression.

These results suggest that depression may define a specific population of people with fatigue and would be a high-value target for treatment to improve fatigue.

Opioids deleteriously influence sleep quality. The work here shows yet another negative outcome from opioid use in this population. Opioid use has been previously linked to poor IBD-related outcomes and worse QoL. The analysis in this thesis has also shown that opioid use is associated with worse sleep quality. There were also associations seen with the higher fatigue latent profiles described here, suggesting a role in fatigue in people with IBD.

Further research directions

Future research directions stemming from the work in this thesis are suggested below (see Figure 12.1).

Longitudinal studies incorporating polysomnography. A small number of longitudinal studies have incorporated subjective sleep quality with varying results, including some suggesting that IBD outcomes are related to sleep quality. No studies have utilised polysomnography to determine sleep quality and then consider longer-term IBD-related outcomes.

Interventional studies targeting sleep quality. Future research could consider interventional studies targeting improving sleep quality as a means of improving QoL in people with IBD and of improving IBD activity. Insomnia is likely the most common sleep disorder in people with IBD.[183] A pilot study of CBTi has been published, showing that this approach is feasible and acceptable to people with IBD.[190] Future research should extend this important work to show efficacy and consider the influence of this intervention on the IBD population.

Which population should be targeted for sleep-directed intervention needs careful consideration. Targeting sleep in someone with severely active IBD may have some benefit but it may be difficult to demonstrate any meaningful difference in outcomes given the severe nature of IBD-related symptoms in this group. Insomnia in people with inactive IBD may provide a target for CBTi where benefits may be readily shown in improving sleep and associated QoL. Similarly, people with mildly active IBD and poor sleep may be a suitable population to target.

Also of interest is the influence that successfully treating insomnia may have on the course of IBD itself. One may postulate that treating poor sleep in someone with inactive IBD may

extend the period of time they stay in remission, and perhaps yield a long-term reduction in rates of hospitalisation and medication escalation.

Develop a screening tool to identify those suitable for a sleep-targeted intervention. If interventional studies utilising methods such as CBTi prove efficacious, screening tools need to be developed to encourage identification and utilisation of CBTi.

Quantify the influence of IBD-related pro-inflammatory cytokines on sleep. Other areas of future research include attempting to quantify the influence of pro-inflammatory cytokines resulting from active IBD on sleep quality. The research here incorporating objective IBD activity and sleep quality was unable to achieve this because of the influence of IBD-related symptoms. A study could be considered including only people with no IBD-related symptoms and objectively active IBD on colonoscopy or MRI. Measurement of cytokines could be undertaken, and at-home sleep studies in the form of polysomnography performed.

This is of interest as consideration could be given to long-term monitoring of sleep in people with IBD. The identification of sub-clinical active IBD in people in long-term remission may allow treatment changes that prevent IBD activity ever reaching the level of symptoms. Sub-clinical IBD activity may be apparent in specific sleep changes as a result of pro-inflammatory cytokines. Future research might consider the use of under-the-mattress sleep monitoring as a potential means to detect sub-clinically active IBD.

This work is also relevant to the many other IMID, with the likelihood that similar gains in QoL could be made and similar approaches to disease monitoring might also be considered.

Longitudinal outcomes of latent profiles of fatigue. This research has defined latent profiles of fatigue. Further research is required to determine the longitudinal significance of these latent profiles and should incorporate objective measurement of IBD activity.

Evaluating treatment strategies for fatigue in IBD. The work in this thesis has, through SEM, identified depression as a high-value contributor to fatigue. Furthermore, latent profile analysis identified a profile with high rates of severe fatigue defined by high rates of depression. Interventional studies can now be designed using the insights from SEM to more accurately identify depression-mediated fatigue and determine the outcomes of conventional treatment of depression in this setting.

Obstructive sleep apnoea screening. Obstructive sleep apnoea has been demonstrated to be more common in IBD than in the general population, with the work in this thesis describing a

screening tool for identifying OSA in an IBD population. This screening tool should be trialled in an IBD clinic to further determine and validate its properties.

Conclusions

Sleep is an important biologic function and critical to overall health. The work in this thesis has established the existence of objective sleep quality differences between active and inactive IBD. It has also demonstrated complex factors influencing sleep because those in remission still experience higher levels of sleep dysfunction than the general population. The longitudinal implications of differences in objective sleep quality among those in IBD in remission remain to be determined. The role of IBD-related inflammatory cytokines in sleep requires further research, which could lead to development of a method of non-invasive monitoring of sub-clinical IBD activity.

Improving sleep quality has the potential to improve QoL in people with IBD and may influence IBD activity. Insomnia was associated with reduced QoL and has potentially suitable treatment in the form of CBTi, the effectiveness of which remains to be determined in an IBD population.

The work in this thesis has furthered the understanding of fatigue in IBD through SEM and latent profile analysis. This work has identified depression as a potential high-value target to improve fatigue. Interventional studies of treating depression in suitable subsets of IBD people with fatigue should be considered.

These new findings provide an important basis for further work with the aim of improving sleep and QoL in individuals living with IBD. The implications of this work extend to other IMID.

Appendices

Abstracts arising from thesis

Sleep disruption is associated with reduced quality of life in inflammatory bowel disease through its interaction with pain

A Barnes, R Mountifield, P619 Sleep disruption is associated with reduced quality of life in inflammatory bowel disease through its interaction with pain, *Journal of Crohn's and Colitis*, Volume 18, Issue Supplement_1, January 2024, Pages i1192–i1193, https://doi.org/10.1093/ecco-jcc/jjad212.0749

Abstract

Quality of life is reduced in people with inflammatory bowel disease. Poor sleep is prevalent in people with inflammatory bowel disease. This study aimed to investigate the influence of sleep on quality of life in people with inflammatory bowel disease.

Methods

An online questionnaire was administered through three tertiary IBD centres, social media and through Crohn's Colitis Australia. The questionnaire included the EQ-5D-5L measures of health-related quality of including EQ-5D utility score, EQVAS – visual analogue scale from 0-100 of quality of life and domains mobility, self-care, activities, pain and depression and anxiety. Measures of sleep included the Insomnia Severity Index (ISI), and the Pittsburgh Sleep Quality Index (PSQI). IBD activity was assessed using validated patient-reported scores. Demographic data and mental health scores were also obtained.

Results

Quality of life was lower in people IBD than the general South Australian population (utility score mean (SD) 0.79 (0.15) v 0.91(0.14)). Poor sleep and clinically significant insomnia were associated with lower quality of life (utility score 0.77 (0.15) and 0.71 (0.16) respectively, cohort 0.79 (0.15), $p < 0.0001$). Sleep quality scores moderately correlated with EQ-5D domains pain (Ro = 0.35), usual activities (Ro = 0.32), and depression–anxiety (Ro = 0.37) but not domains self-care or mobility. After adjusting for demographic variables, IBD anxiety, depression, and anxiety the pain domain continued to be influenced by sleep quality, sleep disturbance and sleep duration, and the usual activities domain continued to be influenced by daytime dysfunction (see Table 1).

Clinically significant insomnia was associated with a reduction of 13.6 (10.42–16.91) (univariate regression) in quality of life measured by EQVAS. Following introduction of demographic and IBD activity the reduction in EQVAS for clinically significant insomnia remained significant (10.11 (6.96–13.27)). Health-related quality of life scores (EQVAS) were significantly worse in those with clinically significant insomnia and active IBD than with active IBD alone (see Figure 1).

Conclusion

Health-related quality of life in IBD is influenced by aspects of sleep quality irrespective of IBD activity and mental health conditions. The presence of insomnia is associated with a significant decline health-related quality of life. Consideration should be given to sleep-targeting interventional studies in an IBD population.

Table 1: Pittsburgh Sleep Quality Index (PSQI) components and EQ-5D domains with univariate regression and multivariate regression for each PSQI component separately. Multivariate regression was then conducted with demographic variables, and then sequentially with IBD activity (as a binary variable with active IBD defined by Harvey–Bradshaw Index ≥ 5, Simple Clinical Colitis Activity Index >5) as well and then finally including depression and anxiety scores (Patient Health Questionnaire-9, Generalised Anxiety Disorder-7).

	Univariate	**Multivariate[a]**	**Multivariate[a] with IBD activity**	**Multivariate[a] with IBD activity, depression and anxiety**
	Coefficients (95% CI)	Coefficients (95% CI)	Coefficients (95% CI)	Coefficients (95% CI)
PSQI-sleep quality Depression–anxiety Pain Activities	0.44 (0.32-0.55)* 0.44 (0.34-0.54) * 0.29 (0.19-0.38) *	0.42 (0.31-0.53) * 0.36 (0.27-0.46) * 0.23 (0.14-0.33) *	0.38 (0.26-0.49) * 0.29 (0.19-0.38) * 0.19 (0.09-0.28) *	-0.03 (-0.12-0.06) 0.18 (0.09-0.29)* -0.012 (-0.11-0.084)
PSQI-daytime dysfunction Depression–anxiety Pain Activities	0.57 (0.45-0.68) * 0.43 (0.32-0.54) * 0.46 (0.37-0.55)*	0.54 (0.42-0.65) * 0.34 (0.24-0.44) * 0.40 (0.31-0.49) *	0.50 (0.38-0.62) * 0.24 (0.15-0.34) * 0.36 (0.27-0.46) *	-0.04 (-0.15-0.06)* 0.09 (-0.027-0.20) 0.12 (0.006-0.22) [#]
PSQI-disturbance Depression–anxiety Pain	0.55 (0.41-0.69) * 0.60 (0.48-0.72) *	0.52 (0.38-0.66) * 0.47 (0.35-0.59) *	0.46 (0.32-0.61) * 0.36 (0.24-0.48) *	0.0073 (-0.11-0.12) 0.25 (0.12-0.37)*

	Univariate	**Multivariate[a]**	**Multivariate[a] with IBD activity**	**Multivariate[a] with IBD activity, depression and anxiety**
	Coefficients (95% CI)	Coefficients (95% CI)	Coefficients (95% CI)	Coefficients (95% CI)
Activities	0.40 (0.29-0.52)*	0.32 (0.21-0.44) *	0.26 (0.14-0.38) *	0.068 (-0.050-0.19)
PSQI-duration Depression–anxiety Pain Activities	 0.20 (0.11-0.30) * 0,32 (0.24-0.41) * 0.15 (0.07-0.23)*	 0.18 (0.09-0.29) * 0.27 (0.20-0.36) * 0.11 (0.03-0.19) *	 0.15 (0.06-0.25) * 0.22 (0.15-0.30) * 0.08 (0.001-0.15)[#]	 -0.048 (-0.12-0.02) 0.17 (0.10-0.25)* 0.015 (-0.059-0.088)

*$p < 0.0001$, #$p < 0.05$

[a] Age, gender, IBD subtype, weight, biologic usage, smoker, alcohol, IBD surgery, opioid usage.

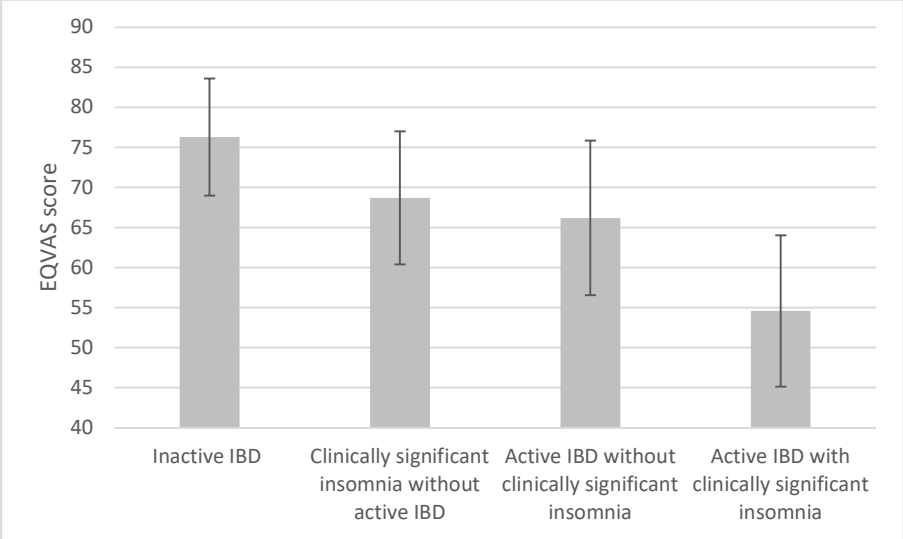

Figure 1: Differences in EQ-5D utility score and EQVAS for groups active IBD, active IBD with clinically significant insomnia (Insomnia Severity Index >15), and inactive IBD. One-way ANOVA for EQVAS (df = 3, F = 36.97, $p < 0.0001$) , all comparisons significant ($p < 0.001$), except 1v0 ($p = 0.21$) and 2v1 ($p = 0.94$).

Active inflammatory bowel disease is associated with reduced sleep efficiency and sleep architecture changes: Preliminary results of IBD-SLEEP

Barnes A, Mountifield R. Active inflammatory bowel disease is associated with reduced sleep efficiency and sleep architecture changes: Preliminary results of IBD-SLEEP, Australian Gastroenterology Week, Sept 2023, Brisbane, Australia.

Background and aim: Sleep abnormalities in the general population have been associated with increased all-cause mortality, and adverse health effects including cardiovascular disease and metabolic syndrome. Sleep disruption is associated with upregulation of pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF-α, that have also been implicated in the pathogenesis of IBD. Furthermore, disrupting sleep quality increases inflammation in mouse models of IBD. Subjectively reported sleep quality suggests active IBD is associated with poor sleep, reduced sleep efficiency, and longer sleep latency. Subjectively reported IBD activity has been associated with objectively assessed reduced sleep efficiency. This study aimed to assess the relationship between objective IBD activity and objective sleep quality.

Methods: Participants were recruited from a tertiary IBD unit and a private IBD service. Participants were required to be adults and have a confirmed diagnosis of IBD by a gastroenterologist. Participants were required to have a home sleep study in the form of polysomnography within 4 weeks of an objective assessment of IBD activity performed as per usual care. Objective assessment of IBD activity included MRI, colonoscopy, and faecal calprotectin (>250 ug/g). Pathology results within 4 weeks of the sleep study were also recorded. Current medications including corticosteroids were recorded. Associations assessed using Wilcoxon rank sum test or Student's t-test as appropriate.

Results: Twelve participants were recruited. Median age was 42 years, majority female (60%) and mostly Crohn's disease (75%). Objective IBD activity was assessed with MRI (5 cases), colonoscopy (7 cases – histology was available in 5 of these cases) and calprotectin (4 cases). One participant had histological active inflammation in the absence of endoscopic inflammation. No participant had an abnormal CRP. No participant was on corticosteroids during the sleep study. A quarter of the cohort had active IBD. Polysomnography (Table 1) showed that active IBD was associated with reduced sleep efficiency with a trend towards longer sleep latency. Total time available for sleep was also lower in those with active IBD. Sleep architectural (Table 1) changes saw similar REM sleep between active and inactive

IBD, with decreased NREM sleep in those with active IBD primarily as a reduction in stage 2 sleep.

Conclusion: Preliminary results suggest that active IBD is associated with overall reduced sleep time along with reduced sleep efficiency and sleep architecture changes. These alterations in sleep may reflect the disruptive effect of overnight bowel symptoms but may also conversely exacerbate IBD associated inflammation in addition to the established deleterious effects of poor sleep on quality of life and cardiovascular morbidity. Further data is required to examine these effects and longitudinal data is required to evaluate their significance.

Table 1: Polysomnography results and basic demographics by objectively active IBD. Comparisons made using Student's *t*-test or Wilcoxon rank sum test as appropriate.

	Active IBD	**Inactive IBD**	***p***
n	4	8	
Age (years)	42.5	41	
Female gender (*n*)	2	5	
Crohn's disease (*n*)	4	5	
Sleep efficiency (%)	73 .4 (2.0)	86.6(1.8)	0.0012
Time for sleep (mins)	422.4 (56.9)	497.9 (43.5)	0.028
Sleep latency (mins)	49.2 (25.7-68.5)	14.7 (10.2-19.0)	0.07
REM latency (mins)	118.7 (32.4)	125.8 (47.2)	0.79
Total sleep (mins)	303.5 (29.9)	432 (40.6)	0.0002
NREM sleep (mins)	228.4 (49.7)	354.9 (39.4)	0.0004
REM sleep (mins)	75 (7.7)	77 (7.1)	0.86
Stage1 (mins)	22.5 (13.4-35.1)	18.8 (11.5-42.6)	0.93
Stage 2 (mins)	136 (18.8)	223.4 (53.8)	0.016
Slow-wave sleep (mins)	64.2 (36.6-95.1)	110.2 (85.6-115.0)	0.23

Influence of inflammatory bowel disease activity on fatigue in Crohn's disease is mediated via sleep and depression.

Barnes A, Mountifield R. Influence of inflammatory bowel disease activity on fatigue in Crohn's disease is mediated via sleep and depression. Australian Gastroenterology Week, Sept 2023, Brisbane, Australia.

Background and aim: Fatigue is a common symptom in people with inflammatory bowel disease with a systemic review and meta-analysis reporting a prevalence of 48%. Frequently reported associations with fatigue in an inflammatory bowel disease population include IBD activity, sleep disturbance, anxiety and, depression. This study aimed to investigate the relationship between fatigue, sleep and IBD activity through correlation analysis, and structural equation modelling.

Methods: An online questionnaire was administered through three tertiary IBD centres, social media and through Crohn's Colitis Australia. Fatigue was assessed via the Functional assessment of chronic illness measurement system fatigue subscale (FACIT-FS), a validated assessment of fatigue and its severity. Validated measures of anxiety (GAD7), depression (PHQ9), IBD activity (HBI) and sleep quality (PSQI) were also included. Variables with significant correlations based on correlational analysis were then included in a structural equation model for an outcome of fatigue score (FACIT-FS) and with sleep as a mediating variable. Direct and indirect effects were then calculated.

Results: There were 575 responses to the online questionnaire, with 328 of these having Crohn's disease which were subsequently included in the analysis. The median age was 41, majority female (77%), median disease duration 12 years, with the majority on biologics (63%).

A structural equation model with sleep as a mediating variable for fatigue was developed from correlation analysis and following optimising demonstrated good fit (see Figure 1). The effect of anxiety on fatigue is via its effect on sleep and depression and its direct influence appeared to improve fatigue. The indirect effect of depression on fatigue, mediated via its influence on sleep, was negligible. The effect of IBD activity on fatigue was primarily via indirect paths – via its influence on depression and sleep. A reduction of severe depression (PHQ9 = 15) to mild depression (PHQ9 = 5) will result in a decrease in fatigue score of 15 points – to put this in context this would take someone with a score indicated severe fatigue and move them into the moderate fatigue range.

Conclusion: A structural equation model was developed for an outcome of fatigue with sleep and depression as mediating variables. IBD activity influenced fatigue largely through its effects on depression and sleep. The influence of anxiety on fatigue was largely indirect. In a Crohn's patient with fatigue consideration should be given to treating depression or active IBD given their relative contribution to fatigue score.

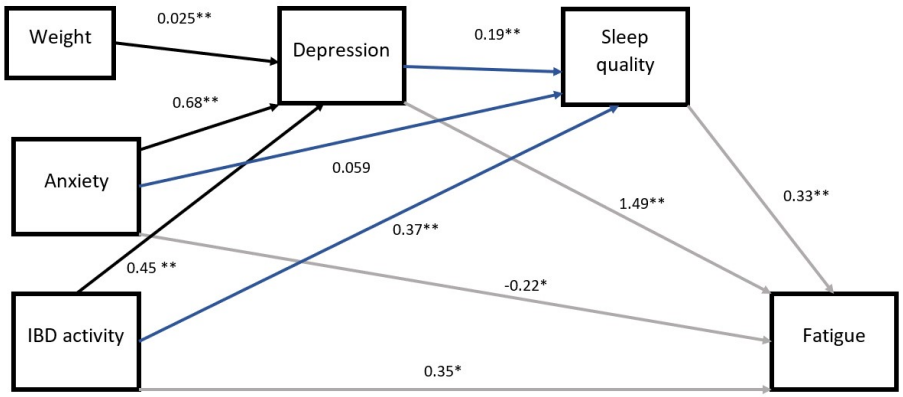

Figure 1: Structural equation modelling using multivariate linear regression. Incorporated all significant variables from correlational analysis. RMSEA 0.026, SRMR 0.016, CFI 0.99, TLI 0.99, $\chi^2(N) = 2.51$, $\chi^2 p = 0.28$. Regression coefficients included on paths. *$p < 0.05$, ** $p < 0.001$.

Table 1: Direct and indirect effects of structural equation model for fatigue score incorporating depression, anxiety, sleep quality, IBD activity, and weight.

Variable	Total effects	Indirect effect	Direct effect	Clinically relevant contribution
Depression	1.56**	0.066*	1.49**	15.6
Sleep quality	0.33**	No path	0.33**	1.6
IBD activity	1.18 **	0.83 **	0.36*	5.8
Anxiety	0.85 **	1.01 **	-0.23*	8.5
Weight	0.039 *	0.039*	No path	-

* $p < 0.05$, ** $p < 0.005$.

Should patients with inflammatory bowel disease and depression be given anti-tumor necrosis factor therapy?

Barnes A, Mountifield R. Should patients with inflammatory bowel disease and depression be given anti-tumor necrosis factor therapy? Australian Gastroenterology Week, Sept 2023, Brisbane, Australia.

Background and aim: Depression is common in the inflammatory bowel disease population. There has been investigation in the influence of anti-TNF biologics on depression in IBD and non-IBD populations with longitudinal studies and small randomised controlled trials showing conflicting results. We performed an analysis regarding the relationship between anti-TNF biologics and depression.

Methods: An online questionnaire was administered through three tertiary IBD centres, social media and through Crohn's Colitis Australia. IBD activity (SCCAI and HBI), IBD data, demographic and IBD medication were recorded. Depression was assessed with patient health questionnaire 9 (PHQ9) with clinically significant depression defined as PHQ9 >15. Inadequate completion of any score or index led to that result not being included.

Results:There were 575 responses to the online questionnaire, with 328 of these having Crohn's disease, median age of 42 years, 77% female and IBD disease duration of 10 years (median). Clinically significant depression was seen in 20.8% of the cohort (see Table 1). Anti-TNF usage was present in 30.4% of the cohort. The rate of clinically significant depression in those on anti-TNF was (13.7% v 24.0% $p = 0.005$) – both adalimumab ($p = 0.026$) and infliximab ($p = 0.046$) had lower rates of clinically significant depression than the non-anti-TNF population. Whilst Anti-TNF monotherapy was associated with lower rates clinically significant depression, combination therapy with immunomodulator and anti-TNF was not associated with significant risk reduction ($p = 0.15$). Corticosteroids and anti-depressants were associated with higher rates of clinically significant depression.

Clinically significant depression was associated with female gender ($p = 0.042$), obesity ($p = 0.001$) and increased body weight ($p = 0.0005$). There was a trend to younger age ($p = 0.06$), and shorter IBD disease duration ($p = 0.056$). Depression was not associated with previous surgery for IBD, or IBD subtype. There was no difference in the anti-TNF and non-anti-TNF groups for any of these variables. An odds ratio for clinically significant depression for those on anti-TNF was 0.52 (0.32–0.85) $p = 0.01$.

Conclusion: In our cohort anti-TNF was associated with lower rates of clinically significant depression in IBD patients compared with those treated with other therapies. This apparent benefit was lost with combination therapy. This finding was not explained by IBD activity or other demographic nor disease-specific variables. Consideration could be given to favouring anti-TNF as preferred IBD treatment in people with concurrent depression.

Table 1: IBD medications and opioids and anti-depressants by proportion with clinically significant depression as defined by Patient Health Questionnaire 9 >15.

	Clinical depression (%)	***p***
N = 575	20.8	
5ASA	19.8	0.7
Corticosteroid	32.7	0.028
Immunomodulator	21.1	0.90
Thiopurine	20.6	0.92
Methotrexate	22.9	0.71
Biologic	17.4	0.032
Vedolizumab	18.0	0.60
Ustekinumab	25.0	0.75
Anti-TNF	13.7	0.005
Anti-TNF and immunomodulator	16.8	0.15
Anti-TNF monotherapy	12.1	0.005
Opioids	24.7	0.36
Ant-depressants	40.5	0.0001

Fatigue in patients with inflammatory bowel disease can be described as three distinct classes.

Barnes A, Mountifield R. Fatigue in patients with inflammatory bowel disease can be described as three distinct classes. Australian Gastroenterology Week, Sept 2023, Brisbane, Australia.

Background and aim: Fatigue is prevalent in people with inflammatory bowel disease (IBD) and has been associated with IBD activity, sleep quality, depression, and anxiety. This study aimed to identify fatigue profiles through latent class analysis.

Methods: An online questionnaire was administered through three tertiary IBD centres, social media and through Crohn's Colitis Australia. Fatigue was assessed via the Functional assessment of chronic illness measurement system fatigue subscale (FACIT-F), a validated assessment of fatigue and its severity with a score below 32 suggestive of severe fatigue, with population norm score of 43. Validated measures of anxiety (GAD7), depression (PHQ9), IBD activity (HBI and SCCAI) and sleep quality (PSQI) were also included. Latent class analysis was performed including severe fatigue, poor sleep (PSQI >5), clinically active IBD (HBI >5 or SCCAI >2), and clinically significant depression (PHQ9 >15) and anxiety (GAD7 >10).

Results: In a cohort of 559 respondents the median age was 41 years (32–52), with the majority female (77%), the majority had Crohn's disease (62%). Severe fatigue was seen in 62%. Latent class analysis identified three classes (see Figure 1) differing by probability of severe fatigue—low fatigue class (p = 0.46), poor sleep and active IBD class (p = 0.66), and a poor mental health class (p = 0.93)—the only class with moderate–high levels of anxiety or depression. Those in the poor mental health class were more likely to have ulcerative colitis, be under sixty years of age, be female, and be on opioids or corticosteroids. Those in the poor sleep and active IBD class were more likely to be on opioids and be over sixty years of age.

Conclusion: Latent class analysis identifies three classes of fatigue in an IBD cohort with associations with specific risk factors for fatigue along with specific IBD and demographic attributes. These classes include a poor mental health class associated with a high level of severe fatigue and a poor sleep and active IBD class associated with moderate levels of severe fatigue. This has implications for the classification of fatigue in IBD and treatment algorithms.

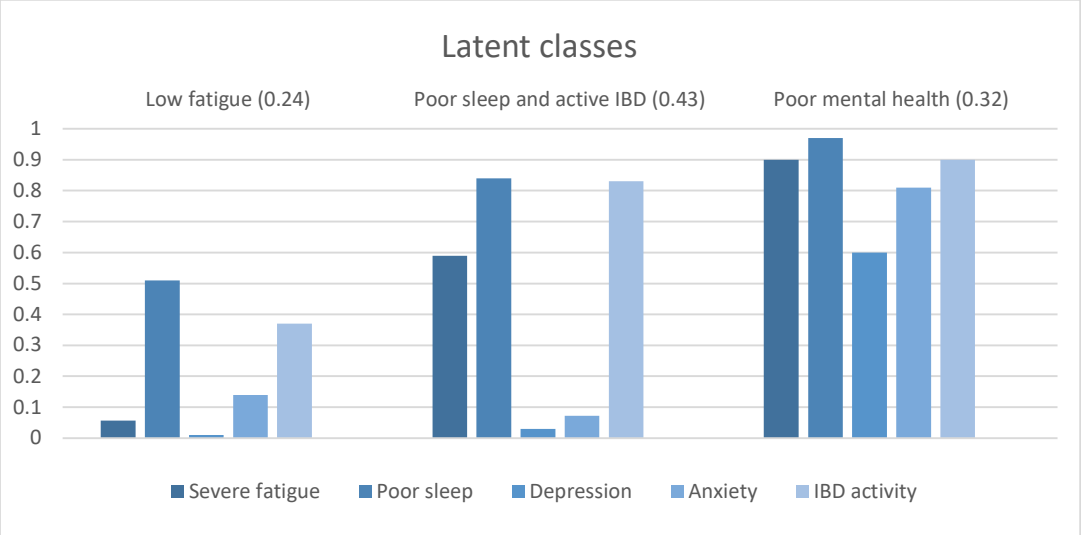

Figure 1: Latent classes – low fatigue, poor sleep and active IBD, poor mental health – defined by probability of severe fatigue (0.42, 0.66, 0.93 respectively). Proportion of cohort in each as follows: low fatigue (0.24), poor sleep and active IBD (0.43), and poor mental health (0.32).

Insomnia is common in IBD and associated with increased disability and abdominal pain.

Barnes A, Andrews J, Bryant RV, Mountifield R. P847 Insomnia is common in IBD and associated with increased disability and abdominal pain. *Journal of Crohn's and Colitis*, Volume 17, Issue Supplement_1, February 2023, Page i972, https://doi.org/10.1093/ecco-jcc/jjac190.0977

Background

Insomnia is common in those with chronic medical conditions. Insomnia is associated with decreased quality of life and is readily treatable through cognitive behavioural therapy for insomnia (CBTi). This study aimed to describe the associations with insomnia in an IBD population and its relationship with IBD-related disability.

Methods

An online questionnaire was administered through three tertiary IBD centres, social media and through a patient advocacy group (Crohn's Colitis Australia). The questionnaire included the Insomnia Index Severity (ISI), a validated assessment of insomnia and its severity, with a score over 14 considered clinically significant insomnia. Validated measures of anxiety (GAD-7), depression (PHQ-9), physical activity (sIPAQ), and disability (IBD-DI-SR) were also utilised. IBD activity was assessed clinical IBD activity scores (HBI or SCCAI).

Results

There were 670 responses included in the analysis. Median age was 41 years (32–70), with the majority being female (78%), and 57% having Crohn's disease. The mean disease duration was 11.9 years (10.4), 30% had undergone surgery for IBD and around half were on biologics (50.5%).

The mean ISI score was 12.7 (6.09). Over a third of the cohort had at least moderate insomnia (ISI >15). A one-way ANOVA revealed differences in disability scores (IBD-DI-SR) (see Table 1) between insomnia severity groups ($F(3,619) = 20.99$, $p < 0.001$), with disability scores worsening with increasing severity of insomnia.

Multivariable logistic regression analysis (see Table 2) revealed that clinically significant insomnia was significantly associated with clinically active IBD, abdominal pain, clinically significant anxiety, and clinically significant depression.

Conclusion

Insomnia is common in people with IBD with at least one-third reporting moderate insomnia. Given that insomnia was associated with increased disability, consideration should be given for routine screening for insomnia in IBD patients. Mental health conditions and ongoing pain should be addressed with consideration given to referral for CBTi.

Table 1: Insomnia Severity Index (ISI) threshold scores with ANOVA used to demonstrate significant difference between disability scores between groups (IBD-DI-SR), $F(3,619) = 20.99$, $p < 0.001$). IBD-DI-SR: IBD-Disability Index self-report form.

ISI thresholds	***n* (%)**	**IBD-DI-SR scores, mean (SD)**
No significant insomnia	125 (20)	-0.56 (4.6)
Subthreshold insomnia	268 (43)	-2.6 (5.1)
Moderate insomnia	178 (29)	-5.1 (6.5)
Severe insomnia	52 (8)	-5.9 (7.4)

Table 2: Univariate and multivariate regression for outcome of clinically significant insomnia. This was optimised by minimising the maximum likelihood ratio. IBD – inflammatory bowel disease. Clinically active IBD assessed using the Harvey–Bradshaw Index and the Simple Clinical Colitis Activity Index as appropriate.

	Univariate regression, odds ratio, 95% CI, *p* value	**Multivariate regression, odds ratio 95% CI, *p* value**
Age	0.99 (0.94-1.01) $p = 0.57$	
Gender	0.84 (0.56-1.24) $p = 0.39$	
Obesity	1.23 (0.88-1.74) $p = 0.21$	
Crohn's disease	0.88 (0.63-1.22) $p = 0.44$	
IBD disease duration	0.99 (0.98-1.01) $p = 0.52$	
Previous surgery for IBD	0.88 (0.62-1.24) $p = 0.46$	
Mediations for sleep	1.30 (0.82-2.07) $p = 0.26$	
Corticosteroids	1.33 (0.77-2.29) $p = 0.31$	
Opioids	1.74 (1.12-2.72) $p = 0.014$	
Biologic	0.86 (0.65-1.24) $p = 0.51$	
Immunomodulators	1.05 (0.75-1.47) $p = 0.77$	
Current smoker	1.69 (0.91-3.15) $p = 0.096$	
Clinically active IBD	3.89 (2.31-6.57) $p < 0.001$	2.07 (1.17-3.69) $p = 0.013$
Abdominal pain	2.52 (1.79-3.54) $p < 0.001$	2.17 (1.45-3.24) $p < 0.001$
Nocturnal diarrhoea	1.33 (0.84-2.09) $p = 0.22$	
Clinically significant anxiety	4.54 93.19-6.43) $p < 0.001$	2.52 (1.65-3.84) $p < 0.001$
Clinically significant depression	6.06 (4.12-8.92) $p < 0.001$	3.91 (2.44-6.28) $p < 0.001$
Total METs	0.99 (0.99-1.00) $p = 0.45$	
Vigorous METs	0.99 (0.99-1.00) $p = 0.37$	
Methotrexate	1.79 (1.00-3.20) $p = 0.048$	

Is the burden of obesity in IBD bigger than just weight?

Madigan S, Mountifield R, Barnes A. P679 Is the burden of obesity in IBD bigger than just weight? *Journal of Crohn's and Colitis*, Volume 17, Issue Supplement_1, February 2023, Page i810, https://doi.org/10.1093/ecco-jcc/jjac190.0809

Background

In the past IBD has been thought to cause low body weight however current estimates show that 15–40% of those with IBD are obese. Obesity is a pro-inflammatory state and has been linked to disease processes such as psoriasis and rheumatoid arthritis. There is some limited data to suggest that obesity also affects disease activity in IBD. In addition, medical therapy for IBD such as corticosteroids and TNF-α inhibitors are associated with weight gain. The aim was to determine the relationship between obesity and IBD disease severity. And also to determine the relationship between obesity, depression, anxiety and QoL in those with IBD.

Methods

As part of the IBD-SLEEP study a survey was emailed to patients via tertiary hospital IBD unit email lists, private gastroenterology group email lists and advertised online. IBD activity was assessed using the Harvey–Bradshaw Index and the Simple Crohn's Colitis Index as appropriate. The survey included measures of clinically significant depression (PHQ9 >10) and anxiety (GAD7 >10), as well as disability (IBD-DI reduced form) and quality of life (EQ-5D-5L).

Results

They were 585 responses with mean age of 42 years (SD 13). The majority were female (80%) and had Crohn's disease (61%). Mean weight of cohort was 79.2kg (SD 20), mean BMI was 28 (SD 7), with 61% overweight (BMI >25), and 38% obese (BMI >30). People with obesity were more likely to have active disease (HBI or SCCAI >5) in those with Crohn' disease (OR 2.39 (1.47-3.89), $p < 0.001$) but not ulcerative colitis (OR 1.26 (0.68–2.31), $p = 0.46$). Obese patients were also found to have higher levels of disability (IBD-DI reduced form, $p < 0.001$) and lower quality of life (EQVAS, $p < 0.001$). Interestingly there was an association between obesity and depression (PHQ9 >10, OR 2.06 (1.42–2.99), $p < 0.001$) but not obesity and anxiety (GAD7 >10, OR 1.03, (0.74–1.45), $p = 0.16$).

Conclusion

Obesity is not only a risk factor for metabolic disease but is also associated with active IBD in those with Crohn's disease. Obesity was also associated with clinically significant depression, increased disability, and lower quality of life. Although causation is not established, consideration should be given to more aggressive management of obesity in an IBD outpatient setting.

A systematic review and meta-analysis of sleep quality in inactive inflammatory bowel disease.

Barnes A, Mountifield R, Bampton P, Murkherjee S. A systematic review and meta-analysis of sleep quality in inactive inflammatory bowel disease. UEG Week, Oct 2022, Vienna Austria.

Objective

Poor sleep in people with inflammatory bowel disease (IBD) has been demonstrated to be prevalent and has been associated with disease activity. This meta-analysis aimed to assess the prevalence of poor sleep in inactive inflammatory bowel disease and in controls by considering cohort and cross-sectional studies.

Methods

Electronic databases were searched for publications from inception to November 1st, 2021. Meta-analysis was performed according to the preferred reporting item for systematic reviews and meta-analyses (PRISMA) guidelines. Quality of studies was assessed using the modified Newcastle–Ottawa Scale or Newcastle–Ottawa Scale as appropriate. Poor sleep and IBD activity were defined according to self-reported subjective sleep measures. A random effects model was used to determine the standardised mean difference between poor sleep in inactive IBD and healthy controls. Publication bias was assessed by funnel plot and Egger's test.

Results

519 studies were screened with 9 studies included in the meta-analysis incorporating a total of 729 people with IBD and 508 controls. Publication date ranged from 2006 to 2020. A random effects model showed a standardised mean difference with poor sleep being more frequent in those with inactive IBD than controls with moderate effect size (Hedge's g 0.41, CI (0.22–0.59) and no significant heterogeneity. Funnel plot was symmetric and Egger's negative (p = 0.37).

Conclusion

Poor sleep is more common in individuals with inactive IBD than healthy controls. This finding suggests that IBD activity may not be the sole driver of the observed poor sleep in this population. Further studies should consider potential mechanisms to explain this result

including the role of sub-clinical inflammation and psychosocial factors that may influence sleep quality in people with IBD.

Poor sleep in IBD is associated with active disease and mental health conditions and outcomes such as increased fatigue, increased disability, and poor quality of life.

Barnes A, Mountifield R, Andrews J, Bampton P, Mukherjee S. Poor sleep in IBD is associated with active disease and mental health conditions and outcomes such as increased fatigue, increased disability, and poor quality of life. UEG Week, Oct 2022, Vienna Austria.

Objective: Sleep has become of increasing interest in inflammatory bowel disease (IBD) as a patient report outcome and as a possible exacerbating factor or extra-intestinal manifestation. This study aimed to document the associations with poor sleep in a IBD and its relationship to other significant patient report outcomes such as disability and quality of life.

Methods: As part of the IBD-SLEEP study a questionnaire was distributed to tertiary hospital IBD mailing lists and advertised through social media and Crohn's Colitis Australia. The questionnaire included validated instruments assessing IBD activity (HBI and SCCAI), sleep quality (Pittsburgh Sleep Quality Index), physical activity (international physical activity questionnaire), depression (PHQ9), anxiety (GAD7), fatigue (FACIT-F), disability (IBD-DI reduced form), and quality of life (EQ-5D-5L). Participants were also asked about their inflammatory bowel disease including medications, complications, and other comorbidities.

Results: There was 544 participants who completed the entire questionnaire. Mean age was 42 years (SD 13), 61% had Crohn's disease, and median disease duration was 10 years (IQR 3–17). Poor sleep quality as assessed by PSQI >5 was associated with female gender (p = 0.043), increased body weight (p = 0.0005), patient-reported active IBD (HBI >5, SCCAI >5, $p < 0.0001$), clinically significant depression (PHQ9 >15, $p < 0.0001$), and clinically significant anxiety (GAD7 >10, $p < 0.0001$), but not physical activity in the form of total sitting time, vigorous activity, and total activity (METs). Poor sleep quality was associated with increased disability (IBD-DI reduced form, $p < 0.0001$), worse quality of life (EQVAS, $p < 0.0001$), and higher reported fatigue levels (FACIT-F, $p < 0.0001$).

Conclusion: IBD patient-reported sleep quality was associated with patient-reported active disease and mental conditions. Poor sleep quality was associated with worse patient-reported outcomes such as fatigue, disability and quality of life. Consideration should be given in IBD clinic to assessing and addressing sleep quality.

Poor sleep in patients with clinically inactive inflammatory bowel disease is characterized by longer sleep latency, lower sleep efficiency, and insomnia and is associated with greater anxiety and disability.

Barnes A, Mountifield R. Poor sleep in patients with clinically inactive inflammatory bowel disease is characterized by longer sleep latency, lower sleep efficiency, and insomnia and is associated with greater anxiety and disability. Australian Gastroenterology Week, Sept 2022, Sydney, Australia.

Background: Sleep has become of increasing interest in inflammatory bowel disease (IBD) as a patient report outcome and as a possible exacerbating factor or extra-intestinal manifestation. Poor sleep in active IBD has been largely attributed to IBD symptom related sleep disturbance, with the causes of poor sleep in inactive IBD more complex. This study aimed to examine sleep in inactive IBD and its associations with mental health and disability.

Methods: As part of the IBD-SLEEP study a questionnaire was distributed to tertiary hospital IBD mailing lists and advertised through social media and Crohn's Colitis Australia. The questionnaire included validated instruments assessing IBD activity (HBI and SCCAI), sleep quality (Pittsburgh Sleep Quality Index, PSQI), depression (PHQ9), anxiety (GAD7). Participants were included in this analysis if they met criteria for clinically inactive IBD (SCCAI <5 or HBI <5). Poor sleep was defined as PSQI >5. An active mental health condition was defined as clinically significant anxiety (GAD7 >10), or clinically significant depression (PHQ9 >10). Regression was performed to examine associations between sleep parameters in participants with inactive IBD and psychological and disability variables.

Results: 148 responses met inclusion criteria—median age 40 (32–50), Crohn's disease in 63%, female gender in 31%. Severe excessive daytime sleepiness was seen in 9.2% (ESS >15), and clinically significant insomnia was seen in 24.5% (ISI >15). Those with poor sleep exhibited longer sleep latency ($p < 0.001$) and lower sleep efficiency ($p < 0.001$). Univariate regression was significant for higher disability, clinically significant anxiety, clinically significant depression, higher levels of fatigue, lower quality of life scores and clinically significant insomnia. The final model included clinically significant insomnia (OR 1.53 (0.25–2.81)), clinically significant anxiety (OR 1.43 −0.13–3.04), and higher disability (OR 0.16 (0.01–0.31)).

Conclusions: Poor sleep in clinically inactive IBD was characterised by longer sleep latency and lower sleep efficiency, which is consistent with the rates of clinically significant

insomnia seen in this cohort. Poor sleep was associated with clinically significant anxiety and greater disability, and thus has the potential to negatively affect quality of life even when inflammation is well controlled.

Active IBD and mental health conditions have an additive deleterious effect on sleep quality.

Barnes A, Mountifield R. Active IBD and mental health conditions have an additive deleterious effect on sleep quality. Australian Gastroenterology Week, Sept 2022, Sydney, Australia.

Background: Sleep is of increasing interest in inflammatory bowel disease (IBD) as a patient-reported outcome and as a possible exacerbating factor or extra-intestinal manifestation of IBD. IBD activity and mental illness have both been seen as contributors to poor sleep in this population. This study aimed to look at the relative contributions of active disease and mental health conditions to aspects of sleep quality, sleepiness and insomnia.

Methods: As part of the IBD-SLEEP study a questionnaire was distributed to tertiary hospital IBD mailing lists and advertised through social media and Crohn's Colitis Australia. The questionnaire included validated instruments assessing IBD activity (HBI and SCCAI), sleep quality (Pittsburgh Sleep Quality Index, PSQI), physical activity (international physical activity questionnaire), depression (PHQ9), anxiety (GAD7). Participants were included in the analysis if they met criteria for poor sleep quality (PSQI >5). An active mental health condition (AMHC) was defined as clinically significant anxiety (GAD7 >10), or clinically significant depression (PHQ9 >10). Active IBD was defined by SCCAI ≥5 or HBI ≥5. Patients were classified into groups as inactive IBD and no active mental health condition, active IBD and no active mental health condition, active mental health condition and inactive IBD, an active mental health condition and active IBD. One-way ANOVA was performed, with pairwise comparison performed (Tukey), Bernoulli's correction applied as appropriate.

Results: 490 participants met criteria for poor sleep quality (PSQI >5), with mean age 42.1 (SD 13.0), with 56.1% having Crohn's disease, and mean disease duration 11.8 years (SD 10.5). The majority (55.7%) met criteria for clinically significant insomnia (ISI >15). Criteria for clinically significant anxiety (GAD7 >10) were seen in 47.3%, and clinically significant depression (PHQ9 >10) seen in 35.9%.

Table 1 reports sleep scores using ANOVA for group comparisons. Sleep scores overall were better in those with inactive IBD and without mental health conditions. Sleep efficiency (a measure of time asleep as opposed to time in bed) and sleep duration were worse in those with active IBD alone, with an additive effect again seen if mental health disorders coexisted. Sleep efficiency and sleep duration were not impaired in the presence of anxiety and depression alone. An additive effect with active IBD and active mental health condition was

seen in overall sleep quality, sleepiness, insomnia severity and most sleep scores, with the exception of sleep latency which was similar across groups. No significant difference in sleep medication usage was seen across groups.

Conclusion: In an IBD cohort with poor sleep, IBD activity and mental health conditions both contributed to poor sleep quality, sleepiness and insomnia severity. Active IBD was associated with worse sleep efficiency and sleep duration, whereas anxiety and depression alone were not associated with a difference in sleep duration. However, there was an additive effect on various aspects of sleep quality with concurrence of an active mental health condition along with active IBD.

Opioids, steroids and medications for anxiety and depression are associated with worse sleep quality, higher disability, and lower quality of life in people with IBD.

Barnes A, Mountifield R. Opioids, steroids and medications for anxiety and depression are associated with worse sleep quality, higher disability, and lower quality of life in people with IBD. Australian Gastroenterology Week, Sept 2022, Sydney, Australia.

Background: Sleep has become of increasing interest in inflammatory bowel disease (IBD) as a patient-reported outcome and as a possible exacerbating factor or extra-intestinal manifestation. This study aimed to explore the influence of medications on sleep quality and quality of life.

Methods: As part of the IBD-SLEEP study a questionnaire was distributed to tertiary hospital IBD mailing lists and advertised through social media and Crohn's Colitis Australia. The questionnaire included validated instruments assessing IBD activity (HBI and SCCAI), sleep quality (Pittsburgh Sleep Quality Index), fatigue (FACIT-F), disability (IBD-DI reduced form), and quality of life (EQ-5D-5L). Participants were also asked about their inflammatory bowel disease including medications, complications, and other comorbidities. Medications were subdivided into groups: amino salicylate type medications (5ASA), immunomodulators, biologics and corticosteroids. Other medications including medications for sleep, pain and mental health conditions were recorded.

Results: There was 544 participants who completed the questionnaire. Mean age was 42 years (SD 13), 61% had Crohn's disease, and median disease duration was 10 years (IQR 3–17). IBD-related medications included biologics in 50.6% of the cohort, immunomodulators in 34.5%, 5ASA in 32.1%, and steroids in 9.1%. People on steroids had comparatively worse sleep quality ($p = 0.0027$), were more likely to have active disease and lower quality of life (EQVAS $p < 0.0001$) and higher disability scores ($p < 0.0001$). Those on biologics and immunomodulators had comparatively lower levels of sleepiness (ESS, $p = 0.001$, and $p = 0.003$ respectively) and biologics were associated with lower insomnia scores ($p = 0.003$), with no difference in IBD activity ($p = 0.62$). Opioid medications were associated with lower sleep quality ($p < 0.0001$), higher levels of fatigue (FACIT-F, $p = 0.0063$), lower quality of life scores (EQVAS, $p = 0.0001$), and higher disability scores ($p = 0.0032$). People who had medications for anxiety or depression had worse sleep quality scores ($p = 0.0004$), higher sleep apnoea screening scores ($p < 0.0001$, noting a higher BMI in this group), higher levels

of fatigue (FACIT-F, $p = 0.0056$), lower quality of life scores (EQVAS, $p < 0.0001$), and higher disability scores ($p < 0.0001$).

Conclusion: Sleep quality, disability and quality life were adversely associated with steroid usage, opioid medication use, and anxiety or depression medication use. Biologic or immunomodulator usage may be associated with decreased sleepiness and lower rates of insomnia.

A systematic review and meta-analysis of inflammatory bowel disease activity and sleep quality

Barnes A, Spizzo P, Mountifield R, Bampton P, Andrews J, Fraser R, Mukherjee S. P008 A systematic review and meta-analysis of inflammatory bowel disease activity and sleep quality. *SLEEP Advances*, Volume 2, Issue Supplement_1, October 2021, Page A24, https://doi.org/10.1093/sleepadvances/zpab014.057

Background

Poor sleep quality has been associated with active inflammatory bowel disease (IBD) in several studies. This review examines sleep quality in people with active IBD and in those in remission, with meta-analyses performed, considering subjective and objective sleep quality and IBD activity.

Methods

Electronic databases were searched from inception to December 1st 2020. A random effects model was used with separate meta-analyses performed for objective and subjective sleep and IBD activity, considering sleep quality in active and inactive IBD.

Results

19 studies were included in the qualitative review representing 4972 IBD patients. Subjective IBD activity (11 studies) was associated with subjective sleep quality with pooled odds ratio (OR) for subjective poor sleep in active IBD compared to remission of 3.04 (95% CI 2.41–3.83). Including only studies with objective sleep measures (5 studies), sleep efficiency was lower in those self-reporting active IBD and time awake post sleep onset was higher in those with active IBD. Objective IBD activity was associated with subjective poor sleep (4 studies), with pooled OR of 6.64 95% CI (3.02–14.59). Insufficient data was available to consider objective IBD activity and objective sleep quality.

Conclusion

IBD activity is associated with poor sleep using subjective and objective measures of sleep quality. This poor sleep manifests as decreased sleep efficiency and increased number of waking episodes post sleep onset. The relationship between objective IBD activity and sleep requires further investigation.

Co-authorship declaration form

In accordance with Clause 5, 7 and 8 in the HDR Thesis Rules, a student must sign a declaration that the thesis does not contain any material previously published or written by another person except where due reference is made in the text or footnotes. There can be no exception to this rule.

a. Publications or significant sections of publications (whether accepted, submitted or in manuscript form) arising out of work conducted during candidature may be included in the body of the thesis, or submitted as additional evidence as an appendix, on the following conditions:
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   II. they are formatted in the same way as the other chapters (i.e. not presented as reprints unless as an appendix), whether included as separate chapters or integrated into chapters
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STUDENT DETAILS

Student Name	Alexander Barnes
Student ID	
College	College of Medicine and Public Health
Degree	PhD
Title of Thesis	Dissecting the complex interaction between inflammatory bowel disease and sleep

PUBLICATION 1

This section is to be completed by the student and co-authors. If there are more than four co-authors (student plus 3 others), only the three co-authors with the most significant contributions are required to sign below.

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Full Publication Details	Alex Barnes, Réme Mountifield, Justin Baker, Paul Spizzo, Peter Bampton, Jane M Andrews, Robert J Fraser, Sutapa Mukherjee, A systematic review and meta-analysis of the prevalence of poor sleep in inflammatory bowel disease, *SLEEP Advances*, Volume 3, Issue 1, 2022, zpac025, https://doi.org/10.1093/sleepadvances/zpac025
Section of thesis where publication is referred to	Chapter three

Student's contribution to the publication

80	%	Research design
80	%	Data collection and analysis
75	%	Writing and editing

Outline your (the student's) contribution to the publication:

Alex Barnes: responsible for study concept and design, data acquisition, analysis and data interpretation, drafting of manuscript, critical revision of the manuscript.

APPROVALS

By signing the section below, you confirm that the details above are an accurate record of the students contribution to the work.

Name of Co-Author 1 Réme Mountifield Signed  Date:7/2/24

/

Name of Co-Author 2 Sutapa Mukherjee Signed  Date 30/1/24

Name of Co-Author 3 Paul Spizzo Signed  Date 8/1/24

PUBLICATION 2

This section is to be completed by the student and co-authors. If there are more than four co-authors (student plus 3 others), only the three co-authors with the most significant contributions are required to sign below.

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Full Publication Details	Barnes A, Mountifield R, Baker J, Spizzo P, Bampton P, Mukherjee S. Systematic review and meta-analysis of sleep quality in inactive inflammatory bowel disease. JGH Open. 2022 Sep 29;6(11):738-744. doi: 10.1002/jgh3.12817. PMID: 36406652; PMCID: PMC9667405.
Section of thesis where publication is referred to	Chapter six

Student's contribution to the publication			
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	75	%	Writing and editing

Outline your (the student's) contribution to the publication:

Alex Barnes: responsible for study concept and design, data acquisition, analysis and data interpretation, drafting of manuscript, critical revision of the manuscript.

APPROVALS

By signing the section below, you confirm that the details above are an accurate record of the students contribution to the work.

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PUBLICATION 3

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Full Publication Details	Barnes, A., Spizzo, P., Bampton, P., Andrews, J.M., Fraser, R.J., Mukherjee, S. and Mountifield, R. (2023), Examining the influence of inflammatory bowel disease medications on sleep quality. JGH Open, 7: 190-196. https://doi.org/10.1002/jgh3.12871
Section of thesis where publication is referred to	Chapter 7

Student's contribution to the publication			
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	80	%	Data collection and analysis
	75	%	Writing and editing

Outline your (the student's) contribution to the publication:

Alex Barnes: responsible for study concept and design, data acquisition, analysis and data interpretation, drafting of manuscript, critical revision of the manuscript.

APPROVALS

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PUBLICATION 4

This section is to be completed by the student and co-authors. If there are more than four co-authors (student plus 3 others), only the three co-authors with the most significant contributions are required to sign below.

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Full Publication Details	Barnes A, Andrews JM, Mukherjee S, Bryant RV, Bampton P, Fraser RJ, Mountifield R. Insomnia is common in inflammatory bowel disease (IBD) and is associated with mental health conditions as well as IBD activity. Intest Res. 2023 Nov 1. doi: 10.5217/ir.2023.00028. Epub ahead of print. PMID: 37904322.
Section of thesis where publication is referred to	Chapter 8

Student's contribution to the publication

80	%	Research design
80	%	Data collection and analysis
75	%	Writing and editing

Outline your (the student's) contribution to the publication:

Alex Barnes: responsible for study concept and design, data acquisition, analysis and data interpretation, drafting of manuscript, critical revision of the manuscript.

APPROVALS

By signing the section below, you confirm that the details above are an accurate record of the students contribution to the work.

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PUBLICATION 5

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Full Publication Details	Alex Barnes, Jane M Andrews, Sutapa Mukherjee, Robert V Bryant, Peter Bampton, Paul Spizzo, Robert J Fraser, Réme Mountifield, Simple Novel Screening Tool for Obstructive Sleep Apnea in Inflammatory Bowel Disease, *Crohn's & Colitis 360*, Volume 5, Issue 2, April 2023, otad016,
Section of thesis where publication is referred to	Chapter 9

Student's contribution to the publication			
	80	%	Research design
	80	%	Data collection and analysis
	75	%	Writing and editing

Outline your (the student's) contribution to the publication:

Alex Barnes: responsible for study concept and design, data acquisition, analysis and data interpretation, drafting of manuscript, critical revision of the manuscript.

APPROVALS

By signing the section below, you confirm that the details above are an accurate record of the students contribution to the work.

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PUBLICATION 6

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Full Publication Details	Insomnia is associated with reduced quality of life in inflammatory bowel disease Under review
Section of thesis where publication is referred to	Chapter 4

Student's contribution to the publication			
	80	%	Research design
	80	%	Data collection and analysis
	75	%	Writing and editing

Outline your (the student's) contribution to the publication:

Alex Barnes: responsible for study concept and design, data acquisition, analysis and data interpretation, drafting of manuscript, critical revision of the manuscript.

APPROVALS

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PUBLICATION 7

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Full Publication Details	Latent profiles of fatigue in inflammatory bowel disease Under review
Section of thesis where publication is referred to	Chapter 11

Student's contribution to the publication			
	80	%	Research design
	80	%	Data collection and analysis
	75	%	Writing and editing

Outline your (the student's) contribution to the publication:

Alex Barnes: responsible for study concept and design, data acquisition, analysis and data interpretation, drafting of manuscript, critical revision of the manuscript.

APPROVALS

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PUBLICATION 8

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Full Publication Details	Depression influences fatigue in inflammatory bowel disease amongst other factors: a structural modelling approach Under review
Section of thesis where publication is referred to	Chapter 10

Student's contribution to the publication			
	80	%	Research design
	80	%	Data collection and analysis
	75	%	Writing and editing

Outline your (the student's) contribution to the publication:

Alex Barnes: responsible for study concept and design, data acquisition, analysis and data interpretation, drafting of manuscript, critical revision of the manuscript.

APPROVALS

By signing the section below, you confirm that the details above are an accurate record of the students contribution to the work.

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Name of Co-Author 3	Jane Andrews	Signed		Date	29/01/2024

PUBLICATION 9

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Full Publication Details	Active inflammatory bowel disease is associated with polysomnography parameters consistent with sleep deprivation Under review
Section of thesis where publication is referred to	Chapter 5

Student's contribution to the publication			
	80	%	Research design
	80	%	Data collection and analysis
	75	%	Writing and editing

Outline your (the student's) contribution to the publication:

Alex Barnes: responsible for study concept and design, data acquisition, analysis and data interpretation, drafting of manuscript, critical revision of the manuscript.

APPROVALS

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Name of Co-Author 1: Réme Mountifield Signed [signature] Date 7/2/24

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