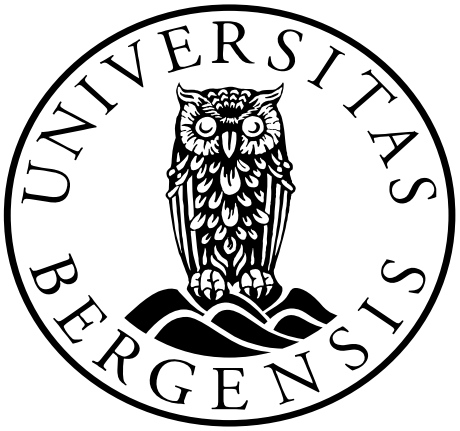
Fatigue and its relation to sleep problems in patients with irritable bowel syndrome

Siri Margreta Gjernes Thomsen



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Veileder: Astri J. Lundervold, Institutt for Biologisk og Medisins psykologi

Biveileder: Jelena Mrdalj og Birgitte Berentsen

Abstract

This thesis aims to investigate fatigue and its relations to sleep problems in patients with irritable bowel syndrome (IBS). The master study is part of the Brain-Gut project at Haukeland University Hospital in Bergen. IBS is defined within the umbrella term "disorders of gut-brain interaction" to include characteristics that are not directly related to the gastrointestinal symptoms. Several patients with IBS report chronic fatigue and sleep problems. The two symptom clusters share several characteristics, indicating that they are closely linked. However, several studies have shown that some patients struggling with chronic fatigue do not show more sleep problems than healthy controls. This study investigates patients' subjective reports regarding both sleep and fatigue, how they are associated with each other and with the severity of gastrointestinal symptoms. The participants include 56 patients with IBS and 39 healthy controls. The participants completed the IBS-Severity Scoring System (IBS-SSS), Chalders Fatigue Scale (CFQ-11), and Bergen Insomnia Scale (BIS). The results showed that patients with IBS have a higher prevalence of sleep problems and fatigue than healthy controls. A positive correlation between severity of IBS symptoms and sleep problems and between severity of IBS and fatigue was found when the entire dataset was included in the analysis. However, these associations were non-significant when analysis was constrained to the IBS group. Sleep problems and fatigue were positively correlated. The strength of the correlation was stronger between fatigue and experience of not being adequately rested, daytime impairment and dissatisfaction with current sleep than between fatigue and measures of prolonged sleep onset, long nocturnal awakenings, and early morning awakenings. These results support a systemic view of IBS, where the rich communication between the gut and the brain contributes to a syndrome that are not restricted to gastrointestinal symptoms.

Key words: Irritable bowel syndrome, fatigue, sleep, gut-brain-axis

Sammendrag

Denne masteroppgaven har som hensikt å undersøke utmattelse og hvilken relasjon det har til søvnproblemer hos pasienter med irritabelt tarm-syndrom (IBS). Denne studien er del av Brain-Gut prosjektet ved Haukeland universitetssykehus i Bergen. IBS er definert som en forstyrrelse av hjerne-tarm-aksen. Flere IBS pasienter rapporterer konisk utmattelse og søvnproblemer. De to symptomgruppene deler flere karakteristika noe som indikerer at de er overlappende. Flere studier har imidlertid vist at pasienter som sliter med kronisk utmattelse ikke nødvendigvis sliter mer med søvnproblemer enn kontrollgruppen. Denne studien utforsker pasientenes subjektive rapporter angående utmattelse og søvn, hvordan de er assosiert med hverandre og med alvorlighetsgrad av gastrointestinale symptomer. Deltakerne svarte på spørreskjemaene IBS-Severity Scoring System (IBS-SSS), Chalder Fatigue Scale (CHQ-11), og Bergen Insomnia Scale (BIS). Resultatene viste at pasienter med IBS har en høyere forekomst av søvnproblemer og utmattelse enn kontrollgruppen. Når hele datasettet ble inkludert i analysen så vi en positiv korrelasjon mellom alvorlighetsgrad av IBS symptomer og søvnproblemer, og mellom alvorlighetsgrad av IBS symptomer og utmattelse. Denne korrelasjonen var derimot ikke-signifikant når analysen kun inkluderte pasienter fra IBS gruppen. Søvnproblem og utmattelse var positivt korrelert. Korrelasjonen var sterkere mellom utmattelse og opplevelse av å ikke være godt nok uthvilt etter å ha sovet, svekket funksjon på dagtid og misnøye med søvnkvalitet, enn mellom utmattelse og forlenget søvnlatens, lange oppvåkninger i løpet av natten og tidlig oppvåkning om morgenen. Disse funnene gir støtte til en system-tilnærming av IBS, der den rike kommunikasjonen mellom tarmen og hjernen bidrar til et syndrom som ikke er begrenset til å omfatte kun gastrointestinale symptomer.

Acknowledgements

Going into this project I was excited and motivated to learn more about IBS and how symptoms of fatigue and sleep problems are related to it. I am grateful to Birgitte Berentsen and Astri Lundervold for allowing me to join the Brain-Gut project and dive even deeper into the world of IBS and learn so much more in the process. Not just about the main topic, but also about myself and what I am capable of. Astri, you have followed me all the way from the beginning, inspired and encouraged me all the way to the end. Thank you for being so incredibly understanding, and sticking with me even when things took longer than planned. Together with Jelena Mrdalj you have given me guidance, feedback, and support through this long and hard process. When I was stuck you both helped me get out of my mental hole with encouraging words and advice. Birgitte has also provided valuable feedback to the thesis, helping it become what it is. Further I would like to thank Tina and Tine, my fellow brain nerds, who have always been there for mental support and brainstorming. I want to thank my wonderful parents for supporting me through this in every possible way. And lastly I want to thank Ketil and Inger Anita, without you I would not be where I am today.

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Irritable Bowel Syndrome

IBS is a gastrointestinal disorder characterised by reoccurring abdominal pain, often in association with defecation, bloating and disordered bowel habits such as constipation and/or diarrhoea (Lacy et al., 2016). Patients suffering from IBS often have negative experiences when seeking help for their symptoms (Halpert & Godena, 2011), feeling like their health care provider does not understand the severe impact the IBS symptoms have on their life quality, and that it is due to more than just a stomachache. The goal of this thesis is to investigate the relationship between two common symptoms in patients with IBS: fatigue and sleep problems.

Why some people develop IBS is still uncertain, but we know that genetics, environmental and psychosocial factors do play a role (Lacy et al., 2016). Developmental and maintaining factors of IBS include anxiety, stress, food intolerances, infections (Camilleri et al., 2012), and the use of antibiotics (Collins, 2014). Another factor that is linked to developing IBS is childhood trauma, either in the form of one or several traumatic incidents, or in the form of a prolonged stress response (Ålander et al., 2008; Klooker et al., 2009; van Tilburg et al., 2010). A common perpetuating factor is chronic stress. The IBS symptoms can by themselves be a major cause of negative stress, meaning stress that the individual cannot cope with. This negative stress created by the IBS symptoms can enter a feedback loop that can be hard to get out of. Other examples of chronic stress are unfavourable living situations, co-existent somatic illness, drug abuse or interpersonal conflicts. All which also may contribute to the perpetuation of IBS symptoms.

To illustrate how IBS affects people in their lives I will introduce the case of a 57-year-old woman suffering from IBS. This case is an amalgamation of several different interviews of

patients with IBS and is used here to illustrate the severe impact IBS has on the life quality of the sufferers.

"Woman born in 1966, from now on referred to as Woman (57). She has experienced gastrointestinal symptoms in varying degrees for as long as she can remember but did not receive help from health care providers as a child or teenager. Instead, she was told that it was something she just had to learn how to live with, and that it might pass with age. In her early 20s the symptoms became debilitating to the point that it severely affected her daily life. She also experienced nausea and dizziness together with intense gastrointestinal pains, as well as fatigue, muscle and joint pains and problems falling asleep in the evening. Any free time she had as a student was spent resting and recharging for the next day. After seeing a doctor as an adult, her gastrointestinal symptoms were interpreted as food intolerance, but no valid treatments were available. After she started working, she needed a sick leave after a few months, and this pattern continued until she eventually ended up on a disability pension in her mid-50s. She developed cognitive symptoms such as problems with memory, language, processing speed, and general difficulties performing tasks that require mental effort. She also developed migraines and tinnitus, however the migraines got milder with age, while the tinnitus got worse. In 2013 she was diagnosed with IBS and was put on the lowFODMAP-diet (see section "Treatments of IBS"). It was difficult to stick to its regime, and she found that the small relief it gave her did not outweigh the social and financial downsides. At this point in her life, she had adapted to her health issues, and she accepted that her symptoms would be permanent. It did also help a lot that her health care provider listened to her and validated her symptoms. After getting disability pension she could use her energy on activities that were neglected for a long time".

Symptoms

> *"I always experienced stomach aches and intense urge but was told that I just had to learn to live with it. It was not until my early 20s that it was so bad that I sometimes could not leave the house. I would either sit on the toilet or lay curled up on the bathroom floor with a heating pad, trying to minimize the pain" – Woman (57).*

Aside from gastrointestinal symptoms, such as bloating, pain, urge and change in bowel movements and consistency, IBS has also been associated with symptoms such as fatigue and muscle and joint pains (Berstad et al., 2012), as well as altered or disturbed sleeping patterns (Khanijow et al., 2015). IBS is a complex disorder that involves the gastrointestinal system, immune system, and the nervous system (Camilleri et al., 2012), and affects a large number of people. Approximately 11,2% of the world population is diagnosed with IBS according to the ROME III criteria (Lacy et al., 2016), and they experience symptoms that not only impair the quality of life of the affected individuals (Cassar et al., 2020), but it has also become a socioeconomic problem affecting the society as a whole.

Diagnosis

There is no specific biomarker that confirms an IBS diagnosis. An IBS diagnosis is rather based on symptom mapping according to the ROME criteria, and the exclusion of other disorders with symptoms similar to IBS through endoscopy and biopsy, such as Crohn's disease, Ulcerative Colitis, and celiac disease (Lacy et al., 2016). The ROME IV criteria were introduced in 2016, but the ROME III criteria are still in use in some studies (see Table 1 for description of the criteria).

Table 1

Comparison of ROME III and ROME IV

ROME IV (Lacy et al., 2016)	Recurring abdominal pain on average at least 1 day/week in the last 3 months associated with two or more of the following criteria: 1. Related to defecation. 2. Associated with a change in frequency of stool. 3. Associated with a change in form (appearance of stool). Criteria fulfilled for the last 3 months, with symptom onset at least 6 months before diagnosis.
ROME III (Longstreth et al., 2006)	Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with two or more of the following: 1. Improved with defecation. 2. Onset associated with a change in frequency of stool. 3. Onset associated with a change in form (appearance) of stool. Criteria fulfilled for the last 3 months, with symptom onset at least 6 months prior to diagnosis.

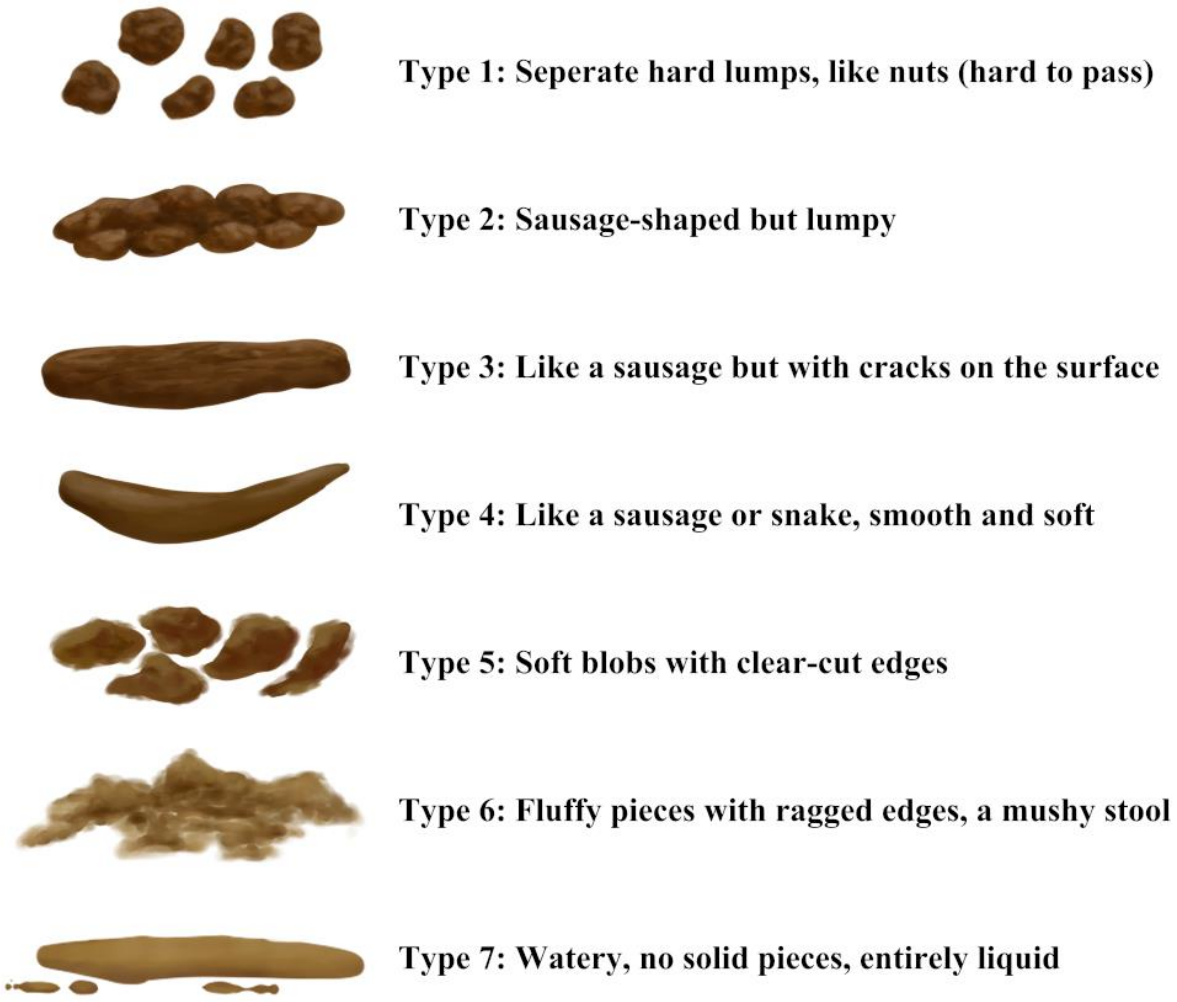
Subgroups

IBS is categorized into four subgroups based on defecation patterns. The Bristol stool form scale is a tool used when diagnosing IBS (Lewis & Heaton, 1997). The Bristol stool form scale consists of seven items describing the consistency of the faecal matter, where number one represents the stool with the lowest water content, and seven with the highest (see Figure 1). Diagnostics of IBS sub-types are based on the self-reports of The Bristol stool form scale. In IBS-D (diarrhoea) at least 25% of the stool must be type 6 or type 7, and less than 25% must

be type one or type two. In IBS-C (constipation) at least 25% of the stool must be type one or type two, and less than 25% must be type six or type seven. Some patients experience a mix between IBS-C and IBS-D and will be classified as IBS-M (mixed), where more than 25% of the stool must be type one or type two and more than 25% of the stool must be type six or type seven. A few patients do not fit into any of those three subgroups and may be placed in the subgroup IBS-U (unclassified) (Lacy et al., 2016).

Figure 1

Bristol Stool Form Scale



Note. Modified from original by (Lacy et al., 2016)

The gut-brain-axis

IBS is defined under the umbrella term “disorder of the gut-brain interaction”. This emphasises the importance of the gut-brain-axis, referring to the bidirectional communication between the central and the enteric nervous system. By this, it allows emotional and cognitive processes to be connected with the functions in the gastrointestinal system and vice versa (Carabotti et al., 2015; Koloski et al., 2012). This communication occurs through the central nervous system, the enteric nervous system, the autonomic nervous system, and the hypothalamic pituitary adrenal (HPA) axis (Al Omran & Aziz, 2014; Carabotti et al., 2015). The autonomic nervous system is involved in both afferent and efferent signals. Afferent signals from the intestines are transmitted through enteric, spinal and vagal pathways to the central nervous system, and efferent signals from the central nervous system to the intestines (Carabotti et al., 2015). The HPA-axis is another important part of the communication between the brain and the gut as it is one of our main stress regulation systems. When exposed to a stressor the hypothalamus produces and secretes corticotropin releasing hormone which travels by the capillary system to the anterior pituitary gland, where it stimulates the production of adrenocorticotropic hormone. Adrenocorticotropic hormone is then released into the bloodstream and travels down to the adrenal glands, stimulating the glands to produce cortisol. Cortisol has important functions such as increasing availability of nutrients in the blood and acting on the immune system. It also works as a negative feedback mechanism in the HPA-axis by binding to receptors in the hypothalamus. However, in cases of chronic stress the body may experience cortisol resistance, where cortisol is unable to bind to the receptors (Cohen et al., 2012). A malfunctioning HPA-axis can have several negative consequences that affects the digestive system, somatic pain perception and the autonomic nervous system response (Mayer, 2000). There have been very few studies done on IBS and cortisol resistance, but Patacchioli et al. (2001) found that patients with IBS had higher

cortisol levels in the morning, and lower cortisol levels in the evening compared to a healthy control group. Patacchioli et al. (2001) used saliva to test cortisol levels to avoid any extra stressors from drawing blood, with the assumption that the concentration of cortisol in the saliva would be comparable to the concentration of cortisol in the blood. Weaver et al. (2018), on the other hand, tested blood level cortisol and found no significant difference between a group of patients with IBS and a healthy control group. Despite the similarities in blood cortisol levels, patients with IBS reported higher perceived stress and lower quality of life than the healthy control group.

How much stress people can handle varies between individuals. Park et al. (2018) found that individuals struggling with IBS generally have a lower tolerance for stress than individuals who do not. We also know that individuals who have experienced trauma generally have a lower tolerance of stress, or "window of tolerance" as it is often described in literature (Corrigan et al., 2011). Those with a very small window of tolerance will have a higher risk of experiencing hyperarousal or hypoarousal. Hyperarousal is characterised by an overactive nervous system, while hypoarousal is characterised by fatigue. The nervous system is only able to stay in hyperarousal for a certain amount of time before the resources are exhausted, and it will then end in a hypoaroused state (Corrigan et al., 2011). Those who experience higher perceived stress, as experienced by many patients with IBS, may have a smaller window of tolerance when it comes to stress, and thus find it difficult to regulate stress. Whereas people without IBS may be able to utilise the stress activation, a person with IBS may find themselves overwhelmed and unable to do anything in a similar situation, because they tend to find themselves stuck in a hyper- or hypoaroused state.

Gut microbiota is a core part of the gut-brain-axis. Not only does it communicate with the cells in the digestive system or the enteric nervous system, but it also communicates with the central nervous system through neuroendocrine and metabolic pathways (Carabotti et al.,

2015). A disruption in the gut microbiota, called dysbiosis, can impact the functions of the gut-brain-axis, such as changes in intestinal motility and cause visceral hypersensitivity (Kennedy et al., 2014; Mayer & Tillisch, 2011). Under normal circumstances afferent signals from the gut would not be consciously registered by the individual, but in patients with IBS the signals might reach the somatic sensory system and cause discomfort, nausea and pain (Mayer & Tillisch, 2011; Raskov et al., 2016). This can be one of the explanations as to why individuals with IBS experience more pain and discomfort from bowel activation than healthy individuals.

Several studies show how important gut microbiota, and the gut-brain-axis communication are for IBS symptoms. Crouzet et al. (2013) investigated what happened when gut microbiota was transferred from patients with IBS with visceral hypersensitivity, into germ-free rats. They found that it triggered visceral hypersensitivity in the rats. This indicated that the bacteria that constitute the gut microbiota have a very direct impact on IBS symptoms. Using this knowledge for treatment options, faecal microbiota transplant from healthy donors to patients with IBS has been shown to significantly improve IBS symptoms (El-Salhy et al., 2020; Halkjær et al., 2018; Johnsen et al., 2020). This shows that by considering IBS as a disorder of the gut-brain interaction, it brings new and improved possibilities for treatment options for patients with IBS.

Treatments of IBS

> *"I've tried out the lowFODMAP diet, cognitive behavioural therapy, and meditation. Honestly, none of them really worked for me. Perhaps I'm too set in my ways to change the way I think, or to learn how to not be stressed. It is also really frustrating when you are in immense pain or so exhausted you can't take a shower, to be told that you just*

need to change the patterns of your thoughts, emotions and behaviours. No one would say that to someone with, let's say diabetes, right?" – Woman, 57.

There is currently no cure for IBS, and most available treatment options focus on minimising and accepting symptoms. Symptoms can vary between individuals, and treatment should be based on the patient's symptoms and needs (Lacy et al., 2016). Information and psychoeducation should be the first step in any treatment, so that patients can gain understanding and knowledge of their own condition. Since stress can trigger IBS symptoms, it is important to minimize the amount of fear and uncertainty the patient experience from their own diagnosis. Learning about the condition and its symptoms is an important step in the process of removing unnecessary stress and fear. This could create an understanding that although the symptoms may be painful and debilitating, they are not dangerous. Lowering the level of worry and fear might in and of itself lower the level of symptoms.

As already stated, the gut-brain-axis implies a two-way communication between the enteric nervous system in the gut and the brain. Because of this, thoughts and feelings will have an effect on somatic symptoms, and any symptoms experienced will again affect thoughts and feelings. Cognitive behavioural therapy has been successful in reducing IBS symptoms in some cases, probably because of its influence on the gut through the brain. Cognitive behavioural therapy is used to help the patient understand how their own thought patterns contribute to worsen or improve their physical symptoms. The patient is therefore instructed to manage their symptoms by interrupting or changing their thought patterns through rehearsal and skill learning (Hutton, 2005). Stress management might also be a part of the treatment for patients who experience worsening in symptoms due to negative stress or have a low tolerance for stress. Stress management can include exercises in mindfulness or meditation, and learning of breathing techniques that will calm the activity of the autonomous

nervous system (Naliboff et al., 2020). However, as Woman (57) states, she has been through treatment programs such as cognitive behavioural therapy and meditation, without any positive effect. The downside of these types of treatment is that they require a lot of effort from the patients, and they will only succeed if they are adhering to the treatment over time. For many patients it can be too difficult to stick to the treatment long enough to obtain positive results, and for some the improvement in symptoms is considered to be too minor if there are other aspects, such as dysbiosis, that are the main cause of the symptoms.

> *"Some days I feel perfectly fine, until I'm about to leave the house. It took me a long time to understand that it was my own worries that triggered it. Subconsciously worrying about what would happen if I had to find a toilet while on the bus, or standing in line, or in the middle of a store. The fear alone of what might happen when I was outside of the comfort of my own home, was enough to trigger the symptoms." – Woman, 57.*

Another common treatment recommended for patients with IBS is dietary interventions. A diet low in fermentable oligo-, di-, monosaccharides and polyoids (FODMAPs) has gained support as treatment for patients with IBS (Moayyedi et al., 2015). FODMAPs are carbohydrates that are difficult to absorb in the small intestines, which attracts water into the bowels and can lead to diarrhoea. FODMAPs are also quickly fermented by bacteria in the intestines, which can create symptoms such as bloating, pain, nausea and disturbed bowel movements (Gibson & Shepherd, 2010). By eliminating certain FODMAPs from the diet, the bacteria that use these carbohydrates as nutrients, will no longer have access to those nutrients, and the population of that specific bacteria will diminish in the gut. Hence, changing the diet will subsequently change the gut microbiota composition.

The lowFODMAP diet is an elimination diet that is to be strictly followed for 4-6 weeks, before introducing each of the FODMAP groups one by one. By following this regime, the patient can figure out how they react to the different groups of carbohydrates, and decide which to continue excluding from their diet, and which to reintroduce. The lowFODMAP diet may not only improve gastrointestinal symptoms, but also quality of life as a whole (Eswaran et al., 2017). A challenge with this treatment option is that the diet requires a lot of effort from the patient and can be hard to follow. It can even lead to nutrition deficiencies and social difficulties due to food restriction. It should thus be followed under the guidance of a dietitian to ensure that the patient gets all their micro- and macronutrient needs covered and ensure sustainability over time.

There are also pharmacological treatments, such as laxatives to relieve constipation for those mainly struggling with IBS-C, and antidiarrheals for those mainly struggling with IBS-D. However, this brings its own set of challenges, as it can be difficult to regulate the correct dosage over time and IBS-C will often turn to IBS-D with medical treatment. For those struggling with IBS-M or IBS-U it might be extra difficult to find a good balance between these two groups of pharmacological agents, as the symptoms keep alternating between constipation and diarrhoea. For pain management low dose of antidepressants have been shown to have a positive effect in some individuals (Törnblom & Drossman, 2015). Moreover, once the pain is removed a lot of the worry and anxiety around the condition may also cease. However, for any pharmacological treatment, it is important to weigh the effects up against the potential side effects.

As already mentioned, faecal microbiota transplant has recently been reported as a successful treatment option for patients with IBS. Not only does it improve symptoms directly involving the gastrointestinal system, but also symptoms related to fatigue (Johnsen et al., 2020). Faecal microbiota transplant changes the gut microbiota, and this change is reported to

be maintained over time, with patients reporting that the effects on IBS symptoms and their quality of life in general were maintained a year after the transplantation (El-Salhy et al., 2022).

Hypnosis is another treatment that has proven to relieve symptoms in patients with IBS (Palsson, 2015; San Miguel, 2019) usually after 7-12 sessions over 2-3 months. Based on the meta-analysis by Schaefert et al. (2014) about 54% of patients who had no improvement with conventional therapy (pharmacological and dietary interventions) benefited from hypnotherapy. Besides improving core IBS symptoms, hypnotherapy is also shown to reduce non-gastrointestinal symptoms and generally improves quality of life, and these effects may last for years after the treatment (Palsson, 2015).

Fatigue

Characteristics and diagnostic criteria

Fatigue is characterized by a feeling of extreme lack of energy that is not related to an excessive amount of exertion. Patients describe fatigue as being ever-present, fluctuating throughout the day or from day to day and beyond one's own control (Mengshoel et al., 2014).

> *"It's difficult to describe fatigue to someone who has never experienced it. I sometimes say it is like having the flu, with 40°C fever. Your body does not work, your mind does not work. A simple task such as going to the toilet feels impossible. Just turning around in bed makes you feel out of breath and your muscles ache. And people tell me I should just pull myself together? How?" – Woman, 57.*

Fatigue is a symptom spectrum experienced by patients across several diseases and disorders. In the lower part of the spectrum, the fatigue generally has a clear trigger and will be

relieved once the trigger is removed. Typical triggers can be temporary illness, demanding labour, episodic stress, malnourishment, and sleep deprivation. When fatigue is discussed in this thesis, we are referring to a chronic fatigue that does not have an obvious trigger but is a core symptom embedded in the chronic illness. However, we still cannot prove that chronic illness causes fatigue, or if there is a common cause that triggers both fatigue and the chronic illness. Although fatigue is a subjective symptom, it can to some extent, be measured objectively by testing a person's physical or cognitive performance. However, the findings on these tests do not always match with the patient's subjective experience of the severity of their fatigue symptoms (Sharpe, 2006).

Fatigue that cannot directly be explained by an underlying disorder is defined as Chronic Fatigue Syndrome (CFS), also called Myalgic Encephalomyelitis (ME) (Fukuda et al., 1994; Institute of Medicine, 2015). The diagnostic ME criteria from 1994 state that the severe fatigue must have been present for longer than 6 months, and that the patients must have at least four of the following symptoms; headache of new type, pattern, or severity; joint pain without swelling or erythema; muscle pain; postexertional malais for longer than 24 hours; significant impairment in short-term memory or concentration; sore throat; tender lymph nodes; unrefreshing sleep (Fukuda et al., 1994). Institute of Medicine (2015) proposed new diagnostic criteria for CFS/ME and a new name: Systemic Exertion Intolerance Disease (SAID), arguing that this is a better description of the condition than myalgic encephalomyelitis, and that the literal definition of chronic fatigue syndrome carries too much stigma. According to the new diagnostic criteria for SAID the three symptoms shown in Table 2 must be present. In addition, at least one of the following manifestations must be present: cognitive impairment such as problems related to thinking, memory, executive functions and information processing, and orthostatic intolerance, i.e., that the patient shows a worsening of symptoms while standing in an upright position. The symptoms should be present at least half the time with moderate,

substantial or severe intensity (Institute of Medicine, 2015). In 2021 National Institute of Health and Care Excellence (NICE) updated their criteria from 2007. These are quite similar to Institute of Medicine's criteria, with the exception that the symptoms should have persisted for at least 3 months instead of 6 months (The NICE Guideline Development Group, 2021).

Table 2

SAID diagnostic criteria

A substantial reduction or impairment in the ability to engage in pre-illness levels of activity	Lasts for more than 6 months Is accompanied by fatigue that is: • Often profound • Of new onset (not life-long) • Not the result of ongoing or unusual excessive exertion • Not substantially alleviated by rest
Postexertional malais	Worsening of symptoms after physical, mental or emotional exertion. May lasts days, weeks or longer.
Unrefreshed sleep	Not feeling better or less tired even after a full nights sleep despite no objective sleep alterations

Note. (Institute of Medicine, 2015). Abbreviation: SAID = Systemic Exertion Intolerance Disease

Despite the slight variations in aetiology the symptoms of fatigue are debilitating and have a negative impact on the patient's life. The study in this thesis focuses on fatigue that is associated with an IBS diagnosis, while the introduction and discussion include results from research that has been done on CFS/ME and fatigue caused by other chronic illnesses.

Fatigue in IBS

> *"I remember the first time someone told me that fatigue was a very common symptom in people with IBS, it blew my mind. Up until that point I had the impression that IBS was just something that affected your digestive system, and nothing else. Why are we not given more information about our condition by our health care providers? Is it because they lack knowledge on IBS? Or do they simply not consider it to be serious enough to properly educate the patients?" – Woman, 57.*

In a study on IBS, 17% of the participants reported that fatigue was the symptom they struggled with the most, while 51% reported that fatigue was just as bad as their gastrointestinal symptoms (Piche et al., 2007). Fatigue can have negative consequences both cognitively, physically and socially (Fisk et al., 1994), and will by this affect physical activities, work, domestic labour, and social interactions (Frändemark et al., 2017), which all contribute to impairing the life quality of the patients. IBS patients with fatigue who were given a faecal microbiota transplantation noticed an improvement in their fatigue after the treatment (Johnsen et al., 2020). Still, we know very little about the interplay between IBS and fatigue, and why only some patients with IBS experience fatigue.

Fatigue and diseases/disorders in general

What exactly causes fatigue is thus still mainly unknown. Fatigue in and of itself is a natural defence mechanism for when we get sick (Dantzer et al., 2008). This sickness behaviour forces our bodies to rest, allowing it to fight for instance a pathogen or an infection. However, in some cases, the fatigue does not stop after the sickness has passed. Just as the immune system can start attacking the body's own cells, or a natural fear response can turn into an anxiety

disorder, fatigue can become disabling, but exactly how or why this happens is still mostly unknown.

We do know that fatigue is associated with several chronic disorders, both physical and mental, including IBS (Frändemark et al., 2017; Han & Yang, 2016). However, we do not know if IBS triggers fatigue or if there is a third condition that triggers both IBS and fatigue, such as for instance a prolonged stress response or emotional trauma. Fatigue can also be experienced after a viral infection, such as mononucleosis (Katz et al., 2009), and it was recently discovered that some patients develop chronic fatigue after a Covid-19 infection (Raveendran et al., 2021) also known as long-covid. Carfì et al. (2020) found that over half the patients who were infected with Covid-19 developed fatigue after the viral infection had passed, and they found no correlation between the severity of the Covid-19 infection and the development of fatigue. Long-covid is still a quite newly identified set of symptoms and the research is in its infancy. It has, however, been suggested that such a post-viral fatigue is associated with dysregulation of the immune system and abnormalities in the HPA-axis (Katz et al., 2009; Koralnik & Tyler, 2020), which are some of the same factors that are used to explain IBS.

Fatigue has also been associated with an increased inflammatory activation, and is often seen in patients suffering from inflammatory and autoimmune conditions (Lee & Giuliani, 2019). Microglia cells can respond to inflammatory stimuli by producing pro-inflammatory cytokines (Dantzer et al., 2008), which stimulate the immune system. Sometimes cytokines are produced even when there are no inflammatory stimuli, such as when we experiencing a stress response (Maes et al., 1998). If the stress response becomes chronic the immune system will respond to the increase in pro-inflammatory cytokines even though there are no specific pathogen or infection in the body, and this can lead to increased inflammation in the body (Tian et al., 2014).

Treatment of fatigue

To find the best possible treatment for fatigue Fukuda et al. (1994) recommended to search for its underlying cause. They argue that patients with CFS should be evaluated for their medical and psychosocial history at the onset of the fatigue; depression and other psychiatric disorders; medically unexplained symptoms; substance abuse; current prescribed or over-the-counter medication. Further, their mental state and cognitive abilities should be evaluated, and a physical examination and laboratory testing should be conducted. Any detected comorbidities such as sleep disturbance, depression and pain should be treated to see if this can reduce the severity of fatigue.

In addition to the most common treatment options in a medical setting, cognitive behavioural therapy (see section "Treatments of IBS") is shown to have positive effect on the severity of fatigue symptoms (Malouff et al., 2008). Graded exercise therapy is another treatment option where the patient and therapist together decide on a realistic daily goal for the patient regarding physical activity. Over time the goal is to increase the frequency of the activity, and eventually the duration and intensity. It is important that the patient does not overexert themselves, and they should not experience postexertional malais or any other negative symptoms from the exercise (Larun et al., 2019). Adaptive pacing therapy is another treatment option where the patient learns to regulate their activity level on a day-to-day basis, and therefore limit symptoms triggered by exertion. This type of therapy are appropriate for patients who are near or on their maximum level of functioning (Goudsmit et al., 2012). A comparison between the three treatment options have shown that cognitive behavioural therapy and graded exercise therapy used in addition to medical care moderately improve the symptoms of fatigue, while adaptive pacing therapy had no additional effect to medical care (White et al., 2011). However, a survey done by the ME Association (2010) showed that patients experienced

most improvement when offered adaptive pacing therapy, experienced no difference with cognitive behavioural therapy, and felt worse after taking part of graded exercise therapy.

Stress management through certain mindfulness exercises have also shown to improve fatigue symptoms over time (Stubhaug et al., 2018). Furthermore, some studies show positive effects of treatment using low-dose hydrocortisone (5-10mg) as a short-term treatment for fatigue. Treatment that lasted for 28 days showed a reversal of the dysfunction of the HPA-axis in some of the patients (Cleare et al., 1999; Cleare et al., 2001). Why some patients experience less fatigue after his treatment is still unexplained.

Sleep

Sleep and sleep regulation

Sleep is an active, reversible process which is associated with muscle relaxation and reduced responsiveness to external stimuli (Zepelin, 1994). Most adults need 7 hours or more sleep per night (Watson et al., 2015), with great individual variation. Ursin et al. (2005) found that the average sleep duration of 40–45-year-olds was 6 hours and 52 minutes (+/- 55min) for men and 7 hours and 11 minutes (+/- 57min) for women.

Sleep can be divided into two main stages, non-rapid eye movement (NREM) sleep which comprises 75-80% of the time spent asleep, and rapid eye movement (REM) sleep which comprises 20-25% of the time spent asleep (Khanijow et al., 2015). NREM sleep is divided into three stages, N1, N2 and N3. One sleep cycle usually lasts 90 minutes and includes all sleep stages. N1 is the transition between wakefulness and sleep. While in this stage, external stimuli can easily awaken the individual (Carskadon & Dement, 2017). Stage N2 is light sleep, while N3 is deep sleep, requiring increasingly more stimuli to awaken the individual. REM sleep is characterized by rapid eye movements and complete muscle

relaxation (Bathory & Tomopoulos, 2016) and is where dreams are most frequently experienced (Institute of Medicine, 2006).

There are mainly two processes that regulate sleep and wakefulness. Process C represents the circadian rhythm and Process S represents the homeostatic factor (Gillette & Abbott, 2005). The circadian rhythm is regulated by our inner, biological clock that creates near 24-oscillations in almost all physiological functions including sleep and wakefulness, the body temperature, hormone secretion and blood pressure. This clock is usually slightly longer than 24 hours, but is synchronised to 24 hours by the light-dark cycle which is the main zeitgeber (time giver) (Bathory & Tomopoulos, 2016). The homeostatic process represents the subjective need for sleep, which is higher the longer we have been awake.

Sleep has many functions and is not only important for creating complex memories and for mental health. Getting enough and regular sleep helps maintain both the metabolism and the immune system (Sen et al., 2021). A disturbed sleeping pattern or chronic sleep loss can lead to a range of negative consequences such as impaired concentration and mood and increased risk of depression, but also risk of obesity, diabetes and hypertension (Cooper et al., 2018; Horne, 1985; Knutson & Van Cauter, 2008; Lustberg & Reynolds, 2000; Palagini et al., 2013). Specific cytokines are known to affect the sleep-wake cycle and increase fatigue and promote sleep (Santos et al., 2007), and sleep deprivation has been linked to increased levels of pro-inflammatory cytokines (McEwen, 2006).

Sleep and the Gut

The interaction between sleep and gut microbiota has been shown in several studies. In a study of rats, the gut microbiota was altered by the use of antibiotics. This led to changes in sleep with longer time spent in NREM sleep and less time in REM sleep (Ogawa et al., 2020). Several studies on both rats and humans investigating effects of sleep deprivation have not only

reported increased cognitive failure, but also increased proinflammatory cytokines, and changes in the gut microbiota (Ma et al., 2019; Poroyko et al., 2016; Ramesh et al., 2012). This suggests that disturbed sleep will likely have a negative effect on the symptoms in patients with a disorder like IBS. Another study showed that gut microbiota can have a direct effect on sleep. In this study patients with IBS received gut microbiota from a healthy donor through faecal microbiota transplant, and reported thereafter better sleep, and less depression and anxiety symptoms (Kurokawa et al., 2018). Gut microbiota in patients with insomnia (see section "Sleep in patients with IBS" for a description of insomnia) was found to be significantly different than in healthy controls (Jiang et al., 2020). A small pilot study has shown that behavioural therapy for insomnia in patients with IBS, did not only improve insomnia, but also improved the IBS related symptoms (Ballou et al., 2020). This gives an interesting insight into how all the symptoms in patients with IBS are interconnected, and how it might be better to have a holistic approach for treatment instead of treating separate diagnoses.

Sleep in patients with IBS

> *"When I was younger, I did not understand the importance of sleep and its effects on my symptoms. As I became older, I started noticing very clear worsening of symptoms in periods where I did not sleep well. I would have more pain, both in my stomach and in my body in general, my fatigue would be worse, and it was harder to think. Despite knowing this, I can't always sleep. Sometimes I lay awake until 4 o'clock in the morning without knowing why. It's very frustrating" – Woman, 57.*

Wang et al. (2018) found that the prevalence of sleep disorders was higher in patients with IBS compared to healthy controls. Lee et al. (2016) found that a person with insomnia has higher odds of having IBS than a person without insomnia. Insomnia is one of the most common

sleep disorders with 8-18% of the general population experiencing symptoms of insomnia, while 6% of the population is diagnosed with insomnia (Ohayon, 2002). Insomnia is characterised by reoccurring difficulties with falling asleep, waking up in the night, waking up too early in the morning and/or perceived bad sleep quality, which may results in fatigue, irritability, general discomfort or cognitive failure during daytime (World Health Organization, 2018). Insomnia can be divided into primary and secondary insomnia. In primary insomnia the cause is unknown, while in secondary insomnia the cause is often a psychological or somatic disorder (Bjorvatn et al., 2009). A small pilot study has also shown that behavioural therapy for insomnia in patients with IBS improved insomnia as well as IBS related symptoms in the participants (Ballou et al., 2020). This points to how all the symptoms are interconnected and support the importance of a holistic attitude to treatment of patients with this and similar disorders.

One study among shift workers found that compared to day-time shift workers only, rotating shift workers have a higher prevalence of IBS, which is believed to be associated with the disturbance in circadian rhythm created by the irregular shifts (Kim et al., 2013). Using anorectal manometry to measure pain sensitivity in patients with IBS it has been shown that patients with IBS reporting lower sleep quality have a lower threshold for rectal pain sensitivity and urge compared to participants without IBS (Chen et al., 2011). Results from these studies support a conclusion that low sleep quality may – at least partly – be a risk factor of developing IBS symptoms. However, anxiety and depression are also quite common in patients with IBS (Whitehead et al., 2002), and sleep disturbance is commonly a co-existent symptom of both anxiety and depression (Alvaro et al., 2013). This comorbidity might be important in understanding how sleep and IBS symptoms affect each other.

Patients with IBS-like symptoms (their symptoms were mapped using the Izumo scale and not the ROME criteria) had a higher prevalence of day-time sleepiness compared to healthy

controls (Morito et al., 2014) and self-reported sleep disturbances predicted higher levels of abdominal pain and fatigue the next day (Buchanan et al., 2014). Patel et al. (2016) also found that abdominal pain is more severe after a night of disturbed sleep, while frequency, stool consistency and other IBS symptoms did not seem to be affected by sleep quality. Disturbed sleep did also affect somatic pain perception in general (Patel et al., 2016), which suggests that the effect disturbed sleep has on IBS is more related to pain perception than the actual IBS symptoms. Song et al. (2005) explored the effects of melatonin as a sleeping medication on IBS symptoms and found that the use of melatonin for 2 weeks gave patients with IBS a higher threshold for both urgency and pain, despite no improvement in sleep disturbance and psychological distress, suggesting that melatonin's effect on abdominal pain is perhaps independent of sleep. However, it did not alter gut motility, and the patients still experiences the same frequency of defecation and stool consistency, and self-reports revealed that despite the lowered abdominal pain the treatment had not improved their quality of life.

Fatigue and Sleep

Based on the studies presented so far, the relationship between fatigue and sleep problems is not clear. Some studies have found that sleep as short as a 20-min nap may contribute to relieve the symptoms of fatigue (Cooke et al., 1998; Hayashi et al., 1999). On the other hand, in one study patients with chronic fatigue reported less sleep problems than patients with depression (Morriss et al., 1997). Waking up without feeling rested is more frequently reported by patients with fatigue than problems related to initiation and maintaining sleep (Sharpley et al., 1997). Chronic fatigue is in other words different from being exhausted after mental or physical effort, a condition that is normally remediated by a good night's sleep. Healthy individuals who experience this kind of fatigue describe it as temporary, relaxing, fulfilling, normal and pleasant, while those struggling with chronic fatigue describe it as

frustrating, exhausting and frightening (Gielissen et al., 2007). Fatigue due to underlying illnesses thus seems to be qualitatively and quantitatively different from the fatigue and tiredness commonly experienced by most people, due to the different responses to sleep and rest. Ream and Richardson (1996) sums this up by stating that severe fatigue will not improve with rest, while mild fatigue can be improved by resting. Taken together, these differences suggest that fatigue can be considered along a dimension, with chronic fatigue representing the most severe end of the spectrum.

Conflicting results along the dimension of fatigue and its association with different aspects of sleep problems call for future studies. How sleep problems are measured seems to have an impact on the study results. In one study using subjective reports it was found that sleep quality was a stronger predictor for fatigue than measurements of prolonged sleep onset, long nocturnal awakenings and early morning awakenings (Lavidor et al., 2003). Whereas another study found that patients with CFS who complained about unrefreshing sleep did not have abnormal polysomnography data compared to healthy controls (Sharpley et al., 1997). Hence, fatigue seems to be more closely connected to the subjective sleep quality than objective sleep measures.

As far as we know no study has investigated the association between self-reported fatigue and sleep problems in patients with IBS. This motivated the present study to investigate this association in participants with IBS and a healthy control group using validated questionnaires with dimensional measures.

Aim and Hypotheses

The aim of this study was to investigate fatigue and its relation to sleep problems in patients with IBS. From the literature presented above, we had the following expectations:

H1: Patients with IBS would report more severe fatigue and sleep problems than a group of healthy controls, and the severity would be closely related to the severity of IBS symptoms.

H2: Self-reported severity of fatigue would be positively correlated with severity of self-reported sleep problems. This correlation would be strongest for items reflecting not being adequately rested, daytime impairment and dissatisfaction with current sleep.

H3: A subgroup of patients with IBS would report a fatigue at a severity level above a cut-off score indicating a need of medical attention. This subgroup would report more severe sleep problems and IBS symptoms.

Method

Participants

The participants and the data used in this master thesis have been collected as part of a larger project, the Bergen Brain-Gut project (see braingut.no). Participants were recruited through posters hung up in different locations at Haukeland University Hospital and the University of Bergen, as well as through posts on social media. All who volunteered to participate were screened by a nurse via a phone call to make sure that they fulfilled the inclusion criteria and did not have any of the exclusion criteria (see section "Inclusion and Exclusion Criteria"). After the screening process 102 participants were included in the study (see Figure 2).

Inclusion and Exclusion Criteria

The Bergen Brain-Gut project had several strict inclusion and exclusion criteria.

Inclusion criteria: age between 18-65 years, meeting the ROME IV criteria: abdominal pain at least one day per week for the least three months, with symptom onset at least six months ago, as well as two or more of the following criteria: pain related to defecation; pain related to

change in frequency of stool; pain related to change in form of stool. The participants were also required to have a score of at least 175 according to the IBS-Severity Score System (IBS-SSS).

Exclusion criteria: pharmacological treatment that can affect the gastrointestinal tract (including medication for anxiety and depression); organic disorders such as celiac disease, inflammatory bowel diseases, diabetes, active Helicobacter pylori infection, polycystic ovarian syndrome, or neurological illnesses such as multiple sclerosis, Parkinson's disease and amyotrophic lateral sclerosis; treatment with antibiotics the last 3 months; probiotic or lowFODMAP diet the past 3 months; being a vegan or vegetarian; regular use of pain medication; pregnancy; previous intestinal surgery except from appendectomy; claustrophobia or metallic implants that are not compatible with MRI; travel outside of Europe the last 3 weeks (or plan of travelling in the near future); participation in other clinical studies at the same time as this one; lacking ability to understand and respond to questions or following diet instructions (Berentsen et al., 2020).

Measurements

Irritabel Bowel Syndrome – Severity Scoring System (IBS-SSS)

IBS-Severity Scoring system (IBS-SSS) is a questionnaire used to assess the severity level of IBS. The questionnaire contains five questions related to abdominal pain, distention, bowel habits and quality of life. Each of the five questions has a max score of 100, meaning that the max score of the test is 500. A score between 75-175 defines mild, 175-300 moderate and >300 severe symptoms (Francis et al., 1997). Most of the patients with IBS included in the Bergen Brain-Gut project obtained an IBS-SSS score that was at least 175 points.

Chalder Fatigue Scale (CFQ-11)

The Chalder Fatigue Scale (CFQ-11) is a questionnaire containing 11 questions regarding how the responder perceives their own level of fatigue. There are four options to choose from: “less than usual”, “not more than usual”, “more than usual” and “much more than usual”, or variations of that depending on the nature of the question. There are two scoring systems available for this questionnaire, the bimodal system, and the Likert system. For the present study the bimodal system was used, which counts the number of symptoms, where the two first response categories give 0 points, while the two latter response categories give 1 point. Minimum point score is 0, maximum point score is 11. A participant is defined with “severe fatigue” if they obtain a score of 4 or above. (Chalder et al., 1993). In the present study this cut-off is used to define patients with and without fatigue.

Bergen Insomnia Scale (BIS)

The Bergen Insomnia Scale is a questionnaire containing six questions about sleep. The responders rank each question on a Likert scale from 0-7, indicating how many days a week during the past month they have experienced the symptom in question (Pallesen et al., 2008).

In the present study we used a quantitative scoring system, where scores on all items were added. To check for the presence of insomnia, we used the following definition from the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (Bell, 1994): a score of at least 3 or more on one of the items 1-4 and a score of 3 or more on one of the items 5-6 to get the diagnosis insomnia vs. a score of 2 or less on all the items 1-4 or a score of two or less on all the items 5-6 for no insomnia diagnose. The first three items of BIS (BIS 1-3) give measures of prolonged sleep onset, long nocturnal awakenings, and early morning awakening, while answers on the last three reflect the participant’s experience of not being adequately rested, daytime impairment and dissatisfaction with current sleep (BIS 4-6).

Ethical considerations

The Bergen Brain-Gut project at Haukeland University Hospital was approved through the Regional Ethical Committee for medical research ethics. All the participants were informed about the procedures and that they could withdraw their participation at any time. All the data were anonymised and saved at a secure server connected to Helse Bergen, and physical paper has been stored at a secure archive at Haukeland University Hospital. All the participants signed a consent form, they were also informed that they could withdraw from the study at any time and that they could ask for information about results. Any medically relevant information that was discovered during the assessment procedure would be disclosed to the participant.

Data analysis

All the data were transferred from FileMakerPro (CFQ-11), CheckWare (IBS-SSS) and manually (BIS) into an Excel sheet. The data was transferred into Jamovi 2.2.5 for analysis. Shapiro-Wilks tests were performed to measure normality. For the data used in H1 it was significant for IBS-SSS (p = < .001) and CFQ-11 (p = < .001), but not for BIS (p = .061) when the entire dataset was included. Because the analysis would also include data where the IBS group and the healthy control group were isolated, a Shapiro-wilks test was also performed for these groups separately. Isolating the IBS group IBS-SSS (p = < .001) and CFQ-11 (p = < .001) were significant, while BIS (p = .719) was not. Isolating the HC group, IBS-SSS (p = .006), CFQ-11 (p = < .001) and BIS (p = .007) were all significant. Because of this Mann Whitney U test and Spearman's rho will be used in the analysis in H1. In H2 BIS 1-3 (p = < .001) and BIS 4-6 (p = .007) were both significant when the entire dataset was included. When the IBS group was isolated BIS 1-3 (p = .22) and BIS 4-6 (p = .11) were not significant, but when the healthy control group was isolated BIS 1-3 (p = < .001) and BIS 4-6 (p = .01) were significant. Because CFQ-11 will also be used in the analysis in H2, all analysis will be non-parametric. In H3 we

are only looking at those with and without severe fatigue within the IBS group. For the group with severe fatigue IBS-SSS (p = < .001) was significant, while BIS (p = .89) was not. For the group without fatigue IBS-SSS (p = .66) and BIS (p = .58) neither were significant. Any results from analysis including IBS-SSS in the severe fatigue group will be reported using non-parametric measures. QQ plots were used for visual observation and to remove any extreme outliers. One outlier from the IBS group was removed based on these observations. Levene's test was performed to test the violation of equal variance. Non-parametric results will be described using median (Md) and range (R), while the normally distributed data will be described with mean (M) and +/- one standard deviation (SD). The level of statistical significance was set to p = < .05, and effect sizes will be reported.

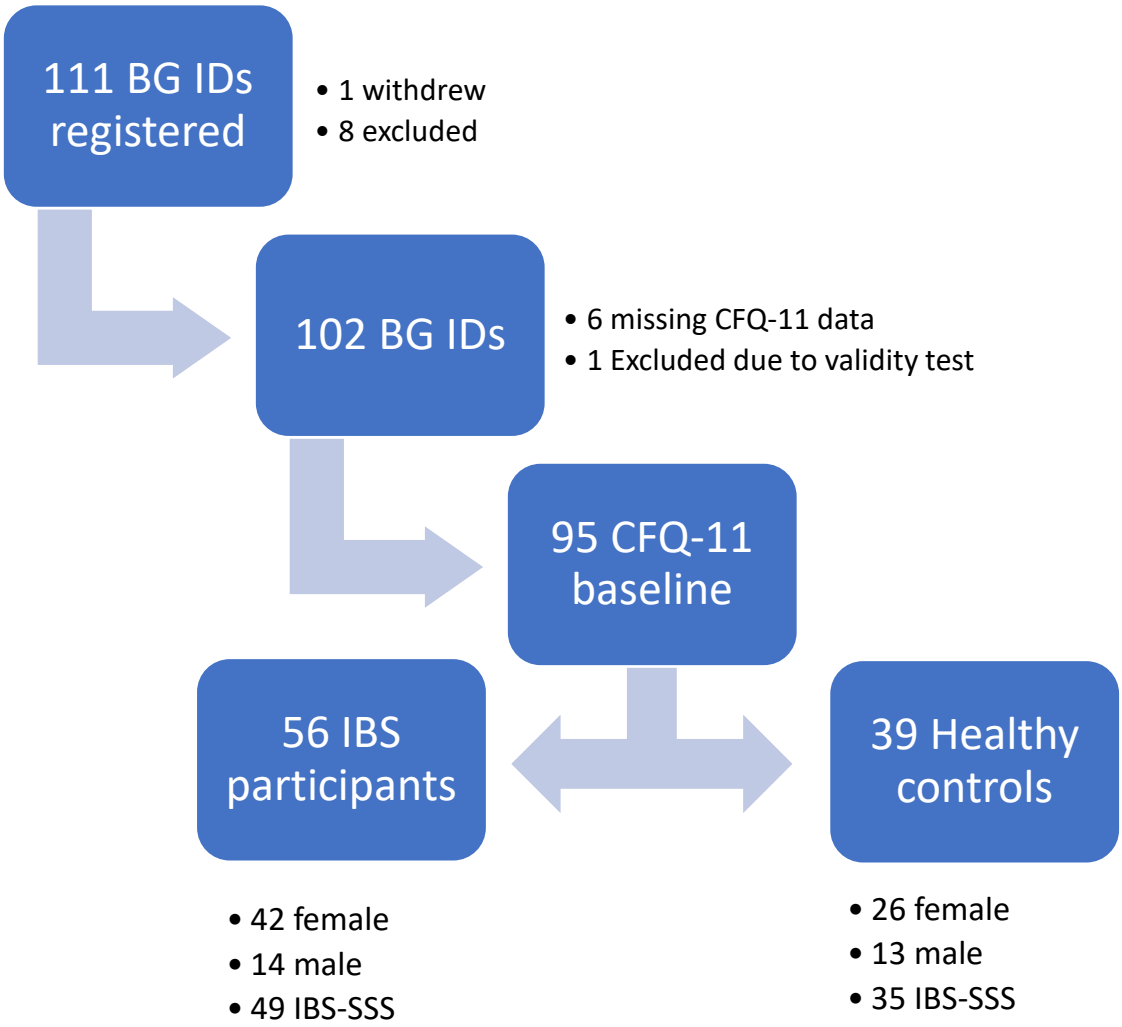
Results

Characteristics of the IBS and the healthy control group

Out of the 111 participants of the Bergen Brain-Gut project, 95 participants were included in the data analysis, 69 females and 27 males, with an age range from 19-61 years. Out of 95 participants, 56 were categorised in the IBS group, and 39 participants were in the healthy control group (Figure 2). Only 49 participants in the IBS group and 35 participants in the healthy control group completed the IBS-SSS. Forty-nine participants were defined as having "severe fatigue" (i.e., a score equal to or above 4 on the CFQ-11), of whom 40 were from the IBS group. In the IBS group 41 (73%) participants were defined with insomnia based on their reports on BIS, while the number was 16 (41%) in the healthy control group.

Figure 2

Sample characteristics



Note. Abbreviations: BG = Brain Gut, ID = Identification, CFQ-11 = Chalder Fatigue Scale, IBS = Irritable Bowel Syndrome, IBS-SSS = Irritable Bowel Syndrome-Severity Scoring System

A Chi square test revealed no significant difference between the IBS group and the healthy control group regarding gender (X^2 = .785, N = 95, p = .376, Φ = .09). Table 3 shows that on average participants in both groups were in their thirties, with a non-significant difference between the groups.

Table 3

Characteristics of the IBS and HC group

	IBS (N = 56)	HC (N = 39)	Statistics	
	M ± SD	M ± SD	p	Effect size (rrb)
Age	37.5 ± 11.2*	36.4 ± 12.3	.583	.066
IBS-SSS (0-500)	275 ± 71.7	33.7 ± 30.3	< **.001**	1.00
CFQ-11 (0-11)	6.41 ± 3.61	1.56 ± 2.49	< **.001**	.724
BIS (0-42)	17.5 ± 7.06*	10.3 ± 6.91	< **.001**	.544

Note. * Mean and standard deviation used on parametric data. Statistics: p = Mann-Whitney U test. Abbreviations: N = Number, M = Mean, SD = Standard deviation, IBS = Irritable Bowel Syndrome, HC = healthy controls, IBS-SSS = Irritable Bowel Syndrome-Severity Scoring System, CFQ-11 = Chalder Fatigue Scale, BIS = Bergen Insomnia Scale.

Table 3 shows that the IBS group scored significantly higher on all the questionnaires compared to the healthy controls. Because of lack of normal distribution, a Mann-Whitney U test was used and revealed a significant difference *(p* = <.001*)* between the IBS group and the healthy control group on the measures of IBS severity, fatigue, and sleep problems, with large and medium effect sizes for all the three scales (see Table 3).

Severity of IBS and results on the fatigue and sleep problems subscale

Next, we investigated the correlation (Spearman's rho) between the IBS-SSS score and the CFQ-11 score, and the correlation between the IBS-SSS score and the BIS score. A moderate correlation was found between scores on the CFQ-11 (*N* = 95, *Md* = 4, *R* = 11) and the IBS-SSS (*N* = 84, *Md* = 207, *R* = 426) (Figure 3a), and a moderate correlation between the BIS score (*N* = 95, *M* = 14.5, *Sd* = 7.81) and the IBS-SSS score (Figure 3b). Figure 3c and 3d show the results separately for the two groups and reveal non-significant correlations between the IBS-SSS score and each of the CFQ-11 and the BIS scores.

Figure 3a

Correlation between fatigue and IBS severity

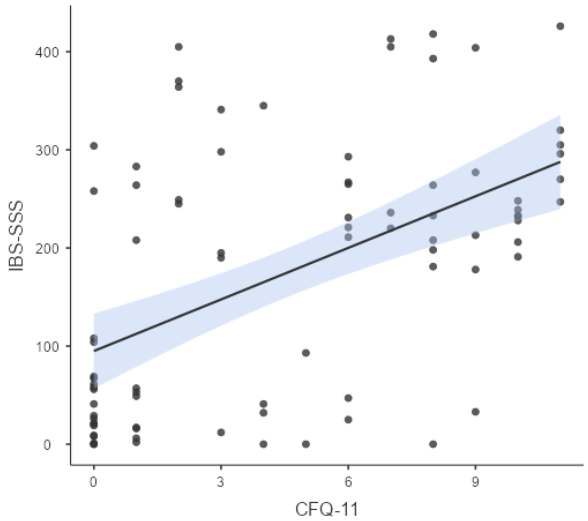


Figure 3b

Correlation between sleep and IBS severity

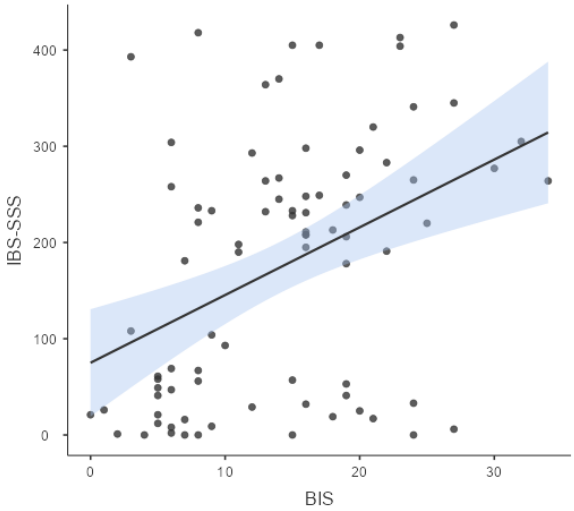


Figure 3c

Correlation between sleep and IBS severity

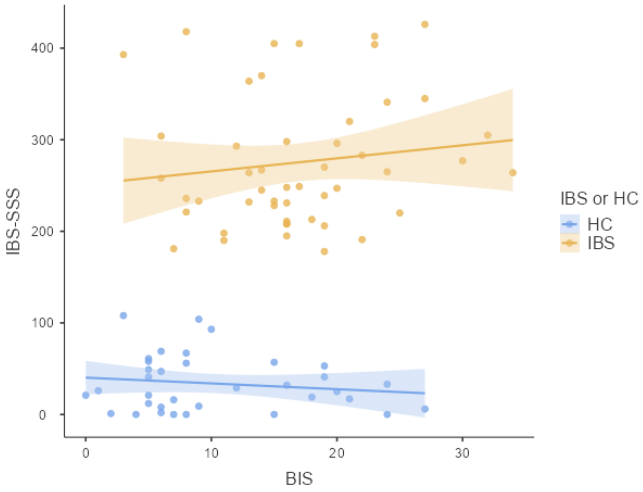
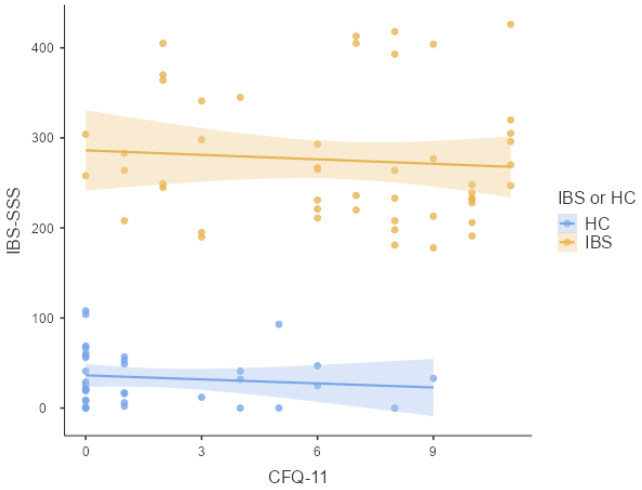


Figure 3d

Correlation between fatigue and IBS severity



Note. 3a) Entire dataset is included. N = 84, p = <.001, rho = .495. 3b) Entire dataset is included. N = 84, p = <.001, rho = .390. 3c) BS and healthy control groups separated. IBS: N = 49, p = .204, *rho* = .185. HC: N = 35, p = .670, *rho* = -.075. 3d) IBS and healthy control groups separated. IBS: N = 49, p = .593, *rho* = -.078. HC: N = 35, p = .351, *rho* = -.163. Abbreviations: HC = Healthy Control, IBS = Irritable Bowel Syndrome, IBS-SSS = Irritable Bowel Syndrome-Severity Scoring System, BIS = Bergen Insomnia Scale, CFQ-11 = Chalder Fatigue Scale.

Fatigue and its relation to sleep problems

The correlation (Spearman's rho) between the CFQ-11 and the BIS scores was moderate (Figure 4a) when results from both the IBS and the healthy control group were included in the analysis. When analysed within the IBS group, the results showed a positive correlation with a

medium effect size (Figure 4b) between the CFQ-11 score and the BIS score, and a positive corelation with medium effect size for the healthy control group (Figure 4b).

Figure 4a

Correlation between fatigue and sleep

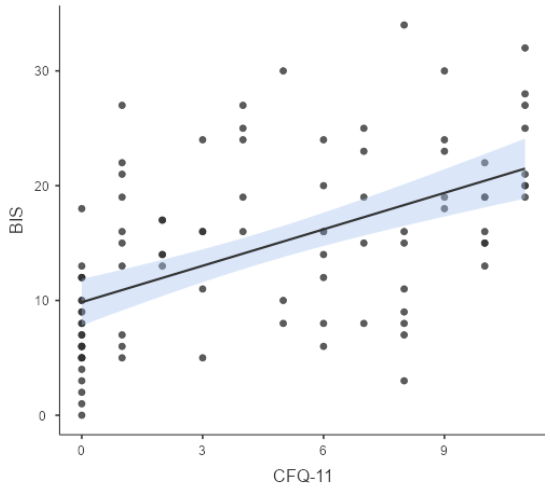
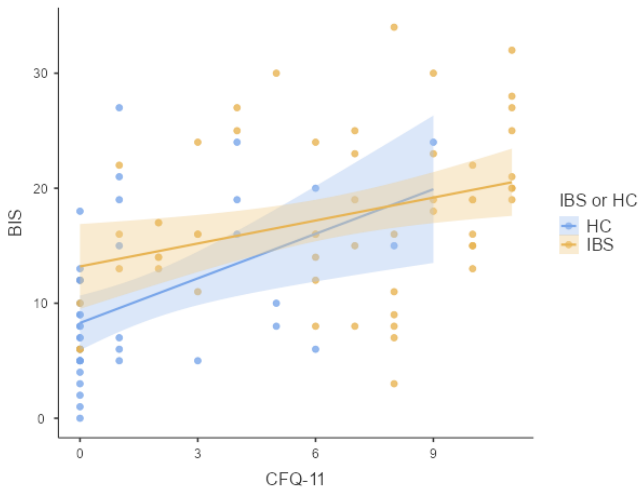


Figure 4b

Correlation between fatigue and sleep



Note. 4a) Entire dataset is included. *N* = 84, *p* = < .001, *rho* = .594. 4b) IBS and healthy control groups separated. IBS: *N* = 49, *p* = .003, *rho* = .386. HC: N = 35, *p* = .001, *rho* = .503.
Abbreviations: HC = Healthy Control, IBS = Irritable Bowel Syndrome, BIS = Bergen Insomnia Scale, CFQ-11 = Chalder Fatigue Scale.

When splitting the BIS into a sum of items reflecting prolonged sleep onset, long nocturnal awakenings, and early morning awakenings (BIS 1-3) (*N* = 95, *Md* = 5, *R* = 16) and a sum of items reflecting not being adequately rested, daytime impairment and dissatisfaction with current sleep (BIS 4-6) (*N* = 95, *Md* = 9, *R* = 21), the results showed that the correlation with the CFQ-11 score was significantly stronger for the BIS 4-6 items (Figure 5b) than the BIS 1-3 items (Figure 5a). When the analysis was restricted to the IBS group, statistical significance was retained for the correlation between the CFQ-11 the BIS 4-6 (*N* = 56, *M* = 11.1, , *Sd* = 5.13) items (Figure 5d) but not for the BIS 1-3 (*N* = 56, *M* = 6.41, *Sd* = 3.82) items (Figure 5c).

Figure 5a

Scatterplot for BIS 1-3 and fatigue

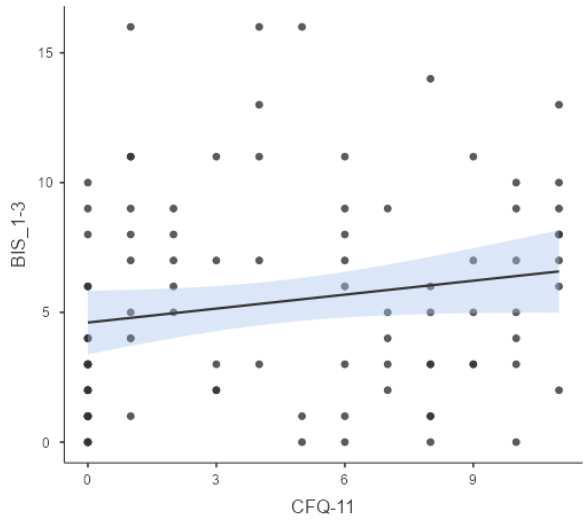


Figure 5b

Scatterplot for BIS 4-6 and fatigue

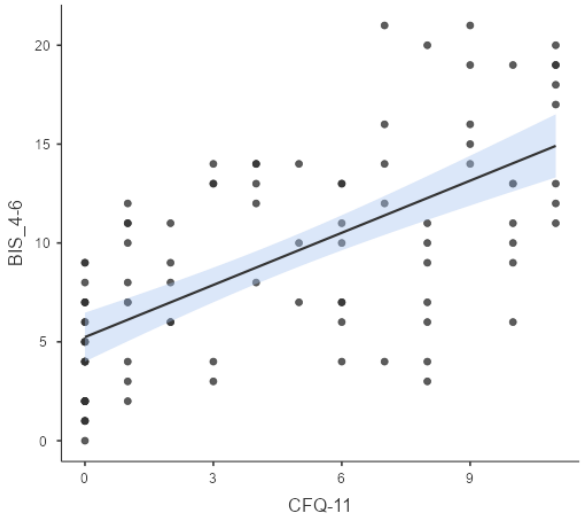


Figure 5c

Scatterplot for BIS 1-3 and fatigue

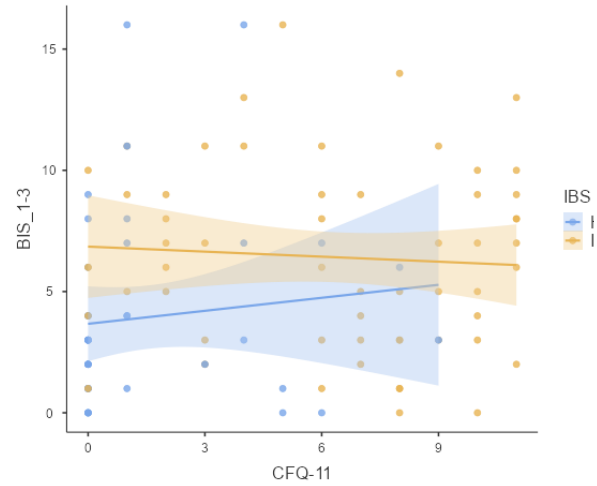
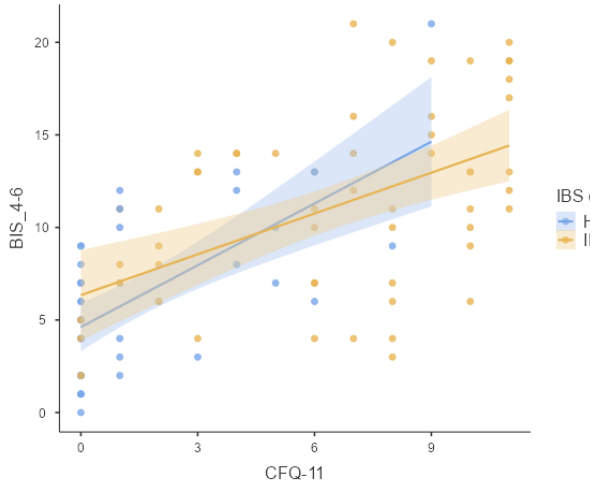


Figure 5d

Scatterplot for BIS 4-6 and fatigue



Note. 5a) Entire dataset is included. *p* = .014, *rho* = .251. 5b) Entire dataset is included. *p* = < .001, *rho* = .669. 5c) IBS and healthy control groups separated. IBS: *p* = .736, *rho* = .126. HC: *p* = .152, *rho* = .234. 5d) IBS and healthy control groups separated. IBS: *p* = < .001, *rho* = .500. HC: *p* = .006, *rho* = .433.
Abbreviations: IBS = Irritable Bowel Syndrome, HC = Healthy controls, CFQ-11 = Chalder Fatigue Scale, BIS 1-3 = Bergen Insomnia Scale items 1-3. BIS 4-6 = Bergen Insomnia Scale items 4-6.

Sleep and IBS symptoms in patients with IBS defined with severe fatigue

A total of 40 patients with IBS were defined with severe fatigue according to the definition given in the method section (a score equal to or above 4 on the CFQ-11). A Chi

square test revealed no significant difference between the fatigue groups regarding gender (X^2 = .00, N = 56, p = 1, Φ = .00). There were also no significant differences between the two groups regarding age and IBS severity, but the "severe fatigue" group had significantly higher scores on the BIS scale compared to the rest of the group (Table 4).

Table 4

Demographics of the fatigue and no-fatigue group (IBS)

	Severe Fatigue		**No-Fatigue**		Statistics	
	N	M ± Sd	N	M ± Sd	p-value	Effect size
Age	40	37.5 ± 11.71	16	37.4 ± 10.3	.969	.011
IBS-SSS (0-500)	35	272 ± 74.1	14	284 ± 67.2	.465*	.136**
BIS (0-42)	40	18.8 ± 7.42	16	14.2 ± 4.85	.027	.674

Note. Statistics: p = Student's t. *Mann-Whitney U test. Effect size = Cohen's d. **Rank biseral correlation. Abbreviations: N = number, M = mean, Sd = standard deviation, IBS-SSS = Irritable Bowel Syndrome-Severity Scoring System, BIS = Bergen Insomnia Scale.

A student's t-test showed that the group defined with severe fatigue showed statistically higher score on the BIS scale (Table 4) compared to the rest of the IBS group. A Mann-Whitney U test was not significant for the IBS-SSS score. This means that those suffering from severe fatigue also had higher levels of sleep problems, but they did not experience more severe IBS symptoms than those without severe fatigue. Out of the 40 patients with severe fatigue, 32 (80%) have a BIS score indicating an insomnia diagnosis.

Discussion

The aim of the present study was to investigate the presence of fatigue in patients with IBS and its relation to sleep problems. Based on self-reports on a set of questionnaires, the patients with IBS reported significantly more severe fatigue and sleep problems compared to healthy controls, with a high percentage of patients with IBS reporting fatigue at a level that should lead to medical attention. Severity of fatigue was significantly correlated with severity level of sleep problems in the IBS group. A more detailed analysis showed that the correlation was substantially stronger between fatigue and sleep problems reflecting not being adequately rested, daytime impairment and dissatisfaction with current sleep, than between fatigue and problems related to prolonged sleep onset, long nocturnal awakenings, and early morning awakening. Surprisingly, our selected measure of IBS symptom severity (i.e., IBS-SSS) was not significantly correlated with fatigue nor sleep problems when analysed separately for the group of healthy controls and patients with IBS. These results will be discussed in the following paragraphs.

Fatigue and sleep problems in patients with IBS

The present study confirmed expectations of more severe fatigue and more severe sleep problems in patients with IBS compared to a group of healthy controls. These results are in accordance with results from several previous studies focusing on sleep problems (Khanijow et al., 2015; Lee et al., 2016; Wang et al., 2018) and fatigue in patients with IBS (Frändemark et al., 2017; Han & Yang, 2016; Piche et al., 2007). All these studies, including a meta-analysis of 36 studies conducted by Wang et al. (2018), showed a higher prevalence of sleep problems and fatigue in patients with IBS. Some of these studies contributed with more specific information about the biological underpinnings of fatigue and sleep problems in patients with IBS. A review by Khanijow et al. (2015) focused on the interplay between sleep disorders,

immune function, and gastrointestinal disorders. They found that poor sleep has been associated with the exacerbation of gastrointestinal symptoms, and that many gastrointestinal diseases affect the sleep-wake cycle and by this lead to poor sleep. The review also investigated how the immune system and gastrointestinal diseases are associated with sleep problems. They referred to Santos et al. (2007) who has shown that the sleep-wake cycle is affected by the release of cytokines, where specific cytokines promote fatigue and sleep behaviour. This has also been shown in another study (Vgontzas et al., 2002) reporting that some of the same cytokines were activated after sleeping only 6 hours per night instead of the recommended 8 hours. Maes et al. (1998) discovered that stress and anxiety can stimulate the production of pro-inflammatory cytokines. The production of pro-inflammatory cytokines which is tiggered by lack of sleep, stress and anxiety will in turn promote fatigue and sleep problems, and possibly also negatively affect IBS symptoms associated with the gastrointestinal tract. Frändemark et al. (2017) found that patients with IBS who suffered from severe fatigue also struggled more with anxiety and thus also experienced a higher stress response. Considering the biological underpinnings of stress, it would be interesting to investigate if patients with IBS and healthy controls would differ on a biochemical level. Weaver et al. (2018) investigated this and surprisingly found that patients with IBS and healthy controls did not differ on blood levels of cortisol and adrenocorticotropic hormone (hormones that are part of the HPA-axis). Despite this, patients with IBS had significantly higher perceived stress than the healthy controls. Results from this single study are not sufficiently strong to conclude that patients with IBS have a well-functioning HPA-axis. A previous study by Patacchioli et al. (2001) did find higher cortisol levels in saliva in patients with IBS than in a control group. The conflicting findings indicate that more studies on the biological aspects of stress in patients with IBS are required. There is however no question about the fact that patients with IBS do experience a higher level of perceived stress than healthy controls. It has been suggested that patients with IBS have a

decreased stress resilience, meaning that it is harder for them to bounce back after being exposed to stressors, that their tolerance for stressors are lower, and/or that being exposed to stress passing their limits will result in a worsening of symptoms (Park et al., 2018). To sum up, the associations between fatigue and sleep problems in IBS seems to not only impact each other but are also impacted by stress. A heightened stress response can also be the result of gastrointestinal symptoms, fatigue, and sleep problems, creating a downward spiral of symptoms that can be hard to break.

Associations between fatigue and sleep problems

The present study confirmed our expectations about positive correlations between self-reported severity of fatigue and severity of self-reported sleep problems. The BIS scale was also divided into two parts where one part included items related to not being adequately rested, daytime impairment and dissatisfaction with current sleep, while the other included items related to prolonged sleep onset, long nocturnal awakenings and early morning awakenings. We found that the correlation with fatigue was strongest for items related to not being adequately rested, daytime impairment and dissatisfaction with current sleep. The division of the BIS scale into two parts based on the nature of the questions shows the clinical validity of this questionnaire when assessing patients with IBS and probably also other patient groups with similar problems related to fatigue. By this separation, the BIS scale gave results that are in accordance with experiences commonly reported by patients with IBS. This can be exemplified by the following quote from a conversation with the case referred to in the introduction (Woman, 57):

> *"I almost never feel rested, no matter how long I sleep. Some nights I'm fast asleep for 10 hours, I do not remember waking up in the middle of the night, but I'm still exhausted when I wake up in the morning. On the worst days I'm not even able to get out of bed before I've rested an additional hour after waking up. Having to explain someone who has not experienced fatigue themselves that I have to rest after sleep before I'm able to start my day is quite difficult" – Woman, 57.*

In this example woman (57) clearly experiences not being adequately rested, daytime impairment and dissatisfaction with current sleep, and experiences no noticeable difference between the nights when she is getting 8+ hours of sleep, and the nights where she is not able to fall asleep until 3-4 o'clock in the morning. Consistent sleep deprivation over time would probably make her feel even worse, but even nights with the full 8 hours of sleep do not help to reduce her fatigue and improve her daytime functioning.

This dependency on the nature of the questions about sleep problems was intriguing and elucidates the importance of sleep quality. This was supported by Lavidor et al. (2003) who investigated subjective sleep quality as a predictor of fatigue and the impact of quantitative sleep measures such as sleep onset, nocturnal awakenings, and early morning arousals. They measured fatigue in a random sample by using three different questionnaires: the 5-items Tiredness Questionnaire, the 29-item Fatigue Assessment Instrument, and the Masuda Fatigue Questionnaire. Sleep was assessed by self-reports on four questions regarding prolonged sleep onset, number of nocturnal awakenings, and early morning awakening. The fourth question asked about subjective sleep quality rated on a scale from 1 (poor) to 5 (excellent). They also measured symptoms of depression and somatization (e.g., backache, nausea, loss of appetite, allergy), and found that these measures together with the subjective sleep quality ratings were

better predictors of fatigue than prolonged sleep onset, number of nocturnal awakenings, and early morning awakenings.

Even stronger arguments for the importance of including measures of perceived sleep quality in studies of fatigue have been given by studies including objective measures of sleep. Already in the late 1990s Sharpley et al. (1997) discovered that patients with chronic fatigue who did not feel rested after sleep, did not have abnormal polysomnography data, meaning that their objective sleep measures was the same as in a group of healthy controls. This suggests that despite having objectively normal sleep, the participants in these studies suffered from fatigue and subjectively considered their own sleep to be unfulfilling. Furthermore, Patel et al. (2016) reported that patients with IBS slept longer per night than healthy controls but still felt less rested. However, patients with IBS had more awakenings during the night meaning that they experienced worse sleep quality than the healthy control group, despite sleeping longer. These nocturnal awakenings were associated with worsening of abdominal pain and lower general- and IBS-specific quality of life. A large study by Lee et al. (2016) showed that participants with insomnia were more likely to have IBS than participants without insomnia. Based on ROME II criteria they identified 374 participants with IBS in a pool of 3429 participants. Insomnia was determined by asking questions about sleep onset, nocturnal awakenings, and early morning awakenings, with a similar content as the first 3 items on the BIS scale. The participants were not asked any questions about perceived quality of sleep or daytime functioning. Despite this the authors found a higher prevalence of patients with IBS amongst patients with than without insomnia. In the present study we found no correlation between IBS-SSS score and BIS 1-3 items (prolonged sleep onset, long nocturnal awakenings, and early morning awakening) when the analysis was restricted to the IBS group, and only a small correlation when the entire dataset was included.

Chronic fatigue is not restricted to patients with IBS. We still do not know exactly why some patients with IBS experience fatigue, and if the pathophysiology of fatigue in patients with IBS are different from patients with post-viral fatigue. Fatigue after a viral infection is well recognised, for example after mononucleosis (Katz et al., 2009). Recently it has also been reported after a Covid-19 infection, commonly referred to as long-covid (Raveendran et al., 2021). Even though the cause of this post-viral fatigue is still mostly unknown Katz et al. (2009) suggested that the development of chronic fatigue after mononucleosis infection may be associated with dysregulation of the immune system, as well as abnormalities in the HPA-axis. They also found no correlation between the severity of the initial infection and the development of chronic fatigue. Similarly, in long-covid, fatigue was found in over half of the patients after recovering from the covid-19, also including those who had mild covid-19 symptoms (Carfì et al., 2020; Townsend et al., 2020). Research on long-covid is still in its early stages, but some theories suggest that chronic fatigue may be related to inflammation and immune dysregulation (Koralnik & Tyler, 2020). Dantzer et al. (2008) theorised that fatigue was natural sickness behaviour, but in some cases the fatigue response might continue after the initial infection has passed. Future studies will probably show us similarities and differences between disorders characterised with fatigue.

In the present study we found no correlation between severity of IBS symptoms and severity of sleep problems and fatigue when the analysis was isolated to the IBS group. However, the association was statistically significant when the control group was included in the analysis. This may imply that fatigue and sleep problems are associated with severity of IBS symptoms when analysed along the full spectrum of symptoms assessed by the IBS-SSS, but that the inclusion criteria led to a low inter-group variability by defining IBS primarily in patients with an IBS-SSS score of 175 and above. This effect may also have been exaggerated by the low number of included patients with IBS in the present study.

IBS patients with severe fatigue

More than 70% (n=40) of the patients with IBS in the present study were defined with severe fatigue, i.e., a score equal to or above 4 on CFQ-11. When comparing IBS patients with and without fatigue, we saw that sleep issues were less prominent in the latter group, and 32 out of 40 (80%) patients in the severe fatigue group scored high enough on the BIS scale to meet the criteria for insomnia. However, the severity of IBS symptoms was not higher in the severe fatigue group, compared to the group without fatigue.

Similar findings were reported in a study by Piche et al. (2007) where 62.7% of the IBS participants suffered from fatigue based on a score equal to or above 4 on the fatigue impact scale, a percentage significantly higher than in the healthy control group. Frändemark et al. (2017) investigated the impact of fatigue in patients with IBS compared to the impact of symptoms of depression and anxiety. Using the fatigue impact scale total score, they found that 40% of the patients had severe fatigue, 35% had moderate fatigue, 26% mild fatigue, and 44% of the patients reported that fatigue was one of their most distressing symptoms, and 4% that it was their most distressing symptom. In the present study 71.43% of the IBS participants were defined with severe fatigue by scoring equal to or above 4 on CFQ-11. For comparison, in a meta-analysis of 17 studies Han and Yang (2016) found that the frequency of fatigue in patients with IBS was 54.2%.

Considering the high prevalence of fatigue in IBS patients, and that 17% of the patients reported that fatigue is the symptom they struggle with the most, and over half of patients report that fatigue is just as bad as their gastrointestinal symptoms (Piche et al., 2007), it is indeed important to take fatigue into account when designing treatment options for this group of patients. As has been shown through the literature presented in the introduction, every symptom tends to affect other symptoms. It is not a simple linear structure, where sleep problems cause IBS and IBS cause fatigue, and that everything would be fine if you fix the sleep problem or

fatigue. Sleep, pain, fatigue, anxiety, food, physical activity, depression, gut microbiota, stress, and social support are some of the challenges that affect our health. In this thesis we have only focused on fatigue and sleep, and we expect that the interaction between the two affects both symptom severity and everyday behaviours. Some of the triggers for IBS symptoms such as anxiety and stress (acute or chronic) (Ålander et al., 2008; Camilleri et al., 2012) are the same that trigger or maintain symptoms of fatigue. A malfunctioning HPA-axis, which can be the result of trauma or chronic stress, has negative consequences that affects the digestive system (Mayer, 2000), and a disrupted gut microbiota, dysbiosis, can lead to IBS-symptoms such as changes in intestinal motility and visceral hypersensitivity (Kennedy et al., 2014; Mayer & Tillisch, 2011). These symptoms can work in a feedback loop that increase the amount of stress, physical and psychological distress that the person experience, which again may trigger symptoms of fatigue. A correlation between fatigue and sleep does not mean causation. It is possible that a third factor, such as childhood abuse or trauma (van Tilburg et al., 2010) is responsible for developing both IBS and fatigue symptoms. It may in some cases only be responsible for one of them, as not everyone with IBS struggles with fatigue, and not everyone with fatigue experiences gastrointestinal problems. Based on the results of this study, showing a significant correlation between severity of fatigue and sleep problems, and that those with severe fatigue also experience the most severe sleep problems, we can support a conclusion that both symptoms affect each other, positively or negatively. This means that when a patient is left untreated for a long period of time, it may lead to more severe symptoms. This is of course not restricted to sleep and fatigue. What started as “just” gastrointestinal pain may in other words develop into fatigue, muscle-joint pains, anxiety, and depression, making the symptom pattern fairly complex. It may also mean that if one of the symptoms is treated, it will probably also be easier to treat another symptom, and by this both would be less prominent. Somatic symptoms from an emotional or psychological trauma might cease once the trauma has been

treated. In the same sense IBS symptoms that are an expression of untreated trauma or anxiety might cease once the trauma or anxiety have been processed through treatment.

> *"I do wonder what my life would have been like if the doctors had taken me seriously earlier. Perhaps I would have been able to work full time, have hobbies and a social life? I have no doubt that the stress created from the symptoms themselves have made me worse. Being chronically ill is a fulltime job."* – *Woman, 57.*

Limitations and methodological issues

The main strength of the present study was the inclusion of participants from an ethically approved project supported by grants from the Research Council of Norway and Health West. All participants were evaluated by medical specialists at the Haukeland University Hospital.

There is, however, several limitations that should be mentioned, both regarding the measures included and the criteria used to define a patient with IBS.

Although CFQ-11 is a valid measure of fatigue its response options may seem strange for those who have been struggling with chronic fatigue over a long period of time. Some severe cases may still respond "not more than usual" to many of the questions, and by this indicating that they do not have fatigue, while they really have struggled with severe fatigue for a long time. Even though the instructions state that the responder should compare their current symptoms with the last time they felt well, those who have had fatigue for 6 months or more, may not have a reference for what it feels like to be without fatigue symptoms, and thus ends up responding "not more than usual". This scale is good at measuring individual/group improvement over time but might not give the most accurate picture of baseline fatigue in a group of people. Using a questionnaire such as for instance Fatigue Impact Scale (Fisk et al., 1994) would probably have been a better choice for the present study.

The BIS scale was used to measure sleep problems. The BIS scale was originally developed as a diagnostic tool for insomnia, but the six questions still provide a good insight into the level of the participants' sleep problems and what they struggle with the most. In this study the BIS scale was divided into two parts, one measuring prolonged sleep onset, long nocturnal awakenings, and early morning awakenings (BIS 1-3), and the other measuring the participant's experience of not being adequately rested, daytime impairment and dissatisfaction with current sleep (BIS 4-6). There were no objective sleep measures included in the present study. Still, we will argue for the validity of self-reports on the BIS scale. In the present study we showed that a difference between BIS 1-3 and BIS 4-6 could be used to show that items reflecting not being adequately rested, daytime impairment and dissatisfaction with current sleep is more closely related to symptoms of fatigue and gastrointestinal symptoms than prolonged sleep onset, long nocturnal awakenings, and early morning awakenings. Furthermore, studies that have included objective sleep measures, such as polysomnography, show that these data are worse as predictors of fatigue and gastrointestinal symptoms than the subjective reports of sleep quality.

Parts of the criteria for including patients with IBS was to have a minimum score of 175 on the IBS-SSS, meaning that the patients should have moderate to severe IBS symptoms. Because of this we have ended up with an IBS group with less variation than what would be expected among patients with IBS in the general population. All patients with mild IBS symptoms were by this not included. In the present study we detected that three of the participants in the healthy control group obtained scores above 75 on the IBS-SSS scale. Expecting to find a high prevalence of mild IBS symptoms in the population, inclusion of healthy controls and IBS patients irrespective if IBS-SSS scores would have given us a sample that would have covered the whole spectrum from none to severe symptoms on this IBS-SSS scale. This inclusion procedure is recommended when designing future studies.

This study used the ROME IV criteria as part of the inclusion criteria for the IBS group, while many of the cited studies have used the ROME III criteria or earlier versions. The new criteria are not vastly different from the old, but there are some key differences. For instance, according to ROME IV abdominal pain should be related to defecation, while in ROME III pain or discomfort should be improved with defecation. Although, a lot of patients with IBS do feel an improvement in pain after defecation, this is not always the case. ROME IV would therefore also include those who do not feel immediate relief after defecation. The two other criteria of ROME IV are as follows: [pain is] associated with a change in frequency of stool and with a change in form of stool. In comparison the ROME III criteria states: Onset [of pain] associated with a change in frequency of stool and change in form of stool. Again, the ROME IV criteria are more inclusive, as for some sufferers the pain would not necessarily only be associated with the onset of change in frequency or form. ROME IV include those who experience pain before, during and after defecation, and those who experience pain in regard to change in frequency or form of stool in general, and not just those who start experiencing pain when the frequency or form changes. Another change from ROME III to ROME IV was the removal of the word “discomfort”. On the one hand the word discomfort can be quite vague and might in some cases include people who do not have gastrointestinal issues above what is considered normal. However, patients with IBS do sometimes explain their symptoms on a range from pain to discomfort, where discomfort is not as intense or debilitating as pain, but still enough to draw attention to. Spiegel et al. (2010) found that patients do not have a shared understanding of what “discomfort” means. However, the new criteria in ROME IV without the word “discomfort”, may make it easier for patients to respond, as the word “pain” may be less open for individual interpretation than “discomfort”. The requirement of frequency of symptoms also changed from at least 3 days/month for the last 3 months in ROME III to 1day/week for the past 3 months in ROME IV.

Clinical implications and future research

The findings of the current study show that the included patients with IBS struggle more with sleep problems and fatigue than the participants in the healthy control group. This is in line with previous studies pointing to the complexity of IBS and underscores that IBS should be defined under the umbrella term of disorders of the gut-brain interaction. Further, this study showed that sleep problems related to being adequately rested, daytime impairment and dissatisfaction with current sleep was more closely related to fatigue than sleep problems related to prolonged sleep onset, long nocturnal awakenings, and early morning awakenings. These results are essential as they must be taken into account when designing future studies investigating the relationship between sleep and fatigue more closely. In such a study, we would recommend that the CFQ-11, with response categories asking for change, should be exchanged by a fatigue scale giving a wide range of responses, for example the Fatigue Impact Scale (Fisk et al., 1994). Furthermore, the study should include physiological and psychometric cognitive to enable comparisons between self-reported symptoms of fatigue and objective sleep measures and measures of what the patients commonly refer to as a brain-fog. From Sharpe (2006) we have learned that self-reported and psychophysiological measures seems to assess different aspects of sleep problems. This calls for studies in a group of patients with IBS, both regarding different measures of sleep and between subject reports of cognitive problems related to brain-fog and performance on psychometric tests of cognitive function. Regarding sleep, the results of the present study should definitely inspire researchers to assess objective sleep measures of sleep onset, number of awakenings, time spent in the different sleep stages and investigate how these are associated with self-reported symptoms of IBS and fatigue.

The high frequency and severity of sleep problems and fatigue in patients with IBS, underscore the importance of developing treatment options targeting fatigue and sleep problems in patients with IBS. Although IBS is defined as a disorder of the gut-brain interaction, there

are patients who still experience that treatment options are only directed towards their gastrointestinal symptoms, and that any other experienced symptoms are not taken into consideration as a treatment target. Some may not even be informed by their health care provider that fatigue and sleep problems are common symptoms in IBS sufferers.

> *"When I first read about IBS, years before I was diagnosed officially, I got the impression that it just affected the digestive system. There was no information about how it also affects and is affected by sleep, or how it can also give symptoms such as muscle pains or fatigue, or even how it will affect you cognitively. I guess I thought IBS was just a 'really bad stomachache', the same way some people have told me that they think a migraine is just a 'really bad headache'. Those are people who have never experiences a migraine attack by the way." – Woman, 57.*

The first step of treatment should always be to educate the patient on the complexity of their own diagnosis. A problem with this is that not all health care providers have the knowledge about the complexity of IBS. The "IBS-School" at Haukeland University Hospital in Bergen is a great tool for educating patients and next of kin. The "IBS-School" aims to educate the participants about IBS, how to live with it and how they can positively affect their own health. The course consists of lectures by doctors, psychologists, dietitians, physiotherapists and patients with IBS talking about their own experiences. It is also a good place to exchange experiences and connect with other people with the same disorder.

> *"I attended the IBS-school when I was diagnosed. One thing I struggled with was experiencing that my own thoughts could trigger the symptoms. I had been told by so many people, doctors included that 'it is all in your head', and the fact that symptoms*

could be triggered by my thinking could prove that? But the explanation I got at the IBS-school helped me realize that it is not just about thinking the right or wrong things, and that IBS is a complex illness that are affected by so many different things. I think many people have a tendency to think that anything that does not have a very clear, objective and physical cause is not really real. Thoughts and emotions are only part of it what triggers my IBS, but just because pain or urge is triggered by worry or anxiety does not mean it is not real. And it helped a lot to hear that from health care professionals" – Woman, 57.

Besides educating the patients about their own diagnosis, it is important to offer them treatment options that can help lessen or relieve their main symptoms. It is thus important for the health care provider and patient to define the severity of symptoms and figure out what treatment option is best suited. It is of course a challenge that every patient with IBS may have an idiosyncratic set of challenges, but this should rather inspire a thorough examination that covers gastrointestinal, social, emotional, and cognitive factors. This is indeed important, because the experience of starting a course of treatment that you are not able to finish, might be more detrimental for the patient's mental health than never trying that treatment option at all. This may also discourage the patient from seeking other treatment options in the future, in fear of failing once more. Based on my own personal experience and through communications with other patients with IBS, it seems like the health care system generally are negative towards patients who are not able to finish a treatment program. Instead of giving the patient support, the health care provider may give up on the patient and even clearly demonstrate a wish to move on to the next patient (which is an understandable response in a system that has too many patients and too few health care providers, but still clearly detrimental for the patients who do

need some extra support). In other words, there is room for improvement of importance of symptoms of fatigue, sleep problems as well as a wide range of other health parameters.

As presented in the introduction, there are some treatment options for IBS that have shown positive results on fatigue and sleep problems. Reducing the severity level of fatigue as well as gastrointestinal symptoms have for example been shown in studies on faecal microbiota transplant treatment (Johnsen et al., 2020). However, faecal microbiota transplant is still in the early stages of research and is not yet offered as a treatment option for IBS through the public health care service in Norway. More research is thus needed on this treatment approach. It would for example be interesting to know if results of the present study could be confirmed by results from a longitudinal study on fatigue and sleep problems.

The lowFODMAP diet is another intervention that seems to be more available for patients with IBS. In addition to improving gastrointestinal symptoms, this diet us shown to improve overall quality of life and suboptimal physical activity (Eswaran et al., 2017), and by this probably also reducing the severity level of symptoms of fatigue. Here, it should be mentioned that reduced severity of fatigue as well as sleep problems have been presented from preliminary analyses of data from the Bergan Brain-Gut study, where a subgroup of the IBS patients have been part of a 12-week lowFODMAP intervention program (personal communication). A downside of this intervention program is that it can be difficult to follow a strict dietary procedure, and a positive effect may be difficult to maintain after the treatment period is finished. This could indeed be challenging for patients experiencing severe fatigue and sleep problems. For those patients it should be of great importance to have regular contact with a dietitian and other health care professionals to personalise this treatment program for the given IBS patient. Both the faecal microbiota transplant and the lowFODMAP intervention are treatment programs start from the gut microbiota part of the disorder, faecal microbiota transplant by introducing a new culture of bacteria to the intestines, and lowFODMAP by

excluding the intake of certain carbohydrates and thereby altering the gut microbiota and improving IBS symptoms.

Cognitive behavioural therapy is another commonly used treatment for patients with IBS that primarily start with cognitive and emotional functions that at least until recently have been linked primarily to brain functions. This form of treatment is used to remediate both symptoms of IBS, fatigue, and sleep problems as well as anxiety and stress, with a positive effect shown on them all (Malouff et al., 2008). Graded exercise therapy and adaptive pacing therapy are two therapies inspired by cognitive behavioural therapy but are more targeted toward fatigue. Graded exercise therapy focuses on increasing the amount, duration and intensity of physical activity that the patient is capable of, by slowly increasing in, without overexerting the patient (Larun et al., 2019). Adaptive pacing therapy focuses on teaching the patient how to regulate their activity based on how they are feeling on that day, meaning that some days they are able to do more or less than other days (Goudsmit et al., 2012). It is vividly debated which of these forms of therapy is the most efficient for a given patient. White et al. (2011) found that cognitive behavioural therapy and graded exercise therapy used in addition to medical care resulted in a moderate improvement of symptoms, while adaptive pacing therapy had no additional effect. However, ME Association (2010) conducted a survey and found that patients experiences most symptom improvement using adaptive pacing therapy, no difference using cognitive behavioural therapy and felt worse using graded exercise therapy.

The studies referred to above show the need of more knowledge about the efficiency of different treatment programs and how to develop new programs targeting symptoms like fatigue and sleep problems in patients with IBS. The following two studies including patient groups with other disorders characterised by severe fatigue, may be used to inspire such studies. White et al. (2011) recruited 641 patients with CFS and divided them into four groups based on treatment, cognitive behavioural therapy, graded exercise therapy, adaptive pacing therapy and

specialist medical care. The patients were given instructions on the therapy form they would follow and would then be followed up to record their progress. In a ME Association (2010) survey with over 4000 ME/CFS patients, 997 had experience with cognitive behavioural therapy, 906 with graded exercise therapy and 2137 with adaptive pacing therapy. These patients were not followed up or given a treatment program in coherence with the survey but relied on previous experience with the given forms of therapy. Adaptive pacing therapy allowed and taught the patients to listen to their own bodies and their needs, and in a situation where they constantly push their limits, they were encouraged by a health care provider to relax and not cross their body's boundaries. For a patient who normally is not pushing their boundaries adaptive pacing therapy might not do much to improve their symptoms. It is expected to have the best results for those who are close to their maximum limit on a daily basis.

As with the lowFODMAP intervention, cognitive behavioural therapy requires a lot of effort from the patient. They have to follow more or less strict rules and conduct challenging tasks to learn how to handle gastrointestinal symptoms and other features associated with having a disorder of the gut-brain interaction. Graded exercise therapy for example put an extra load on already severe problems but may still be of help in a longer time perspective. Overall, it is important to discuss limits and conduct a thorough examination of the symptom pattern of individual patients.

No matter what treatment option is selected for the patient, it is important to take all their challenges and strengths into account. The results of the present study supports that fatigue and sleep problems should be taken into account when assessing treatment options. Someone struggling with fatigue might not be able to start a new diet or attend classes for cognitive behavioural therapy as well as someone without. It is important to see the entire patient and how they function, instead of looking at each symptom in isolation.

Conclusion

IBS is defined within the umbrella term of disorders of the gut-brain interaction. By this the awareness of the widespread symptomatology of IBS has improved. This has made it easier for patients, relatives and health workers to understand the widespread symptomatology that characterise many patients with IBS. The present study has contributed by investigating these symptoms, fatigue ad sleep problems, their relations with each other and a measure of the severity of gastrointestinal symptoms. A more specific association between fatigue and sleep problems are related to not being adequately rested, daytime impairment and dissatisfaction with current sleep should also be considered a main contribution. With the study, we also showed that future research is indeed called for. It is important to understand pathophysiological mechanisms, but also to understand how to develop treatment programs targeting a symptom like fatigue. In this work it is important to take the complexity of IBS into account. This motivated the Bergen Brain-Gut group to conduct a multidisciplinary study on IBS. By providing data to the present study, this master thesis may have made a small contribution to its aim to obtain more knowledge about the rich communication between the brain and the gut in a disorder like IBS.

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Appendix

Appendix 1: Bergen Insomnia Scale

BERGEN INSOMNIA SCALE

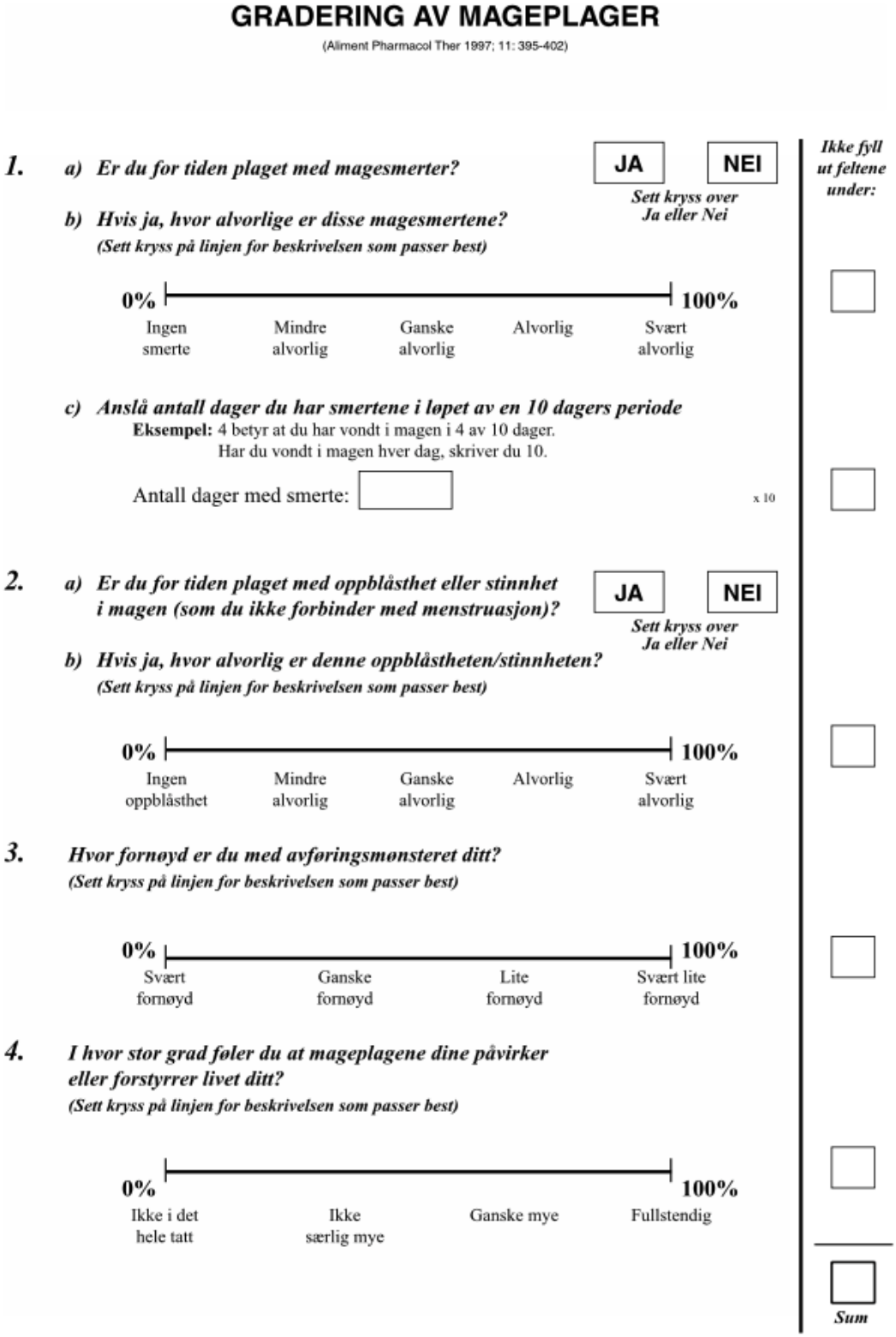
Instruksjon. På spørreskjemaet under er det 6 spørsmål knyttet til søvn og tretthet. Vær vennlig å sett ring rundt det alternativet (antall dager pr uke) som passer best for deg. 0 er ingen dager i løpet av en uke, 7 er alle dager i løpet av en uke.

Eksempel
Hvis du 3 dager i løpet av en uke har brukt mer enn 30 minutter på å sovne etter at du har slukket lyset, setter du ring rundt alternativ 3.

	I løpet av den siste måneden, hvor mange dager pr. uke har du brukt mer enn 30 minutter for å sovne inn etter at lysene ble slukket?	0 1 2 (3) 4 5 6 7

		Antall dager pr. uke
1.	I løpet av den siste måneden, hvor mange dager pr. uke har du brukt mer enn 30 minutter for å sovne inn etter at lysene ble slukket?	0 1 2 3 4 5 6 7
2.	I løpet av den siste måneden, hvor mange dager pr. uke har du vært våken mer enn 30 minutter innimellom søvnen.	0 1 2 3 4 5 6 7
3.	I løpet av den siste måneden, hvor mange dager pr. uke har du våknet mer enn 30 minutter tidligere enn du har ønsket uten å få sove igjen?	0 1 2 3 4 5 6 7
4.	I løpet av den siste måneden hvor mange dager pr. uke har du følt deg for lite uthvilt etter å ha sovet.	0 1 2 3 4 5 6 7
5.	I løpet av den siste måneden, hvor mange dager pr. uke har du vært så søvnig/trett at det har gått ut over skole/jobb eller privatlivet?	0 1 2 3 4 5 6 7
6.	I løpet av den siste måneden, hvor mange dager pr. uke har du vært misfornøyd med søvnen din?	0 1 2 3 4 5 6 7

Apendix 2: Irritable Bowel Syndrome – Severity Scoring System



GRADERING AV MAGEPLAGER

(Aliment Pharmacol Ther 1997; 11: 395-402)

Ikke fyll ut feltene under:

1. *a) Er du for tiden plaget med magesmerter?* JA NEI

Sett kryss over Ja eller Nei

b) Hvis ja, hvor alvorlige er disse magesmertene?
(Sett kryss på linjen for beskrivelsen som passer best)

0% — 100%

Ingen smerte | Mindre alvorlig | Ganske alvorlig | Alvorlig | Svært alvorlig

c) Anslå antall dager du har smertene i løpet av en 10 dagers periode
Eksempel: 4 betyr at du har vondt i magen i 4 av 10 dager.
Har du vondt i magen hver dag, skriver du 10.

Antall dager med smerte: ☐ x 10 ☐

2. *a) Er du for tiden plaget med oppblåsthet eller stinnhet i magen (som du ikke forbinder med menstruasjon)?* JA NEI

Sett kryss over Ja eller Nei

b) Hvis ja, hvor alvorlig er denne oppblåstheten/stinnheten?
(Sett kryss på linjen for beskrivelsen som passer best)

0% — 100% ☐

Ingen oppblåsthet | Mindre alvorlig | Ganske alvorlig | Alvorlig | Svært alvorlig

3. *Hvor fornøyd er du med avføringsmønsteret ditt?*
(Sett kryss på linjen for beskrivelsen som passer best)

0% — 100% ☐

Svært fornøyd | Ganske fornøyd | Lite fornøyd | Svært lite fornøyd

4. *I hvor stor grad føler du at mageplagene dine påvirker eller forstyrrer livet ditt?*
(Sett kryss på linjen for beskrivelsen som passer best)

0% — 100% ☐

Ikke i det hele tatt | Ikke særlig mye | Ganske mye | Fullstendig

☐ *Sum*

Appendix 3: Chalder Fatigue Scale

Tretthet (Fatigue)

Vi vil gjerne vite om du har følt deg sliten, svak eller i mangel av overskudd den siste måneden. Vennligst besvar ALLE spørsmålene ved å krysse av for det svaret du synes passer best for deg. Vi ønsker at du besvarer alle spørsmålene selv om du ikke har hatt slike problemer. Vi spør om hvordan du har følt deg i det siste og ikke om hvordan du følte deg for lenge siden. Hvis du har følt deg sliten lenge, ber vi om at du sammenlikner deg med hvordan du følte deg sist du var bra. (Ett kryss for hver linje)

1. Har du problemer med at du føler deg sliten?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

2. Trenger du mer hvile?
☐ Nei, mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

3. Føler du deg søvnig eller døsig?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

4. Har du problemer med å komme i gang med ting?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

5. Mangler du overskudd?
☐ Ikke i det hele tatt ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

6. Har du redusert styrke i musklene dine?
☐ Ikke i det hele tatt ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

7. Føler du deg svak?
☐ Mindre enn vanlig ☐ Som vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

8. Har du vansker med å konsentrere deg?
☐ Mindre enn vanlig ☐ Som vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

9. Forsnakker du deg i samtaler?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

10. Er det vanskeligere å finne det rette ordet?
☐ Mindre enn vanlig ☐ Ikke mer enn vanlig ☐ Mer enn vanlig ☐ Mye mer enn vanlig

11. Hvordan er hukommelsen din?
☐ Bedre enn vanlig ☐ Ikke verre enn vanlig ☐ Verre enn vanlig ☐ Mye verre enn vanlig

12. Hvis du føler deg sliten for tiden, omtrent hvor lenge har det vart? (Ett kryss)
☐ Mindre enn en uke
☐ Mindre enn tre måneder
☐ Mellom tre og seks måneder
☐ Seks måneder eller mer

13. Hvis du føler deg sliten for tiden, omtrent hvor mye av tiden kjenner du det? (Ett kryss)
☐ 25 % av tiden
☐ 50 % av tiden
☐ 75 % av tiden
☐ Hele tiden

Appendix 4: REK approval

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Claus Henning Thorsen	22845515	09.10.2015	2015/1621/REK sør-øst C
			Deres dato:	**Deres referanse:**
			18.08.2015	

Vår referanse må oppgis ved alle henvendelser

Trygve Hausken
Haukeland Universitetssjukehus

2015/1621 Magefølelse

Forskningsansvarlig: Haukeland Universitetssjukehus
Prosjektleder: Trygve Hausken

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 17.09.2015. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikkloven § 4.

Prosjektomtale
Studien ønsker å sammenligne mål på mage-tarm aktivitet, symptomer, hormoner og metabolske produkter ved ulike måltider mellom pasienter med funksjonelle mage-tarm plager og friske frivillige. I tillegg vil en vurdere effektene av modifikasjoner i diett på de samme parametrene. Studien vil benytte ulike bildemodaliteter som MR og ultralyd for å få informasjon om aktivitet i koblingen mellom hjerne og tarm. Det vil i tillegg bli tatt blod- og avføringsprøver. Deltagere vil svare på ulike skjema for å sikre klassifisering av deltagerne. Gjennom studien ønsker vi å få en større forståelse for aktivitet i hjerne-tarm aksen hos pasienter med funksjonelle mage-tarm lidelser. Dette vil kunne gi kunnskap nyttig for ulike behandlingsstrategier, og generere kunnskap for fremtidig forskning på pasientgruppen.

Vurdering
Komiteen mener dette er et godt beskrevet prosjekt.

Prosjektets formål er å undersøke koblingen mage-tarm hos pasienter med

Besøksadresse:
Gullhaugveien 1-3,
0484 Oslo

Telefon: 22845511
E-post: post@helseforskning.etikkom.no
Web: http://helseforskning.etikkom.no/

All post og e-post som inngår i saksbehandlingen, bes adressert til REK sør-øst og ikke til enkelte personer

Kindly address all mail and e-mails to the Regional Ethics Committee, REK sør-øst, not to individual staff

funksjonelle mage-tarm plager, og sammenligne disse med friske frivillige. Dette skal man gjøre ved hjelp av diett, MR, ultralyd, blod- og avføringsprøver, i tillegg til utfylling av spørreskjema.

Komiteen bemerker at dietten (FODMAP) synes utfordrende å følge, men deltakerne vil få opplæring i dietten. Utover dietten fremstår prosjektet som ikke spesielt invasivt.

Komiteen mener det bør etableres en beredskap i forhold til eventuelle funn på MR/ultralyd, og setter dette som vilkår for godkjennelsen.

Friske frivillige skal ifølge søknaden rekrutteres gjennom annonse i media, og komiteen ber for ordens skyld om å få se annonseteksten.

Informasjonsskriv og samtykkeerklæring
Punktet om stedfortredende samtykke i selve samtykkeerklæringen må fjernes, da dette aspektet ikke er relevant i denne studien. Komiteen ber også om at forkortelsene som benyttes i skrivet, skrives fullt ut.

Ut fra dette setter komiteen følgende vilkår for prosjektet:

1. Det skal etableres beredskap ved MR-funn.

2. Annonseteksten til friske frivillige sendes komiteen til orientering

3. Informasjonsskrivet revideres i henhold til ovennevnte og sendes komiteen til orientering.

Vedtak
Prosjektet godkjennes under forutsetning av at ovennevnte vilkår oppfylles, jf helseforskningslovens §§ 9 og 33.

I tillegg til vilkår som fremgår av dette vedtaket, er tillatelsen gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden og protokollen, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Tillatelsen gjelder til 30.06.2019. Av dokumentasjons-og oppfølgingshensyn skal opplysningene likevel bevares inntil 30.06.2024. Opplysningene skal lagres avidentifisert, dvs. atskilt i en nøkkel-og en opplysningsfil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Komiteens avgjørelse var enstemmig.

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jfr. helseforskningsloven § 10, tredje ledd og forvaltningsloven § 28. En eventuell klage sendes til REK sør-øst C. Klagefristen er tre uker fra mottak av dette brevet, jfr. forvaltningsloven § 29.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK sør-øst på eget skjema senest 31.12.2019, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK sør-øst dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK sør-øst. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Britt-Ingjerd Nesheim prof.dr.med
leder REK sør-øst C

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Leena Heinonen	22845522	15.03.2018	2015/1621 REK sør-øst C
			Deres dato:	Deres referanse:
			22.02.2018	

Vår referanse må oppgis ved alle henvendelser

Trygve Hausken
Helse Bergen HF

2015/1621 Magefølelse

Forskningsansvarlig: Haukeland Universitetssjukehus, Helse Bergen HF - Haukeland universitetssykehus
Prosjektleder: Trygve Hausken

Vi viser til søknad om prosjektendring datert 22.02.2018 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK sør-øst C på fullmakt, med hjemmel i helseforskningsloven § 11.

Det søkes følgende endringer i prosjektet:

1.- en ny prosjektmedarbeider: Astri J. Lundervold
2.- utsettelse av prosjektslutt til 31.12.2023
3.Innhenting av nye data fra samme utvalgsgruppe:
- innhente dataene via spørreskjema som spørreskjema og nevropsykologisk testing
- Biopsier vil innhentes via kolonoskopi dersom det uansett er nødvendig som del av klinisk utredning for pasientene (ikke friske kontroller)
- Blodprøver vil være det samme innsamling, men vil analyseres annerledes
4. Ny/endret forespørsel om deltakelse og samtykkeerklæring, vedlagt
5. revidert protokoll, vedlagt

Vurdering
REK har vurdert de omsøkte endringene, og har ingen forskningsetiske innvendinger til endringene slik de er beskrevet i skjema for prosjektendring.

Vedtak

REK godkjenner prosjektet slik det nå foreligger, jfr. helseforskningsloven § 11, annet ledd.

Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknad, endringssøknad, oppdatert protokoll og de bestemmelser som følger av helseforskningsloven med forskrifter.

Godkjenningen gjelder til 31.12.2023. Av dokumentasjonshensyn skal opplysningene likevel bevares inntil 31.12.2028. Forskningsfilen skal oppbevares atskilt i en nøkkel-og en opplysningsfil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Klageadgang

EKs vedtak kan påklages, jf. forvaltningslovens § 28 flg. Eventuell klage sendes til REK sør-øst C.

Besøksadresse: Gullhaugveien 1-3, 0484 Oslo
Telefon: 22845511
E-post: post@helseforskning.etikkom.no
Web: http://helseforskning.etikkom.no/

Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst C, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Vi ber om at alle henvendelser sendes inn på korrekt skjema via vår saksportal: http://helseforskning.etikkom.no. Dersom det ikke finnes passende skjema kan henvendelsen rettes på e-post til: post@helseforskning.etikkom.no.

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen

Britt Ingjerd Nesheim Prof.dr.med,
Leder REK sør-øst C

Kopi til: *lnes@helse-bergen.no; postmottak@helse-bergen.no*

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Claus Henning Thorsen	22845515	10.04.2019	2015/1621/REK sør-øst C
			Deres dato:	Deres referanse:
			15.02.2019	

Vår referanse må oppgis ved alle henvendelser

Trygve Hausken
Gastroenterologisk seksjon

2015/1621 Magefølelse

Forskningsansvarlig: Haukeland Universitetssjukehus, Helse Bergen HF - Haukeland universitetssykehus
Prosjektleder: Trygve Hausken

Vi viser til søknad om prosjektendring datert 15.02.2019 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK sør-øst C på fullmakt.

Vurdering

De omsøkte endringene er beskrevet i skjema for prosjektendringer datert 15.02.2019 ,samt i tilleggsdokumentasjon mottatt 18.02.2019, og består av følgende:

1. Ny prosjektleder
Birgitte Berentsen blir ny prosjektleder

2. Nye prosjektmedarbeidere
Elisabeth Kjelsvik Steinsvik, Gülen Arslan Lied, Katarina Lundervold, Mattis Bekkelund, Tarek Mazzawi, Camilla Thuen, Espen Handeland Øvrehus, Dag Andre Sangnes, Jan Gunnar Hatlebakk og Linda Bratli blir nye prosjektmedarbeidere.

3. Endringer i humant biologisk materiale i forskningsbiobank
I tillegg til vanlige blodprøver, biopsi fra tykktarm og avføringsprøver, skal biopsimateriale fra tynntarm og magesekk lagres i generell biobank. Innsamling skjer ved vanlig klinisk undersøkelse ved gastroskopi med vanlig biopsitaking i ventrikkel og duodenum.

I tillegg skal man samle inn spyttprøver før og etter lavFODMAP-diett-intervensjon. Disse prøvene skal analyses for microbiota-komposisjon, lik de fekale analysene man allerede har godkjenning på. Det vises til at det er et interessant forskningsspørsmål om pasienter med IBS har en mikrobiell komposisjon i spyttet som kan korreleres, og muligens predikere, tarmens flora. Spyttprøvene skal også lagres i generell biobank.

4. Økning i antall forskningsdeltaker
Man ønsker å øke antall deltakere i studien til 200 (100 pasienter og 100 frivillige).

5. Ny/endret forespørsel om deltakelse og samtykkeerklæring.

Komiteen har vurdert søknaden og har ingen forskningsetiske innvendinger til endringen av prosjektet.

Vedtak

Besøksadresse: Gullhaugveien 1-3, 0484 Oslo
Telefon: 22845511
E-post: post@helseforskning.etikkom.no
Web: http://helseforskning.etikkom.no/

Komiteen har gjort en forskningsetisk vurdering av endringene i prosjektet, og godkjenner prosjektet slik det nå foreligger, jf. helseforskningsloven § 11.

Komiteen gjør samtidig oppmerksom på at etter ny personopplysningslov må det også foreligge et behandlingsgrunnlag etter personvernforordningen. Det må forankres i egen institusjon.

Tillatelsen er gitt under forutsetning av at prosjektendringen gjennomføres slik det er beskrevet i prosjektendringsmeldingen og de bestemmelser som følger av helseforskningsloven med forskrifter.

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. helseforskningsloven § 10, 3 ledd og forvaltningsloven § 28. En eventuell klage sendes til REK sør-øst C.

Klagefristen er tre uker fra mottak av dette brevet, jf. forvaltningsloven § 29.

Vi ber om at alle henvendelser sendes inn via vår saksportal: http://helseforskning.etikkom.no eller på e-post til: post@helseforskning.etikkom.no

Vennligst oppgi vårt referansenummer i korrespondanse

.

Med vennlig hilsen

Britt -Ingjerd Nesheim
Prof.dr.med,.
Leder REK sør-øst C

Claus Henning Thorsen
Seniorrådgiver

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