

# Factors of importance for work productivity in Irritable Bowel Syndrome

Åsa Frändemark

Department of clinical and molecular medicine  
Institute of medicine  
Sahlgrenska Academy, University of Gothenburg



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[asa.frandemark@gu.se](mailto:asa.frandemark@gu.se)

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Åsa Frändemark

Department of clinical and molecular medicine, Institute of medicine  
Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

## ABSTRACT

Disorders of gut-brain interaction (DGBI) are highly prevalent in the general population, and irritable bowel syndrome (IBS) is one of the most common DGBI. Having IBS, and many of the DGBI, can impact work life. However, this has not been fully explored. The overall aim of this thesis was to investigate factors that affect the ability to work in patients with DGBI and IBS.

In **study I**, work productivity impairment was examined in patients with IBS. There was a substantial work impairment, and gastrointestinal(GI)-specific anxiety, IBS symptom severity and general fatigue were independently associated with overall work impairment. In **study II**, as fatigue was identified as an important factor for the reduced ability to work in patients with IBS, fatigue was explored further. Patients with IBS and severe fatigue had more severe IBS symptoms, more depression and anxiety, and lower sense of coherence compared to patients with moderate or mild fatigue. Fatigue impacted many aspects of daily life, and negative effects on stamina and control over bodily processes were prominent. In **study III**, constructivist grounded theory was used to explore work life in patients with IBS. The core category *Balancing work life under threat of symptoms*, consisted of the categories *being prepared*, *restricting impact*, *adjusting* and *reconciling*, all while being under threat of symptoms. The categories were understood as different strategies, and outcomes of strategies, used to lessen and restrict the threat of symptoms, where adjusting was seen as an obstacle, leaving the persons more susceptible to symptoms. In **study IV**, a multinational, population-based cohort was used to investigate work productivity impairment in persons with DGBI. Persons with DGBI were demonstrated to have significantly higher degrees of work productivity and activity impairment compared to those without, and for persons with DGBI in several anatomical regions, work productivity impairment increased for every additional region.

In conclusion, the results from this thesis confirm a substantial negative impact on work life for persons with IBS and DGBI, and that fatigue, psychological distress and somatic symptoms, not only confined to the GI tract, contribute to this impairment. Further, we found that behaviors and strategies can be applied to lessen impact on work life. These results highlight the importance of a broad view on the management of persons with DGBI and IBS, and that the overall symptom burden, both physical and mental, should be considered to optimize the outcome.

Keywords: Irritable bowel syndrome, disorders of gut-brain interaction, work productivity impairment, work, fatigue

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# SAMMANFATTNING PÅ SVENSKA

Funktionell mag-tarmsjukdom är mycket vanligt och drabbar ca 40% av världens befolkning. En av de vanligaste funktionella mag-tarmsjukdomarna är irritable bowel syndrome (IBS), en sjukdom som innebär återkommande buksmärta tillsammans med rubbade avföringsvanor, med antingen diarré, förstoppning eller omväxlande diarré och förstoppning. Utöver dessa symtom är det vanligt att IBS och andra symtom och sjukdomar samexisterar, till exempel ångest, depression, fibromyalgi och fatigue, d v s trötthet som är något mer, som begränsar och upplevs som kraftlöshet eller utmattning. IBS är kopplat till nedsatt arbetsproduktivitet med både ökad sjukfrånvaro och sjuknärvaro, men kunskapen kring arbete och IBS är begränsad. Därför var syftet med denna avhandling att utforska arbetslivet hos personer med funktionell mag-tarmsjukdom i allmänhet och IBS i synnerhet. Specifika syften var att undersöka graden av nedsatt arbetsproduktivitet samt hitta faktorer som påverkar sjukfrånvaro och sjuknärvaro hos personer med IBS, att undersöka fatigue hos personer med IBS, att utforska hur personer med IBS upprätthåller sitt arbetsliv, samt att undersöka arbetsproduktivitet hos personer med funktionell mag-tarmsjukdom i en stor, multinationell, populationsbaserad studie.

I **studie I** identifierades en påtagligt nedsatt arbetsproduktivitet hos patienter med IBS, och att denna nedsatthet var kopplad till svårighetsgraden av IBS-symtom, fatigue, och ångest kopplat till mag-tarmsymtom.

I **studie II** påvisade vi att uttalad fatigue hos patienter med IBS är kopplat till svårare IBS-symtom, mer depressions- och ångestsymtom och en lägre känsla av sammanhang. Fatigue påverkade flera aspekter av det dagliga livet, såsom arbete, familjeliv och hobbies, och påverkan på uthållighet var framträdande.

I **studie III** utforskades hur personer med IBS upprätthåller arbetslivet och denna process beskrevs som *Att balansera arbetslivet under ständigt symtomhot* och består av fyra kategorier som beskriver olika strategier och rutiner, och hinder för dessa, som personerna använde sig av för att minska eller förebygga risken att utsättas för symtom.

I **studie IV** påvisades nedsatt arbetsproduktivitet hos personer med funktionell mag-tarmsjukdom i populationen, och att detta är kopplat till manligt kön, fatigue, svårighetsgraden av kroppsliga och psykiska symtom, samt antal delar av mag-tarmkanalen med funktionell mag-tarmsjukdom.

Sammanfattningsvis visar resultaten från denna avhandling att funktionell mag-tarmsjukdom i allmänhet, och IBS i synnerhet, har en påtaglig negativ påverkan på arbetslivet och att mag-tarmsymtom, och andra faktorer, såsom fatigue, ångest och andra kroppsliga symptom, bidrar till detta. Att upprätthålla rutiner och att använda sig av olika strategier kan minska påverkan på arbetslivet. Resultaten understryker vikten av att möta hela patienten och alla besvär och symtom, och att inte bara fokusera på magen för att optimera utfallet av omhändertagandet.

# LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. Frändemark Å, Törnblom H, Jakobsson S, Simren M. *Work Productivity and Activity Impairment in Irritable Bowel Syndrome (IBS): A Multifaceted Problem*. Am J Gastroenterol 2018;113(10):1540-9
- II. Frändemark Å, Jakobsson Ung E, Törnblom H, Simrén M, Jakobsson S. *Fatigue: a distressing symptom for patients with irritable bowel syndrome*. Neurogastroenterol Motil 2017;29(1):e12898
- III. Frändemark Å, Törnblom H, Simrén M, Jakobsson S. *Maintaining work life under threat of symptoms: a grounded theory study of work life experiences in persons with Irritable Bowel Syndrome*. BMC Gastroenterol 2022;22(1):73
- IV. Frändemark Å, Törnblom H, Hreinsson J, Andresen V, Benninga M.A, Corazziari E.S, Fukudo S, Mulak A, Santos J, Sperber A.D, Bangdiwala S.I, Palsson O.S, Simrén M. *Work productivity and activity impairment in subjects with Disorders of Gut-Brain Interaction: data from the Rome Foundation Global Epidemiology Study*. Submitted.



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# ABBREVIATIONS

DGBI	Disorders of gut-brain interaction
FAM	Fatigue adaptation model
FIS	Fatigue impact scale
GI	Gastrointestinal
GT	Grounded theory
HAD	Hospital Anxiety and Depression scale
IBS	Irritable bowel syndrome
IBSQOL	Irritable Bowel Syndrome Quality of Life Questionnaire
IBS-SSS	IBS Severity scoring system
MFI-20	Multidimensional Fatigue Inventory 20
PHQ-15	Patient health questionnaire-15
PHQ-4	Patient health questionnaire-4
SOC	Sense of coherence
VSI	Visceral Sensitivity Index
WPAI	Work productivity and activity impairment questionnaire
WPAI:GH	WPAI: General health
WPAI:IBS	WPAI: Irritable bowel syndrome

# 1 INTRODUCTION

## 1.1 PURPOSE OF THE THESIS

The purpose of this thesis is to gain more knowledge of work life in persons with disorders of gut-brain interaction (DGBI), with emphasis on irritable bowel syndrome (IBS), one of the most common DGBI. In the four studies of this thesis, different research methods have been used to examine various aspects of work and work life in persons with IBS and DGBI. In study I we used questionnaires to get an overview of factors related to work productivity impairment in IBS. We found that fatigue was an important factor for this and focused on that in study II. In study III we explored work life in persons with IBS further with interviews, using grounded theory to understand and construct a theory for what we could not capture using only questionnaires. In study IV, we broadened the perspective by investigating the entire DGBI group in a large, multinational cohort (figure 1).

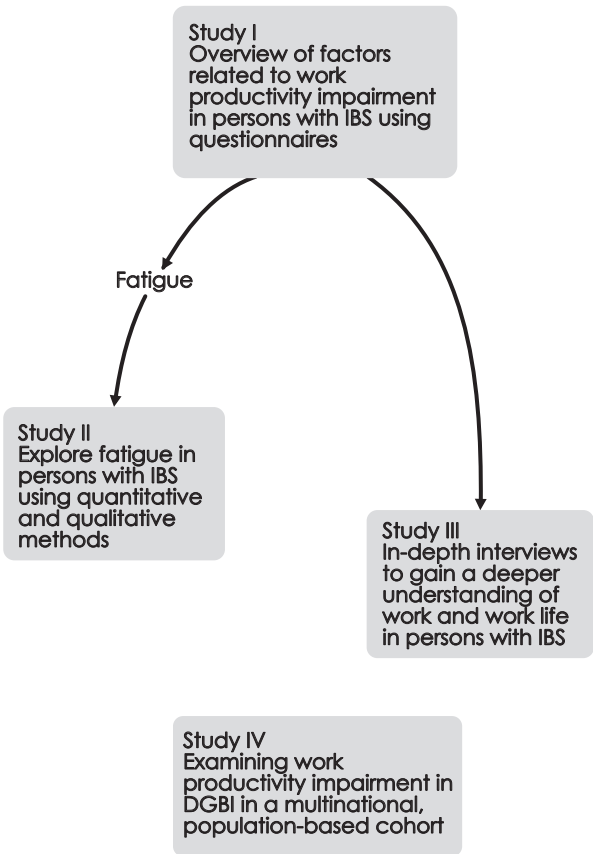


Figure 1. Overview of the studies in this thesis.

## 1.2 DISORDERS OF GUT-BRAIN INTERACTION

Disorders of gut-brain interaction (DGBI) are a group of disorders affecting the gastrointestinal system classified by the Rome Foundation and diagnosed through symptom patterns with the Rome diagnostic criteria.<sup>1</sup> DGBI were previously referred to as functional gastrointestinal disorders, but with the latest version of the Rome criteria, Rome IV, the shift to the new term DGBI was made to better reflect the underlying multifactorial pathophysiology of these disorders. From what is known today, visceral hypersensitivity, altered gut microbiota, altered central nervous system (CNS) processing, motility disturbance and altered mucosal and immune function, alone or in any combination are important factors in explaining the symptoms in DGBI.<sup>1</sup> More women than men are affected by DGBI and having DGBI is associated with poorer quality of life, higher health care consumption and more severe psychological distress compared to the general population.<sup>2,3</sup>

The prevalence of any DGBI in the general population is 40.3%.<sup>3</sup> Of the six groups of DGBI, bowel disorders are the most prevalent, and of the bowel disorders, functional constipation is most prevalent, followed by functional diarrhea and IBS (figure 2).<sup>3</sup>

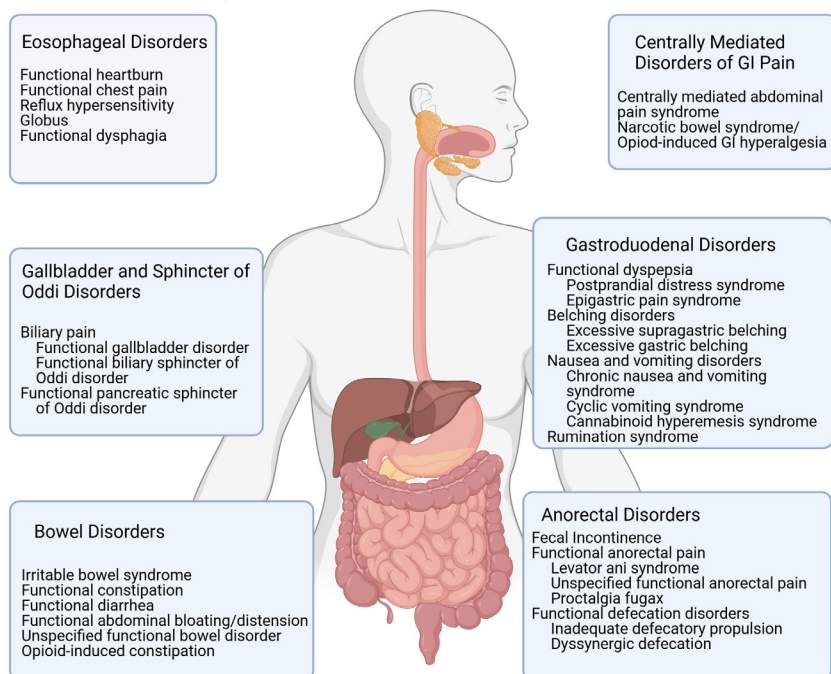


Figure 2. DGBI according to the Rome IV criteria for adults. Created with BioRender.com.

## 1.3 IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is one of the six bowel disorders characterized by the Rome IV criteria.<sup>1</sup> All persons with IBS experience abdominal pain together with altered bowel habits. The altered bowel habits vary among different persons with IBS, and can vary over time with either predominantly diarrhea, constipation or alternating between both. Other GI symptoms, e.g. bloating and flatulence, are common but are not part of the diagnostic criteria. As for most DGBI, women are affected to a larger extent than men by IBS.<sup>4</sup>

### 1.3.1 DIAGNOSTIC CRITERIA

The diagnostic criteria for Rome III and Rome IV IBS can be seen in table 1 and 2.<sup>1,5</sup> The definition of IBS is stricter in Rome IV compared to Rome III, with the removal of discomfort and a need for more frequent symptoms in the Rome IV diagnostic criteria. The association between pain and defecation has also been adjusted. The stricter Rome IV criteria resulted in a drop in the prevalence from Rome III to Rome IV criteria for IBS, which was evident in the recent Rome Foundation Global Study assessing the global population-based rates of DGBI (10.1 vs 4.1%).<sup>3</sup> The drop in IBS prevalence with the Rome IV criteria can primarily be explained by the raised threshold for frequency of pain, followed by the removal of discomfort and lastly the changing of stool-associated criteria.<sup>6, 7</sup> In agreement with the stricter diagnostic criteria, Rome IV IBS is associated with more severe symptoms compared to Rome III IBS.<sup>6</sup> However, the majority of persons who "lose" their IBS diagnosis from Rome III with the updated Rome IV criteria, end up in another diagnostic entity within the bowel disorders, e.g. functional constipation or functional diarrhea. This can explain why the prevalence rates of the other functional bowel disorders have increased in Rome IV in parallel with a decrease in the prevalence of IBS.<sup>7</sup>

Table 1.

<b>Rome III diagnostic criteria* for irritable bowel syndrome<sup>5</sup></b>
Recurrent abdominal pain or discomfort** at least 3 days/month in the last 3 months associated with <i>two or more</i> of the following:
1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool
*Criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis **"Discomfort" means an uncomfortable sensation not described as pain

### 1.3.2 DIAGNOSING IBS

Diagnosing IBS usually requires a thorough medical history, a physical exam and a limited number of additional tests to rule out other diagnoses.<sup>8,9</sup> The medical history focuses on GI symptoms and alarm symptoms that could indicate other causes for the symptoms present. Regarding GI symptoms, it is important to identify which symptoms the patient experience, and using visual aids such as the Bristol stool scale<sup>10</sup> can enable a joint understanding between the patient and the physician.<sup>9,11</sup> Apart from current symptoms, the onset of symptoms (at least six months' duration), the progression, and worsening or alleviating factors as well as presence of non-GI symptoms, including psychological comorbidities, can help guide in the diagnostic approach, treatment options and prognosis.<sup>11</sup> Alarm symptoms that require further investigations are onset of symptoms after 50 years of age, rectal bleeding, weight loss, family history of inflammatory bowel disease or GI cancer, nocturnal diarrhea or laboratory abnormalities.<sup>8, 9, 12</sup> The physical exam should include an abdominal examination, a digital rectal exam, and depending on the symptom profile, a rigid sigmoidoscopy, which all should be normal. Blood tests that should be part of the routine investigation when diagnosing IBS are complete blood count, C-reactive protein and serologic testing for celiac disease. Fecal calprotectin (in diarrhea predominant IBS), thyroid tests and stool testing for e.g. giardia can be considered depending on the symptom pattern and the medical history.<sup>8, 9, 12</sup>

With a typical medical history without alarm symptoms, fulfillment of the Rome IV diagnostic criteria for IBS, and a normal physical examination, a confident IBS diagnosis can be made at the first visit with the physician, clearly conveying that the blood tests are expected to be normal and thereby confirming the diagnosis.

Table 2.

<b>Rome IV diagnostic criteria* for irritable bowel syndrome<sup>1</sup></b>
Recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with <i>two or more</i> 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
*Criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

### 1.3.3 TREATMENT

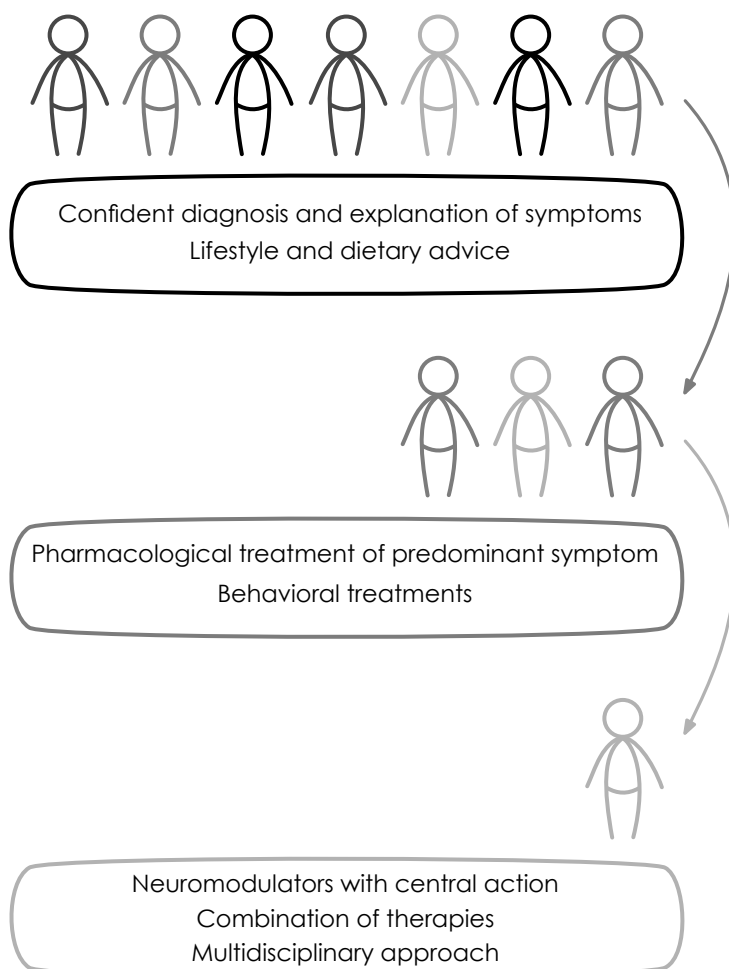
The treatment approach for IBS is based on a stepwise strategy (figure 3).<sup>8,9,11</sup> Establishing a good alliance between the physician and the patient is important for the outcome of the treatment and this includes conveying a confident diagnosis to the patient. A thorough explanation of what IBS is and reassurance of the benign nature of the disorder, are important parts of the first step that should be provided to all patients. In addition, lifestyle advice with information about stress management, physical activity, sleep, smoking and basic dietary advice should also be included in the initial standard management of IBS patients.<sup>8,9,11</sup> The advice can be given verbally by the physician during the visit at the outpatient clinic, ideally supported by information included in information material, or as structured patient education when available (e.g. “IBS school”).<sup>13</sup> If needed, patients can later be referred to a dietician for consideration of further dietary interventions, such as a low FODMAP diet (a diet where fermentable oligosaccharides, disaccharides, monosaccharides and polyols are excluded and thereafter reintroduced in a structured manner).<sup>14</sup> For many patients, the first treatment steps including explanation, reassurance, lifestyle advice and information about diet are sufficient, but some are in need of additional interventions / treatment options in step two in the treatment strategy.

The second step consists of pharmacological and behavioral treatments. The target for the pharmacological treatment is the predominant symptom, and it is important for the patient to identify their most bothersome symptoms, as this might sometimes differ from what the physician expects.<sup>8,9,11</sup> If the most bothersome symptom is abdominal pain, antispasmodic drugs (hyoscyamine, papaverine or peppermint oil) are first line treatment options. For diarrhea, the antidiarrheal agent loperamide is a logical first line pharmacological treatment option, while bulking agents such as psyllium or sterculia are used for constipation. The dose for all treatments is titrated based on the effect and potential side effects, and a follow-up visit or a scheduled telephone call after one to two months of treatment is often helpful for both the patient and the physician.<sup>8,9,11</sup> Behavioral treatments that have been shown to be effective in IBS are cognitive behavioral therapy, hypnotherapy and psychodynamic and interpersonal psychotherapy.<sup>11</sup> However, although effective, the use of these treatment options in clinical practice to large groups of patients is limited by poor availability.

The third step in the treatment approach for patients with IBS with refractory symptoms, where previous treatment alternatives have not offered sufficient relief of the symptoms, consists of centrally acting neuromodulators (e.g. antidepressants), combinations of therapies and a multidisciplinary approach.<sup>8,9,11</sup> These patients often have both severe IBS symptoms and psychological and/or somatic comorbidities, and this combination will influence the choice of treatment. Neuromodulators, in



particular antidepressants, are used for their effects on gastrointestinal (GI) symptoms, such as abdominal pain, as well as non-GI somatic and psychiatric comorbidity. Tricyclic antidepressants in low dose are the first line treatment, but SSRI (selective serotonin reuptake inhibitor) and SNRI (serotonin–norepinephrine reuptake inhibitors) are also frequently used, depending on the symptom profile of the patient.<sup>8, 9, 11</sup> As for all medical treatments, the physician-patient alliance is of great importance for treatment compliance as well as outcome. It is important that the physician conveys a realistic view of what effect can be expected from the treatment and informs about potential negative effects, and that these may disappear despite continued use.<sup>11</sup>



*Figure 3. Stepwise treatment strategy for IBS.*

### **1.3.4 BURDEN OF DISEASE**

Although IBS is benign from a medical point of view, IBS substantially impacts daily life negatively. It is associated with lower quality of life than the general population and comparable to other disease such as ulcerative colitis, gastroesophageal reflux disease, diabetes mellitus and migraine.<sup>15-17</sup> IBS is also associated with increased healthcare utilization compared to the general population<sup>2</sup> and reduced work productivity, leading to substantial costs for both the individual and the society (discussed in greater detail under “Work and IBS”). IBS is also associated with several other symptoms and conditions, such as fibromyalgia, chronic fatigue, endometriosis, migraine, chronic back pain, anxiety and depression.<sup>18</sup>

### **1.3.5 FATIGUE**

Fatigue is a symptom with a definition that is not well known to the general population, and therefore often described as a feeling of being “so tired” or “too tired” by the patients.<sup>19</sup> There are both mental and physical components in the complex nature of fatigue, and fatigue is perceived differently depending on health status and depending on level of fatigue. Mild fatigue in healthy individuals is described as temporary, and something that can be rested away, whereas severe fatigue in patients does not improve with rest and is described as exhausting, frustrating and frightening.<sup>20, 21</sup> Fatigue is the most common extraintestinal symptom reported by patients with IBS, affecting more than 50%, with higher prevalence among patients with IBS in tertiary care and females.<sup>22, 23</sup> Of those reporting fatigue, more than half report fatigue to be as distressing as or worse than their GI symptoms.<sup>24</sup> With different diagnostic criteria used, the impact of fatigue also changes, with persons with Rome IV IBS having more severe fatigue than patients with Rome III IBS.<sup>4</sup>

## 1.4 SIGNIFICANCE OF WORK LIFE

To work does not only supply economic means to live and participate in society, but it can also create a sense of purpose and belonging and be central to the identity of individuals.<sup>25</sup> Even though there are health risks associated with professions, and some jobs can be harmful, on a group level the overall effects on health of being employed are positive, with increased well-being, and better physical and mental health.<sup>25</sup> Socioeconomic status, which is largely influenced by employment status, is associated with health and mortality.<sup>25, 26</sup> In line with employment being positive for health and well-being, unemployment affects health and well-being negatively on a group level, with poorer general health, higher health care consumption, lowered quality of life and increased mortality.<sup>25, 27</sup> This is partly due to lowered socioeconomic status.<sup>25-27</sup> Going from unemployment to employment promotes health, with improved mental and physical health, further strengthening the association between work and well-being.<sup>25, 27</sup>

Poor health can influence the ability to work. When assessing work productivity in relation to health, there are two main types of impairment; absenteeism, sick leave from work due to health problems; and presenteeism, a lowered ability to perform and be productive while at work due to health problems.

### 1.4.1 WORK AND CHRONIC DISEASE

Almost half of the population in Sweden have at least one chronic disease<sup>28</sup> and the work impairment in relation to chronic diseases is substantial. Due to the beneficial effects of work for both the individual and for the society at large, maintaining work or returning to work when living with a chronic disease, is the goal. This is also reflected in policies for sickness benefit from the Social Insurance Agency, where the ability to work, and not the diagnoses or disabilities in themselves, decides if the individual qualifies for benefits.<sup>29</sup> The three most common reasons for sick leave in Sweden are musculoskeletal conditions in the back and neck, mental illnesses and cardio-respiratory conditions.<sup>30</sup> It can be hard to return to work for persons living with long term conditions, and a recent qualitative systematic review by Reed et al.<sup>31</sup> identified that e.g. having a proactive collaboration between the job seeker, employing organization and other agencies and services, work-focused skill development and workplace adjustment and accommodations can facilitate the process.<sup>31</sup> Apart from absenteeism, chronic disease also affects presenteeism, but these effects are, due to the nature of it, not part of the records provided by the Social Insurance Agency.

## 1.4.2 WORK AND IBS

As mentioned above, having IBS affects the ability to work, with both higher degrees of absenteeism and presenteeism than the general population.<sup>32</sup> The work productivity impairment reported by patients with IBS is often driven by presenteeism, and treatment of IBS symptoms was shown to reduce work impairment in a recent study where patients with IBS receiving a comprehensive self-management program based on cognitive behavioral therapy, reduced their presenteeism by close to 13% nine months after the intervention.<sup>33</sup> The reasons behind the work productivity impairment persons with IBS have, have not been fully examined, but having abdominal pain as the worst symptom, anxiety and depression have all been found to be associated with work productivity impairment.<sup>34</sup> In addition, some patients with IBS describe how abdominal pain can lead to an inability to move, making work-life hard.<sup>35</sup> Patients with IBS have also described how access to bathrooms and embarrassment around toilet visits at work influence work life negatively.<sup>36, 37</sup> Apart from absenteeism and presenteeism in employed persons with IBS, earlier studies have shown that more than ten percent of patients with IBS do not work at all because of their IBS, and that having IBS can influence what kind of positions you apply to or pursue promotions for.<sup>37</sup>

Since IBS is a highly prevalent disease the work productivity loss associated with this disorder causes substantial consequences for both the affected individual and the society. A systematic review published in 2013 evaluating the economic burden of patients with IBS found that the indirect cost of IBS, including the cost of sick leave days, ranged from \$791 to \$7,737 per year,<sup>38</sup> and a review from 2014 estimated the annual cost related to IBS for employers to range from £400 to £900 per patient.<sup>39</sup> A more recent study examining patients with IBS according to the Rome IV criteria in the United Kingdom, estimated 90.5 hours of work lost because of IBS per patient and year, giving an estimated of total 71,956,139 hours of work lost due to IBS in the United Kingdom each year.<sup>34</sup>

## 2 AIM

The overall aim of this thesis was to investigate factors that affect the ability to work in patients with DGBI and IBS. Furthermore, we also aimed to specifically explore how patients with IBS perceive their work.

The specific aims for the studies of this thesis were:

- I. To investigate the association between work impairment and physical and psychological symptoms in patients with IBS
- II. To describe the impact and manifestations of fatigue in patients with IBS and investigate the relationship between fatigue severity and illness-related and health-promoting factors
- III. To explore how patients with IBS perceive their work life/work situation
- IV. To investigate work productivity and activity impairment in persons with DGBI in a population-based, multinational cohort

## 3 METHODS

### 3.1 DESIGN

An overview of the study design, participants, data, and analytical methods of studies I-IV can be seen in table 3.

Table 3.

Study	Participants	Design	Data	Data analysis
I	525 patients with IBS	Quantitative	Questionnaires	Spearman's rank order correlation, Kruskal–Wallis tests, Mann–Whitney <i>U</i> tests, linear regression analyses
II	160 patients with IBS	Qualitative and quantitative	Questionnaires	Chi-squared test, Kruskal–Wallis tests, Mann–Whitney <i>U</i> tests. Content analysis based on key domains of the Fatigue Adaptation Model <sup>19</sup>
III	23 patients with IBS	Qualitative	Individual in-depth interviews	Constructivist grounded theory
IV	16820 persons from the general population	Quantitative	Questionnaires	Kruskal–Wallis tests, Mann–Whitney <i>U</i> tests, linear trend analysis, linear regression analyses

### 3.2 STUDY PARTICIPANTS

Characteristics of the participants in the studies of this thesis can be seen in table 4. The study participants were either recruited at our clinical research unit (study I-III) or recruited globally (study IV). The participants recruited at the clinical research unit were all patients with IBS and there was some overlap of participants in study I-III (figure 4). Study I included patients with IBS from two different cohorts; baseline data from a study evaluating the effect of group-based patient education (cohort 1);<sup>13</sup> and data from a study focusing on the pathophysiology of IBS (cohort 2).<sup>40, 41</sup> The participants in cohort 1 were diagnosed with IBS in primary or secondary care by the referring physician, and the participants in cohort 2 were diagnosed with IBS at the clinical research unit upon inclusion by experienced gastroenterologists. Study II also used data from the previously mentioned study focusing on the pathophysiology of IBS and the participants in study III were recruited among patients who had participated in the same study.

Table 4.

	Study I		Study II	Study III	Study IV	
Participants	Patients with IBS		Patients with IBS	Patients with IBS	General population	
	Cohort 1	Cohort 2			DGBI	No DGBI
Rome criteria	Rome II	Rome III	Rome III	Rome III	Rome IV	Rome IV
Number of subjects included (female)	370 (307)	155 (108)	160 (110)	23 (15)	7111 (4193)	9709 (4240)
Age, median (range), years	35 (17-80)	31 (18-60)	30.5 (18-60)	44 (26-64)	43 (18-86)	47 (18-89)

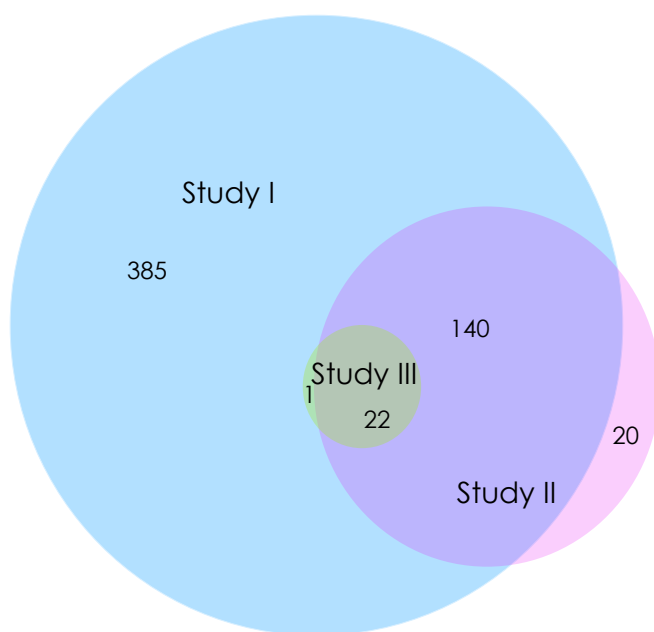


Figure 4. Venn diagram showing the overlap among subjects in the cohorts for study I, II and III.

Study participants in study IV participated in the internet part of a study examining the global epidemiology of DGBI in the general population.<sup>3</sup> The data collection was done through a company specialized in internet surveys. The aim was to collect data from 2000 participants from each of the 26 countries participating the internet survey and fulfilling preset goals of age quotas, as well as an equal sex distribution. In our study, we included persons from the general population from 8 countries (out of 26 countries included in total in the survey), where the participants completed a questionnaire to assess work productivity and activity (see below).

## 3.3 QUESTIONNAIRES

### 3.3.1 DISORDERS OF GUT-BRAIN INTERACTION

The adult Rome IV diagnostic questionnaire is based on the Rome IV diagnostic criteria and assesses 22 DGBI.<sup>42</sup> When used in combination with complementary questions assessing factors that can cause a respondent to wrongfully fulfill the diagnostic criteria, e.g. having another disease explaining the same symptoms, a diagnosis of the 22 DGBI can be made. As an example, a respondent who fulfills any DGBI criteria but also reports inflammatory bowel disease was excluded from the DGBI group in our studies. In study IV, we used the Rome IV diagnostic questionnaire to identify the 22 DGBI that are part of the questionnaire. The individual diagnoses were used to group participants with or without any DGBI; participants with any painful DGBI or non-painful DGBI; and to create four groups based on the anatomical regions defined in the Rome IV diagnostic criteria and thereafter group participants with DGBI in 1, 2, 3 or 4 affected anatomical regions (figure 5).

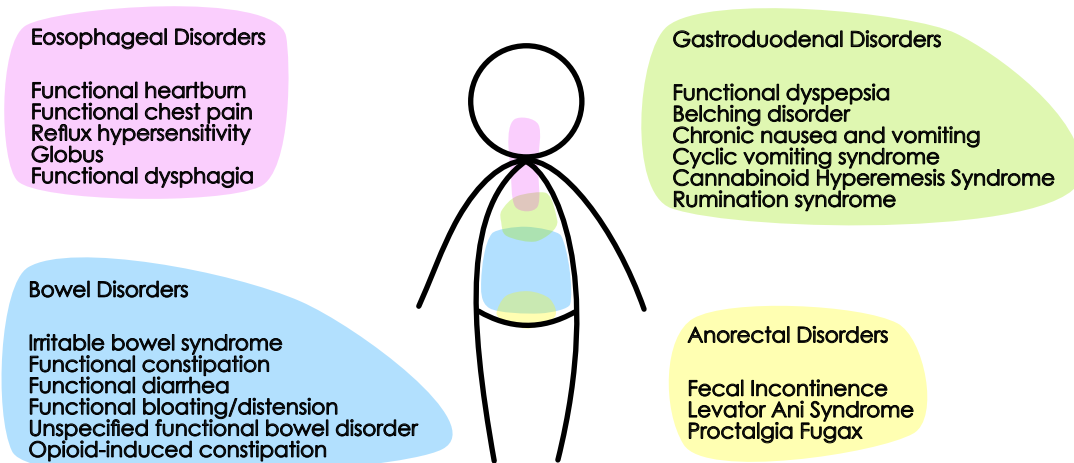


Figure 5. Four anatomical regions of DGBI, with their corresponding disorders.



### 3.3.2 WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT

The Work Productivity and Activity Impairment questionnaire: general health (WPAI:GH) was developed in the 1990's as a way of evaluating the magnitude and the costs of work productivity impairment and has since been adapted for several different diseases and disorders.<sup>43</sup> The questionnaire evaluates different aspects of work productivity and activity; absenteeism, i.e. absence from work due to health problems; presenteeism, i.e. impaired productivity at work due to health problems; overall work productivity impairment, i.e. absenteeism and presenteeism combined; and activity impairment, i.e. impairment in daily activities outside of work due to health problems (figure 6). The questionnaire consists of six questions, starting with "Are you currently employed (working for pay)?". Those answering yes to the first question are thereafter asked four additional questions about the last seven days; how many hours they worked; how many hours they were absent from work due to health reasons; how many hours they were absent due to other reasons than health; and how much their health impacted on their productivity while working on a scale from 0 to 10. Finally, all respondents are asked to rate how their health impacted daily activities outside of work on a scale from 0 to 10.<sup>43</sup>

Employed respondents get a score from 0-100% impairment for all four dimensions of the questionnaire: absenteeism, presenteeism, overall work productivity impairment and activity impairment. Those not working for pay get a score for activity impairment solely. From the scores, it is possible to calculate costs of the impairment by multiplying the impairment score with an annual income of the respondent or if that data is not available, data on annual income available from e.g. Statistics Sweden.<sup>43</sup>

In the studies in this thesis we have used two different versions of this questionnaire: Work productivity and activity impairment questionnaire: general health (WPAI:GH)<sup>43</sup> and the disease-specific Work productivity and activity impairment questionnaire: Irritable bowel syndrome (WPAI:IBS).<sup>44</sup> The difference between the two versions is that where WPAI:GH asks about impairment because of your health problems, WPAI:IBS asks about impairment related to IBS symptoms.

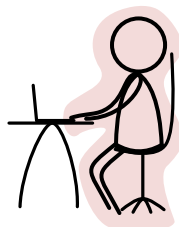


Figure 6. Visualization of work productivity impairment.

### 3.3.3 FATIGUE

#### FATIGUE IMPACT SCALE

In study II, which focused on fatigue (figure 7), the Fatigue impact scale (FIS) was used.<sup>45</sup> FIS is a questionnaire that was developed as a detailed measure of fatigue, where respondents rate functional limitations because of fatigue on activities during the last month. Rating impact on activities rather than just fatigue in general was chosen in this questionnaire since it was thought to have a higher sensitivity and was in line with previous research.<sup>46</sup> FIS consists of two parts. The first part of the questionnaire evaluates the magnitude of fatigue; frequency as days per month with fatigue; duration as hours per day with fatigue; distress as rating of no problems with fatigue to fatigue being the worst symptom; to what extent fatigue has a negative impact on daily life on a 0-10 numeric rating scale; and as two open-ended questions where respondents can describe affected daily activities and how fatigue influence daily life. The second part consists of 40 statements (“Because of my fatigue...”) rated on a five-point Likert-scale (0=no problem, 1=small problem, 2=moderate problem, 3=big problem, 4=extreme problem) with a total score ranging from 0 to 160. The total score consists of three domains: cognitive functioning (0-40), physical functioning (0-40) and psychosocial functioning (0-80), and a high score indicates greater functional limitations due to fatigue.<sup>45</sup>

In study II a new way of assessing fatigue was introduced based on FIS. The first part of the questionnaire was used and we formulated three criteria to define different severity categories of fatigue; frequency of fatigue  $\geq 10$  days a month; fatigue being ranked as one of the worst symptoms; and rating  $\geq 4$  on the numeric rating scale of to what extent fatigue has a negative impact on daily life. Respondents fulfilling all three criteria were classified as having severe fatigue, respondents fulfilling one or two were classified as having moderate fatigue and those fulfilling none were classified as having mild fatigue.

#### MULTIDIMENSIONAL FATIGUE INVENTORY 20

In study I and III, The Multidimensional Fatigue Inventory 20 (MFI-20) was used to assess fatigue.<sup>47</sup> MFI-20 rates five dimensions of fatigue with four statements each rated on a 5-point Likert-scale (1=“Yes, that is true” to 5=“No, that is not true”): general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity. The scores on each dimension ranges from 4 to 20 and a high score indicates greater fatigue.<sup>47</sup>

## FATIGUE IN STUDY IV

In study IV, fatigue was evaluated with one question from the Patient-Reported Outcomes Measurement Information System (PROMIS) global-10 questionnaire.<sup>46</sup> Respondents answered “How would you rate your fatigue on average?” on a 5-point Likert scale (“None”, “Mild”, “Moderate”, “Severe”, “Very severe”) giving a score from 1 to 5, with higher scores indicating greater fatigue.<sup>46</sup>



Figure 7. Visualization of fatigue.

### 3.3.4 SOMATIC SYMPTOMS

We have used two different questionnaires in this thesis to evaluate somatic symptoms (figure 8), the Irritable Bowel Syndrome Severity Scoring System (IBS-SSS)<sup>49</sup> and the Patient Health Questionnaire-15 (PHQ-15).<sup>50</sup> To evaluate symptoms specific to IBS, the IBS-SSS was used in study I, II and III. This questionnaire has four visual analogue scales (VAS) evaluating abdominal pain (together with a question on number of days with abdominal pain during the last ten days), abdominal bloating, satisfaction with bowel habits, and interference of IBS on daily life. The questionnaire gives a total score from 0-500, with scores indicating mild (<175), moderate (175–300) or severe (>300) overall IBS symptoms.<sup>49</sup>

To evaluate overall somatic symptoms, PHQ-15 was used in study I and IV. The questionnaire consists of 15 questions, evaluating somatic symptoms (such as headaches, shortness of breath and trouble sleeping) during the past 4 weeks on a 3-point Likert scale (“Not bothered at all”, “Bothered a little”, “Bothered a lot”), and gives a score of 0-30 with scores indicating no (0–4), low (5–9), medium (10–14) and high ( $\geq 15$ ) symptom severity.<sup>50</sup>

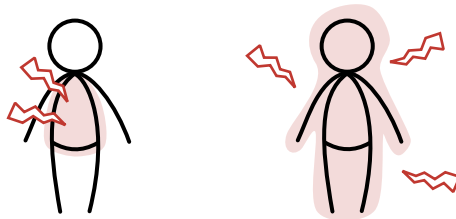


Figure 8. Visualization of IBS symptoms (left) and somatic symptoms (right).

### 3.3.5 PSYCHOLOGICAL FACTORS

Two different questionnaires have been used to evaluate general anxiety and depression (figure 9) in this thesis, the Hospital Anxiety and Depression scale (HAD) and the Patient Health Questionnaire-4 (PHQ-4).<sup>51, 52</sup> In study I, II and III HAD was used, and this is a questionnaire with two subscales, measuring anxiety and depression. Each of the 14 items is scored 0-3, giving subscale scores of 0-21 with score ranges indicating no anxiety/depression (0–7), possible anxiety/depression (8–10), and probable anxiety/depression (11–21).<sup>51</sup> In study IV, PHQ-4 was used. PHQ-4 consists of four questions divided into 2 subscales, measuring anxiety and depression.<sup>52</sup> The subscales can be used separately or combined into a total score (0-12) of psychological distress, where scores indicate normal (0-2), mild (3-5), moderate (6-8), and severe (9-12) psychological distress.<sup>53</sup>

To target GI-specific anxiety, the Visceral Sensitivity Index (VSI) was used in study I.<sup>54</sup> VSI consists of 15 statements capturing different cognitions and behaviors related to GI symptoms; worry, fear, vigilance, sensitivity and avoidance. The respondents either agree or disagree with the statements (e.g. “I am constantly aware of the feelings I have in my belly” and “Because of fear of developing abdominal discomfort, I seldom try new foods”) on a 6-point scale. The total score ranges from 0 to 75 and higher scores indicate greater GI-specific anxiety.<sup>54</sup>

Quality of life was evaluated with the Irritable Bowel Syndrome Quality of Life Questionnaire (IBSQOL) and used in study I.<sup>55</sup> The questionnaire consists of nine dimensions of quality of life with scores of 0-100 of each dimension: emotional health, mental health, sleep, energy, physical functioning, diet, social role, physical role and sexual relations. High scores indicate high quality of life.<sup>55</sup>

To evaluate coping, ability to handle and endure stressful situations and trauma, the Sense of Coherence (SOC) Scale was used in study II.<sup>56</sup> In the SOC scale, which is based on a theoretical framework that aims to explain universal resources promotes successful coping, three components are assessed; comprehensibility, manageability, and meaningfulness. Out of the three components, meaningfulness (a sense of meaning in life and a that life is worthy of engagement) is the most important, and without it, comprehensibility and manageability will falter. The SOC scale consists of 29 items rated on a 7-point Likert scale with scores for each component, and a total score of 29-203, where higher scores indicate higher ability to cope with stressful situations.<sup>56</sup>

Figure 9. Visualization of psychological distress.



### 3.4 STATISTICAL ANALYSIS

In all studies, descriptive data was presented as n (%) for categorical variables, median (range) or median (IQR) for numerical variables. Primarily, non-parametric tests have been used due to non-normal distribution of the different dependent variables, primarily absenteeism, presenteeism, overall work productivity impairment and activity impairment derived from WPAI. The significance level used is  $p < 0.05$ .

Correlations between work productivity and activity impairment, and physical and psychological symptoms were made using Spearman's rank order correlation. Differences between two groups were analyzed using Mann-Whitney U tests and differences between more than two groups were analyzed with Kruskal–Wallis tests (study I, II and IV), and if significant, Mann–Whitney U tests were used as post-hoc analyses for differences among the individual groups (Study I and II). Chi-squared test was used in study II to compare differences in the distribution of categorical variables. In study IV, one-way between-group analysis of variance with linear trend analysis was used to investigate associations between absenteeism, presenteeism, overall work productivity impairment and activity impairment and number of anatomical regions affected by DGBI. To find factors independently associated with work productivity and activity impairment stepwise linear regression (study I) and multiple linear regression models (study IV) were used.

## 3.5 QUALITATIVE ANALYSIS

Two different qualitative approaches were used in this thesis to explore fatigue in IBS (content analysis, study II), and to explore and construct a theory around how to maintain work life in IBS (constructivist grounded theory, study III). The approaches were chosen based on research questions and the nature of the data used.

### 3.5.1 DEDUCTIVE CONTENT ANALYSIS

In study II, the aim of the qualitative analysis was to find patterns of fatigue for patients with IBS within a previously developed model (the Fatigue adaptation model (FAM)),<sup>19</sup> described in detail below), and furthermore, to explore if these patterns were related to the novel categorization of mild, moderate and severe fatigue. Using the two open-ended questions in FIS (which activities that were affected by fatigue, and how tiredness and lack of energy influence life), content analysis was performed in two different ways. Analysis of the answers on affected activities focused on manifest content, where responses were categorized based on type of activity and then quantified as proportion of patients reporting the different categories. Manifest content is content of the text that is observable and without interpretation and does not rely on a high level of abstraction. Deductive content analysis was used when analyzing the responses to the question on how fatigue influences life. The answers were categorized into the domains in FAM and placed on the continuum of adaptation in the model. Finally, an investigation of patterns for patients with mild, moderate and severe fatigue was done.

### 3.5.2 FATIGUE ADAPTATION MODEL

The Fatigue adaptation model (FAM) was used as a basis for the deductive analysis of how tiredness and lack of energy influenced life.<sup>19</sup> FAM presumes a continuum of adaptation on which tiredness, fatigue and exhaustion exist as distinctive states (figure 10). The term adaptation was chosen as it had previously been used by Selye<sup>57</sup> to describe how stress triggers the general adaptation syndrome, which if activated long enough depletes energy reserves and eventually leads to exhaustion. Selye's description was in line with the changes in behavior in the different states (tiredness, fatigue and exhaustion) that Olson saw when creating FAM. Individuals can move between the different stages by gaining or losing adaptive responses.<sup>19, 57</sup>

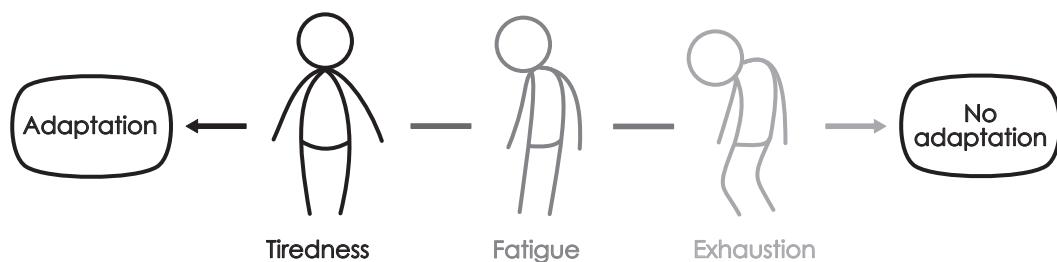


Figure 10. Fatigue adaptation model.<sup>19</sup>

There are six main domains in FAM (figure 11), and different behaviors characterize the different stages of tiredness, fatigue and exhaustion for each domain. Exhaustion as a state is mortal if not alleviated by an adaptive response (and thereby moving to fatigue) and is characterized by insomnia or hypersomnolence (sleep pattern), confusion (cognition), sudden loss of energy disproportional to energy expended (stamina), emotional numbness (emotional reactivity), a withdrawal from all social activity (social interaction), and a feeling of the body taking over (control over body processes). Fatigue is characterized by difficulties sleeping and not achieving restful sleep (sleep pattern), inability to concentrate (cognition), gradual loss of energy disproportional to energy expended (stamina), feeling anxious (emotional reactivity), heightened sensitivity towards sensory input, and a mental persuasion of the body to carry out daily activities and social events (control over bodily processes and social interaction). In the state of tiredness, no changes in sleep pattern, control over body processes and social interaction are seen. Tiredness is instead characterized by forgetfulness (cognition), gradual loss of energy proportional to energy expended (stamina) and feeling impatient (emotional reactivity).<sup>19</sup>

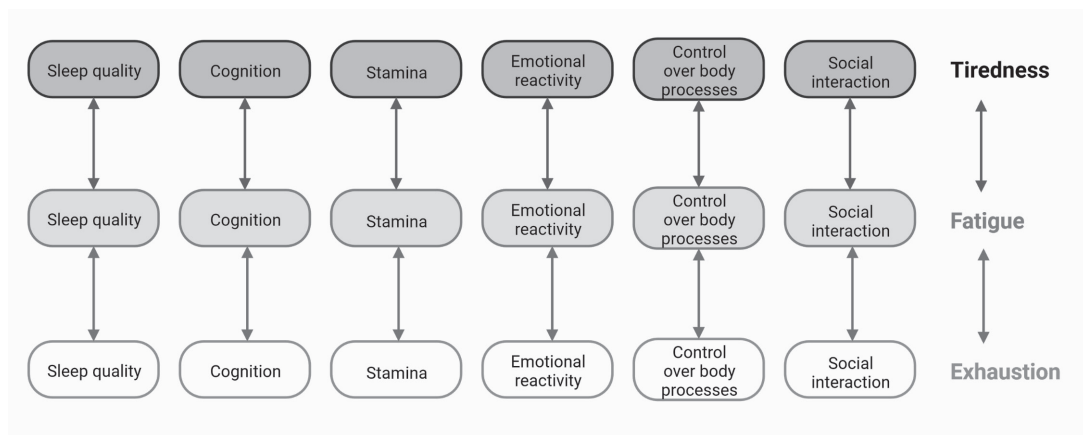


Figure 11. Key dimensions of Fatigue adaptation model.<sup>19</sup> Created with BioRender.com

### 3.5.3 GROUNDED THEORY

In study III, we used a slightly modified version of grounded theory, inspired by Charmaz' Constructivist Grounded Theory (2014).<sup>58</sup> This method was chosen since we wanted to explore a largely unknown research area and we aimed at constructing a theory for how persons with IBS maintain their work life.

Grounded theory (GT) is a qualitative method that creates theories grounded in the data studied. This is in contrast to deductive methods that test already created theories. In 1967, the sociologists Glaser and Strauss published "The Discovery of Grounded Theory: Strategies for Qualitative Research", where they describe a systematic approach where data collection and analysis are two simultaneous processes, in which codes and categories are created from the data and where memos aids the analysis.<sup>59</sup> In 2006, Kathy Charmaz published *Constructing Grounded theory* (2nd edition 2014) where she presents another form of GT, constructivist GT, that differs from classical GT in that the researcher is not seen as a passive observer but as a part of the social construction that makes up the reality.<sup>58</sup> The researcher's perspective, privileges and interactions have to be taken into account and questioned during the research process. In this method, instead of discovering theories, you construct them.<sup>58</sup>

### DATA COLLECTION AND ANALYSIS

Data in study III was collected in the form of individual interviews with persons with IBS at our clinical research unit. The interviews were unstructured and opened with the question "Can you tell us about your work situation as it is today?". Further open-ended questions, as well as probing questions, where the respondents were asked to elaborate and exemplify their answers, were asked to obtain a deeper understanding. During the interviews, it was possible to ask about topics that had been raised in previous interviews and during the analysis since data collection and analysis were made simultaneously. Interviews were held during two time periods, the interviewers wrote memos after and between the interviews, and data collection stopped when reaching saturation. The interviews were tape recorded and transcribed verbatim. The transcripts were coded line-by-line and then entered into Nvivo software (QSR International, 2018), a software used for qualitative analysis. There it was coded incident-by-incident and categories were formed using a constant comparative method to ensure that codes and categories are representative of the data. From the data, codes and categories, a core category was constructed, describing the process of maintaining work life.



## 4 RESULTS

### 4.1 MAIN FINDINGS OF STUDIES

#### 4.1.1 STUDY I

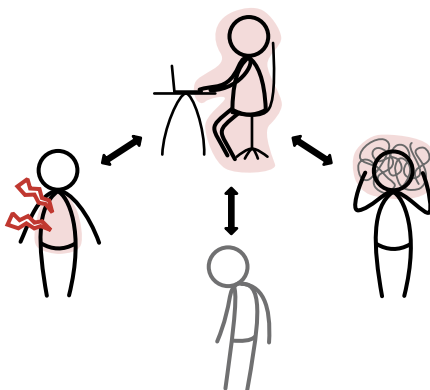


Figure 12. Schematic visualization of Study I.

In study I, work productivity and activity impairment was examined in patients with IBS in two large cohorts (figure 12). We found that having IBS was associated with a substantial work productivity and activity impairment, and that this impairment was even higher for those with severe IBS symptoms, possible or probable depression or severe somatic symptoms (figure 13).

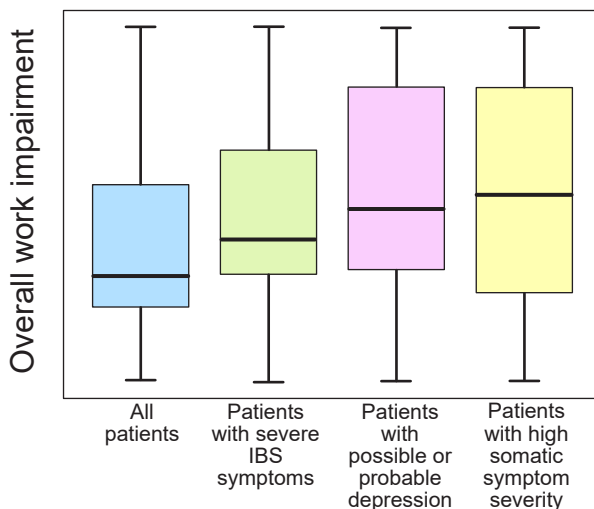


Figure 13. Summarizing and schematic boxplots of overall work impairment scores for all patients in study I, patients with severe IBS symptoms, patients with possible or probable depression and patients with high somatic symptom severity.

There was a negative correlation between work productivity and activity impairment and quality of life, i.e., higher degrees of work productivity and activity impairment were associated with low quality of life in patients with IBS. In the stepwise linear regression model, GI-specific anxiety was independently associated with absenteeism and overall work impairment; general fatigue was independently associated with presenteeism and overall work impairment; IBS symptom severity was independently associated with presenteeism, overall work impairment and activity impairment; and somatic symptom severity was independently associated with activity impairment. In figure 14, a summary of the regression model for overall work impairment is shown.

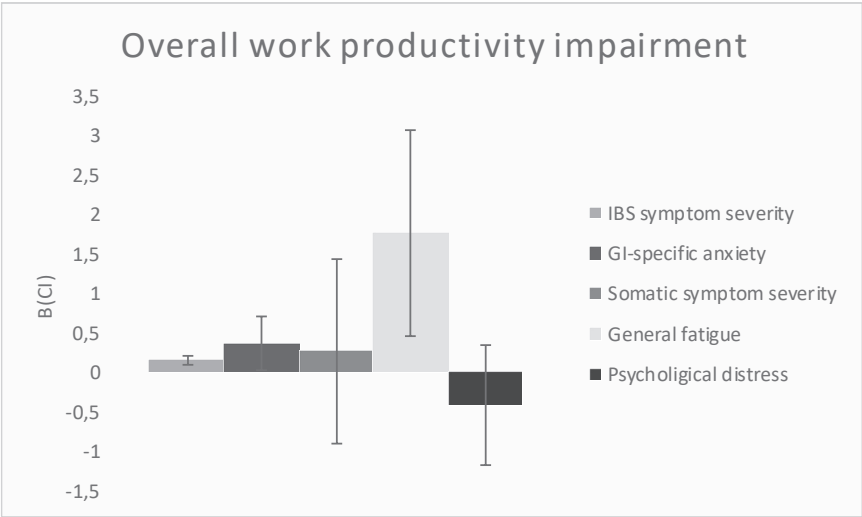
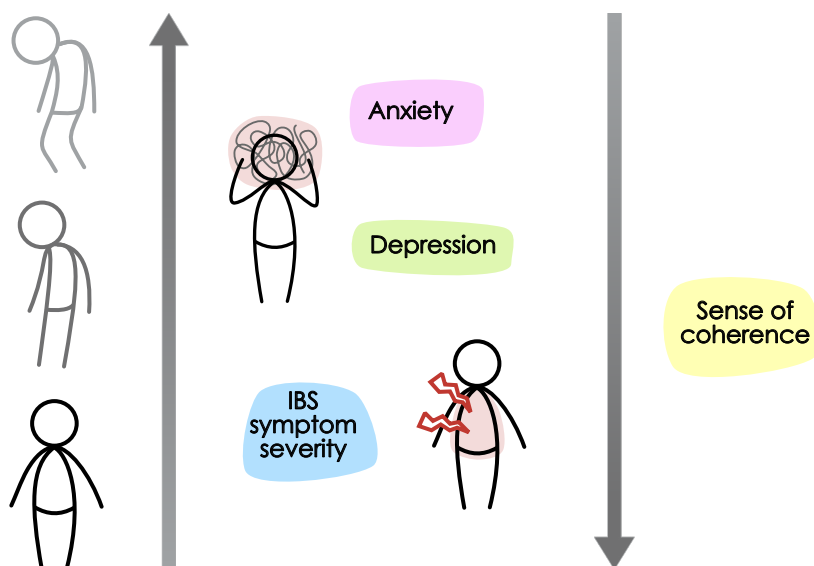


Figure 14. Regression model for Overall work impairment. The diagram shows  $\beta$ (CI) for the independent variables IBS symptom severity (measured with IBS-SSS), GI-specific anxiety (measured with VSI), somatic symptom severity (measured with PHQ-15), the general fatigue domain from MFI and psychological distress (measured with HAD total score). In this model, IBS symptom severity, GI-specific anxiety and general fatigue were independently associated with overall work impairment.

## 4.1.2 STUDY II

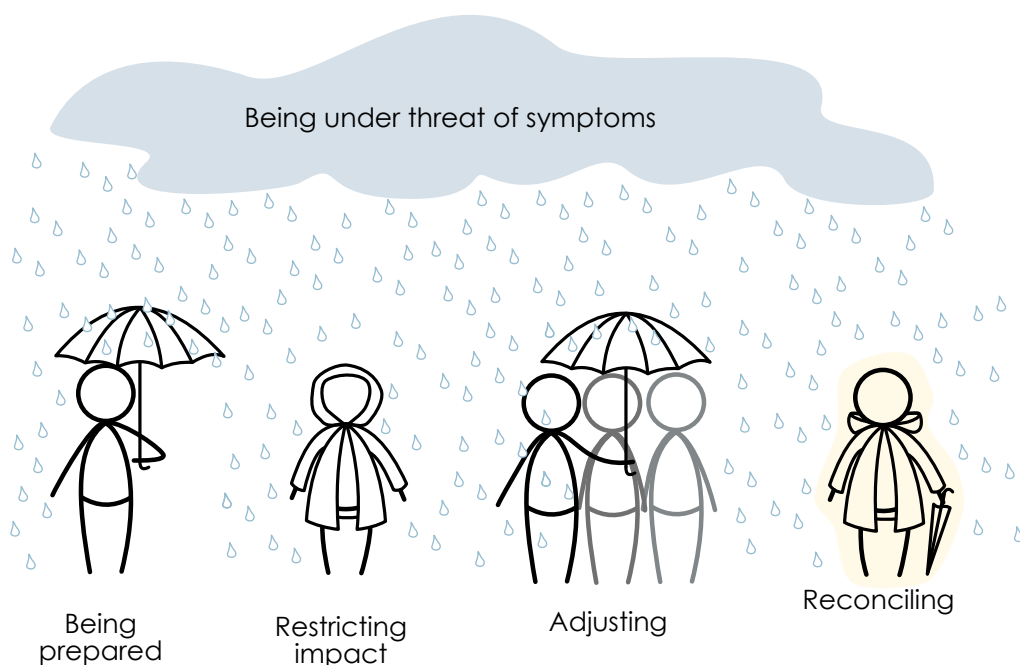


*Figure 15. Patients with IBS and severe fatigue had more severe anxiety and depression, more severe IBS symptoms and lower sense of coherence than patients with IBS and mild or moderate fatigue.*

In study II, a new way of characterizing patients with mild, moderate and severe fatigue was introduced in a cohort of patients with IBS using the Fatigue impact scale (FIS). There were distinct differences between the patients with moderate and severe fatigue. The patients with IBS classified as having severe fatigue had higher scores for IBS symptom severity (IBS-SSS), higher scores on the depression and the anxiety subscales of HAD, as well as lower scores on SOC scale, indicating lower ability to endure and mobilize resources during stressful situations, compared to those with mild or moderate fatigue (figure 15). Furthermore, we demonstrated that fatigue interferes with work/studies, physical activity, hobbies, domestic work, family life and social activities, and that stamina and control over body processes were two prominent domains influenced by fatigue. The patients with severe fatigue according to our classification more often expressed fatigue and exhaustion in FAM compared to those with mild and moderate fatigue.

### 4.1.3 STUDY III

Study III examined the process of maintaining work life while living with IBS. The core category “Balancing work life while being under threat of symptoms” describes the processes patients with IBS go through to maintain their work life. It consists of the categories being prepared, restricting impact, adjusting and reconciling, all of which relates to being under threat of symptoms (figure 16).



*Figure 16. Visualization of the process of Balancing work life under threat of symptoms in persons with IBS. In the figure, being under threat of symptoms is conceptualized as a raincloud always present when the persons with IBS are working. To not be susceptible to symptoms, pictured as getting wet, the persons with IBS prepare and restrict impact of the symptoms, pictured as rain. One challenge in work life is having to adjust to others, and this often led to not being able to take advantage of being prepared or restricting impact, making them at risk of the threat of symptoms, getting wet. Reconciling was understood as having the tools of being prepared and restricting impact, but also something more profound, a way of understanding the world and the outlook of life and work life, pictured as having protection against the rain but also emitting a force field that protects against rain.*

The categories presented in the model represent:

- Being under threat of symptoms: The threat of symptoms loomed over the respondents and the unpredictable nature of symptoms caused them to spend a lot of time listening to and worrying about their gut. Pain, fatigue, bloating, flatulence and altered bowel habits interfered with work life in different ways, and the respondents tried to limit this the best they could.
- Being prepared: The respondents tried to prevent or decrease symptom burden at work by being prepared. This was done by using different strategies to control and adapt work life, e.g. by scheduling meetings and work trips at certain time slots or sometimes by working from home
- Restricting impact: By maintaining routines that could reduce symptom burden, the respondents tried to restrict impact of IBS on work life. This was done by e.g. controlling food intake at lunch and at home, doing physical activities, reducing stress and having routines for bowel movements.
- Adjusting: Having to adjust or relate to others was a challenge for the respondents who could then not fully use their tools of being prepared or restricting impact. This left them more vulnerable to the threat of symptoms.
- Reconciling: When reconciliation of work life and IBS worked well, the respondents experienced less severe symptoms, or was not as affected of their effect during work. There were two levels of reconciliation, one superficial level where the respondents had learnt how to take advantage of being prepared and restricting impact, and a more profound level that had to do with basic outlook of life and work life.

### 4.1.4 STUDY IV

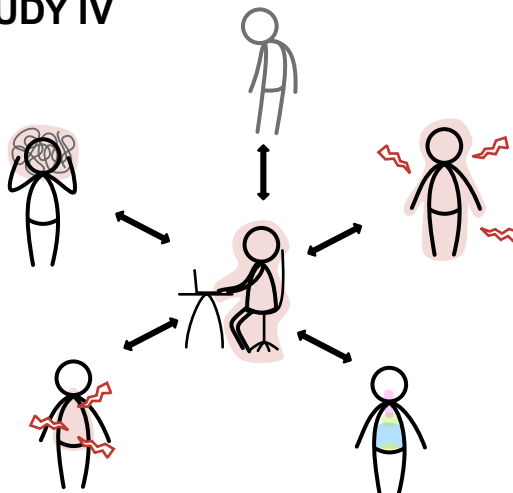


Figure 17. Schematic visualization of Study IV.

In study IV, work productivity and activity impairment in persons with DGBI was examined in a large, population-based, multinational cohort. Persons with any DGBI had higher degrees of work productivity and activity impairment compared to the general population. Among the persons with any DGBI, those with a painful DGBI, those with medium or high somatic symptom severity and those with moderate or severe psychological distress had even higher degrees of work productivity and activity impairment (Figure 18).

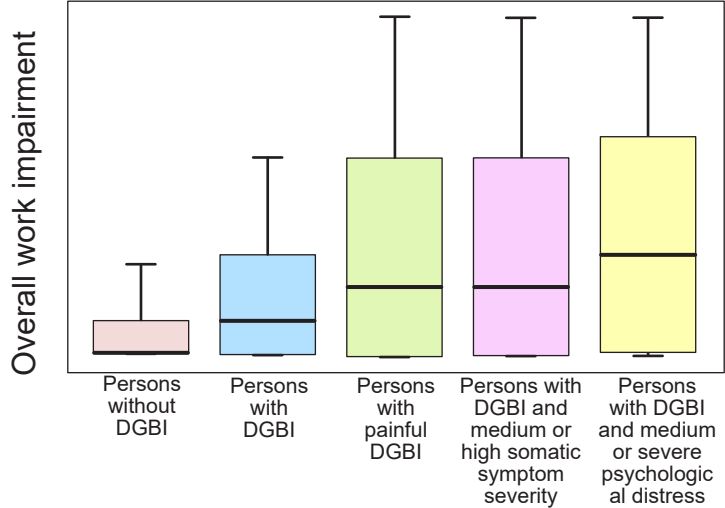
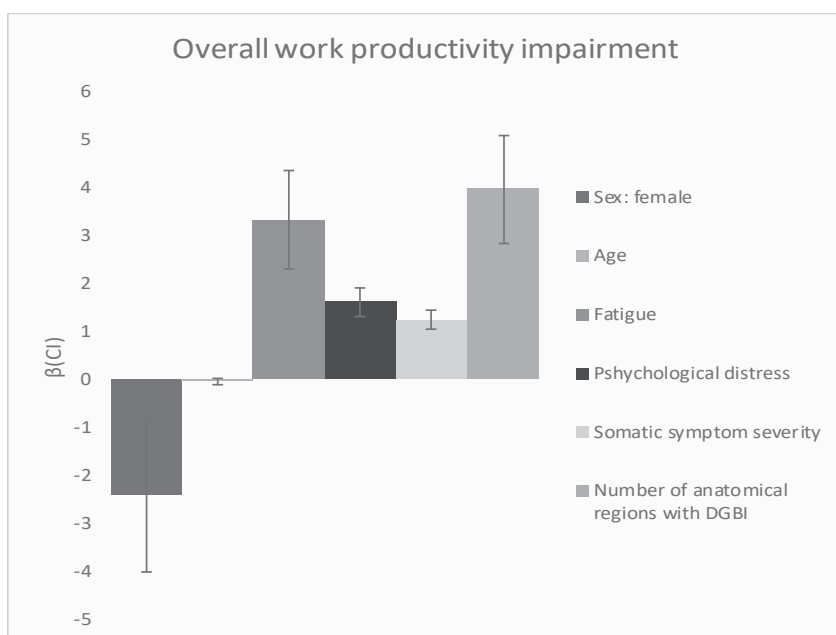


Figure 18. Summarizing and schematic boxplots of overall work impairment scores for persons with and without DGBI, persons with painful DGBI, persons with DGBI and medium or high somatic symptom severity, and persons with DGBI and medium or severe psychological distress.

Using multiple regression analysis, we found that having DGBI in overlapping anatomical regions, reporting more severe fatigue, psychological distress and non-GI somatic symptom severity were independently associated with work productivity and activity impairment (figure 19). Examining work productivity and activity impairment among persons with DGBI between participating countries (Germany, Israel, Italy, Japan, the Netherlands, Poland, Spain and Sweden), there were significant differences in both scores and proportion reporting any health-related work productivity and activity impairment.

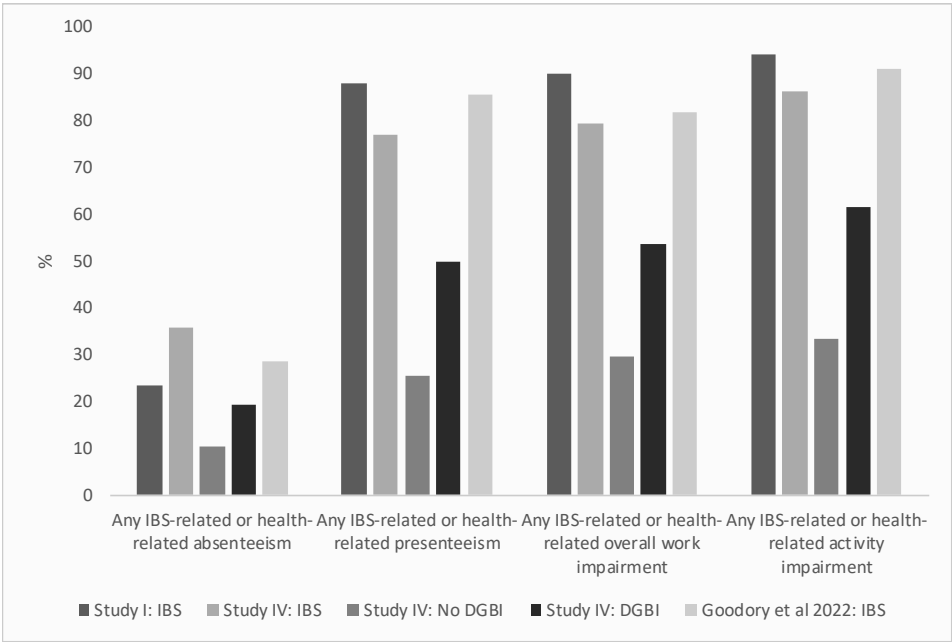


*Figure 19. Regression model for Overall work impairment. The Diagram shows  $\beta$ (CI) for independent variables sex, age, fatigue, psychological distress (measured with PHQ-4), somatic symptom severity (measured with PHQ-15), and number of anatomical regions affected by DGBI. In this model, male sex, fatigue, psychological distress, somatic symptom severity and number of anatomical regions affected by DGBI were all independently associated with overall work impairment.*

## 4.2 SYNTHESIS OF THE RESULTS

### 4.2.1 MAGNITUDE OF WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT

In manuscript I, a larger proportion of subjects with IBS reported work productivity and activity impairment than the subjects with at least one DGBI in study IV (figure 20). When comparing the subjects with IBS from the general population in study IV and the subjects (patients with IBS) in study I, the difference is smaller, with the proportion reporting absenteeism being higher in study IV, while the proportion reporting presenteeism, overall productivity impairment and activity impairment is still higher in study I.



*Figure 20. Percent reporting any IBS- or health-related work productivity and activity impairment of the patients with IBS in study I, the persons with IBS in study IV, the persons with DGBI in study IV. For comparison, data from another recent publication on work productivity and activity impairment in IBS from the UK is also included in the figure.<sup>34</sup>*



## 4.2.2 FATIGUE AND WORK PRODUCTIVITY

Fatigue was the main focus of study II and 48% of the participants reported fatigue as one of or their worst symptoms. Fatigue was also examined to some extent in study I and IV, where fatigue was independently associated with work productivity impairment for both patients with IBS (study I) and persons with DGBI (study IV). In study III, fatigue was a prominent theme as it was one of the most common symptoms reported by the respondents, in addition to the GI symptoms. The respondents also described how pain led to fatigue, interfering with work and daily life. One respondent described:

*"The body gets very tired when it hurts all the time. You become more tired than what you should be" Respondent 23*

Descriptions in study III ranged from tiredness to exhaustion in the continuum of adaptation from FAM<sup>19</sup> used in study II, with an emphasis on fatigue and exhaustion, table 5.

*Table 5. Quotes from respondents in study III exemplifying different domains of FAM<sup>19</sup> on the continuum of adaptation.*

Term	Domain	Quote from respondents in study III
Tiredness	Stamina: Gradual loss of energy in proportion to energy expended	"If it is as intense at work as it is now, then of course I get tired earlier in the day. But if I have a normal workload, I don't feel tired until I get home" Respondent 18
Fatigue	Cognition: Inability to concentrate	"Tiredness and also inability to concentrate... Memory and concentration is affected. I've come to realize the importance of doing one thing at a time" Respondent 8
Exhaustion	Control over body processes: Body over mind	"I feel tired. The mind wants more, but I go to bed instead" Respondent 2

### 4.2.3 SOMATIC SYMPTOMS, WORK PRODUCTIVITY AND FATIGUE

Severe somatic symptoms were associated with work productivity impairment in patients with IBS in study I, and in persons with DGBI in study IV, and to severe fatigue in patients with IBS in study II. IBS symptom severity was associated with work productivity in study I and with fatigue in study II. In study III, the treat of symptoms was always present for the respondents, both in and outside of work life.

*“I feel as if I’m always thinking of my stomach” Respondent 11*

Always thinking of the gut and trying to predict and prevent GI symptoms could affect work performance during work hours. This led to the respondents using the strategies of being prepared and restricting impact by controlling different aspects of their work, such as food intake, planning breaks to suitable times, and sometimes choosing to work alone. Symptom flare-ups made it difficult and sometimes impossible to work. In study I, apart from interference of IBS on daily life, the question on satisfaction with bowel habits correlated strongest with absenteeism of the questions in IBS-SSS (Spearman’s rho 0.273,  $p < 0.001$ ). One respondent from study III described recurring episodes where there was no possibility to work through his symptoms and sick leave was the only choice:

*“Every third or fourth week when I’m on the toilet in the morning, my entire body empties itself. Without going into details, I completely run out of everything and need to go to bed directly afterwards. It can happen at home or at work. If I’m at home I have to call in and say that I can’t come, and if I’m at work I have to go home, I don’t have energy left for anything” Respondent 7*

Pain, especially abdominal pain, was described as difficult to handle during work. This is in line with study I where pain intensity correlated with presenteeism and overall work impairment (Spearman’s rho 0.377 respectively 0.408,  $p < 0.001$  for both), and the same pattern was seen for pain frequency (Spearman’s rho 0.334 respectively 0.341,  $p < 0.001$  for both). In study IV, persons with painful DGBI had higher degrees of absenteeism, presenteeism and overall work productivity impairment than those with non-painful DGBI. As mentioned above, pain was also often described in relation to fatigue, where pain could lead to being tired and tiredness sometimes made the respondents more susceptible to pain. This is in line with the findings in study II where 24 % of the subjects reported that fatigue interfered with work and studies and having severe fatigue was associated with having more severe IBS symptoms.

*“It’s probably those two things [affecting my work the most]. Pain and when I feel extra tired” Respondent 6*

## 4.2.4 PSYCHOLOGICAL DISTRESS AND WORK PRODUCTIVITY

Psychological distress was investigated in all studies in this thesis. In study I, GI-specific anxiety correlated with absenteeism, presenteeism, overall work impairment and activity impairment (Spearman's rho 0.237-0.557,  $p < 0.05$  for all), HAD anxiety scores correlated with absenteeism, presenteeism and overall work impairment (Spearman's rho 0.200-0.217,  $p < 0.05$  for all), and HAD depression scores correlated with presenteeism, overall work impairment and activity impairment (Spearman's rho 0.270-0.302,  $p < 0.05$  for all). In study II, patients with IBS and severe fatigue had higher scores for HAD anxiety and depression than the patients with mild or moderate fatigue. In study IV, psychological distress, measured with PHQ-4 total score, was independently associated with presenteeism, overall work productivity and activity impairment in persons with DGBI. Of the 23 respondents in study III, 5 had probable depression and 9 had probable anxiety. Several respondents shared that they had been on sick leave because of depression or stress reactions due to "burn-out", and three were on sick leave during the time of the interview. Stress and anxiety were described to affect both GI symptoms and work performance negatively. One respondent described:

*"I don't get more gas when I'm stressed but I know that I get more alternating diarrhea and constipation then. So, there's something happening in the stomach then" Respondent 15*

Not having job security caused anxiety and stress, affecting both IBS symptoms and work life. One self-employed respondent shared:

*"I feel as if I'm at a high level of stress all the time, with not knowing from day to day if I will be able to pay for rent. Especially when the jobs are far apart and nothing new comes in, then I get so f\*cking worried and can't sleep. So, I feel that my worry and stress levels are high all the time. And I believe that is the biggest thing that affects [work] actually" Respondent 20*

Using different techniques, such as relaxation, yoga, and hypnosis, to manage stress and anxiety was described as useful to maintain work life. One respondent described:

*"I have a relaxation playlist on Spotify that I can play in my car or on headphones. The gut, it reacts before I notice myself that I am stressed. So, if I'm in my car in a traffic jam which I find stressful, I put that on" Respondent 14*

## 5 DISCUSSION

In this thesis, we have examined work life in persons with IBS and DGBI from different perspectives, using different methods to capture different aspect of this complex phenomenon. In study I, we evaluated the magnitude of work productivity among patients with IBS using questionnaires and found a substantial work impairment, and that fatigue, IBS symptom severity and general fatigue were independently associated with overall work impairment. In study II, as fatigue was found to be of importance for work productivity in IBS, we explored fatigue in patients with IBS using both quantitative and qualitative methods, and patients with IBS and severe fatigue had more severe IBS symptoms, more depression and anxiety, and lower sense of coherence compared to patients with moderate or mild fatigue. Fatigue impacted many aspects of daily life, and negative effects on stamina and control over bodily processes were prominent, with only patients with moderate or severe fatigue reporting effects in line with exhaustion. In study III, we used in-depth interviews and constructivist grounded theory to explore the process of maintaining work life in patients with IBS and constructed a model with the core category Balancing work life under threat of symptoms. In study IV, we broadened the perspective and examined all DGBI in a large population-based, multinational cohort and found that persons with DGBI have significantly higher degrees of work productivity and activity impairment compared to those without, and that those with a painful DGBI, or more psychological distress or somatic symptoms, have more work impairment than those with non-painful, no or low psychological distress, mild or moderate somatic symptoms.

In study I and IV, we found a substantial work productivity and activity impairment in patients with IBS and persons with DGBI, and as mentioned in the results, there were some differences between the two studies. This difference of magnitude of work productivity and activity impairment of the patients with IBS in study I and the persons with IBS in study IV can be due to several reasons, e.g. that the two studies used different versions of the work productivity and activity impairment questionnaire (study I used WPAI:IBS and study IV used WPAI:GH), the multinational vs Swedish cohorts, and that the subjects in study I are patients while the participants in study IV were from the general population. Comparing the proportion reporting any IBS-related absenteeism, presenteeism, overall work productivity and activity impairment in the patients with Rome III IBS from study I to what Goodoory et al.<sup>34</sup> reported for their patients with Rome IV IBS showed comparable numbers (23, 88, 90 and 94 % in study I vs 29, 86, 82 and 91% in Goodoory et al.<sup>34</sup>), indicating that patients with IBS seeking health care for their symptoms have greater overall work productivity impairment than persons with IBS in the general population, regardless of which version of the Rome criteria that was used to define IBS.

To evaluate work productivity we used WPAI:IBS and WPAI:GH. There are some limitations to this questionnaire that should be taken into account when interpreting the results. The short time period evaluated, the last seven days, is good because of the low risk of recall bias, but makes estimating the yearly productivity impairment risky. Data must be collected reasonably consistent over the year to reflect the average work impairment so that seasonal variations does not cause over- or underestimation. Another limitation with this questionnaire is the subjective evaluation of presenteeism, where the respondents themselves estimate their presenteeism on a scale from 0 (no) to 10 (total impairment). Because of the nature of presenteeism, we cannot compare how accurate the subjective perception is compared to an objective measurement of presenteeism in this type of study, and things like culture, gender, perceptions and expectations of oneself might impact how the respondents answer the question. This could be one of the reasons behind differences between the countries in persons with DGBI in study IV. However, since all responds to the same questionnaire, on a group level, there is still a difference on how patients with IBS, and persons with DGBI, evaluate their work productivity compared to the general population. Having the possibility to evaluate presenteeism adds much value to the evaluation of work productivity impairment, since absenteeism alone only captures part of the productivity impairment.

In study III, we explored a previously uncharted territory by using qualitative methods to address work life in IBS. Because of the lack of previous knowledge, we chose a methodology, constructivist GT, that was inductive, i.e., we did not work after a predefined theory or aimed to prove or disprove a hypothesis, but tried to discover a new theory/create a model for the process of maintaining work life while living with IBS. The core category “Balancing work life under threat of symptoms” and its categories of being prepared, restricting impact, adjusting, and reconciling contain aspects that in several ways are very specific to IBS, with a lot of focus on food, breaks, access to bathrooms etc., but some aspects might be useful for workers with most chronic diseases and even healthy workers. The respondents highlighted being able to control different aspects of work themselves, e.g. worktime control (flexible hours, control over work schedule, etc.) the possibility to alter work tasks over the work day, or to alter workplace, sometimes working from the office and sometimes working from home. This is called employee-oriented flexible work, and especially worktime control has been shown to have modest beneficial effects on psychological distress, fatigue, depressive symptoms, burnout and emotional exhaustion.<sup>60</sup> Telework (working from anywhere, anytime), and home-based telework, has become even more common after the Covid-19 pandemic. Telework has been found to have both negative and positive effects on health. The negative effects are in part due to the physical workspace with poor ergonomics and working conditions, with increased risks of work-related musculoskeletal disorders, eye strain and migraines.<sup>61</sup>

Positive effects are in part due to the beneficial impact on work-life balance.<sup>61</sup> In line with what the respondents in study III reported, the participants in a study of teleworkers' relationship between work and health reported that teleworking allows working with symptoms that if not being able to work from home would cause absenteeism.<sup>62</sup>

There were differences in work productivity and activity in persons with DGBI between the countries in study IV. As mentioned previously, cultural differences can partly explain this through the way individuals report presenteeism, but there are of course many other potential reasons for this. A recent multinational study of patients with inflammatory bowel disease in 12 European countries also showed differences in absenteeism, presenteeism and overall work impairment between the participating countries, and speculated that socio-economic factors, differences in healthcare systems or labor policies could be underlying reasons for the differences.<sup>63</sup> These are all factors that we did not examine in study IV, and this motivates further that investigations on country differences in work life for persons with IBS.

## 6 CONCLUSION AND FUTURE PERSPECTIVES

In conclusion, the results from this thesis highlight a substantial negative impact on work life for persons with IBS and DGBI, and that fatigue, psychological distress and somatic symptoms, not only confined to the GI tract, contribute to this impairment. Further, we found that behaviors and strategies can be applied to lessen impact on work life. These results highlight the importance of a broad view on the management of persons with DGBI and IBS, and that the overall symptom burden, both physical and mental, should be considered to optimize the outcome.

When I started working on this thesis, the area of work life and IBS had not gained much attention, but over the last years this has changed. There are now more studies assessing work productivity impairment, and it is not uncommon to even have work productivity as a secondary outcome in treatment studies. For future perspectives, evaluating if treatment of symptoms does in fact help with work life would be of great interest, as well as comparing the effect on work life with different treatment strategies and different treatments targeting different symptoms. It would also be of interest to expand on the results from study III, to evaluate if it is possible to develop a behavioral treatment option that targets the important aspects we found for maintaining work life. In addition, it would also be worthwhile to determine if this treatment can also be applied to other DGBI or even to other chronic diseases. Moreover, in our regression models only parts of the variances of the different aspects of work productivity and activity impairment in IBS and DGBI were explained. Hence, other aspects, not covered in our studies are also of importance for work life in these large groups of patients. This should be further explored in future studies to optimize the management of persons with DGBI and IBS with the goal to improve their work life.

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