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LIVING WITH INFLAMMATORY BOWEL DISEASE - HEALTH-RELATED QUALITY OF LIFE, WORRIES, AND STRESS



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“Det är svårt att förstå det som inte syns”

Medlem i Mag- och tarmförbundet

To my mother

ABSTRACT

Background: Patients with inflammatory bowel disease have a number of worries and concerns related to the disease, and in comparison with a general population their health-related quality of life is impaired. These patients need disease-related information and education. However, it remains unclear how this information should be provided in order to decrease their worries and concerns, and improve their health-related quality of life. Disease activity is one of the most important factors for reduced health-related quality of life. Therefore it is also important to assess more information about trigger factors for relapses in inflammatory bowel disease.

Aim: The general aim of this thesis was to gain scientific evidence about worries and concerns, health-related quality of life, and trigger factors for relapses, and to develop and evaluate an education programme.

Method: In all four studies the patients included were diagnosed with inflammatory bowel disease, and in remission. In **Study I**, 93 patients were included and randomized to an intervention group or a control group. The intervention group attended a group-based education programme. Health-related quality of life was measured at baseline and after six months, by using four questionnaires. The intervention group also completed the questionnaires after one month. In **Study II**, 197 patients were included and divided into a Crohn's disease group and an ulcerative colitis group. Each group was also divided into separate groups according to whether the patients had short disease duration or long disease duration. Health-related quality of life was measured using four questionnaires. In **Study III**, a sample of 195 patients was included. They filled in the RFIPC, and two other questionnaires measuring health-related quality of life. Confirmatory factor analysis was performed to validate the factor structure in the Swedish version of the RFIPC and to examine fit of different hypothesized models of factor structure. In **Study IV**, 60 patients were included. They filled in a structured diary daily during six months in order to collect information about symptoms and potential trigger factors, such as perceived stress.

Results: No difference could be found in health-related quality of life between patients with ulcerative colitis and Crohn's disease. Scores of health-related quality of life were lower for patients with short disease duration than for patients with long disease duration. Patients with Crohn's disease and short disease duration had the lowest health-related quality of life. After attending an education programme, an improvement was found in the intervention group when measurements were made after one month. After six months, no improvement could be shown in health-related quality of life when comparing the intervention group with the control group. The RFIPC is the most appropriate choice when measuring health-related quality of life, worries and concerns. Using the single-factor model (sum score) displayed poor fit indices. The factorial structure of the RFIPC, as suggested in the original version, could be replicated with a slight modification in the Swedish version and showed the most adequate fit. Perceived stress can act as a trigger for relapses in inflammatory bowel diseases. A high level of perceived stress was found to have an effect when stratifying level of stress. High level of stress one day increased the risk of relapse the next day.

Conclusion: CD patients with short disease duration have the greatest need of education and support. No improvement could be seen in health-related quality of life after attending an education programme. The separate factors in RFIPC provide more

detailed information about patients' disease-related worries and concerns in both research and clinical settings. This may help healthcare professionals to provide each patient with the appropriate education and support. Identification of trigger factors for relapses in inflammatory bowel disease also makes it possible to influence the trigger. By extension, this could decrease the number of relapses and improve health-related quality of life.

Keywords: Inflammatory bowel disease, Crohn's disease, ulcerative colitis, health-related quality of life, worries, stress

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LIST OF ABBREVIATIONS

IBD	Inflammatory Bowel Disease
UC	Ulcerative colitis
CD	Crohn's Disease
HRQOL	Health-related Quality of Life
HI	Health Index
IBDQ	Inflammatory Bowel Disease Questionnaire
RFIPC	Rating Form of Inflammatory Bowel Disease Patient Concerns
SOC	Sense of Coherence
ANOVA	Analysis of variance
MANCOVA	Multivariate Analysis of Covariance
CFA	Confirmatory Factor Analysis
HBI	Harvey Bradshaw Index
UC-DAI	Ulcerative Colitis Disease Activity Index

1 INTRODUCTION

Patients with inflammatory bowel disease (IBD) have to cope with a lifelong condition and make many lifestyle adjustments. Living with IBD and its unpredictable course may influence several aspects of life. Worries and concerns related to IBD may affect the patient's adjustment to the illness and compliance with treatment [1, 2]. Patients with IBD rate their health-related quality of life (HRQOL) lower than a general population [3-6], and disease activity is one of the most important factors for decreased HRQOL [3, 5-9]. Therefore, patients with IBD need both treatment for the bowel symptoms as well as disease-related information, particularly concerning factors that may trigger relapses (especially if the trigger can be influenced). By extension, this might lead to fewer relapses, a decrease in patients' worries and concerns, and also to improvements in HRQOL.

I became interested in patients with IBD because of their complex life situation. It is not only the disease that needs to be treated; several aspects of life also have to be considered. All patients with chronic diseases require information and education to help them have a better life in spite of their illness. It is important to support these patients in their efforts to cope with the disease, and provide them with as much disease-related knowledge as possible. Living with IBD may affect several aspects of life and patients have to deal with different lifestyle adjustments. Many questions may arise when dealing with for example pregnancies, travelling, symptoms, financial issues and different treatments. Availability at the clinic is very important [10]. Patients with IBD are often in the middle of life and may find it difficult to keep to fixed telephone hours due to their own working- or school hours. In our clinic we changed our way of working with IBD patients in 2003, when a clinic especially for IBD patients and managed by nurses was started. Availability is one of the most important aspects of the clinic. The telephone line is open during the whole day, with an answering machine that takes calls when it is not possible to answer. It is the nurses who are in charge of patients' annual visits. Before the IBD clinic was started it was the gastroenterologists who took care of these visits, but they could not prioritize the annual visits since they had to take care of acute visits and new patients. The nurses also provide patients with more structured information, especially those who are newly diagnosed but also those who need further knowledge. Today our IBD patients receive both group-based as well as individual information, and the aim is to be as available as possible. There is still much to learn about IBD. We can learn more from other specialities that work with chronic diseases, for example in the area of diabetes, but we also learn a great deal by studying our IBD patients. What are their needs and how can we help them to improve the way they live and cope with their disease? This thesis tries to clarify a number of questions, and by extension this may help nurses and doctors to provide better help for IBD patients.

2 BACKGROUND

2.1 INFLAMMATORY BOWEL DISEASE – IBD

IBD includes ulcerative colitis (UC) and Crohn's disease (CD), comprising chronic diseases that are characterized by alternating periods of remission and relapses [11, 12]. The most common symptoms of UC are diarrhoea, rectal bleeding, and abdominal pain [13, 14]. The inflammation is non-transmural and restricted to the colon. The extent of the inflammation may vary: proctitis, left-sided colitis (involving the sigmoid colon with or without involvement of the descending colon), or fulminant colitis [13]. In CD the inflammation is transmural and may affect the entire gastrointestinal tract, from the mouth to the anus [13, 15]. The inflammation is often discontinuous (in contrast to UC, where the inflammation is always continuous) and complications including strictures, abscesses, or fistulas may occur. At diagnosis the disease is located in the terminal ileum in 47% of cases, in the colon for 28%, the ileocolon for 21%, and in the upper gastrointestinal tract for 3%. The symptoms depend on disease location and may include diarrhoea, abdominal pain, fever, clinical signs of bowel obstruction, passage of blood or mucus or both [13]. CD and UC are most commonly diagnosed in late adolescence and early adulthood but may occur in all ages [16]. Endoscopy with biopsy sampling is the gold standard for diagnosing IBD, but blood- and stool samples are also necessary [14].

Current IBD medications include corticosteroids, 5-aminosalicylates (5-ASA), immunomodulators, biologic agents, and antibiotics [13, 14]. Despite improvements in medical treatment, surgery still plays an important role. Indications for surgery include bowel perforation, intractable disease despite medical treatment, dysplasia, strictures, and fistulas [14].

Patients with IBD have an increased risk of colorectal carcinoma when they have had the disease for a long time. Risk factors for colorectal carcinoma are long-term disease (more than 8-10 years), young age of onset, extensive colonic involvement, family history of colorectal carcinoma, and concomitant inflammatory manifestations, for example primary sclerosing cholangitis [17]. The risk is the same in both CD and UC. Colonoscopies for screening should begin 8-10 years after the onset of IBD symptoms in patients with fulminant UC and patients with CD involving at least one third of the colon [17-19]. How often the surveillance colonoscopies should be repeated depends on the presence of dysplasia. According to guidelines, the survey should be done every 1-2 years [17].

2.1.1 Relapses

The course of UC is characterized by relapses that alternate with periods of remission, but for a minority of patients there is a more continuous course. Both the severity of the relapses as well as patient response to treatment vary and are difficult to predict [15]. For CD patients the course is generally also characterized by alternating periods of relapses with remission of varying durations. However, 10-15% of these patients have a more chronic, continuous course [15].

Both CD and UC seem to become less severe over time. A decrease in symptoms is the most common course of the diseases [12, 20, 21]. Five years after diagnosis, the majority of UC patients have no symptoms and 40% do not take any medication for IBD [20]. Direct costs are highest in the first year after diagnosis and greater in CD patients compared with UC patients [21]. A more benign course can be seen in both CD patients and UC patients with increasing disease duration [12, 21, 22], but even patients with long periods in remission may experience a severe relapse or complication that requires surgery.

2.1.2 Aetiology

The aetiology of IBD is still unknown but it is likely that genetic predisposition, environmental factors, and immune dysfunction are all important [23]. The association between smoking and IBD is well established. Smokers are at higher risk of developing CD than non-smokers, whereas ex-smokers run an increased risk of developing UC [15, 24-27]. It has also been suggested that there may be a specific effect of antibiotics in early life which may increase the risk of developing IBD, particularly CD, later on [24], and possible infectious events may also influence the risk of IBD [27]. A family history of IBD is an important risk factor for developing the disease. On average, 8-10% of CD patients and 6% of UC patients have one or more relatives with IBD [25].

2.1.3 Incidence and Prevalence

The highest incidence rates have been reported in northern and western Europe and North America [15, 28]. Previous low-incidence areas of eastern Europe, Asia, North Africa, and Central and South America have demonstrated a recent increase in the incidence and prevalence of IBD [15, 28]. In paediatric IBD, significant increases in both incidence and prevalence can be seen [14]. Over the past 50 years the incidence of UC has increased and then stabilized, or even decreased, whereas the incidence of CD has continually increased [15]. In the United States and Canada there are approximately 780 000 persons with UC, and 630 000 persons with CD. In Europe, there are approximately 2.2 million persons suffering from IBD [16].

2.2 TRIGGER FACTORS OF RELAPSES

It is still unknown whether any factors/variables can be triggers of disease relapses. However, diet, smoking, infections, antibiotics, and stress have all been reported to be potential triggers of relapses in IBD.

2.2.1 Lifestyle Factors

It has been suggested that specific diet could impact the course of the disease. It is possible that an intake of high-fibre, rice-based, and high-fish diets could work as a protection against relapse. On the other hand, diets including large amounts of red meat, simple sugar, and low fibre could be trigger factors [29]. Studies have shown that the course of the disease cannot be influenced by avoiding certain foodstuffs, or by adopting a specific diet. Nevertheless, there is evidence that some diet therapy is effective in treating the diseases [30, 31]. Some studies have found that a diet with low doses of refined carbohydrate is beneficial for patients, while other studies have been

unable to confirm this [30]. Research has shown that an increase in intake of animal protein and an increase in intake of omega 6 fatty acid compared with omega 3 fatty acid correlated with a high risk of IBD [29].

Patients with UC who smoke are more likely to have a relapse if they quit smoking [32], and patients with CD are more likely to be smokers [33]. The properties of cigarette smoking that lead to a negative development in CD and protect against disease activity in UC are, however, still unknown.

2.2.2 Infection and Antibiotics

It is suggested that there is a link between systemic or respiratory infection and relapse in IBD, but the evidence for this is minimal. It is possible that these infections lead to relapses in IBD patients, but it may be that IBD-affected tissues allow for increased cell membrane permeability, therefore implying greater potential for pathogenic infection [34]. It has also been suggested that enteric infections, for example *Clostridium difficile*, cause relapse in IBD, but it is possible that they cause symptoms of their own, rather than inducing a relapse [34]. It remains unclear whether the use of antibiotics directly triggers a relapse in IBD, and there is as yet no evidence that this should be classified as a trigger. The hypothesis is that antibiotics can change beneficial microbial flora, which can be injurious in IBD [34].

2.2.3 Stress

It has been suggested that high stress is associated with relapse in IBD [35-39]. Stress is a condition in which person-environment interactions lead to a perceived discrepancy between the demands of the situation and the biological, psychological and social resources of the person. Stress has been defined as *a process in which environmental demands tax or exceed the adaptive capacity of an organism, resulting in psychological and biological changes that may place persons at risk for disease* [40]. Stress can be looked at from different perspectives: environmental stress, which includes life events; psychological stress, focusing on individuals' perceived stress; and finally biological stress, which focuses on the activation of physiological systems [40].

Some studies have examined the possible association between stress and relapses in IBD, and there is some evidence that perceived stress is a trigger [34-37, 39, 41]. However, there are studies where no connection could be found [42-44], and other studies showing that short-term stress does not trigger relapses but long-term stress increases the risk [38]. Others have found an association between stress and relapse in UC but not in CD [41]. On the other hand, depressive symptoms seem to have a negative effect on the course of CD [45].

Studies have been made to investigate the effect of stress reduction programmes. Stress management psychotherapy does not improve disease activity but improves HRQOL, especially in UC patients [46]. So far, the stress reduction programmes that have been developed have had little effect on CD patients [45, 46].

Acute psychological stress has several proinflammatory effects at both systemic and mucosal levels. For example, stress increases the production of ROM (reactive oxygen metabolite), which may contribute to mucosal damage. Stress has also been shown to reduce the RMBF (rectal mucosal blood flow), causing mucosal ischaemia which may trigger relapses. Increases in both platelet activation and PLA formation (platelet-leucocyte aggregate) might also be partly responsible for stress-induced symptoms in IBD [39].

There are several issues involved in studying the link between stress and relapse in IBD. There are, for example, several ways to measure stress. Some studies utilize reports of stressful life events. Others use stress diaries or standardized questionnaires, while there are also studies that focus on physiological correlates/indices of stress. The physiological response to stressful experiences can be studied by measuring urinary metabolites of catecholamines or cortisol, making serial measurements of serum or salivary cortisol, or by monitoring cardiovascular or immune responses to stress [45]. Since a relapse in IBD is a stressful event in itself it may be difficult in cross-sectional data to establish whether stress is the cause or the consequence of the relapse.

2.3 HEALTH-RELATED QUALITY OF LIFE (HRQOL)

Quality of life has been defined as *individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns* [47]. HRQOL is the value assigned to duration of life as modified by the impairments, functional states, perceptions and social opportunities that are influenced by disease, injury, treatment or policy [48]. HRQOL is determined by the patient's physical, psychological and social status, and by attitudes, concerns and behaviours in response to the disease [2].

IBD is a disease which has a major impact on patients' lives. Several studies have examined HRQOL in patients with IBD, and it is clear that their HRQOL is impaired compared with that of a healthy population [6, 49-55]. Symptom severity is one of the most important associations with reduced HRQOL [4-7, 49, 53, 56-60]. In some studies it can be demonstrated that CD patients have lower HRQOL compared with UC patients [2, 3, 8, 51, 52, 61], but in other studies no differences have been found [6, 54, 62, 63]. Women are another subgroup for whom HRQOL seems to be reduced [1, 3-5, 49, 54, 61-64]. So far, few studies have examined the association between HRQOL and disease duration. Those that have been conducted have displayed various results. Two studies have shown that longer disease duration is associated with better HRQOL [5, 65], whereas one study did not find any difference between short and long disease duration [9].

CD patients in remission, who have low disease activity and no need for medical treatment to maintain remission, have 3.5 times lower costs (both direct medical costs and costs for lost productivity) than patients with a more active disease. Also, patients that respond to treatment have lower costs and better HRQOL compared with patients where disease activity is high but no treatment is given or there is no response to treatment [66].

There seems to be a complex relationship between biopsychosocial factors and HRQOL. Different aspects of well-being interact with various biopsychosocial factors in determining the IBD patient's well-being [67]. Psychological factors, such as depressive mood associated with anxiety and poor HRQOL, seem to have a negative influence on the course of IBD [68].

2.4 WORRIES AND CONCERNS

Everyone worries from time to time, even those who do not suffer from a chronic disease. Worry involves a predominance of negative verbal thoughts. We talk to ourselves about negative things and what may happen in the future [69]. The highest rated reasons for worrying are that it helps to discover ways of avoiding negative future events and it prepares us for the worst scenario if this cannot be avoided [70]. Most people with a chronic disease have many worries and concerns. Even if they do not have any symptoms they may feel worried since they do not know how they are going to feel tomorrow. High levels of worry are associated with increased threat and negative content in cognitive representations of illness [71]. Worry predicts anxious and depressive symptoms and correlates positively with a disengagement of coping efforts, and negatively with perceived coping effectiveness [72].

Among the many worries and concerns of IBD patients in relation to the disease, the most important are related to surgery, energy level, having an ostomy bag, the uncertain nature of the disease, the effects of medication, being a burden on others, loss of bowel control, developing cancer, the ability to achieve full potential, pain or suffering [1, 2, 63, 64, 73]. The illness may lead to several consequences in the person's life affecting work, education, family life, sexual life and social relationships. Making adjustments becomes part of everyday life. The patient's worries and concerns may also decrease HRQOL and affect the clinical outcome.

Some young people with CD describe life as a roller coaster of fears and hopes, the known and the unknown. They experience extreme exhaustion, debilitating surgery, and near-death experiences as they seesaw between wellness and illness, and hope for a better future [74]. Many patients with IBD spend considerable time thinking and worrying, and planning around the disease [75]. Some patients have described that even in remission they find it difficult to feel secure because the habit of being ill is so strong. It can take them several months of remission before they feel confident enough to participate in different activities [10].

2.5 DEPRESSION AND ANXIETY

There is a higher rate of depression and anxiety in IBD patients than in the general population [76]. There also seem to be more severe depressive and anxiety symptoms when the IBD is active [8, 76]. Patients with CD have more anxiety and depression compared with UC patients [8, 53].

Patients with IBD may have great psychosocial restrictions due to their disease and express a greater need for psychological interventions than patients with rheumatoid arthritis. The psychological factors are mainly worries about the impact of the disease and anxiety [77].

2.6 COPING

People with chronic diseases may have major limitations in physical, emotional, social and occupational functioning. It has been shown that psychological factors, in particular cognitive representations, coping efforts, and appraisals of coping efforts, play a crucial role in adaptation to a chronic disease. Coping behaviours are influenced by the person's representation of the illness and appraisals of coping efforts. Coping efforts aim to avoid or reduce the negative consequences of the illness [78]. Coping has been defined as *constantly changing cognitive and behavioural efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of a person* [79]. The threat of illness may produce an emotional response. This emotion might increase or decrease the intensity of illness symptoms and generate symptoms that could be confused with those of the illness. This could lead a person to concentrate on the most negative consequences of the illness [80].

Coping is a process that changes over time and across situations. During the process of coping, the situation itself or the person's feelings about it change; this requires new appraisals, which in turn leads to new coping strategies [79]

In patients with IBD, the most frequently used coping strategies are characterized by optimism, self-reliance, confrontation, acceptance, and seeking emotional support [8, 81]. IBD patients often wished that the problem would go away, tried to keep the situation under control, or hoped that things would get better [8, 82]. Many patients also tried to think positively and tried to keep their feelings under control [8].

Less effective coping strategies such as substance use, expressing anger, self-distraction and self-blame are associated with higher disability, psychological distress and poorer physical and mental health [81]. Depressive coping is characterized by social withdrawal, irritable behaviour towards others, self-pity, and pessimistic thinking. Depressive coping is dysfunctional with regard to emotional and physical well-being and is strongly and negatively associated with reduced HRQOL [60, 63].

2.7 COMPLIANCE AND ADHERENCE

Non-adherence and non-compliance is common in IBD and may result in more relapses. Those who are most non-adherent are young patients, when they are in remission and taking maintenance therapies for IBD [83]. This may result in an overuse of health resources with a shift from cost-effective preventive care to more emergency treatment of relapses. It may also lead to financial loss due to the patients' inability to work, or that family members have to take time off work to take care of patients [84]. Shared decision-making between patients and physicians appears to be more powerful when it comes to encouraging the patient regarding adherence and compliance [83-85]. Patient education is another way to deal with this [83, 84].

2.8 INFORMATION AND EDUCATION

Perceived level of IBD information correlates with patients' concerns. Lower scores for the level of information are associated with more concerns [73]. Patient education can

lead to more effective coping strategies, less anxiety and depression, and reduced IBD symptoms [86]. IBD patients call for information about their disease and how to manage it, but they want more than they are given [87, 88].

How should IBD patients be educated about their disease? Among the different ways that have been tested, group-based education programmes have been very much appreciated by patients, and knowledge scores have been improved. These programmes include between four and nine sessions, of around two to three hours per session, covering various topics, which are most often presented by gastroenterologists, dieticians, surgeons, psychologists, social workers, and nurses. The groups contain about 8-12 patients and in some education programmes family members are welcome [86, 89-91].

It is important to give disease-related information to newly diagnosed patients. These patients often need several clinical visits at the beginning of their disease to ensure that all important issues are covered [84, 92].

Self-management is a way to teach patients with a chronic disease to be more involved in their own care. This has been tested in the form of a patient guidebook, which contains information about investigation and treatment. It also contains self-management of IBD and indicated areas where patient choice might influence treatment decisions. Guided self-management is a written plan to which patients can refer when making decisions about treatment and the need for service contact [93]. They need to work in partnership with their doctors, and this can be achieved by using patient-centred consultants. The gastroenterologists or specialist nurses should however be trained in patient-centred communication for the self-management to be as effective as possible [94].

Many patients with IBD are young and eager to learn more about their disease. A considerable amount of medical information is readily accessible on the Internet and it is quite common that newly diagnosed IBD patients are already well informed on their first visit to the clinic. Gastroenterologists and specialist nurses need to learn more about the information that is available on the Internet in order to help the patients find and use appropriate websites [84].

Knowledge about the disease and how to manage it is essential for patients with a chronic disease such as IBD. This may have a positive influence on HRQOL and the capacity to handle treatment.

3 RATIONALE

The incidence of IBD has increased. Due to the increasing number of patients and the fact that the number of healthcare professionals is not increasing, it is becoming essential to learn more about HRQOL. Which patients have the greatest need for education and support? It has been shown in the literature that patients with IBD have poor HRQOL compared with a healthy population. They also have a number of worries and concerns. IBD patients need and call for disease-related information, but there are still some questions remaining about how this information should be provided in order to increase HRQOL. It is also important to gain more knowledge about the issues that are most burdensome for IBD patients. This helps to individualize patient education and support. Healthcare professionals can then focus on these topics, with the aim of reducing patients' IBD symptoms and stress, and promoting effective coping strategies. In the long run this could lead to fewer worries, improved HRQOL, and fewer relapses.

Several studies have shown that disease activity is the most important factor for reduced HRQOL. It is therefore fundamental to gain more information about what may trigger relapses in IBD, especially if the trigger can be influenced. In this way patients can be better informed and better supported in this area, which could lead to fewer relapses and increased HRQOL.

It is extremely important to have a deeper insight into HRQOL and the worries and concerns of IBD patients, in order to better understand them. In this way we can develop more effective nursing intervention programmes, providing the best possible education and support. It is essential to have the right measurements in order to identify which patients have the greatest need of education and support, and to identify which issues patients are most worried about. For further studies in this area it is also important to find a good tool for measuring trigger factors for relapses. All this may influence the clinical course for the patients.

4 AIMS OF THE THESIS

4.1 GENERAL AIM

The general aim of this thesis was to gain scientific evidence about worries and concerns, HRQOL, and trigger factors for relapses, and to develop and evaluate an education programme.

4.2 SPECIFIC AIMS

The specific aims for each study were:

- To create an education programme which would be suitable for patients with newly diagnosed IBD and which could be readily applied at the clinic, and to investigate whether a group-based education programme could improve HRQOL among patients with IBD (**Study I**).
- To identify predictors of low HRQOL among patients with IBD and make a comparison between CD and UC with respect to disease duration (**Study II**).
- To validate the factor structure in the Swedish version of the RFIPC and to explore how these hypothesized different factors are associated with HRQOL and general health (**Study III**).
- To examine whether perceived stress has a short-term acute effect, i.e. whether it acts as a trigger, for the risk of relapse in IBD (**Study IV**).

5 METHODS

Table 1. Overview of Studies I-IV

	Study I	Study II	Study III	Study IV
Design	Randomized controlled trial	Cross sectional study	Methodological study	Case-crossover study
Inclusion criteria	CD or UC <2 years duration Clinical remission No other chronic disease Swedish language	CD or UC < 2 years or > 5 years of duration Clinical remission No other chronic disease Swedish language	CD or UC Clinical remission No other chronic disease Swedish language	CD or UC < 2 years of duration Clinical remission No other chronic disease Swedish language No surgery due to IBD
Participants	N=93	N=197	N=195	N=60
Main outcome	Education, HRQOL	HRQOL	Worries and concern	Stress

5.1 INSTRUMENTS

A combination of generic and disease-specific questionnaires was used in Studies I and II, to describe and measure HRQOL and worries and concerns in patients with IBD. In Study III, the same combination was used but in order to validate one of the disease-specific questionnaires. In Study IV, a structured diary was used.

Table 2. Overview of instruments used in Studies I-IV

Instruments	Study I	Study II	Study III	Study IV
The Health Index	x	x	x	
The SOC	x	x		
The IBDQ	x	x	x	
The RFIPC	x	x	x	
Evaluation of education	x			
The Diary				x
HBI		x	x	x
UC-DAI		x	x	x
Truelove & Witts Index				x

5.1.1 The Health Index

The Health Index (HI), used in Studies I, II, and III, is a generic questionnaire. It contains nine questions describing the patient's general health [95], and includes questions regarding energy, temper, fatigue, loneliness, sleep, vertigo, bowel function, pain and mobility. Each question is graded: 1=very poor, 2=rather poor, 3=rather good,

4=very good. The total score ranges from 9 (very poor general health) to 36 (very good general health). The internal consistency reliability measured with Cronbach's alpha coefficient reached acceptable levels in all studies using the HI.

5.1.2 The Sense of Coherence Scale

The short form of the Sense of Coherence (SOC) questionnaire, used in Studies I and II, is a generic instrument that measures coping capacity [96]. The concept of SOC includes three components: the perception of comprehensibility, manageability, and meaningfulness. The questionnaire contains 13 questions, each with a scale graded from 1 to 7. Possible scores range from 13 to 91. A high score indicates a strong sense of coherence. With a strong sense of coherence, it is more likely that a person will cope successfully with stressful situations. The rationale for using this questionnaire is based on an increased interest in the phenomenon of coping related to stress, and the way in which this is related to illness and health. The SOC questionnaire has been shown to have adequate reliability and validity in Sweden [97, 98]. The internal consistency reliability measured with Cronbach's alpha coefficient reached acceptable levels in all studies using the SOC.

5.1.3 The Inflammatory Bowel Disease Questionnaire

The Inflammatory Bowel Disease Questionnaire (IBDQ), used in Studies I, II, and III, is a disease-specific questionnaire used for assessing HRQOL in patients with IBD. It has 32 items, divided into four subscales: bowel symptoms (bowel movements and abdominal pain), systemic symptoms (fatigue and sleep), emotional function (irritation, depression and aggression), and social function (ability to work and participate in social activities). The IBDQ has been shown to be a reliable and sensitive measure of HRQOL [99, 100] and it has been validated in Sweden [101, 102]. In Studies I, II, and III, we used the response option that is used in the UK version of the IBDQ, since it is more differentiated [103]. In this version, a 4-graded Lickert scale is used instead of the 7-graded Lickert scale that was developed by Guyatt et al. [99]. Score 1 represents the "best function" and score 4 represents the "worst function". We used all 32 items [99] and the total score ranges from 32 (optimal HRQOL) to 128 (worst HRQOL). The modified version of the IBDQ was tested for reliability and validity in Study I by using Cronbach's alpha coefficient and Rasch analysis [104]. The internal consistency reliability measured with Cronbach's alpha coefficient reached acceptable levels in all studies using the IBDQ.

5.1.4 The Rating Form of Inflammatory Bowel Disease Patient Concerns

The Rating Form of Inflammatory Bowel Disease Patient Concerns (RFIPC), used in Studies I, II, and III, is a disease-specific questionnaire that rates important worries and concerns of patients with IBD. The RFIPC contains 25 items or concerns that are graded on 100 mm visual analogue scales, where the extremes are 0 mm="not at all", and 100 mm="a great deal". The basic formulation is "Because of your condition, how concerned are you about...?" The items or concerns are for example "having surgery", "feeling alone", "uncertain nature of the disease", "effects on medication", "being a burden on others", "loss of sexual drive". It has been shown that the RFIPC is a reliable

and sensitive measure of the worries and concerns expressed by patients with IBD, for use in clinical care and in research [1]. In the original version of the RFIPC, the 25 items are divided into four factors: impact of the disease, sexual intimacy, complications of the disease and body stigma. In Sweden it is mostly the sum score (the mean of the 25 items) that is reported in the studies using the questionnaire. In Studies I and II, we reported the results of the RFIPC by displaying the sum score. In Study III, we validated the factor structure. The internal consistency reliability measured with Cronbach's alpha coefficient reached acceptable levels in all studies using the RFIPC.

5.1.5 Evaluation of the Education Programme

The patients in the intervention group in Study I filled in a questionnaire for evaluation of the group-based education programme. The patients were asked about the point of time for the sessions, how the group was composed and how satisfied they were with the education programme. Response alternatives were graded from 1 to 7, where 1 was the worst score and 7 the best possible score. The patients were also asked about their general opinion of the education programme.

5.1.6 The Diary

To collect information regarding symptoms of IBD and a number of potential triggers, a diary was constructed for Study IV. The potential triggers included were based on previous literature reported on possible triggers for relapse [34, 105]. Questions in the diary were used to identify relapses and concerned number of loose stools during daytime and night-time, occurrence of urgency, blood in stools, and abdominal pain, with a scale graded from 0 to 4 (0 = no problem to 4 = all the time). One question concerned the patients' general well-being, with a response scale graded from 0 to 4 (0 = very good to 4 = very bad). Perceived stress was measured with the question "Have you felt stressed today?" and a five-graded response scale ranging from 0 to 4 (0 = not at all to 4 = a lot). Another question concerned changes in food intake regarding sugar, fat, and fibre graded on a three-point scale. A further question dealt with smoking; 0 = no (non-smoker) and 1 = yes (smoker), and if "yes" the patients had to state the number of cigarettes per day. The non-smokers were asked if they had stopped smoking and if so, when. The last question dealt with having an infection, for example a cold or an enteric infection, and whether they had taken antibiotics, with two response alternatives, 0 = no and 1 = yes. In the diary it was also possible for patients to state if their medical treatment had been changed, and to give information about additional trigger factors such as divergences from their normal life situations.

Patients were instructed to fill in the diary every day during 26 weeks.

5.1.7 The Truelove and Witts Index

The Truelove and Witts Index is commonly used to assess disease severity. The severity of the illness is assessed according to *severe*, *moderate*, and *mild*. Severe disease is when the patient has diarrhoea six or more times a day with macroscopic blood in the stools, fever, tachycardia, and anaemia. Mild disease is when the patient has mild diarrhoea (maximum four times per day) with no more than a small amount of macroscopic blood in the stools, no fever, no tachycardia, and no severe anaemia. Moderate disease is between severe and mild [106]. In Study IV, the Truelove and Witts Index was used to identify relapses.

5.1.8 The Harvey-Bradshaw Index

The Harvey-Bradshaw Index (HBI) was developed to assess the degree of illness in patients with CD. The criteria included are: number of liquid or soft stools per day, abdominal pain rating (0-3), general well-being rating (0-4), presence of abdominal mass (0=none, 1=dubious, 2=definite, 3=definite and tender), complications: arthralgia, uveitis, erythema nodosum, pyoderma gangrenosum, anal fissure, new fistula, abscess (score 1 per item). An HBI score of less than five is defined as being in remission, 5 to 7 as mildly active disease, 8 to 16 as moderately active disease, and >16 as severely active disease [107, 108]. The HBI was used in Studies II, III, and IV to assess whether the patients were in remission before inclusion.

5.1.9 The Ulcerative Colitis Disease Activity Index

The Ulcerative Colitis Disease Activity Index (UC-DAI) is used to measure degree of illness in UC. The UC-DAI is the sum of scores from four criteria: stool frequency, rectal bleeding, mucosal appearance, investigator’s rating of disease activity. Each of the criteria can be ranked from 0-3. UC in remission is defined as two or fewer points. Severe disease is defined as greater than nine points [109]. The UC-DAI was used in Studies II, III, and IV to determine if patients were in remission before they were included.

5.2 PARTICIPANTS AND PROCEDURE

In Studies I, II, and III, missing values are accounted for by using the mean substitution procedure. The missing values for a variable are replaced by a mean value of that variable, calculated from all valid responses [110].

5.2.1 Study I

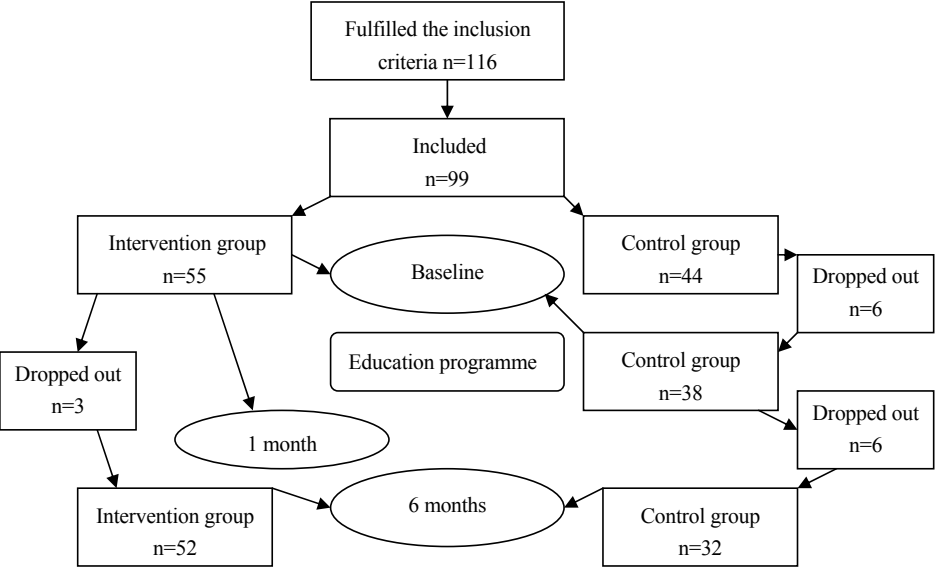


Figure1. Overview of participants and dropouts in Study I

Participants

Patients suffering from CD or UC for less than two years, who were in clinical remission and visited the IBD clinic at Danderyd Hospital between November 2002 and November 2004, were invited to participate in the study. To be included, they were to suffer from no other chronic diseases, have a good understanding of the Swedish language and be able to fill in a questionnaire. Clinical remission was defined as having no bowel symptoms associated with active disease, i.e. no diarrhoea or blood in the stools, and undergoing no acute treatment. A total of 116 patients fulfilled the inclusion criteria and were invited to participate in the study. Ninety-nine patients (85%) gave their informed consent. Fifty-five patients were randomized to the intervention group and 44 patients were randomized to the control group. Six patients in the control group dropped out when they were informed that they had not been randomized to the intervention group. The control group therefore remained at 38 patients.

Procedure

The 116 patients who fulfilled the inclusion criteria were sent a letter enclosing written information about the study, and the questionnaires. Randomization was performed by using blocks of 20 patients: 10 were allocated to either an intervention group or a control group. Both groups completed the questionnaires at baseline and after six months. The intervention group also completed the questionnaires after the group-based education programme, one month after baseline.

Three patients in the intervention group and six patients in the control group did not return the questionnaires at the six-month measurement. After two reminders they were excluded from the study. The analyses are therefore restricted to “per protocol” analyses.

When the patients were included in the study they were in clinical remission. The patients’ files were scrutinized to identify illness activity during the six-month study period.

The multi-professional group-based education programme

The content of the multi-professional, group-based education programme was first tested in a pilot study including eleven participants. The result showed that the content was well suited for patients with IBD with the exception of the number of sessions. Many of the patients had difficulty finding time to participate in an education programme. Therefore, after the evaluation, the number of sessions was reduced from four to three. The intervention group was divided into groups of eight to ten patients, and each patient was invited to bring a significant other of his/her own choice. The patients with CD and the patients with UC were divided into separate groups. The education programme was held once a week and consisted of three two-hour sessions. It was scheduled in the evening for the convenience of the patients. A specialist nurse, gastroenterologist, dietician and a medical social worker gave the lectures. The specialist nurse worked as a coordinator and attended every meeting. The content was based on clinical experience, literature studies and contacts with other gastroenterological clinics with experience of similar education programmes. The topics for the sessions were aetiology and nature of the diseases, examinations, treatments, side effects, new research, nutrition, financial issues, psychological

reactions, coping, behavioural changes, information concerning the organization and care of IBD patients at the clinic, and demonstration of a sigmoidoscope. During every session there was time to ask questions and to discuss personal experiences. At the last session, the patients received a written summary of the contents of the education programme.

5.2.2 Study II

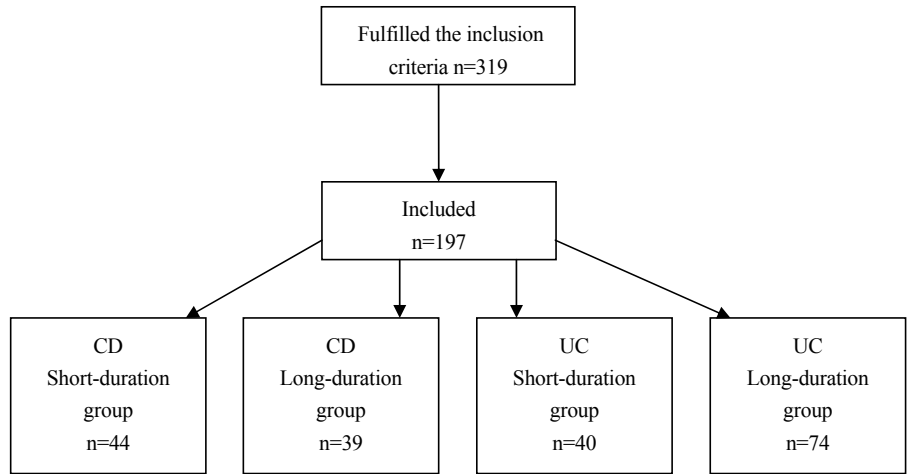


Figure 2. Overview of participants in Study II

Participants

Patients with CD or UC who were in clinical remission and receiving care at the IBD clinic at Danderyd Hospital were invited to participate in the study. To be included, they were to suffer from have no other chronic diseases, have a good understanding of the Swedish language and be able to fill in a questionnaire. They were to have had the disease for less than two years (short-duration group) or more than five years (long-duration group). Clinical remission was defined as having no bowel symptoms associated with active disease, i.e. no diarrhoea, no blood in stools and no acute treatment. Furthermore, UC patients were to have an UC-DAI score of 2 or less [109], and CD patients were to have a HbIc score of less than 5 [107, 108]. A total of 319 patients matched the inclusion criteria and were invited to participate in the study. A total of 197 patients (61%) gave their informed consent and were included. The study population was then divided into a CD group and an UC group. Each group was also divided into separate groups based on short disease duration (less than two years) or long disease duration (more than five years). In the CD group there were 44 patients with short disease duration and 39 patients with long disease duration. In the UC group there were 40 patients with short disease duration and 74 patients with long disease duration.

Procedure

A letter with information about the study and the four questionnaires was sent to the 319 patients that fulfilled the inclusion criteria. One reminder was sent to non-responders after six weeks. The questionnaires were completed on one occasion.

5.2.3 Study III

Participants

A total of 195 patients with CD and UC who were receiving care at the IBD clinic at Danderyd Hospital were included in the study. They were to be in clinical remission, suffer from no other chronic diseases, have a good understanding of the Swedish language, and be able to fill in a questionnaire. Clinical remission was defined as having no bowel symptoms associated with active disease, i.e. no diarrhoea, no blood in stools and no acute treatment. Furthermore, UC patients were to have an UC-DAI score of 2 or less, and CD patients were to have an HBI score of less than 5.

Procedure

The patients were sent a letter including information about the study, the RFIPC, the IBDQ and the HI. The patients filled in the questionnaires on one occasion.

5.2.4 Study IV

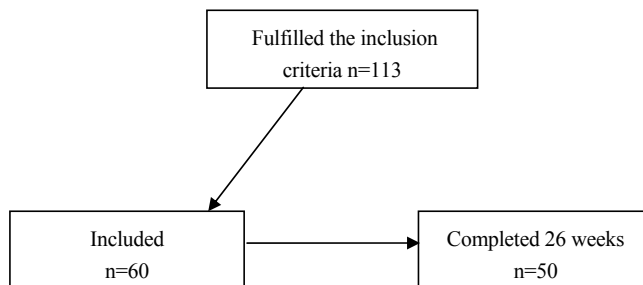


Figure 3. Overview of participants in Study IV

Participants

A nurse specially trained in IBD, identified the patients from a local register at the IBD clinic at Danderyd Hospital. Those who were eligible for participation were patients with CD or UC, who had suffered from the disease for less than two years, had no other chronic diseases, had not undergone surgery due to their IBD, and were in clinical remission. Clinical remission was defined as having no bowel symptoms associated with active disease, i.e. no diarrhoea, no blood in stools and no acute treatment. Furthermore, UC patients were to have an UC-DAI score of 2 or less, and CD patients were to have an HBI score of less than 5. A total of 113 non-consecutive patients were invited to participate, and 60 (53%) accepted and were included. Of these 60 patients, 50 (84%) participated throughout the whole study. The ten patients who discontinued stated reasons such as low motivation or forgetting to fill in the diary, or they experienced that it was not meaningful since there was no variation in the reported variables.

Procedure

After identification, the patients were sent a letter including information about the study. Those who gave informed consent were then given detailed information by telephone. After being included, the patients were instructed to fill in a diary every day during a 26-week period. They were asked to send in completed diary pages every fourth week. If the pages were not sent in, a reminder was sent after four weeks.

A pre-test study was conducted before the main study. Two patients tested the designed diary by filling it in every day for one month. After the pre-test study the diary was slightly adjusted. For example, an open question was added to give the participants the opportunity to provide other subjective information.

Relapse of IBD was defined in the diary according to Trulove and Witt criteria [106], i.e. blood in stools for patients with UC and for patients with CD in the colon. For patients with CD in the small bowel, relapse was defined as more than two consecutive days of abdominal pain. Identified relapses in the diary were checked by scrutinizing the medical files.

Onset of a relapse was considered as the first day with a relapse. A relapse was considered as over when 14 consecutive days had passed with no blood in stools, no diarrhoea, or no abdominal pain.

The case-crossover design was used. This is an epidemiological design developed to study triggers for acute events, and constitutes a valuable methodology for establishing causality between stress and relapses in IBD [111]. The method departs from the assumption that if there are factors influencing the onset of an outcome, in this case a relapse in IBD, these would more often be present during a period just before the onset than during periods further from the onset [112]. Only cases were examined and were self-matched by serving as their own controls.

5.3 DATA ANALYSIS

Table 3. Overview of statistical analysis used in Studies I-IV

Statistical analysis	Study I	Study II	Study III	Study IV
Student's t-test	x	x		
Chi-squared test	x	x		
ANOVA	x			
Mann-Whitney U-test	x		x	
Spearman's correlation	x		x	
Pearson's correlation		x		
Second-order factor analysis		x		
MANCOVA		x		
CFA			x	
Cronbach's alpha			x	
Matched-pair interval				x
Usual frequency				x

Student's t-test and the chi-squared test were performed to compare demographic background data between the intervention group and the control group (Study I), and between the short-duration groups and the long-duration groups (Study II). Cronbach's alpha coefficients were calculated for the instruments HI (Studies I, II, III), SOC (Studies I, II), the IBDQ (Studies I, II, III), and the RFIPC (Studies I, II, III) to provide measures of internal consistency.

5.3.1 Analysis Study I

In order to compare the intervention group with the control group at baseline and at six months, and for comparisons in the intervention group at baseline, one month, and six months, analysis of variance (ANOVA) with repeated measures was performed. The Mann-Whitney U-test was used for more detailed analysis of the changes over time. Correlation between variables was calculated using Spearman's rank correlation.

5.3.2 Analysis Study II

Correlation between variables was calculated by using Pearson's correlation coefficient. Significant correlations were displayed for both CD patients and UC patients between the HI, the IBDQ and the RFIPC. A 2 x 2 multivariate analysis of covariance (MANCOVA) with SOC and natural log-transformed number of relapses as covariates was performed to examine the impact of diagnosis and disease duration.

5.3.3 Analysis Study III

Confirmatory factor analysis (CFA) was performed on the variance-covariance matrix of the RFIPC items to assess the fit of the factorial structure of the RFIPC to the data. Cronbach's alpha coefficient was calculated to test reliability. In order to follow up the results from the CFA, Spearman's correlation analysis and the Mann-Whitney U-test were performed.

5.3.4 Analysis Study IV

Exposure frequency during the period just before onset of a relapse (the case period) was compared with exposure frequency during one or several control periods during remission. The matched-pair interval approach and the usual frequency approach were performed. The matched-pair interval approach uses exposure status during a matched time period, e.g. the same weekday as the day before the onset of a relapse, but a week earlier. The usual frequency approach was based on the frequency of exposed days during the control period. The 1-7 days prior to the onset of a relapse were considered as the case period and the 8-14 days prior to the onset of a relapse were considered as the control period. Hazard periods of varying length were tested.

Conditional logistic regression was used in the matched-pair interval approach for estimation of odds ratio (OR) and 95% confidence intervals. Standard Mantel-Haenszel estimates for sparse data were used for analysis in the usual frequency approach for estimation of OR and 95% confidence intervals.

6 ETHICAL CONSIDERATIONS

The four studies were all approved by the local Ethics Committee, Karolinska Institutet (Dnr. 01-224, 04-813T).

In all four studies, the patients received written information about the study. The information included the aim of the study and assurance of confidentiality. The patients were also informed that participation was voluntary and that they could withdraw from the study at any time. The patients were asked to give their informed consent if they wanted to participate in the study.

All data were handled anonymously. The questionnaires used in Studies I, II, III and the diary in Study IV were provided with a patient code to ensure confidentiality. The patient codes and the information about the patients' names are stored in two different locked safes.

In Study I, the patients in the control group were invited to participate in the education programme after completion of the questionnaires at the six-month measurement.

7 RESULTS

7.1 HRQOL AND PATIENT EDUCATION (STUDY I)

There were no differences between the intervention group and the control group regarding demographic and disease-related factors.

A significant difference was found when comparing the RFIPC at baseline and one month later, showing that patients had lower RFIPC scores immediately after the education programme. When comparing with the control group, no improvement could be seen in HRQOL in patients with IBD at the six-month follow-up. The education programme was highly appreciated by the patients.

A significant correlation was found for all patients between the HI and the IBDQ, and the HI and the RFIPC, in the measurements at baseline and at six months, indicating that the higher the perceived general health, the better the perceived HRQOL. There were no differences in gender for any of the measurements.

7.2 PREDICTORS OF LOW HRQOL (STUDY II)

There were no differences between the groups regarding demographic and disease-related factors, except for patients in the long-duration groups who had a significantly larger number of relapses compared with patients in the short-duration groups.

Disease duration had a significant effect on HRQOL; scores of HRQOL were lower for patients with short disease duration than for patients with long disease duration. There were no significant differences in HRQOL between patients diagnosed with CD and UC. The analysis showed a significant interaction between diagnosis and disease duration with regard to HI and the IBDQ. The analysis displayed significantly lower scores on the HI (low HRQOL) and higher scores on the IBDQ (low HRQOL) for CD patients with short disease duration than the other groups.

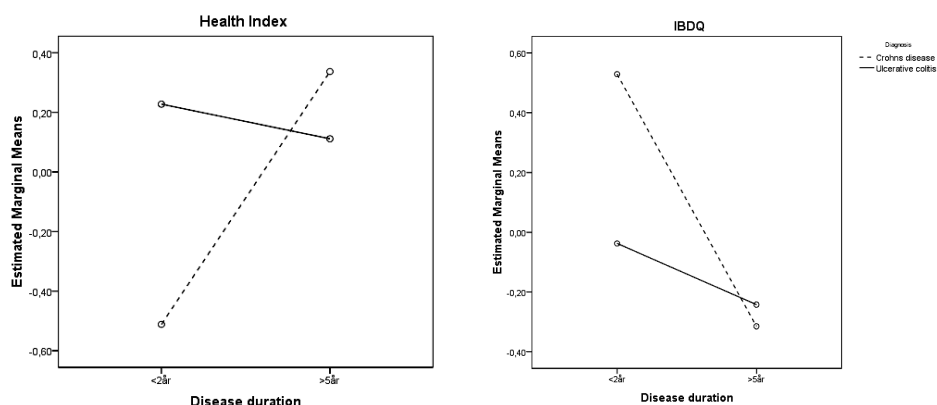


Figure 4. The Health Index and the IBDQ as dependent variables in a MANCOVA with Sense of Coherence and log-transformed number of relapses as covariates, and disease duration and Diagnosis x Disease duration as independent variables with significant effects. Estimated means in the figure are presented as z-scores at Sense of Coherence $Z=0.08$, and log-transformed number of relapses $Z=0.90$.

7.3 WORRIES AND CONCERNS (STUDY III)

Three models of the RFIPC were tested. The first model to be validated was the single-factor model of the RFIPC, which is based on the assumption that the variance in the questionnaire could be placed in one single factor of worry. The one-single factor model is the most commonly used scoring procedure in Sweden. The second model was the four-factor model according to Drossman et al. [1], in which the RFIPC consists of four distinct factors: *impact of disease*, *sexual intimacy*, *complications*, and *body stigma*. The third and final model was the four-factor model with the addition of correlated error terms between item 5 (developing cancer) and item 6 (dying early), and item 16 (having surgery) and item 17 (having an ostomy bag). Inclusion of correlated error terms for subgroups of items is generally not recommended. However, it was considered to be appropriate in this analysis due to clinical observations. An ostomy bag is often the consequence of having surgery, and the fear of dying early is normally related to concerns about developing cancer.

The analysis showed that the single-factor model had poor fit indices. The four-factor model displayed better fit compared with the single-factor model, but failed to approximate the established thresholds for the fit indices. The four-factor model permitted correlated error terms between items 5 and 6, and items 16 and 17 displayed the most adequate fit. All Cronbach's alpha coefficients for the factors in the final model were acceptable (all alphas >0.88).

Significant correlations were found between the four factors of the RFIPC and the four factors of the IBDQ and the HI. The correlation between the four factors of the RFIPC and emotional function (the IBDQ) showed the highest correlation coefficients, while correlation coefficients regarding systemic symptoms showed the lowest correlations. Greater worries and concerns regarding *impact of disease* were reported by CD patients than by UC patients (statistically significant).

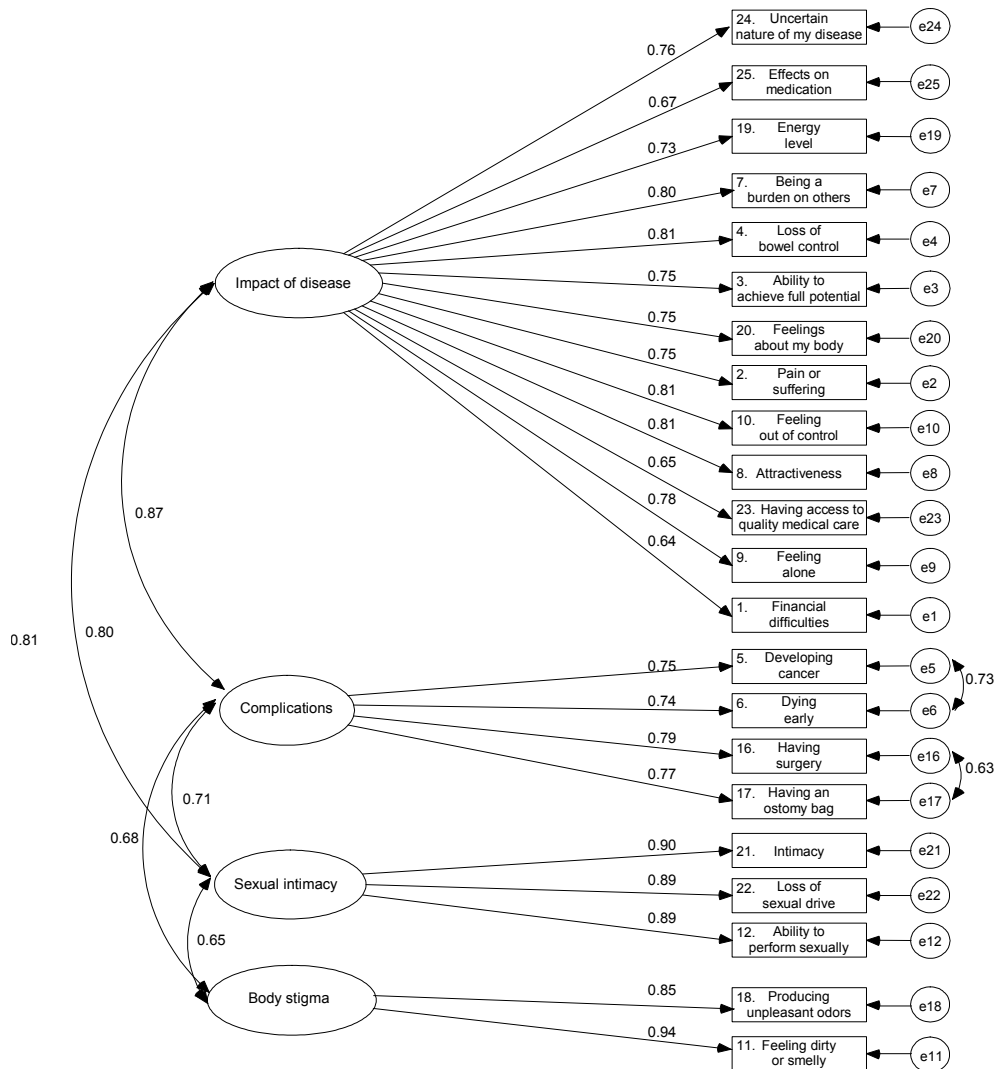


Figure 5. Graphical representation of the correlated four-factor model of the RFIPC. The factor loadings are standardized loadings.

7.4 STRESS AS A TRIGGER FACTOR (STUDY IV)

Twenty-five patients experienced one or several relapses during the data collection, and a total of 42 relapses were identified. Of the potential trigger factors included in the diary it was only perceived stress that displayed an effect. In 19 of the 42 relapses the patients were exposed to stress on the day before the onset of a relapse. Stress on one day increased the risk of relapse on the next day with an OR of 2.48 (95% CI 1.07-5.78) for the usual frequency, and 2.67 (95% CI 0.71-10.05) for the matched-pair interval analyses. No increased effect estimates were found for hazard periods further than one day from onset.

When stratifying level of stress, the analysis showed an effect for high levels of perceived stress. When reporting “quite a lot” of stress, an OR of 4.8 (95% CI 1.09-21.10) was found. No statistically increased risk for lower levels of perceived stress was displayed, although elevated effect estimates were found for “some” stress. No one reported having “a lot” of stress during the day before onset of a relapse. Stratification of the analysis with respect to diagnosis gave an OR of 7.33 (95% CI 0.94-57.33) for CD patients, and 1.88 (95% CI 0.94-4.87) for UC patients.

If the analysis was restricted to the first relapse during follow-up, this did not change the results.

Table 4. Odds ratio (OR) for relapse in IBD after exposure to stress during the previous day, 95% confidence interval (95% CI)

Analytical approach	Level of stress							
	1		2		3		4	
	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval		
Usual frequency (95% CI)	1.38	(0.60-3.16)	2.57	(0.55-11.93)	4.8	(1.09-21.10)	-	
Matched-pair interval	1.00	(0.32-3.10)	3.00	(0.31-28.84)	4.00	(0.45-35.79)	-	

8 DISCUSSION

The general aim of this thesis was to gain scientific evidence about worries and concerns, HRQOL, and trigger factors for relapses, and to develop and evaluate an education programme. In Studies II and III, newly diagnosed CD patients were found to have the lowest HRQOL, and a questionnaire for measuring worries and concerns was validated. In Study IV, perceived stress was identified as an important factor in triggering relapses in IBD. In Study I, a group-based education programme was developed and evaluated. The education programme was highly appreciated by the patients but no improvements in HRQOL could be found.

In the following sections, the discussion will focus on each topic in this thesis.

8.1 HRQOL AND PATIENT EDUCATION

The multi-professional group-based education programme was highly appreciated by the patients. An improvement in HRQOL could be seen in the intervention group immediately after the education programme. However, no improvement in HRQOL could be found six months after attending the education programme when comparing with a control group. These results correspond with other studies where HRQOL was also investigated in IBD patients after attending group-based education programmes. No improvement in HRQOL was found in any of these studies, but the education programmes were highly appreciated by the patients [86, 89, 90, 113]. Another study found that a group-based education programme improved patient knowledge and patient satisfaction, but no improvement could be found in HRQOL here either [91]. Moser et al. found a significant correlation between patients' worries and concerns and their perceived level of information. Lower scores of information level were associated with greater concerns [73].

HRQOL is positively influenced by "providing information" [114], but several questions still remain about the best way of doing this. Being part of a group can provide support simply due to the group dynamic. In one study it could be shown that there was an improvement in emotional and social aspects of HRQOL after attending a support group [115]. There are some differences between this study and Study I in this thesis. They had meetings once a month for 24 months, while we had a total of only three meetings, once a week.

The intervention group had better HRQOL scores immediately after attending the education programme. However, this improvement could not be found six months after the education programme. This short-term effect is similar to a result in a study that analyzed the effect of a comprehensive lifestyle modification programme using an intervention group and a control group [116]. A significant great improvement in Short-Form 36 scale physical function and a significant great reduction in anxiety scores could be seen three months after the programme. An improvement could also be seen in the IBDQ scores, although not significant, but no significant differences between the intervention group and the control group were found after twelve months. In another study, a short-term effect could be detected when CD patients were given access to a

nurse-led counselling service. An improvement could be seen in HRQOL after six months but the effect was not sustained for 12 months [117].

In one study, disease-related information was found to result in deteriorated HRQOL [118], but the information was given in the form of information booklets and it may be ineffective to provide disease-related information without the opportunity to discuss questions or concerns that arise. Furthermore, the participants may not have bothered to read the information booklets. Another explanation for the fact that there was no improvement in HRQOL in either this study or our study might be that the patients were perhaps not in remission. Symptom severity is one of the most important associations with reduced HRQOL [4-7, 49, 53, 56-60].

The education programme could readily be applied in the clinic. It was held at the hospital and lectures were given by the working staff, so rooms and lecturers were easy to organize. Even if no improvement could be found in HRQOL after attending a multi-professional group-based education programme, the patients were positive and satisfied overall.

8.2 PREDICTORS OF LOW HRQOL

Study II showed that HRQOL was poorer for patients with short disease duration than for patients with long disease duration. There were no differences between CD and UC patients. However, a significant effect on the interaction between diagnosis and duration was found, indicating that patients with CD and short disease duration have the poorest HRQOL.

These results contradict the results from another study where no differences in HRQOL could be found between CD patients with long disease duration and patients with short disease duration [9]. However, it is difficult to compare these results with those of Study II, since they compared patients who had been diagnosed less than 10 years earlier with patients whose diagnosis was more than 20 years old. The patients in the short-duration group in this study were comparable with the patients in the long-duration group in Study II.

Several studies have examined whether there are any differences in HRQOL between CD patients and UC patients. In Study II, no differences could be found between CD patients and UC patients when only diagnosis was considered. This correlates with other studies [5, 62, 63]. However, some studies have found that CD patients have poorer HRQOL [3, 8, 53, 61]. CD patients are more often in hospital compared with UC patients, and they also have more re-admissions [119]. Since CD and UC differ in several ways, for example in symptoms and complications, it makes sense not to treat the diseases in the same way, also with regard to giving disease-related information.

Few studies have investigated whether there are differences in HRQOL due to disease duration. One study compared CD patients and UC patients in their first relapse with patients who had reported at least three relapses [65]. In contrast to Study II, no difference in HRQOL could be found, indicating that it is similar in debut and recurrent relapses for both CD patients and UC patients. However, the designs in the two studies

are very different, making it difficult to compare them. For example, for the patients in the group with several relapses, disease duration was five years at the most. In Study II, the mean number of years for disease duration of the patients in the long-duration group was 14 years for CD patients and 12 years for UC patients. As in Study II, other studies have found that patients with long disease duration have better HRQOL [5, 7, 120]. The most common course seems to be a decrease in symptoms over time [20, 21]. Since disease activity is the most important factor for decreased HRQOL, this may be one reason why the patients in the long-duration group had better HRQOL. However, here too, there are some contradictory findings. Etienney et al. examined CD patients and could find no evidence that CD activity burned out in time [121].

One study found that 20% of IBD patients expressed a need for psychotherapy. Anxiety, worries and short disease duration were some of the reasons for this [77]. Non-adherence is a common problem in IBD. Non-adherence increases when the patients are < 40 years old and have disease duration < 5 years. Poor adherence may result in more frequent relapses and a disabling disease course [83]. One way of increasing adherence is to give the patients disease-related education. Since the number of patients with IBD is increasing, it is important to know which patients have the greatest need of education. It is also important to gain more insight into which issues an education programme should concentrate on. In this way an education programme that focuses on the most important topics could be provided for a special patient group. The results in Study II suggest that it is newly diagnosed CD patients that need disease-related education most. This correlates with a study that found an improvement in HRQOL in a group of IBD patients with disease duration ≤ 3 years after attending an education programme. No improvement in HRQOL could be found in patients with disease duration ≥ 3 years [90]. Bregenzer et al. also conclude that patients should be educated at the beginning of their disease in order to achieve the optimal effect [89].

8.3 WORRIES AND CONCERNS

IBD patients have many worries and concerns related to the disease. Worries and concerns about IBD may affect the patient's adjustment and compliance to the illness [2]. Patients are influenced by the seesawing of their fears and hopes. This seems to be linked to what they know and what they do not know, and what cannot be known because of the nature of the illness [74]. Very few patients ask friends or neighbours for help when they need it. They either do not want people outside their closest family to know about their condition or they do not want to impose on people [122]. However, patients have also expressed a feeling of increasing the burden when discussing their worries and concerns with a family member [10]. It is important for healthcare professionals to recognize and address the worries and concerns that are important for the patient, not only the issues that the healthcare professionals feel are important.

In both the clinical and the research setting it is essential to have validated instruments in order to assess and measure worries and concerns in IBD patients. A more detailed assessment of the worries and concerns provides useful information about HRQOL. Two IBD-specific questionnaires, the IBDQ and the RFIPC, have shown adequate validity and reliability. The RFIPC is better for reflecting the psychological and social aspects of IBD from the patient's point of view, while the IBDQ provides a better

reflection of disease activity [123]. Therefore, when measuring worries and concerns in IBD, the RFIPC is the most appropriate choice.

In Study III, the factor structure of the Swedish version of the RFIPC was validated. The study focused on validation of the factor structure that was suggested by Drossman [1], with a differentiation of the components of worries. In Sweden the RFIPC is most often used by reporting the sum score or ranking the items [4, 58, 124]. The results in Study III suggest that use of a single-factor model (sum score) of the RFIPC is an unacceptable structure of this measure. This model suggests that a single underlying uni-dimensional latent variable of the patient's worries is manifested in the items of the RFIPC. No matter what the worries and concerns are about, the patient is characterized by a degree of worries and concerns. Study III displayed that a slightly modified model of the original factor structure of RFIPC had the most acceptable fit. In this version, the patient's worries and concerns can be divided into distinct components: *impact of disease*, *sexual intimacy*, *complications*, and *body stigma*. To be able to address worries and concerns in clinical practice it is important to know specifically what each patient is worried about. This approach provides more nuanced data and useful information in both clinical and research settings. Healthcare professionals gain information about what each patient is worried about and this enables them to provide the patient with appropriate education and support. Using the RFIPC by reporting each item and/or ranking the items is another method, although in this way it may be difficult to get an overview of patients' worries and concerns. The factorial structure according to Drossman that was replicated in Study III makes it easier to gain information in a clinical setting about which issues are most worrying for each patient. It also provides important data in subgroups of patients. Some may have worries related to complications, while another subgroup may worry about the impact of the disease. In Study III, significantly greater worries and concerns in the factor impact of disease were reported by CD patients than by UC patients. These findings give more detailed information about patients' worries and concerns compared with using a sum score or ranking of items.

The RFIPC has been validated in Sweden, both in UC patients [125] and in CD patients [126]. In the study with CD patients, an exploratory factor analysis was conducted and four factors similar to those of Study II and Drossman were found. However, in some ways the factors are different from Drossman's original factors. In this study, the factors *complications*, *achievements*, *intimacy*, and *stigma* were found. A Norwegian study also validated the RFIPC using exploratory factor analysis [127], finding six factors, only one of which, *sexual intimacy*, was identical to a factor in Drossman's original validation. Another study that conducted an exploratory factor analysis could not distinguish any factors in the RFIPC questions [128]. It was therefore concluded that no interpretation of answers regarding different aspects of patient concerns could be made.

Study III also displayed significant correlations between the factors of RFIPC and the factors of IBDQ (bowel symptoms, systemic symptoms, social function, and emotional function) and the HI. Furthermore, the findings showed that social function is associated with worries concerning impact of disease and sexual intimacy but not with

complications or body stigma. The results also suggest that bowel symptoms are unrelated to worries about complications.

The more detailed assessment provided by using the factorial structure of the RFIPC, as suggested by Drossman and replicated in Study III, gives more detailed information about disease-related worries and concerns of IBD patients in both research and clinical settings, as these components of worries are differently related to HRQOL and general health.

8.4 STRESS AS A TRIGGER FACTOR

Study IV showed that perceived acute stress can be considered as a trigger factor for relapses in IBD. Patients with IBD believe that the severity of the disease is affected by stress and their attitude to life [10]. Levels of stress and the nature of what is stressful are very similar for patients with IBD and healthy controls [129]. Those in remission even reported lower levels of daily stress compared with the healthy controls. This may reflect a positive rebound effect of having some relief from the disease [129]. Also, the use of active coping strategies to deal with stress is similar no matter whether an individual suffers from IBD or not [130].

Studies that examined the association between stress and relapses in IBD are inconclusive. Some studies have found that stressful life events do not trigger relapses in IBD [42, 43, 131]. In studies where no association between stress and relapses in IBD has been found, it is most often stressful life events that are investigated. However, other studies have shown that perceived stress may trigger a relapse in IBD [35-38]. Bernstein et al. examined both stressful life events and perceived stress, and found that both could be considered as trigger factors for relapses in IBD [35]. Mawdsley et al. displayed that experimental stress causes increases in a range of inflammatory variables. Each of these variables may contribute to cause relapses in IBD [39].

It has also been suggested that studies of stress should analyze CD and UC separately [41, 45]. UC has more often proved to be a trigger of relapses than CD. This might be due to difficulties in defining clear criteria for relapses and remission in CD [41]. This contradicts the results from Study IV where the trigger effect of stress seemed to be higher in CD patients. Bitton et al. were also able to show that high stress influenced relapse in CD patients [36].

In Study IV, high levels of stress are found to increase the risk of relapse the next day. This contradicts the results of Levenstein et al., where it is rather long-term perceived stress that is considered as a trigger factor [38]. The patients were followed for 45 months or until the patient experienced a relapse. Relapse status could be monitored for up to 68 months. In this study, no increase in stress levels just before a relapse could be found. The results suggest 8-11 months before symptoms began. Levenstein et al. also conclude that it is perceived stress that appears to be a trigger factor for relapses and not stressful life events or depressive symptoms. A strength of this study is that the patients were followed with proctoscopy to establish the relapses. Examination with proctoscopy not only identifies the relapses, but also classifies them in normal mucosa, minimal, mild, moderate, or severe activity. In Study IV, the relapses were identified

according to symptoms that the patients stated in the diary. Patients' files were however scrutinized after the data collection in order to check the identified relapses. But since not all patients seek hospital care when they have a relapse, this method does not provide complete information. Eighteen of the 42 identified relapses had not been recorded in the hospital. This does not mean that the patients did not have real relapses. Often patients with IBD start a treatment on their own without contacting the IBD clinic. Another difference between these studies is the duration of disease. In Study IV, patients with disease duration of less than two years were included, while the patients in the study by Levenstein had a mean disease duration of 6.5 years. Patients with a chronic disease and with long disease duration may have changed some factors in their way of life in order to feel better. There may therefore be some difficulties in examining and comparing patients with different disease duration. In Study IV, patients were followed on a daily basis, whereas patients were followed monthly in the study by Levenstein. This difference in design could also explain the differences in result. In Study IV, patients were only followed for six months and therefore no long-term effects could be examined.

It is also unclear whether stress management programmes have an effect in reducing relapses. Stress management psychotherapy does not improve disease activity or disease course in IBD patients [46]. However, one study found that patients who received a brief behavioural intervention, targeting stress and disease self-management experienced a reduction in risk of relapse [132]. One study gave 60 patients with UC a structured training programme which included stress management training. The use of relaxing techniques proved to be a significant predictor of improvement in the psychological sum score after three months of therapy [116].

The strength of Study IV is its design. The patients acted as their own controls and were followed on a daily basis during a period of six months. The case-crossover design eliminates all confounding factors.

8.5 METHODOLOGICAL CONSIDERATIONS

In Study I, all patients were in remission at baseline. In order to examine if the patients were still in remission at the six-month measurement, the patients' files were scrutinized. The investigation showed that 42% in the intervention group and 22% in the control group had relapsed or had symptoms of their disease. Disease activity influences the HRQOL negatively, and this may have made it difficult to measure HRQOL after six months and compare with the baseline measurement.

In Study I, it is possible that it is not HRQOL that should be measured to evaluate an education programme. Instead it may be the patient's worries and concerns or knowledge score that should be measured.

In Study III, the analysis is performed in a single primary sample. Therefore it is not cross-validated. To establish the results more firmly, a cross-validation of the suggested factor structure of the RFIPC in other samples is advisable.

In Study III, correlated error terms were included. This is generally not recommended, but correlation of error terms of these items was considered appropriate. For example, having an ostomy bag is associated with surgery, and the fear of dying early can be related to developing cancer.

One limitation in Study IV is the small number of patients. It is difficult to include patients in a study where they are asked to fill in a diary on a daily basis. Even if the diary was easy to fill in, and only took about one minute per day, several patients felt it was too much work and did not want to participate.

In Study IV, the patients were asked about their perceived stress in only one question. Other studies that measured perceived stress have used validated questionnaires [35-38]. We chose the one single question since we wanted to measure the presence and degree of perceived stress on a daily basis during a period of six months. Under these circumstances it is imperative to use an easy and fast instrument for the patients to fill in, otherwise they might drop out.

Another limitation in Study IV was the risk of recall bias. If the patients forgot to fill in the diary one day they might have done it retrospectively. However, this retrospective reporting is most likely when there was no variation in the reported variables. If symptoms were present or if some factors in life were unusual, patients would probably have been reminded of the study that they were included in. Nevertheless, in spite of the potential for misclassification due to memory recall, the strength of the design is that the patients did not know about the definition of relapse or the time periods of interest.

Of the potential trigger factors included in the diary in Study IV, it was only stress that displayed an effect. Diet, smoking, infections, and antibiotics did not show an effect. The sample size was small and difficulties in measuring, for example, diet may be one reason for the non-effect. The patients were asked to fill in if they had more or less sugar, fat, and/or fibre compared with their normal food intake. In the diary there was an explanation of what sugar, fat and fibre could be classified as. But it might nevertheless have been a problem for them to interpret the information and give an adequate answer.

9 CONCLUSION

A multi-professional group-based education programme could readily be applied in the clinic. Patients had improved RFIPC scores immediately after the education programme, although when comparing with the control group, no improvement could be seen in HRQOL at the six-month follow-up. The education programme was highly appreciated by the patients.

HRQOL is poorer for patients with short disease duration than for patients with long disease duration. No differences could be found between CD and UC patients. Patients with CD and short disease duration have the poorest HRQOL.

The factorial structure of the RFIPC as suggested by Drossman [1] was replicated in a Swedish version. The four separate factors identified in this structure provide more detailed information about disease-related worries and concerns of IBD patients than the sum score.

Perceived stress may act as a trigger for relapses in IBD. A high level of stress one day increases the risk of relapse the next day.

10 CLINICAL IMPLICATIONS AND FUTURE STUDIES

10.1 CLINICAL IMPLICATIONS

No improvement could be found in HRQOL after attending an education programme, but the patients were positive and satisfied overall. They became better informed about how to manage their disease. The increased knowledge may improve compliance, and lead to a better understanding of treatment, and, by extension, to fewer relapses.

Patients with CD and short disease duration have the lowest HRQOL and are in most need of education and support. It is important for healthcare professionals to identify patients with the greatest need for education and support, in order to develop effective nursing intervention programmes. The more detailed version of the RFIPC may help to provide each patient with the appropriate education and support.

By identifying potential trigger factors for relapses in IBD there is also a potential for preventing relapses by influencing for example stress levels and optimizing the clinical care of these patients.

10.2 FUTURE STUDIES

Further investigations with larger power are needed to confirm the findings regarding stress as a trigger for relapses in IBD. The case-crossover design is a valuable method and the structured diary would be a useful tool in further studies.

Further investigations are needed to examine the worries and concerns of IBD patients in order to develop more adequate intervention programmes. The RFIPC with four factors is a useful tool for future studies. There is also a need for more qualitative studies in order to more deeply examine HRQOL, as well as the worries and concerns of IBD patients.

11 POPULÄRVETENSKAPLIG SAMMANFATTNING

Inflammatorisk tarmsjukdom (Inflammatory Bowel Disease=IBD) är en sjukdomsgrupp som omfattar sjukdomarna Crohns sjukdom och ulcerös colit. Dessa är kroniska sjukdomar som går i skov (sjukdomsattacker). De vanligaste symtomen är diarré, blodtillblandad avföring, buksmärtor, trötthet och viktnedgång. Vanligaste åldern att insjukna är 15-35 års ålder. Varför man får IBD är ännu okänt men man tror att det är en kombination av flera faktorer. Hur sjukdomsbilden ska komma att se ut och hur ofta en patient med IBD kommer att få skov är okänt. Stress verkar dock vara en potentiell så kallad triggerfaktor till skov i IBD.

Patienter med IBD måste anpassa sig till en livslång sjukdom och göra många anpassningar i livet. Studier har visat att de har en sämre hälsorelaterad livskvalitet (Health-Related Quality of Life=HRQOL) jämfört med en frisk population. Det som påverkar HRQOL mest negativt är skov i sjukdomen. Patienter med IBD känner också mycket oro relaterat till sjukdomen. Det som ger mest oro är relaterat till kirurgi, energinivå, att få en påse på magen, osäkerhet kring sjukdomens natur, effekt av medicinering, att bli en börda för andra, tappa kontroll över tarmen och att utveckla cancer.

Patienter med kroniska sjukdomar som IBD behöver kunskap om sjukdomen samt hur den ska hanteras. Att vara väl utbildad inom sin sjukdom kan ge en positiv påverkan på HRQOL samt en god kapacitet till att hantera sin behandling.

Det övergripande syftet med denna avhandling var att samla vetenskaplig fakta om oro och bekymmer, HRQOL och triggerfaktorer till skov samt att skapa och utvärdera ett utbildningsprogram.

Syftet med **delstudie I** var att skapa ett utbildningsprogram anpassat till nydiagnostiserade patienter med IBD och som lätt kunde appliceras på kliniken samt att undersöka om ett gruppbaserat utbildningsprogram kan förbättra HRQOL hos patienter med IBD. 93 patienter med Crohns sjukdom eller ulcerös colit deltog i studien. Hälften lottades till en interventionsgrupp och fick delta i ett gruppbaserat utbildningsprogram medan hälften lottades till en kontrollgrupp. HRQOL mättes med hjälp av fyra frågeformulär som fylldes i när de inkluderades i studien samt efter sex månader. Interventionsgruppen fyllde dessutom i frågeformulären efter en månad (direkt efter avslutat utbildningsprogram). Ingen skillnad framkom i HRQOL mellan interventionsgrupp och kontrollgrupp vid mätningen efter sex månader. Interventionsgruppen hade dock förbättrade värden i HRQOL vid mätningen efter en månad, direkt efter utbildningsprogrammet. Det gruppbaseade utbildningsprogrammet var uppskattat av patienterna.

Syftet med **delstudie II** var att identifiera vad som kan förutsäga nedsatt HRQOL hos patienter med IBD samt göra en jämförelse mellan Crohns sjukdom och ulcerös colit och med sjukdomsduration. 197 patienter med Crohns sjukdom eller ulcerös colit deltog i studien. De fyllde i fyra frågeformulär som mätte HRQOL vid ett tillfälle.

Ingen skillnad i HRQOL framkom mellan patienter med Crohns sjukdom och patienter med ulcerös colit. Patienter med kort sjukdomsduration (< 2 år) hade sämre HRQOL när de jämfördes med patienter med lång sjukdomsduration (> 5 år). De som hade sämst HRQOL var patienter med Crohns sjukdom och kort sjukdomsduration.

Syftet i **delstudie III** var att utvärdera frågeformuläret Rating Form of Inflammatory Bowel Disease Patient Concerns (RFIPC) utifrån svenska förhållanden. 195 patienter med Crohns sjukdom eller ulcerös colit deltog i studien. De fyllde i RFIPC samt ytterligare två frågeformulär vid ett tillfälle. RFIPC används för att mäta oro och bekymmer hos patienter med IBD. Det innehåller 25 områden angående oro relaterat till IBD. Dessa områden kan till exempel handla om ”att bli opererad”, ”att få cancer”, ”att kunna få barn”, ”att lukta illa”. RFIPC används i Sverige men oftast utan att använda den struktur som förslogs i originalversionen. Där delades de 25 områdena in i fyra faktorer medan i Sverige räknas oftast en totalsumma på alla områden. Resultatet i delstudien visar otydliga anpassningsmått då RFIPC används med totalsumma. Originalversionen, med lätt förändring, visade det bästa anpassningsmättet.

Syftet med **delstudie IV** var att undersöka om upplevd stress kan starta ett skov i IBD. 60 patienter med Crohns sjukdom eller ulcerös colit deltog i en dagboksstudie. Dagboken innehöll frågor angående symtom i deras sjukdom samt en fråga om stress. Patienterna fyllde i dagboken varje dag under sex månader. Analyserna visade att hög grad av stress en dag kan öka risken för skov dagen efter.

Sammanfattning

Ingen förbättring i HRQOL framkom efter att patienterna deltagit i ett gruppbaserat utbildningsprogram. Utbildningen var dock uppskattad av patienterna. Patienter med Crohns sjukdom och kort sjukdomsduration har sämst HRQOL och har störst behov av utbildning och stöd. Genom att använda frågeformuläret RFIPC med de fyra faktorerna som föreslagits i originalversionen ges en mer detaljerad information om patienternas sjukdomsrelaterade oro både i forskningssammanhang och i den kliniska vården. Detta kan hjälpa sjukvårdspersonalen att erbjuda varje enskild patient lämplig utbildning och stöd. Det som försämrar HRQOL mest negativt är skov. Att identifiera faktorer som triggat skov ger en möjlighet att också om möjligt påverka denna trigger. Hög grad av stress verkar kunna öka risken för skov.

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