HEALTH-RELATED QUALITY OF LIFE, SYMPTOMS AND COMORBIDITY IN INFLAMMATORY BOWEL DISEASE

JOHANNA HAAPAMÄKI

ACADEMIC DISSERTATION

To be presented, with the permission of the Medical Faculty of the University of Helsinki, for public examination in Auditorium 2 of Meilahti Hospital, Haartmaninkatu 4 on the 8th of April 2011, at 12 noon.

Helsinki 2011
Supervised by

Docent Perttu Arkkila, MD, PhD
Division of Gastroenterology, Department of Medicine
Helsinki University Central Hospital
Helsinki, Finland

Professor Martti Färkkilä, MD, PhD
Division of Gastroenterology, Department of Medicine
Helsinki University Central Hospital
Helsinki, Finland

Reviewed by

Docent Seppo Niemelä
Division of Gastroenterology, Department of Medicine
Oulu University Hospital
Oulu, Finland

Docent Kari Puolakka
Helsinki University and
South Karelia Central Hospital, Department of Medicine
Lappeenranta, Finland

To be discussed with

Docent Katri Kaukinen
School of Medicine, University of Tampere and
Department of Gastroenterology and Alimentary Tract Surgery
Tampere University Hospital
Tampere, Finland

ISBN 978-952-10-6808-9 (PDF)

Kyriiri Oy
Helsinki 2011
To Aino and Veikko
List of original publications ........................................................................................................... 8
Abbreviations .................................................................................................................................. 9
Abstract ........................................................................................................................................... 11
1 Introduction .................................................................................................................................... 13
2 Review of the literature ............................................................................................................... 14
    2.1 Aetiopathogenesis .................................................................................................................... 14
        2.1.1 Aetiology and pathogenesis ....................................................................................... 14
        2.1.2 Genetics ...................................................................................................................... 14
        2.1.3 Environmental factors ............................................................................................... 15
        2.1.4 Immune response ....................................................................................................... 15
    2.2 Epidemiology ......................................................................................................................... 16
    2.3 Diagnosis and natural history of IBD .................................................................................... 17
        2.3.1 Clinical presentation ...................................................................................................... 18
        2.3.2 Clinical course .............................................................................................................. 18
        2.3.3 Extraintestinal manifestations of IBD ............................................................................ 20
        2.3.4 Endoscopic, radiological and laboratory examinations .............................................. 20
            2.3.4.1 Endoscopy ........................................................................................................... 20
            2.3.4.2 Radiological techniques ...................................................................................... 21
            2.3.4.3 Laboratory findings ............................................................................................ 21
            2.3.4.4 Histology ............................................................................................................. 22
        2.3.5 Assessment of disease activity ....................................................................................... 22
        2.3.6 Surgery .......................................................................................................................... 23
    2.4 Medical therapy ..................................................................................................................... 24
        2.4.1 Aminosalicylates .......................................................................................................... 25
        2.4.2 Corticosteroids ............................................................................................................ 25
        2.4.3 Immunomodulators ..................................................................................................... 25
        2.4.4 TNFα blocking agents ................................................................................................. 26
        2.4.5 Calcineurin inhibitors ................................................................................................. 27
        2.4.6 Antibiotics .................................................................................................................... 27
        2.4.7 Nutritional therapy ...................................................................................................... 27
    2.5 Comorbidity ........................................................................................................................... 28
        2.5.1 Autoimmune diseases .................................................................................................. 28
        2.5.2 Pulmonary diseases ...................................................................................................... 28
        2.5.3 Thromboembolic and vasculatory disease .................................................................... 28
        2.5.4 Malignancies ................................................................................................................ 29
        2.5.5 Psychiatric conditions .................................................................................................. 29
    2.6 Education level and working capacity .................................................................................. 30
2.7 Health-related quality of life (HRQoL) ........................................................................ 31
2.7.1 Definition of HRQoL ........................................................................................................ 31
2.7.2 Applications of quality of life measurement .................................................................. 31
2.7.3 Assessment of HRQoL ..................................................................................................... 32
2.7.4 Types and structure of HRQoL instruments .................................................................. 32
2.7.5 Properties of HRQoL instruments .................................................................................. 33
2.7.6 Generic HRQoL instruments .......................................................................................... 34
    2.7.6.1 Medical Outcomes Study Short-Form ................................................................. 34
    2.7.6.2 EuroQoL .................................................................................................................. 34
    2.7.6.3 Sickness Impact Profile ......................................................................................... 35
    2.7.6.4 Nottingham Health Profile ..................................................................................... 35
    2.7.6.5 Psychological General Well-Being ........................................................................ 35
    2.7.6.6 15D ........................................................................................................................... 36
2.7.7 Disease-specific HRQoL instruments ........................................................................... 38
    2.7.7.1 Inflammatory Bowel Disease Questionnaire ............................................................... 38
    2.7.7.2 Rating Form of IBD Patient Concerns ........................................................................ 39
    2.7.7.3 Cleveland Clinic IBD Scale ..................................................................................... 39
2.7.8 Worries and concerns of IBD patients ........................................................................... 42
2.7.9 Predictors of HRQoL in IBD ......................................................................................... 42
    2.7.9.1 Disease-related factors ............................................................................................... 42
    2.7.9.2 Patient-related factors .................................................................................................. 43
2.7.10 Impact of individual IBD symptoms on HRQoL .......................................................... 44
2.7.11 Impact of therapy on HRQoL ...................................................................................... 44
2.7.12 Comparison of HRQoL with the general population and with other disease groups .... 45

3 Aims of the study ............................................................................................................... 46

4 Patients and methods ........................................................................................................ 47
4.1 Patients and data collection ............................................................................................. 47
4.2 Questionnaires .................................................................................................................. 47
4.3 Control groups .................................................................................................................. 48
4.4 Statistical methods .......................................................................................................... 48
4.5 Ethical considerations ..................................................................................................... 50

5 Results ............................................................................................................................... 52
5.1 Recruited patients (I, II, III, IV) .................................................................................... 52
    5.2 Demographic characteristics of the patients and comparison with the European study (I, III) .......................... 52
    5.2.1 Rates of surgery (I) ....................................................................................................... 54
    5.2.2 Symptoms and extraintestinal manifestations (I) .......................................................... 55
    5.2.3 Frequency and impact of symptoms on daily life (I, II and III) ..................................... 55
    5.2.4 Current therapy (I, III) ................................................................................................ 56
    5.2.5 Patient satisfaction (I) ................................................................................................ 57
5.3 Comorbidity (IV) .......................................................................................................... 57
List of original publications

This thesis is based on the following publications:


The publications are referred to in the text by their roman numerals, and reprinted by permission of the copyright holders.
Abbreviations

5-ASA  5-aminosalicylate
15D   15-dimensional
ANOVA analysis of variance
CARD caspase-activating recruitment domain
CD Crohn’s disease
CDAI Crohn’s disease activity index
CDEIS Crohn’s disease endoscopic index of severity
CHD coronary heart disease
CI confidence interval
CIA confidence interval analysis
CRC colorectal cancer
CRP C-reactive protein
CT computed tomography
DBE double-balloon enteroscopy
EFCCA European Federation of Crohn’s and Colitis Associations
ESR erythrocyte sedimentation rate
HRQoL health-related quality of life
IBD inflammatory bowel disease
IBDQ inflammatory bowel disease questionnaire
IBS irritable bowel syndrome
IC indeterminate/unspecified colitis
IL interleukin
IPAA ileal pouch-anal anastomosis
IRR incidence rate ratio
MRI magnetic resonance imaging
NHP Nottingham health profile
NOD nucleotide oligomerisation domain
NSAID non-steroidal anti-inflammatory drug
OEGD oesophagogastroduodenoscopy
OR odds ratio
PDAI perianal Crohn’s disease activity index
PGWB psychological general well-being
PSC primary sclerosing cholangitis
QALY quality adjusted life year
RFIPC rating form of inflammatory bowel disease patient concerns
SBE small bowel barium examination
SD standard deviation
SES-CD simple endoscopic score for Crohn’s disease
SF-36 medical outcomes study short form
SIBDQ short-form inflammatory bowel disease questionnaire
SIP sickness impact profile
TLR toll-like receptor

9
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF</td>
<td>tumour necrosis factor</td>
</tr>
<tr>
<td>UC</td>
<td>ulcerative colitis</td>
</tr>
<tr>
<td>VAS</td>
<td>visual analogue scale</td>
</tr>
<tr>
<td>WCE</td>
<td>wireless capsule endoscopy</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Abstract

**Background:** During the last decades, health-related quality of life (HRQoL) measurement has become an important outcome in treatment studies and in health policy decisions. Inflammatory bowel diseases (IBDs) are chronic gastrointestinal diseases of unknown aetiology. Symptoms of IBD can be bothersome and sometimes painful. In earlier studies, impairment of health-related quality of life was evident in IBD, especially when the disease was active. In addition to the physical symptoms, the mental state and social support were also found to affect HRQoL. Data about the impact of demographic characteristics or comorbidity of the patients on HRQoL are partly controversial.

HRQoL can be measured by using generic or disease-specific tools. Generic instruments can be used for comparing health status among patients in different health states, conditions and diseases. However, these instruments do not focus specifically on the issues relevant to a particular disease, as they were developed for general populations. Disease-specific tools may be more responsive to changes within a specific condition.

The disease-specific Inflammatory Bowel Disease Questionnaire (IBDQ) used in this study has been utilized in many earlier surveys with smaller patient samples. In contrast, data about the feasibility of using the generic 15D tool in IBD are scarce. The aims of this study were to compare HRQoL, the frequency of symptoms, and the arrangement of therapy of Finnish IBD patients with those of European IBD patients. The health-related quality of life in Finnish IBD patients using both the IBDQ and 15D instruments was also examined. Furthermore, comorbidity of IBD patients and influence of comorbidity on HRQoL were evaluated.

**Patients and methods:** The study questionnaire was mailed to 3852 adult (over 18 years of age) members of the Crohn’s and Colitis Association of Finland in September 2006, and to an additional 1490 adult patients selected from the Social Insurance Institution register of Finland in February 2008. In study I, the differences in the diagnosis of IBD, current and previous therapies, frequency of IBD symptoms, and impact of symptoms on HRQoL of Finnish patients were compared with those of patients who participated in an earlier European study that comprised 5576 IBD patients from seven countries. Study II evaluated the disease-specific IBDQ scores in Finnish IBD patients. In study III, the generic 15D scores of IBD patients were compared with scores of a gender and age matched general population sample obtained from two national health surveys. Moreover, the 15D scores were compared with the IBDQ scores to evaluate the feasibility of 15D as a HRQoL tool for IBD. In study IV, two age, gender, and hospital district matched control subjects for each participant were selected from the Social Insurance Institution register for a comparison of comorbidity between IBD patients and the general population. Data of other chronic diseases were obtained from the Social Insurance Institution’s reimbursement register.

**Results:** The response rate was 57%. Of these patients, 37% reported that they suffered from disturbing IBD symptoms weekly. In 17% of the patients, the symptoms greatly affected their ability to enjoy leisure activities, and 14% stated that these symptoms greatly...
affected their capacity to work. Despite that, the great majority (93%) of patients expressed satisfaction with their current treatment and only 1.4% were very dissatisfied.

43% of the Crohn’s disease (CD) patients had undergone surgery, whereas the percentage was 12% for ulcerative colitis (UC). Rates of surgery were lower than in the previous European survey. Over a quarter of operated patients reported postoperative complications in both surveys.

The IBDQ scores ranged from 43 to 224, whereas the possible range is 32 to 224. The mean total score was 163, and disease activity was the most strongly correlated factor with HRQoL. Older age, comorbid diseases, and female gender were also related to impairment of HRQoL. Lower HRQoL scores were also seen in newly-diagnosed patients and in those with a history of surgery, especially after stoma or ileal pouch-anal anastomosis (IPAA) operation.

The range of 15D scores was 0.30-1.00, with a mean of 0.87. As found with the IBDQ, disease activity was strongly correlated with the score, but not even those who reported infrequent symptoms could reach the 15D level of the control group. Sex of the patient or disease type had no significant impact on the score, but older age and a history of surgery were related to lower scores. Newly-diagnosed patients and patients with a long-lasting disease had lower scores than average after adjusting for age. The 15D tool appeared to be a feasible and easy-to-use instrument to assess HRQoL for IBD, and the 15D scores were strongly correlated with the IBDQ scores.

Comorbidity with other chronic diseases was found in 29% of IBD patients. Connective tissue diseases, asthma and chronic obstructive pulmonary diseases, pernicious anaemia, and coronary heart disease were significantly increased among patients with IBD. Females with IBD appeared to be especially at increased risk of CHD with a 1.6-fold prevalence to that of their peers (p=0.014), and those who reported weekly symptoms had a higher risk of having other chronic diseases in addition to IBD. Comorbidity impaired HRQoL as measured by using both the generic and disease-specific tools.

Conclusions: IBD had a considerable impact of the daily life of the patients. Symptoms that affected leisure activities, work, and HRQoL were common in IBD. Disease activity was the most important factor related to HRQoL, and older age, comorbidity, and female sex also impaired HRQoL. Newly-diagnosed patients and those with a history of surgery, especially for stoma or IPAA operation, had low HRQoL scores.

The risk for many other chronic diseases, such as CHD, connective tissue diseases, asthma and chronic obstructive pulmonary diseases was increased with IBD. The increased prevalence of CHD in IBD predisposes to more efficacious management of other possible underlying cardiovascular risk factors in addition to the inflammatory activity of IBD. The increased risk for preterm cardiovascular disease should be borne in mind especially in females.

The burden of IBD symptoms on various aspects of general well-being was most marked in those patients with the active disease. However, patients with inactive disease may also have impaired HRQoL, and the impact of the chronic disease on their daily lives may be remarkable. An understanding of predictors of HRQoL will help to recognise patients needing special support.
1 Introduction

The primary aim of medical care is to improve or maintain the overall functional capacity and the general health of patients. The success of a treatment has been traditionally measured by biomedical or clinical end points such as survival, response rates, time to progression, relapse or treatment failure, mortality, morbidity and duration of hospital stay (Sajid 2008).

Edwards and Truelove were probably the first to include a measurement of “invalidism being experienced by the surviving members” in their study on the course and prognosis of ulcerative colitis. In their study, 88% of the patients reported living entirely or essentially normal lives in spite of their disease and the prerequisite hospital visits (Edwards and Truelove 1963). During the last decades, the measurement of health-related quality of life (HRQoL) has become an important outcome in treatment studies in addition to being a factor in health policy decisions (Garratt et al 2002). Chronic diseases, which include inflammatory bowel disease (IBD), were found to have a marked impact on HRQoL, especially when frequent symptoms or complications exist (Irvine et al 1994, Mili et al 2003, Wändell 2005).

Although numerous instruments for HRQoL evaluation have been developed, there is no gold standard for HRQoL. The World Health Organization (WHO) defined HRQoL as:

“Individuals’ perception 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. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment”.

WHO 1997

Having a chronic disease influences HRQoL in many ways. IBDs are chronic diseases that are characterized by remission and relapse periods. Patients often have bothersome symptoms that affect their daily lives, and there is also a risk of having to undergo surgery or having a malignancy. The HRQoL of IBD patients has been surveyed earlier in many studies. However, little is known about the overall quality of life of Finnish IBD patients, or about the impacts of IBD symptoms, comorbidities and given therapies on their daily lives.

This thesis investigated the HRQoL for a large cohort of Finnish IBD patients by using a disease-specific inflammatory bowel disease questionnaire (IBDQ) and a generic 15D questionnaire. The former is used in many earlier IBD studies throughout the world, but to the best of the author’s knowledge the latter has not been used in specific IBD studies before. Another aim was to evaluate factors that affect HRQoL in patients with IBD, and to survey comorbidities and their impacts on HRQoL of IBD patients.
2 Review of the literature

Inflammatory bowel diseases, namely Crohn’s disease (CD) and ulcerative colitis (UC), are chronic inflammatory diseases of the gastrointestinal tract. The first description of IBD as a separate entity from epidemic dysentery was made by the British physician Samuel Wilks in 1859. In the same year, he also described a case report entitled “Morbid appearances in the intestine of Miss Bankes” in the London Medical Gazette, a case resembling ileocaecal CD (Kirsner 1988). CD was formerly called regional enteritis or terminal ileitis, and is named after Dr. Burrill B. Crohn, who described the disease along with his colleagues Ginzburg and Oppenheimer in 1932 (Crohn et al 1932).

2.1 Aetiopathogenesis

2.1.1 Aetiology and pathogenesis

Although the knowledge of immunological mechanisms has increased during the past years, the aetiology and pathogenesis of IBD remains incompletely understood. The most widely accepted hypothesis is that the damage to the bowel mucosa occurs as a result of a dysregulated immune response to multiple mucosal antigens comprised within the constituents of the normal intestinal flora (Baumgart and Carding 2007, Brown and Mayer 2007). Dysbiosis of mucosa-associated intestinal microbiota is one of the major characteristics in IBD (Ott et al 2004, Tamboli et al 2004, Manichahn et al 2006, Rehman et al 2010) but its contribution to disease pathogenesis has been controversial (Ott et al 2004, Gophna et al 2006, Ott et al 2008, Nell et al 2010).

Intestinal microvascular ischaemia has also been suggested to play a role in the pathogenesis of IBD (Wakefield et al 1989, Maconi et al 1996, van Oostayen et al 1994). An inverse association between appendectomy and UC has been reported in many studies, whereas appendectomy has a positive correlation with CD. The mechanism is unknown, but the appendix may have a role in the mucosal immune system (Kourtoubakis and Vlachonikolis 2000).

2.1.2 Genetics

A significant proportion of IBD patients have a positive family history in up to 22% of cases in population-based studies (Gaya et al 2006, Ben-Horin et al 2009). Moreover, for those IBD patients diagnosed at younger than 20 years of age, over one-third were found to have other family members with IBD (Farmer 1989). The onset of disease in familial IBD cases often occurs at younger age than in sporadic cases (Yang et al 1993, Polito et al 1996).
In recent years, advances on genome-wide association studies and linkage analysis methods have aided the understanding of the genetics of IBD, as more than 30 IBD susceptible loci have been found (Ishihara et al 2009). The findings indicate the polygenic aetiology of CD and UC (Gaya et al 2006). The first IBD susceptible gene found was the nucleotide oligomerisation domain 2 (NOD2). This was previously known as the caspase activated recruitment domain protein 15 (CARD15) and is located in chromosome 16 (Hampe et al 2001, Hugot et al 2001, Ogura et al 2001). NOD2/CARD15 mutation has been associated mainly with CD, especially when ileal involvement, fistulizing or stricturing disease phenotype, and/or familial occurrence of CD are present (Ahmad et al 2002, Lesage et al 2002, Radlmayr et al 2002, Heliö et al 2003). In the initial study by Hugot et al, allelic variants of the CARD15 gene were found to be present in 43% of patients with CD (Hugot et al 1996). However, since that study evidence of ethnic variation in the contribution of the gene has become evident. In Northern Europe, Asia, Ireland and Scotland the contribution of the gene to CD susceptibility is much lower than elsewhere in Europe (Heliö et al 2003, Gaya et al 2006), and in Finland the allelic frequency in CD patients is only about 5% (Heliö et al 2003).

Recently, linkage analyses have drawn the attention of researchers to the IBD3 region (major histocompatibility complex) of chromosome 6p, the IBD5 locus in chromosome 5 (5q31-33) and CARD4 gene in chromosome 7 (7p14) (Gaya et al 2006).

2.1.3 Environmental factors

Genetics alone is insufficient to explain the development of IBD. Several environmental triggers have been investigated, and no single factor has been found to be responsible for the development of IBD. Agents that break the mucosal barrier of the intestine such as nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, and viral and bacterial infections, have been identified as triggers of IBD (Mayer 2010). Smoking is a risk factor for the development of CD, and is associated with a more active disease, whereas in UC, the effect of smoking seems to be protective (Calkins 1989, Russell et al 1998). Stress is not clearly linked to the development of IBD, but it can alter the host immune response or gut flora thus predisposing the subject to the disease (Hunter 2008, Levenstein 2008). A high linoleic acid intake has recently been associated with increased risk of UC. An estimated 30% of cases could be attributed to having dietary intakes higher than the lowest quartile of linoleic acid intake (The IBD in EPIC Study Investigators 2009). Moreover, vitamin D3 has very recently been shown to modify T-cell proliferation and increase IL-6 levels in CD patients (Bendix-Struve et al 2010), and vitamin D3 levels have been found to be lower in CD patients than in controls (McCarthy et al 2005).

2.1.4 Immune response

The mechanisms responsible of maintaining oral tolerance to microbes and food-derived antigens in a healthy gut are still incompletely understood. The response of a defective
mucosal immune system to mucosal microflora and other luminal antigens in IBD lead to damage and increased permeability of the bowel mucosa (Baumgart and Carding 2007).

There are two basic components to the immune response: the innate and the adaptive response. The innate immunity, which is responsible for the early initial immune response, is more primitive and lacks the specificity and the ability to augment responses upon reinfection. In the intestine, the innate immunity includes the epithelial barrier and phagocytic cells within the lamina propria (macrophages, dendritic cells, and neutrophils). The incidence of IBD is increased in patients with genetic defects in the innate immunology (Dieckgraefe and Korzenik 2002). The expression of α-defensins is needed for prevention of microbial invasion through the intestinal mucosa, and in ileal CD it is lower than in CD patients with unaffected ileum or the ileum of healthy controls (Wehkamp et al 2007).

The adaptive immunity, although slower than the innate immunity, complements the immune system and is characterized by specificity and memory. The adaptive immune system is mostly based on T- and B lymphocytes that express antigen receptors on their surfaces (Mayer 2010). Current evidence indicates that defective T-cell apoptosis and impairment of intestinal epithelial barrier play crucial roles in the pathogenesis of IBD (Dignass et al 2004). Without the appropriate control of T-cell proliferation and death during an immune response, accumulation of T-cells and intestinal inflammation may occur.

Recently, proinflammatory Th17 cytokines, such as IL-17, IL-22, and IL-23, have been found to play crucial roles in intestinal protection and homeostasis by recruiting neutrophils and macrophages at infected tissues (Shen and Durum 2010).

Toll-like receptors (TLRs) recognise specific microbial components and trigger innate and adaptive antimicrobial responses. In IBD, changes in TLR expression have been found, which leads to the impairment of the elimination of microbes, and also to chronic inflammation (Baumgart and Carding 2007).

2.2 Epidemiology

The peak incidence of IBD occurs between 16-26 years of age (Vind et al 2006) and in CD, a slight predominance of females can be seen (Loftus 2004, Vind et al 2006).

In many epidemiological studies, a north-south gradient with higher incidence of IBD in northern countries and even within southern and northern parts of the United States, exists (Loftus 2004, Sonnenberg et al 1991). A Norwegian study reported that the incidence of IBD was higher in municipalities inhabited by people with the highest level of education and in urban municipalities (Aamodt et al 2008). There are also ethnic differences in incidence and prevalence of IBD. The incidence of UC is 3 to 5 times higher in Jews than in non-Jews, which implicates their genetic susceptibility to the disease. Ashkenazi Jews in Israel have a lower incidence of UC than those living in the United States or Northern Europe, which suggests that environmental factors also play an
important role in the pathogenesis of IBD (Niv et al 2000). In North America, the prevalence of CD is higher in white individuals and African-American individuals than in Hispanic or Asian people, and differences in disease location and extraintestinal disease complications between ethnic groups have also been observed (Kurata et al 1992, Nguyen et al 2006). In South Africa, the incidence of IBD in the coloured population is markedly lower than in whites (Wright et al 1986). Although IBD incidence in Western countries shows stabilization or decline, rates of IBD continue to rise in many Asian countries (Al-Ghamdi et al 2004, Leong et al 2004, Asakura et al 2009).

A population-based study conducted in Olmsted County, Minnesota, found that the incidence rates of CD and UC increased after 1940, but have remained stable since the 1980’s. Today, the prevalence of UC is decreasing, whereas that of CD is increasing due to earlier age of onset and low mortality (Loftus et al 2007). Another population-based study reported, that the incidence of CD in Sweden increased until the 1990’s, but has been decreasing since 1996 (Lapidus 2006). In Denmark, increasing incidences of both UC and CD have been observed (Vind et al 2006). A recently published study of IBD incidence in Pirkanmaa county in Finland in 1986-1999 showed an increase of annual incidence of IBD from 19.5 to 29.2 per 100 000 inhabitants with the increase observed for both UC and CD. The prevalences were 291/100 000 for UC and 124/100 000 for CD (Manninen et al 2010). The highest prevalence of CD reported, 319/100 000, was in the province of Nova Scotia, Canada (Bernstein et al 2006). The incidence of IBD in children is increasing in many countries (Kolek et al 2004, Turunen et al 2006, Malaty et al 2010). In 2009, the register of the Social Insurance Institution in Finland comprised 33 445 individuals who were eligible for reimbursement for their IBD medication, which equals a prevalence of about 620/100 000 (Statistical Yearbook of the Social Insurance Institution 2010).

### 2.3 Diagnosis and natural history of IBD

No single specific test for diagnosing IBD is available. Lennard-Jones and Shivananda have defined widely accepted macroscopic and microscopic criteria for diagnosing IBD (Lennard-Jones and Shivananda 1997). Clinical evaluation with a combination of endoscopic, histological, biochemical and sometimes radiological investigations are needed to confirm the diagnosis (Van Assche et al 2010a). A Working Party of the 2005 Montreal World Congress of Gastroenterology introduced a classification of IBD, and provided recommendations for clinical classification in practice (Silverberg et al 2005).

The classification for CD was a modification of the earlier Vienna classification (Gasche et al 1998). UC and CD can most often be differentiated by their clinical characteristics. The term “colitis yet to be classified” describes a situation where definitive distinction between UC, CD and other causes of colitis cannot be made after appropriate diagnostic tests (Satsangi et al 2006). “Indeterminate colitis” refers to pathological-anatomical diagnosis, which is made usually from a colectomy specimen that has overlapping features of both UC and CD (Price 1978, Satsangi et al 2006). In five years follow-up, change of
diagnosis occurred in 9% of the patients originally classified as UC, CD, unclassified colitis or possible IBD. A change to non-IBD was more frequent than change between UC and CD (Henriksen et al 2006b).

### 2.3.1 Clinical presentation

The most pronounced symptoms of UC are loose stools or diarrhoea, which are almost invariably associated with rectal bleeding (Lennard-Jones and Shivananda 1997, Stange et al 2008). Patients with the active disease also present with rectal urgency, tenesmi, passage of mucopurulent exudates, crampy abdominal pain, and nocturnal and postprandial defaecation. Constipation or feeling of incomplete evacuation, usually with visible blood in the stools, can also occur in active colitis (Rao et al 1988). The onset of UC is often insidious. Systemic symptoms, such as weight loss, fever, tachycardia, nausea and vomiting, are features of severe attack (Baumgart and Sandborn 2007).

Clinical presentation and symptoms in CD depend on disease severity and location. Chronic diarrhoea is the most common symptom that occurs in up to 85% of patients (Nikolaus and Schreiber 2007). Abdominal pain presents in 70% and weight loss in 60% of patients before diagnosis. Blood and mucus in the stools are found less frequently than in UC, but are reported for between 40 and 50% of sufferers (Lennard-Jones and Shivananda 1997). In population-based studies, fistulas occur in about 20% of CD patients and the cumulative incidence increases with duration of the disease (Schwartz et al 2002).

As UC is limited to the colon, CD can involve any part of the gastrointestinal tract, most often the ileum and the colon, however (Cosnes et al 2002, Silverberg et al 2005, Stange et al 2008). UC affects the rectum and a variable extent of the colon in continuity. The Montreal Working Group suggests a classification of UC into proctitis, left-sided colitis and extensive colitis (beyond the splenic flexure) and also takes into account disease behaviour and age at diagnosis in addition to disease location (Silverberg et al 2005). In a US study, 28% of the patients had proctitis, 25% left-sided colitis and 47% extensive colitis (Loftus et al 2000). The extent of UC influences the management and frequency of surveillance of patients (Katsanos et al 2007, Stange et al 2008). However, the extent of the disease is not a fixed parameter and can change over time. Proximal extension of UC has been observed in up to 53% of patients with a left-sided UC or proctitis (Langholtz et al 1996, Moum et al 1999). Infrequently, appendiceal skip lesions and backwash ileitis are seen in UC (Ladefoged et al 2005, Haskell et al 2005).

### 2.3.2 Clinical course

IBD primarily presents at late adolescence or early adulthood and affects both sexes (Loftus 2004, Stange et al 2008). The disease is characterized by chronic inflammation and typically has a relapsing and remitting course (Friedman and Blumberg 2008).
In CD, 80% of the patients will experience at least one relapse during a 10-year follow-up (Wolters et al 2006a) and 60% of the patients will develop a stricturing or penetrating complication of the disease in the long run (Cosnes et al 2002). Patients with small bowel involvement are especially prone to stricturing complications and those with perianal lesions to penetrating complications (Cosnes et al 2002). Predictors of progressive disease are age younger than 40 years, perianal disease, and the need for steroids (Beaugerie et al 2006).

In UC, a relapsing disease has been reported in over 80% of patients, but some other studies found that nearly half (48%) had stayed in remission for years (Solberg et al 2009). Figure 1 shows the different course patterns of UC (Solberg et al 2009). A decrease in symptoms has been observed in 59% of patients in a five year follow-up (Henriksen et al 2006a), and in a large Norwegian study, 40% of UC patients had been in remission for the last five years of a 10-year follow-up after diagnosis (Solberg et al 2007).

No significant increase in mortality has been observed for UC, whereas for CD, there is excess mortality from gastrointestinal causes and, in some studies, from cancer (Masala et al 2004, Wolters et al 2006b, Höie et al 2007, Solberg et al 2009).

**Figure 1.** Different courses of ulcerative colitis in ten years follow-up. Figure from: Solberg et al. Scand J Gastroenterol 2009;44:431-440.
2.3.3 Extraintestinal manifestations of IBD

The most important extraintestinal manifestations of IBD include arthropathies (peripheral and axial), cutaneous manifestations (erythema nodosum, pyoderma gangrenosum, Sweet’s syndrome), ocular manifestations (uveitis, episcleritis) and hepatobiliary manifestations (primary sclerosing cholangitis). Peripheral arthritis, erythema nodosum, oral aphthous ulcers and episcleritis are related to IBD activity, whereas pyoderma gangrenosum, uveitis, spondylarthropathy and primary sclerosing cholangitis are independent of it (Van Assche et al 2010b, Biancone et al 2008).

The most common extraintestinal manifestations are inflammatory arthropathies with a prevalence of between 10 to 20%. Radiological evidence of sacroilitis can be detected in up to 25% of the patients, but clinical ankylosing spondylitis, as defined by accepted criteria, can be diagnosed in 3 to 10% (Bernstein et al 2001a, De Vos 2004). Non-inflammatory joint pain, i.e. joint pain without underlying arthrosis or arthritis, was reported by 16% of IBD patients (22% in CD) with no association to the extent of the disease, medication, surgery or markers of systemic inflammation (Palm et al 2005). Primary sclerosing cholangitis (PSC) markedly increases risk for cholangiocarcinoma and colon cancer (MacFaul and Chapman 2004). The incidence of PSC is up to 16 in 100 000 in the general population, and over three quarters of PSC patients have also been diagnosed with IBD (Lindqvist et al 2010). On the other hand, PSC affects up to 5% of IBD patients (Saich and Chapman 2008). Currently, PSC is the most common indication for liver transplantation in the Nordic countries (www.scandiatransplant.org).

IBD has also been found to be associated with increased risk of osteoporosis and osteopenia, nephrolithiasis, amyloidosis, idiopathic pancreatitis, myocarditis and pleuropericarditis (Danese et al 2005).

2.3.4 Endoscopic, radiological and laboratory examinations

2.3.4.1 Endoscopy

Ileocolonoscopy, and systematic mucosal biopsies from each anatomic segment should be performed to establish the diagnosis of IBD. A minimum of two biopsy samples from each of five sites of the colon and the ileum should be obtained for a reliable diagnosis of IBD (Van Assche et al 2010a).

Endoscopic appearance is useful in differentiating UC from CD. UC typically presents with continuous, uniform inflammation that extends proximally from the rectum. The inflammation is normally limited to the colon, but occasionally a “backwash” ileitis occurs in total colitis. Rectal sparing has been described in children prior to treatment, and in adults following topical or systemic therapy for UC (Kim et al 1999, Rajwal et al 2004). The endoscopic features of CD are discontinuous involvement, anal lesions and cobblestone appearance of the ileum. The inflammation can involve any part of the
gastrointestinal tract, and the rectum can be spared. Small, deep aphthous lesions or longitudinal, polygonal ulcerations occur (Nikolaus and Schreiber 2007).

Colonoscopy is used for diagnosis, and also for follow-up of IBD patients. Chromoendoscopy improves detection of pre-malignant and malignant mucosal lesions (Thorlacius and Toth 2007). Oesophagogastroduodenoscopy (OEGD) is recommended for both CD and UC patients with upper gastrointestinal symptoms. OEGD can be useful in patients with unclassified colitis, as focal active gastritis in the absence of ulceration may be a CD feature (Van Assche et al 2010a, Stange et al 2008). Formerly, only radiographical techniques were available for examinations of the entire small bowel. In recent years, new radiation-free techniques for small bowel examinations have been introduced. Small bowel wireless capsule endoscopy (WCE) serves in making a diagnosis and is used for assessing the severity of small bowel CD, but is contraindicated if suspected or documented intestinal strictures exist (Leighton et al 2007). Double-balloon enteroscopy (DBE) is a novel technique that enables endoscopic examination of the entire small bowel. The scope can be inserted either by oral or anal route (Yamamoto et al 2001).

2.3.4.2 Radiological techniques

Radiological techniques are mainly used for the examination of the small bowel and extramural complications of IBD. The gold standard for small bowel examination has traditionally been small bowel barium examination (SBE), with either by using an enteroclysis or a small-bowel follow-through. As SBE is invasive and requires ionizing radiation, it is not suitable for follow-up (Horsthuis et al 2007). Computed tomography (CT) and magnetic resonance imaging (MRI) are accurate methods for examining extramural complications of IBD, although CT can not be considered suitable for repeat use because of its associated radiation burden. MRI is more suitable for fistula imaging because of its high contrast resolution (Horsthuis et al 2007). MRI enteroclysis is superior to conventional SBE in imaging of small bowel lesions in CD (Rieber et al 2000). However, as superficial lesions are not accurately visualized with CT or MRI enteroclysis, WCE is preferred in examining inflammatory lesions especially in the jejunum (Gölder et al 2006). In the hands of an experienced operator, abdominal ultrasound can reveal small bowel or colonic inflammation in 80-90%, though this is unspecific. It can also be used for detecting fistulas and abscesses (Parente et al 2003).

2.3.4.3 Laboratory findings

Initial laboratory investigations of IBD should include a full blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), creatinine, electrolytes and liver enzymes. Microbiological testing for infectious enteritis including clostridium difficile toxin is needed for differential diagnosis. Anaemia and thrombocytosis are common in the blood count of patients with active IBD (Stange et al 2008). Especially in CD, CRP
correlates with disease activity (Vermeire et al 2004) and it helps to identify those UC patients with severe exacerbation that needs colectomy (Travis et al 1996). Low serum protein or low serum albumin is indicative of protein loss or malabsorption (Nikolaus and Schreiber 2007). Faecal calprotectin can be used for monitoring disease activity, but is not specific for IBD (Konikoff and Denson 2006, Sipponen et al 2008).

2.3.4.4 Histology

Histological examination of biopsies taken from the colon and ileum are required for the diagnosis of IBD. In the initial ileocolonoscopy examination, multiple mucosal biopsies should be taken from each segment of the colon (right, transverse, left, sigmoid colon and the rectum) and the ileum. Histology helps in distinguishing between UC and CD, and between IBD and other inflammatory disorders of the gastrointestinal tract (Van Assche et al 2010a).

Typical microscopic features of CD include focal or patchy inflammation with granulomas, crypt architectural irregularity, increased basal cellularity (mainly plasmacytes and lymphocytes), erosions, and mucin depletion. In ileal biopsies, the same features, and also irregular villous architecture can be seen. Crypt atrophy is more pronounced in UC. Basal plasmacytosis, mucosal atrophy and crypt epithelial neutrophils are also seen. Inflammation in UC is typically continuous with a decreasing gradient of inflammation from the distal to the proximal colon. Basal plasmacytosis decreases and can disappear during treatment (Jenkins et al 1997, Stange et al 2008, Van Assche et al 2010a).

2.3.5 Assessment of disease activity

A global measurement of IBD activity that comprises clinical, endoscopic, biochemical and pathological features is not available (Sostegni et al 2003) but activity can be measured by endoscopic or clinical activity scores. The most commonly used clinical activity score in CD studies is the Crohn’s disease activity index (CDAI). The CDAI comprises eight clinical variables, which are: the number of liquid stools, abdominal pain, general well-being, extraintestinal complications, the use of antidiarrhoeal drugs, abdominal mass, hematocrit, and body weight. The CDAI scores range from 0 to approximately 600. The limit between remission and active disease is CDAI 150 and the cut-off value between active and severe disease is 450 points (Sostegni et al 2003). Another widely used clinical activity index for CD is the Harvey Bradshaw index, which is based on five variables, namely: the number of liquid stools, abdominal pain, general wellbeing, extraintestinal manifestations and abdominal mass (Harvey and Bradshaw 1980). A score of less than five in the Harvey Bradshaw index is usually the limit for clinical remission (Tibble et al 2000). As patients with fistulising disease may score very low in the CDAI and the Harvey Bradshaw indices, the Perianal Crohn’s disease Activity Index (PDAI) was introduced. The PDAI includes five items: discharge, pain, restriction
of sexual activity, type of perianal disease, and degree of duration. The PDAI is considered at present the gold standard for evaluating the severity of perianal disease (Irvine et al 1995, Sostegni et al 2003).

Endoscopic activity in CD can be measured against a Crohn’s disease endoscopic index of severity (CDEIS) that ranges from 0 to 44 according to mucosal lesions present and distribution of the disease (Mary et al 1989). The scoring system is time-consuming and requires an analogue scale transformation that makes it unsuitable for everyday clinical practice (Sostegni et al 2003). It also correlates poorly with clinical activity (Cellier et al 1994). Simple endoscopic score for Crohn’s disease (SES-CD) is a simpler assessment that is based on four endoscopic variables scored in five endoscopic segments, which yields scores ranging from 0 to 60 (Daperno et al 2004). For postsurgical disease activity evaluation, the Rutgeert’s score is the gold standard (Sostegni et al 2003).

The most commonly used activity indices for UC are modifications of Truelove and Witt’s criteria, such as the Lichtiger score and the Mayo score (Truelove and Witts 1955, Lichtiger et al 1994). These activity indices include some or all of the following items: stool frequency and form, urgency/incontinence, nocturnal diarrhoea, use of anti-diarrhoeal medications, blood per rectum, abdominal pain, well-being, extraintestinal symptoms, rectal prolapse, fever, laboratory tests, physician’s assessment, anorexia, and nausea/vomiting (Turner et al 2009). The Mayo Score is the most commonly used index that combines both endoscopical and clinical findings. It consists of four items with three-point scales for the following: stool frequency, rectal bleeding, findings of flexible sigmoidoscopy, and physician’s general assessment. Scores range from 0 to 12 points, and patients in complete remission score 0 points (Schroeder et al 1987). Clinical improvement is usually defined as a decrease from baseline of the score ≥ 3 points. The Mayo Score has not been validated. (D’Haens et al 2007). The non-invasive 9-point Mayo score has been found to perform as well as the full Mayo score for assessing clinical response (Lewis et al 2008).

2.3.6 Surgery

Indications for colectomy in UC are severe acute colitis that does not respond to therapy, chronically active disease that causes steroid dependency, and dysplasia or cancer of the colon (Andersson and Söderholm 2009). Nowadays, restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the standard care for elective surgery for UC (Travis et al 2008). A total abdominal colectomy with an end ileostomy and the rectal stump left behind is a good alternative for patients requiring emergent surgery for UC. In such cases a restorative operation can be performed when the patient has fully recovered (Grucela and Steinhagen 2009). Total colectomy with ileostomy is recommended for individuals with impaired sphincter function, advanced age, significant comorbidities or distal rectal cancer (Cohen et al 2005).

Surgery for CD may be necessary for disease-related complications and emergencies, such as perforation or intestinal obstruction. It may also be used for the control of symptoms when medical therapy is not useful or has failed, such as in case of strictures,
fistulas or neoplasia (Penner et al 2005, Kiran et al 2010). After ileocaecal resection for CD, 52-72% of patients develop a recurrence and 35% have had repeat resection surgery within 10 years follow-up (Rutgeerts et al 1984, Cullen et al 2007). Smoking is a risk factor for recurrence (Papay et al 2010).

The cumulative 10-year colectomy rate for UC is about 10% (Solberg et al 2009). The 10-year cumulative surgery rate for CD is higher, 40% (Wolters et al 2006a, Solberg et al 2007), and within a year from diagnosis, 12% of CD patients will have undergone resection (Vind et al 2006). More than three quarters of CD patients will require surgery at some point of their disease (Penner et al 2005). In northern Europe, colectomy rates for UC and overall surgery rates for CD are higher than in southern Europe, which suggests a more severe disease course in the north (Wolters et al 2006a, Wolters et al 2007). Although immunosuppressants have been used more frequently during the last 25 years, no significant decrease in the need of surgery has occurred (Cosnes et al 2005, Domènech et al 2010). The overall pouch function is good for most patients after IPAA surgery, and the majority of the patients are satisfied with their pouch function (Ferrante et al 2008).

However, the functional result of the pouch is not always satisfactory. In a Swedish study that comprised 370 IPAA patients, median bowel frequency was six times per 24 hours and 76% of the patients had to empty the reservoir during the night. In addition, 23% of patients experienced urgency, 12% evacuation difficulties and 17% soiling during the day (Berndtsson et al 2007).

Idiopathic inflammation of the pouch mucosa, “pouchitis”, occurs in up to 58% of operated CU patients (Kuisma et al 2004, Ferrante et al 2008). Patients with associating PSC (Penna et al 1996) or ankylosing spondylitis (Kuisma et al 2004) are particularly at risk. Chronic pouchitis, stricturing or pouch fistulas can lead to pouch failure and the need for permanent ileostomy in about 5% of the cases (Lepistö et al 2002, Ferrante et al 2008). However, of 19 patients with chronic pouchitis and impaired HRQoL, over 80% would still undergo IPAA operation again (Turina et al 2006).

2.4 Medical therapy

Medical therapy of IBD is designed in conjunction with the patient according to disease activity, location (ileal, ileocolonic, colonic, rectal) and disease behaviour (relapse frequency, response to previous medications, fistulas, strictures, and extraintestinal manifestations). Patients should be encouraged to participate in therapeutic decisions. In some CD patients with a mild disease, no medication can be an option. In contrast, therapy is usually needed for rectal bleeding and urgency occurring often even in mild rectal inflammation for UC (Stange et al 2008, Van Assche et al 2010a). As smoking cessation is associated with a more benign disease course for CD, and non-smoking patients have higher rates of response to infliximab therapy, smoking cessation should be recommended to all smokers with CD (Cosnes et al 2001, Parsi et al 2002).
2.4.1 Aminosalicylates

Oral 5-aminosalicylate (5-ASA) containing compounds are the preferred first-line maintenance treatment for UC. The minimal effective dose of oral 5-ASA is around 1 g/day and higher doses up to 2.4 g/day may be more effective in patients with extensive disease. Sulfasalazine is equally effective to mesalazine but has more adverse effects than mesalazine (Travis et al 2008).

Mesalazine suppositories or foam enemas (1 g/day) are the preferred initial treatments for mild or moderately active proctitis, and have a better effect than oral mesalazine alone (Gionchetti et al 1998). A combination of oral and topical 5-ASA appears to provide further benefit. Mild to moderate, active UC should be initially treated with mesalazine at a dose of >2 g/day, preferably in combination with topical mesalazine. However, oral aminosalicylates alone can induce remission in a minority of patients (Travis et al 2008).

The effect of 5-ASA on the induction or maintenance of remission in active ileal or colonic CD is limited (Hanauer and Strömberg 2004). After curative surgery for ileal CD, mesalazine is useful in decreasing the rate and severity of endoscopic recurrences and can be used in low-risk patients (Brignola et al 1995).

2.4.2 Corticosteroids

Corticosteroids have been used since the 1950’s when Truelove and Witts published their study regarding the positive effect of cortisone therapy in active UC (Truelove and Witts 1955). Corticosteroids are used as a first-line therapy for active IBD, and over 50% of UC patients have an associated remission (Ho et al 2006). In comparison, 38% of CD patients had remission for a year after corticosteroid therapy (Ho et al 2006). No difference between classic corticosteroids and placebo exists after 6, 12, and 24 months with maintenance therapy for CD (Steinhart et al 2003).

Enteric-coated budesonide has a high anti-inflammatory activity combined with low systemic and steroid activity. Moreover, it has fewer systemic side-effects than conventional corticosteroids because of its rapid hepatic conversion to metabolites. In mildly active ileal or ileocaecal CD, it has been found to be beneficial. However, for maintenance therapy that exceeds one year, the relapse rates equal those of placebo (Greenberg et al 1994, Greenberg et al 1996). Budesonide is less effective than prednisolone, and severely active or extensive ileocaecal or ileal CD should be treated initially with systemic corticosteroids (Dignass et al 2010).

2.4.3 Immunomodulators

The immunomodulative medications, thiopurines (azathioprine and 6-mercaptopurine) and methotrexate are recommended for steroid-dependent or steroid-refractory patients (Travis et al 2008). Thiopurines are also recommended for the postoperative prophylaxis of complex CD and for the extensive small bowel CD (Dignass et al 2010). A study reported
that 53% of patients that received azathioprine for steroid-dependent UC achieved clinical and endoscopic remission after six months, whereas the rate was 21% for those that received mesalazine (Ardizzzone et al 2006). Thiopurines are effective therapy for inducing remission in active CD (Prefontaine et al 2010). In those cases that need rapid induction of remission, thiopurines alone may be insufficient, as the onset of action is slow (Travis et al 2008, Dignass et al 2010).

Methotrexate is beneficial in inducing remission in active CD at an intramuscular dose of 25 mg weekly, and it is also significantly more effective than placebo in maintaining remission (Feagan et al 1995, Patel et al 2009). For the present, data on methotrexate for maintenance of remission in UC are few (Travis et al 2008).

2.4.4 TNFα blocking agents

Infliximab is an intravenously administered, chimeric anti-tumour necrosis factor (TNF) monoclonal antibody with a potent anti-inflammatory effect. It is indicated for moderate to severe corticosteroid refractory or corticosteroid dependent IBD, or after failure of other immunosuppressive therapy (Dignass et al 2010). Infliximab is usually given as an induction regimen at 0, 2, and 6 weeks at a dose of 5 mg/kg, followed by a maintenance regimen of 5 mg/kg every 8 weeks. A dose of 10 mg/kg can be considered for those patients who lose their response after initially responding (Rutgeerts et al 2004).

Infliximab is effective for inducing remission and healing endoscopic lesions in active CD. Up to 80% of patients clinically respond and over 30% go into remission (Targan et al 1997). In a large multicenter study, 42% of the patients who received systematic maintenance therapy after successful induction therapy were in remission at 1 year follow-up (Hanauer et al 2002). Infliximab is also effective in fistulizing CD, and closure of all fistulas appears in up to 50% of patients after three infliximab infusions. The median time to relapse was 12 weeks, which shows the necessity of maintenance therapy for the majority of patients (Present et al 1999).

Infliximab is also an effective rescue therapy for patients who experienced an acute severe or moderately severe attack of UC, and it decreases the rate of colectomy significantly in a three months follow-up (Järnerot et al 2005). However, only 24% of patients having maintenance therapy were reported to achieve steroid-free remission at 12 months' follow-up (Rutgeerts et al 2005).

Adalimumab, a fully human anti-TNFα monoclonal antibody, was shown to be effective for inducing remission in TNFα-naïve CD patients at a dose of 160 mg at week 0 followed by 80 mg at week 2 (Hanauer et al 2006). Moreover, 46% of patients were reported to be in remission after one year (Sandborn et al 2007). Adalimumab is usually administered subcutaneously every other week at a dose of 40 mg in maintenance therapy. There is also some preliminary evidence that adalimumab is clinically beneficial for about 20% of UC patients who have lost their response or are intolerant to infliximab (Afif et al 2009).
2.4.5 Calcineurin inhibitors

Calcineurin inhibitors are an option for a rescue therapy for steroid-refractory UC. Because of their nephrotoxicity, they are recommended for induction therapy for only 3 to 6 months, until slower-acting immunomodulators, such as azathioprine become effective (Travis et al 2008). Intravenous cyclosporine is effective for patients with severe corticosteroid-resistant UC with a seven-day mean length of time to a response (Lichtiger et al 1994). Calcineurin inhibitors reduce the short-term colectomy rate, but the relapse risk remains high in the first year after treatment (Cohen et al 1999, Moskovitz et al 2006).

Tacrolimus may have an effect in the short-term clinical improvement of refractory UC patients. More data are needed to determine the long-term efficacy and safety (Baumgart et al 2008). Calcineurin inhibitors are of limited value for CD (Dignass et al 2010).

2.4.6 Antibiotics

For mild to moderate flare-up of CD, ciprofloxacin has been found to have similar efficacy to that of 5-ASA with a response rate of 40-50% after 6 weeks of therapy (Colombel et al 1999). Metronidazole can be used alone, or in combination with ciprofloxacin. They can be used for the therapy of pouchitis, for which both metronidazole and ciprofloxacin have proved to be beneficial (Pardi and Sandborn 2006). However, antibiotics can not be considered effective in inducing or maintaining remission for UC (Travis et al 2008).

2.4.7 Nutritional therapy

Malnutrition, caused by reduced food intake, presence of active inflammation and enteric loss of nutrients, is a common problem with active IBD, especially for CD (Hartman et al 2009). IBD is associated with disturbances in body composition, so both bone mineral content and lean body mass are lower than those of healthy subjects. This is most striking for males with CD (Jahnsen et al 2003). Enteral nutrition, usually liquid preparations containing aminoacids or whole protein, can be used to induce or maintain clinical remission, and to improve nutritional status and body composition. Nowadays parenteral nutrition is mainly used for treatment of severe malnutrition and as a pre- or postoperative nutritional support, as enteral nutrition is as effective with lower costs and fewer side effects (Hartman et al 2009). Elemental or polymeric diets are less effective than corticosteroids in the treatment of active CD (Dignass et al 2010). No convincing data on effects of different elimination diets for the treatment of IBD exist (Yamamoto et al 2009).

Because of the increased risk for osteoporosis, sufficient intake of calcium and vitamin D is necessary (Ali et al 2009). Anaemia is a common finding with IBD, and it should be
treated by optimizing therapy of active IBD, and by administrating oral, or in some cases, intravenous iron supplements (Gisbert and Gomollón 2008).

2.5 Comorbidity

2.5.1 Autoimmune diseases

In a recent population-based study from the US, the risk for ankylosing spondylitis was found to be substantially higher for IBD patients than in the general population with an odds ratio (OR) of up to 7.8. Moreover, prevalences of atopic dermatitis, psoriasis or multiple sclerosis were increased by approximately 1.5-fold. No increased risk for type I diabetes mellitus was observed (Cohen et al 2008). The risk for demyelinating diseases has been found to be increased in other surveys, as well (Gupta et al 2005). The risk for rheumatoid arthritis is also increased with IBD (OR 1.8-2.7) (Bernstein et al 2005, Cohen et al 2008). Clustering of many autoimmune diseases in the first-grade relatives of IBD patients has also been observed (Hemminki et al 2010).

2.5.2 Pulmonary diseases

A broad spectrum of respiratory symptoms (such as wheeze, cough, dyspnoea and sputum production) and lung diseases have been associated with IBD. The most commonly reported lung diseases are bronchiectasies, acute and chronic bronchitis and asthma (Bernstein et al 2005, Black et al 2007). Incidences of many pulmonary diseases, such as bronchiectasies, bronchiolitis and interstitial pulmonary disease, are increased in IBD independently of smoking habits or medication (Mahadeva et al 2000).

2.5.3 Thromboembolic and vasculatory disease

Many predictors of atherosclerotic disease, such as levels of carotid arterial stiffness, homocysteine, high-sensitivity CRP, and insulin resistance that support the increased risk for early atherosclerosis are evident in IBD (Papa et al 2005, Brezenger et al 2006, Dagli et al 2010). On the other hand, IBD patients with coronary heart disease (CHD) have been found to have lower Framingham risk scores (fewer risk factors) than patients with only CHD (Sappati Biyyani et al 2009).

A large population-based study from Manitoba, Canada reported that the risk for ischaemic heart disease was increased in both sexes with CD and with UC, and reported an incidence rate ratio (IRR) of 1.26 (CI 1.11-1.44). Furthermore, an increased risk for cerebrovascular disease was seen in CD (IRR 1.32, CI 1.05-1.66) (Bernstein et al 2008).
In another study, increased risk for myocardial ischaemia could be confirmed only in females aged over 40 (hazard ratio 1.6) (Ha et al 2009). However, mortality for cardiovascular diseases has not been found to be elevated in IBD patients (Dorn and Sandler 2007).

Coagulation and fibrinolysis, rate of venous thromboembolic complications, which have been shown to be interrelated with inflammation, are also increased with IBD (Danese et al 2007). The most common thromboembolic complications are pulmonary embolism and deep vein thrombosis with over a three-fold risk compared to the general population (Miehsler et al 2004).

2.5.4 Malignancies

UC has long been known to be associated with increased risk of colorectal cancer (CRC) and the risk increases with a longer duration and with the extent of the disease. More recently, increased risk of CRC has been associated with CD, as well (Bernstein et al 2001b). In a meta-analysis, the cumulative probability of CRC in UC was 2% by 10 years, 8% by 20 years and 18% by 30 years of disease duration (Eaden et al 2001). In IBD patients, 3% of CRC diagnoses are made coincidentally on pathological specimens after colectomy for other reasons (Kiran et al 2010). In a 20 years follow-up study, dysplasia or cancer was detected in 43% of UC patients who attended surveillance colonoscopies. The mortality of all the patients who attended the study was not increased, however. This was probably due to the surveillance program and frequent medical check-ups (Lindberg et al 1996). The risk of small bowel carcinoma in CD is increased 40-fold (Jess et al 2006).

The risk of hepatobiliary carcinoma is also increased with both UC and CD, and most cases are associated with PSC (Bernstein et al 2001b). A study showed that in some patient cohorts cholangiocarcinoma can be found in 50% of PSC patients within one year after the diagnosis (Fevery et al 2007).

A large population-based study reported an increased risk of lymphoma in male CD patients (IRR 3.63, CI 1.53-8.62) (Bernstein et al 2001b). Lung cancer appears to be increased for CD compared to UC or the general population, probably due to the high prevalence of smoking in CD (Masala et al 2004).

2.5.5 Psychiatric conditions

Psychological comorbidity, mainly anxiety and depression, are frequent findings with IBD (Addolorato et al 1997, Miehsler et al 2008). Both depression and anxiety are found significantly more often for IBD than for control populations, and they are related to frequency of disabling symptoms and also to the nutritional level (Addolorato et al 1997). Increased levels of anxiety, depression and distress have been found in inactive IBD patients, as well (Farrokhyar et al 2006, Graff et al 2009). An Austrian study used a validated questionnaire, which evaluated the need for psychological treatment, and found
that 24% of IBD patients expressed a need for psychosomatic support. The rate was significantly higher than for age matched and sex matched rheumatoid arthritis patients. Inadequate social support and anxiety appeared to increase the need for psychological intervention especially in younger age (Miehsler et al 2008).

Higher levels of depression or anxiety at baseline may be related to more frequent relapses of IBD (Mittermaier et al 2004). Furthermore, increasing the number of stressful events appeared to increase risk of relapse in previously inactive UC patients after controlling for demographic factors (Bitton et al 2003). In another study, short-term stress was not associated with exacerbations for UC patients, but long-term stress was a risk factor for relapses, which emphasizes the biopsychological origin of diseases (Levenstein et al 2000). However, some studies found no evidence of impact of psychosocial stress on disease exacerbations. Instead, an increase of physical symptoms led to increased level of psychological disturbance (North et al 1991). In some studies, IBD patients with active disease were more likely to use maladaptive, avoidant coping strategies than patients with inactive disease or the general population (Graff et al 2009), but in others, no differences in coping strategies were found between inactive and active patients or between patients with CD and UC (Larsson et al 2008). Evidence of the effect of cognitive-behavioral treatment for reducing psychological distress and disease-related concerns in IBD patients exists (Mussell et al 2003).

2.6 Education level and working capacity

The level of education of young IBD patients in Scotland was similar to their peers although 40/70 (57%) of the patients reported absences of two months or more from school because of their disease, and many reported that their education had been adversely affected by the disease. 6/70 (8.5%) of IBD patients were involuntarily unemployed (Ferguson et al 1994). A Norwegian study reported that 11.7% of the patients were unemployed at five years follow-up after diagnosis of IBD, whereas the average unemployment rate in the Norwegian population was 4.1%. A rise in disability pension rates was recorded for UC patients aged 30 to 50 years. Furthermore, CD patients had twice as many sick-leave days as the general population, whereas the rate for UC was only slightly elevated. Unemployment was associated with significantly lower HRQoL scores for UC patients (Bernklev et al 2006). The ACT 1 and 2 studies examined the efficacy of infliximab in therapy of UC, as well as the employment status of patients and their HRQoL. At week 30, among the 257 patients who were unemployed at the beginning of the study, a greater percentage of those in remission were employed than of those not in remission (58.8% versus 20.0%, p<0.05), and the number fully productive hours worked was greater for those in remission (Reinisch et al 2007).

In a study comprising both UC and CD patients with permanent ileostomy, 36% reported that before surgery their illness prevented them from pursuing a career of their choice. After surgery, 64% of the patients had the same job status as held preoperatively,
and 13% worked more and 22% less than before surgery. Moreover, 15% had lost their jobs after surgery, and nearly half of them thought that it was because of the ileostomy (McLeod et al 1986).

2.7 Health-related quality of life (HRQoL)

2.7.1 Definition of HRQoL

The WHO’s defined health in 1948 as: “a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity”, which should be considered more as an ideal rather than a reality. The concept of “quality of life” describes the general well-being of an individual or a society. It is distinct from health, but health is one of the parameters most strongly associated with experienced quality of life. Other parameters of quality of life include wealth and employment, environment, education, recreation, leisure time, and social inclusion or exclusion (Flanagan 1978). The relative importance of essential issues related to the quality of life has been studied. In an UK study, respondents most often mentioned relationships with family or relatives (31%), their own health (23%), the health of another person (20%), and finances/standard of living (10%) as the most important issues related to quality of life. Those who reported their health to be impaired, were most likely to mention their own health as the most important issue affecting quality of life (Bowling 1995).

HRQoL indicates the overall effect of a disease on a person’s ability to enjoy life. It is a measure of the functional impact of a (chronic) illness and a given therapy on the daily life of an individual, as seen from that individual’s viewpoint (Fitzpatrick 1992, Wilson 1995).

Most conceptualistic models of HRQoL include the dimensions of physical, social and role functioning, in addition to mental health and general perceptions of health (Wilson 1995). These dimensions impinge on each other, and they are affected by the patient’s personality characteristics, social support, economical support, and non-medical factors, such as political and cultural factors (Fitzpatrick 1992, Wilson 1995).

2.7.2 Applications of quality of life measurement

The need for HRQoL evaluation has arisen to meet the objective of medical therapy to improve patients’ general well-being, which is the most important reason for HRQoL measurement (Ebrahim 1995). HRQoL measurement helps to identify the most appropriate choice between different therapies with their benefits and adverse effects (Sajid 2007). On the population level, HRQoL measurement can be used for monitoring population health and changes in it, for evaluating the effects of health and social policies, and for allocating health care resources in relation to need. On an individual level,
HRQoL measurement serves to evaluate the effects of treatment, to describe the nature and severity of a disease, and to assess prognosis (Ebrahim 1995).

HRQoL measurement has become an essential outcome of cost-effectiveness and cost-utility analyses, as well. A quality-adjusted life year (QALY) can be thought as a year of life that is lived at an optimal state of health. If a medical intervention adds 10 years of life, and each of these years is associated with a HRQoL score of 0.7 (of the maximum being 1.0), that medical intervention will result in a gain of seven years (10 x 0.7) of perfect health or QALYs (Muennig 2002). Therefore, HRQoL instruments measure the impact of a treatment on the quality of life without incorporating influence on the length of life, whereas QALY assessment combines both quantity and quality of life into a single value. In addition, the cost of the intervention is integrated into the cost-effectiveness analyses (Raisch 2000). The accepted cost-effectiveness threshold varies across different countries depending on the availability of health-care resources and technology, as well as on general valuations (Ebrahim 1995, Devlin and Parkin 2004).

2.7.3 Assessment of HRQoL

The purpose of the HRQoL instruments is to calculate a score based on a person’s perception of his/her quality of life. The HRQoL score is therefore a valuation of life lived in a particular state of health (Muennig 2002). The primary source of information for HRQoL measurement should be the patient him- or herself (Bjordal 2004). HRQoL questionnaires are administered by trained interviewers, proxies or by patients themselves (self-administration). Surrogate respondents can be used to predict results that cannot be obtained directly from the patient, for example, if the patient is too sick to complete the questionnaire (Guyatt et al 1993).

2.7.4 Types and structure of HRQoL instruments

There are two main types of HRQoL instruments, generic and disease-specific. Generic instruments can be further divided into two groups: health profiles containing instruments that attempt to measure separately all important aspects of HRQoL, and utility measures comprising instruments that reflect preferences of patients for treatment process and outcome, and yield a single score. The latter can be used for cost-utility analyses (Guyatt et al 1993). Some generic instruments have features of both groups. Global HRQoL assessment refers to a simple summary of overall HRQoL by using a visual analogue scale (VAS), which is usually a horizontal line with one end indicating the worst health and the other end the best health, and the respondent indicates the point that best reflects his/her response to the question by placing a mark on the line. A graded scale with a single attribute can also be used. These assessments are easy to perform, but do not identify specific areas of dysfunction (Borgaonkar and Irvine 2000).

A questionnaire usually consists of several questions or items, which can be grouped into domains or dimensions, which measure physical or emotional function, for example.
Answers to questions are usually scored on a scale. The Likert scale is a category scale by which respondents specify their level of agreement to a statement, such as: 1 = strongly disagree, 2 = disagree, 3 = neither disagree nor agree, 4 = agree, 5 = strongly agree. The questions may have various number of answer options depending on the questionnaire. In some questionnaires, the score is calculated by summing the answers to all the individual items. However, some others use more complex calculations by utilizing preference weights for each question.

2.7.5 Properties of HRQoL instruments

All useful HRQoL measurements must have the prerequisite characteristics that make them useful for the purpose intended (Ebrahim 1995).

First, the instrument must be reliable. The concept of reliability consists of three aspects: test-retest repeatability, inter-observer repeatability, and internal consistency. Internal consistency is a measure of the extent to which the items of the scale are related to each other, i.e. the extent to which they measure consistent underlying concepts (Guyatt et al 1993).

Another important characteristic of an instrument is validity. Validity refers to the ability of the instrument to measure a predefined parameter. The criterion validity refers to the ability of an instrument to correspond to results of the criterion standard (i.e. a shorter version of an instrument versus the full-length instrument, “the gold standard”). Face validity is the property of an instrument to appear to test the parameter intended, whereas content validity refers to the extent to which a measure represents all facets of the issue in question. Construct validity is the agreement between HRQoL scale and predefined expectations about how it should behave in different situations, for example, the ability to show similarity among like groups (Guyatt et al 1993, Irvine et al 1994).

Responsiveness, or sensitivity to change, is the instrument’s ability to detect change in HRQoL. The terms “ceiling effect” and “floor effect” are linked with responsiveness. If the ceiling effect of an instrument is high, many patients gain the best score, and for these individuals, the instrument is not capable of detecting any further improvement in HRQoL. Conversely, the floor effect prevents the detection of HRQoL impairment in those subjects with the worst possible scores (Guyatt et al 1993, Ebrahim 1995).

A good HRQoL instrument is also feasible for the researcher, acceptable for the patient, interpretable, and useful in providing tools for clinical and political decision making (Sajid et al 2007). An adequate validation of the instrument is important prior to its application in clinical practice or research to minimize the risk of missing important observations or focusing on inconsequential problems (Irvine 1996). After these criteria have been taken into account, there are no uniformly ‘worst’ or ‘best’ performing instruments. Consequently, the instrument selection should be made by using the characteristics that are considered most relevant to the study (Coons et al 2000).
2.7.6 Generic HRQoL instruments

Generic instruments are often preference-based and designed to provide a summary of HRQoL. The questionnaires have been developed by obtaining importance weights of each dimension of the questionnaire, and also by obtaining the values assigned to a particular state of health from a general population sample (Muennig 2002). Their aim is to create a standardized health state descriptive system by choosing the correct dimensions in which health is to be measured and by dividing each dimension into discrete levels that correspond to different health states (Sintonen 1994). Generic instruments can be used for comparing health status among patients with different health states, conditions and diseases. However, as developed for general populations, these instruments do not focus specifically on the impact of a particular condition on HRQoL, and they may be less capable of detecting small but clinically important changes over time or changes related to treatment of a specific disease (Cramer et al 2002). Their most important function is to enable comparisons between populations with different diseases, and also comparisons with the general population. Generic instruments are suitable for calculating QALYs for cost-effectiveness analyses of different therapies (Raisch 2000). Properties of the most important standardized generic HRQoL instruments used in IBD are discussed below.

2.7.6.1 Medical Outcomes Study Short-Form

The Medical Outcomes Study Short-Form (SF-36) was designed to study health status in the Medical Outcomes Study. It is suitable to be used in clinical practice and for research, health policy evaluations and general population surveys, and it has been widely used. It has 36 questions, so is relatively fast and easy to use, and can be self-administered or interviewer-administered (Ware and Sherbourne 1992, Brazier et al 1992). In a study by Essink-Bot et al, SF-36 had superior validity to that of the EuroQoL and the Nottingham Health Profile (Coons et al 2000). Abbreviated versions (SF-20 and SF-12) of SF-36 have been developed, but their reliability and validity are slightly lower than those of the SF-36 questionnaire (Stewart et al 1988).

2.7.6.2 EuroQoL

The EuroQoL (EQ-5D) comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with three answer options, in addition to a VAS that describes the current general health state at a scale from 0 to 100. EQ-5D was developed with the intent of constructing a simple, self-administered instrument that was particularly useful when used alongside with other measures of health status. It can be used for clinical studies, and for population surveys. EQ-5D provides a simple descriptive profile, and a single index value that describes health status. In total 243 health states can be differentiated according to answers to the five items of the questionnaire and the VAS scale (www.euroqol.org). EQ-5D has a good reliability but it has a high ceiling effect, as with many other generic tools (Coons et al 2000).
2.7.6.3 Sickness Impact Profile

The Sickness Impact Profile (SIP) is one of the first validated and extensively used health state measures. It is behaviourally based and serves both as an evaluative and as a discriminative measure (Gilson et al 1975). SIP comprises 136 items in 12 categories. The minimum score of 0% indicates absence of dysfunction, and 100% maximal dysfunction. High test-retest reliabilities have been reported for SIP. However, its administration is time-consuming (20 to 30 minutes when interviewer-administered). Moreover, the SIP may fail to detect small, but existing differences in HRQoL, or to detect small changes in health after treatment in those patients with mild disease because of its high ceiling effect (Yacavone et al 2001).

2.7.6.4 Nottingham Health Profile

The Nottingham Health Profile (NHP) was developed in the UK for being used in epidemiological studies. NHP assesses subjective health by using 38 statements in 6 sections requiring “yes” or “no” for an answer. The score is calculated using weighted values, which yield scores ranging from 0 (no problems) to 100 (maximal problems) for each section. NHP has a high degree of relevance and acceptability to patients and it is simple to complete and score (Yacavone et al 2001). In reliability testing it has shown good test-retest correlations (Coons et al 2000). Its main disadvantage is a relatively high floor effect which limits its usefulness in the general population (Coons et al 2000). The ceiling effect is similar to that of SIP (Yacavone et al 2001), and NHP is less sensitive to minor levels of discomfort than SF-36 (Brazier et al 1992, Ebrahim 1995).

2.7.6.5 Psychological General Well-Being

The Psychological General Well-Being (PGWB) is a 22-item questionnaire that measures subjective feelings of well-being and distress. Responses are graded on a six-point Likert scale with higher values indicating better well-being. Six dimensional scores (anxiety, depression, general health, positive well-being, self-control, and vitality), comprising three to five items, are calculated. The total score is the sum of the domain scores with a maximum of 110 points. A shorter, 6-item version of PGWB has also been developed, but hitherto it has not been fully validated (Grossi et al 2006). Reliability testing has shown tendency of initially low scores to rise and initially high scores to fall in the event of re-testing, which indicates the need for caution in interpreting results in longitudinal studies (Yacavone et al 2001).
15D is a 15-dimensional, comprehensive instrument that yields both a profile and a single index score measure. 15D is designed to be self-administered, though interviewer or proxy administration can also be used. 15D includes the following dimensions: breathing, mental function, speech (communication), vision, mobility, usual activities, vitality, hearing, eating, elimination, sleeping, distress, discomfort and symptoms, sexual activity, and depression. Each dimension is rated against a five-point scale and the score is calculated by utilizing preference weights obtained from the general population. The maximum score is 1 (no problems on any dimension), and minimum 0 (deceased). 15D has been used in the Finnish National Health Survey 1995/96 and the Health 2000 Survey, thus it provides a large general population sample for comparison studies (Sintonen 2001). With regards to the ceiling and floor effects, 15D is superior to NHP and EQ-5D and equivalent to SF-20 (Sintonen 1994). Responsiveness to change has been found to be roughly comparable between 15D, NHP and SF-20 (Sintonen 2001). Completion rates of 15D questionnaires have generally been 96-100%, and a small number of missing answers can be fairly accurately predicted by regression models with the responses on the other dimensions, age, and gender as explanatory variables. A change of ≥0.03 in 15D score can be sensed by an individual (Sintonen 1994). 15D has been used in several conditions, drug evaluations, rehabilitation and treatment studies (www.15d-instrument.net/15d). The mean 15D score was 0.91 for the general population of the Health 2000 Survey. Impairment of 15D scores occurs with increasing age (Saarni et al 2006). Two versions of 15D exist for studying children and adolescents; 17D for children aged 8-11 years and 16D for adolescents aged 12-15 years (Apajasalo et al 1996a, Apajasalo et al 1996b). The most important studies that have used 15D are shown in Tables 1 and 2.
Table 1. Overview of 15D studies

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Disease</th>
<th>Number of patients</th>
<th>Purpose of study</th>
<th>15D score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stavem 1998</td>
<td>Epilepsy</td>
<td>57</td>
<td>Comparison of different HRQoL tools</td>
<td>0.89</td>
</tr>
<tr>
<td>Stavem 1999</td>
<td>Chronic obstructive pulmonary disease</td>
<td>77</td>
<td>Comparison of different HRQoL tools</td>
<td>0.80</td>
</tr>
<tr>
<td>Hahl <em>et al</em> 2002</td>
<td>Diabetes mellitus</td>
<td>539</td>
<td>Measurement of HRQoL in diabetes, and impact of diabetes-related complications and age on HRQoL</td>
<td>Impairment of HRQoL with increasing age and with diabetic complications</td>
</tr>
<tr>
<td>Haapaniemi <em>et al</em> 2004</td>
<td>Parkinson’s disease</td>
<td>260</td>
<td>Assessment of feasibility of 15D in Parkinson’s disease</td>
<td>0.77 (matched controls 0.86)</td>
</tr>
<tr>
<td>Dahlberg <em>et al</em> 2005</td>
<td>Spinal cord lesion</td>
<td>117</td>
<td>Evaluation of HRQoL</td>
<td>0.78 (matched controls 0.95)</td>
</tr>
<tr>
<td>Yildirim 2006</td>
<td>Renal insufficiency</td>
<td>646</td>
<td>Evaluation of HRQoL in renal transplant patients</td>
<td>0.94 (transplantation), 0.57 (haemodialysis), 0.46 (peritoneal dialysis)</td>
</tr>
<tr>
<td>Saarni <em>et al</em> 2007</td>
<td>Various diseases</td>
<td>6166</td>
<td>Impact of chronic diseases on 15D scores (Health 2000)</td>
<td>0.91 (population)</td>
</tr>
<tr>
<td>Gvozdenovic <em>et al</em> 2008</td>
<td>Sarcoidosis</td>
<td>81</td>
<td>Comparison of patients with pulmonary and with extrapulmonary sarcoidosis</td>
<td>0.76</td>
</tr>
<tr>
<td>Miettola <em>et al</em> 2009</td>
<td>Metabolic syndrome</td>
<td>480 (metabolic syndrome 181)</td>
<td>Examination of HRQoL in metabolic syndrome</td>
<td>Significantly lower 15D score in patients with metabolic syndrome</td>
</tr>
<tr>
<td>Pirkola <em>et al</em> 2009</td>
<td>Anxiety/ depression</td>
<td>6986 (685 with anxiety or depression)</td>
<td>Impact of anxiety or depression disorder on HRQoL</td>
<td>0.91 (no anxiety)/0.89 (anxiety), 0.80 (current depression)</td>
</tr>
<tr>
<td>Tikkinen <em>et al</em> 2010</td>
<td>Nocturia</td>
<td>3474 (nocturia 1530)</td>
<td>Evaluation of association between frequency of nocturia and HRQoL</td>
<td>0.94 (no nocturia)/0.83 (over two voids per night)</td>
</tr>
<tr>
<td>Mattila <em>et al</em> 2010</td>
<td>Alexithymia</td>
<td>5090</td>
<td>Assessment of HRQoL in alexithymia</td>
<td>Impairment in all 15D items in alexithymia</td>
</tr>
<tr>
<td>Ahola <em>et al</em> 2010</td>
<td>Type I diabetes</td>
<td>1023</td>
<td>Impact of diabetes and its complications on HRQoL</td>
<td>0.90 (all), impairment of scores if diabetic complications present</td>
</tr>
</tbody>
</table>

HRQoL = health-related quality of life
Table 2. Overview of intervention studies with 15D

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Disease</th>
<th>Number of patients</th>
<th>Intervention/therapy</th>
<th>Time of follow-up</th>
<th>15D score before/after intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kauppinen et al 2000</td>
<td>Asthma</td>
<td>134</td>
<td>Patient education and supervision for self-management for novel asthmatics</td>
<td>5 years</td>
<td>0.03 points' improvement of 15D score</td>
</tr>
<tr>
<td>Räsänen et al 2006</td>
<td>Cataract</td>
<td>219</td>
<td>Cataract surgery</td>
<td>6 months</td>
<td>0.82/0.83</td>
</tr>
<tr>
<td>Räsänen et al 2007</td>
<td>Various conditions affecting joints</td>
<td>223</td>
<td>Hip and knee replacement surgery</td>
<td>12 months</td>
<td>0.81/0.86 (primary hip arthroplasty), 0.81 (primary knee arthroplasty)</td>
</tr>
<tr>
<td>Laas et al 2009</td>
<td>Rheumatoid diseases</td>
<td>295</td>
<td>Patients with new referral to clinic of rheumatology</td>
<td>8 months</td>
<td>0.82/0.84</td>
</tr>
<tr>
<td>Loponen et al 2009</td>
<td>Coronary artery disease</td>
<td>469</td>
<td>Coronary artery bypass surgery (CABG)/percutaneous coronary intervention (PCI)</td>
<td>36 months</td>
<td>0.82/0.86 (CABG, 6 months), 0.83/0.85 (PCI, 6 months)</td>
</tr>
<tr>
<td>Salo et al 2010</td>
<td>Chronic neck pain</td>
<td>180</td>
<td>Neck strength training</td>
<td>12 months</td>
<td>0.90/0.93</td>
</tr>
<tr>
<td>Kantola et al 2010</td>
<td>Acute liver failure</td>
<td>90</td>
<td>MARS (molecular adsorbent recirculating system)</td>
<td>median 49 months</td>
<td>0.30/0.70</td>
</tr>
</tbody>
</table>

2.7.7 Disease-specific HRQoL instruments

Specific instruments focus on aspects of health status that are specific to the area of interest, such as a certain disease, condition, function or problem, or a population of patients (Guyatt et al 1993). Disease-specific instruments are usually more responsive to changes in evaluation of HRQoL in a specific condition (Irvine et al 1994). Clinical trials that evaluate specific therapeutic interventions most often utilize disease-specific HRQoL tools (Yacavone et al 2001). Disease-specific HRQoL tools have been developed for numerous diseases and conditions. Several disease-specific tools exist for evaluating HRQoL in IBD, the most important of which are presented below.

2.7.7.1 Inflammatory Bowel Disease Questionnaire

The most commonly used HRQoL instrument in IBD, translated into over 40 languages, is the Inflammatory Bowel Disease Questionnaire (IBDQ) (ip.mcmaster.ca/questionnaires/questionnaires).

The questionnaire consists of 32 questions rated most important to the HRQoL by IBD patients and their physicians. The questionnaire has four domains: gastrointestinal
symptoms, systemic symptoms, emotional function and social function, with each domain comprising five to 12 items. Responses range from 1 (worst) to 7 (best). The total score ranges from 32 to 224, and is calculated by summing all the answers to the 32 questions. Mean scores per item for each domain (range 1 to 7) can also be calculated. The questionnaire has been validated and it is sensitive to change in IBD patients (Guyatt et al 1989). However, systemic function (such as fatigue, sleep, and energy level) is more responsive to change than emotional or social scores. In remission, scores are generally 170 points or more, and a mean decrease in relapse is about 32 points (Irvine et al 1994, Cregor et al 1997).

Alternative versions of the IBDQ have been developed. A short-form IBDQ (SIBDQ) consists of 10 questions and has been developed for clinical use. It is useful in both UC and CD (Han et al 2000). A version designed for stoma patients is also available. The most important surveys utilizing IBDQ are presented in Tables 3 and 4.

2.7.7.2 Rating Form of IBD Patient Concerns

The Rating Form of IBD Patient Concerns (RFIPC) was developed to evaluate disease-related worries and concerns of IBD patients. The questionnaire is self-administered and has 21 items. Items are in the form “Because of your condition, how concerned are you with...?” Patients rate concerns from 0 to 100 on a VAS, and the total score is the mean of all answers (Drossman et al 1989). This instrument is well suited to guiding patient education and counselling because of its focus on patient concerns (Yacavone et al 2001) but it has also been used in HRQoL studies (Stjernman et al 2010).

2.7.7.3 Cleveland Clinic IBD Scale

The Cleveland Clinic IBD Scale was developed for use as a routine management tool for ambulatory IBD patients. It has 47 items, of which 45 are scaled and two require descriptive answers. The questionnaire comprises four categories: functional/economic, social/recreational, affect/life in general, and medical/symptoms. The questionnaire has not yet been fully validated (Yacavone et al 2001).
### Table 3. Overview of earlier studies with Inflammatory Bowel Disease Questionnaire (IBDQ)

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Number of patients</th>
<th>Disease</th>
<th>Main result</th>
<th>Study purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hjortswang et al 2001</td>
<td>276</td>
<td>UC</td>
<td>202 (remission)/ 167 (relapse)</td>
<td>Validation of Swedish version of IBDQ</td>
</tr>
<tr>
<td>Casellas et al 2001</td>
<td>289</td>
<td>CD 129, UC 160</td>
<td>Disease activity affected HRQoL</td>
<td>Study the influence of IBD on different dimensions of HRQoL</td>
</tr>
<tr>
<td>Nordin et al 2001</td>
<td>492</td>
<td>CD 161, UC 331</td>
<td>Anxiety and depression impair HRQoL</td>
<td>HRQoL and distress in IBD</td>
</tr>
<tr>
<td>Casellas et al 2002</td>
<td>354</td>
<td>CD 169, UC 185</td>
<td>CD: mean per item 6.1 (remission)/4.2 (active), UC: 6.3 (remission)/4.1 (active)</td>
<td>Impact of health status and socio-demographic factors on HRQoL</td>
</tr>
<tr>
<td>Rubin et al 2004</td>
<td>409</td>
<td>CD 163, UC 239 IC 7</td>
<td>Lower HRQoL scores for women, in CD and for those under specialist care</td>
<td>HRQoL in established IBD, community-based study</td>
</tr>
<tr>
<td>Casellas et al 2005a</td>
<td>1156</td>
<td>CD 628, UC 528</td>
<td>Mean per item 6.1 (remission)/ 4.5 (active)</td>
<td>Impairment of HRQoL in IBD</td>
</tr>
<tr>
<td>Bernklev et al 2004, 2006</td>
<td>497</td>
<td>CD 169, UC 328</td>
<td>CD: 157 (sick leave)/187 (no sick leave), 173 (♀)/186 (♂); UC:174 (sick leave)/192 (no sick leave), 183 (♀)/191 (♂)</td>
<td>Impact of demographic variables, sick leave and unemployment on HRQoL</td>
</tr>
<tr>
<td>Stjernman et al 2006</td>
<td>448</td>
<td>CD</td>
<td>193 (remission), 161 (active)</td>
<td>Evaluation of validity of IBDQ in Swedish CD patients</td>
</tr>
<tr>
<td>Watanabe et al 2006</td>
<td>64</td>
<td>UC with IPAA</td>
<td>IBDQ mean 165.7</td>
<td>IBDQ in IPAA patients</td>
</tr>
<tr>
<td>Moreno-Jiménez et al 2007</td>
<td>120</td>
<td>CD 60, UC 60</td>
<td>Neuroticism impaired all four IBDQ subscores</td>
<td>Influence of personality factors on HRQoL</td>
</tr>
<tr>
<td>Gibson et al 2007</td>
<td>143</td>
<td>CD</td>
<td>180.6 (CDAI &lt;150), 115.4 (CDAI ≥220)</td>
<td>Impact of disease severity on HRQoL and health-care resource use</td>
</tr>
<tr>
<td>Vidal et al 2008</td>
<td>147</td>
<td>CD 76, UC 71</td>
<td>Hospital Anxiety and Depression Score was negatively correlated with IBDQ scores</td>
<td>Impact of anxiety and depression on HRQoL</td>
</tr>
<tr>
<td>Kuriyama et al 2008</td>
<td>331</td>
<td>UC</td>
<td>mean per item 5.9 (disease duration &lt;5 years), 6.0 (≥10 years)</td>
<td>Impact of disease duration on HRQoL</td>
</tr>
<tr>
<td>Hyphantis et al 2010</td>
<td>185</td>
<td>CD 64, UC 121</td>
<td>198.5 (low anxiety), 146.4 (high anxiety)</td>
<td>Impact of psychological distress on HRQoL</td>
</tr>
</tbody>
</table>

CD = Crohn’s disease; HRQoL = health-related quality of life; IBD = inflammatory bowel disease; IPAA = ileal pouch-anal anastomosis; UC = ulcerative colitis
<table>
<thead>
<tr>
<th>Author and year</th>
<th>Number of patients</th>
<th>Disease</th>
<th>Time of follow-up</th>
<th>IBDQ score before/after intervention</th>
<th>Intervention/therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irvine et al 1995</td>
<td>305</td>
<td>CD</td>
<td>18 months</td>
<td>168/impairment in those requiring surgery</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Casellas et al 2000</td>
<td>119</td>
<td>CD</td>
<td>median 34.5 months</td>
<td>No difference between groups</td>
<td>Comparison of HRQoL in medically and in surgically induced remission</td>
</tr>
<tr>
<td>Borgaonkar et al 2002</td>
<td>59</td>
<td>CD 36 UC 23</td>
<td>2 weeks</td>
<td>HRQoL impaired for the group receiving information</td>
<td>Impact of disease-related information on HRQoL</td>
</tr>
<tr>
<td>Feagan et al 2007a</td>
<td>728</td>
<td>UC</td>
<td>54 weeks</td>
<td>Significant improvement in all IBDQ subscores for the infliximab group</td>
<td>Infliximab/placebo</td>
</tr>
<tr>
<td>Langhorst et al 2007</td>
<td>60</td>
<td>UC</td>
<td>12 months</td>
<td>Mean per item 5.1/5.4 (intervention group), 5.2/5.4 (placebo), NS</td>
<td>Comprehensive lifestyle modification programme</td>
</tr>
<tr>
<td>Reinisch et al 2007</td>
<td>493 (206 in remission)</td>
<td>UC</td>
<td>30 weeks</td>
<td>130/195</td>
<td>Impact of remission induced by infliximab on HRQoL</td>
</tr>
<tr>
<td>Feagan et al 2007b</td>
<td>339</td>
<td>CD</td>
<td>60 weeks</td>
<td>Significant improvement in IBDQ subscores for the natalizumab group</td>
<td>Natalizumab/ placebo</td>
</tr>
<tr>
<td>Rutgeerts et al 2008</td>
<td>292</td>
<td>CD</td>
<td>12 weeks</td>
<td>132.2 (certolizumab pegol)/ 122.9 (placebo)</td>
<td>Certolizumab pegol/placebo</td>
</tr>
<tr>
<td>Loftus et al 2008</td>
<td>499</td>
<td>CD</td>
<td>56 weeks</td>
<td>Significant improvement in IBDQ subscores for the adalimumab group</td>
<td>Adalimumab maintenance therapy</td>
</tr>
<tr>
<td>Feagan et al 2009</td>
<td>425</td>
<td>CD</td>
<td>26 weeks</td>
<td>122.6/175.7 (certolizumab pegol), /167.9 (placebo)</td>
<td>Certolizumab pegol/placebo</td>
</tr>
<tr>
<td>Dudley-Brown et al 2009</td>
<td>509</td>
<td>CD</td>
<td>12 weeks</td>
<td>123.6/150.3 (natalizumab) 122.5/137.7 (placebo)</td>
<td>Natalizumab/ placebo</td>
</tr>
<tr>
<td>Ng et al 2009</td>
<td>26</td>
<td>CD</td>
<td>12 months</td>
<td>137/176</td>
<td>TNFα-inhibitors in fistulizing CD</td>
</tr>
<tr>
<td>Bastida et al 2010</td>
<td>92</td>
<td>CD 68 UC 24</td>
<td>12 months</td>
<td>4.98/6.10 (mean score per item)</td>
<td>Thiopurines</td>
</tr>
</tbody>
</table>

CD = Crohn’s disease; HRQoL = health-related quality of life; UC = ulcerative colitis
2.7.8 Worries and concerns of IBD patients

The most intense concerns of IBD patients in a US study were the uncertainty of the disease course, the effects of medication, the impact of the disease on energy level, the risk of having surgery or an ostomy bag, being a burden on others, loss of bowel control, and the risk of developing cancer. In CD, concerns about energy level, being a burden on others, not achieving full potential, having pain, and incurring financial costs were more pronounced than in UC, whereas concerns of developing cancer or other complications of the disease were more often seen in UC. Females were generally more concerned about issues associated with the body image, and younger individuals were more worried about impact of the disease on sexual intimacy (Drossman et al 1991). Females, patients with active disease, and overweight patients have higher levels of worries and concerns (Stjernman et al 2010).

The most intense concerns of patients with ileostomy were issues related to intimacy, access to medical care, energy level, loss of sexual drive, loss of ability to perform sexually, producing unpleasant odours, being a burden on others, attractiveness, and feelings about the body (Carlsson et al 2003).

2.7.9 Predictors of HRQoL in IBD

2.7.9.1 Disease-related factors

Disease severity and activity are the most important determinants of HRQoL as measured by the IBDQ (Irvine et al 1994, Casellas et al 2002, Hjortswang et al 2003) and the SF-36 (Hjortswang et al 2003). The need for hospitalization reflects the disease activity and is associated with lower HRQoL scores (Blondel-Kucharski et al 2001, Casellas et al 2002).

In most surveys, there were no significant differences in HRQoL between UC and CD patients after severity of disease had been taken into account (Casellas et al 2002, Guthrie et al 2002). A US study found that CD patients with colonic disease had better disease-specific (IBDQ) and generic (SF-36) HRQoL scores than had patients with small bowel disease or those with fistulizing or stricturing disease (Lix et al 2008). This finding was not seen in an earlier European study, in which disease activity determined the IBDQ scores, not the Vienna Classification (Casellas et al 2005b). The knowledge about impact of age on HRQoL is controversial, but longer disease duration may predict better HRQoL scores at least for some disease groups (Casellas et al 2002, Canavan et al 2006, Zahn et al 2006). Little is known about HRQoL in patients with both IBD and PSC. A recent study comprising 26 IBD-PSC patients and IBD patients without PSC, who were matched for gender, age, disease type and disease duration, found that both groups had similar SIBDQ scores (Ananthakrishnan et al 2010).

Patients who have undergone surgery for CD report worse HRQoL, as evaluated by IBDQ, than reported by non-surgical CD patients (Canavan et al 2006). After surgery for CD, HRQoL was improved 3 and 6 months postoperatively. After 12 months, due to
disease recurrences, there was no significant difference for RFIPC score compared to preoperative values. However, for those patients still in remission, the postoperative HRQoL was significantly better than that preoperatively (Tillinger et al 1999).

The post-surgical situation of UC patients is different. After ileostomy and IPAA surgery, the function of the stoma or pouch is the most important determinant for HRQoL (McLeod et al 1986, Lepistö et al 2002). The impact of stoma on body image and self-esteem of adolescents is probably more pronounced (Nicholas et al 2008). In some studies, patients with stoma reported better quality of life than did those with an IPAA (Nordin et al 2002).

### 2.7.9.2 Patient-related factors

Psychiatric disorders (anxiety, depression, neuroticism and alexithymia) are important and independent predictors of poor quality of life in many surveys, and they affect the domain of social function most strongly (Guthrie et al 2002 Moreno-Jiménez et al 2007). Patients with psychological disorders also have significantly worse scores for domains that measure physical function, pain, and health perception in SF-36 (Guthrie et al 2002). In a study that controlled patients for disease activity, psychological factors were strongly associated with perceived health in IBD (Graff et al 2009). The negative impact of psychiatric disorders on perceived quality of life and symptom burden has been noted in other chronic diseases, as well (Katon and Ciechanowski 2002, Scott et al 2007).

Males are associated with better HRQoL scores in most surveys (Casellas et al 2002, Hjortswang et al 2003, Bernklev et al 2004), but not all (Han et al 2005). Concurrent smoking has a negative impact on HRQoL especially in CD (Blondel-Kucharski et al 2001, Casellas et al 2002, Bernklev et al 2004). However, a Canadian study found that smoking was related to a better quality of life for inactive IBD as measured by SIBDQ and EQ-5D (Farrokhyar et al 2006). A higher level of education was associated with better IBDQ scores in a Spanish study comprising 354 IBD patients, which probably was related to socioeconomical differences between the educational groups (Casellas et al 2002). In a Swedish study, the educational level did not affect generic or disease-specific HRQoL, nor did civil status, disease duration or disease extent (Hjortswang et al 2003). Even if disease duration does not have a significant impact on HRQoL, factors that affect HRQoL may change along with disease duration. In UC patients with disease duration of over 10 years, complications due to corticosteroids, such as osteoporosis, were thought to be the most striking factors that impaired HRQoL in a study performed in Japan (Kuriyama et al 2008). However, the medication of the study patients differed somewhat from preferred therapy in Finland.

A Canadian study found that patients with inactive IBD have significantly more functional gastrointestinal disorders than the general population as determined by Rome II criteria. These symptoms increase anxiety, and impair both generic (as measured by EQ-5D) and disease-specific (SIBDQ) HRQoL (Farrokhyar et al 2006). There is evidence that co-existing diseases impair HRQoL in IBD (Hjortswang et al 2003). Nevertheless, IBD
severity is the most important predictor of HRQoL for those with other chronic conditions in addition to IBD (Pizzi et al 2006).

Short-term benefits of some aspects of HRQoL and general well-being have been achieved with a comprehensive lifestyle modification programme which included stress reduction, stress management, and dietary and exercise guidance for 10 weeks. Three months after the intervention, patients of the intervention group showed significant improvement in the SF-36 scale compared with the usual-care control group. However, 12 months after the intervention, no difference was observed between the groups (Langhorst et al 2007). A group-based education programme for particularly anxious IBD patients did not improve their anxiety levels or HRQoL, although patients reported satisfaction with the programme and found information given on disease-related items useful (Larsson et al 2003). In another study, the provision of disease-related information in the form of educational booklets worsened short-term HRQoL as measured by IBDQ (Borgaonkar et al 2002). The same was seen in a Swedish study, in which a group-based intervention programme comprising educational lectures and therapy sessions was given. Those with short disease duration (≤3 years) benefited from the programme, whereas the HRQoL of patients with longer disease duration worsened during the follow-up (Oxelmark et al 2007).

2.7.10 Impact of individual IBD symptoms on HRQoL

During the development of the IBDQ, 77 ambulatory patients were asked about their problems related to IBD. The most disturbing symptoms were frequent or loose stools, abdominal pain and rectal bleeding. Patients experienced constitutional symptoms, such as fatigue, sleeping difficulties, and problems in maintaining weight as being more disturbing than emotional problems (irritability, anger and depression) or social problems (such as the need to cancel social events, or being unable to attend leisure-time activities, work or school). Even so, social and emotional problems were still seen as noteworthy. UC patients reported less fatigue and better well-being (p<0.05) than did the CD patients (Mitchell et al 1988). Non-inflammatory joint pain, which is common in IBD, significantly impairs IBDQ and SF-36 scores (Bemklev et al 2004, Palm et al 2005).

2.7.11 Impact of therapy on HRQoL

A Spanish survey reported that HRQoL (measured by IBDQ, EQ-5D, and PGWB) was similar for CD patients in remission, irrespective of whether remission had been achieved medically or surgically. The survey also included stoma patients (Casellas et al 2000). A large European survey found that two-thirds of patients (both UC and CD) rated their quality of life after surgery as greatly improved. However, after surgery, 65% of patients reported a recurrence of symptoms, and 58% reported postoperative complications (Ghosh and Mitchell 2007). In UC patients who had undergone colectomy and IPAA surgery, HRQoL highly depended on pouch function, and the patients with poor pouch function or
pouch failure had significantly lower SF-36 scores than did those with good pouch function (Lepistö et al. 2002, Berndtsson et al. 2007). In comparison, there were no significant differences in HRQoL scores (SF-36 and IBDQ) for UC patients with IPAA or permanent ileostomy after surgery, but those with restorative proctocolectomy appeared to have a better perception on body image (Camilleri-Brennan et al. 2003).

HRQoL evaluations of most drugs used for IBD are available. Mesalazine has been shown to improve HRQoL significantly in mildly and moderately active UC (Irvine et al. 2008). The use of immunomodulators is associated with a better HRQoL, whereas the use of corticosteroids has a negative impact on HRQoL of CD patients (Blondel-Kucharski et al. 2001). Improved HRQoL, as measured by VAS and a questionnaire designed for evaluation of outcomes after surgery (Öresland et al. 1999), was observed in patients with severe UC treated successfully with intravenous cyclosporine, compared to their peers who were treated surgically (Cohen et al. 1999).

Infliximab has been shown to have a beneficial impact on HRQoL, as measured by IBDQ, and the increase is in parallel with improvements of CDAI (in CD) and Mayo (in UC) scores (Hanauer et al. 2002, Reinisch et al. 2007). With active or fistulizing CD, a rapid improvement in the IBDQ score was already evident after a single infusion of infliximab (van Balkom et al. 2002).

2.7.12 Comparison of HRQoL with the general population and with other disease groups

Examined with a general HRQoL tool (SF-36) and a VAS, patients with colonic CD in remission did not differ from the general population. In contrast, patients with active disease scored lower for all the eight domains of SF-36, and those patients who had undergone surgery had lower scores for those domains that measured general health and physical role (Andersson et al. 2003). A Swedish study found that inactive UC patients scored even better for the SF-36 dimensions of “physical function” and “bodily pain” than did the general population (Hjortswang et al. 2003). UC patients with a well-functioning IPAA had similar SF-36 scores to those of the general population (Berndtsson et al. 2007), although impaired scores for the domain that measures energy levels have also been reported (Lepistö et al. 2002).

Psychological distress and impairment of HRQoL as measured by SF-36 were similar in irritable bowel syndrome (IBS) and IBD in a referral center setting (Pace et al. 2003).

The 15D has earlier been used for IBD patients in a population-based survey that measured the impact of various chronic conditions on 15D and EQ-5D scores in a sample of citizens over 30 years of age. The respondents were matched for age, sex, income, education, marital status and other chronic conditions. The mean 15D score of IBD patients was 0.868, compared to the mean of all respondents of 0.910. Lower scores inter alia were determined for diabetes (0.833), urinary incontinence (0.835), rheumatoid arthritis (0.831), Parkinson’s disease (0.748) and macular degeneration (0.798). Patients with psoriasis (0.888), migraine (0.903), a loss of hearing (0.872) or disturbing allergy (0.894) had better scores than IBD patients (Saarni et al. 2006).
3 Aims of the study

The aims of the present study were to find answers to the following questions:

1. Do Finnish IBD patients have symptoms as frequently as other European patients, and are the arrangements of their therapy different from those of other patients in Europe? (Study I)
2. Which demographic and therapy-associated factors influence HRQoL as measured by the disease-specific IBDQ instrument? (Study II)
3. Is the generic 15D instrument useful for the evaluation of HRQoL in IBD, and do IBD patients have lower 15D scores than those of the general population sample? (Study III)
4. Do IBD patients have more comorbidities than those of the general population, and do comorbidities impair HRQoL? (Study IV)
4 Patients and methods

4.1 Patients and data collection

The study was performed in cooperation with a patient organization, the Crohn’s and Colitis Association of Finland. Most of the study patients were recruited from the patient organization member register, but an additional sample of individuals who had received special reimbursement for IBD medication, as recorded in the register of Social Insurance Institution of Finland, was recruited. The study was performed as a postal survey, by which the study questionnaire was first mailed to 3852 adult (over 18 years of age) members of the patient organization in September 2006. The study questionnaire was posted to an additional 1490 adult patients selected by random sampling from the national register in February 2008. The national register included about 30 000 individuals who were eligible for reimbursement for IBD medication. The two study populations included an overlap of the same individuals (total of 82 respondents), and for those, the latter response was included in the analysis. No reminders were sent.

4.2 Questionnaires

The study questionnaire comprised the 32-item, disease-specific IBDQ and the 15-item, generic 15D questionnaires. These were complemented by the European Federation of Crohn’s and Colitis Associations’ (EFCCA) questionnaire with 31 questions about the following: the diagnosis and history of the disease, current and previous therapies, IBD symptoms and their frequency, and the impact of the given therapy and symptoms on the experienced HRQoL. The study questionnaire also included a section that inquired about the utilization of health care services (not in the scope of this thesis). The IBDQ was used under licence from McMaster University, Hamilton, Canada, and the EFCCA gave permission to use their questionnaire. Small modifications were made to the EFCCA questionnaire (such as including additional questions about the education level of the respondents).

The IBDQ and EFCCA questionnaires were translated into Finnish and Swedish by official translators of the Helsinki University Language Services. A back-translation to English was performed to confirm the linguistic accuracy of the translation. The 15D was originally available both in Finnish and in Swedish. The questionnaire was then tested on a group of 60 IBD patients who were members of the Crohn and Colitis Association and all the questions were easily understood.

Some patients did not answer all the questions in the questionnaire. In such cases, the mean scores of IBDQ were calculated from the other items of the domain. If two or more questions per domain were unanswered, or if the total number of unanswered items
exceeded four, the patient was omitted from analyses, as the results and scores would not have been reliable. If the subject had left one to three questions of the 15D unanswered, the missing data were replaced by predictions from linear regression analysis, based on the other dimensions and using age and gender as the independent variables (www.15d-instrument.net). For the EFCCA questionnaire, percentages were calculated of those patients who had given an answer to the relevant question.

The Finnish versions of the 15D and EFCCA questionnaires are presented in Appendix A. Per the terms of the license agreement, the IBDQ questionnaire can not be published.

4.3 Control groups

In study I, the differences in the diagnosis of IBD, current and previous therapies, frequency of IBD symptoms, the impact of symptoms and given therapies between the Finnish and the European patients were compared. The European control group comprised the 5576 IBD patients who had participated in a survey conducted by EFCCA with seven of its national organizations. The participating countries were Denmark, Italy, The Netherlands, Portugal, Spain, Switzerland, and the United Kingdom (Ghosh and Mitchell 2007).

The examination of the generic 15D scores of IBD patients in study III used a general population sample obtained from the national Health 2000 Survey (for subjects ≥30 years of age) (Aromaa et al 2004) and from the Finnish National Health Survey 1995/96 (for subjects 18-29 years of age). These population samples were matched for age and sex, and served as a control group.

In study IV, two control subjects for each participant that were matched for age, gender and hospital district were chosen from the Social Insurance Institution register. The aim of study IV was to compare patients with IBD with the general population, and the reference group included patients with IBD in proportion to their prevalence in that particular population (0.7%). No HRQoL data were available for the control group.

4.4 Statistical methods

Statistical analyses were performed using SPSS for Windows versions 14.0-16.0 statistical software (SPSS Inc, Chicago, Ill., USA). In study I, Confidence Interval Analysis version 2.1.2 (CIA, Statistics with confidence; BMJ Publishing Group Ltd., London, UK) software was utilized.

The results are presented as percentages, means with standard deviations (SD), or medians. In study I, 95% confidence intervals (CI) were used. The percentages are reported as integral numbers when they exceed 10, and to one decimal place for percentages less than 10. In studies I and IV, comparisons of continuous variables
between the groups were performed by using analysis of variance (ANOVA). Moreover, ANOVA was used in study II to examine how differences in the frequency of symptoms, the level of satisfaction with current treatment, and the arrangement of therapy affected the IBDQ scores. In studies II and III, linear regression analysis served to estimate how individual demographic factors, symptoms and medications affected HRQoL scores. Linear regression was also used for studying the patient characteristics and risk factors for CHD in study IV.

In study III, the 15D scores were not normally distributed, thus differences in continuous variables were analysed by the Kruskal-Wallis test when more than two groups were present, or by the Mann Whitney U-test to examine differences between two groups. Furthermore, in study III, correlations between 15D and IBDQ scores were tested by using Pearson’s correlation coefficient whereas differences in the 15D scores between study patients and the reference population were analysed by the independent samples t-test.

In study IV, the Cox regression model was used for examining the differences in the occurrences of chronic diseases between IBD patients and their controls. The analysis was performed using a conditional logistic regression model that was technically implemented by using the Cox regression model. The matched case-control group variable was handled as a stratum, and the follow-up time within each matched case-control subject was set to 1 so that the cases and controls were at risk at the same time. Further, partial correlation with matching for age was used for estimating the impact of various chronic diseases on HRQoL scores. For categorical variables, tests were performed with the chi-square test in all studies.

Many patients reported taking several different medications. Therefore, dummy variables were used for investigating the impact of separate therapies on IBDQ scores in study II. The dummy variables comprised subjects with no medical treatment, subjects with only 5-ASA medication, subjects with immunosuppressive therapy but no biological medication or corticosteroids, subjects with biological treatment but no corticosteroids and subjects who were having corticosteroid treatment (with any other treatment) at the time of the survey. In study II, the impacts of each demographic factor and given therapy on the IBDQ score were examined by using a sequential ANOVA approach, in which the symptoms were first accounted for in the model. Thereafter, the effect of each factor in turn was evaluated based on its respective residual variability in the IBDQ score.

The study population was divided into four subgroups according to the following diagnoses: UC, CD, proctitis and indeterminate or unspecified colitis (IC). As the last two subgroups were considerably smaller than the first two, statistics were in some cases calculated only for the UC and CD groups. In study IV, statistical analyses were performed only for UC and CD groups, and patients with proctitis were included in the UC group.

A p-value of less than 0.05 was considered statistically significant.
4.5 Ethical considerations

The study protocol was approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District (registration number 94/E5/06). All participants gave their written informed consent for the HRQoL study and for the access and acquisition of their data from the Social Insurance Institution register. Non-respondents and control patients selected from earlier population-based HRQoL studies or from the Social Insurance Institution register could not be identified.
Figure 2. Flow chart of the patients in studies I-IV

Questionnaires mailed to patient association members, n=3852
- Not returned, n=1405
- Returned, n=2447
  - Invalid, n=23
    - under 18 years, n=2
    - no IBD, n=8
    - no informed consent, n=13
  - Valid for study I, n=2424
    - IBDQ filled in inadequately, n=38
    - 15D filled in inadequately, n=5
    - Responded twice, n=82

Questionnaires mailed to national register patients, n=1490
- Not returned, n=866
- Returned, n=624
  - Invalid, n=53
    - demographic questions not completed, n=5
    - 15D or IBDQ inadequately completed, n=29
    - no informed consent, n=11
    - suspicion of IBD diagnosis, n=8

Valid for study I, n=2424
- Valid for study II, n=2386
  - Valid for study III, n=2870
    - Missing or incomplete social security number, n=39
    - Valid for study IV, n=2831
5 Results

5.1 Recruited patients (I, II, III, IV)

Of the total of 5342 questionnaires mailed, 3071 (57%) were returned. Of those questionnaires sent to patient association members, 64% were returned, whereas the percentage was 42% for those mailed to patients who were selected from the Social Insurance Institution register. Of all the respondents, two were under 18 years, 16 reported or were suspected of not having IBD, and 24 had not signed the informed consent. An additional 116 subjects had omitted their social identity numbers, which made their reimbursement data unobtainable from the Social Insurance Institution, or had failed to complete either of the HRQoL questionnaires adequately for the accurate calculation of the HRQoL scores. A total of 82 patients had responded twice. For each study, all the suitable patients were included. Figure 2 shows the flow chart of the study population.

5.2 Demographic characteristics of the patients and comparison with the European study (I, III)

The results are given for the patient association cohort, as the control population in the European EFCCA study also comprised members of IBD patient associations. Differences between patient association members and patients recruited from the Social Insurance Institution register are given in Table 5.

Of the respondents with valid responses, the majority were female. The gender difference was mostly due to the female predominance among the members of Crohn and Colitis Association, for which about two-thirds are female. A predominance of females, (57%) was also observed in the European EFCCA study (Ghosh and Mitchell 2008). In the current study, the majority (53%) were diagnosed with UC, 37% with CD and the rest with proctitis or unspecified colitis. The distribution of diseases was somewhat different in the European study with 57% of patients having CD. In the European study, patients were divided into groups of CD and UC, and the smaller group of those having IC was excluded from the analyses. Demographic characteristics of the study population are shown in Table 5.
Table 5. Demographic characteristics of patients and differences between samples (studies I & III)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patient association sample</th>
<th>Social Insurance Institution sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n=2424)</td>
<td>CD (n=961)</td>
</tr>
<tr>
<td></td>
<td>(\text{CD}^*) (\text{n}=154)</td>
<td>(\text{UC}^*) (\text{n}=337)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>43.3*</td>
<td>43.7*</td>
</tr>
<tr>
<td>Median</td>
<td>42.2</td>
<td>41.9</td>
</tr>
<tr>
<td>Range</td>
<td>18-85</td>
<td>18-85</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>67.0%*</td>
<td>67.1%*</td>
</tr>
<tr>
<td>Male</td>
<td>33.0%</td>
<td>32.9%</td>
</tr>
<tr>
<td>Duration of IBD (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>9.5*</td>
<td>10.2*</td>
</tr>
<tr>
<td>Median</td>
<td>8.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Range</td>
<td>0-50</td>
<td>0-40</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>16.7%</td>
<td>17.8%</td>
</tr>
<tr>
<td>Married/common-law</td>
<td>73.5%</td>
<td>72.1%</td>
</tr>
<tr>
<td>Widowed</td>
<td>2.3%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Divorced</td>
<td>7.5%*</td>
<td>7.5%*</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comprehensive school</td>
<td>13.4%*</td>
<td>15.3%</td>
</tr>
<tr>
<td>Vocational school</td>
<td>21.5%*</td>
<td>22.9%</td>
</tr>
<tr>
<td>High school</td>
<td>10.2%</td>
<td>10.2%</td>
</tr>
<tr>
<td>College/institute</td>
<td>40.7%*</td>
<td>39.3%*</td>
</tr>
<tr>
<td>University</td>
<td>14.1%</td>
<td>12.2%</td>
</tr>
<tr>
<td>Symptoms prior to meeting specialist (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.9</td>
<td>4.0</td>
</tr>
<tr>
<td>Median</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Range</td>
<td>0-50</td>
<td>0-50</td>
</tr>
<tr>
<td>Family history of IBD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13.5%*</td>
<td>13.6%*</td>
</tr>
<tr>
<td>No/no answer</td>
<td>86.5%</td>
<td>86.4%</td>
</tr>
</tbody>
</table>

\(\text{CD} = \text{Crohn's disease}; \text{UC} = \text{ulcerative colitis}; \text{IBD} = \text{inflammatory bowel disease}\)

*indicates significant difference between the patient association and the Social Insurance Institution samples
The females were younger than the males (43 years vs. 45 years, p<0.001). The mean duration of the disease was 9.6 years (SD 7.8) and 277 (11%) had been diagnosed with IBD at least 20 years earlier. In those patients, rates of CD and UC were close to each other (48% versus 50%). The mean duration of the disease was shorter than that found in the European study, for which almost three-quarters of the patients had been diagnosed more than five years earlier. This contrasts with the current study in which only 61% had had the disease for over five years. The study population included 190 patients who had been diagnosed within a year and a majority (54%) of them had UC. At least one first-grade relative (parent, sibling or child) diagnosed with IBD was reported by 16% of CD patients and by 14% of UC patients, which was slightly more than that observed in the European survey (12% for the whole study population). UC patients had received tertiary education significantly more often than the CD patients (p=0.014). The reason for the educational difference remains unexplained, and the level of education was not explained by current activity of the disease or by the history of surgery.

The European study inquired as to whether the patients had been diagnosed by a family physician, gastroenterologist, or other type of physician. Due to the different arrangement of the health care system in Finland, in the current study the patients were asked whether they had been diagnosed by a health center physician or occupational physician, specialist (gastroenterologist, surgeon, or specialist in internal medicine), or by any other type of physician. A marked difference emerged in the way that diagnosis of IBD was made in Finland and elsewhere in Europe. In the European study three-quarters of respondents were diagnosed by a gastroenterologist, whereas the percentage in the current Finnish study for those diagnosed exclusively by a specialist was 96%. No difference in the rates could be seen for those patients diagnosed more than 20 years ago and for those diagnosed more recently. Moreover, 81% of the patients reported being currently followed-up only by a gastroenterologist and for the remaining 19%, an occupational or general physician took part in the therapy. In Europe, a quarter of patients reported at least some involvement of their family physician.

Both in the current study and in the previous European study patients reported long delays before seeing a gastroenterologist after the emergence of the first IBD symptoms. In our study, over 50% stated that they had experienced symptoms for a year or longer before meeting a specialist, and 13% had waited for over five years. For the CD group the delay was particularly long, a mean 4.0 years (median 2.0 years) and 19% reported delay of over five years.

5.2.1 Rates of surgery (I)

The rate of patients who had undergone surgery was high, 43%, for CD, and five patients had undergone 10 or more operations due to their illness. The percentage of surgery for UC was considerably lower, 12%. Rates of surgery were even higher in the European survey for both CD (58%) and UC (14%). Over a quarter of operated patients reported serious postoperative complications in both surveys. Furthermore, 4.6% of CD patients and 1.4% of UC patients had a stoma after surgery and 8.5% of UC patients had an IPAA.
The rates of surgery are shown in Table 6. Although postoperative recurrence of symptoms was reported by 67% of CD and 34% of UC patients, over 90% of CD patients and 85% of UC patients stated that their quality of life had improved in the months following surgery. Similar rates could also be seen in the European study.

Those CD patients who had undergone surgery, experienced more disturbing symptoms than did those treated conservatively. After surgery, 22% of CD patients had symptoms that greatly interfered with their leisure activities (13% in the non-surgery group, p<0.001) and 19% had symptoms that greatly affected their ability to work (11% in the non-surgery group, p<0.001). In addition, UC patients with either stoma or IPAA felt more disabled than did the patients who had not undergone surgery.

**Table 6. Rates of surgery (study I)**

<table>
<thead>
<tr>
<th></th>
<th>Crohn's disease (n=961)</th>
<th>Ulcerative colitis (n=1257)</th>
<th>Proctitis (n=121)</th>
<th>Indeterminate or unspecified colitis (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operations for IBD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>42.6%</td>
<td>12.3%</td>
<td>2.5%</td>
<td>6.0%</td>
</tr>
<tr>
<td>No/no answer</td>
<td>57.4%</td>
<td>87.7%</td>
<td>97.5%</td>
<td>94.0%</td>
</tr>
<tr>
<td>Postoperative situation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stoma</td>
<td>4.6%</td>
<td>1.4%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>IPAA</td>
<td>0.4%</td>
<td>8.5%</td>
<td>0.0%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

*IBD=inflammatory bowel disease; IPAA= ileal pouch-anal anastomosis*

**5.2.2 Symptoms and extraintestinal manifestations (I)**

The most common IBD symptoms reported were painful abdominal cramps, persistent or recurrent diarrhoea, rectal bleeding, and fatigue. Over half of the CD patients had suffered from joint pain associated with their disease. The percentage for UC was also high, 47%. In the small group of patients with proctitis, fewer than 30% reported a history of joint pain.

Comorbidity with ankylosing spondylitis was reported by 3.3% of patients, with the highest percentage being in the CD group, 5.3%. The results were similar for the European study.

**5.2.3 Frequency and impact of symptoms on daily life (I, II and III)**

Impact of the disease on daily life was notable: 37% reported suffering from disturbing symptoms weekly, as the percentage was 10% in the European study. The symptoms
greatly affected the ability to enjoy leisure activities in 17% of the patients, and in 14% of the patients they greatly affected the person’s capacity to work. In addition, many patients reported inconvenience during leisure activities (51%) or at work (45%). In the European survey, the rate of patients who experienced difficulties at work or during the pursuit of leisure activities was somewhat higher. No significant gender or age difference was seen for disease activity. Patients recruited from the patient organization and from the national register had no differences in disease activity as measured by the frequency of symptoms. CD patients with a history of surgery reported a more active disease than did those who had not undergone surgery (p=0.025) with 45% suffering from weekly IBD symptoms. Table 7 shows the rates of symptoms associated with IBD.

Table 7. Symptoms of inflammatory bowel disease (study I)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Crohn's disease (n=961)</th>
<th>Ulcerative colitis (n=1257)</th>
<th>Proctitis (n=121)</th>
<th>Indeterminate or unspecified colitis (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful abdominal cramps</td>
<td>71.3%</td>
<td>64.3%</td>
<td>52.9%</td>
<td>70.6%</td>
</tr>
<tr>
<td>Persistent or recurrent diarrhoea</td>
<td>76.5%</td>
<td>81.5%</td>
<td>60.3%</td>
<td>75.3%</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>39.8%</td>
<td>31.0%</td>
<td>17.4%</td>
<td>34.1%</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>54.6%</td>
<td>83.4%</td>
<td>82.6%</td>
<td>71.8%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>48.5%</td>
<td>44.7%</td>
<td>26.4%</td>
<td>43.5%</td>
</tr>
<tr>
<td>Fever</td>
<td>43.0%</td>
<td>30.9%</td>
<td>10.7%</td>
<td>32.9%</td>
</tr>
<tr>
<td>Joint pain</td>
<td>53.9%</td>
<td>46.5%</td>
<td>29.8%</td>
<td>54.1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>54.7%</td>
<td>51.8%</td>
<td>30.6%</td>
<td>45.9%</td>
</tr>
<tr>
<td>Skin tags</td>
<td>22.4%</td>
<td>12.8%</td>
<td>14.9%</td>
<td>12.9%</td>
</tr>
<tr>
<td>Fistulas</td>
<td>19.9%</td>
<td>3.3%</td>
<td>2.5%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Sores around the anal area</td>
<td>32.2%</td>
<td>26.2%</td>
<td>33.9%</td>
<td>28.2%</td>
</tr>
</tbody>
</table>

Adapted from: Haapamäki et al 2008

5.2.4 Current therapy (I, III)

Only 4.2% of the patients reported not taking any IBD medications at the time of the survey, compared with as many as 18% in the European study. Two-thirds reported a previous intake of corticosteroids and over one-fifth were taking corticosteroids at the time of the survey. The current use of immunomodulators was reported by 33% of all patients, as the rate for CD was significantly higher 44% (p<0.001). The numbers are higher than in the European survey, which found that 31% of CD patients and 19% of UC patients were receiving immunomodulators. At the time of the first mailing of the questionnaires (in 2006), infliximab was the only biological medical treatment indicated for IBD. A few patients reported that they were receiving adalimumab off-label. Current or previous use
of biologicals was reported by 193 patients (8.0%) in the patient association sample, and over 80% of them had CD. The percentage was lower, 3.9%, for the national register sample, mainly due to different disease distribution (CD 26%, UC 59%).

5.2.5 Patient satisfaction (I)

Despite the burden of symptoms on daily life, the great majority (93%) of patients expressed satisfaction with their current treatment and only 1.4% were very dissatisfied. Dissatisfaction was at least partly related to treatment resistant disease activity, as 60% of the very dissatisfied subjects had weekly symptoms of IBD. When asked about the impact of different therapies (steroids, immunomodulators, biologicals and surgery) on the quality of life, all therapies were associated with at least some level of increased quality of life during the months following treatment for over 70% of the patients. Those consulting a specialist during follow-up, expressed satisfaction more often with their current therapy than those being followed-up by general practitioners or occupational doctors (94% versus 89%, p=0.02).

The level of satisfaction was higher in the current study than that found in the previous European EFCCA study, in which only 76% expressed satisfaction with their current treatment.

The majority of the patients (60%) stated that their doctors had never asked about the impact of their IBD symptoms on their quality of life.

5.3 Comorbidity (IV)

Reimbursements for chronic diseases in addition to IBD were observed in 29% of the patients. On the other hand, 0.7% of the control subjects, who were matched for age, gender and hospital district, had reimbursement for IBD, a percentage that was proportional to the actual prevalence of IBD in the population (Statistical Yearbook of the Social Insurance Institution 2008).

Significant increases in frequencies of connective tissue diseases (p<0.001), asthma and chronic obstructive pulmonary diseases (p<0.001), pernicious anaemia (p<0.001) and coronary heart disease (p=0.004) were associated with IBD. No differences in the occurrence of malignant diseases were seen. Malignancies were relatively rare for both IBD patients and for the controls, with a prevalence of less than 1%. The most prevalent comorbid diseases are presented in Table 8.

Females with IBD in particular appeared to be at increased risk of CHD (1.6-fold, p=0.014) compared with their peers in the general population. The comparable CHD risk of the male IBD patients was only just significantly increased (p=0.046), but it was still over two-fold compared to the female IBD patients (1.4% versus 3.4%, p=0.043 after controlling for age). For those patients diagnosed with IBD at over 50 years of age (n=299, current mean age 64 years), the CHD prevalence was only just significantly
higher than for their peers in the general population (9.7% versus 6.0%, \( p=0.045 \)). Patients with both IBD and CHD were slightly, but non-significantly, younger than patients with only CHD (64.5 versus 66.2 years). IBD had been diagnosed earlier than CHD in 66% of the cases.

Those with the most active disease (weekly symptoms) had a higher risk of having other chronic diseases in addition to IBD, than did those patients with less active disease (\( p=0.028 \) between the groups). IBD activity was especially related to prevalence of CHD (\( p=0.030 \)), chronic cardiac insufficiency (\( p=0.030 \)), pernicious anaemia (\( p=0.022 \)), epilepsy (\( p=0.010 \)), and glaucoma (\( p=0.007 \)).

**Table 8.** The most important diseases conferring entitlement to a special refund under national health insurance

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency in controls ((n=5662))</th>
<th>Frequency in IBD patients ((n=2831))</th>
<th>Frequency in CD ((n=1054))</th>
<th>Frequency in UC (including proctitis) ((n=1661))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic cardiac insufficiency</td>
<td>0.3%</td>
<td>0.5%</td>
<td>0.4%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Connective tissue diseases, rheumatoid arthritis</td>
<td>2.0%*</td>
<td>3.9%*</td>
<td>5.4%†</td>
<td>3.0%†</td>
</tr>
<tr>
<td>Chronic asthma and obstructive pulmonary diseases</td>
<td>4.3%*</td>
<td>7.1%*</td>
<td>7.0%</td>
<td>7.3%</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>7.5%</td>
<td>8.1%</td>
<td>8.3%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Chronic coronary heart disease</td>
<td>1.4%*</td>
<td>2.2%*</td>
<td>2.2%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Chronic arrhythmias</td>
<td>0.6%</td>
<td>0.6%</td>
<td>0.6%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.6%</td>
<td>2.3%</td>
<td>1.7%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Thyroid insufficiency</td>
<td>1.7%</td>
<td>1.9%</td>
<td>1.6%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>0.2%*</td>
<td>4.1%*</td>
<td>10.3%†</td>
<td>0.3%†</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>0.2%</td>
<td>0.1%</td>
<td>0.0%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Epilepsy and comparable convulsive disorders</td>
<td>1.4%</td>
<td>1.1%</td>
<td>0.9%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Severe psychotic and other severe mental disorders</td>
<td>2.3%*</td>
<td>1.6%*</td>
<td>1.7%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>0.7%</td>
<td>0.9%</td>
<td>0.9%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Cancer or leukemia</td>
<td>0.9%</td>
<td>0.8%</td>
<td>0.9%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

*† significant difference between groups (controls/IBD patients, or CD/UC); IBD, inflammatory bowel disease; CD, Crohn’s disease; UC, ulcerative colitis
5.4 IBDQ scores (II, III, IV)

Of all the patients, 63 had filled in the IBDQ inadequately for calculating the scores, and a further 171 patients had left single IBDQ questions unanswered. The total IBDQ scores ranged from 43 to 224 in the current study, as the possible range is 32-224. The mean total score was 163 (SD 35.1). As in many earlier studies, females had significantly lower scores (161, SD 34.8) than did males (168, SD 35.5) (p<0.001), and males had higher scores for all dimensions except for social functions. However, the medians of the total scores were closer to each other, 166 in females and 168 in males. The sample taken from the patient association scored significantly worse (mean 163) than that of the national register (mean 170) (p<0.001).

Those who had been diagnosed within the last five years, scored significantly lower than those with a longer-lasting disease, and particularly low scores were seen in those who had been diagnosed during the previous year (154, SD 34.8, p<0.001). Older age also affected the scores, and patients over 50 years of age had significantly lower scores than did younger patients, 159 (SD 35.4) versus 165 (SD 34.9) (p<0.001).

There was a statistically significant difference in the scores between UC and CD, but the difference disappeared, when the groups were adjusted for disease activity.

Disease activity had a great impact on the IBDQ scores as shown in Figure 3. The mean score was 136 (SD 32.1) for patients with weekly symptoms, compared to 177 (SD 26.8) for those who suffered from IBD symptoms only occasionally (p<0.001). Satisfaction with current treatment also reflected the scores, and for those who expressed satisfaction, the mean score was 166 (SD 33.4) compared to 124 (SD 34.7) for dissatisfied subjects (p<0.001). No significant differences existed between patients who were being followed-up by specialists and those who were being followed-up by occupational doctors or general practitioners.

The history of surgery impaired IBDQ scores in this survey, and a mean IBDQ score was 158 (37.2) for those who had undergone surgery compared to 166 (SD 33.7) for non-surgical patients (p<0.001). No significant post-surgical difference between UC and CD was detected. In general, the patients with IPAA (156, SD 40.8) or stoma (153, SD 36.1) had even lower scores compared to all surgical patients.

Comorbidity with other chronic reimbursed diseases was also associated with significantly impaired IBDQ scores. As IBD patients without other chronic diseases had a mean IBDQ score of 168 (SD 34.3), those who had any other reimbursed disease scored 157 (SD 36.2) (p<0.001). Patients with hypertension, pernicious anaemia and severe mental disorders in particular had lower scores than average (p<0.001).
Figure 3. Mean 15D and Inflammatory Bowel Disease Questionnaire (IBDQ) scores and frequency of inflammatory bowel disease symptoms

Possible range is 0 to 1 for the 15D and 32 to 224 for the IBDQ. A higher score indicates better quality of life.

Figure adapted from: Haapamäki et al 2010

5.5 15D scores (III, IV)

More than three 15D questions were unanswered by five respondents who were therefore omitted from the analyses. Single questions were left unanswered by some respondents, and the total number of unanswered questions was 188. The question that considered sexual activity had been left unanswered by 64 respondents. The range of 15D scores was 0.30-1.00, with a mean of 0.87 (SD 0.097). A ceiling effect was observed as 6.2% of patients scored 1.00 (perfect health). Disease activity was strongly associated with the score even after differences in scores were adjusted for age, gender and diagnosis (p<0.001). Figure 4 shows the 15D profiles in groups of different disease activity. Gender or disease type had no significant impact on the scores but older age was related to lower scores. Both groups of newly-diagnosed patients and patients with a long-lasting disease had lower scores even after adjusting for age. After surgery, the mean score was
Figure 4. 15D profiles by frequency of inflammatory bowel disease symptoms.

Figure adapted from: Haapamäki et al 2010

significantly lower than in patients who had not had surgery, 0.85 versus 0.88 (p<0.001) and it was 0.84 for stoma patients. No significant differences emerged between patients who were being followed-up by specialists and patients who were being followed-up by occupational doctors or general practitioners. Again, patient association subjects had significantly lower scores than other patients (0.87 versus 0.88) (p=0.002).

As observed with IBDQ, comorbidity with other chronic conditions was associated with impaired 15D scores. Suffering from any other chronic reimbursed disease impaired significantly the 15D score (p<0.001). Most strikingly this was seen for hypertension, obstructive pulmonary diseases and severe mental disorders (p<0.001).

The 15D score appeared to be strongly related to the total IBDQ score (Pearson’s correlation coefficient of 0.733, p<0.001), which indicates its applicability for the measurement of HRQoL in IBD patients (Figure 3).

The age and gender-standardized population sample had significantly higher scores for all dimensions, except for speech (Figure 5). Not even the IBD patients who reported symptoms less often than monthly could achieve the 15D level of the controls (mean scores 0.902 for IBD versus 0.927 for controls). Differences in 15D scores in addition to other results between the two samples are shown in Table 9.
Figure 5. 15D profiles of the study group and of an age- and sex-standardized sample from the general population

All differences are significant except for speech (mobility, $p=0.023$; vision, $p=0.003$; eating, $p=0.032$; for other dimensions, $p<0.001$).

Figure adapted from: Haapamäki et al 2010

Table 9. Comparison of results of the patient association and of the Social Insurance Institution samples (III, IV)

<table>
<thead>
<tr>
<th></th>
<th>Patient association sample</th>
<th>Social Insurance Institution sample</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active disease (weekly symptoms)</td>
<td>37%</td>
<td>36%</td>
<td>NS</td>
</tr>
<tr>
<td>Satisfaction with current therapy</td>
<td>93%</td>
<td>92%</td>
<td>NS</td>
</tr>
<tr>
<td>Rate of surgery</td>
<td>25%</td>
<td>16%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IBDQ score</td>
<td>163</td>
<td>170</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>15D score</td>
<td>0.87</td>
<td>0.88</td>
<td>0.002</td>
</tr>
<tr>
<td>Frequency of connective tissue diseases</td>
<td>4.2%</td>
<td>2.7%</td>
<td>0.014*</td>
</tr>
<tr>
<td>Frequency of CHD</td>
<td>1.9%</td>
<td>3.4%</td>
<td>NS*</td>
</tr>
<tr>
<td>Frequency of asthma or chronic obstructive pulmonary disease</td>
<td>6.9%</td>
<td>8.0%</td>
<td>NS*</td>
</tr>
</tbody>
</table>

*IBDQ = Inflammatory Bowel Disease Questionnaire; CHD = coronary heart disease; NS = not significant; *= analyzed after controlling the groups for age
6 Discussion

6.1 Patients and methods

At the end of year 2007, the Social Insurance Institution register comprised 30,051 patients (both children and adults) who were eligible for reimbursement for IBD medication (Statistical Yearbook of the Social Insurance Institution 2008). Therefore, the study subjects represented over 9% of Finland’s IBD population. The questionnaires were mailed only once, and no reminders were subsequently sent. Nevertheless, the response rate was still 57% (63% for members of Crohn and Colitis Association), which can be considered as satisfactory.

The Social Insurance Institution register comprises mainly patients with current or earlier IBD medication, and for example UC patients who end up to colectomy very soon after the diagnosis may not have claimed for reimbursement for their IBD medication. Nonetheless, the reimbursement register can be considered as very representative of the whole IBD population.

Most of the surveyed patients were members of the patient association. The possible differences between members and non-members are not fully known, but being a member may indicate that the subject has found his/her disease problematic in some way. The patient association members had significantly lower HRQoL scores than those of the patients who were recruited from the national register, although no differences in disease activity were detected between them and the patients recruited from the national register. It should be noted, however, that the rating of disease activity was based solely on the subjective information obtained from the respondents, not on clinical or endoscopic scores. Consequently, the ‘activity of the disease’ as experienced by the respondent does not necessarily equal that of the true activity of the disease. Moreover, the division of activity into three levels according to frequency of symptoms is robust. Nevertheless, getting more specific data would have been difficult with self-administered questionnaires.

Due to confidentiality regulations, no information about the non-respondents was available. Returning of the questionnaires was optional, and it is possible that those who returned the questionnaire may have felt more disabled due to their disease, or may have been more aware of issues concerning HRQoL. Some respondents did not answer all the questions in the questionnaire. At less than 1%, the number of unanswered questions was relatively small, however.

No significant difference in the prevalence of IBD between genders has been evident in epidemiological surveys (Loftus 2004, Vind et al 2006), but due to the gender distribution of the patient association, our sample had a predominance of females. In the sample obtained from the national register, 52% of the respondents were female, which indicates no significant differences in response rates between the sexes. The study population included patients of different age groups and from different parts of the country, who lived in either a city and or in rural areas, thus the samples can be considered representative of the IBD population in Finland.
The postal survey design of the survey had its advantages and disadvantages. We reached patients from all over the country by mailing the questionnaires, and the patients were followed-up in various hospitals instead of a single or a few centers. On the other hand, the only information about the diagnoses, symptoms and therapies came from the patients themselves. The Social Insurance Institution register included systematic data on exact diagnoses for those diagnosed in 2000 and later. However, most patients appeared to be well aware of their diagnosis and a few patients who were unsure of the diagnosis were classified into the group of unspecified colitis, which was mostly not used for statistical calculations because of its small size.

The study population included 58 subjects with a stoma. In all respects, the IBDQ questionnaire is not ideal for them, as it includes questions about frequency of bowel movements and continence. Nevertheless, the views of stoma patients were still of importance, so they were included in the analyses. The IBDQ has also been used in stoma patients in other surveys (Nordin et al 2002, Camilleri-Brennan et al 2003, Watanabe et al 2006).

### 6.2 Symptoms and therapy (I, II, III)

The time from first IBD symptoms to diagnosis was strikingly long in our study, as over half of the respondents reported symptoms for a year or longer before having an examination by a specialist. The delay was especially long for CD patients, and exceeded the time intervals reported in earlier studies (Vind et al 2006). As there were a few very long reported delays, the median is probably a more informative parameter of the actual situation. It is noteworthy, that the time before diagnosis was not significantly shorter for the patients diagnosed during the past 10 years. This finding suggests that despite the new diagnostic tools and an increased number of gastroenterologists, a suspicion of CD does not always arise because of the sometimes obscure or indefinite symptoms. Many of the patients who reported long delays before meeting a gastroenterologist, at the time of the survey lived outside big cities, and sometimes in areas where only a few gastroenterologists or other specialists are available. After diagnosis, most of the patients were in the follow-up of a specialist, however. In many cases, a specialist took part in the therapy in addition to the family or occupational doctors.

As IBD is a relatively rare disease that in many cases needs immunosuppressive therapy and regular laboratory and endoscopic examinations, it is logical that specialists be involved in treatment decisions. Even so, it is unclear, whether being in the follow-up under the care of a specialist improves HRQoL. The problem in interpreting this is that patients with the most severe disease usually remain under the care of specialists, whereas patients with non-problematic disease course are usually followed-up in primary care. In an UK community based study, being under specialist care was related to lower IBDQ scores (Rubin et al 2004). In the current study, patients who were followed-up at least in part by a specialist expressed significantly more often satisfaction with their current
therapy than those who were solely followed-up by occupational or family doctors. Despite this, no differences appeared in 15D or IBDQ scores between the groups.

Differences in treatment practices of IBD exist between different countries (Odes et al 2006). Compared to the earlier European EFCCA survey, Finnish patients used 5-ASA medication more frequently than did patients in the earlier study. 5-ASA appears to have a protective effect from CRC for both UC and colonic CD (Munkholm 2003, Winther et al 2004) but it has been rated no more effective than a placebo for active ileal CD (Dignass et al 2010). In the Finnish Current Care treatment guideline published in 2005, it is stated that 5-ASA is still a standard therapy for CD, which partly explains the common use of the medication. The use of immunomodulative and biological therapy was also more common in the current study, whereas rates of surgery for the CD patients were lower. Most patients reported an improved quality of life shortly after surgery, which is indicative of successful patient selection for surgery. After the favourable situation immediately following surgery, recurrences of symptoms were common in the long run for both CD and UC patients. Maintaining postoperative remission in CD remains a challenge, even though novel therapies have reduced the rates of postoperative recurrences (Regueiro et al 2009, Dignass et al 2010, Papay et al 2010). It has been reported that after IPAA surgery, chronic pouchitis and other pouch-related problems are common and can lead to the need for permanent ileostomy in 5% of the patients (Lepistö et al 2002, Cohen et al 2005).

Differences in treatment practices of IBD in different parts of Finland have been examined, as well. The rates of surgery varied somewhat between different university hospital districts, but otherwise treatment modalities, and also patient satisfaction were found to be equal (Haapamäki et al 2010).

The burden of IBD symptoms on the lives of patients and on society as a whole is remarkable. In spite of most patients being under the care of specialists, over one-third of the patients suffered from weekly IBD symptoms and many patients stated that the symptoms affected their capacity to work. A cost-analysis was not included in our survey, but in earlier surveys, a great amount of direct (hospitalizations, medications and surgery) and indirect costs (lost workdays, restricted activity days and early retirements) have been related to IBD, and these costs are higher in those with a more active disease (Gibson et al 2007). The mean annual costs of IBD vary considerably from country to country depending on the arrangement of therapy. In a European study, mean annual costs were 1524€ for UC and 2548€ for CD (Odes et al 2006). In the US, the annual costs were higher, $8265 (≈6140€) for CD and $5066 (≈3764€) for UC in 2008, and hospitalizations, medications and outpatient care were all attributable for about one-third of the costs (Kappelman et al 2008). Novel therapies, such as biological medications, have been found to improve the HRQoL and reduce resource use (Rubenstein et al 2002, Hanauer et al 2002) at least in the short term. Maintenance therapies that last under four years have been found to be cost-effective in selected CD patients (Bodger et al 2009). The additional costs caused by using biological medications in long maintenance therapies may exceed the conventional benchmarks for affordability. The problem with these models is the lack of real-patient data and lack of data of effect of infliximab on the long-term course of IBD (Bodger 2005).
6.3 Comorbidity (I, IV)

The self-reported rate of IBD patients for ankylosing spondylitis was 22 times higher and that of rheumatoid arthritis about three times higher than the corresponding values in the general population (Kaipiainen-Seppänen et al 1997, Aho et al 1998). Furthermore, the frequency of joint pain was remarkable. In addition to the impairment of HRQoL caused by these complaints, there are other problems related to joint and axial pain associated with IBD. The therapy of joint or axial pain in IBD patients may be problematic. Although the question about whether NSAIDs cause exacerbations of IBD is still unclear, in some cases at least their gastrointestinal and other side-effects can be detrimental to IBD patients (Feagins and Cryer 2010).

According to reliable data obtained from the Social Insurance Institution register, the prevalences of connective tissue diseases, asthma and obstructive pulmonary diseases, CHD, and pernicious anaemia were significantly higher for IBD patients than for their controls. However, regarding the diagnosis of pernicious anaemia in IBD patients, many of these patients are in fact CD sufferers who have undergone ileal resections that have led to a reduction in the absorption of vitamin B12.

Females with IBD appeared to be at increased risk for CHD compared to their non-IBD counterparts. The comparable risk for CHD in IBD males was only just significantly increased, but was still more than two-fold compared to female IBD patients, which indicates the much higher overall risk for CHD in males. In the national reimbursement register, 33 035 males aged 15-64 years have CHD, whereas the number is 9968 in females of the same age (a 3.3-fold difference). The difference between the older age cohorts is much smaller (Statistical Yearbook of the Social Insurance Institution 2009). IBD may contribute to the preterm development of CHD, although in this study no significant age difference was found between patients with both IBD and CHD and those patients with CHD alone. The use of acetylsalicylic acid preparations may have induced gastrointestinal bleeding leading to the discovery of earlier unsymptomatic or quiescent IBD in those patients initially diagnosed with CHD. Long-lasting and active IBD was a risk factor for CHD in both sexes. Chronic inflammation is suspected to accelerate atherosclerosis, and increased CHD risk has also been found in other inflammatory disorders, such as in rheumatoid arthritis (Sattar et al 2003, Snow and Mikuls 2005). However, in some studies no relationship between chronic inflammation and atherosclerosis has been determined after the appropriate corrections for known risk factors (Hansson 2005, Hamirani et al 2008). It is unfortunate, that no data on the smoking habits (or on lipid values) of our study subjects were available due to nature of the study.

The accuracy of IBD diagnoses in elderly patients with CHD needs to be considered. Ischaemic colitis has been suspected to be misdiagnosed as IBD on certain occasions (Brandt 2005). In such a case, one would expect the rate of CHD to be significantly higher in those patients diagnosed with IBD in their late middle age or in old age. However, no convincing evidence of this was found in our study.
6.4 Health-related quality of life and patient satisfaction (I, II, III, IV)

Disease activity was found to be the most important factor that predicted HRQoL, as noted in earlier studies (Irvine et al 1994, Casellas et al 2002, Guthrie et al 2002, Hjortswang et al 2003). The history of surgery was also related to both generic and disease-specific lower scores, which reflected the frequent postoperative recurrence of the disease and high reported rates of postoperative complications in study patients. The observed HRQoL of IPAA and stoma patients was lower than those reported by earlier surveys (Camilleri-Brennan et al 2003, Berndtsson et al 2007). Nevertheless, one must remember that those who had no problems may have considered it unnecessary to return the questionnaire. Disease activity probably also explains the lower HRQol scores for the newly-diagnosed patients. Another study on paediatric patients showed a similar result (Otley et al 2006), whereas in some other surveys a short disease duration was not associated with impaired HRQoL (Han et al 2005).

The differences in IBDQ scores of patients who receive different medications are mostly explained by the severity of the disease. Even the most effective and modern pharmaceutical preparations can not completely prevent the negative impact of disease on HRQoL. When compared to a placebo or to other medications, most of the medications currently in use have been shown to improve HRQoL (Feagan et al 2007a, Irvine et al 2008, Bastida et al 2010).

Despite the frequency of disturbing IBD symptoms, the great majority of patients expressed satisfaction with their current treatment. More patients in the current study were satisfied with their treatment than were found the in the other European countries (Ghosh and Mitchell 2007). The separate rates for each of the seven participating countries in that study have not been published. The sociodemographic characteristics of the patients, the local health care systems, and other conditions vary within and between different European countries, which is probably the main reason for the differences. Other reasons are the variation in accessibility to treatment and also the actual differences between treatment practices among the countries. However, the level of satisfaction expressed by the patients is indicative of good treatment practices in Finland.

The fact that 60% of the patients reported that their doctor never asked them about the impact of IBD symptoms on the quality of life is striking. Health care personnel often focus on reducing the actual disease symptoms, which indeed is one of the most important aspects in improving HRQoL. However, there are other important factors of HRQoL, such as psychological problems or comorbidity with other diseases, and their impacts can be difficult to detect by only looking at the patient’s symptoms and objective medical findings.

In this survey, females reported worse disease-specific HRQoL than did males. This gender difference is a common finding in HRQoL studies, and the reason for it is mainly unresolved (Hunt and Annandale 1999, Guallar-Castillón et al 2005, Gallicchio et al 2007). Disease activity per se was not different between the sexes, but it is possible that
females experience symptoms of IBD as being more awkward and disturbing than do males.

15D appeared to be a feasible and applicable instrument for evaluating HRQoL in IBD patients. It had a ceiling effect of 6.2%, which is comparable or better than in other generic HRQoL tools. In a Finnish population sample, EQ-5D had a ceiling effect of 47% compared to 15% for 15D, which is indicative of the better discriminative power of 15D (Saarni et al 2006). 15D scores were more impaired with increasing age, which has also been reported in other 15D studies, and in studies that used other generic HRQoL instruments (Saarni et al 2006, Hopman et al 2009, Sørensen et al 2009). When compared to other studies of chronic conditions, the 15D scores of IBD patients have been similar to those of patients with epilepsy, diabetes-related complications, or anxiety (Stavem 1998, Hahl et al 2002, Pirkola et al 2009), but lower than those of patients who had undergone renal transplantation (Yildirim 2006).

6.5 Patient groups at risk of HRQoL impairment

The most striking impairment in HRQoL was seen in those patients with active, symptomatic disease. In addition, newly-diagnosed patients, many of whom were still having frequent IBD symptoms, and also older patients with increased rates of comorbid diseases had lower HRQoL scores. Perhaps surprisingly, HRQoL was impaired in patients who had undergone surgery, a feature very clearly observed in both CD patients and in UC patients after IPAA surgery. Similar to many other HRQoL studies, females in general had lower IBDQ scores than males. However, in this study, the generic 15D scores did not differ significantly between the sexes. Patients with comorbid diseases, or with extraintestinal manifestations of IBD, also had impaired HRQoL.
7 Conclusions

IBD is a chronic, relapsing disease that often occurs at a young age. It is common for IBD patients to have symptoms that affect leisure activities, work and their HRQoL. The frequency of symptoms was higher in Finnish IBD patients in this current study than in patients recruited in an earlier European study. Nevertheless, Finnish patients found their symptoms to be less disturbing, and the patients were more satisfied with their current therapy compared to the patients of the other European countries.

HRQoL has become an essential outcome of health care, though no gold standard for HRQoL exists. Generally, the use of both generic and disease-specific HRQoL instruments has been considered optimal in HRQoL assessment. In this study, both generic 15D and disease-specific IBDQ instruments were used.

Disease activity, as experienced by the patient, was the most important factor related to HRQoL. Of the demographic factors, older age, comorbid diseases, and female gender reduced the IBDQ scores. Other patient groups at risk of lower HRQoL were those with a newly-diagnosed disease and those with a history of surgery, especially after having had a stoma or an IPAA operation.

The generic 15D instrument appeared to be a feasible instrument for estimating the level of HRQoL in IBD. The 15D scores were significantly lower for IBD patients than for the general population sample. Active disease, older age and a history of surgery were associated with lower scores. IBDQ and 15D scores were strongly correlated in IBD patients, an observation that justifies the use of 15D as a fast and easily applied questionnaire for examining HRQoL of IBD patients.

The risks of many other chronic diseases, such as CHD, connective tissue diseases, asthma and chronic obstructive pulmonary diseases, were increased in IBD, and the comorbidities had a negative impact on the HRQoL. The increased prevalence of CHD in IBD encourages more efficacious management of other possible underlying cardiovascular risk factors (e.g. smoking and hypertension) and the inflammatory activity of IBD. The increased risk of preterm cardiovascular disease should be borne in mind especially in females. Furthermore, health-care personnel should be aware of the negative impact of comorbid diseases on the HRQoL of IBD patients.

HRQoL assessment helps to identify patients who need special support. With novel IBD therapies, symptoms and relapse rates of IBD are fewer for many patients. In such patients, the emphasis in examining the impact of the disease on their HRQoL should be directed at other areas in contrast to the approach that should be taken for patients with the active disease. Even when quiescent, the disease may have marked adverse impacts on the lives of the patients. Patients with an inactive disease often worry about the side-effects of medication, body-image issues, and the increased risks of surgery or of having cancer. The emphasis for patients with the inactive disease should be as much on addressing these issues than on easing individual IBD symptoms, especially in those patient groups that are prone to a low HRQoL. Correspondingly, for patients with the active disease, the main emphasis should be on ameliorating IBD symptoms and on improving various aspects of general well-being. These could be realised by therapeutic interventions to achieve improvement in both the patient’s physical condition and his or her quality of life.
Acknowledgements

This study began in 2006, and was carried out at the Division of Gastroenterology at Helsinki University Central Hospital.

I wish to express my deepest gratitude to the following:

My supervisors,
Docent Perttu Arkkila, who suggested the topic of this study and guided me into the world of science, and Professor Martti Färkkilä who made my specialization in gastroenterology possible and whose encouragement and support have been invaluable during this process. I have been privileged to have supervisors like them.

Docent Seppo Niemelä and Docent Kari Puolakka, the official reviewers of this thesis, for their valuable advice and constructive criticism concerning final manuscript.

Docent Risto P. Roine for his practical help and rapid responses to my numerous questions, and my dear colleague and co-author MD Ulla Turunen for her support and contribution during this process.

Professor Harri Sintonen for allowing me to use the 15D and for making the calculations for general population comparisons.

The great people in the Crohn and Colitis Association of Finland for helping in the recruitment of patients for this study.

My colleagues in our clinic for support and interest in this work. I especially want to thank Pauliina Molander, MD, Henna Rautiainen, MD, PhD, and Taina Sipponen, MD, PhD, for their help and friendship. I also want to thank all my other friends for their support and encouragement during this work.

My warm thanks also go to

Professor Pasi Korhonen for his excellent statistical advice.

Alisdair Mclean, PhD, Carol Norris, PhD, and Carol-Ann Pelli, BSc(Hons), for reviewing the language of my articles and thesis.

Special thanks go to

My parents, my grandmother and my brother Mikko for all the help and love they have shown to me during my life. Without their support this work would not have been possible.
And most of all, to my dear children Aino and Veikko for bringing love and happiness to my life. Thank you for your understanding and patience during the periods of intensive research work.

I wish to express my thanks to everyone who has contributed in one way or another, also to those who are not separately mentioned.

This work was supported by Schering Plough Corporation and by the Finnish Foundation for Gastroenterological Research.

Helsinki, February 2011,

Johanna Haapamäki
References


Leighton JA, Legnani P, Seidman EG. Role of capsule endoscopy in inflammatory bowel disease: where we are and where we are going. Inflamm Bowel Dis 2007;13:331-337.


Mayer L. Evolving paradigms in the pathogenesis of IBD. J Gastroenterol 2010;45:9-16.


Palm Ø, Bernklev T, Moum B, Gran JT. Non-inflammatory joint pain in patients with inflammatory bowel disease is prevalent and has a significant impact on health-related quality of life. J Rheumatol 2005;32:1755-1759.


inflammatory intestinal disorders and identifying their anatomical location within the bowel. Aliment Pharmacol Ther 2003;18:1009-1016.


Prefontaine E, MacDonald JK, Sutherland LR. Azathioprine or 6-mercaptopurine for induction of remission in Crohn’s disease. Cochrane Database of Systematic Reviews 2010, Issue 6, Art No.: CD000545.


### Terveyteen liittyvän elämänlaadun kyselylomake (15d⁰)

Lukea ensin läpi huolellisesti kunkin kysymyksen kaikki vastausvaihtoehtot. Merkitä sitten rasti (x) sen vaihtoehdon kohdalle, joka parhaiten kuvaa nykyistä terveydentilaanne. On tärkeää, että vastaatte kaikkiin 15 kysymykseen rastittamalla kustakin yhden vaihtoehdon.

### 1. Liikuntakyky

1. Pystyn kävelemään normaalisti (vaikeuksitta) sisällä, ulkona ja portaissa.
2. Pystyn kävelemään vaikeuksitta sisällä, mutta ulkona ja/tai portaissa on pieniä vaikeuksia.
3. Pystyn kävelemään ilman apua sisällä (apuvälisein tai ilman), mutta ulkona ja/tai portaissa melkoisin vaikeuksin tai toisen avustamana.
4. Pystyn kävelemään sisälläkin vain toisen avustamana.
5. Olen täysin liikuntakyvytön ja vuoteenoma.

### 2. Näkö

1. Näen normaalisti eli näen lukea lehteä ja TV:n tekstejä vaikeuksitta (silmälaseilla tai ilman).
2. näen lukea lehteitä ja/tai TV:n tekstejä pienin vaikeuksin (silmälaseilla tai ilman).
3. Näen lukea lehteitä ja/tai TV:n tekstejä huomattavin vaikeuksin (silmälaseilla tai ilman).
4. En näe lukea lehteää enkä TV:n tekstejää ilman silmälaseja tai niiden kanssa, mutta näen kulkia ilman opasta.
5. En näe kulkia oppaatta eli olen lähes tai täysin sokea.

### 3. Kuulo

1. Kuulen normaalisti eli kuulen hyvin normaalia puheääntä (kuulokojella tai ilman).
2. Kuulen normaalia puheääntä pienin vaikeuksin.
3. Minun on melko vaikea kuulla normaalia puheääntä, keskusteluissa on käytettävä normaalia kovempaa puheääntä.
4. Kuulen kovaakin puheääntä heikosti; olen melkein kuuro.
5. Olen täysin kuuro.

### 4. Hengitys

1. Pystyn hengittämään normaalisti eli minulla ei ole hengenahdistusta eikä muita hengitys-vaikeuksia.
2. Minulla on hengenahdistusta raskaassa työssä tai urheilussa, reippaassa kävelyssä tasamaalla tai lievässä ylimäessä.
3. Minulla on hengenahdistusta, kun kävelen tasamaalla samaa vauhtia kuin muut ikäiseni.
4. Minulla on hengenahdistusta pienenkin rasituksen jälkeen, esim. peseytyessä tai pukeutuessa.
5. Minulla on hengenahdistusta lähes koko ajan, myös levossa.
5. **Nukkuminen**

1. Nukun normaalisti eli minulla ei ole mitään ongelmia unen suhteen. □
2. Minulla on lievä uniongelmia, esim. nukahtamisvaikeuksia tai satunnaisia yöheräilyä. □
3. Minulla on melanopsia uniongelmia, esim. nukun levottomasti tai un ei tunnu riittävältä. □
4. Minulla on suuria uniongelmia, esim. joudun käyttämään usein tai säännöllisesti unilääkettä, herään säännöllisesti yöllä ja/tai aamuisin liian varhain. □
5. Käräin vaikeasta unettomuudesta, esim. unilääkkeiden runsaasta käytöstä huolimatta nukkuminen on lähes mahdotonta, valvon suurimman osan yöstä. □

6. **Syöminen**

1. Pystyn syömään normaalisti eli itse ilman mitään vaikeuksia. □
2. Pystyn syömään itse pienin vaikeuksin (esim. hitaasti, kõmpeästi, vavisten tai erityisapuneuvoin). □
3. Tarvitsen hieman toisen apunäytöksessä. □
4. En pysty syömään itse lainkaan, vaan minua pitää syöttää. □
5. En pysty syömään itse lainkaan, vaan minulle pitää antaa ravintoa letkun avulla tai suonensisäisesti. □

7. **Puhuminen**

1. Pystyn puhumaan normaalisti eli selvästi, kuuluvasti ja sujuvasti. □
2. Puhuminen tuottaa minulle pieniä vaikeuksia, esim. sanoja on etsittävä tai ääni ei ole riittävän kuuluvaa tai se vaihtaa korkeutta. □
3. Pystyn puhumaan ymmärrettävästi, mutta katkonesi, ääni vavisten, sammaltaen tai äntyttäen. □
4. Muilla on vaikeuksia ymmärtää puhettani. □
5. Pystyn ilmaisemaan itseäni vain elein. □

8. **Erittystoiminta**

1. Virsarakon ja suoliston toimivat normaalisti ja ongelmittaa. □
2. Virsarakon ja/tai suoliston toiminnassa on lievä ongelmia, esim. minulla on virtsaamisvaikeuksia tai kova tai löysä vatsa. □
3. Virsarakon ja/tai suoliston toiminnassa on melkoisia ongelmia, esim. minulla on satunnaisia virtsanpäätysvaikeuksia tai vaikea ummetus tai ripuli. □
4. Virsarakon ja/tai suoliston toiminnassa on suuria ongelmia, esim. minulla on säännöllisesti ”vahinkojen” tai peräruiskojen tai katetroinnin tarvetta. □
5. En hallitse lainkaan virtsaamista ja/tai ulostamista. □

9. **Tavanomaiset toiminnat**

1. Pystyn suoriutumaan normaalisti tavanomaisista toiminnosta (esim. ansiotyy, opiskelu, kotityö, vapaa-ajan toiminnat). □
2. Pystyn suoriutumaan tavanomaisista toiminnosta hieman alentuneella teholla tai pienin vaikeuksin. □
3. Pystyn suoriutumaan tavanomaisista toiminnosta huomattavasti alentuneella teholla tai huomattavin vaikeuksin tai vain osaksi. □
4. Pystyn suoriutumaan tavanomaisista toiminnosta vain pieneltä osin. □
5. En pystyn suoriutumaan lainkaan tavanomaisista toiminnosta. □

10. **Henkinen toiminta**

1. Pystyn ajattelemaan selkeästi ja johdonmukaisesti ja muistin toimii täysin moitteettomasti. □
11. Vaivat ja oireet

1 Minulla ei ole mitään vaivoja tai oireita, esim. kipua, särkyä, pahoinvointia, kutinaa jne. □
2 Minulla on lievä vaivoja tai oireita, esim. lievää kipua, särkyä, pahoinvointia, kutinaa jne. □
3 Minulla on melkoisia vaivoja tai oireita, esim. melkoista kipua, särkyä, pahoinvointia, kutinaa jne. □
4 Minulla on voimakkaita vaivoja tai oireita, esim. voimakasta kipua, särkyä, pahoinvointia, kutinaa jne. □
5 Minulla on sietämättömiä vaivoja ja oireita, esim. sietämätöntä kipua, särkyä, pahoinvointia, kutinaa jne. □

12. Masentuneisuus

1 En tunne itseäni lainkaan surulliseksi, alakuloiseksi tai masentuneeksi. □
2 Tunnen itseäni hieman surulliseksi, alakuloiseksi tai masentuneeksi. □
3 Tunnen itseäni melko surulliseksi, alakuloiseksi tai masentuneeksi. □
4 Tunnen itseäni erittäin surulliseksi, alakuloiseksi tai masentuneeksi. □
5 Tunnen itseäni äärimmäisen surulliseksi, alakuloiseksi tai masentuneeksi. □

13. Ahdistuneisuus

1 En tunne itseäni lainkaan ahdistuneeksi, jännittyneeksi tai hermustuneeksi. □
2 Tunnen itseäni hieman ahdistuneeksi, jännittyneeksi tai hermostuneeksi. □
3 Tunnen itseäni melko ahdistuneeksi, jännittyneeksi tai hermostuneeksi. □
4 Tunnen itseäni erittäin ahdistuneeksi, jännittyneeksi tai hermostuneeksi. □
5 Tunnen itseäni äärimmäisen ahdistuneeksi, jännittyneeksi tai hermostuneeksi. □

14. Energisyys

1 Tunnen itseäni terveeksi ja elinvoinnialueeksi. □
2 Tunnen itseäni hieman uupuneeksi, väsyneeksi tai voimattomaksi. □
3 Tunnen itseäni melko uupuneeksi, väsyneeksi tai voimattomaksi. □
4 Tunnen itseäni erittäin uupuneeksi, väsyneeksi tai voimattomaksi, lähes ”loppuun palaneeksi”. □
5 Tunnen itseäni äärimmäisen uupuneeksi, väsyneeksi tai voimattomaksi, täysin ”loppuun palaneeksi”. □

15. Sukupuolielämä

1 Terveydentilani ei vaikuta mitään sukupuolielämää. □
2 Terveydentilani vaikuttaa hieman sukupuolielämää. □
3 Terveydentilani vaikuttaa huomattavasti sukupuolielämää. □
4 Terveydentilani tekee sukupuolielämän lähes mahdottomaksi. □
5 Terveydentilani tekee sukupuolielämän mahdottomaksi. □

15D©/Harri Sintonen
**EFCCA Survey Questionnaire**

(EFCCA = European Federation of Crohn's and Ulcerative Colitis Association)

Kyselyä on modifioitu Suomen oloihin sopivaksi.

**Merkitä rastilla vastauksenne kussakin kohdassa olevaan ruutuun.**

### Henkilön tietoihin ja sairaushistoriaan liittyvät kysymykset

1. **Sukupuoli**
   - a) Mies □
   - b) Nainen □

2. **a) Siviilisääty**
   - Naimaton □
   - Naimisissa □
   - Avoliitossa □
   - Leski □
   - Eronnut tai asumuserossa □

2. **b) Mikä on koulutuksen (korkein loppuun suoritettu koulutus) peruskoulu tai vähemmän**
   - Lukio □
   - Opistotasoinen koulutus □
   - Ammattikorkeakoulu □
   - Yliopisto □

2. **c) Minkäläista työaikaa noudatatte saannollinen päivätyö □**
   - 2-vuorotyö □
   - 3-vuorotyö □
   - Yötyö □
   - Muu epäsäännöllinen työ □
   - Osa-aikatyö □
   - En ole töissä □

2. **d) Jos olette eläkkeellä, onko eläkkeen peruste**
   - Suolistosairaus □
   - Muu sairaus □
   - Muu syy, esim. ikä □

3. **Äidinkieli**
   - a) Suomi □
   - b) Ruotsi □

4. **Jokin muu, mikä □**

4. **Onko Teillä diagnosoitu?**
   - a) Crohnin tauti □
   - b) Haavainen paksusuolen tulehdus eli ulceratiivinen koliitti □
   - c) Vain peräsuo oleva haavainen paksusuolen tulehdus (proktiitti) □
   - d) Välitmuotoinen (indeterminate) koliitti □
   - e) Ei mikään näistä □

5. **Muu tulehdus sairaus suolistosairaus**
   - a) Mikroskooppinen koliitti (lymfos-täärinen tai kollageenikoliitti) □
   - b) Jokin muu tulehdus sairaus suolistosairaus, mikä □
   - c) Ei mitään tulehdus sairaus suolistosairautta □

*(Jos olette vastannut kohti 4–5 Ei, Teidän ei tarvitse jatkaa tämän kyselyn täyttöä.)*

6. **Onko yhteys, jota olette tuntenut myös siltä, että Teidän on tehty diagnoosi Crohcin tauti tai haavainen paksusuolen tulehdus?**
   - a) Kyllä □
   - b) Ei □

7. **Mikä alan lääkäri diagnoosi Teillä Crohnin tautia tai haavainen paksusuolen tulehdusen?**
   - a) Terveyskeskus- tai työterveyslääkäri □
   - b) Erikoislääkäri tai sairaalalääkäri (sisä- tai lautalääkäri, gastroenterologi tai kirurgi) □
   - c) Muu lääkäri □
   a) Terveyskeskus- tai työterveyslääkäri [1]
   b) Erikoislääkäri tai sairaalalääkäri (sisätäululääkäri, gastroenterologi tai kirurgi) [2]
   c) Muu lääkäri [3]

10. Jos vastauksenne edellisessä oli “Erikoislääkäri (sisätäululääkäri, gastroenterologi tai kirurgi)”, kuinka monta vuotta Teillä oli oireita ennen kuin tapasitte erikoislääkärin? ________ vuotta

11. Onko Teillä diagnosoiotto jokin seuraavista sairauksista?
   a) Nivelreuma [1]
   b) Selkärankareuma [2]
   c) Psoriasis [3]
   d) Psoriasiseen liittyvä nivelvaiva [4]
   e) Silmän värilkalvon tulehdus tai vastaava [5]

**Hoito**

   a) Solunsalpaajahoito (Azamun®, Imurel®, Merkaptopurin®, Trexan®).
      Hoidon kesto vuosina [1]
   b) Kortisoni (Prednison®, Prednisolon®, Medrol®, Entocort®)
      Hoidon kesto vuosina [2]
   c) 5-aminosaliksylaattti (5-ASA)
      (Asacol®©, Pentasa®, Dipentum®, Salazopyrin®)
      Hoidon kesto vuosina [3]
   d) Antibiootit (Trikozol®, Flagyl®, Ciprofloxac®)
      Hoidon kesto vuosina [4]

   a) Solunsalpaajahoito (Azamun®, Imurel®, Merkaptopurin®, Trexan®).
      Hoidon kesto vuosina [1]
   b) Kortisoni (Prednison®, Prednisolon®, Medrol®, Entocort®)
      Hoidon kesto vuosina [2]
   c) 5-aminosaliksylaattti (5-ASA)
      (Asacol®, Pentasa®, Dipentum®, Salazopyrin®)
      Hoidon kesto vuosina [3]
   d) Antibiootit (Trikozol®, Flagyl®, Ciprofloxac®, Zeclar®)
      Hoidon kesto vuosina [4]
   e) Siklosporiini (Sandimmun Neoral®, Hoidon kesto vuosina [5]
   f) Biologiset lääkkeet (Remicade®, Hoidon kesto vuosina [6]
   g) Leikkaushoito [7]
   h) Adacolumn® hoito [8]
   i) En tiedä mitä hoitoja olen saanut [9]
   j) Toistaiseksi ei ole ollut käytössä hoitoja [10]
   k) Paikallishoitovalmisteet (peräpuikot, peräruiskeet) [11]
   l) Muu lääke tai hoito suolistosairautenne [12]

4 5 6 7 8 9 10 11 12
14. Jos vastasitte edellisten kysymysten kohtiin 12 f) ja 13 f) kyllä, minkälainen vaikutus hoidolla oli elämänlaatuunne hoitoa seuraavien kuukausien aikana?
   a) Elämänlaatu parantui selvästi □ 1
   b) Elämänlaatu parantui jonkin verran □ 2
   c) Elämänlaatu ei parantanut □ 3
   d) Elämänlaatu huononi □ 4

15. Jos vastasitte kortisonihoitoa koskeviin kysymyksiin 12 b) ja 13 b) kyllä, minkälainen vaikutus hoidolla oli elämänlaatuunne hoitoa seuraavien kuukausien aikana?
   a) Elämänlaatu parantui selvästi □ 1
   b) Elämänlaatu parantui jonkin verran □ 2
   c) Elämänlaatu ei parantanut □ 3
   d) Elämänlaatu huononi □ 4

16. Jos vastasitte solunsalpaajahoitoa koskeviin kysymyksiin 12 a) ja 13 a) kyllä, minkälainen vaikutus hoidolla oli elämänlaatuunne hoitoa seuraavien kuukausien aikana?
   a) Elämänlaatu parantui selvästi □ 1
   b) Elämänlaatu parantui jonkin verran □ 2
   c) Elämänlaatu ei parantanut □ 3
   d) Elämänlaatu huononi □ 4

17. Oletteko tyttäväinen tämän hetkiseen hoitoonne?
   a) Hyvin tyttäväinen □ 1
   b) Melko tyttäväinen □ 2
   c) Melko tyttymätön □ 3
   d) Hyvin tyttymätön □ 4

18. Onko Teille tehty leikkuuksia liittyen Crohnnin tautiin tai haavaiseen paksunsumoisen tulehdukseen?
   a) Kyllä □ 1
       Kuinka monta____________________
   b) Ei (siirtykää kysymyseen 22) □ 2

19. Jos vastasitte edelliseen kysymykseen 18 kyllä, kuinka määritelisitte leikkaus- hoidon vaikutuksen elämänlaatuunne leikkausta seuraavien kuukausien aikana?
   a) Elämänlaatu parantui selvästi
   b) Elämänlaatu parantui jonkin verran
   c) Elämänlaatu ei parantanut
   d) Elämänlaatu huononi

20. Jos vastasitte kysymykseen 18 kyllä, ovatko taudin oireet uusineet Teillä leikkauskseen jälkeen?
   a) Kyllä □ 1
   b) Ei □ 2

21. Jos vastasitte kysymykseen 18 kyllä, onko Teillä ollut leikkauskseen jälkeisiä vakavia komplikaatioita?
   a) Kyllä □ 1
   b) Ei □ 2

22. Mikäli jatkossa Teille harkitaan leikkaushoitoa Crohnnin taudin tai haavaiseen paksunsumoisen tulehdukseen vuoksi, olisitteko haluska kokeilemaan uuden tyypistä lääkehoitoa leikkaushoidon vaihtoehtona?
   a) Kyllä □ 1
   b) Ei □ 2

23. Onko lääkärinne ottanut esille Crohnin taudin tai haavaisessa paksunsumoisen tulehdukseen hoidossa käytettävät uudet hoidot?
   a) Kyllä □ 1
   b) Ei □ 2

Oireiden vaikutus elämänlaatuun

24. Mitä seuraavista oireista Teillä on esiintynyt liittyen Crohnnin tautiin tai haavaiseen paksunsumoisen tulehdukseen? Merkattakaa kaikki sopivat vaihtoehdot.
   a) Kivuliaat vatsak rampit □ 1
   b) Pysyvä tai toistuva ripuli □ 2
   c) Ruokahaluttomuus □ 3
   d) Verentulo peräsuolesta □ 4
   e) Painon putoaminen □ 5
   f) Kuume □ 6
   g) Nivelkipu □ 7
h) heikotus
i) peräaukon suulla ihokielekkeet eli skin tagit
j) avanne eli määräkäytävä (fisteli)
k) haavauma peräaukon seudussa

25. Kuinka usein Teillä esiintyy häiritseviä oireita?
   a) Viikottain
   b) Kuukausittain
   c) Muutaman kuukauden välein

26. Kuinka paljon oireet häiritsevät vapaa-ajan toimintaanne tai aktiviteettejanne (esim. matkustamista, ruokailua, urheilua)?
   a) Merkittävästi
   b) Jonkin verran
   c) Eivät lainkaan

27. Kuinka paljon oireet vaikuttavat työntekoonne?
   a) Merkittävästi
   b) Jonkin verran
   c) Eivät lainkaan

29. Oatteko oireiden vaikutuksen elämänlaatuunne esille käydessänne lääkärissä?
   a) Kyllä
   b) Ei

30. Kysykö lääkärinne oireiden vaikutusta elämänlaatuunne?
   a) Kyllä
   b) Ei (voitte siirtyä tämän sivun lopun)

31. Jos vastasitte edelliseen kysymyksen 30 kyllä, onko lääkärinne tehnyt muutoksia hoitoonne vähentääkseen oireiden vaikutusta elämänlaatuunne?
   a) Kyllä
   b) Ei
1. Kuinka monta kertaa viimeisen vuoden aikana olette käynyt vatsaaviojen takia terveyskeskulääkärin vastaanotolla? ______ kerta

2. Kuinka monta kertaa viimeisen vuoden aikana olette käynyt vatsaaviojen takia työterveyslääkärin vastaanotolla? ______ kerta

3. Kuinka monta kertaa viimeisen vuoden aikana olette käynyt vatsaaviojen takia sairaalan ajanvarauspoliklinikalla (sisätäntien tai kirurgian poliklinikalla)? ______ kerta

4. Kuinka monta kertaa viimeisen vuoden aikana olette käynyt vatsaaviojen takia sairaalan päivystyspoliklinikalla (ensiapupoliiklinikalla)? ______ kerta

5. Kuinka monta kertaa viimeisen vuoden aikana olette käynyt vatsaaviojen takia yksityislääkärin vastaanotolla? (Tässä ei tarkoiteta käyntejä yksityisellä lääkäriasiemalla työterveyslääkärin luona) ______ kerta

6. Kuinka monta päivää olette ollut vatsaaviojen vuoksi sairaalahoidossa viimeksi kuluneen vuoden aikana yhteensä ______ päivää

7. Kuinka monta kertaa viimeisen vuoden aikana olette ollut vatsaaviojen vuoksi yhteydessä puhelemitse sairaanhoitajan tai lääkärin? ______ kerta

8. Kuinka monta kertaa viimeisen vuoden aikana olette käynyt lääkärin vastaanotolla muiden syiden kuin vatsaaviojen vuoksi? ______ kerta

9. Kuinka usein viimeksi kuluneen 3 kuukauden aikana vatsaaviojeen ovat haitanneet Teidän työntekoanneen töissä ollessanne?
   • Ei ollenkaan □
   • Harvemmin kuin 2 päivänä kuukaudessa □
   • 2–3 päivänä kuukaudessa □
   • 1–2 päivänä viikossa □
   • 3 päivänä viikossa tai useammin □
   • En ole ollut töissä viimeisten 3 kuukauden aikana □

10. Kuinka monta päivää olette ollut vatsaaviojen takia poissa töistä viimeisen vuoden aikana? ______ (päivää)
    ______ (X, jos ette ole olleet työelämässä viimeisen vuoden aikana)

11. Kuinka monta kertaa Teille on tehty vatsaaviojen vuoksi seuraavia tutkimuksia viimeisen vuoden aikana?
   • Paksusuolen tähystys? ______ kerta
   • Paksusuolen röntgenkuvaus? ______ kerta
   • Mahalaakun tähystys? ______ kerta
   • Vatsan alueen ultraäänitutkimus? ______ kerta
   • Vatsan alueen tietokonotomografikuvaukset? ______ kerta
   • Vatsan alueen magneettikuvaukset? ______ kerta

Kiitos vaivannäöstänne.