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Crohn's Disease in Sickness and in Health

Studies of Health Assessment Strategies and
Impact on Health-Related Quality of Life

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”Fundera flitigt. Försök förstå.”

Ur Alfabetets Användning Anar Aporna Aldrig – en ABC-bok av Alf Henriksson

Dedicated to those who suffer from Crohn's disease

ABSTRACT

Background and aims. Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) with potentially deleterious effects on well-being and daily-life functioning. A complete picture of health status in CD therefore comprises both disease activity (DA) and health-related quality of life (HRQL). Several measures of DA and HRQL in CD have been developed. Some have gained prominence as standard endpoints in clinical trials, but none has been validated in Swedish CD patients and their use in clinical practice has been limited. A conceptual health status model of five dimensions (Biological variables, Symptoms, Function, Worries, and Well-being) has been proposed for IBD health assessment, enabling the construction of the Short Health Scale (SHS), a four-item questionnaire intended to facilitate assessment and interpretation of HRQL in IBD.

The aims of this thesis were: (1) to evaluate the Swedish versions of the Inflammatory Bowel Disease Questionnaire (IBDQ) and the Rating Form of IBD Patient Concerns (RFIPC); (2) to evaluate the Short Health Scale; (3) to study the relationship between DA and HRQL variables by identifying determinants of DA outcome and by validating the SHS health status model; (4) to describe the spectrum of disease-related worries and repercussions on general HRQL in a context of social variables, sickness, and disability.

Methods. The thesis is based on clinical variables and HRQL data measured in a population-based cohort of 505 CD patients, consecutively included in conjunction with their regular outpatient visits at three hospitals (Jönköping, Örebro, Linköping). The HRQL questionnaires were evaluated regarding construct validity, reliability, and responsiveness. Multivariate analyses were used to investigate the relationship between Crohn's Disease Activity Index (CDAI) and physician-assessed DA. The SHS health status model was validated with structural equation modelling (SEM). Disease-related worries and concerns, general HRQL, social variables, sickness, and work disability were compared with data from background population or patients with ulcerative colitis (UC).

Results. The IBDQ had good validity, reliability, and responsiveness, but the original dimensional structure was not supported. The RFIPC was valid, and reliable, but less sensitive to change in disease activity. The SHS had the highest completion rate and proved adequate psychometric properties. The CDAI correlated weakly with the physician's appraisal of disease activity, being more influenced by subjective health perception than objective disease activity. SEM showed that the SHS model had a good fit to measured data, explaining >98% of the covariance of the variables. Worries and general HRQL impairment were greater in CD than in UC, especially for women. Disease complications and impaired life achievements elicited most worries. CD patients had lower educational level. Female patients were more often living single. The rates of long-term sickness and disability were doubled compared with background population, with worse outcome for women.

Conclusions. The IBDQ, the RFIPC, and the SHS all demonstrated adequate psychometric properties. The SHS was easier to administer and provided a more comprehensive picture of subjective health status. The weak correlation between CDAI and physician-assessed DA was explained by a strong influence of subjective variables on CDAI, stressing the importance of assessing DA and HRQL separately. The SHS health status model was further supported by SEM. CD has tangible effects on subjective health perception, worries and work capacity, especially for women.

LIST OF PAPERS

- I. Stjernman H, Grännö C, Ockander L, Blomberg B, Järnerot G, Tysk C, Almer S, Bodemar G, Ström M, Hjortswang H. Evaluation of the Inflammatory Bowel Disease Questionnaire in Swedish patients with Crohn's disease. *Scand J Gastroenterol* 2006;41(8):934-43
- II. Stjernman H, Tysk C, Almer S, Ström M, Hjortswang H. Worries and concerns in a large unselected cohort of Crohn's disease patients. *Scand J Gastroenterol* 2010;45(6):696-706
- III. Stjernman H, Blomberg B, Järnerot G, Tysk C, Ström M, Hjortswang H. Short health scale: a valid, reliable, and responsive instrument for subjective health assessment in Crohn's disease. *Inflamm Bowel Dis* 2008;14(1):47-52
- IV. Stjernman H, Tysk C, Almer S, Ström M, Hjortswang H. Factors predicting the outcome of disease activity assessment in Crohn's disease. *Inflamm Bowel Dis* 2009;15(12):1859-66
- V. Stjernman H, Svensson E, Hjortswang H. Structural equation modelling of the relationship between disease activity and health-related quality of life variables in Crohn's disease. Submitted for publ.
- VI. Stjernman H, Tysk C, Almer S, Ström M, Hjortswang H. Unfavourable outcome for women in a study of health-related quality of life, social factors, and work disability in Crohn's disease. Submitted for publ.

ABBREVIATIONS

CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
CFA	Confirmatory factor analysis
CRP	C-reactive protein
EIM	Extraintestinal manifestation
GI	Gastrointestinal
Hb	Haemoglobin
HBI	Harvey-Bradshaw Index
HRQL	Health-related quality of life
IBD	Inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
LCS	Living Conditions Survey
MCS	Mental Component Summary
NSAIDs	Non-steroidal anti-inflammatory drugs
PCS	Physical Component Summary
PGA	Physician's global assessment of disease activity
PGWB	Psychological General Well-being
RFIPC	Rating Form of IBD Patient Concerns
SEM	Structural equation modelling
SES-CD	Simple Endoscopic Score for CD
SF-36	Short Form -36
SHS	Short Health Scale
TNF	Tumour Necrosis Factor
UC	Ulcerative colitis
VAS	Visual Analogue Scale
VHI	Van Hees Index

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INTRODUCTION

Crohn's disease

Historical background

In 1929, a 17-year old boy, durably suffering from abdominal pain, fever, and diarrhoea, was admitted to Mt Sinai Hospital in New York. The doctor in charge, an experienced gastroenterologist by the name of Burill B. Crohn, noticed a tender palpable mass in the patient's lower right abdominal quadrant. He suspected intestinal tuberculosis, a fairly common explanation for a clinical picture like this in the overcrowded and socially deprived city of New York, on the cusp of the Great Depression. (Crohn later recalled a Medical School professor who skipped the chapter about the small intestine in a lecture "since there are no recognized diseases of the small intestine, except tuberculosis.") Four hospital admissions later, and after several fruitless treatments with intra-peritoneal oxygen insufflation, the poor boy had succumbed into such a state that desperate and dangerous measures had to be taken. A bowel resection was performed and the young man luckily survived the ordeal. However, Crohn could not find any tubercle bacilli when he subsequently perused the resected specimen under the microscope. Instead he wrote in the young man's journal: "terminal ileitis". By then, he and his colleagues had experienced several other cases with similar clinical and histological findings of necrotic and cicatrizing inflammation confined to the terminal part of the ileum, sometimes associated with stenosis and fistula formation, but always devoid of tubercle bacilli. These features differed noticeably from the only known non-infectious inflammatory bowel disease, ulcerative colitis, though a few similar case reports had been published (Dalziel 1913, Tietze 1920). In 1932, he submitted the landmark paper in collaboration with Leon Ginzburg and Gordon Oppenheimer, describing 14 cases of this new disease entity (Crohn et al. 1932). Within a year, a new eponym was born, Crohn's disease, gradually replacing the original term along with the growing acknowledgement that the disease also could affect the large bowel, as well as any part of the gastrointestinal tract (Baron 2000, Janowitz et al. 2003).

Diagnosis

Crohn's disease (CD) has a heterogeneous appearance and the diagnosis relies on a combination of clinical features and multimodal investigational findings and the exclusion of other causes such as infection or malignancy (Lennard-Jones 1989). The most common symptoms, typically insidious in onset, are chronic diarrhoea and abdominal pain, often accompanied by systemic symptoms like fatigue and weight loss (Travis et al. 2006). Symptoms from other organ systems (joints, skin, or eyes) may also occur (see below). Complications from ulcerations and strictures can result in abdominal or perianal fistulous tracts and abscesses, gastrointestinal (GI) bleeding, or intestinal obstruction. Typical macroscopic findings at endoscopy or radiology are discontinuous lesions of aphthoid or deep linear mucosal ulcers, cobblestone formation of mucosa, thickened bowel wall and luminal narrowing. Microscopic investigations may reveal a focal deep inflammation, crypt irregularities, and submucosal fibrosis,

sometimes with the pathognomonic finding of epithelioid cell granuloma in lamina propria (Riddell 2000). Although diagnostic criteria have been stipulated and serological and molecular tools are emerging, the current view is that the diagnosis rests on a judgemental assembly of the clinical picture. In 5-10% of newly diagnosed inflammatory bowel disease (IBD) restricted to colon, reliable distinction between CD and ulcerative colitis cannot be made and the term 'indeterminate colitis' is used, although most of these cases will be classified in the long run (Henriksen et al. 2006).

Classification

The most recent consensus on CD classification (Montreal Classification) is based on disease phenotype (Silverberg et al. 2005). Three parameters linked to prognosis, serological and genetic characteristics are used: age at onset (A1≤16 years, A2=17-40 years, A3>40 years), location (L1=ileal, L2=colonic, L3=ileocolonic, L4=upper GI disease, p=perianal disease), and behaviour (B1=inflammatory, B2=stricturing, B3=penetrating). The behaviour of the disease is dependent on time, with a potential non-recursive progress from B1 to B3. In B2, intestinal obstruction has occurred, and in B3 fistulas and abscesses are encountered. Earlier onset and ileal disease have been associated with particular susceptibility genes and a more severe disease course of stricturing and penetrating disease behaviour (Polito et al. 1996, Russell et al. 2005). The role of serological and genetic markers in CD classification has yet to be settled.

Pathogenesis

The understanding of CD pathogenesis spans over molecular genetics, innate and adaptive immune systems, epithelial barrier function, gut microbiota, and environmental factors (Xavier 2007, Mayer 2010). Evidence of genetic association derived from twin studies and identification of susceptibility genes has furthered the paradigm from a maladaptive immune system to abnormalities in gut microbe–host interaction (Tysk et al. 1988, Barrett et al. 2008). Partially identified noxious agents in the environment (e.g. smoking, NSAIDs, infection) and in the largely uncharted commensal gut flora are inadequately averted by an insufficient mucosal defence system. Dysfunction of the epithelial barrier and of the innate immune system linked to genetic aberrations are believed to be key elements in the initiation process promoting localized tissue damage. The cascade of downstream adaptive immune responses, including T-cell activation, cytokine secretion, and expression of chemokines and endothelial adhesion molecules, is insufficiently controlled by regulatory T-cells, thus augmenting and perpetuating the inflammation. In the evolving field of psychoneuroimmunology, interesting pathways from the central nervous system to the gut immune system are being investigated, adding new fuel to the debate on the psychosocial influence on CD development and course (Mawdsley et al. 2005). Thus far, limited evidence has been adduced for such a linkage (Maunder et al. 2008, Goodhand et al. 2008).

Epidemiology

CD occurs worldwide but has a varying incidence and prevalence. The Swedish incidence and prevalence rates have been shown to increase continuously during the 20th century and are among the highest reported, with an incidence of $8.3/10^5$ person-years and a prevalence of $213/10^5$ inhabitants in the latest report (Lindberg et al. 1991, Lapidus 2006). A similar increase is seen internationally. An estimate of nearly 1.5 million affected individuals in Europe and USA was made in 2004 (Loftus 2004). Higher rates in the northern Europe and North America and in more industrialized countries are well known but the differences are levelling (Lakatos 2006). CD is most commonly diagnosed in late adolescence or early adulthood but the disease may present itself at any age. In general, studies have shown a slight female predominance, especially in the age group 15-35 years (Loftus 2004). Disease location has varied between studies and over time. At diagnosis 15-27% had ileitis, 42-45% colitis, and 26-37% ileocolonic CD in two European population-based studies (Henriksen et al. 2007, Wolters et al. 2006b). Epidemiological studies have also given etiological insights. The injurious effects of smoking on disease development and course are firmly established (Calkins 1989). The weak but persistent association between female CD and oral contraceptives has not been discounted (Godet et al. 1995). Recent studies suggest a CD promoting effect of appendectomy (Andersson et al. 2003b), but purported associations with dietary factors, breastfeeding, or childhood infections remain to be proved (Loftus 2004).

Associated health problems

CD has been associated with a wide array of diseases (Veloso 1996, Danese et al. 2005), many of which reflect susceptibility to autoimmune disorders (rheumatoid arthritis, psoriasis, diabetes mellitus type 1, thyroid disorders, etc.). Other links with concomitant ill-health may be malnutrition, smoking, and adverse effects of therapy. Conditions with a closer association to the IBD, extraintestinal manifestations (EIM), may develop in up to 30% of the cases, engaging peripheral or axial joints (arthritis, sacroiliitis), the skin (pyoderma gangrenosum, erythema nodosum), or the eyes (iritis, episcleritis). Primary sclerosing cholangitis is a chronic IBD-associated hepatobiliary disease with a prevalence of 1.4-3.5% in CD, potentially causing liver failure or cholangiocarcinoma (Navaneethan et al. 2010). Gallstones, pancreatitis, kidney stones, and renal failure are also over-represented. Increased risks of colorectal cancer, and small bowel cancer have been reported (Munkholm 2003, Jess et al. 2005), and an excess risk of lymphoproliferative disorders in IBD associated with immunosuppressive treatment is currently suspected (Beaugerie et al. 2009). Malnutrition, micronutrient deficiencies, and metabolic bone disease are reported in 20-50% of CD outpatients (Scott et al. 2000, Hartman et al. 2009). Short bowel syndrome with intestinal failure as a result of extensive disease or bowel resection is rare but highly influential on morbidity and mortality (Thompson et al. 2003). CD patients are also liable to functional GI disorders, either idiopathic or secondary to bowel resection (Nyhlin et al. 1994, Castiglione et al. 2000, Simrén et al. 2002, Farrokhyar et al. 2006). Finally, published data indicate a higher prevalence of psychiatric disorders, especially depression, in CD compared with background population (North et al. 1994, Graff et al. 2009).

Medical treatment

Treatment of CD aims at relieving symptoms and preventing complications (Hanauer & Sandborn 2001, Travis et al. 2006, Dignass et al. 2010). Treatment choice depends on inflammatory activity, disease location, disease behaviour, previous complications, and the patient's preference and susceptibility to side effects. Most patients experience a mild disease type and abstention from pharmacological treatment is not uncommon. Traditionally a "step-up" approach of adding therapies is used, but the advantages of the "top-down" strategy with early potent treatment in more severe cases have been brought to the fore. Aminosalicylates are often used in milder disease, but its efficacy is debated. Antibiotics may have some effect in colitis, but are mostly restricted to septic or perianal complications. Corticosteroids are effective in inducing remission, but maintenance therapy is usually avoided due to lack of relapse preventing effect and the risk of side effects (e.g. osteoporosis, infection, hyperglycaemia, and hypertension). Thiopurines (6-mercaptopurine, azathioprine) and secondarily methotrexate are opted as immunosuppressants in corticosteroid-dependent or refractory cases. Biological immunosuppressive therapies (anti-TNF, anti- α_4 -integrin) have emerged during the last decade as efficacious but expensive options in severe cases not amenable to conventional strategies. Immunosuppressive treatment needs careful monitoring in view of intolerance, opportunistic infections, and the possible long-term risk of malignancies. Enteral or parenteral nutrition are other temporary options when acute alleviation of symptoms and sustainment of nutrition are of primary interest.

Surgical treatment

During recent decades, surgery in CD has moved away from extensive bowel resection to more restrictive efforts against complications such as stenosis, abscesses and fistulae recalcitrant to medical treatment (McLeod 2003). Strictureplasty and endoscopic dilatation are two techniques that in selected cases further reduce the need for bowel resection. Complicated perforating ano-rectal disease requires a close collaboration between medical and surgical specialists. Abscess incision and various techniques to drain or seal fistulae may be combined with antibiotic or immunosuppressive treatment. In some cases temporary or permanent diversion of the faecal stream with an ostomy may be necessary.

Course of disease and prognosis

Many studies describe the course of the disease but with varying results due to different study populations, time eras and differing classifications and treatment policies (Hellers 1979, Gollop et al. 1988, Munkholm et al. 1995, Faubion et al. 2001, Solberg et al. 2007, Jess et al. 2007). It is important to note that most data represent the situation before the widespread use of immunomodulators or the introduction of biological therapy.

A recent review concluded from population-based studies that disease location remains mainly stable over time (Peyrin-Biroulet et al. 2010), whereas disease behaviour progresses, the proportion of patients with penetrating disease (B3) increasing from 12-19% at diagnosis to

50% after 20 years. The risk of relapse within 10 years of the initial disease episode is 80-90%, but 50% can expect a full year of remission within 3 years and only a few percent will have a continuously active disease for a decade. Corticosteroids are used in 50-75% of cases within the first 5 years. One third develop corticosteroid dependency and one fifth will be primary non-responders. About half of all CD patients will undergo bowel surgery. Symptomatic postoperative recurrence rate is approximately 50% after 10 years, and 10-30% undergo at least two operations within 10 years of diagnosis.

Even though the disease course is often described as chronically remitting and relapsing, this pattern was only described by 32% of the patients 10 years after diagnosis (Solberg et al. 2007). Forty-three percent had experienced continuous remission, and 19% continuously active disease. An illustrative estimation of expected disease course in newly diagnosed CD was afforded by a Markov model study in the USA based on 1,957 person-years of observation (Silverstein et al. 1999). A representative CD patient diagnosed at the age of 28 and with an expected further life span of 46 years will spend 30 years (65%) in medication-free remission, with or without previous surgery. For 13 years (28%), disease activity will be mild and the treatment limited to aminosalicylates and/or topical corticosteroids, while 3 years (7%) will be affected by a more severe disease course treated with corticosteroids and/or immunosuppressants. In a recent multinational European Markov model study, CD patients were classified as having medical remission (no treatment) or mild disease (aminosalicylates, antibiotics) 68% of the time during the first 4-10 years after diagnosis (Odes et al. 2010).

In referral centres, the rates of perianal fistula are 14-26% depending on duration of follow-up (Lapidus 2006, Schwartz et al. 2002). In the latter study, 24% were managed medically, while 52% and 24% respectively had undergone minor surgery or proctocolectomy.

Although death caused by CD is very rare, the all-cause mortality rate in CD is slightly raised (40-50%) according to the most recent meta-analyses (Canavan et al. 2007, Duricova et al. 2010). Diseases associated with smoking partly explain the findings, but 25-50% of the excess mortality is believed to be more directly related to CD.

Effects on social life, sickness, and disability

CD may harbour debilitating symptoms and often commences early in life, before or during the crucial period when education, career, relationships, and family are moulded. Studies have nevertheless produced ambiguous results regarding the impact of CD on life prospects.

The likelihood of marrying and starting a family has in many studies been used as an indicator of life prospects, albeit crude and obsolete as markers of a happy life. The proportion of married (or cohabitant) CD patients has been equal or lower, than in the background population (Sainsbury et al. 2005). Some indications of fewer children born to CD parents and a lower parenthood rate (Sørensen et al. 1987, Andersson et al. 2003a), especially for male CD (Narendranathan et al. 1986) have been purported. In contrast, larger population-based studies on female CD have shown infertility rates similar to the general population (5-14%), though the risk of adverse pregnancy outcome (e.g. pre-term delivery, low birth weight) was increased (Mahadevan 2006, Staphansson et al. 2010).

Most studies have found no difference in attained educational level, compared with background population for IBD in general or CD in particular (Sørensen et al. 1987, Longobardi et al. 2003a, Andersson et al. 2003a, Marri et al. 2005). Nevertheless, 15-21% of CD patients have experienced hindrance in examination performance or lack of understanding from teachers (Mayberry et al. 1992), and 60% reported that the disease had adversely affected their educational goals (Ferguson et al. 1994). Registry studies have indicated a higher rate of skilled (“white-collar”), indoor, and sedentary occupations among IBD patients in general (Sonnenberg 1990, Bøggild et al. 1996, Bernstein et al. 2003). Income and socioeconomic status have otherwise been on a par with controls for IBD and CD (Sørensen et al. 1987, Bernstein et al. 2001, Andersson et al. 2003a).

Increased rates of sick leave and disability pensions attributable to CD are quoted in most reports, although the magnitude of the issue is hard to compare due to differing social security systems and definitions (Marri et al. 2005). Munkholm et al. (1995) reported that approximately 15% of Danish CD patients had obtained disability pension 15 years after diagnosis. Bernklev et al. (2006) found a doubled rate of working days on sick leave and a doubled disability pension rate in Norwegian CD patients, compared with the general population. A Dutch study estimated that CD accrued 7 additional sick days per patient-year and a threefold likelihood of obtaining disability pension (Boonen et al. 2002). Andersson et al. (2003) reported an excess of 24 sick days per year compared with controls in colorectal CD from a Swedish referral centre (Linköping). Although insufficiently studied, most IBD patients (80%) perceived a helpful attitude from co-workers and employers (Wyke et al. 1988), though a minority of CD patients (24%) stated that their disease had restricted their employment or promotion prospects (Mayberry et al. 1992).

Blomqvist et al. (1997) found (albeit before the era of biological therapy) that 2/3 of total IBD costs in Sweden 1994 were attributable to sick leave or disability pension. CD incurred doubled health care costs and 3-4 times higher costs for sickness and disability compared with UC, despite a 50% lower prevalence. One recent study estimated an annual cost of 184 million € for CD in Sweden, of which the indirect cost secondary to loss of work productivity accounted for 64% (Mesterton et al. 2009).

Health assessment

What is health?

“Health is a state in which we neither suffer from pain, nor are hindered in the functions of daily life”

Claudius Galenus, 200 A.D.

Health is a complex and abstract construct. The Proto-Indo-European origin of the word is related to key concepts such as whole, heal, holy, and hail (Klein, 1971). The definition of health has been a matter of debate in different arenas since ancient times, and still is. Two main streams have appeared.

The *biostatistical view* starts from the definition of disease as an impairment of the statistically normal functions necessary for survival and reproduction of an organism, while health is merely the absence of disease (Boorse 1977). This standpoint emanates from traditional medical science and evolutionary biology, developed during times when improved survival was the primary goal.

During the 20th century, as survival became less of a problem in many diseases, the ambitions of health care widened. In 1948, the World Health Organization defined health as ‘not merely the absence of disease or infirmity, but a state of complete physical, mental, and social well-being’ (WHO 1948). Protagonists of this *holistic view* consider health from the individual’s point of view (Nordenfelt 2007). Complete health can only be achieved in a state in which the individual’s goals of achieving well-being are fulfilled. Disease is only one of several possible causes of ill-health. The general view of health has thus shifted from a merely objective definition to a dualistic concept with both value-free objective (disease) and value-laden subjective (illness) components (Fig. 1).

Some theorists include sickness as a third dimension (Fig. 2), representing society’s view of an individual’s health status, with reference to performance of societal duties, sick role, sickness benefits and disability (Hofman 2002). This ‘triad of health’ perspective is employed in the International Classification of Functioning, Disability, and Health (ICF) endorsed by the WHO as a framework for assessment of health and disability from medical, individual, and societal perspectives (WHO 2001).

It may well be that the 1,800-year-old holistic statement by the Roman-Greek physician Galenus quoted above is buoyant even today (Temkin 1963).

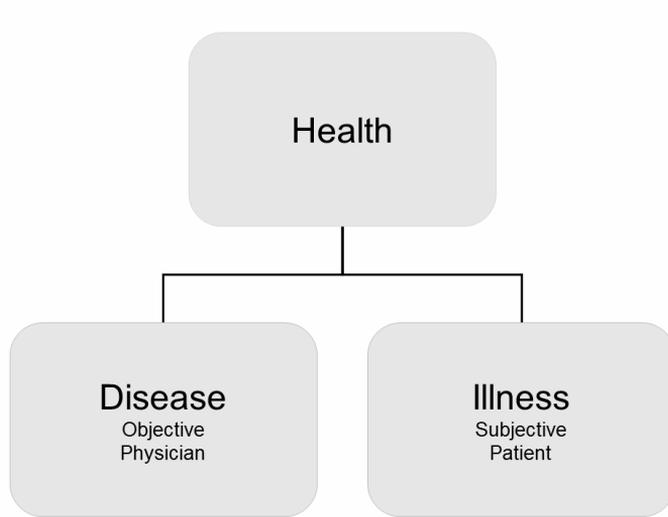


Figure 1. The dualistic concept of health.

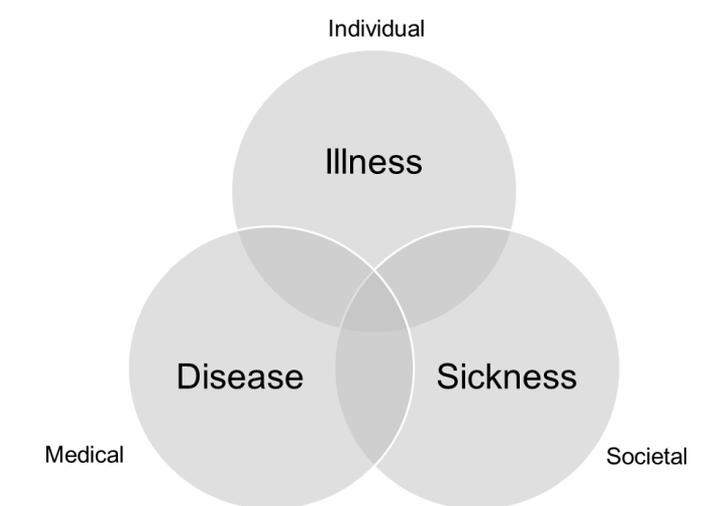


Figure 2. The triad of health.

Inflammatory activity

Monitoring the inflammatory activity is crucial in clinical decision-making and management of IBD. In CD, the assessment of inflammation may be difficult due to limited endoscopic access to the site of inflammation. Furthermore, abdominal symptoms may be unspecific and related to causes other than bowel inflammation, and patients with significant inflammation may be asymptomatic.

Attempts to create indices of microscopic inflammation (histological disease activity) have been discouraging due to the considerable variability and the poorly verified clinical relevance of histological appearance (Sandborn et al. 2002). Several standardized and reproducible endoscopic measures of mucosal inflammation have been developed. Crohn's Disease Endoscopy Index of Severity (CDEIS) and the Simple Endoscopic Score for CD (SES-CD), which summarize macroscopic findings of ulcerations and stenosis with acceptable inter-observer agreement, are used in clinical trials to assess mucosal healing after treatment (Mary et al. 1989, Daperno et al. 2004). Rutgeerts's Score is an endoscopic index of recurrence of lesions after bowel resection, proven useful to predict symptomatic post-surgical relapse (Rutgeerts et al. 1990). All these measures are limited to the colon and the last part of ileum. Despite the development of capsule endoscopy, enteroscopy and other new gut imaging techniques, an index to encompass the lesions of the entire GI tract has yet to be established.

Several blood tests are used as indirect markers of inflammation. Serum level of C-reactive protein (CRP), a sensitive and rapid acute-phase reactant to systemic inflammation, is the most widely used. Elevated levels demonstrably predict response to anti-inflammatory therapy and future relapse of active disease (Vermeire et al. 2006, Minderhoud et al. 2007). However, neither the sensitivity nor the negative predictive value of CRP for significant endoscopic lesions is optimal (Denis et al. 2007, Sipponen et al. 2008). Other blood tests associated with inflammation (sedimentation rate, albumin, orosomucoid, β_2 -microglobulin, white blood cell and platelet counts) have not consistently proved superior to CRP or have been insufficiently studied in this regard. More specific markers of gut inflammation have been searched for in stools. Calprotectin is one of several neutrophil-derived faecal proteins associated with intestinal inflammation, permeability and leukocyte migration to the GI tract, that have been suggested as more sensitive IBD activity markers (Sutherland et al. 2008). Several studies on calprotectin have revealed a close correlation with mucosal inflammation and good ability to predict relapse (Sipponen 2008, Gisbert et al. 2009), but elevated levels may occasionally have other explanations (neoplasm, infection, NSAIDs).

Clinical disease activity indices

In the absence of a universal benchmark of disease activity in CD, attempts have been made to assemble clinical variables into a single disease activity index. Best et al. (1976) devised the Crohn's Disease Activity Index (CDAI) by using the physician's overall appraisal of "how the patient was doing" (very poor, poor, fair to good, very well) as outcome variable in a multiple linear regression analysis of 18 clinical variables and symptoms from the last 7 days, as

reported by the patient. Eight independent variables were ultimately chosen to form the index, each weighted by the relative magnitude of its regression coefficient (Table 1). The cut-off limits between quiescent/active disease (“very well/fair to good”) and active/very severe disease (“poor/very poor”) were set to 150 and 450 points respectively. Subsequently, an additional limit was arbitrarily drawn at 220 points between mild and moderate disease activity and a reduction of 70-100 points has been deemed to indicate treatment response (Travis et al. 2006, Sandborn et al. 2002). CDAI has been adopted as the ‘gold standard’ for outcome assessment in clinical trials, its use being a prerequisite for regulatory approval of new therapies by authorities in the USA and Europe (Fredd 1995).

The Harvey-Bradshaw index (HBI) is a derivative of the CDAI, excluding the laboratory variables and only recalling symptoms from the last 24 hours (Table 1, Harvey, 1980). HBI correlates strongly ($r>0.90$) with CDAI and has been used to simplify disease activity assessment.

Adapted versions of CDAI have been constructed for use in children and in patients with perianal fistulizing disease (Hyams et al. 1991, Irvine 1995a). Concerns were raised against CDAI as being largely determined by subjective variables (van Hees et al. 1980). This led to the development of an index governed by laboratory parameters, the van Hees Index (VHI, Table 1). As expected, the correlation with CDAI was weak, but neither did it predict endoscopic severity in a subsequent study (Simonis et al. 1998), and its use in clinical trials has been limited.

Emerging CD concepts emphasize the progressive and irreversible character of the tissue damaging process (Louis et al. 2001, Cosnes et al. 2002). To capture this aspect, a multinational project has been launched to develop a global score of cumulative bowel damage, taking into account location and extent of stricturing or penetrating lesions, and bowel resection (Pariente et al. 2010).

CDAI

x_1 : Number of liquid stools in 1 week

x_2 : Sum of 7 daily abdominal pain ratings (0=none, 1=mild, 2=moderate, 3=severe)

x_3 : Sum of 7 daily ratings of general well-being (0=well, 1=slightly below par, 2=poor, 3=very poor, 4=terrible)

x_4 : Total number of the following symptoms or findings present during the week:

(1) arthritis or arthralgia

(2) skin or mouth lesions, e.g. pyoderma gangrenosum, erythema nodosum, aphthous stomatitis

(3) iritis or uveitis

(4) anal fissure, fistula, or perirectal abscess

(5) other external fistula, e.g. enterovesical, enterovaginal, enterocutaneous

(6) febrile episode exceeding 100°F during week

x_5 : Taking any Lomotil or other opiate for diarrhea during the week (0=no, 1=yes)

x_6 : Abdominal mass (0=no, 2=questionable, 5=definite)

x_7 : Anaemia (47-haematocrit for males, 42-haematocrit for females)

x_8 : Body weight (100 x [1-body weight/standard weight])

$$\text{CDAI} = 2x_1 + 5x_2 + 7x_3 + 20x_4 + 30x_5 + 10x_6 + 6x_7 + x_8$$

Harvey-Bradshaw Index

x_1 : General well-being (0=well, 1=slightly below par, 2=poor, 3=very poor, 4=terrible)

x_2 : Abdominal pain (0=none, 1=mild, 2=moderate, 3=severe)

x_3 : Number of liquid stools

x_4 : Abdominal mass (0=no, 1=dubious, 2=definite, 3=definite and tender)

x_5 : Complications: arthralgia, uveitis erythema nodosum, pyoderma gangrenosum, aphthous stomatitis
anal fissure, fistula, abscess (score 1 per item)

$$\text{HBI} = x_1 + x_2 + x_3 + x_4 + x_5$$

van Hees Index

x_1 : Serum albumin (g/L)

x_2 : Erythrocyte sedimentation rate, SR (mm/h)

x_3 : Quetelet index [weight (kg) x 10/height (cm²)]

x_4 : Abdominal mass (no mass=1, dubious=2, diameter <6 cm=3, diameter 6-12 cm=4, >12 cm=5)

x_5 : Sex (male=1, female=2)

x_6 : Body temperature (°C)

x_7 : Stool consistency (1-3)

x_8 : Intestinal resection (no=1, yes=2)

x_9 : Extraintestinal lesion (no=1, yes=2)

$$\text{VHI} = -209 - 5.48x_1 + 0.29x_2 - 0.22x_3 + 7.83x_4 - 12.3x_5 + 16.4x_6 + 8.46x_7 - 9.17x_8 + 10.7x_9$$

Table 1. The variables and formulas of the CDAI, HBI and VHI.

Health-related quality of life

*“We should not worry about how long we live but rather how satisfactorily;
for in order to live a long time, you only require fate,
but living satisfactorily requires understanding.
Life is long if it is full.”*

From *Epistularum Moralium ad Lucilium* by Lucius Annaeus Seneca (4 BC – 65 AD), a Roman philosopher and author who suffered from bad health throughout life and was forced by the emperor Nero – his former pupil – to commit suicide, accused of conspiracy.

It is a truism in daily clinical practice that any worthwhile assessment of a patient’s health status should include the question ‘how are you feeling?’. Medical science, however, has by tradition focused on biological abnormalities in the assessment of disease severity and treatment outcome. As the definition of health and the ambitions of health care widened to embody the individual’s own perception of health, health-related quality of life (HRQL) became established as an important part of outcome assessment. The potential benefits of this development in clinical practice are numerous. The change from an objective to a subjective perspective improves patient influence and empowerment in health care (Rubenstein et al. 1995, McLachlan et al. 2001, Detmar et al. 2002). The holistic overall view deepens and broadens our understanding of the interactions between health-related problems on physical, mental and social levels (Guyatt et al. 2007). This can facilitate decision-making in patient management and resource allocation, minimizing disease impact on individual lives and mitigating the societal burden of health care utilization (Blumenthal 1996).

Crohn’s disease has many characteristics rendering HRQL assessment particularly important: an onset in early life, a chronic unpredictable course, and multiple symptoms with associated health problems potentially impeding daily function, social interactions, and self-image. Moreover, the biological disease process is difficult to assess, and the most potent treatment options are expensive or flawed with side effects.

The challenge lies in how to define and measure such an elusive concept as quality of life. Some authors have likened it to measuring the beauty of a rose (Mount & Scott 1983). Different contexts (philosophical/ethical, political/economic, sociological, psychological) have provided different concepts of quality of life (human existence, welfare, social interaction, happiness). Although the “health-related” prefix is intended to direct focus on issues of medical concern, there is no distinct boundary toward the most all-embracing definition. The terms HRQL, well-being, life satisfaction and subjective health status are often used interchangeably. HRQL may be described as the patient’s perception of disease impact on well-being and function in physical, emotional and social domains of life (Bergner 1989, Staquet et al. 1998, Frayer & Machin 2007). Another eloquent delineation reads ‘all those things one might want to measure in clinical trials beyond the traditional outcomes of death and physiological measures of disease activity’ (Guyatt et al. 1991). Patient-reported outcome (PRO) is an emerging term used in clinical trials replacing HRQL, better capturing the intention to measure the effect of treatment interventions, seen from the patient’s perspective (Wiklund 2004).

Modes of assessment

In-depth interviews

HRQL can be evaluated in a qualitative manner by in-depth interviews with individual patients or relatives. This approach gives a valuable and detailed insight into patients' daily lives and preferences, but is resource consuming and dependent on the interviewer's interpretation. It is not quantifiable and therefore not usable in clinical trials, but has been important in the initial item selection process of HRQL questionnaire development (Guyatt et al. 1989, Drossman et al. 1989) and also in efforts to characterize and conceptualize HRQL (Hall et al. 2007, Pihl-Lesnovska et al. 2010).

Health utility measures

In utility measures, respondents evaluate their general health status with a single score in relation to how they value survival. Time trade-off (TTO) is one example of this technique where the respondent exchanges life-years for perfect health (Torrance 1972). The gain for a given health care effort can be translated into quality-adjusted life years (QALY) and inserted in cost-utility analyses and studies of health economy. Utility measures do not provide any specific information about which areas of HRQL are affected. Furthermore, they have shown weak correlations with other measures of HRQL and low sensitivity to change in disease activity in IBD and CD (Mitchell et al. 1988, Gregor et al. 1997).

Health indices and profiles

The most commonly used type of HRQL instrument in CD research is the health index (Cohen 2002). This can consist of a single global question, but more often several items are included to cover different aspects of HRQL. The responses to each item may be chosen from a rating scale with two or several labelled options (Likert scale), or they can be graded with a tick on a continuous line between two extremes (Visual Analogue Scale, VAS). The items can be sub-grouped into putative dimensions to form a health profile, or be summed into a single score. Some instruments weigh the importance of each item in the summation algorithm, based on pre-established patient preference.

General or generic HRQL questionnaires cover general aspects of health and allow for comparisons between different health conditions. Many of them have been used in large health surveys to obtain reference scores for background population.

Specific HRQL questionnaires have been adapted to increase their accuracy for health problems of particular concern for certain diseases or sub-populations (e.g. elderly). They may also focus on selected areas of interest, e.g. sleep, worries, or sexual functioning. Compared with generic instruments, specific instruments give a more detailed picture, and are more sensitive to change in health condition.

HRQL questionnaires may be completed by an interviewer (face-to-face/ by phone) or more commonly, by the respondents themselves (Wiklund 2004). The interview approach enhances motivation, comprehension and response rate, but has been shown to bias the score toward better HRQL and inhibit willingness to disclose sensitive information (Bowling 2005, Hays et al. 2009). Computerized self-administration has emerged as an effective way to collect data, but can lead to selection bias of the study population.

Development and evaluation of an HRQL index

The initial step in health index development is defining the theoretical concepts and purpose of the instrument (Kirshner et al. 1985). Do the concepts intended to be measured really exist and what is their relevance to the purpose? The importance of an instrument's psychometric properties is dependent on the purpose. If the investigator wishes to distinguish HRQL between different groups of individuals in order to detect determinants of outcome or to predict morbidity, the items need to be intra-individually stable and have an inter-individually uniform meaning and generalizability. If the instrument is used to evaluate an intervention effect (e.g. a clinical trial), sensitivity to change is of greater importance, and the items must reflect areas that are intended to be affected by the intervention. The choice of item scaling is also influenced by these considerations. A Likert scale has greater reproducibility and interpretability, while VAS yields greater variability and sensitivity to change (Revicki & Leidy 1998). Item selection usually starts with in-depth interviews or open-ended questionnaires, followed by item reduction with ranking procedures in the population of interest and other focus groups having valuable knowledge (relatives, health professionals).

The preliminary questionnaire is thereafter subjected to a thorough evaluation process comprising assessment of *validity*, *reliability*, and *responsiveness* in a larger sample of the population (Kirshner et al. 1985, Guyatt et al. 1993).

Validity is the extent to which an instrument measures what it is intended to measure. In the absence of a gold standard for HRQL, validation relies heavily on qualitative judgemental assessment of whether the instrument and the selected items reflect and cover the domain(s) of interest (*face validity*), and whether the wording is lucid, comprehensive, and unambiguous (*content validity*). *Construct validity* is a more quantitative attribute of how closely collected data adhere to pre-constructed hypotheses of correlation with other measures (concurrent validity) or distinguish between groups of theoretically different levels of HRQL (known-group comparison).

Reliability is a gauge of an instrument's precision, i.e. the ratio of overall variability explained by true difference, and not by systematic or random error measurement. An often applied technique is the test-retest procedure, in which the concordance between two measurements in unchanged respondents is estimated. Internal consistency, i.e. how closely the items of a questionnaire or a dimension covariate, has also been used as an indirect measure of reliability.

Responsiveness, or sensitivity to change, describes the ability to detect relevant changes in the measured variable. The change in score of respondents with hypothetically changed HRQL is compared with the change in score of respondents with hypothetically unchanged HRQL.

The application of an instrument expressed in a different language necessitates careful translation procedures including forward and backward translation (Berkanovic 1980). To be fully confident in the validity of the instrument in the new linguistic and cultural setting, the evaluation process needs to be repeated (Deyo 1984, Hunt 1998).

It should also be noted that a single evaluation of an instrument does not guarantee its psychometric properties. Rather, the evaluation proceeds with repeated use of the instrument, strengthening or weakening its validity, according to performance.

HRQL instruments used in CD studies

Over the years, a host of generic or specific HRQL instruments have been developed. One web-based quality of life instrument database (QOLID, www.proqolid.org) lists more than 1,000 different questionnaires. This may indicate redundancy of some measures, but also reflects the complexity of the subject studied. Although there is considerable value in standardized use of a few instruments for comparison, the wide disparity in the objectives and conditions for each research field justifies continuous development and refinement of instruments. The basic outlines of the most commonly employed HRQL indices in CD research and other instruments of interest in this thesis are compiled in Table 2.

Generic

Short form-36 (SF-36) is the most frequently used generic questionnaire in HRQL studies overall, and normal population databases are available in many countries including Sweden (Ware 1992, Sullivan et al. 1998). The SF-36 generates eight dimensional scores, and two norm-based (physical and mental) summary scores. A more condensed version (SF-12) and a version adapted for cost-utility studies are available (SF-6D). Furthermore, an improved version (SF-36 v2.0) has been presented more recently but data from CD patients are sparse. Sickness Impact Profile (SIP) has a rather complex calculation algorithm with weighting of 136 items according to their importance, yielding 12 dimensions, two sub-scores and an overall score (Bergner et al. 1981). SIP has been used in health surveys yielding background population reference and in many of the early explorative and developmental HRQL studies in IBD, but infrequently in CD studies. The Psychological General Well-Being index (PGWB) taps domains with closer association to mood, distress and mental well-being (Dupuy 1984). It has been used in studies on other gastrointestinal diseases to complement symptom-based instruments with a more general assessment of well-being (Borgaonkar & Irvine 2000). An even stronger focus on mental aspects is evident in the Hospital Anxiety and Depression Scale (HADS), designed to assess psychological symptoms in patients with physical illness (Zigmond 1983). EuroQol-5D contains both a health profile with five dimensions and a global score, making it useful for utility studies (Kind 1996). However, some domains of Euro-QoL 5D pertain to aspects rarely affected by IBD (self-care, mobility). The Cleveland Global Quality of Life index (CGQL) was developed on IBD patients, but was intended for generic use (Kiran et al. 2003). It has been utilized mostly in evaluations of surgical interventions in CD.

Specific

The Inflammatory Bowel Disease Questionnaire (IBDQ) was one of the first IBD-specific HRQL instruments in the arena (Guyatt et al. 1989). It contains 32 items graded on a seven-point Likert scale and subgrouped into four dimensions. The IBDQ was developed in Canada, but has been translated and validated extensively (Pallis & Mouzas 2000). The use of IBDQ as a standard secondary outcome measure in prospective randomized controlled trials of CD therapies has been recommended (Sandborn et al. 2002). Both extended and shorter versions have been developed, and some translated versions have been modified regarding the internal dimensions. It has not been adapted for use in patients with ostomy or perianal disease. The Rating Form of IBD Patient Concerns (RFIPC) was developed from videotaped interviews with IBD patients regarding their disease-related worries (Drossman et al. 1989). The questionnaire contains 25 items scored on a horizontal 100 mm VAS, with higher scores signalling more disturbing worries. RFIPC has been used mostly in descriptive studies of HRQL in various subpopulations of IBD (Mussell et al. 2004, Levenstein et al. 2001).

Dimensions		No. of items	Scale	Modified versions	No. of CD studies 1995-2008
Generic					
SF-36		36	Likert	SF-6D	47
	Physical function	10	1-3	SF-12	
	Physical role	4	1-2	SF-36 v2.0	
	Bodily pain	2	1-5/6		
	General health	5	1-5		
	Vitality	4	1-6		
	Emotional role	3	1-2		
	Social function	2	1-5		
Mental health	5	1-6			
HADS		14	Likert (0-3)		10
	Anxiety	7			
Depression	7				
PGWB		22	Likert (1-6)		9
	Anxiety	5			
	Depressed mood	3			
	Positive well-being	4			
	Self-control	3			
	General health	3			
	Vitality	4			
EuroQol-5D			Likert (1-3)		8
	Mobility	1			
	Self-care	1			
	Daily activities	1			
	Pain	1			
Depression/anxiety	1				
CGQL		3	0-10		5
	Quality of life				
	Quality of health				
Energy level					
SIP		136	Dichotomous		3
	Physical (3)				
	Psychological (4)				
Social (5)					
Disease-specific					
IBDQ		32		IBDQ-36	93
	Bowel symptoms	10		SIBDQ	
	Systemic symptoms	5		N-IBDQ	
	Social function	5		UK-IBDQ	
	Emotional function	12			
RFIPC		25	VAS (0-100)		9

Table 2. The most frequent HRQL instruments in adult IBD research, obtained from the search log of a systematic review of HRQL studies in IBD using standardized electronic search procedures (Hoivik et al. 2010). This review identified a total of 216 HRQL studies on CD between 1995 and July 2008.

Determinants of HRQL

*“It is more important to know
what kind of patient has the disease
than to know what kind of disease the patient has.”*

Sir William Osler (1849-1919), “the father of modern medicine”

For an appropriate interpretation of HRQL outcome, the impact of influential factors needs to be taken into account. In comparative cross-sectional or case-control studies the results may be biased by differing population characteristics (Irvine 1995b). Although the variation within each subject is of greater importance in interventional studies, there may be interaction between intervention effect and population attributes. The determinants of the wide concept of HRQL are innumerable, but may be grouped into intrinsic and extrinsic factors.

Intrinsic factors

Intrinsic factors are the characteristics of the respondent in mental (gender, age, personality, coping strategy, preference, life goals, experience, knowledge, education, psychiatric disorder) and in physical (co-morbidity, disease severity and duration, complication, general physical health status) aspects. Female gender has in most (but not all) studies been associated with worse HRQL in CD, in other diseases, and in the general population (Sullivan 1994, Sainsbury 2005, Cherepanov et al. 2010). The elderly have reduced generic HRQL in general population health surveys, particularly as regards physical domains (Sullivan 1994). In several studies on HRQL in IBD and CD, however, age has had minor or no effect (Blondel-Kucharski et al. 2001, Casellas et al. 2002, Hjortswang et al. 2003). Personality traits, coping strategies and mental illness have been found influential on HRQL in IBD (Verissimo et al. 1989, Petrak et al. 2001, Guthrie et al. 2002, Mussel et al. 2004, Moreno-Jimenez et al. 2007). The individual ability to cope with ill-health is not necessarily unchanged over time. Impairment of health status may elicit a process of accommodation in which the internal standards, values, and conceptualization of subjective health evaluation are changed. This phenomenon – termed ‘response shift’ – has been acknowledged as an important factor for HRQL outcome, possibly explaining improvements of HRQL over time and counter-intuitive findings of enhanced HRQL in patients with severe disease (Sprangers & Schwarz 1999). Despite this phenomenon, and the generally described mitigating long-term disease course (Munkholm et al. 1995, Henrikssen et al. 2007, Solberg et al. 2007), HRQL seems not to be affected by disease duration in CD (Casellas et al. 2002, Mussel et al. 2004, Canavan et al. 2006, Pizzi et al. 2006, Moreno-Jimenez et al. 2007). A higher educational level has been associated with better IBD-related HRQL (Drossman et al. 1991a, Casellas et al. 2002), but specific IBD education programmes have not improved HRQL (Borgaonkar et al. 2002, Larsson et al. 2003). Low socioeconomic status and smoking have also been linked to a poorer HRQL in CD (Russell et al. 1996, Rubin et al. 2004). Disease activity or severity has in many studies been the strongest predictor of HRQL in IBD (Guthrie et al. 2002, Andersson et al. 2003a, Graff et al. 2006), even though disease phenotype (as classified by age at diagnosis, location, and behaviour) had no effect on HRQL in a study by Casellas et al. (2005). Finally, co-morbidity has been detrimental on HRQL in both physical and mental respects, also when measuring with IBD-specific instruments (Hjortswang et al. 2003, Pizzi et al. 2006).

Extrinsic factors

Extrinsic factors are characteristics of the social surroundings (family, social network, quality of care, social security, infrastructure, occupation, cultural, and religious values). The role of extrinsic factors in HRQL is less well studied in IBD. The significance of family and social support has been elucidated in some studies (Sewitch et al. 2001, Janke et al 2005, Pihl-Lesnowska et al. 2010). A role for quality of care as judged by the IBD patient, was demonstrated in one large European study (van der Eijk et al. 2004). Levenstein et al. (2001) found a moderate correlation between patient-reported IBD-related concerns and adverse national economic parameters. Ethnic and religious differences have also been put forward as predictors of HRQL outcome in CD and IBD (Straus et al. 2000, Farrokhyar et al. 2006).

The key dimensions of HRQL

The ample and protean character of HRQL as a concept has prompted developers of multi-item HRQL questionnaires to sub-group the items into underlying comprehensive dimensions. The resulting models of HRQL structure have varied according to the purpose of the measurement and the population under study. Symptoms often have a dominant role in instruments intended for clinical trials, as well as in palliative medicine, in which symptom relief is the primary goal. Some researchers claim that symptoms do not belong to HRQL, but instead are part of objective disease assessment. However, symptoms are by definition based on the individual's perception, feelings, or beliefs concerning one's physical state, and hence ineluctably interwoven with the term subjective health perception (Pennebaker 1982). Studies of symptoms from various medical fields have shown a closer correlation with psychosocial factors and emotional status than with objective physiological parameters (Barsky et al. 1992). In medical fields with large elements of rehabilitation (orthopaedics, neurology, rheumatology), emphasis is placed upon function and independence in daily self-care, mobility, and livelihood. Function can be gauged objectively in many ways (e.g. walking distance, grip strength, joint mobility, or cognitive tests). Other more esoteric aspects of function in daily life (e.g. career, social life, leisure, intimate relations) need to be subjectively assessed, and are more dependent on individual goals, expectations, and adaptability, as well as on supportive or inhibitory factors in the environment. Psychological HRQL indices have an even greater degree of subjectivity, tapping domains of mood, sense of well-being, energy, and life satisfaction, thus integrating psychosocial factors with general health perception and well-being on a higher level of complexity.

Wilson and Cleary (1995) proposed a five-dimensional model of health status, linking the biological parameters of disease process with the subjective overall quality of life through a causal pathway including symptoms, function, and general health perception (Fig. 3a). This pathway connects the biostatistical definition of disease with the holistic concept of quality of life along a continuum of increasing complexity and subjectivity. Although the causal structure implies unidirectional relationships between the dimensions, the authors acknowledged the possibility of reciprocal associations. Based on experiences of HRQL assessment in IBD, Hjortswang et al. (1999) further elaborated the model, adding disease-related worries as a dimension and merging general health perception with overall quality of life into a single dimension of general well-being (Fig. 3b). Keeping the idea of a gradient of increasing psychosocial influence and subjectivity from disease to HRQL, Hjortswang et al. also suggested that the dimensions may interact in a network, rather than on a line. This conceptual health status model formed the theoretical basis for the development of the four-item IBD-specific HRQL questionnaire, the Short Health Scale (SHS, Table 5), containing one global VAS-scored question for each of the four subjective dimensions (Hjortswang et al. 2006).

(a)



(b)

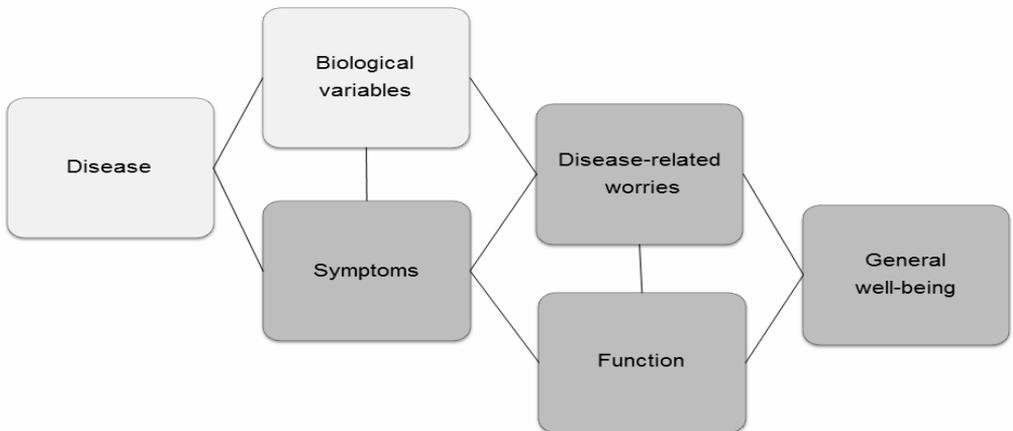


Figure 3. (a) The conceptual health status model of Wilson & Cleary (1995). (b) The conceptual health status model proposed by Hjortswang et al. (1999). Boxes in darker grey represent dimensions of subjective health perception.

1. How severe symptoms do you suffer from your bowel disease?

No |-----| Very severe symptoms
symptoms

2. Does your bowel disease interfere with your activities in daily life?

Not at all |-----| Interferes to a very high degree

3. How much worry does your bowel disease cause?

No worry |-----| Constant worry

4. What is your general sense of well-being?

Very well |-----| Dreadful

Table 5. The English translation of the Short Health Scale (SHS).

AIMS OF THE THESIS

1. Evaluation of the Swedish versions of two disease-specific measures of health-related quality of life in CD: IBDQ and RFIPC (papers I and II)

Several translations of the most popular HRQL instruments exist, facilitating international studies and comparisons of subjective health status. Translation of a questionnaire necessitates a re-evaluation of the new version, to ensure that the psychometric properties have been retained throughout the translation process. Two IBD-specific HRQL questionnaires, the IBDQ and the RFIPC, have been translated into Swedish and further evaluated in patients with UC (Hjortswang et al. 1997, and 2001). However, it cannot be assumed that the results of the UC evaluations can be extrapolated to CD, since the two diseases differ in several clinical and demographical respects.

Thus, the first aim was to evaluate the Swedish versions of the IBDQ and the RFIPC in patients with CD.

2. Evaluation of the Short Health Scale in CD: a new concept for health assessment (paper III)

Most HRQL instruments are multi-item questionnaires in which the outcome is presented as a summation of the items into one single score. Using a one-dimensional estimation withholds important information on how the different aspects of HRQL are affected. Although subscales have been constructed to overcome this problem, the grouping of the items has not always been well-founded and psychometrically verified in repeated studies. Furthermore, the complexity of the HRQL concept makes it difficult to cover all possible aspects, even with a lengthy list of items. Many instruments are therefore cumbersome to complete and compile, yet omitting important issues for each specific respondent. Hjortswang et al. (1999) suggested a strategy of health assessment based on a conceptual health status model, comprising five dimensions (biological variables, symptoms, function, worries, and general well-being), inter-related in a network along a gradient of increasing psychosocial influence and subjectivity. This model was further elaborated into a four-item questionnaire, the Short Health Scale (SHS), in which each of the four subjective dimensions of the model was represented by a global question. The SHS was subsequently evaluated and proved to be valid, reliable, and responsive in patients with UC (Hjortswang et al. 2006).

The second aim was thus to evaluate the psychometric properties of the SHS in patients with CD.

3. Analysis of the relationship between disease activity and health-related quality of life (papers IV and V)

Health assessment involves an integration of objective (disease activity) and subjective (HRQL) components. The term ‘disease activity’ is poorly defined, and often understood as ‘inflammatory activity’. Crohn’s Disease Activity Index (CDAI) has become the ‘gold standard’ for disease activity assessment in clinical trials. Since the development of the CDAI in the mid–1970s, the aim of CD treatment has changed from mere symptom relief to a more active approach to inflammatory activity and mucosal lesions in order to prevent complications. In addition, improvements in the field of endoscopy and laboratory analyses have enhanced the ability to more directly monitor inflammatory activity. Concerns have been raised against a weak correlation between CDAI and clinical apprehension of disease activity, but few studies have addressed this issue. The CDAI consists of both subjective and objective variables, but little is known about how much each variable contributes and what aspect of health status CDAI actually measures.

The health status model behind the Short Health Scale was an attempt to conceptualize the structure and interactions of the underlying dimensions explaining the relationship between disease activity and HRQL variables. Although based on clinical experience and reasoning, the model is a theoretical construct, and as such difficult to substantiate or validate. Structural Equation Modelling (SEM) is a statistical technique by which theoretical models can be tested and modified. Based on the correlation matrix of measurable variables representing each abstract dimension, the goodness-of-fit between a theoretical model and empirical data can be estimated.

The third aim was thus to study the relationship between disease activity and HRQL in CD

- (a) by investigating the compatibility of the CDAI formula to the apprehension of disease activity in current clinical practice, and by identifying the main variables contributing to the outcome of disease activity assessment*
- (b) by testing how the SHS health status model fits the measured data, using SEM.*

4. Describing health-related quality of life and social characteristics of patients with CD (papers II and VI)

Crohn’s disease is a lifelong diagnosis with a minimal effect on survival, but with a potential to seriously impair quality of life and life prospects. The worries and concerns that come with the disease have been purported to constitute a unique component of HRQL, having a substantial influence on mood, life satisfaction and health perception even in patients with quiescent disease. The RFIPC, a multi-item questionnaire devised to measure this dimension, was evaluated in the previously discussed study (see aim 1). The RFIPC data afforded us a unique opportunity to describe the nature and degree of disease-related worries, including modifying factors, in a large population-based cohort of CD patients only.

In trying to understand and describe how life in general turns out for Swedish CD patients two different aspects were elucidated. First, the subjective perception of general health status, both physical and mental, compared with the general population and with ulcerative colitis patients. Secondly, the prospects of achieving full potential in life in terms of family life, education, and livelihood. The second aspect entails the societal view of health status: sickness and disability, recognized as the most burning issues in health economics, driving the cost and adding weight to the overall burden of illness in CD.

The fourth aim was thus to study the impact of CD on HRQL and life prospects in a regional Swedish patient cohort

(a) by characterizing the nature and degree of disease-related worries and concerns

(b) by describing general HRQL and social characteristics, sickness, and disability in comparison with background population.

PATIENTS AND METHODS

Patient inclusion and data collection

Adult patients with a firmly established diagnosis of Crohn's disease were consecutively invited in conjunction with their regular visits at the outpatient clinics of three hospital-based gastroenterology units (Ryhov County Hospital [Jönköping], Örebro University Hospital, and Linköping University Hospital). The invitation and the study questionnaires were sent by mail together with the regular notice of appointment to all CD patients registered for follow-up at the clinics during 1999 to 2001. In general, all patients with Crohn's disease in the primary catchment areas of the three hospitals are intended to be followed-up once a year. Participants were instructed to complete five different HRQL questionnaires and to leave blood samples during the week before the visit. In addition, they completed a questionnaire regarding demographic data (family, work/sickness, education, smoking habits), and a 7-day symptom diary including a daily report of stool consistency and frequency, abdominal pain, general well-being, and extra-intestinal symptoms graded according to the disease activity indices listed in Table 1. The nurses were instructed to check for incomplete questionnaires and answer any study-related questions from the patients. The physicians performed a regular examination and made a four-level global assessment of disease activity (remission, mild, moderate, or severe disease activity) based on anamnesis, physical examination, and relevant medical data, but were 'blinded' for the HRQL questionnaires (Physician's Global Assessment, PGA). For the purpose of reliability analysis, a sub-group of patients ($n=40$) who were deemed to be in remission by the physician at the inception, and reported unchanged health status 4 weeks later, completed the HRQL questionnaires a second time (test-retest method). All study patients were offered a follow-up visit 6 months later, or earlier in case of disease deterioration, in which all procedures from the first visit were repeated.

HRQL questionnaires used in the study

Inflammatory Bowel Disease Questionnaire (IBDQ)

The IBDQ is a disease-specific questionnaire with 32 items sub-grouped into four dimensions (Guyatt et al. 1989): bowel symptoms (e.g. abdominal pain, loose stools), systemic symptoms (e.g. energy, weight problems), social function (e.g. work/school, social engagement), and emotional function (e.g. frustration, worries, embarrassment). Responses are graded on a 7-point Likert scale with higher scores indicating better HRQL (1=very severe problem, 7=no problem at all). The total score is the sum of the individual scores, ranging from 32 to 224. The original American-English IBDQ was translated into Swedish by two of the investigators in our study group and subsequently back-translated into English by a bilingual person living in the USA (Hjortswang et al. 2001). Any resulting discrepancies were discussed by all translators and a final Swedish version was agreed upon. The IBDQ is not applicable to patients with stoma and their results were therefore omitted.

Rating Form of IBD Patient Concerns (RFIPC)

The RFIPC is a self-administered disease-specific 25-item questionnaire that rates important worries and concerns of patients with IBD (Drossman et al. 1991). For each of the items, the respondent is asked ‘Because of your condition, how concerned are you with . . .?’. The degree of concern is marked on a 100 mm horizontal visual analogue scale (VAS). Zero mm represents ‘not at all’ and 100 mm ‘a great deal’. The ‘sum score’ is the mean of the 25 item scores. The RFIPC was translated into Swedish by members of our group and an English teacher (Hjortswang et al. 1997). A native-speaking English teacher then translated back into English. The result was discussed by all the translators and a consensus reached about the final Swedish wordings

The Short Health Scale (SHS)

The SHS is a self-administered questionnaire containing four questions, one for each of four major HRQL dimensions in IBD postulated by Hjortswang et al (1999): symptoms of the bowel disease, impairment of daily function caused by the bowel disease, disease-related worries, and general well-being (Table 5, p. 30, Hjortswang et al. 2006). The responses are graded on a 100 mm VAS, with higher values indicating worse outcome. The results are presented as an individual score for each dimension.

Short Form-36 (SF-36)

The SF-36 is a generic 36-item questionnaire subdivided into eight dimensions (physical function, physical role, bodily pain, general health, vitality, social function, emotional role, and mental health), and one single item concerning change in health status (Ware 1992, Sullivan et al. 1998). The item scores are weighted and transformed according to a standard algorithm into eight dimensional scores, ranging from 0 (worst possible state) to 100 (best possible). Dimensional scores can also be aggregated into two higher-order component scores (physical and mental) based on normal population reference values and dimensional weightings obtained from a factor analysis.

Psychological General Well-Being (PGWB)

The PGWB is a generic 22-item questionnaire measuring subjective feelings of well-being and distress (Dupuy 1984, Wiklund & Karlberg 1991). Responses are graded on a six-point Likert scale. Higher values correspond to better well-being. The items are grouped into six subscales, each representing an emotional state reflecting subjective well-being (*anxiety, depressed mood, positive well-being, self-control, general health, and vitality*). The sum score is the sum of the item responses, ranging from 22 to 132.

Methods of evaluation of IBDQ, RFIPC, and SHS (papers I, II and III)

Construct validity was evaluated by (1) assessing the pattern of correlation between the questionnaire under study and other HRQL measures, and by (2) comparing the scores of patients in remission with patients having active disease (mild, moderate, or severe) according to the PGA. The sum score or the subscales of a valid instrument should perspicuously correlate more strongly with measures of similar aspects of HRQL and vice versa. Furthermore, significantly better HRQL scores should be found in patients in remission, compared with pa-

tients having an active disease. Factor analysis was performed to study the interrelationships of the items and to define the underlying dimensions. The internal structure of the IBDQ, i.e. the sub-grouping of the items into the four dimensions, was further validated by studying the pattern of correlations between items, between items and dimensions, and between dimensions. In the evaluation of the RFIPC, face validity was assessed by encouraging patients to suggest additional items of worries and concerns related to their bowel disease that they felt were missing in the questionnaire.

Reliability was assessed using the test–retest method, in which the concordance between two measurements with purportedly unchanged conditions was analysed. Patients in remission at the first visit, who reported unchanged health status four weeks later, completed the HRQL questionnaires a second time. For the IBDQ subscales and the RFIPC, the internal consistency was assessed at the first visit by calculating Cronbach’s α .

Responsiveness was studied by comparing the change in score of patients who were stable in remission vis-à-vis the change in score of patients whose condition deteriorated or improved between the two study visits. Improvement or deterioration was defined as a change in either direction between remission and active disease (mild, moderate or severe).

The relationship between disease activity and HRQL (papers IV and V)

Factors predicting the outcome of disease activity assessment in CD (paper IV).

The correlation between the Crohn’s disease activity index (CDAI), and the physicians’ global assessment of disease activity (PGA) was analysed. A multiple linear regression analysis was performed to rederive the regression coefficients of the eight CDAI variables (loose stools, abdominal pain, general well-being, extra-intestinal complication, anti-motility drugs, abdominal mass, haematocrit, and body weight) using the PGA as the dependent variable. The contribution of each CDAI variable to the final score was assessed. The influence of demographic and disease-related factors on the CDAI and the PGA outcome was analysed by multiple linear regression analysis. The factors influencing total CDAI score were further studied regarding which of the CDAI variables they affected, by comparing the CDAI variable scores for different factor categories.

Structural equation modelling of the relationship between disease activity and HRQL (paper V).

The conceptual model of the five health dimensions (biological variables, symptoms, function, worries, and general well-being) and their interactions were validated with structural equation modelling (SEM). In SEM, theoretical models of how measured variables (manifest variables) are sub-grouped into dimensions (latent variables), and how these dimensions are related, can be assessed by analysing the correlation or covariance matrix of the measured variables.

A set of measured variables was chosen to represent each postulated dimension (Table 6, Fig. 4). ‘Biological variables’ were represented by haemoglobin (Hb), serum-orosomucoid (Om), and the van Hees index (VHI); ‘Symptoms’ by loose stools (LS) and abdominal pain (AP)

from the symptom diary; 'Function' by the subscales of social function from the IBDQ (ISF) and the SF-36 (SSF); 'Worries' by the four subscales of the RFIPC identified in the factor analysis in paper II: complications (RC), achievements (RA), intimacy (RI), and stigma (RS). Finally 'General Well-being' was represented by three subscales of PGWB identified by exploratory factor analysis: mood (PM), energy (PE), and stress (PS).

<u>I. Biological variables</u>			
Haemoglobin (Hb)	Orosomuroid (Om)	Van Hees Index (VHI)	
<u>II. Symptoms</u>			
Loose stools (LS)	Abdominal pain (AP)		
<u>III. Function</u>			
IBDQ Social function (ISF)	SF-36 Social function (SSF)		
4. Work/school activities	6. Limitation social activities		
8. Social engagements	9j. Limitation social visits		
12. Leisure/sports activity			
16. Avoid events			
28. Sexual activity			
<u>IV. Worries</u>			
RFIPC Achievements (RA)	RFIPC Complications (RC)	RFIPC Intimacy (RI)	RFIPC Stigma (RS)
1. Financial difficulties	5. Developing cancer	8. Attractiveness	11. Dirty
2. Pain or suffering	6. Dying early	9. Feeling alone	15. Treated different
3. Achieving full potential	7. Being a burden on others	12. Sexual performance	18. Odours
4. Loss of bowel control	16. Having surgery	20. Feelings about body	
10. Feeling out of control	17. Ostomy	21. Intimacy	
19. Energy level	23. Access to quality care	22. Sexual drive	
	24. Uncertain nature		
	25. Effects of medication		
<u>V. Well-being</u>			
PGWB Mood (PM)	PGWB Energy (PE)	PGWB Stress (PS)	
3. Depressed	1. Feeling in general	8. Tense	
4. Control of emotions	2. Illness, bodily disorder, pain	19. Relaxed	
5. Nervousness	6. Energy/vitality	22. Strain/pressure	
7. Downhearted/blue	9. Happy/satisfied personal life		
11. Discouraged/hopeless	10. Healthy enough to function		
13. Worried about health	12. Fresh/rested		
14. Losing mind	15. Interested		
17. Anxious/upset	16. Active/vigorous		
18. Emotionally stable	20. Cheerful/lighthearted		
	21. Tired/exhausted		

Table 6. The five dimensions (latent variables, I–V) of the conceptual SHS health status model and the measured (manifest) variables (the subscales and their specific items as numbered in the questionnaires) representing each dimension.

The measurement model (i.e. the grouping of the measured variables into the dimensions, and the covariance of the dimensions) was first validated with confirmatory factor analysis (CFA). If the measurement model was corroborated by the CFA, the structural model (i.e. the structural pathways or the causal linkages between the dimensions stipulated in the model) was tested with SEM. The structural model is depicted in Fig. 4.

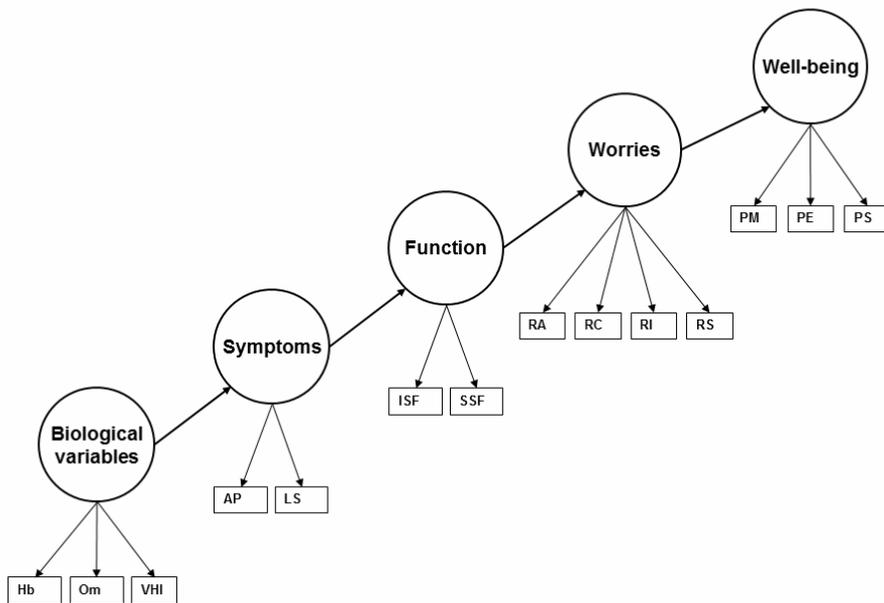


Figure 4. The structural model tested in the SEM analyses. Circle=latent variable/dimension, rectangle=manifest/measured variable, thick arrows=regression paths, thin arrows=factor loadings

Although a more network-like interaction between the dimensions was discussed originally (Hjortswang et al. 1999), the simplest linear model was chosen as a starting point. Based on results obtained in the subsequent analyses (modification indices), the model could be adjusted with additional interactions. In the CFA and the SEM, all parameters (the variances and co-variances of the dimensions, the regression weights of dimensions on measured variables, the variances of measurement errors of the measured variables, and the regression weights of the inter-dimensional pathways) were estimated by the maximum likelihood method. Statistical significance of the estimates was tested by dividing the estimate by its standard error (critical ratio). A critical ratio >1.96 was considered significant. The goodness-of-fit of the measured data to the model was assessed with three indices: The chi-square (χ^2) likelihood ratio test, the comparative-fit-index (CFI), and the root mean square error of approximation (RMSEA). Based on recommendations in the literature (Bentler 1990, Hu 1999), the following thresholds for adequate goodness-of-fit were used: $CFI \geq 0.90$, and $RMSEA < 0.08$. The χ^2 value should ideally correspond to a non-significant p -value (≥ 0.05), since the discrepancy between observed and expected data should be the smallest possible. However, this is rarely fulfilled in SEM research due to a high sensitivity of the test to the large sample sizes that are critical in order to obtain precise parameter estimation, and the inexact properties of psychometric measurements (Mc-Callum et al. 1996, Byrne 2001). The χ^2 likelihood ratio test is therefore preferably used for comparison between alternative models. Analysis of model misspecification was based on modification indices of the parameter estimates, and any model adjustment made was based on the magnitude of the modification index as well as theoretical reasoning.

Describing health-related quality of life and social characteristics of patients with CD (papers II and VI)

Worries and concerns of patients with CD (paper II)

A rank list of the patients' most worrying IBD-related issues was made, based on median values of the RFIPC item scores. Underlying dimensions of the RFIPC items were explored with factor analysis, and predictors of the degree of worries and concern for these dimensions and the total score were identified with multiple linear regression analysis.

General HRQL and social characteristics in CD (paper IV)

The SF-36 results were compared with the SF-36 results of a large Swedish health survey data base ($n=8930$, Sullivan et al. 1998) with match-case analysis. The means and standard deviations of the SF-36 subscales in the control group were obtained by randomly selecting two sex- and age-matched controls per study patient from the survey database. To further elucidate any HRQL issues specific for CD, comparisons were made with ulcerative colitis (UC). SF-36 data for UC were available from a HRQL study performed a few years earlier in Linköping and Örebro by Hjortswang et al. (2001). The methods of patient recruitment and data collection were identical, except for the exclusion of patients with an ileostomy in the UC study. Direct comparison between CD and UC was hampered by differing age and gender distributions in the two populations. To overcome this, the UC population was compared with gender- and age-matched controls selected from the SF-36 database in a procedure identical to the one for CD patients.

The PGWB results of the CD patients were compared directly with the results of the UC patients in the study by Hjortswang et al. (2001). To control for the demographic differences between the two IBD populations, multiple logistic regression analysis was employed.

Social characteristics (educational level, smoking status, marital status, parenthood, sickness, disability pension, and employment) collected in the demographic data questionnaire were compared with Swedish background population, adjusting for age and gender with indirect standardization.

Background population data grouped by gender and age were obtained from Statistics Sweden (Living Conditions Survey, Swedish Population Registry, and Labour Force Survey), and the registry of the Swedish Social Insurance Agency. The Living Conditions Survey (LCS) is a health survey of the Swedish population performed every second year by Statistics Sweden. Approximately 15,000 randomly selected persons representative of the Swedish population are interviewed regarding their living conditions. The LCS provided the rates of education limited to compulsory school, post-secondary school education, current daily smoking, and single living persons. In addition, the LCS rate of 'a long-lasting disease (or injury or other weakness) that reduces the working capacity to a high degree', were compared with the rate of CD patients reporting long-lasting sickness compensation and/or disability pension. Background population parenthood rate and number of children per parent were obtained from the Swedish Population Registry. The unemployment rate, defined as the proportion of the labour force (excluding students, sick leave, parental leave, disability pension) being unemployed at the end of 2000, was obtained from the Labour Force Survey. Disability pension

rates in the three participating counties (Jönköping, Örebro, and Linköping) at the end of 2000, were collected from the Swedish Social Insurance Agency.

Statistical analyses

As the results of the HRQL questionnaires do not follow a normal distribution and can be considered as ordered categorical data, non-parametric statistics were preferably used with exceptions made when necessary as discussed below. The risk of falsely rejecting a null hypothesis by chance was considered by lowering the significance level ($p < 0.01$ in general) when interpreting the significance tests for hypotheses with large numbers of comparisons.

Basic analyses

Averages and distributions of scores, and demographic variables were generally reported as medians and inter-quartile ranges. Chi-square tests were used for comparison of nominal data. Mann-Whitney U-test was used to compare ordered categorical data in two-sample cases and Kruskal-Wallis one-way analysis of variance to compare more than two groups. Wilcoxon signed rank test was used to compare two related samples in the analysis of responsiveness. To facilitate comparison of the responsiveness with previous evaluations, we also calculated the responsiveness ratio defined as mean difference in score of changed subjects divided by the standard deviation of difference in score of unchanged subjects (Deyo et al. 1991). A greater responsiveness ratio indicates better responsiveness. Correlations between ordered categorical variables were analysed with Spearman rank order correlation coefficient (r_s). The analysis of the concordance between repeated measurements (test–retest) was supplemented with calculation of intra-class correlation coefficient (ICC) to adjust for systematic differences between the measurements. As only means and standard deviations were available for SF-36 reference values, Student's t-test was used for comparisons. To evaluate the importance of any difference detected in SF-36 comparisons, effect size (Cohen's d) was calculated as the difference in means divided by the pooled standard deviation.

Multiple regression analyses

In paper IV, multiple linear regression analysis was performed with backward stepwise deletion to rederive the CDAI variable regression coefficients, replicating the methods used in the original study by Best et al. (1976). The method for estimating each variable's fractional contribution to the total CDAI was also replicated, i.e. the product of the regression coefficient and the standard deviation of each variable was divided by the sum of such products of all eight variables. To further estimate each variable's contribution to the final score, the mean absolute value of each variable was calculated and compared for the different levels of disease activity according to CDAI. Multiple linear regression analysis with backward stepwise deletion was also employed to identify disease-related and demographic variables independently associated with the CDAI, and with the PGA outcome. The variables were first analysed with univariate regression analysis, and variables with some degree of association ($p < 0.25$) were entered into the multiple regression analysis. Co-linearity between independent variables was evaluated with variance inflation factor (VIF). The same method of multiple linear regression analysis was used in paper II to identify predictors of the RFIPC outcome. Logistic regression analysis was used to control for discrepancies in demography between CD and UC patients,

when comparing PGWB and RFIPC scores between the two IBD-types. Score worse than the 25th percentile was used as dependent variable, and IBD-type, gender, smoking, age, and disease duration as independent variables. Logistic regression analyses were also performed to analyse the influence of gender on reduced work capacity and disability pension controlling for age, education, current smoking, co-morbidity, disease location (ileal, colonic, ileocolonic), disease behaviour (inflammatory, stricturing, penetrating), extraintestinal manifestation, and disease course in current year.

Exploratory factor analyses

The exploratory factor analyses performed in papers I and II were made using principal component analysis or maximum likelihood ratio with varimax rotation as extraction method. The number of factors was selected with latent root criterion (Eigen value >1). Each item was affiliated to the factor on which it exerted the greatest loading. Factor loadings below 0.40 were deemed non-significant.

Indirect standardization

In paper VI, indirect standardization was performed to adjust for gender and age distribution in the comparison of social characteristics with background population. For each gender, rates of specific age groups in the background population were applied to the corresponding age groups in the study population in order to obtain the standardized ratio between expected and observed number of cases. This ratio was further used to calculate the age- and gender-adjusted rate in the study population. The significance of any difference found was appraised with the Mantel-Haenszel χ^2 -test. The age-group interval varied for the different social factors, depending on available background population data.

Software

Calculations were made using the Statistical Package for Social Sciences (SPSS) v 13.0. All SEM analyses were made using SPSS AMOS v 18.0. The indirect standardization procedure was performed manually, using Microsoft Office Excel 2003 spreadsheet.

Ethical considerations

The study was approved by the Committee of Research Ethics at the Faculty of Health Sciences, Linköping University and Örebro University Hospital. The participants gave their informed consent before participating.

RESULTS AND DISCUSSION

Study cohort and study populations

Of 593 invited patients, 505 (85.2%) consented to participate in the study. Patient enrolment took place from the end of 1999 to the end of 2001. Demographic and disease-related data of the basic study cohort are presented in Table 7. Non-participants had a lower frequency of previous bowel resection (48.9% vs. 63.6 %, $p<0.01$), but did not differ from the participants regarding age, gender distribution, disease duration or disease location. Four-hundred and forty-nine patients (88.9%) participated in the follow-up visit. As the IBDQ is not adapted for use in patients with ostomy, only patients without ostomy were included in paper I ($n=448$). In paper II, only patients who returned a complete RFIPC questionnaire at the first visit were included in the analyses ($n=447$), except for the compilation of suggested additional items which included all returned RFIPC questionnaires ($n=503$). Only patients in Jönköping and Örebro were administered the SHS necessary for inclusion in paper III ($n=367$). In paper IV, only patients with complete CDAI and PGA assessments were included ($n=405$). In paper V, a valid SF-36 was needed for inclusion in the case-control analysis of general HRQL ($n=497$). When comparing the social characteristics with the different background population sources in paper V, all available data from the cohort of 505 patients were used. In paper VI only patients with complete data for all the manifest variables of the structural model could be included ($n=283$). The basic characteristics remained reasonably stable throughout the six papers, despite the varying inclusion criteria (Table 7).

	Frequency (%)	Range in the papers
Female gender	58.8	57.9–59.1
Age (years)	46 (33–56)*	44–46
Smokers	35.3	33.2–35.8
Compulsory school/University	39.2/23.0	35.0–39.0/22.8–24.1
Disease duration (years)	15 (6–25)*	12–15
Remission according to PGA	68.5	67.0–69.4
CDAI	103 (51–178)*	96–103
Disease classification (Montreal)		
<i>A (Age at diagnosis)</i>		
1. <16 years	12.8	13.1–13.3
2. 16–40 years	66.3	62.6–66.1
3. >40 years	20.9	20.5–24.1
<i>L (Location)</i>		
1. Ileal	34.8	34.7–37.5
2. Colonic	28.6	27.9–28.7
3. Ileocolonic	36.4	33.6–36.4
4. Isolated upper GI †	0.2	0.2–0.4
<i>B (Behaviour)</i>		
1. Inflammatory	40.4	40.0–43.1
2. Stricturing	21.4	21.5–23.2
3. Penetrating	38.2	37.8–38.7
Perianal disease	27.5	23.3–27.7
Extraintestinal manifestation	17.6	17.7–19.4
Previous bowel resection	63.6	58.0–63.7
Ostomy bag	11.3	0–11.3
Corticosteroids	24.8	24.7–27.6
Immunomodulators	25.9	26.2–26.6

Table 7. Demographic and disease-related characteristics of the total study cohort ($n=505$), and range of the characteristics in the papers. *) Median (25th–75th percentile). †) 6.1 % had L4 added to L1-3.

1. Evaluation of the Swedish versions of two disease-specific measures of health-related quality of life in Crohn's disease

IBDQ (Paper I)

The questionnaire was incompletely answered in 8.2% of the cases, mostly older patients omitting questions about sexuality, work, and leisure/sport activities. The IBDQ subscales generally correlated closely with their corresponding measures ($r_s=0.61-0.86$, $p<0.001$). The validity was further corroborated by significantly worse scores in patients with active disease ($p<0.001$ for all subscales and total score). The reliability assessment showed high test-retest correlations for total score ($r_s=0.92$) and subscales ($r_s=0.85-0.88$). Adequate responsiveness was indicated by the significant change in scores in the expected direction in patients who went from remission to active disease or vice versa ($p<0.001$ for all subscales and total score).

However, several findings in the analysis of the correlations between items, including the factor analysis, cast doubt upon the original grouping of the items into the four subscales. Fewer than 20% of the items correlated convincingly more strongly with their own subscale than with the other subscales, and five items correlated even more strongly with some of the other subscales. The subscales *Systemic symptoms* and *Emotional function* seemed to be closely related, and were mainly merged into one single dimension by the factor analysis. The subscale *Social function* was relatively consistent as a dimension, whereas the items of the subscale *Bowel symptoms* correlated rather weakly (median $r_s=0.38$), being splintered into three main dimensions by the factor analysis: *abdominal discomfort* (pain, cramps, bloating, nausea), *ano-rectal dysfunction* (soiling, passing gas, defecation need, embarrassment) and *diarrhea* (stool frequency and consistency, fear of not finding a toilet).

A similar problem with the internal validity of the Swedish IBDQ was noted in the evaluation on UC patients (Hjortswang et al. 2001). For UC, six dimensions were identified. Symptoms such as bloating, passing gas, and soiling did not load on any factor in UC. On the other hand did rectal bleeding load heavily together with loose stools on a *symptom* factor in UC, as opposed to a weak loading on a *Social function* factor in CD.

The original grouping of the items has been questioned also in evaluations of IBDQ translations into other languages (Cheung et al. 2000, Bernklev et al. 2002, Hashimoto et al. 2003, Vlachonikolis et al. 2003). The alternative groupings of the items, however, have differed between these studies and interpretation is hampered by the inclusion of both CD and UC patients in most of the analyses.

The IBDQ is therefore valid and reliable when used as an overall score, but conclusions regarding the different dimensions of HRQL are difficult to draw when comparing results between UC and CD and between different translations.

RFIPC (Paper II)

Similar to the IBDQ, about 10% of the questionnaires had unanswered items, typically items concerning procreation and sexuality omitted by the older patients. Another problematic item was *having an ostomy bag*, omitted by 2.6%, all of whom already had an ostomy. This could be explained by the translation of the English verb “having” an ostomy into the Swedish “få” an ostomy bag, which limits the meaning to *acquiring*, and not already *having* or *living with* an ostomy. Additional items were suggested by 22.5% of the patients (Table 8, p.46). Some of these items closely resembled the existing items and may have been added due to misinterpretation or due to an urge to express their strongest concerns more exhaustively. Examples of worrying issues seemingly not covered by the RFIPC are extraintestinal manifestations, long-term complications, concomitant health problems, ageing, and the chronic nature of the disease. The length of the list in Table 8 illustrates the abundance of variation in CD-related worries, and also the difficulty of capturing all individual concerns even when using a multi-item questionnaire.

The RFIPC sum score demonstrated a good validity by correlating more strongly with corresponding health measures than less related measures ($r_s=0.61-0.86$, $p<0.001$), and by showing a significantly higher degree of worry in patients with active disease vis-à-vis those in remission (median 32.0 vs. 18.0, $p<0.001$). For each of the 25 items the score was numerically higher in active disease but for some items the difference was not significant (e.g. *cancer*, *dying early*, *access to quality care*). The test-retest reliability of the sum score was excellent ($r_s=0.90$).

The assessment of responsiveness showed a significant change in sum score ($p=0.002$) accordant with the change in disease activity, but the change in median score was merely 5 points (25 vs.30). Only two specific items displayed a significant change (*uncertain nature of disease* and *pain*) in this group of patients. Furthermore, the responsiveness ratio of 0.84 was lower than for the IBDQ total score (1.43). Thus, the RFIPC seems to be less sensitive to change in disease activity, which makes it less useful as an endpoint in clinical trials.

The low responsiveness may be a characteristic of the disease-related worries per se, and not necessarily attributed to the specific instrument. Disease-related worries are probably more weakly associated with disease activity, and changes in this dimension may take place at a slower pace. Although a patient has achieved remission during the 6 months between visits, worries about future ill-health or effects of medication may persist. This emphasizes that disease-related worries constitute an important health dimension, which needs to be measured separately.

Topics	Items	<i>n</i>	Corresponding RFIPC items
Medical care	Waiting time Correct diagnosis Optional treatment Future cut downs	15	23. Access to quality medical care
Side effects of medication	Liver or kidney injuries Osteoporosis Teratogenicity	10	25. Effects of medication
Family	Taking care of family Absence from family life	10	10. Being a burden on others
Heredity	Will my children inherit CD?	9	14. Passing the disease to others
Extraintestinal manifestations	Joint or back pain Eye disease	9	2. Pain or suffering?
Long-term complications	Osteoporosis Kidney disease Vitamin deficiency Bowel perforation	9	-
Work and maintenance	Unemployment Coping with work tasks Living on sickness ben.	7	1. Financial difficulties 3. Achieve full potential
Concomitant health problems	Urinary incontinence Dental problems Allergy	5	-
Chronicity of disease	Will I ever get well? Life-long medication?	5	24. Uncertain nature of disease?
Surgery	How many times?	5	16. Having surgery
Fatigue	Constant lassitude	5	19. Energy level
Ageing	How to manage the disease in old age?	5	-
Psychological symptoms	Insomnia Anxiety Mood instability	5	10. Feeling out of control?
Bowel control	Finding a toilet in time Urgency after meals	4	4. Loss of bowel control
Ostomy	Bandaging problems Sounds and leakage Will it be permanent?	4	17. Having an ostomy bag
Anal problems	Incontinence Pain	4	4. Loss of bowel control ? 2. Pain or suffering ?
Social function	Journeys and visits Restaurants	3	9. Feeling alone? 11. Feeling dirty?
Other gastrointestinal symptoms	Heartburn, nausea Abdominal cramps	3	2. Pain or suffering?
Clinical procedures	Endoscopy	2	-
Weight problems	Over-/underweight	2	-

Table 8. Additional items of worries and concerns suggested by 113 patients. The items are grouped into 20 main topics with corresponding RFIPC items suggested when possible (*n*=number of patients).

2. Evaluation of the Short Health Scale: a new concept and instrument for health assessment (paper III)

Psychometric properties

The pattern and strength of correlations between the SHS items and corresponding HRQL measures ($r_s=0.50-0.83$) supported a good validity, on a par with IBDQ and RFIPC. Further evidence of good validity was provided by the significantly worse scores in patients with active disease, compared with patients in remission ($p<0.001$). This finding was consistent also when only patients with mild disease activity were compared with patients in remission.

Test-retest reliability was adequate ($r_s=0.69-0.82$), although the Spearman correlation for SHS *Well-being* did not reach the stipulated standard level of 0.70 (Nunnally 1978) and showed a trend toward better scores at the retest. This item, however, is intended to cover all aspects of well-being and is expected to have the weakest association with disease activity according to the SHS model.

All four SHS items showed a significant change in score in the expected direction in patients whose disease activity classification changed from remission to active disease, or vice versa ($p<0.001-0.004$). Patients in stable remission, on the other hand, had unchanged scores. Again, these significant differences persisted also when only patients with mild disease activity were analysed. The SHS responsiveness ratios were 1.98, 1.50, 1.06, and 1.41 for *Symptoms*, *Function*, *Worries*, and *General well-being* respectively. This is on a par with or even superior to the corresponding ratios for IBDQ (1.43) and RFIPC (0.84). The lowest responsiveness was noted for *SHS Worries*, consistent with the finding in paper II of a relatively weak association between worries and current disease activity.

When comparing the psychometric properties of SHS in CD with the previous SHS evaluation in UC, the results are similar (Hjortswang et al. 2006). The validity assessed by concurrent validity and known-group comparison and the sensitivity to change were equally good. The test-retest correlations were somewhat stronger for UC ($r_s=0.71-0.91$), but this can be attributed to the shorter retest interval (2 weeks vs. 4 weeks).

The pros and cons of SHS

The SHS is easy to complete (completion rate 99.7% in the study) and requires no further processing. As opposed to many of the multi-item questionnaires summing up into a single score, the four-item structure provides a comprehensive overview of how the most important dimensions of HRQL are affected. Whether perceived illness is caused by a heavy symptom burden, functional limitations, disease-related worries or general distress is important information in the decision making process in clinical practice, as well as in outcome assessment of clinical trials. The SHS does not draw a detailed picture of the patient's HRQL. Structured interviews or exhaustive multi-item questionnaires may be superior tools in this aspect. The SHS can, however, serve as a catalyst and a basis for a deeper discussion around problematic areas specific for the patient in the clinical encounter.

Several items of the IBDQ and the SF-36 questionnaires ask respondents to quantify *how often* or *how much of the time* the respondent has experienced hindrance in certain areas, omitting the *quality* aspect. A patient might have been able to participate in an activity, but with an impaired performance or pleasure due to their health status. The open-ended phrasing of the SHS items allows the respondent to consider both quality and quantity in their rating. Moreover, the respondent can individually define and weigh the importance of the symptoms, limitations in function, worries, and sense of well-being. By contrast, most existing questionnaires focus on detailed items, some of which may be irrelevant for the individual respondent and therefore left unanswered. As pointed out in the evaluation of the 25-item questionnaire RFIPC, additional items of concern were easily elicited when asking the patients, and even a 32-item questionnaire such as IBDQ lacks questions concerning arthralgia, fistulae, skin or eye manifestations.

The representation of one single item for each dimension in SHS increases the element of random error, which was reflected in the lower test-retest reliability compared with the two multi-item questionnaires. However, aggregation of multiple items can mask or dilute information about changes, leading to a lower responsiveness (Staquet et al. 1998). For instance, a patient may experience increased intensity of one single symptom (e. g. rectal bleeding due to proctitis) which highly influences his or her HRQL. This significant change would probably be detected with an open-ended symptom question, but may be dispersed and unnoticed if aggregated with several other unchanged symptoms. One disadvantage of letting the respondent define the symptoms could be the inclusion of symptoms irrelevant to the bowel disease, e.g. those caused by a functional gastro-intestinal disorder or concomitant disease. This problem, however, is difficult to avoid even when detailed questions are asked. The universal character of the SHS items could well explain why the psychometric standard was equally good in CD and UC, despite the different characters of the diseases. This generalizability is promising, indicating applicability to other chronic diseases as well.

The use of VAS is not without complications. The items (symptom, function, worries, and well-being) are theoretical constructs that must be operationalized into measurable variables. The numerical values obtained from the measurement are ordered categorical data. This means that they do not contain information about size or distance of the construct, although the use of millimetres on a visual scale may mislead the investigator to believe so. The information lies solely in the ranking of the measured values. Forty mm on SHS *Worries* is more than 20 mm, but not necessarily twice as much worries. A rise in SHS *Symptom* from 30 mm to 40 mm is an increase in symptoms, but not necessarily by 30%. It is therefore important to use non-parametric statistical methods to the largest possible extent. The use of a Likert-scale, with a few ordered and labelled categories, could have been pleaded in this regard. For example, the result of SHS *Symptoms* could be presented as the proportion of patients with no or only mild symptoms. This may be more informative if the instrument is used to describe or compare HRQL in different populations. However, the low variability of this type of scale may hamper its use in studies evaluating the effect of interventions.

3. Analysis of the relationship between disease activity and health-related quality of life (papers IV and V)

Factors predicting outcome of disease activity assessment (paper IV)

The CDAI was relatively weakly correlated ($r_s=0.44$) with the physician's assessment of disease activity (PGA) (Fig. 5). Of patients with a CDAI score above the limit for active disease (>150 points), only 55.6% were classified by their physician as having active disease. Of patients deemed to have active disease according to their physician, only 58.1% were classified by the CDAI as having active disease.

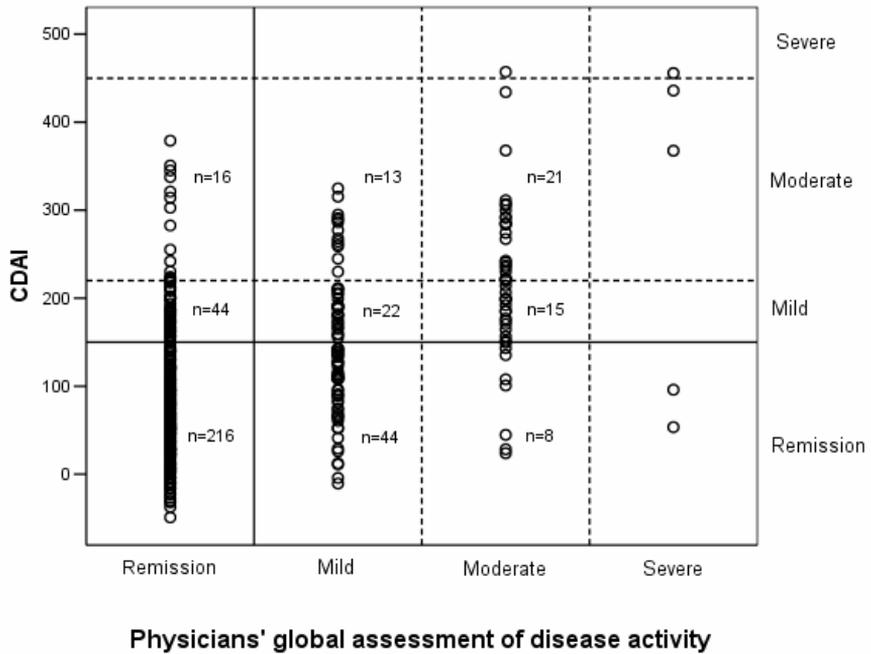


Figure 5. Scatter diagram of the PGA plotted against the CDAI. Spearman correlation (r_s) = 0.44 ($p<0.001$). Whole reference lines delimit remission from active disease. Dotted reference lines mark the limits between mild, moderate and severe disease activity.

The distribution of CDAI scores among the eight variables for different levels of CDAI score is shown in Fig. 6. The subjective patient-reported variables loose stools, abdominal pain, and general well-being increasingly dominate the overall CDAI score as it increases, while the contribution from the objective variables of disease activity is relatively constant throughout the different levels of overall CDAI scores. In an attempt to rederive the CDAI formula, a different set of coefficients for the CDAI variables was obtained. In contrast to the original study by Best et al. (1976), general well-being did not reach a significant level in the model and its fractional contribution diminished from 23% to 10%. In our study, the physicians attached a greater importance to extraintestinal complications, abdominal mass, and loose stools when assessing disease activity.

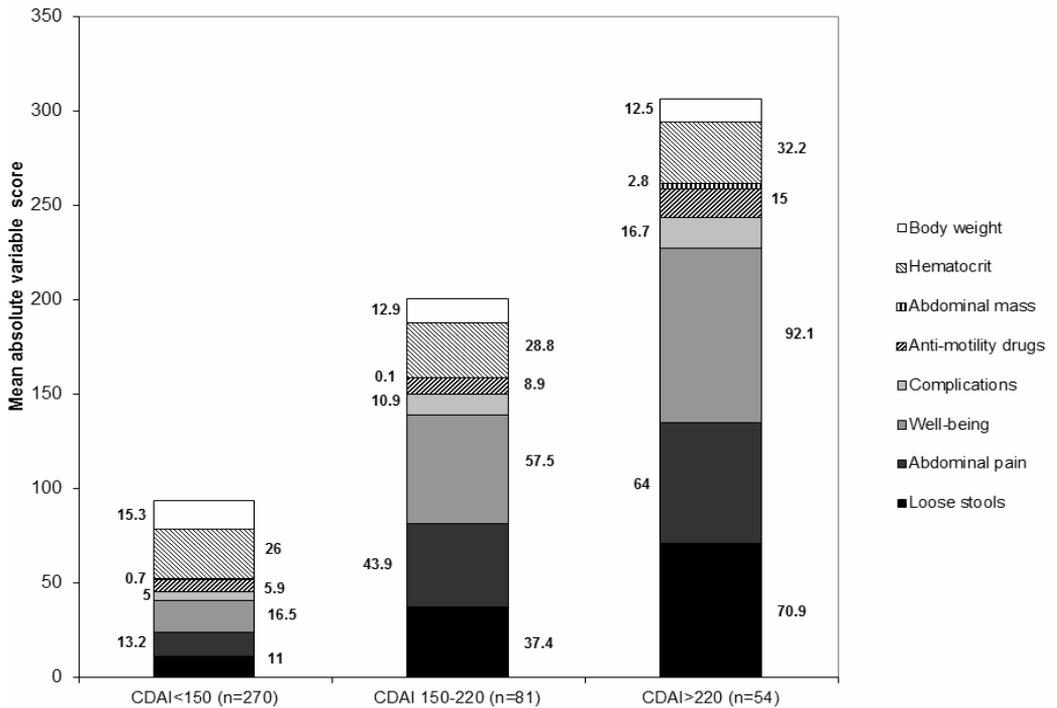


Figure 6. Mean absolute values of the CDAI variables for patients in remission (CDAI < 150), with mild disease activity (CDAI 150-220) and with moderate to severe disease activity (CDAI > 220).

The regression analyses showed that the outcome of the PGA could be predicted by factors traditionally associated with disease activity, such as CRP, fistula, and luminal stenosis (Table 9). For CDAI, however, the list of predictors also included factors with no obvious relation to current disease activity (female gender, concomitant disease, and previous bowel resection).

Predictor	PGA		CDAI	
	β	p	β	p
CRP	0.234	<0.001	0.195	<0.001
Intestinal stenosis	0.159	0.001	0.107	0.02
Fistula	0.162	0.002	-	-
Previous bowel resection	-	-	0.246	<0.001
Smoking	-	-	0.167	0.001
Concomitant disease	-	-	0.111	0.02
Female gender	-	-	0.097	0.048

Table 9. Predictors of PGA and CDAI outcome obtained from multiple linear regression analyses. β = standardized regression coefficient.

Women had higher scores, but only for the two most subjective CDAI variables (abdominal pain and general well-being). No objective indications of a more severe inflammatory activity in women were found in this study, and none have been reported elsewhere. However, female gender has in numerous studies been independently associated with worse outcome in subjec-

tive health perception (Sullivan 1994, Sainsbury 2005, Cherepanov et al. 2010). Patients with concomitant disease received higher scores due to a poorer general well-being. Previous bowel resection increased the CDAI score due mainly to higher scores for loose stools, and use of anti-diarrheal drugs. Patients with a history of bowel resection can develop diarrhea due to short bowel syndrome, bile acid malabsorption, or intestinal bacterial overgrowth, unrelated to bowel inflammation (Nyhlén et al. 1994, Castiglione et al. 2000).

This study shows that CDAI only partly measures disease activity, as appreciated objectively by the physicians, and to a greater extent measures subjective health perception, i.e. HRQL. CDAI correlated more strongly with the HRQL instrument IBDQ ($r_s=-0.71$) than with the PGA ($r_s=0.44$). This is in contrast with the general view of the CDAI as a surrogate marker of inflammatory activity, which makes it the preferred outcome measure in most clinical trials. When the CDAI was constructed, however, the authors clearly expressed their intention to create an index whose numerical value “would be proportional to degree of *illness*”. They also acknowledged that the subjective aspects constituted an important part of the evaluation of disease severity. In line with this they used a more holistic PGA as the dependent outcome variable, asking the physicians to rate “how the patient was doing”. In our study, we more explicitly instructed the physicians to rate the “disease activity”. Moreover, our investigators could have been more influenced by inflammatory activity due to the closer endoscopic monitoring available in modern clinical practice.

The advantages of including HRQL in CD outcome assessment is widely acknowledged, but the mix of both disease activity and HRQL variables in the CDAI leads to difficulties in sorting out what aspect of health one actually measures. This can lead to inclusion of patients in clinical trials on the basis of a low subjective health perception secondary to psychosocial factors, or functional GI disorders, thus biasing the results of the trial. Although the overall assessment of health status must include both objective and subjective variables, they should be measured separately.

Structural equation modelling of the relationship between disease activity and HRQL (paper V)

Complete data were available for the 14 manifest variables in 283 cases. Despite a rather strict selection of patients (56% of those originally invited), the basic characteristics of the patients remained stable. The only difference was shorter disease duration in included patients. All parameter estimates (variances and co-variances of the dimensions, error variances, and factor loadings of the manifest variables) were significant in the confirmatory factor analyses of the measurement model. Modification indices suggested a measurement covariance between *loose stools* (LS) and IBDQ *Social Function* (ISF), and between RFIPC *Intimacy* (RI) and RFIPC *Self-image* (RS) to be allowed in the model. This was theoretically plausible, as loose stools can interact strongly with ability to work or participate in social activities, and issues concerning intimacy can very well be associated with self-image. The goodness-of-fit indices of the measurement model were more than adequate (CFI=0.965, RMSEA=0.062), thus supporting the existence of the dimensions and their mutual correlation. The structural model (Fig. 4, p.39), in which the stipulated regression paths between the dimensions are included,

could therefore be tested. The regression weights of the pathways were all significant and in the expected directions. Modification index suggested a cross-loading for the dimension symptoms on RFIPC *Achievements* (RA), which was added to the model. This was motivated by the inclusion of *worries about pain* and *loss of bowel control* in RFIPC *Achievements* (see Table 6, p. 38), which should be associated with *abdominal pain* and number of *loose stools* in the symptom dimension. Moreover, the model would gain a significant drop in χ^2 -value (i.e. significant improvement of goodness-of-fit) by adding a regression path directly between function and well-being. The resulting model, including the regression weights and the goodness-of-fit indices, is shown in Fig. 7.

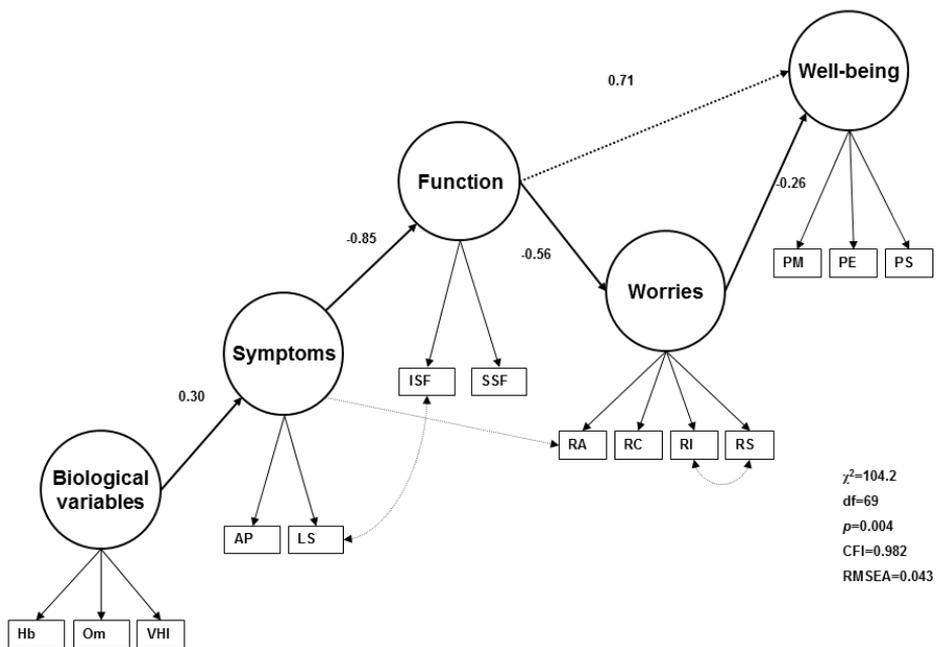


Figure 7. Structural pathways of the SHS health status model with standardized regression weights and goodness-of-fit indices. Abbreviations are explained in Methods. Circle=latent variable, rectangle=manifest variable, thick single-headed arrow=regression path, thin single-headed arrows=factor loadings, double-headed arrow=measurement covariance. Dotted lines are modifications.

The CFI passed the threshold for adequate fit by a wide margin (0.982), even reaching the level (>0.95) which is suggested to be a good fit (Bentler 1990, Hu 1999). This level indicates that 98% of the variance in our sample is explained by the model. The RMSEA evaluates the error of approximation and how well a model fits the population covariance matrix. A value below 0.05 is deemed to be good to excellent, a goal reached by our model (0.043).

Summarizing the model in Fig. 7, biological abnormalities induce symptoms, which impair function, which in turn elicits worries, and worries are associated with a lower level of well-being. Multiple interactions between the dimensions in a network rather than a sequential line were hypothesized in the original thesis (Fig. 3b, p.29, Hjortswang et al. 1999). For instance, biological variables can affect worries directly, as when a patient without symptoms is informed about abnormal blood samples or severe inflammation found during endoscopy. Also, worries may elicit symptoms of abdominal pain or loose stools. Indeed, the modification indices obtained in the SEM showed that the model was improved by adding a positive association directly between *Function* and *Well-being*. However, further associations between the dimensions did not improve the model fit. Nevertheless, more complex network-like or recursive interactions among the dimensions cannot be excluded. The SEM yields a compromise between degree of explanation and complexity. A more parsimonious model is rewarded in the goodness-of-fit assessment, at the expense of degree of explanation. Only the strongest paths between the dimensions may be justified in the modelling process, even though more complex interactions may be true in reality.

An interesting finding was the rather low standardized regression weight between *Biological variables* and *Symptoms* (0.30). This means that biological variables are relatively distant from the other variables, which is consistent with our clinical experience that disease activity, as defined by biological abnormalities (e.g. CRP elevation or mucosal lesions), is rather vaguely connected with the dimensions of HRQL.

Factor correlations	BV	SY	FU	WO	GW
Biological Variables (BV)	-	-	-	-	-
Symptoms (SY)	0.35	-	-	-	-
Function (FU)	-0.21	-0.84	-	-	-
Worries (WO)	0.20	0.66	-0.68	-	-
General Well-being (GW)	-0.22	-0.70	0.85	-0.75	-

Table 10. Factor (latent variable) correlations from the confirmatory factor analysis.

In the correlation matrix of the dimensions (Table 10), the correlations should generally decrease from main diagonal to left lower cell, as the associations should weaken with the distance in the postulated sequence: *Biological variables* → *Symptoms* → *Function* → *Worries* → *Well-being*. However, the correlations increase in the last row (*Well-being*). This could be an empirically based argument for placing *Worries* last in the sequence (Fig. 8). This model had equal goodness-of-fit indices. Therefore, the SEM analysis cannot firmly establish which model fits the data best. In theory, worries could be a reaction or response to the perception of well-being, rather than a determinant. Worries may have a greater influence of relatively uncontrollable and irrational emotions or fears, encompassed in the personality or trait (Borkovec et al. 1983), while symptoms, daily function, and general well-being are assessments of states, having larger elements of reasoning, comparing and calculating. This may question the importance of measuring worries if these do not determine well-being. However, knowledge of the type and magnitude of patients' worries helps us to understand their fears and unmet needs. It also reflects patients' ability to meet the challenge of ill-health. This ability can be an important determinant of health care utilization, treatment compliance and patient preference in choice of treatment.

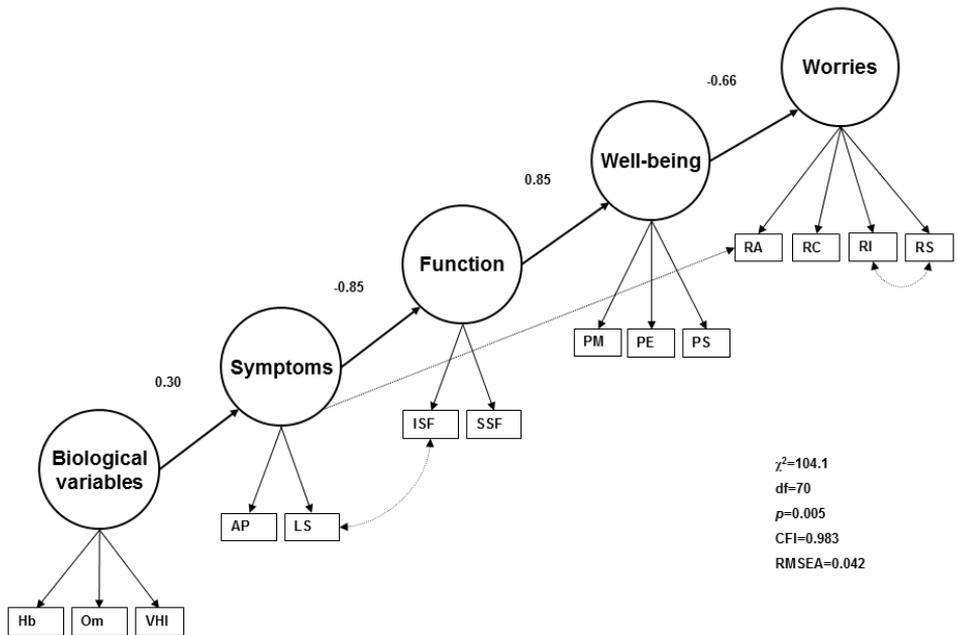


Figure 8. Alternative structural pathways of the SHS health status model with standardized regression weights and goodness-of-fit indices.

It should be noted that SEM has its limitations. Firm conclusions regarding causality in the structural pathways cannot be drawn. Furthermore, the proposed model only represents an approximation of the reality and the fit indices merely imply that the model is a plausible solution. Another problem is the assumption of multivariate normality made in SEM, a criterion rarely met in psychometric research. However, SEM analyses are considered to be fairly robust against this violation, especially when larger sample sizes are used and the scaling of the measured variables has more than four levels. In addition, the consequence of multivariate non-normality ought rather to be underestimation of the goodness-of-fit statistics (Byrne 2001). The results of the SEM therefore strongly support the SHS model as a valid conceptualization of health status in CD, and call for further evaluations of the model also in other chronic diseases.

4. Describing health-related quality of life and social characteristics of patients with Crohn's disease (papers II and VI)

Worries and concerns (paper II)

The CD patients were (in descending order) most worried about *having an ostomy bag*, *low level of energy*, *loss of bowel control*, *effects of medication*, and *having surgery* as ranked by the median item score (Fig. 9). Placed at the bottom of this list were in reverse order *ability to have children*, *passing the disease to others*, and *being treated as different*. The list is fairly comparable with the one found in Swedish UC patients (Hjortswang et al. 2001), although they ranked worries about *developing cancer* higher and *energy level* lower (Fig.9). The RFIPC sum score was higher in CD patients (median 22.2 vs. 14.3, $p<0.001$). This finding was consistent even when excluding CD patients with an ostomy and when controlling for the other differences in gender distribution, smoking rate, age, and disease duration, using logistic regression analysis (Odds ratio for IBD-type [CD/UC]: 1.85, 95% CI: 1.28–2.63, $p=0.005$, see Methods p.41). Of the specific item scores, two thirds were significantly ($p<0.01$) higher in CD.

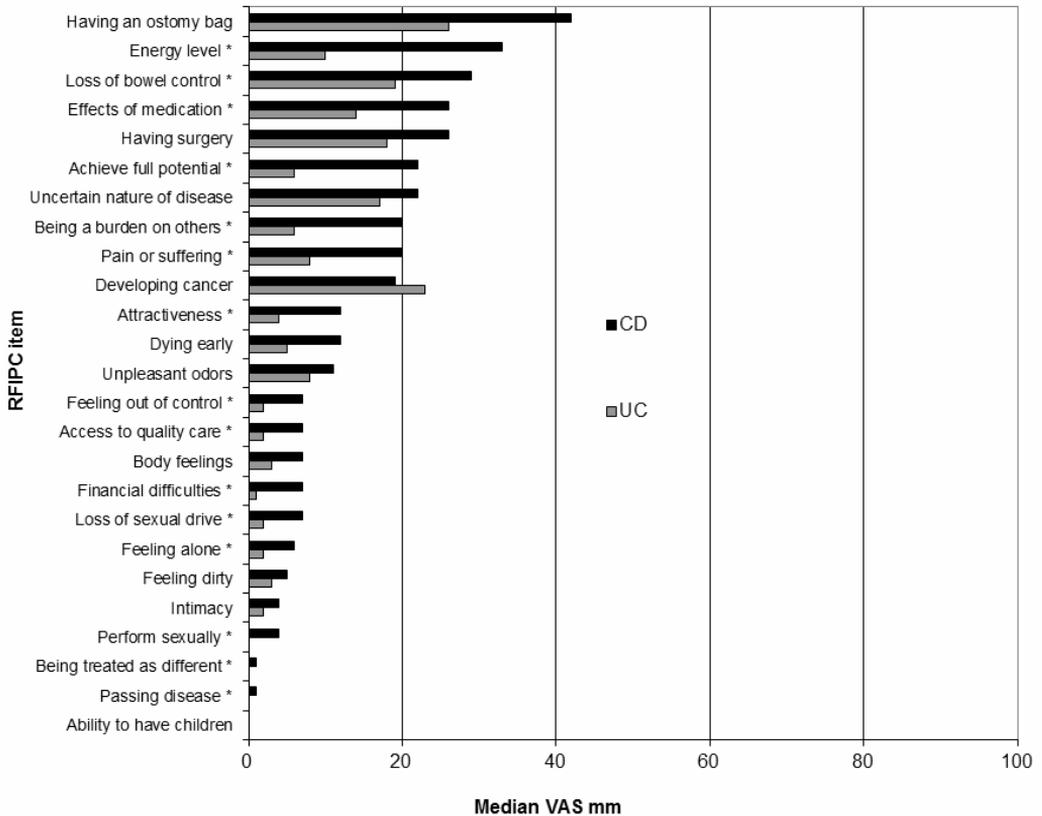


Figure 9. Median RFIPC item scores for CD ($n=406$, ostomists excluded) compared with UC (Hjortswang et al. 2001, $n=292$). Asterisks designate significant differences ($p<0.01$).

Compared with a previous study that compiled RFIPC results from 1141 CD patients in Europe (including 37 Swedish patients), North America, and Israel (Levenstein et al. 2001), our patients seemed generally less worried (mean sum score 28.7 vs. 40.0). Interestingly, the international study described a north to south gradient across Europe, with higher values in Mediterranean countries. The authors noted an association between worse RFIPC score and lower national economic prosperity, but also speculated that better doctor–patient continuity and emphasis on patient education and self-management may have allayed worries in northern countries. The ranking list based on mean scores (median scores were not presented in the international study) was similar except for *uncertain nature of disease*, *body feelings* and *intimacy* being ranked higher (more worried), and *dying early*, *developing cancer*, and *loss of bowel control* being ranked lower (less worried) in the international cohort (Table 11). Further speculation regarding cultural characteristics to explain these differences is dubious. Suffice it to notice that cultural differences regarding the degree and ranking of worries should be taken into account in international comparisons of RFIPC results.

Swedish Ranking	Item	Swedish Mean score (n=447)	International Mean score (n=1141)	International Ranking	Ranking difference
1	Having an ostomy bag	44.3	55.2	3	-2
2	Loss of bowel control	39.1	47.2	7	-5
3	Energy level	37.7	59.2	2	+1
4	Having surgery	36.0	52.9	5	-1
5	Being a burden on others	35.6	47.1	8	-3
6	Effects of medication	35.2	55.2	4	+2
7	Achieve full potential	32.5	47.9	6	+1
8	Developing cancer	32.5	37.3	13	-5
9	Uncertain nature of disease	32.4	60.0	1	+8
10	Pain or suffering	30.8	44.9	9	+1
11	Unpleasant odours	30.2	44.8	10	+1
12	Dying early	28.6	31.8	19	-7
13	Loss of sexual drive	25.7	33.7	17	-4
14	Access to quality care	25.3	35.2	15	-1
15	Financial difficulties	24.8	33.6	18	-3
16	Attractiveness	24.3	35.6	14	+2
17	Feeling out of control	23.8	37.4	12	+5
18	Body feelings	22.5	43.5	11	+7
19	Feeling alone	22.4	31.8	20	-1
20	Perform sexually	22.3	29.8	21	-1
21	Feeling dirty	22.2	27.7	22	-1
22	Intimacy	21.5	35.0	16	+6
23	Passing disease	20.5	26.2	23	0
24	Being treated as different	15.3	24.5	24	0
25	Ability to have children	9.8	23.4	25	0

Table 11. Mean RFIPC item scores of the study cohort compared with a compilation of international results (Levenstein et al. 2001)

Factor analysis identified four underlying dimensions of the RFIPC items (Table 12). The first dimension (Complications) collected worries about threats to life and limb (*having surgery, ostomy, cancer, effects of medication*) and expectations of receiving aid against these threats (*burden on others, access to quality care*). In the second dimension (Achievements) we found issues concerning achievements in daily life (*financial difficulties, feeling out of control, achieving full potential*) and disease-related impediments to reaching their goals (*energy level, pain, loss of bowel control*). The third and fourth dimensions (Intimacy and Stigma) gathered repercussions on intimate relations and self-image.

Complications Sum score: 33.9	Achievements Sum score: 31.2	Intimacy Sum score: 22.2	Stigma Sum score: 21.7
Having an ostomy bag (1)	Energy level (2)	Attractiveness (11)	Feeling dirty (18)
Effects of medication (4)	Loss of bowel control (3)	Body feelings (15)	Treated as different (23)
Having surgery (5)	Achieving full potential (6)	Loss of sexual drive (18)	Unpleasant odours (13)
Uncertain nature of dis. (7)	Pain or suffering (9)	Feeling alone (20)	
Being a burden (7)	Feeling out of control (14)	Intimacy (21)	
Developing cancer (10)	Financial difficulties (15)	Perform sexually (21)	
Dying early (11)			
Access to quality care (15)			

Table 12. The four dimensions of the RFIPC as suggested by factor analysis, and their sum scores. The overall ranking of each item is presented within parentheses.

Two items failed to load on any factor (*passing the disease to others* and *ability to have children*). These items also had the lowest median scores, and have been ranked the lowest in several other studies. However, even though an item fails to load on a factor, or has a low median score, it may still be important to certain subgroups of patients. For instance, *ability to have children* was ranked 10th with a median score of 19 mm in female patients under 30 years of age.

The two most salient variables independently associated with more worry were disease activity assessed by the physician (PGA), and female gender (Table 13). Disease activity has been presented as a strong predictor of RFIPC in several studies (Drossman et al. 1991a, Moser et al. 1995, de Rooy et al. 2001, Mussell et al. 2004, Canavan et al. 2006), but only one previous study used a physician-based objective assessment of disease activity similar to our study (Blondel-Kucharski et al. 2001). A strong association between patient-reported disease activity and disease-related worries is not surprising as both variables are dimensions of subjective health perception. The use in our study of a physician-based disease activity definition confirms that also objective aspects of disease activity influence worries.

Regarding gender, the previous results have been diversified. Half of the studies reported a negative influence of female gender (Drossman et al. 1991a, Blondel-Kucharski et al. 2001, Mussell et al. 2004) though comparisons are hampered by differing populations (CD, or mixed CD and UC), inclusion methods (postal questionnaires, or office visits), different RFIPC versions, and definitions of disease activity (subjective or objective). In our study, the worries were greater for women in all items except for two: worries about *having an ostomy bag* and *attractiveness* did not differ significantly between genders.

Greater body mass index was also associated with a worse RFIPC outcome. This has not been reported before, and was unexpected as a more severe disease course is more likely to result in weight loss. However, the association is reasonable, considering that it was limited to the areas of attractiveness, intimacy and self-image.

Six other variables were associated with more worry: use of corticosteroids, extraintestinal manifestation, older age, previous bowel resection, ostomy bag, and living alone. However, their regression coefficients were borderline significant and any conclusions should be drawn with caution.

Predictors	Sum Score		Complications		Achievements		Intimacy		Stigma	
	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>
Disease activity (PGA)	0.234	<0.001	0.204	<0.001	0.230	<0.001	0.241	<0.001	0.163	0.001
Female gender	0.183	<0.001	0.127	0.01	0.154	0.002	0.119	0.015	0.140	0.005
Body Mass Index	0.134	0.008	-	-	-	-	0.161	0.001	0.161	0.002
Corticosteroids	0.103	0.049	-	-	0.116	0.023	0.123	0.016	-	-
Extraintestinal manifest.	-	-	0.111	0.044	0.115	0.021	-	-	-	-
Age	-	-	0.105	0.044	-	-	-	-	-	-
Previous bowel resection	-	-	-	-	-	-	-	-	0.125	0.014
Ostomy bag	-	-	-	-	-	-	0.100	0.04	-	-
Living single	-	-	-	-	-	-	0.103	0.036	-	-

Table 13. Independent predictors of RFIPC outcome identified by multiple linear regression analysis. β =standardized regression coefficient.

General HRQL compared with background population and UC (paper VI)

SF-36

The SF-36 scores were significantly lower on all subscales in CD patients, compared with the sex- and age-matched controls (Table 14). Although significant, a difference may not be of practical importance. To further estimate the relevance of any difference found, effect size (Cohen’s *d*) was calculated. A large negative effect size ($d > 0.8$) was seen only for *general health* (0.98). In this subscale the patients assess their health state or propensity to get sick in comparison with other people, and their expectations of suffering worse health. The second most negatively affected subscale was *vitality*, with a medium ($d=0.5-0.8$) effect size (0.58). This is consistent with the high rank of the RFIPC-item *energy level* in paper II. Moreover, fatigue has been recognized as an important and prevalent feature of CD (van Langenberg & Gibson 2010, Romberg-Camps et al. 2010). *Role physical, social function, mental health, bodily pain, and role emotional* were all impaired, but with a small ($d=0.2-0.5$) effect size (0.28–0.45). The reduced score in *physical function* had the smallest effect size (0.18), which is understandable since it contains items of low relevance for bowel diseases (walking, dressing, carrying groceries et cetera). Both the physical and mental summary measures (PCS and MCS) were reduced, but the effect size was larger for the physical component (0.53 vs. 0.43).

SF-36 subscale	CD			UC				
	Sample (n=497)	Controls (n=994)	<i>p</i>	Effect size (<i>d</i>)	Sample (n=284)	Controls (n=568)	<i>p</i>	Effect size (<i>d</i>)
Physical Function	83.5	87.1	<0.001	-0.18	90.5	86.5	0.004	0.22
Role Physical	65.1	82.2	<0.001	-0.45	79.0	81.8	0.256	-
Bodily Pain	65.7	73.5	<0.001	-0.29	76.0	73.5	0.185	-
General Health	54.3	75.4	<0.001	-0.98	65.9	75.5	<0.001	-0.43
Vitality	55.1	69.0	<0.001	-0.56	64.6	68.8	0.015	-0.18
Social Function	79.8	88.7	<0.001	-0.40	85.6	88.2	0.082	-
Role Emotional	75.9	85.2	<0.001	-0.28	82.2	84.6	0.291	-
Mental Health	74.7	81.9	<0.001	-0.38	78.1	81.5	0.015	-0.18
Physical Summary	44.3	49.7	<0.001	-0.53	49.4	49.6	0.776	-
Mental Summary	45.9	50.5	<0.001	-0.42	47.6	50.1	0.002	-0.23

Table 14. SF-36 scores compared with background population controls for CD and UC.

When separating the genders, the pattern of subscale and component score impairment was similar, but with a strikingly larger effect size for women (Fig.10). For women all subscales were significantly reduced, of which three subscales with a medium effect size, and one with large effect size (*general health*). Men did not have significantly reduced scores on three of the subscales (*physical function, bodily pain, and role emotional*), and only one of the subscales (*general health*) was reduced with a medium effect size.

In UC, only *general health* was significantly reduced ($p<0.001$) vis-à-vis the controls, and only with a small effect size. There was only a borderline reduction of *vitality* with an uncertain relevance ($d=-0.18$), a finding in accordance with previous reports of less pronounced fatigue in UC compared with CD (Romberg-Camps et al. 2010). *Physical function* was even better than the background population for male patients ($p<0.01$), but with a small effect size (0.28). In contrast to CD, only the mental dimension (MCS) was reduced, although with a small effect size (0.23). Women had a worse outcome also in UC, but the differences were less pronounced, compared with CD (Fig. 10).

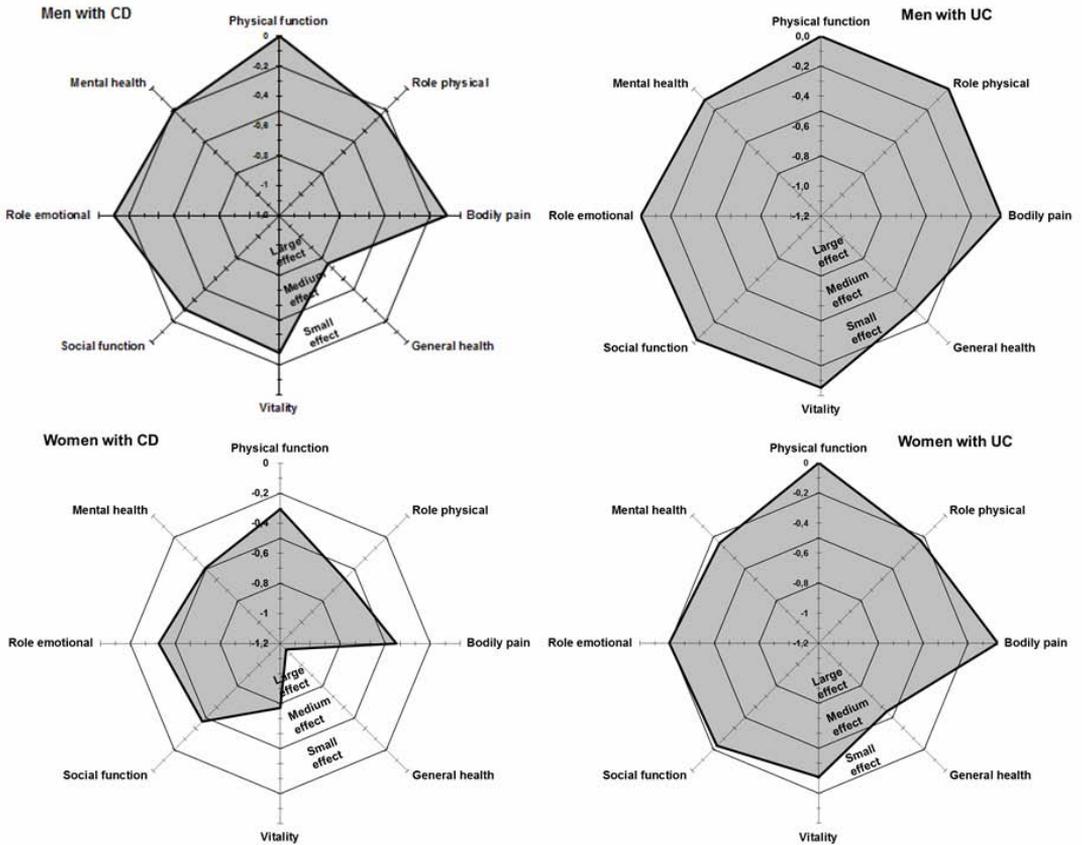


Figure 10. Gender- and disease-specific spider web diagrams of effect size for SF-36 subscale difference in patients with CD ($n=497$) and ulcerative colitis ($n=284$) compared with controls. The eight radiating scales of each diagram represent the effect size of reduced scores for each subscale, with the effect size verging into the centre.

Most previous studies have shown significantly reduced SF-36 for CD both when compared with a background population and with UC (Blondel-Kucharsky et al. 2001, Juan et al. 2003, Bernklev et al. 2005). One population-based study of Swedish IBD patients presented similar results, albeit without age-adjustment or assessment of effect size (Nordin et al. 2002). In that study, the impact for CD was greater on the mental component (MCS) than on the physical (PCS). That study had a lower participation rate (70%) and was performed entirely by mail, which might have biased patient selection.

A worse outcome for women has not been a consistent finding in studies using multivariate techniques to identify predictive factors of SF-36 outcome (Petрак et al. 2001, Pallis et al. 2002, Pizzi et al. 2006). In those studies, subjectively reported health status in various forms (e.g. symptom burden, subjectively perceived disease activity) has been included as one of the independent variables. These variables have such a strong association with the domains tapped by the SF-36 that other variables of importance may be rejected as insignificant in the multivariate analyses.

PGWB

The PGWB was included in our study to represent the most subjectively and psychosocially determined aspects of health perception. In the absence of reliable background population data, comparisons were limited to the UC cohort from the study by Hjortswang et al. (2001). CD patients had worse scores than UC patients for all PGWB subscales and for the sum score (Table 15). The differences were consistent also when CD patients with an ostomy were excluded. However, when adjusting for differences in other population characteristics (age- and gender distribution, disease duration, and smoking habits) with logistic regression analysis, only the subscales *general health* and *vitality* had significantly ($p<0.01$) worse scores. The more mentally oriented subscales (covering states of nervousness, mood, general spirit, and emotional stability) did not differ convincingly between the two IBD entities.

The logistic regression analysis also showed a negative impact of female gender, with significantly increased odds ratios for all subscales and sum score (OR=1.63–1.96, $p=0.001$ – 0.009). The results were robust whether age and duration were included together or separately in the model to control for collinearity. Unsurprisingly, older age had a negative impact on *general health* (OR 1.02, 95% CI 1.01–1.03, $p=0.004$), while disease duration and smoking habits had no significant effect.

	CD (n=493) Median (iqr)	UC (n=284) Median (iqr)	<i>p</i>	OR (95% CI)	<i>p</i>
Anxiety	24 (20–27)	25 (22–28)	<0.001	1.44 (1.04–2.29)	0.029
Depression	16 (14–18)	17 (15–18)	<0.001	1.27 (0.86–1.88)	0.225
Pos. well-being	17 (13–19)	17 (14–19)	0.006	1.18 (0.80–1.74)	0.413
Self-control	16 (14–17)	16 (15–17)	0.024	1.29 (0.84–1.99)	0.240
General health	14 (11–16)	16 (13–17)	<0.001	2.33 (1.53–3.57)	<0.001
Vitality	15 (12–19)	18 (14–20)	<0.001	1.96 (1.29–3.00)	0.002
Sum score	102 (86–114)	109 (95–119)	<0.001	1.50 (1.01–2.21)	0.045

Table 15. PGWB sum score and subscale scores for CD and UC compared with Mann-Whitney U-test. Independent influence of IBD-type investigated with logistic regression, controlling for gender, age, duration, and smoking. Iqr=interquartile range, OR= Odds ratio of IBD-type (CD/UC) with 95% confidence interval (CI) for score worse than the 25th percentile.

Comparisons of HRQL with UC

The generally poorer outcome in RFIPC, SF-36 and PGWB for CD, compared with UC, may in part be explained by differing population characteristics. The longer disease duration and larger proportion of smokers in CD was not controlled for in the SF-36 comparison. Patients with an ostomy and patients from Ryhov County Hospital were not included in the UC cohort. However, none of these variables seemed to have any pivotal effect on any of the HRQL questionnaires in multivariate analyses (data not shown). A poorer HRQL in CD tallies with most studies comparing the two IBD-types (Petрак et al. 2001, de Rooy et al. 2001, Nordin et al. 2002, Bernklev et al. 2005). The clinical manifestations of UC and CD differ in many ways; the frequency of abdominal pain, the occurrence of strictures and fistulas, and the greater need for surgery being the most distinctive features for CD (Vatn 2009). Moreover, greater rates of systemic symptoms (including fatigue), functional gastrointestinal disorders, and health care utilization have all been reported for CD (Simrén et al. 2002, Farrokhyar et al. 2006, Longobardi & Bernstein 2006, Guthrie et al. 2002, Romberg-Campus et al. 2010).

Higher degree of anxiety and depression for CD has been found, but this has been explained by more severe physical symptoms in multivariate analyses (Drossman et al. 1991b, Nordin et al. 2002, Graff et al. 2006). Differences in psychological functioning, coping strategies, or personality traits seem not to account for the disparity in HRQL between the two IBD entities (Sewitch et al. 2001, Guthrie 2002, Mussell et al. 2004, Boye et al. 2008, Larsson et al. 2008, Lix et al. 2008, Graff et al. 2009).

Social characteristics, sickness, and disability compared with background population (paper VI)

Education

Compared with the population in the Living Condition Survey (LCS), CD patients had an increased gender- and age adjusted rate of low education defined as schooling limited to nine-year compulsory school (Table 16). As described above (see Introduction) most previous studies have not shown lower educational levels in CD or IBD. One study, though, reported a lower rate of advanced educational achievements in patients with active IBD compared with durably asymptomatic patients (Longobardi et al. 2003b). The finding in our study is probably not attributable to the disease per se, since patients diagnosed later in life had an even greater rate of low education. One explanation could be the higher smoking rate in the patient group (adjusted rate 38.1% vs. 21.4%, $p < 0.001$). Smoking is associated with a lower educational level in Sweden and many other countries (Cavelaars et al. 2000). The high smoking rate among patients was expected, given the firmly established link between smoking and CD development (Calkins 1989). When comparing patients who had reached post-secondary school education, the adjusted rate of further educational achievements (university degree or equivalent) was unaffected (Table 15). However, patients for whom the disease could have a possible effect on education, i.e. patients with diagnosis early in life (<26 years of age), this rate was lower compared with LCS (31.5 %, $p < 0.05$). Although borderline significant, this may reflect a real effect of the disease on the prospects of attaining higher education.

	Background rate (%)	Adjusted rate in CD (%)	p
Compulsory school only			
Women	13.9	38.0	<0.001
Men	16.8	32.3	<0.001
Total	15.3	35.9	<0.001
Post-Secondary school*			
Women	42.1	37.4	ns
Men	38.9	35.7	ns
Total	40.6	36.5	ns

Table 16. Age-adjusted rates for each gender and gender-age adjusted rates for the total (in bold) of educational levels in the study population (age 25-64 years) compared with the Living Conditions Survey (LCS).*) Proportion of patients with at least secondary school education that also have university degree or equivalent.

Family

The proportion of parents did not differ from the Swedish Population Registry (Table 17), and neither did the mean number of children per parent (2.16, 95% CI 2.07–2.25 vs. 2.17 in the population registry). However, the adjusted rate of living single was greater in CD for women, but not for men (Table 17). For women diagnosed later in life (≥ 26 years of age) this rate was even higher (29.4%), but for men with late diagnosis the trend was opposite (20.0%).

	Background rate (%)	Adjusted rate in CD (%)	<i>p</i>
Parenthood			
Women	70.4	67.1	ns
Men	61.7	65.7	ns
Total	66.0	65.5	ns
Living single			
Women	15.7	28.2	<0.001
Men	23.2	22.1	ns
Total	19.4	26.7	<0.001

Table 17. Age-adjusted rates for each gender and gender-age adjusted rate for the total (in bold) of parenthood and living single in the CD population compared with the Swedish Population Registry (parenthood) and the Living Conditions Survey (living single).

Interestingly, a similar finding of more singles among CD women compared with controls (25.7% vs. 12.0%, $p < 0.05$) was reported in a study from Örebro, comparing smoking habits in CD with background population controls (Lindberg et al. 1988). A Canadian study (Bernstein et al. 2001) reported that for IBD patients who were married at diagnosis, the probability of being single at a long-term follow-up was twice as high for women vis-à-vis men (20% vs. 10%). These findings may be attributable to a higher proportion of women becoming widowed rather than divorced. However, the proportion of widows/widower or divorcées among the singleton patients in our study did not differ between the genders. The results may indicate that CD exerts a more severe strain on female patients' family life and relationships, perhaps with gender inequalities in partner-related support and demands playing a role.

Work

The adjusted rate of reduced work capacity, defined as long-term sickness compensation and/or disability pension, was more than doubled in the study population compared with the LCS (Table 18). It must be noted that it is not two identical variables that are compared. In the study, patients reported if they received any long-term sickness benefit or disability pension for any reason, while the LCS asked for "long-term illness or sequelae from accidents or other weakness or regular medication for something that greatly reduces work capacity". The LCS question is broader and more subjective. The difference in the rate of reduced work capacity may therefore have been underestimated.

A more direct comparison of disability pension rate was made possible by data from the Social Security Agency of the three counties. The result was similar: a two-fold increase of the rate in CD patients. The increase in rate was greater for women in both comparisons. The logistic regression analysis confirmed an independent association between female gender and reduced work capacity (OR 2.34, 95% C.I. 1.24–3.66, $p = 0.003$) or disability pension (OR 2.04, 95% C.I. 1.03–3.85, $p = 0.04$). Other predictors of reduced work capacity or disability

pension identified in the regression analysis were: higher age, co-morbidity, and active disease the preceding year, while education, smoking, disease location, disease behaviour, and extraintestinal manifestation had no significant effect. The adjusted unemployment rate was similar to the background population; women had a higher rate, though with a borderline significance (6.3% vs. 1.5%, $p < 0.05$).

	Background rate (%)	Adjusted rate in CD (%)	<i>p</i>
Reduced work capacity			
Women	13.3	31.1	<0.001
Men	9.4	19.7	<0.001
Total	11.4	25.7	<0.001
Disability pension			
Women	8.4	19.2	<0.001
Men	6.4	11.3	<0.005
Total	7.4	15.2	<0.001

Table 18. Age-adjusted rates for each gender and gender-age adjusted rate for the total (in bold) of reduced work capacity, disability pension, and unemployment in the CD population, compared with the Living Conditions Survey, Social Insurance Agency statistics, and Labour Force Survey respectively.

Comparison of sickness and disability data from previous CD studies is difficult due to differing populations, time eras, and social security systems. Disability pension rates have ranged from 2–5.3% in British and North American studies (Wyke et al. 1988, Bernstein et al. 2001, Ananthkrishnan et al. 2008) to 32% in one Dutch study (Boonen et al. 2002). The Scandinavian countries are fairly comparable in this regard. Previous Danish and Norwegian studies have reported disability pension rates equivalent to this study (Binder et al. 1985, Munkholm et al. 1995, Bernklev et al. 2006). It is noteworthy that Munkholm et al. (1995) found that up to 15% of CD patients obtained disability pension 15 years after diagnosis. The crude rate in our study was 15.9% and the median disease duration was 15 years. Bernklev et al. (2006) reported a crude rate of 14.9% (1.7 times higher than the background population), also with higher rates for women (24.6% vs. 8.5%).

Why was outcome worse for women?

A consistent finding in the characterization of the patients' social variables and HRQL (both in terms of disease-related worries and the more general aspects measured by SF-36 and PGWB), was that whenever a gender difference was detected, a worse outcome was noted for women. Worse SF-36 scores among women are well-documented in Swedish and international general population health surveys (Sullivan et al. 1998, Hanmer et al. 2006), though the gender adjustment in our study excludes this explanation. Figure 10 depicts rather illustratively that CD affects HRQL more seriously in women than in men, and this discrepancy is more pronounced than for UC.

Did women have a more severe disease activity or course? The CDAI score was slightly higher for women (113.5 vs. 92.3, $p=0.027$). However, the CDAI variables responsible for this difference were the subjectively reported symptoms *general well-being* and *abdominal pain*. We found no convincing objective evidence of a more severe disease course for women. The physicians' global assessment of disease activity, disease course the preceding year, disease location or behaviour, orosomucoid level, proportions of patients with CRP elevation, anaemia, previous bowel resection or ileostomy, were all independent of gender. Extraintestinal manifestations, of which 91% were arthralgia, were more common among women, possibly contributing to the difference in HRQL. A negative influence of arthralgia on HRQL in IBD has been reported (Palm et al. 2005, Bernklev et al. 2004). Women may also have had worse HRQL due to a higher prevalence of irritable bowel syndrome (IBS). The prevalence of IBS was not investigated in our study, but has been more prevalent in women (Chang et al. 2006). IBS has also been associated with poorer HRQL in IBD patients (Simrén et al. 2002, Minderhoud et al. 2004, Farrokhyar et al. 2006). The higher degree of abdominal pain among women in our study is interesting, considering reports of greater visceral pain sensitivity in women, varying in time with menstrual cycle (Heitkemper et al. 2008).

Are there gender differences in coping strategies and psychological functioning? As pointed out in the Introduction, several studies have shown that the type of coping strategy affects the outcome of HRQL in IBD (Verissimo et al. 1998, Petrak et al. 2001, Mussell et al. 2004, Moreno-Jimenez et al. 2006). However, none of these studies reported any gender differences. Coping strategies in the general population and other patient categories have differed between genders, but the results have been diverse, mainly leaving the gender differences in perceived health status unexplained (Davis et al. 1999, Heo et al. 2007, Nagase et al. 2009, Colodro et al. 2010). No significant gender differences were found regarding which health-related factors the respondent considered and valued, when rating their perceived health status in a Swedish community-based survey (Undén & Elofsson 2006). There seems to be a genuine female preponderance of depressive and anxiety disorders, partly attributed to differences in coping skills and vulnerability to stressful life events (Piccinelli & Wilkinson 2000, Lepine 2002). However, gender has not been found influential on the level of depression and anxiety in IBD patients assessed with the HADS questionnaire (Nordin et al. 2002, Janke et al. 2005, Larsson et al. 2008).

Are there gender inequalities in external supportive factors? Marital status seems to be important for HRQL outcome (Liu & Umberson 2008). Especially formerly married (divorced/-widowed) singletons have a poorer HRQL, a finding more pronounced in women. Whether the higher rate of single living for women in our study was a mediator or a consequence of worse subjective health status cannot be established. Socio-economic gender inequalities may be important. In a general population survey Cherepanov et al. (2010) found that when HRQL scores were adjusted for women's higher rate of single living, and lower income, their shortcoming in HRQL was greatly reduced. For patients with coronary artery disease, weaker social support (from relatives or friends) for women partly explained the gender gap in HRQL (Norris et al. 2008). However, a gap persisted despite full adjustment for disease severity, depression and level of social support. Further SEM analyses suggested that other societal factors associated with the gender role may be explanatory mechanisms (Norris et al. 2010).

Do the physicians (of whom 90% were male in our study) interpret anamnesis and choose treatment differently, depending on the patient's gender? This issue has been discussed in other areas of health care (Scirica et al. 1999, Cook et al. 2009). Although our study was not constructed to answer this question, we did not find any support for the hypothesis. In the PGA questionnaire, the physicians designated the causes of the patient's symptoms (luminal inflammation, stricture, fistulae, post-resection diarrhea or functional bowel disorder). The proportions of patients whose symptoms were interpreted as unrelated to disease activity (post-resection diarrhea or functional bowel disorder) were similar for male and female patients (39% and 43% respectively), as were the proportions having symptoms solely explained by functional bowel disorder (8% and 11% respectively). The rates of previous bowel surgery and on-going corticosteroid or immunosuppressive treatment did not differ significantly between genders.

CONCLUSIONS

1. The Swedish IBDQ exhibited a proper external validity, reliability, and responsiveness. However, the grouping of the items was not corroborated. Hence, only the total score can be used. The Swedish RFIPC showed a good validity and excellent reliability, but was less sensitive to change in disease activity.

2. The SHS proved valid and sensitive to change. The test-retest reliability was lower compared with the IBDQ and the RFIPC, but adequate for comparisons on group level. The SHS is easier to use and provides a more comprehensive overview of subjective health status.

3. The composite CDAI score is heavily weighted by traditional HRQL variables, resulting in an influence by non-CD-related factors, and a weak correlation with the physicians' clinical appraisal of disease activity. CD health assessment would benefit from a more intelligible division of health status into separate subjective and objective dimensions. Structural equation modelling showed that the SHS health status model describes the relationship between disease activity and HRQL with a sustainable goodness-of-fit to measured data. In contrast to the original hypothesis, however, worries may be the most psychosocially influenced dimension.

4. CD patients have a poorer general HRQL compared with background population and UC, with the greatest impairment in the physical domain. The impact is more pronounced for women. A direct influence by the disease on educational level or family building was not established, although female patients were more often living single compared with controls. The rates of long-term sickness and disability pension were doubled, with female gender as a negative predictor. The level of disease-related worries is higher in CD than in UC. Disease complications and impact on achievements in daily life arouse more concern than issues of intimacy and self-image. Disease activity, female gender, and greater BMI are independently associated with a higher degree of worries. The generally worse outcome for CD women in subjective health perception and sickness was not echoed in objective disease assessment.

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POPULÄRVETENSKAPLIG SAMMANFATTNING

Crohns sjukdom (CS) är en inflammatorisk tarmsjukdom (IBD), som oftast börjar tidigt i livet och har ett livslångt förlopp. Alla delar av mag-tarmkanalen kan drabbas och för den sjuke kan hälsan påverkas på många olika sätt. En utmaning i patient-läkarmötet är att rätt bedöma sjukdomens allvarlighetsgrad och försöka förstå orsaken till patientens besvär. För detta krävs ett helhetsperspektiv, där traditionella undersökningsmetoder och mått på inflammation (sjukdomsaktivitet) vägs samman med patientens egen upplevelse av hur sjukdomen påverkar livet (hälsorelaterad livskvalitet, HRQL). Denna studies huvudsyfte var att utvärdera olika strategier för bedömning av hälsotillståndet vid CS, samt att beskriva sjukdomens inverkan på olika aspekter av HRQL.

Studien genomfördes på mag-tarmmottagningarna i Jönköping, Linköping och Örebro under 2 år. Drygt 500 patienter med CS deltog genom att fylla i livskvalitetsformulär och symtomdagbok, samt lämna blodprov i samband med sitt planerade återbesök och vid ett uppföljningsbesök. Patienternas mag-tarmläkare registrerade sjukhistoria och värderade sjukdomsaktiviteten.

I de två första artiklarna utvärderades de svenska versionerna av två befintliga IBD-specifika HRQL-enkäter (IBDQ och RFIPC). Båda enkäterna hade adekvata mätgenskaper, men skiljde sig åt i vissa avseenden. IBDQ gav bristfällig information om vilken aspekt av HRQL som var påverkad och RFIPC var mindre känsligt för förändring i hälsotillståndet.

I tredje artikeln undersöktes motsvarande egenskaper hos ett nytt HRQL-instrument, Short Health Scale (SHS), som utvecklats för att förenkla livskvalitetsmätning vid IBD i klinisk vardag. SHS består av endast fyra frågor, som var och en representerar viktiga aspekter av HRQL vid inflammatorisk tarmsjukdom (symtom, funktion, oro och välbefinnande). SHS hade adekvata mätgenskaper och kunde tydligt skilja friskare från sjukare patienter. Det var känsligt för förändring i hälsotillståndet och hade det lägsta bortfallet.

Fjärde artikeln studerade det internationellt mest accepterade måttet på sjukdomsaktivitet, Crohn's Disease Activity Index (CDAI). Formuläret består av fem kliniska och tre patientrapporterade variabler som sammanräknas i en slutpoäng. Måttets överensstämmelse med läkarens kliniska bedömning av sjukdomsaktivitet var sämre än förväntat. Poängen styrdes till största delen av typiska livskvalitetsvariabler som patientens symtom och välbefinnande. Faktorer som inte borde vara associerade med aktuell sjukdomsaktivitet (som t ex kön, annan samtidig sjukdom, och tidigare operation) påverkade resultatet, medan läkarnas bedömning av sjukdomsaktivitet enbart påverkades av inflammationsprov och sjukdomskomplikationer. Slutsatsen blir att CDAI till största delen är ett livskvalitetsmått, samt att sammanslagningen av både subjektiva och objektiva variabler försvårar tolkningen av vad som egentligen är påverkat.

SHS bygger på en teoretisk modell som delar in hälsomätningen i fem huvudsakliga dimensioner (biologiska variabler, symtom, funktion, oro och välbefinnande). I modellen interagerar dessa dimensioner i en logisk sekvens som startar med att sjukdomen ger biologiska föränd-

ringar, som ger symtom, som påverkar funktion, vilket ger oro, som slutligen påverkar välbefinnandet. I den femte artikeln testades denna modell statistiskt med strukturell ekvationsmodellering, som är en matematisk metod att värdera hur väl en teoretisk modell passar med variabler uppmätta i verkligheten. Resultaten visade att modellen kunde förklara de uppmätta variablernas samvariation i hög grad, med en god överensstämmelse mellan modell och verklighet. Analyserna visade också på en alternativ slutsekvens där graden av oro påverkas av graden av välbefinnande.

Slutligen jämfördes olika aspekter av HRQL vid CS med bakgrundsbefolkningen och med ulcerös colit (UC), en annan inflammatorisk tarmsjukdom. CS gav högre grad av sjukdomsrelaterad oro än UC. Patienterna verkade vara mer bekymrade över risker för sjukdomskomplikationer och förmågan att klara av vardagen, än över intimare frågor som sexualitet och självbild. Kvinnligt kön, aktiv sjukdom och övervikt medförde högre grad av oro. HRQL var tydligt sämre för CS än för bakgrundsbefolkningen och UC, främst inom fysiska områden och framför allt för kvinnor. Någon direkt negativ effekt av CS på utbildningsnivå eller familjebildning kunde inte påvisas, även om patienternas utbildningsnivå generellt var lägre och kvinnliga patienter var ensamstående i större utsträckning än i befolkningen. Kön- och åldersjusterad andel långtidssjukskrivna eller förtidspensionerade var dubbelt så hög som i befolkningen, återigen med sämre resultat för kvinnliga patienter. Det överlag sämre utfallet för kvinnor i studien kunde inte förklaras med skillnader i sjukdomens svårighetsgrad eller behandling.

Sammanfattande slutsatser:

1. Svenska versionerna av livskvalitetsformulären IBDQ och RFIPC är adekvata och användbara.
2. Livskvalitetsmätning kan göras mer överblickbar och lätthanterlig i den kliniska vardagen med hjälp av livskvalitetsformuläret SHS.
3. Sjukdomsaktivitetsmättet CDAI mäter huvudsakligen hälsorelaterad livskvalitet. Sammanslagningen av både subjektiva och objektiva variabler försvårar tolkningen.
4. Förhållandet mellan sjukdomsaktivitet och hälsorelaterad livskvalitet enligt den teoretiska SHS modellen har en statistiskt bevisad god överensstämmelse med uppmätta variabler.
5. CS har en påtagligt negativ effekt på livskvalitet och arbetsförmåga, och vållar högre grad av oro än UC, framför allt för kvinnor. Områden som bekymrar mest är risken för sjukdomskomplikationer och tillkortakommanden i vardagen.

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