Long-term disease course, cost and prognosis of inflammatory bowel disease: Epidemiological studies of a European and a Danish inception cohort

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Bente Merete Stallknecht, Dean of Faculty

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Abbreviations

CD	Crohn's disease
IBD	Inflammatory bowel disease
IBDU	Inflammatory bowel disease unclassified
IQR	Interquartile range
SD	Standard deviation
UC	Ulcerative colitis
5-ASA	5-aminosalicylates
95% CI	95% confidence interval

Preface

This thesis summarises the epidemiological research that I carried out from 2013 to 2021 during my employment at the Department of Surgery at Nordsjællands Hospital, the Abdominalcenter K at Bispebjerg Hospital and the Gastrounit at Hvidovre Hospital. Much of it is a direct continuation of my epidemiological work with the European *Epi-IBD* cohort on which I based my Ph.D. thesis in 2013. Therefore, most of the following words of thanks have been written before, but they nonetheless need repeating.

I would like to express my deepest appreciation and gratitude to Pia Munkholm for her continuous guidance and inspiration, which started almost fifteen years ago when she first introduced me to the world of research and clinical epidemiology in inflammatory bowel diseases. I also wish to thank Ebbe Langholz for being an encouraging collaborator and friend throughout these years. Both have taught me the importance of always putting the patients at the centre of one's research. I am also grateful for the opportunity to work with "their" *Copenhagen County* cohort and to dive into Danish IBD epidemiological history. Although no longer with us, my grandfather, professor, Dr.med and gastroenterologist Povl Riis, has been ever-present during this process, as well as while writing up this thesis.

I would like to thank all of the physicians and nurses in the *Epi-IBD* study group for their perseverance in following up the cohort and for their enthusiasm throughout the years. Special thanks go to Selwyn Odes of Israel and his team for their extraordinary support and contributions to the cost analysis. Thanks also go to Søren Lophaven, Omicron A/S, and Henrik Wachman, Larix A/S for their invaluable statistical assistance and cooperation, and to Martin McLean for reviewing the English language of the papers, as well as this thesis.

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Johan Burisch
Virum, April 2021

List of papers

The present thesis is based on the following manuscripts:

I. Burisch J, Lophaven S, Langholz E et al. The clinical course of Crohn's disease in a Danish population-based inception cohort with more than fifty years of follow-up 1962-2017. Aliment Pharmacol Ther 2021, in press

II. Burisch J, Lophaven S, Munkholm P, et al. Surgery, cancer and mortality among patients with ulcerative colitis diagnosed 1962-1987 and followed until 2017 in a Danish population-based inception cohort. Aliment Pharmacol Ther 2021, in press

III. Burisch J, Kiudelis G, Kupcinskas L, et al. Natural disease course of Crohn's disease during the first 5 years after diagnosis in a European population-based inception cohort: an Epi-IBD study. Gut 2019;68:423–433.

IV. Burisch J, Katsanos KH, Christodoulou DK, et al. Natural Disease Course of Ulcerative Colitis During the First Five Years of Follow-up in a European Population-based Inception Cohort-An Epi-IBD Study. J Crohns Colitis 2019;13:198–208.

V. Burisch J, Zammit SC, Ellul P, et al. Disease course of inflammatory bowel disease unclassified in a European population-based inception cohort: An Epi-IBD study. J Gastroenterol Hepatol 2019;34:996–1003.

VI. Burisch J, Vardi H, Schwartz D, et al. Health-care costs of inflammatory bowel disease in a pan-European, community-based, inception cohort during 5 years of follow-up: a population-based study. Lancet Gastroenterol Hepatol 2020;5:454–464.

VII. Burisch J, Bergemalm D, Halfvarson J, et al. The use of 5-aminosalicylate for patients with Crohn's disease in a prospective European inception cohort with 5 years follow-up - an Epi-IBD study. United Eur Gastroenterol J 2020;8:949–960.

1. Introduction

The term 'inflammatory bowel disease' (IBD) describes a group of chronic, immune-mediated inflammatory disorders of the gastrointestinal tract. The aetiology of IBD is not entirely understood, but it is generally accepted that the diseases result from a complex interplay between genetic susceptibility, environmental factors and intestinal microbiota, resulting in a self-perpetuating abnormal mucosal immune response and inflammation[1]. The two most common forms of IBD are Crohn's disease (CD) and ulcerative colitis (UC), both of which typically debut in young adulthood and are characterized by a chronic disease course with alternating periods of remission and active intestinal inflammation, resulting in symptoms such as abdominal pain, bloody or non-bloody diarrhoea, and weight loss that in some cases require hospitalisation.

The incidence of IBD is increasing worldwide and globally more than 6.8 million individuals are estimated to suffer from it[2]. IBD has a significant impact on patients' quality of life, but it also places a considerable financial burden on society with its direct costs, as well as its indirect costs related to work disability and sick leave[3]. The disease course of IBD is heterogeneous. Some patients experience frequent flare-ups, progression of disease and/or the need for biological therapy or surgery, while others have a mild disease course with few flare-ups, stationary disease and only limited need for medication. Furthermore, a subset of patients develop extra-intestinal manifestations or cancers[4].

At present, no cure for IBD exists and treatment consists of anti-inflammatory drugs used to induce and maintain remission, reduce disability and ultimately to improve quality of life. Over the past two decades, treatment options and strategies for IBD patients have evolved significantly. Biological therapies such as anti-TNFα antibodies were introduced at the end of the nineties and are able to effectively induce and maintain remission in cases of moderate-to-severe IBD, as well as reduce the need for hospitalisation and surgery[5,6]. Furthermore, pivotal trials have demonstrated that early and aggressive immunomodulating treatment might hold disease-modifying potential[7,8]. Such promising results have led to earlier and more widespread use of immunomodulators and biological therapies in clinical practice. However, it remains uncertain whether these changes in the treatment of IBD have improved long-term outcomes in *real-world settings*. Outside of rigorous clinical trials, there is much greater variability in patient selection and monitoring capacity, and this is likely to reduce the efficacy of drugs. Furthermore, the availability of treatments differs between countries and regions such as Eastern and Western Europe, which might too influence treatment outcomes and the natural course of IBD[9,10].

The term *'natural course'*, as applied to chronic diseases, traditionally describes how the disease will proceed without any medical or surgical intervention. While one can argue that the placebo arm of a controlled trial can provide information about the short-term *natural* disease course, studies of the long-term natural disease course, at least according to its original definition, do not exist as very few patients in the long term will remain untreated[11]. A more relevant definition of the *natural course*, therefore, could be the course of the disease when treated according to contemporary, well-established treatment guidelines[12]. That is the definition used in this thesis and the papers accompanying it.

The gold standard in epidemiological research of disease course and prognosis is a regional and unselected population-based cohort study. Such studies are able to capture the *true* natural disease course of IBD as they include all patients within a specific area representing the entire, broad spectrum of disease severity. Such studies are important for informing both patients and health care providers about long-term prognoses and risk factors in modern medical treatments. Furthermore, they can demonstrate the efficacy of treatment strategies in the community setting[13]. Comparing cohorts of patients from periods before potent drugs and close monitoring were available to physicians with more recent cohorts can therefore offer insights into whether disease outcomes have improved over time.

The research program presented here pursued that gold standard. It aimed at investigating the contemporary natural disease course of IBD, as well as geographic differences in a European population-based cohort of patients diagnosed in 2010. These patients were followed for five years. Additional data were gleaned from a Danish population-based cohort of patients diagnosed between 1962-1987 and followed for more than fifty years. This cohort stands out in that immunomodulating and biological therapies were not available until very late in the observation period, and as such it can serve as a reference point for comparisons with subsequent cohort studies.

2. Material and methods

2.1 Study populations

Patient populations originated from two population-based inception cohorts, the *Epi-IBD* cohort (Papers I-V) and the *Copenhagen County* cohort (Papers VI and VII).

The *Epi-IBD* cohort is a collaborative prospective cohort of 1,289 incident patients with IBD (CD: 488, UC: 717, IBD Unclassified (IBDU): 84) diagnosed between January 1 and December 31, 2010 in 20 European countries and Israel[9]. A total of 29 gastroenterological departments (centres) from 12 western European countries (Denmark, Sweden, Finland, Faroe Islands, UK, France, Spain, Portugal, Italy, Malta, Greece, and Cyprus) and Israel, as well as eight eastern European countries (Lithuania, Estonia, Russia, Croatia, Hungary, Moldova, Czech Republic, and Romania) participated in the study, covering a total population of 9.7 million people (7.1 million in western Europe and 2.6 million in eastern Europe). The terms 'eastern' and 'western' Europe were chosen to differentiate these two groups of countries for the sake of the present studies. All participating centres were required to have a well-defined primary uptake area, as well as an established network of general practitioners, gastroenterologists and colorectal surgeons within those uptake areas. These individuals were contacted twice during the inclusion period to ensure complete coverage and maximal inclusion of patients. Additionally, endoscopy lists, pathology reports and patient lists were searched for all incident cases by the end of the inclusion period[14].

The *Copenhagen County* cohort is a prospective cohort of 1,534 incident IBD patients (CD: 373, UC: 1,161) diagnosed between January 1, 1962 and December 31, 1987 in the former area of *Copenhagen County*[15,16]. This administrative region existed from 1970 to 2006 and included the greater parts of the population of Copenhagen and the capital city of Denmark. By the end of the inclusion period in 1987, the total population was approximately 10% of the Danish population, or 554,533 inhabitants. Patients were diagnosed and treated in one of four university hospitals in Herlev, Gentofte, Glostrup and Rigshospitalet, which were the only gastroenterological clinics treating IBD within the uptake area. All general practitioners, gastroenterologists, colorectal surgeons and paediatricians were contacted at the end of the inclusion period in 1987 in order to capture incident patients that had not been referred to the hospital. Sixteen patients were identified, but as their diagnostic data were incomplete or missing, they were not added to the cohort[17,18].

For papers VI and VII, patients were matched by sex, date of birth and municipality at the date of study entry with a control group of up to fifty individuals from the general population. The control population was retrieved from the Danish Civil Registration System, none of whom had an IBD diagnosis. As the Civil Registration System only started recording data about municipalities in 1980, patients diagnosed between 1962 and 1979 were matched with controls whose municipality was not necessarily the same as on the date of diagnosis.

2.2 Case definition

Patients in both cohorts were required to fulfil the *Copenhagen Diagnostic Criteria* for IBD after exclusion of infectious gastroenteritis, endamoeba and intestinal cancer. The criteria included the following:

Copenhagen Diagnostic Criteria for CD (at least two of the criteria present)[15]:

1. History of abdominal pain, weight loss and/or diarrhoea for more than three months
2. Characteristic endoscopic findings of ulceration (aphthous lesions, snail track ulceration) or cobble stoning *or* radiological features of stricture or cobble stoning
3. Histopathology consistent with Crohn's disease (epithelioid granuloma of Langerhans type or transmural discontinuous focal or patchy inflammation)
4. Fistula and/or abscess in relation to affected bowel segments.

Copenhagen Diagnostic Criteria for UC (all three of the criteria present)[16]:

1. History of diarrhoea and/or rectal bleeding and pus for more than one week or repeated episodes
2. Characteristic endoscopic findings of continuous ulceration, vulnerability or granulated mucosa
3. Histopathology consistent with ulcerative colitis (neutrophils within epithelial structures, cryptitis, crypt distortion, crypt abscesses).

Cases in which not all criteria for CD or UC were fulfilled, and yet subsequent IBD treatment was necessary, were classified as IBDU[19]. In the *Epi-IBD* cohort, only patients 15 years or older at the time of diagnosis were included because most departments in the study did not treat paediatric IBD patients. In the *Copenhagen County* cohort, all patients were included, regardless of age.

2.3 Data collection and follow-up

Incident patients in the *Epi-IBD* cohort were followed prospectively from diagnosis until December 31, 2015, their emigration or death. The participating physicians collected data prospectively about demographics, disease classification, clinical disease activity, medical and surgical therapy, hospitalisation, changes in disease classification, cancers and deaths. Data were collected in the web-based Epi-IBD database[20]. Audit visits were performed at a selection of the centres to secure data quality and protocol adherence[20].

Patients in the *Copenhagen County* cohort were followed prospectively and clinically from diagnosis until December 31, 1987, their emigration or death, by annual assessments of demographics, disease location, clinical disease activity, medical and surgical therapies, mortality and cancers. In addition, follow-up of surgeries, cancers and deaths was extended from January 1, 1988 until December 31, 2017, by linking the cohort to the Danish national registries using the unique personal identification number that is given to all Danish citizens at birth. Data on surgical procedures were retrieved from the National Patient Registry, which contains information on all hospitalisations, diagnoses, surgical and other procedures performed in Danish hospitals on an individual level since 1977, as well as in ambulatory outpatient settings since 1995[21]. Information on migrations and dates of death were retrieved from the Danish Civil Registration System. Specific causes of death were obtained from the Danish Register of Causes of Death[22], and information on

incident cancers, including their type, anatomical location, and date of diagnosis were retrieved from the Danish Cancer Registry[23].

In both cohorts, treatment choices, as well as in- and outpatient visits, took place at the treating physician's discretion.

2.4 Classifications

The *Montreal Classification*[24] was used to classify patients in terms of disease behaviour and location for CD and disease extent for UC. In the *Copenhagen County* cohort, the extent of disease was recorded for each segment of the colon, as well as the ileum and jejunum. However, specific information about the terminal ileum or involvement of the upper gastrointestinal tract was not available. Therefore, UC patients could be retrospectively reclassified according to the *Montreal Classification*, while CD patients' disease behaviour remained classified as either small intestine, colon, or small intestine and colon.

Information on medical treatments was only available for the *Epi-IBD* cohort, while data on surgeries were available for both cohorts. Treatments were classified in order of ascending potency: 5-aminosalicylates (5-ASA) (oral and/or topical 5-ASA treatment ± topical steroids), glucocorticosteroids (oral steroids ± 5-ASA or topical steroids), immunomodulators (azathioprine, 6-mercaptopurine, cyclosporine or methotrexate ± steroids), biologicals (alone or in combination with any of the above), and surgery (regardless of medical treatment prior to surgery). Surgery was defined as total or subtotal colectomy for UC, and small or large bowel resection for CD.

Disease activity in the *Epi-IBD* cohort was assessed using the *Simple Clinical Colitis Index* (SCCAI)[25] for UC patients and the *Harvey-Bradshaw Index* (HBI)[26] for CD patients. For those in the *Copenhagen County* cohort, disease course during follow-up years two to five was classified as being either in remission (no clinical disease activity during any of the years), intermittent (years in remission as well as years with active disease), or chronic continuous (clinical disease activity during all years of follow-up)[27,28].

Types of cancer were classified according to the 7th revision of the International Classification of Diseases and Related Health Problems (ICD-7) between 1943 and 1977, and from 1978 according to ICD-10. Causes of death were coded according to ICD-8 between 1970 and 1993, and from 1994 according to ICD-10.

2.5 Statistical analysis

Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and SPSS version 23 (SPSS Inc., Chicago, IL, USA). In Paper IV, quantile regression was performed using STATA 12.0 (StataCorp, College Station, TX, USA). Categorical variables were summarized as proportions and results for continuous variables expressed as median values (inter-quartile ranges). Continuous variables were analysed using Student's *t*-test. Differences in the time to events were compared using the Wilcoxon two-sample test. Categorical data were analysed using χ^2-test or Fisher's exact test, as appropriate. A *p*-value smaller than 0.05 was considered to be statistically significant.

2.6.1 Disease course

In papers I and II, associations between endpoints (surgery, cancer, and mortality) and multiple covariates (sex, age at diagnosis, disease location in CD and disease extent in UC at diagnosis, disease course type, and observation period) were analysed by Poisson regression. In papers III-V, associations between endpoints (including changes in disease classification, surgery, hospitalisation, and a need for biological treatment) and multiple covariates (age at diagnosis, sex, diagnosis, diagnostic delay, geographic region, Montreal classification at diagnosis, treatment potency, smoking status, extra-intestinal manifestations at diagnosis, use of immunomodulators, use of biologicals and a need for corticosteroids within thirty days of the diagnosis) were analysed by Cox regression analyses using the proportional hazards assumption. In Paper VII, associations between the aforementioned covariates and the group of CD patients being treated only with 5-ASA in the first year following their diagnosis were analysed by logistic regression analysis. In all papers, associations of interest were visualized in Kaplan-Meier plots and analysed with the log-rank test.

2.6.2 Cost analysis

In Paper IV, the costs of resources were supplied by each country and prices were set at their 2015 levels. Prices were not discounted over the follow-up period. Costs were calculated for the following categories: total costs, biological therapy, non-biological conventional therapy, investigations, hospitalisations and surgeries. As the distribution of costs was non-parametric, median costs were deemed more representative of the typical patient than mean costs. However, mean costs allow for the calculation of overall expenditure and therefore some results of costs are also presented as mean values (standard deviation, SD). Predictors of costs were determined by quantile regression analysis (5%, 25%, 50%, 75%, 95%), using the following variables: use of biological therapy, geographic region, sex, age, smoking status, year of follow-up (years 2, 3, 4 and 5), most severe disease behaviour in CD, and most severe disease extent in UC and IBDU.

Collinearity between years and total cost was tested by Pearson correlation coefficient and Spearman's Rho correlation analysis. The significance of cost differences between different groups, such as types of IBD or geographic regions, was calculated by Kruskal-Wallis one-way ANOVA. The association between the cost of biologicals and the total cost excluding biological medication between follow-up years 2 and 5 was analysed by UNI-ANOVA. The first year of follow-up was excluded as this is when the costs of care are usually highest, so they could have obscured the association being tested[29,30].

2.6.3 Mortality and cancer

In papers I and II, observed rates of cancer and mortality among IBD patients were compared to those in the matched control population and risk differences were assessed as relative risk (95% confidence interval). Furthermore, cumulative survival curves in patients and in the control population were visualized as Kaplan–Meier plots and analysed with the log-rank test.

Patients who underwent a colectomy or proctocolectomy were censored from the date of the procedure when analysing the risk of colon cancer. Similarly, patients undergoing a proctocolectomy or proctectomy were excluded from the analysis of rectal cancer following their procedure. No censoring was made in the case of colonic resections.

3. Results and discussion

3.1 Natural disease course of Crohn's disease

3.1.1 Own results (Papers I and III)

In the *Copenhagen County* cohort, 373 CD patients were diagnosed between 1962 and 1987 and followed for a median of 33 years (Interquartile range (IQR): 20-39). By the end of follow-up, three out of four patients had needed surgery at least once. Most surgeries took place within the first years after a diagnosis. The cumulative rate of surgery increased steadily during the first 20 years and then plateaued.

The median time to a first surgery was one year (IQR: 0-5) and after five years half of the population had undergone surgery. The cumulative surgery rates 5, 10, 20, 30, 40 and 50 years after diagnosis were 53% (CI95%: 48-59%), 62% (CI95%: 57-67%), 71% (CI95%: 66-75%), 72% (CI95%: 67-76%), 74% (CI95%: 69-79%), and 74% (CI95%: 69-79%), respectively, Figure 1. Risk factors for needing surgery included disease location, initial disease course following diagnosis, and time period, as shown in Table 1. Additionally, more than half of patients operated upon needed additional surgery, with 26% needing two, and 28% needing three or more, resections in total.

In the more recent *Epi-IBD* cohort, a total of 488 CD patients were diagnosed in 2010 and followed for a median of five years (IQR: 0-5). As described in the Methods chapter, clinical data were available for this cohort throughout the entire observation period, which allowed for more detailed analysis. Clinical disease activity in the cohort improved during follow-up. Most CD patients were diagnosed with non-stricturing, non-penetrating disease and this remained the case throughout the observation period. However, as shown in Figure 2, 14% of these patients eventually developed either strictures or intra-abdominal fistulas/abscesses. Furthermore, 11% of patients with strictures at diagnosis also developed intra-abdominal fistulas. While smoking was not found to be associated with the risk of disease progression, colonic disease location, as compared with small intestinal involvement, was found to be associated with disease progression, Table 2. In contrast, the development of perianal fistulas, which had occurred in 14% of patients by the end of follow-up, predominantly occurred in patients with colonic disease. In terms of disease location, 12% of patients were found to have developed more extensive disease during follow-up, Figure 2. In the multivariate analysis, stricturing or penetrating disease behaviour, longer diagnostic delay, and being female were found to influence the risk of progression in disease location.

One-third of all patients needed at least one hospitalisation for their CD, most (65%) shortly after their diagnosis. The median time to first hospitalisation was six months (IQR: 1-22). When excluding hospitalisations due to surgery, 24% of patients were hospitalized after a median of nine months (IQR: 4-25). As shown in Table 2, complicated disease behaviour at diagnosis and diagnostic delay increased the risk of hospitalisation, while the use of immunomodulators decreased the risk. Finally, the five-year surgery rate among patients was 22%, more than half (13%) of whom needed to be operated upon during the first year following their diagnosis, Figure 3. The median time to first surgery was seven months (IQR: 1-30). In subsequent years, the annual surgery rate was 2% per year for a first intestinal resection. Again, complicated disease behaviour at diagnosis and delays in establishing the diagnosis increased the risk of surgery, while treatment with immunomodulators lowered the risk. In total, 6% of patients needed an additional operation. These observations did not differ between Eastern and Western European patients.

3.1.2 Discussion

The treatment options available for CD up until the mid-nineties consisted of 5-aminosalicylates (5-ASA), for which there is no evidence of their long-term efficacy in maintaining remission, except perhaps in the post-operative setting[31,32], and steroids, which have no relapse-preventing effect[33]. Paper IV and other population-based cohorts of patients diagnosed during the 1960s, 1970s and 1980s[34–36] demonstrate that without treatments to maintain remission, only one-in-four patients were able to avoid surgery and that most of these surgeries took place within the first five-to-ten years following a diagnosis. Surgery, however, is not curative and without prophylactic therapy clinical and surgical relapses are frequent[37]. Consequently, and as suggested by other studies[36], the proportion of patients needing several additional surgeries was approximately 50%, with a few patients needing up to eight resections (Paper I).

Most patients with CD follow a chronic intermittent disease course, but some 20-25% of patients will experience a mild or indolent course with few flare-ups and only a limited need for treatment and/or surgery[27,38,39]. An individual's disease course remains difficult to predict even to this day. However, a previous analysis of the *Copenhagen County* cohort found that the course of the disease during the initial two years could be used to predict the frequency of flare-ups in the subsequent five years[27]. This initially mild clinical disease course was associated with a markedly lower risk of surgery compared to patients with an intermittent or chronic continuous course. Clinical symptoms are not, however, a reliable measure of mucosal inflammation in CD[40], and even asymptomatic patients in the long term can accumulate intestinal damage and develop disease-related complications[41,42]. Consequently, almost half of patients with an initially mild disease course were in need of surgery by the end of follow-up. CD is a progressive disease that, without effective immunosuppressive treatment to maintain remission and prevent flare-ups, can lead to the accumulation of intestinal damage, the development of complications such as strictures, and will eventually need surgery.

Several measures since the 1980s have improved the disease course of CD. Better diagnostic tests, as well as their wider availability, have resulted in patients being diagnosed earlier. This has reduced the proportion of patients with strictures or features of penetrating disease at diagnosis[43,44]. However, 20-25% of patients still present with such complications today[9,19,45], either due to delays in making the diagnosis[46] or because of a pre-clinical disease phase with asymptomatic inflammation[47]. Since the 1980s treatment options have also improved, first with the introduction of immunomodulators such as thiopurines, and then with an increasing number of biological therapies and small molecules for the treatment of IBD. Finally, evolving disease monitoring and treatment strategies have led to earlier and more aggressive immunosuppressive treatment (as will be discussed in 3.3), as well as more vigilant monitoring[7,48].

In parallel with these developments, surgery rates have decreased over time[34,43,44,49,50]. As shown in Paper III, as well as in a recent systematic

review[51], today one-in-five patients requires surgery within five years of a diagnosis. Most of these patients are operated upon within the first year following their diagnosis, highlighting the inability of current treatments to prevent surgery – at least in patients with severe disease at the time of diagnosis. During subsequent years, surgery rates increase only slowly – 2% per year, described in Paper III – as has been found in other recent cohorts[52].

The progression from non-stricturing, non-penetrating disease to either stricturing and/or penetrating disease occurs in approximately 15-20% of patients within five years of a diagnosis. This has also been observed in other population-based cohorts[43,53,54], including in cohorts of patients diagnosed in the pre-biological era[43,55]. In contrast to surgery rates, which are also influenced by factors not directly related to the disease, such as physician and patient preferences, reducing the rates of disease progression over time might prove more difficult. The number of long-term follow-up studies of contemporary cohorts is still limited. However, a recent Swedish study of patients diagnosed between 2005 and 2009 who were followed for ten years found that, similar to findings in Paper II, disease progression appears to stabilize after the first five years[52]. In contrast, disease location in CD tends to remain stable throughout[56] and only 10-15% of patients will develop lesions at sites other than those first diagnosed (Paper I). Disease location at diagnosis is an important predictor of the subsequent disease course and patients with small bowel, rather than colonic, involvement at the time of diagnosis are at higher risk of disease progression[57]. Progressing disease behaviour, on the other hand, is a major predictor for the need for surgery[35,36]. Interestingly, and in contrast to a recent systematic review of both population-based and selected cohort studies[58], smoking at the time of diagnosis was not associated with a worse prognosis in patients of the *Epi-IBD* cohort, nor was the association found in other population-based cohorts[55,59].

	Crohn's disease		**Ulcerative colitis**	
	Major surgery	**All-cause mortality**	**Colectomy**	**All-cause mortality**
	Relative risk [95% CI]	**Relative risk [95% CI]**	**Relative risk [95% CI]**	**Relative risk [95% CI]**
Sex				
Female	1.30 [1.00; 1.68]	0.78 [0.56; 1.09]	0.96 [0.77; 1.20]	0.73 [0.60; 0.89]
Male	*Reference*	*Reference*	*Reference*	*Reference*
Age at diagnosis				
0-17 years	1.60 [0.73; 3.50]	0.00 [0.00; .]	1.84 [1.06; 3.17]	0.05 [0.01; 0.39]
18-39 years	2.24 [1.50; 3.33]	0.05 [0.02; 0.11]	1.45 [1.05; 1.99]	0.05 [0.03; 0.08]
40-59 years	1.77 [1.16; 2.69]	0.24 [0.16; 0.35]	1.08 [0.79; 1.48]	0.15 [0.11; 0.19]
60+ years	*Reference*	*Reference*	*Reference*	*Reference*
Period				
1962-1986	11.63 [3.67; 36.90]	2.48 [1.19; 5.19]	2.19 [1.33; 3.63]	1.43 [1.01; 2.05]
1987-2011	2.26 [0.70; 7.28]	3.30 [1.72; 6.34]	0.80 [0.49; 1.33]	1.60 [1.19; 2.14]
2012-Present	*Reference*	*Reference*	*Reference*	*Reference*
Disease course during follow-up years 2 to 5				
Remission	0.28 [0.17; 0.48]	0.67 [0.35; 1.30]	0.59 [0.38; 0.91]	1.23 [0.82; 1.85]
Intermittent	0.92 [0.66; 1.29]	0.94 [0.58; 1.54]	0.84 [0.59; 1.19]	1.24 [0.86; 1.79]
Chronic continuous	*Reference*	*Reference*	*Reference*	*Reference*
Disease location / extent at diagnosis				
Small intestine / proctitis	0.70 [0.52; 0.95]	1.02 [0.66; 1.59]	0.38 [0.30; 0.49]	0.79 [0.63; 0.99]
Colon / left-sided colitis	0.66 [0.48; 0.90]	1.65 [1.10; 2.48]	0.53 [0.39; 0.70]	0.88 [0.67; 1.14]
Small intestine and colon / extensive colitis	*Reference*	*Reference*	*Reference*	*Reference*

Table 1. Risk factors associated with surgery and all-cause mortality (relative risk, 95% confidence interval) among patients with Crohn's disease and ulcerative colitis in the population-based Copenhagen County cohort.

	Progression in behaviour (*n*=347)	Progression in location (*n*=373)	Hospitalisation (*n*=488)	Hospitalisation, medical (*n*=488)	Surgery (*n*=488)
Age at diagnosis (per year)	1.0 (1.0-1.0)	0.99 (0.97-1.00)	0.99 (0.98-0.99)*	0.99 (0.98-1.0)	0.99 (0.98-1.00)
Sex					
Female	*0.8 (0.5-1.5)*	*0.5 (0.3-0.9)**	*1.0 (0.7-1.3)*	*0.9 (0.6-1.3)*	*0.8 (0.5-1.3)*
Male	*Reference*	*Reference*	*reference*	*reference*	*reference*
Diagnostic delay (per day)	1.0 (1.0-1.0)	1.004 (1.001-1.008)*	1.0 (1.0-1.1)	1.004 (1.001-1.008)*	1.005 (1.001-1.009)*
Geographic region					
Eastern Europe	0.6 (0.3-1.4)	0.7 (0.3-1.4)	0.7 (0.4-1.1)	0.8 (0.4-1.3)	0.8 (0.4-1.4)
Western Europe	*reference*	*Reference*	*Reference*	*reference*	*Reference*
Smoking status at diagnosis					
Currently	1.3 (0.7-2.5)	1.6 (0.9-3.0)	1.2 (0.8-1.7)	1.2 (0.8-1.8)	1.2 (0.7-2.0)
Former	1.5 (0.7-3.3)	0.8 (0.4-1.8)	1.3 (0.8-2.1)	1.1 (0.3-2.0)	1.4 (0.8-2.5)
Never	*reference*	*reference*	*reference*	*reference*	*Reference*
Disease behaviour					
B2: stricturing	-	2.5 (1.3-4.7)*	3.0 (2.1-4.4)*	1.7 (1.1-2.8)*	4.7 (2.8-7.9)*
B3: penetrating		2.6 (1.1-6.1)*	2.7 (1.6-4.5)*	1.3 (0.6-2.6)	4.8 (2.5-9.1)*
B1: non-stricturing, non-penetrating		*reference*	*reference*	*reference*	*reference*
Disease location					
L2: Colon	0.4 (0.1-0.96)*		1.2 (0.7-1.9)	1.3 (0.7-2.2)	1.1 (0.6-2.1)
L3: Terminal Ileum + colon	1.0 (0.4-2.3)	-	0.9 (0.6-1.6)	0.7 (0.4-1.3)	1.1 (0.5-2.0)
L4: Upper GI (± L1-L3)	1.5 (0.7-3.4)		1.3 (0.8-2.0)	1.3 (0.8-2.3)	1.2 (0.7-2.2)
L1: Terminal ileum	*Reference*		*reference*	*reference*	*reference*
Extra-intestinal manifestations at diagnosis	0.3 (0.1-0.9)*	0.5 (0.2-1.2)	0.8 (0.5-1.3)	0.7 (0.4-1.3)	0.8 (0.4-1.6)
Use of immunomodulators	0.6 (0.3-1.1)	1.2 (0.6-2.2)	0.3 (0.2-0.5)*	0.4 (0.2-0.6)*	0.4 (0.2-0.6)*
Use of biologicals	1.1 (0.5-2.2)	0.7 (0.4-1.4)	0.7 (0.5-1.2)	0.8 (0.5-1.4)	0.8 (0.4-1.3)
Need for early corticosteroids	1.4 (0.7-2.6)	1.2 (0.7-2.2)	1.2 (0.8-1.7)	1.1 (0.7-1.7)	1.0 (0.6-1.7)

* $p<0.05$

Table 2. Predictors associated with progression in behaviour and location, hospitalisation and surgery in Crohn's disease patients in the Epi-IBD cohort

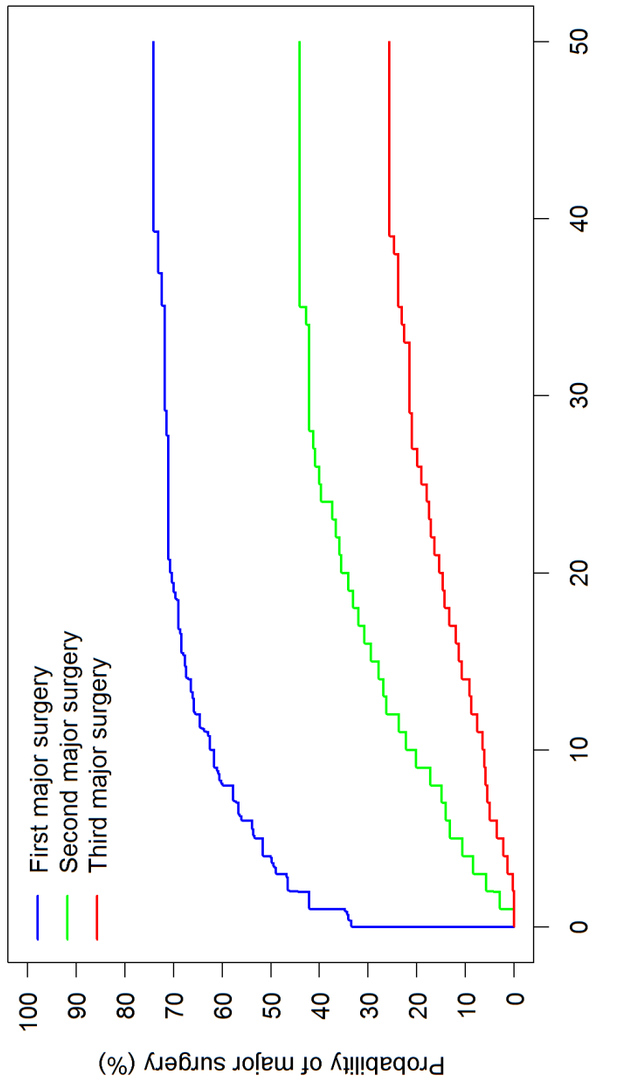


Figure 1. The cumulative risk of a first, second and third major surgery in a Danish population-based cohort of patients with Crohn's disease diagnosed between 1962 and 1987.

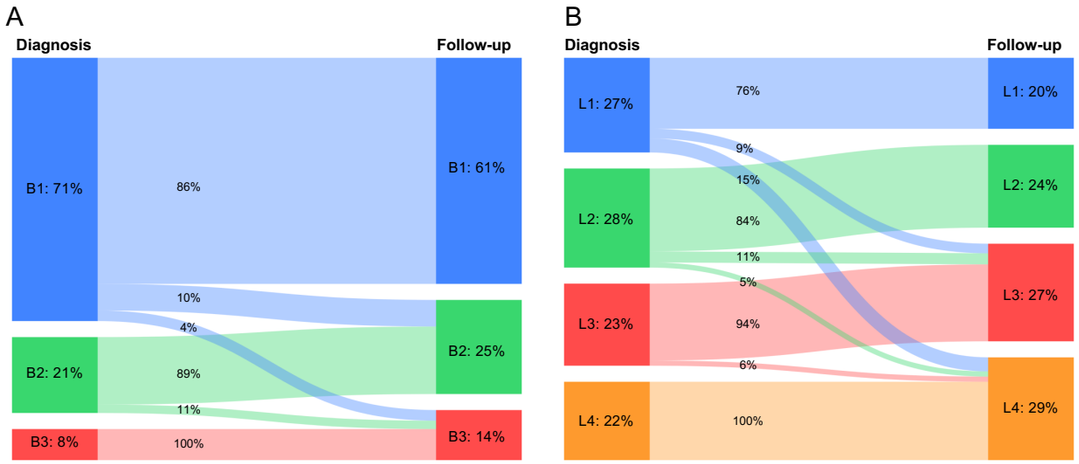
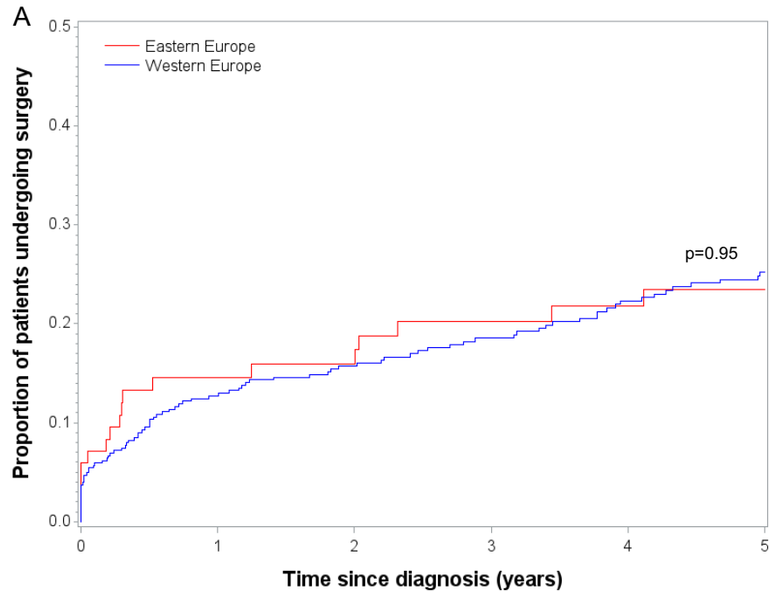


Figure 2. Changes in disease behaviour (A) and location (B) during five years of follow-up among patients with Crohn's disease in a European population-based inception cohort. The central column represents the proportion of patients within each category that changed to one of the other categories.

B1: non-stricturing, non-penetrating; B2: stricturing; B3: penetrating; L1: terminal ileum; L2: colon; L3: terminal ileum and colon; L4: upper gastrointestinal tract (all patients with upper GI involvement)



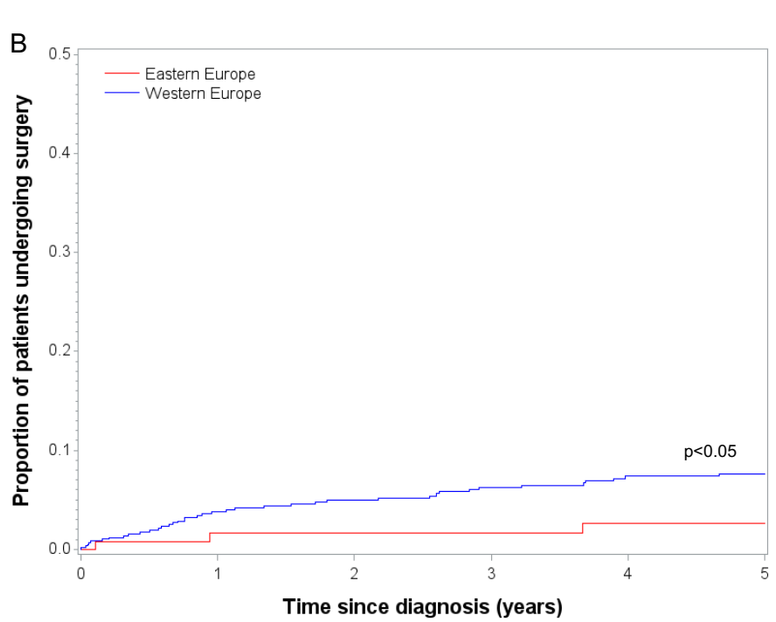


Figure 3. Cumulative probability for surgery in (A) Crohn's disease and (B) ulcerative colitis during the first five years of disease in a European population-based cohort.

3.2 Natural disease course of ulcerative colitis

3.2.1 Own results (Papers II and IV)

The *Copenhagen County* cohort included 1,161 patients with UC that were followed for a median of 34 years (IQR: 21-42). The cumulative probability of needing a colectomy 5, 10, 20, 30, 40 and 50 years after diagnosis was 17% (CI95%: 15-20%), 22% (CI95%: 20-25%), 27% (CI95%: 25-30%), 31% (CI95%: 28-34%), 34% (CI95%: 31-37%), and 40% (CI95%: 36-44%), respectively, Figure 4. The median time to colectomy was 4.0 years (IQR: 0.5-13.2). The risk of colectomy varied according to the disease extent at diagnosis. Most patients needing a colectomy had extensive colitis at diagnosis (47%), and their crude colectomy rate was 43% compared to 21% among patients with proctitis, and 28% among patients with left-sided colitis. Besides disease extent, the multivariate analysis found that young age at diagnosis and an initial remitting disease course were associated with a greater risk of needing a colectomy, Table 1.

The *Epi-IBD* cohort consisted of 717 UC patients that were followed for a median of five years (IQR: 0-5). At diagnosis, 61% of patients had either proctitis or left-sided colitis. During follow-up, 21% of those progressed to extensive colitis. This happened within a median of 12 months (IQR: 1-62) from diagnosis. In addition, 25% of patients diagnosed with extensive colitis, and 34% of patients progressing from limited to extensive colitis, experienced a regression in disease extent, Figure 5. Predictors associated with changes in disease extent are shown in Table 3.

Hospitalisation was necessary for 23% of patients, mainly due to the need for medical treatment. The median time to medical hospitalisation was ten months (IQR: 3-23). Hospitalisations occurred more frequently among Western, than Eastern, European patients (24% compared to 17%, $p<0.05$). Extensive disease and the need for corticosteroids increased the risk of hospitalisation. Residing in Eastern Europe and using immunomodulators decreased the risk of hospitalisation, Table 3. The five-year colectomy rate was 6% and two-thirds of these took place within the first two years after a diagnosis, Figure 3. A total of 56% of these patients subsequently received a pouch during the follow-up period. The colectomy rate was higher in Western (7%), than in Eastern, Europe (2%, $p<0.05$); however, the multivariate analysis did not find this geographic difference to be significant, and only extensive disease was found to be associated with the risk of colectomy, Table 3. In the subgroup of patients that did not achieve mucosal healing at endoscopy during the first year following a diagnosis, the risk of colectomy in subsequent years was non-significantly increased (HR: 2.3 CI95%: 0.8-6.2).

3.2.2 Discussion

Unlike CD, the foundations for controlling long-term UC were laid as early as the 1960s, when sulfasalazine was introduced. However, as the findings in Paper II demonstrate, many patients still needed a colectomy despite the ability of sulfasalazine and, later, 5-ASA to successfully reduce the frequency of flare-ups in UC. Similarly, in Sweden patients diagnosed prior to 1980 had a surgery rate of 21% at ten years disease duration[60] and 45% at 25 years[61], while in Olmsted county, United States of America, the colectomy rate was 25% after twenty years[62]. A significant proportion of patients in the *Copenhagen County* cohort (9%) had undergone surgery within the first year after their diagnosis[63] and half of colectomies took place within the first decade of disease.

Surgery rates in UC patients since then have declined significantly. Cohorts from the 1990s and early 2000s have reported lower colectomy rates of approximately 10% after ten years of disease[51,64–67]. As in CD, the reasons for this decline are multifactorial and include progress made in diagnosing, treating, and monitoring UC patients[51]. Whether the need for colectomy has further decreased more recently remains undetermined due to a lack of long-term follow-up of cohorts during the last decade. The five-year colectomy rates available are approximately 5%[64,68].

It is not clear why the colectomy rates in Paper IV are lower in eastern Europe, despite patient characteristics there being similar to their counterparts in western Europe[9,69]. Previous studies had demonstrated significant geographic variations in surgery rates in IBD due to differences in health care settings, and patient and physician attitudes towards surgery[65]. Indications for colectomy have changed over time from being almost exclusively due to medically refractory disease before 1990, to now include colorectal neoplasia and fulminant colitis[70]. Regardless of the time period, a significant proportion of patients needing a colectomy will do so within less than two years of a diagnosis[71], including almost half of patients with extensive colitis, which underlines the potential fulminant course of UC. Acute severe colitis remains a clinical situation in which early colectomy rates, as well as mortality, are high[72] and therapeutic options are not sufficiently effective[73]. However, the number of early colectomies performed within six months of a diagnosis are decreasing in some populations[64].

While the long-term prognosis of UC is always uncertain, it is clearly affected by the area of inflamed colonic mucosa, which is one of the most important predictors. Patients with extensive colitis are at higher risk for several major outcomes, including colectomy, than are those with limited extent. This has been reported consistently in both early[74,75] and more modern studies[71,76,77], including those presented here. However, UC is a dynamic disease and the extent to which the colon is involved can change over time. Progression in disease extent occurs in approximately 20% of patients within ten years of their diagnosis[60,76,78] and is an important indicator of the severity and activity of the disease. Accordingly, disease progression is associated with as similarly high risk of colectomy as is being diagnosed with extensive disease[76]. Regression of extensive colitis during the course of disease, in contrast, was associated with a lower risk of hospitalisation in Paper IV. Regression in extent has previously been described in the *Copenhagen County* cohort as occurring in 71% of patients with pancolitis after 10 years[79], whereas 22% of patients in a Norwegian population-based cohort experienced disease regression within a median of 14 months of follow-up after their diagnosis[80].

Population-based data about age at diagnosis as a predictor for colectomy are conflicting. While colectomy rates in some regions are higher among children than adults[81–84], in other cohorts they are not[85]. In Norway, being diagnosed at 40 years or older was associated with a reduced risk of colectomy over a twenty year period[71], whereas colectomy rates were higher in the group of elderly-onset group of patients (older than 60 years at diagnosis) than in younger adults[86]. Finally, achieving mucosal healing has been associated with a reduced risk of colectomy[87,88], even after 20 years of follow-up[71]. In Paper IV, endoscopic assessment of the mucosa was only performed at the treating physicians' discretion and this could explain why the association could not be confirmed.

	Progression in extent (*n*=435)	Regression in extent (*n*=273)	Hospitalisation, all (*n*=717)	Hospitalisation, only medical (*n*=717)	Colectomy (*n*=717)
Age at diagnosis (per year)	0.98 (0.96-0.99)*	1.00 (0.99-1.02)	0.98 (0.97-0.99)*	0.98 (0.97-0.99)*	0.99 (0.97-1.01)
Sex					
Female	0.9 (0.6-1.5)	0.7 (0.4-1.3)	1.3 (0.9-1.7)	1.3 (0.9-1.8)	1.2 (0.7-2.4)
Male	*reference*	*reference*	*reference*	*reference*	*reference*
Diagnostic delay (per day)	1.0 (1.0-1.0)	1.0 (0.9-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Geographical region					
Eastern Europe	0.6 (0.3-1.2)	0.9 (0.4-1.8)	0.6 (0.4-0.9)*	0.6 (0.4-0.97)*	0.3 (0.1-1.1)
Western Europe	*reference*	*reference*	*reference*	*reference*	*reference*
Smoking status at diagnosis					
Currently	1.1 (0.5-2.8)	0.7 (0.3-2.1)	0.7 (0.4-1.4)	0.7 (0.4-1.4)	0.3 (0.1-2.4)
Former	1.2 (0.7-2.1)	1.1 (0.6-1.9)	1.1 (0.7-1.5)	1.1 (0.8-1.7)	1.3 (0.7-2.7)
Never	*reference*	*reference*	*reference*	*reference*	*reference*
Disease extent					
E3: Extensive colitis	-	-	1.4 (1.4-4.1)*	2.2 (1.3-3.8)*	3.5 (1.01-12.3)*
E2: Left-sided colitis			1.5 (0.9-2.6)	1.4 (0.8-2.3)	2.3 (0.7-8.1)
E1: Proctitis			*reference*	*reference*	*reference*
Extra-intestinal manifestations at diagnosis	1.3 (0.6-2.8)	0.6 (0.3-1.4)	1.4 (0.9-2.2)	1.4 (0.9-1.0)	1.3 (0.5-3.1)
Use of immunomodulators	0.6 (0.3-1.1)	0.7 (0.4-1.3)	0.5 (0.3-0.8)*	0.5 (0.3-0.8)*	1.3 (0.7-2.7)
Use of biologicals	0.7 (0.2-2.2)	1.5 (0.8-2.8)	0.8 (0.3-1.7)	0.6 (0.1-1.4)	1.4 (0.6-3.2)
Need for early corticosteroids	1.1 (0.6-2.2)	1.4 (0.8-2.3)	1.7 (1.2-2.4)*	1.8 (1.3-2.6)*	0.9 (0.5-1.9)

* $p<0.05$

Table 3. Factors associated with changes in disease extent, hospitalisation and colectomy in ulcerative colitis patients in the Epi-IBD cohort

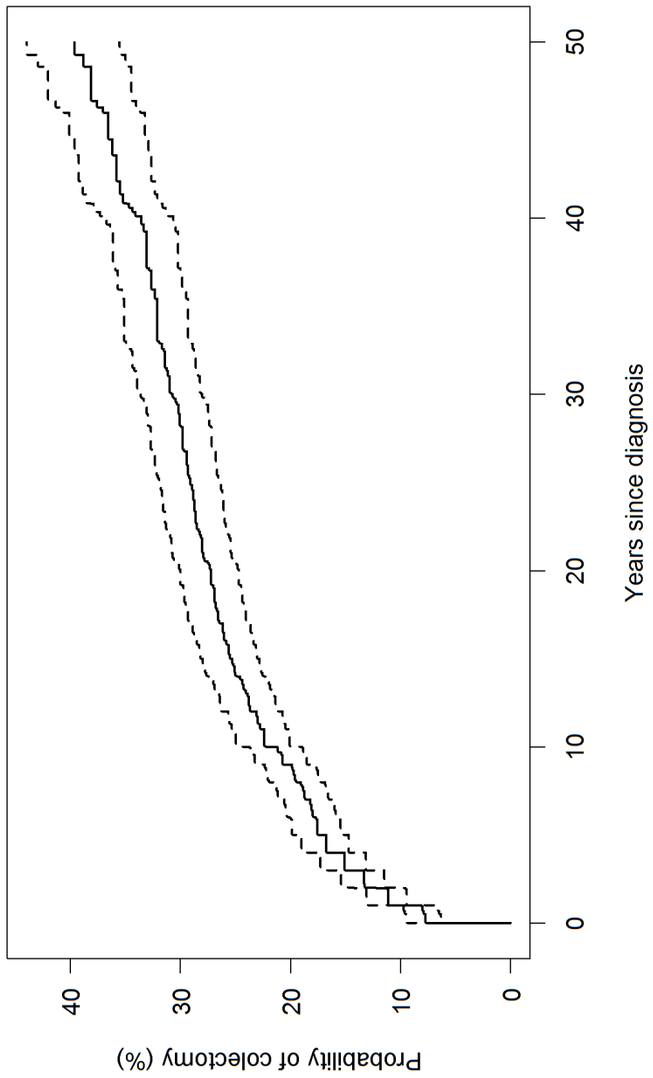


Figure 4. The cumulative risk of colectomy in a Danish population-based cohort of patients with ulcerative colitis diagnosed between 1962 and 1987.

Figure 5. Disease extent and changes in extent in ulcerative colitis patients during five years of follow-up in a European population-based inception cohort. The figure shows disease extent at diagnosis, the greatest extent during follow-up, and the extent by the end of follow-up.

3.3 Treatment strategies in European patients with Crohn's disease and ulcerative colitis

3.3.1 Own results (Papers III, IV and VII)

Within five years of a diagnosis, approximately two-thirds of CD patients were started on immunomodulators and 30% were started on biological therapy (all received anti-TNFα therapy), while this was the case in 29% and 11% of UC patients, respectively. Most patients started therapy during the first year, Figure 6. The treatment patterns differed between Eastern and Western Europe, as shown in Table 4. More Western European UC and CD patients were treated with immunomodulators and biological therapies, and the drugs were introduced earlier, than in Eastern Europe, while the use and duration of 5-ASA in CD patients was higher in Eastern Europe. The distribution of patients across treatment steps at any given time during follow-up is shown in Figure 7 and the treatments prior to initiation of biological therapy or surgery are shown in Table 5. The proportion of patients in need of treatment with steroids for more than six consecutive months was 9% in CD and 7% in UC, with no geographical difference observed between the two.

Three-in-five CD patients had received 5-ASA for a median treatment duration of 28 months (IQR: 6–60), which prompted further analysis of this subgroup of patients. In 26% of CD patients, 5-ASA was the only medical treatment initiated for maintenance therapy during the first year after a diagnosis. These patients were treated with 5-ASA for a median duration of 34 months (IQR: 12-60 months) and were older and had fewer complications at diagnosis than other CD patients. Their disease course was mild as surgery, hospitalisation and disease progression occurred less frequently than among the rest of the cohort, Figure 8, and 76% never needed treatment escalation beyond 5-ASA. However, in all cases where treatment escalation was deemed necessary, 5-ASA were continued in combination with immunomodulators or biological therapy. An additional 44% of CD patients also received 5-ASA, in 97% of cases as the first maintenance treatment, but eventually three-quarters of these patients were escalated to immunomodulators (35%), biological therapy (23%) or needed surgery (18%) within the first year.

3.3.2 Discussion

Ultimately, the goals of IBD treatment are to induce and maintain steroid-free remission with mucosal healing, to reduce disease-related disability and to avoid hospitalisations and surgery[89,90]. Over the last two decades, this has led physicians to introduce immunomodulators and biological therapies earlier in the disease course and more frequently for IBD patients, as has been demonstrated in several other recent population-based cohorts[43,44,50,64,91,92]. These efforts are made with the hope of shifting disease management from symptom control to long-term mucosal healing and, potentially, disease modification.

However, real-world data are conflicting as to the impact of modern treatment strategies on disease outcomes. The number of patients ever exposed to steroids appears to have been stable during previous decades[93], but whether the cumulative number of days of corticosteroid use has decreased is uncertain[94,95]. Similarly, changes in disease progression and surgery rates over time have not been demonstrated to have been significantly impacted by the introduction of biological therapies[43,96]. The outcomes in Papers III and

IV are largely similar to what has been observed in cohorts from the preceding decade.

Several reasons might explain such underperformance of modern treatment strategies in population-based cohorts. Besides the patient population being different from those included in trials, strategies to optimize biological therapy such as accelerated start-up[97], therapeutic drug monitoring[98,99] and close monitoring with faecal calprotectin or intestinal MR[100–102] are not uniformly implemented due to limited access across Europe. Furthermore, the ability of physicians to predict the disease course or response to treatments among IBD patients is limited and might be leading to overtreatment of patients in the community setting who might otherwise have responded to alternative treatment approaches[103,104]. Still, the difference in use of biological therapies between Eastern and Western European centres is striking considering that patient characteristics and disease outcomes are similar. Despite the availability of evidence-based treatment recommendations[105,106], choices regarding investigations, medical and surgical treatments and the availability of such treatments are all closely linked to extramedical considerations and health care systems, treatment practices, access to biological treatments and the highly variable costs of drugs in Europe[10]. Reimbursement guidelines in Eastern European countries are more restrictive, for example, than those in Scandinavian countries; Eastern countries reserve biological therapies for more severely ill patients or only for later on in the disease course[107], as is also clear from the way in which patients were treated before starting biological therapies or undergoing surgery. Macro-economic indicators (such as GDP) have been shown to correlate with access to, and use of, biological therapies, but they do not explain the relationship entirely. Differences in the use of biological therapies have also been observed between Eastern European countries, as well as between different inflammatory conditions (such as IBD, rheumatoid arthritis or ankylosing spondylitis) within the same country[108].

Such differences in treatment practices are also reflected in the use of 5-ASA in CD patients. Several other cohorts have demonstrated that almost half of CD patients are exposed to 5-ASA at some point and that treatment continues for long periods of time[34,109–112]. Several systematic reviews have concluded that 5-ASA used to treat CD is no better than a placebo and therefore guidelines do not recommend it[105,113]. As such, the widespread clinical use of 5-ASA to treat CD takes place in sharp contrast to the limited scientific evidence supporting it. The reasons for this remain unknown. It takes time before research evidence becomes incorporated into clinical practice, and physicians might be driven by patient expectations of being started on maintenance therapy following their initial flare-up. On the other hand, the use of 5-ASA is frequent among elderly patients and those with comorbidities and could therefore be partly explained by physicians being hesitant to use more potent and toxic drugs in these patients[82,86,114]. Despite evidence to the contrary, many physicians endorse 5-ASA as a valid therapy for mild CD[110,115–117]. Findings from Paper IV suggest that physicians had indeed identified CD patients that were at low risk for a severe disease course and treated them with 5-ASA. Previous studies have demonstrated that approximately 20% of CD patients show a quiescent disease course with minimal disease activity, as well as low rates of progression and surgery[27,55,118].

Type of treatment	Western Europe		Eastern Europe		All patients	
	n (%)	Months, median (IQR)	*n* (%)	Months, median (IQR)	*n* (%)	Months, median (IQR)
Crohn's disease						
5-aminosalicylates	227 (56%)	22 (5-55)	76 (90%)	47 (15-63)	303 (62%)	28 (6-60)
Budesonide	122 (30%)	6 (3-10)	13 (15%)	7 (3-22)	135 (28%)	4 (3-10)
Prednisolone	243 (60%)	3 (2-6)	51 (61%)	3 (2-7)	294 (60%)	3 (2-6)
Immunomodulators	266 (66%)	36 (11-58)	45 (54%)	39 (21-57)	311 (64%)	37 (12-58)
Biological therapy	132 (33%)	32 (13-49)	12 (14%)	29 (12-45)	144 (30%)	32 (13-49)
Ulcerative colitis						
5-aminosalicylates	535 (91%)	49 (19-62)	126 (100%)	45 (24-63)	661 (92%)	49 (20-62)
Prednisolone	305 (52%)	4 (1-3)	56 (44%)	3 (2-6)	361 (50%)	4 (2-6)
Immunomodulators	176 (30%)	29 (8-49)	34 (27%)	25 (9-48)	210 (29%)	28 (8-49)
Biological therapy	70 (12%)	14 (5-28)	10 (8%)	19 (10-32)	80 (11%)	14 (6-29)

Table 4. Frequency and duration of oral treatment in patients with Crohn's disease and ulcerative colitis after five-years of follow-up in the Epi-IBD cohort

	Crohn's disease			Ulcerative colitis		
	Western Europe	Eastern Europe	All patients	Western Europe	Eastern Europe	All patients
Most potent treatment step before biological therapy, *n* (%)						
No treatment	3 (3%)	0 (0%)	4 (3%)	0 (0%)	0 (0%)	0 (0%)
5-aminosalicylates	1 (1%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	1 (1%)
Corticosteroids	20 (15%)	3 (25%)	23 (16%)	32 (46%)	2 (20%)	34 (43%)
Immunomodulators	97 (73%)	7 (58%)	104 (72%)	36 (51%)	8 (80%)	44 (55%)
Surgery	10 (8%)	2 (17%)	12 (9%)	1 (1%)	0 (0%)	1 (1%)
Most potent treatment step before surgery, *n* (%)						
No treatment	22 (25%)	7 (39%)	29 (27%)	1 (3%)	0 (0%)	1 (2%)
5-aminosalicylates	2 (2%)	2 (11%)	4 (4%)	1 (3%)	1 (33%)	2 (4%)
Corticosteroids	20 (23%)	1 (6%)	21 (20%)	8 (19%)	0 (0%)	8 (19%)
Immunomodulators	20 (22%)	8 (44%)	28 (26%)	16 (40%)	2 (67%)	18 (42%)
Biological therapy	25 (28%)	0 (0%)	25 (23%)	14 (35%)	0 (0%)	14 (33%)

Table 5. Treatment steps reached prior to biological therapy or surgery in a European inception cohort of patients with Crohn's disease and ulcerative colitis

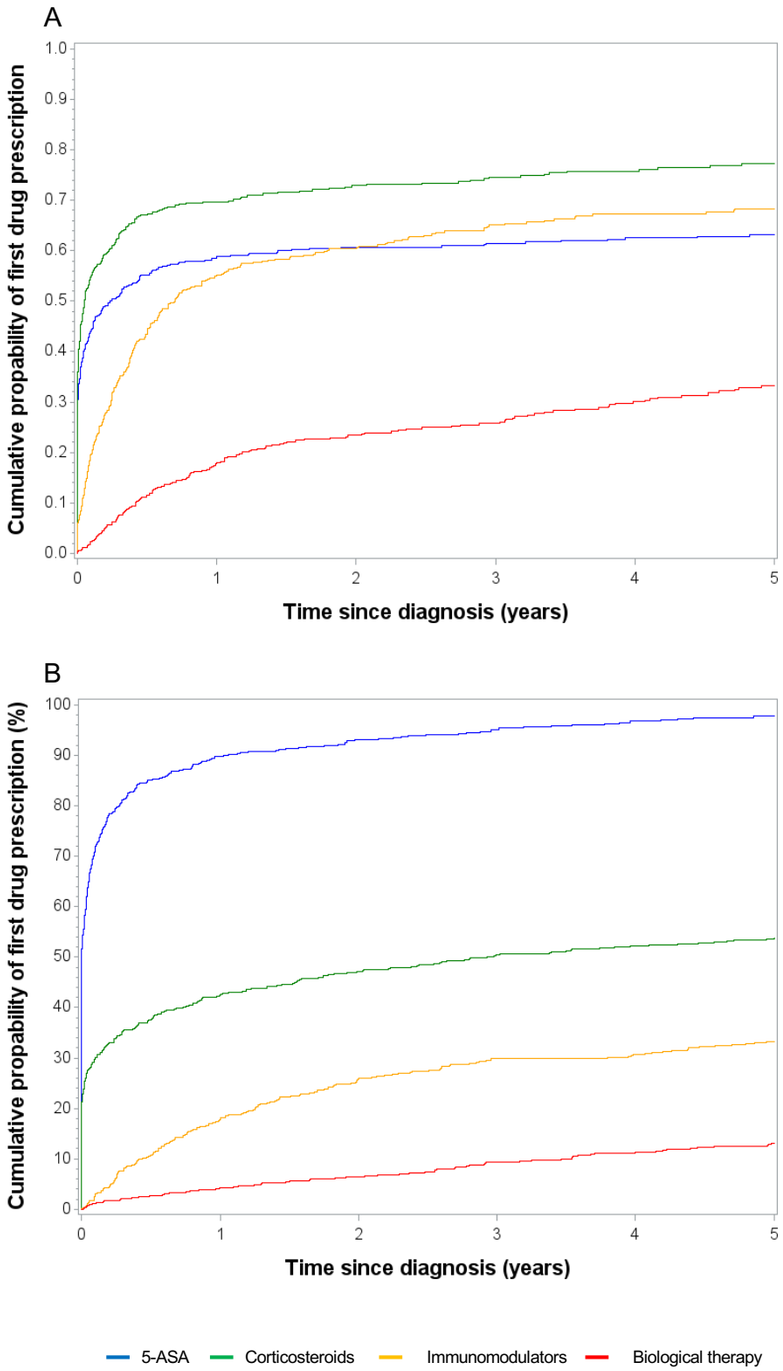
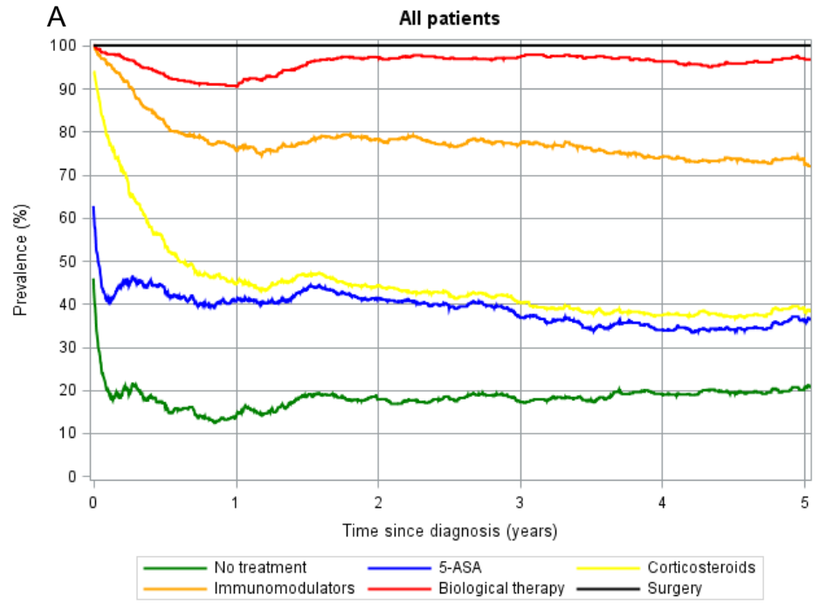


Figure 6. Cumulative five-year exposures for medical treatment among patients with (A) Crohn's disease and (B) ulcerative colitis in a European inception cohort.
** 5-ASA, 5-aminosalicylates*



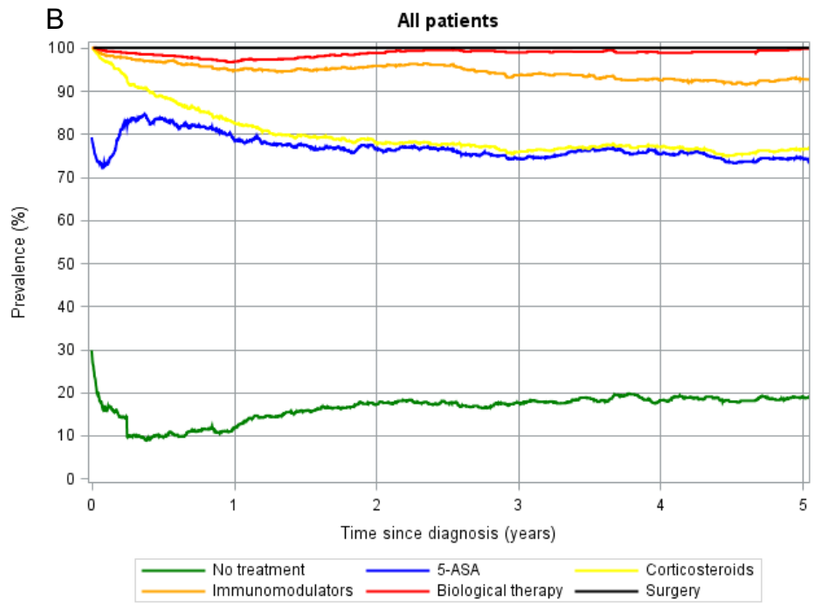


Figure 7. The time-varying distribution of patients with (A) Crohn's disease and (B) ulcerative colitis receiving different potencies of treatment on any given day during follow-up. At any time, the distribution totals 100%. Patients receiving combination therapy are categorized according to the most potent treatment step.
** 5-ASA, 5-aminosalicylates*

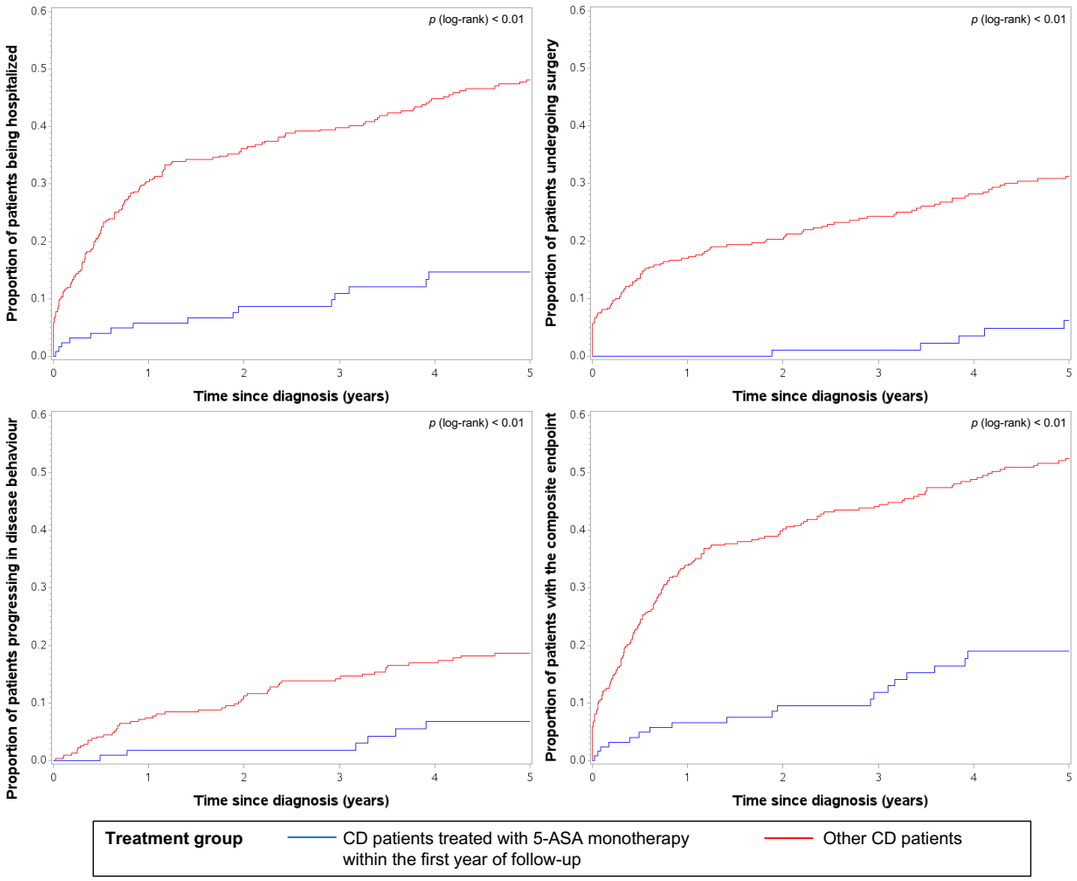


Figure 8. Cumulative probability for (A) hospitalisation, (B) surgery, (C) disease progression and (D) the composite endpoint of all three outcomes in patients with Crohn's disease (CD) treated with 5-aminosalicylate (5-ASA) monotherapy within the first year of follow-up in a European inception cohort.

3.4 Costs and resource utilization of patients with inflammatory bowel disease

3.4.1 Own results (Paper VI)

Total expenditure for CD patients between 2010 and 2015 was €6,768,173 (Western Europe €6,283,777; Eastern Europe €484,396). For UC patients it was €5,945,501 (Western Europe €5,615,040; Eastern Europe €330,461). In the case of CD patients, half of the total was spent on biological therapies (€3,406,233). Hospitalisation and diagnostic procedures accounted for more than half of total costs in UC (€3,429,415).

The total costs corresponded to median costs per patient-year of €717 (IQR: € 214–3512) in CD and €408 (IQR: € 92–1228) in UC. Costs were higher in Western than in Eastern Europe across all categories and in all follow-up years in both CD and UC. Furthermore, in CD, males, current smokers, younger patients and patients with stricturing or penetrating disease behaviour carried higher median costs per year. In UC, patients with elderly-onset IBD and those who were current smokers had lower median costs; costs increased with increasing disease extent.

Costs were highest in the first year of treatment and then decreased significantly during follow-up. At the same time, the cost profile changed. Hospitalisations and diagnostic procedures accounted for more than 50% of costs for both CD and UC patients during the first year. Expenditure on biologicals increased in subsequent years and accounted for 73% of costs in CD and 48% in UC during the final year of follow-up, Figure 9.

The mean annual costs for biological therapy increased from €918 (SD: €2,684) on year one to €2,539 (SD: €5,145) in year five in CD, and from €109 (SD: €568) to €548 (SD: €2,226) in UC. The increase in expenditure on biologicals was paralleled by a significant decrease in all other costs in UC, but not in CD, Figure 10. CD patients that were smoking at diagnosis or had stricturing or penetrating disease carried higher mean annual costs for biological therapy. In UC, patients with a current or previous smoking habit, or with extensive disease at diagnosis, had higher costs. In both CD and UC, patients older than 60 years at diagnosis had lower costs for biological therapy than did patients diagnosed at a younger age.

The quantile regression analysis confirmed that biological therapy, severe disease phenotype at diagnosis and smoking status predicted higher total costs in the cohort, and that the level costs during the first year following diagnosis also predicted high costs in subsequent years.

3.4.2 Discussion

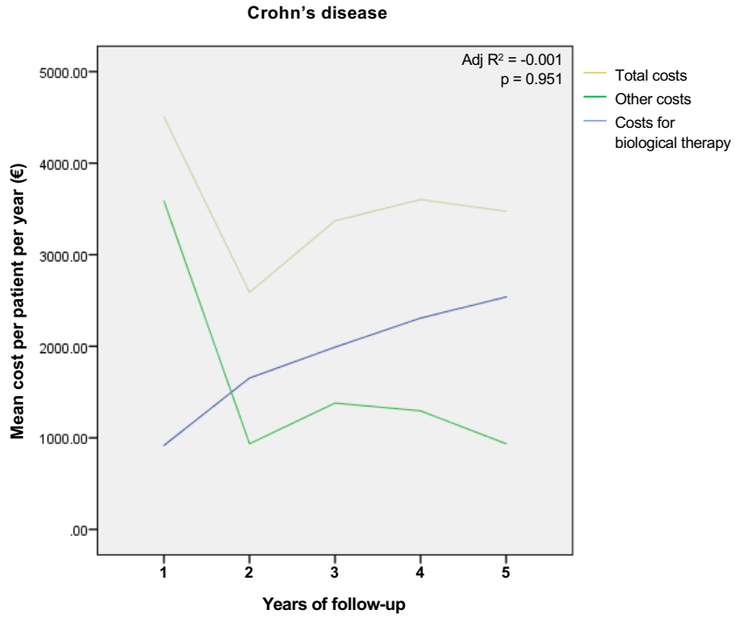
Before 2000, which for practical purposes can be defined as the pre-biological era, the direct costs of treating IBD were strongly driven by hospitalisation and surgery[29,119]. With the introduction of biological therapies, the costs and cost profile of IBD changed significantly. Firstly, the uptake of biological therapies has increased dramatically. In addition, and due to a high risk of relapse[120], biological drugs are usually continued indefinitely in patients who respond positively to them[120]. Expenditures for IBD management, which have increased over the past two decades, are now mostly driven by the cost of biological therapies[121–125].

Following diagnosis, costs during the initial year are determined by expenditures on diagnostic and monitoring procedures. By the second year, biological therapies account for more than half of costs in CD. In UC, due to the efficacy of 5-ASA[126], this change in cost profile takes longer to emerge, as procedures and hospitalisations continue to account for a large proportion of costs.

It remains to be proven whether in the long term the increasing costs for biological therapies cause direct cost reductions in hospitalisations and surgeries. In Paper IV, expenditures on biologicals increased as costs for other drugs, surgeries, hospitalisations and diagnostic procedures decreased. In contrast, in a Swiss cohort the mean expenditure on inpatients remained stable over a ten-year period despite an increase in the use of biological therapy. These findings suggest no direct substitution of costs between inpatient and outpatient/pharmaceutical care[121]. In a Canadian population-based cohort, while savings were made in inpatient costs among patients started on anti-TNFα antibodies, these savings were less than expenditures on maintenance therapy. Overall, the high medical costs of patients on biological therapy persisted throughout the follow-up[127]. In a cost-effectiveness analysis based on the Swiss IBD cohort, early (i.e., within two years of a diagnosis) treatment with biological therapy was associated with a significant cost burden, but did not sufficiently improve health outcomes over a patient's lifetime to justify the expense[128]. However, there are a number of contextual and methodological differences between these studies which likely affect their findings. Furthermore, work presented in Paper VI and a previous European population-based study[29] demonstrate that the costs of care and drugs vary considerably between countries due to differences in health care financing and delivery systems.

While biological therapies have improved disease management, the cost-effectiveness of these agents is a growing concern in a time of ever-pressing budget constraints[129]. However, the cost-benefit analysis changes somewhat if the indirect costs of IBD, such as reductions in work productivity and absenteeism, are included[123,125]. If biological therapies are able reduce indirect costs, this might justify their increasing use. A small number of studies suggest that they do so[130,131], but these studies are limited by their short follow-up times. It remains to be proven whether this holds true in the long term. Furthermore, the increasing number of available biosimilars[132] might eventually lower costs, although this could depend on prices dropping further still, as has been suggested in a Canadian study[127]. Lower prices for biological therapies can, however, also result in increased access and hence increasing use and overall costs. One final consideration is that interventions targeted at modifiable cost drivers, such as smoking in CD[133,134], can improve the efficacy of biological therapies and consequently reduce overall costs.

Figure 9. Annual distribution of costs for patients with Crohn's disease and ulcerative colitis in a European population-based inception cohort.



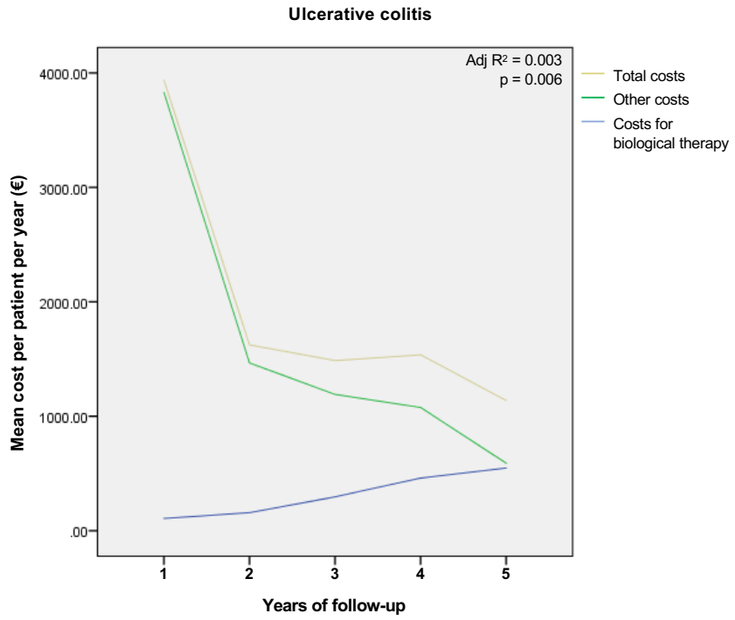


Figure 10. Changes in mean costs per year of follow-up for biological therapy and other costs (other drugs, surgeries, hospitalisations, investigations) for patients with Crohn's disease and ulcerative colitis in a European population-based inception cohort*.

**The statistical analysis model relates to years 2 to 5 as year 1 is a high-cost year based principally on investigations. The adjusted R2 values are very low. In IBDU (not shown) p=0·727.*

3.5 The prognosis of inflammatory bowel disease unclassified

3.5.1 Own results (Paper V)

A total of 112 patients (9%) in the *Epi-IBD* cohort were initially diagnosed with IBDU. In 63% of cases this was because they did not fulfil all diagnostic criteria for UC, most often the histological criteria. During follow-up, after a median of six months (IQR: 4-12) 25% of IBDU patients received a definitive diagnosis of either UC (71%) or CD (29%). However, 46% of IBDU patients had no further endoscopy or imaging performed. Therefore, by the end of follow-up 84 (7%) patients in the cohort had been diagnosed with IBDU.

The cumulative rates of medical treatment and surgery are shown in Figure 11. Almost all (96%) patients were treated with 5-ASA and only few patients needed escalation to immunomodulators or biological therapies. This applied particularly to those that remained as IBDU throughout the observation period. A total of eight patients with IBDU underwent surgery after a median of 19 months (IQR: 8-35). Six surgeries were performed on patients whose diagnosis changed to UC either before or after colectomy, whereas the remaining two colectomies did not result in a definitive UC diagnosis. One-third of IBDU patients whose diagnosis had been changed to UC experienced a progression in disease extent, and half of those eventually needed a colectomy. One IBDU patient developed cancer in the male genital organs and three patients died during the follow-up period; none of these deaths were related to their IBD.

3.5.2 Discussion

There is no gold standard for the diagnosis of CD and UC. But distinguishing between IBD types can be of pivotal importance for tailoring clinical management, particularly in the case of surgical managment[135]. Approximately 10% of patients in population-based cohorts either lack classic features and/or present with overlapping features of CD and UC at diagnosis. Consequently, their IBD cannot be more precisely categorized[136]. However, no uniform terminology or clear definitions for such cases exist. While the European Crohn's and Colitis Organization (ECCO) recommends using the term IBDU[137,138], other studies use different definitions and terminologies (for example, 'uncertain colitis' or 'indeterminate colitis'), making it difficult to compare studies and to make evidence-based decisions about treatment[139]. The *Copenhagen Diagnostic Criteria* also allows patients with small bowel inflammation to be classified as IBDU, whereas other definitions include only patients with colonic inflammation[139]. In many cases, IBDU is an interim diagnosis made while further investigations take place to reach a definitive classification of IBD type. Even then some patients may remain unclassifiable in the long term[136,140,141].

The frequency of IBDU varies between cohorts[9,136]. Microscopic features of IBD depend on time and treatment. They may not be present early on in the disease course, which can make a definitive diagnosis difficult[139,142]. The ability to recognize features of CD and UC also depend on the experience of the pathologist and there is significant inter-observer variation in the evaluation of biopsies[143]. Serologic testing can help in identifying the *true* IBD subtype[140,144], however such testing is not widely available and is expensive to carry out.

In cases of IBDU, ECCO guidelines recommend follow-up procedures after the first and fifth years in order to reconfirm the diagnosis, as well as update

earlier biopsies[137]. But as is apparent in Paper V, many patients will not be investigated beyond their initial workup. As many IBDU patients are clinically similar to UC[145–147], clinicians might not be motivated to carry out further diagnostic procedures as the implications for treatment choices can appear limited. Hence, the number of *true* IBDU patients is difficult to determine and studies of the disease course of IBDU might well be influenced by cohorts consisting of both IBDU patients and UC or CD patients.

Surprisingly little is known about the disease course of IBDU. A Swedish cohort of patients diagnosed between 1958 and 1982 found that patients with IBDU, in the study restricted to patients with colitis, had a higher risk of relapse[148] and colorectal cancer[149] than patients with UC. A Chinese study of twenty-seven IBDU patients observed a mild short-term disease course, with three-quarters of patients going into remission on 5-ASA and only eight needing steroids[150]. A mild disease course was also observed in a multicentre cohort of paediatric IBDU patients with lower frequencies of immunomodulators, biological therapies and surgeries than among patients with definitive diagnoses of CD or UC[151]. Similar observations were made in Paper VI of patients who remained classified as IBDU throughout follow-up. However, patients whose diagnosis did change to UC were more likely to need biological therapy and colectomy. The results could have been affected by physicians treating IBDU patients differently; alternatively, it may point to a distinct phenotype of IBD.

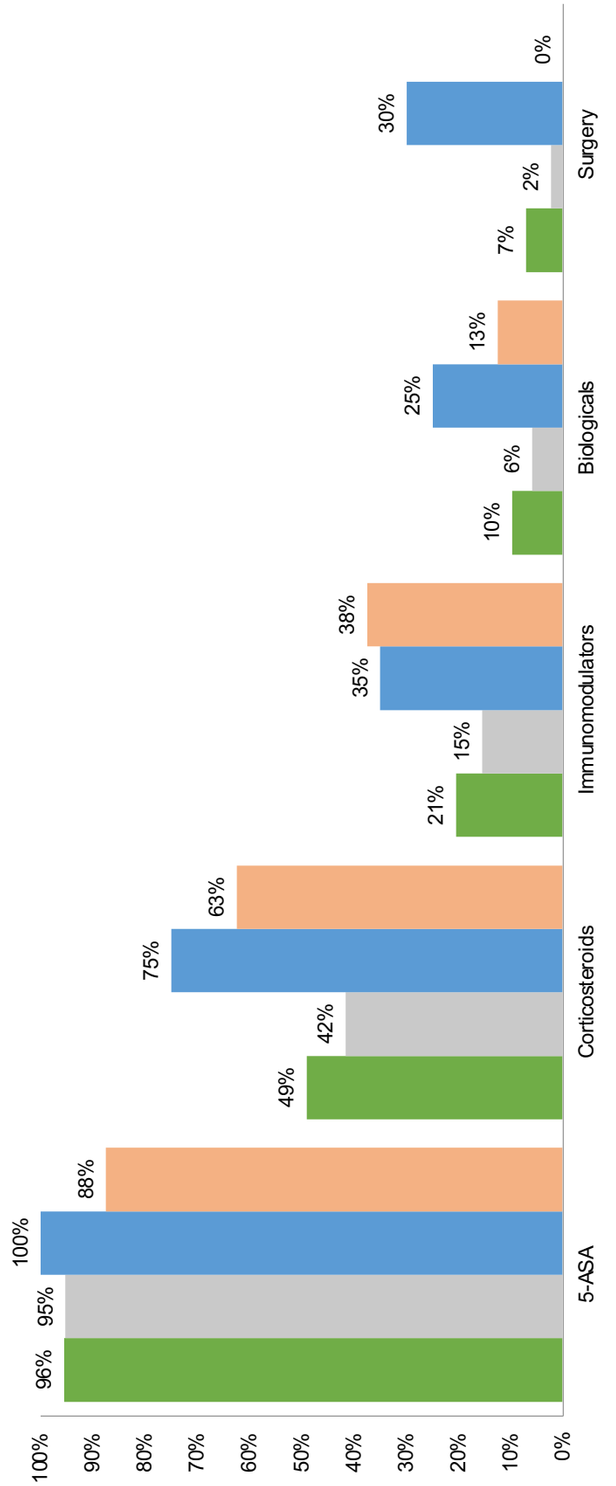


Figure 11. Cumulative five-year exposures for treatment among patients in a European inception cohort with inflammatory bowel disease unclassified (IBDU) at diagnosis.
* *5-ASA, 5-aminosalicylates*

3.6 Cancer in patients with inflammatory bowel disease

3.6.1 Own results (Papers I-V)

In the *Copenhagen County* cohort, five patients with CD developed small intestinal cancer, seven patients developed colon cancer, six patients developed rectal cancer and one patient cancer in the anus. Except for one case of rectal cancer, all cancers occurred after at least ten years of disease. The median time from diagnosis of CD to small intestinal cancer was 19.5 years (CI95%: 13.2-26.2), 22.1 years (CI95%: 16.7-27.0) for colon cancer, and 31.4 years (CI95%: 18.6-33.1) for rectal cancer. One patient developed anal cancer after 38 years.

As shown in Table 6, only the relative risk of small intestinal cancer was found to be higher among IBDU patients than among controls. The cumulative prevalence 50 years after diagnosis was 2% (CI95%: 1-6%). However, a high relative risk of rectal and anal cancer was found in the subgroup of patients with colonic disease location at diagnosis. Additionally, cancers of the respiratory organs and skin (non-melanoma skin cancer and basal cell carcinoma) occurred more frequently among these patients, and the overall risk of cancer was slightly greater than for controls (RR: 1.36; CI95%: 1.13-1.63). In a Poisson regression analysis only age at diagnosis (older than 60 years) was identified as a risk factor for developing cancer.

Among UC patients in the *Copenhagen County* cohort, four patients developed small intestinal cancer, 32 developed colon cancer, 19 developed rectal cancer and three patients developed anal cancer. UC patients were found to be at greater risk of small intestinal, colon, rectal and anal cancer than controls, Table 7. With three exceptions, these intestinal cancers appeared late in the disease course (i.e., more than 10 years after diagnosis). The median time from diagnosis for colon cancer was 29.0 years (CI95%: 23.5-39.9), while it was 30.9 years (CI95%: 22.5-39.1) for rectal cancer, 32.0 years (CI95%: 31.0-32.1) for anal cancer, and 29.1 years (CI95%; 18.8-38.9) for small intestinal cancer. The cumulative prevalence 50 years after diagnosis was 1% (CI95%: 0%-5%) for small intestinal cancer, 8% (CI95%: 5-12%) for colon cancer, and 5% (CI95%: 3-9%) for rectal cancer. The overall risk of cancer among UC patients was higher than among controls (RR: 1.18 CI95%: 1.06-1.31), and extra-intestinal cancers in the pancreas, thyroid, as well as in the skin, occurred more frequently in UC patients than in controls. Among the risk factors, older age at diagnosis was associated with increased risk for all types of cancers. Disease extent was only found to be associated with the risk of overall cancer, but not for any specific types of cancer.

In the *Epi-IBD* cohort, eight CD patients (2%), 14 UC patients (2%) and one (1%) patient with IBDU developed cancer within five years of a diagnosis. Two patients with UC developed colon cancer, while all other cases involved extra-intestinal cancers.

3.6.2 Discussion

It has long been recognised that patients with CD and UC are at increased risk of developing intestinal cancers[152]. This risk is thought to arise as a consequence of chronic inflammation that promotes the transformation of inflamed mucosa to dysplasia and, eventually, cancer[153,154]. Accordingly, clinical surrogates of chronic inflammation such as extensive disease, longer disease duration and young age at diagnosis are known to increase the risk of cancer[155], as is also shown in Papers I and II. While multiple studies and

meta-analyses have estimated the risk of colorectal, small intestinal and anal cancer in IBD patients[156], risk estimates are difficult to quantify due to methodological differences between studies, including how patients were identified, length of follow-up and the granularity of clinical data, all of which can result in risk estimates that are either too high or too low[157]. For example, similar to findings described in Paper II the overall risk of colorectal cancer in UC patients was found to be increased in population-based cohorts from Sweden[158] and Norway[159], while it was not increased in more recent cohorts from the Netherlands[160] and Italy[161], and only in patients with extensive disease in Olmsted county[162].

Risk estimates for CD patients are less clear[162–164]. The risk of colorectal cancer in patients with colonic disease location appears to be equivalent to that of UC patients[165], as described in Paper I. But a recent Scandinavian cohort study found the risk of colorectal cancer to be 40% higher overall in CD compared to controls[166], while a Danish study found the risk of rectal cancer to only be increased in the subgroup of patients with perianal disease[167]. However, a recent meta-analysis that pooled data from population-based cohorts found the incidence rate of colorectal cancer to be 70% higher in patients with CD and UC than in controls[163]. The risk of colorectal cancer seems to have decreased over the past three decades in some populations, which would suggest that this risk is modifiable, but via a mechanism that remains unknown[163,166,168].

Besides methodology, such disparities between studies might be explained by doctors' heterogeneous treatment approaches. Patients undergoing maintenance treatment tend to have a lower risk of colorectal cancer due to better control of chronic inflammation[169,170]. High rates of colectomy in the *Copenhagen County* cohort might have resulted in lower rates of colorectal cancer by removing the target at risk[63,171–173]. Furthermore, as cancers take years or decades to develop, sufficient follow-up is important in order to quantify any excess risk. In this sense it is notable that an increased risk of colon and rectal cancer in the *Copenhagen County* was only observed when the median length of follow-up was almost twice as long as that in previous reports[172,173].

Patients with CD are at increased risk of small intestinal cancer compared to the background population, as has been demonstrated in several cohorts, including the *Copenhagen County* cohort[162,172,174–176], as well as in meta-analyses[165]. Risk estimates for small intestinal cancer vary significantly and can be as much as 70-fold higher than the lowest estimates. However, despite the relative risk being high, small intestinal cancer remains rare and the absolute risk is low. In 2019, small intestinal cancers accounted for approximately 0.5% of all cancers in Denmark[177]. The extended follow-up of CD patients in Paper I only resulted in one additional case of small intestinal cancer.

Findings in studies of UC patients are less consistent. A Swedish study found a more than two-fold increased risk of cancer in UC patients compared to controls[178], while a Danish study did not find any increased risk[176]. However, a more recent Scandinavian cohort study found an almost two-fold increased risk, similar to the earlier Swedish one[174]. But as in CD, the absolute risk of cancer remains low. Little is known about the link between IBD and anal cancer, which is also a rare neoplasm. Two recent studies have found the risk of anal cancer to be higher in patients with perianal CD[167,179], whereas an Italian population-based cohort found a higher risk in both CD and UC[161].

Patients with CD and UC are also at risk of developing extra-intestinal cancers, such as of the skin (including melanoma and non-melanoma skin cancer), respiratory organs, thyroid, pancreas hepato-biliary system, as well as of lymphoproliferative disorders[4,180,181]; however, risk estimates vary across studies and are not found to be consistently higher for IBD patients[159,160].

Some differences in the risk of cancer between patients with IBD and the general population are the result of differences in the distribution of lifestyle factors. For example, in the case of lung cancers, smokers are overrepresented among patients with CD, while non-smokers are overrepresented among patients with UC[182]. Other cancers are caused by IBD-related medications. Immunomodulators play a key role in the development of extra-intestinal cancers by impairing immunosurveillance of cancer cells or inducing DNA damage[183] and their association with the risk of lymphoproliferative disorders and skin cancers is well-established[156]. The underlying immune dysfunction of IBD itself may also play a role in cancer development[184,185], but distinguishing the role of IBD per se from the effects of immunosuppressant therapies is difficult. Patients in Papers I and II were exposed to immunosuppressant drugs late in their disease course as they became widespread only in the late 1990s. It remains unclear whether the observations made of these patients are to be explained by their advanced age, or by how long they had been exposed to immunomodulators, or by the longer follow-up. What can be said is that no additional risk of extra-intestinal cancers was observed after a median of 17 years of following up the *Copenhagen County* cohort[172,173].

	All cancers	Small intestine	Colon	Rectum	Anus and anal canal	Melanoma	Non-melanoma skin cancer (excl. basal cell carcinoma)
All patients	1.18 [1.06; 1.31]	6.26 [2.25; 17.47]	1.45 [1.02; 2.08]	1.87 [1.19; 2.95]	4.27 [1.34; 13.65]	1.71 [1.06; 2.77]	1.36 [1.11; 1.66]
Sex							
Male	1.20 [1.03; 1.41]	4.83 [1.15; 20.33]	1.47 [0.90; 2.42]	1.90 [1.04; 3.45]	3.77 [0.50; 28.33]	2.08 [1.07; 4.03]	1.43 [1.08; 1.90]
Female	1.14 [0.98; 1.31]	9.63 [2.21; 41.93]	1.45 [0.87; 2.41]	1.85 [0.92; 3.73]	4.42 [1.07; 18.36]	1.44 [0.71; 2.90]	1.28 [0.96; 1.71]
Age at diagnosis							
0-17 yrs	1.95 [1.24; 3.09]	-	19.52 [4.61; 82.66]	7.92 [0.89; 70.33]	-	-	1.09 [0.26; 4.61]
18-39 yrs	1.37 [1.18; 1.58]	10.36 [2.29; 46.94]	1.78 [1.03; 3.07]	4.03 [2.37; 6.85]	6.37 [1.50; 27.12]	1.68 [0.89; 3.17]	1.57 [1.20; 2.06]
40-59 yrs	1.12 [0.92; 1.35]	12.05 [2.73; 53.15]	1.39 [0.78; 2.47]	0.28 [0.04; 2.00]	4.64 [0.62; 34.77]	2.42 [1.14; 5.13]	1.43 [1.02; 1.99]
60+ yrs	0.68 [0.49; 0.96]	-	0.41 [0.10; 1.67]	0.48 [0.07; 3.47]	-	-	0.41 [0.15; 1.10]
Disease location at diagnosis							
Proctitis	1.07 [0.91; 1.25]	3.20 [0.44; 23.23]	1.54 [0.94; 2.53]	0.79 [0.30; 2.12]	2.80 [0.39; 20.24]	1.61 [0.80; 3.23]	1.03 [0.74; 1.42]
Left-sided colitis	1.01 [0.80; 1.27]	12.81 [3.09; 53.11]	0.78 [0.29; 2.08]	3.29 [1.64; 6.60]	6.74 [0.93; 48.75]	0.93 [0.23; 3.75]	1.52 [1.03; 2.25]
Extensive colitis	1.50 [1.25; 1.79]	6.52 [0.90; 47.36]	1.91 [1.02; 3.55]	2.46 [1.10; 5.50]	5.55 [0.77; 40.13]	2.70 [1.28; 5.69]	1.82 [1.29; 2.58]
Disease course during follow-up years 2 to 5							
Remission	1.03 [0.81; 1.31]	6.88 [0.94; 50.12]	0.44 [0.11; 1.76]	0.45 [0.06; 3.22]	22.69 [7.07; 72.74]	1.05 [0.26; 4.20]	0.80 [0.45; 1.41]
Intermittent	1.18 [1.03; 1.34]	4.80 [1.16; 19.79]	1.62 [1.08; 2.45]	1.92 [1.11; 3.32]	-	2.09 [1.23; 3.55]	1.55 [1.23; 1.96]
Chronic continuous	1.50 [1.10; 2.06]	19.01 [2.62;138.06]	2.23 [0.84; 5.95]	3.49 [1.12; 10.84]	-	1.02 [0.14; 7.22]	1.65 [0.91; 2.99]

Relative risk was not calculated for cancers that did not occur in either controls or patients with Crohn's disease.

Table 6. Risk of selected cancers (relative risk, 95% confidence interval) among patients with Crohn's disease compared to a matched control group in a population-based inception cohort.

	All cancers	Small intestine	Colon	Rectum	Anus and anal canal	Melanoma	Non-melanoma skin cancer (excl. basal cell carcinoma)
All patients	1.18 [1.06; 1.31]	6.60 [2.37; 18.39]	1.45 [1.02; 2.08]	1.87 [1.19; 2.95]	1.21 [1.08; 1.34]	1.80 [1.11; 2.92]	1.44 [1.17; 1.76]
Sex							
Male	1.20 [1.03; 1.41]	5.06 [1.20; 21.27]	1.47 [0.90; 2.42]	1.90 [1.04; 3.45]	3.95 [0.53; 29.65]	2.16 [1.12; 4.20]	1.49 [1.13; 1.98]
Female	1.14 [0.98; 1.31]	10.24 [2.35; 44.60]	1.45 [0.87; 2.41]	1.85 [0.92; 3.73]	4.71 [1.13; 19.53]	1.52 [0.76; 3.07]	1.36 [1.02; 1.82]
Age at diagnosis							
0-17 yrs	1.95 [1.24; 3.09]	-	19.52 [4.61; 82.66]	7.92 [0.89; 70.33]	-	-	1.23 [0.29; 5.17]
18-39 yrs	1.37 [1.18; 1.58]	10.85 [2.40; 49.02]	1.78 [1.03 3.07]	4.03 [2.37; 6.85]	6.69 [1.57; 28.40]	1.77 [0.94; 3.35]	1.67 [1.27; 2.20]
40-59 yrs	1.12 [0.92; 1.35]	12.53 [2.85; 55.14]	1.39 [0.78; 2.47]	0.28 [0.04; 2.00]	4.81 [0.64; 36.03]	2.50 [1.18; 5.29]	1.49 [1.06; 2.08]
60+ yrs	0.68 [0.49; 0.96]	-	0.41 [0.10; 1.67]	0.48 [0.07; 3.47]	-	-	0.43 [0.16; 1.15]
Disease location at diagnosis							
Proctitis	1.07 [0.91; 1.25]	3.24 [0.45; 23.57]	1.54 [0.94; 2.53]	0.79 [0.30; 2.12]	2.85 [0.39; 20.56]	1.63 [0.81; 3.28]	1.04 [0.75; 1.44]
Left-sided colitis	1.01 [0.80; 1.27]	13.36 [3.22; 55.43]	0.78 [0.29; 2.08]	3.29 [1.64; 6.60]	6.95 [0.96; 50.29]	0.97 [0.24; 3.87]	1.56 [1.06; 2.32]
Extensive colitis	1.50 [1.25; 1.79]	7.51 [1.03; 54.51]	1.91 [1.02; 3.55]	2.46 [1.10; 5.50]	6.58 [0.91; 47.52]	3.11 [1.48; 6.56]	2.16 [1.53; 3.06]
Disease course during follow-up years 2 to 5							
Remission	1.03 [0.81; 1.31]	7.28 [1.00; 53.04]	0.44 [0.11; 1.76]	0.45 [0.06; 3.22]	23.67 [7.38; 75.90]	1.10 [0.27; 4.39]	0.84 [0.48; 1.48]
Intermittent	1.18 [1.03; 1.34]	5.03 [1.22; 20.76]	1.62 [1.08; 2.45]	1.92 [1.11; 3.32]	-	2.19 [1.29; 3.72]	1.63 [1.29; 2.06]
Chronic continuous	1.50 [1.10; 2.06]	20.23 [2.79; 146.92]	2.23 [0.84; 5.95]	3.49 [1.12; 10.84]	-	1.08 [0.15; 7.71]	1.81 [1.01; 3.28]

Relative risk was not calculated for cancers that did not occur in either controls or patients with ulcerative colitis.

Table 7. Risk of selected cancer (relative risk, 95% confidence interval) among patients with ulcerative colitis compared to a matched control group in a population-based inception cohort.

3.7 Survival of patients with inflammatory bowel disease

3.7.1 Own results (Papers I-V)

In the *Copenhagen County* cohort, 148 (40%) patients with CD died within the observation period and 22 (6%) deaths were due to CD, Figure 12. CD-related deaths occurred a median of 24 years (IQR: 12-47 years) after diagnosis. All-cause mortality for CD patients was higher (RR: 1.22, CI95%: 1.04-1.43) than in controls. Analysis of subgroups of patients found that female patients (RR: 1.33, CI95%: 1.07-1.66), patients diagnosed between the ages of 0-17 (RR: 3.86, CI95%: 1.57-9.51) and 40-59 years (RR: 1.46, CI95%: 1.16-1.85), and those with an intermittent (RR: 1.33, CI95: 1.10-1.60) or chronic continuous disease course (RR: 1.84, CI95: 1.18-2.89) had an increased risk of death.

In UC, a total of 457 (39%) patients died and 26 (2%) deaths were due to UC, Figure 12. UC-related deaths occurred a median of 29 years (IQR: 14-48 years) after diagnosis. All-cause mortality for UC patients was slightly lower (RR: 0.90, CI95%: 0.82-0.99) than among controls, as was mortality due to diseases or cancer of the respiratory system. In subgroup analyses, mortality was lower among male patients (RR: 0.85, CI95%: 0.74-0.96) and higher in those diagnosed between the ages of 0-17 years (RR: 3.20, CI95%: 1.84-5.57). In both CD and UC, the risk of death due to gastrointestinal cancer was comparable to that of controls. In the multiple Poisson regression model, age at diagnosis, as well as disease location and disease extent at diagnosis, were associated with mortality in CD and UC, respectively, Table 1.

In the *Epi-IBD* cohort, 16 (3%) CD patients died within five years of a diagnosis. Two patients died because of sepsis after CD surgery, while the remaining patients died of non-CD-related causes. A total of eight (1%) UC patients died, one of whom died because of respiratory complications following colectomy. Of IBDU patients, three (3%) patients died of causes unrelated to IBD.

3.7.2 Discussion

To date, there have been numerous studies published on mortality in cases of IBD, including four meta-analyses[186–189]. Most of these studies have found that CD is associated with an increased risk of mortality, while the data on whether UC is associated with increased mortality are equivocal.[190–194] In the *Copenhagen County* cohort, the risk of death among CD patients was 22% higher than among their matched controls, especially patients diagnosed at an older age and with colonic disease location, while it was slightly lower among UC patients than among controls. Methodological differences between studies in how causes of death were captured, length of follow-up, as well as how mortality rates were compared with those of the background population, all contribute to the heterogeneity of their findings[195]. Furthermore, populations differ in terms of risk factors, such as smoking habits or the medical care available.

Several risk factors have been identified that increase the risk of death, including older age at diagnosis, as well as being early on in the disease course[196–198]. However, in UC this increased risk of death in the initial years following diagnosis diminishes over time, as demonstrated in the *Copenhagen County* cohort and in Manitoba, Canada[63,196]. Surgery has also been shown to increase mortality in IBD[190,194,196], probably due to a combination of direct postsurgical complications and pre-existing, preoperative risk factors,

including malnourishment and immunosuppression[72,199]. In Paper II, patients with proctitis, who carry a lower risk of colectomy, had lower mortality rates than those with extensive colitis, and this was also found in a recent systematic review[200]. CD patients with colonic disease were at increased risk of all-cause mortality similar to that found in a European population-based cohort[201], while females were at lower risk of death compared to males, a finding also reported by others[196,202]. However, these findings have not been made consistently and many studies have not included analysis of risk factors or of patient subgroups, which makes comparisons difficult[189].

Despite the findings of an increased risk of intestinal and extra-intestinal cancers described above (3.6), cancer-related mortality was not found to be higher among IBD patients. This is in line with the results of several other cohorts[191,193,201,203], but not with the most recent meta-analysis[189]. However, this meta-analysis included studies of both unselected and selected patient cohorts, the latter potentially including more severely ill patients. Furthermore, death due to respiratory diseases, including cancer, did not occur more frequently among CD patients, as was found in other cohorts, and despite their higher prevalence of smoking[191,193,201]. In contrast, mortality due to respiratory diseases was lower among UC patients than controls, which might be related to their lower prevalence of smoking. Interestingly, the previous follow-up of the *Copenhagen County* cohort[204] did indeed find an increased mortality due to respiratory diseases; some reasons for this might include the longer follow-up or that a matched controlled group was used in Paper II instead of sex- and age-specific mortality rates for the Danish.

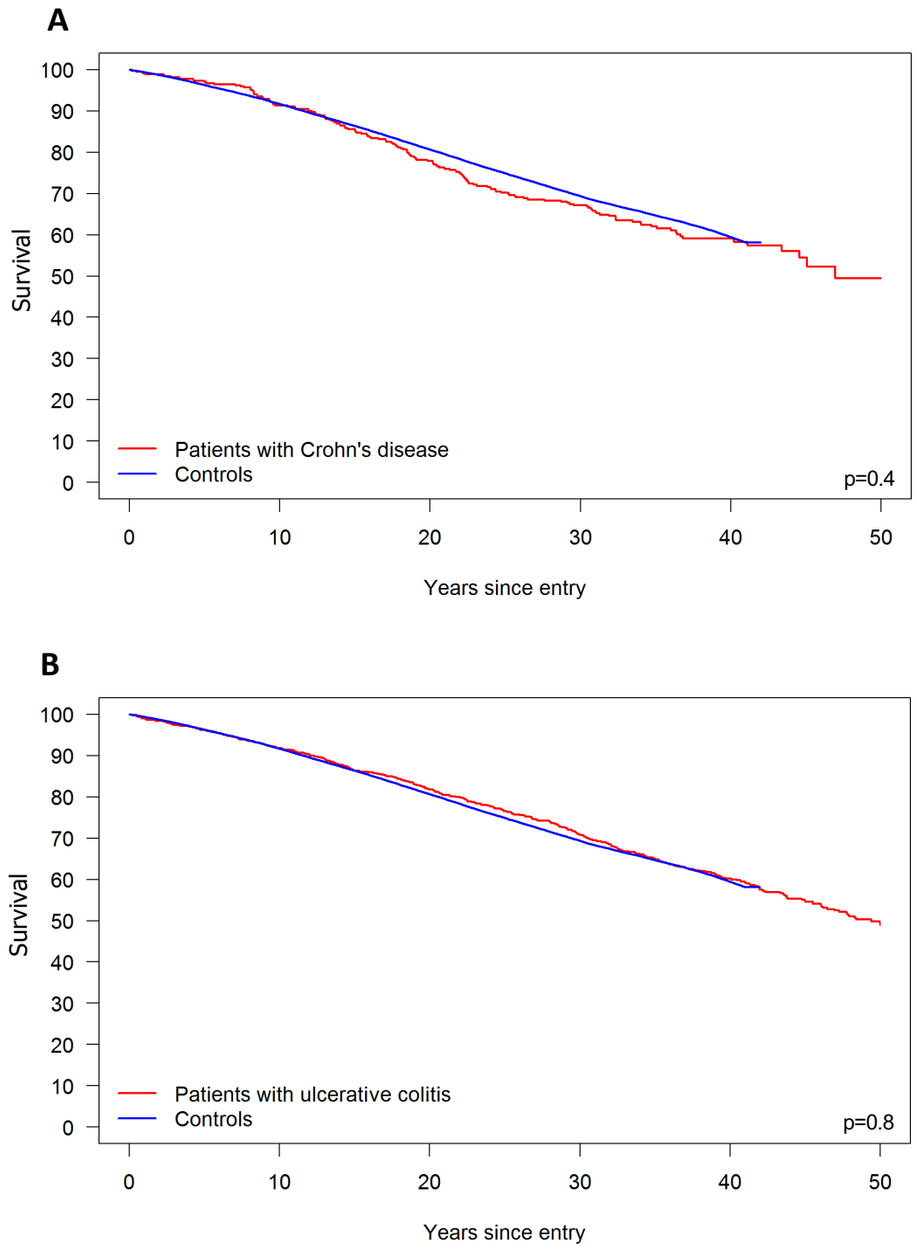


Figure 12. Survival rates of patients with (A) Crohn's disease and (B) ulcerative colitis diagnosed between 1962 and 1987 in a Danish population-based inception cohort.

4. Conclusions and perspectives

The present thesis and its accompanying papers have described the disease course and prognosis of patients with IBD based on population-based inception cohorts representing two different time periods and the treatments and outcomes occurring therein. Findings from the *Copenhagen County* cohort studies demonstrate the high rates of surgery that characterise the *natural* disease course of CD and UC, which is to say without potent immunosuppressive therapies and modern monitoring practices. Furthermore, over the life-long course of IBD, patients will sometimes develop intestinal and extra-intestinal cancers and, in the case of CD, be at higher risk of mortality. The consequences of long-term, uncontrolled inflammation in CD and UC are evident from these studies, which support the way we envision the course of IBD without immunosuppressive treatment[100]. The findings also underline that IBD patients need life-long monitoring and treatment to maintain remission and prevent disease progression, as well as the need for new, potent disease- modifying drugs.

The epidemiological studies of the *Epi-IBD* cohort show that, despite improvements in the care of IBD, the *natural* disease course of CD, UC and IBDU still leads to a significant number of patients developing disease- related complications, experiencing disease progression, or needing surgery. This should be of interest to physicians who have incorporated into their practice early and aggressive treatment with potent immunomodulators and/or biological therapies with the aim of preventing said complications. The *Epi-IBD* cohort has highlighted differences in treatment practices and strategies across Europe. The true impact of these treatment strategies in a real-world setting – beyond increasing the costs of care and shifting the cost profile of IBD towards drugs – has yet to be determined.

Evidence-based advice about treatment and monitoring take a long time to reach clinical practice. Changes to clinical practice, and the choices made regarding investigations, medical and surgical treatments and the availability of such treatments, are closely linked to extra-medical considerations. Future studies of the community efficacy of treatments must consider factors such as the structure of the health care system, reimbursement systems, local restrictions in how and when patients can be treated with biological therapies, and a physician's experience when evaluating outcomes.

Cohorts with a very long follow-up, such as the *Copenhagen County* cohort, will serve as reference points for future cohorts used to assess the prognosis of IBD patients. But studying the *natural* disease course of IBD, as well as the changes it undergoes, in new cohorts will remain important as the armoury of treatments for IBD continues to expand.

Findings from clinical trials cannot be replicated in a real-world setting, and therefore studies of the real-world efficacy of treatments and treatment plans, and their cost-effectiveness, are needed to guide physicians, patients and policy makers. Furthermore, long-term follow-up of contemporary cohorts such as *Epi-IBD* are needed in order to assess the cost-effectiveness of current treatment practices and their impact on the natural disease course of IBD in the long-run, and how they affect the risk of long-term outcomes such as cancer and mortality.

Finally, in the future population-based cohort studies must go further than simply observing clinical outcomes. There is an urgent need for better prediction of the disease course, as well as for risk stratification, at the time of diagnosis. Modifying or changing the disease course will involve personalized treatment, including choosing which molecular pathways to target and which drugs to use at specific time points, as well as individualized disease monitoring. eHealth technologies enable patients to be monitored tightly and remotely based on clinical symptoms and objective markers of inflammation and have been shown to improve the short term disease course[205,206].

Furthermore, we need a better understanding of how environmental factors, including diet and gut microbiota, influence the disease course. This will require studying well-described inception cohorts, in combination with prospective collections of biological material and detailed information about environmental exposures, to inform disease modification trials and improve clinical care. Such studies are, however, time-consuming and massive undertakings that require both sufficient funding and dedicated personnel. Initiatives such as PREdiCCt (www.predicct.co.uk) and the GEM study (www.gemproject.ca), or the Danish-based IBD PROGNOSIS study and the Danish IBD Biobank[207], will hopefully advance the field, yet there is still, in the words of Cecil Rhodes, *"so little done, so much to do."*

5. Summary

The two main forms of inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are chronic, immune-mediated inflammatory disorders of the gastrointestinal tract. The aetiology of IBD is not fully understood and its disease course is heterogeneous. Some patients experience frequent flare-ups, progression of disease and/or the need for surgery, while others have a mild disease course with few flare-ups, stationary disease and only a limited need for medication.

The present thesis is based on seven epidemiological papers investigating the natural disease course of IBD in two population-based cohorts of newly-diagnosed patients. Papers I and II investigated the long-term disease course of CD and UC in the Danish *Copenhagen County* cohort consisting of IBD patients diagnosed between 1962 and 1987 and followed for more than fifty years. This cohort stands out in that immunomodulating and current biological therapies were not available until very late in the observation period. The papers highlight the potential severity of IBD, as three-out-of-four CD patients and two-out-of-five UC patients needed surgery during the observation period, at least half of whom with CD required additional surgeries. The risk of intestinal and extra-intestinal cancers was higher among both CD and UC patients and mortality was found to be higher among CD patients than among controls, while among UC patients it was comparable to the background population. Mortality due to gastrointestinal cancers in CD and UC was similar to that of the background population.

Papers III to VII investigated the contemporary disease course of IBD in the European multicentre *Epi-IBD* cohort of patients diagnosed in 2010 and followed for five years. Papers III and IV found that the disease course of CD and UC even today involves many patients experiencing a progression of their disease, the need for rapid escalation of treatment to biological therapies, and surgery within just a few years of their diagnosis. Furthermore, significant geographic differences in treatment strategies and choices exist across Europe, with a greater use of biological and immunomodulating therapies in Western Europe than in Eastern Europe. These differences did not, however, result in differences in disease outcomes, and the precise impact of modern treatment strategies in a real-world setting has yet to be determined. Paper V investigated the disease course of patients with IBD unclassified (IBDU) and shows that most IBDU patients can expect a mild disease course, with a light treatment burden and low frequencies of surgery and hospitalisation.

Paper VI investigated the resource utilization and cost profile of the *Epi-IBD* cohort. The costs of IBD today are mainly driven by expensive medical therapies, where biological therapies accounted for almost half of all costs among the cohort by the final year of follow-up. In parallel with increasing expenditure on biologicals, expenditure on conventional medical treatments, hospitalisations, and surgeries decreased. Considering the high costs associated with biological therapy, more cost-effective treatment strategies are needed to reduce the economic burden of IBD.

Finally, Paper VII investigated the use of 5-aminosalicylates (5-ASA) among patients with CD. Despite international guidelines advising against using 5-ASA to treat CD, their use was common and often the first treatment prescribed following a diagnosis. A substantial group of patients, however, received only 5-ASA as their maintenance treatment and experienced a quiescent disease course; this suggests that 5-ASA may, in some cases, have a role to play in modifying the disease course.

6. Dansk resumé

De inflammatorisk tarmsygdom (IBD) Mb. Crohn (CD) og ulcerøs colitis (UC), er kroniske og immunmedierede inflammatoriske sygdomme i mavetarmkanalen. De bagvedliggende årsager for hvorfor sygdommene opstår er fortsat ukendte og sygdomsforløbet varierer betydeligt. Nogle patienter oplever hyppig opblussen af sygdommen, sygdomsprogression og / eller behov for kirurgi, mens andre har et mildt sygdomsforløb med få tilbagefald, stationær sygdom og begrænset behov for medicin.

Nærværende afhandling er baseret på syv epidemiologiske studier, der undersøger naturforløbet af IBD baseret på to populationsbaserede kohorter af nydiagnosticerede patienter. Artikel I og II undersøgte sygdomsforløbet ved CD og UC i en kohorte fra det tidligere Københavns Amt bestående af IBD-patienter diagnosticeret mellem 1962 og 1987. Kohorten blev fulgt i over halvtreds år og udmærker sig ved, at immunmodulerende og biologiske behandlinger ikke var tilgængelige før meget sent i observationsperioden. Artiklerne fremhæver det potentielt alvorlig sygdomsforløb af IBD, da tre ud af fire patienter med CD (for mindst halvdelen af disse patienter var yderligere operationer også nødvendige) og to ud af fem patienter med UC havde behov for operation i observationsperioden. Risikoen for cancer i og uden for fordøjelseskanalen var øget ved både CD og UC. Dødelighed var højere blandt CD-patienter mens den var sammenlignelig med baggrundsbefolkning i UC. Dødelighed på grund af gastrointestinal cancer var lige med baggrundbefolkningens.

Artikel III til VII undersøgte sygdomsforløbet ved IBD i den nutidige europæiske *Epi-IBD*-kohorte, der består af patienter diagnosticeret i 2010 og fulgt i fem år. Artikel III og IV viste, at sygdomsforløbet af CD og UC stadig i dag indbefatter at mange patienter vil opleve sygdomsprogression, behov for hurtig eskalering af behandlingen til biologiske terapier og behov for kirurgi allerede inden for få år efter deres diagnose. Derudover fandtes der betydelige geografiske forskelle i behandlingsstrategi og -valg i Europa med en højere anvendelse af biologiske og immunmodulerende terapier i Vesteuropa sammenlignet med Østeuropa. Disse behandlingsforskelle resulterede imidlertid ikke i forskelle i forhold til sygdomsoutcome såsom kirurgi eller progressionsrater. Fundene viser, at effekten af moderne behandlingsstrategier i den kliniske hverdag stadig er uklar. Artikel V undersøgte sygdomsforløbet hos patienter med uafklaret IBD (IBDU) og viste, at de fleste IBDU-patienter kan forvente et mildt sygdomsforløb, da behandlingsbyrden var let og hyppigheden af operationer og hospitalsindlæggelser var lav.

Artikel VI undersøgte ressourceudnyttelsen og omkostningsprofilen i *Epi-IBD*-kohorten. Omkostningerne ved IBD i dag er hovedsageligt drevet af dyre medicinske terapier, da biologiske terapier ved slutningen af opfølgningsperioden tegnede sig for næsten halvdelen af alle omkostningerne. Parallelt med stigende udgifter til biologiske behandlinger faldt udgifterne til konventionelle medicinske behandlinger, indlæggelser og operationer. I betragtning af de høje udgifter forbundet med biologisk terapi er der behov for omkostningseffektive behandlingsstrategier for at reducere den økonomiske byrde ved IBD.

Endelig undersøgte artikel VII brugen af 5-aminosalicylater (5-ASA) blandt patienter med CD. På trods af at internationale retningslinjer fraråder anvendelse af disse lægemidler til patienter med CD, blev 5- ASA brugt i høj grad i kohorten. Det tjente dog for det meste kun som den initiale behandling efter diagnosen var stillet. En betydelig gruppe patienter modtog imidlertid kun 5-ASA som vedligeholdelsesbehandling og oplevede et mildt sygdomsforløb. Disse fund tyder på, at 5-ASA i nogle tilfælde kan resultere i et tilfredsstillende sygdomsforløb for både patienter og læger.

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