Epidemiological and therapeutic aspects of inflammatory bowel disease
To my family
Epidemiological and therapeutic aspects of inflammatory bowel disease
Abstract

Introduction: The two main forms of inflammatory bowel disease (IBD) are Crohn’s disease and ulcerative colitis. These are chronic inflammatory disorders, mainly affecting the gastrointestinal tract.

Aims: The overall aims of this thesis were to study the epidemiology of ulcerative colitis in Örebro, Sweden; to examine certain aspects of anaemia in IBD; and to determine the clinical effectiveness of medical treatments.

Material and methods: Cohort studies with the sampling frame defined by the geographic boundaries of the primary catchment area of Örebro University Hospital (Papers I–III), or by the entire IBD population in Sweden registered in the Swedish national quality registry for IBD (SWIBREG; paper IV), were performed to determine the epidemiology of ulcerative colitis, the incidence and prevalence of anaemia in IBD, and the clinical effectiveness of thiopurine drugs and vedolizumab in routine care.

Results: A fivefold increase in the incidence and a tenfold increase in the prevalence of ulcerative colitis was observed in Örebro during the past 50 years. In parallel, the prognosis, in terms of risk for colectomy within 10 years from diagnosis, improved during the same time period. Earlier and more widespread use of thiopurine drugs may have contributed to the decrease in colectomies. Anaemia is common in IBD, particularly in Crohn’s disease. Vedolizumab, a new drug targeting leucocyte migration to the gut, appears to be well tolerated and effective in Swedish real-world IBD care.

Conclusion: Ulcerative colitis is on the rise, and data from Örebro indicate that the number of IBD patients in Sweden already exceeds 70,000. Improved knowledge of long-term outcomes of medical therapy may have far-reaching implications for future IBD management.

Keywords: Inflammatory bowel disease; ulcerative colitis; Crohn’s disease; cohort study; population-based; colectomy; disease course; anaemia; azathioprine; 6-mercaptopurine; vedolizumab

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## Abbreviations

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<th>Description</th>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CDAI</td>
<td>Crohn’s disease activity index</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>HBI</td>
<td>Harvey-Bradshaw index</td>
</tr>
<tr>
<td>IBD</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>IBD-U</td>
<td>Inflammatory bowel disease unclassified</td>
</tr>
<tr>
<td>ICD</td>
<td>International Statistical Classification of Diseases and Related Health Problems</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>LOD</td>
<td>Lowest limit of detection</td>
</tr>
<tr>
<td>MCS</td>
<td>Mayo Clinic score</td>
</tr>
<tr>
<td>P-HBI</td>
<td>Patient Harvey-Bradshaw index</td>
</tr>
<tr>
<td>P-SCCAI</td>
<td>Patient Simple Clinical Colitis Activity index</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>SWIBREG</td>
<td>Swedish national quality registry for IBD</td>
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<tr>
<td>TNF</td>
<td>Tumour necrosis factor</td>
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</table>
Introduction

The two main forms of inflammatory bowel disease (IBD) are Crohn’s disease and ulcerative colitis. These are chronic, relapsing and remitting inflammatory disorders, mainly affecting the gastrointestinal tract.

Despite having some common features, the two forms can usually be distinguished by differences in clinical, endoscopic, and histopathological characteristics. Crohn’s disease affects any region of the intestine, often discontinuously,1 while ulcerative colitis always involves the rectum and to a varying extent the colon in a continuous fashion.2, 3 In Crohn’s disease, transmural inflammation is common, whereas in ulcerative colitis—with the exception of acute severe ulcerative colitis—the inflammation is restricted to the colonic mucosa.4 However, the term IBD unclassified (IBD-U) is used in a small proportion of cases in whom there is evidence of chronic colonic inflammation but no evidence to favour a definitive diagnosis of either Crohn’s disease or ulcerative colitis,5 while the term indeterminate colitis is reserved for cases where a reliable distinction is impossible after colectomy.4, 6

Historical remarks

Ulcerative colitis was the first subtype of IBD to be characterized as a distinct disease entity. The term is generally ascribed to Sir Samuel Wilks (1824–1911) who, in a case report written in 1859, described a condition similar to what is understood as being ulcerative colitis today (even though it has later been argued that Wilks actually described a patient with Crohn’s disease).7, 8 The first series of Crohn’s disease patients was published in 1913 by the Scottish surgeon Thomas Kennedy Dalziel (1961–1924). His report included nine patients who had been treated surgically and in whom the pathologist observed giant cells, granulomas, but no signs of infectious agents. In the report, Dalziel described the bowel as having “the consistence and smoothness of an eel in a state of rigor mortis” and proposed a radical surgical approach: “one does not hesitate in resecting large proportions of the intestine”.9

Although Dalziel’s and several other reports preceded Burrill Crohn’s (1884–1983), Leon Ginzburg’s (1898–1988), and Gordon Oppenheimer’s (1900–1974) contribution by nearly 20 years,9-11 it was their landmark article (published in 1932) that alerted the medical world to the existence of Crohn’s disease.12 Dr. Crohn himself strongly discouraged the use of the eponym Crohn’s disease, which was attributed to him through an odd set
of circumstances. Ginzburg and Oppenheimer were the ones who discovered the pattern of disease, collected the first 12 cases, and proposed the term “regional ileitis”. However, in order to increase the number of patients in their report, they were put in contact with Crohn who contributed with two additional patients and became a co-author of the report. In the 1930s, the journal’s policy was to arrange the authors alphabetically by surname. In Scotland Crohn’s disease is sometimes still termed Dalziel’s disease, as many Scots considered his description to be the first. In 1956, when President Eisenhower, who suffered from Crohn’s disease, required an emergent operation in the middle of the night due to bowel obstruction, the disorder went from a being a medical curiosity to a relatively well-known disease.

**Definitions and diagnosis**

An accurate definition and classification of IBD is crucial, both from a clinician’s and a basic scientist’s point of view. However, at present no pathognomonic feature of either Crohn’s disease or ulcerative colitis has been identified. Instead, these diagnoses are established based on clinical presentation and confirmed by objective laboratory, histopathological, and endoscopic or radiological findings. The diagnostic criteria and classification of IBD have improved over the past six decades along with advancements in diagnostic methods, particularly with the introduction of fibre-optic endoscopy and the possibility of obtaining biopsies from the entire colon. Today, in the absence of an international consensus, the Lennard-Jones criteria published in 1989 are often regarded to be the gold standard for diagnosis of Crohn’s disease and ulcerative colitis (Table 1).
Table 1. The Lennard-Jones criteria for diagnosis of ulcerative colitis and Crohn’s disease\textsuperscript{22}

<table>
<thead>
<tr>
<th>Ulcerative colitis</th>
<th>Crohn’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria for exclusion:</td>
<td>Criteria for exclusion:</td>
</tr>
<tr>
<td>- infective colitis</td>
<td>- infections</td>
</tr>
<tr>
<td>- ischaemic colitis</td>
<td>- ischaemia</td>
</tr>
<tr>
<td>- irradiation colitis</td>
<td>- irradiation</td>
</tr>
<tr>
<td>- solitary ulcer</td>
<td>- lymphoma/carcinoma</td>
</tr>
<tr>
<td>- abnormalities suggesting Crohn’s disease</td>
<td></td>
</tr>
<tr>
<td>- complex anal lesion</td>
<td></td>
</tr>
<tr>
<td>- granulomata</td>
<td></td>
</tr>
<tr>
<td>Criteria for inclusion:</td>
<td>Criteria for inclusion:</td>
</tr>
<tr>
<td>- rectum ± colon</td>
<td>- mouth to anus</td>
</tr>
<tr>
<td>- continuous</td>
<td>- discontinuous</td>
</tr>
<tr>
<td>- mucosal</td>
<td>- transmural (fissure, abscess, fistula)</td>
</tr>
<tr>
<td>- muscular thickening</td>
<td>- fibrosis</td>
</tr>
<tr>
<td>- mucin depletion</td>
<td>- lymphoid ulcers, aggregates</td>
</tr>
<tr>
<td>- glandular damage</td>
<td>- granuloma</td>
</tr>
</tbody>
</table>

**Classification of Crohn’s disease**

Crohn’s disease is a heterogeneous condition with a spectrum of intestinal and extra-intestinal manifestations.\textsuperscript{1} The first attempt to classify Crohn’s disease using recognizable clinical features was presented in 1975 by Farmer et al., and indicated that the anatomical disease location at diagnosis had an impact on symptomatology, on the clinical course, and on the risk of requiring surgery.\textsuperscript{23} Some years later, Greenstein recognized that patients with perforating disease behaviour had a higher risk of surgery than patients with a non-perforating phenotype.\textsuperscript{24} These observations were further refined by an international working party in the development of the “Rome classification”, which emerged in 1991.\textsuperscript{25} In addition to location (stomach-duodenum; jejunum; ileum; colon; rectum; anal-perianal) and behaviour (inflammatory; fistulizing; fibrostenotic), the Rome classification also included the extent of disease (localized or diffuse) and surgical history (primary or recurrent). However, the Rome classification was not widely accepted in its original form, since as many as 756 subgroups of Crohn’s disease were possible and the inter-observer agreement, especially concerning disease behaviour, was poor.\textsuperscript{26} Thus, the Rome system was exchanged in preference for the Vienna classification a few years later.\textsuperscript{27} With the purpose of making the system more feasible in clinical practice, the components regarding extent of disease and surgical history were removed, the number of possible anatomical locations was reduced (ileum; colon; ileocolon; upper gastrointestinal tract), and in order
to avoid combinations, a hierarchy regarding disease behaviour was established (inflammatory; stricturing; penetrating). Furthermore, the variable “age at diagnosis” was implemented (less than 40 years; 40 years or older). The current classification system, which in contrast to previous versions also provides recommendations for ulcerative colitis, was presented at the World Congress of Gastroenterology in Montreal, 2005 (Table 2A).28

**Classification of ulcerative colitis**

It has been recognized for years that the disease extent of ulcerative colitis has implications for the long-term prognosis in terms of medication use,29 hospital admissions,30, 31 surgical resection rates, and the risk of colorectal cancer.32 However, it is important to note that these associations were established when the extent of disease was assessed by macroscopic findings from double-contrast barium enema or endoscopy, and that the significance of histological changes in an endoscopically normal mucosa remains uncertain. However, there are some data to suggest that the histological extent of disease is associated with the risk of developing colorectal cancer.33 Furthermore, proximal disease progression of proctitis or left-sided colitis may occur in 12–70% of cases within 10 years of diagnosis.28 As a consequence of these obstacles, the Montreal classification working party proposes that the disease extent of ulcerative colitis should be defined as the maximal macroscopic extent of disease at endoscopy (Table 2B). In general, rectal involvement and continuous distribution of inflammation are essential characteristics of ulcerative colitis. However, “rectal sparring” has been described in children at the time of diagnosis and in adults who have received topical therapy.34, 35 Furthermore, involvement of the cecum or the orifice of the appendix may be observed in patients with left-sided colitis, and “backwash ileitis” occurs in about 20% of patients with extensive colitis.36, 37
Table 2A. The Montreal classification of Crohn’s disease  
[adapted from Silverberg et al. 28]

<table>
<thead>
<tr>
<th>Age at diagnosis (A)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A1 16 years or younger</td>
<td></td>
</tr>
<tr>
<td>A2 17–40 years</td>
<td></td>
</tr>
<tr>
<td>A3 Over 40 years</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location (L)</th>
<th>Upper GI modifier (L4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1 Terminal ileum</td>
<td>L1+L4 Terminal ileum + upper GI</td>
</tr>
<tr>
<td>L2 Colon</td>
<td>L2+L4 Colon + upper GI</td>
</tr>
<tr>
<td>L3 Ileocolon</td>
<td>L3+L4 Ileocolon + upper GI</td>
</tr>
<tr>
<td>L4 Upper GI</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Behaviour (B)</th>
<th>Perianal disease modifier (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1 Inflammatory</td>
<td>B1+p Inflammatory + perianal disease</td>
</tr>
<tr>
<td>B2 Stricturing</td>
<td>B2+p Stricturing + perianal disease</td>
</tr>
<tr>
<td>B3 Penetrating</td>
<td>B3+p Penetrating + perianal disease</td>
</tr>
</tbody>
</table>

Table 2B. The Montreal classification of ulcerative colitis  
[adapted from Silverberg et al.28]

<table>
<thead>
<tr>
<th>Extent (E)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>E1 Proctitis</td>
<td></td>
</tr>
<tr>
<td>E2 Left-sided colitis</td>
<td></td>
</tr>
<tr>
<td>E3 Extensive colitis</td>
<td></td>
</tr>
</tbody>
</table>

**Histopathological aspects of IBD**

The histological appearance of Crohn’s disease is similar irrespective of disease location. The three microscopic features with the highest diagnostic value are: focal discontinuous chronic inflammation, focal distortion of crypt architecture, and presence of giant-cell granulomas.4, 38 The term “focal” reflects the fact that a variable intensity of inflammation is often present in a single biopsy sample.4 Additionally, an irregular villous architecture is characteristic in samples from the small intestine.

Correspondingly, the three main histological findings of ulcerative colitis are: distorted crypt architecture,39 transmucosal inflammatory infiltrate with basal plasmacytosis, and signs of cryptitis—as well as crypt abscesses if samples are collected from a patient with active inflammation.38, 40

Several scoring systems have been developed for histological assessment of disease activity in ulcerative colitis,41, 42 whereas in Crohn’s disease,
microscopic evaluation of inflammatory activity is difficult because of the segmental disease distribution and because none of the existing indexes have been fully validated.\textsuperscript{43, 44} The main histological changes in IBD are summarized in Table 3.\textsuperscript{4}

Table 3. The main histological changes in inflammatory bowel disease
[adapted from Magro et al.\textsuperscript{4}]

<table>
<thead>
<tr>
<th></th>
<th>Ulcerative colitis</th>
<th>Crohn’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crypt architectural irregularity</td>
<td>Diffuse (continuous)</td>
<td>Focal (discontinuous)</td>
</tr>
<tr>
<td>Chronic inflammation</td>
<td>Diffuse (continuous)</td>
<td>Focal (discontinuous)</td>
</tr>
<tr>
<td>Patchiness</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Localization</td>
<td>Superficial</td>
<td>Transmural</td>
</tr>
<tr>
<td></td>
<td>Sometimes in submucosa</td>
<td></td>
</tr>
<tr>
<td>Serositis</td>
<td>Absent except in fulminating colitis</td>
<td></td>
</tr>
<tr>
<td>Lymphoid aggregates</td>
<td>Frequent in mucosa, submucosa</td>
<td>Common, transmural</td>
</tr>
<tr>
<td>Granulomas</td>
<td>Absent, except with ruptured crypts</td>
<td>Present</td>
</tr>
<tr>
<td>Acute inflammation</td>
<td>Diffuse (continuous)</td>
<td>Focal (discontinuous)</td>
</tr>
<tr>
<td>Crypt epithelial polymorphs</td>
<td>Diffuse (continuous)</td>
<td>Focal (discontinuous)</td>
</tr>
<tr>
<td>Crypt abscesses</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Mucin depletion</td>
<td>Present, pronounced</td>
<td>Uncommon, mild</td>
</tr>
<tr>
<td>Neuronal hyperplasia</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Muscular hypertrophy</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Paneth cell metaplasia</td>
<td>Present</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Pyloric gland metaplasia</td>
<td>Rare</td>
<td>Present</td>
</tr>
</tbody>
</table>

**Clinical features of IBD**

The clinical manifestations of Crohn’s disease are more variable than those of ulcerative colitis. At presentation, diarrhoea, abdominal pain, weight loss, and fever are common features of Crohn’s disease while patients with ulcerative colitis usually present with diarrhoea, which may be accompanied by rectal bleeding, urgency, tenesmus, incontinence, and abdominal pain.\textsuperscript{45, 46} Some data indicate that a prodromal phase may precede the development of IBD, particularly of Crohn’s disease, by approximately 10 years.\textsuperscript{47-49} In addition, extra-intestinal manifestations that may involve almost any organ system frequently occur in both diseases.\textsuperscript{50, 51} Anaemia appears to be the most common extra-intestinal manifestation and has been associated with a wide range of complications such as im-
paired quality of life, increased rate of hospital admissions, and even mortality. The occurrence of anaemia in IBD is still uncertain, however, as most data come from tertiary referral centres or cohorts of newly diagnosed patients.

Traditionally, IBD has been renowned for an episodic behaviour with periods of relapses and remissions. However, recent studies have shown that the clinical course varies substantially between patients, ranging from an indolent disease with minimal symptoms to a severe disease that strongly interferes with the individual’s daily life and has a pronounced adverse effect on quality of life. At the 10-year follow-up of patients diagnosed with IBD in southeastern Norway during the period 1990–1994, only 35% of them reported the classic episodic pattern of disease whereas a decrease in the severity of symptoms over time was the most common course in both Crohn’s disease and ulcerative colitis (Figure 1). Even so, a sizeable proportion of the patients suffered from chronic relapsing—or even chronic continuous symptoms. Ulcerative colitis patients with proctitis or left-sided colitis at diagnosis may have a progression in extent of disease during follow-up. In Crohn’s disease, the disease location is usually rather stable, while the majority of patients will have a change in disease behaviour from purely inflammatory to strictureing and/or penetrating disease, suggesting that the latter phenotypes are merely complications of chronic inflammation. Furthermore, the all-cause mortality is slightly increased in both Crohn’s disease and ulcerative colitis compared to the general population, and both disorders have been associated with an increased risk of colorectal cancer, although the risk has been studied more extensively in ulcerative colitis. Even though medical treatment is the mainstay of management in IBD, about 50% of Crohn’s disease patients and 15% of patients with ulcerative colitis will require surgery within 10 years of diagnosis. Nowadays, the most common surgical procedure in Crohn’s disease is ileocaecal resection, whereas a total colectomy is the operation of choice in ulcerative colitis. There is emerging evidence that the resection rate in Crohn’s disease has decreased in recent decades, while with ulcerative colitis the literature is inconsistent. However, indications and timing of surgery have changed over time, and whether improvements in medical management in recent decades have been associated with reduced resection rates and a decreased risk of long-term complications remains largely unknown for both diseases.
<table>
<thead>
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<th>Curve (1-4):</th>
<th>Definitions:</th>
<th>Outcome:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Curve 1:</strong> Decrease in the severity of bowel symptoms during the follow-up period</td>
<td></td>
<td>Crohn’s disease: 43% Ulcerative colitis: 55%</td>
</tr>
<tr>
<td><strong>Curve 2:</strong> Increase in the severity of bowel symptoms during the follow-up period</td>
<td></td>
<td>Crohn’s disease: 3% Ulcerative colitis: 1%</td>
</tr>
<tr>
<td><strong>Curve 3:</strong> Chronic continuous bowel symptoms during the follow-up period</td>
<td></td>
<td>Crohn’s disease: 19% Ulcerative colitis: 6%</td>
</tr>
<tr>
<td><strong>Curve 4:</strong> Chronic relapsing bowel symptoms during the follow-up period</td>
<td></td>
<td>Crohn’s disease: 32% Ulcerative colitis: 37%</td>
</tr>
</tbody>
</table>

Figure 1. Four predefined curves reflecting different patterns of IBD in terms of the severity of bowel symptoms from diagnosis to 10-year follow-up. Data were missing in 3% of Crohn’s disease patients and in 1% of ulcerative colitis patients. Reprinted with permission from Taylor & Francis® and from Magne Henriksen.58, 59, 78, 79
### Monitoring of disease activity

Today, we have limited ability to predict the disease course in individual patients. Adequate disease monitoring is therefore essential to evaluate the response to medical interventions, in order to identify therapies that are ineffective and also avoid complications.\(^1\,^2\) During the past decade, “treat to target” has emerged as a concept in the clinical management of IBD.\(^8^0\) The simplest way of monitoring IBD is to assess clinical symptoms. In both Crohn’s disease and ulcerative colitis, a strong association between clinical disease activity and quality of life has been observed.\(^8^1\,^8^2\) In ulcerative colitis, the number of stools and the presence of blood in stool are associated with the endoscopic activity,\(^8^3\) while in Crohn’s disease there is a greater discrepancy between the presence of inflammatory lesions at endoscopy and clinical symptoms.\(^8^4\) For example, in a randomized controlled trial involving Crohn’s disease patients treated with anti-tumour necrosis factor (anti-TNF) agents and/or immunomodulators, 47% of patients in clinical remission still had lesions visible at colonoscopy, whereas 35% of patients with persistent clinical symptoms did not have any active inflammation visible at colonoscopy.\(^8^5\) Thus, the absence of clinical symptoms is no guarantee that the underlying inflammation is adequately controlled, indicating that a symptomatic response alone is insufficient to prevent future complications of IBD.

### Endoscopy

Endoscopic examination to determine the mucosal inflammation is the gold standard for assessment of disease activity in the colon and ileum. In both Crohn’s disease and ulcerative colitis, endoscopic improvements and mucosal healing (absence of visible signs of active inflammation) have been associated with better long-term outcomes, including reduced resection rates.\(^8^6\,^8^7\) There are several endoscopic scoring indices for evaluation of disease activity, and the best validated include the Mayo Clinic endoscopic sub-score for ulcerative colitis, Crohn’s disease endoscopic index of severity, and the simple endoscopic scale for Crohn’s disease.\(^8^8\,^8^9\) However, frequent endoscopies are not always feasible because of poor acceptability by patients, the risk of complications, high cost, and poor availability.

### Disease activity indices

The first disease activity index to be used in IBD, the Trulove and Witts severity index, dates back to 1955 when hydrocortisone was shown to be
effective in ulcerative colitis.\textsuperscript{90} Since then, numerous instruments have been developed, although none of these indices have been completely validated.\textsuperscript{91, 92} Nowadays, the Crohn’s disease activity index (CDAI) and the Mayo Clinic score (MCS) are the most common outcome measures used in clinical trials.\textsuperscript{93, 94} However, these indices have several limitations. The CDAI, which consists of 18 clinical items and ranges from 0 to 600, is generally far too complex to be used in clinical practice and correlates poorly with endoscopic and biochemical measures of inflammation.\textsuperscript{92, 95, 96}

The Harvey-Bradshaw Index (HBI) has a high correlation with CDAI and was introduced in order to simplify the assessment.\textsuperscript{97, 98} Remission is defined as an HBI of < 5 and corresponds to a CDAI score of < 150, while a 3-point change in HBI correlates with a 100-point change in the CDAI.\textsuperscript{98} The MCS is a composite instrument, ranging from 0 to 12, including both clinical and endoscopic items.\textsuperscript{93} The main limitation of the MCS is that its sub-components are not easy to properly interweave. For this reason, both symptom-based and endoscopic criteria of response and remission are commonly used in clinical trials.\textsuperscript{99} The Patient Harvey-Bradshaw index (P-HBI) and the Patient Simple Clinical Colitis Activity index (P-SCCAI) are validated, patient-based, disease activity questionnaires developed to facilitate assessment of disease severity in clinical practice.\textsuperscript{100, 101}

**Biomarkers**

Although numerous biomarkers that can be detected in blood, faeces, or urine have been evaluated in IBD, the most widely used in both clinical practice and in research include C-reactive protein (CRP) and calprotectin.\textsuperscript{102}

CRP was originally discovered by Tillett et al. in 1930, and is an acute-phase protein synthesized by the liver in response to inflammatory cytokines.\textsuperscript{103} Early studies found increased levels of CRP in nearly 100\% of patients with active Crohn’s disease and in approximately 50\% of those with ulcerative colitis.\textsuperscript{104-106} However, according to recent data the sensitivity of CRP to detect active disease, based on colonoscopy, is only about 50\% in both conditions and it has been estimated that as many as 20\% of healthy individuals do not generate CRP under inflammatory conditions.\textsuperscript{107, 108} Furthermore, levels of CRP can be confounded by age, sex, body mass index, and other inflammatory conditions.\textsuperscript{109} Faecal biomarkers have the potential to detect mucosal inflammation with higher sensitivity and specificity.
Calprotectin is a calcium- and zinc-binding protein secreted by activated neutrophil granulocytes; it was discovered in 1983. Soluble calprotectin is stable in faeces for up to seven days, and in a meta-analysis of diagnostic accuracy studies, the sensitivity and specificity for active IBD according to endoscopy was 88% and 73%, respectively.

Epidemiology

Epidemiology is the science of the frequency and distribution of disease in the general population. Although it is common to associate the discipline with the study of acute outbreaks of infections, epidemiology still remains important as variations in incidence across geographical regions and changes in the incidence over time may provide clues about the aetiology and pathogenesis of diseases of unknown cause. Fifty years after the publication of John Snow’s seminal work “On the Mode of Communication of Cholera” in 1849, the first epidemiological study of IBD was presented at a symposium at the Royal Society of Medicine in London. One hundred and seventy-seven patients with ulcerative colitis had been identified at three London hospitals, and the report included observations on the common presentation (diarrhoea and haemorrhage) and on risk factors for the disease (early adult and middle age). Since then, more than 1,000 publications have appeared.

The occurrence of IBD varies considerably, both within and between geographic regions. Traditionally, there has been a north-south gradient in the occurrence of IBD, with the highest incidence in “westernized” nations including northern Europe, United Kingdom and North America, while IBD was rare in southern areas with the exceptions of Israel, Australia and South Africa. Intriguingly, a change in the incidence pattern has occurred in recent decades, with increasing incidence in eastern Europe, Asia, and Latin America.

It is believed that IBD is associated with the industrialization of nations, and the observed increase in southern areas is possibly a result of adaptation to a “westernized” way of living. In parallel with the increase in IBD in previous low-incidence areas, some reports have indicated a plateau or even a decline in traditional high-incidence regions, although by far the highest age-standardized incidence rate of IBD, with no signs of levelling off (74 per 100,000 inhabitants) has been reported from the Faroe Islands, which are located far north. One must also remember that there are several methodological challenges in the assessment of epidemiological data that may easily have influenced the incidence patterns observed in
recent decades.\textsuperscript{135} For example, advances in healthcare systems and the availability of diagnostic modalities necessary for recognition of IBD, such as endoscopy, may be associated with industrialization.\textsuperscript{136} In addition, most recent epidemiological studies lack the necessary observation time to allow analysis of temporal trends.\textsuperscript{113}

Within one country, the incidence of IBD is higher in urban areas than in rural areas.\textsuperscript{137-139} Individuals living in cities are exposed to completely different environmental risk factors than people living outside these regions. In the late 1980s, Strachan proposed that improved childhood hygiene and reduced contact with microorganisms in terms of decreased family size, increased use of antibiotics and vaccinations, clean drinking water, and a “westernized” diet, could explain the increase in incidence of autoimmune and allergic diseases associated with industrialization and urbanization.\textsuperscript{140} The “hygiene hypothesis”, however, may not apply perfectly to IBD. For instance, in India, proxy markers of low hygiene were found to be associated with an increased risk of ulcerative colitis,\textsuperscript{141} and several other theories that might explain the increased incidence in urban societies have also emerged, including smoking, air-pollution, and occupational exposure associated with urban employment.\textsuperscript{139, 142-144}

Within countries, the incidence of IBD can also vary among different ethnic groups living in the same area. Early studies demonstrated that Ashkenazic Jews of western Europe, the United States, and South Africa were at increased risk of developing IBD compared to their non-Jewish neighbours.\textsuperscript{145, 146} The consistency of this finding over time, across different geographical areas, with studies demonstrating a higher prevalence of CARD15/NOD2 mutations in Ashkenazic Jews, indicates that this difference may be explained by genetic factors.\textsuperscript{147} (CARD15/NOD2 was the first Crohn’s disease susceptibility gene to be identified).\textsuperscript{148, 149} In contrast, studies of migrants from low-incidence areas to the United Kingdom and Canada have demonstrated that immigrants—and particularly their offspring—have incidence rates that are comparable with those of the native population.\textsuperscript{150, 151} The fact that age at the time of migration appears to be critical, with the highest risk of IBD in children who have grown up in the adoptive country, suggest that differences in incidence depending on ethnicity might be more related to lifestyle and environmental factors, particularly early in life, than to genetic factors. These results emphasize the importance of including both children and adults in epidemiological surveys of IBD.
Although IBD affects individuals of all ages, the disease is commonly diagnosed during late adolescence or early adulthood, with a median age of onset of approximately 20–30 years.\textsuperscript{113} Some early studies demonstrated a second incidence peak later in life,\textsuperscript{152, 153} while most current epidemiological studies have not shown such a bimodal age distribution.\textsuperscript{113} In a systematic review of 109 studies reporting the sex-stratified incidence of IBD, no gender-related difference in the incidence was observed in either Crohn’s disease or ulcerative colitis.\textsuperscript{113}

Another reason for performing epidemiological surveys is that studies of incidence and prevalence may provide important information about the burden of disease in a population, which is valuable to politicians and planners of healthcare resources. As Crohn’s disease and ulcerative colitis are incurable conditions with low mortality, the global prevalence is expected to grow exponentially over the next few decades through an epidemiological phenomenon termed compounding prevalence.\textsuperscript{154}

**Aetiology and pathogenesis**

The cause of IBD is currently unknown, although particularly in Crohn’s disease it appears that affected individuals develop an inappropriate immune response to commensal gut bacteria.\textsuperscript{155-157} Several studies have indicated that the strongest independent risk factor for IBD is having a family history of the disease, and the concordance rates of Crohn’s disease in monozygotic twins range from 20% to 55% as compared to from 0% to 3.6% in dizygotic twins.\textsuperscript{158-162} In ulcerative colitis, the corresponding figures are 6.3% to 18.8% and 0% to 6.3%, respectively, suggesting that genetic susceptibility is more important in the development of Crohn’s disease than in development of ulcerative colitis.\textsuperscript{158-162} To date, genome-wide association studies have identified 240 distinct loci that modulate the risk of IBD.\textsuperscript{163} Despite these great efforts, there does remain a substantial “missing heritability”, as the loci identified only explain about 20% of the heritability of IBD.\textsuperscript{164} However, subsequent studies of the identified loci have revealed several pathways that appear to be of importance in the pathogenesis of IBD, including intestinal barrier function, epithelial restoration, innate immune regulation, formation of reactive oxygen species, autophagy, and regulation of adaptive immunity.\textsuperscript{165}
Environmental risk factors

Genetic predisposition cannot, however, explain the rapid rise in IBD observed in certain geographic regions, and one must remember that more than 50% of individuals with identical genetic constitution are discordant regarding IBD. Thus, environmental influences play an equally important role in the development. Numerous environmental factors have been proposed to influence the risk of IBD, although with few exceptions the data are inconsistent. This might be because combinations of harmful exposure interplay to cause IBD, influences early in life may be more important than later exposures, or the impact of a certain environmental factor may differ depending on an individual’s genetic susceptibility. In addition, methodological limitations may have interfered with the results, since the majority of studies determining risk factors for IBD have been observational. In the following sections, the most commonly studied environmental risk factors are critically reviewed (Table 4).

Table 4. Environmental risk factors for IBD*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Ulcerative colitis</th>
<th>Crohn’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoker</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Never a smoker</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Appendectomy</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>Oral contraceptive agents</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>↑</td>
<td>?</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Protein</td>
<td>↑</td>
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</tr>
<tr>
<td>- Fats</td>
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<td>- Fibre</td>
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<tr>
<td>- Carbohydrates</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Microbial dysbiosis</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

*↑ Increased risk; ↓ decreased risk; ↔ equivocal risk; ? no data: from a minimum of one randomized controlled trial or a cohort study.
Smoking

The first environmental risk factor for IBD to be identified was cigarette smoking. In a thesis from 1976, Samuelsson reported that the occurrence of ulcerative colitis was considerably higher in former smokers and in non-smokers than in active smokers. However, the thesis was written in Swedish and the observation passed unnoticed until 1982 when the same finding was made from a mail questionnaire used in Cardiff, United Kingdom. Since then, many studies have confirmed the inverse association between smoking and ulcerative colitis. Interestingly, cigarette smoking has also been associated with a reduced risk of colectomy and hospital admission due to ulcerative colitis, although the mechanism of action remains to be explained. However, the effect does not seem to be mediated by nicotine alone, as three randomized controlled trials did not find any positive effect on the clinical remission rate of transdermal nicotine treatment. Correspondingly, the use of oral moist snuff does not appear to affect the risk of developing IBD.

In contrast to the beneficial effects observed in ulcerative colitis, cigarette smoking appears to be one of the most important risk factors for Crohn’s disease. Similarly, active smoking has been associated with complications such as increased risk of Crohn’s disease-related surgery and of recurrent disease after an operation.

Appendectomy

Another influence that has been associated with the development of ulcerative colitis is appendectomy. The inverse association was first noticed in an multi-centre case-control study of newly diagnosed patients with IBD. A subsequent Swedish cohort study involving 425,000 individuals found that patients who had undergone appendectomy for an inflammatory condition such as appendicitis or lymphadenitis before the age of 20 had a reduced risk of developing ulcerative colitis, while in a large Danish cohort a 13% decrease in the relative risk of ulcerative colitis was observed, but the association was not statistically significant.

Studies on the risk of Crohn’s disease after appendectomy have been conflicting. In a meta-analysis, past appendectomy was associated with a future risk of Crohn’s disease, although no significant association remained five years after the operation. At presentation, Crohn’s disease may mimic appendicitis and according to a large Swedish-Danish population-based study, the association between appendectomy and Crohn’s disease may be explained by diagnostic bias. The mechanism by which
appendectomy may be protective against ulcerative colitis is not known, but several hypotheses have been proposed. The appendix may act as a reservoir for enteric bacteria, and the development of an appendicular dysbiosis may be a priming event in the development of ulcerative colitis.\(^{188}\)

### Oral contraceptive agents
Several studies have investigated the effect of oral contraceptive agents on the occurrence of IBD. In a meta-analysis of 14 studies, a modest association with both Crohn’s disease and ulcerative colitis was observed.\(^{189}\) The risk of Crohn’s disease increased with prolonged exposure, while in ulcerative colitis no dose-response effect was evaluated because of an insufficient sample size. Similarly, in a recent cohort study of more than 230,000 women, an increased risk of Crohn’s disease was observed in users of oral contraceptive agents whereas in ulcerative colitis, the association was restricted to women with a history of smoking.\(^{190}\) Oral contraceptive agents may influence the risk of IBD through the effects of oestrogen, which has immune-enhancing properties with regard to secretion of TNF and macrophage proliferation.\(^{189}\) Correspondingly, hormone therapy in postmenopausal women has also been associated with the risk of IBD.\(^{191,192}\)

### Non-steroidal anti-inflammatory drugs
Several studies have demonstrated that the use of non-steroidal anti-inflammatory drugs is associated with relapse in patients with quiescent IBD.\(^{193-195}\) A possible explanation for this finding may be the effect on the intestinal permeability of these drugs.\(^{196}\) Increased permeability of the intestinal epithelium has been demonstrated in both Crohn’s disease and ulcerative colitis, although whether the barrier impairment is a consequence of the inflammatory response or a primary defect is a matter of debate.\(^{197,198}\) One large cohort study has assessed the effect of non-steroidal anti-inflammatory drugs on the development of IBD and found an association in terms of an increased risk of both Crohn’s disease and ulcerative colitis in heavy users (at least 15 days per month). However, the absolute increase in risk was small and the adjusted risk estimate in Crohn’s disease was not statistically significant.\(^{192,199}\)

### The gut microbiota
While most of the above-mentioned risk factors have been known for decades, one environmental factor that has gained increasing attention in
recent years is the community of bacteria that colonizes the human intestine, the microbiome. The highest concentration of microbiota is found in the colon, with a level of $10^{11}$–$10^{12}$ cells/g, thus out-numbering the cells of the entire human body. The microbiome has been found to carry out a range of useful functions for the host, including repression of harmful microorganisms, education of the mucosal immune system, and digestion of nutrients that are inaccessible to the host. One model to explain how the intestinal microbiota might contribute to chronic inflammation in IBD is the concept of dysbiosis. This model suggests that an imbalance between protective/aggressive commensal bacteria may drive host inflammatory responses in the gut. The most consistent observation regarding dysbiosis in IBD includes a decrease of bacteria in the Firmicutes phylum, an increase in the Proteobacteria phylum, and a reduced diversity of the gut microbiota. Interestingly, the composition of the gut microbiota has been associated with the IBD phenotype and the risk of relapse of inactive Crohn’s disease. Furthermore, several epidemiological risk factors for IBD including diet, age, drug treatment, and smoking appear to have an interplay with the microbial composition, and there is some evidence that faecal microbiota transplantation may induce remission of ulcerative colitis. However, despite these promising results, it is still not clear whether the dysbiosis observed in IBD is just a consequence of chronic inflammation or a triggering event in the pathogenesis. Prospective longitudinal studies to address this question will be essential for further investigation.

**Antibiotics**

The first data to support the idea that the use of antibiotics might contribute to the development of Crohn’s disease were from two retrospective case-control studies. Since then, several studies have confirmed this finding. In a prospective, nationwide Danish cohort study, childhood antibiotic use was found to be associated with Crohn’s disease. The association appeared to be stronger within 3 months of initiation of treatment and in children with seven or more courses of antibiotics, whereas no increase in the risk of ulcerative colitis was observed. Two studies demonstrated that the association between antibiotics and Crohn’s disease was stronger in boys than in girls, while the type of antibiotics used did not appear to affect disease development.

Interestingly, antibiotic use does not appear to influence the occurrence of ulcerative colitis. This finding supports the idea that different pathogenic mechanisms are involved in the development of Crohn’s disease and...
ulcerative colitis. The most conceivable explanation of how antibiotics affect the risk of Crohn’s disease is by alteration of the intestinal microbiota.

**Diet**

It has been proposed that the global variation in dietary habits is the most plausible explanation for the differences in incidence of IBD observed between different geographic regions. However, despite numerous studies of dietary influences on the risk of IBD, no consensus has emerged. One possible explanation is that these studies are difficult to perform because of poor recall of diet, the time-varying nature of dietary habits, and the possibility that dietary habits change due to symptoms of incipient disease. However, in recent years some large cohort studies have highlighted some potentially important dietary factors. A large French prospective cohort study of more than 67,000 women aged 40–65 years found that a high total protein intake, specifically animal protein, was associated with an increased risk of IBD. However, the study was under-powered for evaluation of the impact in Crohn’s disease and ulcerative colitis separately. Data from the Nurses’ Health Study, with a cohort of more than 170,000 women followed over 26 years with food frequency questionnaires collected every 2 years, indicated that a high fibre intake—especially from fruits and to a lesser extent from vegetables and cruciferous vegetables—reduces the risk of Crohn’s disease but not of ulcerative colitis. Reverse causation is an unlikely explanation of this finding, as the association remained despite a lag of 4–8 years between the assessment of fibre intake and diagnosis. In a subsequent study of the Nurses’ Health cohort, high intake of long-chain n-3 polyunsaturated fatty acids was found to be associated with a trend of lower risk of ulcerative colitis whereas high intake of trans-unsaturated fatty acids was associated with a trend of an increased incidence of ulcerative colitis. Neither total fat intake nor specific fatty acids modified the risk of Crohn’s disease. Similar results were achieved in a large European, nested case-control study. Although several case-control studies have suggested that a high intake of carbohydrates and refined sugars increases the risk of IBD, no such association has been established in more rigorous cohort studies. There are several biologically plausible mechanisms by which diet may affect gut inflammation, including antigen presentation, change in prostaglandin balance, and modification of the microbiota. Interestingly, in newly diagnosed children with Crohn’s disease, nutritional therapy with exclusive enteral nutrition appears to be effective in inducing remission, but no beneficial effect has been observed in adults.
Treatment of IBD
There is no cure for IBD, but once the diagnosis has been established, the goal of therapy is to induce and sustain remission with the use of medication. It has been hypothesized that control of chronic inflammation may prevent long-term complications such as progression in disease extent, stenosis, or penetrating disease, but there is no proof. Both single-drug therapy and combination therapy are used.

Aminosalicylates
In an attempt to treat the arthritis of his King, Gustav V of Sweden, Nanna Svartz (1890–1986) combined the anti-inflammatory substance 5-aminosalicylic acid with the antibacterial substance sulfapyridine and created sulphasalazine. When the new drug was serendipitously found to improve ulcerative colitis in patients with both joint symptoms and IBD, sulphasalazine also came in to use in IBD. Because of adverse drug reactions caused by the sulfapyridine component, 5-aminosalicylate preparations without sulphapyridine (mesalazin, balsalazid, and olsalazine) were developed and have successively replaced sulphasalazine. In ulcerative colitis, 5-aminosalicylates are effective and safe both in inducing remission of active disease and in preventing disease relapse, whereas these drugs play a limited role in treatment of Crohn’s disease.

Glucocorticosteroids
In 1955, just a few years after the discovery of cortisol by Hench et al., Truelove published the first randomized controlled trial on treatment of IBD in the British Medical Journal, demonstrating improvement and reduced mortality in ulcerative colitis patients who received corticosteroid treatment. However, subsequent studies have revealed that corticosteroids are a poor choice for maintenance therapy and carry an undesirable side-effect profile. Thus, systemic corticosteroids are mainly used for induction of remission in the setting of disease flares.

Immunomodulators
6-mercaptopurine and its pro-drug azathioprine are among the first designer drugs to be developed, and were initially intended for use as chemotherapeutic agents. Being structural analogues of nucleic acids, they interfere with DNA synthesis and inhibit the growth of rapidly dividing cells such as cancer cells or inflammatory cells. In 1958, it was documented that 6-mercaptopurine inhibited the formation of antibodies to protein
antigens given to rabbits, and the first study of thiopurines in IBD was published in 1962. Subsequent randomized controlled trials demonstrated that thiopurines are effective in maintaining remission in both Crohn’s disease and ulcerative colitis, and that thiopurines prevent recurrence of Crohn’s disease after surgery. However, thiopurines have a slow onset of action and there is no clear evidence that these drugs are effective in inducing remission in either Crohn’s disease or ulcerative colitis. Furthermore, there is no evidence that thiopurines reduce the risk of colectomy in ulcerative colitis. An unfortunate disadvantage of thiopurines is the risk of adverse drug reactions, which occur in about 15–30% of patients and include skin rash, nausea, fever, pancreatitis, hepatotoxicity, and bone marrow toxicity. In 1980, it was found that patients with polymorphisms in the gene encoding the enzyme thiopurine methyltransferase (TPMT) were at increased risk of bone marrow toxicity and gastrointestinal symptoms because of reduced drug inactivation. Thus, TPMT gene variation and also levels of the active metabolites, thioguanine nucleotides, are increasingly being measured in patients on thiopurine treatment.

Biological agents

The first biological agents used in common diseases such as IBD were monoclonal antibodies directed at the pro-inflammatory cytokine tumor necrosis factor alpha (TNF). Early studies associated TNF-alfa with the pathogenesis of septic shock, and the first human trials of anti-TNF agents were conducted for sepsis during the late 1980s. Although anti-TNF agents were never approved for clinical use in sepsis, these studies led other laboratories to investigate the role of TNF-alfa in other diseases such as rheumatoid arthritis and Crohn’s disease. In 1995, van Dullemen et al. reported that eight out of 10 Crohn’s disease patients showed normalization of CDI scores and improved endoscopic activity within 4 weeks after a single infusion of anti-TNF, and in 1998 infliximab was the first biological agent to be approved for IBD. Even though anti-TNF agents have markedly improved the management of both Crohn’s disease and ulcerative colitis that are refractory to conventional treatment, many patients do not respond, lose response over time, or become intolerant towards the treatment. For instance, patients may develop anti-drug antibodies, which can lead to a loss of response, and anti-TNF therapy has been associated with safety issues such as increased susceptibility to infections and exacerbation of congestive heart failure. Thus, drugs with
other mechanisms of action are being developed. Vedolizumab is a monoclonal antibody targeting the alpha4beta7 integrin, blocking the adhesion and migration of leucocytes into the intestinal mucosa. Randomized controlled trials have demonstrated that vedolizumab is effective in both Crohn’s disease and ulcerative colitis, although future studies will be required to define the long-term efficacy, the clinical effectiveness, and the safety of this drug.

**Surgery**

Despite the increasing array of pharmacological treatments for IBD, surgical management has remained a mainstay of therapy for patients who do not respond to medical treatment, suffer intolerable side effects of drug therapy, or develop complications such as dysplasia, adenocarcinoma, perforation, or bowel obstruction.

Operations for IBD during the early 1900s such as appendicostomy, intestinal bypass, therapeutic pneumo-peritoneum, and vagotomy were sporadic, were mainly experimental, and were later abandoned. However, surgical interventions gradually became more standardized. Beginning in 1913, ileostomy was performed to “rest” the inflamed colon. Although subsequent studies found that this procedure settles the inflammation distal to the stoma, particularly in Crohn’s disease, wide resections to remove all histologically detectable disease with the hope of curing the disease were advocated by Dr. Crohn and others.

In ulcerative colitis, early colectomy for patients refractory to steroids was a major advancement, reducing the mortality in acute severe ulcerative colitis from approximately 30–40% down to less than 1%. Proctocolectomy with permanent ileostomy was considered the gold standard of surgical management until the early 1980s, when the currently favoured operation, proctocolectomy with restorative ileal pouch-anal anastomosis, emerged. In Crohn’s disease, however, it soon became clear that excision of the affected bowel segment did not cure the disease and that postoperative recurrence was common regardless of resection margins. It was also discovered that repeated surgery may produce the short-bowel syndrome. Nowadays, surgery is deferred for as long as possible and bowel-preserving operations with minimal resections and techniques for strictureplasty that conserve the bowel length have been widely adopted in the surgical management of Crohn’s disease.

With the exception of colectomy in the setting of acute severe ulcerative colitis that is refractory to corticosteroids, there is still not much evidence
from randomized controlled trails to support decisions regarding surgery in IBD. Joint care by multidisciplinary teams remains vitally important for safe management.
Aims

The overall aim of the work described in this thesis was to study the epidemiology of ulcerative colitis in Örebro, Sweden, to examine certain aspects of anaemia in IBD, and to determine the clinical effectiveness of medical treatment.

Paper I
To study time trends in the incidence and prevalence of ulcerative colitis and in the risk of progression in disease extent and of colectomy, in the primary catchment area of Örebro University Hospital during the period 1963–2010.

Paper II
To determine the incidence, prevalence, and clinical outcome of anaemia in a population-based IBD cohort and to identify risk factors for anaemia in IBD.

Paper III
To study the impact of thiopurines in ulcerative colitis in terms of 10-year risk of colectomy, hospital admission, progression in disease extent, and need for anti-TNF therapy.

Paper IV
To describe the vedolizumab-treated IBD population in Sweden, to assess the long-term clinical effectiveness in real-world, and to identify predictors of successful treatment.

Ethics

The studies were approved by the Uppsala Regional Ethics Committee (studies I–III; DNR: 2010/304 and 2010/304/1) or by the Linköping Regional Ethics Committee (study IV; DNR: 2014/375-31 and 2015/247-32).
Material and methods

Papers I–III

Patients
Papers I–III were population-based cohort studies with the sampling frame defined by the geographic boundaries of Örebro University Hospital primary catchment area, including the following five municipalities: Askersund, Hallsberg, Kumla, Lekeberg, and Örebro. The catchment area covers both urban and rural areas and is representative of the whole of Sweden in terms of migration, demographic profile, and socio-economic features. During the period 1963–2010, the population increased by 26% from 150,177 to 189,603 and the median age increased from 36 years (interquartile range [IQR] 18–57) to 39 years (IQR 20–59). Within the area, there are no private gastroenterologists and everyone with a suspected or verified IBD is referred to Örebro University Hospital. Similarly, all colonoscopies, radiological examinations, and histopathological examinations are performed at the University Hospital and all medical records—including endoscopy, laboratory, radiological, and histopathological data on patients with inflammatory bowel disease—have been stored at the private archive of the Department of Gastroenterology since the opening in 1976. We identified patients with possible ulcerative colitis by evaluation of all the medical records in this archive. We also performed computerized searches in the County Council’s digital diagnostic database of in-patients and out-patients, which was established in 1988, in order to identify additional cases. The following International Statistical Classification of Diseases and Related Health Problems (ICD) codes were used in the searches: the ICD-10 codes K510-K519 (ulcerative colitis), K528-K529 (colitis UNS), K500-K509 (Crohn’s disease), M074-M076 (IBD-associated arthropathy), and M091-M092 (IBD-associated juvenile arthritis); and the ICD-9 codes 555 (regional enteritis), 556 (ulcerative colitis), and 558 (other and unspecified non-infectious gastroenteritis and colitis).

Inclusion criteria
Individuals who were resident in the catchment area of Örebro University Hospital were included in paper I if they were diagnosed with ulcerative colitis according to the Lennard-Jones criteria before 31 December 2010. Patients who were diagnosed during the period 1963–2010 and who lived
within the catchment area at the time of diagnosis were considered to be incident cases. Patients were surveyed until death, until migration, or to the end of follow-up, i.e. 31 December 2015. All incident patients who had received treatment with thiopurine drugs at any time during their disease course until the end of follow-up were included in paper III, while a random subset of patients with IBD who were living in the catchment area on 31 December 2010 was included in paper II. The Crohn’s disease patients included in paper II were identified in previous epidemiological studies conducted in the area.77, 115, 288, 289

**Data collection**

Age- and sex-stratified data on the study population were obtained from Statistics Sweden.287 Medical records of the included patients, from the Department of Gastroenterology, and, if relevant, from the Departments of Surgery, Paediatrics, Infectious Diseases, Clinical Chemistry, and Pathology, were evaluated using a standardized case report form including the following key information:

**Descriptive epidemiology:**
- Date of diagnosis, death, and migration.
- Demographic information including sex and date of birth.

**Exposure:**
- Start and stop dates of medical treatments and reasons for discontinuation.

**Outcomes:**
- Dates of surgical procedures.
- Extent of disease at diagnosis and during follow-up, according to the Montreal classification.28
- Dates of hospital admissions because of ulcerative colitis or infectious diseases.
- Haemoglobin levels recorded during the period 2011–2013 (for patients included in study II).
Paper IV

Patients
The Swedish National Quality Registry for Inflammatory Bowel Disease (SWIBREG) is a large, prospectively maintained national quality registry, established in 2005. The purpose of SWIBREG is to continuously improve treatment and follow-up of patients with IBD. Currently, the registry contains information on more than 40,000 patients from 45 hospitals, and the national coverage rate is about 60%. The list of variables has been updated on a regular basis, and includes clinical data such as date of diagnosis, disease characteristics according to the Montreal classification, surgery, endoscopy, prescribed and administered drugs, reasons for drug discontinuation, clinical and biochemical disease activity, and measures of quality of life. Information is captured both at out-patient visits and at hospital admissions. According to a recent study, the data registered in SWIBREG have high validity with a positive predictive value of 99% for IBD diagnoses.

Inclusion criteria
In paper IV, we used SWIBREG to identify patients with IBD who started on vedolizumab therapy during the inclusion period, 1 June 2014 until 30 May 2015, and to survey the included patients until death, emigration, or the end of follow-up, i.e. June 2016.

Data collection
The following information was extracted from SWIBREG:

Descriptive epidemiology:
- Date of diagnosis.
- Demographic information including sex and date of birth.
- Disease characteristics at baseline according to the Montreal classification.

Exposure:
- Start and stop dates of medical treatments including vedolizumab, and reasons for discontinuation according to the criteria used in SWIBREG: lack of or loss of response (termination because of primary non-response or secondary loss of response); intolerance (dis-
continuation due to side effects including infusion reactions); or other reasons, including pregnancy.

Outcomes:
- Clinical disease activity indices including P-HBI and P-SCCAI at baseline and during follow-up.\textsuperscript{100,101}
- Results from biochemistry such as CRP and faecal calprotectin levels at baseline and during follow-up.

\textbf{Statistics}

Continuous variables that were not normally distributed—including age, disease duration, and biochemical measurements, and also data on an ordinal scale such as clinical disease activity—are presented as median (IQR). Non-parametric methods including the Mann-Whitney U-test were used to compare these variables between groups and Wilcoxon signed-rank test was used to investigate changes in one individual over time.\textsuperscript{294,295} Bonferroni correction was used to adjust for multiple comparisons.\textsuperscript{296} Results from clinical laboratory measurements below the lowest limit of detection (LOD) were generally transformed to LOD/\sqrt{2}.\textsuperscript{297} Pearson’s chi-squared test (or Fisher’s exact test when appropriate) was performed to compare categorical data such as disease phenotype and previous medication use between groups.\textsuperscript{298,299} Life tables and survival plots were constructed by Kaplan-Meier analysis and the log-rank test was used to compare survival data between groups.\textsuperscript{300,301} One-sample z-tests were conducted to determine whether observed proportions differed from hypothesized proportions.\textsuperscript{302} All tests were two-tailed and any p-value of $< 0.05$ or a 95\% confidence interval of a relative risk estimate, not involving 1.0, was considered statistically significant.

\textbf{Incidence rate}

In epidemiology, most rates such as incidence, prevalence, and mortality are strongly age-dependent. For example, IBD is commonly diagnosed early in life—during adolescence or early adulthood.\textsuperscript{113} Since the age structure of a population may change over time and differ considerably between geographic regions, comparisons of age-specific rates may be misleading. Thus, several methods for adjusting age-specific rates have been developed. In paper I, the crude age-specific incidence and prevalence were weighted using the characteristics of the Örebro population in 1999 (as the standard population). This method for age-adjustment is termed direct standardization and requires age-specific rates for each stratum of the
population. In contrast, indirect standardization can be performed when data are missing from some strata.\textsuperscript{303} We used the Örebro population of 1999 as the standard population to adjust for changes in population structure over time, while for international comparisons other standard populations—such as the world or European standard populations—might be more appropriate.\textsuperscript{303, 304}

**Regression analysis**

In papers I–IV, multiple regression models were constructed in order to adjust the observed results for influences of confounding factors. In all regression analyses, covariates were selected on the basis of their potential biological association with the outcome and no statistical methods for variable selection such as forward selection, backward elimination, or stepwise method were applied.\textsuperscript{305}

Binary logistic regression is a model developed by Cox during the 1950s.\textsuperscript{306} This method can be used to estimate the probability (odds ratio) of a dichotomous outcome, given the values of one or more explanatory variables. Dichotomous means that the outcome variable can take one of two values, “yes” or “no” (e.g. dead or alive), and dichotomous outcomes are common endpoints in medical research. Variables that are not naturally binary can often be transformed using a cut-off level. The explanatory variables however, can be either categorical or continuous. Logistic models use “maximum likelihood estimation” to determine the effect of explanatory variables on the results.\textsuperscript{307} This process begins with a tentative solution, then revises it slightly and repeats the process until no more improvements can be made. In some instances, however, no solution is possible. For example, logistic regression requires that there is little or no multi-collinearity among the independent variables. This means that the explanatory variables should not be to highly correlated to each other. Furthermore, maximum likelihood estimation requires a large sample size. A widely used guideline states that at least 10 cases with the outcome per every explanatory variable are necessary to achieve consistent results.\textsuperscript{308}

Cox proportional hazard regression is a method for investigating the effect of explanatory variables on the time to a specified event, the “survival time”. In this type of analysis, it is uncommon that the event of interest is observed in all subjects, so individuals without events are censored at the end of follow-up. When censoring individual subjects, it is important to make sure that the continuation of follow-up does not depend on a participant’s medical condition. The distribution of survival time is often un-
known and may vary depending on the outcome of interest. To deal with this problem, Cox demonstrated in 1972 that if the effect of a predictor on the survival time is constant over time, i.e. the proportional hazard assumption holds, no assumptions regarding the distribution of survival times is necessary.\textsuperscript{309} The proportional hazard assumption can be tested visually from Kaplan-Meier curves and, additionally, there are several statistical methods that can be used to verify the assumption, including testing the significance of time-dependent covariates and plotting Schoenfeld residuals.\textsuperscript{310} The output of a Cox regression model is a hazard ratio for each explanatory variable and, as in logistic regression, the model is fitted by maximum likelihood estimation.

Poisson regression was introduced by von Bortkiewicz in 1898, and is an appropriate method when data is a count of events, particularly rare events—for example, the number of new IBD patients during a period of time, in a specified geographical region. However the method is named after the French mathematician Poisson, who derived the mathematical form of the distribution. As with logistic regression and Cox regression, estimation of the influence of explanatory variables is done using maximum likelihood and the output from a Poisson regression is an incidence rate ratio.\textsuperscript{311}

All statistical analyses in this thesis were performed using SPSS version 22 (IBM Corporation, Armonk, NY, 2013) or STATA version 14 SE (Stata Corporation, College Station, TX, 2013)
Results

Paper I

Incidence rate
During the study period 1 January 1963 to 31 December 2010, 1,007 patients in the study area were diagnosed with ulcerative colitis and the age-standardized incidence rate (IR) increased from 3.5 per 100,000 inhabitants in the period 1963–1965 to 18.1 per 100,000 inhabitants in the period 2006–2010. Results from Poisson regression analysis demonstrated that the observed increase was statistically significant in both men (p < 0.01) and women (p < 0.01).

Table 5. Crude and age-standardized incidence rates of ulcerative colitis per 100,000 inhabitants, aggregated over 5-year periods

<table>
<thead>
<tr>
<th>Period</th>
<th>No of incident cases</th>
<th>Crude IR (95% CI)</th>
<th>Age-standardized IR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1963–1965</td>
<td>12</td>
<td>3.4 (1.8–6.0)</td>
<td>3.5 (1.5–5.5)</td>
</tr>
<tr>
<td>1966–1970</td>
<td>34</td>
<td>4.8 (3.3–6.6)</td>
<td>4.5 (3.0–6.0)</td>
</tr>
<tr>
<td>1971–1975</td>
<td>46</td>
<td>5.7 (4.2–7.6)</td>
<td>5.7 (4.0–7.3)</td>
</tr>
<tr>
<td>1976–1980</td>
<td>111</td>
<td>13.6 (11.2–16.4)</td>
<td>13.7 (11.1–16.2)</td>
</tr>
<tr>
<td>1981–1985</td>
<td>104</td>
<td>12.7 (10.4–15.4)</td>
<td>12.6 (10.2–15.1)</td>
</tr>
<tr>
<td>1986–1990</td>
<td>114</td>
<td>13.7 (11.3–16.5)</td>
<td>13.4 (10.9–15.9)</td>
</tr>
<tr>
<td>1991–1995</td>
<td>137</td>
<td>15.9 (13.4–18.8)</td>
<td>16.0 (13.3–18.7)</td>
</tr>
<tr>
<td>1996–2000</td>
<td>140</td>
<td>15.9 (13.4–18.7)</td>
<td>15.9 (13.3–18.6)</td>
</tr>
<tr>
<td>2001–2005</td>
<td>137</td>
<td>15.3 (12.8–18.0)</td>
<td>15.2 (12.6–17.8)</td>
</tr>
<tr>
<td>2006–2010</td>
<td>172</td>
<td>18.5 (15.8–21.5)</td>
<td>18.1 (15.4–20.8)</td>
</tr>
</tbody>
</table>

In total, 570 of 1,007 incident patients were male and the age-adjusted incidence rate ratio for men vs. women was 1.34 (95% CI 1.18–1.52). The median age at diagnosis was 35 years (IQR 24–51). A higher proportion of men were diagnosed with extensive colitis than women (age-adjusted odds ratio [OR] = 1.55; 95% CI 1.17–2.05) whereas a lower proportion of men had proctitis at diagnosis (age-adjusted OR = 0.54; 95% CI 0.42–0.70).

Prevalence
The age-standardized point prevalence of ulcerative colitis increased from 44 per 100,000 inhabitants on 31 December 1965 to 474 per 100,000 inhabitants on 31 December 2010.
Long-term outcome of ulcerative colitis

To assess temporal trends and to be able to compare our results with studies of Crohn’s disease conducted in the Örebro catchment area, we evaluated the risk of progression in the extent of disease, of colectomy, and of medication exposure in three time periods according to year of diagnosis: 1963–1975, 1976–1990, and 1991–2005. Patients diagnosed after 31 December 2005 were excluded from this part of the analysis, in order to achieve at least 10 years of follow-up for all patients.

Progression in extent of disease

The cumulative probability of progression in the extent of disease within 10 years from diagnosis was 34.5% and 18.5% in patients with proctitis and left-sided colitis, respectively. In the Cox regression model, age > 40 years (adjusted hazard ratio [HR] = 0.47; 95% CI 0.25–0.90) and left-sided colitis (adjusted HR = 0.48; 95% CI: 0.36–0.65) were associated with a reduced risk of progression in disease extent after making adjustment for sex and study period.
Colectomy

In patients diagnosed during 1963–2005, the cumulative probability of colectomy within 10 years from diagnosis was 13.5%. Indications for colectomy were acute severe colitis that was refractory to medical therapy (47% of patients), chronic active disease (43%), colorectal dysplasia or cancer (8%), and other indications in 2% of patients (sarcoma, colon metastasis from testicular cancer, and iatrogenic perforation because of colonoscopy). In the Cox regression model, left-sided colitis (adjusted HR = 1.67; 95% CI 1.04–2.69) and extensive colitis (adjusted HR = 4.27; 95% CI 2.81–6.50) were associated with an increased risk of colectomy while diagnosis during the last study period, 1991–2005, was associated with a reduced risk of colectomy (adjusted HR = 0.61; 95% CI 0.39–0.94), after adjustments for sex and age.

Temporal trends in medical therapy
Between the two earliest study periods, 1963‒1975 and 1976‒1990, there was a significant increase in the cumulative probability of receiving oral 5-aminosalicylates (79% vs. 92%; p < 0.01) and corticosteroids (37% vs. 70%; p < 0.01) within 10 years of diagnosis. Thiopurines were introduced in selected cases during the 1980s and an increasing probability of receiving thiopurines within 10 years was observed between the two most recent study periods (7% vs. 34%; p < 0.01). The first anti-TNF agent, infliximab, was approved in 2005 and 9% of patients diagnosed during the last study period received anti-TNF within 10 years from diagnosis.

Table 6. Indications for colectomy, according to study period

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Acute severe colitis</td>
<td>9 (26)</td>
<td>31 (48)</td>
<td>35 (58)</td>
</tr>
<tr>
<td>Chronic active disease</td>
<td>23 (66)</td>
<td>26 (41)</td>
<td>20 (33)</td>
</tr>
<tr>
<td>Colorectal dysplasia or cancer</td>
<td>3 (8)</td>
<td>5 (8)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Other indications</td>
<td>0 (0)</td>
<td>2 (3)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Chi-squared test for trend, p = 0.04.

Paper II

Patients
A random sample of 342 IBD patients, diagnosed with Crohn’s disease (n = 171) or ulcerative colitis (n = 171) in the period 1963‒2010 and resident in the Örebro University Hospital catchment area on 31 December 2010, was obtained from the IBD cohort of Örebro University Hospital.77,289,312
One hundred and seventy-seven (52%) of the patients were male, the median age was 57 years (IQR 41–66), and the corresponding disease duration was 19 years (IQR 9–31).
Inflammatory Bowel Disease

Incidence rate
In total, 124 of the 342 patients had an instance of anaemia during the period 1 January 2010 to 31 December 2013, corresponding to a mean annual incidence rate of 15.9 per 100 person years. The incidence rate was 19.3 per 100 person years for Crohn’s disease and 12.9 per 100 person years for ulcerative colitis (Figure 4). In the logistic regression model, Crohn’s disease was associated with an increased risk of anaemia compared to ulcerative colitis, after making adjustment for age and sex, (adjusted OR = 1.60; 95% CI 1.02–2.51). Correspondingly, in the sensitivity analyses performed to minimize the influence of surveillance bias, Crohn’s disease was found to be associated with an increased risk of anaemia in both a model where patients treated with immunomodulators and/or anti-TNF agents were excluded (adjusted OR = 1.89; 95% CI 1.10–3.24) and in a model that only included patients who had had out-patient clinic visits during the study period (adjusted OR = 1.69; 95% CI 1.00–2.86).

Figure 4. Kaplan-Meier plot showing the cumulative probability of anaemia in patients with Crohn’s disease and in patients with ulcerative colitis.
Period prevalence
Overall, 76 patients had an episode of anaemia during 2013, corresponding to a period prevalence of 22.6%. For Crohn’s disease, the prevalence was 28.7% as compared to 16.5% for ulcerative colitis. In the logistic regression model, Crohn’s disease was found to be associated with an increased risk of anaemia, after making adjustment for age and sex (adjusted OR = 2.04; 95% CI 1.20–3.46). The association between Crohn’s disease and increased risk of anaemia remained in both a model where patients treated with immunomodulators and/or anti-TNF agents were excluded (adjusted OR = 1.96; 95% CI 1.03–3.37) and in a model that only included patients who had had out-patient clinic visits during the study period (adjusted OR = 2.25; 95% CI 1.22–4.14).

Risk factors for anaemia
Cox proportional hazard regression was used in the assessment of risk factors for anaemia. For Crohn’s disease, stricturing disease behaviour was found to be associated with an increased risk of anaemia (adjusted HR = 2.59; 95% CI 1.00–6.79), after making adjustment for sex, disease duration, disease location, and past bowel surgery. For ulcerative colitis, extensive disease was found to be associated with a higher risk of anaemia (adjusted HR = 2.40; 95% CI 1.10–5.36), after making adjustment for sex, disease duration, and past colectomy.

Treatment and outcome of anaemia
In total, 51 (41%) of the 124 patients who were diagnosed with anaemia during the study period received supplementation therapy (oral iron, n = 18; iron intravenously, n = 22; oral folic acid, n = 3; or oral vitamin B12, n = 8) and eight patients received a blood transfusion within 3 months of diagnosis of anaemia. Similarly, 42 patients (34%) received intensified anti-inflammatory treatment (introduction or dose optimization of oral 5-aminosalicylates, n = 8; immunomodulators, n = 15; anti-TNF, n = 4; leukocyte apheresis, n = 1; or corticosteroids, n = 14). However, none of the patients were treated with erythropoietin, and 42 (36%) of the patients diagnosed with anaemia received no treatment at all within 3 months.

Repeated measurement of haemoglobin was performed 12 months after the diagnosis of anaemia in 123 of the 124 patients, and at this point 80 (65%) had a restored haemoglobin level. Although, Crohn’s disease patients received more specific therapy (supplementation or anti-
inflammatory therapy) than patients with ulcerative colitis (72% vs. 55%; p = 0.05), Crohn’s disease was associated with a worse prognosis than ulcerative colitis in terms of resolution of anaemia within 12 months (56% vs. 75%; p = 0.03). Correspondingly, females received more specific therapy than males (73% vs. 56%; p = 0.05) and were more likely to have resolution of the anaemia within 12 months (75% vs. 54%; p = 0.02)

**Paper III**

**Patients**

Of the 1,007 patients who were diagnosed with ulcerative colitis in the period 1963–2010 in the catchment area of Örebro University Hospital, 253 patients had received at least one dose of a thiopurine drug before the end of follow-up on 31 December 2015 and were included in this study. Within 12 months of commencement, 76 of the 253 (30%) stopped therapy because of intolerance, whereas 177 patients continued treatment or stopped for other reasons. Fifty-eight percent of the patients included were male, the median age was 30 years (IQR 21–42), and the median disease duration was 2 years (IQR 0–6) at baseline, i.e. initiation of first thiopurine drug. There were no significant differences between the two groups in terms of age, sex, smoking habits, family history of IBD, disease duration, extent of disease, hospital admission at diagnosis, or previous medical or surgical treatment at baseline.

**Colectomy**

The cumulative probability of colectomy within 10 years was 19.5% in patients who tolerated thiopurines, as compared to 29.0% in patients who stopped treatment because of intolerance. In the Cox regression analysis, thiopurine tolerance was found to be associated with a reduced risk of colectomy (adjusted HR = 0.39; 95% CI 0.21–0.73) after making adjustment for sex, age, extent of disease, previous medical or surgical therapy, hospital admission at diagnosis, and year of thiopurine initiation in 5-year intervals.

**Hospital admission**

The cumulative probability of hospital admission because of ulcerative colitis or ulcerative colitis-related conditions within 10 years of first thiopurine exposure was 34.0% in tolerant patients as compared to 56.2% in
patients who discontinued treatment due to adverse drug reactions. In the Cox regression model, thiopurine tolerance was found to be associated with a reduced risk of hospital admission (adjusted HR = 0.36; 95% CI 0.23–0.56) after making adjustment for sex, age, extent of disease, previous medical or surgical therapy, hospital admission at diagnosis, and year of thiopurine initiation in 5-year intervals.
Figure 4. Kaplan-Meier plot showing the cumulative probability of colectomy in patients who tolerated thiopurines and in those who discontinued treatment because of an adverse drug reaction.

Figure 5. Kaplan-Meier plot of the cumulative probability of hospitalization in patients who tolerated thiopurines and in those who discontinued treatment because of an adverse drug reaction.
Progression in extent of disease

The risk of progression in the extent of disease within 10 years in thiopurine-tolerant patients with proctitis or left-sided colitis was 20.4%, and the corresponding figure in intolerant patients was 48.8%. Cox regression analysis gave an adjusted HR of 0.45 (95% CI 0.21–0.97) for disease progression in thiopurine-tolerant patients, after making adjustment for sex, age, extent of disease, previous medical or surgical therapy, hospital admission at diagnosis, and year of thiopurine initiation in 5-year intervals.

Figure 6. Kaplan-Meier plot showing the cumulative probability of progression in the extent of disease in patients with ulcerative proctitis or left-sided colitis who tolerated thiopurines and in those who discontinued treatment because of an adverse drug reaction.
Anti-TNF exposure
At 10 years from initiation of thiopurines, 16.1% of tolerant patients and 27.5% of intolerant patients had received anti-TNF therapy. In the regression model, thiopurine tolerance was associated with a reduced risk of anti-TNF exposure (adjusted HR = 0.49; 95% CI 0.26–0.92), after making adjustment for sex, age, extent of disease, previous medical or surgical therapy, hospital admission at diagnosis, and year of thiopurine initiation in 5-year intervals.

Figure 7. Kaplan-Meier plot showing the cumulative probability of anti-TNF therapy in patients who tolerated thiopurines and in patients who discontinued treatment because of an adverse drug reaction.
Paper IV

Patients
Altogether, 246 IBD patients (Crohn’s disease, n = 147; ulcerative colitis, n = 92; and IBD-U, n = 7) who started treatment with vedolizumab between 1 June 2014 and 30 May 2015 were identified through SWIBREG. In the cohort, 67% were males, the median age was 38 years (IQR 26–49), and disease duration at baseline was 7 years (IQR 2–16). At the start of vedolizumab treatment, 86% had had failed TNF antagonist and 48% of the Crohn’s disease patients had undergone at least one surgical resection. Furthermore, 94 patients (38%) were treated concomitantly with an immunomodulator, i.e. a thiopurine (n = 85) or methotrexate (n = 9), and 66 (27%) were on corticosteroids at baseline.

Drug continuation rate
During a median follow-up time of 17 months (IQR 14–20), 104 of the 246 patients (42%) discontinued vedolizumab therapy (due to lack of or loss of response, 66%; intolerance, 23%; or for other reasons, 11%). The 12-month continuation rates were 61% for Crohn’s disease and 65% for ulcerative colitis (p = 0.51).

Figure 8. Kaplan-Meier plot showing the cumulative survival on vedolizumab in patients with Crohn’s disease and ulcerative colitis. The numbers of patients at risk are listed according to time points in months.
Predictors of discontinuation

Cox regression analyses to assess risk factors for discontinuation of vedolizumab because of lack of or loss of response and because of intolerance were performed separately. Previous TNF exposure and CRP > 2.87 mg/mL at baseline were associated with an increased risk of termination due to a lack of or loss of response in the univariate analysis. However, after making adjustment for sex, IBD diagnosis, age, type of hospital (regional or university hospital), disease duration, smoking status, and concomitant treatment (corticosteroids and/or immunomodulators), only CRP > 2.87 mg/mL (adjusted HR = 2.22; 95% CI 1.10–4.35) but not previous TNF exposure (adjusted HR = 4.03; 95% CI 0.96–16.75) remained significantly associated with the risk of terminating vedolizumab because of lack of or loss of response.

Female sex (adjusted HR = 2.75; 95% CI 1.16–6.48) was associated with a higher risk of termination due to intolerance, after making adjustment for the above-mentioned covariates.

Clinical and biochemical effectiveness in Crohn’s disease

At last follow-up, after a median treatment duration of 17 months (IQR 15–19), 82 out of 147 of the Crohn’s disease patients (56%) were still being treated with vedolizumab. Altogether, 36 out of 71 of the patients with P-HBI available at baseline and at last follow-up (51%) had a clinical response; 38 (54%) were in clinical remission and 36 (51%) were in steroid-free clinical remission. Correspondingly, significant decreases in median P-HBI (8 to 4; p < 0.01), CRP (6 to 3; p < 0.05), and faecal calprotectin (746 to 201; p < 0.01) were observed between baseline and last follow-up.

Clinical and biochemical effectiveness in ulcerative colitis

At last follow-up, after a median time of 16 months (IQR 14–20), 57 out of 92 (62%) of the ulcerative colitis patients had continued vedolizumab treatment. In the group of 44 patients with data available on P-SCCAI scores at baseline and at last follow-up, 29 (66%) had a clinical response, 28 (64%) were in clinical remission, and 27 (61%) were in steroid-free clinical remission. Similarly, significant decreases in median P-SCCAI (7 to 2; p < 0.01) and faecal calprotectin (1,162 to 101; p < 0.01) were observed between baseline and last follow-up.
Discussion

Despite the great variation in occurrence of IBD geographically and in spite of reports indicating a plateau or even a decline in some parts of Europe,\textsuperscript{133, 313-315} data from the Örebro region—including the results of paper I—show a clear increase in both the incidence and the prevalence of IBD in the area over the past 50 years.\textsuperscript{115, 119, 288, 289} Our findings, which are supported by some recent Scandinavian studies including reports from the neighbouring county of Uppsala,\textsuperscript{118, 316-319} indicate that the total number of IBD patients in Sweden already exceeds 70,000 and that this number will continue to grow during the next few decades as IBD is diagnosed primarily in young individuals, since the mortality is low and there is no cure.

The growing number of IBD patients will pose a significant challenge to gastroenterologists and gastrointestinal surgeons in Sweden, which may necessitate innovations in healthcare delivery to meet the increasing demand. However, just in the last few years the pharmacological armamentarium of IBD has been augmented with several new biological agents, and many new therapies, targeting novel pathogenic pathways, are under development.\textsuperscript{320, 321} Short-term follow-up of participants in clinical trials supports the idea that anti-TNF therapy is associated with a reduced risk of surgery, a reduced risk of hospital admission, and better quality of life in IBD patients, compared to conventional treatment.\textsuperscript{99, 322} In the future, having a number of drugs with different mechanisms of action available may allow clinicians to customize therapy for the individual patient. This new paradigm of IBD management will possibly have far-reaching implications—not only for patients and clinicians, but also for society as a whole.

On the other hand, numerous questions remain regarding the optimal use of the therapies that are already on the market. Traditionally, the approach to managing active IBD has been based on progressive intensification of medical treatment as symptoms become worse.\textsuperscript{323, 324} In recent years, however, a top-down approach in medical therapy has been introduced for patients with risk factors for a severe outcome already at diagnosis.\textsuperscript{325, 326} It also appears that treatment targeting the underlying inflammation in terms of biomarkers and endoscopic findings is more effective than traditional management, aimed at the control of symptoms only.\textsuperscript{327}

More aggressive treatment algorithms, including combination of drug therapies, and more ambitious goals with the treatment may, however, be associated with increased toxicity. Unfortunately, clinical trials are rarely
designed to study long-term events such as uncommon but potentially life-threatening side effects.\textsuperscript{328} For example, the risk of progressive multifocal leukoencephalopathy, which affects about four per cent of patients exposed to the integrin antagonist natalizumab, was not detected in the pivotal trials.\textsuperscript{329-332} This severe viral disease of the central nervous system has a 6-month mortality rate of 25\% and highlights the importance of large observational studies with long-term observation periods to assess the safety and clinical effectiveness of new pharmacological treatments.\textsuperscript{333}

In paper IV we found that vedolizumab, another integrin antagonist that is gut-selective, appears to be well tolerated and effective in Swedish clinical practice. However, previous exposure to anti-TNF agents and elevated CRP at start of treatment were associated with a less favourable clinical response, and women were more likely to discontinue therapy because of intolerance.

Given that complications of IBD, such as disease progression or events necessitating a surgical resection, often arise after years of disease, another advantage of observational studies with a long duration of follow-up is the possibility to investigate outcome measures other than the endpoints commonly used in clinical trials.

In paper I, we observed that patients diagnosed with ulcerative colitis during the last study period, 1991–2005, had a reduced risk of colectomy compared to patients diagnosed during the first study period, 1963–1975. This finding is supported by recent Danish observational studies and also by a meta-analysis of population-based studies of patients diagnosed between 1955 and 2006.\textsuperscript{70, 76, 334} Interestingly, we observed that the reduction in colectomies was temporally associated with increased use of thiopurines and anti-TNF agents, but this finding should be interpreted with caution, since associations were at the group level only.

The aim of paper III was to further investigate the long-term effect of thiopurine drugs on the disease course and risk of colectomy in ulcerative colitis. However, the fact that patients exposed to thiopurines represent a treatment-refractory group challenges the assessment of the long-term effectiveness of thiopurines in a real-world setting, since the thiopurine-exposed population has a different risk of colectomy and other long-term outcomes compared to the general ulcerative colitis population.\textsuperscript{335}

In order to avoid differential bias due to confounding by indication, a novel study approach was adopted. We only included patients exposed to thiopurines, and compared patients who stopped treatment because of adverse drug reactions within 12 months from initiation of treatment with
patients who continued treatment or who discontinued the therapy for other reasons. Using this method, we observed that thiopurine therapy is associated with a reduced risk of colectomy and that these drugs have a profound beneficial effect on the natural history of the disease. Perhaps increased and earlier use of thiopurine drugs may explain the decrease in colectomies seen in the catchment area of Örebro University Hospital in 1991–2005.

Although the occurrence of IBD has been studied in many parts of the world during the latter part of the twentieth century, there have only been a few continuous surveys with a total observation time of more than 50 years: ulcerative colitis in Uppsala, 1945–2007; ulcerative colitis and Crohn’s disease in Olmsted county, 1940–2000; and Crohn’s disease in Cardiff, 1931–2005. The Örebro region has a long tradition of epidemiological studies of IBD, and the incidence and prevalence of ulcerative colitis have previously been studied over two time periods, 1939–1958 and 1963–1987. In addition, the epidemiology of Crohn’s disease has been reported for the period 1963–2010 and that of microscopic colitis for the period 1984–2008. Having a well-characterized population-based cohort of patients covering the whole spectrum of IBD, followed up during many years, allows almost endless possibilities for performing further research.

In paper II, we studied the incidence and prevalence of anaemia in a randomized subset of patients with established IBD allocated from the entire IBD cohort. We found that anaemia is a common complication even beyond the first years after diagnosis of IBD. The risk of developing anaemia was higher in Crohn’s disease than in ulcerative colitis. Interestingly, the prognosis of anaemia in terms of resolution within 12 months was also worse in Crohn’s disease. Unfortunately, the study also indicated that despite current guidelines, many patients did not receive adequate therapy. The risk factors for anaemia, strictureing behaviour in Crohn’s disease, and extensive disease in ulcerative colitis should be recognized and current treatment guidelines should be better implemented in clinical practice.

Methodological considerations

Randomized controlled trials (RCTs) are generally regarded to be the best source of medical data on the effects of clinical interventions. However, RCTs are unethical for testing the causes of disease, and cannot be used to quantify the occurrence of a disease in a population. Cohort studies are
the best available substitute when an RCT would be inappropriate or impossible.  

A cohort is a group of individuals who share a defining characteristic, e.g. people who live in the same area or have a specific disease. At the start of a study, participants are divided into groups depending on exposure. The subjects are then followed up over a period of time to determine the proportion in each group who develop the outcome of interest.

Cohort studies are either prospective (where participants are followed up forward from the present) or retrospective (where participants are followed up from a date in the past). Prospective cohort studies are generally expensive and time consuming whereas retrospective studies are not. All the papers in the current thesis describe retrospective cohort studies, although the capture of data was prospective and based on medical records (papers I–III) or registry data (paper IV).

**Bias and random error**

There are two broad types of errors in medical research: random error and systematic error. Random error is a difference between the observed value and the true value that is due to chance or imprecise measurement. Random errors can be reduced by increasing the sample size or averaging of multiple measurements. A confidence interval can be computed from the observed data to estimate the interference of random variation, and statistical methods may be applied in hypothesis testing. Type-II error occurs when a hypothesis is rejected even though the hypothesis is true, and the power of the test expresses the probability of committing a type-II error. (The power is determined by the sample size, the precision with which the data are measured, and the magnitude of the effect or difference of interest). Type-I error occurs when the hypothesis is not rejected even though it was false, and the risk of committing a type-I error is determined by the significance level (p-value).

Bias is a systematic error i.e. results have been obtained that consistently deviate from the truth (by under- or over-estimation). Bias cannot be eliminated by increasing the sample size. Instead, it is minimized by proper study design and conduction of the study. There are virtually dozens of types of bias that might distort the estimation of a scientific measure, although two general types are important to remember: selection bias and information bias. Selection bias is error because of systematic differences between individuals who take part in a study and those who do not, while information bias arises from inaccurate measurement of exposures and
Outcomes. Bias in a study does not necessarily mean that the conclusion of the study should be disregarded. However, the impact of systematic errors on the study results and the methods used to minimize the influence of bias should be openly presented.

Confounding
A confounding factor is independently associated with both the exposure and the outcome of a test, and should always be considered as a possible explanation for an observed association. In non-randomized studies, the influence of confounding can be reduced by proper study design and by adjustments for potential confounders using methods such as regression analysis. However, only known and measured confounders can be adjusted for.

Validity
For a study to be regarded as valid, it must be shown that the conclusions of the study can be logically drawn from the results and that the results are based on an appropriate methodology. Internal validity reflects the extent to which a conclusion is correct for the participants of a study and may be threatened by bias, confounding, and random error. External validity relates to the value of the conclusion to other populations (generalizability).

Limitations
A main limitation of all the studies in this thesis was the retrospective study design, i.e. the studies were conducted after the events of interest had already occurred. In studies I–III, data were extracted from medical records whereas in study IV information was obtained from the Swedish national quality registry for IBD (SWIBREG). Thus, data on relevant exposures and outcomes were collected from existing records and were not originally gathered to answer our specific research questions.

In paper I, patients with ulcerative colitis were identified by assessment of all medical records in the private archive of the Department of Gastroenterology, Örebro University Hospital, amended by computerized search in digital records. Since there are no private gastroenterologists in the area, and as all colonoscopies and histopathological examinations are performed at the University Hospital, we believe that our ability to detect patients diagnosed with ulcerative colitis during the study period was good. However, we cannot exclude the possibility that patients with an
indolent disease and few episodes of inflammation were more often overlooked in the early part of the study period. Correspondingly, the retrospective study design did not allow the assessment of disease activity and other potentially interesting covariates, such as smoking habits over time. On the other hand, one advantage of the retrospective ascertainment of data and the follow-up of all patients until 31 December 2015 was the possibility of correcting the diagnosis, based on information recorded later during the follow-up period. As a consequence of these limitations, we may have underestimated the incidence of ulcerative colitis during the first study period, 1963–1975. Correspondingly, the reduced risk of colectomy observed between the periods 1963–1975 and 1991–2005 may to some extent be artificial, reflecting improved detection of patients with indolent disease in recent years. However, the proportion of patients who were colectomised because of acute severe ulcerative colitis that was refractory to steroids (Table 6) was stable over the study period, and there was no significant change in the proportion of patients with extensive colitis at diagnosis during the study period, suggesting that the method used for case ascertainment was valid. Unfortunately, data on hospital admission at the time of diagnosis, which could have been used as a surrogate marker of disease severity at presentation, were not recorded.

In paper II, we examined the incidence and prevalence of anaemia in a randomized subset of IBD patients, obtained from the entire Örebro IBD cohort and consisting of (1) patients with ulcerative colitis identified in paper I and (2) Crohn’s disease patients identified through corresponding studies of Crohn’s disease in Örebro, 1963–2010.77, 115, 289 IBD patients with anaemia may often present with unspecific symptoms such as fatigue, pallor, and dyspnea on exertion, although patients with mild anaemia may be asymptomatic.346 During the study period 1 January 2011 to 31 December 2013, haemoglobin levels were measured in 332 of 342 (97%) of the patients included, with a median of 6 (2–13) samples per individual. Despite the large number of haemoglobin measurements, the incidence and prevalence estimates may have been influenced by bias—and since patients without haemoglobin measurements were considered non-anaemic, we may have underestimated the true occurrence. At the Department of Gastroenterology, Örebro University Hospital, patients with second-line IBD therapy (i.e. immunomodulators and anti-TNF agents) are followed with blood sampling—including haemoglobin measurement—every third month, while patients without these medications are followed less rigorously. To confirm that the occurrence of anaemia was
increased in Crohn’s disease compared to ulcerative colitis, we performed subgroup analysis with patients on second-line therapy excluded, and by only including patients with out-patient clinic visits during the study period.

In order to include an adequate number of patients in this study, a power calculation was performed. However, the power analysis was used to calculate the minimum sample size required to detect a difference in the occurrence of anaemia between patients with Crohn’s disease and patients with ulcerative colitis in the overall study population. The study was possibly under-powered for assessment of risk factors for anaemia and also for the subgroup analyses that were performed.

All patients diagnosed with ulcerative colitis within the catchment area of Örebro University Hospital in 1963–2010 who were treated with thiopurine drugs at any time during their disease course were included in paper III. Patients who stopped therapy within 12 months because of an adverse drug reaction were compared with patients who continued the therapy or stopped for other reasons. Generally, it was not difficult to classify patients into these two groups based on information from medical records.

The main limitation of this study is probably that no patients diagnosed after 31 December 2010 were included. The first anti-TNF agent, infliximab, was approved for maintenance therapy of ulcerative colitis in 2005; this was followed by adalimumab in 2012 and by golimumab in 2013. Furthermore, the integrin antagonist vedolizumab became available during 2014 Biological therapies have markedly improved the medical management of ulcerative colitis in patients who do not respond to or do not tolerate conventional treatment. Since the availability of other treatment options in thiopurine-intolerant patients have varied over time, all main analyses in the study were adjusted for the year of thiopurine initiation in 5-year intervals. Despite this, most of the study period was during the pre-biologic era, and the study may have over-estimated the impact of thiopurines in the medical management of ulcerative colitis in 2018.

In paper IV, SWIBREG was used to identify patients who had received vedolizumab treatment in Swedish routine care at any time since the approval (in June 2014) until 30 May 2015. The reason for not including patients who started on vedolizumab after this time was that these patients were included in a prospective study being run through the registry.

SWIBREG contains information from a broad sample of hospitals and has a national coverage rate of about 60%, although we believe that the
coverage is even better for some subgroups of patients—such as patients on biologic treatment. Data are prospectively recorded at acute referrals, at hospital admissions, and at scheduled appointments. Although the coverage of SWIBREG is not 100%, we believe that the study population in study IV was fairly representative of the vedolizumab-treated patient population in Sweden. However, participation in this study was optional for the patients. Furthermore, patients who received just a single dose of vedolizumab and then stopped might have been more easily overlooked and unrecorded by the treating clinician than patients who received several doses of the drug.

Thus, it cannot be excluded that the observed drug continuation rate was slightly over-estimated. Another limitation of the study was that data on clinical and biochemical activity were missing for some patients during follow-up. In general, these data are gathered at out-patient clinic visits, and (theoretically) patients who do well might be more likely to miss scheduled appointments. Attrition analysis, i.e. the comparison of known characteristics between patients with and without data, can be used to evaluate whether data are missing at random or whether individuals without data differ from the overall population. Unfortunately, no such analysis was done in this study. Instead, paired statistical methods to assess changes in disease severity over time were applied, i.e. only patients with data available both at baseline and during follow-up were included. In theory, the observed results could be either an over-estimation or an under-estimation of the true clinical effectiveness, although the most conservative and probably the best approach would have been to consider patients with missing data as being non-responders.

A third limitation was the absence of detailed data on intolerance. Almost one of every 10 patients stopped vedolizumab treatment because of adverse drug reactions. However, we were unable to retrieve information on type of intolerance, since this information is not recorded in SWIBREG.
General conclusions

I. Both the incidence and the prevalence of ulcerative colitis are increasing in the catchment area of Örebro University Hospital. Patients diagnosed in the period 1991–2005 had a lower risk of colectomy than patients diagnosed in the period 1963–1975. The decrease in colectomies was temporally associated with increased use of thiopurines and anti-TNF agents.

II. Anaemia is a common complication, even beyond the first years after diagnosis of IBD. The risk of developing anaemia is higher in Crohn’s disease than in ulcerative colitis. Stricturing behavior in Crohn’s disease and extensive disease extent in ulcerative colitis is associated with an increased risk of anaemia. The prognosis of anaemia, in terms of resolution of anaemia within 12 months, is worse in Crohn’s disease.

III. Thiopurine drugs have a profound beneficial effect on the natural history and long-term colectomy rates of ulcerative colitis.

IV. Despite the fact that vedolizumab-treated patients in Sweden are generally a treatment-refractory group, the majority continued the therapy after a median follow-up period of almost 1.5 years. Previous exposure to anti-TNF and elevated CRP appear to be associated with a less favourable clinical response, and female sex was found to be associated with an increased risk of intolerance.
Future perspectives

- To deal with the above-mentioned limitations in paper IV, including the absence of detailed data on adverse drug reactions and problems with missing data, a prospective observational study of vedolizumab-treated patients in Swedish clinical practice is currently being undertaken.

- Clinical trials have demonstrated the efficacy of golimumab in ulcerative colitis. However, randomized trials do not readily reflect everyday clinical practice, and the efficacy of golimumab in Crohn’s disease has not been evaluated. Two observational studies to address the clinical effectiveness of golimumab in Crohn’s disease and ulcerative colitis are currently being performed.

- Active smoking has an impact on the risk of developing IBD and also on the risk of having a complicated disease course (decreased risks in ulcerative colitis and increased risks in Crohn’s disease). On the other hand, there are no data on the effect of oral moist snuff on the disease course of IBD, and a study to address this issue is currently under way.

- Concomitant infections with *Clostridium difficile* appear to be a growing problem in IBD, and are associated with increased morbidity and mortality. A study to investigate the epidemiology and clinical outcome of *Clostridium difficile* infections based on data from our population-based IBD cohort is currently being planned.

- Sweden offers exceptional conditions for epidemiological research in the field of IBD, since almost all healthcare is publicly financed and because the Swedish personal identity number allows large-scale linkage of data from different nationwide computerized registries. Studies on the epidemiology of IBD at a national level have several advantages over single-centre studies.

- In recent years, several new drugs have been approved for use in IBD. In most cases however, the efficacy of these drugs has only been shown to be superior to that of placebo. Studies that com-
pare the efficacy of new drugs to the efficacy of currently available therapies, such as anti-TNF agents, are very much needed. In the future, it might be possible to include a randomization module in SWIBREG and to perform this type of study through the registry. In this way, the advantages of a randomized trial could be combined with the strengths of a large, unselected clinical registry.
Sammanfattning på svenska

De kroniska inflammatoriska tarmsjukdomarna (IBD) utgörs av Chrons sjukdom och ulcerös kolit. Dessa tillstånd kännetecknas av inflammation i gastrointestinal-kanalen, debuterar ofta tidigt i livet och har starkt negativ inverkan på den drabbades dagliga liv, livskvalité och arbetsförmåga. Behandlingen är i första hand medicinsk men en betydande andel av de drabbade behöver någon gång opereras på grund av sjukdomskomplikationer eller bristande svar på medicinering.

Orsaken till inflammatorisk tarmsjukdom är fortfarande okänd men under 1900-talet rapporterades en kraftig ökning i insjuknande i många delar av västvärden. Under senare år har det kommit rapporter om utplanande eller till och med minskande insjuknande i länder som tidigare haft hög förekomst, samtidigt som insjuknandet ökat i medel och låginkomstländer, där IBD tidigare varit ovanligt. Förändringarna i insjuknande har gått för fort för att kunna förklaras av genetiska faktorer och forskarvärlden har dragit slutsatsen att de betingas av okända miljöfaktorer. I delarbete I påvisar vi en femfaldig ökning av antalet insjuknande i ulcerös kolit i Örebrou under perioden 1963-2010. Orsaken till denna ökning kan inte fullständigt förklaras men minskning av cigarettrökning har sannolikt bidragit. Studien påvisar också att andelen patienter som behöver opereras gått ner, möjligen till följd av förbättrad medicinsk behandling.


Syftet med delarbete III var att undersöka långtidseffekter av behandling med så kallade thiopuriner vid ulcerös kolit. Thiopuriner är läkemedel som minskar mängden vita blodkroppar genom att hämma celldelning och användningen vid ulcerös kolit har gradvis ökat i Sverige sedan 80-talet. Omkring 30% av individer som får thiopurinbehandling slutar inom 1 år på grund av biverkningar och hittills har det varit okänt hur dessa läkemedel påverkar sjukdomsförloppet på lång sikt. I genomförandet av studien utnyttjade vi det faktum att många patienter avbryter behandlingen på grund av biverkningar och jämförde effekten mellan de som slutat
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