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MEDICAL AND SURGICAL TREATMENT OF INFLAMMATORY BOWEL DISEASE

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Medical and surgical treatment of inflammatory bowel disease

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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For past, present and future family and friends.

ABSTRACT

Inflammatory bowel disease (IBD), with its two main entities Crohn's disease (CD) and ulcerative colitis (UC), is a chronic and relapsing inflammatory condition affecting the entire gastrointestinal tract. IBD is associated with reduced health-related quality of life, substantial loss of work productivity and increased morbidity. In Sweden alone, around 70 000 persons are estimated to be affected by IBD. Treatment includes both medical and surgical therapy. In case of failure or intolerance to conventional medical therapies, remaining treatment options are surgery or newer medical therapies such as biological agents. However, a sizeable number of patients do not respond or lose response to a certain biological agent, hence there is still a need to expand the knowledge about therapeutic options in IBD. This thesis therefore aimed to explored real-world clinical outcomes of a recent biological therapy. Using registered-based data, the thesis also investigated epidemiological aspects of IBD including the validity of IBD-related surgical procedure codes and the incidence of IBD in Sweden.

In **Study I**, we validated IBD-related surgical procedure codes in the Swedish National Patient Register (NPR). We conducted the validation through patient chart review in a nationwide random sample of 262 patients with registered IBD diagnoses in the NPR between 1966 and 2014. We found high validity and high sensitivity for IBD-related surgical procedure codes in the NPR with a positive predictive value of 96.8% and a sensitivity of 94.5%. Our study indicated that the NPR is a reliable data source for researchers wanting to identify patients with a history of IBD-related surgery.

In **Studies II** and **III**, we conducted a nationwide prospective observational real-world study of clinical, biochemical and health-related quality of life outcomes in CD patients treated with ustekinumab according to clinical practice. We included a total of 114 patients initiated on ustekinumab treatment during 2017 and 2018 at 20 different hospitals. We found significant improvements of almost all outcome measures and both short-term (Study II) and long-term (Study III) response and remission to treatment. Our study contributes to the knowledge about the real-world effectiveness and safety of ustekinumab for treatment of moderate to severe CD.

In **Study IV**, we estimated the nationwide incidence of IBD and subtypes (CD, UC and IBD-unclassified) and investigated differences between age-groups and sexes in Sweden 1990-2014. We used a combination of diagnostic codes for IBD in the NPR and biopsy data from the ESPRESSO histopathology cohort to identify incident cases (N=65 908) during the study period. We found evidence of increasing incidence rates (IRs) in all subtypes 1990-2001, but signs of stabilising or decreasing IRs 2002-2014. We also showed differences in IRs between males and females related to age and calendar period. Our results contribute to the knowledge about temporal trends of IBD incidence in Sweden of importance for future research, and possibly also for healthcare resource planners.

In conclusion, this thesis gave evidence of the NPR as a reliable and valid data source for researchers wanting to identify patients with previous IBD-related surgery. It also enhanced knowledge about the real-world effectiveness of ustkinumab, beneficial for patients suffering from CD. Finally, it shed light on previous contradicting estimates of the temporal trends of the incidence of IBD in Sweden.

LIST OF SCIENTIFIC PAPERS

I. **Forss, A**, Myrelid, P, Olén, O, Everhov H, Å, Nordenvall, C, Halfvarson, J, Ludvigsson, JF
Validating surgical procedure codes for inflammatory bowel disease in the Swedish National Patient Register.
BMC Medical Informatics and Decision Making 19:217 (2019)

II. **Forss, A**, Clements, M, Myrelid, P, Strid, H, Söderman, C, Wagner, A, Andersson, D, Hjelm, F, The PROSE SWIBREG study group, Olén, O, Ludvigsson, JF, Halfvarson, J
Prospective observational study on Stelara (ustekinumab) assessing effectiveness in Crohn's disease (PROSE): a 16-week follow-up.
Scandinavian Journal of Gastroenterology, 56:6;680-686 (2021)

III. **Forss, A**, Clements, M, Myrelid, P, Strid, H, Söderman, C, Wagner, A, Andersson, D, Hjelm, F, The PROSE SWIBREG study group, Olén, O, Halfvarson, J, Ludvigsson, JF
A two-year prospective observational study on ustekinumab assessing effectiveness and health-related quality of life in Crohn's disease (PROSE)
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IV. **Forss, A**, Clements, M, Bergman, D, Roelstraete, B, Kaplan, G, Myrelid, P, Halfvarson, J, Olén, O, Ludvigsson, JF
A nationwide cohort study of the incidence of inflammatory bowel disease in Sweden from 1990-2014.
Alimentary Pharmacology & Therapeutics, doi:10.1111/apt.16735 (2021)

CONTENTS

LIST OF ABBREVIATIONS

aTNF	Anti-tumour necrosis factor
CD	Crohn's disease
CRP	C-reactive protein
eCRF	Electronic case report form
EIM	Extra intestinal manifestation
EQ-5D-5L	EuroQual 5-Dimensions 5-Levels
ESPRESSO	Epidemiology strengthened by histopathololology reports in Sweden
f-calprotectin	Fecal-calprotectin
Hb	Haemoglobin
HBI	Harvey-Bradshaw Index
HRQoL	Health-related quality of life
IBD	Inflammatory bowel disease
IBD-U	Inflammatory bowel disease - unclassified
ICD	International classification of disease
IPAA	Ileal pouch-anal anastomosis
IR	Incidence rate
IRR	Incidence rate ratio
NBHW	National Board of Health and Welfare
NPR	Swedish National Patient Register
NOMESCO	Nordic Medico-Statistical Committee
PIN	Personal identity number
RCT	Randomized controlled trial
SHS	Short Health Scale
SnoMed	Systematised Nomenclature of Medicine
SWIBREG	Swedish inflammatory bowel disease registry
UC	Ulcerative colitis

1 INTRODUCTION

Inflammatory bowel disease (IBD) mainly refers to the two disease entities of Crohn's disease (CD) and ulcerative colitis (UC), although microscopic colitis [1] is sometimes included as a third entity. IBD is characterised by chronic and relapsing inflammation in the gastrointestinal tract. The history of IBD likely stems back far beyond the modern medical history writing when pathologist Samuel W. Wilks in 1859 described a middle-aged woman with severe bowel symptoms, fever and diarrhea, calling it 'ulcerative colitis'[2]. However, she was later re-classified as having CD based on the classical signs of transmural inflammation in CD found in her autopsy. This historical note exemplifies the difficulties to sometimes distinguish between CD and UC at disease onset. In some cases, the diagnostics of IBD remains a challenge even with today's advanced technique. The clinical features of CD were first described in more detail in a research article published in 1932 by Crohn *et al*. [3] The authors referred to CD as 'regional ileitis'.

Most common signs and symptoms of IBD range from abdominal pain, anemia, anorexia, fever, weight loss and fatigue, to bloody diarrhea and severe surgical emergencies such as peritonitis and perforation [4-6]. Many patients suffer from weight loss, anemia and diarrhea already at the time of IBD diagnosis. Symptoms also vary with disease location and IBD subtype [4-6]. Symptoms do not always correlate to disease activity and severity.

IBD can have a substantial negative impact on the patients' health-related quality of life (HRQoL) and cause increased sick leave and lower work participation [7-12]. There is also evidence of subjective reductions of HRQoL such as negative impact on intimate relations [13, 14]. Monitoring of disease course with adequate and timely treatment decisions is of fundamental importance for the HRQoL of IBD patients.

This thesis investigates clinical outcomes of medical treatment and surgical and epidemiological aspects of IBD.

2 BACKGROUND

2.1 CLINICAL FEATURES OF INFLAMMATORY BOWEL DISEASE

2.1.1 Crohn's disease

CD can affect any part of the gastrointestinal tract from mouth to rectum, although the area around the ileocecal valve is a common disease location [6]. There is evidence suggesting ileal and colonic CD could be different disease entities [15]. CD is characterised by transmural inflammation involving both mucosal and submucosal layers of the intestines, causing a development of fibrosis and subsequent stenosis of the intestines [16]. The inflammation is non-continuous with so-called skip lesions, i.e. inflamed followed by non-inflamed sections of the intestines [6]. Histopathological characteristics include granulomas [16]. Clinical symptoms of CD often depend on the location of inflammation. Most common symptoms are diarrhea, often with blood or mucus, followed by weight-loss and gastrointestinal pain and fatigue [17]. Many patients suffer from complications associated with CD such as fistulas, abscesses, strictures, perianal and extra-intestinal manifestations (EIMs) [6]. EIMs are more common in CD than UC and presence or absence of EIMs can be of guidance when distinguishing CD from UC [4, 6, 17].

2.1.2 Ulcerative colitis

UC is a colorectal disease which after initial involvement of the distal part of the colon, including rectum, spreads more proximally [4]. In contrast to CD, the inflammation in UC is continuous and limited to the mucosa, however, severe UC can also present with transmural inflammation [4]. Histological characteristics of UC include irregular crypt architecture and crypt abscesses estimated to be prevalent in over than 60% of UC cases [16]. UC presents symptoms similar to those of CD. Diarrhea is the most common symptom in UC. While blood and mucus in the stool are present in around 50% of CD cases, it is even more frequent in UC [17, 18]. Patients with pancolitis often suffer from tenesmus, nocturnal defecation, rectal urgency and abdominal pain. Patients with isolated proctitis more often experience symptoms such as rectal bleeding and sometimes constipation [18]. The disease onset of UC can be severe with symptoms such as high fever, tachycardia and vomiting [4].

2.1.3 Aetiology and risk factors

The chronic inflammation characterising IBD is believed to be initiated and maintained by a complex chain of interactions between the innate and adaptive immune response, genetic susceptibility, intestinal microbiota composition, impaired epithelial barrier function and environmental factors such as smoking, food intake and use of antibiotics [19-21]. However, the aetiology of IBD is still not fully understood.

Hereditary aspects and genetic susceptibility is an important factor in the development of IBD[21]. To date, studies on the genetics of IBD suggest over 200 genetic loci associated with IBD [22, 23]. Some of which are shared between UC and CD, while others are suggested to be disease specific[22, 23]. The majority of associated genes are believed to be linked to the functioning of the immune system in the gastrointestinal tract[21, 24, 25] such as the interleukin 23 receptor (IL23R) and NOD2 genes.

There are several known environmental risk factors associated with the onset, disease progression and prognosis of IBD[19]. Smoking can be protective in UC, showing lower risk of developing UC in current than former smokers, while considered a risk factor in CD[26-29]. Medication, such as early-life exposure to antibiotics[30-32], nonsteroidal anti-

inflammatory drugs (NSAIDs)[33, 34] and oral contraceptives[35-38] has also been associated with an increased risk of developing CD and UC.

Although a causal relationship between microbial gut dysbiosis and the pathogenesis of IBD has not been shown in humans, current knowledge implies a major role of the microbiota. The potential influence of over a 100 trillion different species of bacteria, viruses, protozoa and fungi is not to be underestimated [39]. The gut microbiota plays a central role in the development of the immune system [39, 40] and IBD patients show a dysregulated immune response prone to development of chronic inflammation. There is also evidence of dysbiosis and change in the composition of the gut microbiota species compared to healthy individuals[41-49].

2.1.4 Comorbidities

Comorbidities are common in both CD and UC and can involve almost any organ systems[50]. EIMs are present in as many as 25-50% of patients with IBD[50]. Most common manifestations include spondyloarthritis[50, 51], skin manifestations, including erythema nodosum and pyoderma gangrenosum [50], and eye inflammation such as uveitis and episcleritis[52]. IBD patients have an increased risk of thromboembolic events, partly due to the systemic inflammation caused by active disease [53, 54]. There is also evidence suggesting higher risk of anxiety and depression than in the general population [55]. A particularly feared comorbidity is primary sclerosing cholangitis (PSC), [50]. The condition is associated with cholangiocarcinoma and colorectal cancer [56, 57].

2.1.5 Mortality and risk of cancer

Several studies have shown an overall increased mortality for both CD and UC compared to the general population [58-65]. This increase has been be attributed to the disease itself and to an increased risk of cardiovascular disease, serious infections and development of cancer [59]. The risk of cancer is increased for both intestinal and extra-intestinal malignancies, such as lymphoma and non-melanoma skin cancer[66, 67]. IBD patients show higher prevalence of colorectal cancer and increased mortality in such cancer compared to non-IBD controls[68, 69]

2.2 EPIDEMIOLOGY

2.2.1 Prevalence

The prevalence of IBD worldwide is influenced both by changes in incidence but also by decreasing all-cause and IBD-related mortality due to improved general health and better treatment of IBD during the past decades. Prevalence estimates for CD and UC range from around 1 and 5 cases per 100 000 persons in low prevalence countries, respectively, to around 300 and 500 per 100 000 persons in high prevalence areas like the Nordic countries and North America[70, 71]. In Sweden, more than 60 000 individuals had an IBD diagnosis in 2010, accounting for an overall prevalence of 0.65% of the Swedish population (the authors required ≥2 records of IBD in the Swedish National Patient Register (NPR) for an IBD diagnosis)[72]. There is evidence of growing prevalence globally when new cases, driven by increasing incidence rates (IRs) world-wide, induce an exponential increase in the number of prevalent IBD cases in the world[73]. Differences in sex-specific prevalence have been reported from several regions and UC is generally more common in males and CD in females[70, 74, 75].

2.2.2 Incidence

The peak onset of IBD is bimodal with the first and highest peak occurring between 15 and 25 years of age and the second between 50 and 70 years [76]. The incidence of IBD is increasing globally, with Europe, North America and Oceania showing the highest IRs[70]. A majority of studies investigating the incidence of IBD during the 20th century have shown steadily rising IRs of both UC and CD in the Western world[71]. However, since the beginning of the 21st century, several countries in the Western world report stabilising or declining IRs [73]. The most rapid increase in IBD incidence is now seen in developing countries in Africa and South America[70]. The reasons for the stabilising or declining IRs in the Western world are not fully known but could be related to changes in environmental factors, while the increasing IRs in developing countries have been suggested partly to be due to the introduction of less healthy diets and lifestyle changes[70, 77]. Some studies suggest geographical gradients of the incidence rates with decreasing incidence from West to East and North to South [77-79]. The reasons for this are not fully understood, but differences in dietary intake, genetics, environmental factors, awareness of the disease and diagnostics have been suggested as possible explanations[79, 80].

UC commonly have higher IRs than CD[70]. There are known differences in incidence between the sexes[74]. In Europe, females have lower IRs of CD than males during childhood, then shifting to higher IRs for males in adults. UC show similar IRs in males and females during childhood, while males have higher IRs than females after 45 years of age[74]. Worldwide, the IRs of CD ranges from 0.1 to around 25 per 100,000 person-years, and for UC from 0.2 to around 40 per 100 000 person-years[70]. In the Nordic countries, including Sweden, IRs between 26-40 (IBD), 16-47 (UC) and 8-22 (CD) per 100,000 person-years have been reported [81-89].

2.3 TREATMENT OF INFLAMMATORY BOWEL DISEASE

2.3.1 Treatment options

Treatment of IBD stands on three pillars: medical treatment, surgery and nutritional support. The treatment aims to achieve and maintain disease remission, avoid complications and hospitalization and reduce disease impact on HRQoL. Treatment decisions must be based on a multidisciplinary approach involving several medical specialties, including gastroenterology, surgery, radiology and pathology[90]. Despite existing advanced treatment options, complications and disease flares are common in both UC and CD. Hence, there is still a need for novel therapeutic alternatives.

2.3.2 Medical treatment

Medical treatment of IBD is traditionally based on a step-up approach where corticosteroids, aminosalicylates and thiopurines form the therapeutic basis. In case of intolerance or failure to such treatment, remaining treatment alternatives include methotrexate and biological agents.

When the first biological agent, anti-tumour necrosis factor (aTNF), was introduced some 20 years ago it was seen as a major paradigm shift in the treatment of IBD, especially in severe cases[91]. Treatment with aTNF agents have since then become the mainstay of medical therapy for both UC and CD. Today's aTNF alternatives include infliximab, adalimumab, golimumab and certolizumab. Treatment with aTNF has shown effectiveness in achieving both short-term and long-term remission [92-94] and reduced risk of both hospitalisation and surgery[95]. However, a sizeable number of around 40% treated are non-responders, intolerant to or experience secondary loss of response to aTNF treatment[96-100]. For those

patients, a class switch to other biologics such as anti-integrin antibody (vedolizumab) [101, 102], IL-12/23-inhibitor (ustekinumab) [103-106] or JAK-inhibitor (tofacitinib)[107, 108] treatment are possible options. According to Swedish clinical treatment guidelines, aTNF, anti-integrin antibody and IL-12/23-inhibitor therapies are recommended in both UC and CD, depending on disease location and phenotype [109, 110].

The IL-12/23-inhibitor ustekinumab was approved in Europe in 2016 for treatment of adults with moderate to severe CD. In pivotal trials, ustekinumab has shown efficacy in achieving response and remission as induction and maintenance therapy in moderate to severe CD[106, 111] and in UC[112]. The follow-up pivotal trial on maintenance therapy with ustekinumab in CD showed that between 38-43% of initial responders were in remission after 152 weeks[103]. Several short-term observational studies have confirmed the efficacy of ustekinumab in CD[113-119], however long-term studies are limited and further studies with longer follow-up time are warranted[120-123]. Furthermore, the optimal dosing intervals and drug concentration levels need to be further investigated in a real-world setting.

Despite the recent development of IBD treatment and new medical treatment options, sufficient knowledge about optimal dosage intervals, possible combination therapies with immunomodulators and biologics in different disease phenotypes and age-groups, optimisation of drug concentration levels as well as predictors for response and remission are still largely lacking. There is also a need for head-to-head randomized controlled trials (RCTs) comparing clinical outcomes between existing biological agents in different patient cohorts and with different patient phenotypes.

2.3.3 Surgical treatment

The benefits of surgery as treatment of severe UC was demonstrated already in the 1950s by the British surgeon Sidney Truelove and his colleagues [124]. The introduction of surgery lowered the mortality in UC. The surgical methods have since then steadily evolved, via introduction of ileal pouch-anal anastomosis (IPAA) in the 1980s [125], through development of minimal invasive laparoscopic and robotic surgery [126, 127]. Today's surgical options in CD[128] include strictureplasty[129], segmental resections[130], ileorectal and ileocolonic anastomosis and temporary or permanent ileostomy/colostomy, whereas in UC[131] the primary options are subtotal colectomy with ileostomy or ileorectal anastomosis, proctocolectomy with permanent ileostomy, IPAA or continent ileostomy according to Kock[132, 133].

In cases of severe or treatment refractory disease, surgery is sometimes the only remaining treatment alternative. About approximately 50% and 20% of patients with CD and UC respectively undergo surgery during their lifetime[126, 134-139]. There is some evidence of decreasing surgery rates in Sweden with lower rates of colectomies in patients with UC during the most recent decades[85]. Similar trends with decreasing rates of primary, however, not secondary surgery, have also been shown for CD in Sweden and other regions[135, 140]. This is thought to be, at least partially, a consequence of the introduction of more effective medical treatment with immunomodulators and biological agents during the past decades.

Because of the disease characteristic with skip lesions, surgery is rarely curative in CD, whereas colectomy in UC can radically decrease the disease burden, improving short- and long-term HRQoL[141-143]. IBD-related abdominal surgery is elemental also for the treatment of colorectal cancer, a feared complication of long-standing colonic IBD[144]. It is sometimes said that "less is more" for surgery in CD, while for UC it is somewhat the other way around. However, the role and timing of IBD-surgery in the era of biologics remain to be further investigated[126, 145-147].

2.3.4 Other treatment options

Nutritional support is an integral part of IBD treatment mainly focusing on avoiding dietary triggers of disease flares and preventing malabsorption, a common problem in IBD. In children with CD, nutritional treatment may even constitute a primary treatment option[148, 149]. Different diets are suggested to be involved in the pathogenesis and disease activity of IBD, where dietary components such as high fibre or fat intake have been investigated[19, 150, 151]. Even with a large number of studies in this field, evidence supporting a specific diet or dietary supplement for treatment of IBD is lacking[152-155].

Fecal microbiota transplantation can modify the gut microbiota, however the biochemical and immune response mechanisms involved are still largely unknown[156, 157]. Optimal donor and host match is not clear, neither are there any consensus on the way to administer the fecal transplant. Further research in this field is therefore warranted.

3 AIMS AND RESEARCH QUESTIONS

The studies included in this thesis address research questions related to medical and surgical treatment as well as epidemiological aspects of IBD. The overarching aim is to provide further knowledge about advanced medical treatment of IBD for improved treatment decision making, ultimately beneficial for the individual IBD patient. Furthermore, it aims to provide epidemiological evidence on the temporal trends of the occurrence of IBD to support health care planning to meet the needs of the IBD patient population. Finally, it also aims to validate register-based data of surgical procedure codes used by researchers to study the epidemiology and outcomes of IBD-related surgical interventions. The study-specific research questions are summarised in Figure 3.

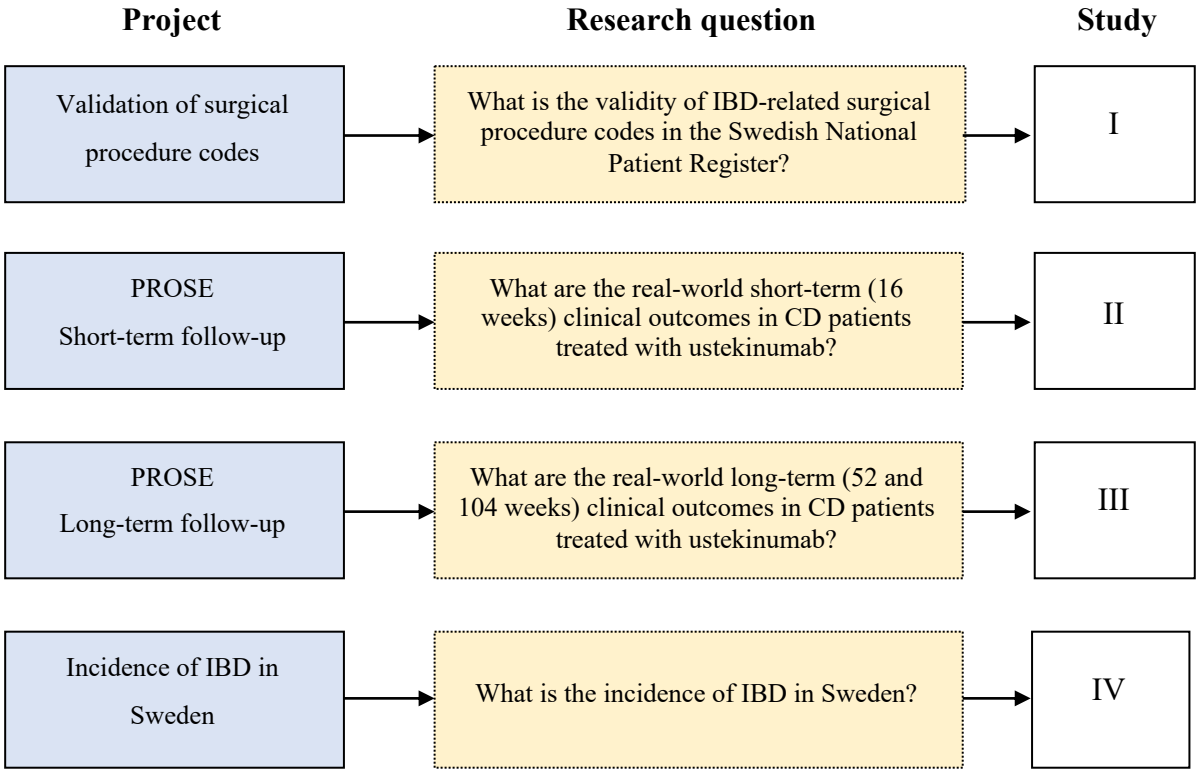

Figure 3 Overview of studies and research questions included in this thesis

CD, Crohn's disease; IBD, inflammatory bowel disease; PROSE, PRospective Observational study on Stelara assessing the Effectiveness in Crohn's disease.

4 DATA SOURCES AND LINKAGE

4.1 TOTAL POPULATION REGISTERS

Swedish National Patient Register
The Swedish National Patient Register (NPR) was formed in 1964. It is governed and maintained by the National Board of Health and Welfare (NBHW). In 1987, the NPR became nationwide. It contains data about inpatient care such as discharge diagnoses according to the International classification of disease (ICD) codes, dates of hospital admission and discharge alongside data on medical and surgical procedure codes. All data in the NPR are linked to the Swedish personal identity number (PIN) assigned to all legal residents in Sweden [158]. Since 2001 the NPR also includes information on outpatient visits in specialised medical and surgical healthcare lending the NPR an almost 100% coverage of all inpatient visits. The coverage of outpatient visits is estimated to around 80% [159]. Both public and private caregivers are mandated according to Swedish laws and regulations to register patient data in the NPR, however primary care providers is not subject to these regulations [159].

Surgical procedure codes have been registered in the NPR since the founding of the register in 1964. However, in 1993 it became mandatory to register such codes, and in 1997 mandatory registration of day surgery was also introduced [160]. Since 2001, all types of medical procedures (i.e. also non-surgical) became mandatory to report [159]. A new classification system for surgical procedure codes based on an American classification version was introduced by the NBHW when the NPR was founded. The system used four digit-codes (e.g. 4642 ileocaecal resection). It was replaced in 1997 by an adapted version of the Nordic Medico-Statistical Committee Classification (NOMESCO) of Surgical Procedures using five-character alpha-numeric coding (e.g. JFB20 ileocaecal resection) [161]. This system is still in place and codes are continuously revised by the NBHW. All procedures with codes are listed in the publication Swedish Classification of surgical and medical procedures (in Swedish: “KVÅ” – klassifikation av vårdåtgärder) [162].

4.2 OTHER REGISTERS AND DATABASES

Swedish inflammatory bowel disease register
In addition to the NPR, the Swedish Inflammatory Bowel Disease Register (SWIBREG)[163] is an important source of data in IBD research. SWIBREG is a nationwide quality register for IBD formed in 2005. To date, it covers more than 80% of the Swedish IBD population (n=53 885 patients) (annual report 2021). SWIBREG includes data on CD phenotype, disease activity, treatment (including extensive data on biological treatment), smoking and HRQoL measurements. Together with the NPR it provides extensive data about the Swedish IBD population for epidemiological and clinical research [164].

Epidemiology strengthened by histopathology reports in Sweden - ESPRESSO cohort
The nationwide gastrointestinal ESPRESSO histopathology cohort [165] comprises histopathology reports from 2.2 million unique individuals with around 6.1 million separate data entries. Data includes histopathology reports between 1965-2017 collected from all (n=28) pathology departments in Sweden. Through the unique PIN, data in the ESPRESSO cohort were linked to the NPR. Histopathology reports include codes of topography and morphology, according to a Swedish modification of the Systematised Nomenclature of Medicine (SnoMed) coding system.

4.3 ETHICAL CONSIDERATIONS

The obligation to minimize the impact of research studies on the mental, physical and social integrity of the individual in research involving human subjects is specifically underlined in the 2013 Declaration of Helsinki [166]. Ethical aspects of studies included in this thesis were thoroughly discussed before initiation and adequate measures to minimize potential harm and breach of integrity of the individual study participants were taken.

In **Study I**, all medical charts used for validation had been created under a patient-doctor confidentiality. Reviewing such charts violates this confidentiality without the consent of patient or doctor. As discussed elsewhere, the principle of informed consent does not necessarily apply to a register-based study such as chart review in Study I [167]. However, absence of informed consent warrants a considerable degree of confidentiality from the investigator when reviewing patient data in the charts. Number of investigators given access to the charts was therefore kept to a minimum and the charts were safely stored at the Department of Medical Epidemiology and Biostatistics (MEB), according to the guidelines for good data management practice at Karolinska Institutet. One gold standard for validating surgical procedure codes in the NPR is through manual chart review and the aim of Study I could not have been achieved by other research methods. The results of this study allow researchers to assess the efficacy of IBD-related surgery and study complications among various subgroups of IBD patients based on the knowledge of the sensitivity, specificity, positive and negative predictive value of the validated codes.

Studies II and **III** included human subjects and were therefore subject to the regulations about informed consent according to national and international law [166, 168]. Ethical aspects such as informed consent, and the right of withdrawal of such at any point after inclusion, and strict confidentiality of collected data are stipulated in the study protocol of Studies II and III. Collected data were securely stored on encrypted servers and only the research team had access to the full set of collected data. To ensure the integrity of study participants, data were managed and analysed anonymously with a key file stored separate from the dataset used for statistical analyses. The individual treating physician independently decided to initiate the patient on the studied treatment according to clinical practice and treatment guidelines. Studies II and III did not impose any additional risk to the participating patient since only observational data were collected. The potential benefits for a large group of patients with moderate to severe CD outweighs the possible breach of integrity of the study subjects in these studies.

Study IV is a register-based study and therefore exempted from the regulations about informed consent as discussed above. Data from the included registers (NPR) and databases (ESPRESSO) were compiled in a dataset through which no individual could be identified. Personal identity numbers were only used for linkage and data were analysed anonymously. The breach of patient integrity was therefore be kept to a minimum. Possible breaches of patient integrity must be weighed against the contribution to the understanding of temporal trends of the incidence of IBD in Sweden. Such knowledge is fundamental for observing time-dependent trends and possible influence and changes of risk factors for IBD.

5 METHODS

An overview of study design, study population, main outcome measures and statistical methods applied in the studies included in the thesis is presented in Figure 5.

Study	Study design	Study population	Outcome measures	Statistical analysis
I	Register-based study with patient chart review	Random nationwide sample of patients with IBD diagnosis in the NPR during 1966-2014	PPV and NPV Sensitivity and Specificity	Bootstrap analysis
II	Multicenter prospective observational study	Patients with active CD initiated on ustekinumab in Sweden during Jan 23, 2017 to Nov 22, 2018	Clinical and biochemical response and remission HRQoL	Survival analysis Univariable/multivariable logistic regression
II	Multicenter prospective observational study	Patients with active CD initiated on ustekinumab in Sweden during Jan 23, 2017 to Nov 22, 2018	Clinical and biochemical response and remission HRQoL	Survival analysis Univariable/multivariable logistic regression
IV	Register-based study	Patients in Sweden with IBD diagnosis in the NPR during 1990-2014	Incidence rates Incidence rate ratios Cumulative lifetime incidence	Poisson regression

Figure 5 Overview of study design, study population, outcomes and statistical methods in studies included in the thesis

CD, Crohn's disease; HRQoL, health-related quality of life; IBD, inflammatory bowel disease; NPV, negative predictive value; PPV, positive predictive value.

5.1 STUDY DESIGN AND STUDY POPULATION

5.1.1 Validation of diagnostic codes in healthcare registers

The use of quality data from healthcare registers is elemental for medical research. Knowledge about the validity of register-based data is important when designing studies and also for the interpretation of results. Validation studies can answer research questions about the validity and quality of data and expose potential sources of misclassification and administrative biases in registers. One gold standard for validating diagnostic and procedure codes is manual patient chart review. Such review allows for accurate comparison of the actual notes in the patient chart with codes in the register. However, chart review is time-consuming, needs a structured methodological approach and the quality of the results depends on the competence of reviewers.

In Study I, we validated surgical procedure codes in the NPR through manual patient chart review. A total of 262 patient charts from a nationwide random sample between 1966 and 2014 were reviewed for IBD-related surgical procedure codes and checked against data in the NPR. The review used a study specific standardised methodology for validating procedure codes in the patient charts against the NPR described in Figure 5.1.1.

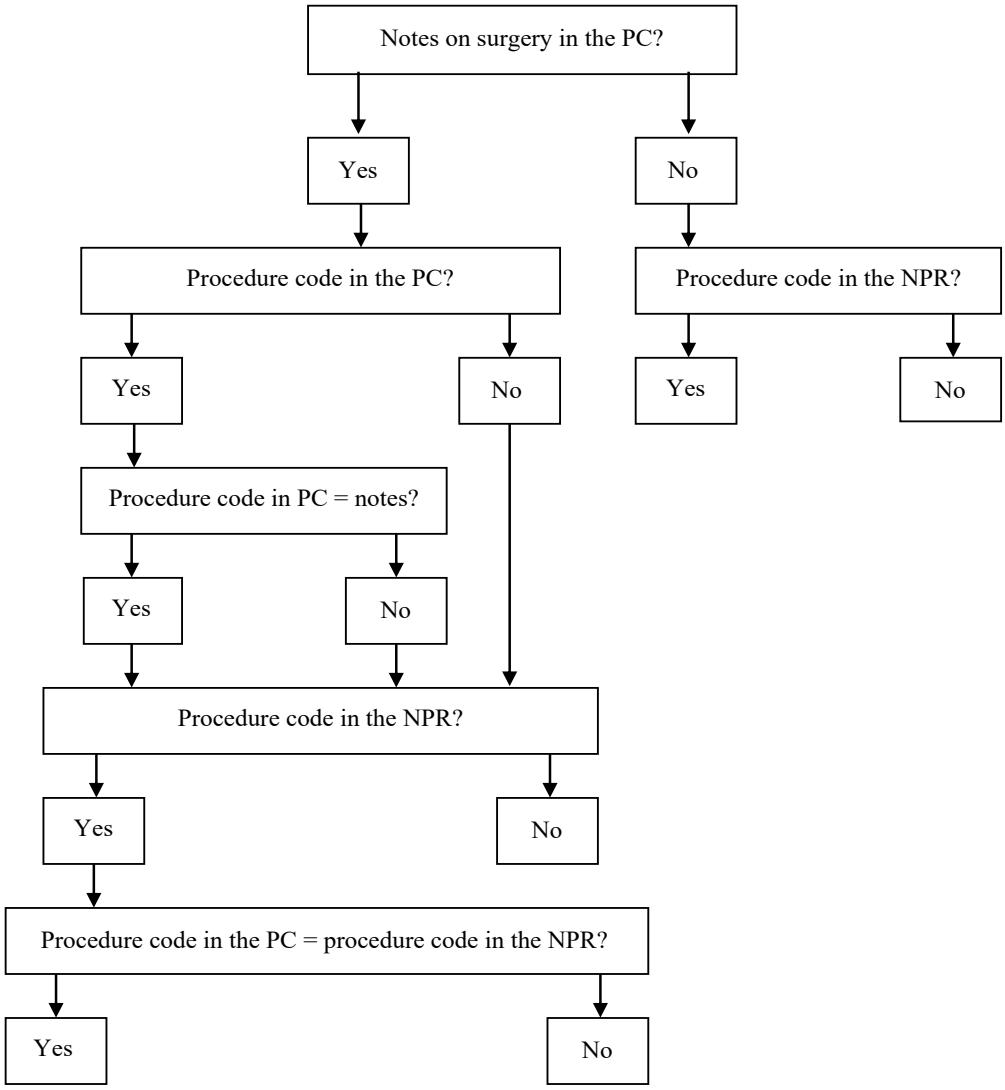

Figure 5.1.1 Flowchart of chart review for IBD-related surgical procedure codes
PC = patient chart, NPR = national patient register

5.1.2 Prospective observational cohort study design

Important elements of a cohort study design include recruiting and longitudinal follow-up of a selected study population. To enter the cohort the study participant needs to be free from the outcome at entry. The cohort is followed for a period (follow-up time) to observe and detect the outcome of interest. A prospective observational study cohort design observes study participants longitudinally from time of inclusion until end of study period or end of follow-up by other reasons such as death, emigration, lost-to follow up and withdrawal of consent. Strengths of a prospective observational cohort study design include clear temporal pattern of the outcomes and reduced risk of reporting bias since data are reported at follow-up time points and not retrospectively.

Studies II and **III**, used a multicenter prospective observational study design to collect real-world clinical data about patients treated with ustekinumab. In these studies, the individual physician independently decided on the initiation of ustekinumab treatment according to national clinical treatment guidelines and clinical practice. Data were collected at pre-defined follow-up timepoints using a study specific electronic case report form (eCRF). Collected data included biochemical inflammatory markers and clinical information on disease activity in accordance with standard clinical practice. No additional study specific data were requested. A total of 114 patients were included between 23 January 2017 and 22 November 2018. At end of study period (104 weeks), 69 patients remained on ustekinumab.

5.1.3 Register-based epidemiological study design

Register-based study designs to investigate the occurrence of disease enable researchers to include large study populations. By linking data in different registers together through an individual identification number epidemiological outcomes can be studied in a cost-efficient and less time-consuming way than requiring data from each individual. However, the robustness of the results depends on the quality and validity of the data in the registers. The Swedish national population registers (4.1 and 4.2 above) provide unique opportunities for epidemiological research in large populations cohorts.

To study the incidence of IBD and subtypes during 1990-2012, **Study IV** used data on IBD diagnoses in the NPR and biopsy data in the ESPRESSO cohort linked together with an individual PIN for each patient. A total of 65 908 incident cases of IBD (UC, n=38 261; CD, n=18 577; IBD-unclassified (IBD-U), n=9 070) were identified between 1990-2014. The main strengths of this study are the large number of included cases and the combination of biopsy data and diagnostic codes. This diagnostic approach has previously showed high validity for similar data[32, 164].

5.2 MAIN DEFINITIONS AND MEASUREMENTS

5.2.1 Inflammatory bowel disease

There is no existing single gold standard for diagnosis of IBD and subtypes[169]. The diagnostic assessment includes a combination of endoscopic, clinical and histopathological data. In the studies included in this thesis, different definitions of IBD and subtypes were used to fit the study designs applied.

In the validation study (**Study I**) we included IBD patients with at least one ICD diagnosis of IBD (ICD-9: CD 555, UC 556 or ICD-10: CD K50, UC K51) registered in the NPR. In the observational study of utstekinumab (**Studies II** and **III**), our diagnosis of CD was based on the clinical assessment of the including physician. In **Study IV**, we used data on SnoMed classified biopsies from the ESPRESSO cohort consistent with CD (SnoMed codes: T62-68,

D6216, M41-M44, M463 and M47), UC (T67-68, D6255, M41-M44, M463 and M47) and IBD-U (T67-68, D6214, D6216, D6255, M41-M44, M463 and M47). These codes were combined with ≥1 biopsy consistent with IBD (UC, CD or IBD-U). To define incident cases we also requested ≥1 concordant ICD code for IBD (CD (ICD-9/10: 555/K50 all sub-classifications), UC (ICD-9/10: 556/K51 all sub-classifications) and IBD-U (ICD-10: K52.3)) registered in the NPR.

5.2.2 Measures of validity

Main outcome measures in **Study I** were sensitivity, specificity and PPV and NPV. Sensitivity was calculated as the proportion of surgical procedure codes in the patient charts also present in the NPR and specificity as the proportion of charts negative for IBD-surgery also negative for such surgery in the NPR. PPV was expressed as surgical procedure codes in the NPR with concordant surgery in the patient charts and NPV as absence procedure codes in the NPR and also absence of codes in the patient charts.

5.2.3 Clinical and biochemical outcomes

Different clinical assessment indices are used to monitor disease activity in IBD. Crohn's Disease Severity Index (CDAI)[170] and Mayo Score (DAI) [171, 172] are commonly used indices in CD and UC respectively. They include both objective data such as number of soft/liquid stools last day/days and subjective self-assessed well-being. Harvey-Bradshaw Index (HBI), is used for clinical assessment in both UC and CD[173]. It captures items presented in Figure 5.3.2. HBI is often used when assessing treatment response and remission in clinical studies, were a HBI score of ≤4 points commonly is defined as remission and a ≥3-point-decrease of HBI as response. **Studies III** and **IV** used HBI to assess remission and response, applying above presented cut offs. For evaluation of biochemical outcomes we used haemoglobin (Hb), C-Reactive Protein (CRP) as a general marker of inflammation and faecal-calprotectin (f-calprotectin) as a marker of gastrointestinal inflammation. In contrast to HBI, the latter inflammatory markers have shown a potential to predict active mucosal healing [174-176].

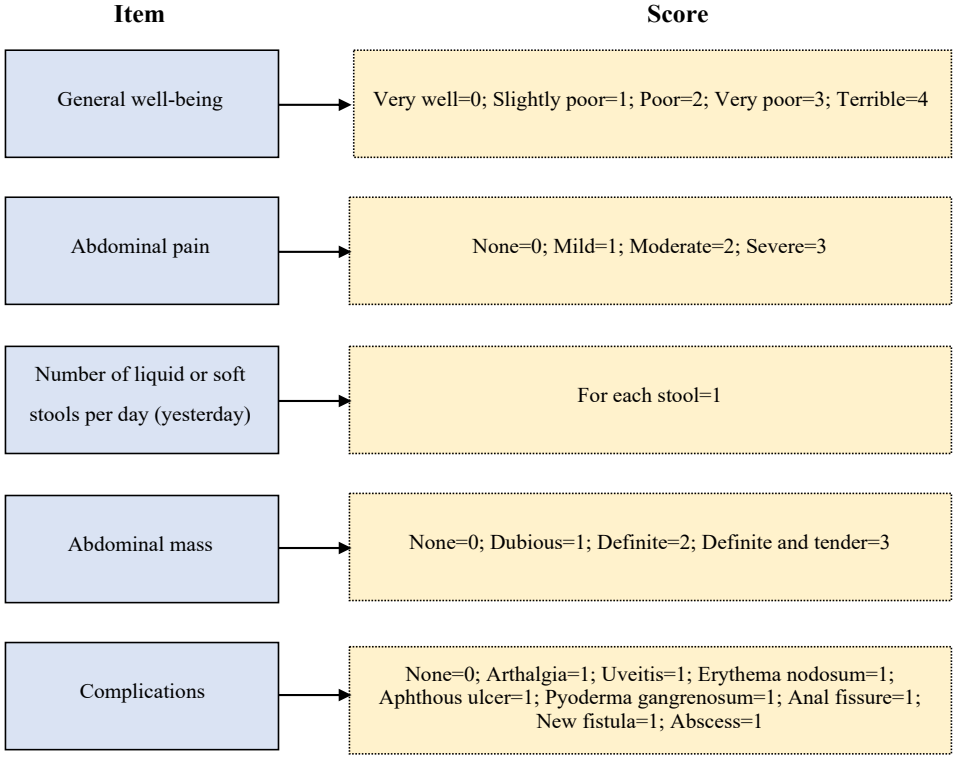

Figure 5.3.2 Harvey-Bradshaw Index

5.2.4 Health-related quality of life

To capture the possible impact on HRQoL in CD patients treated with ustekinumab in **Studies II** and **III** we used Short Health Scale (SHS)[177, 178] and EuroQual 5-Dimensions 5-Levels (EQ-5D-5L)[179]. The SHS is a valid instrument for assessing subjective HRQoL in both CD and UC [177, 178]. SHS includes four patient-reported dimensions of HRQoL, including social function/activity, bowel symptom burden, worry and general well-being. Each item is scored from 0 to 5, ranging from no problem (0) to worst imaginable state (5)[177]. The EQ-5D-5L includes five self-reported generic dimensions of HRQoL, mobility, self-care/hygiene, usual/daily activities, pain/discomfort and anxiety/depression[179]. It also includes a visual analogue scale (VAS) for assessment of current health state, ranging from 0 to 100, representing the worst (0) to the best possible state (100). The responses to each dimension are converted into a compound index score where 1.0 represents best possible wellbeing. The EQ-5D-5L instrument is often used for reasons of simplicity and comparability. It has been validated and shown comparably high validity also in an IBD population[180].

5.2.5 Incidence

Incidence describes the number of new cases of disease in a population at risk of getting the disease. In **Study IV**, we calculated the incidence of IBD and subtypes (according to the definition described above, 5.2.1) in Sweden between 1990 and 2014 presented as IRs per 100 000 person-years in the total Swedish population. We also calculated incidence rate ratios (IRRs) comparing the IRs between males and females, defining IRR as the IR for males divided by the IR for females.

5.3 STATISTICAL METHODS

In **study I**, measures of validity (PPV, NPV, sensitivity and specificity) were calculated with 95% confidence intervals (CIs) using a two-step bootstrap analysis clustered for hospital in strict hierarchy with a total of 10 000 re-samplings [181, 182].

In **studies II and II,** we calculated proportions of patients with response or remission and changes in median values for biochemical outcome measures with interquartile ranges. Comparisons between groups were tested by Wilcoxon signed-rank test. Drug survival rates were presented in a plot using the Kaplan-Meier curves. Univariable and multivariable logistic regression [183] was used to investigate possible predictors for remission (binary outcome). The threshold for statistical significance was set to *p-value* >0.05.

In **study IV**, Poisson regression [184] was used to calculate the age-standardised IRs per calendar year and age-group. We also used Poisson regression to investigate if the IRRs between the sexes vary by introducing an interaction term between sex and calendar period or age. Cumulative life-time incidence of IBD was calculated using a competing risk, which is interpreted as a probability of an IBD diagnosis across a life-time [185]. We used a threshold for statistical significance of *p-value* >0.05.

6 MAIN FINDINGS

6.1 VALIDITY OF IBD-RELATED SURGICAL PROCEDURE CODES IN THE SWEDISH NATIONAL PATIENT REGISTER (STUDY I)

We validated IBD-related surgical procedure codes through manual patient chart review in a nationwide random sample of 262 patients with IBD diagnoses registered in the NPR between 1966 and 2014. We identified 57 patients (22%) with a total of 158 individual surgical procedure codes in the NPR, representing 60 different types of codes. Of these, 155 were also present in the patient charts and 153 were concordant with the surgical notes in the patient charts, corresponding to a PPV (n=153/158) of 96.8% (95%CI=93.9-99.1). In the patient charts, we identified 164 surgical procedure codes, of which 155 were registered in the NPR, corresponding to a sensitivity of 94.5% (95%CI=89.6-99.3). The specificity of the NPR for these codes were 98.5% (95%CI=97.6-100).

Table 6.1 Positive predictive value, sensitivity and specificity of the Swedish National Patient register for IBD-related surgical procedure codes (n=258 patients)

	Chart review	
NPR	Patient chart positive for IBD-related surgery (n=53 patients; N=164 codes)	Patient chart negative for IBD-related surgery (n=205 patients)
Code for IBD-related surgery (Concordant code in NPR)	155 (153)	3
No corresponding code for IBD-related surgery	9	202
Patients with no code in the NPR	2	
PPV (true positives, 95%CI)	98.7 (96.3-100) 153/155	
PPV (concordant codes, 95%CI)	96.8 (93.9-99.1) 153/158	
Sensitivity of the NPR (95%CI)	94.5 (89.6-99.3) 155/164	
Specificity of the NPR (95%CI)		98.5 (97.6-100) 202/205

CI = confidence interval, IBD = inflammatory bowel disease, NPR = national patient register, PPV = positive predictive value
PPV of true positives calculated from surgical procedure codes in the NPR present in the charts (n=155) and codes confirmed by chart review. (n=153). PPV of concordant codes calculated from all surgical procedure codes in the NPR (n=158) and codes confirmed by chart review (n=153).

6.2 REAL-WORLD CLINICAL OUTCOMES OF USTEKINUMAB TREATMENT IN CROHN'S DISEASE (STUDIES II AND III)

In a nationwide prospective multicentre observational study of 114 patients initiated on ustekinumab according to routine clinical care in Sweden at 20 Swedish hospitals we assessed clinical (HBI) and biochemical response (Hb, CRP and f-calprotectin) at weeks 16, 52 and 104 compared to baseline. We also reported changes in HRQoL measures (EQ5D-5L and SHS) during follow-up. Of included patients, nearly all (94%, n=107) had a history of treatment with one previous biological drug and half (51%, n=58) had failed ≥2 such treatments. One third (35%, n=40) had failed treatment with anti-integrin antibody agents. At initiation of treatment, concomitant treatment with corticosteroids and immunomodulators was seen in 18% (n=21) and 23% (n=26) of patients, respectively. At baseline, 72% (n=69/96, missing: n=18/114) had a HBI score ≥5.

We observed clinical remission (≤4 points) in 26%, 32% and 29% of included patients after 16, 52 and 104 weeks, respectively (Figure 6.2.1). The corresponding clinical response rates (≥3-point-decrease of HBI) were 33%, 36% and 29% (Figure 6.2.1). Weeks 52- and 104-response or remission was observed in 44% and 32%, respectively. The median HBI

decreased at all follow-up timepoints compared to baseline (Figure 6.2.2). We also saw statistically significant reductions of median levels of CRP and improvement in HRQoL measures throughout the study period compared to baseline. Drug survival rates were 92% (n=104/114), 70% (n=80/114) and 61% (n=69/114) at weeks 16, 52 and 104, respectively.

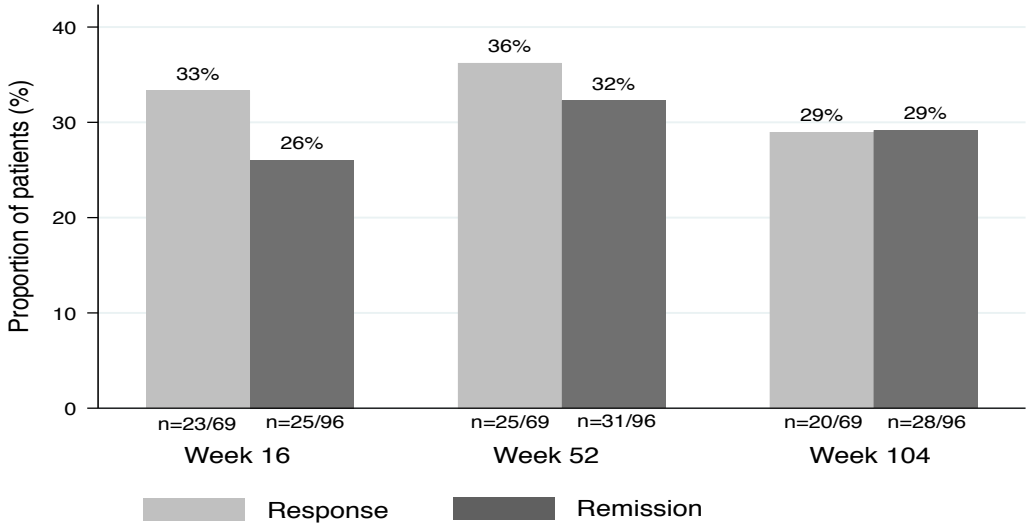

Figure 6.2.1 Clinical response and remission
Proportion of patients (%) with Harvey-Bradshaw Index (HBI) score ≥5 at baseline (n=69) and response (≥3-point-decrease of HBI) after 16, 52 and 104 weeks. Proportion of patients (%) in clinical remission (HBI score ≤4 points) after 16, 52 and 104 weeks among patients with HBI scores at baseline (n=96).

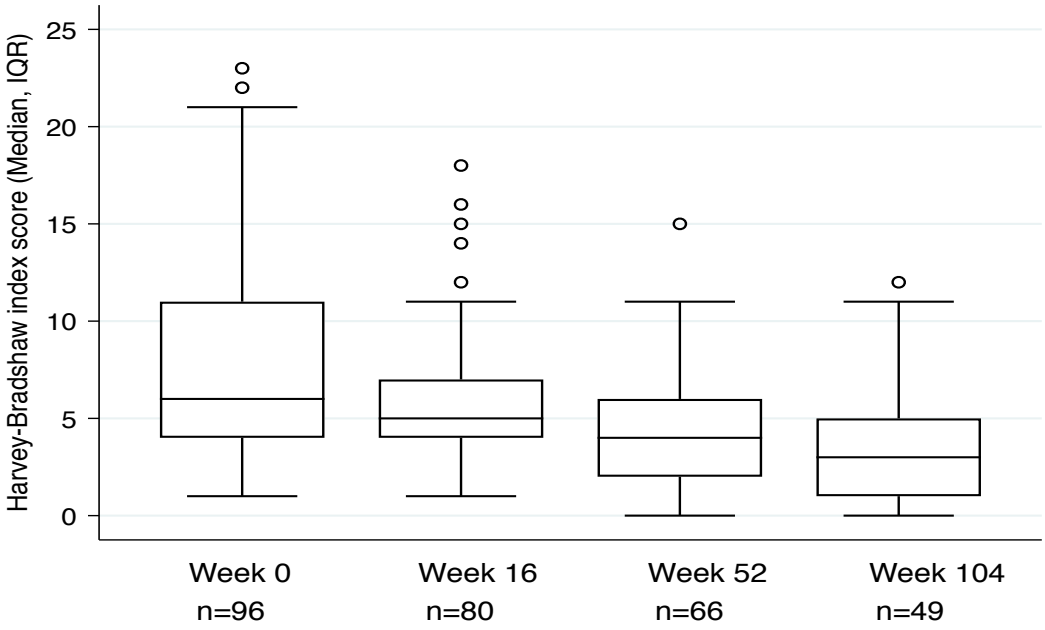

Figure 6.2.2 Median Harvey-Bradshaw Index score during follow-up
Box plot of Harvey-Bradshaw Index scores at baseline, weeks 16, 52 and 104.

6.3 INCIDENCE OF INFLAMMATORY BOWEL DISEASE IN SWEDEN (STUDY IV)

We calculated the incidence of IBD and subtypes in Sweden based on biopsy reports and ICD diagnoses registered between 1990 and 2014. We identified a total of 65 908 incident cases of IBD. The mean annual age-standardised IR per 100 000 person-years for IBD during 1990 to 2014 is 29.0 (95%CI=27.3-30.7) (Table 6.3.1). The corresponding numbers for UC and CD are 16.9 (95%CI=15.9-17.9) and 8.1 (95%CI=7.7-8.6), respectively. The annual IR for IBD, UC and CD increased by around 7% (p<0.001) between 1990 and 2001 but decreased by 1-2% (p <0.001) between 2002 and 2014 (Table 6.3.2).

Table 6.3.1 Mean annual age-standardised incidence rates of overall IBD and by subtype per 100,000 person-years in Sweden 1990-2014

	IBD	UC	CD	IBD-U†
Period	**Incidence rate/100,000 person-years (mean, 95% CI)**			
1990 - 2014	29.0 (27.3-30.7)	16.9 (15.9-17.9)	8.1 (7.7-8.6)	-
1990 - 2001	25.6 (22.7-28.6)	15.8 (13.9-17.7)	7.3 (6.5-8.0)	-
2002 - 2014	32.1 (31.4-32.8)	17.9 (17.2-18.7)	9.0 (8.7-9.3)	5.2 (4.9-5.6)

CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease unclassified; UC, ulcerative colitis.
†For IBD-U we restricted the period to 2002-2014 as a diagnostic code for IBD-U was introduced only in 1997 and outpatient data were included in the Swedish National Patient Register since 2001.

Table 6.3.2 Mean annual change of incidence rates of overall IBD and by subtype per 100,000 person-years in Sweden 1990-2014

	IBD	UC	CD	IBD-U†
Period	**Change in incidence rate/100,000 person-years (mean %, 95% CI)‡**			
1990-2014	1.8 (1.7–2.0)	1.0 (0.9–1.2)	1.7 (1.5–1.9)	-
1990-2001	7.6 (7.2–7.9)	6.9 (6.4–7.4)	7.0 (6.3–7.7)	-
2002-2014	-1.1 (-1.3 – -0.8)	-2.2 (-2.5 – -1.8)	-1.3 (-1.8 – -0.8)	3.1 (2.4–3.7)

CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease unclassified; UC, ulcerative colitis.
†For IBD-U we restricted the period to 2002-2014 as a diagnostic code for IBD-U was introduced only in 1997 and outpatient data were included in the Swedish National Patient Register since 2001.
‡ Adjusted for age and sex.

Our results show differences in IRs and temporal trends between males and females. Males show higher overall IRs for IBD, UC and IBD-U, while the IR for CD is higher in females (Figure 6.3.1). The male to female incidence rate ratio (IRR) varies by age for UC (p=0.013) and CD (p=0.006) with increasing IRRs in UC and decreasing in CD with older ages (Figure 6.3.2). The IRRs also vary by calendar periods for IBD (p=0.009), UC (p <0.001) and CD (p=0.009) with attenuation of the IRRs over time. We estimate that 1 in 40 individuals in Sweden is expected to be diagnosed with IBD during their lifetime.

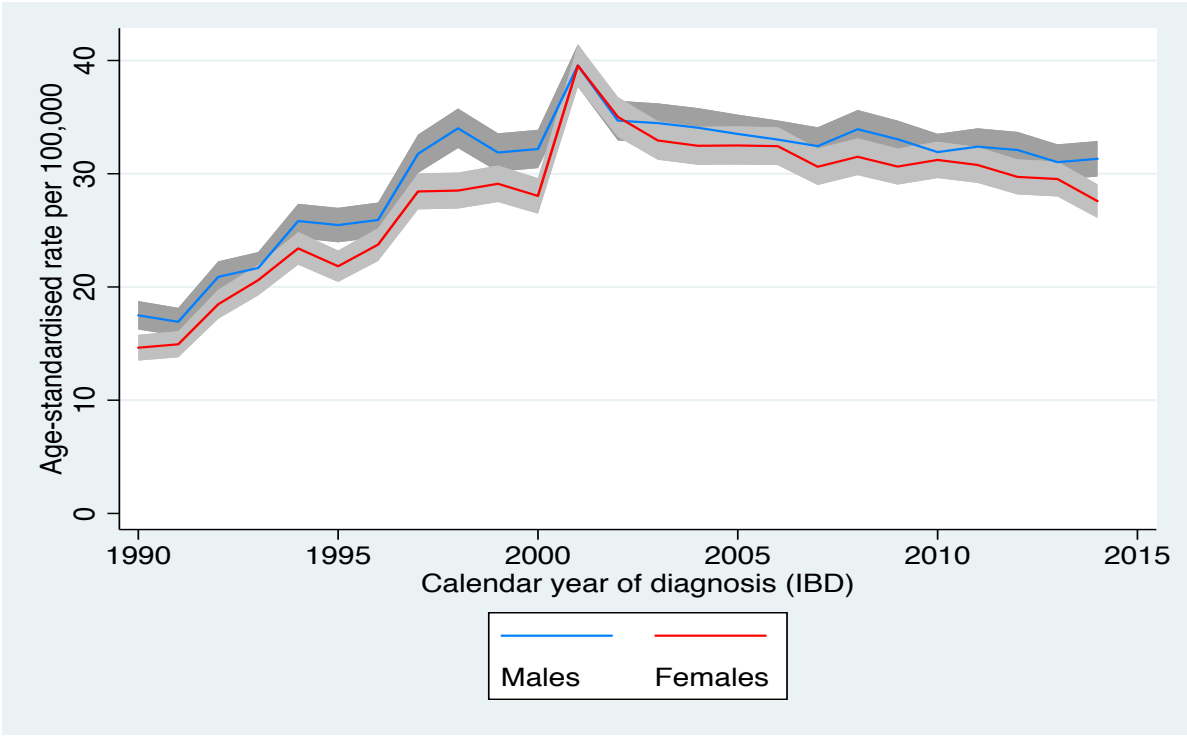

Figure 6.3.1 Age-standardised incidence rates of inflammatory bowel disease (IBD) per calendar year, stratified by sex.

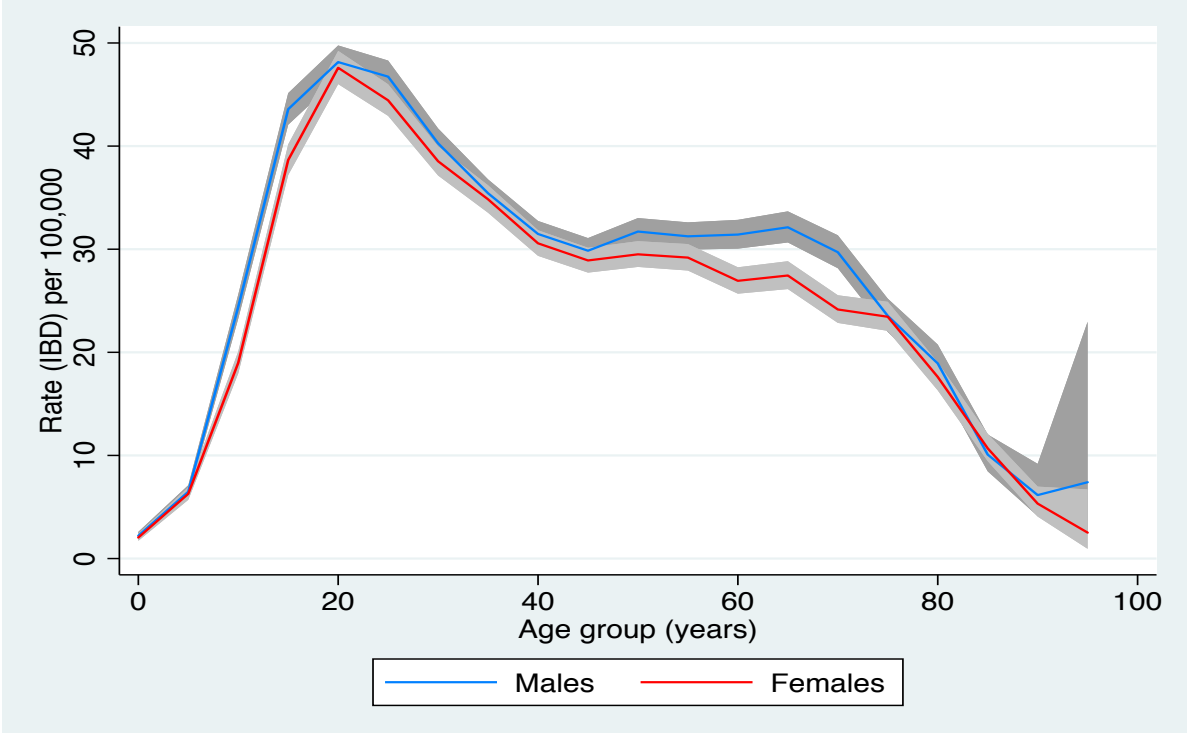

Figure 6.3.2 Age-specific incidence rates of inflammatory bowel disease (IBD)

7 DISCUSSION

7.1 METHODOLOGICAL CONSIDERATIONS

7.1.1 Study design

In **Study I**, we performed manual chart review to validate surgical procedure codes in the NPR using a predefined review methodology. Manual chart review is one of existing gold standards for validating diagnostic codes in registers. Other methodologies include patient examination and interviews of physicians who performed the procedures. Such approaches could potentially increase the accuracy of the classification of performed surgery. However, these methods are time-consuming and meet practical challenges. In our study, the assessment of the surgical notes in the charts is strengthened by pathology reports from surgical specimens and notes from follow-up visits after surgery.

Studies II and **III** applied an observational prospective study design to investigate real-world clinical outcomes associated with ustekinumab treatment of CD patients. RCTs include an often homogenous and highly selected group of patients, chosen on the basis of narrow inclusion and wide exclusion criteria. The intervention is rigidly controlled and patients in the same group receive similar treatment regimens. However, in real-world clinical practice, treating physicians adopt far a more varied treatment patterns in a heterogeneous patient population.

A prospective observational study design facilitates collection of a sufficient quantity of well-defined clinical variables to address the objectives of Studies II and III. In contrast, retrospective database mining is typically only able to provide a limited amount of clinical data. Compared to previous RCTs [103, 111] evaluating ustekinumab in CD, we included a heterogenous group of patients with a homogenous treatment regimen representing 20 regional and university hospitals, thus likely to reflect the CD patient population in Sweden.

One limitation of Studies II and III is the comparably high rates of missing data at follow-up time points, owing the study design where clinical practice is only observed without intervening in or mandating reporting of all data items collected during follow-up. Another limitation is the lack of comparison group, limiting the conclusions about the associations between treatment and main outcome measures.

Study IV used a register-based data to identify incident cases by combining ICD codes for IBD in the NPR and biopsy data in the ESPRESSO cohort. Using both ICD codes and biopsy data, we are likely to achieve higher accuracy than with ICD codes only and especially a better date for diagnosis. Other methods/study designs used in incidence studies include manual chart review and clinical assessment alone or in combination. In a previous validation study based on chart review, using ICD codes and biopsies, our diagnostic approach had a PPV of 95% (95%CI=88-99) [32].

7.1.2 Confounding

Confounding occurs when the effect of the exposure on the outcome is influenced also by the effect of other variables[186]. A confounder is related to both exposure and outcome, but not part of the causal pathway between them.

Previous exposure to biologics and the number of treatments with such agents in **Studies II** and **III** may indicate severe and treatment resistant CD, hence more likely to be initiated on

ustekinumab, and possibly less likely to respond to treatment. Similarly, concomitant treatment with immunomodulators may increase the likelihood of response and remission, especially in patients previously naïve to immunomodulators.

7.1.3 Bias and misclassification

Selection bias is systematic errors deriving from selection of study participants based on factors affecting the outcome of the study[186]. In **Studies I** and **IV**, we used the total Swedish population as source population when selecting the respective nationwide study populations. This approach reduces the potential effects of underrepresentation caused by selection bias.

The chart review in **Study I** was performed by a single reviewer with medical training but lacking specialist surgical training. Cases of uncertainty of the performed surgery, as noted in the patient charts, were discussed with an experienced IBD-surgeon. Despite this approach, it cannot be excluded that biases in the assessment of surgical notes were introduced by the single reviewer. Such biases could potentially lead to misclassification of the performed surgery. However, misclassification is unlikely to be differential in our case, but can influence the results in cases when the surgery was incorrectly classified. Misclassification could also be introduced by the surgeons themselves in their notes, and by the person assigning a procedure code and when reporting it to the NPR. Since procedure codes and surgical notes are generally recorded in real time the risk of introducing recall or reporter biases is low. We performed a bootstrap analysis to calculate 95%CIs to account for differences in coding practice between hospitals.

In the multicenter prospective **Studies II** and **III** patients initiated on ustekinumab and fulfilling the inclusion criteria were included based on independent decisions of treating physicians. Despite efforts to enroll all patients who consented to study participation, regardless of geographical residence, health status and previous treatment history, we cannot exclude that prior biologic and immunosuppressive treatment influenced the selection of study participants. This could introduce selection bias related to previous treatment, disease severity and history of surgery limiting the generalizability and comparison to other studies.

Patient-reported data may introduce recall bias in outcome measures of HBI and HRQoL measurements. Overestimation and underestimation of existing symptoms and signs of disease may therefore be introduced. However, through prospective collection of real-world clinical data we aimed to reduce the risk of recall bias. To further limit this risk, we applied strict criteria for all clinical and biochemical outcomes and included only data reported within tight time-windows (±2 weeks) of physician's follow-up visits in the analyses.

Study IV included diagnostic data of IBD diagnosis from the NPR and pathology data from the ESPRESSO cohort. Incident cases were defined as a combination of at least one ICD code of UC, CD or IBD-U in the NPR and a consistent biopsy report (SnoMed code) in the ESPRESSO data cohort. Year of diagnosis was set to first registered ICD/SnoMed code. With this definition, we were not able to identify changes in diagnoses from one subtype to another. However, potential misclassification is unlikely to be differential. Previous studies show that such changes occur both to and from subtypes with proportions of subtypes largely unchanged over longer periods[65, 187]. Taking the advantage of biopsy data in defining incident cases, we are able to more accurately assign year of IBD diagnosis of incident cases than with a case definition based on ICD codes alone.

7.1.4 Missing data

During the study period of **Studies II** and **III**, patients were lost to follow-up, withdrew consent or discontinued treatment. Due to the observational study design, not mandating reporting of all data items, we encountered a considerable amount of missing data. To limit the effect on the main outcomes (response and remission) of patients discontinuing the study and of missing data we applied an intention-to-treat like approach. Missing data and discontinuation, regardless of the reason for discontinuation, were hereby classified as treatment failure in the analysis, thus avoiding overestimation of the main outcomes.

7.1.5 Generalizability

Generalizability (or external validity) aims to measures to what extend the findings are applicable also in other settings than the studied[186].

In **Study I** we validated surgical procedure codes used in IBD-related surgery. Since these codes are also used for other abdominal surgical conditions the results of our study can be generalized also to other diagnoses than IBD.

The findings of **Studies II** and **III** represent clinical outcomes of ustekinumab for treatment of CD patients in a Swedish clinical setting. The current system for reimbursement of treatment and drug expenses on administrative and hospital levels can potentially influence the use of ustekinumab in Sweden as compared to other countries. We cannot exclude that financial aspects or regional differences in clinical practice influence treatment decisions for biologics, including ustekinumab. However, the study population represent a nationwide sample of both university and regional hospitals and we found no evidence of significant differences in basic patient characteristics between hospitals. With some caution, our findings can be generalized to a CD patient population in clinical settings outside Sweden such as countries with similar demographics, healthcare systems and treatment traditions. Possible selection bias limiting this generalizability is addressed above (7.1.3).

The incidence and temporal trends of IBD were investigated in a nationwide sample of IBD patients in **Study IV**. The large sample size (N=65 908) lends considerable statistical power to the analyses. We did not perform any regional analyses and therefore cannot capture existing regional epidemiological trends. A regional Swedish study showed contradicting IBD prevalence numbers of UC and CD when comparing municipalities within the same region[188]. It is not fully known if such regional differences also exist in the incidence of IBD. The results of our study can possibly be generalized to countries with healthcare systems, demographics, diet and lifestyles similar to those in Sweden.

7.2 INTERPRETATIONS AND IMPLICATIONS

7.2.1 Validity of IBD-related surgical procedure codes in the Swedish National Patient Register (Study I)

We found high validity (PPV 96.8%) and high sensitivity (94.5%) for IBD-related surgical procedure codes in the NPR (Study I). Our results confirm previous findings of high validity for procedure codes of other types of surgery registered in the NPR[189-191]. Part of the incorrectly registered codes we found were possibly due to technical errors occurring when manually transferring the codes from patient charts to the NPR, such as shifting letters in the codes (for example JFB--- to JBF---). We also found that the actual IBD-related surgery took place on average 2.1 (SD 3.1) days after admission date registered in the NPR. These findings highlight the importance of validating not only diagnostic and procedure codes in health-care registers, but also the need for thorough understanding of the administrative and technical

aspects of registers when applying register-based data in research studies. In all, the NPR is a reliable and important data source for clinical and epidemiological studies based on IBD-related surgical procedure codes.

7.2.2 Real-world clinical outcomes of ustekinumab treatment in Crohn's disease (Studies II and III)

Treatment of CD with ustekinumab according to recommended doses showed evidence of achieving both short-term response and remission and long-term remission in a real-world Swedish clinical setting. The study population in our study showed patient characteristics at baseline similar to comparable observational studies [114, 192] with 94% of included patients having previous exposure to biologic treatment. Response rates in our study (weeks 52 and 104, 36% and 29%, respectively) were comparable to the those of the only currently fully multicenter prospective long-term observational study by Straatmijer et al [192]. However, we showed lower remission rates of 32% and 29% at weeks 52 and 104, respectively, compared to 44% and 37%, respectively, in their study. It is possible that our lower rates are due to differences in data collection methodology, timing of treatment initiation, disease severity and concomitant treatment with corticosteroids and immunomodulators. As previously discussed, we applied an intention-to-treat like approach, treating patients who were lost to follow-up or discontinued ustekinumab as treatment failures in the analyses. The response and remission rates in our study are therefore more likely to underestimate the impact of ustekinumab treatment on the main outcomes than the opposite.

CD can have substantial negative impact on the HRQoL of patients. We found significant improvement of HRQoL measurements throughout the 104-week-study period. This confirms the findings of the previous long-term pivotal study of ustekinumab in CD[193]. Emphasis on the value of also reporting HRQoL outcomes as part of treatment evaluation in IBD is gradually growing[194]. Our findings indicate that improvement of HRQoL may not always correlate to high response and remission rates.

It must be acknowledged that the absence of a comparison group in our studies make it difficult to evaluate the true association between ustekinumab treatment and main outcome efficacy measures. As for similar observational studies, the results must be interpreted with caution. In a meta-analysis of RCTs of the efficacy of medical treatment, including both biologics and conventional treatment, as many as 30% and 28% in the placebo group showed long-term response and remission, respectively[195]. In our study, we showed similar response and remission rates. However, disease severity, previous biologics exposure and disease duration were associated with lower response and remission rates in the meta-analysis, and as pointed out in this thesis (7.1.1), patient populations in RCTs may differ substantially from those in observational studies.

7.2.3 Incidence of inflammatory bowel disease in Sweden (Study IV)

In a large cohort (N=65 908) We found evidence of rapidly increasing incidence between 1990 and 2001 in UC and CD, followed by decreasing incidence from 2002 onwards. We also reported annual age-standardised IRs for the study period 1990 to 2014 (IBD, 29.0; UC, 16.9; CD, 8.1; IBD-U (2002-2014), 5.2 per 100 000 person-years) comparable to those of previous Swedish and Nordic studies [81-84, 87, 89, 196, 197]. Differences in IRs can partly be explained by different case definitions. We also found that the IRR between males and females varies by age and calendar period for both UC and CD, however, in different directions by age in UC and CD.

The increasing incidence in the first half of the study period may be explained by a rapid rise in number of endoscopies during that period. The underlying reasons for the following shift

to declining IRs are not known. The statistical significance of our findings is strengthened by the fact that even with a continuous growing number of endoscopies since 2002, potentially increasing the likelihood of becoming an incident IBD with our case definition, we found decreasing IRs. It is possible that unknown environmental factors and gradual changes in smoking habits and lifestyle over the years may eventually lead to decreasing incidence. There are no previous consistent findings on the temporal trends in Sweden. A regional study found increasing incidence of UC during 1990-2010, notably, using a different case definition than ours in a smaller study population[85].

Differences in the IRRs between the sexes have not fully been investigated in previous Swedish studies. The differences we found by age may be explained by female exposure to oral contraceptives and hormonal changes during puberty, and also by menopausal hormonal changes [74].

Although our study was based on a large population-based cohort over a 25-year study period, the decreasing incidence rates from 2002 onwards need to be followed-up with incidence data up until today to confirm if this trend still holds. Furthermore, we did not explore any regional differences in IRs and therefore cannot exclude that such differences exist.

8 CONCLUSIONS

Based on the studies included in this thesis the following main conclusions are noted:

- The NPR shows high validity and high sensitivity for IBD-related surgical procedure codes indicating that it is a reliable data source for researchers aiming to identify and study patients with a history IBD-related surgery. (**Study 1**)

- In a real-world setting, ustekinumab treatment is associated with improvement of short- and long-term clinical outcomes and improved HRQoL in patients with moderate to severe CD. (**Studies II** and **II**)

- The incidence of IBD in Sweden increased overall and by subtype in both males and females during the 1990-2014. However, increasing incidence rates up until 2001 were followed by decreasing rates from 2002 onwards. The incidence varies between the sexes, across calendar periods and by age groups. It is expected that 1 in 40 individuals will be diagnosed with IBD during their lifetime, indicating a significant IBD burden of disease. (**Study IV**)

9 FUTURE PERSPECTIVES

The global incidence and prevalence of IBD is expected to grow in coming years[198]. At present, about one third of patients with IBD are treatment refractory or lose response to aTNF treatment[97]. Remaining medical or surgical treatment options are still comparably few. Knowledge about the optimal timing, dosing intervals, drug concentration levels and combination of medical IBD therapies is still limited. Against this background, the importance of investigating these aspects through epidemiological and real-world data cannot be underestimated.

Epidemiological evidence of disease occurrence and validity of register-based data are fundamental to healthcare planning and for design and interpretation of research studies. Although validating register-based data can be time-consuming it can identify important technical and administrative reasons for misclassification and errors. We validated IBD-related surgical procedure codes, however future research on IBD would also benefit from validation of other IBD-related data in registers, such as endoscopic procedure codes, pathology reports and data on prescribed IBD drugs. At present, no consensus guidelines on validation methods for data in healthcare registers exist. Introduction of such guidelines to ensure sufficient quality of validation studies would be beneficial for future research.

This thesis explored the temporal trends of the incidence of IBD in Sweden and reported decreasing incidence during the last 20 years. This is an encouraging development, however, the underlying reasons remain to be elucidated. Public healthcare policies, promoting healthy lifestyles and diets, may have impacted on the incidence. Repeated studies on the IBD incidence in Sweden and similar countries, with focus on regional and socioeconomic differences, can hopefully shed light on current and future temporal trends. Comparisons with other regions in the world may also help identify and understand differences in environmental and genetic impact on disease onset and sex related differences. Accurate estimates, and preferably also forecasts, of IBD incidence and prevalence are important for healthcare resource allocation.

During the past two decades, new biologic therapies have been introduced for treatment of UC and CD. These additions, including ustekinumab, have mainly benefited patients with moderate to severe IBD. In parallel, surgery remains a central pillar of treatment of both UC and CD. In this thesis, we demonstrated that ustekinumab can achieve clinical response and remission in CD in a real-world setting. Further observational studies on ustekinumab and other recent biological agents are needed. Results of observational studies cannot replace RCTs, which are the only study design able to accurately assess the clinical effectiveness of treatment compared to no treatment. However, regardless of inherent limitations of clinical observational treatment studies discussed in this thesis, they can contribute with highly important data if systematically and prospectively collected in a real-world setting. Pivotal trials are typically not large enough to provide enough clinical data on safety profiles, optimal dosing patterns, drug concentration levels and concomitant treatment. We are still largely lacking knowledge on these important aspects of treatment with biologic agents. Furthermore, the positioning of a certain biologic agent relative to other biologics and surgery need to be better understood. Head-to-head RCTs in large patient cohorts, including different disease presentation and patient phenotypes, are therefore warranted. Especially challenging disease presentations, such as perianal CD, sadly still lack efficient treatment. Against this background, future research applying observational study designs, focusing on both short- and long-term treatment outcomes, is welcomed.

To facilitate the quality of pooled results of clinical observational studies through systematic reviews and meta-analysis, adherence to existing guidelines of observational studies is important.

Finally, as a gastroenterologist, one can hope for future prediction models and biomarkers able to accurately guide clinical treatment decisions, predict treatment response, and possibly also map phenotype and forecast the disease course of individual IBD patients.

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