Magnetic Resonance Imaging of a Population-based Cohort of Patients with Long-term Inflammatory Bowel Disease

Primary sclerosing cholangitis, bowel damage and inflammation

By

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“You only see what you know”
JW von Goethe
Table of contents

Acknowledgements ........................................................................................................ vii

Abstract ....................................................................................................................... viii

List of papers ................................................................................................................ xi

Abbreviations ............................................................................................................... xii

1. Introduction ............................................................................................................. 1
   1.1 IBD .................................................................................................................... 2
       1.1.1 UC ........................................................................................................... 4
       1.1.2 CD ........................................................................................................... 4
   1.2 EIMs of IBD ...................................................................................................... 6
       1.2.1 PSC .......................................................................................................... 6
   1.3 Assessment of disease activity in IBD ................................................................. 9
   1.4 Cross-sectional imaging ....................................................................................... 11
       1.4.1 MRE ....................................................................................................... 13
       1.4.2 MRC ....................................................................................................... 16

2. Study aims .............................................................................................................. 17
   2.1 Primary aim ....................................................................................................... 17
   2.2 Secondary aims ................................................................................................ 17

3. Patients and methods ........................................................................................... 18
   3.1 Study design .................................................................................................... 18
   3.2 Study population ............................................................................................. 18
       3.2.1 Paper I ................................................................................................... 19
       3.2.2 Paper II ................................................................................................... 21
       3.2.3 Paper III .................................................................................................. 22
   3.3 Assessment of clinical disease activity .............................................................. 22
   3.4 Imaging ............................................................................................................ 23
       3.4.1 MRC ....................................................................................................... 23
       3.4.2 MRE ....................................................................................................... 23
   3.5 Image evaluation ............................................................................................. 24
       3.5.1 Detection of PSC-like lesions ................................................................ 24
3.5.2 Assessment of accumulated bowel damage .................................................. 24
3.5.3 Assessment of bowel inflammation .............................................................. 25
3.6 Statistics ........................................................................................................ 26
3.7 Ethics ............................................................................................................. 28

4. Summary of results .......................................................................................... 29
  4.1 Paper I ........................................................................................................... 29
  4.2 Paper II ......................................................................................................... 31
  4.3 Paper III ....................................................................................................... 33

5. Discussion ....................................................................................................... 35
  5.1 Study design and population ....................................................................... 35
  5.2 PSC ............................................................................................................. 37
    5.2.1 PSC prevalence in IBD .......................................................................... 38
    5.2.2 MRC screening .................................................................................... 39
    5.2.3 PSC-IBD ............................................................................................. 41
  5.3 Bowel damage in CD .................................................................................... 42
    5.3.1 LI ......................................................................................................... 42
    5.3.2 Accumulated bowel damage ................................................................. 43
    5.3.3 Predictors of bowel damage ................................................................. 44
  5.4 Added value of MRE assessment ................................................................. 46
  5.5 Bowel inflammation ...................................................................................... 47
    5.5.1 MEGS .................................................................................................. 47
    5.5.2 Inflammatory activity .......................................................................... 49
    5.5.3 Predictive value of MRE ..................................................................... 50

6. Conclusions and future perspectives ............................................................... 51

List of references ................................................................................................ 54

APPENDIX 1-6

PAPERS I-III
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Abstract

Background:
Inflammatory bowel disease (IBD) is a chronic disease of the gut with an unknown etiology and increasing incidence rates worldwide. Persistent inflammation can lead to serious complications and permanent bowel damage. Additionally, IBD is often complicated by extraintestinal manifestations (EIMs), such as primary sclerosing cholangitis (PSC). PSC is a chronic cholestatic liver disease that is usually progressive and ultimately leads to liver failure. There is no single gold standard for the diagnosis of these conditions. In recent years, cross-sectional and magnetic resonance imaging (MRI) have emerged as reliable, consistent and well-tolerated diagnostic modalities.

Aims:
The primary aim of this thesis was to assess the disease extent and distribution of intestinal and EIMs in a population-based study of patients with long-term IBD by means of MRI. Specifically, the aim was to examine the prevalence of PSC by magnetic resonance cholangiography (MRC) and to assess bowel damage and inflammation in patients with Crohn’s disease (CD) 20 years after the diagnosis by magnetic resonance enterography (MRE).

Results:
The accumulated prevalence of PSC among patients with IBD in Southeast Norway was 2.2 %. In Paper I, MRC screening was performed in 322 patients; 26 patients (8.1 %) had PSC-like lesions, out of which 9 (35 %) had known PSC. Patients with suspected PSC had significantly more extensive colitis, a higher prevalence of colectomy, and more chronic and continuous symptoms of IBD than patients without PSC (P=0.029, P=0.002, and P=0.012, respectively). The MRC progression score for PSC at baseline (mean=0.94, SD=0.75) increased
significantly (P=0.046) when patients were re-examined after a median of 3.2 years (mean=1.18, SD=0.95).

In Paper II, 96 patients with CD were examined by MRE. The Lémann index (LI), which is a measure of accumulated bowel damage, was calculated. The median LI was 4.6 (interquartile range (IQR): 17.5), and the score was associated with a younger age (P=0.02), the complicated ileocolonic phenotype (P<0.001) and the use of biological (P<0.001) or immunosuppressive treatments (P=0.045). Sixty-five patients (67.7 %) had imaging findings indicating CD, and the disease classification was changed for 8 patients (8.3 %) solely based on MRE findings. Complicated disease, C-reactive protein (CRP) and thrombocyte levels and the use of medication during the follow-up period were positively associated with LI, while age, hemoglobin and albumin levels were negatively associated with LI at the 20-year follow-up.

In Paper III, the inflammatory activity in 95 patients with CD was assessed by the MRE Global Score (MEGS). Thirty-five (36.8 %) patients had active inflammation, with a median MEGS of 5 (IQR: 18.5). The interobserver Bland-Altman limits of agreement for the MEGS were to -9.53 to 6.77, and the intraclass correlation coefficient was 0.98 (95 % CI: 0.97 to 0.99). The MEGS associated positively with the CRP level (P=0.01), elevated fecal calprotectin (P=0.001), mucosal ulceration on endoscopy (P=0.03), complicated disease (P=0.04), chronic disease pattern (P=0.006) and use of medication (P=0.007).

Conclusions:
MRC screening of patients with IBD revealed a prevalence rate of PSC 3-fold higher than that detected based on symptoms. Sixty-five percent of the patients had subclinical PSC associated with progressive IBD.
Half of the patients with long-term CD had imaging findings of bowel damage that were associated with a young age, complicated disease and ongoing active
disease. Additionally, approximately one-third of patients had moderate or severe inflammation 20 years after the diagnosis. MRE proved its role as an indispensable supplement in the clinical assessment of CD location and behavior.
List of papers

Paper I

Paper II

Paper III
Abbreviations

ADC – apparent diffusion coefficient
ANOVA - analysis of variance
5-ASA – 5-aminosalicylate
ASCA - anti-Saccharomyces cerevisiae antibodies
b-SSFP- balanced steady state free precession
CCC - cholangiocellular carcinoma
CD – Crohn’s disease
CDAI - Crohn's disease activity index
CDEIS - Crohn's disease endoscopic index of severity
CRC – colorectal cancer
CRP – C-reactive protein
CT – computer tomography
DWI – diffusion weighted imaging
EIMs – extra intestinal manifestations
ERCP - endoscopic retrograde cholangiography
FSE – fast spin echo
GADO - Gadolinium enhancement after intravenous contrast medium administration
GRE – gradient echo
HBI – Harvey Bradshaw index
IBD – inflammatory bowel disease
IBSEN - Inflammatory Bowel Disease South-East Norway
ICC - intraclass correlation coefficients
IQR – interquartile range
LI – Lemann index
MARIA - magnetic resonance index of activity
MEGS - magnetic resonance enterography global score
MIP - maximum intensity projection
MRC - magnetic resonance cholangiography
MRE – magnetic resonance enterography
MRI – magnetic resonance imaging
PABAK - prevalence-adjusted bias-adjusted kappa
PACS - picture-archiving and communication system
pANCA - perinuclear anti-neutrophil cytoplasmic antibodies
PSC – primary sclerosing cholangitis
RCE - relative contrast enhancement
SCCAI - Simple Clinical Colitis Activity Index
SES-CD - Simple Endoscopic Score for Crohn Disease
T - Tesla
TNF-α – tumor necrosis factor α
TSE – turbo spin echo
UC – ulcerative colitis
US - ultrasound
1. Introduction

Over the last two decades, radiological imaging has become an essential part of the assessment of patients with known or suspected inflammatory bowel disease (IBD). Several factors have contributed to this development. There has been an increasing understanding of IBD as a complex, multifaceted disease that cannot be assessed fully by clinical, laboratory and endoscopic evaluations. Clinical indices have shown poor correlations with inflammatory activity (1), and there is increasing evidence that inflammation, structural bowel changes and bile duct affection have gone undetected in patients with IBD (2-4). In this setting, magnetic resonance imaging (MRI) is an important, noninvasive supplemental modality with little or no complications. Moreover, therapeutic advances in the management of IBD call for the reproducible, objective monitoring of disease activity. MRI has shown a high sensitivity and specificity for detecting bowel inflammation, penetrating lesions, strictures and extraintestinal disease manifestations (5-7) and is increasingly being used to monitor medical therapy (8-10). Additionally, standardized assessments are evolving through new scoring systems, which will hopefully facilitate patient follow-up visits and therapeutic decision-making.

The etiopathogenesis of IBD is elusive. Good epidemiological studies are crucial for providing clues to the etiology of the disease and identifying areas that warrant further study. However, reliable epidemiology data are dependent on accurate disease assessment. To date, there are relatively few data on the radiological long-term outcomes of IBD. This thesis proceeds from a population-based cohort study of patients with IBD in Southeast provinces of Norway. It examines the intestinal and extraintestinal MRI findings of patients who have had the disease for approximately two decades. In the long term, acquiring detailed knowledge on the natural extent and behavior of IBD will help improve our understanding of this challenging disease.
First, a brief introduction to IBD, primary sclerosing cholangitis (PSC) and the diagnostic work-up, which is relevant to the results and interpretation of the studies, is presented. Study aims are then presented, followed by a review of the applied methods and summarized results. Finally, findings and methodological considerations are discussed.

1.1 IBD

IBD involves chronic inflammation of the digestive tract and primarily includes ulcerative colitis (UC) and Crohn’s disease (CD). Both conditions usually involve such clinical symptoms as diarrhea, abdominal pain and fatigue. Serious local and systemic disease complications can be debilitating for the patient. IBD affects mostly young people, usually in late adolescence and early adulthood (11, 12). The prevalence of IBD varies greatly in different parts of the world and among different ethnicities (13). Caucasians in northern parts of the world are at the greatest risk, and prevalence as high as 0.5 % has been reported in the Western world (13). It is estimated that approximately 3 million people in Europe suffer from IBD (14). Additionally, both the prevalence and incidence of IBD are increasing worldwide (13) (Figure 1).
IBD is a complex disease that arises as a result of the interaction of environmental and genetic factors leading to immunological responses and inflammation in the intestine (16). The exact etiology is unknown. It is suspected that the disrupted interplay of genetic and epigenetic factors and a defective immune response in a dysbiotic gut combined with several environmental and psychological factors results in chronic inflammation of the gut. UC causes inflammation and ulcers in the innermost lining of the colon and rectum, while CD causes deep, transmural inflammation that can involve all areas of the digestive tract – from mouth to anus. Patients with IBD often experience extraintestinal manifestations (EIMs), such as arthritis, dermatological and ocular complications and PSC (17, 18). Additionally, these patients are at a higher risk than the general population of developing serious complications, including colorectal cancer (CRC) and cholangiocellular carcinoma (CCC) (19, 20).
1.1.1 UC

UC is confined to the colon, typically starting in the rectum and extending proximally in a continuous pattern. It is the most prevalent of the IBD disorders, affecting 505/10^5 persons in Norway (13). The classification of UC is based on the colonic disease extension, as follows: proctitis (limited to the rectum, extending ≤15 cm); left-sided colitis (extension distal to the splenic flexure); and extensive colitis (extension proximal to the splenic flexure) (21), with approximately a third of patients falling into each group at diagnosis (22-24). However, the disease extends from proctitis to pancolitis in many patients over time (12). Reported long-term cumulative relapse rates range from 67–83 % (22, 25), and according to the 10-year follow-up of patients from the IBSEN study cohort, 40 % of patients report chronic symptoms (22).

Current medical treatments, such as 5-aminosalicylate (5-ASA), corticosteroids, immunosuppressants and biological treatments, either alone or in combination, aim to induce and maintain remission. In patients who are unresponsive to medical therapy, resective surgery is recommended. The reported cumulative colectomy rates vary from 3 % to 17 % in different cohorts (26), and the rates have been decreasing gradually over time (27, 28). Patients with extensive, longstanding active disease are at a higher risk of developing CRC (20), and they are offered regular surveillance colonoscopies (29). Currently, the mortality rates of patients with UC are comparable to those of the general population (30, 31).

1.1.2 CD

CD is a chronic inflammatory disease that can affect any part of the gastrointestinal tract. The reported prevalence in Norway is 262/100,000 persons (32). The disease varies in extent and presentation. Most patients have an intermittent disease course, but up to 20 % exhibit continuous symptoms (33). The classification of CD is based on age at diagnosis, disease location and disease
behavior. The Vienna classification (34), used in this cohort study, was developed in 1998 and later evolved into the Montreal classification (21). Modifications included an additional age category, and a modifier for proximal disease location (L4) and perianal disease (P) (Table 1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vienna Classification</th>
<th>Montreal Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at diagnosis (A)</strong></td>
<td>A1: &lt; 40 years</td>
<td>A1: ≤ 16 years</td>
</tr>
<tr>
<td></td>
<td>A2: ≥ 40 years</td>
<td>A2: 17-40 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A3: &gt; 40 years</td>
</tr>
<tr>
<td><strong>Disease location (L)</strong></td>
<td>L1: ileal</td>
<td>L1: ileal</td>
</tr>
<tr>
<td></td>
<td>L2: colonic</td>
<td>L2: colonic</td>
</tr>
<tr>
<td></td>
<td>L3: ileocolonic</td>
<td>L3: ileocolonic</td>
</tr>
<tr>
<td></td>
<td>L4: upper GI tract</td>
<td>L4: isolated upper GI tract¹</td>
</tr>
<tr>
<td><strong>Disease behavior (B)</strong></td>
<td>B1: inflammatory</td>
<td>B1: inflammatory</td>
</tr>
<tr>
<td></td>
<td>B2: stricturing</td>
<td>B2: stricturing</td>
</tr>
<tr>
<td></td>
<td>B3: penetrating</td>
<td>B3: penetrating</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P: perianal disease²</td>
</tr>
</tbody>
</table>

Table 1. The Vienna and the Montreal classification for Crohn’s disease.

¹added to L1-L3; ²added to B1-B3

At the time of diagnosis, roughly one-third of patients presents with ileal, colonic or ileocolonic affection (35). It has been reported that some 1–2% of patients present with upper gastrointestinal tract affection only (36, 37). Most patients have an inflammatory disease type to begin with, but over time, they develop stricturing and/or penetrating disease, i.e., complicated disease that eventually affects over 50% of patients (33, 38-41). Additionally, population-based studies pre-dating biological therapies have described high long-term relapse rates ranging from 75–90% (38, 42, 43).

The treatment of CD often requires a multidisciplinary approach. Simplified inflammation is treated with medical therapy, such as corticosteroids, immunosuppressants (methotrexate and thiopurines), biological therapy (mainly anti-TNF agents) and occasionally antibiotics or sulfasalazine. The
main indications for surgery are complicating strictures, abscesses and fistulas. Within ten years of onset, approximately 50 % of patients undergo intestinal resection, and one in three of these will subsequently need a second surgical intervention within 10 years (44). Studies have shown that ileal affection, complicated disease, and young age at onset, among other factors, predict surgical resection (33, 38, 40, 45, 46). Most studies have indicated a modest increase in the mortality of patients with CD, mainly due to malignancies in the gastrointestinal tract and in the lungs (47, 48).

1.2 EIMs of IBD

IBD is a systemic disease that affects organs other than the gut (49, 50), such as joints (51, 52), skin, eyes (53) and the hepatobiliary system (54). These conditions presumably share an immunological pathogenesis with the coexisting IBD. Some EIMs are secondary to the bowel disease and caused by metabolic processes, malnutrition and drug-related side effects. These include metabolic bone disease and various urogenital, pulmonary and cardiovascular manifestations (55). The EIMs of IBD have reported prevalence rates that vary from 6 % to 38 % in different studies (56, 57). The reported accumulated prevalence of EIMs in Norway is 16.9 % (58).

1.2.1 PSC

PSC is a chronic inflammation of the intra- and extra-hepatic bile ducts causing biliary strictures and recurrent cholangitis that can ultimately lead to end-stage liver disease and cancer (Figure 2).
Figure 2. Illustration of bile duct pathology in PSC. Chronic inflammation and fibrosis lead to multifocal biliary strictures and dilatations both inside and outside of the liver. Reprinted with permission © Kari C. Toverud, CMI.

PSC mostly affects young male adults (59, 60), and up to 80 % of PSC patients in Northern Europe have concomitant IBD (61). PSC has often been considered an EIM of IBD, but the causative relationship between these diseases is still uncertain. PSC-IBD is a distinct phenotype that is generally colonic, with a right-sided predominance, high frequency of “backwash” ileitis, and rectal sparing (62). Genetically, there is also substantial evidence suggesting that PSC is a condition separate from or only partly overlapping with IBD (63). The reported prevalence of PSC in IBD ranges from 0.8 % to 7.5 % in patients with UC and from 0 to 6.4 % in patients with CD, with the highest prevalences reported by non-population-based studies (Table 2). These discrepancies may be due to different patient populations and other methodological differences; thus, the true prevalence of PSC in IBD remains unclear.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Region</th>
<th>Study period</th>
<th>No. of patients</th>
<th>No. (%) of PSC patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population based studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monsen U. (64)</td>
<td>Sweden</td>
<td>1955-79</td>
<td>1274 UC</td>
<td>13 (I)</td>
</tr>
<tr>
<td>Olsson R. (65)</td>
<td>Sweden</td>
<td>1988</td>
<td>1500 UC</td>
<td>55 (3.7)</td>
</tr>
<tr>
<td>Aitola P. (66)</td>
<td>Finland</td>
<td>1994</td>
<td>534 UC</td>
<td>11 (2)</td>
</tr>
<tr>
<td>Broome U. (67)</td>
<td>Sweden</td>
<td>1955-79</td>
<td>1274 UC</td>
<td>29 (2.3)</td>
</tr>
<tr>
<td>Bernstein C.N. (56)</td>
<td>Canada</td>
<td>1984-96</td>
<td>4454 IBD</td>
<td>90 UC (2) 18 CD (0.4)</td>
</tr>
<tr>
<td>Mendes F.D. (68)</td>
<td>US</td>
<td>2000-01</td>
<td>544 IBD</td>
<td>25 (4.6)</td>
</tr>
<tr>
<td>Isene R. (58)</td>
<td>EU + Israel</td>
<td>1991-2004</td>
<td>1145 IBD</td>
<td>9 (0.8)</td>
</tr>
<tr>
<td>Rönnblom A. (69)</td>
<td>Sweden</td>
<td>2005-09</td>
<td>526 UC 264 CD</td>
<td>9 (1.7) 8 (3)</td>
</tr>
<tr>
<td>Fraga M. (70)</td>
<td>Switzerland</td>
<td>2006-2013</td>
<td>1188 UC 1556 CD</td>
<td>48 (4.0) 9 (0.6)</td>
</tr>
<tr>
<td><strong>Non-population based studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lupinetti M. (71)</td>
<td>US</td>
<td>1966-77</td>
<td>202 IBD</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Schrumpf E. (72)</td>
<td>Norway</td>
<td>1974-78</td>
<td>336 UC</td>
<td>14 (4.2)/25 (7.5)*</td>
</tr>
<tr>
<td>Shepherd HA. (73)</td>
<td>UK</td>
<td>NR</td>
<td>681 UC</td>
<td>17 (2.5)</td>
</tr>
<tr>
<td>Tobias R. (74)</td>
<td>South Africa</td>
<td>1975-81</td>
<td>250 UC 164 CD</td>
<td>8 (3.2) 2 (1.2)</td>
</tr>
<tr>
<td>McGarity B. (75)</td>
<td>UK</td>
<td>1986-87</td>
<td>125 CD</td>
<td>8 (6.4)</td>
</tr>
<tr>
<td>Wewer V. (76)</td>
<td>Denmark</td>
<td>NR</td>
<td>396 UC 125 CD</td>
<td>3 (0.8) 0</td>
</tr>
<tr>
<td>Hashimoto E. (77)</td>
<td>Japan</td>
<td>1984-90</td>
<td>163 UC</td>
<td>5 (3.1)</td>
</tr>
<tr>
<td>Rasmussen H.H. (78)</td>
<td>Denmark</td>
<td>1976-87</td>
<td>305 UC</td>
<td>11 (3.6)</td>
</tr>
<tr>
<td>Veloso F.T. (79)</td>
<td>Portugal</td>
<td>1975-94</td>
<td>449 UC 343 CD</td>
<td>9 (2) 2 (0.7)</td>
</tr>
<tr>
<td>Rasmussen H.H. (80)</td>
<td>Denmark</td>
<td>1976-91</td>
<td>262 CD</td>
<td>9 (3.4)</td>
</tr>
<tr>
<td>Parlak E. (81)</td>
<td>Turkey</td>
<td>1993-2000</td>
<td>386 UC 110 CD</td>
<td>9 (2.4) 4 (3.6)</td>
</tr>
<tr>
<td>Lakatos L. (82)</td>
<td>Hungary</td>
<td>NR, 25 y follow-up</td>
<td>619 UC 254 CD</td>
<td>10 (1.6) 2 (0.8)</td>
</tr>
<tr>
<td>Ye B.D. (83)</td>
<td>Korea</td>
<td>1977-2009</td>
<td>1849 UC</td>
<td>21 (1.1)</td>
</tr>
<tr>
<td>Roberts H. (84)</td>
<td>Kentucky, US</td>
<td>1996-2013</td>
<td>269 UC 488 CD</td>
<td>8 (3) 7 (1.4)</td>
</tr>
</tbody>
</table>

*later follow-up (85)

Table 2. Summary of studies reporting prevalence of PSC in IBD.
The diagnosis of PSC can be a challenge. Some patients have clinical and biochemical signs of cholestasis, but this may fluctuate over time (86, 87). The diagnosis of PSC is based on findings compatible with sclerosing cholangitis and the exclusion of secondary causes, such as cholelithiasis, cholangiocarcinoma, iatrogenic bile duct strictures and cirrhosis caused by other liver diseases. Magnetic resonance cholangiography (MRC) is currently the primary modality for diagnosing PSC (88). Endoscopic retrograde cholangiography (ERCP) is sometimes performed when there are uncertain MRC findings or for therapeutic purposes. There are no histological features pathognomonic for PSC, and liver biopsy is usually only performed when there is doubt about the diagnosis or suspicion of an overlapping condition with autoimmune hepatitis. Some patients have hepatic histology compatible with a diagnosis of PSC but normal cholangiography results. This condition has a slightly better long-term outcome (89, 90), and it is termed small-duct PSC (91, 92).

PSC has a variable disease course that generally progresses to liver failure after a median of 12 to 21 years (93, 94). Currently, there are no established medical treatments, and liver transplantation is the only potentially curative therapy. PSC is the leading indication for liver transplantation in Norway, accounting for 18% of all first liver transplantations performed from 2004 to 2013 (95). Additionally, patients with PSC have an increased risk of cholangiocarcinoma, hepatocellular carcinoma, and gallbladder cancer (96-99), as well as CRC in patients with colitis (19, 100).

1.3 Assessment of disease activity in IBD

IBD is a heterogeneous disease entity that varies in extension, severity and activity over time in the same patient as well as among patients. There is no single gold standard for the diagnosis of IBD. The diagnosis is based on clinical presentation, laboratory tests, endoscopy findings with histopathological
evaluation and radiological imaging (101, 102). However, discrepancies between clinical symptoms and inflammatory lesions have been reported, more so in CD than UC (103, 104). Although ileocolonoscopy is considered the gold standard for assessing disease activity in patients with IBD, the procedure is invasive and associated with patient discomfort and the risk of bowel perforation. Furthermore, the method evaluates the superficial mucosa only, it can be incomplete (105), and it does not assess the whole small bowel. Still, the small bowel mucosa can be assessed by capsule endoscopy. The technique has been improving in recent years with high sensitivity for detecting small bowel inflammation that is comparable to that of MRE (106, 107). However, it is a logistically demanding and invasive procedure whose use is limited by low specificity (108) and potential capsule retention (109).

The most commonly used biomarkers for evaluating inflammation are C-reactive protein (CRP) and fecal calprotectin. CRP is an acute-phase protein that increases rapidly in response to systemic inflammation. Calprotectin is a cytosolic protein found in the inflammatory cells of the gut. It is released during inflammation and reflects the level of inflammatory activity in the intestinal mucosa (110). Fecal calprotectin screening in patients with suspected IBD has shown high sensitivity and specificity rates (111, 112). Both CRP and fecal calprotectin correlate to endoscopic activity and mucosal healing (113-115). Unfortunately, these markers can be influenced by other inflammatory activities, genetic factors and nutritional status. CRP levels can be low in patients with active disease (116, 117), and patients with CD have higher CRP levels than patients with UC (118). Additionally, fecal calprotectin levels correlate better with colonic disease than ileal disease (119).

The comprehensive diagnostics and disease monitoring methods are supplemented by radiological imaging. The choice of imaging modality is based
on patients’ symptoms and presentation, but it usually encompasses trans-abdominal ultrasound (US), computed tomography (CT) or MRI.

The demands for quantifying disease activity in recent years, especially in clinical trials, have led to an introduction of clinical indices. There are a variety of clinical scores, which can be symptom-based, patient-reported or endoscopic. The purpose of these scores is to improve the objectivity of clinical assessments, facilitate the follow-up examinations and evaluate the treatment response. The most commonly used indices are summarized in Table 3. Still, there are no validated definitions of overall disease severity. Additionally, we have limited ability to predict disease course and treatment response for individual patients.

1.4 Cross-sectional imaging

The field of gastrointestinal radiology has advanced and expanded considerably during the last four decades, from single barium radiography studies to fast imaging MRI sequences of the bowel. Cross-sectional imaging techniques offer an accurate and reliable overview of the intestinal, extramural and extraintestinal signs of the disease. CT is rapid and available, making it a preferred modality in acute clinical settings. Sensitivity and specificity rates of approximately 90 % have been reported for CT enterography (120-123). The diagnostic accuracy of US is comparable to that of CT and MRE (124), but it is highly operator-dependent and sensitive to disturbances due to bowel gas or a large body habitus. However, it can play a role in the follow-up examination of known lesions (125, 126) and in interventional procedures (127). Since the mid-1990s, MRI has gradually become the preferred modality for imaging the small bowel. It exhibits excellent image contrast combined with dynamic sequences, multiplanar possibilities and a lack of ionizing radiation. MRI examinations used in this thesis will be discussed in more detail below.
### Ulcerative colitis

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>Thresholds</th>
<th>Score</th>
<th>Description</th>
<th>Thresholds</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCCAI (128)</td>
<td>Stool frequency, urgency, blood in stool, general health and other manifestations.</td>
<td>≤2 (129) or &lt;2.5 (130) = remission</td>
<td>CDAI (131)</td>
<td>Clinical and laboratory variables: stool frequency, pain, general well-being, medication use and complications in the past week, adjusted with a weighting factor.</td>
<td>&lt;150 = remission 150-450 = mild/moderate &gt;450 = severe disease (132)</td>
</tr>
<tr>
<td>Partial Mayo Score (133)</td>
<td>Stool frequency, rectal bleeding, physicians' global assessment.</td>
<td>&lt;2 = remission 2-8 = mild/moderate disease 9-12 = severe disease (134)</td>
<td>HBI (135)</td>
<td>General well-being, abdominal pain and stool frequency previous day. Complications and EIMs.</td>
<td>&lt;8 = mild 8-16 = mild/moderate &gt;16 = severe (1)</td>
</tr>
</tbody>
</table>

### Crohn’s Disease

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>Thresholds</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDEIS (137)</td>
<td>Type and extent of ulceration and stenosis in up to 5 pre-defined colon segments.</td>
<td>&lt;3 = remission 3-12 = mild/moderate ≥ 12 = severe (138)</td>
</tr>
<tr>
<td>SES-CD (139)</td>
<td>Simplified CDEIS. Extent of ulceration and the presence of stenosis.</td>
<td>≤2 = remission 3-15 = mild/moderate ≥15 = severe (140)</td>
</tr>
</tbody>
</table>

**Abbreviations:**

SCCAI - Simple Clinical Colitis Activity Index  
CDAI - Crohn’s Disease Activity Index  
HBI – Harvey-Bradshaw Index  
CDEIS - Crohn’s Disease Endoscopic Index of Severity  
SES-CD - Simple Endoscopic Score for Crohn Disease

**Table 3.** Symptom based and endoscopic scoring systems in UC and CD for assessment of disease activity.

12
1.4.1 MRE

The first report of MRI of the small bowel came in the mid-nineties (141). Since then, several systematic reviews have shown high diagnostic accuracy and reliability for the detection of small bowel pathologies (124, 142, 143). Meta-analyses have reported pooled sensitivities and specificities ranging from 88–93 % and 88–90 %, respectively (124, 144). The inter-reader agreement is also good (145-147). Studies have shown that MRE findings correlate well with endoscopic and histological findings and surgical specimens (123, 145, 148-153). Additionally, MRE can provide valuable information on colonic disease. Sensitivity and specificity rates ranging from 78 % to 100 % and 46 % to 100 % have been reported by a per-patient analysis (127). However, mild colonic disease is easily overlooked (154), although diagnostic accuracy in the colon can be improved with bowel preparation and adequate luminal distention (155).

Several MRE parameters have been connected with bowel inflammation and damage. Studies have shown that bowel wall thickness is one of the most sensitive indicators of bowel inflammation (5, 156). A T2-weighted sequence is usually included in the MRE protocol to visualize bowel wall edema, another good marker of bowel inflammation (142, 157). T2 hyperintensity and mucosal lesions are the most specific signs of inflammation on MRE, with specificity estimates surpassing 90 % at the patient level (7). Finally, increased signal intensity of the bowel wall on post-contrast T1 sequences is a sensitive sign of bowel inflammation (158, 159) and fibrosis (6). Additionally, the pattern of contrast enhancement can provide valuable information. Three patterns have been described: homogeneous enhancement of the entire thickness of the bowel; stratified enhancement of the mucosa and muscularis/serosa, but not the submucosa; and mucosal enhancement with superficial mucosal enhancement only. Layered patterns have been correlated with severe disease activity, while
mucosal and homogeneous enhancement patterns are considered decreasingly less severe in that order (5, 6, 149, 160). A meta-analysis from 2015 concluded that the most consistently accurate signs of damage were abscess and fistula (7).

However, isolated findings are probably too inaccurate for assessing disease activity, and combining them may improve the accuracy of MRE. There have been several attempts to create a composite MRE-based scoring system for disease assessment in recent years (Table 4). The purpose is to create a good surrogate marker of the disease activity in CD. The most applied scores based on conventional MRE techniques are the magnetic resonance index of activity (MaRIA) score (161) and the magnetic resonance enterography global score (MEGS). The MEGS combines seven imaging variables in addition to extramural findings into a global inflammatory score. The MaRIA score is also a multi-item measure of mural inflammation based on an extensive MRE protocol with bowel cleansing and a rectal enema. Both scores have shown good correlation to endoscopic and biological inflammation markers (162-164).

Although inflammation is a crucial element that needs to be assessed and controlled, the resulting structural bowel damage is equally important. CD is usually intermittent, and immediate measures of activity fail to assess the overall impact of the disease. The Lémann index (LI) was developed to assess bowel damage in CD by incorporating resective surgery burden and endoscopic and imaging findings from all segments of the digestive tract into one composite score (165). The goal is to assess the broader effects of the disease on the patient in a systemized manner.
<table>
<thead>
<tr>
<th>Type</th>
<th>Score</th>
<th>Description</th>
<th>Thresholds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Protocol</td>
<td>Segments</td>
</tr>
<tr>
<td>Conventional</td>
<td>MARIA (161)</td>
<td>Bowel cleansing. Oral and rectal preparation. Contrast delay: 1, 2, 5, 7 min.</td>
<td>Distal ileum, ascending, transverse, descending, sigmoid colon, and rectum.</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nancy score (155)</td>
<td>No bowel cleansing or oral/rectal preparation. Contrast delay: 25 sek, 70 sek, 2, 3, 5 min.</td>
<td>Ileum, right, transverse, left colon, sigmoid, rectum.</td>
</tr>
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<td></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>Clerkont score (168)</td>
<td>No bowel cleansing. Oral preparation. No contrast. Diffusion: b=800 s/mm²</td>
<td>Jejunum, proximal ileum, distal ileum, right, transverse, left, sigmoid colon, rectum.</td>
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</tbody>
</table>

**Formula:**
- MARIA: 1.5 x wall thickness (mm) + 0.02 x RCE + 5 x edema + 10 x ulceration
- MEGS: Total score = (Σ (Segmental score x length score)) + extraintestinal score
- Nancy score: Total score = Σ Segmental scores (1 point per positive imaging variable per segment)
- Clermont score: Formula: 1.646 x bowel thickness - 1.321 x ADC + 5.613 x edema + 8.306 x ulcers + 5.039

**Abbreviations:**
- DWI – Diffusion Weighted Imaging
- GADO – Gadolinium enhancement after intravenous contrast medium administration
- ADC – Apparent Diffusion Coefficient

*Table 4. MRI based scores of Crohn’s disease activity.*
MRC is the first-choice modality in the initial diagnosis of PSC (88, 170). It has replaced ERCP because it is a noninvasive, comparably accurate, and less expensive method (171). ERCP is an invasive method associated with serious complications and mostly reserved for interventional procedures. Current MRC techniques are based on heavily T2-weighted fast spin echo (FSE) pulse sequences, which produce a high-intensity signal in fluid-filled structures, such as bile ducts and the gall bladder. The T2-weighted hyperintensity of bile outlines the biliary tree against a hypointense background, demonstrating the biliary tree optimally. The first MRC results, obtained in the beginning of the 1990s, were produced by two-dimensional (2D) acquisitions. 3D imaging techniques provide better image quality than 2D sequences, and they are usually acquired in the coronal orientation (172). Maximum intensity projections (MIPs) can then be obtained in any plane, providing high resolution in all three spatial planes. The performance of MRC in detecting PSC is comparable to that of conventional cholangiography, with a sensitivity of 86 % and a specificity of 94 % (171). MRC is usually complemented with other MRI sequences that provide additional information on both PSC and its complications (173).

Radiographical features of PSC are mural irregularities, multiple short segmental strictures, biliary dilatation, a pruned-tree appearance, alternating strictures and bile duct dilatations or beading (174). The developed MRI progression risk score is based on the combination of predictive radiological features, such as dilatation of intrahepatic bile ducts, liver dysmorphy and portal hypertension (175). The score is associated with PSC progression, but it is not presently used as a prognostic marker. Annual PSC surveillance is usually performed due to the increased risk of cholangiocarcinoma (176-178), but the scientific evidence for this practice is lacking.
2. Study aims

2.1 Primary aim

The principal aim of this thesis is the MRI assessment of long-term IBD and its complications in a Norwegian population-based cohort of IBD patients – the IBSEN (Inflammatory Bowel Disease South-East Norway) study.

2.2 Secondary aims

i. To estimate the frequency and distribution of MRC lesions indicating PSC in patients with IBD 20 years after the initial diagnosis and to identify clinical characteristics associated with these findings.

ii. To investigate the extent and behavior of long-term CD by MRI.

iii. To evaluate the accumulated bowel damage by MRI in patients with long-term CD and search for predictors of the latter.

iv. To assess bowel inflammation by MRI in patients with CD and relate the radiological findings to clinical data.
3. Patients and methods

3.1 Study design

All patients in this thesis came from the IBSEN study. The IBSEN study is a prospective, population-based inception study initiated in the early nineties. From January 1990 to December 1993, all newly diagnosed IBD patients from four Southeastern Norwegian counties (Oslo, Østfold, Telemark and Aust-Agder) were recruited by local physicians (179). Patients were diagnosed with IBD according to the Lennard-Jones criteria (180). The study included 519 patients with UC and 237 patients with CD in a catchment area of nearly 1 million people. The included patients were offered prescheduled follow-up examinations at 1, 5, 10 and 20 years, which consisted of a standardized interview, clinical examination, colonoscopy and blood tests. Additional procedures were performed if clinically indicated. At the 10-year follow-up, the final diagnosis was made, and the patients with CD were categorized according to the Vienna classification (Table 1).

The 20-year follow-up examination was performed between February 2011 and October 2014. All patients were offered MRC, and patients with CD were offered MRE. The data were recorded on paper and subsequently entered into a central database. Ten percent of all the records were checked; the proportion of incorrect data was acceptable (<0.5 %).

3.2 Study population

Three different patient cohorts were studied, as presented in the three papers that constitute this thesis (Table 5). All patients were prospectively included from the IBSEN cohort. The exclusion criteria included pregnancy, the presence
of foreign bodies that were incompatible with a magnetic field, severe claustrophobia and patient noncompliance.

<table>
<thead>
<tr>
<th></th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong></td>
<td>322</td>
<td>96</td>
<td>95</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>IBD</td>
<td>CD</td>
<td>CD</td>
</tr>
<tr>
<td><strong>Main imaging mode</strong></td>
<td>MRC</td>
<td>MRE</td>
<td>MRE</td>
</tr>
<tr>
<td><strong>Study objectives</strong></td>
<td>Screening for PSC</td>
<td>Accumulated bowel damage</td>
<td>Bowel inflammation</td>
</tr>
</tbody>
</table>

Table 5. Overview of the papers.

3.2.1 Paper I

All patients from the IBSEN study, with a confirmed diagnosis of IBD, were invited to an MRC screening for PSC at the 20-year follow-up visit. Of 470 patients who attended the 20-year follow-up visit, 327 (69.6 %) completed the study (Figure 3). Four patients were excluded due to the presence of foreign bodies (n=2), pregnancy (n=1) or noncompliance (n=1), and 5 MRC results were discarded due to poor image quality. Additionally, earlier MRC results were collected retrospectively (n=3) for patients with known PSC in whom an MRC had not been performed as part of the study.
Figure 3. Flowchart of patients in Paper I.
3.2.2 Paper II

All eligible patients from the IBSEN cohort, with a confirmed diagnosis of CD, were invited to undergo MRE at the time of the 20-year follow-up visit. Of 156 patients who completed the 20-year follow-up visit, MRE was performed successfully in 96 patients (Figure 4). Also upper endoscopy results performed as part of the clinical follow-up were collected from local hospitals (n=1).

Figure 4. Flowchart of patients in Paper II.
3.2.3 Paper III

The study population in the third paper was similar to the one in the second paper. Out of 96 patients who successfully underwent MRE, one patient had an examination that lacked contrast-enhanced images. For that reason, the patient was excluded, and the final study population included 95 patients.

3.3 Assessment of clinical disease activity

Basic demographic data, blood tests, medication use, endoscopic and histological findings and surgical interventions were recorded at all follow-up timepoints. Clinical course was assessed using visual curves, each reflecting a different predefined disease pattern (Appendix 1) (33). Medication use was recorded retrospectively at each prescheduled visit. The endoscopic evaluation did not follow any scoring system, and the endoscopists recorded the presence and the extent of mucosal inflammation and ulceration. Surgery was defined as any resective, intra-abdominal procedure for active CD during the follow-up period. The results of the serological analysis for the presence of perinuclear anti-neutrophil cytoplasmic antibodies (pANCAs) and anti-Saccharomyces cerevisiae antibodies (ASCAs) performed at the 10-year follow-up visit were available for analysis.

Additional data were collected at the 20-year follow-up visit. The Harvey-Bradshaw Index (HBI) was calculated, and values ≥8 were considered to represent moderate/severe disease (1). Fecal samples were collected and investigated for calprotectin by ELISA (Bühlmann fCAL™, Bühlmann Laboratories AG, Schönenbuch, Switzerland). An overview of all recorded variables that were used in this thesis is presented in Appendix 2.
3.4 Imaging

All MRI examinations were performed at 5 locations with different 1.5-T Achieva/Ingenia (Philips Healthcare, Amsterdam, Netherlands), Avanto/Aera (Siemens, Erlangen, Germany) and Excelart Vantage (Toshiba, Tokyo, Japan) scanners.

3.4.1 MRC

The MRC examinations were performed between March 9, 2011 and March 26, 2015. A shared MRI protocol was developed, consisting of a coronal and axial turbo spin echo (TSE) T2-weighted sequence, an in- and opposed-phase axial T1-weighted gradient echo sequence, a 3D single-shot TSE MRC sequence with maximum intensity projection reconstruction, and 1 of the following 2 sequences: 2D single-shot TSE MRC or thick-slab single-shot TSE MRC. More details on the MRI protocol are provided in Appendix 3.

3.4.2 MRE

The MRE examinations were performed between January 14, 2011 and March 26, 2015. The MRE protocol consisted of coronal and axial balanced steady-state free precession (b-SSFP) sequences, axial and coronal T2-weighted half-Fourier sequences with and without fat suppression and coronal fat-suppressed spoiled gradient echo T1-weighted sequences with axial reconstruction, including unenhanced and contrast-enhanced portal phase images. More details on the MRI protocol are provided in Appendix 4.

Patients fasted for 4 h prior to the study and consumed 1-1.5 L of 3 % sorbitol solution 1 h before the exam. The examination was performed in the prone position. Patients received an intravenous injection of 20 mg of scopolamine-N-butyl bromide (Buscopan; Boehringer Ingelheim, Ingelheim am Rhein, Germany) to reduce motion artifacts from bowel peristalsis. An intravenous
injection of 0.2 mL/kg body weight of gadolinium contrast medium (Dotarem, Guerbet, Roissy, France) was administered, and patients were scanned 1 min after the injection.

3.5 Image evaluation

3.5.1 Detection of PSC-like lesions

Two experienced abdominal radiologists individually evaluated MRC images on a picture-archiving and communication system (PACS) workstation. The reviewers were blinded to the patients’ previous imaging findings and clinical data. The reading procedure was initially rehearsed with 10 MRC examinations. Bile duct strictures, focal dilatation, wall irregularities, and beading at the level of extra- and intrahepatic biliary ducts were graded as being present or absent. The presence of PSC lesions was graded from 1 to 5 (1, present; 2, probably present; 3, uncertain; 4, probably not present; 5, not present). Disagreements were resolved by consensus when the final diagnosis was made. Ratings of “definitely present” and “probably present” were considered positive. The MRI progression risk score (175) was assessed in all patients with positive MRC findings. Images were reviewed in consensus, and the score was calculated as follows: 1 × dilatation of the intrahepatic bile ducts + 2 × liver dysmorphism + 1 × portal hypertension.

3.5.2 Assessment of accumulated bowel damage

A gastroenterologist and a radiologist jointly calculated the LI retrospectively based on the exams that were performed as part of the 20-year follow-up visit. The investigators scored according to the already-published protocol (Appendix 5). All patients underwent MRE. They were offered a colonoscopy, while upper endoscopy was performed at the investigator’s discretion. Perianal disease was evaluated by clinical examination and MRI. A detailed history of
previous surgery was collected for each patient. Calculation of the LI was done using the Microsoft Excel (Microsoft Corporation, Redmond, WA)-based calculator provided by the LI study group.

3.5.3 Assessment of bowel inflammation

Two experienced abdominal radiologists blinded to the patients’ previous imaging findings and clinical data individually evaluated MRE images. The reading procedure was initially rehearsed with 10 MRE examinations not included in the study. Disagreements were resolved by consensus when the final diagnosis was made. Next, the observers retrospectively applied the MEGS scoring system individually for each patient.

The bowel was divided into nine segments (jejunum, ileum, terminal ileum, coecum, ascending, transverse and descending colon, sigmoid and rectum), and each segment was scored in relation to the following MRI features: mural thickness, mural and perimural T2 signal, the level and pattern of post-contrast T1 enhancement and evaluation of colonic haustral loss (Table 6). The segmental score was multiplied by a factor depending on the length of the affected segment (0–5 cm: factor 1, 5–15 cm: factor 1.5, >15 cm: factor 2). The global score was calculated by summing the scores for all nine segments. Another 5 points per patient were added for the presence of any extra-enteric complications, such as enlarged mesenteric lymph nodes (≥1 cm measured in shortest diameter), the comb sign, abscesses and fistulas.
Table 6. Scoring method for each bowel segment according to Magnetic resonance enterography score (MEGS), modified from ref. (162).

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mural thickness</td>
<td>&lt;3 mm</td>
<td>&gt;3-5 mm</td>
<td>&gt;5-7 mm</td>
<td>&gt;7 mm</td>
</tr>
<tr>
<td>Mural T2 signal*</td>
<td>Equivalent to normal bowel wall</td>
<td>Dark grey bowel wall on fat-sat images</td>
<td>Light grey bowel wall on fat-sat images</td>
<td>High bowel wall signal approaching luminal content</td>
</tr>
<tr>
<td>Peri-mural T2 signal</td>
<td>Equivalent to normal mesentry</td>
<td>Increase in mesenteric signal</td>
<td>Small fluid rim (≤2 mm)</td>
<td>Large fluid rim (≥ 2 mm)</td>
</tr>
<tr>
<td>T1 enhancement**</td>
<td>Equivalent to normal bowel wall</td>
<td>Bowel wall signal increased, but significantly less than nearby vascular structures</td>
<td>Bowel wall signal increased, but somewhat less than nearby vascular structures</td>
<td>Bowel wall signal approaches that of nearby vascular structures</td>
</tr>
<tr>
<td>Mural enhancement pattern</td>
<td>N/A or homogeneous</td>
<td>Mucosal</td>
<td>Layered</td>
<td></td>
</tr>
<tr>
<td>Haustral loss (colon only)</td>
<td>None</td>
<td>&lt;1/3 segment</td>
<td>1/3-2/3 segment</td>
<td>&gt;2/3 segment</td>
</tr>
</tbody>
</table>

*compared with normal bowel
**compared with nearest vessel

3.6 Statistics

Continuous variables are described as the mean or median, including suitable measures of variability. Categorical variables are described as proportions and percentages. All statistical analyses were performed using SPSS v. 23.0 (Paper I) and v. 24.0 (Papers II and III). The criterion of statistical significance was P<0.05. The statistical tests applied in this thesis are summarized below (Table 7).
Table 7. Summary of statistical tests used in each paper.
*PABAK – prevalence-adjusted bias-adjusted kappa

Student’s t-test was used to compare continuous variables. Alternatively, Wilcoxon’s rank sum test was used to compare non-normally distributed continuous data. The chi-square test was used to compare categorical variables. In cases of violation of the assumptions of the chi-square test, Fisher’s exact test was applied. Analysis of variance (ANOVA) was used when comparing the mean scores of more than two groups.

The intra- and interobserver agreements were examined by kappa (κ) statistics for categorical data and Bland-Altman plots and intraclass correlation coefficients (ICCs) for continuous data. A κ value of <0.20 represented poor agreement, 0.21–0.40 was deemed fair, 0.41–0.60 moderate, 0.61–0.80 good, and 0.81 represented excellent agreement. The independent associations between the accumulated damage and bowel inflammation scores and several clinical variables were examined by univariate linear regression analysis.
3.7 Ethics

The IBSEN study was approved by the Regional Committee for Medical Research Ethics in Southeastern Norway (REK, Helse Sør-Øst). The study was conducted in accordance with the Helsinki declaration. All patients gave their informed written consent and could withdraw from the study at any time point.
4. Summary of results

4.1 Paper I


Primary sclerosing cholangitis (PSC) is a chronic inflammatory disease of the bile ducts, which is highly correlated with inflammatory bowel disease (IBD). The true prevalence of PSC among patients with IBD remains unclear. Determining the exact prevalence of PSC in IBD is important because concomitant PSC demands an extended follow-up period due to an increased risk of cholangiocarcinoma and colon cancer. Patients with IBD might be screened for PSC using magnetic resonance cholangiography (MRC). In this study, we aimed to estimate the frequency and distribution of MRC-detected lesions that indicate PSC in patients with IBD 20 years after their initial diagnosis and to identify clinical characteristics associated with these findings.

We performed a 20-year follow-up analysis of a population-based cohort of 756 patients in Southeastern Norway. Of these subjects, 470 attended the follow-up evaluation, in which they were offered routine clinical blood testing and ileocolonoscopy. MRC was performed in 222 patients with ulcerative colitis and 100 patients with Crohn’s disease. In the MRC examination, 24 patients (7.5 %) were found to have PSC-like lesions; only 7 of these patients (2.2 %) were known to have PSC. One patient was initially missed, and 1 had small-duct PSC; thus, the final prevalence of PSC was 8.1 %. Extensive colitis, a high prevalence of colectomy, and chronic and continuous symptoms of IBD occurred in significantly more patients with suspected PSC than without PSC (P=0.029, P=0.002, and P=0.012, respectively). Among patients with subclinical features of
PSC, the MRC progression score for PSC increased when they were re-examined after a median of 3.2 years (P=0.046).

In conclusion, the MRC screening of patients with long-term IBD showed that the prevalence of PSC was approximately 3-fold higher than that detected based on symptoms (Figure 5). Sixty-five percent of patients had subclinical PSC associated with progressive IBD, with no biochemical abnormalities and mild disease, based on radiology findings. The extended follow-up period of the subclinical cases revealed subtle radiological progression.

**Figure 5.** Prevalence of primary sclerosing cholangitis in patients with long-standing IBD. Reprinted from Weersma et al. (181) with permission from Elsevier.
4.2 Paper II


Magnetic resonance enterography (MRE) has been implemented in patient care as a valuable supplement to endoscopy and provides detailed information on the extent and complications of Crohn’s disease (CD). MRE findings are used in the calculation of the Lémann index (LI), a standardized score developed for the assessment of bowel damage in CD. This index characterizes accumulated bowel damage by combining clinical findings, diagnostic imaging results and surgical resection history. The long-term outcomes of CD are uncertain; in this study, we aimed to assess bowel disease and damage in patients with CD using MRE and the LI score.

We performed a follow-up analysis of a population-based cohort of 237 patients in Southeastern Norway diagnosed with CD from 1990 to 1993. Twenty years after diagnosis, 156 attended the evaluation, in which they were offered routine clinical blood tests and colonoscopies. Ninety-six patients were examined by MRE, and LI scores were calculated for these patients. The independent associations of the LI with clinical variables were examined by univariate analysis.

Sixty-five patients (67.7 %) had CD manifestations based on findings from MRE (36.9 %), colonoscopy (29.2 %), or both (33.9 %). MRE findings changed the disease classification for 8 patients (8.3 %). The median LI was 4.6 (interquartile range: 17.5) and was associated with a younger age (P=0.02), the complicated ileocolonic phenotype (P<0.001), and the use of biological (P<0.001) or immunosuppressant therapies (P=0.045). Factors independently
associated with the LI during the follow-up period were age, complicated
disease, medication use, and markers of inflammation.

In summary, we found that two-thirds of the examined patients had imaging
features of CD, half of which were only detectable by MRE (Figure 6). Bowel
damage was associated with a young age and complicated and ongoing active
disease two decades after diagnosis. Additionally, MRE proved its role as a
necessary supplement in the clinical assessment of CD location and behavior.

Figure 6. Unexpected finding in a 48-year-old man who reported that the disease was
quiescent; the colonoscopy exam was normal. The image shows an intra-abdominal
fistula between the terminal ileum and sigmoid (arrow). There were additional
findings in the ascending colon (not shown). The resulting LI score was 12.3. Reprinted
from Lunder et al. (182).
4.3 Paper III


We performed a 20-year follow-up analysis of a population-based cohort of CD patients in Norway, where ninety-five patients were examined by MRE and the calculated MEGS. Observer agreement was assessed with kappa statistics, intraclass correlation coefficients (ICCs) and Bland-Altman plots. The independent associations of the MEGS with clinical variables were examined by univariate analysis.

Thirty-five (36.8 %) patients had active inflammation mostly affecting the ileum (53.1 %). The median MEGS was 5 (IQR: 18.5), and it was associated with the C-reactive protein level (P=0.01), elevated fecal calprotectin (P=0.001), mucosal ulceration on endoscopy (P=0.03), complicated disease (P=0.04), chronic disease patterns (P=0.006) and medication use (P=0.007). The interobserver Bland-Altman limits of agreement for the MEGS were -9.53 to 6.77. The ICC for the MEGS was 0.98 (95 % CI: 0.97 to 0.99).

In conclusion, approximately one-third of patients had moderate or severe inflammation according to the MRE-based activity score (MEGS) 20 years after the diagnosis (Figure 7). The MEGS had a high reproducibility, and it was significantly associated with the clinical and biochemical parameters of active inflammation in a population with longstanding CD.
**Figure 7.** Intra-abdominal fistula involving terminal ileum and transverse colon (arrow). A 47-year-old male treated with immunosuppressives for the past 9 years reported no bowel symptoms at the 20-year follow-up. There was an additional affection of the rectum (not shown). The mean MEGS was 29.5.
5. Discussion

The incidence and prevalence rates of IBD are increasing globally. The disease strikes young individuals with substantial personal and socioeconomic consequences. The etiology of IBD is still unclear, and the treatment is symptomatic. In general, there is a paucity of population-based studies with long follow-up periods because the work is expensive, tedious, and requires transparent and well-organized medical systems. However, fully assessing the disease course in a general IBD population is valuable and necessary to direct further research and evaluate and guide treatment strategies.

In recent years, diagnostic imaging has entered the world of gastroenterology, offering the reliable, consistent and gentle work-up of patients with IBD. Today, it is an integral part of patient care. However, a standardized assessment of the disease extent and behavior in a general IBD population by means of MRI has never been done before. The general objective of this thesis was to investigate MRI findings in patients with long-term IBD. We aimed to establish the prevalence of PSC in patients with IBD and to assess the bowel damage and inflammation in patients with CD. This thesis has hopefully shed some light on the long-term effects of IBD in a general population. The methodological approach, results and futures perspectives are discussed in more detail below.

5.1 Study design and population

The IBSEN study is a longitudinal, observational study of patients diagnosed with IBD between 1990 and 1994 in four counties of Southeastern Norway with an estimated population count of approximately 1 million. General practitioners and private practice gastroenterologists recruited the patients. Although it is possible that some patients were missed, we are quite confident that the cohort is close to complete. The Norwegian health system is well organized and
transparent. The population is consistent, and patients are usually loyal to their care providers. Inherently, this population-based study should provide results that are generalizable to the whole IBD population. Furthermore, the diagnosis of IBD was based on standardized criteria, including endoscopic and histological parameters, within a short period of time, ensuring uniform assessment.

Patients were invited to prescheduled standardized follow-up visits at 1, 5, 10 and 20 years after diagnosis. Large amounts of data were gathered prospectively at each time point, making it is less susceptible to bias than other observational study designs. However, prospective cohort studies are sensitive to attrition, especially when the follow-up time is long. During the follow-up period of 20 years, patients have disappeared due to relocation, death and loss of interest in the study. The 20-year follow-up analysis included 470 of all living patients with confirmed IBD (78.5%). MRC and MRE were performed in 322 patients with IBD (53.7%) and 96 patients with CD (48.2%), respectively. The fact that only half of the patients still living 20 years after the initial diagnosis were examined calls into question the generalizability of the reported results. Was there a selection bias in favor of patients who experienced abdominal symptoms and for that reason accepted an MRI examination? Still, the study of basic demographic and clinical data revealed no statistically significant differences between the initial patient population and the subgroups of patients examined by MRI. The losses to follow-up seem to be undifferential. Although this suggests that our findings might be valid for the whole population, the results should be interpreted with some caution.

In the first paper, the main goal was to assess the accumulated prevalence of PSC in patients with IBD. The prospective cohort design is less practical when the outcome of interest is rare, as in the case of PSC. The disease can have a long latency, and the long-term follow-up examination of patients can lead to differential loss to follow-up and bias. According to the mortality data collected
from the Norwegian Causes of Death registry and hospital records, there was only one case of cholangiocarcinoma in a patient with known PSC. One patient died of cancer in the papilla of Vater region, which could have been related to undiagnosed PSC. Overall, the risk of CCC is low, and unrecognized PSC does not seem to be a major cause of death in the cohort. This is in accordance with other studies reporting an annual CCC risk of 0.5–1 % (94). Additionally, this study was a cross-sectional analysis at the 20-year follow-up timepoint, and a longer follow-up time could possibly reveal more cases of PSC. In sum, the reported prevalence estimate might be considered relatively conservative.

Another major limitation of the first paper is the lack of a control group. The ideal group would be a non-IBD population group matched in gender and age and screened for bile duct changes by MRC. Retrospectively assembling a group of patients who had MRC performed at our institution would be achievable. However, this was considered as an inappropriate strategy because there would already exist an indication for MRC in these patients. Consequently, that would not be a screening for bile duct abnormalities in presumably healthy patients. At present, there are no published reports on PSC-like bile duct changes in healthy individuals.

5.2 PSC

The true prevalence of PSC in IBD is still uncertain, but it is important to determine because concomitant PSC demands an extensive follow-up period due to an increased risk of cholangiocarcinoma and colon cancer. Additionally, the identification of an ongoing PSC-like pathology might have implications beyond the follow-up examination of the individual patients. Clinically, the IBD in PSC has particular clinical characteristics, such as pancolitis with rectal sparing, right-sided dominance and backwash ileitis, suggesting that it could represent a "third" IBD type (62). Increasing amounts of data suggest that PSC is something more than just a complication of IBD. For studies of pathogenesis,
it is therefore extremely important to be able to separate IBD patients without PSC from individuals with a PSC-like pathology, as these may differ significantly. In this study, we used standard cholangiographic features to diagnose PSC.

5.2.1 PSC prevalence in IBD

The prevalence of clinically recognized PSC in the entire IBSEN cohort was 2.2 %. This is in line with what has previously been reported in population-based cohorts (Table 2). Studies from tertiary care centers inherently report higher prevalence rates due to selection bias. The MRC screening revealed subclinical PSC in 8.1 % of patients. Given the slightly lower sensitivity of MRC than ERCP in detecting PSC (183-186), this result might be an underestimation of PSC-like changes in this population of IBD patients.

There are few data available for comparison. In a pediatric IBD cohort (187), MRC identified 15 % of patients with PSC-like lesions. A previous study only published in abstract format in 2008 reported that 18 % of IBD patients with normal liver enzyme levels and colitis had MRC appearances consistent with PSC (188), actually representing some of the rationale for the present study. Our results align well with those data, but the reason why those were never published in a peer-review journal is unknown. Still, taken together, the data suggest that PSC may be more prevalent in IBD than previously acknowledged.

MRC is well tolerated, noninvasive and quick, making MRC a good screening method for PSC. However, we do not know whether these changes will result in overt PSC or if it means that there is an increased risk of colorectal and biliary malignancy in these patients. Another question is whether MRC findings should be classified as PSC and receive clinical follow-up accordingly. Although no medical therapy has been shown to improve the prognosis of PSC, the increased risk of serious malignancies might justify MRC screening and surveillance colonoscopy. Furthermore, diagnosing subclinical PSC in IBD
patients can help us understand the pathogenesis of IBD and possibly provide better treatments for these patients.

5.2.2 MRC screening

In our study, we performed an MRC screening. Screening is a strategy to identify the presence of an undiagnosed disease in individuals without signs or symptoms (189). While the clinical diagnosis of PSC is often made using a combination of elevated liver biochemistry levels and typical MRC findings, liver biochemistry levels were not elevated in patients with no previous history of PSC. The MRC findings were not accompanied by any evident clinical signs of PSC up to the last follow-up examination, which was performed approximately three years after the initial examination. Therefore, the obvious concern is the clinical significance of radiographical findings alone, which calls into question the value of diagnosing subclinical PSC.

MRC has become the preferred imaging modality for the initial diagnosis of PSC. Typical findings of multifocal strictures and alternating dilatations are not pathognomonic, but they are highly indicative of sclerosing cholangitis (174). Imaging patterns on MRC can vary from minor irregularities to apparent liver fibrosis depending on the stage and type of the disease. This range of cholangiographic findings from subtle to obvious can to some extent explain the moderate interobserver agreement in our study. Additionally, the low PSC prevalence rate in the current study affects the agreement calculation. Although kappa is a widely used measure of agreement, paradoxes due to the effects of marginal distributions have been described (190). The prevalence effect occurs when the trait prevalence is very different from 50%. Both high and low prevalence rates generate lower kappa coefficients. To bypass the paradoxes of kappa, it is recommended to report additional values of agreement, including prevalence-adjusted bias-adjusted kappa (PABAK) values. PABAK values reduce the influence of the prevalence and bias by using the
mean of the agreement and disagreement numbers.

Moreover, kappa is considered a rather conservative measure of agreement, and it does not necessarily reflect accuracy. The final diagnosis was made by the consensus of two experienced MRI readers based on preliminary rounds of individual, blinded assessments. With the lack of a reference standard, the consensus of experienced clinicians is the only possible basis for the determination of a final diagnostic decision. Supplementary tests, such as liver biopsy or ERCP, were not considered suitable to perform in a screening context because of potential complications. A meta-analysis of MRC performance in diagnosing PSC reported on how the prevalence of PSC would influence the posttest probability of a test result being correct (171). They found that in cases of low clinical suspicion, negative MRC results would be correct in 95% of the cases, and there would only be a 5% risk of a false-negative test result. Conversely, posttest probability given a positive MRC result would be 84%. These results indicate that in a low-prevalence patient cohort such as ours, MRC is sufficient to at least exclude PSC.

The MRC findings may well represent early signs of PSC or subclinical PSC. Normal liver biochemistry test results are not uncommon among PSC patients, and they can fluctuate over time (86, 87). Additionally, the subclinical PSC patients had mild liver involvement on MRC and a low MRI progression score, indicating a non- or slowly progressive form of PSC. The extended follow-up examination of newly detected cases revealed significant subtle radiological progression. These findings illustrate that perhaps there is a spectrum of PSC disease, supporting the notion that most diseases exist on a continuum, rather than as discrete conditions (191). The manifestations may also vary over time, or as in the case of PSC, have a long subclinical phase (59).
5.2.3 PSC-IBD

The literature suggests that patients with PSC-IBD have a quiescent IBD phenotype (192-195). In our study, subclinical PSC was associated with extensive colitis, chronic, continuous bowel symptoms and higher rates of colectomy. Contrary to previous reports, almost all PSC patients, regardless of having clinically known or subclinical PSC, had characteristics of progressive IBD. This is a surprising finding, adding to the mounting scientific evidence of a wide and overlapping disease spectrum of systemic immune-mediated disorders of the gut and liver (196).

More than two-thirds of patients with subclinical PSC were female, and the overall gender distribution in the PSC group was approximately 1:1. Other studies have shown that more than 60 % of patients with PSC are men, with a median age of onset of 30–40 years (197-200). This finding is compatible with a model where women and men have a similar predisposition to developing PSC, but women acquire a milder phenotype later in life, perhaps due to hormonal factors. These observations are supported by data from a large multi-center study of patients with PSC, which showed a later PSC onset and a lower risk of liver transplantation and death for female patients (200). Another study showed that pregnancies were associated with later PSC onset (201), indicating that hormonal factors in women may act protectively and contribute to the observed gender differences.

Another observation, in particular, deviates from the current literature: a higher prevalence of PSC-like lesions in CD than in UC was observed. This collides with the typical categorization of PSC as a disease mainly affecting patients with UC (62, 80, 87, 202). Still, there are studies that have reported similar findings. A Swedish population-based study reported PSC in 3.0 % of CD patients compared with 1.7 % in UC patients during a 4-year period (69). Other studies have confirmed comparable frequencies, up to 6.4 % in patients
with CD (75). In our study, the clinical profile was similar across the IBD subtypes in patients with PSC, supporting the notion that PSC-IBD is a separate IBD phenotype altogether. Several investigators have already suggested that making the distinction between CD and UC less relevant. It has been proposed that both IBD and PSC embody several disease entities with partly diverging and partly overlapping clinical characteristics, all existing on an immune-mediated hepato-intestinal disease spectrum (196).

5.3 Bowel damage in CD

CD is a life-long disease that is usually progressive and destructive over time (203). Persistent inflammation can lead to serious complications and permanent bowel damage, which frequently requires surgery. The full impact of the disease over time can be hard to grasp. Available instruments measure certain aspects of the disease activity at one point in time. The Crohn's Disease Digestive Damage Score (the LI score) was designed to measure cumulative structural damage to the bowel by taking into account the history of surgical resections and damage severity and extent measured by suitable diagnostic imaging modalities.

5.3.1 LI

The LI assessment of bowel damage in CD makes it possible to measure the accumulated damage over time in a standardized manner. In the final IBSEN 20-year follow-up visit, 96 patients were examined by MRE and the LI was calculated. All data were gathered prospectively, but the LI calculation was not envisioned at the 20-year follow-up; hence, the calculation was done retrospectively. The original protocol advises mandatory investigations per segment regardless of symptoms and a maximum delay of 120 days in obtaining all mandatory exams. Unfortunately, not all patients were willing to go through a complementary colonoscopy. Gastroscopy and pelvic MRI were performed at
the investigator’s discretion based on the symptoms presented at the 20-year follow-up visit. This is clearly a deviation from the original protocol. However, this is a study of disease outcome in patients with long-term CD who exhibit little or no change in symptoms and/or medication.

These deviations from the original protocol may have influenced the LI calculation. One can argue that the influence was only minor, bearing in mind the scarce contribution endoscopy findings have made in this long-term CD cohort. Additionally, in cases where colonoscopy was not performed, MRE was used as a substitute for evaluating the colon. Although the sensitivity of MRE for detecting mild lesions is lower than that of endoscopy, several studies have shown that MRE is a reliable tool for assessing colonic lesions (154, 155, 204). Nevertheless, this is a careful estimate of bowel damage 20 years after the diagnosis, and some lesions may have gone undetected.

There are also some general limitations regarding the LI calculation. It is complex to calculate because it demands interdisciplinary skills, as it comprises the results of a clinical evaluation, disease history, endoscopy and cross-sectional imaging. The interpretation of these findings can sometimes be difficult, especially if there is a mismatch in findings between different modalities. The Microsoft Excel–based calculator facilitated the LI calculation, but the consistency of the evaluation among different evaluators has not been assessed. Additionally, no clear cut-offs for bowel damage and what constitutes a significant clinical change over time have been established.

5.3.2 Accumulated bowel damage

Approximately two-thirds of the examined patients had extensive, fibrostenosing and penetrating disease, which is consistent with earlier clinical reports (40, 205, 206). Irreversible bowel damage is the main indication for surgery and according to the LI rationale, resective surgery is the ultimate bowel damage. The cumulative rate for bowel resection was 35.4 % 10 years
after the diagnosis, increasing to 42.7 % at the 20-year follow-up timepoint. In the paper by Gilletta et al. (207), LI=2 represented the 75th percentile of the pre-operative values in patients who underwent intestinal resection. These patients had symptoms that were unresponsive to medical therapy and hence had significant damage. Another study reported that an LI of 4.8 was a cut-off for bowel damage based on a clinical evaluation by a gastroenterologist (208). In our cohort, the LI had a median of 4.6 after 20 years of disease. In the original construction cohort, a mean score of 19.0 for disease duration >10 years was reported (165). Following studies have reported LI scores of 8 to 9.2 points 5-12 years after the diagnosis (207-209). However, these studies were retrospective and conducted in referral centers with a bias toward severe CD. The lower LI of 4.6 in the present study reflects that the findings come from a general CD population.

The bowel damage and LI in early CD (<2 years) range from 2.5 to 3 (207, 210). All LI-based studies hitherto have shown increasing LI values with disease duration. Additionally, the LI score and bowel damage seem to progress regardless of clinical or endoscopic activity (208). These findings lend support to other studies that have reported a discrepancy between patient-reported symptoms and objective signs of active disease (104). Consequently, these findings underline that the use of a routine assessment by cross-sectional imaging is merited in patients with CD at baseline and during the follow-up period.

5.3.3 Predictors of bowel damage

In our study, the LI was associated with ongoing active disease, indicating that surgical resections do not necessarily induce long-term remission. A retrospective cohort of 221 patients with CD found that an increasing LI over a 5-year period was associated with persistent active disease (207). Another study repeatedly assessed LI changes in patients who underwent intestinal resection
over a median follow-up period of 29 months. They found that approximately half of the patients had an increased LI and that equally many demonstrated endoscopic disease recurrence as quantified by the Rutgeerts score (scores of 3 to 4) (211). These findings are supported by large population-based studies reporting high postoperative relapse rates in long-term CD (46, 212, 213).

A young age and complicated disease were to some extent predictive of bowel damage. Several studies have reported that a young age and complicated disease behavior (stricturing and penetrating) at diagnosis predict a more serious disease course (33, 38, 214). Elevated CRP levels at the 5- and 10-year follow-up visits correlated positively with the LI, underlining that persistent inflammation plays a crucial role in bowel damage. Hemoglobin levels were negatively associated with the LI at all previous follow-up visits, inversely correlating with the inflammatory activity (215, 216). In a prospective 5-year follow-up analysis of 389 CD patients, Bhagya et al. showed that patients with anemia (hemoglobin <13 g/dL in men and <12 g/dL in women) had significantly higher LI, greater health care utilization and more clinically active disease. Additionally, there was a significant correlation between anemia status and increasing bowel damage (217).

A history of immunosuppressant and biological use was positively associated with the LI. The present cohort was initiated before the introduction of such biologicals. Consequently, patients received treatment late in the disease course and in a sporadic manner usually due to their advanced and aggressive disease. The therapy seems to have had a limited impact on the 20-year outcome. Studies have indicated that patients who received early treatment with biological therapy achieved better outcomes than those treated in the later stages of disease (218).

Few studies have investigated the effect of medical therapy on bowel damage progression by means of the LI. A recent retrospective study examined the
efficacy of different therapies on LI reduction and found that although the LI score tends to increase over time, the use of biological drugs appears to limit the progressive bowel damage (219). A single-center study prospectively followed 30 patients over a median of 32.5 months and found that anti-TNF therapy reversed bowel damage in 83 % of patients (208). The LI seems to be responsive to therapy and could potentially serve as a new endpoint in clinical trials.

5.4 Added value of MRE assessment

Half of the CD-related findings on MRE were not detectable by other exams. Additionally, the disease location and behavior status were changed in 8.3 % of the patients based on the MRE findings alone so long after the diagnosis. In a prospective study of 79 CD patients with a median disease length of 5.7 years, Greener et al. reported that the original disease classification (Montreal) changed in 47 % subjects (2). A large CT enterography study found that 12 % of the examined patients had non-acknowledged penetrating disease and extraintestinal IBD (220). A paper by Fiorino et al. (209) reported that approximately 40 % of patients with CD had bowel damage at the time of the first cross-sectional imaging study. Data from population-based cohort studies have shown that less than 20 % of patients have stricturing or penetrating CD (40, 206). In line with our findings, this discrepancy illustrates the importance of a comprehensive evaluation including cross-sectional imaging at and after diagnosis. Suboptimal assessment of the bowel, extramural and EIMs may delay the diagnosis and adequate treatment. Diagnostic delay has been reported in CD (221, 222), and it has been shown to be associated with disease complications (223).
5.5 Bowel inflammation

Measuring the location and extent of the bowel inflammation is crucial for making optimal decisions on therapy. Endoscopy is considered the gold standard for assessing mucosa. However, CD is a transmural disease with extramural findings and complications that cannot be visualized by ileocolonoscopy. CRP and calprotectin can easily be measured and used to some extent to differentiate between active and inactive disease. However, CRP levels can be normal in up to one-third of CD patients with active disease (116, 117), and calprotectin reflects colonic disease better than ileal disease (119). MRE depicts the bowel wall, surrounding structures and associated complications with a high sensitivity and specificity. Together with the abovementioned examinations, it has become indispensable in the modern care of CD patients. The MEGS maps intestinal and extraintestinal signs of inflammation both in the small and the large bowel.

5.5.1 MEGS

Recent studies have reported good interobserver agreement for the MRE-based inflammation score (MEGS) (162, 224). Additionally, in our study of patients with long-term CD, the MEGS had a high reproducibility. The calculation was based on the consensus data from two experienced observers. In the initial independent assessment, the interobserver agreement was good and moderate for the small bowel and the large bowel, respectively. Colonic preparation was not included in the MRE protocol, resulting in a somewhat lower kappa for the large bowel agreement. Impaired luminal distention of the colon challenges the evaluation and may have led to an underestimation of colonic findings in our study. This is an inherent drawback of the MEGS protocol.

Another limitation is the lack of a gold standard. Although, the MEGS is positively associated with severe inflammation with ulceration on endoscopy,
the endoscopic evaluation was descriptive and not related to any scoring system. The endoscopists recorded the presence and the extent of mucosal inflammation and ulceration. Biopsies were taken and confirmed the endoscopic findings to some extent. Therefore, there was no topographical reference standard with which we could compare the MRE results. However, this study was not aiming to assess or compare diagnostic accuracies. Several studies have assessed the performance of available modalities for the assessment of CD. After all, different modalities complement each other at best, and one cannot really talk about one gold standard. Additionally, the time span between the MRE and the clinical assessment of patients was lengthy. Still, this is a study of patients with long-term CD who exhibit little or no change in symptoms and/or medication. In addition, only patients who did not have exacerbation or a change in their medical therapy were included in the analysis.

The MEGS is a partly qualitative score and is thus somewhat subjective. Certain reader variability is expected, and usage would likely require training (225) in order to achieve acceptable accuracy. Additionally, it can be overly time consuming in clinical practice. An alternative MRE-based inflammation score, the MaRIA score, has comparable accuracy and reproducibility (224, 226), and it was initially considered for use in this cohort. However, several aspects of the MaRIA score made its use unfeasible. The score was developed in a cohort of patients with severe CD via the use of an extensive protocol, including bowel cleansing and a rectal enema. The protocol is frankly unachievable in a clinical setting. Additionally, the MaRIA score does not take into account extramural findings or the total length of the affected segments, failing to assess the full disease burden and extent.
5.5.2 Inflammatory activity

Approximately one-third of patients had moderate or severe inflammation at the 20-year follow-up visit. The median MEGS for the whole population was 5, which is considered to represent mild inflammation. There are few other studies for comparison. In the initial validation study by Makanyanga et al., 71 patients with a median disease duration of 6 years had a pooled mean MEGS of 15. In a study of patients with severe CD requiring TNF-alpha inhibitor therapy, the median baseline MEGS ranged from 26 to 28. Approximately 15 % of patients in our cohort had a MEGS within or above the same range 20 years after diagnosis.

Thirty percent of patients had a fibrostenosing phenotype at the 20-year follow-up visit according to the Vienna classification. Studies have shown that fibrosis coexists with inflammation and are often in the same segment (6, 227-229). It can be practically impossible to differentiate between the two, as the cells and processes act and influence each other in the confined space of the bowel wall. Fibrosis, muscular hypertrophy, fat infiltration and hypervascularization are all characteristic features of CD that influence the imaging findings. In this setting, the demarcation between inflammation and fibrosis is challenging. Some reports have indicated that there is a homogeneous contrast enhancement on delayed images due to slow diffusion of contrast in the dense fibrotic tissue (228, 229). Preliminary results from the IBSEN cohort indicate that over 40 % of patients with moderate/severe inflammation according to the MEGS also had fibrotic components as evaluated on delayed images (>5 minutes) (unpublished).
5.5.3 Predictive value of MRE

Studies have shown that the MEGS correlates with objective markers of inflammation, such as fecal calprotectin and CRP levels (162). This observation coincides with our results, as it appears that the MEGS can moderately predict disease activity and severity in patients who have had the disease for two decades. The MEGS has been shown to reflect long-term clinical responses and therapy-induced responses (8, 9). These studies suggest that the MEGS can serve as a surrogate biomarker of inflammation and a good marker of treatment outcomes in patients with CD.

Other studies have shown that MRI is not only a supplement to endoscopy but can predict disease progression over time. Jauregui-Amezaga et al. followed 112 patients for a median of 49 months and found that MRI findings, such as strictures and fistulas, were associated with the risk of resective surgery over time (230). Another study by Deepak et al. showed that radiological responses to treatment are associated with a reduced risk of surgery in patients with CD in the small bowel (231).

Until now, clinical trials have relied on clinical endpoints and endoscopic findings, including mucosal inflammation and healing. However, CD is a transmural disease, and there is suitable evidence that cross-sectional imaging reflects transmural disease and therapy responses adequately. Fernandez et al. showed that transmural healing was associated with improved long-term outcomes in CD (232), whereas Van Assche et al. reported that the anti-TNF agent infliximab induced the rapid improvement of transmural inflammation as assessed by MRE. Other studies, such as the Impact of early MRI ReMission As therapeutic target in Crohn’s disease patients (IRMA) study, are underway (233). In sum, transmural healing is a promising endpoint for monitoring disease progression and therapeutic responses. Treating patients to a radiological endpoint may hopefully alter the natural history of CD.
6. Conclusions and future perspectives

This work assesses the extent and severity of CD and PSC in patients with IBD by means of MRI. Moreover, it applies standardized methods and scores to quantify bowel damage, inflammation and progression in PSC. Standardized assessments are important for determining and monitoring disease activity and severity. Clinical indices are particularly important for research purposes where objective and reproducible quantification is mandatory to establish and compare the effect of treatment strategies. In recent years, radiology practice has moved from purely descriptive to more quantitative imaging. Our studies revealed unexpected PSC-like changes in patients with IBD and showed that bowel damage and inflammation are extensive in patients with long-term CD. These findings make MRI a cornerstone of the modern care of IBD patients.

6.1 PSC

PSC remains a clinical and diagnostic challenge. There are no effective medical treatments for the disease, and patients face an unpredictable risk of cancer. The link between the IBD and PSC is still a puzzle to scientists. Prospective, interdisciplinary research is needed to further characterize the disease spectrum, course and prognosis. However, there are great limitations in detecting and monitoring this disease. Diagnostic tools should ideally enable us to detect the disease early on, stage and assess the treatment response and detect cholangiocarcinoma in time for treatment. Unfortunately, the cholangiographic changes are often unspecific and appear late in the disease process. Additionally, the varying quality of protocols and images among institutions is a limiting factor in this regard. A recent publication addressed this issue by providing a minimum standard protocol for performing MRI/MRCP in PSC (173).

Future research will need to concentrate on defining the degree and extension
of inflammation and fibrosis on MRC and correlate these changes with histology and ERCP results in different disease stages. Differentiation between other forms of cholangitis and more importantly, cholangiocarcinoma, is essential. Hepatobiliary contrast agents will probably play an important role in this work. Novel quantitative techniques, such as diffusion-weighted imaging (DWI), T1 mapping and MR elastography, are promising for the assessment of liver function (234-236). DWI measures the diffusion of water molecules, which is impaired in fibrotic tissue. T1 mapping or relaxometry quantifies liver function based on T1 relaxation times after the administration of hepatospecific contrast agents. MR elastography measures liver stiffness as a surrogate marker of fibrosis. Additionally, the development and validation of MRI-based severity and prediction scores for the assessment of liver function should be a priority.

6.2 CD

Assessing disease severity in CD is difficult. Short-term measures of disease activity fail to grasp the true burden of CD, and there is a lack of validated tools with distinct thresholds. The bowel inflammation, damage and complications can go undetected for a long time, and the imaging findings do not always match the reported symptoms. Biomarkers of disease severity are needed as surrogate endpoints and stratification tools in clinical trials. They should be easy to use and compare, as well as responsive to change. Hopefully, they would facilitate risk stratification and prediction of the course of the disease. This work has just started with the LI and the MEGS. Future research should integrate MRE scores for the exact categorization of patients and as outcome measures. Transmural healing assessed by MRI is being conceptualized as an important endpoint. However, these indices need further modifications and validation before they can be incorporated into clinical routines.

Additionally, new imaging protocols are emerging. The differentiation between
active inflammation and fibrosis is challenging. Magnetization transfer MRI is sensitive to the changes in collagen content, potentially correlating with fibrosis (237). Dynamic contrast enhanced MRI quantifies tissue perfusion in the bowel wall after intravenous administration of gadolinium, adding valuable information (6, 238, 239). DWI depicts the restricted diffusion of water molecules observed in acute inflammation (240). As it can be quite unspecific, it is usually used as a supplement to conventional imaging (241). However, it can potentially replace contrast-enhanced imaging in the detection of bowel inflammation, as concerns have been raised about gadolinium contrast accumulation in the brain due to repeated imaging in individuals with normal kidney function (242, 243). In sum, cross-sectional imaging is likely to play an important role in the future management of CD.
List of references


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Radiological Potential


APPENDIX 1-6
Appendix 1. Predefined curves reflecting the course of CD symptoms over time. Reprinted from Solberg et al. (i), with permission from Elsevier.

<table>
<thead>
<tr>
<th>Curve (1-4):</th>
<th>Definitions:</th>
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<tr>
<td><img src="image1.png" alt="Curve 1" /></td>
<td><strong>Curve 1:</strong> Decrease in the severity of bowel symptoms during the follow-up period</td>
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<tr>
<td><img src="image2.png" alt="Curve 2" /></td>
<td><strong>Curve 2:</strong> Increase in the severity of bowel symptoms during the follow-up period</td>
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<td><img src="image3.png" alt="Curve 3" /></td>
<td><strong>Curve 3:</strong> Chronic continuous bowel symptoms during the follow-up period</td>
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<td><img src="image4.png" alt="Curve 4" /></td>
<td><strong>Curve 4:</strong> Chronic relapsing bowel symptoms during the follow-up period</td>
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Appendix 2. Prospectively gathered clinical variables during the follow-up used in this thesis.

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<td>Fecal calprotectin</td>
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<td>Flares in the last year of follow-up</td>
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<td>Chronic fatigue</td>
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**Appendix 3.** Magnetic resonance cholangiography (MRC) protocol. Technical parameters utilized for MRC sequences acquisition – Philips.

<table>
<thead>
<tr>
<th>Sequence</th>
<th>T2W TSE</th>
<th>T2-weighted TSE FS</th>
<th>T1W in- and out of fase</th>
<th>MRC SS 2D</th>
<th>MRC radial stack (thick slab)</th>
<th>MRCP 3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR (ms)</td>
<td>394-409</td>
<td>496-509</td>
<td>112-113</td>
<td>1082-1091</td>
<td>8000</td>
<td>1204-2110</td>
</tr>
<tr>
<td>TE (ms)</td>
<td>40</td>
<td>80</td>
<td>2.3/4.6</td>
<td>330</td>
<td>800</td>
<td>650-722</td>
</tr>
<tr>
<td>Slice thickness/gap (mm)</td>
<td>3/1</td>
<td>3/1</td>
<td>5/1</td>
<td>3/0.9</td>
<td>40</td>
<td>1,02-1.7 x 1.27-1.5 x 0.8</td>
</tr>
<tr>
<td>Orientation</td>
<td>Coronal</td>
<td>Axial</td>
<td>Axial</td>
<td>Coronal</td>
<td>Coronal</td>
<td>Coronal</td>
</tr>
<tr>
<td>Field of view</td>
<td>380 x 332-333</td>
<td>298-300 x 375</td>
<td>375/297</td>
<td>350/327</td>
<td>300 x 300</td>
<td>260-300 x 260-267</td>
</tr>
<tr>
<td>Matrix</td>
<td>216 x 208</td>
<td>340 x 234-238</td>
<td>288 x 229</td>
<td>240 x 178</td>
<td>320 x 256</td>
<td>256 x 182-205</td>
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<tr>
<td>Breath hold</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No/respiration triggered</td>
</tr>
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</table>

**Abbreviations:**
- T2W – T2 weighted
- TSE – Turbo Spin Echo
- FS – Fat suppressed
- T1W – T1 weighted
- SS – Single Short
- 3D – 3 dimensional
- TR – repetition time
- TE – time to echo
### Appendix 4. Magnetic resonance enterography (MRE) protocol. Technical parameters utilized for MRE sequences acquisition – Philips

<table>
<thead>
<tr>
<th>Sequence</th>
<th>b-FFE</th>
<th>SS T2W TSE</th>
<th>SS T2W TSE FS</th>
<th>3D THRIVE FS pre-, early- and late- post iv contrast</th>
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</thead>
<tbody>
<tr>
<td><strong>Orientation</strong></td>
<td>Axial/Coronal</td>
<td>Coronal</td>
<td>Axial</td>
<td>Coronal/axial reconstruction</td>
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<tr>
<td><strong>Slice thickness (mm)</strong></td>
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<td>4</td>
<td>4</td>
<td>Voxel size: 2.07 x 2.1 x 2</td>
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<tr>
<td><strong>Field of view</strong></td>
<td>300/420 x 400</td>
<td>375x311</td>
<td>400x300</td>
<td>405x405</td>
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<tr>
<td><strong>Matrix</strong></td>
<td>400x300/268x470</td>
<td>252x204</td>
<td>364x234</td>
<td>196x193</td>
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<td><strong>TR (ms)</strong></td>
<td>6</td>
<td>1045</td>
<td>490</td>
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<tr>
<td><strong>TE (ms)</strong></td>
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<td>80</td>
<td>80</td>
<td>1.96</td>
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<td><strong>Flip angle</strong></td>
<td>70</td>
<td>90</td>
<td>90</td>
<td>10</td>
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<tr>
<td><strong>Breath hold</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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**Abbreviations:**
- b-FFE – Balanced Fast Field Echo
- SS – Single Short
- T2W – T2 weighted
- TSE – Turbo Spin Echo
- FS – Fat suppressed
- 3D – 3 dimensional
- THRIVE - T1-weighted High Resolution Isotropic Volume Examination
- Iv – intravenous
- TR – repetition time
- TE – time to echo
### Appendix 5. Protocol for the calculation of Lemann Index. Provided by New Indexes in Crohn’s disease (IPNIC) group.

<table>
<thead>
<tr>
<th>Upper Tract/Grade</th>
<th>Strictureing lesions (so-3)</th>
<th>Penetrating lesions (po-3)</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>MRI or CT: Wall thickening &lt;3 mm or segmental enhancement without prestenotic dilatation</td>
<td>Endoscopy: superficial ulceration</td>
</tr>
<tr>
<td>2</td>
<td>Endoscopy: Lumen narrowing, passable. MRI or CT: Wall thickening ≥3 mm or mural stratification without prestenotic dilatation</td>
<td>Endoscopy: deep ulceration MRI or CT: Deep transmural ulceration</td>
</tr>
<tr>
<td>3</td>
<td>Endoscopy: Stricture, non passable MRI or CT: Stricture with prestenotic dilatation</td>
<td>Endoscopy: Fistula MRI or CT: Phlegmon or any type of fistula</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Small bowel/Grade</th>
<th>Strictureing lesions (so-3)</th>
<th>Penetrating lesions (po-3)</th>
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<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Wall thickening &lt;3 mm without prestenotic dilatation</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Wall thickening ≥3 mm without prestenotic dilatation</td>
<td>Deep transmural ulceration</td>
</tr>
<tr>
<td>3</td>
<td>Stricture with pre-stenotic dilatation</td>
<td>Abscess or fistula</td>
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</table>

<table>
<thead>
<tr>
<th>Colon/Rectum Grade</th>
<th>Strictureing lesions (so-3)</th>
<th>Penetrating lesions (po-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>MRI or CT: Wall thickening &lt;3 mm without pre-stenotic dilatation</td>
<td>Colonoscopy: superficial ulceration</td>
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<tr>
<td>2</td>
<td>Colonoscopy: lumen narrowing, passable. MRI or CT: Wall thickening ≥3 mm or mural stratification without pre-stenotic dilatation or &lt;50% of the lumen</td>
<td>Colonoscopy: deep ulceration MRI or CT: Transmural ulceration</td>
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<tr>
<td>3</td>
<td>Colonoscopy: lumen narrowing, non passable. MRI or CT: Stricture with pre-stenotic dilatation or &gt;50% of the lumen</td>
<td>Colonoscopy: Fistula MRI or CT: Phlegmon or any type of fistula</td>
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<table>
<thead>
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<th>Anus/Grade</th>
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<th>Penetrating lesions (po-3)</th>
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<tr>
<td>1</td>
<td>Clinical examination: Mild stricture</td>
<td>Clinical examination: anal ulceration MRI or CT: Simple fistula (i.e., fistula extending from the anal canal to the perianal skin, but involving only the lowermost, or none, of the anal sphincter muscles, and without any secondary tracks)</td>
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<td>2</td>
<td>Clinical examination: Frank stricture, passable</td>
<td>Clinical examination: Multiple fistulas MRI or CT: Branching fistula, multiple fistulas, or any type of abscess &gt;1 cm</td>
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<tr>
<td>3</td>
<td>Clinical examination: Frank stricture, non-passable</td>
<td>Clinical examination: Multiple fistulas with extensive anal and perianal tissue destruction MRI or CT: Extensive anal and perianal suppuration, horseshoe abscess, or fistula(s) involving or extending above the levator plate.</td>
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**Appendix 6. Errata**

Abbreviations for different types of corrections:
Cor – correction of language
Cpltf – change of page layout or text format

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<th>Type of correction</th>
<th>Corrected text</th>
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<td>i. To estimate the frequency and distribution of MRC lesions indicating PSC in patients with IBD 20 years after the initial diagnosis and to identify clinical characteristics associated with these findings........................... ii. To investigate the extent and behavior of long-term CD by MRI............</td>
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