Epidemiological aspects of Microscopic Colitis
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Epidemiological aspects of Microscopic Colitis
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Abstract


Microscopic colitis (MC) constitutes the main entities collagenous colitis (CC) and lymphocytic colitis (LC), diseases that are relatively recently described (in 1976 and 1989, respectively).

The aims of this thesis were to study the epidemiology of MC, to describe how these diseases affect patients in terms of symptom burden and health-related quality of life (HRQoL), to study potential risk factors such as familial factors, childhood circumstances, educational level, marital status, smoking and comorbidity, and to describe a cohort of patients with ulcerative colitis (UC) or Crohn’s disease (CD) and subsequent MC, and vice versa.

During 1999–2008 in Sweden, the mean annual incidence of MC was 10.2 per 10^5 inhabitants, compared with 5.2 per 10^5 inhabitants for CC, and 5.0 per 10^5 inhabitants for LC. The prevalence of MC on 31 December 2008 was 123 per 10^5 inhabitants. Women appeared to be especially affected – the female:male ratio was 3.6:1 in CC and 4.6:1 in LC.

Patients’ HRQoL is impaired both in active CC and in LC. Patients with CC in clinical remission have persisting symptoms: abdominal pain, fatigue, arthralgia and myalgia; LC patients in remission have persistent fatigue compared with controls. This illustrates that the long-term outcome is different in CC compared with LC.

Microscopic colitis is associated with a family history of MC, indicating that familial factors may play a role in the pathogenesis of this disease. We confirm earlier reports that smoking is a risk factor in MC.

In the present study population, CC was associated with rheumatic disease and previous appendicectomy. Moreover, CC and LC were associated with thyroid disease and coeliac disease and, interestingly, with a history of UC.

Most patients with UC or CD and subsequent MC, or vice versa, had UC or CD first and later developed MC. The majority had extensive UC and later onset of CC. Microscopic colitis should be considered in patients with UC or CD if there is onset of chronic watery diarrhoea without endoscopic relapse of mucosal inflammation.

Key words: microscopic colitis, epidemiology, risk factors, comorbidity, health-related quality of life

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## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>anti-TNF</td>
<td>anti-tumour necrosis factor</td>
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<td>ASR</td>
<td>age-standardized incidence rate</td>
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<tr>
<td>CC</td>
<td>collagenous colitis</td>
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<tr>
<td>CCC</td>
<td>chronic continuous course</td>
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<tr>
<td>CCI</td>
<td>incomplete collagenous colitis</td>
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<tr>
<td>CD</td>
<td>Crohn’s disease</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CIC</td>
<td>chronic intermittent course</td>
</tr>
<tr>
<td>F-ECP</td>
<td>faecal eosinophil cationic protein</td>
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<tr>
<td>F-EPX</td>
<td>faecal eosinophil protein X</td>
</tr>
<tr>
<td>GSRS</td>
<td>Gastrointestinal Symptom Rating Scale</td>
</tr>
<tr>
<td>HLA</td>
<td>human leucocyte antigen</td>
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<tr>
<td>HRQoL</td>
<td>health-related quality of life</td>
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<tr>
<td>IBD</td>
<td>inflammatory bowel disease</td>
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<tr>
<td>IBD-U</td>
<td>unclassified inflammatory bowel disease</td>
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<tr>
<td>IBS</td>
<td>irritable bowel syndrome</td>
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<tr>
<td>IBS-D</td>
<td>irritable bowel syndrome with diarrhoea</td>
</tr>
<tr>
<td>ICD</td>
<td>International Statistical Classification of Diseases and Related Health Problems</td>
</tr>
<tr>
<td>iNOS</td>
<td>inducible nitric oxide synthase</td>
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<tr>
<td>IQR</td>
<td>inter-quartile range</td>
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<tr>
<td>LC</td>
<td>lymphocytic colitis</td>
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<tr>
<td>LCI</td>
<td>incomplete lymphocytic colitis</td>
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<tr>
<td>MC</td>
<td>microscopic colitis</td>
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<tr>
<td>MCI</td>
<td>incomplete microscopic colitis</td>
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<tr>
<td>NO</td>
<td>nitric oxide</td>
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<tr>
<td>NSAID</td>
<td>non-steroidal anti-inflammatory drug</td>
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<tr>
<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>QoL</td>
<td>quality of life</td>
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<tr>
<td>SA</td>
<td>single attack</td>
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<tr>
<td>SHS</td>
<td>Short Health Scale</td>
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<tr>
<td>SOIBD</td>
<td>Swedish Organization for the study of Inflammatory Bowel Disease</td>
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<tr>
<td>SRR</td>
<td>standardized rate ratio</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin re-uptake inhibitor</td>
</tr>
<tr>
<td>UC</td>
<td>ulcerative colitis</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Introduction

History of collagenous and lymphocytic colitis

Microscopic colitis (MC) is an umbrella term for the two diseases collagenous colitis (CC) and lymphocytic colitis (LC). The first report of CC was published in 1976 by a Swedish pathologist, Clas Lindström, who reported on a woman with chronic watery diarrhoea without mucus or blood, whose rectal biopsies showed a thick collagen deposit under the colonic epithelium. In analogy with collagenous sprue, which was histologically characterized by a marked collagen layer under the surface epithelium in the jejunal mucosa as described in case reports in 1947 and 1963, Lindström chose the term collagenous colitis (CC). A few years later, in 1980, Read et al reported the results of a thorough investigation of 27 patients with severe diarrhoea of unknown origin. In eight of these patients the pathology reports revealed mild inflammatory changes despite an endoscopically normal appearance, findings that were not diagnostic of ulcerative colitis (UC). The authors named these findings microscopic colitis, although they did not correlate these mild inflammatory changes with the patients’ symptoms. In 1989 Lazenby et al performed a comparative study with CC and other forms of colitides, defining a similar condition with the same symptoms (chronic watery diarrhoea, abdominal pain, weight loss and faecal incontinence), but where the most characteristic feature of the histopathologic examination of the colorectal biopsies was intraepithelial lymphocytosis, and so the term lymphocytic colitis (LC) was coined. Over the next few years, case reports and small patient series of CC or LC were published, and by the end of 1992, it was estimated that about 446 patients with CC had been described in the medical literature. The clinical and scientific knowledge has increased considerably during the last 20 years (Figure 1) and today both CC and LC are well established causes of chronic watery diarrhoea.

Clinical presentation and diagnosis

Microscopic colitis mainly affects older people and especially women. Collagenous colitis and LC are indistinguishable by the clinical and endoscopic presentation, but the histopathologic definitions of the two diseases are separate and well defined. The main symptoms of MC are chronic watery diarrhoea, abdominal pain, weight loss and faecal incontinence. Routine blood tests as well as stool cultures are normal. There are as yet
no biomarkers available in MC. The diagnostic accuracy of the widely available faecal test, calprotectin, is low in MC in contrast to UC and Crohn’s disease (CD). However, Wagner et al reported elevated levels of the faecal eosinophil cationic protein (F-ECP) and eosinophil protein X (F-EPX) in CC patients with active disease. After treatment with budesonide and achievement of clinical remission the levels of F-ECP and F-EPX were normalized. The macroscopic appearance of the colonic mucosa is generally normal although minor endoscopic abnormalities (changes in vascular pattern or mucosal nodularity) or major ones (colonic mucosal defects) can be seen. Histopathologic assessment of colon biopsies is therefore necessary in order to make a diagnosis of MC. In both CC and LC, there are signs of chronic inflammation with mainly lymphocytes in lamina propria and epithelial damage. In addition to these findings, in CC there is a thickened sub-epithelial collagen layer of ≥10 μm underneath the basement membrane, and in LC there is an increased number of intraepithelial lymphocytes of >20 per 100 epithelial cells (Figure 2).
Figure 2a. Normal colon mucosa

Figure 2b. Collagenous colitis with a subepithelial collagen layer of ≥10 µm underneath the basement membrane and mild inflammation in the lamina propria.

Figure 2c. Lymphocytic colitis with an increased number of intraepithelial lymphocytes, of >20 per 100 epithelial cells, and mild inflammation in the lamina propria.
Epidemiology
The first epidemiologic study of CC ever, published in 1995, was conducted in Örebro, Sweden, by Bohr et al and studied the period 1984–1993.8 Until 2005, only a few centres, Terrassa in Spain,15 Iceland,16 and Örebro in Sweden,9 had reported epidemiological data on MC. The studies performed in Spain and Iceland reported similar incidence figures for CC and LC, around 2–3/10^5 person years in Spain and around 5/10^5 person years in Iceland. Both of these studies reported a 5-year period, in Spain from 1993 to 1997 and in Iceland from 1995 to 1999. The study by Olesen et al from Örebro, Sweden, in 1993–1998,9 together with the study by Bohr et al,8 gave the longest continuous study, with a total observation time of 15 years. During that time, the incidences of both CC and LC were increasing, with a tendency to level off to around 5/10^5 person years for each disorder during the last few years of the study period. All studies consistently reported a median age at diagnosis of 50–70 years, and the overwhelming majority of patients have been women, with female: male ratios having varied from 9:1 in a study on CC,8 to 2.1:1 in LC.9 Since then, the knowledge about MC epidemiology has been increasing, and there have been epidemiological reports from Olmsted County, MN, USA,17, 18 Calgary, Canada,19, 20 southern Sweden,21 Uppsala, Sweden,22 Denmark,23, 24 Terrassa, Spain,25 Central Spain,26 northern France27 and the Netherlands.28

Pathophysiology
The pathogenesis of MC is not well known. It is considered to be multifactorial. Collagenous colitis and LC may represent specific mucosal responses to different, unknown luminal agents (for example, bacterial components and several suspected drugs) in the faecal stream in predisposed individuals, leading to an uncontrolled mucosal immune response.29 This theory is supported by the observation that diversion of the faecal stream by an ileostomy normalized or reduced the characteristic histopathologic changes in CC.30 Closure of the ileostomy resulted in recurrence of symptoms and histopathologic changes.

The origin of diarrhoea in MC is considered inflammatory, and studies indicate a mix of secretory and osmotic components.31-34 The intestinal barrier function is impaired in MC,35 but the complete set of mechanisms underlying this phenomenon have not yet been revealed. Nitric oxide (NO) has been shown to affect the tight junctions between the epithelial cells of the colon, leading to increased paracellular permeability.36 Olesen
et al report that inducible nitric oxide synthase (iNOS) in the colonic epithelium is activated in both CC and LC, leading to high levels of intraluminal NO in the colon, correlating to clinical activity of the disease in terms of bowel movements. 

**Clinical course, symptom burden and quality of life**

Compared with UC or CD, the clinical course of MC is usually benign, with either a single attack (SA) or chronic intermittent disease that responds well to standard treatment. However, patients with active CC are socially impaired and report low health-related quality of life (HRQoL), on par with patients with active UC. There have been no previous studies on HRQoL in LC.

Apart from chronic watery diarrhoea, both CC and LC have been associated with abdominal pain, weight loss, fatigue, nocturnal diarrhoea and faecal incontinence, as well as arthralgia and myalgia, but the long-term symptom burden has not been studied, and most studies reporting symptom burden are uncontrolled observational studies. Most often these have reported long-term outcome in terms of improvement of diarrhoea, or have given a general statement of resolution of symptoms. Little is known about the extent of these symptoms and how often they appear in patients with MC, whether they are related to active disease or occur even in clinical remission, and whether they are important to assess in order to improve patients’ quality of life (QoL).

**Treatment and prognosis**

Microscopic colitis generally responds well to treatment and the long-term prognosis is good. Sometimes diarrhoea ceases spontaneously without treatment or after cessation of medication suspected of causing the disease. In mild cases, treatment with loperamide or cholestyramine is often sufficient. In moderate to severe cases, budesonide is the drug of choice and has been found effective in up to 80% of patients. Cochrane meta-analyses of treatment of CC and LC have shown superiority of budesonide compared with placebo, yielding odds ratios (ORs) for clinical response to treatment with budesonide of 12.32 (95% confidence interval (CI) 5.53–27.46) and 9.00 (95% CI 1.98–40.93) respectively. In CC, budesonide has been shown to be effective as maintenance treatment, with 6 mg budesonide once daily for 6 months giving a response rate of 83% and an OR of maintaining remission of 8.82 (95% CI 3.19–24.37), and with
4.5 mg budesonide once daily for 12 months achieving a clinical remission rate of 61.4% compared with 16.7% in the placebo group, yielding a treatment difference of 44.5% in favour of budesonide (95% CI 26.9–62.7%, p<0.001). However, the relapse rate is 46–82% after budesonide withdrawal. In those cases budesonide can be used again, either as intermittent courses or as a low-dose maintenance therapy. It is important to rule out coeliac disease and bile acid malabsorption in patients not responding to budesonide treatment as these diseases may coexist with MC. In patients intolerant or unresponsive to budesonide, immune modulators such as thiopurines or methotrexate have been tried though there are conflicting and no controlled data. Among the small proportion (around 1.3% of the MC cohort) of patients unresponsive to the treatments listed above, treatment with anti-tumour necrosis factor (anti-TNF) has been tried in a few patients, but these treatment options should be considered experimental. Lastly, for the patients with poor response to all medical treatment, surgery with either an ileostomy or colectomy may be a good alternative.

**Risk factors**

As smoking is associated with CD and inversely associated with UC, there is an obvious interest in studying smoking in MC. The first uncontrolled studies revealed frequencies of current smokers of 25% in CC patients and 15–47% in LC patients. Subsequent controlled studies have reported an association with smoking in both CC and LC, and in CC it has been shown that smokers develop the disease around 10 years earlier compared with non-smokers.

Several drugs have been associated with MC, and the most well-known drug in this context is lansoprazole. Other proton pump inhibitors, histamine H2 receptor blockers, non-steroidal anti-inflammatory drugs (NSAIDs) and selective serotonin re-uptake inhibitor (SSRI) have been reported associated with onset of MC.

There have been some reports of family clusterings of MC, in a total of 16 families, with two or more first-degree relatives affected by CC or LC. Whether these case reports reflect random associations, a shared environment or shared familial traits is unknown.

There have been no studies of other potential risk factors such as childhood circumstances, educational level or marital status.
Co-morbidity

Autoimmune disorders have been reported to be overrepresented in MC, especially coeliac disease (2–17%), thyroid diseases (8–21%), diabetes mellitus (5–13%) and rheumatic diseases (3–11%). Most of these studies were uncontrolled. Some used hospital-based controls while population-based control groups were used only in a few studies. Previous appendicectomy, which has been associated with CD and inversely associated with UC has not been associated with MC in previous studies. Bile acid malabsorption has been reported in 27–44% of patients with CC and in 9–60% of patients with LC. As bile acid malabsorption and diarrhoea may occur after a cholecystectomy, studies have been undertaken to analyse a possible association with MC. In these studies, previous cholecystectomy was not associated with MC. Lung cancer has been associated with CC, but the overall risk of malignancy is not increased in MC. The risk of colorectal adenomas and cancer is not increased in MC. Very little is known about other co-morbidities.

Links with ulcerative colitis and Crohn’s disease

The relationship between MC, UC and CD is unknown. There have been a number of case reports on the development of MC in patients with an established diagnosis of UC or CD, or vice versa. Furthermore, there are a few reports about synchronous occurrence of UC and CD and MC. Whether this merely represents a coincidence, or shared pathophysiological pathways, is unknown. In an uncontrolled study on LC by Olesen et al, 7% of patients reported a first-degree relative with UC or CD.
Aims of the studies

The overall aim of this thesis was to conduct epidemiological and clinical studies of MC. The specific aims of the papers were:

Study I

Study II
To report a case-control study of clinical symptoms and HRQoL in patients with CC and LC in comparison with an age- and sex-matched control group.

Study III
To report a case-control study of various background factors such as family history, childhood circumstances, educational level, smoking and overall co-morbidity in MC, using a population-based, age- and sex-matched control group.

Study IV
To describe clinical characteristics of a Swedish cohort of patients with UC or CD who later developed MC, or vice versa, and to review the literature on this topic.

Ethics

Study I: The study was approved by the ethics committee at Örebro University Hospital (500:19, §24, 1997-03-11) and by the Swedish Data Protection Authority (7038:95, 1995-12-15).

Studies II and III: These studies were approved by the regional ethics committee in Uppsala, Sweden (2005/161).

Study IV: This study was approved by the regional ethics committee in Uppsala, Sweden (2005/341).
Materials and methods

Study I

Catchment area
The catchment area of Örebro University Hospital has a mixed urban-rural population and is representative of the population across Sweden with respect to age and sex distribution and socioeconomic status. It had an average population of 180 475 inhabitants during the study period 1999–2008. The population increased by 5% from 1999 to 2008 (from 176 833 to 186 187 persons). All information about the population of the catchment area was obtained from Statistics Sweden. There are 17 primary health care clinics and a few private practitioners in the area, but no private gastroenterologists. All colonoscopies in patients living within the catchment area are performed at the Endoscopy Unit of Örebro University Hospital, and all the biopsy specimens are evaluated at the Department of Pathology at the same hospital.

Patients
Residents in the catchment area of Örebro University Hospital who were diagnosed with MC (either CC or LC) from 1 January 1999 to 31 December 2008 were searched for in the diagnosis register at the Department of Medicine by International Statistical Classification of Diseases and Related Health Problems, 10th revised edition (ICD-10), diagnostic code K52.8 or in the database of the Department of Pathology. The medical records of all cases were reviewed with respect to demographic and clinical features and histopathological findings.

Diagnostic criteria
The diagnosis was based on both clinical and histological criteria, with the clinical criteria being watery diarrhoea of more than 3 weeks’ duration, together with a macroscopically normal or almost normal colonic mucosa, and negative stool cultures.

The histopathological criteria for CC were (1) a sub-epithelial collagen band of 10 µm or more in correctly oriented sections; (2) epithelial damage with or without an increased number of intraepithelial lymphocytes; and (3) inflammation in the lamina propria with mainly lymphocytes. For LC, the histological criteria were (1) increased numbers of intraepithelial...
lymphocytes (>20/100 epithelial cells); (2) epithelial damage; and (3) inflammation in the lamina propria with mainly lymphocytes and no increased collagen layer.7

Statistics
Age at diagnosis is presented as median and range (min-max). Incidence rates, based on the time of diagnosis, were calculated as crude (all ages) and age-standardized incidence rate (ASR) by direct method to allow for the changing population age structure over time. The Örebro population in 2000 was used as the standard population. The 95% CIs of the incidence rates were computed assuming a Poisson distribution.

The patients from the previous study period, 1993–1998, were compared with the current patient cohort using standardized rate ratios (SRRs) based on the same standard population. The 95% CI of the SRR was calculated according to the approximation of Smith.109 The Wilcoxon-Mann-Whitney and age-adjusted logistic regressions were applied to compare age and sex distributions between the study populations of the two periods. Poisson regression was used to compare colonoscopy rates in two periods in the catchment area.

Studies II and III

Patients
Patients diagnosed with CC or LC at Örebro University Hospital from 1980 to 2008, using the same diagnostic criteria as in Study I, were invited to participate in this study.

Controls
Statistics Sweden identified a control group consisting of three controls per patient matched for age, sex and residential municipality. The information about the controls was delivered anonymized.

Questionnaire
In 2008–2009 a questionnaire was sent by post to patients with MC in our primary catchment area and to matched controls. Up to two reminder letters were sent. Questions about symptom burden, HRQoL using the Short Health Scale (SHS), and medications (for bowel disease) and use of analgesics formed the basis for Study II, and questions about childhood circumstances, family history, educational level, marital status, smoking,
and other diseases constituted the basis for Study III. The SHS is a four-item questionnaire representing four health dimensions: (1) symptom burden; (2) social function; (3) disease-related worry; and (4) general well-being. Responses are scored on a 100-mm visual analogue scale and presented as an individual score for each question.

**Definitions**
Active MC was defined as an average of three or more loose or watery stools per day during the week prior to completing the questionnaire, and clinical remission was defined as less than three semi-solid or solid stools per day on average.

**Statistics**

**Study II**
Age is given as median (range), and scores of different aspects of HRQoL are presented as median and inter-quartile range (IQR). Logistic regression was used to calculate OR, presented with a 95% CI. Different models were created using CC/LC patients and their matched controls, or patients with or without active disease, as dependent variables, and the different categorical answers on the questionnaire as independent variables. Adjusted ORs were also calculated with age (patients and controls were categorized into 13 age cohorts with 5-year intervals) and sex as co-factors. However, the differences between unadjusted and adjusted ORs were negligible and therefore unadjusted ORs are presented.

Continuous data from the SHS were analysed using Mann-Whitney U-test.

**Study III**
Differences between patients and controls were calculated using logistic regression, and presented as ORs with 95% CIs, as well as P-values, where a P-value <0.05 was considered statistically significant. The matching factors were age, sex, and municipality. The ORs were calculated, adjusted for age and sex. The reason for not using conditional logistic regression was that we would lose cases and controls in pairs where either was missing. When there were fewer than six variables in any cell, significance was corrected using Fisher’s exact test. When comparing median age at diagnosis in smokers and non-smokers, independent samples Mann-Whitney U-test was used.
Study IV

This retrospective study was conducted among members of Swedish Organization for the study of Inflammatory Bowel Disease (SOIBD). Forty-six Swedish gastroenterology clinics were contacted by letter about patients with diagnosis of both UC or CD and CC or LC. Inclusion criteria were patients with an established diagnosis of either UC or CD, who later in life developed CC or LC, or vice versa. Symptomatic onset of disease 2 referred to a patient with an established diagnosis 1, who later had changes in clinical presentation and presented with clinical symptoms and features of diagnosis 2. An asymptomatic onset of disease 2 was one where a patient with diagnosis 1 in clinical remission underwent a surveillance colonoscopy after long-standing disease and the biopsies gave diagnosis 2 without any new symptoms.

Patients’ files were reviewed (A.W.) with respect to clinical data, endoscopic findings, and available diagnostic biopsies from both disease 1 and disease 2 were reviewed by an expert gastro pathologist (Å.Ö.). The diagnoses of UC and CD relied on a combination of generally accepted criteria: clinical history, endoscopy, histopathology and, in some cases, radiology. The diagnoses of CC and LC were based on a combination of clinical and histopathological criteria consistent with definitions used in our previous studies. The phenotype of UC and CD was assessed using the Montreal classification, and the clinical course of MC was defined as asymptomatic, single attack (SA), chronic intermittent course (CIC), or chronic continuous course (CCC).

In the medical literature, publications for this review were identified by searching PubMed using the following MeSH terms: microscopic colitis, collagenous colitis, lymphocytic colitis, ulcerative colitis and Crohn’s disease. Additional reports were found searching the reference list of pertinent articles.

Statistics
Age, time span between diagnosis 1 and 2, and follow-up time are presented in years as median (range).
Results

Study I
During the study period, from 1 January 1999 to 31 December 2008, 96 patients living in the catchment area of Örebro University Hospital were diagnosed with CC and 90 patients with LC.

Collagenous colitis
Of the 96 incident cases of CC, 75 were female, yielding a female:Male ratio of 3.6:1. The median age (range) at diagnosis was 66 years (27–90 years), 66 (27–90) years in women and 63 (38–84) years in men. The mean annual ASR for the period 1999–2008 was $5.2 \times 10^5$ inhabitants (95% CI; 4.2–6.3/$10^5$), $8.0 \times 10^5$ (95% CI; 6.2–9.8/$10^5$) in women and $2.3 \times 10^5$ (95% CI; 1.3–3.3/$10^5$) in men. Figure 3 shows age- and sex-specific incidence rates with an incidence peak in patients 80–89 years of age.

Lymphocytic colitis
Of the 90 incident cases of LC, 74 were women, yielding a female:Male ratio of 4.6:1. The median age at diagnosis was 67 years (27–90 years), 67 (27–90) years in women and 76 (43–81) years in men. The mean annual
ASR during 1999–2008 was 5.0/10^5 inhabitants (95% CI; 4.0–6.0/10^5), 8.1/10^5 (95% CI; 6.2–9.9/10^5) in women and 1.8/10^5 (95% CI; 0.9–2.7/10^5) in men. Figure 4 shows age- and sex-specific incidence rates, with an incidence peak in patients 70–79 years of age.

![Figure 4. Age- and sex-specific annual incidence of lymphocytic colitis (LC) during the period 1999–2008.](image)

**Prevalence**

On 31 December 2008, 229 patients with MC were living within the catchment area, 126 of whom were diagnosed with CC and 103 with LC. This yields crude prevalence figures of 123.0/10^5 (95% CI 107.6–140.0/10^5) for MC, 67.7/10^5 (95% CI 56.4–80.6/10^5) for CC, and 55.3/10^5 (95% CI 45.2–67.1/10^5) for LC, assuming these are chronic conditions.

**Comparison of the present study period with the previous period, 1993–1998**

A comparison of the patients from the previous study period, 1993–1998, with the present study period showed that the median (range) age at diagnosis increased from 63 (16–89) to 67 (27–90) years (p=0.035) in the whole MC population. However, analyses by diagnosis and sex showed no significant changes except for a trend in female patients with LC, where an increase from 57(29–86) to 67(27–90) years (p=0.07) was seen.
Seventy-six out of 97 MC patients in the period 1993–1998 were women, yielding a female: male ratio of 3.6:1, whereas in the current period 149 out of 186 patients were women, giving a female: male ratio of 4.0:1. Corresponding figures for CC were 7.5:1 and 3.6:1, respectively, and the difference in sex distribution was not statistically significant for MC or CC. However, a statistically significant difference in sex distribution (adjusted for age) was observed for LC, with a female: male ratio of 2.1:1 in the period 1993–1998 vs. 4.6:1 (p=0.02) in the current period.

*Figure 5. Age- and sex-specific annual incidence of collagenous colitis (CC) during the period 1984–2008, divided into three time periods.*
Age-standardized incidence rates in the two time periods were similar for CC and LC, yielding an SRR of 1.1 (95% CI 0.8–1.5) for CC and 1.1 (95% CI 0.8–1.6) for LC (Table 2, Study I). The incidence figures in elderly patients aged >60 years were higher in the period 1999–2008 compared with 1993–1998 (Figures 5 and 6), but this finding was statistically significant only in women with LC, with an SRR of 2.2 (95% CI 1.2–3.7) (Table 2, Study I).

Figure 6. Age- and sex-specific annual incidence of lymphocytic colitis (LC) during the period 1993–2008, divided into two time periods.

Endoscopy data
The number of all annual colonoscopies increased during the entire 25-year period, from 415 in 1984 to 896 in 1993, 1247 in 1998 and 1427 in 2008. Figure 5 in Study I shows age-specific colonoscopy rates in the catchment area during three time periods. Data on endoscopies were missing for 1 year, 1994; therefore, 1994 was excluded from the analyses. The rates for the periods 1999–2003 and 2004–2008 were very similar. The age- and sex-adjusted colonoscopy rate ratio was 1.07 (1.03–1.19) during 1999–2008 compared with 1993–1998. In particular, rates were increased among individuals over 70 years of age (p<0.0001 for the interactions (period by age) in the model adjusted for sex) (Table 3, Study I).
Studies II and III

Characteristics of the study population in Studies II and III

Patients
The demographic data on the patients are shown in Figure 7. The questionnaire was completed by 226/277 (82%) patients. Fourteen of these cases did not meet the diagnostic criteria for MC and were excluded. In seven cases, the diagnosis changed during follow-up, six of them from LC to CC, and one from CC to LC. The most recent diagnosis was registered. There were 115 CC patients (97 female) enrolled in this study, with a median age of 66 (27–91) years, and 97 LC patients (79 female) with a median age of 64 (33–94) years. The patients not replying to the questionnaire (n=51) were older (CC patients, 77 (34–95) years; LC patients, 75 (31–92) years), but did not differ in sex distribution from the participating patients.

Controls
Of the controls, 627/828 (76%) answered the questionnaire (Statistics Sweden had originally selected three more controls, but they died before the questionnaire was sent) (Figure 7). Women between 60 and 79 years
of age were the most frequent respondents, and this was somewhat more prominent in the control group compared with the patient cohort. There were no statistically significant demographical differences between patients and controls. There were no reports of an MC diagnosis in the control group.

Missing data
Missing data were generally few per question; in the CC patient group, between 0% and 5%, and in the CC control group between 0% and 4% were missing items. In both the LC patient group and in the LC control group between 0% and 4% of items were missing.

Results, Study II

Symptom burden

Collagenous colitis
Of CC patients, 24/115 (21%) had active disease, 72 (63%) were in remission, and 19 (16%) were not classified, either because symptoms did not meet criteria for either group, or because data on stool frequency or consistency were missing (Figure 2, Study II). Median disease duration since diagnosis was 9.8 (1.5–18.3) years for patients with active disease and 5.1 (0.5–20.8) years for those in remission. The median age was 68 (27–91) years for those with active disease, and 66 (36–88) years for patients in remission. Current treatment for CC was budesonide (n=26; 23%), loperamide (n=16; 14%), aminosalicylates (n=8; 7%), cholestyramine (n=3; 3%) or prednisolone (n=3; 3%).

Clinical symptoms such as diarrhoea, abdominal pain, fatigue, arthralgia, myalgia, faecal incontinence, and nocturnal defecation were more prevalent in all 115 CC patients compared with controls (Table 1, Study II). A sub-analysis of the 72 patients in clinical remission showed that abdominal pain, fatigue, arthralgia, myalgia and faecal incontinence still were more prevalent compared with matched controls (Table 1, Study II). Abdominal pain was described as cramping in 45%, dull in 27%, unspecified in 21% and related to defecation in 7% of the patients. Severity of pain was reported as mild or moderate in the majority of cases, but ten (14%) patients reported abdominal pain as severe (n=6) or very severe (n=4). Patients reporting abdominal pain were younger than those without pain (63 vs. 70 years; p=0.028), but disease duration (6.0 vs. 6.1 years) or
ongoing budesonide therapy did not differ notably. Fatigue was common both among patients in remission and in patients with active disease, and was reported as severe or very severe in 31% of patients with active disease and 30% of the patients in remission. There were no sex differences in symptom burden.

**Lymphocytic colitis**

Of LC patients, 27/97 (28%) had active disease, 60 (62%) were in remission, and 10 (10%) were not classified because their symptoms did not meet criteria for either group, or because data on stool frequency or consistency were missing (Figure 2, Study II). Duration of disease was 5.6 (0.3–12.1) years for patients with active disease and 6.4 (0.5–14.8) years for patients in remission. The median age was 61 (35–84) years for those with active disease, and 69 (33–89) years for patients in remission. Current treatment for LC included budesonide (n=16; 17%), loperamide (n=12; 13%), cholestyramine (n=6; 6%) or aminosalicylates (n=5; 5%).

Clinical symptoms such as diarrhoea, abdominal pain, fatigue, faecal incontinence, and nocturnal defecation were more prevalent in LC patients compared with controls (Table 2, Study II). A sub-analysis of the 60 patients in remission showed that diarrhoea during the last week, fatigue, and faecal incontinence still were more prevalent compared with matched controls (Table 2, Study II). Abdominal pain was reported by 38% of LC patients in remission, which was not statistically different from controls, 27% of whom reported this (OR 1.7; 95% CI 0.9–3.2). Abdominal pain was described as cramping in 49%, dull in 29%, unspecified in 16% and related to defecation in 6% of the patients. Pain was reported as severe or very severe by five (8%) of the patients. Patients reporting abdominal pain were younger than those without pain (63 vs. 70 years; p=0.017), but disease duration (6.9 vs. 6.1 years) or ongoing budesonide treatment did not differ notably. Nineteen (29%) patients reported severe (n=16) or very severe fatigue (n=3). There were no sex differences in symptom burden.
Assessment of health-related quality of life using the Short Health Scale

Collagenous colitis
Patients with active disease scored significantly worse than patients in remission regarding symptom burden (median 48 (IQR 30–64) vs. 11 (0–36), p<0.001), social function (33 (10–66) vs. 5 (0–32), p<0.001), disease-related worry (60 (23–82) vs. 15 (0–39), p<0.001) and general well-being (43 (17–54) vs. 21 (10–50), p=0.001). Compared with controls, CC patients scored significantly worse regarding well-being (28 (12–51) vs. 17 (0–43), p<0.001), and this was also true when comparing patients in remission with their matched controls (21 (10–50) vs. 17 (0–39), p=0.04) (Figure 8).

Lymphocytic colitis
Lymphocytic colitis patients with active disease scored significantly worse compared with patients in remission on all four SHS dimensions: symptom burden (68 (40–83) vs. 23 (8–40), p<0.001), social function (66 (33–90) vs. 14 (4–28), p<0.001), disease-related worry (56 (42–88) vs. 17 (7–33), p<0.001) and general well-being (44 (25–63) vs. 25 (6–44), p=0.001). Patients with LC scored significantly worse compared with controls on well-being (31 (12–50) vs. 24 (6–45), p=0.04) but no difference was seen
when comparing patients in remission with their matched controls (28 (8–47) vs. 25 (7–47), p=0.31) (Figure 9).

Figure 9. Short Health Scale (SHS) scores illustrated by box plots, for patients with lymphocytic colitis (LC) with clinically active disease or in clinical remission, and matched controls. Higher scores indicate worse subjective health status.

Results, Study III

Family history, childhood circumstances, educational level and marital status

Patients with CC more often reported having a first-degree relative with MC compared with controls (OR 10.3 (95% CI 2.1–50.4, p=0.004)). Compared with their controls the LC patients significantly more often reported having a first-degree relative with MC, inflammatory bowel disease (IBD) or coeliac disease, but the numbers were small (Table 1, Study III). After adjustment for presence of coeliac disease in cases/controls who had reported first-degree relatives with coeliac disease, the association with LC disappeared (OR 2.1(95% CI 0.6–7.7, p=0.28)). Patients with MC did not differ from the controls with respect to growing up on a farm, number of siblings, and birth order, educational level or marital status (Table 1, Study III).

Tobacco use

Smoking affected the risk of MC (Table 2, Study III). In both CC and LC, there was an association with smoking, with 28% in the CC population compared with 13% in the control group (OR 4.7 (95% CI 2.4–9.2,
p<0.001)), and 26% of the LC group compared with 12% of the control group being current smokers (OR 3.2 (95% CI 1.6–6.7, p=0.002)).

We have no data on the temporal relationship between age at diagnosis and time of smoking cessation. Therefore, we included ex-smokers and current smokers in the group of ever-smokers. Ever-smokers with MC had lower age at diagnosis compared with never-smokers. In CC, median age at diagnosis was 58 (IQR 48–65) years in ever-smokers compared with 70 (IQR 56–82) years in the never-smoking group (p=0.001). With LC, median age at diagnosis was 55 (IQR 47–66) years in ever-smokers, and in the never-smoking group it was 64 (IQR 53–73) years (p=0.031).

Association with autoimmune and other diseases

Collagenous colitis
Patients with CC reported significantly more digestive diseases other than CC, as well as diseases of the skin and subcutaneous tissue and diseases from the musculoskeletal system and connective tissue, compared with the control group (Table 3, Study III).

There was an association with occurrence of inflammatory or autoimmune diseases in CC: 47% of CC patients reported one or more concomitant diseases, compared with 29% of the controls (OR 2.4 (95% CI 1.5–3.9, p<0.001)) (Table 4, Study III).

Collagenous colitis was associated with thyroid disease, which was reported by 17% of the patients compared with 9% of controls (OR 2.3 (95% CI 1.1–4.5, p=0.02)) (Table 4, Study III). There was no association with diabetes mellitus (Table 4, Study III).

Collagenous colitis was associated with a history of both UC (OR 8.7 (95% CI 2.2–33.7, p=0.002)) and coeliac disease (OR 13.1 (95% CI 2.7–62.7, p=0.001)), but not of CD (Table 4, Study III). Thirty-six per cent of the CC patients reported diseases from the musculoskeletal system and connective tissue compared with 16% in the control group (OR 3.2 (95% CI 1.9–5.5, p<0.001)) (Table 3, Study III). When restricting the analysis to inflammatory rheumatic disorders (inflammatory polyarthropathies, systemic connective tissue disorders and inflammatory spondylopathies) the difference remained (OR 1.9 (95% CI 1.0–3.5, p=0.042)) (Table 4, Study III).

An association with skin diseases was seen in CC, but the figures are small; 5% of the CC patients reported skin disease, as did 1% in the con-
control group (OR 6.0 (95% CI 1.4–26.0, p=0.018)) (Table 3, Study III). The analysis includes various skin disorders, so the association is uncertain.

Whereas previous appendicectomy was associated with CC (OR 2.2 (95% CI 1.3–3.8, p=0.003)), no association was seen with past cholecystectomy (OR 0.8 (95% CI 0.4–1.6, p=0.589)) (Table 1, Study III). The overall risk of malignancy was not different from controls.

**Lymphocytic colitis**

Patients with LC reported significantly more digestive diseases and diseases of the nervous system compared with controls (Table 3, Study III). Besides having LC, 31% of the LC patients had other gastrointestinal disorders, compared with 11% of the control group (OR 4.0 (95% CI 2.1–7.6, p<0.001)) (Table 3, Study III).

There was an association with several concomitant inflammatory or autoimmune disorders and LC, yielding an overall adjusted OR of 2.5 (95% CI 1.4–4.3, p=0.001) (Table 4, Study III).

Lymphocytic colitis was associated with thyroid disease, which was reported by 14% of LC patients and 7% of controls (OR 2.4 (95% CI 1.1–5.4, p=0.037)), but not with diabetes mellitus. There were associations with a history of UC, which was reported by 7% of LC patients and 1% of controls (OR 6.8 (95% CI 1.7–28.0, p=0.008)) and of coeliac disease, reported by 15% of LC patients and 2% of controls (OR 8.7 (95% CI 2.8–26.7, p<0.001)), but not of CD (OR 2.8 (95% CI 0.4–18.1, p=0.279)) (Table 4, Study III).

There was an association with diseases of the nervous system, which were reported by 7% of the LC patients compared with 2% of the controls (OR 4.1 (95% CI 1.2–14.2, p=0.029)), but the association disappeared when the significance was corrected using Fisher’s exact test (p=0.051) (Table 3, Study III). There was no association with past appendicectomy (OR 0.7 (95% CI 0.4–1.2, p=0.218)) or cholecystectomy (OR 1.5 (95% CI 0.8–2.9, p=0.256)) in LC (Table 1, Study III). The overall risk of malignancy was not different from controls.
Study IV

Swedish cohort

Patients
We reviewed patient files of 55 potential cases reported by 18 out of 46 clinics. Twenty-four patients were excluded as they did not meet the inclusion criteria of having two diagnoses (n=13), or because their medical data were insufficient (n=8), or there were synchronous findings of UC and CC (n=2) or UC and LC (n=1) in biopsies from the same colonoscopy.

The remaining 31 patients were included in the study (Table 1, Study IV). In all cases except one, IBD was the first diagnosis and MC was diagnosed at a later stage. The age of all patients at first diagnosis was 37 (13–73) years, and at second diagnosis 56 (31–81) years and the time period from first to second diagnosis was 20 (2–52) years. The follow-up time after second diagnosis was 2 (0–27) years.

Patients with ulcerative colitis who developed microscopic colitis
Sixteen patients (nine female) with a diagnosis of UC later in life developed CC. The age at diagnosis of UC was 43 (21–73) years. Age at diagnosis of CC was 59 (51–75) years and median the time period from first to second diagnosis was 19 (2–52) years. Fourteen patients had extensive UC (E3). Twelve patients had symptomatic onset of disease 2, i.e. they first had flares with bloody diarrhoea and macroscopically inflamed colonic mucosa typical of UC, and later the clinical presentation changed to watery, non-bloody diarrhoea with a macroscopically normal or almost normal colonic mucosa consistent with CC. The remaining four patients had asymptomatic CC, diagnosed through surveillance colonoscopy because of the long duration of UC. In two cases omeprazole or mirtazapine were possible triggers of onset of CC as treatment had been initiated 1 month before onset of symptoms. The follow-up time after CC diagnosis was 3 (0–12) years. Interestingly, six patients had flares of UC 3.5 (1–10) years after diagnosis of CC.

Five patients (two female) with a first diagnosis of UC subsequently developed LC. The age at diagnosis of UC was 35 (13–45) years, and at diagnosis of LC 56 (31–66) years and the time from first to second diagnosis was 29 (11–30) years. Four patients had extensive UC (E3) and one had left-sided disease (E2). Four patients had symptomatic onset of disease 2 with characteristic symptoms of LC. The follow-up time after LC diag-
nosis was 5 (0–10) years. One patient had a flare of UC 1 year after symptomatic onset of LC.

Patients with Crohn’s disease who developed microscopic colitis
Nine patients (all female) with a diagnosis of CD later developed MC; CC in five and LC in four patients. All five patients who developed CC had characteristic clinical symptoms. The age at diagnosis of CD was 33 (23–40) years; age at diagnosis of CC was 53 (39–79) years, and the time from first to second diagnosis was 22 (4–47) years. The maximal location of CD was ileal (L1) (n=4) and colonic (L2) (n=1), and disease behaviour was non-stricturing and non-penetrating (B1) in all cases but one with unknown behaviour. The follow-up time after CC diagnosis was 2 (1–27) years. Three patients had previously undergone an ileocecal resection for ileocecal CD, and had developed CC 4, 25 and 47 years later, respectively. One of these patients had a relapse of CD 8 years after diagnosis of CC. Lansoprazole, carbamazepine and atorvastatin were possible triggers of onset of CC in three patients.

Four patients with ileocolic CD (L3) developed LC. The age at diagnosis of CD and LC was 32 (28–45) years and 60 (44–81) years, respectively, and the time from first to second diagnosis was 29 (12–35) years. Non-stricturing, non-penetrating disease behaviour (B1) was seen in two patients, stricturing behaviour (B2) in one, and penetrating disease behaviour (B3) in one. Three of the four patients who had LC were symptomatic. The follow-up time after LC diagnosis was 1 (0–5) year.

Patient with microscopic colitis who developed Crohn’s disease
A woman with a diagnosis of CC at 42 years of age developed duodenal CD 6 years later. She was examined for abdominal pain, anaemia and weight loss. Upper and lower endoscopic procedures revealed inflammation and aphthous ulcers in the duodenum, and histopathological examination showed inflammation typical of CD with findings of cryptitis and epithelioid cell granulomas. The terminal ileum and colon were macroscopically normal, but biopsies showed a discontinuous inflammation without granulomas in the terminal ileum and colon, and there were no signs of CC at the time of diagnosis of CD. The patient was treated with azathioprine, as well as two courses of budesonide for flares of CD, and was in clinical but not endoscopic remission 2 years after diagnosis of CD.
Review of the literature

Twenty-seven patients (21 female) had comprehensive reports of IBD and subsequent MC, or vice versa (Table 2, Study IV). The age at first diagnosis was 51 (16–75) years and the time from first to second diagnosis was 7 (0.5–39) years.

Fourteen patients had IBD first and later developed MC; ten patients with UC developed CC (n=6) or LC (n=4). Of the four patients with LC, two were asymptomatic and were diagnosed due to surveillance colonoscopies because of long-standing UC. Four patients with CD developed CC (n=3) or LC (n=1). Thirteen patients with a first diagnosis of MC later developed IBD; eleven CC patients were diagnosed with UC (n=7) or CD (n=4), and two patients with LC developed UC (n=1) and CD (n=1), respectively. All eight patients who developed UC or unclassified IBD (IBD-U) had extensive colitis (E3) and four patients underwent acute colectomy due to severe colitis 0.5–4 years after their initial MC diagnosis.92, 94, 100, 114

Seven additional patients had synchronous findings of UC and CC (n=1), UC and LC (n=1), CD and CC (n=2), and CD and LC (n=3) in biopsy specimens from the same colonoscopy.96, 97, 101, 107, 108 Furthermore, 71 more cases with both IBD and MC were briefly described in a few sentences or in a table, without any clinical data or details of the clinical course given.27, 80, 95, 98, 104, 106, 115, 116
Discussion

Epidemiology of microscopic colitis

According to the World Health Organization (WHO) definition, epidemiology is the study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems. Thus, studies of epidemiology are necessary to assess the impact of a certain disease in the general population, in terms of the frequency and how the natural history of the disease affects the persons carrying the disease. They can also give important clues on risk factors and pathophysiology and, in the long run, help find the best treatment options.

Microscopic colitis, including CC and LC, are relatively recently described disorders. Since the first reports, the knowledge has been steadily increasing and more has become known about the epidemiological characteristics. From the beginning, both CC and LC were considered to be rare, but as the awareness increased, it has become evident that they are common diseases in Western Europe and North America, especially in the elderly population. Still, very little is known about the epidemiology of MC in other parts of the world. There have been reports worldwide of MC in patients with chronic diarrhoea.117-123

Our population-based epidemiological study from Sweden is one of the longest continuous surveys of MC, with a total observation period of 25 years. The methods for finding patients differed in different study periods. In 1993-1998, all patients who were referred for colonoscopy due to nonbloody diarrhoea and having macroscopically normal or almost normal colonic mucosa were reassessed with respect to clinical symptoms and histopathology. Patients fulfilling the diagnostic criteria for CC or LC were then included in the study. In 1984-1993 and 1999-2008 cases already diagnosed with MC were identified by searching diagnosis registers. Clinical data and histopathology were reassessed, and those not meeting the diagnostic criteria for CC or LC were excluded. Since biopsies from patients who underwent colonoscopy due to diarrhoea were regularly reassessed in weekly clinical pathologic conferences, the risk of overlooking MC cases was small. After rising annual incidences of CC in the 1980s and early 1990s,8 the figures have been stable during the last 15 years at around 5/105 Swedish inhabitants each for CC and LC, and around 10/105 for MC.9, 124 The prevalence of MC in the Swedish population on 31 De-
cember 2008 was 123/10^5 inhabitants. These figures are on par with the incidence figures reported in other epidemiological studies performed in Sweden\textsuperscript{21, 22} and Iceland.\textsuperscript{16} The epidemiological study of MC in Olmsted County in the USA had a follow-up time of 25 years.\textsuperscript{17, 18} In the articles reporting the Olmsted study, the pattern of an initial rise in incidence rates of CC and LC which eventually levelled off is similar to the evolution of incidence rates in the current study. The incidence figures from other studies in Europe\textsuperscript{15, 23-28} and North America\textsuperscript{19, 20} are divergent, and the differences may be due to different background populations, environmental exposures, health care systems, referral patterns, study designs and/or diagnostic criteria.

Diagnostic criteria in MC are well defined, and the observer variability regarding the histopathological diagnosis appears to be low.\textsuperscript{125, 126} However, there are still issues that need to be clarified in order to find uniform diagnostic criteria for CC and LC, namely regarding the numbers of positive biopsies and the numbers of involved segments required for a morphological diagnosis. The topographic distribution of histopathologic changes is controversial, as there is no consensus on the extent or distribution of histopathological abnormalities required for diagnosing MC. There have been recommendations to perform a full colonoscopy and to obtain two or more biopsies from the right, transverse, left and sigmoid colon in addition to sampling endoscopically visible abnormalities,\textsuperscript{127, 128} but these recommendations came after most of the epidemiological studies had been carried out. Differences in these respects may account for some of the reported geographic differences in incidence rates (Table 1).

We reported increased age-specific incidence rates among the elderly (aged >60 years), which can be explained by increased disease awareness, an increasingly older population and rising colonoscopy rates among the elderly. Other possible explanations could be the increased use of certain drugs (e.g. proton pump inhibitors, serotonin re-uptake inhibitors and NSAIDs), or the increased presence of other risk factors important for the development of MC in the elderly.

Since the early 2000s, there has been increasing focus on incomplete and variant forms of MC.\textsuperscript{23, 129-135} It is a heterogeneous group which includes incomplete MC (MCi) and variant forms such as cryptal LC,\textsuperscript{136} pseudomembranous CC\textsuperscript{137-142} and MC with giant cells.\textsuperscript{143-145}
Incomplete MC can furthermore be divided into incomplete LC (LCi) and incomplete CC (CCi), and there have been proposed histopathological criteria for these subtypes.\textsuperscript{128} LCi has also been named paucicellular LC.\textsuperscript{129} In incomplete and variant forms of MC, patients present with clinical symptoms indistinguishable from MC, respond well to the same treatments used in MC, but do not meet all the histopathological criteria for CC or LC. A study of MC in Denmark reported the estimated yearly incidence of MCi to be 4.0 per 10\textsuperscript{5} inhabitants during 1999–2010.\textsuperscript{23} We diagnosed five patients with MCi during the study period 1999–2008, but since they did not meet the diagnostic criteria for either CC or LC, they were not included in our study. The inclusion of MCi in the epidemiological study of MC would have given us a more complete understanding of these new disease entities. However, the concept of MCi was not well-defined at the time of planning of the study and has gradually evolved.

<table>
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<th>Region, study period</th>
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Table 1. Reported annual incidence per 100,000 inhabitants in population-based epidemiological studies of collagenous colitis (CC), lymphocytic colitis (LC) and microscopic colitis (MC). The current study is given in italics.
during and after completion of study. A different method of case finding had been required, and re-evaluation of biopsy specimens of all patients examined due to chronic watery diarrhoea had been necessary in order to recognize cases of MCi.

The main message in this study is that MC is common, especially in the population aged ≥60, and therefore patients with chronic diarrhoea should be referred for colonoscopy with biopsies in order to rule in or out MC. Scoring systems based on clinical parameters have been proposed to predict MC prior to colonoscopy. They have been shown to have a sensitivity of >90% and specificity of 45-50%. By using these, it is possible to select which patients to obtain mucosal biopsies from in order to cut costs, but they do not reduce the need for colonoscopy.

**Symptom burden and health-related quality of life**

**Symptom burden**

In Study II we reported that, apart from having diarrhoea, MC patients also suffer from other symptoms, irrespective of disease activity. Abdominal pain, fatigue, faecal incontinence and nocturnal defecation are symptoms associated with both CC and LC. Around half of the patients reporting occurrence of abdominal pain report the character as cramping. In CC patients in remission, abdominal pain was more prevalent than among the controls. These findings may be part of the symptom spectrum of MC, but also raise the question of diagnostic overlap between MC and irritable bowel syndrome (IBS), which will be discussed later. Above these symptoms, arthralgia and myalgia was reported by more than 50% of the CC patients, and the difference compared with the control group persisted even in clinical remission. That MC patients have a heavy symptom burden is known from previous studies, but this is the first comparison with a randomly selected and population-based control group. However, that MC patients in clinical remission still have more symptoms than their controls is a novel finding that emphasizes the necessity to address other symptoms when treating MC patients as these may be of importance to QoL.

**Health-related quality of life**

The assessment of HRQoL is known to be of great importance in both clinical trials and clinical practice. There have been several questionnaires with multiple questions that have the disadvantage of being time-
consuming and complicated to fill in and also to interpret. The SHS is a short, four-item questionnaire representing all four of the health dimensions symptom burden, social function, disease-related worry, and general well-being. It was originally designed and validated for use in UC and CD.\textsuperscript{151, 152} It is simple and quick to complete and does not need further calculations. It is valid, reliable and responsive, i.e. changes in SHS reflect changes in disease activity, and therefore SHS is suitable for repeated use in clinical practice. The SHS has been validated and used in two studies of HRQoL in CC,\textsuperscript{39, 40} and also in IBS.\textsuperscript{153}

Quality of life has been studied to some extent in MC. The first reports were in treatment studies of CC and LC, in which QoL was reported to be significantly better in patients who responded to treatment compared with those who did not.\textsuperscript{154-156} Later, there have been studies of CC reporting a significantly reduced HRQoL in patients with active disease.\textsuperscript{39, 40}

In this study, we confirm the results of previous studies of HRQoL, that CC patients report a significantly reduced HRQoL when having active disease. This is the first case-control study of HRQoL in LC reporting a significantly reduced HRQoL in patients with active disease. All MC patients with active disease had significantly reduced well-being compared with patients in clinical remission and also in comparison with the controls. Collagenous colitis patients in clinical remission had significantly reduced well-being in comparison with their controls, which was not the case in LC.

**Family history, smoking, co-morbidity and other risk factors**

In previous case reports, a total of 16 families have been reported in which two or more first-degree relatives were affected by CC or LC; in ten of these reports, two sisters were affected and in six out of these ten families both siblings had CC.\textsuperscript{66-75} In Study III we report associations with a family history of MC in patients with CC and LC compared with their controls, even though the numbers of observations were small. This finding has not been reported previously, and in combination with earlier reports of family clustering of MC, it may indicate that shared environmental factors and/or family factors are of importance in MC. Further studies of such factors and the impact of genetics in MC are warranted.

We found no association with childhood environment as reported in a previous study on UC and CD.\textsuperscript{157} In that study, growing up on a livestock farm for the first 5 years in life was associated with a lower risk of IBD but only in subjects born after 1952, and it was speculated that lower
microbial diversity in the 1950s and later might explain this finding. In our study, the majority of the subjects were born before 1952, which perhaps explains why place of upbringing had little bearing on the development of MC, in this study population.

Smoking has been associated with several effects in the gut, by altering the mucus layer in the colon, modifying cytokine production, modulating humoral and cellular immunity (both innate and adaptive immune responses), affecting the microvasculature, reducing the smooth muscular tone and activity, and increasing gut permeability.\textsuperscript{158-161} Interestingly, a study of healthy smokers by Biedermann et al reported profound shifts in the gut microbiota and an increase in microbial diversity after smoking cessation.\textsuperscript{162}

The effects of smoking on IBD are well documented. There is an inverse association between smoking and UC, with an increased risk of UC after smoking cessation,\textsuperscript{163, 164} but smoking does not seem to affect the disease course in terms of colectomy rate, flare of disease activity, proximal extension of disease or development of pouchitis.\textsuperscript{165} Smoking is deleterious in CD as it increases the risk of falling ill and worsens the disease course in terms of increased risks of flare of disease activity, abscess and fistula formation and need for surgery.\textsuperscript{163, 164, 166-168} Cessation of smoking alters the disease course in CD; ex-smokers have relapse rates and disease activity comparable to non-smokers.\textsuperscript{168, 169} Smoking is an important risk factor in MC, increasing the risk of developing disease three to fourfold, and smokers develop disease around 10 years earlier than non-smokers. These results are in line with previous studies on smoking in MC.\textsuperscript{22, 57-60} There are insufficient and conflicting data on the effect of smoking on the clinical course of MC. Fernández-Bañares et al report no effect of smoking on clinical symptoms at diagnosis or clinical remission rate, while Münch et al found more severe symptoms and lower remission rates in smokers.\textsuperscript{60, 170}

There are associations with inflammatory autoimmune disorders in both CC and LC, and we have reported associations with coeliac disease, thyroid disease, rheumatic disease and UC in CC, and with coeliac disease, thyroid disease and UC in LC. The association with UC is new; the other associations have been reported in other studies.\textsuperscript{6, 19, 38, 45, 47, 57, 72, 76, 78} In the present study material, previous appendicectomy was associated with CC, but not with LC, and cholecystectomy was not associated with MC at all. Previous studies have reported no association with either appendicectomy or cholecystectomy.\textsuperscript{57, 85} We find the association with UC interesting, and think that it deserves further study.
Ulcerative colitis, Crohn’s disease and microscopic colitis

The purpose of Study IV was to describe patients with IBD who develop MC later in life, and vice versa. We report 30 patients with UC or CD who developed MC 20 (2–52) years later, and one patient diagnosed with CC who developed duodenal CD 6 years later. We searched the medical literature and found 27 detailed cases, 14 of which were patients with IBD who later developed MC while 13 were MC patients who later developed IBD. These 58 detailed cases of IBD and subsequent MC (or vice versa) give us a much clearer view of the phenomenon of interest. The patients in both groups shared many features: around 70% of the patients had UC and around 30% had CD. Among patients with MC, more than 70% in both groups had CC. Of the patients with UC, the majority had extensive colitis, and in all the cases with MC who later developed UC or IBD-U, the colitis was extensive. Four of eight patients with MC first and with later onset of UC or IBD-U had an acute colectomy due to severe colitis.

The main difference between these two groups is that around half of the cases reported in the literature first had MC and later developed IBD; however, only one patient out of 31 in our study showed this pattern. As the incidence peak of IBD in general is between 20 and 40 years of age, and the incidence of MC peaks above 50 years of age, one would expect the development from IBD to MC to be more common. This difference is likely due to publication bias as more spectacular cases will be published as case reports. Another explanation might be that patients with UC or CD who later develop MC may be clinically interpreted and handled as IBS cases. Furthermore, the diagnoses of CC and LC were not well established in the 1980s and 1990s, and the risk of overlooking a diagnosis of MC in a patient who later developed IBD was substantial before the middle of the 1990s.

Of course, we do not know whether these observations may merely represent occurrence of two different bowel disorders in one and the same individual. Alternatively, it may be hypothesized that IBD and MC share common pathophysiological pathways and the type of inflammation depends on which luminal agent(s) triggers inflammation.

This study raises many questions, the most obvious and important of which, in my mind, is how the most common bowel diseases, MC, UC, CD and IBS, are interrelated and sometimes overlap each other. The IBS diagnosis is based on symptom criteria while the other diagnoses are based on combinations of clinical, endoscopic and histopathological criteria. In
Study II, we discussed the potential overlap between MC and IBS. Patients with MC report abdominal pain, diarrhoea and fatigue, despite clinical activity of MC, symptoms that also are typical of IBS. There is considerable overlap of symptoms between MC and IBS, and around 50% of the patients with MC meet the Rome II or Rome III criteria for IBS. In a meta-analysis of prevalence of MC among patients with functional bowel disorders, by Guagnozzi et al, 7% (95% CI 3.6–11.4) were diagnosed with MC. Microscopic colitis and IBS may occur after gut infections. Post-infectious IBS, in which the irritable bowel syndrome with diarrhoea (IBS-D) phenotype predominates, has been associated with low-grade mucosal immune activation and alterations in gut permeability. In MC, an infectious cause has been suspected, especially in patients with a sudden onset of disease. There have been reports of gut infections with Campylobacter jejuni, Yersinia enterocolitica and Clostridium difficile preceding MC.

In UC and CD, several studies have reported IBS-like symptoms in around one-third of UC and half of CD patients in remission. This makes IBS-like symptoms more than twice as common in IBD patients compared with the general population. There are several possible explanations for this phenomenon: persistent low-grade inflammation, IBD-induced dysmotility and IBD-induced increase in mucosal permeability. There also are some similarities between IBS-like symptoms in IBD patients and post-infectious IBS as both seem to be caused by post-inflammatory mechanisms, and there is evidence of an altered gut microbiome in both IBD and IBS.

An altered gut microbiome has also been reported in studies of MC, and it may be speculated that the composition of the faecal microbiota holds the clue to the kind of pathology that will appear in the gut – IBS, LC, CC, UC or CD.

Strengths and limitations
When performing a scientific study or reading the scientific report of a study, it is important to evaluate and understand the quality of the work. There are some important terms to consider that facilitate this process: internal and external validity, systematic errors (confounding factors and bias) and random (chance) errors.

Internal validity has to do with the extent to which the results of a study reflect true associations in the studied population. The presence of systematic errors (confounding factors or bias) and random (chance) er-
rors in a study reduces the internal validity. There are statistical measures that can be taken to reduce the problem of confounding factors and biases, for example increasing sample sizes or adjusting for possible confounders.

**External validity** reflects the extent to which the results of a study can be applied to other populations, and is also referred to as generalizability. A prerequisite for the external validity is the internal validity. In medical research, a common source of reduced external validity is the exclusion criteria used to reduce the problem of confounders or bias in a study (in order to increase the internal validity), which on the other hand results in a study of a defined proportion of the patients with a certain medical problem. The results from such a study may be applicable only to the proportion of patients studied and not to the ones excluded from participation.

**Confounding factors** are risk factors that are associated with exposure and disease, but not as an intermediate between these two. Failure to recognize possible confounding factors may lead to false associations between exposure and outcome.

**Selection bias** is due to the selection of individuals, groups or data for analysis in such a way that proper randomization is not achieved, resulting in a sample not representative of the population intended to be studied.

**Referral bias** is a form of selection bias that can occur, for example, in studies carried out in tertiary patient care centres where a sub-population of patients with the most severe forms of a disease are cared for, as patients with milder cases of the disease will be referred to those clinics to a lesser extent.

**Recall bias** is a systematic error caused by differences in accuracy or completeness of recall of past events or experiences.

**Differential misclassification bias**, or **differential bias**, occurs in a situation where exposure outcomes are registered differently between the outcome groups in a study, and leads to a non-random error, leading to either overestimation or underestimation of the true association depending on the situation.

**Surveillance bias** occurs when one group is followed more closely than another group. This could lead to an outcome being diagnosed more often in the more closely followed group, but not because it truly occurred more often in that group.

**Random errors**, or **chance errors**, are non-systematic errors in a study that always lead to the underestimation of true associations. Statistical
analysis is the method we use to calculate the risk of a found association being due to chance. One way of reducing the risk of chance errors is by increasing the sample size as a larger sample size will dilute them.

**Study I**
The epidemiological study of MC was performed retrospectively, and we collected all patients with MC by searching the diagnosis register system at the Department of Medicine by the diagnostic code for MC (ICD-code K52.8) and the Department of Pathology. The advantage in comparison with a prospective study was the time it took to collect data. The disadvantage is that the quality of data was probably lower than if we had collected them prospectively, as we had to rely on records in which important clinical data were often lacking.

In this study, the quality of data regarding the actual diagnoses was high, and as there is only one endoscopy department and one pathology department in the catchment area it was fairly easy to find all patients diagnosed with MC. All the cases were reassessed to make sure they fulfilled clinical and histological diagnostic criteria, and all the diagnostic biopsies were reviewed by one gastro pathologist, the same person as in the previous epidemiological studies of MC in Örebro. The same diagnostic criteria that were applied in previous epidemiological studies of MC in Örebro were used in this study.

The main weakness of this study was the low quality of data from patients’ files on potential risk factors, such as smoking, pharmacological treatment around the time of diagnosis, family history and the presence of diseases other than coeliac disease, which made it impossible for us to use these data in our study.

There is a risk of slightly underestimating the true incidence rates since we cannot be sure that all patients with MC are actually diagnosed with the disease. There are probably individuals whose MC is undiagnosed because of failure to seek health care or because of no referral for colonoscopy as their symptoms may be interpreted as IBS.

**Studies II and III**
This case-control study was relatively large in terms of being a study of MC. The strength is that was a controlled study, with three matched controls to each case, and high response rates among cases and controls, likely limiting the risk of differential bias. All patients with MC living in our catchment area were invited to participate, which reduced the risk of selec-
tion bias, and all patients were living within our catchment area, which eliminated the risk of referral bias. The absence of these biases increases the internal and external validity of the study.

Another important issue when performing a study where the data are retrieved from answers in a survey, is the wording of the questions asked, and the construction of the questions. Clearly stated questions with concise and reliable answers make the analysis of data easier. This is why it is wise to use validated questionnaires when performing such studies. In this study, the section about HRQoL was based on the SHS which had been previously validated and used in CC.\(^{39, 40}\) Apart from the HRQoL section, the questionnaire we used was constructed by us. Even though we piloted it in a group of patients in advance of the study, the data we received in some of the studied topics were difficult and time-consuming to interpret. If we were to perform a survey like this again, we would use validated questionnaires covering the issues intended to study as this measure most likely would improve the quality of data. Some examples of validated questionnaires used to study different domains in gastrointestinal diseases are the Gastrointestinal Symptom Rating Scale (GSRS), which measures gastrointestinal symptom severity and covers five separate domains (diarrhoea, constipation, abdominal pain, indigestion, and reflux),\(^{199, 200}\) the Patient Health Questionnaire 12 Somatic Symptom scale, which contains twelve questions addressing different extra-intestinal somatic symptoms,\(^{201}\) the Fatigue Questionnaire, which contains eleven questions covering physical and mental fatigue,\(^{202}\) and the Hospital Anxiety and Depression Scale, which contains 14 questions and has been found efficacious for screening anxiety and depression.\(^{203, 204}\) There are also disease-specific questionnaires covering symptom burden and QoL. In IBD, the IBD Questionnaire is used for the assessment of these issues,\(^{204-207}\) and in IBS the IBS Severity Scoring System measures the severity of IBS symptoms,\(^{208}\) the IBS Disease Specific Quality of Life questionnaire measures QoL specific to this disease,\(^{209, 211}\) and the brief Visual Analogue Scale for Irritable Bowel Syndrome questionnaire evaluates symptoms and psychological wellbeing in IBS patients.\(^{212}\) A Microscopic Colitis Disease Activity Index (MCDAI) was created recently.\(^{213}\) It was based on symptoms common in MC: number of unformed stools daily, presence of nocturnal stools, abdominal pain, weight loss, faecal urgency and faecal incontinence. The MCDAI predicted the physician global assessment of disease severity and correlated with the QoL score of the IBD Questionnaire. Validation of MCDAI in
another cohort at a different institution to determine its robustness and general applicability is required.

Active disease in previous studies of HRQoL in CC has been defined, according to Hjortswang et al.,\textsuperscript{39} as three or more stools per day or one or more watery stool per day, and remission as fewer than three stools per day and less than one watery stool per day. When constructing the survey for this study, the Hjortswang criteria for active disease and remission had not yet been defined, which is why our definitions of these items were slightly different from the established ones (active disease was defined as three or more loose or watery stools per day and remission as fewer than three semi-solid or solid stools per day). The differences are, however, small, and are likely of minor importance to our results.

Even though this study is fairly large in comparison with other studies of MC, it is still relatively small in terms of being an epidemiological study. In some of the associations we found, for instance with family history of MC or history of UC, the numbers of observations are small, resulting in wide CIs for the found associations. Another weakness of the study is that we were not able to verify concomitant diseases in either cases or controls. There is a risk of surveillance bias as patients are more likely to be investigated for other diseases because of their symptoms compared with controls, possibly contributing at least to some extent to the associations found here. Some associations were weaker because of possible confounders and recall bias as the patients were probably more aware of their own as well as relatives’ other gastrointestinal disorders compared with the controls.

**Study IV**

This retrospective, observational study of patients with UC or CD who later developed MC, or vice versa, is the biggest of its kind describing this phenomenon. The strengths of the study are the size of the patient cohort and our ability to verify the histopathological diagnoses for the two diseases in each patient. These factors enabled us to describe the clinical course of patients with UC or CD who later develop MC, and vice versa, in a more detailed fashion than has previously been possible.

The main limitations of this study were lack of knowledge about the population size from where the patient cohort were derived and the, in epidemiological terms, small sample size that did not allow us to make any assumption regarding how common this phenomenon is or perform any statistical evaluation of our findings. Therefore we cannot rule out the
possibility of chance associations. Another weakness of the study is the quality of the medical records that was low in some cases, lacking important medical data such as the presence of other diseases, smoking data and data on medical treatment other than the ones used for treatment of the bowel diseases. Such information would have been of great value in this study. Furthermore, there is an aspect of time that needs to be taken into consideration: the diagnoses of CC and LC were not well established in the 1980s and 1990s. Before the mid-1990s the risk of overlooking a diagnosis of MC in a patient who later developed IBD was substantial. Therefore, we may have underestimated the numbers of patients who had MC first and later developed UC or CD.
Conclusions

- For the last 15 years, the annual incidences of CC and LC have been stable at around five cases per $10^5$ inhabitants per year for each disorder.
- The incidence of LC increased twofold in women older than 60 years, yielding an increased female to male ratio from 2.1:1 to 4.6:1.
- The prevalence of MC on 31 December 2008 was 123.0/$10^5$ inhabitants (95% CI 107.6–140.0/$10^5$): 67.7/$10^5$ (95% CI 56.4–80.6/$10^5$) for CC, and 55.3/$10^5$ (95% CI 45.2–67.1/$10^5$) for LC, assuming these are chronic conditions.
- Patients with active CC and LC have impaired HRQoL.
- CC patients in clinical remission report persisting clinical symptoms such as abdominal pain, fatigue, arthralgia and myalgia, while LC patients in clinical remission experience fatigue.
- MC is associated with a family history of MC.
- MC is associated neither with childhood circumstances, such as growing up on a farm or being raised with older or younger siblings, nor with educational level.
- Smoking is a risk factor in MC and ever-smokers develop disease about 10 years earlier than never-smokers.
- CC and LC are both associated with coeliac disease and thyroid disease.
- CC is associated with rheumatic disorders while LC is not.
- CC is associated with previous appendicectomy but LC is not.
- Both CC and LC are associated with a history of UC.
- Altogether 139 patients with occurrence of both UC or CD and MC were found.
- The most common development in our cohort of patients with UC or CD and subsequent MC, or vice versa, was from UC to CC.
- MC should be considered in a patient with UC or CD if there is onset of chronic watery diarrhoea without endoscopic relapse of mucosal inflammation.
Future perspectives

During the process of performing the studies of this thesis many questions arose my mind. Below, I list some suggestions for future studies and one study that is already ongoing.

- We now see stable incidence rates of MC, which makes it easier to study other factors of importance in MC, for example how the use of certain drugs may affect the incidence rates of CC and LC, respectively.
- Studies of best possible treatment in patients intolerant to or not responding to budesonide would be valuable.
- A prospective, multi-centre study of MC in Europe named ProMC, is currently planned and being carried out. This study will hopefully give us high-quality data on tobacco use, medications preceding symptom onset, and comorbidities, as well as give us better opportunities to study the immunology of the colonic mucosa and faecal microbiome in treatment-naïve MC patients.
- Further studies with the aim to find reliable, non-invasive diagnostic markers for CC and LC that may also be used in monitoring the diseases would be of great clinical value.
- Smoking has been shown to be an important risk factor in CC and LC. Smoking in itself has many effects on gastrointestinal function and the gut microbiome. A study of the effects of smoking cessation on symptom burden and HRQoL, as well as inflammatory markers and faecal flora in MC, would be of great interest.
- The study of patients with UC or CD and subsequent MC, or vice versa, has raised the question of how these different disease entities may be interrelated. Detailed studies of mucosa immunology and faecal flora in patients with alternating phases of UC or CD and MC could perhaps give us valuable insights into pathophysiological mechanisms.
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Populärvetenskaplig sammanfattning


Det första delarbetet som är en renodlad epidemiologisk studie av MC visar att CC och LC är relativt vanliga med incidenssiffror kring 5/10^5 invånare vardera. De flesta som insjuknar är 60-70 år, med en klar övervikt för kvinnor som utgör ca 80% av alla fall av MC. Dessa siffror står sig väl med epidemiologiska studier som genomförts i Sverige, Europa och USA. Prevalensen av dessa sjukdomar uppgick till 123/10^5 invånare den 31 december 2008. Det är betydligt lägre än de prevalenssiffror som ses vid andra inflammatoriska tarmsjukdomar som UC och CD, och det förklaras av att åldern vid insjuknande vid både UC och CD är betydligt lägre, i de flesta fall kring 20-40 år.

Vid jämförelse med tidigare epidemiologiska studier av MC som utförts vid USÖ har incidenssiffrorna planat ut, och den incidens och prevalens som nu är närmast de sanna värdena, efter att sjukdomarna sedan de först beskrevs blivit allmänt kända både inom primär- och sekundärvård, och att koloskopier numera rutinmässigt utförs med denna frågeställning.
De andra och tredje delarbetena handlar om symtombörda och livskvalitet hos patienter med CC och LC respektive olika bakgrunds faktorer som årtighet, uppväxtförhållanden, utbildningsnivå, civilstånd, rökning, och annan sjuklighet vid MC. Detta har studerats genom en fall-kontrollstudie, där alla patienter som bor i upptagningsområdet till Universitets sjukhuset i Örebro inbjudits till att svara på enkät med frågor om ovanstående. Till dessa fall har statistiska centralbyrån (SCB) slumpmässigt valt ut 3 kontroller per patient som är matchade för ålder, kön och bostadskommun.

Den andra studien visar att patienter med MC har andra symtom än bara diarré i större utsträckning än kontrollgruppen; nämligen buksmärtor, trötthet och avföringsinkontinens. Patienter med CC har dessutom led- och muskelvärk i betydligt större utsträckning än personerna i kontrollgruppen. Patienter som har aktiv MC har dålig livskvalitet, i nivå med andra sjukdomar som anses vara betydligt mer allvarliga. Andelen patienterna som använder läkemedel för sin tarmsjukdom har studerats, och intressant nog är andelarna ungefär lika stora hos de som är symtomfria och hos de som har aktiv sjukdom. Vilka läkemedel de använder skiljer sig inte heller åt mellan grupperna.

I den tredje studien påvisas att patienter med MC i större utsträckning rapporterar årtighet för MC än kontrollgruppen, vilket kan betyda att det finns genetiska faktorer som predisponerar för MC. Rökning är en stark riskfaktor för både CC och LC, och rökarna insjuknar ca 10 år tidigare än icke-rökarna. Uppväxtförhållanden, utbildningsnivå och civilstånd tycks inte ha betydelse vid MC. Flera sjukdomar kan kopplas till MC; glutenintolerans, autoimmuna sköldkörtelsjukdomar och intressant nog också UC. Reumatiska sjukdomar är associerade till CC vilket kan förklara varför CC-patienterna rapporterat smärta i leder och muskler mer än kontrollgruppen.

I det fjärde arbetet studeras patienter som har fått två tarmsjukdomar; UC eller CD och senare i livet CC eller LC, eller vice versa. Detta har rapporterats i fallrapporter i den medicinska litteraturen sedan slutet av 1980-talet, då mikroskopisk kolit började bli allmänt känt. Genom ett samarbete inom SOIBD (svensk organisation för studier av inflammatorisk tarmsjukdom) har vi kunnat samla ihop ett unikt patientmaterial för att beskriva ett större antal sådana s.k. konverteringsfall i detalj, samt genom sökt den medicinska litteraturen efter sådana fallbeskrivningar. 31 patientfall inkluderades i vår studie och i den medicinska litteraturen fanns ytterligare 27 detaljerade och 71 odetaljerade fall. Vid genomgång av de detal-
jerade patientfallen hade majoriteten av patienterna UC först och senare CC, eller vice versa, och de flesta med UC hade extensiv kolit. Av de 8 som hade MC först och senare fick UC eller obestämbar kolit (IBD-U), behövde 4 akut operation med kolektomi (man opererar bort tjocktarmen) p.g.a. svår kolit. Det viktiga med denna studie är belysningen av ett fenomen som tidigare fått liten uppmärksamhet och sannolikt ofta förbisetts. Att patienter med UC eller CD senare i livet kan få en andra tarmsjukdom som CC eller LC eller vice versa är sannolikt vanligare än man hittills trott och detta arbete kan öka kunskapen, så att patienter med en tarmsjukdom som plötsligt får nya symtom också utreds på misstanke om konvertering till annan tarmsjukdom.
References


Publications in the series
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41. Gustafsson, Sanna Aila (2010). *The importance of being thin – Perceived expectations from self and others and the effect on self-evaluation in girls with disordered eating.*

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52. Loishe, Karin (2011). *Echocardiographic measurements of the heart. With focus on the right ventricle.*


64. Nordin Olsson, Inger (2012). Rational drug treatment in the elderly: "To treat or not to treat”.


67. Thuresson, Marie (2012). The Initial Phase of an Acute Coronary Syndrome. Symptoms, patients’ response to symptoms and opportunity to reduce time to seek care and to increase ambulance use.


75. Gustavsson, Anders (2012): Therapy in Inflammatory Bowel Disease.


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