Thesis for doctoral degree (Ph.D.)
2022

Microscopic colitis: Epidemiology, death and associated disorders

David Bergman

Karolinska Institutet

From Department of Medical Epidemiology and Biostatistics
Karolinska Institutet, Stockholm, Sweden

MICROSCOPIC COLITIS: EPIDEMIOLOGY, DEATH AND ASSOCIATED DISORDERS

David Bergman, M.D.

Karolinska Institutet

Stockholm 2022

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2022

ISBN 978-91-8016-582-2

Microscopic colitis: Epidemiology, death and associated disorders
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

David Bergman

The thesis will be defended in public at Petrén lecture hall, Nobels väg 12B Friday June 3rd, 13.00 p.m.

Principal Supervisor:
Professor Jonas F Ludvigssonme
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics

Co-supervisor(s):
Professor Lars Agréus
Karolinska Institutet
Department of Neurobiology, Care Sciences and Society

Docent Mark Clements
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics

Associate Professor Hamed Khalili
Harvard Medical School
Department of Medicine

Opponent:
Professor Darrell S. Pardi
Mayo Clinic College of Medicine
Division of Gastroenterology and Hepatology

Examination Board:
Professor Bodil Ohlsson
Lund University
Department of Clinical Sciences, Malmö

Associate professor Marte-Lie Høivik
University of Oslo
Institute of Clinical Medicine

Associate professor Elizabeth Arkema
Karolinska Institutet
Department of Medicine, Solna

To Louise, Eyvind, Alexander and Nils.

POPULAR SCIENCE SUMMARY OF THE THESIS

Microscopic colitis is the most recently recognized inflammatory condition of the large intestine. At present, more than 10,000 people in Sweden are estimated to be living with the disease. Previously, insufficient awareness and knowledge of microscopic colitis have led to underdiagnosis of the disorder leaving patients untreated. As the term *microscopic* implies, a microscopic evaluation of a tissue biopsy from the large intestine is required to establish a diagnosis of microscopic colitis. Therefore, access to colonoscopy and knowledge of the typical histopathological findings are required in the diagnostic process. Further, missed diagnoses due to insufficient awareness have hampered the ability of researchers to conduct large-scale studies on prognosis, associated disorders and outcomes. In this thesis, we aim to assess the reliability of histopathological data when identifying patients with microscopic colitis. Also, we examine the incidence of microscopic colitis between 1995 and 2015. Moreover, we assess the risks of death and cancer in patients with microscopic colitis and also the risk of later microscopic colitis in patients with celiac disease.

After having conducted these studies, we confirm a high accuracy regarding microscopic colitis in Swedish pathology registries. Our incidence study reveals a substantial increase of microscopic colitis during the past decades, but with stabilizing rates from 2010–2015. Also, patients with microscopic colitis are at an increased risk of death. However, the increased mortality seems to be associated with concomitant disorders and not with microscopic colitis in itself. Furthermore, we have found a modestly (+8%) increased risk of cancer in patients with microscopic colitis. It is possible that this risk is partly attributable to an increased surveillance of these patients. Finally, we show that patients with celiac disease are at an elevated risk of developing microscopic colitis

ABSTRACT

Microscopic colitis (MC) is the most recently recognized inflammatory condition of the large intestine. MC is an umbrella term for two disease entities, namely lymphocytic colitis (LC) and collagenous colitis (CC). These subtypes are distinguished by their histopathological presentation and cannot be separated based on clinical observation or symptoms. The most prominent clinical presentation is watery, non-bloody diarrhea. However, a proportion of patients also suffer from abdominal pain, weight loss, fecal incontinence and reduced quality of life. MC primarily affects the elderly and shows a clear female preponderance with some 2/3 of patients being women. Large scale, epidemiological research of the disease has historically been hampered by insufficient awareness. Therefore, using data from Swedish health care registers, this thesis aims to elucidate temporal patterns of MC as well as the association with mortality, cancer and celiac disease (CD).

In study I, we examined the validity of having a MC diagnosis recorded in Swedish regional pathology registers. Through manual review of medical charts (n=211), carried out by two independent reviewers, we computed a positive predictive value for MC of 95%. Thus, we concluded that Swedish pathology registers are a reliable source for identifying patients with MC.

In study II, we identified every patient with a first-time diagnosis of MC recorded in Swedish pathology registers from 1995-2015. Using this cohort, we examined temporal trends, age distribution and sex differences in MC. As expected, a majority of patients (72%) were female and mean age at diagnosis was 60.2 years. Incidence rates increased appreciably from 1995 to 2012, after which rates have stabilized. The mean age-standardized incidence rate from 2006 to 2015 was 10.5 cases/100,000 person-years, with a female to male incidence rate ratio of 2.4, adjusted for age and calendar period. When analyzing age-specific incidence, incidence rates increased up to 75-79 years after which they declined. Furthermore, we estimated that during a life-time 1 in 115 women and 1 in 286 men are expected to be diagnosed with MC.

In study III we examined mortality in patients with MC. This was done using a matched cohort study design where each exposed individual (MC) (n=14,333) was matched according to age, sex, county of residence and year of biopsy to five reference individuals from the general population. During the study period (1990 to 2017) patients with MC had a higher probability of death. However, after adjustment for comorbidities the association vanished. Thus, we concluded that the increased risk of death is attributable to the burden of concomitant disease.

Study IV aimed to investigate the association between MC and cancer. Again, this was done using the matched cohort design described above. In total, we identified 11,758 patients diagnosed with MC between 1990 and 2016 with MC that were matched to 50,828 reference individuals. After adjustments for the matching variables and comorbidities (CD and diabetes), we estimated an adjusted hazard ratio (aHR) of 1.08 (95%CI=1.02-1.16) for overall cancer. In secondary analyses, we found a decreased probability of colorectal cancer (aHR, 0.52 (95%CI_0.40-0.66)). The same pattern was observed for gastrointestinal cancers overall (aHR, 0.72(95%CI=0.60-0.85)).

In study V we examined the association between CD and MC. Using the same matched cohort study design described above, we identified 45,267 patients with CD and 224,568 reference individuals between 1990 and 2016. 456 patients with CD were diagnosed with MC during the study period compared to 198 reference individuals that developed MC during the same period. These figures correspond to an aHR of 11.5 (95%CI=9.3-13.7). However, as the

proportional hazards assumption was violated, the main result should not be interpreted as the probability for a CD patient to develop MC at any instant during the study period compared to the reference population, but rather a mean aHR based on all lengths of follow up. However, as the increased risk remained even after >10 years of follow up, our results indicate that the concomitance of these diagnoses should be considered if symptoms persist or reoccur despite a gluten free diet.

LIST OF SCIENTIFIC PAPERS

I. Svensson, M, Bergman, D, Olén, O, Myrelid, P, Bohr, J, Wickbom A, Khalili, H, Münch, A, Halfvarsson, J, Ludvigsson, JF
Validating microscopic colitis (MC) in Swedish pathology registers.
Scandinavian Journal of Gastroenterology, 53:12;1469-1475 (2018)

II. Bergman, D, Clements, M, Khalili, H, Agréus, L, Hultcrantz, R, Ludvigsson, JF
A nationwide cohort study of the incidence of microscopic colitis in Sweden.
Alimentary Pharmacology & Therapeutics, DOI: 10.1111/apt.15246 (2019)

III. Khalili, H, Bergman, D, Roelstraete, B, Burke, KE, Sachs, MC, Olén, O, Ludvigsson JF
Mortality of Patients With Microscopic Colitis in Sweden. Clinical Gastroenterology and Hepatology 2020;18:2491-2499 (2020)

IV. Bergman, D, Khalili, H, Roelstraete, B, Ludvigsson, JF
Microscopic colitis and risk of cancer - a population-based cohort study.
Journal of Crohn´s and Colitis, 2021, 212-221 (2020)

V. Bergman, D, Khalili, H, Lebwohl, B, Roelstraete, B, Green, P, Ludvigsson, JF
Coeliac disease and risk of microscopic colitis: A nationwide population-based matched cohort study.
(Manuscript)

CONTENTS

LIST OF ABBREVIATIONS

MC	Microscopic colitis
CC	Collagenous colitis
LC	Lymphocytic colitis
IBS	Irritable bowel syndrome
CD	Celiac disease
IEL	Intraepithelial lymphocyte
HLA	Human leukocyte antigen
NSAID	Non-steroidal anti-inflammatory drugs
PPI	Proton pump inhibitor
OR	Odds ratio
SSRI	Selective serotonin reuptake inhibitors
HR	Hazard ratio
IRR	Incidence rate ratio
NHL	Non-Hodgkin lymphoma
SNOMED	Systematized Nomenclature of Medicine
ESPRESSO	Epidemiology Stengthened By Histopathology Reports in Sweden
NPR	National Patient Register
ICD	International Classification of Diseases and Related Health Problems
PPV	Positive predictive value
CCI	Charlson comorbidity index
IBD	Inflammatory bowel disease
IR	Incidence rate
SD	Standard deviation

1 INTRODUCTION

Microscopic colitis (MC) is the most recently recognized inflammatory condition of the large intestine. Greater awareness of MC has had a substantial impact on the likelihood of an affected individual receiving a correct diagnosis and adequate treatment. Moreover, a natural consequence of the disease being described rather recently has been the difficulty of studying long-term outcomes and associated disorders on a larger scale.

As the term *microscopic* indicates, a microscopic examination of a biopsy from the colonic mucosa is required to diagnose the condition. As there are no pathognomonic macroscopic aberrations in the colon, a correct diagnosis is further dependent, not only on the access to colonoscopy, but also on the colonoscopist´s inclination to take biopsies that in turn are correctly classified. Based on the histopathological presentation, MC is further characterized as either lymphocytic colitis (LC) or collagenous colitis (CC). Although histologically distinct, there is no difference in the clinical presentation of these entities, which underscores the importance of examining whether they differ in other aspects, for example with regard to patient characteristics or associated outcomes and disorders.

In this thesis, based on five studies, we aim to describe the epidemiology of MC in Sweden as well as to examine associated disorders. Furthermore, we assess the reliability of using data from pathology registries when identifying patients with MC. Our hope is that this knowledge will enable more large-scale studies on MC and to illuminate associated risks in order to minimize detrimental impact on health and quality of life for the affected patients.

2 BACKGROUND

2.1 DEFINITION OF MICROSCOPIC COLITIS

The definition and diagnosis of MC is based on histopathological examination. The phenotypic characteristic for LC is an intraepithelial lymphocyte (IEL) count exceeding 20/100 epithelial cells whereas colitis CC is characterized by a collagenous band in the colonic mucosa measuring more than 10 micrometers.

In cases where patients experience typical symptoms and the histopathological examination reveals an elevated IEL count and/or a thickened collagen layer, but not to the extent to fulfill the criteria for CC or LC, a third subtype, the term "MC incomplete" has been proposed[1].

2.1.1 CLINICAL PRESENTATION

The most prominent symptom in MC is watery, non-bloody diarrhea, although other symptoms such as weight loss and abdominal pain[2] have been reported. Some patients may also experience urgency, nocturnal diarrhea, and fecal incontinence[3]. The severity of symptoms may, however, differ substantially between patients. Although MC is generally considered a benign condition, there is a well-documented detrimental effect on quality of life for the affected individuals[4]. Moreover, even in cases in which clinical remission (defined as ≤2 stools per day) is attained, extra-intestinal symptoms such as fatigue and abdominal pain can persist[4]. In a 2021 prospective cohort study that included 381 MC patients who were followed for one year, 49% had a chronic active or relapsing course of the disease, whereas 40% experienced a prolonged remission after treatment and 11% had no signs of disease[5].

2.1.2 ETIOLOGY

The understanding of the etiology of MC is incomplete. Generally, the pathogenesis is considered multifactorial, including a mucosal inflammatory response to a luminal irritant occurring in a genetically predisposed individual[6].

2.1.2.1 GENETICS

While there are reports on familial clusters of MC[7,8], the analyzed datasets have generally been small and therefore unsuitable to form the basis for firm conclusions regarding heritability. Instead, studies aiming to examine the role of genetics in MC have focused on identifying genetic markers associated with the disease. A Swedish case-control study[9] found a significant connection to alleles contained in the HLA region on chromosome 6 in patients with CC. However, in a follow-up study of patients with LC, the same association could not be seen[10]. Furthermore, the haplotype with the strongest association regarding risk of CC carries the DQ2.5 molecule resembling earlier findings in patients with celiac disease (CD)[11], thus implicating a similar pathogenic mechanism.

2.1.2.2 LUMINAL FACTORS AND THE MICROBIOME

In at least two studies,[12,13] in which a temporary ileostomy had been deemed necessary to alleviate symptoms in therapy resistant CC patients, diversion of the fecal stream was associated with normalization of the colonic mucosa.

Interestingly, the thickened collagen layer reappeared following restoration of colon continuity. These findings highlight the role of luminal factors in the pathogenesis of MC as well as suggesting an important part played by the microbiome. In a 2020 study[14] which

examined the microbiome in stool samples from patients with MC, IBS and healthy controls had an increased dysbiosis index in patients with MC compared to controls (healthy and patients with IBS).

When examining microbiome diversity in the stool samples (i.e. alpha diversity), the authors found diversity was lowered compared to diversity in controls. Furthermore, from a 2019 study[15] examining the effect of budesonide on the microbiome in patients with MC, the alpha diversity increased, mirroring that in healthy controls.

2.1.2.3 BILE ACID MALABSORPTION

Bile-acid malabsorption has been proposed to contribute to the pathogenesis of MC. A Swedish cohort (n=28) consisting of patients with CC was assessed for bile-acid malabsorption with a ^{75}Se-homocholic acid taurine test. The authors noted that bile-acid malabsorption was found in 44% of patients and that these individuals responded to a higher degree to a bile-salt-binding agent. These results were corroborated in 2001 in a Spanish study in which the authors also presented evidence for bile-salt malabsorption often being a concomitant condition in LC.

2.1.2.4 EPITHELIAL FACTORS

An increased epithelial permeability has been observed in patients with MC[16,17]. This, in turn, may facilitate an influx of a noxious luminal agent triggering an inadequate immune response, aided by a dysfunctional HLA system[3]. In the case of LC, the increased epithelial permeability has been attributed to paracellular components, namely tight-junction proteins claudin -4, -5 and -8[17]. As for CC, the thickness of the collagen layer has been reported to correlate to the intensity of symptoms[18]. However, more recent studies[19] indicate that an impaired function of tight-junction proteins cause impaired absorption of sodium and chloride, partly explaining the watery diarrhea which is the most prominent symptom in MC.

2.1.3 RISK FACTORS

2.1.3.1 SEX AND AUTOIMMUNITY

Several risk factors have been established. Female sex and increasing age are the two most important risk factors[20] for both LC and CC. The female preponderance is an attribute shared with many autoimmune diseases which in turn are also considered important risk factors. In a 2004 retrospective cohort study[21] of 199 patients with LC recruited from Swedish gastroenterology clinics, 40% had at least one concomitant autoimmune or inflammatory disease with thyroid disease, CD and diabetes mellitus type 1 being the most common. The relationship to autoimmunity was further examined by a Danish team in 2021[22], where 16 autoimmune conditions were shown to have a significant connection to MC.

2.1.3.2 MEDICATION

A clear correlation between MC and the use NSAIDs and PPIs[23] has been established. In a 2015 systematic review and meta-analysis, Tong[24] et al. reported a significant association (OR 2.41) between MC and the use of selective serotonin reuptake inhibitors (SSRIs). This correlation was corroborated by a 2014 Danish case-control study[25] in which the exposure variable was dispensation of these medications during the year prior to MC diagnosis. Furthermore, the authors also reported significant associations between both LC and CC and the usage of statins (ORs 1.25 and 1.29, respectively). However, when using patients with chronic diarrhea as controls[26], an inverse association with regard to the use of proton-pump inhibitors, H2-blockers and oral diabetes medications was observed. This may suggest that

the cause for colonoscopic evaluation (diarrhea) in this group is a side effect of these medications rather than a triggering event.

2.1.3.3 SMOKING

Several studies have found a correlation between smoking and MC. A prospective study conducted in Spain in 2011 found that smokers, on average, are diagnosed with MC more than 10 years earlier than non-smokers[27]. In a large cohort study, the hazard ratio (HR) of developing MC in smokers or past smokers was 2.5 and 1.5, respectively[28]. These findings were similar to the results reported in a 2019 systematic review and meta-analysis[29] examining the correlation between smoking and MC. The authors found a significantly higher risk for MC among smokers compared to non-smokers. The risk for past smoking was also elevated, albeit to a lesser extent than for current smoking. Since smoking clearly has an impact on the course of MC, it is sometimes an important confounder (e.g. in studies of cancer and mortality). In a Swedish cohort study[2] (n=795) the authors found a prevalence of smokers (current or former) of 58% among patients with CC. The corresponding figure for LC was 51%. A systematic review[30] conducted in 2012 found the pooled prevalence of smokers to be 41% among patients (n=410) with CC and 56% (n=724) amongst those with LC. For comparison, the Public Health Agency of Sweden estimates that, as of March 2022, 6% of the Swedish population between ages 18-64 are daily smokers[31].

To conclude, smoking seems to be associated with an earlier onset of MC. The MC excess risk remains elevated, and to a lesser degree, even after smoking cessation. Moreover, past or current smoking seem to be a common trait amongst patients with MC.

2.1.3.4 SOLID ORGAN TRANSPLANT AND MALIGNANCY

A 2008 population-based cohort study found an increased risk of MC in patients with a solid-organ transplant[32]. ;Moreover, from a North American population-based study[33], an increased relative risk of MC was found among women older than 65 years of age with current or past malignant disease. It is, however, unclear whether the observed associations were due to the disease in itself or the treatment given.

2.1.3.5 INFECTIONS

Enteric infections have been proposed to contribute to the development of MC [34,35], although the underlying data for these claims have generally been limited. In a 2020 population-based study from Denmark, researchers found a significantly increased risk for future MC in patients with a diagnosis of Campylobacter concisus[36]. The nature of this association, however, is currently unclear.

2.2 EPIDEMIOLOGY

2.2.1 INCIDENCE

As pointed out in the introduction, a diagnosis of MC is preceded by a colonoscopy (typically of a patient suffering from watery diarrhea) with representative biopsies which, in turn, are assessed by a pathologist. Consequently, incidence will reflect the rate at which colonoscopies are performed, as well as the inclination to take biopsies and the awareness of these diagnoses among pathologists. As CC was first described in 1976[37], and LC in 1989[38], one can assume that a changing awareness of these diseases has strongly influenced their incidence estimates. Moreover, the general nature and varying degree of severity of the symptoms associated with MC poses a risk of erroneous diagnosis of MC as different functional disorders. In a 2016 systematic review and meta-analysis, the authors found that 9.8% of patients with diarrhea- dominant IBS had a diagnosis of MC[39], whereas

approximately 40% of patients with MC had a diagnosis indicating a functional bowel disorder.

Given the specific procedure needed to identify MC, there is a risk of the condition not being diagnosed. The magnitude of this limitation is difficult to estimate, but access to, as well as the cost of performing, colonoscopies probably affect incidence rates. Also, the number of biopsies will influence the sensitivity of the diagnostic process. Primarily, this applies to CC since the thickened collagen layer associated with this diagnosis tends to occur in patches, whereas the increased count of intraepithelial lymphocytes (in LC) tends to be more general.

As in all epidemiological research, there is a risk of misclassification, resulting in both false positives and false negatives. Since most large-scale incidence studies use histopathological records, the false negatives will remain undetected. However, the risk of false positives may be estimated by validating the histopathological finding according to patient charts. To our knowledge, only one[20] of the nationwide studies is based on validated material.

Previous studies on the incidence of MC generally show an upward trend during the last decades, with figures ranging from a mean annual incidence of 3.4 cases/100,000 person-years in the Netherlands during the period 2000–2012[40] to 21.0 cases/100,000 person-years from 2002–2010, in a regional cohort study performed in Olmsted county, Minnesota, USA[41]. Interestingly, a subsequent incidence study from Olmsted County performed in 2019 showed that incidence rates had stabilized[42] but that prevalence had increased, perhaps due to increased life expectancy. A similar pattern has been observed in Denmark, where a 2015 nationwide incidence study[43] found increasing incidence rates from 2002 to 2011. When reexamining incidence in 2020, the authors found that incidence rates had stabilized since 2012[44]. Apart from an increased access to colonoscopy, these findings may indicate an abating effect of awareness on incidence estimates.

A 2015 systematic review and meta-analysis of 25 studies estimated a combined incidence of LC and CC of 8.99 (4.14 for CC and 4.85 for LC) cases per 100,000 person-years[24]. However, ranges of the annual incidence per 100,000 person-years were wide (0.8-10.8 and 0.55-16 for CC and LC, respectively), reflecting varying distributions of subtypes between studies. Moreover, the authors of this systematic review also examined distribution of subtypes and found that eight of the included studies showed a majority of cases being CC. Of the five nationwide studies conducted to date, four show a preponderance of CC[40,44-46] and only one show a majority of cases being LC[20]. Since LC and CC are difficult to separate clinically, the subtype assigned is determined by the pathologist's evaluation. The issue of observer variability was addressed in a Swedish cohort study[2] in which 92% of cases matched the original assessment when re-evaluated by an experienced pathologist. However, a Danish study[47], designed to assess inter-observer and intra-observer variability found that pathologists were less successful in differentiating MC incomplete from CC and LC.

Female sex is associated with an increased risk of MC. To our knowledge, the female preponderance is supported by all population-based studies on MC. The 2015 meta-analysis[48], in which all included studies observed a female predominance, reported IRRs ranging from 2.8 to 7.9 for CC and 1.1 to 5.0 for LC.

Also, there is compelling evidence that MC predominately affects the elderly. In the 25 studies included in the systematic review and meta-analysis mentioned above[48], the median

age at diagnosis for CC and LC varied between 57.8 and 71.0 years and 59.0 and 70.0 years, respectively.

Due to the limited understanding of the pathophysiology in MC, it is difficult to decide to what degree geographical variations in incidence rates may be related to awareness and access to colonoscopy and not biological. Naturally, the true incidence rates of MC may very well vary between countries due to genetic and environmental factors. Looking at geographic variation, a north-south gradient seems to be present. Tong et al.[48] analyzed incidence rates reported in studies performed in Southern Europe, Northern Europe and North America and found significantly higher incidence rates of CC in the northern regions compared to southern Europe. In the case of LC, however, the findings did not attain statistical significance. Moreover, given the scarcity of incidence studies from developing countries, this gradient is difficult to assess on a global scale. At a national level, substantial regional variation has been reported in Denmark[44]. The observed differences were attributed to varying awareness of the disease and variation in the presence of risk factors[49].

2.2.2 PREVALANCE

The prevalence of MC has been studied on a few occasions. A retrospective cohort study[41] performed in Olmsted County, USA, showed that the prevalence of MC colitis at the end of 2010 was 219 cases per 100,000 inhabitants. In the 2021 follow-up study[42], prevalence, at the end of 2019, had risen to 246 cases per 100,000 inhabitants. In a population-based study[50] conducted in Terrassa, Spain, a prevalence of MC of 107 per 100,000 inhabitants was reported.

2.3 TREATMENT

The corticosteroid budesonide has proven to be an efficient treatment for both CC and LC in randomized controlled trials[51,52]. Both these studies evaluated clinical as well as histopathological remission. Symptomatic treatment, such as loperamide, is often prescribed, although studies to assess the efficiency of these treatments are lacking. Furthermore, the *American Gastroenterological Association Institute´s Technical Review on the Medical Management of Microscopic Colitis*[53] published in 2016 states that Budesonide was the only treatment supported by high-quality evidence. Results for other treatments, (e.g. Mesalazine, Bismuth, probiotics or Prednisolone) were considered inconsistent. In severe budesonide-resistant cases, biological treatment (Anti-TNF) has been successfully prescribed. In 2017, a case series of 73 patients[54] with budenoside-refractory MC, budesonide dependence or budesonide intolerance was published. The majority of cases were given thiopurines. Others received methotrexate or anti-TNF. A majority of cases had a favorable outcome.

To conclude, budesonide is the most well-documented and efficient intervention available for treating MC. Solid evidence on the efficacy of other options is missing.

2.4 ASSOCIATED OUTCOMES

Complications related to MC are considered rare[55]. In a Swedish case-control study from 2012[56] which included 277 MC cases from a regional hospital and 831 matched controls, the authors found that patients with LC or CC were more troubled by abdominal pain and fatigue compared to healthy controls. Cases also had a significantly lower quality of life.

2.4.1 CANCER

MC is considered an inflammatory condition with an immune-mediated etiology. Such disorders are generally considered to be associated with an increased risk of cancer[57]. Many of these conditions, including MC[58-60], have also have been strongly linked to non-Hodgkin

lymphoma (NHL). However, large-scale population-based studies on cancer risk in MC have, until recently, been scarce. Studies have, primarily, been focused on the risk of colorectal cancer, with some results[61-64] pointing toward no association whereas other, more recent and larger studies, are suggesting a significantly lower risk of such cancers[65,66]. There are also reports on extracolonic cancers in patients with MC [20,61,66,67]. Data from those studies indicate an increased risk of lung cancer (which most likely is explained by the higher prevalence of smoking in patients with MC), but also lymphoma. Furthermore, some patients with MC receive anti-TNF-treatment, and a 2006 systematic review and meta-analysis[68] found an increased risk of cancer in patients with rheumatoid arthritis treated with infliximab or adalimumab. Moreover, a French observational cohort study[69] conducted on almost 20,000 patients with inflammatory bowel disease (Crohn´s disease, ulcerative colitis or unclassified inflammatory bowel disease) found a roughly five-fold increased risk (HR 5.28) of lymphoproliferative disorders (mainly NHL) for patients treated with thiopurines compared to those naïve to that drug. A prospective cohort study[70] performed on the same cohort found an increased risk for non-melanoma skin cancer among patients previously or currently treated with thiopurines (hazard ratios 3.9 and 5.9, respectively)

2.4.2 CELIAC DISEASE

The relationship between CD and MC has long been a matter of interest. However, adequately powered studies with a high degree of generalizability are rare. A number of studies examining the association between these disorders have found a significantly increased risk of MC in patients with CD (or CD in patients with MC)[71 72 33 73 74 75 2 76]. However, these studies have generally been small and/or based on data from tertiary centers. A 2021 population-based case-control study from Denmark assessed the presence of various autoimmune disorders in MC and the authors reported an OR of 10.15 for CD.

2.4.3 MORTALITY

As mentioned earlier, autoimmune and inflammatory conditions are overrepresented among patients with MC[77]. Also, some of the pharmacological interventions are associated with an increased risk of cancer[68-70]. Moreover, it is well established that MC is a disease that primarily affects the elderly. Although the intensity of symptoms varies between individuals, a detrimental effect on quality of life has been observed[56]. Other inflammatory conditions affecting the large intestine include ulcerative colitis and Crohn's disease, which are both linked to an increased risk of mortality[78].

Nevertheless, the prevailing view has been that MC is not associated with increased mortality. In 2016, this view was expressed in the *Technical Review and Summary Statement for Management of Microscopic Colitis* from the American Gastroenterology Association[53]. However, this assertion was not backed up by any referenced material. Recently, however, three studies[65,79,80] have focused on the association between MC and mortality. Although crude mortality rates are higher in patients affected by MC, this seems to be connected to the burden of comorbid diseases, and most likely smoking, rather than the disease in itself.

3 RESEARCH AIMS

This thesis aims to elucidate epidemiological aspects of MC as well as investigating associated outcomes. This was done by carrying out five separate studies whose individual aims are included in the figure below:

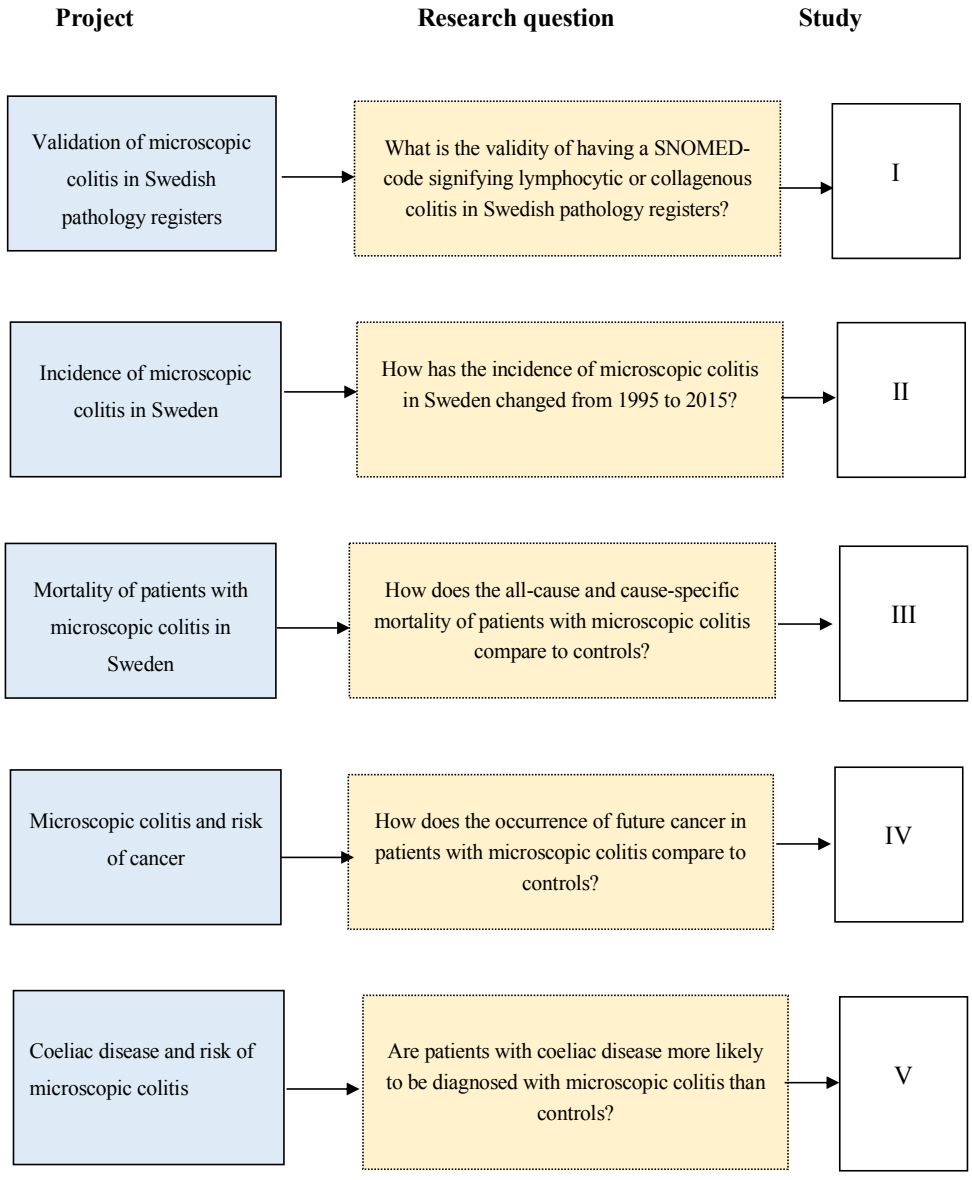

Figure 1 Studies and aims of this thesis

4 DATA SOURCES

4.1 REGISTERS

In Sweden, all citizens are assigned a unique personal identity number. This number carries information on the date of birth but also includes one digit identifying the sex of a person (even numbers for women and uneven numbers for men). This construct enables researchers[81] to link information from various health care registers and follow specific individuals over time.

4.2 REGIONAL PATHOLOGY REGISTERS

Health care in Sweden is generally government funded and managed by the county councils. Each county stores data from biopsies in a pathology register. Each entry in these regional registries contain information on personal identity number, date of biopsy, morphology and topography. All tissue specimens are further characterized using the Systematized Nomenclature of Medicine (SNOMED) which is an international coding system designed to unify and simplify clinical documentation.

4.3 EPIDEMIOLOGY STRENGTHENED BY HISTOPATHOLOGY REPORTS IN SWEDEN (ESPRESSO)

The ESPRESSO study[82] has collected data on all computerized biopsies from the gastrointestinal tract taken in Sweden from 1965 to 2017. The total study population exceeds 13 million people and the study contain biopsy data on 2.1 million unique individuals. Each of these individuals has also been matched (according to age, sex, county and calendar year for biopsy) to five individuals from the general population. These reference individuals were identified through the Total Population Register[83], which is operated by Statistics Sweden, and which includes information on vital status (alive or dead), place of birth, civil status, personal identity number, address and information on emigration/immigration. Moreover, first-degree relatives and spouses to all index individuals and matched controls were identified using the multi-generation register, a component of the Total Population Register, storing data on individuals born from 1932 and their biological parents. Using the longitudinal integrated database for health insurance and labor market studies[84] (LISA), covariates such as educational level and nationality were added to the ESPRESSO study.

Information on comorbid conditions was collected from the national patient register (NPR). Briefly, this register stores data on diagnoses according to the International Classification of Diseases and Related Health Problems (ICD)-coding system. The register is maintained by the National Board of Health and Welfare which initiated data collection (ICD-codes, dates of admission and discharge etc) for the register in 1964. However, nationwide coverage was not attained until 1987 and information from specialized outpatient care is available from 2001. The positive predictive value (PPV) of diagnoses recorded in the NPR is generally considered to be around 90%[85].

Furthermore, the ESPRESSO study contains information from the Swedish Cancer Registry. Starting in 1958, reporting to the Swedish Cancer Registry is mandatory and it has an estimated coverage exceeding 95%[86]. Data on cause of death was imported from the Cause of Death Registry[87]. Reporting to this registry is also mandatory and is considered to record virtually every death occurring in Sweden. The register stores information according to personal identity number and lists the primary cause of death alongside the underlying conditions leading to death.

Finally, the ESPRESSO study stores data on prescribed dispensed medications. This information was retrieved from the Swedish prescribed drug register[88] which commenced recording data on all dispensed prescribed medication from July 1st, 2005. This registry is considered to store data on almost 100% of dispensed medications.

4.4 ETHICAL CONSIDERATIONS

As with all research on humans, there are ethical concerns. With our studies being strictly register-based, there is no risk for physical harm. Hence, our work is in accordance with the principle of no-harm. Furthermore, the studies do not affect the treatment of included patients nor do they cause any extra appointments or testing or lead to any time loss or extra costs for the included study participants.

However, a moral risk is present since the autonomy and integrity of those included in the studies is jeopardized. Particularly, this applies to study I where personal identity numbers and medical charts were made available to us without active consent from the individuals included in the study. As the study was part of a larger register-based study, informed consent was not required[89]. Without this practice, our projects would not be possible to undertake, in part due to the fact that some of the included patients are deceased. Also, had informed consent been required, we would have risked introducing selection bias. Nevertheless, while reviewing charts, information not needed for our study was available to us. In order to limit unwarranted disclosure and viewing of information contained in the charts, we used a standardized protocol for collecting the required data. Unfortunately, our research necessitates a breach of integrity. Nevertheless, as this thesis will include the first nationwide, population-based studies on death and disorders associated with MC, we believe the benefits to outweigh the risks. We also hope the studies will benefit those who have contributed the data as well as their families and others diagnosed with MC.

For studies II-V, the National Board of Health and Welfare linked our data to various national health registers. The final dataset only contained pseudonymized information (personal identity number had been replaced by a serial number but a key file is being stored, for a limited amount of time, by the National Board of Health and Welfare). All charts are stored at the Department of Medical Epidemiology and Biostatistics. Further, all digital data were handled in accordance with good data management and practice at Karolinska Institutet.

From a utilitarian viewpoint, our projects seem sound since the breach of integrity and autonomy are limited to the study participants. Presumably, the results will be applicable to a much larger group of patients. In light of this, it could also be argued that a researcher is obliged to increase knowledge about a condition affecting a large number of patients and that lacking to do so would be objectionable from a moral standpoint. Of course, this is a difficult consideration and should be applied to all ethical viewpoints. What potential findings could motivate the disregard of integrity and autonomy that our studies assume?

Regardless of the findings, our studies will lead to an enhanced knowledge of MC. The Swedish Research Council expresses in its report ”God forskningssed” (loosely translated into “Good research ethics) that knowledge has an intrinsic, absolute value. Provided our studies are properly conducted, this viewpoint suggests that our results will contribute to an increased understanding of MC which may compensate for the lack of informed consent and disregard for study participants´ autonomy.

5 METHODS

Study design, study populations, main outcome measures and statistical methods used in the included studies are presented in Figure 2.

Study	Study design	Study population	Outcome measures	Statistical analysis
I	Register-based study with patient chart review	Random sample of patients with a SNOMED-code indicating LC or CC.	PPV	PPV
II	Nationwide cohort study	All patients in Sweden with a first-time diagnosis of MC from 1995-2015	Incidence of MC/LC/CC	Age-standardization Poisson regression
III	Nationwide matched cohort study	Patients with a first-time diagnosis of MC in Sweden from 1990-2017, their siblings, and matched reference individuals.	All-cause and cause-specific mortality	Cox proportional hazards model
IV	Nationwide matched cohort study	Patients with a first-time diagnosis of MC in Sweden from 1990-2016, their siblings, and matched reference individuals.	Overall cancer Specific cancer	Cox proportional hazards model
V	Nationwide matched cohort study	Patients with a first-time diagnosis of CD in Sweden from 1990-2016, their siblings, and matched reference individuals.	MC, LC, CC	Cox proportional hazards model

Figure 2 Schematic view of study design, study population, outcome measures and the statistical methods applied in the included studies.

PPV, positive predictive value; MC, microscopic colitis; LC, Lymphocytic colitis; CC, collagenous colitis; CD, celiac disease; SNOMED, systematized nomenclature of medicine.

5.1 STUDY DESIGN, STUDY POPULATION AND OUTCOME MEASURES

5.1.1 STUDY I

All the studies in this thesis rely on register-based data to identify MC. We therefore reviewed medical charts belonging to patients with a SnoMed-code signifying LC or CC in pathology registers to assess the validity of the register-based diagnoses. This method is considered to be the gold standard when assessing validity of register-based data. For study 1, pathology departments from 5 counties (Dalarna, Jönköping, Sörmland, Västra Götaland, Örebro län) considered to be representative for Sweden, were asked to identify all histopathology reports with a SnoMed-code for MC. The corresponding medical charts were requested for a random sample (n=231) of these reports. Chart reviews (including physician notes, laboratory reports, x-ray reports) were carried out using a standardized form (including 71 different variables). The gathered data were then independently reviewed by two researchers, and each patient was classified as definite, probable or negative for MC. After discussing uncertain cases with senior colleagues, patients defined as definitive or probable were deemed as confirmed MC.

5.1.2 STUDY II

Data used for study II were gathered as part of the aforementioned ESPRESSO study[82]. We identified all patients with a first-time diagnosis of MC (according to SnoMed-codes M40600 for CC and M47170 for LC) registered in any of the Swedish regional pathology registers (n=28 registers) from 1995 to 2015 (n=13,844 patients). The dataset used for analysis included information on age at diagnosis (according to five-year interval age-brackets), sex, subtype and year of diagnosis. Based on this nationwide cohort, age-standardized incidence rates and age-specific incidence rates (overall and stratified by sex) were calculated.

5.1.3 STUDY III

Leveraging the ESPRESSO study[82], all patients ≥18 years of age, with a diagnosis of MC between 1990 and 2017 were identified (n=14,333). Subsequently, these patients were matched to reference individuals from the general population according to sex, age, county of residence and year of biopsy (n=68,700). Also, all siblings to MC patients were identified (n=14,627) and included in the study, providing a measure for controlling for intrafamilial confounding (early environmental factors and shared genetics). Information on highest attained educational level was retrieved from the national register LISA[84]. In this study, educational level was used as a proxy for socioeconomic status and classified as category 1 (≤9 years of schooling), 2 (10-≤12 years) or 3 (>12 years). In cases with missing data on education, the highest educational level of the parents was imputed. If also these data were absent, study participants were put into a separate missing-category.

Data on comorbid disease were gathered from the NPR. Comorbidity was classified according to the Charlson comorbidity index (CCI)[90,91] at baseline, based on ICD-diagnosis recorded before index date. The burden of comorbidity of the study participants was classified according to CCI-score as no comorbidity (score=0), mild comorbidity (score=1-2) and severe comorbidity (score≥3). Also, data on specific comorbidities such as cardiovascular disease, celiac disease, inflammatory bowel disease (IBD), thyroid disease and diabetes were also added to the dataset.

Data on dispensed medications were collected from the Swedish Prescribed Drug Register. Specifically, dispensed budesonide after MC diagnosis was considered to indicate active treatment for MC.

Information on date of death (the main outcome measure) was retrieved from the Total Population Register. As for cause-specific outcomes (death related to cancer, cardiovascular disease, gastrointestinal disease, infectious disease or other), data were gathered from the Cause of Death Register[87]. Lastly, using a matched cohort study design, we compared mortality rates in patients with MC with corresponding rates in non-exposed comparators.

5.1.4 STUDY IV

For study IV, patients with MC (n=11,758), their siblings (n=11,614) and their corresponding comparators (n=50,828) were identified through the ESPRESSSO study (see section 4.3). Also, data on baseline characteristics and education were gathered and added to the dataset in the same way described for study III. Again, we defined dispensed budesonide as an indicator of active treatment. As the prescribed drug register commenced July 1st, 2005, we considered any dispensed budesonide after January 1st, 2006 initiation of therapy for MC. We also collected information on dispensed immunosuppressants to account for the association between immunosuppressants and lymphoma[92]. As entries for MC in the pathology registers were rare during the 1980s, the study period began January 1st, 1990 and ended December 31st, 2016.

Data on comorbidities (IBD and diabetes) was gathered from the NPR[85]. As there is a known connection between IBD and cancer[93,94], all patients with a prior diagnosis of IBD were excluded. Furthermore, the occurrence of celiac disease was ascertained using histopathology data from the ESPRESSO study[82]. Our main model included adjustments for diabetes and celiac disease.

Data on our primary (any cancer) and secondary outcome (lymphoma, colorectal cancer, any gastrointestinal malignancy, lung cancer, breast cancer, and bladder cancer) measures were retrieved from the Swedish Cancer Register. Again, a matched cohort study design was used to assess cancer rates in MC compared to comparators from the general population.

5.1.5 STUDY V

All patients with CD (exposure) and MC (outcome) were identified using histopathology data from the ESPRESSO study[82]. Matching to reference individuals was performed according to age, sex, county of residence and year of diagnostic biopsy. Siblings to CD patients were identified through the multi-generation register[83]. Again, the study period was set to January 1st, 1990 to December 31st 2016. Follow-up ended on the date of MC diagnosis, date of death, emigration or December 31st, 2016, whichever occurred first. Baseline characteristics and data on educational level were gathered and categorized as described in section 5.1.3. Data on relevant comorbidities (diabetes, IBD, rheumatoid arthritis and thyroid disease) were collected through the NPR. Through the Swedish Prescribed Drug Register, we identified all study participants with dispensed insulin and considered these to have a diabetes diagnosis. Using this data, we conducted a nationwide matched cohort study to assess the risk of MC in CD.

5.2 STATISTICAL METHODS

5.2.1 STUDY I

Our main outcome measure in study I was the PPV of having a diagnosis of MC recorded in Swedish pathology registers. PPV is calculated by the number of people with a disease who test positive for the disease divided by the total number of people testing positive for the disease, regardless of whether they have the disease or not (true positives/true positives+false positives). Power calculations for binomial proportions were performed using the sample size estimator at https://epitools.com.au, assuming 90% of recorded histopathological diagnosis to be correct and requiring a precision of 0.05. The 95% confidence intervals (CI) for binomial proportions were calculated using the Wilson method.

5.2.2 STUDY II

Study II examined the incidence of MC in Sweden 1995-2015. Our main outcome measures were age-standardized incidence rates (IRs) expressed as number of incident cases per 100,000 person-years. To control for changes in the age structure incidence rates were age-standardized to the 2015 Swedish population using the direct method. Results were also presented stratified on sex and MC subtype (LC or CC). Furthermore, age-specific IRs were calculated with 95% CIs based on the Poisson distribution[95]. The Poisson distribution assumes that the events recorded are independent, meaning that the occurrence of one event does not affect the probability of another event occurring. Furthermore, the variance is assumed to be equal to the mean. Using Poisson regression, we examined whether IRRs between sexes were modified by age and calendar period. Based on the sex-specific IRs, we also calculated the lifetime risk of being diagnosed with MC. However, as MC primarily affects the elderly, an adjustment for competing risks becomes important. This adjustment was made by taking the all-cause mortality rates into consideration. A p-value<0.05 was considered statistically significant.

5.2.3 STUDY III-IV

Studies III and IV assessed the association with death and cancer in MC. Crude (unadjusted) survival for MC patients and their corresponding comparators were calculated with a Kaplan-Meier estimator. HRs and 95% CIs were computed by using the Cox proportional hazards model, including adjustments for the matching variables (age (continuous), sex (binary), county of residence (categorical) and year of biopsy (continuous)). The main model in study III also included adjustments for cardiovascular disease, thyroid disease, celiac disease and the Charlson comorbidity index. The main model in study IV included adjustments for the matching variables and education (categorical), together with diabetes and CD. Furthermore, to control for intrafamilial confounding, we performed a separate analysis where siblings to the exposed population were used as reference population. This analysis was stratified according to family. In all analyses, a p-value <0.05 was considered to be statistically significant.

5.2.4 STUDY V

The primary aim of study V was to examine the association between CD and MC. Survival proportions for CD patients and matched reference individuals were calculated by the Kaplan-Meier estimator. HRs and 95% CIs were estimated using the Cox proportional hazards model. To control for the known associations between autoimmune disease and CD (exposure) and autoimmune disease and MC (outcome), we fitted a model including adjustment for IBD, diabetes, rheumatoid arthritis and thyroid disease. However, as a global test provided strong evidence against proportionality, the main result cannot be interpreted as

the probability of the exposed to experience the outcome at any instant during the study period, relative to the non-exposed. Therefore, we also included a model which further adjusted for an interaction between time and exposure. Thus, HRs at various lengths of follow-up could be computed. In order to control for intrafamilial confounding, the same analyses were performed using siblings of CD patients as comparators. Again, the sibling analyses were done according to family strata. In a separate analysis, we also examined the occurrence of prior MC in CD using a logistic regression model (conditional logistic regression in the sibling analysis). The threshold for statistical significance was set to a p-value <0.05.

6 RESULTS

6.1 STUDY I

Study 1 examined the validity of having a diagnosis of MC in the Swedish pathology registers. In total, 215 charts from patients with a SNOMED-code indicating MC were reviewed. Four of these charts had insufficient information for us to be able to ascertain MC and were thus discarded. As expected, a majority of study participants were women (69% for LC and 77% for CC). Mean age at diagnosis was 67 years and 66 years for CC and LC, respectively. Of the 211 patient charts reviewed, 200 patients were considered true MC, yielding a PPV of 95% (95% CI=91-97%). The corresponding figure for CC and LC in the published paper was 95% (95% CI=87-98%) and 85% (95%CI=78-90%), respectively. However, according to the figures contained in Table 1, the PPV for CC and LC should rather be 100% (95%CI=94-100%) and 89% (95%CI=83-94%), respectively. The most common symptom recorded was diarrhea which affected 96% of patients.

Table 6.1 Characteristics of study participants including assigned

SNOMED CT codes (M40600 and M47170)

	All cases, n=215	Confirmed as Microscopic colitis, n=200
Females, n (%)	154 (72)	141 (70)
Age at diagnostic colonoscopy in years, median (range)	66 (17-90)	66.5 (21-90)
Collagenous colitis (M40600), n (%)	75 (35)	75 (38)
Lymphocytic colitis (M47170), n (%)	140 (65)	125 (62)

6.2 STUDY II

Study II assessed the incidence of MC in Sweden 1995-2015. In total, 13,844 patients with a SNOMED-code indicating MC were identified. The age-standardized IR throughout the study period was 7.2 cases/100,000 person-years (95%CI=5.6-8.7) (Figure 6.2.1). When restricting our analysis to 2010-2015 the mean age-standardized IR was 10.7 cases/100,000 person-years (95% CI=7.7-13-7). Mean age at diagnosis of MC was 60.2 years (58.6 years for LC, 63.3 for CC). Looking at age-specific IRs, the incidence increased with age, reaching

a peak in the 75-79-year age-group (Figure 6.2.2). A majority of the identified cases were female (72% of MC). Adjusting for age, the IRR between sexes was 2.7 for MC (2.4 for LC, 3.6 for CC). Testing for interaction between age and sex, we found strong evidence ($p<0.001$) for decreasing IRR between sexes with increasing age ($p<0.001$). The lifetime risk for MC was estimated to 0.87% (95%CI=0.85-0.88%) for women and 0.35% (95%CI=0.34-0.36%) for men. These percentages correspond to 1 in 115 women and 1 in 286 males being diagnosed with MC during a lifetime.

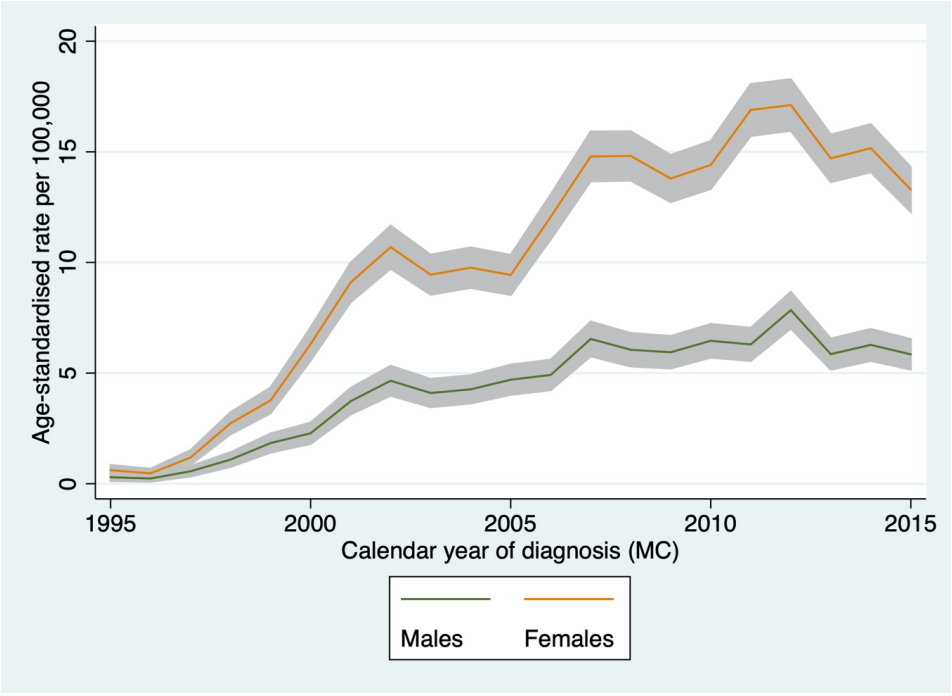

Figure 6.2.1 Age-standardized incidence rates of MC per calendar year, stratified by sex.

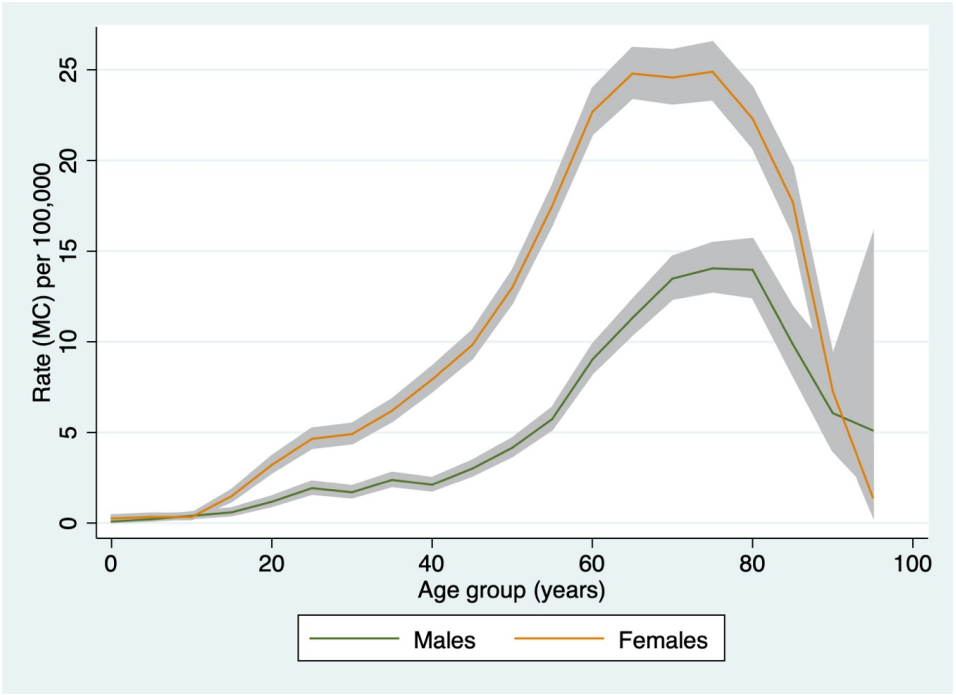

Figure 6.2.2 Age-specific incidence of MC, stratified by sex.

6.3 STUDY III

Study III examined the association between MC and mortality. A total of 14,333 patients with MC, diagnosed between January 1st 1990 and December 31st 2017 were identified. The study also included 68,700 comparators from the general population and 14,267 siblings of the exposed (MC) individuals. The absolute, crude, IR for patients with MC was 27.4 deaths per 1000 person-years. The corresponding figure for the reference individuals was 23.3 deaths per 1000 person-years. These rates translated into an age-adjusted HR of 1.16 (95%CI=1.06-1.17) for the exposed population relative to reference individuals from the general population. However, after adjustments for cardiovascular disease, thyroid disease, celiac disease and the Charlson comorbidity index the association vanished (aHR=0.98; 95%CI=0.96-1.09). Using siblings as comparators yielded a similar result (aHR=1.02; 95% CI=0.92-1.13). When examining cause-specific mortality we found a significantly decreased risk of cancer-related death (aHR=0.83; 95%CI=0.76-0.91), no association between MC and cardiovascular death (aHR=1.02; 95%CI=0.96-1.10), and an increased risk of both gastrointestinal death (aHR=1.68; 95%CI=1.38-2.05) and death related to infections (aHR=1.42; 95%CI=1.11-1.83). Moreover, the risk of death increased with length of follow up. For those with a follow-up-time exceeding 10 years, the aHR was 1.17 (95%CI=1.06-1.30).

6.4 STUDY IV

Study IV aimed to assess the association between MC and cancer. 11,758 patients with a histopathology code used to assign MC were identified alongside 50,828 comparators from the general population and 11,614 siblings to MC patients. From January 1st 1990 to December 31st 2016, 10.5% of MC patients were diagnosed with cancer whereas 9.5% of the reference population received a cancer diagnosis. This disparity in proportions corresponds to one additional cancer event for every 55 patients with MC followed for 10 years. Our main

model included adjustments for the matching variables (age, sex, county of residence and year of biopsy), educational level and comorbid disease (diabetes and celiac disease) and yielded an aHR of 1.08 (95%CI=1.02-1.16). Stratifying on sex did not alter the aHRs significantly. However, during the first year of follow-up the aHR (1.49; 95%CI=1.27-1.73) was higher than subsequent intervals for length of follow-up. Also, a significant effect modification by country of birth was detected ($p<0.0025$). Cancer rates were higher among study participants born outside the Nordic countries (aHR=1.90; 95%CI=1.07-3.39). Furthermore, the associations of specific cancers were assessed. These findings are presented in Figure 6.4.1

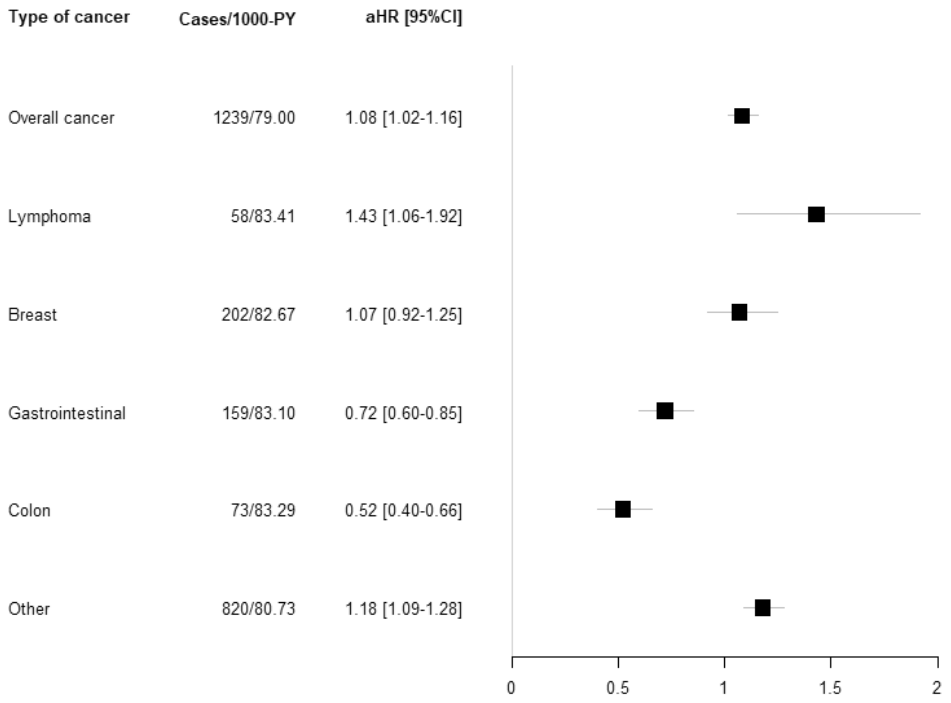

Figure 6.4.1 Adjusted hazard ratios for specific cancers in patients with MC compared to reference individuals

6.5 STUDY V

The primary aim of study V was to investigate the association between CD and subsequent MC. We identified 45,267 patients with a biopsy-verified CD from the ESPRESSO cohort. Moreover, 224,568 reference individuals from the general population and 51,767 siblings to CD patients were included. A proportion 62.4% of CD patients were female and the mean age at diagnosis was 32.4 years (standard deviation (SD)=25.1). From January 1st, 1990 to December 31st, 2016, 456 patients with CD and 198 individuals from the reference population were diagnosed with MC corresponding to IRs of 86.6/100,000 (95%CI=79.1-95.0) person-years in the exposed group and 7.5/100,000 (95%CI=6.5-8.6) person-years among reference individuals. Siblings to CD patients had an IR of 14.8/100,000 (95% CI=12.0-18.3) person-years. Adjustments for the matching variables (age, sex, county of residence and year of biopsy), educational level and comorbidities (diabetes, IBD, thyroid disease, rheumatoid arthritis) resulted in an aHR of 11.5 (95%CI=9.7-13.6) compared to the reference population. Stratification on sex and subtype yielded similar results. Furthermore,

CD patients born in a non-Nordic country had a higher aHR (56.3; 95%CI=12.5-254.5) compared to CD patients of Nordic origin (aHR=10.9; 95%CI=9.2-12.9). However, the discrepancy did not reach statistical significance (p=0.054). When performing similar analysis according to strata defined by length of follow-up, the highest aHR was found in the first year (aHR=36.1; 95%CI=20.6-63.2). To control for a potential misclassification related to remaining lymphocytic infiltration in the colonic mucosa due to an undiscovered celiac disease, we excluded all MC cases diagnosed within a year of CD diagnosis. Nevertheless, when also stratifying on subtype, aHRs remained elevated (10.2 (95%CI=8.1-12.7) for LC, 8.7 (95%CI=6.4-11.6) for CC). As the proportional hazard assumption was not fulfilled, we conducted an analysis including an interaction term between time and exposure. Thus, we could ascertain the aHR at specific lengths of follow up. These results are presented in Table 6.5.1. Using logistic regression, we also examined the association between CD and previous MC. The aOR was 47.4 (95%CI=28.7-78.4).

Years of follow-up	aHR	95% CI
0	19.0	14.5-24.9
1	17.3	13.8-22.8
5	13.4	11.2-16.2
10	9.5	7.9-11.4
20	4.8	3.2-7.0

Table 6.5.1 Adjusted hazard ratios (MC) for CD patients vs reference individuals at x years of follow-up

7 DISCUSSION

7.1.1 METHODOLOGICAL CONSIDERATIONS

Epidemiological studies are observational. The studies included in this thesis are all observational, meaning that we try to answer our research questions through observations of recorded events. Moreover, observational studies can be descriptive (study I-II) or analytic (study III-V) where the former studies aim to describe, compare and measure data and the latter studies focused on the relationship between exposure and outcome. Thus, descriptive observational studies do not test a hypothesis but rather aim at generating new hypotheses whereas observational analytic studies typically test whether there is an association or not between an exposure and an outcome. An observational study is generally considered to be of a lower evidence grade than randomized controlled trials since the latter can remove both known and unknown confounding through randomization of study subjects (if the study population is large enough). However, due to both ethical and practical reasons, not all exposures can be studied in randomized controlled trials. Also, generalizability can be a problem if the study population does not reflect the population to which the findings are to be applied, such as elderly, comorbid individuals who are less often enrolled in randomized controlled trials.

In Study I, we examined the validity of the Swedish pathology registers pertaining to the diagnosis of MC. As the diagnostic traits of MC are assessed by a histopathological examination and subsequently classified according to the SNOMED-system, data from pathology registers are a valuable source of information when trying to identify patients with MC. Also, prior to 2016, there existed no specific ICD-code for MC, thus the pathology registers are pivotal in MC research.

Study II assessed the incidence of MC in Sweden from 1995 to 2015 by collecting data, with a SNOMED-code signifying LC or CC, from Swedish pathology registers, thereby creating a nationwide cohort of MC patients. As the validity of these codes had previously been examined (see above), our results most likely reflect incidence of MC in Sweden as recorded in pathology registers.

Study III-V were carried out using a retrospective, matched cohort study design using register-based data, meaning that we followed a group of patients (the exposed) and their comparators (the non-exposed) and examined whether they developed a certain outcome or not. This design is advantageous for studying rare exposures and allows for the calculation of relative risks for one or several outcomes. Furthermore, temporality can be determined as the study design requires that the exposure occurs before the outcome.

7.1.2 CONFOUNDING

Confounding is a systematic error which should be addressed in all observational studies where the effect of an exposure on an outcome is being examined. Confounding occurs when a variable is associated with both the exposure and outcome of interest and affects the result of the studied observation, disturbing our inference. Researchers try to remove confounding by restriction, randomization, stratification, matching and adjustment using regression models. However, as most biologic systems are complex, a risk for residual confounding remains due to insufficient knowledge of the causal pathway or misclassification of known confounders.

In studies III-V confounding has primarily been dealt with by including possible confounders in the regression models. Study III is a suitable example of confounding by comorbidity where the increased HR of death for patients with MC was attenuated when concomitant

disease was taken into consideration. On the other hand, if a comorbidity reflects a step in the causal pathway, i.e. is a mediator, adjustment would remove the effect of the exposure on the outcome. Furthermore, undue adjustments also risk opening up an alternate causal pathway, thus disturbing our inference.

The elevated aHR for lung cancer in patients with MC compared to reference individuals is most likely attributed to the increased prevalence of smokers among patients with MC. As all of the included studies are based on data originating from registers lacking information on BMI, genetics, use of non-prescription drugs and smoking habits, naturally, there is a risk of residual confounding by these factors.

7.1.3 SELECTION BIAS

Selection bias is a systematic error that occurs if the groups under study are different in other ways than the exposure being studied and these differences are related to the outcome. This phenomenon relates to confounding (see above) in that certain variables may have different associations to the exposure and outcome of interest in the exposed and non-exposed populations. However, selection bias is generally sought to be minimized when including patients to a study whereas confounding is typically addressed when analyzing the gathered data.

In Study I, five counties were assumed to be representative of Sweden. This assumption risks introducing a selection bias if the inhabitants of these counties differ in some way compared to Swedes in general and that difference is associated with the outcome. However, as the counties and hospitals included represented both rural and urban areas as well as university and county hospitals, the impact of a potential selection bias should be fairly limited. Studies II-V were all population-based, thereby minimizing the effect of selection bias.

7.1.4 MEASUREMENT BIAS

Measurement bias is caused by a systematic difference in the method of identifying exposures, outcomes or events of interest in the exposed population compared to reference individuals. Looking at our outcomes of interest (death, cancer, CD), it seems unlikely that these outcomes have been systematically ascertained in a different way among patients with MC compared to matched comparators without MC.

7.1.5 MISCLASSIFICATION

Misclassification of exposure or outcome risks biasing a study. Misclassification is primarily a problem when it is differential. This means that an erroneous classification of exposure and/or outcome is more prevalent in one of the two groups compared introducing a systematic error in the study which can either inflate or reduce the association. Non-differential misclassification means that a flawed classification has occurred haphazardly in both groups, typically attenuating the association. As studies IV and V found significant associations between exposure and outcome, a non-differential misclassification, if present, would most likely attenuate the observed associations. However, in study III, where no association was seen, the potential influence of non-differential misclassification should be addressed but as death is rarely misclassified this becomes a moot issue. Furthermore, in study III-IV our exposure variable was MC which, given the results of our validation study (study I), should be accurate. Outcomes in studies III-IV were death and cancer and the completeness and high validity of the Total Population Register, Cause of Death Register and Cancer Register[83,86,87] lend our results a high degree of validity. In study V we examined the association between CD and MC, two diagnoses that previously have been shown to have a high validity[96,97] as recorded in pathology registers. However, a remaining lymphocytic

infiltration in the colonic mucosa related to an undiagnosed CD may risk being misclassified as LC. To control for this potential error, study V included a sensitivity analyses where all MC diagnoses within a year of the diagnostic biopsy ascertaining CD were excluded. Another kind of differential misclassification is surveillance bias meaning that the groups under study differ in their probability of having the outcome detected. This may have had an impact in study IV and V since patients with MC or CD may be in closer and more frequent contact with health care compared to their non-exposed counterparts from the general population.

7.1.6 RANDOM ERROR

An observed association can be due to a true association, systematic error (see above) or random error. When conducting a study, a null hypothesis and alternative hypothesis is defined. The null hypothesis states that there is no association between the exposure and the outcome, whereas the alternative hypothesis states that there is an association. The precision of a study reflects the probability of falsely rejecting a true null hypothesis (type 1 error) due to a random error. The precision increases with the number of study participants enrolled. The probability of a random error influencing results is quantified by p-values and CIs. Generally, a p-value <0.05 is considered statistically significant, meaning that we accept a 1 in 20 probability that our observed association is a random finding. It should be noted, however, that this threshold (0.05) is arbitrary. While the p-value ascertains the significance of a finding, the CI also estimates the size of the effect. If we use a 95% CI, this means that we are 95% confident that the true value lies within this interval. When computing CIs, the size of the study population is taken into consideration. Thus, as the study population grows, the CI becomes narrower, increasing our confidence in the point estimate. In this respect, the risk of random errors in studies II-V is low since the study populations are large. In study I we based our sample size on a power calculation. However, since the study population only consisted of 211 patients, a risk, albeit small, of a random error is present. In studies III-V, we ascertained, not only the associations to our main outcomes (death, cancer, MC) but also secondary outcomes (cause specific deaths, specific cancers and MC subtypes). As mentioned above, a threshold for statistical significance of $p<0.05$ means that we accept a 1 in 20 probability that our observed association is a chance finding. As we, in studies III-V, test several associations there is a risk that some significant findings are a result of random error. Therefore, the possibility of a type 1 error and also the strength of the underlying hypothesis should be kept in mind when interpreting results pertaining to our secondary outcomes.

7.1.7 GENERALIZABILITY

Generalizability, or external validity refers to the extent to which findings from a study can be applied to different settings other than the one under study. A prerequisite of generalizability is a high degree of internal validity, i.e. the absence of systematic error. In study I our study population originates from a random sample of patients from five different counties, deemed to be representative of Sweden. The internal validity was ascertained by observing a high degree of coherence between pathology register data and information from medical charts and since the included hospitals were from different parts of the country, including both urban and rural settings, we are confident that our findings are valid on a national scale. As studies II-V were all nationwide, the question of generalizability to a Swedish setting becomes superfluous. Our findings should be applicable to countries similar to Sweden, but may not be generalizable to e.g. countries with differing ethnic distributions or lifestyle factors such as smoking patterns.

7.2 FINDINGS AND INTERPRETATIONS

7.2.1 STUDY I

We found a PPV of 95% for MC among patients with a record of MC in Swedish pathology registers. Thus, Swedish regional pathology registers are a reliable source for identifying MC. Moreover, our findings confirmed a high prevalence of smoking (36%) and autoimmune disease (26%) among patients with MC. Surprisingly, given the known association and symptomatic overlap between MC and CD only 50% of patients had been assessed for CD. A possible limitation of study I is that we only had information on risk factors through patient charts. Accordingly, the presence of certain exposures (smoking, medications, etc) not recorded in patient charts may have been underestimated. Furthermore, the PPV was calculated for the entire study population meaning there is a risk that the PPV within certain strata could be lower/higher or has changed (or will change) over time. However, as the incidence (and probably also prevalence and awareness among clinicians) of MC has risen during the past decades[20] the PPV, most likely (as a result of increasing prevalence), would have increased over time. Moreover, as we only collected data on individuals with a biopsy indicating MC, we could not calculate the negative predictive value (the proportion of patients with a biopsy not indicating MC who actually do not have MC), sensitivity (the proportion of patients with MC who are identified by a biopsy indicating MC) or specificity (the proportion of patients without MC identified by a biopsy not indicating MC).

7.2.2 STUDY II

We identified 13,844 patients with a first-time diagnosis of MC in Sweden from 1995 to 2015. As expected, a majority of patients (72%) were female and mean age at diagnosis was 60 years. The female preponderance did not vary during the study period, however the IRR between sexes attenuated with age. We observed a substantial increase in incidence from 1995 to 2012, after which IRs stabilized. This pattern, most likely, is primarily attributed to increasing awareness of MC during the first decades of the study period. The mean age-standardized IR throughout the study period was 7.2 cases/100,000 person-years and age-specific rates increased with age (up to 75-79 years). Patterns for LC and CC were broadly similar. However, 70% of identified MC patients had a diagnosis of LC, which contrasts against other nationwide studies of MC[40,44,46]. The cause of this discrepancy is unclear. Possible explanations entail varying awareness of MC among pathologists, differing routines surrounding the taking of biopsies or impact of environmental factors. With our previous validation study[96] confirming a high accuracy (PPV=95%) in Swedish pathology registers for identifying MC, our study, most likely, does not include a substantial proportion of false positives. However, as IRs historically probably have been kept low by an insufficient awareness there is a risk that some cases of MC remain undiagnosed. Since awareness increased during the study period, a lag in diagnosis may have affected incidence particularly in individuals diagnosed at an older age, skewing age-specific IRs. We estimated that 1 in 115 women and 1 in 286 men will be expected to be diagnosed with MC during a lifetime. These figures indicate that MC carries with it, a substantial, societal burden of disease.

7.2.3 STUDY III

We found that, after adjustment for comorbidities, there was no association between MC (or LC or CC) and death. These results did not change materially when comparing patients with MC to their siblings. Adjusted HRs for death in MC patients treated with budesonide and MC patients without budesonide treatment were not significantly different compared to our main results. When examining cause-specific mortality, we found a decreased HR for cancer-related death and increased HRs for death from infectious and gastrointestinal disease. The increased risk of death related to infections may reflect the dysfunctional immune response

essential for the development of MC. Among diagnoses responsible for the increased risk of mortality related to gastrointestinal disease were diverticular disease and vascular disease of the colon. These findings could generate new hypotheses regarding potentially shared pathogenic mechanisms. However, due to the association between MC and smoking[98], these findings could also include an effect related to residual confounding by smoking[99,100]. The reduced risk of cancer-related death may be attributable to surveillance bias and/or that the colonic inflammation in MC is not sufficient to trigger carcinogenesis. The main limitation of this study is residual confounding since the registers used for this study lacked data on factors such as smoking, BMI and other lifestyle factors.

7.2.4 STUDY IV

We found an 8% increased risk of cancer in MC patients compared to reference individuals from the general population. Further, our result was robust across several sensitivity analyses; e.g. aHRs in MC patients treated and not treated with budesonide did not significantly differ, nor did the aHR change significantly when using siblings to MC patients as comparators. Examining specific outcomes, we found an increased risk of lymphoma and lung cancer, no association with breast cancer nor bladder cancer, and a decreased risk of colorectal cancer and gastrointestinal cancers. The increased risk of lung cancer is likely due to the higher proportion of smokers in patients with MC[98] whereas the decreased risk of colorectal cancer would likely have been even lower if adjustment for smoking was possible. There are a number of explanations for the lower risk of colorectal cancer. Surveillance bias likely partly explains the decreased risk. There is also a possibility that there is negative confounding by BMI[101] or that the adaptive immune response in MC can detect and eradicate cancerous cells before a malignancy is established[102]. Also, as MC is typically diagnosed at age 60-70, the relative mild colonic inflammation that characterizes the disease may not have enough time to trigger cancer development. The significantly increased aHR for lymphoma is in line with previous studies of the association between inflammation and lymphoma[57,103,104].

When examining IRs of cancer according to country of birth (Nordic vs non-Nordic), we found similar IRs of cancer among MC patients born in non-Nordic countries compared to those born in Nordic countries. However, cancer rates among reference individuals of non-Nordic origin were substantially lower, which explains the observed significant effect modification by country of birth. Of course, people without MC of non-Nordic origin could be healthier or have had a cancer diagnosis recorded in another country. However, this discrepancy could also suggest a different health seeking behavior among people of non-Nordic origin which could have important, societal implications.

Limitations of this study include confounding by smoking which we had no way of adjusting for. Also, with MC being a relatively newly recognized condition, the average follow-up time was only 6.6 years which may be an insufficient time span for certain cancers to develop.

7.2.5 STUDY V

There is a known association between CD and MC[22,71,105]. However, our study was the first large, population-based cohort study able to examine the association across several strata. We found a pronounced risk for future MC in CD (aHR 11.5). The risk was most pronounced at the start of follow-up where the aHR was almost 20. This may partially be explained by surveillance bias and misclassification of colonic lymphocytic infiltration caused by an active CD as LC. However, the aHR remained elevated also >10 years of follow up (for both LC and CC). When using siblings of CD patients as comparators, the aHR was appreciably lower, suggesting an influence of early environmental factors and/or shared genetics. As there are reports on common genetic risk factors in CD and CC[9,106], we consider this an interesting

finding. However, the association could not be reproduced when examining a cohort of LC patients[10]. Also, when restricting our analyses to patients with autoimmune disorders, aHR, again, was markedly lower, confirming the known association between autoimmunity and MC[22]. Moreover, we found a suggested, albeit not statistically significant, effect modification by country of birth, caused by lower rates of MC in reference individuals. If this reflects a lower exposure to risk factors (smoking, medications etc), is attributable to genetics or a different health seeking behavior remains an important outstanding question.

Strengths of the study include the nationwide coverage and size of our study population. Based on earlier validation studies we also have a high degree of confidence in the accuracy of our exposure and outcome information[96,97]. We acknowledge some limitations. As the study was strictly register-based, we had no information on lifestyle factors such as smoking. However, as smoking does not seem to be connected to CD[107,108], this lack of data is unlikely to affect our results in a profound way. Moreover, we only used data on biopsy-verified villous atrophy to ascertain CD, meaning that CD patients diagnosed solely by tissue transglutaminase are not included. This should, however, primarily impact the younger population due to the adoption of a non-biopsy routine for diagnosing CD in children[109] established in 2012. When excluding 2012-2015 from our analyses, the aHR for patients <18 did not change substantially compared to analyses for the full study period.

8 CONCLUSIONS

Based on the studies included in this thesis we conclude that:

Swedish pathology registers are a reliable source for identifying MC.

Incidence of MC in Sweden increased appreciably from 1995-2015. However, IRs has stabilized during the past decade. In Sweden, LC is the more common subtype of MC, constituting 70% of MC cases. During a lifetime, 1 in 115 women and 1 in 286 men are expected to be diagnosed with MC.

Patients suffering from MC are at increased risk of dying. This risk, however, is primarily attributable to concomitant disease. Specifically, patients with MC are at an increased risk of dying from gastrointestinal and infectious diseases and at a decreased risk of dying from cancer related causes.

MC is associated with a small (8%) increase in risk of overall cancer. Part of this increase may be attributable to surveillance bias. Specifically, we noted a decreased risk of colorectal cancer. Thus, screening for colorectal cancer in MC patients would likely be superfluous.

Our study confirms a strong association between CD and MC. This finding underlines the importance of evaluating CD patients for MC if symptoms endure or reoccur despite adherence to a gluten-free diet Also, MC patients should be tested for CD when symptoms persist despite adequate treatment.

9 POINTS OF PERSPECTIVE

As pointed out throughout this thesis, the burden of MC has previously likely been underestimated due to insufficient awareness. As we show in study II, IRs increased rapidly from 1995 to 2005. This may be explained by a true increase in incidence and/or improved awareness and diagnostic capabilities. As we lack information on duration of symptoms, we cannot discern whether our observed cases had their onset just prior to being diagnosed with MC or if there is a substantial diagnostic delay. Consequently, temporal patterns and years of follow-up may be skewed. Therefore, as MC nowadays is well-known to clinicians and colonoscopy is easily accessible in Sweden, future studies on incidence, risk of death, cancer and other disorders would be a valuable addition to the body of knowledge. Moreover, additional studies from countries with a differing panorama of risk factors is much needed. Such epidemiological groundwork is pivotal for future large-scale studies aimed to further elucidate the role played by genetic factors and the microbiome in the pathogenesis of MC. Also, smoking is an important confounder. If future, population-based studies could gather data on smoking habits, the effects of smoking and MC could be disentangled and the impact of MC on health-related outcomes could be computed more precisely. Also, a better understanding of the role played by smoking in the development of MC could be gained.

In study II, we also noted that a majority of cases were classified as LC, which contrasts against the distribution of subtypes in other nationwide studies. We have no clear explanation for this discrepancy. However, the relationship between CC and LC and what they actually represent (different stages of the same disease or separate entities with similar symptoms) deserves further study and perhaps our findings could aid in generating new hypothesis regarding the association between subtypes?

Lastly, our finding of the decreased risk of colorectal cancer in MC motivates further study on the mechanisms responsible for this decrease.

10 ACKNOWLEDGEMENTS

Hundreds of thousands of Swedish citizens have contributed to this thesis by inclusion in the Swedish health care registers. I am deeply grateful for having been given the oppurtunity to conduct research based on this material. Furthermore, I would like to thank the following individuals for their precious help during my time as a PhD student:

Professor Jonas Ludvigsson, my main supervisor. Thank you for allowing me the oppurtunity to work with you on this project. I will be forever grateful for all your help and encouragement. Your generous nature and your constant willingness to make your knowledge and time available for the greater good is truly inspiring.

Docent Mark Clements, my co-supervisor. For all the times I've bothered you with questions about statistics, I would like to thank you, not only for your excellent answers, but also for your kind attitude and patience towards me. The questions will keep on coming.

Associate professor Hamed Khalili, my co-supervisor. Thank you for sharing your expertise on MC and for welcoming me to Harvard/MGH. It has been stimulating to work alongside you throughout these years.

Professor Lars Agréus, my co-supervisor. For your help and support throughout my time as a PhD student. However, first and foremost, thank you for providing a shining example of a general practitioner in academia.

Jonatan Hedlund, my mentor**.** For your support, encouragement and friendship since we first met in January 1999. Your mentorship began then and there. Specifically, I would like to thank you for opening the world of punctuation and en-dashes to me. I am genuinly unsurprised that you master such things.

Anders Forss. Thank you for all the help and support throughout our time as PhD students. Many of the obstacles I've faced as a PhD-student would have been overwhelming without your help. Our time spent together at "the office" has been a true pleasure!

Bjorn Roelstraete. Thank you for making statistics seem comprehensible and for always providing help when I've needed it. I would also like to thank you for enrolling in the obviously fraudulent beer-for statistics-program.

Mariam Lashkariani. Thank you for your support and patience with my tendency towards chaotic data management.

Alessandra Nanni, Linn Austin and Gunilla Sonnebring. Thank you for all your help with every administrative detail and specifically for your kind and supportive ways.

Mikael Pettersson, my clinical boss. Thank you for giving me the oppurtunity to pursue a PhD amidst all the challenges of the daily clinical work.

All my colleagues at Brommaplans VC. Thank you for your kindness and support.

Rickard Lidström. For a beautiful friendship. Thank you for sharing every burden and joy and for always supporting me.

Mikael Eriksson. Stata whiz kid and dear friend. The best and brightest of our generation. Thank you for all the help and for all the good times to come.

Jonas Svensson, Peter Asellus and Alexander Liakos. Thank you for the discussions on science in its proper context, i.e. space ships with intergalactic capabilities.

Carl Eckerström. For keeping it real (on the west coast, no less).

Professor Jimmy Ek. Bromma´s finest. Thank you for all your help and for your friendship. No task seems too large or too small. Specifically, thank you for owning and maintaining a printer.

Tomas Hansy and Alexander Fredlund. Thank you for the music. And for every minute spent perfecting our sound.

The Lanser-Erikssons, my dynamic new family. **Kjell** and **Radegundis,** thank you for all the help in every aspect of our lives and for the enriching conversations through the years.

My dear mother and father. Thank you for your unconditional love and encouragement throughout my life. And for helping me value what matters most.

My siblings Linda, Kalle, Gustav and Maja. Thank you for for all your help with all the things I never cared to learn since I knew I could just ask one of you. And for being merry.

Eyvind, Alexander and Nils. My blue-eyed sons, my darling young ones.

Louise, my wife, mother of our children, epidemiological sage and the unsung hero of this thesis. Thank you for our 22 years spent together, for always being by my side and for your "patience" with all my questions about research. Without you, the Penske file would not have happened and each day working on it, I am impressed by your brilliance. You are the love of my life.

11 REFERENCES

1. Guagnozzi D, Landolfi S, Vicario M. Towards a new paradigm of microscopic colitis: Incomplete and variant forms. *World journal of gastroenterology WJG*. 2016;22(38):8459-8471. doi:10.3748/wjg.v22.i38.8459

2. Mellander MR, Ekbom A, Hultcrantz R, Lofberg R, Ost A, Bjork J. Microscopic colitis: a descriptive clinical cohort study of 795 patients with collagenous and lymphocytic colitis. *Scand J Gastroenterol*. 2016;51(5):556-62. doi:10.3109/00365521.2015.1124283

3. Miehlke S, Verhaegh B, Tontini GE, Madisch A, Langner C, Münch A. Microscopic colitis: pathophysiology and clinical management. *Lancet Gastroenterol Hepatol*. 04 2019;4(4):305-314. doi:10.1016/S2468-1253(19)30048-2

4. Nyhlin N, Wickbom A, Montgomery SM, Tysk C, Bohr J. Long-term prognosis of clinical symptoms and health-related quality of life in microscopic colitis: a case-control study. *Alimentary pharmacology & therapeutics*. 2014;39(9):963-972. doi:10.1111/apt.12685

5. Verhaegh BPM, Münch A, Guagnozzi D, et al. Course of Disease in Patients with Microscopic Colitis: A European Prospective Incident Cohort Study. *J Crohns Colitis*. Jul 05 2021;15(7):1174-1183. doi:10.1093/ecco-jcc/jjab007

6. Tysk C, Wickbom A, Nyhlin N, Eriksson S, Bohr J. Recent advances in diagnosis and treatment of microscopic colitis. *Annals of gastroenterology : quarterly publication of the Hellenic Society of Gastroenterology*. 2011;24(4):253-262.

7. Järnerot G, Hertervig E, Grännö C, et al. Familial occurrence of microscopic colitis: a report on five families. *Scand J Gastroenterol*. Sep 2001;36(9):959-62. doi:10.1080/003655201750305486

8. van Tilburg AJ, Lam HG, Seldenrijk CA, et al. Familial occurrence of collagenous colitis. A report of two families. *J Clin Gastroenterol*. Jun 1990;12(3):279-85. doi:10.1097/00004836-199006000-00009

9. Westerlind H, Mellander MR, Bresso F, et al. Dense genotyping of immune-related loci identifies HLA variants associated with increased risk of collagenous colitis. *Gut*. Mar 2017;66(3):421-428. doi:10.1136/gutjnl-2015-309934

10. Westerlind H, Bonfiglio F, Mellander MR, et al. HLA Associations Distinguish Collagenous From Lymphocytic Colitis. *Am J Gastroenterol*. 08 2016;111(8):1211-3. doi:10.1038/ajg.2016.215

11. Koning F. Celiac disease: caught between a rock and a hard place. *Gastroenterology*. Oct 2005;129(4):1294-301. doi:10.1053/j.gastro.2005.07.030

12. Järnerot G, Bohr J, Tysk C, Eriksson S. Faecal stream diversion in patients with collagenous colitis. *Gut*. Jan 1996;38(1):154-5. doi:10.1136/gut.38.1.154-b

13. Daferera N, Kumawat AK, Hultgren-Hörnquist E, Ignatova S, Ström M, Münch A. Fecal stream diversion and mucosal cytokine levels in collagenous colitis: A case report. *World J Gastroenterol*. May 21 2015;21(19):6065-71. doi:10.3748/wjg.v21.i19.6065

14. Morgan DM, Cao Y, Miller K, et al. Microscopic Colitis Is Characterized by Intestinal Dysbiosis. *Clin Gastroenterol Hepatol*. 04 2020;18(4):984-986. doi:10.1016/j.cgh.2019.06.035

15. Rindom Krogsgaard L, Kristian Munck L, Bytzer P, Wildt S. An altered composition of the microbiome in microscopic colitis is driven towards the composition in healthy controls by treatment with budesonide. *Scand J Gastroenterol*. Apr 2019;54(4):446-452. doi:10.1080/00365521.2019.1599064

16. Münch A, Söderholm JD, Wallon C, Ost A, Olaison G, Ström M. Dynamics of mucosal permeability and inflammation in collagenous colitis before, during, and after loop ileostomy. *Gut*. Aug 2005;54(8):1126-8. doi:10.1136/gut.2004.058750

17. Barmeyer C, Erko I, Awad K, et al. Epithelial barrier dysfunction in lymphocytic colitis through cytokine-dependent internalization of claudin-5 and -8. *J Gastroenterol*. 10 2017;52(10):1090-1100. doi:10.1007/s00535-017-1309-2

18. Mogensen AM, Olsen JH, Gudmand-Høyer E. Collagenous colitis. *Acta Med Scand*. 1984;216(5):535-40. doi:10.1111/j.0954-6820.1984.tb05043.x

19. Bürgel N, Bojarski C, Mankertz J, Zeitz M, Fromm M, Schulzke JD. Mechanisms of diarrhea in collagenous colitis. *Gastroenterology*. Aug 2002;123(2):433-43. doi:10.1053/gast.2002.34784

20. Bergman D, Clements MS, Khalili H, Agreus L, Hultcrantz R, Ludvigsson JF. A nationwide cohort study of the incidence of microscopic colitis in Sweden. *Aliment Pharmacol Ther*. Jun 2019;49(11):1395-1400. doi:10.1111/apt.15246

21. Olesen M, Eriksson S, Bohr J, Järnerot G, Tysk C. Lymphocytic colitis: a retrospective clinical study of 199 Swedish patients. *Gut*. 2004;53(4):536-541. doi:10.1136/gut.2003.023440

22. Wildt S, Munck LK, Winther-Jensen M, Jess T, Nyboe Andersen N. Autoimmune diseases in microscopic colitis: A Danish nationwide case-control study. *Aliment Pharmacol Ther*. 12 2021;54(11-12):1454-1462. doi:10.1111/apt.16614

23. Verhaegh BP, de Vries F, Masclee AA, et al. High risk of drug-induced microscopic colitis with concomitant use of NSAIDs and proton pump inhibitors. *Aliment Pharmacol Ther*. May 2016;43(9):1004-13. doi:10.1111/apt.13583

24. Tong J, Zheng Q, Zhang C, Lo R, Shen J, Ran Z. Incidence, prevalence, and temporal trends of microscopic colitis: a systematic review and meta-analysis. *Am J Gastroenterol*. Feb 2015;110(2):265-76; quiz 277. doi:10.1038/ajg.2014.431

25. Bonderup OK, Fenger-Grøn M, Wigh T, Pedersen L, Nielsen GL. Drug exposure and risk of microscopic colitis: a nationwide Danish case-control study with 5751 cases. *Inflamm Bowel Dis*. Oct 2014;20(10):1702-7. doi:10.1097/MIB.0000000000000143

26. Zylberberg HM, Kamboj AK, De Cuir N, et al. Medication use and microscopic colitis: a multicentre retrospective cohort study. *Aliment Pharmacol Ther*. 06 2021;53(11):1209-1215. doi:10.1111/apt.16363

27. Fernandez-Banares F, de Sousa MR, Salas A, et al. Impact of current smoking on the clinical course of microscopic colitis. *Inflamm Bowel Dis*. Jun 2013;19(7):1470-6. doi:10.1097/MIB.0b013e318281f3cc

28. Burke KE, Ananthakrishnan AN, Lochhead P, et al. Smoking is Associated with an Increased Risk of Microscopic Colitis: Results From Two Large Prospective Cohort

Studies of US Women. *J Crohns Colitis*. Apr 27 2018;12(5):559-567. doi:10.1093/ecco-jcc/jjy005

29. Jaruvongvanich V, Poonsombudlert K, Ungprasert P. Smoking and Risk of Microscopic Colitis: A Systematic Review and Meta-analysis. *Inflamm Bowel Dis*. Mar 14 2019;25(4):672-678. doi:10.1093/ibd/izy296

30. Rasmussen MA, Munck LK. Systematic review: are lymphocytic colitis and collagenous colitis two subtypes of the same disease - microscopic colitis? *Aliment Pharmacol Ther*. Jul 2012;36(2):79-90. doi:10.1111/j.1365-2036.2012.05166.x

31. Sweden) TPHAoSSFTPHAo. Tobaksrökning (tobacco smoking), daily [Internet]. . Accessed 2022-04-24,

32. Kaplan GG, Seminowich S, Williams J, et al. The risk of microscopic colitis in solid-organ transplantation patients: a population-based study. *Transplantation*. Jan 15 2008;85(1):48-54. doi:10.1097/01.tp.0000298001.66377.a2

33. Williams JJ, Kaplan GG, Makhija S, et al. Microscopic colitis-defining incidence rates and risk factors: a population-based study. *Clin Gastroenterol Hepatol*. Jan 2008;6(1):35-40. doi:10.1016/j.cgh.2007.10.031

34. Erim T, Alazmi WM, O'Loughlin CJ, Barkin JS. Collagenous colitis associated with Clostridium difficile: a cause effect? *Dig Dis Sci*. Jul 2003;48(7):1374-5. doi:10.1023/a:1024127713979

35. Mäkinen M, Niemelä S, Lehtola J, Karttunen TJ. Collagenous colitis and Yersinia enterocolitica infection. *Dig Dis Sci*. Jun 1998;43(6):1341-6. doi:10.1023/a:1018836614448

36. Nielsen HL, Dalager-Pedersen M, Nielsen H. High risk of microscopic colitis after. *Gut*. 11 2020;69(11):1952-1958. doi:10.1136/gutjnl-2019-319771

37. Lindström CG. 'Collagenous colitis' with watery diarrhoea--a new entity? *Pathol Eur*. 1976;11(1):87-89.

38. Lazenby AJ, Yardley JH, Giardiello FM, Jessurun J, Bayless TM. Lymphocytic ("microscopic") colitis: a comparative histopathologic study with particular reference to collagenous colitis. *Human pathology*. 1989;20(1):18-28.

39. Guagnozzi D, Arias Á, Lucendo AJ. Systematic review with meta-analysis: diagnostic overlap of microscopic colitis and functional bowel disorders. *Alimentary pharmacology & therapeutics*. 2016;43(8):851-862. doi:10.1111/apt.13573

40. Verhaegh BPM, Jonkers DMAE, Driessen A, et al. Incidence of microscopic colitis in the Netherlands. A nationwide population-based study from 2000 to 2012. *Digestive and liver disease*. 2015;47(1):30-36. doi:10.1016/j.dld.2014.09.019

41. Gentile NM, Khanna S, Loftus EV, et al. The epidemiology of microscopic colitis in Olmsted County from 2002 to 2010: a population-based study. *Clinical gastroenterology and hepatology*. 2014;12(5):838-842. doi:10.1016/j.cgh.2013.09.066

42. Tome J, Sehgal K, Kamboj AK, et al. The Epidemiology of Microscopic Colitis in Olmsted County, Minnesota: Population-Based Study From 2011 to 2019. *Clin Gastroenterol Hepatol*. Jun 30 2021;doi:10.1016/j.cgh.2021.06.027

43. Bonderup OK, Wigh T, Nielsen GL, Pedersen L, Fenger-Grøn M. The epidemiology of microscopic colitis: a 10-year pathology-based nationwide Danish cohort

study. *Scandinavian journal of gastroenterology*. 2015;50(4):393-398. doi:10.3109/00365521.2014.940378

44. Weimers P, Ankersen DV, Lophaven S, et al. Incidence and prevalence of microscopic colitis between 2001 and 2016: A Danish nationwide cohort study. *J Crohns Colitis*. Jun 05 2020;doi:10.1093/ecco-jcc/jjaa108

45. Bonderup OK, Wigh T, Nielsen GL, Pedersen L, Fenger-Gr¯n M. The epidemiology of microscopic colitis: a 10-year pathology-based nationwide Danish cohort study. *Scandinavian journal of gastroenterology*. 2015;50(4):393-398. doi:10.3109/00365521.2014.940378

46. Agnarsdottir M, Gunnlaugsson O, Orvar KB, et al. Collagenous and lymphocytic colitis in Iceland. *Digestive diseases and sciences*. 2002;47(5):1122-1128.

47. Fiehn AM, Bjørnbak C, Warnecke M, Engel PJ, Munck LK. Observer variability in the histopathologic diagnosis of microscopic colitis and subgroups. *Hum Pathol*. Nov 2013;44(11):2461-6. doi:10.1016/j.humpath.2013.06.004

48. Tong J, Zheng Q, Zheng Q, et al. Incidence, prevalence, and temporal trends of microscopic colitis: a systematic review and meta-analysis. *The American journal of gastroenterology*. 2015;110(2):265-76; quiz 277. doi:10.1038/ajg.2014.431

49. Weimers P, Vedel Ankersen D, Lophaven SN, et al. Microscopic colitis in Denmark: regional variations in risk factors and frequency of endoscopic procedures. *J Crohns Colitis*. Jul 07 2021;doi:10.1093/ecco-jcc/jjab119

50. Fernández-Bañares F, Salas A, Forné M, Esteve M, Espinós J, Viver JM. Incidence of collagenous and lymphocytic colitis: a 5-year population-based study. *Am J Gastroenterol*. Feb 1999;94(2):418-23. doi:10.1111/j.1572-0241.1999.00870.x

51. Bonderup OK, Hansen JB, Birket-Smith L, Vestergaard V, Teglbjaerg PS, Fallingborg J. Budesonide treatment of collagenous colitis: a randomised, double blind, placebo controlled trial with morphometric analysis. *Gut*. Feb 2003;52(2):248-51. doi:10.1136/gut.52.2.248

52. Miehlke S, Aust D, Mihaly E, et al. Efficacy and Safety of Budesonide, vs Mesalazine or Placebo, as Induction Therapy for Lymphocytic Colitis. *Gastroenterology*. Dec 2018;155(6):1795-1804 e3. doi:10.1053/j.gastro.2018.08.042

53. Pardi DS, Tremaine WJ, Carrasco-Labra A. American Gastroenterological Association Institute Technical Review on the Medical Management of Microscopic Colitis. *Gastroenterology : official journal of the American Gastroenterologic Association*. 2016;150(1):247-274.e11. doi:10.1053/j.gastro.2015.11.006

54. Cotter TG, Kamboj AK, Hicks SB, Tremaine WJ, Loftus EV, Pardi DS. Immune modulator therapy for microscopic colitis in a case series of 73 patients. *Aliment Pharmacol Ther*. Jul 2017;46(2):169-174. doi:10.1111/apt.14133

55. Munch A, Aust D, Bohr J, et al. Microscopic colitis: Current status, present and future challenges: statements of the European Microscopic Colitis Group. *J Crohns Colitis*. Oct 2012;6(9):932-45. doi:10.1016/j.crohns.2012.05.014

56. Nyhlin N, Wickbom A, Montgomery SM, Tysk C, Bohr J. Long-term prognosis of clinical symptoms and health-related quality of life in microscopic colitis: a case-control study. *Aliment Pharmacol Ther*. May 2014;39(9):963-72. doi:10.1111/apt.12685

57. Beyaert R, Beaugerie L, Van Assche G, et al. Cancer risk in immune-mediated inflammatory diseases (IMID). *Mol Cancer*. Aug 29 2013;12(1):98. doi:10.1186/1476-4598-12-98

58. Edwards DB. Collagenous colitis and histiocytic lymphoma. *Ann Intern Med*. Aug 1 1989;111(3):260-1. doi:10.7326/0003-4819-111-3-260

59. Ouyahya F, Michenet P, Gargot D, Breteau N, Buzacoux J, Legoux JL. [Lymphocytic colitis, followed by collagenous colitis, associated with mycosis fungoides-type T-cell lymphoma]. *Gastroenterol Clin Biol*. 1993;17(12):976-7. Colite lymphocytaire puis colite collagene associee a un lymphome T de type mycosis fongoide.

60. Freeman HJ. Lymphoproliferative disorders in collagenous colitis. *Inflamm Bowel Dis*. Aug 2005;11(8):781-2. doi:10.1097/01.mib.0000172559.16896.fe

61. Chan JL, Tersmette AC, Offerhaus GJ, Gruber SB, Bayless TM, Giardiello FM. Cancer risk in collagenous colitis. *Inflamm Bowel Dis*. Feb 1999;5(1):40-3. doi:10.1097/00054725-199902000-00006

62. Bonderup OK, Folkersen BH, Gjersoe P, Teglbjaerg PS. Collagenous colitis: a long-term follow-up study. *Eur J Gastroenterol Hepatol*. May 1999;11(5):493-5.

63. Kao KT, Pedraza BA, McClune AC, et al. Microscopic colitis: a large retrospective analysis from a health maintenance organization experience. *World J Gastroenterol*. Jul 7 2009;15(25):3122-7. doi:10.3748/wjg.15.3122

64. Levy A, Borren NZ, Maxner B, et al. Cancer risk in microscopic colitis: a retrospective cohort study. *BMC Gastroenterol*. Jan 5 2019;19(1):1. doi:10.1186/s12876-018-0926-4

65. Weimers P, Vedel Ankersen D, Lophaven S, et al. Disease Activity Patterns, Mortality, and Colorectal Cancer Risk in Microscopic Colitis: A Danish Nationwide Cohort Study, 2001 to 2016. *J Crohns Colitis*. Apr 06 2021;15(4):594-602. doi:10.1093/ecco-jcc/jjaa207

66. Bergman D, Khalili H, Roelstraete B, Ludvigsson JF. Microscopic colitis and risk of cancer - a population-based cohort study. *J Crohns Colitis*. Jul 25 2020;doi:10.1093/ecco-jcc/jjaa156

67. Larsson JK, Dabos KJ, Höglund P, et al. Cancer Risk in Collagenous Colitis. *J Clin Med*. Nov 11 2019;8(11)doi:10.3390/jcm8111942

68. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA*. May 17 2006;295(19):2275-85. doi:10.1001/jama.295.19.2275

69. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet*. Nov 7 2009;374(9701):1617-25. doi:10.1016/S0140-6736(09)61302-7

70. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, et al. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. *Gastroenterology*. Nov 2011;141(5):1621-28 e1-5. doi:10.1053/j.gastro.2011.06.050

71. Stewart M, Andrews CN, Urbanski S, Beck PL, Storr M. The association of coeliac disease and microscopic colitis: a large population-based study. *Aliment Pharmacol Ther*. Jun 2011;33(12):1340-9. doi:10.1111/j.1365-2036.2011.04666.x

72. Koskela RM, Niemela SE, Karttunen TJ, Lehtola JK. Clinical characteristics of collagenous and lymphocytic colitis. *Scand J Gastroenterol*. Sep 2004;39(9):837-45. doi:10.1080/00365520410006468

73. Pardi DS, Loftus EV, Smyrk TC, et al. The epidemiology of microscopic colitis: a population based study in Olmsted County, Minnesota. *Gut*. 2007;56(4):504-508. doi:10.1136/gut.2006.105890

74. Thorn M, Sjoberg D, Ekbom A, et al. Microscopic colitis in Uppsala health region, a population-based prospective study 2005-2009. *Scand J Gastroenterol*. Jul 2013;48(7):825-30. doi:10.3109/00365521.2013.800993

75. Olesen M, Eriksson S, Bohr J, Jarnerot G, Tysk C. Microscopic colitis: a common diarrhoeal disease. An epidemiological study in Orebro, Sweden, 1993-1998. *Gut*. Mar 2004;53(3):346-50. doi:10.1136/gut.2003.014431

76. Leffler DA, Dennis M, Hyett B, Kelly E, Schuppan D, Kelly CP. Etiologies and predictors of diagnosis in nonresponsive celiac disease. *Clin Gastroenterol Hepatol*. Apr 2007;5(4):445-50. doi:10.1016/j.cgh.2006.12.006

77. Olesen M, Eriksson S, Bohr J, Järnerot G, Tysk C. Lymphocytic colitis: a retrospective clinical study of 199 Swedish patients. *Gut*. Apr 2004;53(4):536-41. doi:10.1136/gut.2003.023440

78. Olen O, Askling J, Sachs MC, et al. Mortality in adult-onset and elderly-onset IBD: a nationwide register-based cohort study 1964-2014. *Gut*. May 15 2019;doi:10.1136/gutjnl-2018-317572

79. Nyboe Andersen N, Munck LK, Hansen S, Jess T, Wildt S. All-cause and cause-specific mortality in microscopic colitis: a Danish nationwide matched cohort study. *Aliment Pharmacol Ther*. 07 2020;52(2):319-328. doi:10.1111/apt.15868

80. Khalili H, Bergman D, Roelstraete B, et al. Mortality of Patients With Microscopic Colitis in Sweden. *Clin Gastroenterol Hepatol*. 10 2020;18(11):2491-2499.e3. doi:10.1016/j.cgh.2019.12.012

81. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *European journal of epidemiology*. 2009;24(11):659-667. doi:10.1007/s10654-009-9350-y

82. Ludvigsson JF, Lashkariani M. Cohort profile: ESPRESSO (Epidemiology Strengthened by histoPathology Reports in Sweden). *Clin Epidemiol*. 2019;11:101-114. doi:10.2147/CLEP.S191914

83. Ludvigsson JF, Almqvist C, Bonamy A-KE, et al. Registers of the Swedish total population and their use in medical research. *European journal of epidemiology*. 2016;31(2):125-136. doi:10.1007/s10654-016-0117-y

84. Ludvigsson JF, Svedberg P, Olén O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. *Eur J Epidemiol*. Apr 2019;34(4):423-437. doi:10.1007/s10654-019-00511-8

85. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health*. Jun 09 2011;11:450. doi:10.1186/1471-2458-11-450

86. Barlow L, Westergren K, Holmberg L, Talbäck M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. *Acta Oncol*. 2009;48(1):27-33. doi:10.1080/02841860802247664

87. Brooke HL, Talbäck M, Hörnblad J, et al. The Swedish cause of death register. *Eur J Epidemiol*. 09 2017;32(9):765-773. doi:10.1007/s10654-017-0316-1

88. Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf*. Jul 2007;16(7):726-35. doi:10.1002/pds.1294

89. Ludvigsson JF, Haberg SE, Knudsen GP, et al. Ethical aspects of registry-based research in the Nordic countries. *Clin Epidemiol*. 2015;7:491-508. doi:10.2147/CLEP.S90589

90. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-83. doi:10.1016/0021-9681(87)90171-8

91. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. Nov 2005;43(11):1130-9. doi:10.1097/01.mlr.0000182534.19832.83

92. Bewtra M, Lewis JD. Update on the risk of lymphoma following immunosuppressive therapy for inflammatory bowel disease. *Expert Rev Clin Immunol*. Jul 2010;6(4):621-31. doi:10.1586/eci.10.36

93. Olén O, Askling J, Sachs MC, et al. Childhood onset inflammatory bowel disease and risk of cancer: a Swedish nationwide cohort study 1964-2014. *BMJ*. Sep 20 2017;358:j3951. doi:10.1136/bmj.j3951

94. Bernstein CN, Blanchard JF, Kliewer E, Wajda A. Cancer risk in patients with inflammatory bowel disease: a population-based study. *Cancer*. Feb 15 2001;91(4):854-62. doi:10.1002/1097-0142(20010215)91:4<854::aid-cncr1073>3.0.co;2-z

95. Brillinger DR. The natural variability of vital rates and associated statistics. *Biometrics*. Dec 1986;42(4):693-734.

96. Svensson M, Bergman D, Olen O, et al. Validating microscopic colitis (MC) in Swedish pathology registers. *Scand J Gastroenterol*. Jan 2 2019:1-7. doi:10.1080/00365521.2018.1543446

97. Ludvigsson JF, Brandt L, Montgomery SM, Granath F, Ekbom A. Validation study of villous atrophy and small intestinal inflammation in Swedish biopsy registers. *BMC Gastroenterol*. Mar 11 2009;9:19. doi:10.1186/1471-230X-9-19

98. Yen EF, Pokhrel B, Du H, et al. Current and past cigarette smoking significantly increase risk for microscopic colitis. *Inflamm Bowel Dis*. Oct 2012;18(10):1835-41. doi:10.1002/ibd.22838

99. Turunen P, Wikström H, Carpelan-Holmström M, Kairaluoma P, Kruuna O, Scheinin T. Smoking increases the incidence of complicated diverticular disease of the sigmoid colon. *Scand J Surg*. 2010;99(1):14-7. doi:10.1177/145749691009900104

100. Hohenwalter EJ. Chronic mesenteric ischemia: diagnosis and treatment. *Semin Intervent Radiol*. Dec 2009;26(4):345-51. doi:10.1055/s-0029-1242198

101. Liu PH, Burke KE, Ananthakrishnan AN, et al. Obesity and Weight Gain Since Early Adulthood Are Associated With a Lower Risk of Microscopic Colitis. *Clin Gastroenterol Hepatol*. 11 2019;17(12):2523-2532.e1. doi:10.1016/j.cgh.2018.11.057

102. Yen EF, Pokhrel B, Bianchi LK, et al. Decreased colorectal cancer and adenoma risk in patients with microscopic colitis. *Dig Dis Sci*. Jan 2012;57(1):161-9. doi:10.1007/s10620-011-1852-2

103. Elfström P, Granath F, Ekström Smedby K, et al. Risk of lymphoproliferative malignancy in relation to small intestinal histopathology among patients with celiac disease. *J Natl Cancer Inst*. Mar 02 2011;103(5):436-44. doi:10.1093/jnci/djq564

104. Baecklund E, Iliadou A, Askling J, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. *Arthritis Rheum*. Mar 2006;54(3):692-701. doi:10.1002/art.21675

105. Green PH, Yang J, Cheng J, Lee AR, Harper JW, Bhagat G. An association between microscopic colitis and celiac disease. *Clin Gastroenterol Hepatol*. Nov 2009;7(11):1210-6. doi:10.1016/j.cgh.2009.07.011

106. Stahl E, Roda G, Dobbyn A, et al. Collagenous Colitis Is Associated with Hla Signature and Shares Genetic Risks with Other Immune-Mediated Diseases. *Gastroenterology*. May 1 2020;doi:10.1053/j.gastro.2020.04.063

107. Ludvigsson JF, Montgomery SM, Ekbom A. Smoking and celiac disease: a population-based cohort study. *Clin Gastroenterol Hepatol*. Sep 2005;3(9):869-74. doi:10.1016/s1542-3565(05)00414-3

108. Ludvigsson JF, Nordenvall C, Järvholm B. Smoking, use of moist snuff and risk of celiac disease: a prospective study. *BMC Gastroenterol*. Jul 03 2014;14:120. doi:10.1186/1471-230X-14-120

109. Husby S, Koletzko S, Korponay-Szabó I, et al. European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. *J Pediatr Gastroenterol Nutr*. 01 2020;70(1):141-156. doi:10.1097/MPG.0000000000002497