Microscopic colitis and risk of incident acute pancreatitis: A nationwide population-based matched cohort study

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Abstract

Introduction: Several gastrointestinal diseases have been linked to acute pancreatitis, but the risk of acute pancreatitis in microscopic colitis (MC) has not been studied.

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Methods: We conducted a nationwide, population-based, matched cohort study in Sweden of 12,140 patients with biopsy-verified MC (diagnosed in 2003–2017), 57,806 matched reference individuals, and 12,781 siblings without MC with follow-up until 2021. Data on MC were obtained from all of Sweden's regional pathology registers (n=28) through the ESPRESSO cohort. Data on acute pancreatitis were collected from the National Patient Register. Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were calculated using Cox regression.

Results: During a mean follow-up of 9.9 years (SD=4.3), 146 MC patients and 437 reference individuals were diagnosed with acute pancreatitis (127.8 vs. 80.1 per 100,000 person-years), corresponding to an aHR of 1.57 (95%CI=1.30–1.90). Moreover, we found a positive association between MC and acute non-gallstone-related pancreatitis (aHR 1.99 (95%CI=1.57–2.51)), but not with acute gallstone-related pancreatitis (aHR 1.08 (95%CI=0.78–1.49)). Comparing patients with MC to their unaffected siblings yielded an aHR of 1.28 (95%CI=0.92–1.78).

The risk of acute pancreatitis remained elevated also for MC patients with a follow-up exceeding 10 years (aHR 1.75 (95%CI=1.14–2.67)).

Conclusion: This nationwide study of more than 12,000 patients with MC demonstrated an increased risk of acute pancreatitis after MC. Hence, clinicians should have a low threshold for evaluation of acute pancreatitis in patients with MC. Also, these patients should receive advice and care aimed at reducing the risk of acute pancreatitis.

INTRODUCTION

Microscopic colitis (MC) is a recently recognized inflammatory condition of the large intestine(1). The disease is usually divided into lymphocytic colitis (LC) or collagenous colitis (CC), depending on the histopathological presentation of a colonic biopsy. The most prominent symptom in MC is watery, non-bloody diarrhea. However, other symptoms, such as abdominal pain, weight loss, fatigue, and arthralgia, have also been reported(2). In a previous study we found a substantial increase in the incidence of MC in Sweden during the past decades(3) with incidence rates (IRs) approaching those of inflammatory bowel disease(4, 5). Acute pancreatitis is an acute inflammation of the pancreatic gland that clinically presents with acute onset of upper abdominal pain, elevated pancreatic enzymes in blood or urine and/or radiological signs of pancreatic inflammation. Risk factors for acute pancreatitis include alcohol abuse(6) and gallstone disease(7). Associations with other gastrointestinal diseases, such as celiac disease(8) and inflammatory bowel disease (IBD) (9, 10), have been described in the literature. However, in a large proportion of acute pancreatitis cases, no underlying risk factor can be determined. The severity of acute pancreatitis and the associated symptoms vary. Some patients require only conservative treatment whereas other patients may need intensive care. The mortality ranges between 3%(11) and 30%(12) depending on the severity of disease.

To our knowledge, no published work exists on the association between MC and acute pancreatitis. There are several reasons to hypothesize that an association between

the two disorders is present. First, MC shares inflammatory characteristics with acute pancreatitis(13, 14). Second, many patients with MC are treated with budesonide, a steroid(15), which has been linked to onset of acute pancreatitis. Third, there is a known association between celiac disease and IBD and acute pancreatitis (of note, both celiac disease(16) and IBD(17) have been associated to MC). As patients with IBD (and likely also patients with MC) risk delayed or missed diagnosis of acute pancreatitis due to shared symptoms(18), added knowledge on the association between MC and acute pancreatitis may lower the threshold for evaluation of acute pancreatitis in MC. Moreover, a detected association between the two disease entities may also aid in generating new hypotheses about shared pathogenic mechanisms. Hence, this study aims to explore the association between MC and acute pancreatitis in a nationwide, population-based cohort.

METHODS

Setting

This study is based on biopsy data derived from Swedish regional pathology registers. All Swedish citizens have a unique personal identity number(19) (PIN) through which we linked data from Swedish healthcare registers. Moreover, health care in Sweden is largely tax-funded, with a policy of providing all Swedish citizens equal access to health care.

Identification of patients with MC

The data used in this study were collected as part of the ESPRESSO study(20), which includes data on all gastrointestinal biopsies in Sweden from 1965 to 2017. The ESPRESSO study contains biopsy data on 2.1 million unique individuals. Classification of biopsies in Sweden is done according to the Systematized Nomenclature of Medicine (SNOMED) system. Based on the histopathological characteristics of a biopsy, the SNOMED system classifies each biopsy by a specific code. We retrieved data on all biopsies coded M40600 for CC and M47170 for LC (Figure 1). Previously, we have examined the validity of these codes, finding a positive predictive value (PPV) of 95% for MC(21). Of 215 randomly selected patients with a SNOMED code indicative of MC, 207 (96%) had diarrhea(21).

General population reference individuals (comparators)

Because this study was based on data from the ESPRESSO study, each exposed individual (MC) was matched to,   5 reference individuals from the general population. Matching was done according to age, sex, county of residence (all at time of diagnosis), and index date (i.e., reference individuals started follow-up on the date of MC diagnosis for their corresponding exposed individual). Reference individuals (with no previous biopsy indicating MC) from the general population were identified through the Total Population Register(22) (Figure 1).

Sibling comparators

Using the Multigeneration Register (part of the Total Population Register(22)), we identified siblings to our exposed population (patients with MC). Access to siblings allowed us to control for intrafamilial confounding (shared genetics and early environmental factors). We identified 12,781 full siblings without MC at index date.

Outcomes

Information on our outcome measure acute pancreatitis (main outcome), acute pancreatitis (gallstone related acute pancreatitis and acute pancreatitis not related to gallstones), was collected from the National Patient Register (NPR). This register stores diagnostic and procedural codes according to the international classification of disease (ICD) system and attained nationwide coverage on inpatient care diagnosis in 1987. Also, data on diagnoses in outpatient care have been available since 2001. The PPV of diagnoses in the NPR is generally approximately 90%(23). The accuracy of ICD codes indicating acute pancreatitis has been assessed in a 2011 validation study(24). The authors reported a PPV of 98% (including definitive and probable cases of acute pancreatitis). We defined incident acute pancreatitis as a first-time record of ICD-codes K850–859. Gallstone-related acute pancreatitis was defined as ICD-code K851 or a procedure code indicating cholecystectomy (listed in the appendix) within 90 days of a diagnosis of acute pancreatitis. Acute pancreatitis not related to gallstones was defined as all acute pancreatitis not considered to be gallstone related. For all outcomes, both primary and secondary diagnostic codes were considered.

Follow-up

Follow-up started on the day of the first biopsy, consistent with MC (for the exposed population) and on the corresponding day for the reference population. To allow access to outpatient data during the study period we commenced follow-up in 2003, using the 2-year time span from 2001–2003 as a washout period for prior diagnosis of acute pancreatitis. Because the ESPRESSO study(20) does not contain data on outcomes beyond 2021, we ended our study period on 31 December 2021. Follow-up ended on the date of acute pancreatitis diagnosis, date of death, date of emigration, or 31 December 2021, whichever occurred first. When examining our secondary outcomes, study participants were not censored if they experienced another outcome than the one under investigation. The end of follow-up also occurred for reference individuals and siblings if they were diagnosed with MC. On the same date, these individuals were reclassified as exposed.

Other covariates

Information on age, sex, county of residence, country of birth, and emigration was collected from the Total Population Register(22). To adjust for socioeconomic status, we gathered data on education level at the time of diagnostic biopsy. This information was retrieved from the longitudinal integrated database for health insurance and labor market studies (LISA)(25). Categories were defined as compulsory school (9 years), upper secondary school (10–12 years), and college (13 years). If information on the level of education was missing, study participants were placed in a missing category.

Data on celiac disease were collected from the ESPRESSO study by identifying all duodenal biopsies coded (according to the SNOMED system) as M58 (including subgroups) or the celiac disease diagnostic code D6218. A validation study using patient charts revealed that 95% of patients with a duodenal biopsy indicating villous atrophy had CD(26). IBD was identified by defining patients with 1 biopsy consistent with IBD and 1 ICD code

indicating IBD. This approach has been found to have a 95% PPV for identifying IBD(4, 27, 28).

We also extracted information on dispensed budesonide (Anatomical Therapeutical Chemical (ATC) code: A07EA06) and thiopurines (ATC codes: L04AX01 and L01BB02). Moreover, there is a well-documented association between thiopurines and acute pancreatitis(29, 30). Thiopurines may also be prescribed to MC patients that cannot be weaned from steroids, which becomes a potential confounder. Beginning on 1 July 2005, the Prescribed Drug Register stores data on almost 100% of dispensed prescribed medications(31).

Exclusion criteria

Figure 1 outlines exclusions. Exclusion criteria were applied equally for all study participants. All study participants who had died, emigrated, or undergone a colectomy on or before index date were excluded. Also, everyone with a previously recorded ICD-code indicating acute or chronic pancreatitis were omitted.

Sensitivity analyses

To examine the robustness of our result, several sensitivity analyses were conducted. First, to enhance the specificity of our exposure, we conducted a sensitivity analysis where all study participants with a prior dispensation of proton pump inhibitors (PPIs (ATC-code=A02BC)), selective serotonin reuptake inhibitors (SSRIs) (ATC-code=N06AB) and non-steroidal anti-inflammatory drugs (NSAIDs (ATC-code=M01A)) prior to enrollment were excluded. Second, we added dispensed prednisolone (ATC-code=H02AB06) prior to enrollment as an exclusion criterion and dispensed prednisolone after enrollment as a censoring event to control for steroid-induced acute pancreatitis. Third and fourth, restricted cohorts were created to evaluate whether dispensed budesonide or thiopurines influenced our results. All additional analyses including data on dispensed medications from the prescribed drug register included all MC patients and matched reference individuals enrolled after or on 2006–01–01. This lag period of 6 months since the starting date for the prescribed drug register (1 July 2005) was intended to rule out prevalent therapy. Fifth, to enhance specificity of our outcome measure, we carried out an analysis where only the primary diagnostic code was considered. Sixth, in an effort to control for smoking we added adjustment for COPD (defined as an ICD code for COPD and age >40 at the time of the first diagnosis) and finally, to assess the influence of intrafamilial confounding (shared genetics and early environmental factors), we used unexposed siblings to our exposed population as comparators.

Patient and Public Involvement

No patient participated in the planning or design of this study.

Statistical analysis

We conducted a matched cohort study comparing the rate of acute pancreatitis in our exposed population (MC) with our reference population. Using a Kaplan-Meier estimator, we computed unadjusted rates for both groups and calculated absolute rate differences at 0, 10, and 15 years of follow-up. Using a Cox proportional hazard model, we also

computed adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs). We confirmed the proportionality assumption by running a Schoenfeld residuals test. To control for a confounding effect by the matching variables (age, sex, county of residence, and year of biopsy) we adjusted for these matching variables(32). Our main model also included adjustment for level of education (as a proxy for socioeconomic status) and comorbidities (IBD and celiac disease, diagnosed before the index date). Employing the same model, we also calculated aHRs for strata defined by sex, calendar period (2003–2010, 2011–2017), calendar period with a maximum of 3 years of follow-up (2003–2010, 2011–2017), age at MC diagnosis (<50 or 50 years), years of follow-up (<1, 1-<5, 5-<10, 10 years), country of birth (Nordic or other), education level (9, 10–12, 13 years), and IBD/celiac disease at baseline. To control for intrafamilial confounding, full siblings to patients with MC were used as comparators. This analysis was based on family-specific strata.

Statistical significance of heterogeneity was tested by introducing an interaction term - MC status and the relevant strata - into the main model. A p-value of <0.05 was considered statistically significant.

All statistical analyses were conducted using Stata/IC 14.2 for Mac (StataCorp, 4905 Lakeway Dr, College Station, TX 77845). Forest plot (Figure 2) was created using the metan package(33). To estimate the influence of unmeasured confounding we used the e-value package by Linden et al.(34)

Ethics

This study was approved by the Stockholm Ethics Review Board. Because the study was strictly register-based, ethical approval or informed consent was not required(35).

RESULTS

We identified 12,140 patients with MC, 57,806 matched reference individuals, and 12,781 siblings (Table 1). As expected, most (72%) patients with MC were female. Mean age at diagnosis was 60.2 years (standard deviation (SD)=16.8). LC was the more common subtype, constituting 68% of all patients with an MC diagnosis. Mean length of follow-up was 9.9 years (SD=4.3). Some 89% of our study population were born in a Nordic country, and over 30% had completed 13 years of schooling.

MC and later acute pancreatitis

During follow-up, 151 patients with MC and 437 reference individuals were diagnosed with acute pancreatitis (Table 1). These figures correspond to an incidence rate (IR) of 127.8 (95%CI=109.0–149.9) per 100,000 person-years for the exposed population and 80.1 (95%CI=73.1–85.6) for the reference population (Table 2). Figure 2 depicts the crude incidence rates for the exposed population (MC) and reference individuals. Average time until acute pancreatitis were comparable for patients with MC and reference individuals, 6.2 years, and 6.5 years respectively.

Siblings without MC had an IR of 85.3 (95%CI=71.0–102.5) per 100,000 person-years compared to 112.3 (95%CI=89.8–140.4) in their siblings with MC.

Our Cox proportional hazards model adjusted for the matching variables (age at start of follow-up, sex, county, calendar year), education level, and comorbidities at baseline (IBD and celiac disease). Compared to the reference population, MC patients were 1.6 times more likely to be diagnosed with acute pancreatitis during follow-up (aHR=1.57, 95%CI=1.30–1.90) (Table 3). Stratifying by sex, the aHR was 1.50 (95%CI=1.07–2.10) for males and 1.62 (95%CI=1.29–2.03) for females. Examining CC and LC separately, the aHR was 1.67 (95% CI=1.22–2.28) for CC and 1.53 (95%CI=1.21–1.94) for LC (Table 3).

Defining age categories as below or above age 50, we found similar aHRs for both groups (Table 3). Examining the association between MC and acute pancreatitis across different calendar periods (2003–2010, 2011–2017), we found a higher aHR (1.92, 95%CI=1.43–2.57) during the past decade compared to the aHR of the earlier calendar period (2003–2010: 1.38, 95%CI=1.08–1.77)). In a separate analysis we restricted follow-up to 3 years to make the different calendar periods more comparable. Again, the same pattern emerged with a higher aHR (1.94, 95%CI=1.18–3.20)) during the most recent calendar period, 2011–2017. The aHR for the earlier calendar period was 1.04 (95%CI=0.56–1.92). The aHR was highest during the first year of follow-up (1.82, 95%CI=0.96–3.43) when stratifying on years of follow-up. However, MC patients followed for 10 years had an almost identical aHR (1.75, 95%CI=1.14–2.67). (Table 3). Excluding all study participants with a follow up less than one year did not materially change our point estimate, aHR (1.56, 95%CI=1.28–1.90)) remained unchanged. Stratifying by educational attainment returned similar aHRs across levels (Table 3).

Secondary outcomes

Classifying acute pancreatitis as gallstone related or gallstone unrelated, aHRs differed with a significant increase for gallstone unrelated acute pancreatitis (n(MC)=106, n(reference population)=250), (aHR=1.99 (95%CI=1.57–2.51)); no association was detected for gallstone related acute pancreatitis (n(MC)=45, n(reference population)=206) (aHR=1.08 (95%CI=0.78–1.49). Table 4 outlines IRs and aHRs for our secondary outcomes.

Sensitivity analysis

To assess the robustness of our observed association, several sensitivity analyses were performed. First, we excluded all study subjects with a prior dispensation of PPIs, NSAIDs or SSRIs. These added exclusions left our estimate virtually unchanged, aHR 1.58 (95%CI=1.28–1.95). Second, omitting all study participants with a prior dispensation of prednisolone and adding dispensation of prednisolone as a censoring event yielded a somewhat lower aHR of 1.33 (95%CI=1.02–1.72). Third, stratifying by use or non-use of budesonide, we found an aHR of 1.84 (95%CI=1.37–2.48) for budesonide users compared to their matched reference individuals. Corresponding figures for MC patients not treated with budesonide were 1.31 (95%CI=0.95–1.80), p for heterogeneity=0.16. Fourth, we performed a similar analysis examining whether the association between MC and acute pancreatitis differed in patients treated with thiopurines. In total, 224 MC patients had been treated with thiopurines. In this restricted cohort five MC patients and one reference individual later developed acute pancreatitis. These figures corresponded to an aHR of 42.1 (95%CI=3.44–514.4). Naturally, the aHR (1.53, 95%CI=1.24–1.90) for MC patients not

treated with thiopurines resembled our main result. Fifth, we investigated the association between MC and acute pancreatitis using only the primary diagnostic code. This restriction, however, had no substantial effect on our our point estimate, aHR 1.59 (95%CI=1.30–1.96). Sixth, to control for intrafamilial confounding we used unaffected siblings as comparators, estimating an aHR of 1.28 (95%CI=0.92–1.78). Finally, in an effort to control for smoking we added adjustment for chronic obstructive pulmonary disease. This additional adjustment, however, did not materially change our results. The aHR for acute pancreatitis in this model was 1.57 (95%CI=1.30–1.90). For non-gallstone acute pancreatitis, the aHR was 1.97 (95%CI=1.56–2.49) when adding adjustment for COPD. Moreover, to estimate the influence of unmeasured confounding, we calculated the e-value for the association between MC and acute pancreatitis finding that the strength of an unmeasured confounder (e.g., smoking) would have to be 2.5-fold to both MC and acute pancreatitis to reduce our observed aHR of 1.57 to 1. To shift the lower limit of the CI below 1, the strength of the association between the unmeasured confounder and the exposure and outcome would have to be 1.93-fold.

Discussion

In this nationwide, matched cohort study of >12,000 patients with MC we found a 1.6-fold increased risk of later acute pancreatitis (95%CI=1.30–1.90). Stratifying on disease duration, we found the highest aHRs for MC patients followed for <1 year and those followed for >10 years. The elevated aHR during the first year of follow-up is likely, partly, explained by surveillance bias. However, when excluding all MC patients diagnosed with acute pancreatitis within 1 year of MC diagnosis, the aHR was still significantly elevated.

Regarding our secondary outcomes, we found an increased risk of acute pancreatitis unrelated to gallstones (aHR=1.99, 95%CI=1.57–2.51), whereas no association was detected for gallstone-related acute pancreatitis (aHR=1.08, 95%CI=0.78–1.49). Our sensitivity analyses strengthened the robustness of our main result, indicating that our observed association, to some extent, is independent of the effects of dispensed medications (e.g., PPIs, SSRIs, NSAIDs, prednisolone, thiopurines) and intrafamilial confounding.

As far as we know, no studies on the association between MC and acute pancreatitis exist. However, there are reports on the relationship between IBD[9, 10] and acute pancreatitis and celiac disease[8] and acute pancreatitis. A nationwide study from Denmark[9] examining the risk of acute pancreatitis in IBD found increased standardized incidence ratios (SIRs) for Crohn's disease (SIR=4.3, 95% CI=2.9–6.1)) and ulcerative colitis (SIR=2.1, 95% CI=1.6–2.8)), whereas a Swedish matched cohort study investigating the risk of pancreatitis in patients with celiac disease[8] found an HR of 2.85 (95% CI=2.53–3.21). There is also a known association between autoimmune pancreatitis (AIP) type2 and IBD; some 15% of patients with AIP type2 are estimated to have a concomitant diagnosis of IBD[36]. A 2019 study[37], outlining holistic prevention strategies for pancreatitis stressed the importance of smoking cessation, healthy foods as well as a cautious use of endoscopic retrograde cholangiopancreatography (ERCP) and drugs known to induce acute pancreatitis. Hence, awareness of our observed association may benefit patients with MC.

Several plausible mechanisms may be involved in the observed association between MC and acute pancreatitis. First, although the heterogeneity between aHRs for MC patients treated

and untreated with budesonide did not attain statistical significance, we noted a tendency towards a higher risk for acute pancreatitis in MC patients on budesonide. This trend may suggest that acute pancreatitis in MC patients is related to disease intensity and/or is iatrogenically caused. The Swedish environmental classification of pharmaceuticals (FASS) lists pancreatitis as a side effect of budesonide, and the risk of steroid-induced acute pancreatitis is well documented(38). To an extent dispensed thiopurines(29) also contributed to our findings. MC patients treated with thiopurines were more prone to develop acute pancreatitis (aHR=42.1 (95%CI=3.44–514.4)) (we urge caution in interpreting this result as it was based on few events). Nevertheless, our result remained essentially unchanged when excluding MC patients with a record of thiopurine treatment. The association with thiopurine, however, corroborates the known association with acute pancreatitis(29).

Second, the inflammatory activity in MC and acute pancreatitis are both characterized by cytokines involved in the Th1/Th17 pathways (13, 14) and there is evidence that IL-6, which is upregulated in active CC(13) also correlates to severity of acute pancreatitis(39). In addition, there are findings from animal-studies indicating that elevated levels of IL-6 increase the susceptibility to acute pancreatitis(40). Third, smoking is associated to both MC(41) and acute pancreatitis(42) and may explain part of our finding. Finally, we found no association between MC and gallstone-related disease, further strengthening the notion that MC and pancreatitis might share environmental or genetic risk factors. This finding is likely explained by the fact that a gallstone wedged in the papilla Vateri suffices to trigger acute pancreatitis regardless of concomitant MC.

One strength of this study is the nationwide coverage, which minimizes selection bias and makes for a sizeable cohort, allowing for precise calculations of relative risks across various strata. Another strength is that the Swedish PIN enabled us to capture our study population's outcomes and exposures of interest. Moreover, our exposure information (biopsy verified MC) was assessed in a validation study, finding a PPV of 95%(43). The accuracy of an ICD code for acute pancreatitis in Sweden has also been examined. Based on a random selection of patients with a primary or secondary diagnosis of acute pancreatitis under inpatient care, the authors reported a PPV of 98%(24). Access to the Prescribed Drug Register permitted us to perform several sensitivity analyses incorporating information on dispensed medication.

We acknowledge some limitations. The registers used for this study lack information on important lifestyle factors such as body mass index (BMI), alcohol and smoking. However, because MC is associated with lean BMI(44) and acute pancreatitis is associated with higher BMI(45), added data on BMI would likely have strengthened our observed association. Moreover, a strong link has been found between alcohol use and pancreatitis(6). However, studies focusing on the relationship between MC and alcohol intake have reported contradictory results ranging from a positive correlation(46) to no association(47, 48). Notably, one of the studies (48) showing no association was performed on a Swedish cohort. Thus, whether alcohol use plays an integral part in the causal pathway is difficult to determine based on *à priori* knowledge. Smoking is more prevalent among patients with MC(41) and is therefore an important confounder. Our attempt to control for smoking did not have a meaningful impact on our main result. Nor did it notably change our aHR for non-gallstone-related acute pancreatitis, which is strongly linked to smoking(49).

However, it should be noted that only a minority of smokers develop COPD and/or receive an ICD-code for the disease. Nevertheless, our calculated e-value suggests our observed association, to some degree, is independent of unmeasured confounding. In addition, as our data only contained information on incident MC, we were unable to contrast the risk of acute pancreatitis in patients with active disease to that of the patients who had been brought to clinical remission.

Furthermore, surveillance bias may partly explain the observed association, as patients with MC generally are followed by a gastroenterologist providing MC patients better access to gastroenterological evaluation and testing for amylase in the event of an episode with acute abdominal pain. Thus, the probability of identifying acute pancreatitis with a less severe presentation increases. Our study was conducted based on Swedish data. We caution that because of genetic dissimilarities and differing exposures to alcohol, tobacco, and other substances, as well as occupational and other factors, our findings cannot unquestionably be extrapolated to other countries.

In conclusion, we found an increased probability of MC patients developing acute pancreatitis. This elevated probability remained after >10 years of follow-up. Our findings suggest clinicians should have a low threshold for evaluating for acute pancreatitis in patients with MC. Our finding of a significantly increased probability of acute pancreatitis unrelated to gallstones motivates further studies on the biologic mechanisms involved in the observed association. Also, our finding stresses the importance of patients with MC being subject to advice and care aimed at avoiding development of acute pancreatitis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Grant support:

Abbreviations used in this article:

MC	Microscopic colitis
LC	lymphocytic colitis
CC	collagenous colitis
CD	celiac disease
IBD	inflammatory bowel disease
PIN	personal identity number
SNOMED	Systematized Nomenclature of Medicine

PPV	positive predictive value
NPR	National Patient Register
aHR	adjusted hazard ratio
CI	confidence interval
SD	standard deviation
IR	incidence rate
aOR	adjusted odds ratio
COPD	chronic obstructive pulmonary disease
SIR	standardized incidence ratio
AIP	autoimmune pancreatitis
BMI	body mass index

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Study highlights:

What is known:

- The association between microscopic colitis and acute pancreatitis has not yet been examined.

What is new here:

- We found a significantly increased risk for acute pancreatitis in patients with microscopic colitis compared to reference individuals.

- Specifically, we found an increased risk for acute pancreatitis not related to gallstones.

- Our findings indicate that the increased risk for acute pancreatitis may be related to disease severity or budesonide.
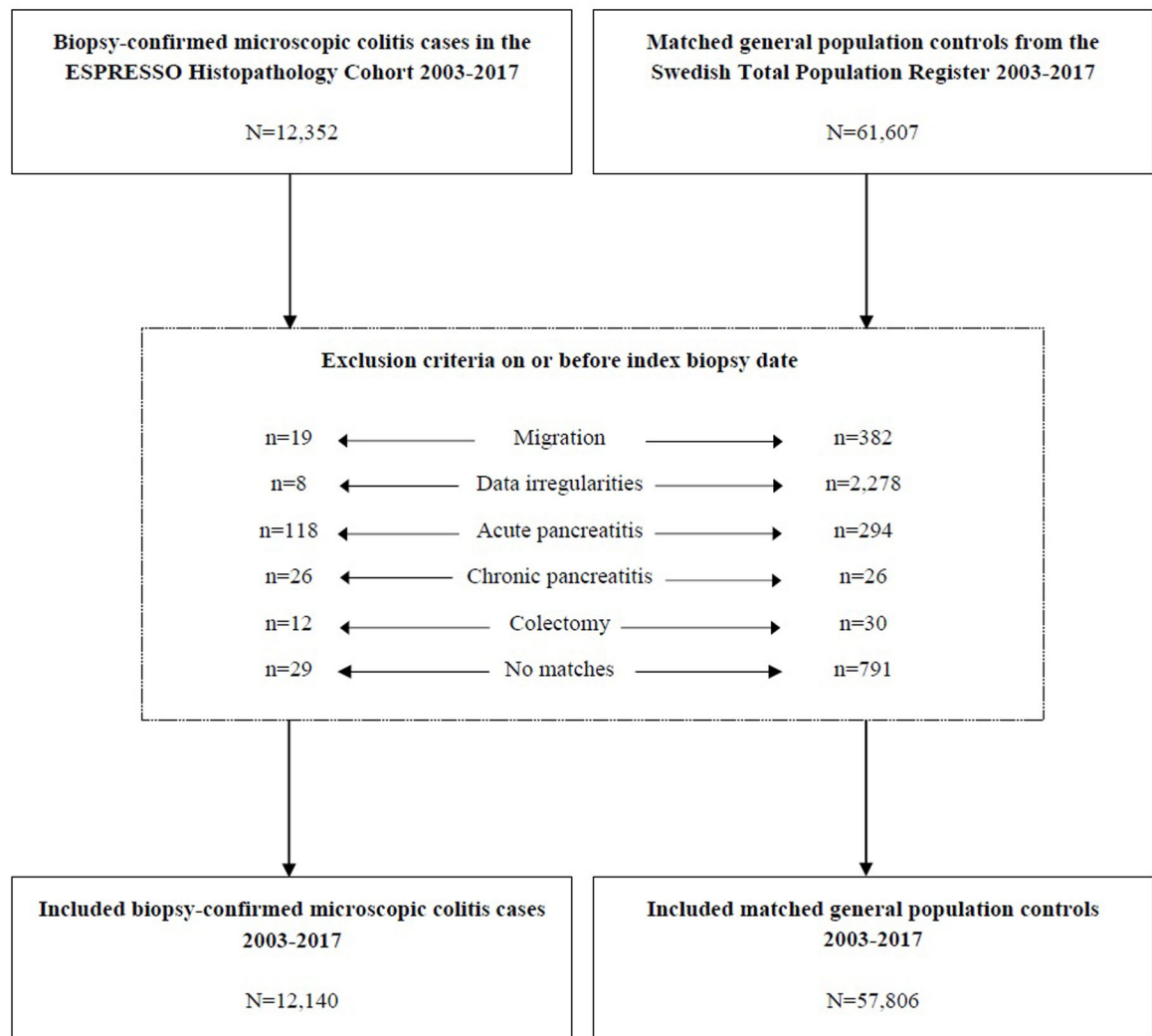
Figure 1.
Flowchart of inclusion of patients with biopsy-confirmed microscopic colitis in the ESPRESSO Histopathology Cohort and matched general population controls from the Swedish Total Population Register 2003–2017.
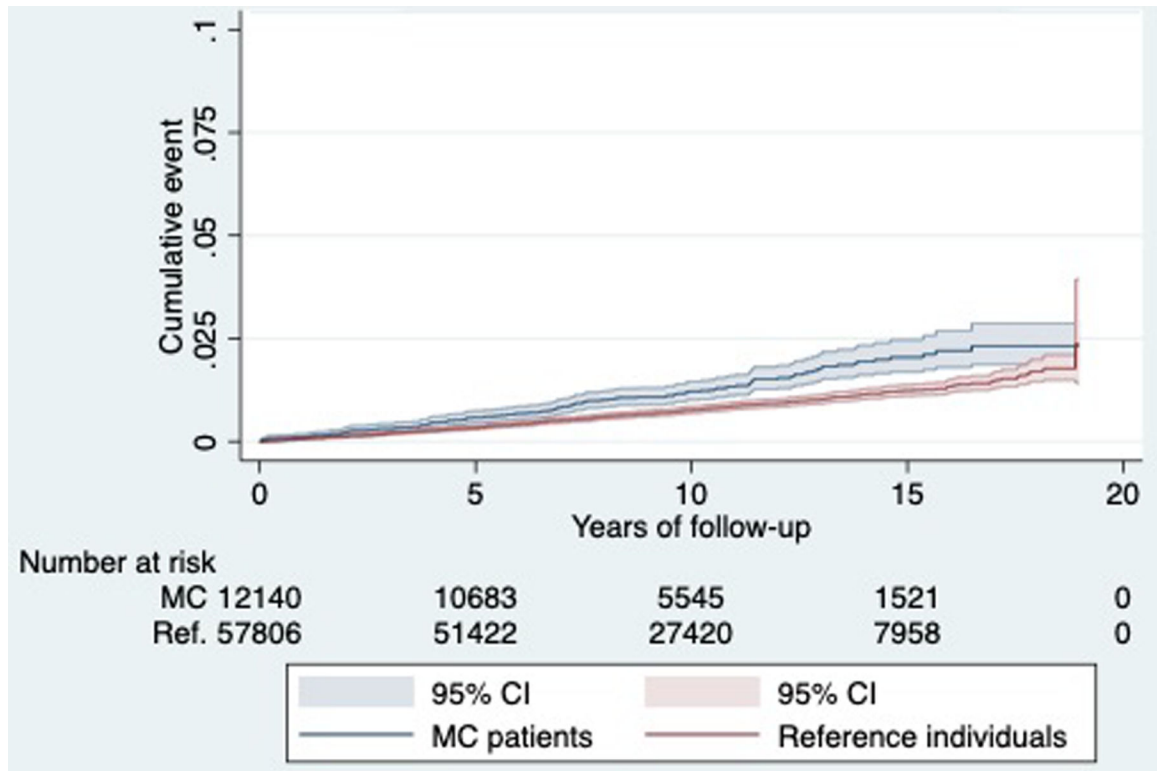ESPRESSO, Epidemiology Strengthened by Histopathology Reports.

Figure 2.
Kaplan-Meier failure estimates

Figure 3:
Forest plot of main and secondary outcomes

Table 1:

Summary statistics for MC patients and matched reference individuals.

	Reference	MC	CC	LC
	n [%]	n [%]	n [%]	n [%]
Total	57,806 [100.00]	12,140 [100.00]	3,905 [100.00]	8,235 [100.00]
Male	16,082 [27.8]	3,400 [28.0]	886 [22.7]	2,514 [30.5]
Female	41,724 [72.2]	8,740[72.0]	3,019 [77.3]	5,721 [69.5]
AGE AT START FOLLOW UP				
Mean [SD] years	60.2 [16.8]	60.8 [16.9]	64.3 [14.8]	59.2 [17.5]
Median [IQR] years	63.0 [50.0–72.6]	63.6 [50.7–73.2]	65.9[55.9–74.9]	62.2 [48.1–72.3]
< 50 years	14,423 [25.0]	2,925 [24.1]	642 [16.4]	2,283 [27.7]
> = 50 years	43,383 [75.0]	9,215 [75.9]	3,263[83.6]	5,952 [72.3]
YEARS OF FOLLOW UP				
Mean [SD] years	9.9 [4.3]	9.7 [4.3]	9.6 [4.3]	9.8 [4.3]
Median [IQR] years	9.7 [6.9–13.1]	9.6 [6.7–12.9]	9.5 [6.8–12.8]	9.6 [6.7–12.9]
< 1 years	1,301 [2.3]	259 [2.1]	107 [2.7]	152 [1.9]
1 < 5 years	5,083 [8.8]	1,198 [9.9]	443 [11.3]	755 [9.2]
5 < 10 years	24,001 [41.5]	5,138 [42.3]	1,597 [40.9]	3,541 [43.0]
> = 10 years	27,420 [47.4]	5,545 [45.7]	1,758 [45.0]	3,787 [46.0]
YEAR OF START FOLLOW UP				
2003 – 2010	30,115 [52.1]	6,305 [51.9]	2,112 [54.1]	4,193 [50.9]
2011 – 2017	27,691 [47.9]	5,835 [48.1]	1,793 [45.9]	4,042 [49.1]
REASON FOR END OF FOLLOW-UP				
Emigration	731 [1.3]	80[0.7]	14 [0.36]	66 [0.8]
31 Dec. 2021	43,667 [75.5]	8,778 [72.3]	2,641[67.6]	6,137 [74.5]
Diagnosed with MC	99 [0.2]	0	0	0
Diagnosed with acute pancreatitis	437 [0.8]	146 [1.2]	54 [1.4]	92 [1.1]
Death	12,872 [22.3]	3,136 [25.8]	1,196 [30.6]	1,940 [23.6]
COUNTRY OF BIRTH				
Nordic	51,118 [88.4]	11,392 [93.8]	3,743 [95.8]	7,649[92.9]
Other	6,688 [11.6]	748[6.2]	162 [4.2]	586 [7.1]
EDUCATION				
Compulsory school (< = 9 yrs)	14,382 [24.9]	3,072 [25.3]	1,151 [29.5]	1,921 [23.3]
Upper secondary school (10–12 yrs)	23,778 [41.1]	4,968 [40.9]	1,633 [41.8]	3,335 [40.5]
College or university (> = 13 yrs)	18,143 [31.4]	3,773 [31.1]	1,030 [26.4]	2,743 [33.3]
NA	1,503 [2.6]	327 [2.7]	91 [2.3]	236 [2.9]
COMORBIDITY AT DIAGNOSIS DATE				
IBD	55 [s0.1]	336 [2.8]	112 [2.9]	224 [2.7]
Celiac disease	39 [0.07]	415 [3.4]	136[3.5]	279 [3.4]
MEDICATION DURING FOLLOW-UP [*]				
Budesonide	132 [0.27]	5,169 [50.1]	1,896 [57.7]	3,273 [46.5]
Thiopurines	5 [0.01]	224 [2.2]	78 [2.4]	146 [2.1]

*
Restricted cohort including study participants enrolled after or on 2006–01–01

Table 2:

Incidence rates (acute pancreatitis) for MC patients diagnosed in Sweden 2003–2017 and for matched reference individuals

	Reference	MC	CC	LC
N Total	57,806	12,140	3,905	8,235
N events	437	151	55	96
Incidence proportion [%]	0.8	1.2	1.4	1.2
Person years	569,367	118,160	37,589	80,571
Incidence rate/100,000 pyears [95% CI]	80.1 [73.1–85.6]	127.8 [109.0–149.9]	146.3 [112.3–190.6]	119.1 [97.5–145.5]
SEX				
Males	98.2 [83.7–115.3]	158.7 [120.3–209.4]	174.9 [103.6–295.2]	153.2 [110.5–212.4]
Females	73.4 [65.7–82.1]	116.6 [95.9–141.7]	138.6 [102.1–188.2]	105.1 [81.6–135.4]
AGE AT START FOLLOW UP				
< 50 years	46.4 [36.9–58.3]	79.9 [54.4–117.3]	110.8 [55.4–221.6]	71.1 [44.8–112.8]
50 years	93.2 [84.3–103.0]	146.0 [122.5–174.0]	154.8 [116.3–206.0]	141.2 [113.1–176.3]
YEARS OF FOLLOW UP				
< 1	64.0 [46.2–88.8]	108.3 [62.9–186.6]	104.0 [39.0–277.0]	110.4 [57.4–212.1]
1 < 5	68.5 [58.3–80.6]	119.2 [91.3–155.7]	146.2 [95.3–224.2]	106.7 [75.9–150.1]
5 < 10	87.9 [75.8–102.0]	126.3 [96.3–165.8]	136.4 [85.9–216.4]	121.6 [86.9–170.2]
>= 10	100.6 [82.7–122.4]	162.4 [114.8–229.6]	194.2 [110.3–342.0]	147.8 [95.4–229.2]
START OF FOLLOW UP				
2003 – 2010	81.6 [72.8–91.5]	116.7 [94.6–144.0]	161.7 [118.2–221.4]	95.2 [71.8–126.3]
2011 – 2017	77.4 [66.4–90.4]	146.7 [114.8–187.4]	118.7 [72.7–193.8]	159.2 [119.9–211.2]
START OF FOLLOW UP (with max 3 years of follow-up)				
2003 – 2010	67.2 [52.0–87.0]	76.9 [45.5–129.8]	82.8 [34.5–198.9]	73.9 [38.5–142.1]
2011 – 2017	67.5 [51.7–88.2]	135.3 [89.9–203.7]	77.0 [28.9–205.2]	161.0 [102.7–252.5]
COUNTRY OF BIRTH				
Nordic	78.1 [70.7–86.2]	121.0 [63.0–232.6]	150.1 [115.0–196.0]	117.7 [95.5–145.1]
Other	95.8 [74.7–122.8]	128.2 [108.8–151.2]	61.9 [8.7–439.1]	137.5 [68.7–274.9]
EDUCATION				
Compulsory school (< = 9 yrs)	108.8 [92.6–127.8]	178.1 [135.0–235.0]	192.3 [124.1–298.1]	169.7 [118.7–242.7]
Upper secondary school (10–12 yrs)	77.0 [66.6–89.0]	122.9 [95.6–158.0]	159.4 [108.6–234.2]	105.0 [75.4–146.3]
College or university (> = 13 yrs)	63.8 [53.1–76.5]	83.1 [58.8–117.5]	75.9 [37.9–151.7]	85.8 [57.5–128.0]
NA	64.4 [33.5–123.7]	410.2 [205.1–820.2]	294.6 [41.5–2091.2]	434.6 [207.2–911.5]
COMORBIDITY				
with IBD	NA [NA-NA] [*]	115.5 [43.3–307.7]	86.1 [12.1–611.0]	130.4 [42.0–404.2]
without IBD	80.1 [73.1–87.8]	128.2 [109.0–150.7]	148.2 [113.5–193.6]	118.8 [97.0–145.6]
with celiac disease	602.1 [150.6–2407.4]	116.1 [79.2–348.4]	69.1 [9.7–490.0]	216.9 [97.5–482.8]
without celiac disease	79.8 [72.8–87.5]	126.4 [107.3–148.8]	149.4 [114.4–195.1]	115.7 [94.1–142.2]

[*]
No events

Table 3:

Acute pancreatitis hazard ratios for MC patients diagnosed in Sweden 2003–2017 compared to matched reference individuals.

Adjusted for age, sex, county, calendar period, level of education, IBD and celiac disease

	MC HR [95% CI]	CC HR [95% CI]	LC HR [95% CI]
Total	1.57 [1.30–1.90]	1.67 [1.22–2.28]	1.53 [1.21–1.94]
SEX			
Males	1.50 [1.07–2.10]	1.69 [0.89–3.21]	1.43 [0.97–2.13]
Females	1.62 [1.29–2.03]	1.66 [1.16–2.37]	1.60 [1.19–2.16]
AGE AT START FOLLOW UP			
< 50 years	1.58 [0.98–2.55]	1.65 [0.75–3.63]	1.56 [0.85–2.84]
50 years	1.57 [1.28–1.94]	1.69 [1.21–2.38]	1.52 [1.17–1.97]
YEARS OF FOLLOW UP			
< 1	1.82 [0.96–3.43]	1.42 [0.47–4.33]	2.07 [0.95–4.50]
1 < 5	1.71 [1.24–2.36]	1.78 [1.07–2.97]	1.68 [1.12–2.54]
5 < 10	1.33 [0.96–1.85]	1.39 [0.80–2.42]	1.31 [0.87–1.96]
> = 10	1.75 [1.14–2.67]	2.38 [1.17–4.82]	1.49 [0.88–2.54]
START OF FOLLOW UP			
2003 – 2010	1.38 [1.08–1.77]	1.74 [1.20–2.51]	1.18 [0.85–1.66]
2011 – 2017	1.92 [1.43–2.57]	1.53 [0.86–42.73]	2.08 [1.48–2.93]
START OF FOLLOW UP (with max 3 years of follow-up)			
2003 – 2010	1.04 [0.56–1.92]	0.83 [0.29–2.39]	1.19 [0.55–2.56]
2011 – 2017	1.94 [1.18–3.20]	1.04 [0.35– 3.07]	2.44 [1.38–4.33]
COUNTRY OF BIRTH			
Nordic	1.62 [1.33–1.98]	1.85 [1.34–2.55]	1.52 [1.18–1.96]
Other	2.32 [0.50–10.8]	NA [NA-NA] **	3.54 [0.61–20.3]
EDUCATION			
Compulsory school (< = 9 yrs)	1.66 [1.19–2.30]	1.65 [0.98–2.77]	1.68 [1.10–2.56]
Upper secondary school (10–12 yrs)	1.64 [1.23–2.21]	2.07 [1.31–3.26]	1.42 [0.97–2.09]
College or university (> = 13 yrs)	1.20 [0.79–1.80]	0.92 [0.39–2.13]	1.29 [0.80–2.07]
NA	5.71 [1.99–16.6]	3.34 [0.33–33.6]	10.62 [2.69–41.9]
COMORBIDITY			
with IBD *	NA [NA-NA]	NA [NA-NA] *	NA [NA-NA] *
without IBD	1.57 [1.30–1.90]	1.65 [1.21–2.26]	1.53 [1.21–1.94]
with celiac disease *	NA [NA-NA]	NA [NA-NA] *	NA [NA-NA] *
without celiac disease	1.59 [1.32–1.93]	1.70 [1.25–2.32]	1.55 [1.22–1.96]

*
No events

**
Only event in reference individuals

Table 4:

INCIDENCE RATES AND ADJUSTED HAZARD RATIOS (ADJUSTED FOR AGE, SEX, COUNTY, CALENDAR PERIOD, LEVEL OF EDUCATION, IBD AND CELIAC DISEASE) FOR SECONDARY OUTCOMES FOR MC PATIENTS DIAGNOSED IN SWEDEN 2003–2017 AND FOR THEIR MATCHED REFERENCE INDIVIDUALS.

ACUTE GALLSTONE RELATED PANCREATITIS				
	Reference	**MC**	**CC**	**LC**
N TOTAL	57,806	12,140	3,905	8,235
N EVENTS	206	45	17	28
INCIDENCE PROPORTION [%]	0.4	0.4	0.4	0.3
PERSON YEARS	570,323	118,617	37,738	80.881
INCIDENCE RATE/100,000 PYEARS [95% CI]	36.1 [31.5–41.4]	37.9 [28.3–50.8]	45.0 [28.0–72.5]	34.6 [23.9–50.1]
ADJUSTED HAZARD RATIO [95% CI]	1.0 [ref]	1.08 [0.78–1.49]	1.09 [0.64–1.85]	1.08 [0.71–1.63]

ACUTE NON-GALLSTONE RELATED PANCREATITIS				
	Reference	MC	CC	LC
N TOTAL	57,806	12,140	3,905	8,235
N EVENTS	250	106	38	68
INCIDENCE PROPORTION [%]	0.4	0.9	1.0	0.8
PERSON YEARS	570,378	118,357	37,672	80,685
INCIDENCE RATE/100,000 PYEARS [95% CI]	43.8 [38.7–49.6]	89.6 [74.0–108.3]	100.9 [73.4–138.6]	84.3 [66.4–106.9]
ADJUSTED HAZARD RATIO [95%CI)	1.0 [ref]	1.99 [1.57–2.51]	2.21 [1.49–3.26]	1.88 [1.40–2.52]