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Moore, M., Coleman, H. G., Allen, P. B., & Loughrey, M. B. (2018). Microscopic colitis: a population-based case series over a nine year period within Northern Ireland. *Colorectal Disease*. <https://doi.org/10.1111/codi.14247>

**Published in:**  
Colorectal Disease

**Document Version:**  
Peer reviewed version

**Queen's University Belfast - Research Portal:**  
[Link to publication record in Queen's University Belfast Research Portal](#)

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## **Microscopic colitis: a population-based case series over a nine year period in Northern Ireland**

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/codi.14247

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## **CONFLICTS OF INTEREST**

None.

## **ABSTRACT**

**Aim:** We report clinicopathological experience of microscopic colitis in a population-based case series in Northern Ireland, over a nine year period.

**Method:** The pathology laboratory information system within a large teaching centre serving two healthcare trusts was interrogated for cases coded between 2008 and 2016 as collagenous colitis (CC) or lymphocytic colitis (LC). Demographic, clinical and follow up information was collected from healthcare records.

**Results:** A total of 326 new diagnoses of MC were identified, an average annual incidence of 6.7 per 100,000 population. The average annual incidence of CC and LC was 5.0 and 1.7 per 100,000 population, respectively. For coding reasons, it is likely LC data is incomplete. Of 191 cases diagnosed by specialist gastrointestinal pathologists, 141 patients had CC and 50 patients had LC. Both CC and LC predominantly involved females aged 60-79. Some 15% demonstrated endoscopic abnormalities. Endoscopic sampling protocols varied widely: 30% of CC and 32% of LC cases had right and left colon sampled separately, with histology concordant in 95% of cases. Of the 191 cases, only one case (of LC) was refractory to treatment, the rest exhibiting a clinical response. Only 35 patients had follow up endoscopy and biopsies, and three of each diagnosis showed persistent disease on histology. .

**Conclusions:** Overall, CC and LC are benign conditions with similar demographics, clinical associations, management and outcomes. Separate sampling of right and left colon is advised at colonoscopy, if this diagnosis is being considered, but left colonic sampling, which can be performed at flexible sigmoidoscopy, will diagnose the vast majority of cases.

### **What does this paper add to the literature?**

We present a population-based series of microscopic colitis diagnoses derived from pathology records, with a focus on epidemiology, clinical associations, endoscopic sampling and outcomes. Incidence is consistent with similar series. Associations with drugs and autoimmune diseases are common for both collagenous colitis and lymphocytic colitis. Endoscopic sampling for diagnosis is highly variable and standardisation of guidelines would be welcomed. If a diagnosis of microscopic colitis is being considered we recommend separate sampling, and specimen labelling, of both right and left colon at colonoscopy. However, sampling of the left colon alone, which can be performed at flexible sigmoidoscopy, will diagnose the vast majority of cases.

### **INTRODUCTION**

Microscopic colitis (MC) is an umbrella term, which comprises two distinct histological entities - lymphocytic colitis (LC) and collagenous colitis (CC). Both LC and CC are chronic inflammatory disorders of the large bowel, that present with non-bloody, watery diarrhoea which can vary in severity and response to treatment. The annual incidence of MC varies somewhat by geography but is approximately 5-15 per 100,000 persons and both LC and CC are reported to be more common in females [1,2]. The incidence of both conditions has increased significantly in recent years probably as a consequence of the greater use of colonoscopy in the diagnostic work-up of patients with chronic diarrhoea [2-4]. MC accounts for 10-15% of cases of chronic, non-bloody diarrhoea in patients undergoing colonoscopy and biopsy [5]. Both LC and CC are associated with a range of drugs and autoimmune disorders [6-10]. Although there is no increased lifetime risk for, or association with, colorectal cancer, symptoms can produce a significant impairment on quality of life [11-13].

Endoscopic specimens taken to exclude a diagnosis of MC now form a large proportion of the routine gastrointestinal workload in any tissue pathology service. Variation in such endoscopic sampling is well recognised and clarity is required on optimal sampling technique. Subtle endoscopic abnormalities are also now increasingly recognised, calling into question the appropriateness of the term 'microscopic colitis' [14-18].

The aim of this study was to describe clinicopathological experiences of a population-based cohort of patients with MC, derived from the pathology records of a large teaching centre, with a focus on epidemiology, clinical associations and endoscopic approach to diagnostic sampling.

## **METHOD**

Study cases were identified through an archival SNOMED search performed within the laboratory information management system of the Belfast Health and Social Care Trust cellular pathology laboratory. This laboratory serves two of five Trusts within Northern Ireland, providing secondary care to a population of approximately 700,000 people (total Northern Ireland population 1.8 million). Incidence data was calculated per 100,000 adult population aged 18 years or older, and residing within the Belfast and South Eastern Health and Social Care Trust regions between 2008-2016 (<https://www.nisra.gov.uk/>). Cases of MC, CC or LC diagnosed from 2008 to 2016 inclusive were searched for using the closest available SNOMED codes "microscopic colitis" (SNOMED code D541725), "collagenous colitis" (D544130) and "lymphocytic-plasmacytic colitis" (D541710). Note no specific code was available for "lymphocytic colitis". The diagnostic term "incomplete MC", although in existence for some time, was not used in Northern Ireland pathology practice during this study period [19-22].

The nine year period was chosen to reflect the introduction of specialist gastrointestinal reporting and to provide sufficient clinical follow up. No pathology slide review was conducted. However, to help ensure robust diagnoses in the absence of slide review, all cases evaluated in detail for this study were diagnosed by a specialist gastrointestinal pathologist, following assessment of routine haematoxylin and eosin (H&E)-stained slides. The use of ancillary investigations,

such as histochemistry for collagen or CD3 to assess intraepithelial lymphocytes, was not recorded for the purpose of this study but such stains are not routinely performed within the practice of this pathology department to assist diagnosis of MC and it is likely the vast majority of diagnoses were made without adjunctive stains [23].

Demographic and clinical characteristics, including follow up information from outpatient review appointments, were collected from electronic healthcare records. Information was collected on age at diagnosis, gender, any history of coeliac disease or other autoimmune conditions, any history of ingestion of drugs recognised to be associated with MC, the treatment instigated following diagnosis of MC and clinical follow up (gastroenterology outpatient review and, where applicable, repeat endoscopy and biopsy), detailing response to treatment and disease evolution. The highest level of medication required to control symptoms was recorded, in the event of multimodality therapy. There was no access to full endoscopy reports (as not incorporated into the electronic healthcare record), however information on endoscopic appearances and biopsy sampling was available from the clinical details provided on pathology request forms. Where this simply stated “exclude microscopic colitis”, it was assumed no significant endoscopic abnormalities were evident. For sampling purposes, the right colon was considered proximal to the splenic flexure and left colon represented the splenic flexure, descending or sigmoid colon. Details on presenting symptoms e.g. duration or severity of diarrhoea, were not collected. A literature review was conducted with regards to identifying the drugs with the strongest reported associations with CC and LC, and in conjunction with common prescribing practice within Northern Ireland, the use of the following four drugs/drug groups were recorded for this study: proton pump inhibitors, aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs) and selective serotonin reuptake inhibitors.

## RESULTS

### *Epidemiology*

A total of 326 new diagnoses of MC were identified over the nine year study period, reflecting an average annual incidence of 6.7 per 100,000 population (Figure 1). This included 244 cases of CC with a range of 10-44 per year and an annual incidence of 5.0 per 100,000 population. Only 82 cases of LC were captured within the same time period, resulting in an annual incidence of 1.7 per 100,000 population. Given the lack of a specific SNOMED code for LC, we consider it unlikely that this reflects the true incidence of LC in this population.

As shown in Figure 1, a peak incidence of MC was observed in 2013 (10.5 per 100,000 population). We then explored the sex ratio of incident cases. Given the caveats with likely incomplete LC data, we restricted this analysis to CC cases. CC incidence was consistently higher in females compared with males (Figure 2), resulting in an average female:male ratio of 3.6 over this time period.

Relationship between age at time of diagnosis and sex is depicted in Figure 3, demonstrating a consistently higher incidence in females across all ages for both CC and LC, and a peak incidence for CC within the eighth decade and for LC within the seventh decade.

Subsequent analysis was restricted to cases diagnosed by specialist gastrointestinal pathologists. A summary overview of the main results for these cases is shown in Table 1. The 191 cases reported by specialist gastrointestinal pathologists comprised 141 cases of CC and 50 of LC. The median age of patients with CC was 64 years (range 27-94) and of patients with LC was also 64 years (range 21-91). There remained a strong female predominance for both CC (78%) and LC (80%).

### *Endoscopic sampling*

In 15% of cases, a range of mild endoscopic abnormalities was reported, including “erythema (patchy)”, “mild injection”, “pancolitis”, “patchy inflammation”, “mild inflammation” and “featureless mucosa”.

In 42 (30%) of the 141 cases of CC both right and left colonic biopsies were obtained (14 cases of which also had rectal sampling). Of these 42 cases, 40 demonstrated concordant histology between the right colon and left colon (the rectal findings were ignored). The left colon was normal in two cases. This equates to a concordance rate of 95%. A total of 67 cases (48%) were diagnosed on random colonic biopsies (site or sites of sampling not further specified), eight of which included normal fragments. Of the remaining 32 cases, five cases sampled the left colon and rectum, 12 cases sampled the left colon only, 13 cases sampled the right colon only and two cases sampled the rectum only. All of these cases provided diagnostic material, including those two cases with rectal sampling only.

Sixteen of the 50 cases of LC (32%) had right and left colon samples (two of which also had rectal sampling). Of these cases, 15 demonstrated concordant histology between the right and left colon. The left colon was normal in one case. This equates to a concordance rate of 94%. 17 (34%) cases were diagnosed on random colonic biopsies, five of which included normal fragments. Of the remaining 17 cases, three cases sampled the left colon and rectum, eight cases sampled the left colon and six cases sampled the right colon only. No cases of LC were diagnosed on sampling the rectum only.

#### *Medication use at diagnosis*

In 80 cases of CC (57%) and 32 cases of LC (64%), the patient was receiving at least one of the recognised associated drugs or drug groups at diagnosis. These included proton pump inhibitors (CC: 35%, LC 34%), aspirin (CC: 21%, LC: 30%), other NSAIDs (CC: 18%, LC: 8%) and selective serotonin reuptake inhibitors (CC: 14%, LC: 14%). In 35 cases of CC (25%) and 9 cases of LC (18%), the patient was receiving two or more of these drugs at diagnosis.

#### *Autoimmune disease prevalence at diagnosis*

In 26 cases of CC (18%) and 20 cases of LC (40%), the patient had at least one autoimmune disease at initial presentation. These included coeliac disease (CC: 4%, LC: 14%), hypothyroidism (CC: 8%, LC: 18%), psoriasis (CC: 3%, LC: 4%), rheumatoid arthritis (CC: 4%, LC: 2%), and others (CC: 2%, LC: 4%). The group listed as "others" contained a combination of type 1 and 2 diabetes mellitus, systemic

lupus erythematosus and polymyalgia rheumatica. Three cases of CC and one case of LC had two or more autoimmune diseases at the time of diagnosis of MC. Only 101 cases of CC (72%) and 24 cases of LC (84%) had coeliac serology tested at any point in their clinical history.

#### *Treatment and clinical follow up*

A variety of treatments were used to control symptoms and these are summarised in Table 2. Eighty two (58%) patients with CC and 25 (50%) patients with LC were managed with pharmacological agents, the majority receiving steroid therapy (ie. prednisolone or budesonide) or 5-ASA therapy (mesalazine). Other drugs less commonly used for symptom control included loperamide and mebeverine, azathioprine, mercaptopurine and, in a minority of cases, combination therapy (see Table 2 for details). Of the 191 cases of MC, only one case (of LC) was refractory to medical treatment and, in this case, compliance with budesonide medication was a potential issue. The rest exhibited clinical benefit in response to withdrawal of a potentially causative drug (CC: 12%, LC: 4%) or no treatment (CC: 28%, LC: 42%). Two cases of CC and one case of LC responded to treatment of coeliac disease. All recorded follow up was in the form of gastroenterology outpatient review. This was predominantly on a planned basis, usually annually until discharge from the service. Occasionally patients with symptom flares were seen more frequently. A total of 114 patients with CC had documented follow up, with a median follow up of 490 days (range 4-2758): 37 patients with LC had documented follow up, with a median follow up of 325 days (range 15-1694): 27 CC patients and eight LC patients had follow up endoscopy and biopsies, three of each showing persistent disease, despite clinical response in the form of improvement in symptoms. Switching of phenotype from CC to LC or vice versa was not observed, nor was histological progression to chronic inflammatory bowel disease.

## DISCUSSION

This is the first cohort of patients with MC reported within the Northern Ireland population. We describe a population-representative series of patients with CC and LC, whose demographic and clinical features are similar to previously reported larger series from the United Kingdom and Ireland [17,24]. Our incidence data for LC is likely to be incomplete, but the average annual incidence of CC (5.0 per 100,000) is similar to that observed in other epidemiological studies, from the United Kingdom and further afield [2,17]. Several findings in the current study provide further insights into clinical practice, in respect of drug and autoimmune disease associations with MC, current and optimal approaches to endoscopic mucosal sampling for diagnosis, treatment plans and clinical follow up.

Although the term MC implies endoscopic normality, a range of minor endoscopic abnormalities, as encountered in this series, is now well documented for both CC and LC, and is most likely related, at least in part, to increased mucosal fragility [14-18]. One recent Swedish study reported endoscopic abnormalities in 37% of patients with CC and 25% of patients with LC [18]. The frequency of endoscopic abnormality in this study (15%) is very similar to that of another recent United Kingdom study [17]. We accept, however, that recording information on endoscopic appearances from pathology request forms alone, may result in incomplete data collection. The frequent finding of endoscopic abnormalities calls into question appropriateness of the term “microscopic” colitis, and supports use of the more specific and accurate terms, CC or LC, whenever possible. This approach is favoured by most pathologists as the histological features of each condition are distinct and “borderline” cases uncommon when sampling has been adequate. . However, the similarities in demographic and clinical features, disease associations, treatments and outcomes lend support to the view that CC and LC should be considered as variations of one condition [25]. Optimal mucosal sampling at colonoscopy to diagnose MC remains contentious.. Some studies have reported that the histological features of MC, and of CC in particular, are less well developed in the distal colon than in the proximal colon, and therefore proximal colonic sampling is required to confidently exclude a diagnosis of MC [26, 27]

This is contradicted by more recent studies which have reported excellent concordance between histology of right and left colonic biopsies in the diagnosis of MC [17, 28, 29] Our right and left colonic biopsy concordance rate of 95% supports the latter studies, and suggests that sampling from the left colon will confidently exclude a diagnosis of MC if histology is normal.

Recent guidance from the American Gastroenterology Association recommends performing full colonoscopy to investigate chronic diarrhoea, with sampling from multiple anatomical segments to exclude MC [30]. If flexible sigmoidoscopy is performed for any reason, sampling from the descending colon is advised [30]. Similarly, a recent United Kingdom consensus statement concluded that all individuals with chronic diarrhoea undergoing colonoscopy should have right and left-sided colonic biopsies [31]. We concur with this advice and add the importance to pathologists of separate labelling of specimens taken from proximal and distal colon. In addition to a subepithelial collagen band (in CC) and surface intraepithelial lymphocytosis (in LC), a key diagnostic feature of both conditions is inflammatory expansion of the lamina propria, typically by a mononuclear inflammatory cell infiltrate. Assessment of this criterion necessitates knowing the site of colonic biopsies as the normal inflammatory content of the lamina propria is greater in the right than the left colonic mucosa and, further, tissue sampled from ileocaecal mucosa can look markedly inflamed if interpreted out of context [32]. Consequently, random colonic samples submitted in one container, are particularly difficult for the pathologist to interpret, and increase the risk of misdiagnosis, particularly if other diagnostic features are borderline.. Additional rectal sampling is probably of little additional value in diagnosing MC.

The spectrum and frequencies of autoimmune diseases observed in this series are very similar to those reported in another Irish series of MC patients [24]. The association with coeliac disease, particularly amongst patients with LC, is higher than most reported series, possibly reflecting the high prevalence of coeliac disease in Ireland [33,34]. Investigation for coeliac disease is advised following any diagnosis of MC, but especially LC [35].

There is a considerable literature suggesting an association between MC, of both subtypes, and specific drugs, in particular proton pump inhibitors, NSAIDs and selective serotonin reuptake inhibitors [2,8]. One recent case-control study reported that concomitant use of NSAIDs and PPIs was associated with the highest risk of developing MC [8]. Although based on small numbers of cases, this study provides some support of an association between certain drugs and MC. . Approximately 20% of MC patients in this series were taking two or more of the drugs which are recognized as being associated with MC. .

Clinical outcomes in this series were largely favourable with all but one of 191 patients responding to a variety of therapeutic strategies. Symptom control usually relied on steroid therapy.

The main limitation of this study relates to the identification of LC. For coding reasons, it is considered likely that our data for LC incidence is incomplete and this is supported by comparing the incidence with that of CC in this series and of LC in other series [2]. Therefore, the extrapolation of LC and MC data to the overall population is not appropriate. Other limitations of this study include the inability to distinguish between patients investigated by colonoscopy or flexible sigmoidoscopy alone, and the lack of pathology slide review to confirm diagnoses. Despite these drawbacks we consider our conclusions reliable as our results were based on efficient and thorough electronic healthcare records, good clinical and follow up information and the fact that we have only included cases diagnosed by specialist gastrointestinal pathologists..

In conclusion, CC and LC, the two subtypes of MC, are generally benign conditions with similar demographics, clinical associations, management and outcomes but distinct histological characteristics. Given increased recognition of subtle associated endoscopic abnormalities, the use of the more specific terms is recommended, rather than MC. Separate sampling of right and left colon is advised at colonoscopy, if this diagnosis is being considered, but left colonic sampling, which can be performed at flexible sigmoidoscopy, will diagnose the vast majority of cases.

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Table 1. Summary of demographic data and clinical associations in a series of patients with microscopic (collagenous and lymphocytic) colitis.

	<b>Collagenous Colitis (n=141)</b>	<b>Lymphocytic Colitis (n=50)</b>
<b>Demographics</b>		
- <b>Age (median)</b>	64	64
- <b>Sex</b>	F= 109 (78%)	F= 40 (80%)
	M= 32 (22%)	M= 10 (20%)
<b>Endoscopic abnormality</b>	22 (16%)	7 (14%)
<b>Drugs associations:</b>	80 (57%)	32 (64%)
- <b>PPI</b>	49 (35%)	17 (34%)
- <b>Aspirin</b>	29 (21%)	15 (30%)
- <b>Other NSAIDs</b>	25 (18%)	4 (8%)
- <b>SSRI</b>	19 (14%)	7 (14%)
<b>Autoimmune diseases:</b>	26 (18%)	20 (40%)
- <b>Coeliac disease</b>	6 (4%)	7 (14%)
- <b>Hypothyroidism</b>	11 (8%)	9 (18%)
- <b>Psoriasis</b>	4 (3%)	2 (4%)
- <b>Rheumatoid disease</b>	5 (4%)	1 (2%)
- <b>Other</b>	3 (2%)	2 (4%)
<b>Coeliac serology</b>	101 (72%)	42 (84%)
<b>Outpatient follow up:</b>		
- <b>Days (median)</b>	490	325
- <b>Follow up endoscopy and biopsy</b>	27 (19%)	8 (16%)

Table 2. Summary of treatment plans in a series of patients with microscopic (collagenous and lymphocytic) colitis.

	<b>Collagenous Colitis (n=141)</b>	<b>Lymphocytic Colitis (n=50)</b>
<b>No treatment</b>	40 (28%)	21 (42%)
<b>Treatment of coeliac disease</b>	2 (2%)	1 (2%)
<b>Cessation of potentially causative drug</b>	17 (12%)*	2 (4%)
- <b>NSAID (ibuprofen, etorocoxib)</b>	8 (47%)	2 (100%)
- <b>Aspirin</b>	3 (17%)	0
- <b>PPI (lansoprazole)</b>	10 (59%)	0
<b>Medical Management**</b>	82 (58%)	25 (50%)
- <b>Symptomatic only (loperamide, mebeverine)</b>	6 (7%)	5 (20%)
- <b>Steroid only (budesonide, prednisolone)</b>	35 (43%)	7 (28%)
- <b>5 ASA only (mesalazine)</b>	27 (33%)	12 (48%)
- <b>Thiopurine only (azathioprine, mercaptopurine)</b>	3 (4%)	1 (4%)
- <b>Steroid + 5ASA in combination</b>	10 (12%)	0
- <b>Thiopurine in combination***</b>	1 (1%)	0
<b>Refractory cases</b>	0	1 (2%)

\*four patients had more than one drug stopped

\*\*highest level of medical treatment required to control symptoms

\*\*\*azathioprine in combination with mesalazine

NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor

Figure 1. Incidence of lymphocytic colitis, collagenous colitis and total cases of microscopic colitis per 100,000 population between 2008 and 2016.

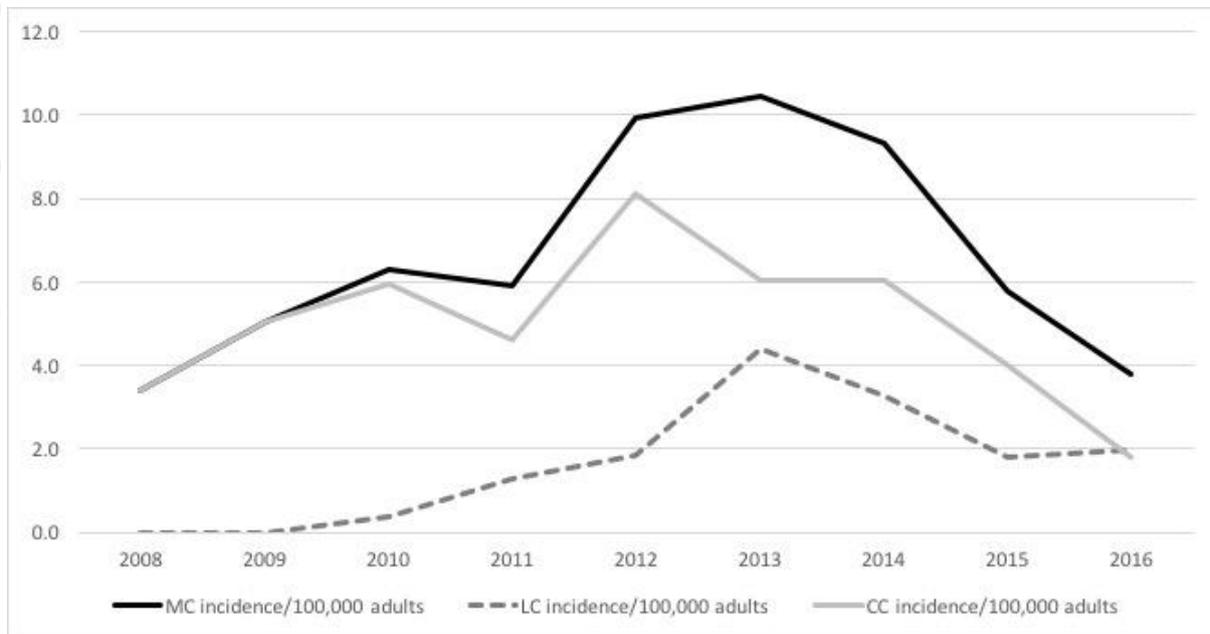


Figure 2. Incidence of collagenous colitis in adult males and females per 100,000 population between 2008 and 2016.

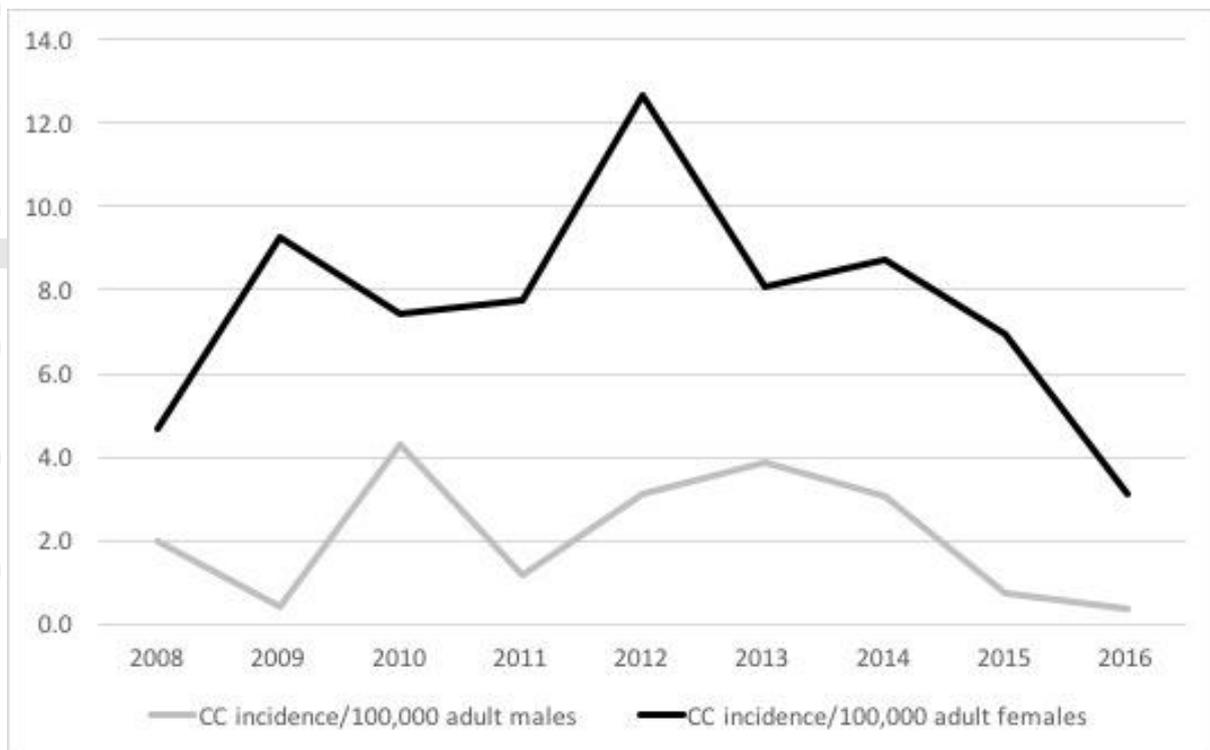


Figure 3. Relationship between age at time of diagnosis and sex in cases of lymphocytic and collagenous colitis between 2018 and 2016.

