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RANCZ ANETT

Transzlációs és klinikai farmakológia

című program

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THE INVISIBLE PRESENCE OF MICROSCOPIC COLITIS

Ph.D. Thesis

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Translational Medicine Program

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"There are no shortcuts to anyplace worth going."

Beverly Sills

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1 LIST OF ABBREVIATIONS

BMD	Bone mineral density
BMI	Body mass index
CC	Collagenous colitis
CI	Confidence interval
DOI	Digital Object Identifier
DXA	Dual-energy X-ray absorptiometry
JBI	Joanna-Briggs Institute (Critical Appraisal Tool)
GI	Gastrointestinal
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HRT	Hormonal replacement therapy
IBD	Inflammatory bowel diseases
iMC	incomplete Microscopic colitis
LBD	Low bone density
LC	Lymphocytic colitis
MC	Microscopic colitis
MD	Mean difference
NSAIDs	Nonsteroidal anti-inflammatory drugs
OCs	Oral contraceptives
ORs	Odds ratios
QUIPS	Quality in Prognosis Studies
PPIs	Proton pump inhibitors
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
RoB	Risk of bias

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SD Standard deviation

SSRIs Selective Serotonin Reuptake Inhibitors

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2 STUDENT PROFILE

2.1 Vision and mission statement

In my vision, general practitioners, gastroenterologists with expertise in endoscopy, and well-informed pathologists collaborate closely to ensure the earliest possible diagnosis of microscopic colitis. To support this goal, my mission is to educate physicians on the clinically relevant risk factors associated with the disease.

2.2 Specific goals

My specific goals during my PhD were to assess the relationship between microscopic colitis and low bone density. Additionally, to further investigate the clinically relevant risk factors for microscopic colitis.

2.3 Scientometrics

Number of all publications:	11
Cumulative IF:	51,50
Av IF/publication:	4,68
Ranking (SCImago):	D1:5, Q1:5, Q2:1,
Number of publications related to the subject of the thesis:	2
Cumulative IF:	7,30
Av IF/publication:	3,65
Ranking (Sci Mago):	D1:-, Q1:2, Q2:-,
Number of citations on Google Scholar:	33
Number of citations on MTMT (independent):	18
H-index:	4

The student's detailed bibliography can be found on pages 65-69.

2.4 Future plans

In the future, I aspire to become a rheumatology specialist who contributes to improving public health by promoting early diagnosis of autoimmune and inflammatory diseases. My goal is to take a holistic approach by combining rheumatology with insights from immunology and gastroenterology, allowing me to better understand and manage complex patient needs.

I am especially interested in applying the most up-to-date immunotherapies available in these fields to offer more effective and personalized treatment options. Alongside my

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clinical work, I plan to stay actively involved in research, both to deepen my professional knowledge and to stay current with the latest clinical methods and innovations.

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3 SUMMARY OF THE THESIS

Microscopic colitis (MC) is considered an underdiagnosed disease as it requires not only an experienced general practitioner to recognize the signs and the joint picture of clinically relevant risk factors for the disease, but also a gastroenterologist with endoscopic expertise and up-to-date pathologists due to its primarily histological appearance. It is characterized by chronic watery diarrhea, stool leakage, and nightly defecations, leading to impaired quality of life and a possible reason for keeping a narrow diet, which can lead to malnutrition and decreased bone mineral density (BMD).

Due to the contradictory vast amount of information about MC's risk factors that might also overlap with those of low bone density (LBD), in study 1, we aimed to investigate if MC contributes to secondary osteoporosis as a risk factor for it, and measured the overall proportion of MC patients' bone mineral loss. In study 2, we focused on assessing the risk factors for MC compared with distinct controls, namely, histologically verified and histologically non-verified, random controls.

In the first study, we observed doubled odds of having LBD in the presence of MC; osteopenia resulted in two and a half odds, while osteoporosis showed only a tendency when MC patients were compared to their age- and sex-matched controls. In the second study, we demonstrated that being elderly, female, and taking nonsteroidal anti-inflammatory drugs and statins are the clinically relevant risk factors for MC when compared to histological controls.

We believe that both studies reflect the need for national and international registries to determine whether patients with MC have secondary osteoporosis by screening their BMD and assessing their negative lifestyle factors like smoking through microbiome interactions, and the dosing of the drugs that might play a role in the development of MC.

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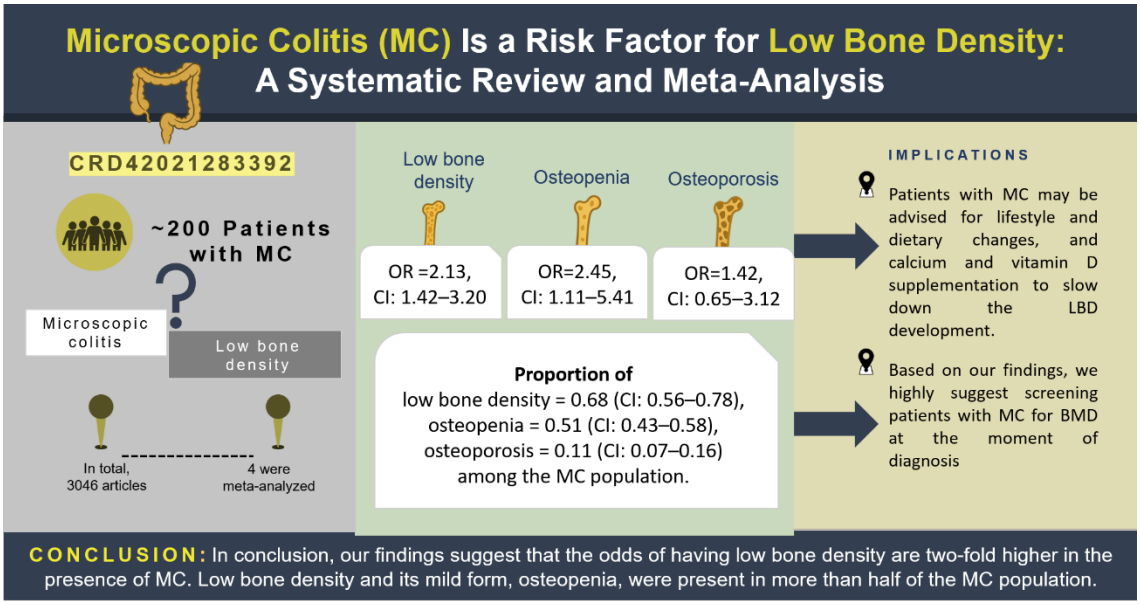
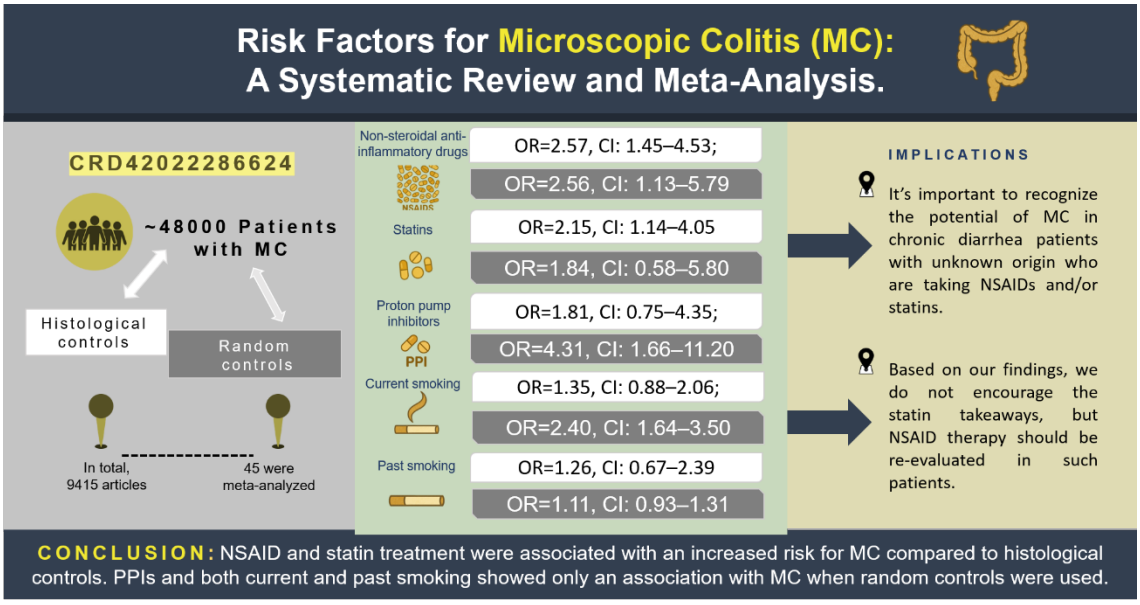
4 GRAPHICAL ABSTRACT

4.1 Study 1



4.2 Study 2



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5 INTRODUCTION

5.1 Overview of the topic

Microscopic colitis (MC) presents a rising incidence in Western countries, with 11.4 cases per 100,000 person-years (1). However, the number of cases is considered to be underestimated as its primary histological diagnosis requires not only well-trained general practitioners (2) but also gastroenterologists with high-endoscopic expertise, and up-to-date pathologists. Therefore, it can be assumed that its diagnosis may take years.

5.2 What is the problem to solve?

5.2.1 MC's risk factors remain debated

A vast amount of contradictory data exists on MC's risk factors. First, MC's discovery shows a higher rate in older women (3) among chronic diarrhea patients undergoing colonoscopy and histopathology; however, child cases and younger age manifestations exist as well (3-5). Second, dysbiosis, chronic inflammation, and immune dysregulation play a role in MC's etiopathology (1, 4), and obesity can also provoke them (5); however, weight gain itself has been reported to have an inverse relationship with the risk of MC (6) and a body mass index (BMI) below 30 is a potential predictive factor for MC (7). Third, smoker MC patients, compared to smoker colonoscopy-referred diarrhea controls, resulted in no association between smoking and MC (8, 9), while an earlier meta-analysis described their strong relationship (10). Last, individual studies (8, 11) have yielded differing results regarding the relationship between MC and hormonal replacement therapy (HRT), and no comprehensive research has been conducted on this topic. Even though MC has a histopathological diagnosis (1), previous studies meta-analyzed its relationship with different medications, with the lack of separate investigation based on more precisely defined control types (12, 13).

5.2.2 MC's risk factors might overlap with those of low bone density (LBD)

Few publications report the potential loss of bone mineral density (BMD) in MC. However, it is characterized by chronic watery diarrhea, contributing to weight loss and mineral deficiencies like calcium and vitamin D, which can ultimately manifest as osteoporosis and osteoporosis-related fractures (14, 15). The additional symptoms, stool leakage, nightly defecations (16), and the fear of them, only worsen the patients' quality

of life, urging them to keep a narrow diet, worsening the bone health maintenance via the poor mineral intake. Furthermore, the gold standard therapy of MC is the locally acting steroid budesonide (1, 17), which has been implicated as a detrimental factor in the development of LBD (18) in long-term therapies. However, one study showed no incidence of osteopenia and osteoporosis in patients receiving budesonide therapy over a five-and-a-half-year follow-up (19). Moreover, both diseases manifest more frequently in elderly women. These women in postmenopausal state can receive hormonal substitution therapy to help maintain their bone health, which in turn can cause microscopic colitis (20). To summarize all points mentioned above, it can be hypothesized that MC may lead to secondary osteoporosis.

5.3 What is the importance of the topic?

Chronic watery diarrhea, which is the leading symptom of MC, is a huge burden for individuals who suffer from it; it not only limits the person's physical abilities but can also have a psychological and emotional impact, not to mention the social and occupational limitations. Therefore, addressing the underlying cause as soon as possible is one of the biggest challenges for both the patients and practitioners.

5.4 What would be the impact of the results?

First, identifying and acknowledging the clinically relevant risk factors for MC would help practitioners in early diagnosis of MC. This could reduce the number of patients who continuously return to the outpatient clinic without a diagnosis. Additionally, it could ease MC patients' psychological welfare impairment (21), anxiety, and depression (22), by ameliorating both their gastrointestinal (GI) symptoms and, therefore, their social limitations, applying MC’s gold standard therapy (1). Plus, the improvement in diagnosis efficiency could decrease the number of unnecessary appointments, repeated endoscopies, and their associated costs.

Second, ascertaining if MC extraintestinal manifestations include BMD loss could point out the need for early screening and prevention of potential osteopenia. It is especially crucial to detect bone mass reduction and bone architecture remodeling that result in skeletal fragility and peaks in fracture risk (23). Highlighting that osteoporotic fractures may lead to complications like thromboembolism and challenging pain management (24). Not to mention, the in-hospital stays, outpatient visits, and nursing home stays, which

contribute to the increased medical costs in these patients' care (24). Therefore, introducing prophylactic therapies like screening for LBD could reduce the osteoporotic fractures-associated morbidity, mortality (25), and cost.

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6 OBJECTIVES

6.1 Study 1

In the first study, we aimed to investigate the relationship between MC and LBD by assessing if MC is a risk factor for LBD development and measuring the proportion of BMD loss in the MC population.

6.2 Study 2

In the second study, we aimed to investigate MC's risk factors to diagnose it as early as possible, comparing MC patients with distinct controls, histologically verified and population-based random controls, taking into consideration MC's primary histological diagnosis (1).

7 METHODS

Both studies had a prospectively registered protocol on the International Prospective Register of Systematic Reviews (PROSPERO), with the following identifiers: CRD42022286624, CRD42021283392 for the first and second studies, respectively.

Both studies were conducted with full adherence to the Cochrane Handbook and to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement.

7.1 Information sources and search strategy

7.1.1 Study 1

We conducted a literature search from inception to October 16, 2021, among five databases: MEDLINE (via PubMed), Embase, Scopus, Web of Science, and Cochrane Library (CENTRAL), using the following search key: "(microscopic colitis OR collagenous colitis OR lymphocytic colitis OR incomplete microscopic colitis) AND (bone OR osteoporosis OR fracture OR osteoporotic OR osteopenia OR dexa OR osteodensitometry OR lbd OR lbm); in Embase a modified search key was applied: "('microscopic colitis' OR 'collagenous colitis' OR 'lymphocytic colitis' OR 'incomplete microscopic colitis') AND (bone OR osteoporosis OR fracture OR osteoporotic OR osteopenia OR dexa OR osteodensitometry OR lbd OR lbm)". There were no restrictions, and our query was applied to all fields/all text in the searched databases. The reference list of eligible studies was checked for additional potentially eligible articles.

7.1.2 Study 2

A primary systematic search was performed on December 18, 2021, that was supplemented on January 6, 2025 in the databases of MEDLINE (via PubMed), Embase, and Cochrane Central Register of Controlled Trials (CENTRAL); using the following search terms: "(microscopic colitis OR collagenous colitis OR lymphocytic colitis OR incomplete microscopic colitis)"; in Embase a modified search key was applied: "('microscopic colitis' OR 'collagenous colitis' OR 'lymphocytic colitis' OR 'incomplete microscopic colitis')", in plus, a backward and forward reference search of the eligible articles on January 28, 2023, and then January 9, 2025.

7.2 Eligibility criteria

7.2.1 Study 1

In the first study two frameworks were used, the first one was the PEO (Population, Exposure, Outcome) framework, assessing whether MC (E) is associated with the development of LBD, osteopenia, or osteoporosis (O) in adult patients (>18 years) (P) (26); including cohort, case-control, and cross-sectional studies, that reported on the number of adult patients with MC diagnosed by histopathologic criteria (1) and their BMD evaluation were available. The second framework was the CoCoPop (Condition, Context, Population) via which we ascertained the proportion of different BMD decreases: LBD, osteopenia, osteoporosis (Co) in the context of MC (Co) (26) in adult patients (>18 years old) (Pop).

7.2.2 Study 2

We formulated the PEO question framework investigating adult patients (P) (>15 years) with different risk factors (E) and the histopathological diagnosis of MC (1) (O), including cohorts, case-control studies, and cross-sectional studies, if they reported on patients with MC and the risk factors for MC compared to distinct histologically verified and histologically non-verified, random controls.

7.3 Study selection and data extraction

During both workflows, the following steps were implemented: a reference management program (EndNote X9, Clarivate Analytics, Philadelphia, PA, USA) (31) was used for the selection process. The search results were integrated, and then duplicates were automatically and manually discarded. Two review authors independently performed all the steps. First, the records were selected by title and abstract, and then by full text. At the end of each step, we calculated the Cohen's kappa coefficient (κ) to preserve the inter-rater reliability (32). Secondly, the extracted data were populated into a pre-designed Excel spreadsheet (Office 365, Microsoft, Redmond, WA, USA). In the case of disagreements that occurred, they were resolved by a third independent investigator.

7.3.1 Study 1

The extracted data were the following: Digital Object Identifier (DOI), first author, publication date: year, country of origin, number of centers, study type, study design,

study period, patient characteristics, number of patients with LBD, osteopenia, or osteoporosis, and number of control cases with the bone pathologies mentioned above. Where the number of patients with LBD was not reported, we added it together with those of osteopenia and osteoporosis.

7.3.2 Study 2

The following data were extracted: first author, year of publication, DOI, study design, study period, country of origin, study centers, MC (including its subtypes: collagenous colitis (CC), lymphocytic colitis (LC), and incomplete microscopic colitis (iMC)), cases: sample size and the percentage of participating females; and control patient characteristics: sample size, control type, and percentage of females.

7.4 Bias and Quality Assessment

Two independent reviewers carried out both assessments, and in the case of disagreements, a third reviewer decided them.

7.4.1 Study 1

In the risk of bias (RoB) evaluation, as different study designs were included, we reported the Joanna Briggs Institute Critical Appraisal Checklists accordingly for our prognostic question (27), and the Checklist for Prevalence Studies (28) for our proportional question.

The quality of evidence was assessed with the 'Grading of Recommendations, Assessment, Development and Evaluation' (GRADE) Working Group (29).

7.4.2 Study 2

In the RoB assessment, we used the Quality in Prognosis Studies (QUIPS) tool.

7.5 Data synthesis and analysis

In both studies, the following steps were applied: a meta-analysis was performed using a minimum of three studies. Forest plots displayed the findings of the meta-analytical calculations. A random-effect model was used with an anticipated substantial between-study heterogeneity to calculate pooled effect sizes. We used the Mantel-Haenszel Method (30-32) (based on raw data) to calculate the pooled event rate for categorical variables and the odds ratios (ORs) with 95% confidence intervals (CIs). To pool the calculated ORs with the extracted ORs (where the raw data were not published), the

inverse variance weighting method was applied (33). We applied the random intercept logistic regression model method to compile the proportions for events with 95% CIs (34, 35). Results were considered statistically significant if $p < 0.05$. Since the number of studies was low (fewer than five), the Hartung-Knapp adjustment was not applied (33, 36).

7.5.1 Study 1

Between-study heterogeneity was tested with Higgins & Thompson's I^2 statistics (37) and Cochran Q tests. The I^2 test represented the presence of statistical heterogeneity in percentages across the analyzed studies (38).

Forest plots displayed the findings of the meta-analytical calculations. Due to the small study number (<10), it was impossible to assess publication bias. The statistical analyses of the data were carried out with R (R Core Team 2021, v4.1.1) using the *meta* (39) and *dmetar* (40) packages.

7.5.2 Study 2

The differences between mean values were used as an effect size measure with 95% confidence intervals (CI) in the case of continuous outcomes. To calculate study mean differences (MDs) and pooled MDs, the sample size, the mean, and the corresponding standard deviation (SD) were extracted from each study (in each group separately) if available.

To estimate the heterogeneity variance measure (τ^2), the Paule-Mandel method (recommended by Veroniki et al.) was used with the Q profile method for confidence intervals for "raw" OR. If only OR was provided, and for MD, the restricted maximum-likelihood estimator was used with the Q profile method for confidence intervals.

In the case of subgroup analysis, a fixed-effects "plural" model (aka mixed-effects model) was used. Different τ^2 values were assumed in the subgroups. A "Cochrane Q" (an omnibus test) was used between subgroups to assess the difference between the subgroups (41). The null hypothesis was rejected at a 5% significance level.

All statistical analyses were made with R (v4.1.2) using base R functions, the meta (v6.2-1) package for basic meta-analysis calculations and plots, and dmetar (v0.0.9000) package for additional influential analysis calculations and plots.

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8 RESULTS

8.1 Search and selection

8.1.1 Study 1

From the total of 3046 records, only three full-text articles (18, 42, 43) and one conference abstract (44) were eligible for analysis (see **Figure 1**).

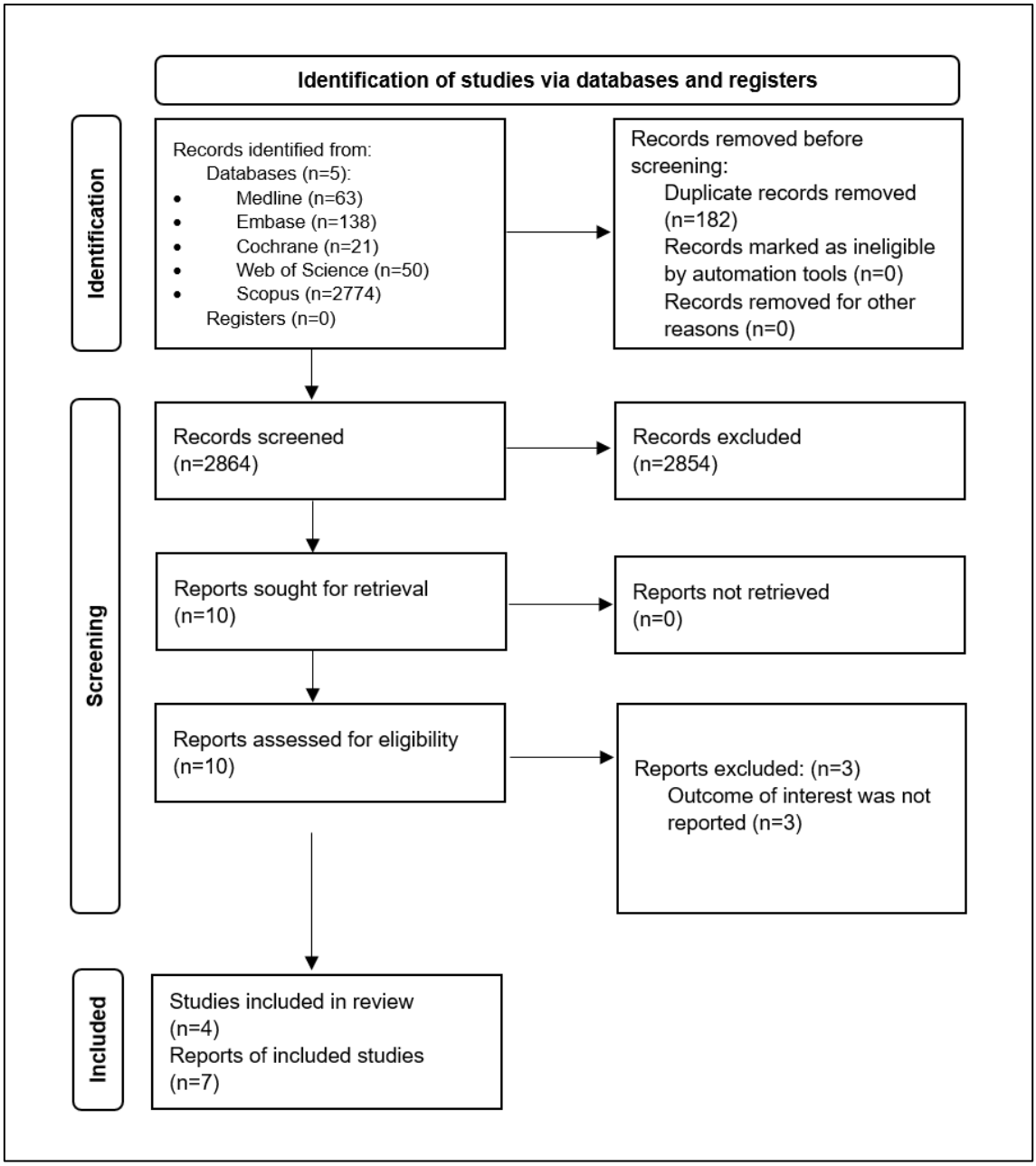

Figure 1. *PRISMA 2020 flowchart representing the detailed systematic search and study selection process (45).*

8.1.2 Study 2

From the total of 6,493 that were yielded from the second and final round of systematic search, an additional 2,922 records were found via the backward and forward citation chases of the suitable studies, 45 (6, 8, 9, 11, 46-86) were eligible for meta-analysis (see **Figure 2**).

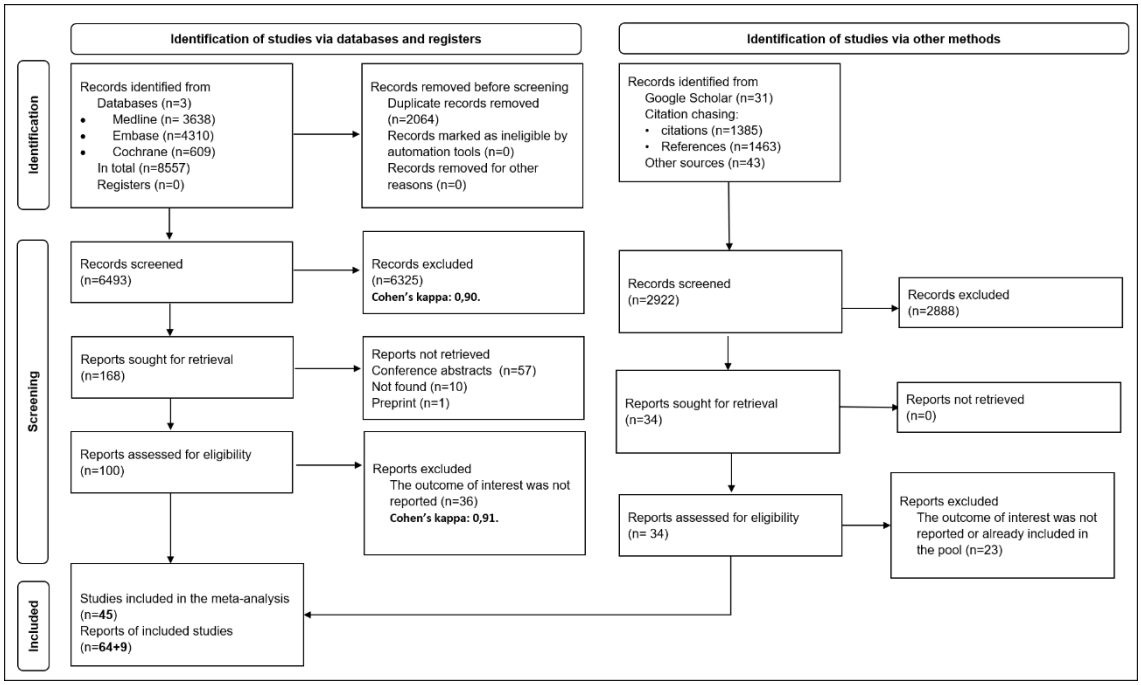

Figure 2. *PRISMA 2020 flowchart representing the detailed systematic search and study selection process (87).*

8.2 Basic characteristics of the included studies

8.2.1 Study 1

The included studies', all of them observational, main characteristics are presented in **Table 1**.

Each study's population consisted of more than two-thirds female participants, and all of them were above the age of 35 years.

In the articles, the patients' disease duration was the following: a mean of 4.33 years with a 1.66 standard deviation (43), a median of 28 months with ranges between 2-163 (18), while an average of 399 days passed between the diagnosis of MC and the dual-energy

X-ray absorptiometry (DXA) measurement (42), and no information (44) from the conference abstract.

Steroid use was reported as inhaled steroid use in around 15% of MC cases (18). Furthermore, intermittent budesonide therapy was used by around 60%, while 30% of them used it as maintenance therapy in the same study (18). In the second article, approximately 10% of the MC patients were on steroid treatment for more than three months before a dual-energy X-ray absorptiometry (DXA) measurement; however, no information was available on budesonide use among them (42). Although approximately 80 percent of the MC participants had less than eight weeks of budesonide treatment before enrollment, no systemic steroids were used in the reports of the third study (43). The conference abstract did not report on any steroid usage of MC patients, while more than two-thirds of them received budesonide (44).

8.2.2 Study 2

Fifteen cohorts, 21 case-control, five cross-sectional, two short reports, one correspondence, and one article of unspecified study design were meta-analyzed. Approximately 48,000 MC cases were investigated, with more than two-thirds of them being female (see **Table 2**).

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Table 1. Basic characteristics of the included articles in Study 1 (45).

Study's first author and year of publication	Study design	Country	Number of patients (N0) MC/CG	Percentage of total females (%)	Age, mean age years±SD or median (ranges)	BMI (kg/m^2), mean±SD or median (ranges) MC/CG	Smoking history (N0) MC/CG	Steroid use (N0) MC/CG
Graziano et al. 2021 (42)	retrospective case-control	USA	47[†]/188	93.60	63.60±10.70	28.40±6.70/29.80±6.60	24/72[§]	5/10[¶]
Greenberg et al. 2019 (44)	retrospective case-control	USA	94/NA	91	69 (42-91)	NA	NA	NA
Wildt et al. 2018 (18)	prospective cohort	Denmark	50/49	87	67 (45-93)	24 (16-34) /25 (17-34)	17/5	7/1[††]
Katalin Lőrinczy et al. 2011 (43)	cross-sectional	Hungary	14/28[‡]	85.71	49.79±13.06	24.23±7.89/25.34±12.40	5/13	none

USA = United States of America. MC = microscopic colitis/CG = control group (patients with MC in comparison to age- and sex-matched controls). BMI = body mass index. NA = not available. SD = standard deviation.

[†] They used 118 patients with MC to investigate the occurrence of bone mineral changes

[‡] matched for age, gender, and menopausal state, not just patients with MC, but patients with Crohn's disease are compared to matched controls

[§] smoking status: current/former/never. (current smoker = active smoker at the moment of dual-energy X-ray absorptiometry)

¶ *prior prednisone > three months*

†† *treatment with inhaled steroids*

Table 2. Basic characteristics of the included articles in Study 2 (87).

Study's first author, year of publication, reference	**Study design**	**Country**	**Total patients with MC (N0)**	**Female patients with MC (N0 [%])**	**Total control patients (N0)**	**Female control patients (N0 [%])**	**Control type**	**CC/LC/MCi patients (N0)**
Abdel-Razeq et al. 2024 (85)	Retrospective cohort	USA (Cleveland, Ohio)	670	370 (55,22)	69312940	37581490 (54,22)	random controls	800/740/none
Batista et al. 2019 (46)	Retrospective cohort	Spain	30	24 (80)	64	51 (79,6)	histopathologically examined controls	13/12/5
Bonagura et al. 2016 (47)	Retrospective cohort	Italy	25	20 (80)	23	19 (82,6)	histopathologically examined controls	2/13/10

Bonderup et al. 2014 (84)	Prospective case-control (incidence-density sampling)	Denmark	5751	CC: 2623 (75,5); LC: 1446 (63,5)	575100	CC: 2623 (75,5); LC: 144600 (63,5)	random controls	3474/227/none
Bonderup et al. 2018	Prospective case-control (risk-set sampling)	Denmark	10652	CC: 4724 (76); LC: 2847 (65)	101381	CC: 45350 (76); LC: 26668 (64)	random controls	6250/4402/none
Burke et al. (Smoking) 2018	Prospective cohort	USA	166	166 (100)	230849	230849 (100)	random controls	78/76/12
Fernández-Bañares et al. 2001	Hybrid cohort (prospective and retrospective)	Spain	51	41 (80,3)	32	21 (65,6)	histopathologically examined controls	26/25/none

Fernández-Bañares et al. 2013	Prospective case-control	Spain	CC: 70; LC: 120	CC: 90 (75); LC: 48 (69)	128 – same control for CC and LC	95 (74)	random controls	120/70/none
Gad et al. 2024	Prospective cohort	Egypt	38	18 (32,7)	78	37 (67,3)	histopathologically examined controls	10/3/25
Gomaa et al. 2017	Retrospective cohort	Egypt	5	2 (40)	37	NA	histopathologically examined controls	1/4/none
Green et al. 2019	Short Report	UK	483	317 (65,6)	450 616	244531 (54,2)	random controls	NA/NA/NA
Gu et al. 2012	Prospective case-control	China (Guangdong)	87	32 (37)	90	34 (38)	histopathologically examined controls	28/59/none

Guagnozzi et al. 2015	Prospective case-control	Central Spain	46	25 (54,3)	317	196 (61,8)	histopathologically examined controls	4/42/none
Holstein et al. 2006	Cross-sectional	Germany	42	30 (72)	43	30 (70)	random controls	26/16/none
Kane et al. 2015	Retrospective derivation cohort	UK	85	64 (75,3)	391	239 (61,1)	histopathologically examined controls	67/18/none
Keszthelyi et al. 2010	Retrospective case-control	Netherlands	95	63 (66)	95	63 (66)	random controls	49/46/none
Koskela et al. 2004	Retrospective case-control; Prospective case-control	Finland	45; 39	NA	84	NA	random controls	21; 9/24; 30/none
Laing et al. 2006	Population based nested case-control	USA (Olmsted County - Minnesota)	130	91 (70)	130	91 (70)	random controls	46/84/none

Larsson et al. 2014	Short Report	Sweden (Malmö)	16	16 (100)	58	41 (70,6)	histopathologically examined controls	10/5/none
Larsson et al. 2016	Prospective cohort	Sweden (Malmö)	135	115 (85)	27960	16918 (60,5)	random controls	73/62/none
Liu et al. (Obesity) 2019	Prospective cohort	USA	244	244 (100)	191857	191857 (100)	random controls	115/117/12
Maret-Ouda et al. 2022	Prospective case-control	Sweden	14520	10428 (71,8)	69491	50062 (72,0)	random controls	4684/9836/none
Masclee et al. 2015	Population-based nested case-control (the data was prospectively collected)	Netherlands	218 - matched to population-based controls (148 - matched to histopatological controls)	116 (78,4); 160 (73,4)	475; 15045	375 (78,9); 11147 (74,1)	histopathologically examined controls; random controls	92/70/56

Misra et al. 2010	Retrospective cohort	India	15	CC: 4 (50); LC 6 (60)	14	9 (64,2)	histopathologically examined controls	5/10/none
Monem et al. 2022	Cross-sectional	Egypt	13	9 (69,2)	47	26 (55,3)	histopathologically examined controls	4/9/none
Morgan et al. 2020	Research Correspondence	NA	20	16 (80)	20; 20	16 (80); 13(65)	random controls	NA/NA/NA
Niccum et al. 2021	Prospective cohort	USA	352	352 (100)	209902	209550 (100)	random controls	167/169/16
Nyhlin et al. 2014	Retrospective cohort	Sweden	212	CC: 97 (84,3); LC: 79 (81,4)	627	NA	random controls	115/97/none
Pagoldh et al. 2019	Cross-sectional	Sweden (Umea°)	57	43 (75,4)	138	104 (75,3)	random controls	24/19/14

Pascua et al. 2010	Retrospective case-control	USA (Pennsylvania)	26	21 (81)	259;259	183 (70); 166 (64)	histopathologically examined controls; random controls	12/14/none
Riddell et al. 1992	Retrospective case-control	Canada	31	28 (90,3)	31	28 (90,3)	histopathologically examined controls	31/none/none
Roth et al. (reproductive) 2013	Cross-sectional	Sweden (County of Skåne)	131	131 (100)	737	737 (100)	random controls	82/49/none
Sandler et al. (Obesity) 2022	Prospective case-control	USA (North Carolina)	110	94 (86,2)	252	176 (69,8)	histopathologically examined controls	NA/NA/NA
Sandler et al. 2021	Prospective case-control	USA (North Carolina)	110	94 (86,2)	252	176 (69,8)	histopathologically examined controls	NA/NA/NA

Sonnenberg et al. (Differences) 2017	Cross-sectional	USA	9848	7371 (74,8)	21,098	10613(50,3)	histopathologically examined controls	NA/NA/NA
Tracy et al. 2022	Nested Case-control within prospective cohort	USA	96	96 (100)	190	190 (100)	random controls	NA/NA/NA
Verhaegh et al. 2016	Retrospective case-control (incidence-density sampling)	UK	1211	886 (73,2)	6041	4423(73,2)	random controls	394/292/525
Verhaegh et al. 2017	Retrospective case-control	Netherlands	171	138 (80,7)	316	250 (79,1)	random controls	81/73/17
Vigren et al. 2011	NA	Sweden	116	92 (79)	6192	3197 (51,6)	random controls	116/none/none

Wickbom et al. 2017	Retrospective case-control	Sweden (Örebro)	CC: 115; LC: 97	CC: 97 (84,3); LC: 79 (81,4)	CC: 263; LC: 224	CC: 228 (86,6); LC: 189 (84,3)	random controls	115/97/none
Yamashiro et al. 2022	Case-control	Japan	161	114 (70,8)	246836	114463 (46,3)	random controls	NA/NA/NA
Yen et al. (Current) 2012	Retrospective case-control	USA (Illinois)	340	259 (76,2)	340	259 (76,2)	random controls	124/216/none
Yen et al. (Decreased) 2012	Retrospective case-control	USA (Illinois)	647	494 (76,3)	647	494 (76,3)	random controls	261/386/none
Yen et al. 2022	Hybrid cohort (prospective and retrospective)	USA (Illinois)	80	65 (81,2)	118	78 (66,1)	histopathologically examined controls	20/60/none

Zylberberg et al. 2021	Retrospective cohort	USA (New York and Minnesota)	344	245 (71,2)	668	478 (71,6)	histopathologically examined controls	131/185/19 +1 unknown

USA: United States of America; UK: United Kingdom; NA: not available; MC: microscopic colitis; CC: collagenous colitis; LC: lymphocytic colitis; MCi: incomplete microscopic colitis

8.3 Results of analyses

8.3.1 Study 1

8.3.1.1 MC as a risk factor for LBD, osteopenia, and osteoporosis

All four articles (18, 42-44) were included in the calculation of the odds of having LBD, and three of them (18, 42, 43) in the odds of osteopenia and osteoporosis in comparison with age- and sex-matched controls. The analysis resulted in doubled odds in the detection of LBD (OR=2.13, CI: 1.42–3.20) with moderate heterogeneity (I^2=37%, CI: 0–78) (see **Figure 3**).

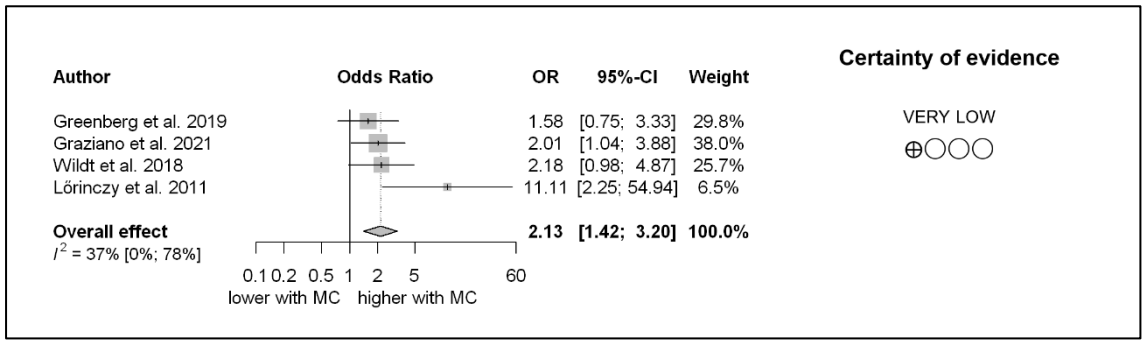

Figure 3. *Forest plot demonstrating that microscopic colitis doubles the odds of having low bone density (45). MC=microscopic colitis. OR=odds ratio. CI=confidence interval.*

The odds of detecting osteopenia were 2,4 times higher (OR=2.45, CI: 1.11–5.41) in the presence of MC with moderate heterogeneity (I^2=35%, CI: 0–79), while osteoporosis occurrence showed an increased tendency (OR=1.42, CI: 0.65–3.12); however, statistical significance was not confirmed, and the I^2 was 0% (CI: 0–90) (see **Figure 4**).

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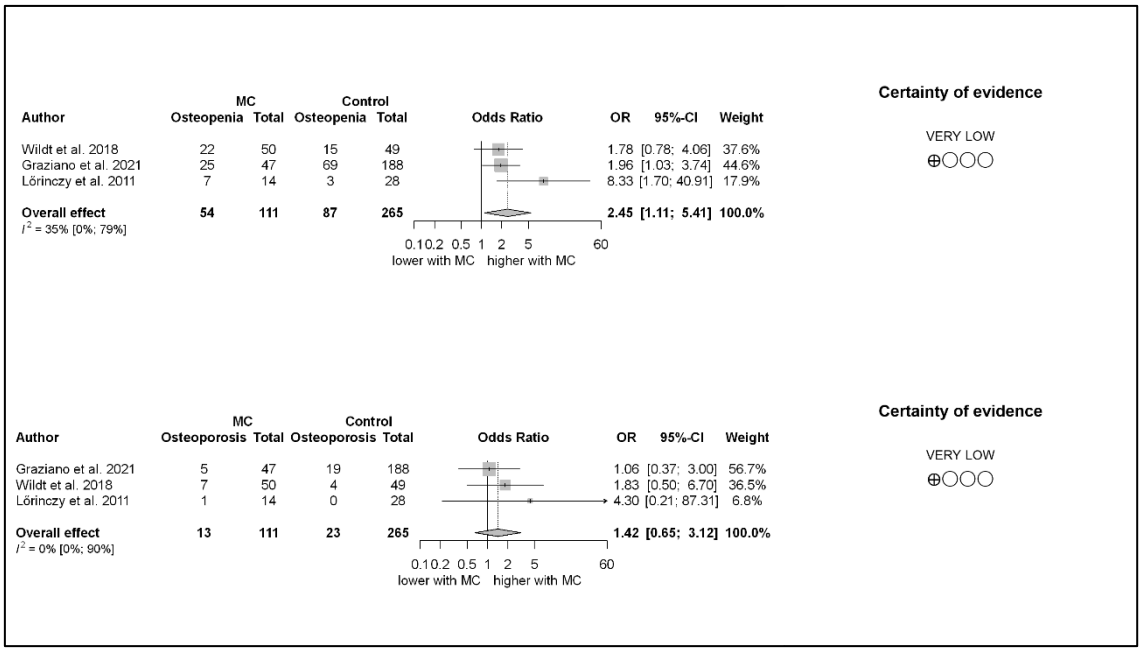

Figure 4. *Forest plots demonstrating the odds of detecting osteopenia were two and a half times higher in the presence of microscopic colitis; osteoporosis occurrence showed a tendency in the case of having MC (45). MC=microscopic colitis. OR=odds ratio. CI=confidence interval.*

8.3.1.2 The proportion of BMD loss in MC

Calculating the proportion of MC patients with BMD loss, we could use all four included studies (18, 42-44). Among the 276, 182, and 182 MC population, there were 189, 92, and 20 cases with LBD, osteopenia, and osteoporosis, respectively. In the conference abstract, only pooled data were available, 77 patients with LBD out of 94. Our results showed a 0.68 (CI: 0.56–0.78) overall proportion of LBD, with considerable heterogeneity (I^2=75%, CI: 31–91). Osteopenia and osteoporosis were present in proportions of 0.51 (CI: 0.43–0.58) and 0.11 (CI: 0.07–0.16), with 0% (CI: 0–79 and CI: 0–90) heterogeneity in both cases (see **Figure 5**).

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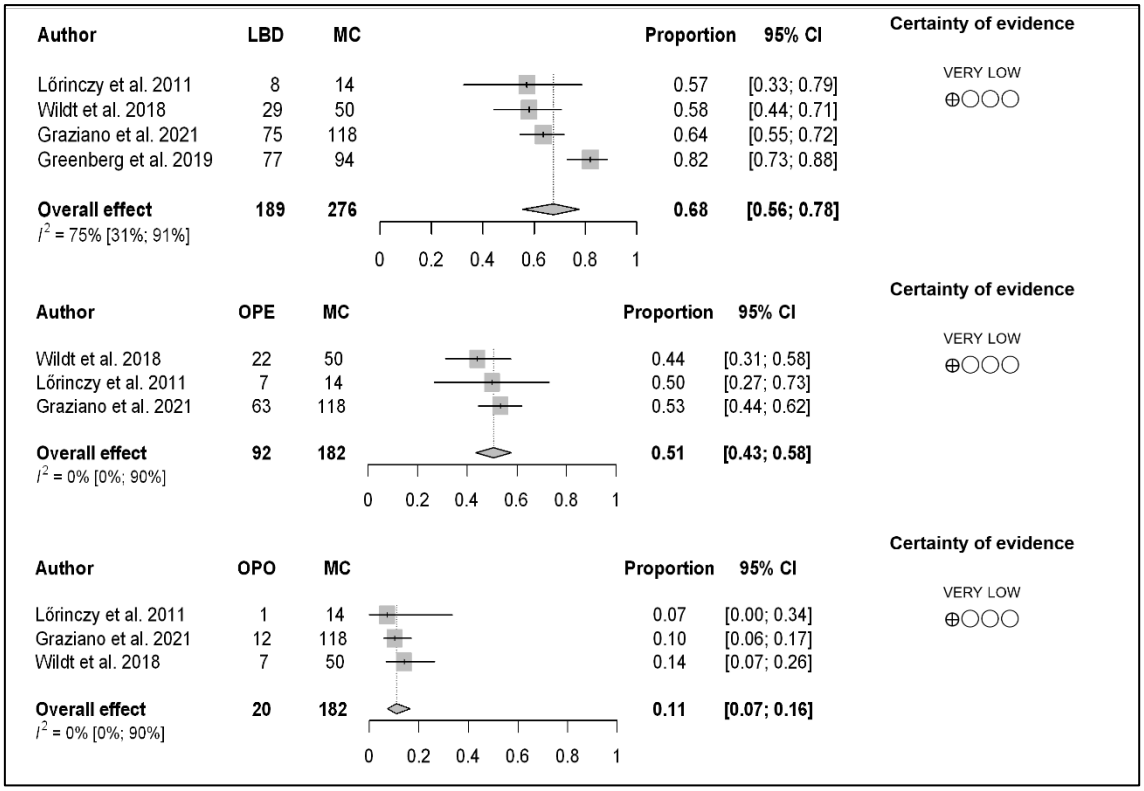

Figure 5. *The forest plot presents the proportions of LBD, osteopenia, and osteoporosis in patients with microscopic colitis (45). MC=microscopic colitis. OPE=osteopenia. OPO=osteoporosis. CI=confidence interval.*

8.3.2 Study 2

8.3.2.1 Unchangeable risk factors for MC

8.3.2.1.1 Age

The age of the MC cases compared to histological controls was given in 13 studies (8, 46, 47, 50, 52, 54, 55, 57, 65, 66, 75, 81, 86). A mean age difference of 5.93 years (CI: 2.08–9.77; I^2=94%, CI: 91–96) was between the MC patients and their controls (see **Figure 6**).

DOI:10.14753/SE.2025.3328

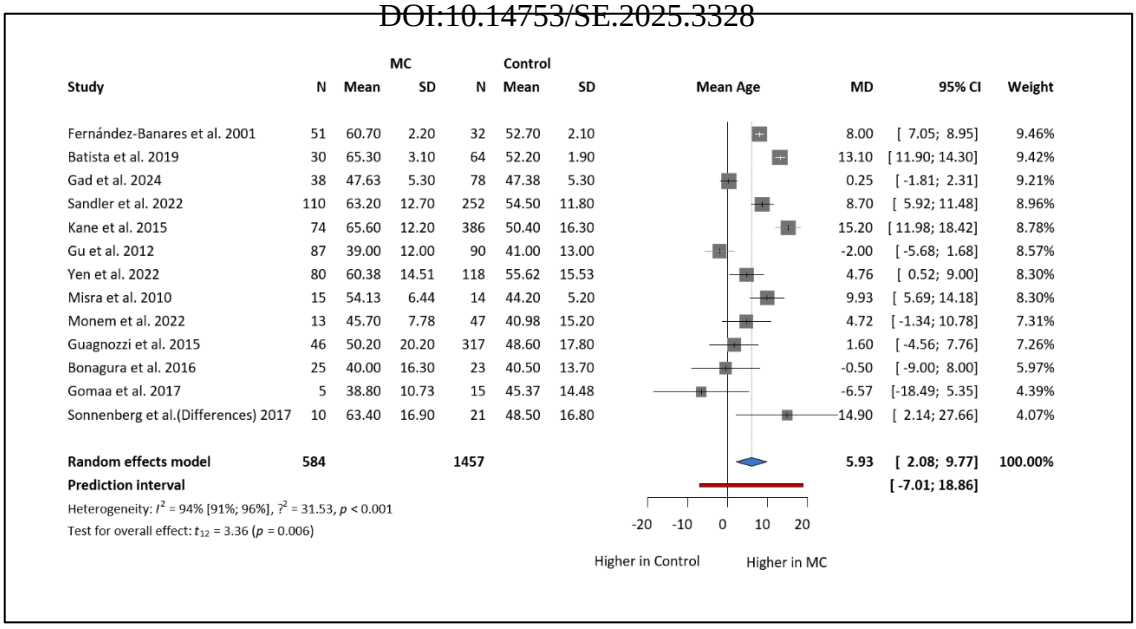

Figure 6*. Forest plot representing the mean age of 5.93 years difference of MC patients in comparison to their histological controls (87). MC=microscopic colitis. N=number. SD=standard deviation. MD=mean difference. CI=confidence interval.*

8.3.2.1.2 Female sex

The female cases among MC patients compared to histological controls were reported in 15 studies (8, 9, 46, 47, 50, 54, 55, 57, 61, 65, 66, 71, 75, 81, 86). This analysis resulted in a 1.48-fold increase in odds for developing MC (CI: 1.13–1.95; I^2=80%, CI: 69–88) (see **Figure 7**).

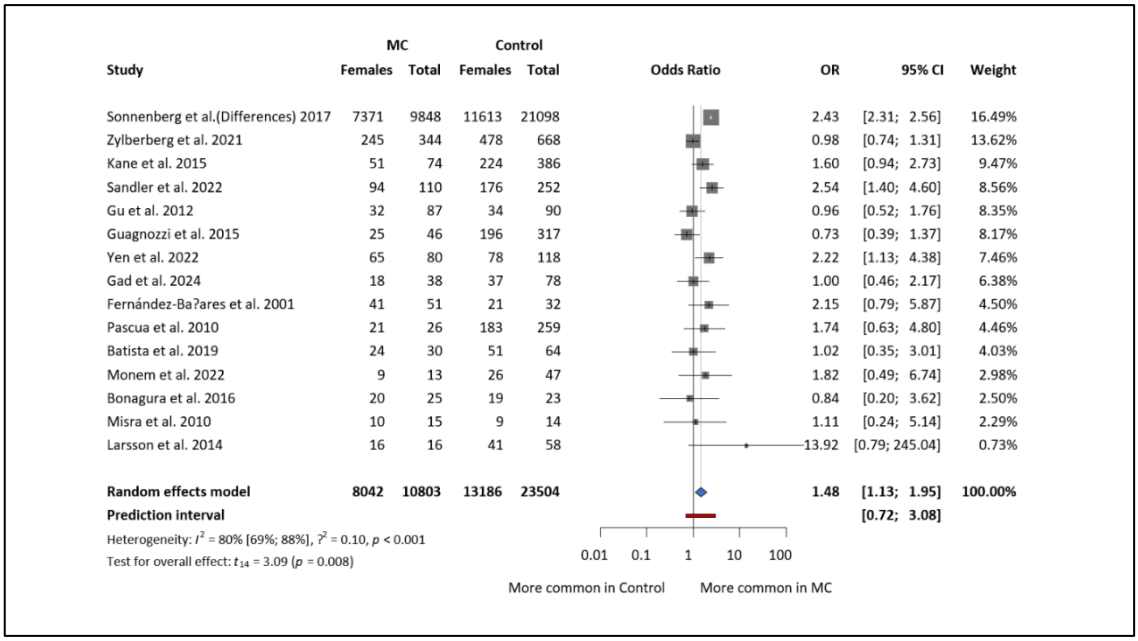

Figure 7*. Forest plot representing a 1.48-fold increase in odds for MC if the patient is female (87). MC=microscopic colitis. OR=odds ratio. CI=confidence interval.*

8.3.2.2 Changeable lifestyle risk factors

8.3.2.2.1 Alcohol consumption

Five studies (62, 68, 73, 76, 82) reported MC patients' alcohol use compared to random controls. We found a 1.64-fold increase in odds (CI: 1.26–2.14; I^2=10%, CI: 0–81) for having MC when cases consume beverages (see **Figure 8**).

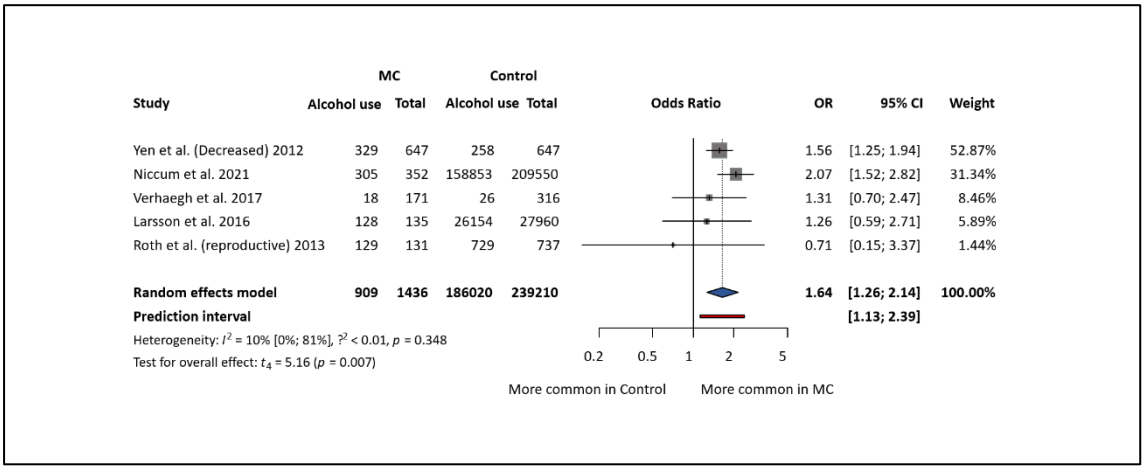

***Figure 8**. Forest plot representing a 1.64-fold increase in odds for MC if the patient consumes beverages (87). MC=microscopic colitis. OR=odds ratio. CI=confidence interval.*

8.3.2.2.2 Smoking

8.3.2.2.2.1 Never smoking

Six studies' data showed (11, 67, 73, 76, 79, 83) that smoking abstinence is a protective factor with a 0.52-odds (CI: 0.39–0.70; I^2=26%, CI: 0–69) compared to MC patients with random controls. However, individual studies (52, 81) comparing MC patients to histological controls found conflicting results. An overall result confirmed the comparison between MC patients with random controls (OR=0.53, CI: 0.42–0.66; I^2=13%, CI: 0–55) (see **Figure 9**).

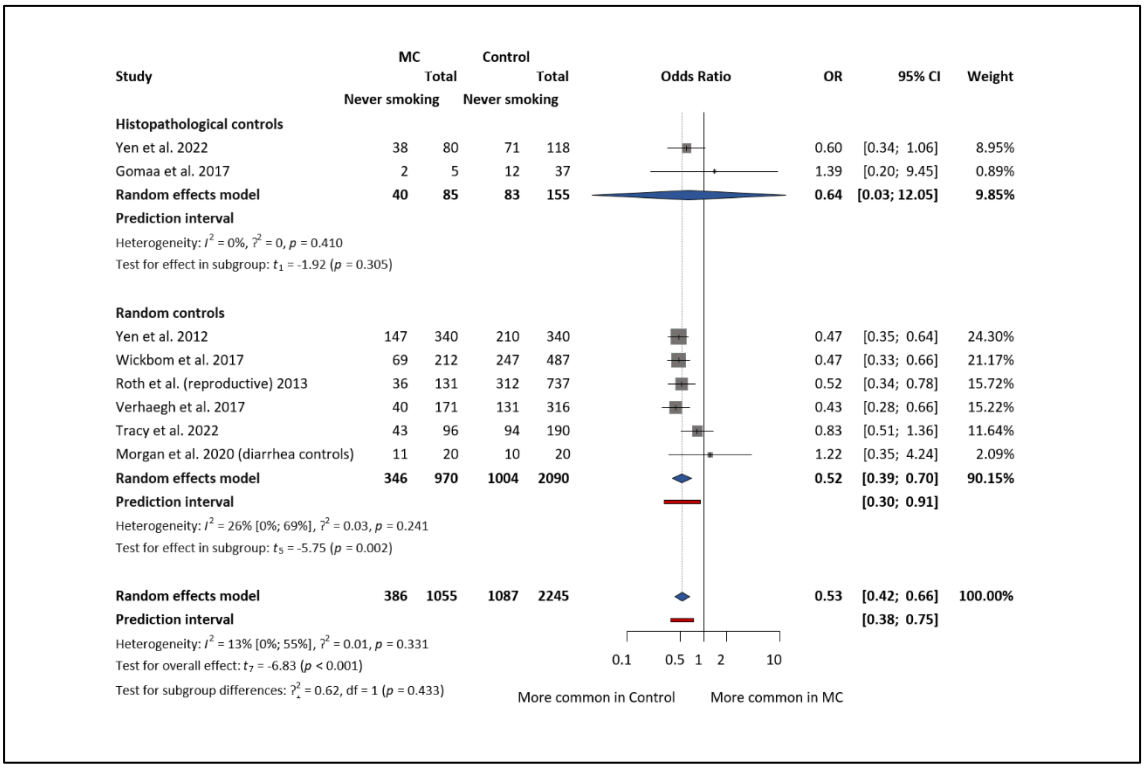

Figure 9. *Forest plot of subgroup analysis of MC patients compared to histological and random controls, showing that smoking abstinence is a protective factor with a 0.53-fold decrease in odds for having MC (87). MC=microscopic colitis. OR=odds ratio. CI=confidence interval.*

8.3.2.2.2.2 Past smoking

Past smoker MC patients compared to histological (8, 9, 55, 81) and random controls (11, 49, 59, 62, 67, 73, 76, 77, 79, 83) resulted in a 1.26- (CI: 0.67–2.39; I^2=58%, CI: 0–86) and a 1.11-fold increase in odds (CI: 0.93–1.31; I^2=28%, CI: 0–65) for having MC, however none of the analysis reached statistical significance (see **Figures 10-11**).

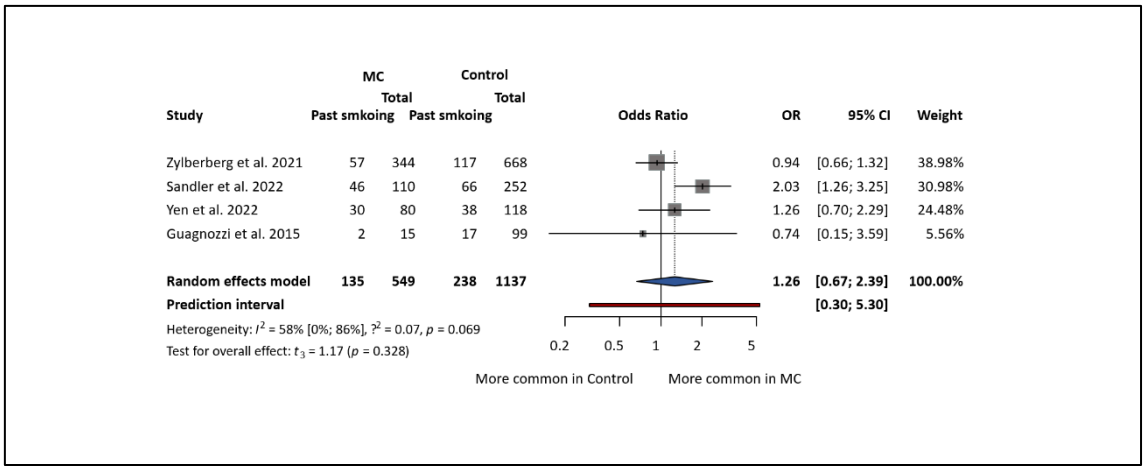

Figure 10. *Forest plot presenting the past smoker MC patients compared to histological controls, resulting in a 1.26-fold increase in odds for having MC (87). MC=microscopic colitis. OR=odds ratio. CI=confidence interval.*

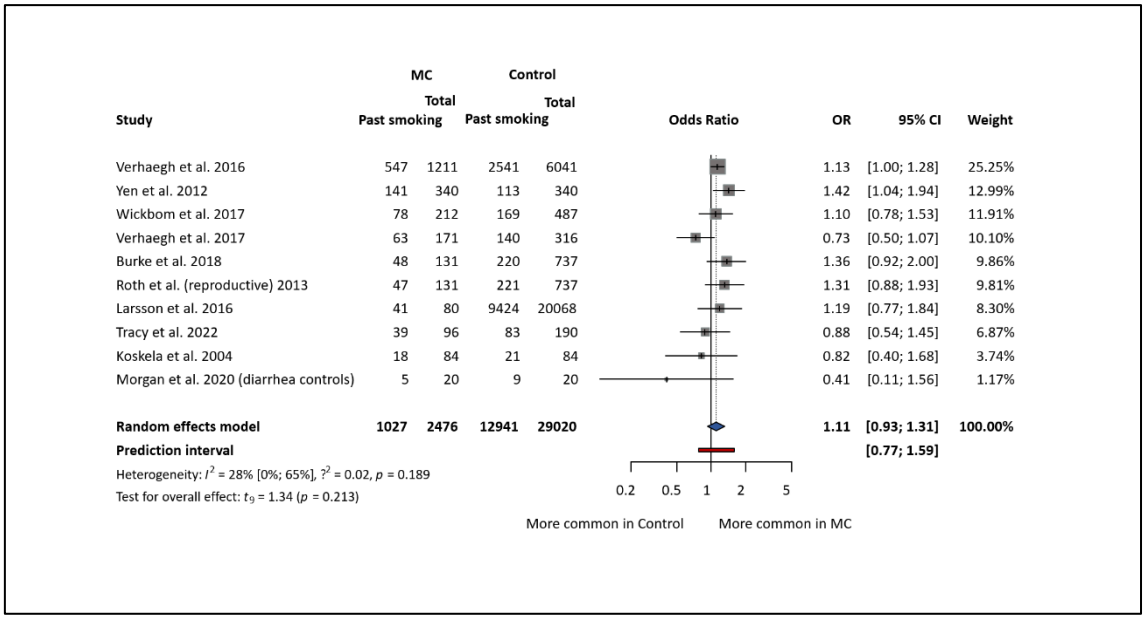

Figure 11. *Forest plot presenting the past smoker MC patients compared to random controls, resulting in a 1.11-fold increase in odds for having MC (87). MC=microscopic colitis. OR=odds ratio. CI=confidence interval.*

8.3.2.2.2.3 Current smoking

The comparison of current smoker MC patients with histological controls (9, 47, 52, 54, 55, 61, 65, 74, 81, 86) resulted in a 1.35-fold increase in odds (CI: 0.88–2.06; I^2=46%, CI: 0–74) for having MC, but did not reach statistical significance, while the comparison of them with random controls (11, 49, 51, 53, 56, 59, 62, 67, 73, 76, 77, 79, 83, 85)

showed more than doubled odds (OR=2.40, CI: 1.64–3.50; I^2=96%, CI: 94–97) for having MC (see **Figures 12-13**).

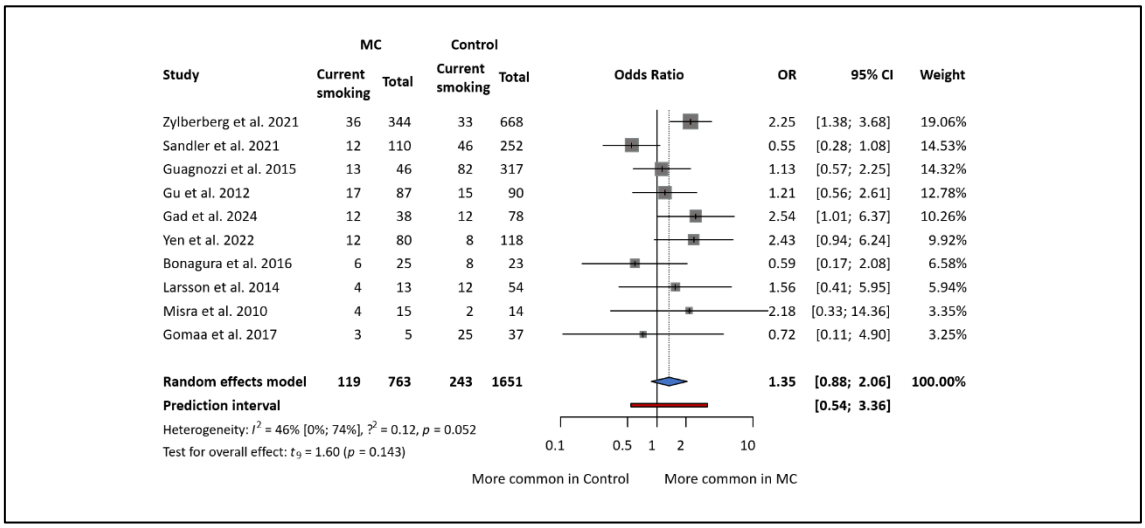

Figure 12. *Forest plot presents the current smoker MC patients compared to histological controls, resulting in a 1.35-fold increase in odds for having MC (87). MC=microscopic colitis. OR=odds ratio. CI=confidence interval.*

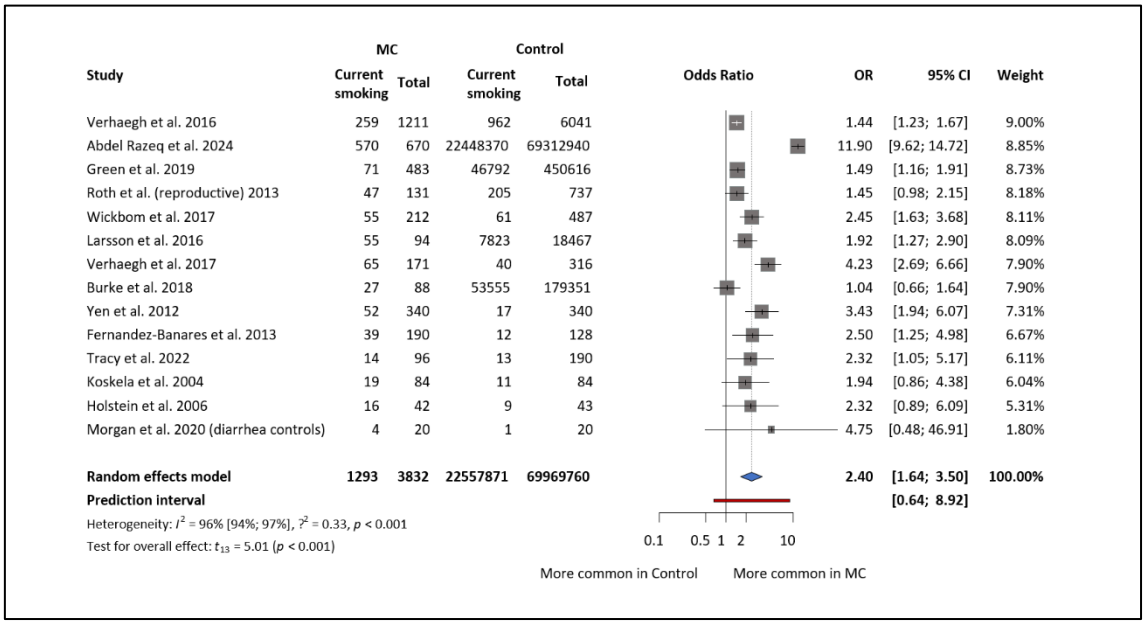

Figure 13. *Forest plot presents the current smoker MC patients compared to random controls, resulting in doubled odds for having MC (87). MC=microscopic colitis. OR=odds ratio. CI=confidence interval.*

8.3.2.3 Medical history risk factors

8.3.2.3.1 HRT

Both (8, 11, 73) HRT ever user and never user MC patients compared to mixed controls (OR=0.87, CI: 0.07–11.66; I^2=90%, CI: 73–96); (OR=1.15, CI: 0.09–14.35; I^2=90%, CI: 72–96) showed non-significant results as a risk factor for MC (see **Figure 14A-B**).

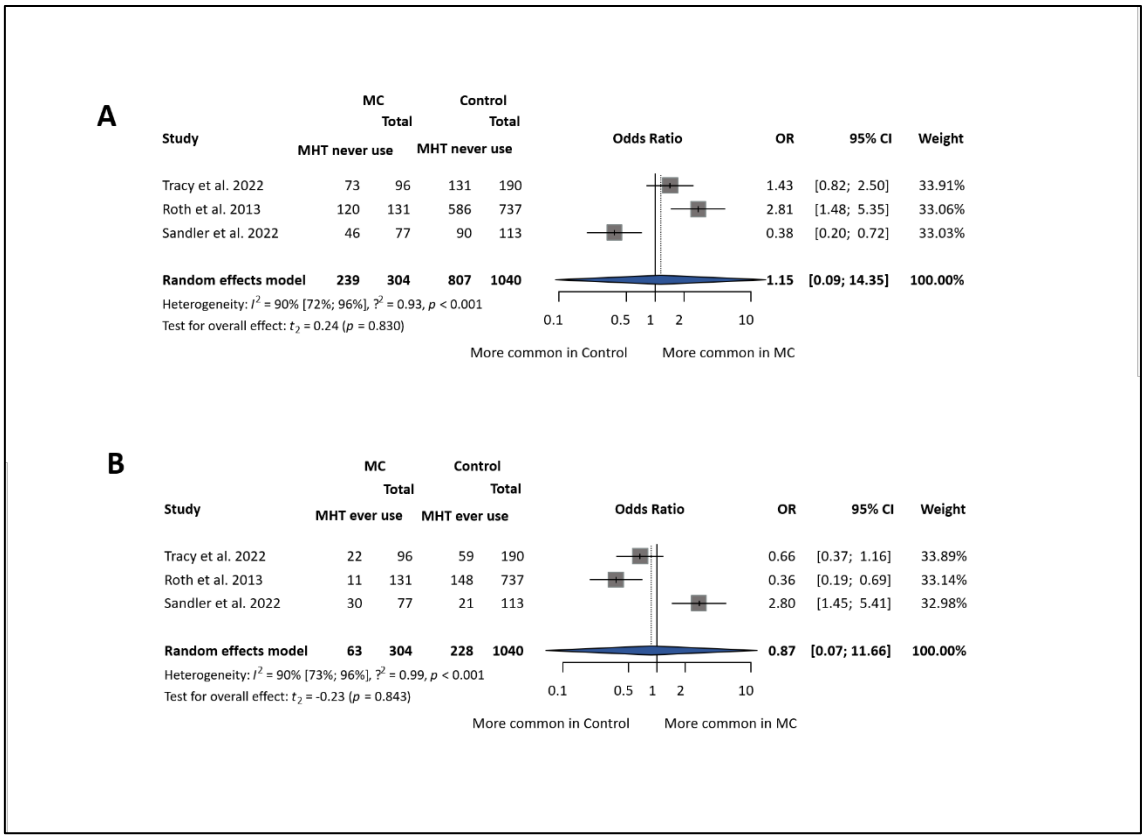

Figure 14*. Forest plot shows the non-significant results of HRT ever and never users, MC females (87). MC=microscopic colitis. MHT=menopausal hormone therapy OR=odds ratio. CI=confidence interval.*

8.3.2.3.2 Proton pump inhibitors (PPIs)

PPI use among MC patients compared to histological controls was reported in 13 studies (9, 46, 47, 52, 54, 55, 57, 64-66, 71, 74, 81). We found a 1.81-fold increase in odds (CI: 0.75–4.35; I^2=88%, CI: 81–92) for having MC if patients took PPIs; however, this was not statistically confirmed. Ten studies'(48, 51, 53, 56, 58, 64, 70, 71, 77, 80, 85) data contained MC cases on PPI therapy compared to random controls; the odds were four times higher (OR=4.31, CI: 1.66–11.20; I^2=97%, CI: 96–98) for having MC (see **Figures 15-16**).

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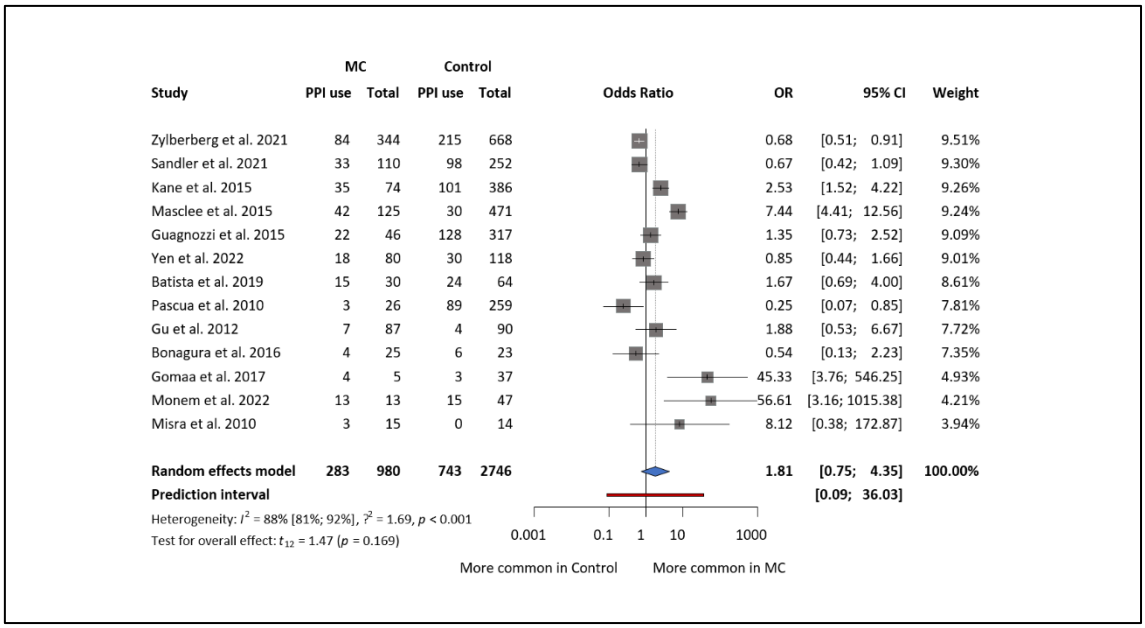

Figure 15. *Forest plot representing proton pump inhibitors investigation as a risk factor for having MC compared to histological controls, resulting in a 1.81-fold increase in odds for having MC (87). MC=microscopic colitis. PPI=proton pump inhibitor. OR=odds ratio. CI=confidence interval.*

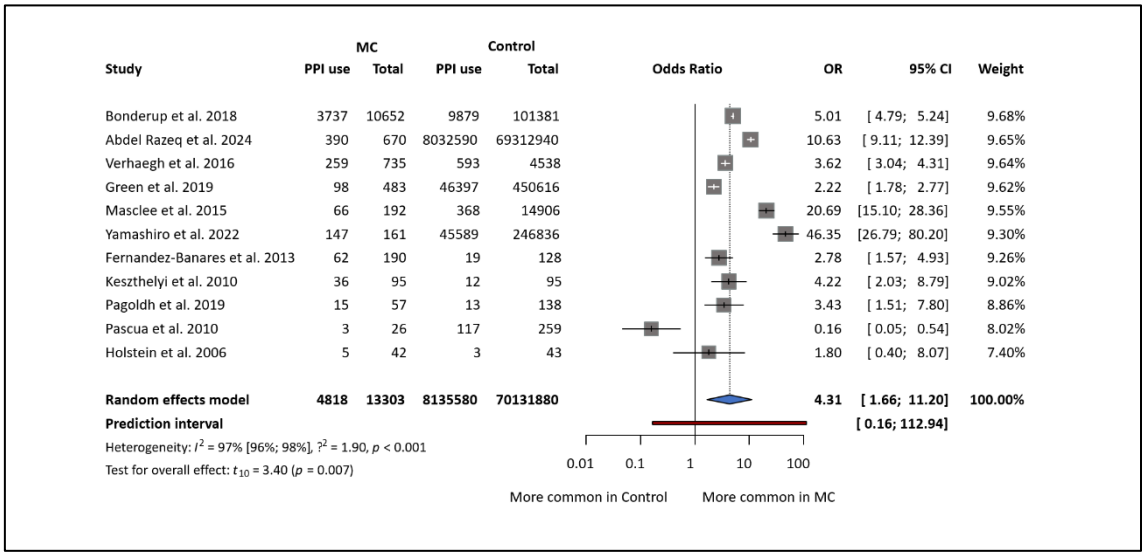

Figure 16. *Forest plot representing proton pump inhibitors investigation as a risk factor for having MC compared to random controls, resulting in four times higher odds for having MC (87). MC=microscopic colitis. PPI=proton pump inhibitor. OR=odds ratio. CI=confidence interval.*

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8.3.2.3.3 Nonsteroidal anti-inflammatory drugs (NSAIDs)

The number of NSAID user MC patients compared to histological and random controls were investigated in 14 (9, 46, 47, 52, 54, 55, 57, 61, 64-66, 71, 74, 83) and 13 studies (11, 48, 51, 53, 56, 58, 59, 64, 69, 70, 77, 80, 85). Both cases resulted in two-and-a-half-fold higher odds (OR=2.57, CI: 1.45–4.53; I^2=69%, CI: 46–82; OR=2.56, CI: 1.13–5.79; I^2=99%, CI: 98–99) for having MC (see **Figures 17-18**).

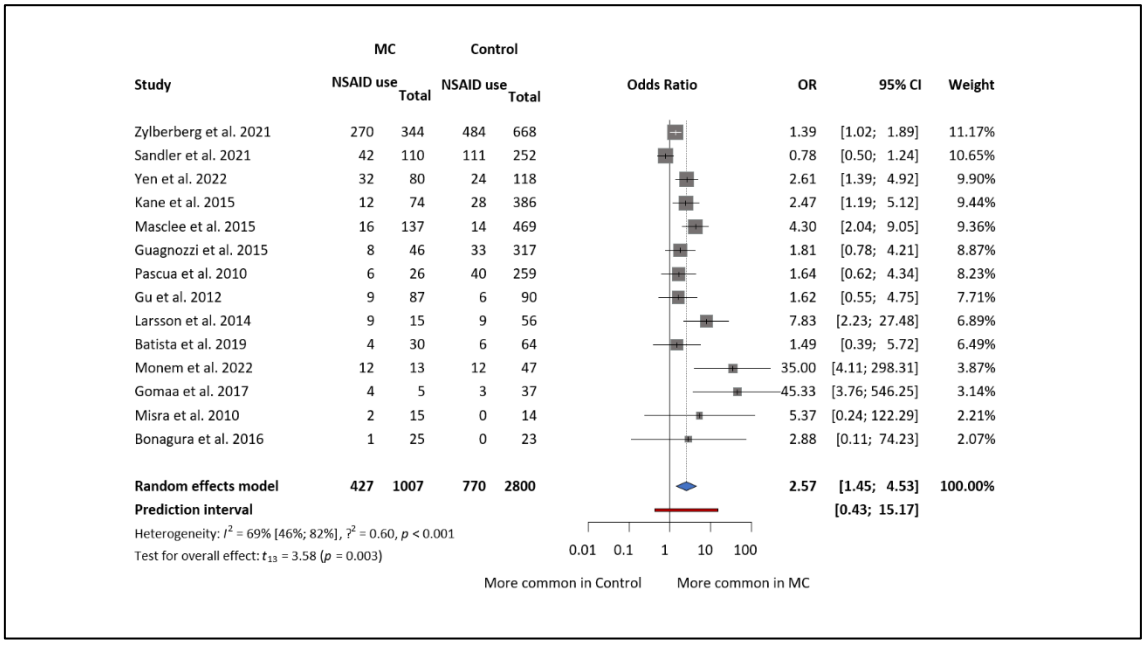

Figure 17*. Forest plot representing nonsteroidal anti-inflammatory drug investigation as a risk factor for having MC compared to histological controls, resulting in two-and-a-half times higher odds for having MC (87). MC=microscopic colitis. NSAID=nonsteroidal anti-inflammatory drug. OR=odds ratio. CI=confidence interval.*

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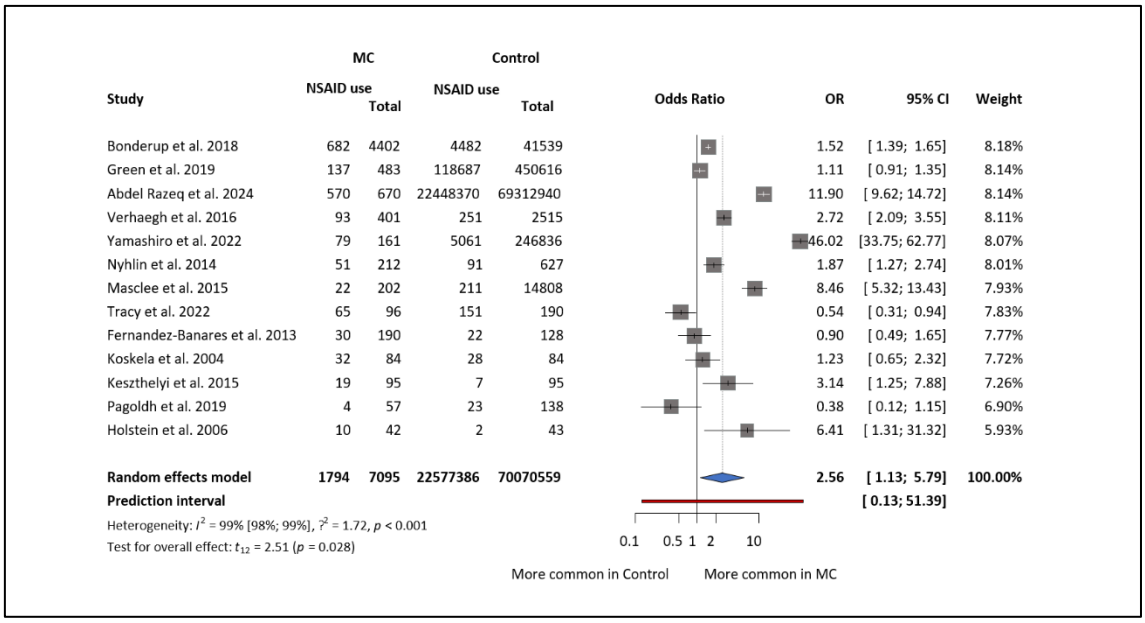

Figure 18. *Forest plot representing nonsteroidal anti-inflammatory drug investigation as a risk factor for having MC compared to random controls, resulting in two-and-a-half times higher odds for having MC (87). MC=microscopic colitis. NSAID=nonsteroidal anti-inflammatory drug. OR=odds ratio. CI=confidence interval.*

8.3.2.3.4 Selective serotonin reuptake inhibitors (SSRIs)

Eight and eight articles reported on SSRI use among MC cases in comparison to histological (9, 46, 55, 64, 66, 71, 74, 81) and random (51, 53, 64, 70, 71, 77, 84, 85) controls. Both analyses showed an increase in the odds for having MC if one is taking SSRIs (OR=1.56, CI: 0.62–3.89; I^2=45%, CI: 0–76; OR=3.30, CI: 1.17–9.31; I^2=98%, CI: 97–98), but only the latter comparison reached statistical significance (see **Figures 19-20**).

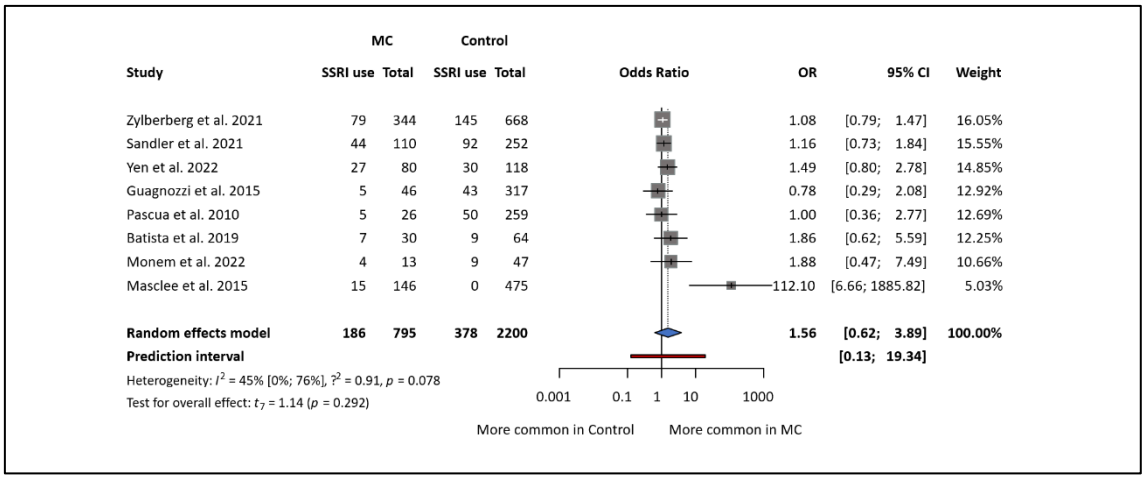

Figure 19. *Forest plot represents investigating the selective serotonin reuptake inhibitor as a risk factor for having MC compared to histological controls, with a 1.56-fold increase in odds for having MC (87). MC=microscopic colitis. SSRI=selective serotonin reuptake inhibitor. OR=odds ratio. CI=confidence interval.*

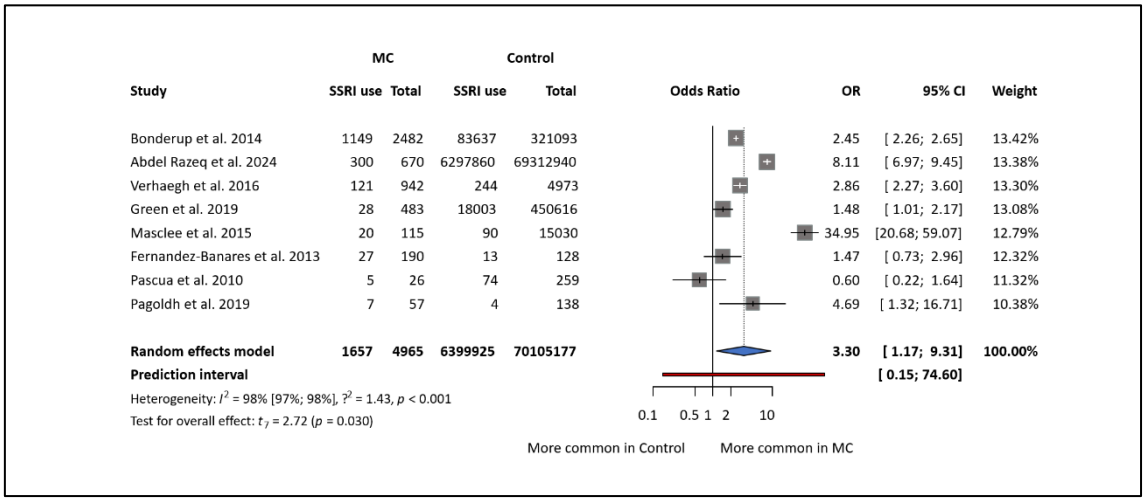

Figure 20. *Forest plot represents investigating the selective serotonin reuptake inhibitor as a risk factor for having MC compared to random controls, resulting in three times higher odds for having MC (87). MC=microscopic colitis. SSRI=selective serotonin reuptake inhibitor. OR=odds ratio. CI=confidence interval.*

8.3.2.3.5 Statins

Six and eight articles reported on statin use among MC cases in comparison to histological (9, 46, 64, 71, 74, 81) and random (51, 53, 56, 70, 71, 77, 80, 84) controls. Both analyses showed an increase in the odds for having MC if one is taking statins (OR=2.15, CI: 1.14–

4.05; I^2=75%, CI: 43–89; OR=1.84, CI: 0.58–5.80; I^2=98%, CI: 98–99), but only the first comparison reached statistical significance (see **Figures 21-22**).

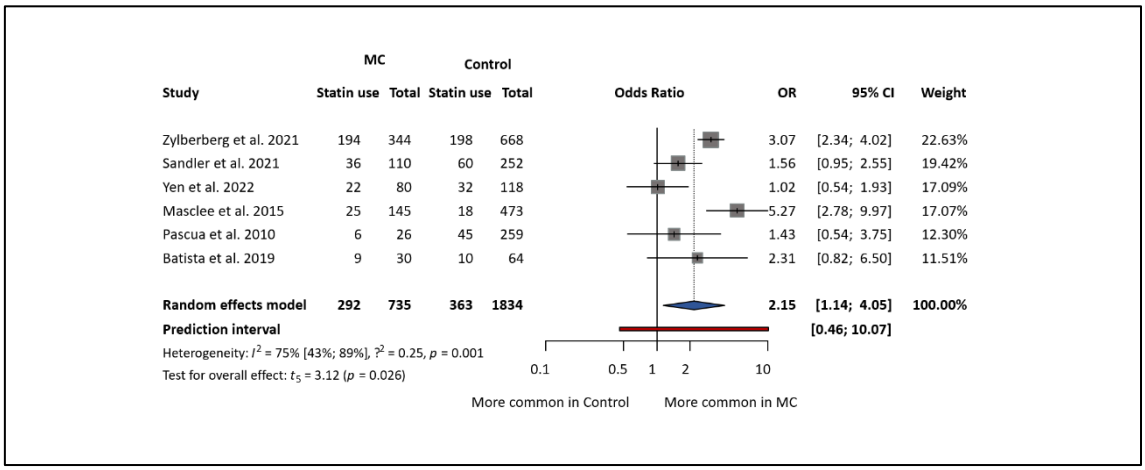

Figure 21. *Forest plot representing statin use investigation as a risk factor for having MC compared to histological controls, resulting in doubled odds for having MC (87). MC=microscopic colitis. OR=odds ratio. CI=confidence interval.*

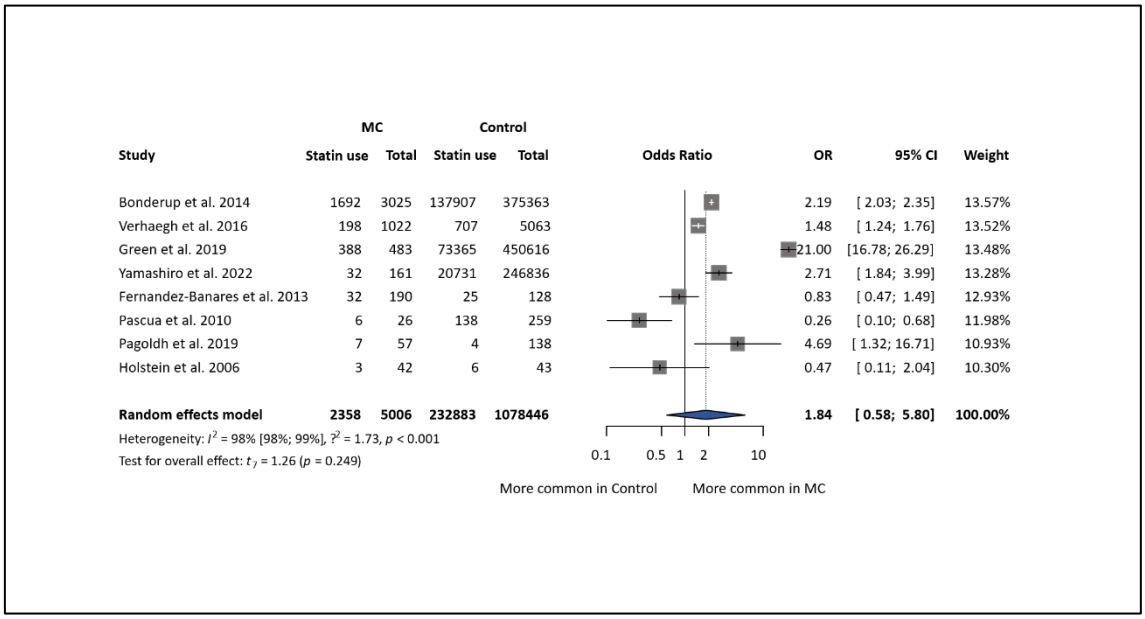

Figure 22. *Forest plot representing statin use investigation as a risk factor for having MC compared to random controls, resulting in a 1.84-fold increase in odds for having MC (87). MC=microscopic colitis. OR=odds ratio. CI=confidence interval.*

8.4 Bias and Quality Assessment

8.4.1 Study 1

First, regarding the PEO framework, all included studies (18, 42-44) lacked a follow-up period for the interested population, and in three cases, adjustment for confounding factors was missing. Therefore, all articles were deemed to have a high RoB. Second, considering the proportional analysis, the same studies (18, 42-44) were again at high risk in the overall appraisal due to the inappropriate patient sampling and small sample size. In addition, all our results ranked in the very low category for the certainty of evidence level, showing wide variance among the OR values, having low patient numbers, and reporting on BMD measurements as a surrogate outcome.

8.4.2 Study 2

Study participation was downgraded in approximately half of the cases, mainly due to the poor patient numbers. Study attrition was deemed a moderate risk of bias if the flow diagram was missing; however, patient dropout was reported in the text. Incomplete risk factor definitions led to the downgrading of the prognostic factor measurement domains, while the outcome measurement was mainly evaluated to have a low RoB. Studies' confounding factors were assessed based on multivariate and/or adjusted values reports. All statistical analysis and reporting domains were confirmed to have low risk of bias.

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9 DISCUSSION

9.1 Summary of findings, international comparisons (including all studies)

Even though MC incidence rates are rising in Western Europe (1), it may still be considered underdiagnosed due to its primarily histological diagnosis (1). The longer it takes to diagnose, the worse the patient's quality of life, as it is affected by MC's GI symptoms. A tremendous amount of data exists in the current literature on MC's risk factors; however, studies show conflicting results. Additionally, MC's relationship with LBD is not well described. Therefore, we investigated MC's risk factors, comparing the MC population with distinct controls: histologically verified and histologically non-verified, random controls. We hypothesized that comparing them with histologically verified controls would yield more precise results. Moreover, we examined whether MC is a risk factor for BMD loss, the proportion of LBD, and its two forms: osteopenia and osteoporosis in MC patients. We found that female sex, increased age, NSAID, and statin therapy are risk factors for MC when compared to histological controls. On the other hand, alcohol use, current smoking, PPI, and SSRI therapy increased the odds of MC only when MC cases were compared to random controls. Additionally, two times higher odds for LBD, around two-and-a-half times higher odds for osteopenia, while only a tendency was found in the case of osteoporosis in the presence of MC when MC cases were compared to sex-and age-matched controls. Lastly, the proportional analysis showed that 68% had LBD, 51% of them had osteopenia, and one in ten patients had osteoporosis among the MC population.

To put the identified risk factors in context, we need to consider MC etiopathogenesis, which is three-pillared: involving genetic, luminal, and immune factors (1). One could say that the unchangeable risk factors form the foundation, much like the soil of MC. On the one hand, the aging immune system contributes to reduced epithelial regeneration, making the colon more susceptible to inflammatory triggers and thereby increasing the risk of elderly individuals to MC. We found a mean age difference of 5.93 between MC patients and their histological controls. On the other hand, women show a higher prevalence of autoimmune diseases (88), hinting at possible shared immune pathways. Our results showed a 1.48 increase in the odds of having MC in women when MC cases

were compared to histological controls. While women's hormonal replacement therapy was suspected to increase MC's incidence (20), we could not confirm that.

The changeable risk factors can be divided into environmental and pharmacological triggers. First, beverage use was found to be associated with having MC, yet all available data come from the comparison of MC patients with random controls. As alcohol may contribute to changed microbial populations (68), an altered gut microbiome has also been linked with MC (4). This phenomenon can further be enhanced by smoking. While past and current smoking barely showed higher odds for having MC compared to histological controls, when compared to random controls, twofold higher odds for MC were found. These results contradict the findings of the previous meta-analysis on this topic (10). Plus, Jaruvongvanich et al. found a "significantly higher risk of microscopic colitis among current smokers compared with never-smokers" (89).

Second, regarding the pharmacological trigger components of this equation, NSAIDs increased the odds of MC by 2.5 times compared to histological controls, and from the included studies, only one publication (74) did not completely align with our findings. As NSAIDs alter the prostaglandin-mediated protective mechanisms and can directly damage epithelial cells, and disrupt the phospholipid barrier of the gut mucosa, leading to "leaky gut" by increasing intestinal permeability and enabling luminal antigens to interact with immune cells, which might lead to MC development. In addition, NSAIDs were linked with gut microbiome shifts (90), which favours the previously mentioned MC development theory.

Statins also stand out, doubling the odds of MC, possibly influencing the modulation of immune responses via T-cell activity and cytokine release. Though single studies' multivariate analysis did not strengthen these findings (9, 74). Therefore, it is assumed that different confounding factors or medications contribute to the statin-attributable risk. Previous meta-analyses did not find a significant relationship between statin use and MC (91, 92).

Our findings contradict previous studies (1, 13, 91, 92), as PPIs showed a tendency to increase the odds of MC; yet, this relationship was statistically significant only when compared to random controls. A 2022 study, lacking from earlier meta-analyses, showed no effect of PPIs on MC development (81). Furthermore, PPIs were also linked to changes

in gut microbiota (93). Moreover, Zylberberg et al. (9) emphasized that histological controls might be potential PPI users with GI symptoms, while non-histological controls are less likely to be on PPI therapy; therefore, chances are higher that they are asymptomatic, highlighting the difference in the comparison of MC patients to the distinct types of controls.

Although a recent meta-analysis of SSRI investigation resulted in a two-and-a-half times increased odds for MC (12), single articles (9, 74, 81) have similar findings to ours. In our investigation, SSRIs tended to increase the odds of MC compared to histological controls; however, it did not reach statistical significance. Among the MC population, some might struggle with anxiety and depression (22) and welfare impairment (21); thus, social limitations and GI symptoms might explain the high SSRI use in MC patients.

To summarize all the points mentioned above, all microbiome alterations may peak with the pathogenesis of MC in genetically predisposed individuals, contributing to the persistent inflammation that is maintained by the constant antigen exposure. Then MC manifests as chronic watery diarrhoea due to the impaired sodium/chloride absorption, mucosal inflammation, and altered gut motility. Because of that, it is a well-grounded question whether MC leads to secondary osteoporosis. These diseases also share common risk factors, like female sex (94), elderly age, alcohol consumption, and smoking (15). MC patients may also choose to stay physically inactive to reduce gut motility, and/or keep a narrow diet – resulting in dietary calcium deficiency – to avoid unpleasant GI symptoms, which are also risk factors for osteoporosis. Additionally, many GI diseases are accompanied by secondary osteoporosis (95-97); for example, coeliac disease which has been associated with MC (98), in which the malabsorption of calcium and vitamin D worsens even more the BMD loss. Besides, one study showed that half of the MC population, due to their active or chronic relapses, struggle with even more frequent diarrhea, deteriorating the LBD (99). Withal, long-term glucocorticoid use is also a contributing risk factor for osteoporosis, via its stimulatory osteoclast activity, and osteoblast and osteocyte apoptosis, elevating the calcium clearance through the kidneys and decreasing the intestinal calcium absorption (100, 101). However, MC's gold standard therapy is budesonide (1), a less detrimental corticosteroid with low systemic bioavailability due to its high first-pass metabolism in the liver. Since a study showed double MC patient numbers with osteoporosis in the lack of budesonide treatment

compared with MC cases on budesonide maintenance therapy, we believe that our results are close to reality, that MC is a risk factor for LBD. Yet, no specific data can be given about the chronological conclusion of their relationship.

To our current knowledge, we provided comprehensive data as the first ones (45) on the MC and LBD association. The four included observational studies reported data on MC cases with LBD compared to age-and sex-matched controls. Our results showed moderate heterogeneity in the doubled odds of LBD in the presence of MC, likely due to the presence of the cross-sectional study (43) that contained the smallest number of patients, who were also the youngest. Our proportional results showed considerable heterogeneity, due to the nature of the data, and even in a small number of patients, little variance is also observed (102). Our results reached a very low certainty level of evidence, using surrogate outcome – BMD measurement. Even though it is accepted as a patient-important outcome, the hardest outcome would have been identifying the number of MC patients with osteoporotic fractures. Only one study elaborated on these numbers, reporting them in the light of budesonide therapy; they found a dose-dependent increase in spinal-fracture risk (103).

9.2 Strengths

The main strength of our first study is that all included articles used DXA to measure BMD (15), while the main strength of the second study lies in distinguishing between histologically examined and histologically non-examined, random controls, acknowledging the primary histopathological diagnosis of MC. Lastly, both studies were conducted following a robust methodology.

9.3 Limitations

The greatest limitation of the first study is the low number of included studies with small patient numbers and the inclusion of a conference abstract, while the greatest limitation of the second study is the huge variance among the definitions of risk factors.

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10 CONCLUSIONS

10.1 Study 1

In conclusion, our findings suggest that MC is a risk factor for LBD, doubling the odds for it and its mild form, osteopenia. In proportion, LBD was in approximately two-thirds, osteopenia in more than half of the MC patients, and one in 10 MC patients had osteoporosis.

10.2 Study 2

Our data confirm that female sex, increased age, NSAID, and statin therapy are risk factors for MC when compared to histological controls. On the other hand, alcohol use, current smoking, PPI, and SSRI therapy increased the odds for MC only when MC cases were compared to random controls.

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11 IMPLEMENTATIONS FOR PRACTICE

11.1 Study 1

MC is an underdiagnosed disease with an increasing incidence. As it might take years to diagnose, the extent of BMD loss can increase further. The mild form of LBD may escalate to osteoporosis, which can peak in osteoporotic fractures. There is a need to prevent this; therefore, we suggest screening of MC populations for BMD at the moment of diagnosis.

MC patients should be advised, especially those with cumulative risk, to implement lifestyle and dietary changes and encourage calcium and vitamin D supplementation to slow down BMD loss. Additionally, the combined training of impact exercise with resistance training is the best fit for pre- and postmenopausal women to maintain their BMD (104).

11.2 Study 2

Given the steadily rising incidence of MC, we aim to raise awareness of its risk factors among gastroenterologists, general practitioners, endoscopists, and pathologists. Accurate diagnosis requires close interdisciplinary collaboration, supported by high-quality colonoscopy and histological assessment. Strengthening these processes could improve diagnostic efficiency, reducing unnecessary consultations, endoscopic procedures, and associated healthcare costs. MC should be considered especially in elderly women with unexplained chronic watery diarrhea who use NSAIDs and/or statins. While statin discontinuation is not warranted, considering other confounding factors or medications' contribution to the statin-attributable risk, NSAID use should be reassessed, and unsupervised NSAID intake should be discouraged in this at-risk group.

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12 IMPLEMENTATION FOR RESEARCH

12.1 Study 1

12.1.1 Methodology issues

There is a lack of long-term, high-quality data on the timeline occurrence of LBD in patients with MC.

12.1.2 Study design

Further prospective observational studies with extended follow-up are needed to determine prevalence indicators (102). Incidence studies should also be conducted to clarify the bone density decrease and fracture risk in MC.

12.1.3 New aspects

Establishing international and national registries that include bone mineral data could provide a valuable resource for future research and improve disease monitoring.

12.2 Study 2

12.2.1 Methodology issues

Current evidence is insufficient due to a lack of prospective data and comprehensive long-term follow-up.

12.2.2 Study design

Future studies should focus on prospective data collection through international and national registries, with an assessment of negative lifestyle factors, smoking history (like pack-years), and medication use (dose, duration, frequency).

12.2.3 New aspects

Deep mapping of MC's risk factors and microbiome interactions could provide novel insights into disease pathogenesis and prevention strategies.

13 IMPLEMENTATION FOR POLICYMAKERS

13.1 Study 1

Given the strong association between MC and low LBD, there is a clear need for health policy adjustments to ensure early detection and prevention of bone-related complications in this patient population. Policymakers should consider incorporating BMD screening into national and international clinical guidelines for MC management, ideally recommending assessment at the time of diagnosis.

Additionally, public health policies should promote physician awareness campaigns to highlight the long-term risks of undiagnosed and untreated MC, including the progression from osteopenia to osteoporosis and the associated fracture risk. Integrating lifestyle and dietary counseling, along with vitamin D and calcium supplementation, into standard care pathways could help mitigate these risks. Policymakers may also support the development of cost-effective, community-based prevention programs focused on physical activity, particularly resistance and impact training for at-risk groups.

13.2 Study 2

MC is a growing public health concern, with a steadily increasing incidence and a clear association with several lifestyle and medication-related risk factors. Policymakers must recognize MC as a significant contributor to chronic GI symptoms, particularly in elderly populations.

To improve early diagnosis and reduce long-term healthcare burdens, we recommend the integration of MC awareness into national screening and diagnostic protocols for the unknown origin of chronic watery diarrhea, especially in elderly women and patients using NSAIDs and/or statins. Diagnostic guidelines should emphasize the importance of high-quality colonoscopy with histological confirmation, supported by specialized training for gastroenterologists, general practitioners, endoscopists, and pathologists.

Educational materials and clinical training curricula should be updated about MC and its risk factors. Further, national healthcare systems should consider reviewing and regulating NSAID prescribing practices in patients with unexplained chronic diarrhea to minimize unnecessary drug exposure and its potential complications.

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Finally, investment should be directed toward establishing centralized MC registries and supporting interdisciplinary clinical networks, which will facilitate consistent care pathways and reduce inefficiencies in diagnosis and treatment.

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14 FUTURE PERSPECTIVES

As I plan to work as a rheumatology resident, I am committed to enhancing the care of MC patients by integrating both GI and extraintestinal considerations into routine clinical practice. The priority will be the early detection and monitoring of LBD through regular screening, particularly in older women and patients with chronic disease, to prevent progression to osteoporosis and reduce fracture risk. I also intend to systematically assess clinically relevant MC risk factors, such as NSAID and statin therapy, smoking history and alcohol consumption, and advanced age, female sex, to identify vulnerable patients sooner, establish MC's diagnosis, and optimize their management. Strengthening interdisciplinary collaboration with gastroenterologists, dietitians, and primary care physicians will be essential to ensure a holistic approach, especially for patients with overlapping autoimmune or metabolic conditions. Alongside clinical management, I plan to develop patient-focused education programs that raise awareness of MC's risk profile, encourage proactive symptom monitoring, promote safe medication use, and highlight strategies for preserving bone health; incorporating lifestyle interventions, such as weight-bearing exercise, adequate calcium and vitamin D intake, and smoking cessation. Ultimately, I aim to contribute to national and international MC registries, generating robust, high-quality data on disease course, treatment outcomes, and long-term complications, driving evidence-based improvements in patient care.

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16.1 Publications related to the thesis

1. **Rancz, Anett**; Teutsch, Brigitta; Obeidat, Mahmoud; Walter, Anna; Weidinger, Gergő; Erőss, Bálint; Hegyi, Péter; Mihály, Emese

Risk Factors for Microscopic Colitis: A Systematic Review and Meta-Analysis

JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY (2025)

Publication: 36257051 | Journal Article (Survey paper) | Scientific

Journal subject: Scopus - Gastroenterology Rank: Q1

Journal subject: Scopus - Hepatology Rank: Q2

IF: 3,4

2. **Rancz, Anett**; Teutsch, Brigitta; Engh, Marie Anne; Veres, Daniel Sandor; Foldvari-Nagy, Laszlo; Eross, Balint; Hosszufalusi, Nora; Juhasz, Mark Felix; Hegyi, Peter; Mihaly, Emese

Microscopic colitis is a risk factor for low bone density: a systematic review and meta-analysis

THERAPEUTIC ADVANCES IN GASTROENTEROLOGY 16 pp. 1-13., 13 p. (2023)

Publication:34039131 | Journal Article (Survey paper) | Scientific

Journal subject: Scopus - Gastroenterology Rank: Q1

IF: 3,9

16.2 Publications not related to the thesis

1. Bednárik, Dániel Steve; Földvári-Nagy, Kincső Csepke; Simon, Viktor; **Rancz, Anett**; Gede, Noémi; Veres, Dániel Sándor; Paraskevopoulos, Panagiotis; Schnabel, Tamás; Erőss, Bálint; Hegyi, Péter et al.

Comparative effectiveness of different therapies for Clostridioides difficile infection in adults: a systematic review and network meta-analysis of randomized controlled trials

LANCET REGIONAL HEALTH - EUROPE 49 Paper: 101151, 14 p. (2025)

Publication: 35663269 | Journal Article (Survey paper) | Scientific

Journal subject: Scopus - Health Policy Rank: D1

Journal subject: Scopus - Internal Medicine Rank: D1

Journal subject: Scopus - Oncology Rank: D1

Journal subject: Scopus - Public Health, Environmental and Occupational Health Rank: D1

IF: 13

2. Gellért, Bálint; **Rancz, Anett**; Hoferica, Jakub; Teutsch, Brigitta; Sipos, Zoltán; Veres, Dániel S; Hegyi, Péter Jenő; Ábrahám, Szabolcs; Hegyi, Péter; Hritz, István

Understanding the Role of Different ERCP Techniques in Post-Roux-en-Y Gastric Bypass Patients: a Systematic Review and Meta-analysis

OBESITY SURGERY 35: 1 pp. 285-304., 20 p. (2025)

Publication: 35647823 | Journal Article (Survey paper) | Scientific

Journal subject: Scopus - Surgery Rank: D1

Journal subject: Scopus - Endocrinology, Diabetes and Metabolism Rank: Q1

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To cut or not to cut? Extended mesenteric excision during intestinal resection does not impact the postoperative recurrence nor the postoperative complications in Crohn’s disease: a systematic review and meta-analysis

TECHNIQUES IN COLOPROCTOLOGY 29: 1 Paper: 79, 15 p. (2025)

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Publication: 35181225 | Journal Article (Survey paper) | Scientific

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One in four patients with gastrointestinal bleeding develops shock or hemodynamic instability: A systematic review and meta-analysis

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Journal subject: Scopus - Gastroenterology Rank: Q1

Journal subject: Scopus - Medicine (miscellaneous) Rank: Q1

IF: 4,3

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Minimally invasive techniques versus opioids in patients with unresectable pancreatic cancer: a systematic review and meta-analysis of randomised controlled trials

TRANSLATIONAL GASTROENTEROLOGY AND HEPATOLOGY 10 PAPER: 45, 19 P. (2025)

Journal subject: Scopus - Gastroenterology Rank: Q2

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