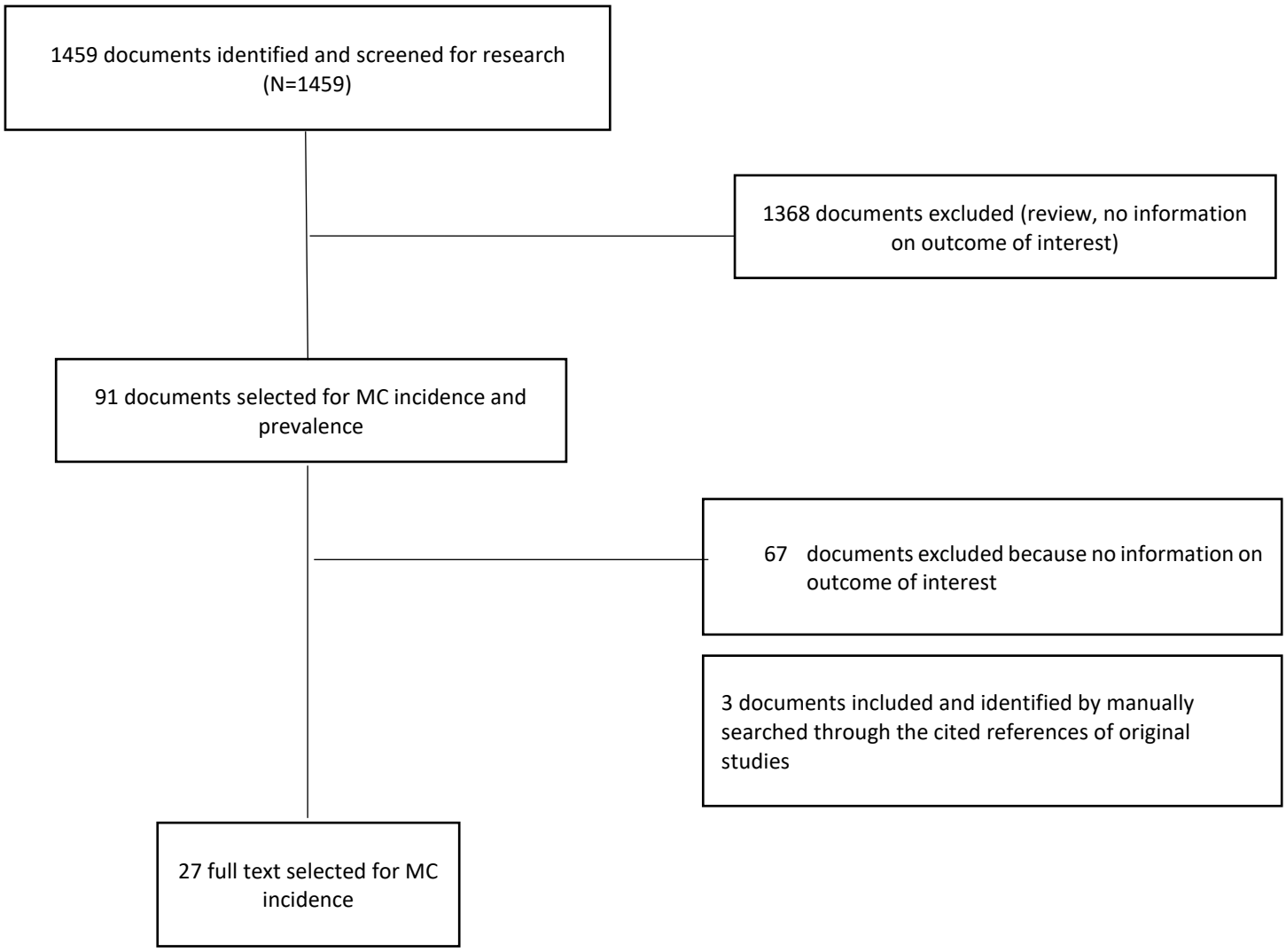
Supplementary material – Appendix A

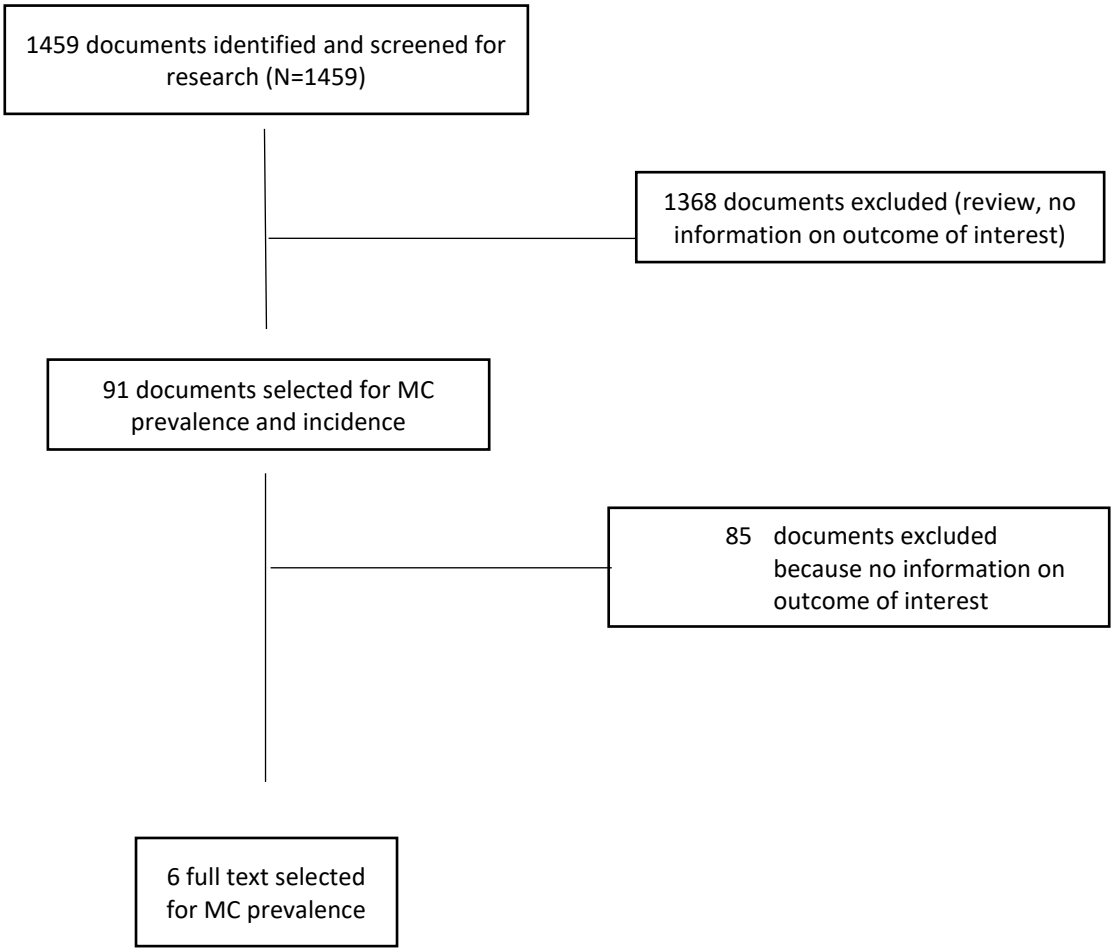
Literature search and flow chart for the process of identifying studies included in and excluded from the systematic review (PRISMA)

Workgroup 1:
PICO 01: What is the incidence of MC?
Combined search in Pubmed and EMBASE data base (using MeSH Terms and correspondent Emtree terms): ((((chronic diarrhea) OR prevalence) OR incidence) OR epidemiology[MeSH Terms])) AND ((((microscopic colitis[MeSH Terms]) OR lymphocytic colitis) OR collagenous colitis) OR incomplete microscopic colitis). Filter activated: Humans.

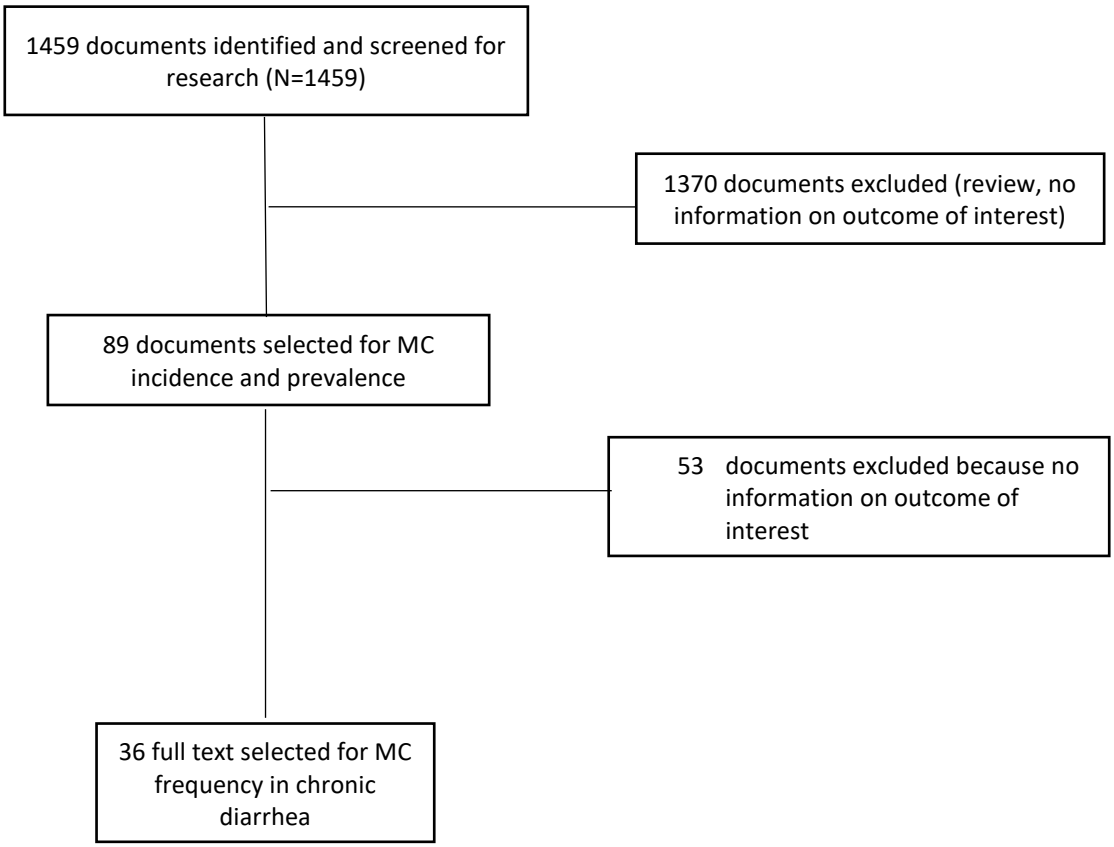


PICO 02: What is the prevalence of MC?

Combined search in Pubmed and EMBASE data base (using MeSH Terms and correspondent Emtree terms): ((((chronic diarrhea) OR prevalence) OR incidence) OR epidemiology[MeSH Terms])) AND ((((microscopic colitis[MeSH Terms]) OR lymphocytic colitis) OR collagenous colitis) OR incomplete microscopic colitis). Filter activated: Humans

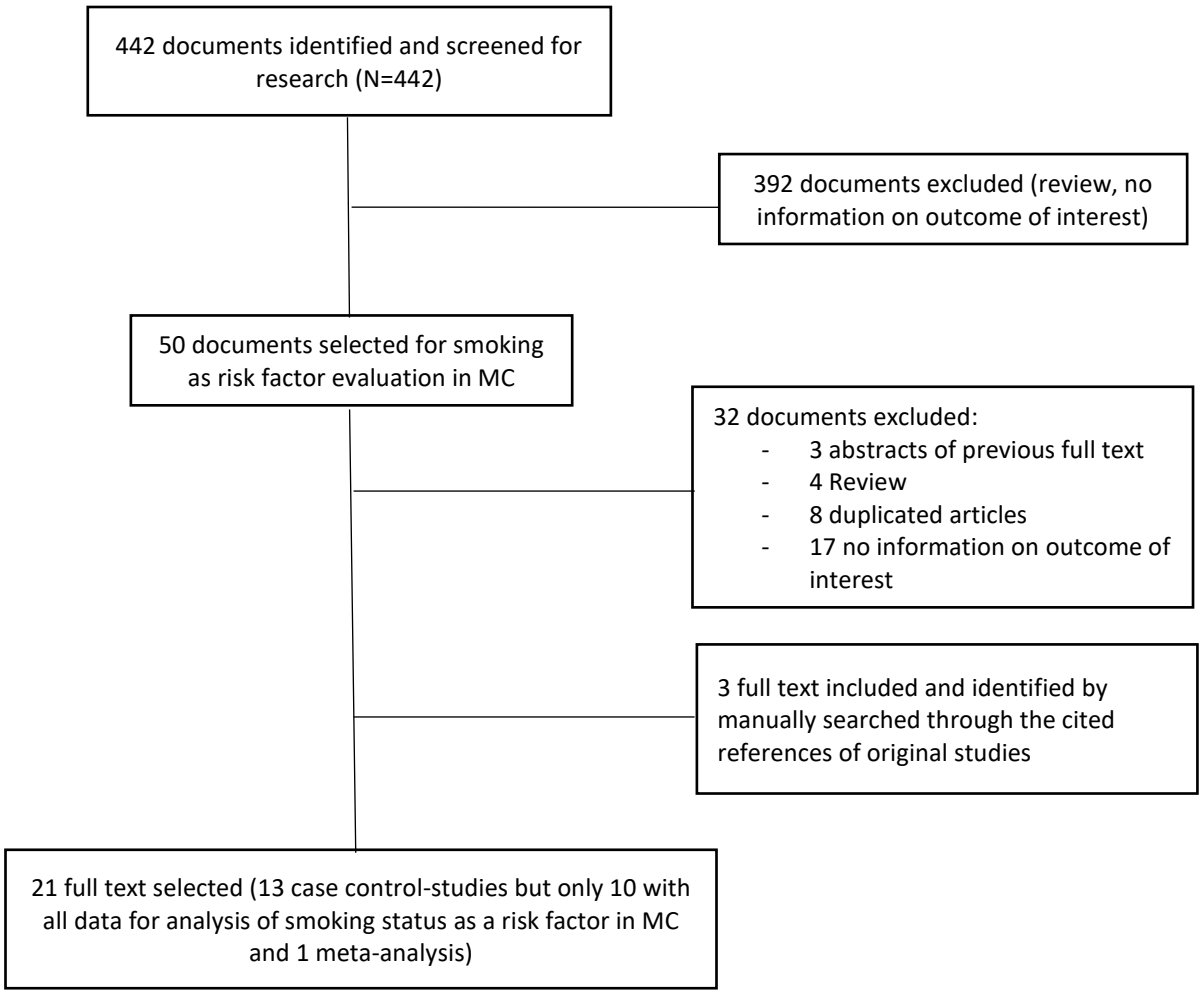


PICO 03: How frequent is MC in patients with chronic diarrhea and normal or near normal colonoscopy?
Combined search in Pubmed and Embase data base (using MeSH Terms and correspondent Emtree terms): ((((chronic diarrhea) OR prevalence) OR incidence) OR epidemiology[MeSH Terms])) AND ((((microscopic colitis[MeSH Terms]) OR lymphocytic colitis) OR collagenous colitis) OR incomplete microscopic colitis). Filter activated: Humans.



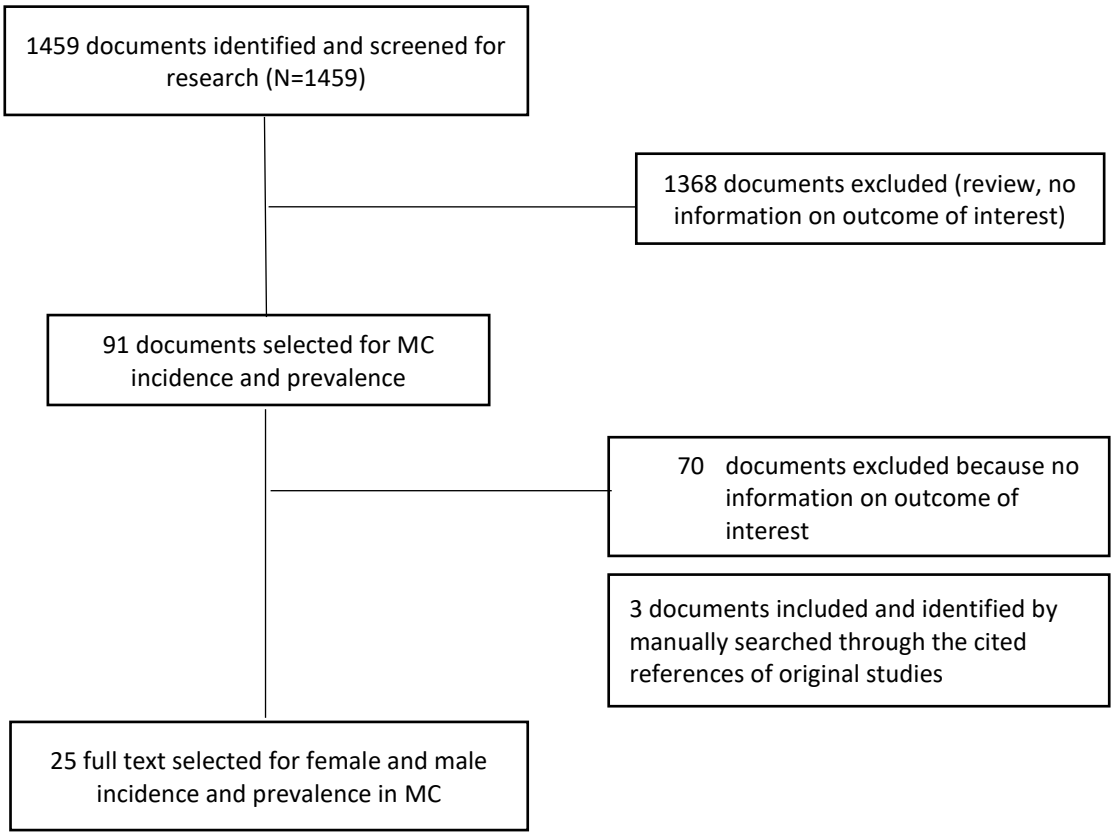
PICO 04: Is smoking a risk factors for MC?

Combined search in Pubmed and EMBASE data base (using MeSH Terms and correspondent Emtree terms): (((smoking) OR tobacco) OR risk factors[MeSH Terms]))) AND ((((microscopic colitis[MeSH Terms]) OR lymphocytic colitis) OR collagenous colitis) OR incomplete microscopic colitis). Filter activated: Humans.



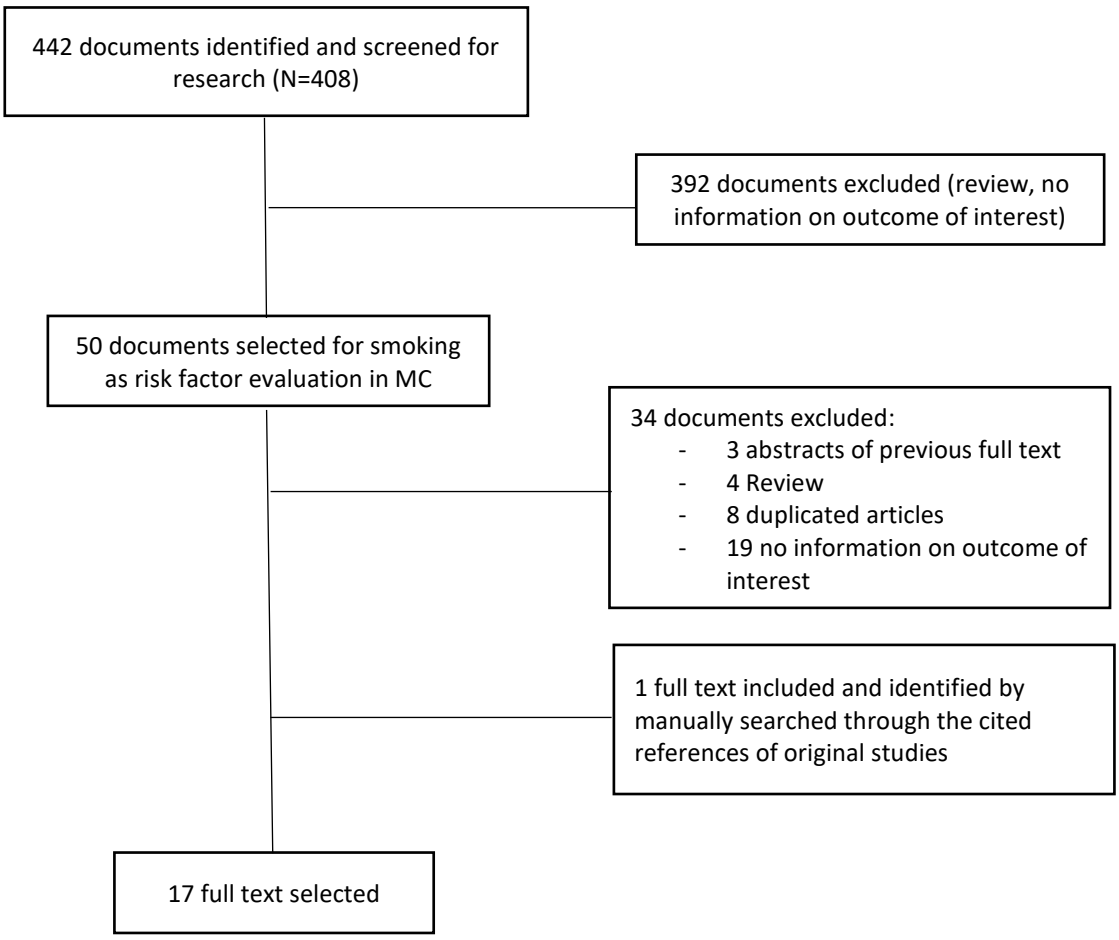
PICO 05: Is female gender a risk factor for MC?

Combined search in Pubmed and EMBASE data base (using MeSH Terms and correspondent Emtree terms): ((((chronic diarrhea) OR prevalence) OR incidence) OR epidemiology[MeSH Terms])) AND ((((microscopic colitis[MeSH Terms]) OR lymphocytic colitis) OR collagenous colitis) OR incomplete microscopic colitis). Filter activated: Humans.



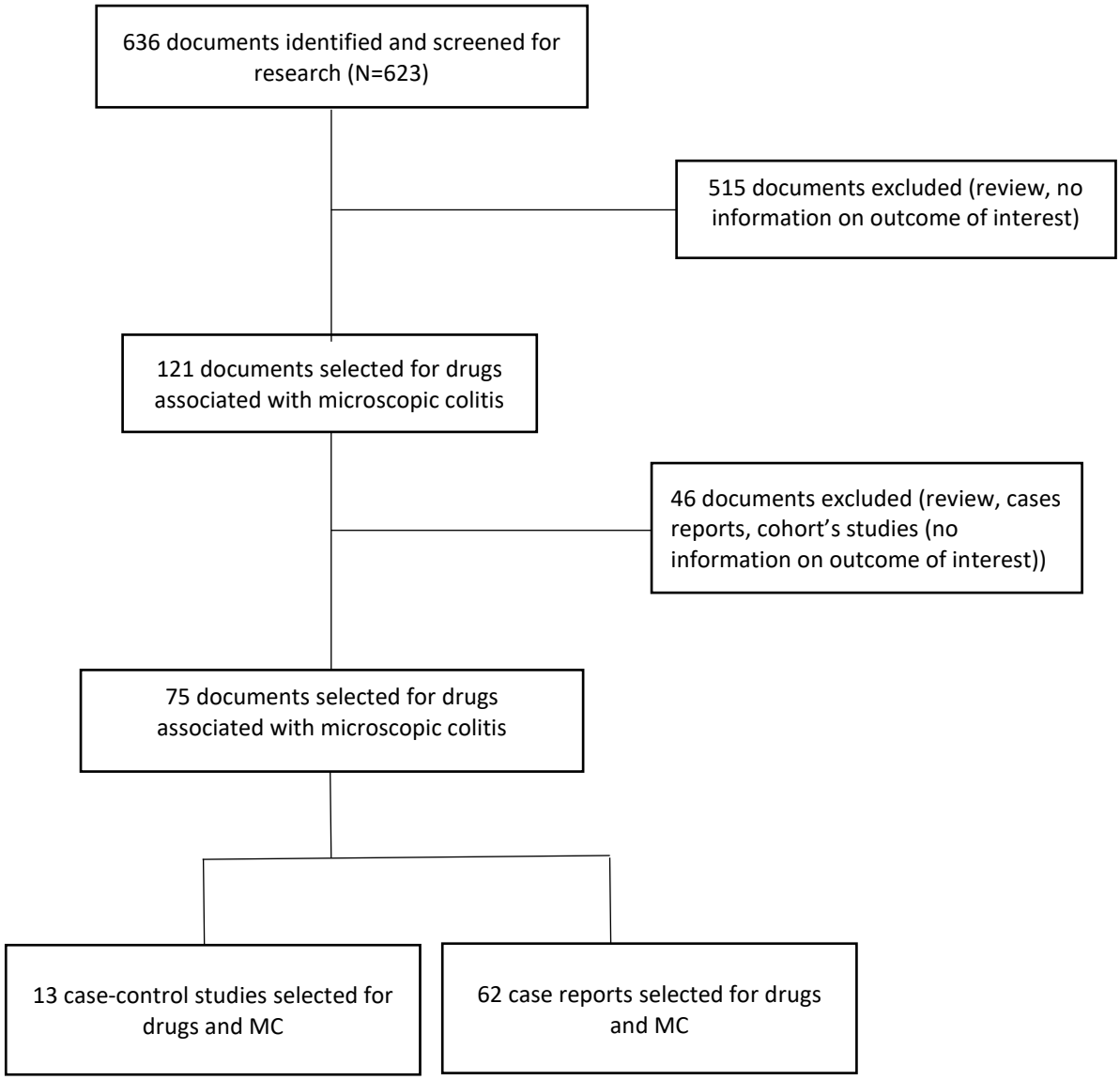
PICO 06: In MC patients does smoking cessation influence the disease course?

Combined search in Pubmed and EMBASE data base (using MeSH Terms and correspondent Emtree terms): (((smoking) OR tobacco) OR risk factors[MeSH Terms]))) AND ((((microscopic colitis[MeSH Terms]) OR lymphocytic colitis) OR collagenous colitis) OR incomplete microscopic colitis). Filter activated: Humans.



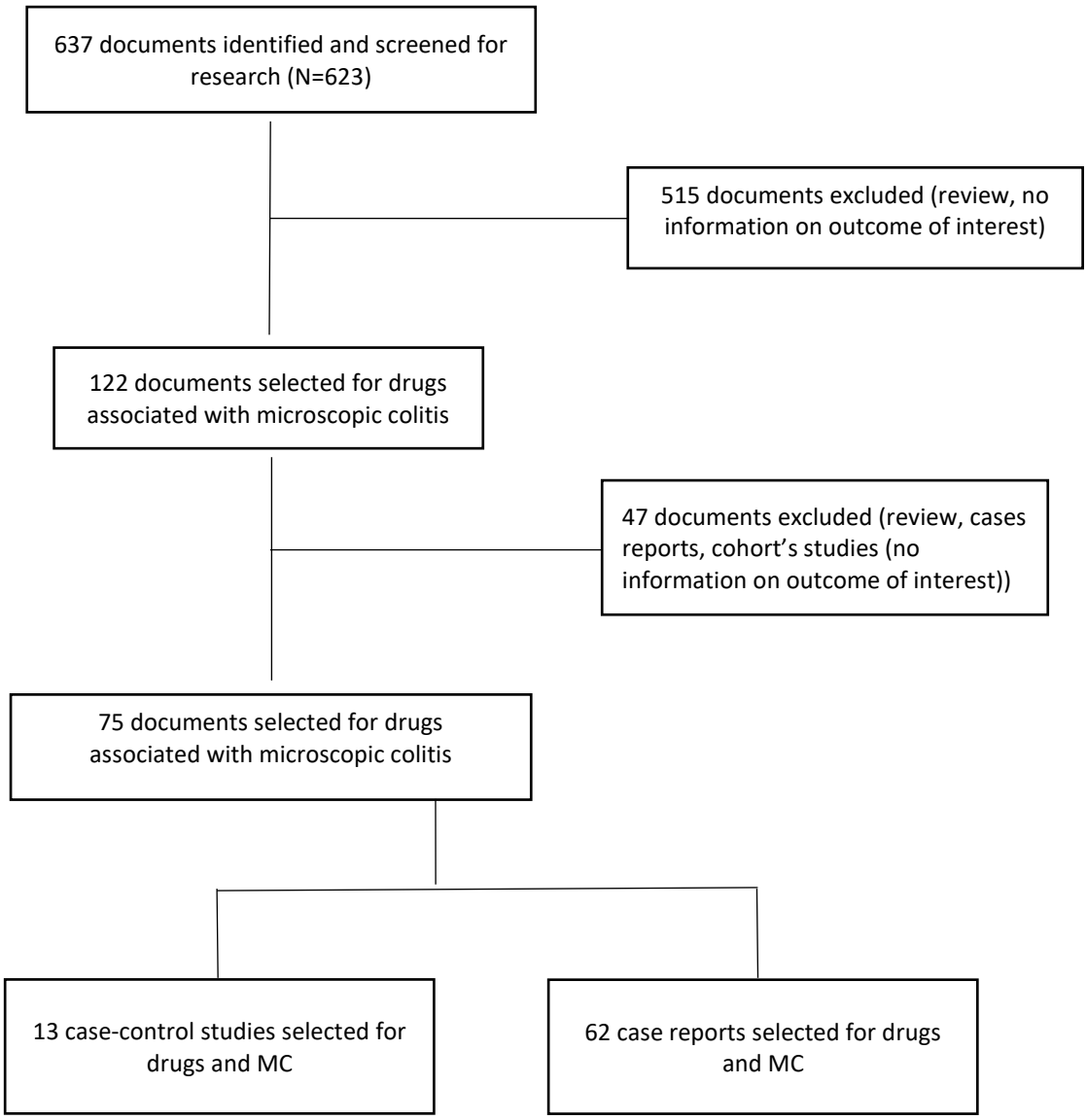
PICO 07: Is drug use associated with a significant increased risk of MC?

Combined search in Pubmed and EMBASE data base (using MeSH Terms and correspondent Emtree terms): ((((chronic diarrhea) OR prevalence) OR incidence) OR epidemiology[MeSH Terms])) AND ((((microscopic colitis[MeSH Terms]) OR lymphocytic colitis) OR collagenous colitis) OR incomplete microscopic colitis). Filter activated: Humans.



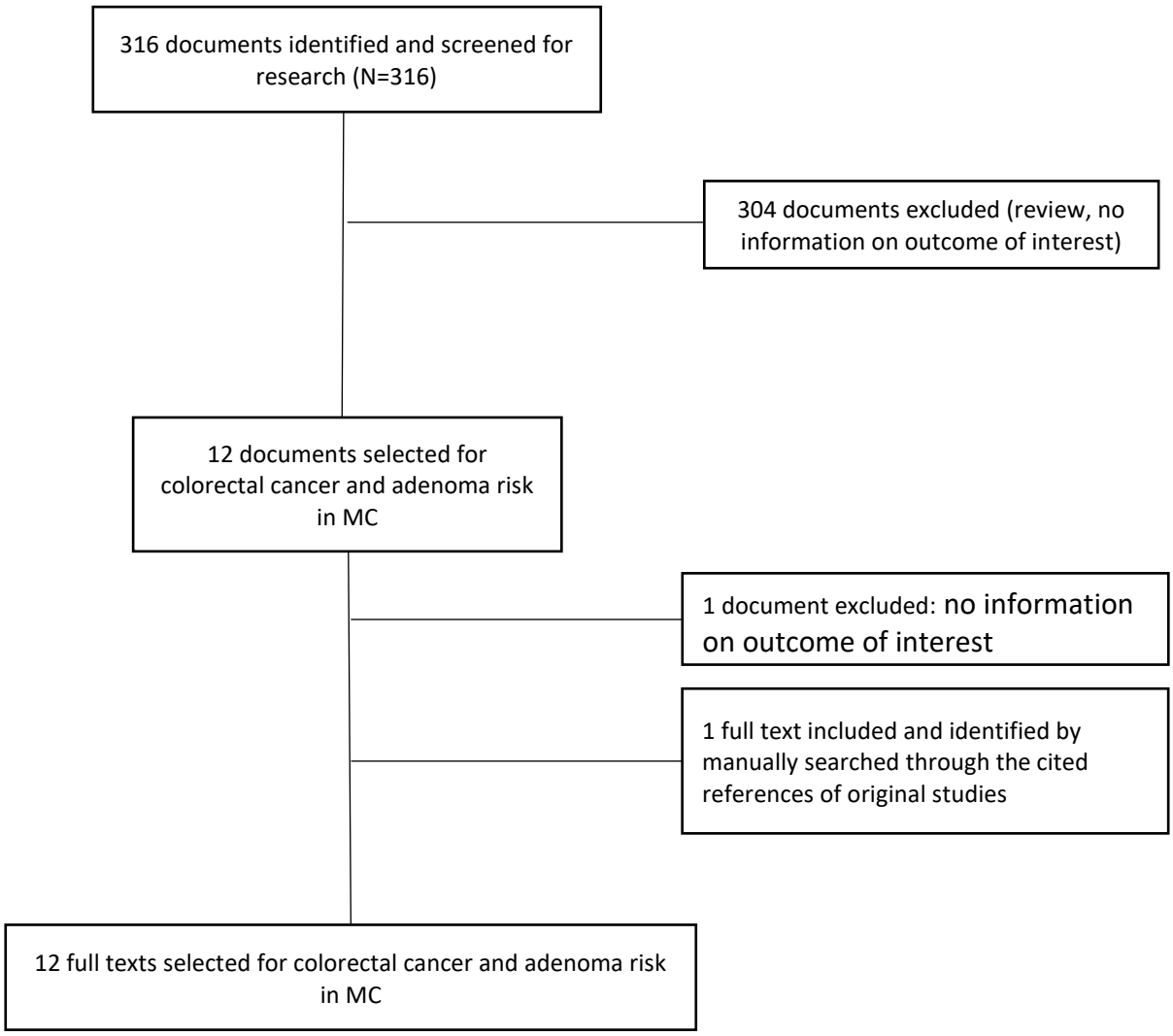
PICO 08: In MC patients does imputable drug withdrawal influence the disease course?

Combined search in Pubmed and EMBASE data base (using MeSH Terms and correspondent Emtree terms): ((((chronic diarrhea) OR prevalence) OR incidence) OR epidemiology[MeSH Terms])) AND ((((microscopic colitis[MeSH Terms]) OR lymphocytic colitis) OR collagenous colitis) OR incomplete microscopic colitis). Filter activated: Humans.



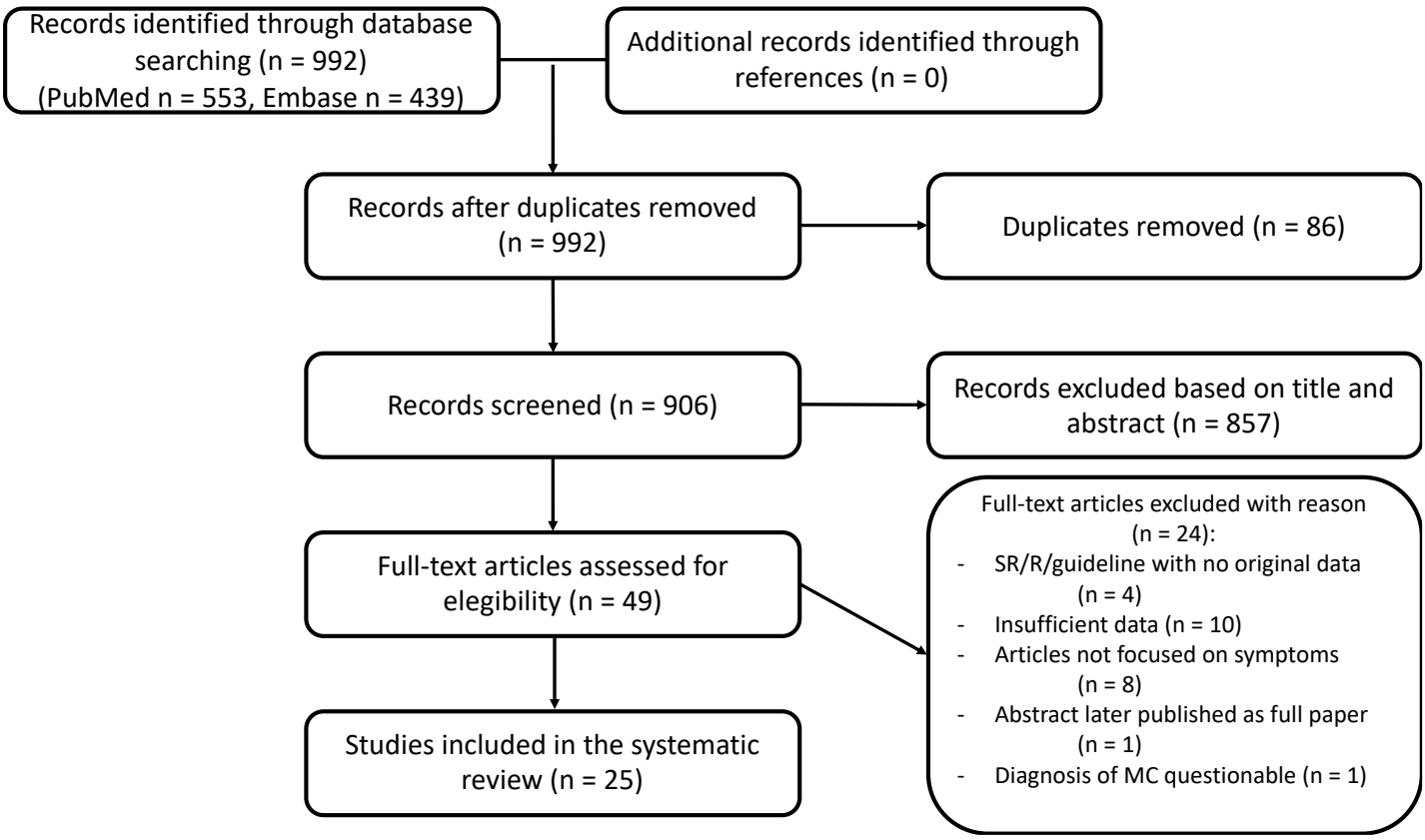
PICO 09: Should MC patients require a special program for colonoscopy surveillance to rule out CRC compared to general population?

Combined search in Pubmed and EMBASE data base (using MeSH Terms and correspondent Emtree terms): ((((colonic polyp) OR colonic adenoma) OR colorectal neoplasia [MeSH Terms])) AND ((((microscopic colitis [MeSH Terms]) OR lymphocytic colitis) OR collagenous colitis) OR incomplete microscopic colitis). Filter activated: Humans.



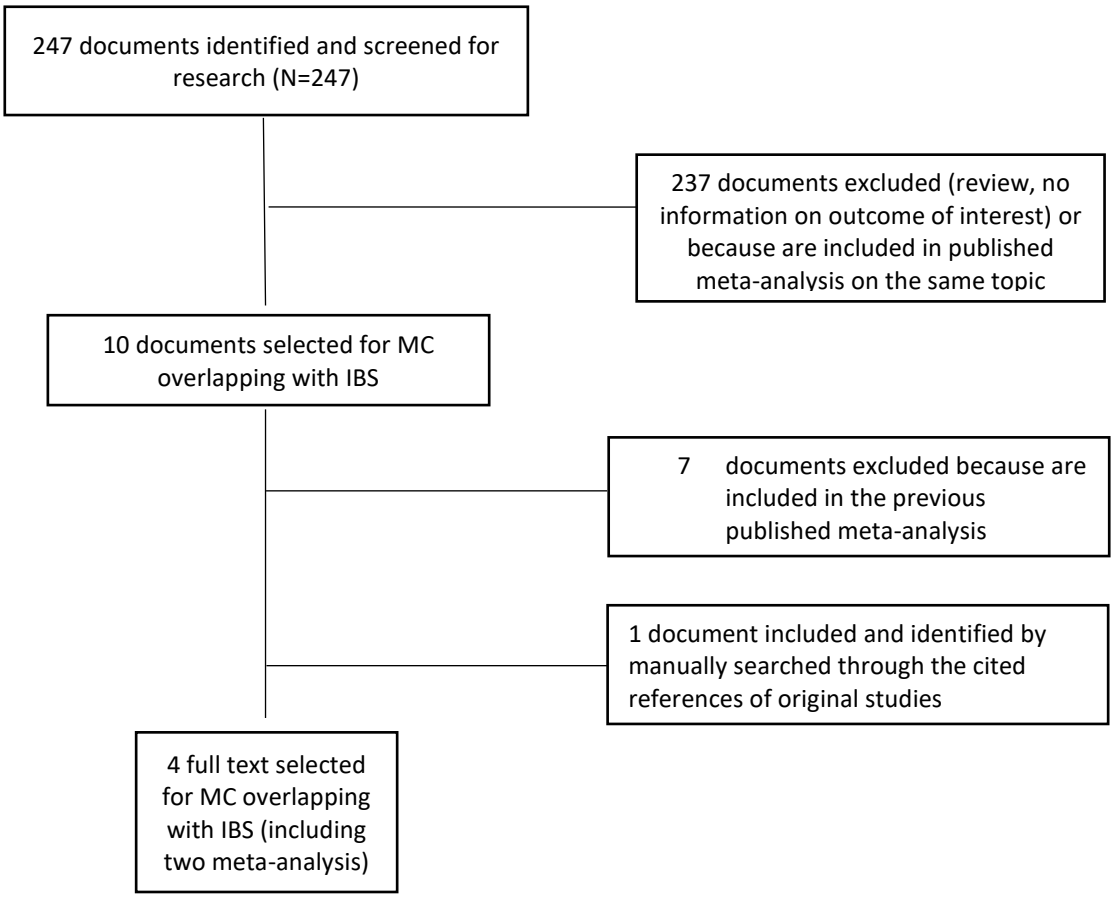
Workgroup 3:

PICO 01: What are the symptoms of MC?

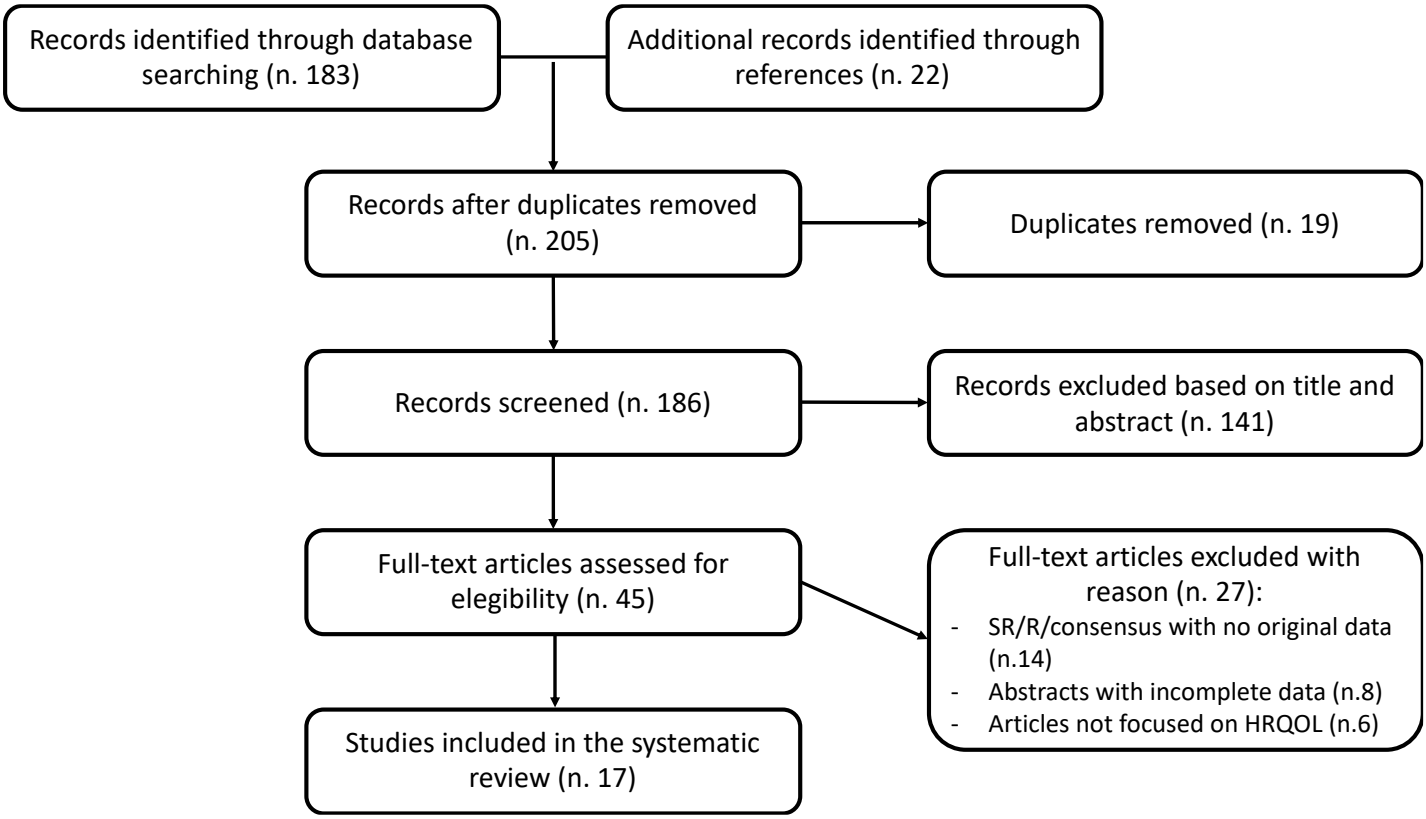


PICO 02: Can MC be distinguished from IBS-D based on symptoms?

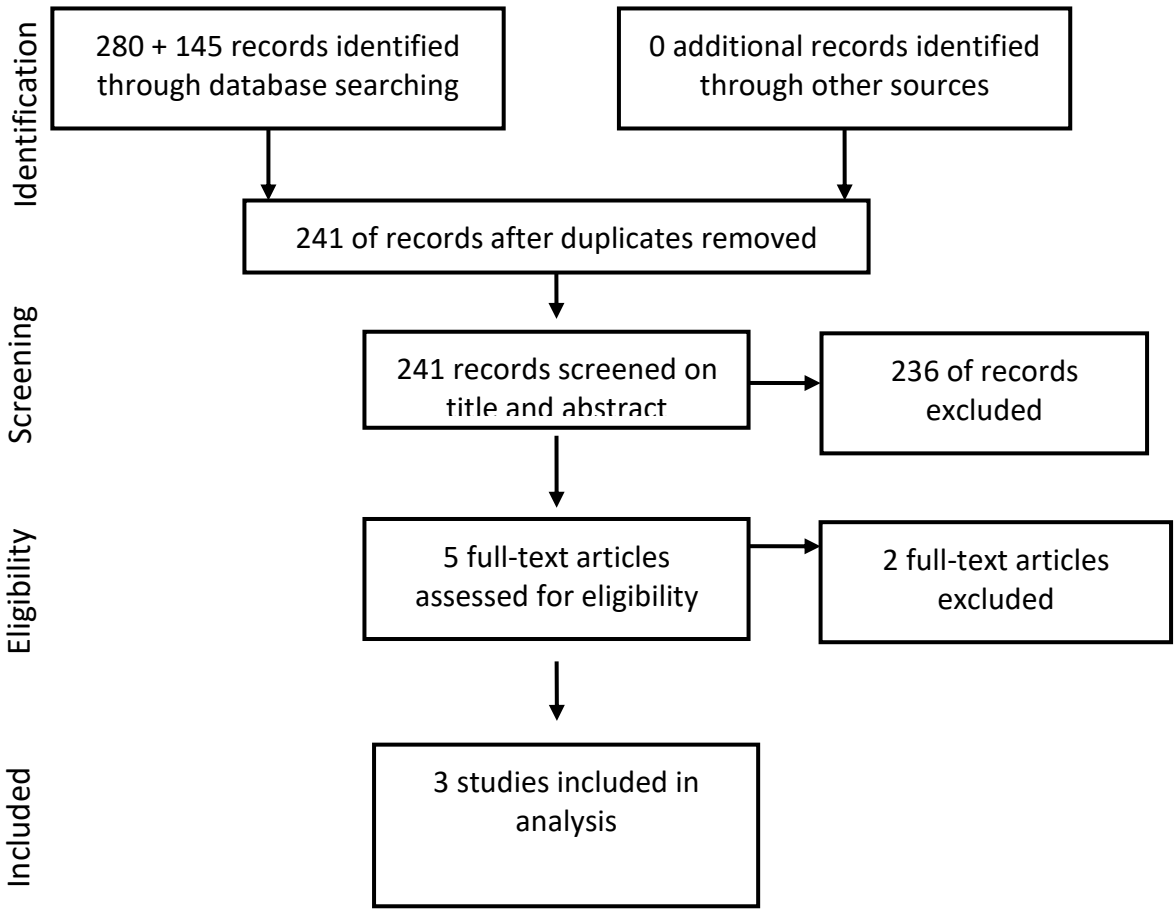
Combined search in Pubmed and EMBASE data base (using MeSH Terms and correspondent Emtree terms): ((Microscopic colitis) OR (microscopic colitides) OR (collagenous colitis) OR (lymphocytic colitis) AND (Rome) OR (Roma) OR (Manning) OR (Kruis) OR (irritable bowel syndrome) OR (functional diarrhea) OR (functional diarrhea) OR (functional disease) OR (functional disorders)) AND ((epidemiology) OR (prevalence) OR (proportion) OR (frequency) OR (incidence) OR (demography)).



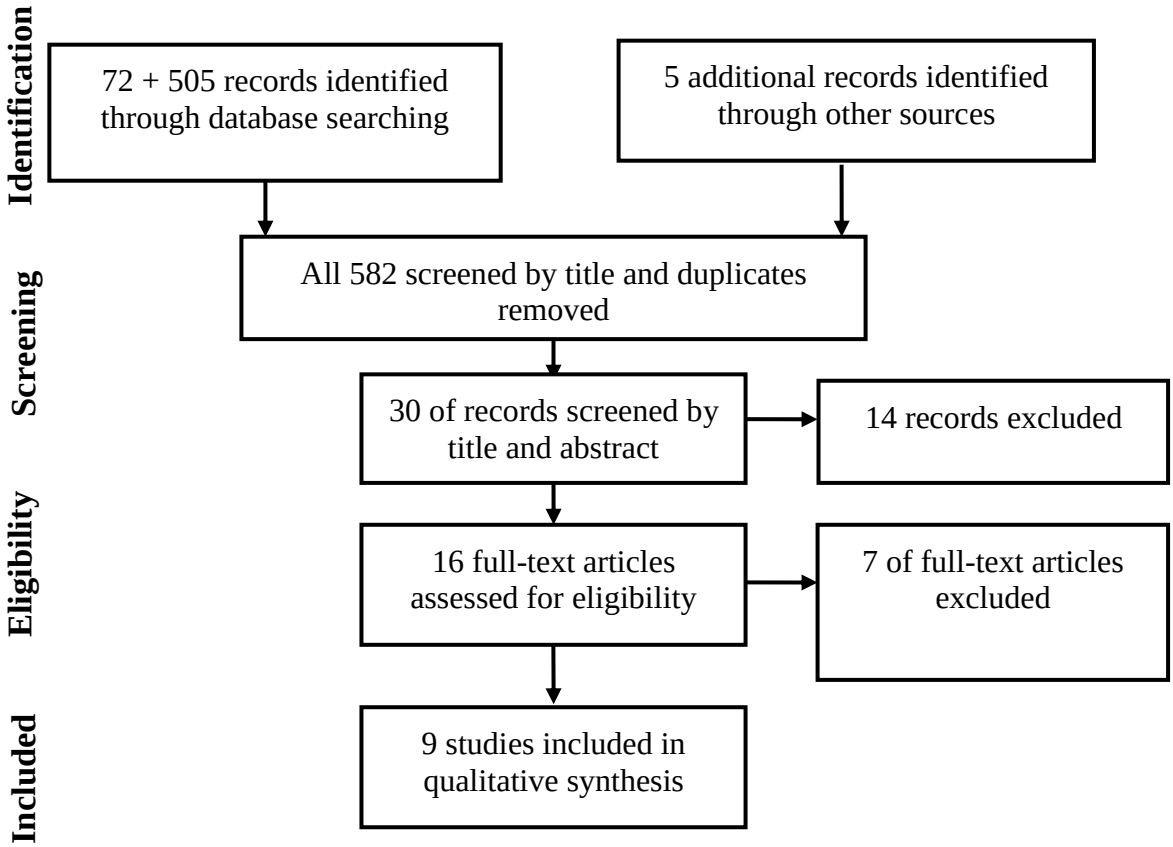
PICO 03: Is the patient health-related quality of life affected by MC?



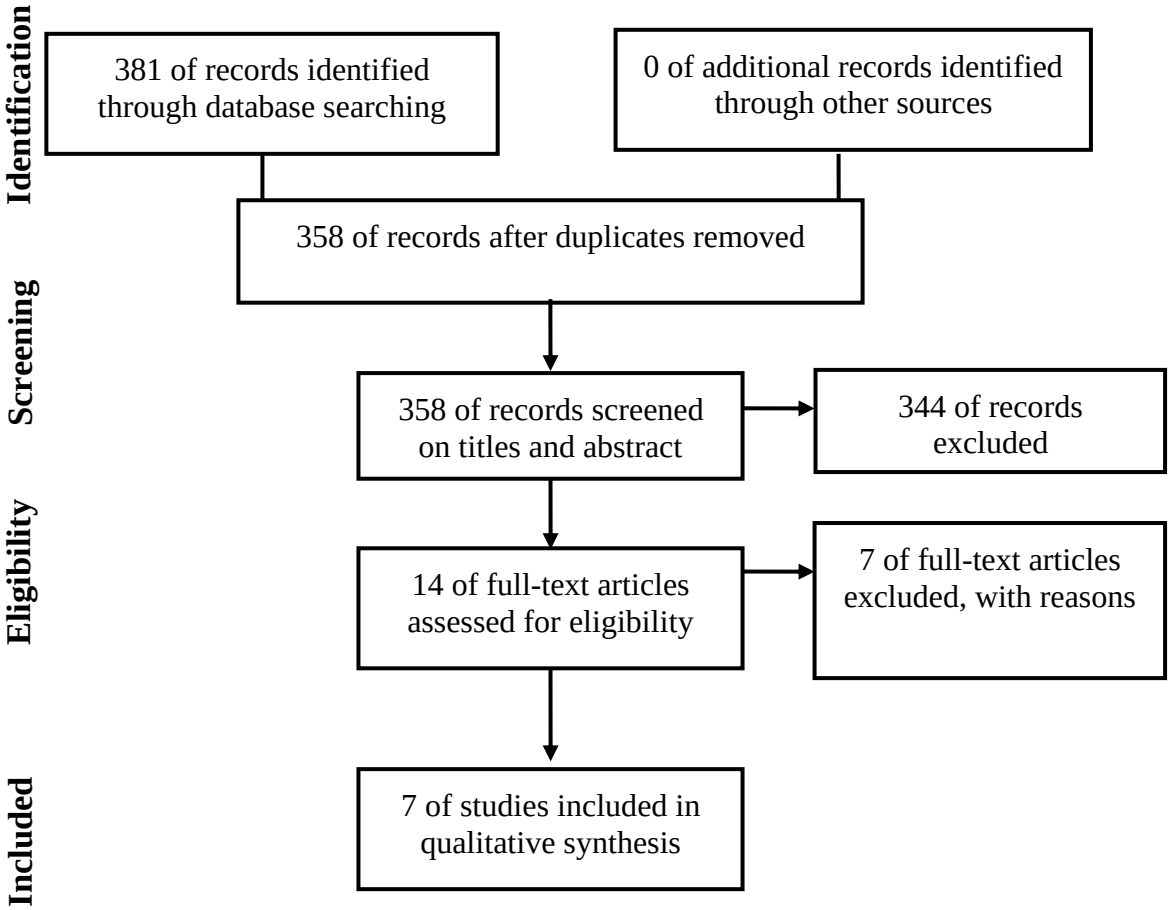
Workgroup 5:
PICO 05: Is there a role for bismuth subsalicylate in MC?



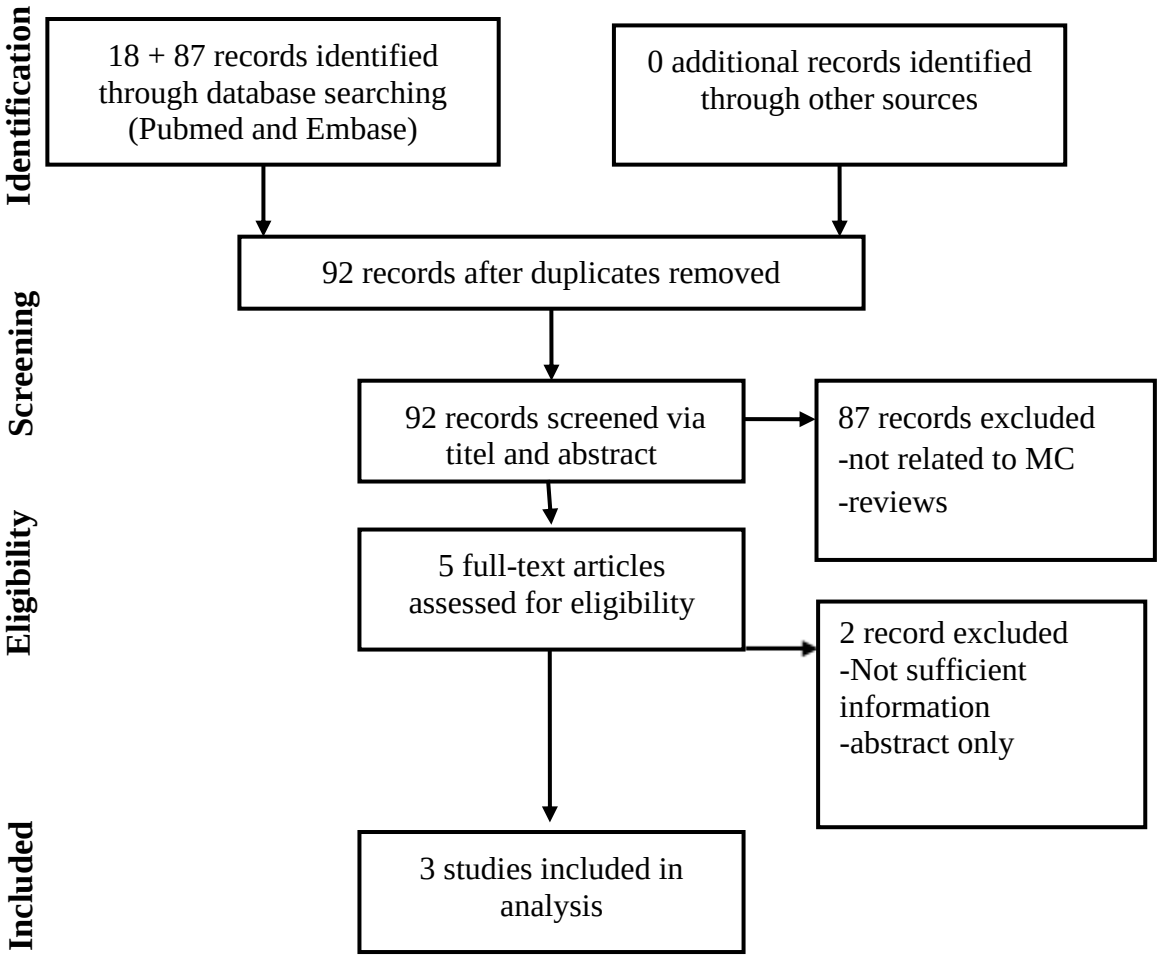
PICO 06: Is there a role for loperamide in MC?



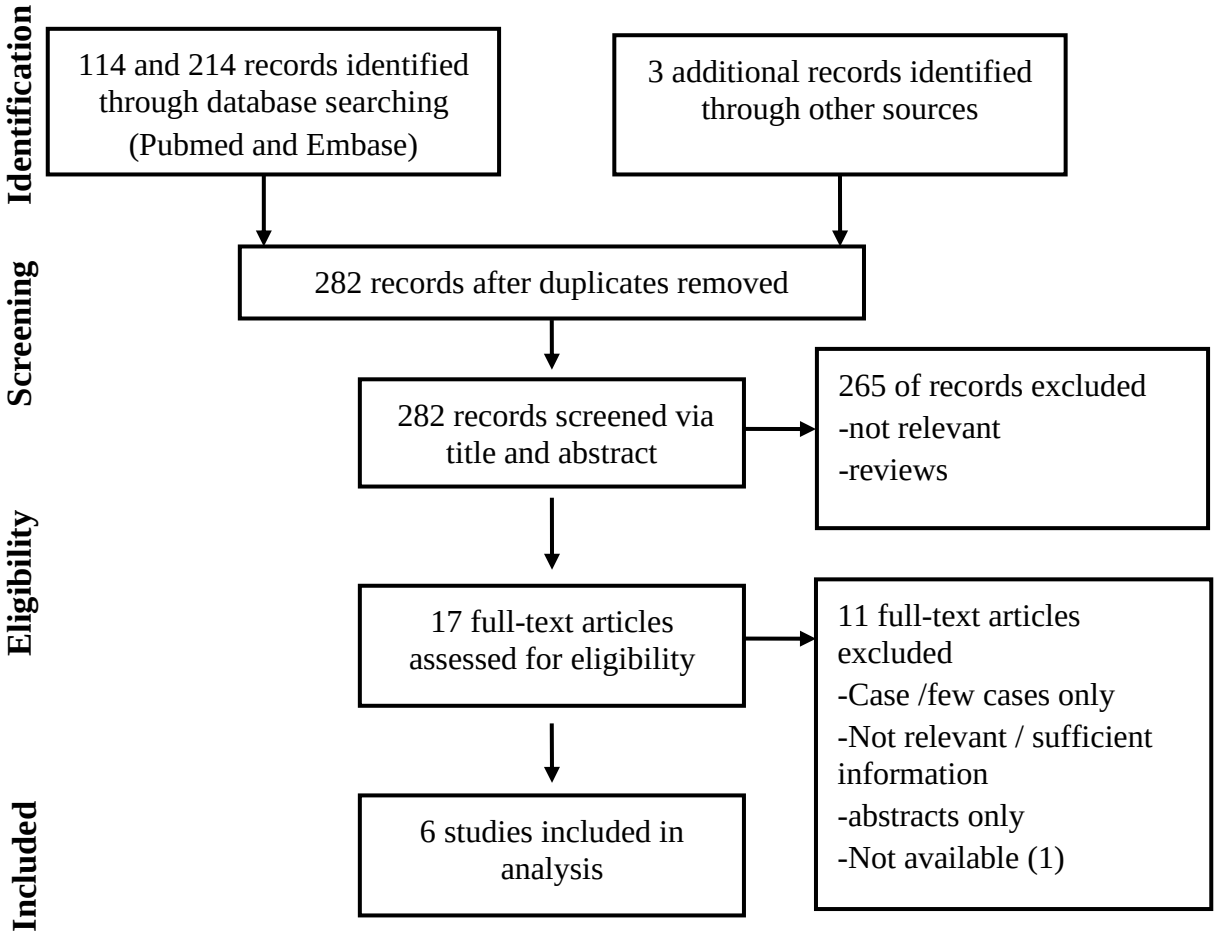
PICO 07: Is there a role for bile acid binding agents in MC?



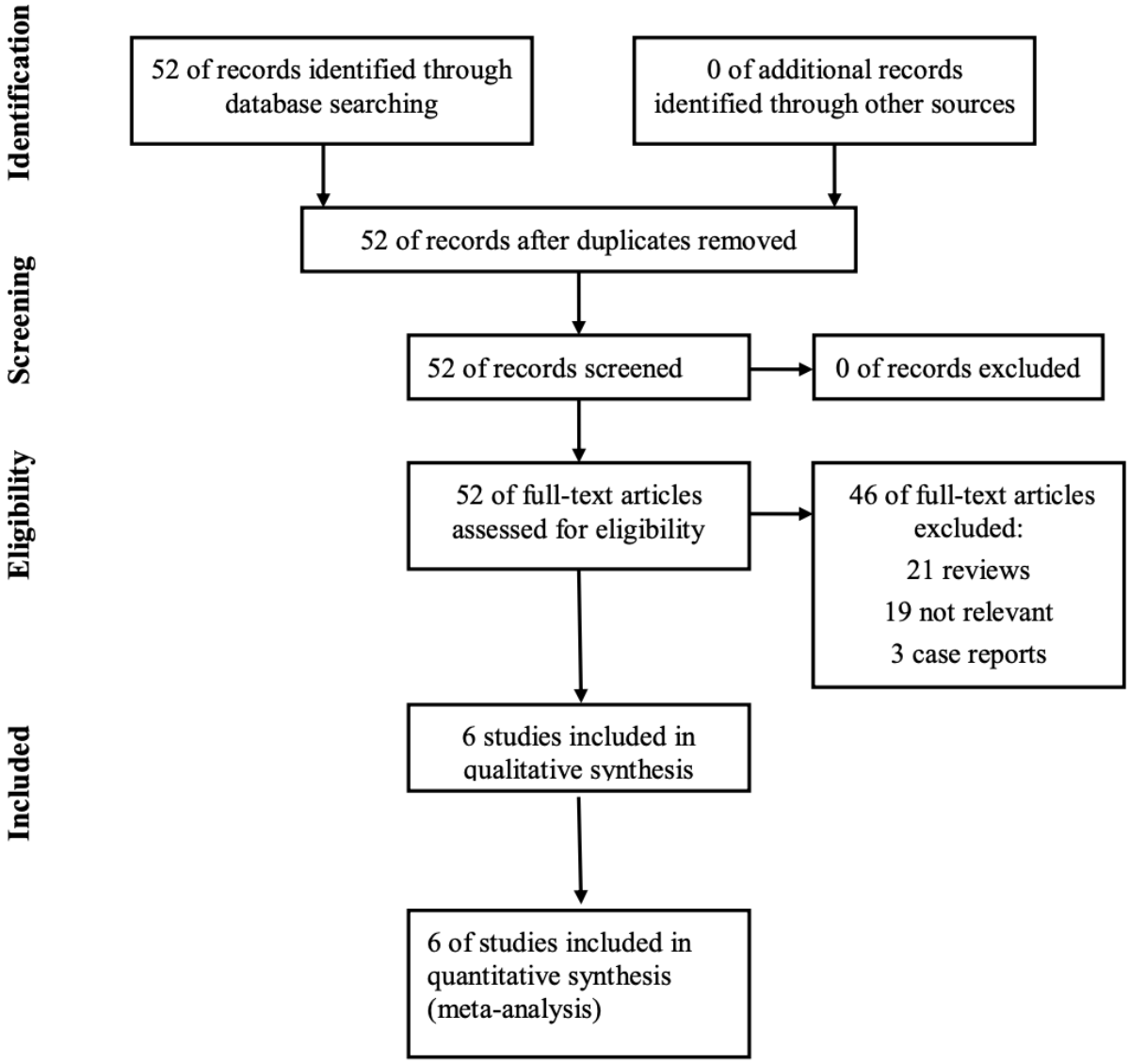
PICO10: Is there a role for probiotics in MC?



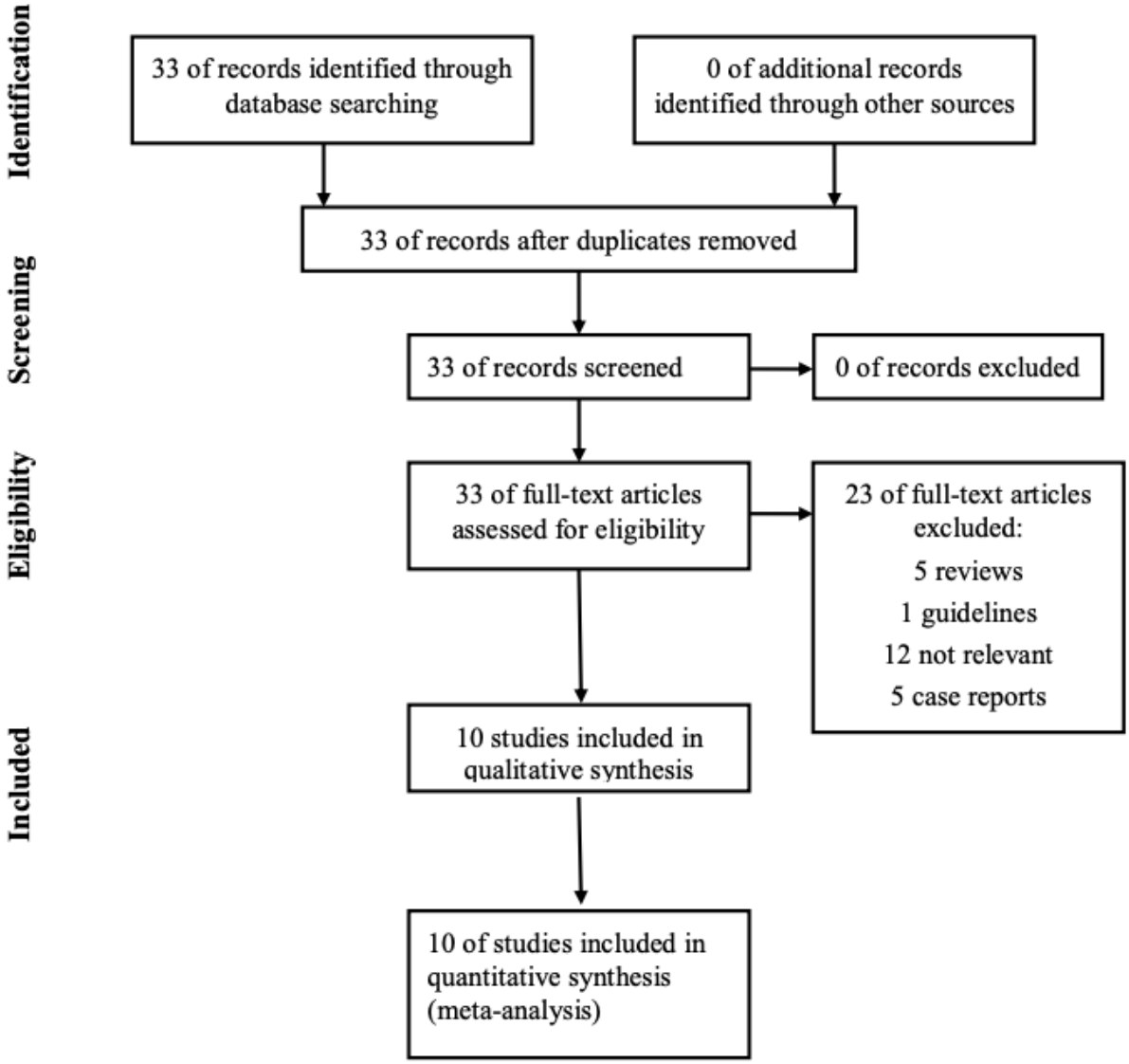
PICO11: Is there a role for other steroids in MC?



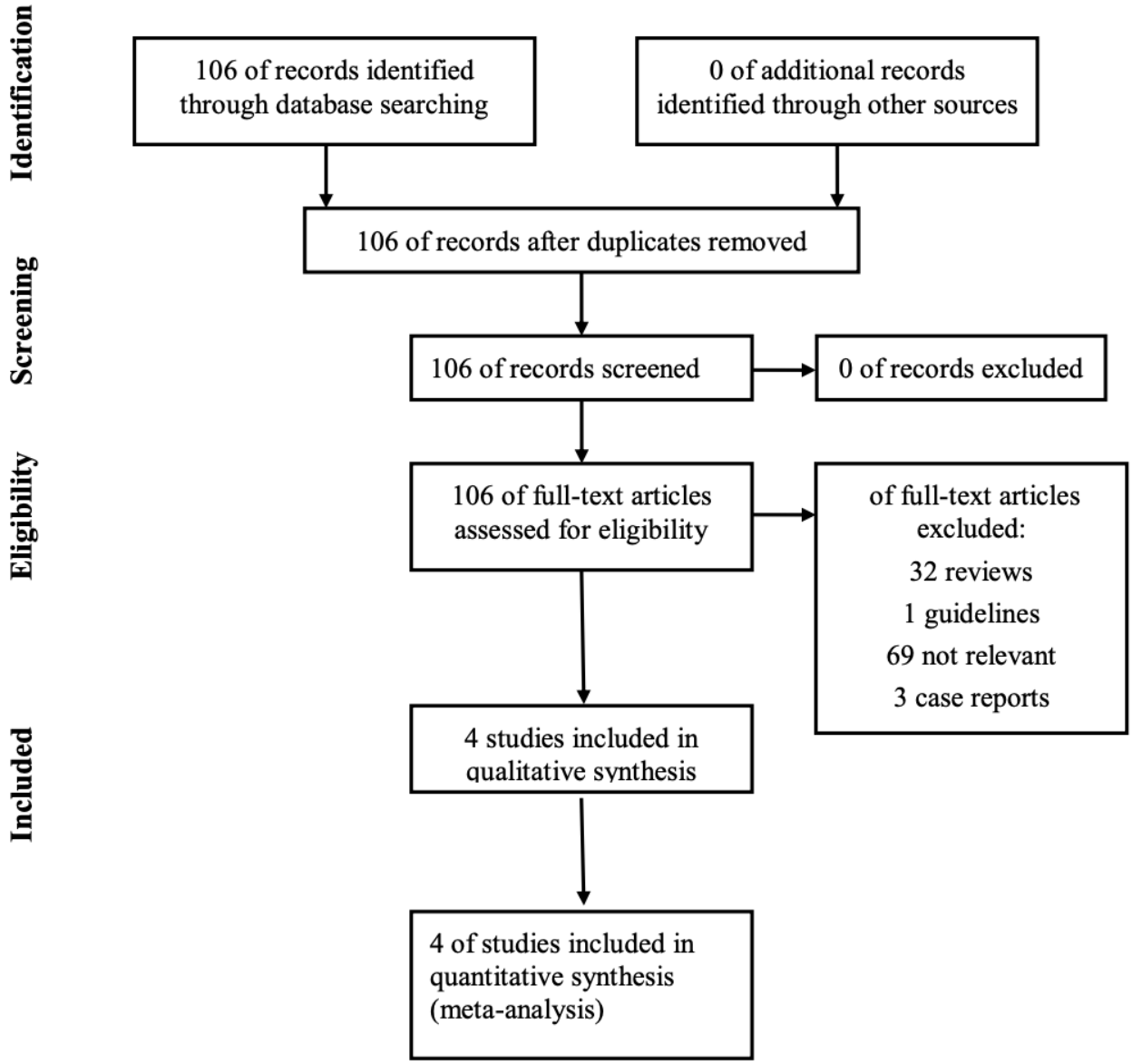
PICO 12: Is there a role for immunomodulators in MC?



PICO 13: Is there a role for biologics in MC?



PICO 14: Is there a role for surgery in MC?



Supplementary material – Appendix B

Data extraction tables

Abbreviations

Abd. = Abdominal
CC = Collagenous Colitis
CI = Confidence Interval
CRC = Colorectal Cancer
CS = Case Study
Erytro = Erythromycin
F = Female
F/M ratio = Female/Male Ratio
GI = Gastro Intestinal
HADS = Hospital Anxiety and Depression Scale
IBDQ = Inflammatory Bowel Disease Questionnaire
IBS = Irritable Bowel Syndrome
LC = Lymphocytic Colitis
MC = Microscopic Colitis
Metro = Metronidazole
n.a. = not applicable
NA = Not Available
NL = Netherlands
Norflox = Norfloxacin
NS = Not significant
NSAID = Nonsteroidal anti-inflammatory drugs
OR = Odds Ratio
PGWB = Psychological General Well-Being
PHQ15 = Patient Health Questionnaire 15
PPI=Proton-Pump Inhibitors
Prosp = Prospective
Pts = patients
RCT = randomized controlled trial
Retrosp = Retrospective
RFIPC = Inflammatory Bowel Disease Patient Concerns
RR = Relative Risk
SeHCAT = 75Se-23-selena-25-homotaurocholate
SF-30
SF-36
SHS = Short Health Scale
SSRI = Selective Serotonine Reuptake Inhibitors
TaC = total antioxidant capacity
UK = United Kingdom
USA = United States of America

* Quality rating established on the basis of Joanna Briggs Institute critical Appraisal Checklists

Workgroup 1:
Data extraction sheet – PICO 01: Incidence

PICO 01: What is the incidence of MC?													
STUDIES	Study time period	INCIDENCE			STUDY METHODS								
First Author (year, Country)		MC incidence (95% CI)	CC incidence (95% CI)	LC incidence (95% CI)	Retrospective/ Prospective	Level of study	Appropriate sample frame	Study participants sampled in an appropriate way	Sufficient coverage of the identified samples	CC and/or LC diagnosis according to standard methods	Valid definition of CC and/or LC used	Quality rating*	
Raclot (1994, France)	1987-1992	NA	0.62 (0.4-0.9)	NA	Retrospective	State/Provincial	Unclear	Unclear	Unclear	Unclear	Unclear	Poor	
Bohr (1995, Sweden)	1984-1993	NA	1.8 (0.5-3.1)	NA	Retrospective	Local	Yes	Yes	Yes	Yes	Yes	Good	
Fernandez-Bañares (1999, Spain)	1993-1997	6 (4.5-7.5)	2.3 (0.5-4.1)	3.7 (1.4-6.0)	Prospective	Local	Yes	Yes	Yes	Yes	Yes	Good	
Agnarsdottir (2002, Iceland)	1995-1999	9.2 (7.6-10.8)	5.2 (2.8-7.6)	4 (1.9-6.1)	Retrospective	National	Yes	Yes	Yes	Yes	No	Moderate	
Olesen (2004, Sweden)	1993-1998	9.3 (7.5-11.2)	4.9 (2.3-7.5)	4.4 (1.9-6.9)	Retrospective	Local	Yes	Yes	Yes	Yes	Yes	Good	
Heron (2005, UK)	1999-2004	1.65 (1.1-2.2)	1.1 (0.7-1.6)	0.6 (0.2-0.9)	Retrospective	State/Provincial	Yes	Yes	Yes	Unclear	Unclear	Poor	
Rajan (2005, UK)	1998-2003	NA	0.8 (0.5-1,1)	NA	Retrospective	State/Provincial	Yes	Yes	Yes	Unclear	Unclear	Moderate	
Pardi (2007, USA)	1985-2001	8.7 (7.3-10.3)	3.1 (1.3-4.9)	5.7 (3.3-8.1)	Prospective	Local	Yes	Yes	Yes	Yes	Yes	Good	
Wiliams (2008, Canada)	2002-2004	10 (8.5-11.6)	4.6 (2.6-6.6)	5.4 (3.2-7.6)	Prospective	State/Provincial	Yes	Yes	Yes	Yes	Yes	Good	
Bjornbak (2011, Denmark)	1999-2010	17.52 (15.9-19.2)	10.8 (8.3-13.3)	6.7 (4.9-8.7)	Retrospective	Local	Yes	Yes	Yes	Yes	Yes	Good	
Stewart (2011, Canada)	2004-2008	14.76 (NA)	4.6 (NA)	10.12 (NA)	Prospective	State/Provincial	Yes	Yes	Yes	Yes	Yes	Good	
Fernandez-Bañares (2011, Spain)	2004-2008	5.2 (4.01-6.4)	2.9 (1.1-4.7)	2.3 (0.7-3.9)	Prospective	Local	Yes	Yes	Yes	Yes	Yes	Good	
Andrews (2012, Canada)	2004	17.9 (16.8-18.9)	6.7 (5.4-8.0)	10.1 (8.6-11.7)	Retrospective	State/Provincial	Yes	Yes	Yes	Yes	Yes	Good	
Guagnozzi (2012, Spain)	2008-2010	17.1 (11.2-23.0)	1.06 (-1.8-4.0)	16 (4.8-27.2)	Retrospective	Local	Yes	Yes	Yes	Yes	Yes	Good	
Vigren (2012, Sweden)	2001-2010	5.4 (NA)	5.4 (4.0-6.9)	NA	Retrospective	State/Provincial	Yes	Yes	Yes	Yes	Yes	Good	
Daferera (2013, Sweden)	1999-2008	13.8 (11.0-16.6)	6.6 (2.8-10.4)	7.2 (3.3-11.2)	Retrospective	Local	Yes	Yes	Yes	Yes	Yes	Good	
Thorn (2013, Sweden)	2005-2009	12.4 (10.9-13.8)	7 (4.8-9.2)	5.4 (3.5-7.3)	Prospective	State/Provincial	Yes	Yes	Yes	Yes	Yes	Good	
Wickbom (2013, Sweden)	1999-2008	10.2 (8.7-11.5)	5.2 (3.2-7.2)	4.9 (2.9-6.8)	Prospective	Local	Yes	Yes	Yes	Yes	Yes	Good	
Gentile (2014, USA)	2002-2010	21 (18-24.1)	9.1 (5.2-13.0)	12 (7.5-16.5)	Retrospective	Local	Yes	Yes	Yes	Yes	Yes	Good	
Bonderup (2015, Denmark)	2002-2011	14.4 (14.1-14.7)	8.8 (8.3-9.3)	5.6 (5.2-6.0)	Retrospective	National	Yes	Yes	Yes	Yes	Yes	Good	
Verhaegh (2015, NL)	2000-2012	3.5 (3.4-3.6)	1.8 (1.7-1.9)	1.3 (1.2-1.4)	Retrospective	National	Yes	Yes	Yes	Yes	Yes	Good	
Fumery (2017, France)	2005-2007	7.8 (6.5-9.2)	5.3 (3.1-7.5)	2.6 (1.1-4.1)	Prospective	State/Provincial	Yes	Yes	Yes	Yes	Yes	Good	
Kane (2017, UK)	2010-2015	11.3 (10.4-12.3)	6.1 (4.7-7.5)	4.2 (3.1-5.4)	Retrospective	Local	Yes	Yes	Yes	Yes	Yes	Good	
Lewis (2017, UK)	2005-2016	18.15 (17.0-19.4)	10.4 (8.6-12.2)	7.7 (6.1-9.3)	Retrospective	State/Provincial	Yes	Yes	Yes	Unclear	Unclear	Poor	
Davidson (2018, Sweden)	2011-2015	8.6 (7.8-9.3)	5.9 (4.7-7.1)	2.64 (1.9-3.4)	Prospective	State/Provincial	Yes	Yes	Yes	Yes	Yes	Good	
Davidson (2018, Sweden)	2010-2016	27.5 (25.9-29.1)	16.4 (14.0-18.3)	11.1 (9.1-13.1)	Prospective	State/Provincial	Yes	Yes	Yes	Yes	Yes	Good	
Moore (2018, Northern Ireland)	2008-2016	6.7 (5.3-8.1)	5 (3.8-6.2)	1.7 (1.0-2.4)	Retrospective	State/Provincial	Yes	Unclear	Unclear	Yes	Yes	Moderate	
Bergman (2019, Sweden)	1995-2015	7.2 (5.6-8.7)	2.4 (2.3-2.6)	4.8 (4.6-5.0)	Retrospective	National	Yes	Yes	Yes	Yes	Yes	Good	

Data extraction sheet – PICO 02: Prevalence

PICO 02: What is the prevalence of MC?													
STUDIES	Study time period		PREVALENCE			STUDY METHODS							
First Author (year, Country)			MC prevalence (95% CI)	CC prevalence (95% CI)	LC prevalence (95% CI)	Retrospective /Prospective	Level of study	Approprite sample Frame	Study participants sampled in an appropriate way	Sufficient coverage of the identified samples	CC and /orLC diagnosis according to standard methods	Valid definition of CC and/or LC used	Quality rating*
Bohr (1995, Sweden)	1984-1993	1993	NA	15.7 (9.9-21.5)	NA	Retrospective	Local	Yes	Yes	Yes	Yes	Yes	Good
Pardi (2007, USA)	1985-2001	2001	103 (83.8-122-2)	39.3 (27.4-51.2)	64.6 (49.4-79.8)	Prospective	Local	Yes	Yes	Yes	Yes	Yes	Good
Guagnozzi (2012, Spaiin)	2008-2010	2009	47.5 (31.1-64.0)	3 (-1.1-7.1)	45 (29.0-61.0)	Retrospective	Local	Yes	Yes	Yes	Yes	Yes	Good
Wickbom (2013, Sweden)	1999-2008	2008	123 (107.1-139.0)	67.7 (56.0-79.4)	55.3 (44.6-66.0)	Prospective	Local	Yes	Yes	Yes	Yes	Yes	Good
Gentile (2014, USA)	2002-2010	2010	219 (194.9-243.1)	128.2 (109.2-146.6)	90.8 (75.3-106.3)	Retrospective	Local	Yes	Yes	Yes	Yes	Yes	Good
Fernandez-Bañares (2016, Spain)	1993-2014	2014	107.1 (91.6-122.6)	52.5 (23.7-76.5)	54.6 (48.2-75.3)	Retrospective	Local	Yes	Yes	Yes	Yes	Yes	Good

Data extraction sheet – PICO 03 a. Frequency

PICO 03: How frequent is MC in patients with chronic diarrhea and normal or near normal colonoscopy?												
STUDIES	NUMBER OF PATIENTS IN STUDY GROUPS					STUDY METHODS						
First Author (year, Country)	N diarrhea group	Definition of diarrhea group	N MC pts (%)	N CC pts (%)	N LC pts (%)	Retrospective/ Prospective	Approprite sample Frame	Study participants sampled in an appropriate way	Sufficient coverage of the identified samples	CC and/or LC diagnosis according to standard methods	Valid definition of CC and/or LC used	Quality rating*
Arcana (2013, Peru)	202	Chronic diarrhea in elderly patientes (median age 73.5 +/- 6.7 years)	71 (35.2%)	NA	NA	Retrospective.	No	Yes	Unclear	Unclear	Unclear	Poor
Batista (2018, Spain)	138	watery chronic diarrhea (non-bloody)	43 (31.2%)	16 (11.6%)	22 (15.9%)	Prospective	Yes	Yes	Yes	Yes	Yes	Good
Carmona-Sanchez (2008, Mexico)	109	chornic diarrhea with norma (N=53) and abnormal endoscopic appearance (N=20)	12 (11.0%)	7 (58.3%)	5 (41.6%)	Retrospective.	Yes	Yes	Yes	Yes	Unclear	Poor
Channaiah (2017, India)	309	chronic diarrhea	18 (5.8%)	NA	NA	Prospective	Yes	Unclear	Yes	Unclear	Unclear	Poor
Cotter (2017, USA)	617	Chronic diarrhea with normal endoscopic appearance (Derivation cohort)	81 (13.1%)	32 (5.2%)	49 (7.9%)	Retrospective.	Yes	Yes	Yes	Yes	Yes	Good
(same above)	309	Chronic diarrhea (Validation cohort) with Cotter scoring system	46 (14.9%	14 (4.5%)	32 (10.4%)							Good
Da Silva (2006, Brazil)	162	Chronic diarrhea with normal endoscopic appearance	31 (19.1%)	19 (11.7%)	12 (6.8%)	Retrospective.	Yes	Yes	No	Unclear	Yes	Poor
Erdem (2008, Turkey)	129	Unexplained chronic diarrhea and normal mucosa appearance	15 (11.5%)	3 (2.3%)	12 (9.3%)	Prospective	Yes	Yes	Yes	Yes	Yes	Moderate
Essid (2005, Tunisia)	150	Chronic diarrhea with normal colonoscopy	44 (29.3%)	19 (43.2%)	25 (57.0%)	Retrospective.	Yes	Yes	No	Unclear	Unclear	Poor
Fernandez-Bañares (2011, Spain)	923	Nonbloody chronic diarrhea	72 (7.8%)	40 (4.3%)	32 (3.5%)	Prospective	Yes	Yes	Yes	Yes	Yes	Good
Fernandez-Bañares (1999, Spain)	375	Chronic or recurrent diarrhea	60 (16%)	23 (6.1%)	37 (9.0%)	Prospective	Yes	Yes	Yes	Yes	Yes	Goos
Fine (2000, USA)	809	Chronic watery non-bloddy diarrhea	80 (9.9%)	NA	NA	Prospective	Yes	Yes	Yes	Yes	Unclear	Moderate
Gado (2011, Egypt)	44	Chronic watery non-bloddy diarrhea with normal endoscopic appearance	22 (50%)	20 (45%)	2 (5.0%)	Retrospective.	Yes	Yes	Yes	Yes	No	Moderate
Garg (1996, India)	77	Chronic diarrhea but bloody also	5 (6.5%)	0	5 (100%)	Retrospective.	Yes	No	No	No	No	Poor
Gonzalez-Nicolas (2010)	180	Chronic diarrhea with normal colonoscopy	16 (9%)	13 (18%)	13 (82.0%)	Retrospective.	Yes	Yes	Yes	Yes	Yes	Moderate

Data extraction sheet – PICO 03 b. Frequency

PICO 03: How frequent is MC in patients with chronic diarrhea and normal or near normal colonoscopy?												
STUDIES	NUMBER OF PATIENTS IN STUDY GROUPS					STUDY METHODS						
First Author (year, Country)	N diarrhea group	Definition of diarrhea group	N MC pts (%)	N CC pts (%)	N LC pts (%)	Retrospective/ Prospective	Approprite sample Frame	Study participants sampled in an appropriate way	Sufficient coverage of the identified samples	CC and/or LC diagnosis according to standard methods	Valid definition of CC and/or LC used	Quality rating*
Gu (2012, China)	613	Chronic diarrhea with normal colonoscopy	87 (14.2%)	28 (4.6%)	59 (9.6%)	Prospective	Yes	Yes	Yes	Yes	Yes	Good
Guagnozzi (2012, Spain)	234	Nonbloody chronic diarrhea with normal endoscopic appearance and normal histology	32 (13.7%)	2 (0.9%)	30 (12.8%)	Retrospective.	Yes	Yes	Yes	Yes	Yes	Good
Hatemi (2011, Turkey)	93	Chronic diarrhea	NA	7 (11%)	NA	Retrospective.	No	Yes	Yes	Unclear	Yes	Poor
Hotouras (2012, UK)	137	Chronic diarrhoea with macroscopically normal mucosa	2 (1.5%)	NA	NA	Prospective	Yes	No	Yes	Unclear	No	Poor
Kagueyama (2014, Brazil)	184	Chronic diarrhe (15 days) with normal endoscopic appearance	10 (5.4%)	3 (1.6%)	7 (3.8%)	Retrospective.	Yes	Yes	No	Yes	Yes	Moderate
Larsson (2014, Sweden)	78	Chronic non bloody diarrhea	15 (19%)	10 (12.8%)	5 (6.4%)	Retrospective.	Yes	Yes	Yes	Yes	Yes	Good
Macaigne (2014, France)	433	chronic non-bloody diarrhea with normal or almost normal colonoscopy	129 (29.8%)	42 (9.7%)	87 (20.1%)	Prospective	Yes	Yes	Yes	Yes	Yes	Good
Marshall (1995, USA)	111	chronic unexplained diarrhoea	0	0	0	Retrospective.	Yes	Yes	Unclear	Unclear	Yes	Poor
Matsubara (2014, Japan)	95	Chroinic diarrhea	6 (6.3%)	6 (6.3%)	0	Retrospective.	Yes	Yes	Unclear	Unclear	Unclear	Poor
Miraglia (2013, Italy)	41	chronic watery diarrhea	3 (6.1%)	2 (2.1%)	1 (11.0%)	Prospective	Yes	Yes	Yes	Yes	Yes	Moderate
Misra (2010, India)	400	Chronic watery diarrhea	15 (3.7%)	5 (1.3%)	10 (2.5%)	Retrospective.	Yes	Yes	Yes	Yes	Yes	Moderate
Olesen M (2004, Sweden)	1018	Chronic non bloody diarrhea	97 (9.5%)	51 (5.0%)	46 (4.5%)	Retrospective.	Yes	Yes	Yes	Yes	Yes	Good
Pardi DS (2007, USA)	929	Chronic diarrhea	130 (14%)	46 (5.0%)	70 (7.5%)	Prospective	Yes	Yes	Yes	Yes	Yes	Good
Sethi (2012, NA)	395	Chronic diarrhea mostly no bloody (97%)	13. (3.3%)	8 (2%)	5 (1.0%)	Retrospective.	Yes	Yes	Yes	Yes	Unclear	Poor
Shah (2001, USA)	168	Unexplained or chronic diarrhea	10 (6%)	1 (0.6%)	9 (5.4%)	Retrospective.	Yes	Yes	Yes	Yes	Unclear	Poor
Shaw (2016, UK)	100	chronic diarrhea	8 (9.2%)	NA	NA	Retrospective.	No	Yes	Yes	Unclear	Unclear	Poor
Sidhu (2012, UK)	294	Chronic diarrhea with colonoscopy normal and 294 with colonic biopsies performed	14 (4.8%)	NA	NA	Retrospective.	No	Yes	Yes	Yes	Unclear	Moderate
Tonitini (2014, Italy)	256	chronic non bloody diarrhoea	43 (16.8%)	33 (12.9%)	13 (5.1%)	Prospective	Yes	Yes	Yes	Yes	Yes	Good
Trembling (2015, NA)	110	chronic diarrhiea	8 (7%)	0	8 (7%)	Retrospective.	Yes	Unclear	Unclear	Unclear	Unclear	Poor
Valle Mansilla (2003, Peru)	110	chronic diarhoa	44 (40%)	2 (1.8%)	42 (95.5%)	Retrospective.	Yes	Unclear	Yes	Yes	No	Poor
Villafuerte (2012, Peru)	162	choinic diarrhoea	NA	NA	58 (35.8%)	Retrospective.	Yes	Yes	doubtful	Yes	Unclear	Poor
Wagner (2016, Sweden)	67	chronic diarrhoea	13 (19.4%)	9 (13.4%)	4 (6.0%)	Retrospective.	Yes	Yes	Yes	Yes	Yes	Good

Data extraction sheet – PICO 04 & 06 a. Smoking

PICO 04: Is smoking a riskfactor for MC? & PICO 06: In MC patients does smoking cessation influence the disease course?																					
STUDIES	Smoking habit results and conclusions																				
Fisrt Author (year, Country)	N total MC	N Current smokers MC (%)	N Former smokers MC (%)	N Never smokers MC (%)	N No smokers never+former MC (%)	N total CC	N Current smokers CC (%)	N Former smokers CC (%)	N Never smokers CC (%)	N No smokers (former+never) CC (%)	N total LC	N Current smokers LC (%)	N Former Smokers LC (%)	N Never smokers LC (%)	N No smokers (former+never) LC (%)	N total controls	Control type	N Current smokers Controls (%)	N Former smokers Controls (%)	N Never smokers Controls (%)	N No smokers (former+never) Controls (%)
Burke (2018, USA)	166	27 (16.3%)	78 (47%)	61 (36.8%)	139 (83.7%)	78	16 (20.5%)	37 (47.4%)	25 (32%)	62 (79.5%)	76	10 (13.2%)	33 (43.4%)	33 (43.4%)	66 (86.8%)	230986	General population	53582 (23.2%)	51547 (22.3%)	125857 (54.5%)	177404 (76.8%)
Cotter (2017, USA)	81	NA	NA	NA	NA	32	NA	NA	NA	NA	49	NA	NA	NA	NA	536	Chronic diarrhea	NA	NA	NA	NA
Fernández-Bañares (2013, Spain)	190	39 (20.5%)	NA	NA	151 (79.5%)	120	22 (18.3%)	NA	NA	98 (81.7%)	70	17 (24.3%)	NA	NA	53 (75.7%)	128	General population	12 (9.4%)	NA	NA	116 (90.6%)
Gu (2012, China)	87	17 (19.5%)	NA	NA	70 (80.5%)	28	5 (17.9%)	NA	NA	23 (82.1%)	51	12 (23.5%)	NA	NA	39 (76.5%)	90	Chronic diarrhea	15 (16.7%)	NA	NA	75 (83.3%)
Guagnozzi (2015, Spain)	46	13 (28.3%)	2 (4.3%)	31 (67.4%)	33 (71.7%)	4	NA	NA	NA	NA	42	NA	NA	NA	NA	317	Chronic diarrhea	82 (25.9%)	17 (5.4%)	218 (68.8%)	235 (74.1%)
Larsson (2016, Sweden)	135	55 (40.7%)	41 (30.4%)	39 (28.9%)	80 (59.3%)	73	NA	NA	NA	NA	62	NA	NA	NA	NA	27960	General population	7878 (28.2%)	9465 (33.9%)	10650 (37.9%)	20115 (71.8%)
Roth (2014, Sweden)	131	47 (35.9%)	48 (36.6%)	36 (27.5%)	84 (64.1%)	82	NA	NA	NA	NA	49	NA	NA	NA	NA	737	General population	205 (27.8%)	220 (29.9%)	312 (42.3%)	532 (72.2%)
Thorn (2013, Sweden)	272	49 (18%)	NA	NA	223 (82%)	154	21 (13.6%)	NA	NA	133 (86.4%)	118	28 (23.7%)	NA	NA	90 (76.3%)	NA	General population	NA (15.3%)	NA	NA	NA
Verhaegh (2017, NL)	171	65 (38.7%)	63 (37.5%)	40 (23.8%)	103 (66.9%)	81	NA	NA	NA	NA	73	NA	NA	NA	NA	316	General population	40 (12.6%)	140 (45%)	131 (42.1%)	276 (87.4%)
Vigren (2011, Sweden)	NA	NA	NA	NA	NA	116	43 (37.1%)	NA	NA	73 (62.9%)	0	NA	NA	NA	NA	6192	General population	1053 (17%)	NA	NA	5139 (83%)
Wickbom (2017), Sweden	212	55 (25.9%)	78 (36.8%)	69 (32.6%)	157 (74.1%)	109	31 (28.5%)	46 (43.4%)	32 (29.4%)	78 (71.6%)	93	24 (26%)	32 (34.4%)	37 (39.9%)	69 (74.2%)	477	General population	61 (12.8%)	169 (26.9%)	247 (39.4%)	416 (87.2%)
Wildt (2018, Denmark)	50	17 (34%)	NA	NA	33 (66%)	35	NA	NA	NA	NA	15	NA	NA	NA	NA	49	General population	5 (10%)	NA	NA	44 (90%)
Yen (2011, USA)	340	52 (15.3%)	141 (41.5%)	147 (43.2%)	288 (84.7%)	124	23 (18.6%)	48 (38.7%)	53 (42.7%)	101 (81.4%)	216	29 (13.4%)	93 (43.1%)	94 (43.5%)	187 (86.6%)	340	General population	17 (5%)	113 (33.2%)	210 (61.8%)	323 (95%)
Fernández-Bañares (2013, Spain)	184	31 (16.8%)	22 (11.9%)	123 (66.8%)	NA	118	22 (18.6%)	17 (14.4%)	79 (66.9%)	96 (81.4%)	66	17 (25.7%)	5 (7.5%)	44 (66.7%)	49 (74.3%)	Not included	-	NA	NA	NA	NA
Fernández-Bañares (2017, Spain)	0	NA	NA	NA	NA	75	NA (21.5%)	NA (5.5%)	NA (7.3%)	NA	0	NA	NA	NA	NA	Not included	-	NA	NA	NA	NA
Fernández-Bañares (2016, Spain)	141	NA	NA	NA	NA	67	NA	NA	NA	NA	94	NA	NA	NA	NA	Not included	-	NA	NA	NA	NA
Gentile (2013, USA)	52	19 (37%)	33 (63%)	NA	NA	27	NA	NA	NA	NA	25	NA	NA	NA	NA	Not included	-	NA	NA	NA	NA
Münch (2016)	0	NA	NA	NA	NA	202	73 (36%)	58 (29%)	71 (35%)	129 (64%)	0	NA	NA	NA	NA	Not included	-	NA	NA	NA	NA
O'Toole (2014, Ireland)	222	38 (17%)	14 (6.3%)	151 (68%)	NA	123	NA	NA	NA	NA	99	NA	NA	NA	NA	Not included	-	NA	NA	NA	NA
Roth (2013, Sweden)	158	53 (33.5%)	64 (40.5%)	41 (25.9%)	NA	92	NA	NA	NA	NA	66	NA	NA	NA	NA	Not included	-	NA	NA	NA	NA

Data extraction sheet PICO 04 & 06 b. Smoking

PICO 04: Is smoking a riskfactor for MC? & PICO 06: In MC patients does smoking cessation influence the disease course?				
STUDIES		STUDY METHODS		
Fisrt Author (year, Country)	Conclusion Note	Study sub-type	Retrospective/Prospective	Quality rating*
Burke (2018, USA)	No association with age of onset MC, association with the intensisty of smoking, the risk of MC decline significantly over time (>5 years), current smoking was associated with an increased risk of CC but not of LC.	Cohort	Prospective	Good
Cotter (2017, USA)	Current smoking is a risk factors for MC in multivariable-adjusted logistic regression model.	Case-control	Retrospective	Moderate
Fernández-Bañares (2013, Spain)	In relation to current smoking there were no differences in either the number of cigarettes per day or the duration of the smoking habit between groups. Frequency of current smokers was higher in young ages, being significant differences both CC and LC and the control group.	Case-control	Prospective	Good
Gu (2012, China)	Not significat asociation of smoking habits with MC.	Case-control	Prospective	Good
Guagnozzi (2015, Spain)	Not significat asociation of smoking habits with MC.	Case-control	Prospective	Good
Larsson (2016, Sweden)	A reduced risk for MC could be seen in both non-drinkers/non-smokers and drinkers/non-smokers, an increased risk was observed, although not statistically significant. There was a strong association between smoking and MC risk (P<0.001).	Case-control	Prospective	Good
Roth (2014, Sweden)	There was an increased risk for both former and current smokers to develop MC (specially for MC with IBS-like symptoms) and no difference between persistent and transiet MC groups was observed.	Case-control	Retrospective	Good
Thorn (2013, Sweden)	Smoking was more prevalent in females compared with the background, however this difference reached significance only for LC patients.	Cohort/case-control	Prospective	Moderate
Verhaegh (2017, NL)	The duration of nicotine exposure enhanched the risk of MC (OR 1.03 95% CI: 1.02-1.06 per years), the average at diagnosis was 58.8 (+/- 9.7 years) vs 59.8 (+/- 12.1 years), p<0.001 for smoking versus nonsmoking at index date, respectively. Passive smoking at work at the index date was also associated with MC (OR: 3.05 95%CI 1.29-7.22) and no association was observed for subjects who had 1 or 2 smoking parents, were exposed to hazardous substances at work or reported a period of excessive alcohol before the index date. The duration of smoking in years was higher in MC patientsvs controls (29.1+/-13.8 vs 23.5+/-13.8 p<0.001).	Case-control	Retrospective	Good
Vigren (2011, Sweden)	Smoking habits did not affect disease activity although there was less activity among those who had never smoked.	Case-control	Retrospective	Good
Wickbom (2017), Sweden	Smokers have a 3-4 fold increased risk for both CC and LC and earlier onset of disease (10 years).	Case-control	Retrospective	Good
Wildt (2018, Denmark)	Smoking was more prevalent among patients with MC (34% vs 10%) than in the control group (p=0.01).	Case-control	Prospective	Moderate
Yen (2011, USA)	Both former and current cigarette smoking was significantly higher in the MC, LC and CC groups, when separated by gender, rates of current or former smoking were still higher in all MC groups across gender.	Case-control	Retrospective	Good
Fernández-Bañares (2013, Spain)	Current smokers developed diarrhea onset >10 years earlier than non smokers. There were no significant differences in either clinical presentation or clinical remission rate.	Cohort	Prospective	Good
Fernández-Bañares (2017, Spain)	Smoking habit is not a risk factor for needing maintenance treatment with budesonide according to the use of NSAIDs.	Cohort	Retrospective	Moderate
Fernández-Bañares (2016, Spain)	There were no differences between patients achieving prolonged disease remission and those not doing so in terms of smoking habits.	Prevalence	Retrospective	Good
Gentile (2013, USA)	Smoking status was not associated with recurrence and the need for maintenance corticoid therapy (p=0.65). Smoking status does not impact initial corticoid treatment response, recurrence or need for maintenance corticoids in patiesnts with MC.	Prevalence	Retrospective	Moderate
Münch (2016)	Current smokers had an increased number of watery stools at baseline compared with non-smokers (p=0.051). No association between the quantity of smoking (cigarettes/day) at baseline and the number of watery stools was observed. An association was found between smoking status (current smokers vs non-smokers OR 0.19 (0.05-0.73), p=0,016) and decreased likelihood of obtaining clinical remission in the logist regression model.	RCTs	Retrospective	Moderate
O'Toole (2014, Ireland)	Smoking habit is not a risk factor for spontaneous remission.	Prevalence	Retrospective	Moderate
Roth (2013, Sweden)	Patients with higher education smoked to a lesser extent than those who had no university degree (MC vs MC with IBS symptoms).	Prevalence	Retrospective	Moderate

Data extraction sheet - PICO 05 Gender risk

PICO 05: Is there a female risk for MC?																		
STUDIES		GENDER									STUDY METHODS							
First Author (year, Country)	Study time period	N MC	N women with MC	N CC	N women with CC	N LC	N women with LC	N total women population	CC F/M Ratio	LC F/M Ratio	Retrospective/ Prospective	Level of study	Appropriate sample frame	Study participants sampled in an appropriate way	Sufficient coverage of the identified samples	CC and/or LC diagnosis according to standard methods	Valid definition of CC and/or LC used	Quality rating*
Bohr (1995, Sweden)	1984-1993	0	0	30	27	0	0	833334	9	NA	Retrospective	Local	Yes	Yes	Yes	Yes	Yes	Good
Fernandez-Bañares (1999, Spain)	1993-1997	60	46	23	19	37	27	500000	4.8	2.7	Prospective	Local	Yes	Yes	Yes	Yes	Yes	Good
Agnarsdottir (2002, Iceland)	1995-1999	125	108	71	63	54	45	679100	7.9	5	Retrospective	National	Yes	Yes	Yes	Yes	No	Moderate
Olesen (2004)	1993-1998	97	76	51	45	46	31	520408	7.5	2.1	Retrospective	Local	Yes	Yes	Yes	Yes	Yes	Good
Heron (2005, UK)	1999-2004	33	22	NA	NA	NA	NA	1000000	NA	NA	Retrospective	State/Provincial	Yes	Yes	Yes	Unclear	Unclear	Poor
Rajan (2005, UK)	1998-2003	0	0	37	28	0	0	2176471	3	NA	Retrospective	State/Provincial	Yes	Yes	Yes	Unclear	Unclear	Moderate
Pardi (2007, USA)	1985-2001	130	91	46	40	84	52	741936	6.7	NA	Prospective	Local	Yes	Yes	Yes	Yes	Yes	Good
Bjornbak (2011, Denmark)	1999-2010	438	308	270	200	168	108	1250000	2.9	NA	Retrospective	Local	Yes	Yes	Yes	Yes	Yes	Good
Fernandez-Bañares (2011, Spain)	2004-2008	72	52	40	31	32	21	689655	3.4	2	Prospective	Local	Yes	Yes	Yes	Yes	Yes	Good
Guagnozzi (2012, Spain)	2008-2010	32	17	NA	NA	NA	NA	93750	NA	NA	Retrospective	Local	Yes	Yes	Yes	Yes	Yes	Good
Vigren (2012, Sweden)	2001-2010	0	0	198	146	0	0	1833333	2.8	NA	Retrospective	State/Provincial	Yes	Yes	Yes	Yes	Yes	Good
Daferera (2013, Sweden)	1999-2008	92	70	44	38	48	32	333334	6	2	Retrospective	Local	Yes	Yes	Yes	Yes	Yes	Good
Thorn (2013, Sweden)	2005-2009	272	204	154	125	118	79	1100000	4.3	2.1	Prospective	State/Provincial	Yes	Yes	Yes	Yes	Yes	Good
Wickbom (2013, Sweden)	1999-2008	186	149	96	75	90	74	923077	3.6	4.6	Prospective	Local	Yes	Yes	Yes	Yes	Yes	Good
Gentile (2014, USA)	2002-2010	182	139	NA	NA	NA	NA	433333	NA	NA	Retrospective	Local	Yes	Yes	Yes	Yes	Yes	Good
Bonderup (2015, Denmark)	2002-2011	7777	5538	4749	3591	3028	1947	2,7E+07	3.1	1.8	Retrospective	National	Yes	Yes	Yes	Yes	Yes	Good
Verhaegh (2015, Netherlands)	2000-2012	6459	4746	3741	2837	2718	1909	1E+08	3.1	2.3	Retrospective	National	Yes	Yes	Yes	Yes	Yes	Good
Fumery (2017, France)	2005-2007	130	101	87	70	43	31	826923	4.1	2.6	Prospective	State/Provincial	Yes	Yes	Yes	Yes	Yes	Good
Kane (2017, UK)	2010-2015	540	379	291	223	203	126	2385246	3.3	NA	Retrospective	Local	Yes	Yes	Yes	Yes	Yes	Good
Lewis (2017, UK)	2005-2016	843	512	NA	NA	NA	NA	2322314	NA	NA	Retrospective	State/Provincial	Yes	Yes	Yes	Unclear	Unclear	Poor
Davidson (Sweden-2018)	2011-2015	549	386	379	279	170	107	3211864	2.8	1.7	Prospective	State/Provincial	Yes	Yes	Yes	Yes	Yes	Good
Davidson (Denmark-2018)	2010-2016	1123	787	670	502	453	285	2042683	3	1.7	Prospective	State/Provincial	Yes	Yes	Yes	Yes	Yes	Good
Bergman (2019, Sweden)	1995-2015	13844	9968	4606	3547	9238	6467	9,6E+07	3.6	2.4	Retrospective	National	Yes	Yes	Yes	Yes	Yes	Good

Data extraction sheet – PICO 07 Drug Risk

PICO 07: Is drug use associated with a significant increased risk of MC?																						
STUDIES	STUDY GROUPS									PPI		SSRI		STATIN		NSAID		ASPIRIN		STUDY METHODS	
Fisrt Author (year, Country)	N MC	N CC	N LC	N controls	Type of control group	N (%) Drugs induced MC	OR[95%IC] or P value MC	N (%) drugs induced Controls	Time retained between start drug and dg of MC	MC	Controls	MC	Controls	MC	Controls	MC	Controls	MC	Controls	Restrospective/ Prospective	Quality rating*
Riddell (1992, Canada)	31	31	0	31	IBS and diverticular disease	19 (61.2%)	< 0.02	4 (12.9%)	> 6 monthes	NA	NA	NA	NA	NA	NA	15	1	11	3	Retrospective	Good
Fernandez-Bañares (2007, Spain)	78	39	39	97	Outpatients attending surgery	CC 92 / CL 90	< 0.05	72.8	not detrmined	14	17	18	1	6	3	23	22	4	6	Retrospective	Good
Keszthelyi (2010, NL)	95	NA	NA	355	Community-based controls	PPIs 37.9	4.5 (2.0-9.5)	PPIs 2.6	6 monthes	36	45	NA	NA	NA	NA	19	26	NA	NA	Retrospective	Good
Pascua (2011, USA)	26	11	15	518	Chronic diarrhea	88	259/259	98/96	12 monthes	3	206	5	124	6	183	NA	NA	NA	NA	Retrospective	Good
Harma (2011, NA)	9	0	9	33	Colonoscopy control	NA	NA	NA	NA	3	12	NA	NA	NA	NA	NA	NA	NA	NA	Retrospective	Moderate
Fernandez-Bañares (2013, Spain)	190	120	70	128	Outpatients attending surgery	NA	NA	NA	15-60 months	62	38	15	13	NA	NA	NA	NA	34	10	Prospective	Good
Macaigne (2014, France)	129	42	87	278	Functional bowel disorder with diarrhea	53	3.7 (2.1–6.6)	24	3 monthes	12	3	6	9	5	1	5	6	NA	NA	Prospective	Good
Bonderup (2014, Denmark)	5.751	3.474	2.277	575.100	Community-based controls	CC 80.5 / CL 73.2	NA	49.8 / 46.7	12 monthes	4039	78704	1158	48332	1643	295659	2075	139545	NA	NA	Retrospective	Good
Guagnozzi (2015, Spain)	46	4	42	317	Chronic diarrhea	33 (71.7)	NA	215 (67.8)	NA	22	128	43	124	NA	NA	8	33	2	28	Retrospective	Good
Masclee (2015, NL)	218	92	70	15.045	Community-based and colonoscopy control	NA	NA	NA	3 months	66	398	20	90	39	349	27	225	32	105	Prospective	Good
Yen (NA)	64	NA	NA	121	Chronic diarrhea	NA	NA	NA	>2 weeks	16	32	6	9	21	30	29	24	16	12	Prospective	Good
Verhaegh (2016, UK)	1.211	394	292	6.041	Community-based controls	64.6	0.38 (0.33-0.44)	43.6	6 monthes	506	1054	186	451	327	1431	250	679	NA	NA	Retrospective	Good
Bonderup (2018, Denmark)	10.652	6.254	4.398	101.381	Community-based controls	PPIs : 11.9%	3.95 (3.60-4.33)	PPIs 3.76%	3 monthes	3737	9879	2449	10252	2456	17400	2024	11341	NA	NA	Retrospective	Good

Data extraction sheet – PICO 08 a. Drug withdrawal

PICO8: Shoul any drug, potentially related to MC onset, been withdrawn?										
STUDIES	PATIENTS			DRUG INTAKE					STUDY METHODS	
Fisrt Author (year)	N MC	N LC	N CC	Time retained between start drug and diagnosis of MC	Clinical remission at drug discontinuation	Histologicalal remission at drug discontinuation	Positive reintroduction test	Drug	MC case definition	Quality rating*
Beaugerie (1994, France)	3	1	0	2 weeks	yes	yes	yes	Ruscus aculeatus and hespéridine méthylchalcone	yes	Good
Beaugerie (1995, France)	1	1	0	2 months	yes	yes	yes	Ranitidine	yes	Good
Macaigne (2002, France)	1	1	0	4 weeks	yes	yes	NA	Oxetorone	yes	Good
Fathallah (2010, Tunisie)	1	1	0	2 weeks	yes	yes	NA	Oxetorone	yes	Good
Brigot (1998, France)	1	1	0	3.5 months	yes	yes	NA	Ticlopidine	yes	Good
Duncan (1997, UK)	1	0	1	NA	yes	NA	NA	Cimetidine	yes	Good
Pierrugues (1996, France)	4	4	0	NA	yes	NA	NA	Cyclo3 Fort	yes	Good
Chauveau (1998, France)	1	1	0	2 weeks	yes	yes	NA	Vinburnine	yes	Good
Mennecier (2001, France)	1	1	0	NA	yes	no	NA	Rustacea flavonoid extract	yes	Good
Fuste (2000, Spain	1	1	0	NA	yes	yes	NA	Ticlopidine	yes	Good
Larzillere (1999, France)	1	1	0	4 months	yes	NA	NA	Ticlid	yes	Good
Macaigne (2008, France)	1	1	0	2 months	yes	yes	NA	Esbeviren (melilot + rutoside)	yes	Good
Lim (2008, France)	1	1	0	1 month	yes	yes	NA	Lévodopa / Bensérazide	yes	Good
Thiolet (2003, France)	1	1	0	NA	yes	no	no	Cyclo3 Fort	yes	Good
Maroy (2010, France)	1	1	0	2 months	yes	yes	NA	Carbamazepine	yes	Good
Mennecier (1999, France)	1	1	0	8 days	yes	NA	NA	Piroxicam fl-cyclodextrin	yes	Good
Macaigne (2001, France)	1	0	1	2 months	yes	yes	NA	Lansoprazole	yes	Good
Bouvet (1998, France)	1	1	0	1 month	yes	yes	NA	Ticlopidine	yes	Good
Hilmer (2006, Australia)	3	1	0	2 months	yes	NA	NA	Lansoprazole	yes	Good
Swine (1998, Belgique)	3	1	0	4 weeks	yes	NA	NA	Ticlopidine	yes	Good
		1	0	5 weeks	yes	NA	NA	Ticlopidine		
		1	0	9 weeks	yes	NA	NA	Ticlopidine		
Wilcox (2002)	1	0	1	< 1 week	yes	yes	yes	Lansoprazole	NA	Moderate
Feurle (1999)	1	1	0	NA	yes	NA	NA	Ticlopidine	yes	Good
Mennecier (1999)	1	1	0	8 days	yes	NA	NA	Piroxicam beta-cyclodextrina	yes	Good
Riddel (1992)	19	0	19	6 months to 15 years	NA	NA	NA	NSAIDs	yes	Good
Maroy (2008)	3	1	0	14 weeks	yes	No	yes	Entacapone	yes	Moderate
Linares Torres (2000)	1	1	0	NA	yes	NA	NA	Carbamazepine	yes	Good
Macaigne (2004)	1	1	0	6 weeks	yes	yes	NA	Saponifiable soy	yes	Good
Dharancy (2000)	1	1	0	1 month	yes	yes	NA	Ruscus aculeatus and hespéridine méthylchalcone	yes	Good
Bouchet (1997)	1	1	0	2 weeks	yes	NA	NA	Tardyferon	yes	Good
Maroy (2009)	1	1	0	3 weeks	yes	yes	yes	Efitoxine	yes	Good
Piche (2000)	1	1	0	4 weeks	yes	yes	yes	Acarbose	yes	Good
Rassiat (2000)	1	1	0	3 months	yes	NA	NA	Lévodopa / Bensérazide	NA	Moderate
Ghilain (2000)	2	1	0	6 weeks	yes	yes	NA	Lansoprazole	yes	Good
Rosa (1999)	1	1	0	2 weeks	yes	yes	NA	Ticlopidine	yes	Good
Kusnik (2009)	1	1	0	4 weeks	yes	NA	NA	Duloxetine	yes	Good
Pelizza (2007)	1	1	0	3 months	yes	yes	yes	Clozapine	yes	Good
Berrebi (1998)	9	9	0	3 to 8 weeks	yes for 9	yes 5/5 tested	NA	Ticlopidine	yes	Good
Thomson (2002)	6	nd	0	1 month	yes	yes	NA	Lansoprazole	NA	Moderate

Data extraction sheet – PICO 08 b. Drug withdrawal

PICO8: Shoul any drug, potentially related to MC onset, been withdrawn?										
STUDIES	PATIENTS			DRUG INTAKE					STUDY METHODS	
Fisrt Author (year)	N MC	N LC	N CC	Time retained between start drug and diagnosis of MC	Clinical remission at drug discontinuation	Histologicalal remission at drug discontinuation	Positive reintroduction test	Drug	MC case definition	Quality rating*
Bouaniche (1996)	1	1	0	1 month	yes	yes	NA	Ruscus aculeatus and hespéridine méthylchalcone	yes	Good
Gwillim (2012)	1	1	1	6 weeks	yes	NA	NA	Duloxetine	yes	Moderate
Kitagawa (2013)	1	0	1	5 months	yes	yes	NA	Lansoprazole	NA	Moderate
Simsek (2007)	2	2	0	1 week	yes	yes	NA	Lansoprazole	yes	Good
Al-Ghamdi (2002)	1	0	1	4 weeks	yes	yes	NA	Diclofenac/ketoprofen	yes	Good
Capurso (2011)	8	0	1	4 weeks	yes	NA	NA	Lansoprazole	NA	Moderate
Rammer (2005)	1	0	1	1 month	yes	yes	NA	Lansoprazole	yes	Good
Milman (2015)	1	0	1	3 days	no	NA	NA	Diclofenac	NA	Moderate
Chiba (2009)	1	0	1	6 months	yes	yes	yes (clinical)	Lansoprazole	yes	Good
Ranjit (2015)	1	1	0	2 weeks	yes	NA	NA	Sertraline	NA	Moderate
Yagi (2001)	1	0	1	6 years (aspirine)	yes	yes (ticlid)	NA	Aspirine-ticlopidine	yes	Moderate
Verschueren (2005)	1	0	1	2 years	yes	NA	NA	Leflunomide	NA	Moderate
Sawada (2010)	1	0	1	6 yeas	yes	yes	NA	Lansoprazole	yes	Good
Salter (2017)	1	1	0	8 weeks	yes	NA	NA	Duloxetine	NA	Moderate
Ozeki (2013)	1	0	1	< 6 months	yes	yes	NA	Lansoprazole	yes	Good
Nomura (2010)	1	0	1	4 months	yes	NA	NA	Lansoprazole	NA	Good
Gugenberger (2008)	1	1	0	6 weeks	yes	NA	NA	Leflunomide	yes	Good
Wilcox (2009)	4	0	1	<6 months	yes	NA	NA	Esomeprazole	no	Good
		1	0	4.5 years	yes	yes	NA	Omeprazole	NA	Good
		0	1	3.5 years	yes	yes	NA	Esomeprazole	NA	Good
		0	1	2 months	yes	NA	yes (clinical)	Omeprazole	NA	Good
Chande (2007)	2	0	2	6 weeks	yes	yes	NA	Lansoprazole	NA	Good
Nielsen (2013)	1	1	0	NA	yes	NA	NA	Olmesartan	yes	Moderate
Mukherjee (2003)	1	1	0	4 weeks	yes	yes	NA	Lansoprazole	no	Moderate
Murasawa (2015)	1	0	1	6 months	yes	NA	NA	Rabeprazole	yes	Good
Giardello (1990)	2	0	1	2 months	yes	NA	NA	Indometacine	yes	Good
		0	1	2 months	s after oral classic cortic	yes	NA	Ibuprofene	yes	Moderate
Umeno (2013)	1	0	1	NA	yes	NA	NA	Lansoprazole	no	Moderate

Data extraction sheet – PICO 09: Adenoma CCR

PICO9: Should MC patients requiere a special programme for colonoscopy surveillance to rule out colorectal cancer compared to general population?																					
STUDIES	COLONIC ADENOMA AND/OR NEOPLASIA RISK IN STUDY GROUPS																		STUDY METHODS		
Fisrt Author (year, Country)	N MC	N Colonic adenomas in MC (%)	N CRC in MC (%)	N CC	N Colonic adenomas in CC (%)	N CRC in CC (%)	N LC	N Colonic adenomas in LC (%)	N CRC in LC (%)	N Controls	N Colonic adenomas in controls (%)	N CRC in controls (%)	OR[95%IC] or P value for colonic adenoma in MC	OR[95%IC] or P value for CRC in MC versus control group	Mean FU of MC patients	Controls type	N of total colonoscopy	Study type	Retrosective/ Prospective	Quality rating*
Chan (1999, USA)	0	NA	NA	117	NA	0	0	NA	NA	NA	NA	22	0.52 (95% CI: 0.05-1 5)	RR 0.52 [95% CI: 0.05-1.5.), P=NS	7 years	General population	NA	Case series	Retrospective	Good
Coyne (2014, UK)	10	10 (100%)	NA	7	7 (100%)	NA	3	3 (100%)	NA	Not include d	NA	NA	NA	NA	NA	Not included	NA	Cohort	Retrospective	Poor
Fernández-Bañares (2016, Spain)	100	15%	0 (0%)	NA	NA	NA	NA	NA	NA	288	53 (18.5%)	1 (0.3%)	0.76 (95% CI 0.4-1.5), P=NS	0.26 (95% CI: 0.08-0.85), P=NS	NA	Chronic diarrhea and population of screening programme	NA	Case series	Retrospective	Good
Gentile (2014, USA)	182	NA	2 (1.1%)	78	NA	1 (1.3%)	104	NA	1 (0.96%)	Not include d	NA	NA	NA	NA	NA	Not included	NA	Prevalence	Retrospective	Poor
Kao (2009, USA)	547	NA	10 (1.8%)	171	NA	1 (0.6%)	376	NA	0 (0%)	547	NA	NA	NA	NA	NA	Normal population	NA	Case-control	Retrospective	Moderate
Levy (2019, USA)	221	79 (35.7%)	9 (4.1%)	112	NA	NA	109	NA	NA	306	121 (39.5%)	10 (3.3%)	1.07 [95% CI 0.69–1.66] p<0.005	0.83 (95% CI 0.20–3.39)	3.5 years	Screening and surveillance programme	306	Case-control	Retrospective	Good
McPhaul (2013, USA)	9521	NA	NA	4183	285 (6.8%)	NA	4784	588 (12.3%)	NA	104,44	20783 (19.9%)	NA	0.57 (95%ci: 0.52-0.62, p<0.0001 for LC and 0.30 (95% CI: 0.26-0.33, p<0.0001) for CC	NA	NA	Chronic diarrhea	NA	Case series	Retrospective	Moderate
Mellander (2016, Sweden)	795	42 (5.3%)	NA	341	NA	NA	453	NA	NA	Not include	NA	NA	NA	NA	NA	Not included	NA	Cohort	Retrospective	Moderate
Mills (1993, Georgia)	36	11 (30.6%)	0	0	NA	NA	33	11 (33.3%)	0	0	NA	NA	NA	NA	NA	Not included	NA	Cohort	Retrospective	Poor
Tontini (2014, Italy)	43	2 (4.6%)	0	30	1 (3.3%)	0	13	1 (7,6%)	0	201	36 (17.9%)	8 (2.6%)	NA	0.22 (95% CI: 0.05–0.97), p=0.035	NA	Chronic diarrhea	8006	Case series	Prospective	Good
Yen (2011, USA)	647	121 (18.7%)	12 (1.9%)	261	40 (15.3%)	5 (1.9%)	386	81 (21.0%)	7 (1.8%)	647	217 (33.5%)	27 (4.2%)	0.46 (95% CI: 0.35–0.59), p<.0001	0.43 (95% CI: 0.22–0.86), p=0.018	147	Sourveillance programme	991	Case series	Retrospective	Good

Workgroup 3:
Data extraction sheet - PICO 01 a. Symptoms

PICO 01: What are the symptoms of MC?																		
Author	Period	Country	Study Type	N tot	N MC	N CC	N LC	N CIs	Sex	Mean Age	% Diarrhea	% Urgency	% Incontin.	% Abd Pain	% Bloating	% Weight L.	% Noctur. S.	%Acute onset	%Constip.
Bjørnbak C (2011)	99-10	Denmark	prosp + retro	539	539	270	168	0	F70%	65/63	90(340/376)	72(122/170)	39(60/152)	50(160/322)	.	55(185/339)	51(85/168)	.	.
Bohr J (1996)	89-95	Sweden	retro CS	163	163	163	0	0	F87%	55(18-87)	100(163/163)	.	.	41(62/163)	.	42(64/163)	27(41/163)	42(48/163)	.
Calabrese (2011)	n.a.	Italy	posthoc of RCT	54	54	35	19	0	F76%	40(19-68)	100(54/54)	69(37/54)	22(12/54)	28(15/54)	.	.	33(18/54)	69(37/54)	.
Chande N (2005)	92-02	Canada	retro CS	104	101	66	35	0	F82%	64 (26-88)	95(96/101)	29(29/101)	16 (16/101)	40(40/101)	7 (7/101)	42(42/101)	23(23/101)	.	.
Cotter TG (2018)	06-12	USA	prosp CS	162	162	80	82	0	F74%	66(57-73)	100(162/162)	90(146/162)	62(101/162)	65(105/62)	.	52(84/162)	67(97/162)	.	.
Fumery M (2017)	05-07	France	prosp CS	130	130	87	43	0	F3.5/1	63 (17-90)	93(119/128)	.	7(7/97)	47(61/129)	.	.	.	.	.
Guagnozzi D (2012)	08-10	Spain	prosp CS	271	32	2	30	234	F53%	50±21.8	100(32/32)	.	.	12(4/32)	.	16(5/32)	.	.	.
Jobse P (2009)	15 y	Netherland	retro CS	83	83	83	0	0	F80%	60(20-87)	97(81/83)	.	.	55(46/83)	.	35(29/83)	17(14/83)	.	.
Kane JS (2017)	10-15	UK	retro CS	540	540	291	203	0	F70%	64.9(±12)	53(286/540)	.	.	22(120/540)	.	28 (152/540)	13(69/540)	.	.
Kane JS (2016)	14-15	UK	prosp CS	242	26	14	12	216	F88%	62.5(±10)	100(26/26)	.	.	53(14/26)	.	54(14/26)	77(20/26)	.	.
Koskela RM (2004)	90-99	Finland	retro+prosp	168	84	30	54	84	F66/18	54.8(±13)	94(79/84)	.	51(43/84)	94(79/84)	81 (68/84)	68(57/84)	60(50/84)	39(33/84)	.
Macaigne G (2014)	10-12	France	prosp CS	433	129	87	42	304	F74%	61(±18.8)	100(129/129)	.	.	53(69/129)	.	48(62/129)	41(53/129)	.	.
Madisch A (2014)	98-04	Germany	prosp CS	494	494	287	207	0	F76%	65/61	90(444/494)	.	.	24(118/494)	.	49(240/494)	63(310/494)	.	.
Maye A (2018)	n.a.	Switzerland	retro CS	200	200	81	108	0	F76%	63.5(±14)	100)	.	.	32(64/200)	.	30(61/200)	.	.	.
Mellander MR (2016)	80-10	Sweden	retro CS	795	795	344	451	0	F76%	61(13-97)	94(745/795)	22(45/204)	.	29(128/442)	.	35(170/481)	23(63/279)	.	.
Nyhlin N (2014)	98-08	Sweden	case control	839	212	115	97	627	F83%	66/64	43/47%	.	36(77/212)	50(106/212)	.	.	15(31/212)	.	.
O'Toole A (2014)	93-10	Ireland	retro CS	222	222	123	99	0	F170/52	64(32-90)	98(218/222)	.	8(18/222)	24(53/222)	.	10(22/222)	.	.	.
Olesen M (2004)	n.a.	Sweden	retro CS	199	199	0	199	0	F2.4/1	59(48-70)	96(191/199)	.	9(18/199)	47(93/199)	11 (21/199)	41(82/199)	39(77/199)	25(50/199)	.
Porras Perez FP (2012)	2009	UK	retro CS	49	49	34	15	0	F38/11	66(34-90)	100(49/49)	.	8(4/49)	24(12/49)	.	6(3/49)	.	.	.
Rubio-Tapia A	95-05	Mexico	retro CS	26	26	10	16	0	F1.8/1	56(26-85)	100(26/26)	.	.	69(18/26)	.	84(22/26)	.	.	.
Sifuentes GWA (2015)	99-14	Spain	retro CS	97	97	29	61	0	F2.1/1	66(15-88)	95(92/97)	7(7/97)	.	44(43/97)	.	51(50/97)	13(13/97)	.	.
Silva M (2017)	08-15	Portugal	retro obs.	25	25	13	12	0	F54%	67(22-83)	96(24/25)	.	.	44(11/25)	.	44(11/25)	.	.	.
Sonnenberg A (2013)	08-11	USA	retro CS	789 568	8 745	3760	4460	780 823	F72-82%	63/66	84(7379/8745)	.	.	10(880/8745)	.	6(542/8745)	.	.	1(97/8745)
Svensson M (2018)	2016	Sweden	cross sectional	211	200	75	125	9	F70%	66(21-90)	99(198/200)	.	2(4/200)	12(23/200)	.	24(48/200)	.	.	.
Verhaegh B (2017)	?-17	Europe	prosp. registry	193	193	87	79	0	F69%	65±14	43	80(154/193)	48(93/193)	48(93/193)	.	.	46(89/193)	.	.

Data extraction sheet – PICO 01 b. Symptoms

PICO 01: What are the symptoms of MC?											
Author	Appropr. Sampling	Appropr. Recruitm.	Adequate S. Size	Setting described	Appropr. Coverage	Proper Dignosis	Reliable Measure	Appropr. Statistics	Adequate Response	Study Quality	Comments
Bjørnbak C (2011)	yes	yes	yes	yes	N/A	yes	yes	yes	N/A	high	101 pts with MCi included
Bohr J (1996)	no	no	yes	no	N/A	yes	yes	N/A	N/A	moderate	only CC patients included
Calabrese (2011)	no	no	no	no	N/A	yes	yes	yes	N/A	low	
Chande N (2005)	no	no	no	no	N/A	yes	yes	N/A	N/A	low	3 patients with both CC and LC
Cotter TG (2018)	no	yes	yes	no	N/A	yes	yes	yes	N/A	moderate	MCDAI, frequency of diarrhea not stated, but it is assumed to be 100%
Fumery M (2017)	yes	yes	yes	yes	N/A	yes	yes	yes	N/A	high	
Guagnozzi D (2012)	yes	yes	no	no	N/A	yes	yes	N/A	N/A	moderate	consecutive pts refered for diarrhea
Jobse P (2009)	unclear	no	no	yes	N/A	no	no	N/A	N/A	low	15 consecutive ys from pathology DB
Kane JS (2017)	yes	yes	yes	yes	N/A	yes	yes	yes	N/A	high	46 patients with MCi included
Kane JS (2016)	yes	yes	no	yes	N/A	yes	yes	yes	N/A	high	cons. pts with diarrhea: MC Vs notMC
Koskela RM (2004)	yes	no	no	yes	N/A	yes	yes	yes	N/A	low	retrospective (pathology based) and prospective design
Macaigne G (2014)	yes	yes	yes	yes	N/A	yes	yes	yes	N/A	high	consecutive pts refered for diarrhea, MC vs FBD-D
Madisch A (2014)	no	no	yes	no	N/A	yes	yes	yes	N/A	moderate	data results section vs data table not fitting
Maye A (2018)	no	yes	yes	no	N/A	unclear	unclear	unclear	N/A	very low	11 patients with MCi, conference ABR
Mellander MR (2016)	no	no	yes	no	N/A	yes	no	yes	N/A	low	some symptoms plotted on diagram without exact%
Nyhlin N (2014)	yes	yes	yes	no	N/A	yes	yes	yes	N/A	high	questionnaire-based case control study: outcome of symptoms and QoL
O'Toole A (2014)	yes	no	yes	yes	N/A	yes	yes	N/A	N/A	moderate	
Olesen M (2004)	yes	yes	yes	no	N/A	no	yes	yes	N/A	moderate	retro CS on patients with LC
Porras Perez FP (2012)	no	no	no	no	N/A	unclear	unclear	N/A	N/A	very low	6-month histopathological report-based case review, conference ABR
Rubio-Tapia A (2007)	no	no	no	no	N/A	yes	yes	yes	N/A	low	retro CS, 26 cases, all with diarrhea
Sifuentes GWA (2015)	no	no	no	no	N/A	unclear	unclear	unclear	N/A	low	7 pts with LC-CC overlap, conference ABR
Silva M (2017)	no	no	no	no	N/A	unclear	unclear	unclear	N/A	very low	
Sonnenberg A (2013)	no	no	yes	no	N/A	yes	yes	yes	N/A	low	computer-based DB: 8745MC, 525(6%) Mci
Svensson M (2018)	yes	no	yes	yes	N/A	yes	yes	yes	N/A	moderate	2 MCi included, histopathological report-based case review
Verhaegh B (2017)	no	no	yes	no	N/A	unclear	unclear	unclear	N/A	low	27 pts with MCi included

Data extraction sheet – PICO 02 Rule out MC

PICO 02: Should MC be ruled out in patients fulfilling the criteria for functional bowel disease with diarrhoea predominant subtype?								
STUDIES	STUDY GROUPS		FREQUENCY OF MC IN IBS			FREQUENCY OF IBS IN MC		
First author (year)	N MC	All IBS	%MC in IBS	%CC in IBS	%LC in IBS	%IBS in MC	%IBS in CC	%IBS in LC
Guagnozzi (2016)	1507	3592	7%	1.4%	4.3%	39.1%	28.4%	40.7%
Kane (2016)	420	1758	7.4%	2.7%	3.2%	33.4%	21.4%	11.5%
Kane (2018)	151	52	NA	NA	NA	34.4%	NA	NA
Hilpüsch (2017)	4	87	4.6%	NA	NA	NA	NA	NA

PICO 02: Should MC be ruled out in patients fulfilling the criteria for functional bowel disease with diarrhoea predominant subtype?												
STUDIES	STUDY METHODS											
First author (year)	Study type	Clearly review question	Appropriate inclusion criteria	Appropriate search strategy	Adequate sources and resources	Critical appraisal by two or more reviewers independently	Method to minimize data extraction error	Appropriate methods used to combine studies	Likelihood of publication bias assessed	Recommendations for policy and/or practice supported by the reported data	Appropriate specific directives for new research	Quality rating*
Guagnozzi (2016)	Systematic review/meta-analysis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Kane (2016)	Systematic review/meta-analysis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Moderate
Kane (2018)	Prospective cohort	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Good
Hilpüsch (2017)	Retrospective cohort	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Moderate

Data extraction sheet – PICO 03 Quality of Life

PICO 03: Is the patient health-related quality of life affected by MC ?																					
Author (Year, Country)	Study Type	N tot	N MC	N CC	N LC	N Controls	Sex	Mean Age	LowQoL in active MC	LowQoL in inactive MC	QoL better with Tx	Symptom-driven QoL severity	Two groupssimilar	Exposures measured similarly	Exposure measured Valid/Reliable	Outcome measured	F-up time	F-up complete	Appropr. Statistics	Study Quality	Remarks
Cotter T (2018, US)	Prosp	162	162	80	82	0	F1.35/1	66(57-63)	Yes	.	.	Unformed s, nocturn s, incontin, weight l,	.	yes	yes	IBDQ, SF-30	8 weeks	yes	yes	high	MCDAI strongly predicted the PGA and correlated with a validated measure of QoL
Hjortswang H (2009, Sweden)	CS	116	116	116	0	0	F3.8/1	62(55-73)	yes	no		s. freequency, watery s.	.	yes	yes	SHS, PGWB, IBDQ, RFIPC	na	na	yes	high	Severity of bowel symptoms had a deleterious impact on HRQOL of pts wit CC
Hjortswang H (2011, Sweden)	CS	116+8931	116	116	0	8931	F3.8/1	62(55-73)	yes	.		s. freequency, watery s.	no	yes	yes	SF-36, PGWB,IBDQ, RFIPC	na	na	yes	high	HRQOL was significantly impaired in pts with CC compared to controls
Kane JS (2018, UK)	CS	129	129	69	50	.	.	.	n.a	n.a.	.	fatigue, ansiety,depression, somatization	.	.	yes	HADS,PHQ15, SF-36, IBDF	.	yes	yes	high	Significant correlation beetwen fatigue severity and psychological comorbidities and impaired HRQOL
Kane JS (2018, UK)	CS	151	151	78	59	.	F75%	68	n.a	n.a.	.	IBS Roma III symptoms, ansiety, depression, somatization	.	.	yes	IBS Roma III criteria, HADS, PHQ15, SF-36	.	na	yes	high	1/3 of MC met diagnostic criteria for IBS and these reported higher levels of anxiety, depression, somatization. impaired HRQOL
Madisch A (2005,	RCT	51	51	29 Bude	.	12 PCB	.	.	yes	no	yes	.	.	yes	yes	GIQLI	6 weeks	yes	yes	high	HRQOL was severely reduced in CC pts; 6 wks Tx with oral budesinide improved HRQOL
Madisch A (2007,	RCT	21	21	16 Bossw	.	15 PCB	Bosw. F87% PCB	Boswellia 64; PCB 53	yes	.	.	s. freequency and consistency	.	yes	yes	SF-36	6 weeks	yes	yes	low	Boswellia serrata had no effects on HRQOL
Miehlke S (2008, Germany)	RCT	48	48	23 Bude	.	23 PCB	F73%	57.5(34-78)	yes	no	yes	S.freequency&consistency, abd pain weight l., duration diarrhoea	.	yes	yes	SF-36, IBDQ	6 weeks	6 mo	yes	high	HRQOL was impaired in CC pts; HRQOL Improvenment was observed during 6 wks of Tx with Bude and during maintenace.
Miehlke S (2009, Germany)	RCT	42	42	.	21 Bude	21 PCB	Bude F13; PCB F15	Bude 61(36-80); PCB 61(23-76)	yes	no	yes	S.freequency&consistency, abd pain, weight l., duration diarrhoea	.	yes	yes	SF-36	6 weeks	.	yes	high	At baseline HRQOL was impaired in LC pts; Bude induced clinical remission and improved HRQOL in LC pts
Munch A (2016, Sweden)	RCT	110	110	44 Bude	.	48 PCB	Bude F4; PCB F10	Bude 57, PCB 61	yes	no	yes	Hjortswang criteria	yes	yes	yes	SHS, PGWBI	8wks induction + 52wks	.	yes	high	Efficacy of Bude to induce clinical remission in CC pts and to improve HRQOL; efficacy of low dose Bude to maintain remission/HRQOL.
Munch A (2013,	series	9	9	9 MTX	.	.	F7	62(44-77)	yes	no	yes	Hjortswang criteria	.	.	yes	SHS	12 weeks	yes	no	low	In Bude refractory CC, MTX had no clinical effect nor improved HRQOL
Munch A (2012,	series	3	3	3 ADA	.	.	F2	45-74	yes	.	yes	Hjortswang criteria	.	.	yes	SHS, PGWBI	6 weeks	yes	no	low	In Bude and MTX refractory CC, ADA appeared to be effective
Nyhlin N (2014, Sweden)	Case Control	277+831	277	115	97	831	.	.	yes	no	.	.	yes	yes	yes	SHS	.	yes	yes	high	HRQOL was impaired in CC and LC; in clinical remission, CC and LC suffer from abdominal pain, fatigue, arthralgia or myalgia.
Roth B (2013, Sweden)	CS	158	158+2162	.	.	2162	MC F 158; Controls F 2162	MC 63(68-67); CTL 51 (19-94)	yes	.	.	Severity of GI symptoms and psycological GWB	no	yes	yes	.GSRS, PGWBI, IBS Roma III criteria	.	.	yes	low	Smoking and IBS symptoms were associated with impaired GI symptoms and psychological well-being in MC
Roth B (2013, Sweden)	CS	158	158	.	.	.	F158	63(27-73)	yes	.	.	GI sympyoms severity, psychological GW-B	no	yes	yes	GSRS,PGWBI, VAS-IBS, IBS Rome III criteria	.	.	yes	low	MC pts fullfilling IBS Roma III criteria experienced more GI symptoms and worse psychological well-being
Wildt S (2006, Denmark)	RCT	29	29	21 Probiot	.	8 PCB	Probiotic F/M 1/20 - PCB 1/7	Probiotic 61 (3-73); PCB 57 (26-	yes	.	.	S. frequency&consistency, abdominal pain, blooting	no	yes	yes	SIBDQ	12 weeks	yes	yes	low	Probiotic had no significant effects both on intestinal symptoms and HRQOL
Miehlke S (2018, Europe)	RCT	57	57	.	19 Bude, 19	19 PCB	Bude F 15; Mesalam. F 14; PCB F	Bude 61; Mesalam. 57; PCB 59	yes	no	yes	S.frequency&consistency, N.sools/day, N.watery s./day	yes	yes	yes	GIQLI, SHS	8 weeks	yes	yes	high	Bude was effective and safe for induction of clinical and histological remission in pts with LC, it also improved HRQOL.

Data extraction sheet – PICO 04 Established Metrics to measure

PICO 04: Are there established metrics to measure disease activity and severity in MC ?																					
Author (Year, Country)	Study Type	N tot	N MC	N CC	N LC	N Ctls	Sex F	Mean Age (r)	Score adopted/developed	Two group similar	Exposures measured similarly	Exposure measured Valid/Reliab	Confoundig factors	Strategies to deal	Groups free of outcome	Outcome measured	Follow up time	Follow up complete	Strategies for incomp FU	Appropr statistics	Study Quality	Comments
Hjorstwang H (2009, Sweden)	CS	116	116	116	0	0	3.83	62(55–73)	HC (a mean of <3 stools/day and <1 watery stool/day.)	na	na	yes	0	yes	na	yes	na	na	na	yes	high	this study defined clinical remission in CC based on symptoms only, the study conclusions received no external nor formal prospective validation but, the HC has been widely adopted in RCT (informal validation in clinical practice, as for the Mayo score in UC)
Pardi D (2018, US)	Prosp	162	162	80	82	0	1.35	66(57-63)	MCDAI less or equal 1.32	na	na	yes	yes	yes	na	yes	yes	yes	no	yes	high (very high)	adeqautely powered cohort, both CC and LC, diagnostic criteria confirmed within 3mo; compared to the HC, this incorporates factors apart from bowel movements (PROs), enables stratification according to disease severity (not only a binomial outcome on disease activity/remission). Not yet formally validated (externally and prospectively) nor used in RCT (up to Dec2019).

Workgroup 5:
Data extraction sheet – PICO 5.1 Budesonide

PICO 5.1: Is oral budesonide effective in inducing remission of MC ?															
Author (year)	Design	Diagnosis	Inclusion criteria	Nº patients		Budesonide dosis, time and Trade Mark	Clinical Remission		P-value	Histological Response		p-value	Adverse events		Considerations
				Budesonide	Placebo		Budesonide	Placebo		Budesonide	Placebo		Budesonide	Placebo	
Baert (2002)	DB-RCT	CC	Active watery diarrhoea CC histological criteria	14	14	9 mg/d, 8 weeks, (Budenofalk caps)	8 out of 11	3 out of 12	0.05	13 out of 13	4 out of 12	0.001	NA	NA	
Bonderup (2003)	DB-RCT	CC	Active watery diarrhoea CC histological criteria	10	10	9 mg/d, 4 weeks and tapering until 8 wks (Entocort caps)	10 out of 10	2 out of 10	<0.001	Significant reduction in lamina propia score and collagen thickness	No effect	NA			
Miehlke (2002)	DB-RCT	CC	Active watery diarrhoea CC histological criteria	26	25	9 mg/d, 6 weeks (Entocort caps)	20 out of 26	3 out of 25	<0.001	14 out of 25	1 out of 26	<0.001	38,5	12	
Miehlke (2014)	DB-RCT	CC	Active watery diarrhoea CC histological criteria	30	37	9 mg/d, 8 weeks, (Budenofalk caps)	24 out of 30 24 out of 30	22 out of 37 14 out of 37 (Hjorts. Criteria)	0.072 0.0006	20 out of 23	11 out of 22	0.01	0,47	0,54	Mesalazine group (n=25); remission: 8/25 (p<0.001 vs BUD)
Miehlke (2009)	DB-RCT	LC	Active watery diarrhoea LC histological criteria	21	21	9 mg/d, 6 weeks, (Budenofalk caps)	18 out of 21	10 out of 21	0.010	11 out of 15	4 out of 13	0.03			
Pardi (2009)	DB-RCT	LC	NA	11	4	9 mg/d, 8 weeks	10 out of 11	1 out of 4	0.03	7 out of 8	1 out of 3		NA	NA	
Miehlke (2018)	DB-RCT	LC	Active watery diarrhoea LC histological criteria	19	19	9 mg/d, 8 weeks, (Budenofalk granules)	15 out of 19	08 out of 19	0.010	13 out of 15	5 out of 14	0.008	47.4%	42.1%	Mesalazine group (n=19); remission: 12/19 (p=NS vs BUD)

Data extraction sheet – PICO 5.2 Budesonide

PICO 5.2: Is oral budesonide effective for maintaining remission of MC ?															
Author (year)	Design	Diagnosis	Inclusion criteria	Nº patients		Budesonide	Clinical Remission		P-value	Histological Response maintained		p-value	Adverse events		Considerations
				Budesonide	Placebo	dosis, time and Trade Mark	Budesonide	Placebo		Budesonide	Placebo		Budesonide	Placebo	
Bonderup (2009)	DB-RCT	CC	Budesonide-induced clinical remission	17	17	6 mg/d, 24 weeks (Entocort caps)	13 out of 17	2 out of 17	<0.001	9 out of 10	4 out of 11		5 out of 17	8 out of 17	
Miehlke (2008)	DB-RCT	CC	Budesonide-induced clinical remission	23	23	6 mg/d, 24 weeks (Entocort caps)	17 out of 23	8 out of 23	0.022	14 out of 15	5 out of 8	0.10	8 out of 23	8 out of 23	
Munch (2016)	DB-RCT	CC	Budesonide-induced clinical remission	44	48	3 and 6 mg on alternate days, 12 months (Budenofalk caps)	27 out of 44	8 out of 48	<0.001	NA	NA		31 out of 44	24 out of 48	

Data extraction sheet – PICO 5.3.2 Budesonide

PICO 5.3.2: Is prolonged use of oral budesonide in MC associated with an increased risk of osteoporosis?									
Author (year)	Country	Design	Inclusion criteria	Nº patients		Outcome: Osteporotic fracture			Considerations
				Cases = MC with fractures	Controls = MC without fractures	Cases exposed /unexposed to budesonide	controls exposed / unexposed to budesonide	Adjusted odds ratio, 95% CI	
Reilev, 2019	Denmark	case-control	MC in DK	9234	1240	309/108	870/ 370	1.13 (0.88-1.47)	Dose-respons association

Author (year)	Country	Design	Inclusion criteria	Nº patients		Outcome: Osteopenia and osteporosis			remarks
				MC cases	Healthy controls	MC cases	Healthy controls	p-value	
Wildt, 2018	Denmark	case-control	MC	50	49	29/50	19/49	0.06	Budesonide dose associated with lower BMD

Data extraction sheet – PICO 5.5 Mesalazine

PICO 5.5: Is there a role for mesalazine in MC ?										
First Author (Year)	Country	Study Period	Study Type	Number of patients with MC	Number of patients treated with mesalazine compounds / placebo	Number of patients treated with mesalazine / mesalazine + cholestyramine	Effect measurement	Number treated with effect, N (%)	p-value	Considerations
Miehlke 2014	Germany	8 weeks	DB-RCT	62 CC	25/37		< 4 stools pr day	44% versus 38%	NS	Included also effective budesonide arm
Meihlke 2018	Germany	8 weeks	DB- RCT	38 LC	19/19		Hjortswang criteria	63% versus 42%	NS	Included also effective budesonide arm
Calabrese 2006	Italy	6 months	Prospective randomised trial, open label	64 (41 LC,23 CC)		31 / 33	Complete resolution of diarrhoea	26 (84%) / 30 (91%)		Very high remission rate in all patients !
Bohr 1996	Sweden	1989 - 1995	retrospective cohort	163 CC	31 / 0		Improved symptoms	12 (39%)		Retrospective, dosage and treatment period unclear. Effect measurement undefined
Olesen 2004	Sweden		retrospective cohort	199 LC	33 / 0		Improved symptoms	15 (45%)		Retrospective, dosage and treatment period unclear. Effect measurement undefined
Bjørnbak 2011	Denmark	2000 - 2010	retrospective cohort	549 (270 CC, 168 LC, 101 MCi)	43/ 0		Improvement in diarrhoea	6 (14 %)		Retrospective, dosage and treatment period unclear. Effect measurement undefined
Jobse 2008	Netherlands	1992-2006	retrospective, cross sectional	83 CC	10 / 0		No diarrhoea complaints	8 (80%)		Retrospective, dosage and treatment period unclear. Effect measurement undefined
Colussi 2015	US	2002-2013	retrospective cohorte	131 (76 CC, 55 LC)	19 LC / 0 23 CC / 0		Resolution of diarrhoea	11 LC (58%) 12 CC (52%)		Retrospective, dosage and treatment period unclear. Effect measurement undefined
Fernandez-Banares 2003	Spain	1992- 2001	retrospective cohort	81 (44 LC, 37 CC)	21 LC / 0 24 CC / 0		Complete resolution of diarrhoea	18 LC (86%) 10 CC (42%)		Retrospective, dosage and treatment period unclear. Effect measurement undefined
Fiedler 2001	US	1991 - 1994	retrospective caseseries	26 CC	13 / 0		Normalisation of bowel function	5 (38%)		Retrospective, dosage and treatment period unclear. Effect measurement undefined

Data extraction sheet – PICO 5.5 Subsalisylate

PICO 5.5: Is there a role for bismuth subsalisylate in MC ?										
First Author (Year)	Country	Study Period	Study type	Number of patients with MC	Number of patients treated with bismuth	Effect mesaurement	Number treated with effect, N (%)	Side effects, N	Quality rating	Considerations
Pardi 2002	US	1997-1999	Retrospective cohorte	170 (LC)	22	Resolution of diarrhea	23%	2	poor	Retrospective. Dosage and treatment period unclear. Effect measurement undefined.
Fine 1998	US		Open -label	6 LC, 7 CC	13	Passage of < 3 formed or semiformed stools/day	11 (85%)	1	fair	small sample size, open label, no placebo
Culossi 2015	US	2002-2013	Retrospective cohorte	131 (76 CC, 55 LC)	10 LC 21 CC	Resolution of diarrhea	46% (LC) 64% (CC)		poor	Retrospective, dosage and treatment period unclear. Effect measurement undefined

Data extraction sheet – PICO 5.6 loperamide

PICO 5.6: Is there a role for loperamide in MC?								
First Author (Year)	Country	Study Period	Study Type	Number of patients with MC	Number of patients treated with loperamide	Effect measurement	Number treated with effect, N (%)	Considerations
Bohr 1996	Sweden	1989-1995	retrospective cohort	163 CC	69	Improved symptoms	49 (71%)	Retrospective, dosage and treatment period unclear. Effect measurement undefined
Olesen 2004	Sweden		retrospective cohort	199 LC	67	Improved symptoms	47 (61%)	Retrospective, dosage and treatment period unclear. Effect measurement undefined
Bjørnbak 2011	Denmark	2000 - 2010	retrospective cohort	549 (270 CC, 168 LC, 101 MCi)	77	Improvement in diarrhoea	46 (60%)	Retrospective, dosage and treatment period unclear. Effect measurement undefined
Jobse 2008	Netherlands	1992-2006	retrospective, cross sectional	83 CC	14	No diarrhoea complaints	8 (57%)	Retrospective, dosage and treatment period unclear. Effect measurement undefined
Fernandez-Banares 2003	Spain	1992- 2001	retrospective cohort	81 (44 LC, 37 CC)	57	Complete resolution of diarrhoea	10 (18%)	Retrospective, dosage and treatment period unclear. Effect measurement undefined
Pardi 2002	US	1997-1999	retrospective cohort	170 (LC)	52	Resolution of diarrhea	14 (27%)	Retrospective, dosage and treatment period unclear. Effect measurement undefined

Data extraction sheet – PICO 5.7 Bile acid binding agents

PICO 5.7: Are bile acid binding agents effective in MC?								
First Author Year	Country	Study Period	Study Type	Number of patients with MC	Number of patients treated with cholestyramine	Effect measurement	Number treated with effect, N (%)	Comments
Bohr 1996	Sweden	1989-1995	retrospective cohort	163 CC	44	Improved symptoms	26/44 (59%)	10 of responders had abnormal SeHCAT. 5 of responders had normal SeHCAT
Olesen 2004	Sweden		retrospective cohort	199 LC	46	Improved symptoms	26/46 (57%)	
Bjørnbak 2011	Denmark	2000 - 2010	retrospective cohort	549 (270 CC, 168 LC, 101 MCi)	95 (CC) 43(LC) 29 (MCI)	Improvement in diarrhoea	39/95 (41%) 29/43 (67%) 22/29 (76%)	Different response rate according to normal or abnormal SeHCAT
Fernandez-Banares 2003	Spain	1992- 2001	retrospective cohort	81 (44 LC, 37 CC)	14 (CC) 18 (LC)	Complete resolution of diarrhoea	7/14 (50%) 15/18 (83%)	
Pardi 2002	US	1997-1999	retrospective cohort	170 (LC)	14	Resolution of diarrhoea	29%	
Calabrese 2006	Italy	6 month	Prospective randomised trial, open label	64 (41 LC,23 CC)	33	Complete resolution of diarrhoea	30/33 (91%)	RCT , mesalamine or mesalamin + colestyramine
Ung 2000	Sweden	36 mdr	open label	28 CC	27	Clear decrease in diarrhoea	21/27 (78%)	92 % response rate in paitents with abnormal SeHCAT 67% response rate in patients wth normal SeHCAT
Colussi 2015	US	2002-2013	Retrospective cohorte	131 (76 CC, 55 LC)	17 (CC) 4 (LC)	Resolution of diarrhoea	7/17 (41 %) 3/4 (75%)	

Data extraction sheet – PICO 5.9 Antibiotics

PICO 5.9: Is there a role for antibiotics in MC?										
First Author (Year)	Country	Study period	Studytype	Studydrug	N of MC	N of patients treated with AB	effect measurement	Number (%) treated with effect	Quality rating	Considerations
Bohr (1996)	Sweden	1989-1995	Retrospective cohort	metronidazol, erythromycin, penicillin	163 CC	metro: 44, Erythro:15, penicillin:8	Improved symptoms	metro: 55%, erythro: 67%, penicillin: 100%	low	retrospective, case series, Dosage and treatment period unclear. Effect measure undefined.
Bjørnbak (2011)	Denmark	1999-2010	Retrospective cohort	Antibiotics unclassified	549 (270 CC, 168 LC, 101 MCi)	33	improvement in stool consistency and frequency	6 / 33 = 18%	low	retrospective, case series. AB drug unknown. Effect measure undefined.
Olesen (2004)	Sweden		Retrospective cohort	metronidazol, norfloxacin	199 LC	metro:23, norflox: 5	Improved symptoms	metro: 61 %, norfloxa: 40%	low	retrospective, case series. Dosage and treatment period unclear. Effect measure undefined.

Data extraction sheet – PICO 5.10 Probiotics

PICO 5.10: Is there a role for probiotics in MC?											
First Author (Year)	Country	Study period	Studytype	Studydrug	N of MC	N active drug / N placebo	N active drug / N mesalamine	Effect size	Number treated with effect, N (%)	p-value	Quality rating	Considerations
Tromm (2004)	Germany	4 weeks	open-label	E.Coli Nissle	14	14 / 0		reduction in stool number and / or consistency > 50%	71%		poor	no placebo group, small sample size
Wildt (2006)	Denmark	12 weeks	DB - RCT	Lactobacillus acidophilus et Bifidobacterium animalis subs Lactis	30	21 / 8		Reduction in number of stools > 50%	6/ 21 (29%) versus 1/8 (13%)	0.640	good	small sample size,
Rohatgi (2015)	India	8 weeks	randomised, open-label	VSL3	30		15 / 15	reduction in bowel movements > 50%	5/11 versus 1/13	0.022	fair	open-label, no placebo group, small sample size

Data extraction sheet – PICO 5.11 Prednisolone and other steroids than Budesonide

PICO 5.11: Is there a role for prednisolone or other steroids than budesonide in MC?										
First Author Year	Country	Study period	Study type	Studydrug	N of MC	N active drug / N placebo	effect measurement	Number treated with effect, N	Quality rating	Considerations
Munck 2003	Denmark	2 weeks	DB - RCT	prednisolone	12 CC	9 and 3	stool volumen and frequcency	2/ 9 and 1 / 3	good	small sample size, short treatment duration
Gentile 2013	US		retrospective cohorte	prednisone	315 MC	17 / 0	50% reduction in bowel movements	9 / 17 had complete response	low	Retrospective, case series, large range of prednisone dosis (7-40mg), no information of treatment duration
Sloth 1991	Denmark	3 months	prospective, open label	prednisolone	7 CC	7 / 0	number of stool before and after treatment	3	low	small sample size, open label
Bohr 1996	Sweden	1989-1995	retrospective cohort	prednisolone	163 CC	39 / 0	Improved symptoms	32 / 39	low	retrospective, case series. Dosage and treatment period unclear. Effect measure undefined.
Olesen 2004	Sweden		retrospective cohort	prednisolone	199 LC	16 / 0	Improved symptoms	15 / 16	low	retrospective, case series. Dosage and treatment period unclear. Effect measure undefined.
Pardi 2002	US	3 years	retrospective cohort	prednisolone	170 LC	15 / 0	clinical remission	6	low	retrospective, case series. Dosage and treatment period unclear. Effect measure undefined.
De Corte 2019	Belgium	10 months	Open - label	beclomethasone dipropionate	30 MC	30 / 0	remission at week 8 (defined from stool number and consistency)	21 / 30 = 70%	fair	open - label

Data extraction sheet – PICO 5.12 a. Immunomodulators and Biologics

PICO 5.12 Is there a role for immunomodulators and biologics in the treatment of patients with MC?														
First Author Year	Country	Study period	Studytype	Studydrug	N of MC	N active drug / N placebo	AZA/6-MP remission, response, no response, N	AZA/6-MP response %	AZA, 6-MP intolerence, N (%)	MTX remission, response, no response, N	MTX response %	MTX intolerence, N (%)	Quality rating	Considerations
Pardi 2001	USA	1996 - 1999	Case series	AZA, 6-MP	9 (6 CC, 1 LC, 2 undefined)	9 / 0	7 / 1 / 1	89					Poor	Not prospective, no placebo control, small sample size
Münch 2013	Sweden	1997 - 2011	Case series	AZA, 6-MP	46 (34 CC, 12 LC)	46 / 0	19 / 0 / 2	41	31 (67 %)				Poor	Not prospective, no placebo control, small sample size
Cotter 2017	USA	1997 - 2016	Case series	AZA, 6-MP, MTX, TAC, CSP	73 (51 CC, 22 LC)	73 (49 AZA/6-MP, 12 MTX, 1 TAC, 1 CSP)	21 / 11 / 17 (AZA) 2 / 0 / 1 (6-MP)	69	17 (35 %)	7 / 2 / 3	75	Not reported	Poor	Not prospective, no placebo control, small sample size.
Riddell 2007	Australia	1986 - 2005	Case series	MTX	19 (all CC)	19 / 0				14 / 2 / 3	84	6 (30%)	Poor	Not prospective, no placebo control, small sample size. Also data on TAC + CSP
Vennamaneni 2001	USA	1995 - 2000	Case series	AZA, 6-MP	6	6 / 0	3 / 0 / 0	50%	3 (50 %)				Poor	Not prospective, no placebo control, small sample size
Münch 2013	Sweden	2010 - 2011	Case series	MTX	9 (all CC)	9 / 0				0 / 0 / 5	0	4 (44 %)	Poor	No placebo control, small sample size

Data extraction sheet – PICO 5.12 b. Immunomodulators and Biologics

PICO 5.12 Is there a role for immunomodulators and biologics in the treatment of patients with MC?														
First Author Year	Country	Study period	Studytype	Studydrug	N of MC	N active drug	IFX response: remission/ response/ no response	Further treatment	ADA response remission/ response/ no response	Further treatment	VDZ response remission/ response/ no response	Further treatment	Quality rating	Considerations
Esteve 2011	Spain, USA	1993 - 2010	Case series	IFX, ADA	4 CC	4 (4 IFX, 3 ADA)	2 / 1 / 1	1 remission → maintenance 2 intolerant → adalimumab 1 refractory → adalimumab	2 / 0 / 1	2 remission → maintenance 1 refractory → colectomy (IFX discontinued after SJS)			Poor	Not prospective, no placebo control, small sample size
Münch 2012	Sweden	2010 - 2011	Case series	ADA	3 CC	3			3 / 0 / 0	2 remission → maintenance 1 intolerant → discontinuation			Poor	No placebo control, small sample size
Ghazaleh 2010	USA	Not reported	Case series	IFX, ADA	2 LC	2 (1 IFX, 1 ADA)	1 / 0 / 0	1 remission → maintenance	1/ 0 / 0	1 remission → maintenance			Poor	Not prospective, no placebo control, small sample size
Cushing 2018	USA	Not reported	Case report	VDZ	1 CC	1					1 / 0 / 0	Remission → maintenance	Poor	Single case report
Casper 2018	Germany	2016 - 2018	Case report	IFX, VDZ	1 CC	1 (1 IFX, 1 VDZ)	0 / 1 / 0	Partial response, but had mucosal rectum prolapse → surgery → discontinuation of IFX → relapse → VDZ			0 / 1 / 0	Partial response → maintenance	Poor	Single case report
Anderson 2016	United Kingdom	Not reported	Case report	ADA	1 LC	1			1 / 0 / 0	Remission → maintenance			Poor	Single case report
Pola 2013	USA	Not reported	Case report	IFX	1 CC	1	1 / 0 / 0	Remission → maintenance					Poor	Single case report
Rivière 2018	Belgium, Sweden, Switzerland, Canada	Not reported	Case series	VDZ	11 (6 CC, 5 LC)	11					5 / 0 / 6	5 remission → maintenance → 1 discontinued after 1 year due to loss of response 6 refractory → rescue therapies (1 budesonide, 1 systhemic steroids, 1 methotrexate, 1 ustekinumab, 2 loop ileostomies)		Not prospective, no placebo control, small sample size
Cotter 2017	USA	1997 - 2016	Case series	IFX, ADA	12 MC	12 (10 IFX, 2 ADA)	3 / 3 / 4	3 remission → maintenance (mean 4 months) 3 partial response → maintenance (mean 23 months) 3 refractory → not reported	1 / 1 / 0	1 remission → maintenance (mean 4 months) 1 partial response → maintenance (mean 23 months)			Poor	Not prospective, no placebo control, small sample size

Data extraction sheet – PICO 5.13 Surgery

PICO 5.13: Is there a role for surgery in MC?											
First Author Year	Country	Study period	Studytype	N of MC	Previous treatment	Indications for surgery	Procedure	Postoperative course	Further Procedures	Quality rating	Considerations
Daferera 2015	Sweden	Not reported	Case report	1 (CC)	Loperamide, cholestyramine, budesonide, methotrexate, adalimumab, prednisolone	All previous treatment measures had failed	Loop ileostomy	Remission for 1 year → bowel reconstruction → relapse		Poor	Single case report Collagen layer thickness normalized during fecal divertsion and increased after recontruction.
Williams 2000	USA	1997	Case report	1 (CC)	Mesalazine, prednisone,	Treatment failure, severe diarrhoea (up to 30 times/day)	Ileostomy → proctocolectomy with ileal pouch anastomosis	Remission (8 - 10 bowel movements/day)		Poor	Single case report
Järnerot 1995	Sweden	1980 - 1995	Case series	9 (CC)	Sulfasalazine, mepacrine, steroids, cholestyramine, loperamide, mesalamine, metronidazole (and othe antibiotics)	Treatment failure, severe diarrhoea with incontinence	Ileostomy (n 8), sigmoidostomy (n 1)	Ileostomy (n 8) → remission, normal collagen layer Sigmoidostomy (n 1) → high sigmoidostomy output → illeostomy → remission	Closure of ileostomy + colectomy (n 2) Closure of ileostomy (n 3) → relapse (clinical and histological) → colectomy (n 3) → remission	Poor	Not prospective, no placebo control, small sample size
Münch 2005	Sweden		Case report	1 (CC)	Loperamide, budesonide, prednisolone, 5-aminosalicylate, cholestyramine, norfloxacine	Treatment failure	Loop ileostomy	Remission, wound infection, C. difficile infection → ileostomy closure → relapse (despite budesonide)		Poor	Singel case report. Permeability was increased before surgery and decreased after loop ileostomy but increased againt after bowl reconstruction (biopsies in Ussing chamber)

Supplementary material – Appendix C

Table 1: Summary of factors and evidence related to the pathogenesis of MC

Luminal factors
• Differences in bacterial composition [p1-p6] • Effect of fecal microbiota transplantation [p7-p10] • Effects of faecal stream diversion [p11] • Bile acids as mucosal inflammation trigger [p12, p13] • Colonic toxicity of drugs [p14]
Autoimmunity phenomena
• Association with autoimmune disorders including celiac disease [p15-p25] • Response to immunosuppressive drugs of even TNF-alpha blockers [p26,p27] • Contradictory evidence related to auto-antibody prevalence [p28-p30]
Innate immune system
• Nitric oxide (effector of innate immune response) concentration [p31] • Lysozyme concentration in MC as a reaction of luminal agents [p32] • Toll-like receptor activation [p33] • Effect of faecal stream diversion on subepithelial collagen thickening regression [p34] • Different chemokines and chemokine receptors expression in active vs. inactive MC [p35] • IKKβ activity, strong NFκB DNA binding [p36] downregulation of E-cadherin and ZO-1 [p37], decreased occludin and claudin-4 expression [p38] and local eosinophil activation, altered mucosal permeability and increased colorectal mucosal secretion of bFGF in CC [p39]
Adaptative immune system
• Increased numbers of $CD4^+$ T lymphocytes in the lamina propria and increased numbers of $CD8^+$ T lymphocytes in the epithelium [p40-p44] • Increased of $CD8^+$ T cells in the lamina propria, with higher numbers of $CD8^+$ and $CD4^+$ $TCR\gamma\delta^+$ T cells [p45-p48] • Both $CD4^+$ and $CD8^+$ in lamina propria as well as intraepithelial T cells with expression of the activation/memory marker CD45RO and the proliferation marker Ki67 [p46] • $CD8^+$ cytotoxic T cells as primary immune cells as seen by gene expression [p49] • Higher numbers of $CD4^+CD25^+FOXP3^+$ regulatory T cells in the mucosa, with higher levels of the anti-inflammatory cytokine IL-10 [p44, p45, p47]

- Th1 or a mixed Th17/Tc17 and Th1/Tc1 mucosal cytokine profile, reduced numbers of Th1 and Th17 cells in MC, and a mixed Th1/Th2 immune response, with expression of both T-bet and the Th2 transcription factor GATA-3 in LC [p37, p50, p51, p52; p48]
- Reduction of mucosa protein levels of most cytokines post-fecal diversion [p53], decreased in $CD8^+$ IELs and both $CD4^+$ and $CD8^+$activated/memory LPLs, with an increased proportion of $CD4^+$ $FoxP3^+$ lamina propria T_{reg}, but a decreased proportion of $CD8^+$ $Foxp3^+$ T cells [p7]
- Increased production of both pro- and anti-inflammatory cytokines by peripheral blood T cells in the presence of soluble factors from the inflamed colonic mucosa in CC [p54]
- Reduced T cell receptor excision circle levels in the colon of MC patients compared to controls [p55]
- Differences in TCRβ repertoire in colonic biopsies of MC patients [p56]

Extracellular matrix (EMC) remodeling

- Subepithelial band consists of collagen type VI (as primary alteration of collagen synthesis) and collagen I and III (probably representing an attempt to repair after a chronic inflammatory damage) [p57-p60]
- Collagen deposition may be reversible [p11, p34, p53, p61]
- Numerous cytokines with pro-inflammatory action and some even with strong pro-fibrotic action are overexpressed in MC (TNF-α, IFN-γ, IL-15 , IL-6, IL-1β, IL-21, IL-22, IL-12, IL-23, IL-17A) [p37, p46, p47, p62]
- Increased expression of TGF-β and TIMP-1 (important regulators of ECM breakdown and fibrosis) in the colonic mucosa of patients with CC as compared to controls [p60, p63]
- Proton pump inhibitors increases expression of fibrosis inducing factors like TGF-β and fibroblast growth factor 2, as well as, collagen types III and IV [p64]
- Increase of mucosal secretion and expression of basic fibroblast growth factor (bFGF), in CC [p65].
- Strong expression for VEGF within the epithelium, inflammatory cells, and fibroblasts in CC leading to collagen accumulation [p66, p67]
- COX-2 increased in colonic mucosa of CC patients [p52,p68], chronic COX-2 inhibition promotes myofibroblast-associated intestinal fibrosis [p69,p70]
- MMP-1 expression, counteracted by increased TIMP-1 expression, suggests locally impaired fibrolysis [p60]. A defect in activation of MMP-9 in CC could contribute to the accumulation of subepithelial collagen [p71, p72]

Genetic factors

- Familial cases where first-degree relatives were generally affected also by other autoimmune diseases [p73-p79]
- Candidate-gene approach including the human leukocyte antigen (HLA) region, nucleotide oligomerization domain containing 2 (*NOD2*), tumor necrosis factor (*TNF*), adrenergic receptor alpha 2A (ADRA2A), matrix metalloproteinase-9 (MMP9), interleukin 6 (IL6), FERM domain containing 4B (FRMD4B), serotonin transporter solute carrier family 6 member 4 (SLC6A4), and phosphatase and tensin homolog (PTEN) [p80-85,p71, p79]
- Predisposing role of the extended HLA haplotype 8.1, which contains variants (HLA-DQ2) known to be relevant also to other immune-related diseases, particularly celiac disease [p80-82; p84], that appear to be specific to CC and not observed in LC [p86, p87]

Pathogenesis of the diarrhoea in microscopic colitis

- *Osmosis*: Normal stool weight restored by fasting in some cases [p88]. Elementary diet can reduce diarrhoea associated with MC [p89]. The faecal osmotic gap is variable among patients with MC [p88;p90].
- *Reduced absorption*: Decrease in absorptive net fluxes of sodium and chloride in CC [p38]. Epithelial Na+ channel is inhibited in human sigmoid colon of LC patients [p91], fecal sodium and chloride concentration are increased [p90], increased level of luminal nitric oxide and epithelial nitric oxide synthase [p31,p37].
- *Increased secretion*: Active electrogenic chloride secretion in CC patients [p38]
- *Epithelial barrier dysfunction*: Colonic epithelial resistance is diminished accompanied by a decrease in transmembrane strand-forming proteins of the epithelial tight junction (E-cadherin, occludin and claudins) [p3, p38, p92].
- Dysregulation of aquaporins [p93].
- *Abnormal motility*: Abnormal motility is uncertain and poorly investigated [p94, p95]
- *Bile acid malabsorption*: preventing water absorption and increasing water secretion by intracellular mediators or intracellular and epithelial barrier permeability [p96]

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Supplementary material – Appendix D

Figures

PICO 03: How frequent is MC in patients with chronic diarrhea and normal or near normal colonoscopy?

Figure 1: Pooled frequency of MC in patients with chronic watery diarrhea. An I^2 value (statistical heterogeneity) of 93.6% indicates a high variability in intra-study differences in the overall effect size.

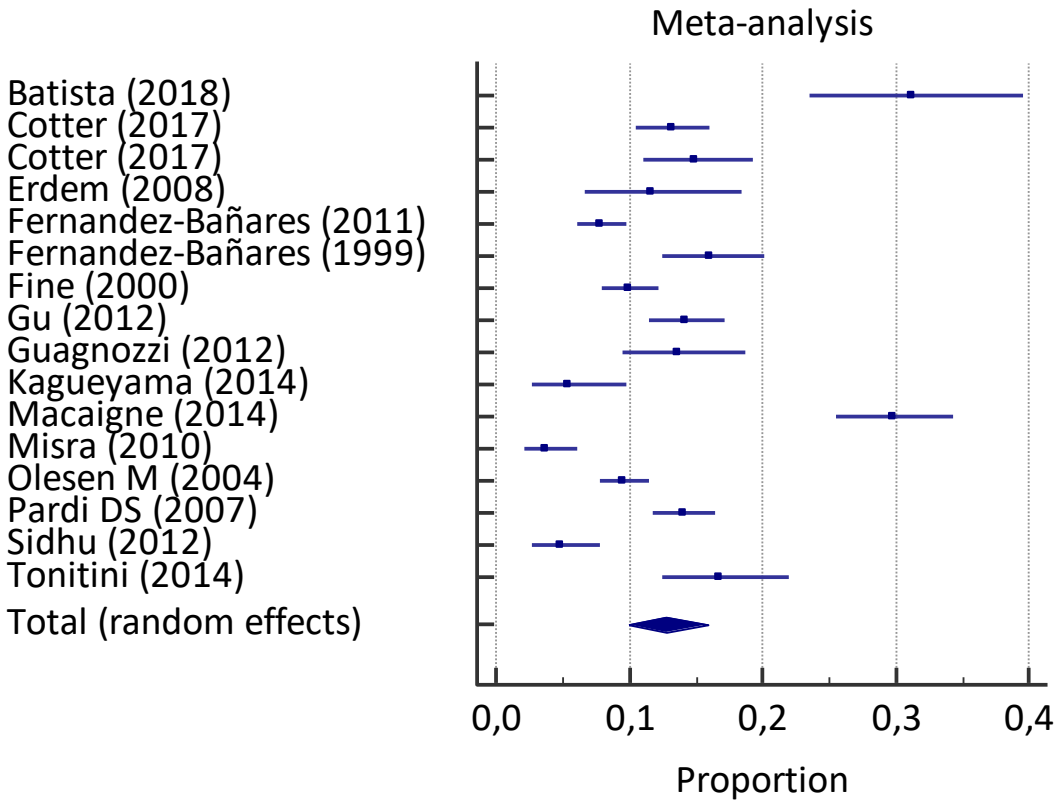


Figure 2. Pooled frequency of CC in patients with chronic watery diarrhea. An I^2 value (statistical heterogeneity) of 85.2% indicates a high variability in intra-study differences in the overall effect size.

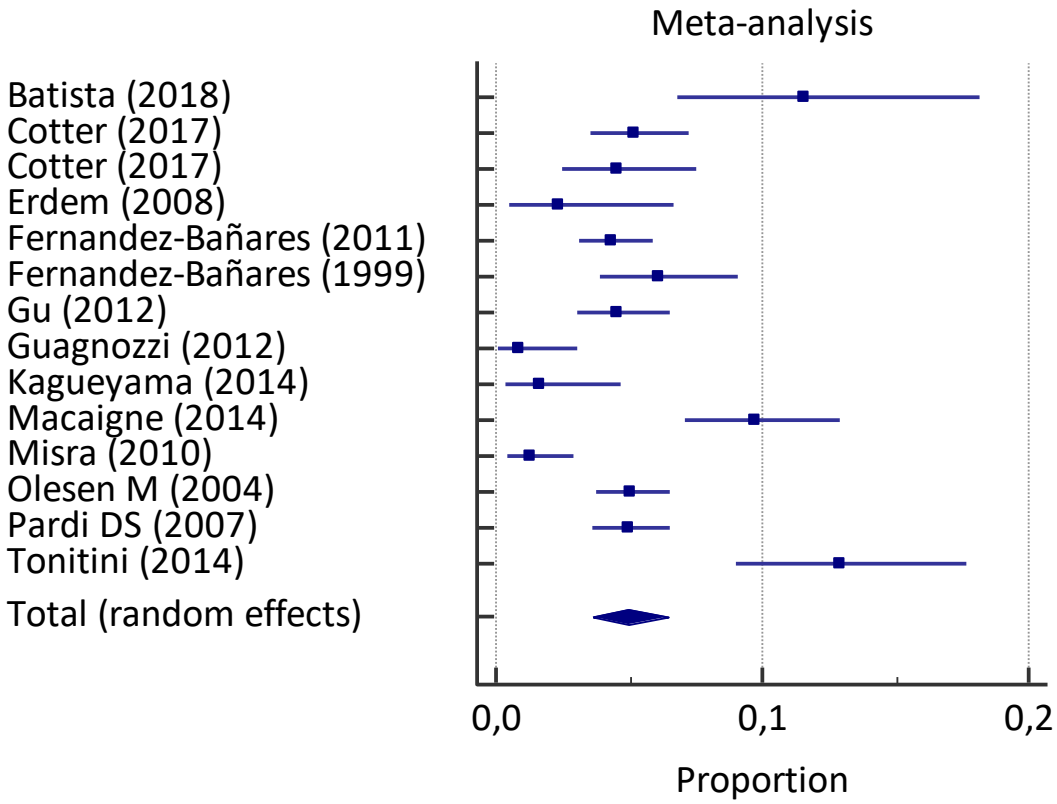
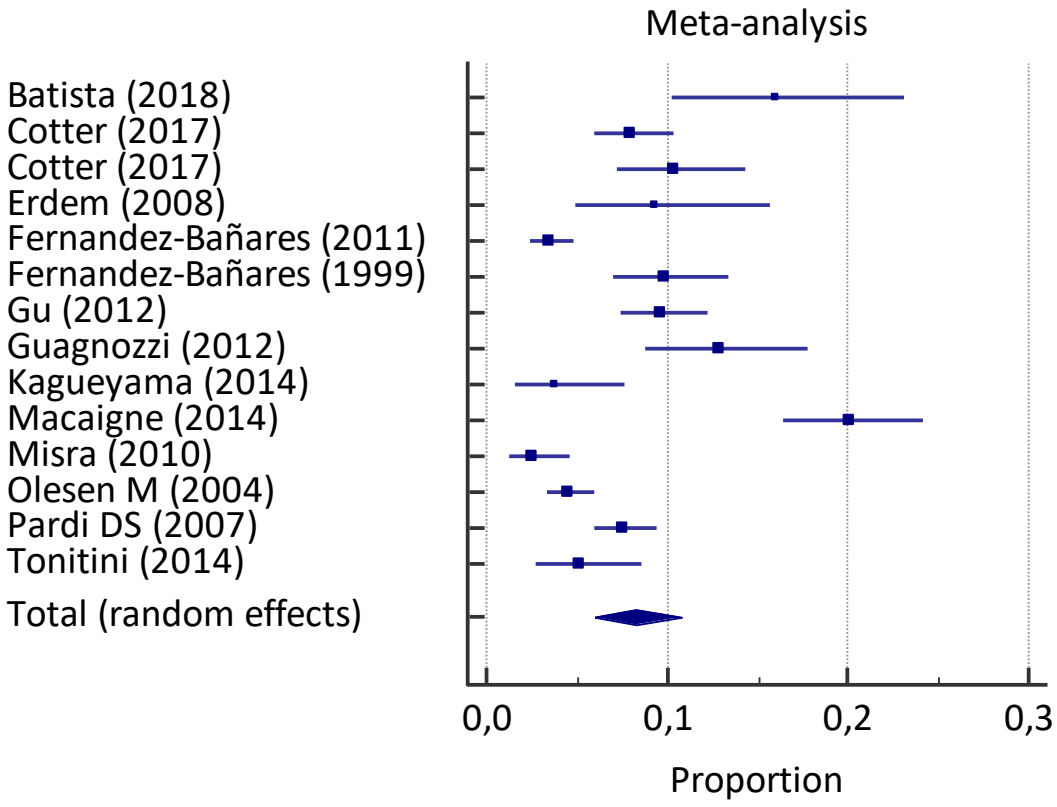


Figure 3. Pooled frequency of LC in patients with chronic watery diarrhea. An I^2 value (statistical heterogeneity) of 92.0% indicates a high variability in intra-study differences in the overall effect size.



PICO 05: Is female gender a risk factor for MC?

Figure 1. Pooled odds ratio of female incidence rate compared to male incidence rate for MC. An I^2 value (statistical heterogeneity) of 89% indicates a high variability in intra-study differences in the overall effect size.

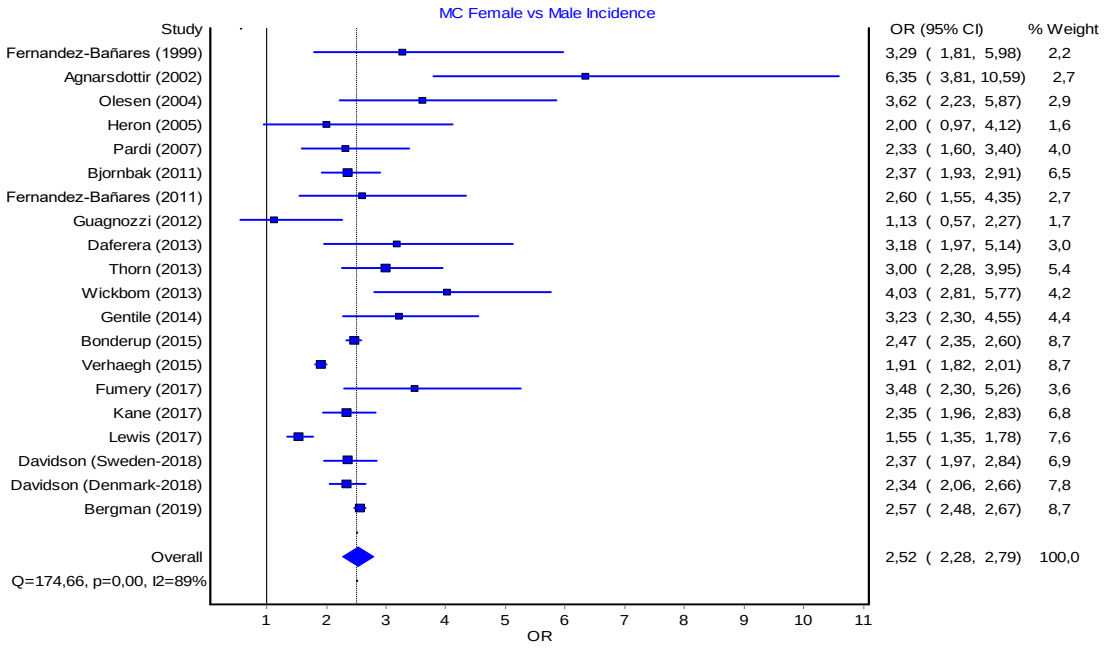


Figure 2a. Pooled odds ratio of female incidence rate compared to male incidence rate for CC. An I^2 value (statistical heterogeneity) of 35% indicates a moderate variability in intra-study differences in the overall effect size.

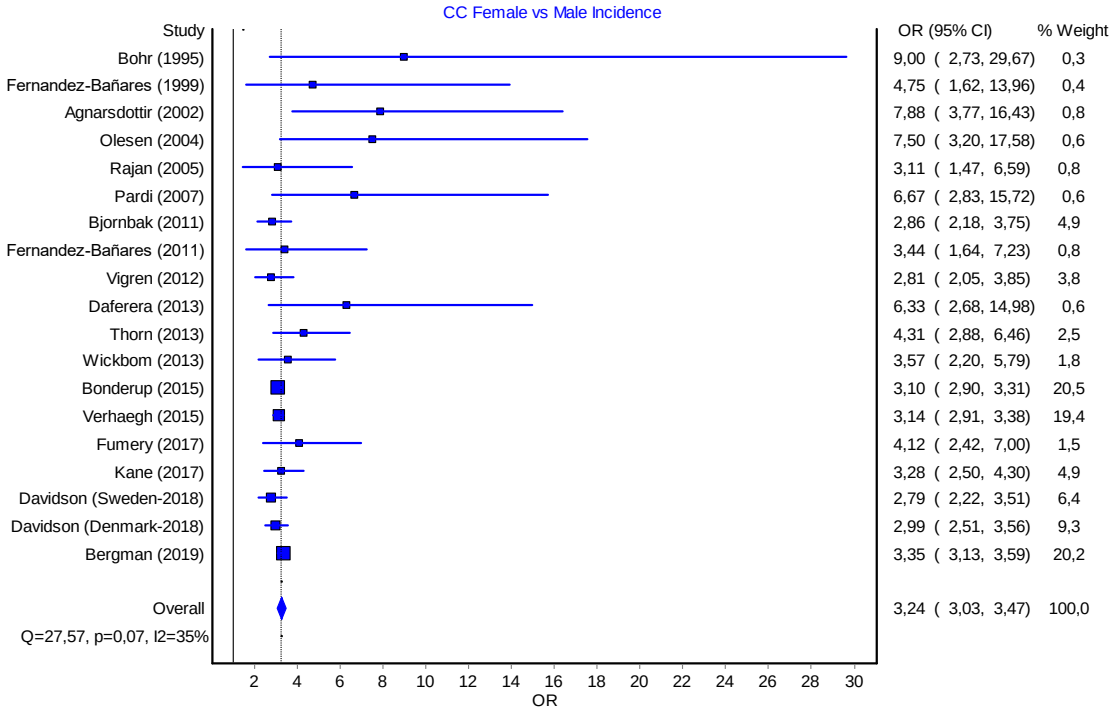
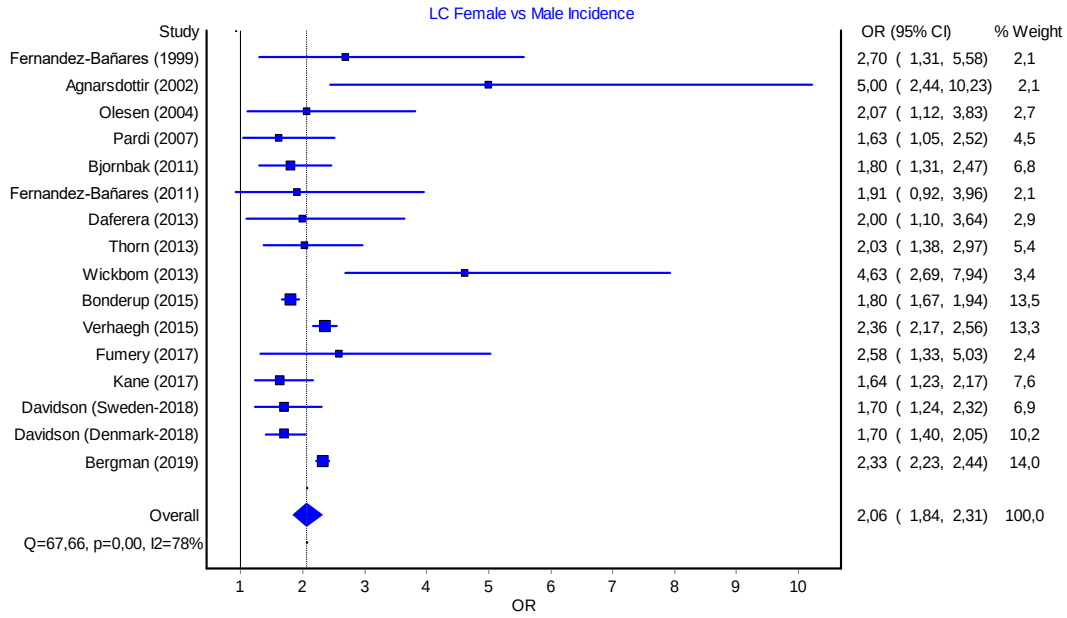
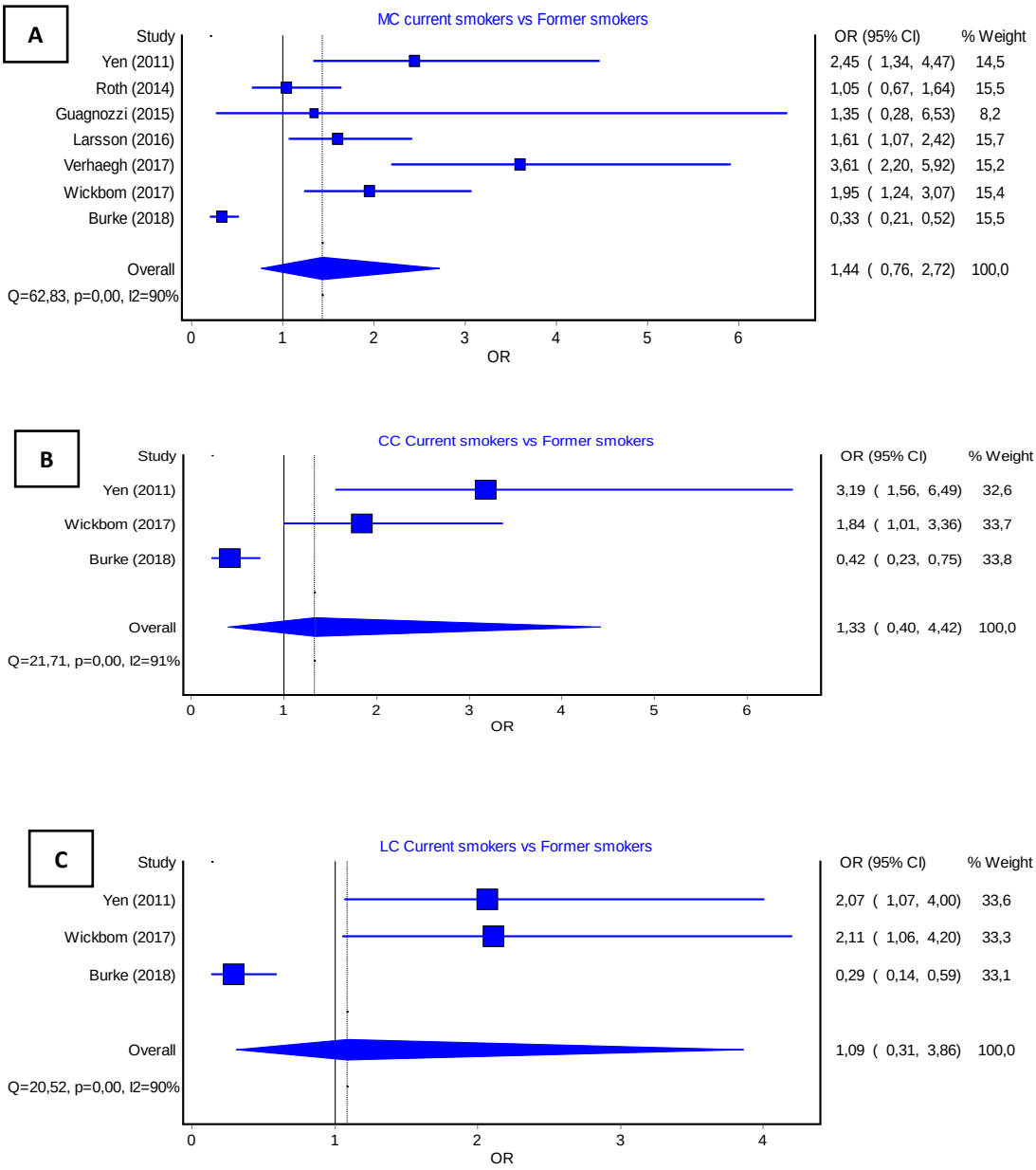


Figure 2b. Pooled odds ratio of female incidence rate compared to male incidence rate for LC. An I^2 value (statistical heterogeneity) of 78% indicates a high variability in intra-study differences in the overall effect size.



PICO 06: In MC patients does smoking cessation influence the disease course?

Figures 1. Summary estimates for smoking status as a risk factor for MC (Figure 1A), CC (Figure 1B) and LC (Figure 1C), expressed as Odds Ratio (OR) between current smokers vs former smokers. An I^2 value (statistical heterogeneity) >75% indicates a high variability.



PICO 07: Is drug use associated with a significant increased risk of MC?

Figure 1. Pooled odds ratio of PPIs exposure in MC patients. An I^2 value (statistical heterogeneity) of 99% indicates a high variability in intra-study differences in the overall effect size.

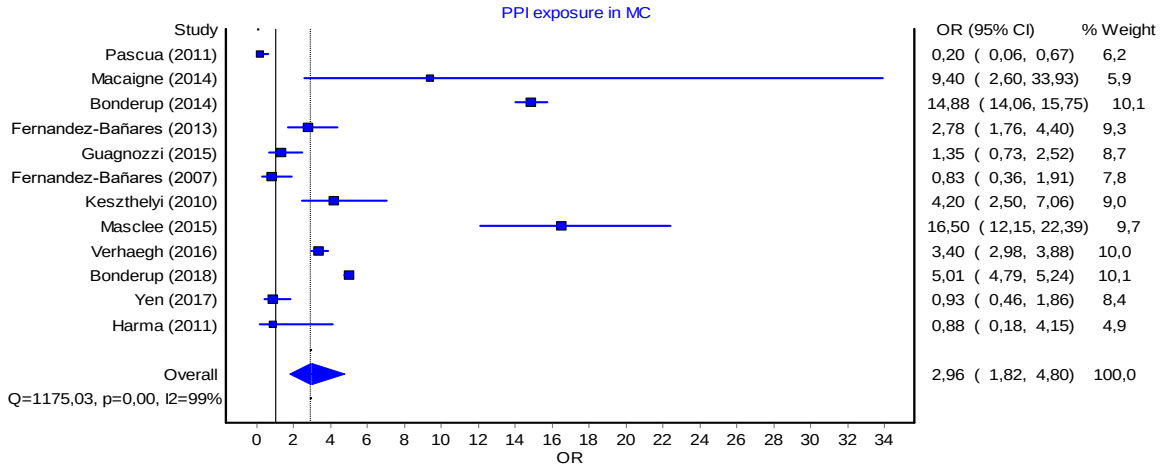
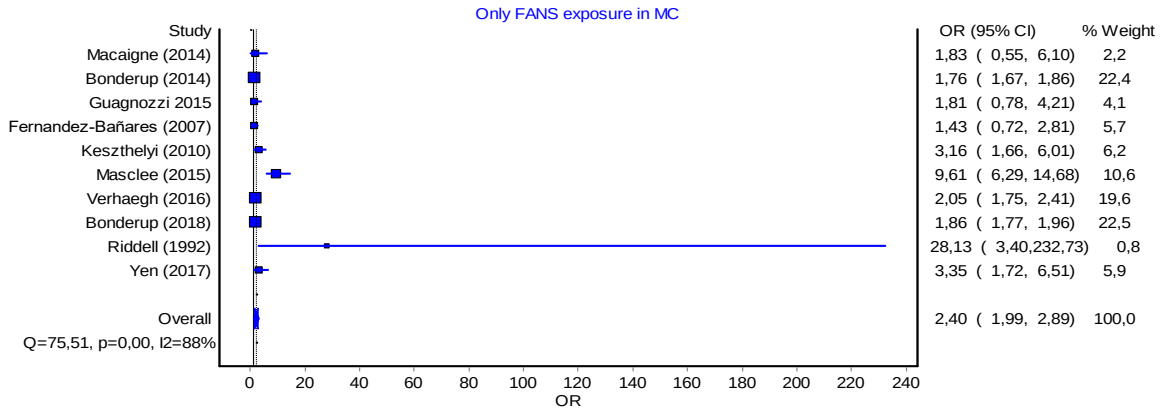


Figure 2. Pooled odds ratio of NSAIDs (excluding aspirin intake) (Figure 2A) and low-dosis aspirin intake (<300 mg) alone (Figure 2B) in MC patients. An I^2 value (statistical heterogeneity) of 88% indicates a high variability in intra-study differences in the overall effect size.

A



B

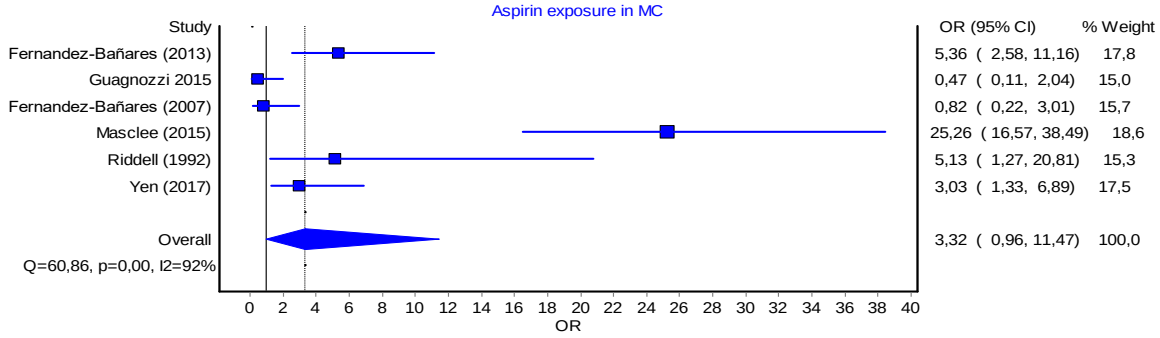
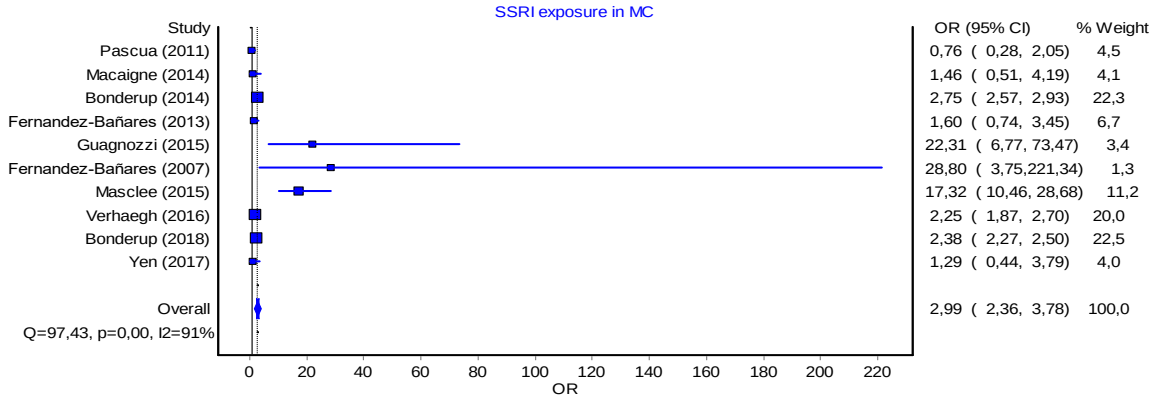


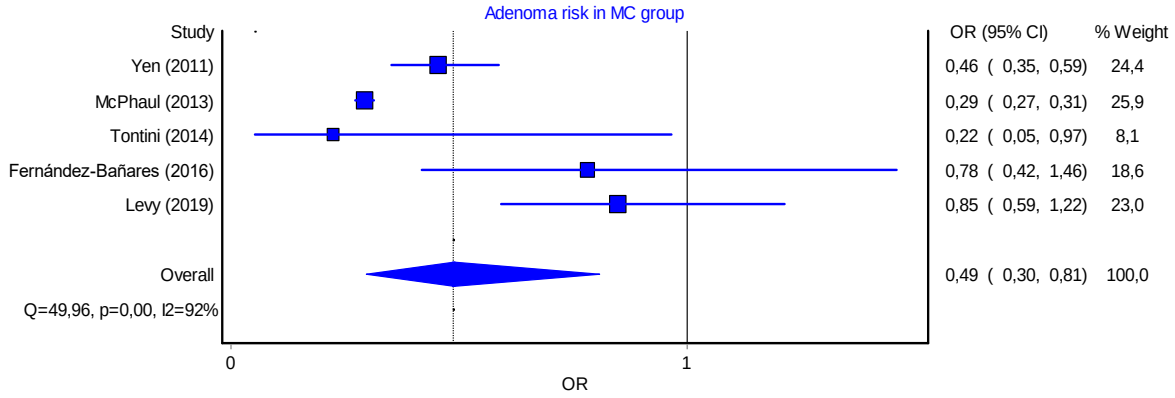
Figure 3. Pooled odds ratio of SSRI exposure in MC patients. An I^2 value (statistical heterogeneity) of 91% indicates a high variability in intra-study differences in the overall effect size.



PICO 09: Do MC patients require a special program for colonoscopy surveillance to rule out CRC compared to general population?

Figure 1. Summary estimates for colonic adenoma (A) and colorectal cancer (B) risk in MC patients expressed as Odds Ratio (OR) between MC and controls. An I^2 value (statistical heterogeneity) >75% indicates a high viability.

A:



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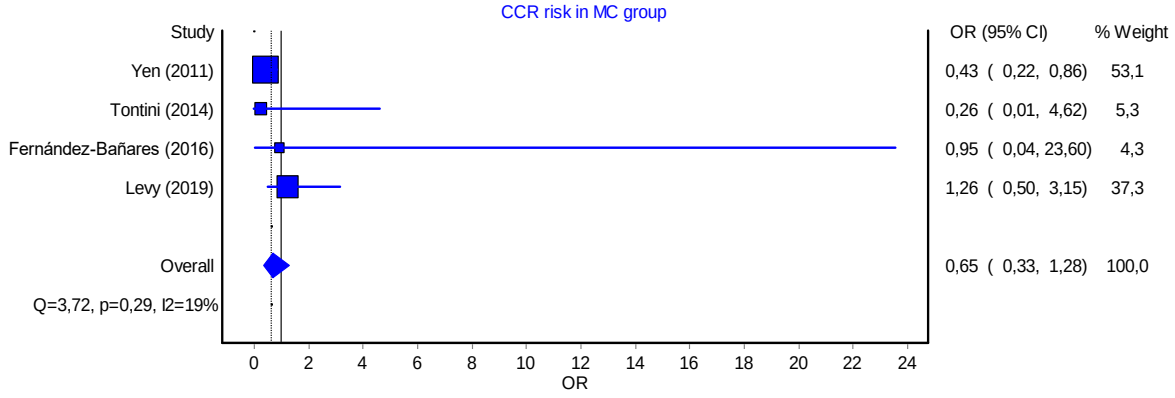

Workgroup 5:

Figure 1. Meta-analysis of trials comparing the efficacy of oral budesonide *versus* placebo in inducing clinical response in patients with collagenous colitis.

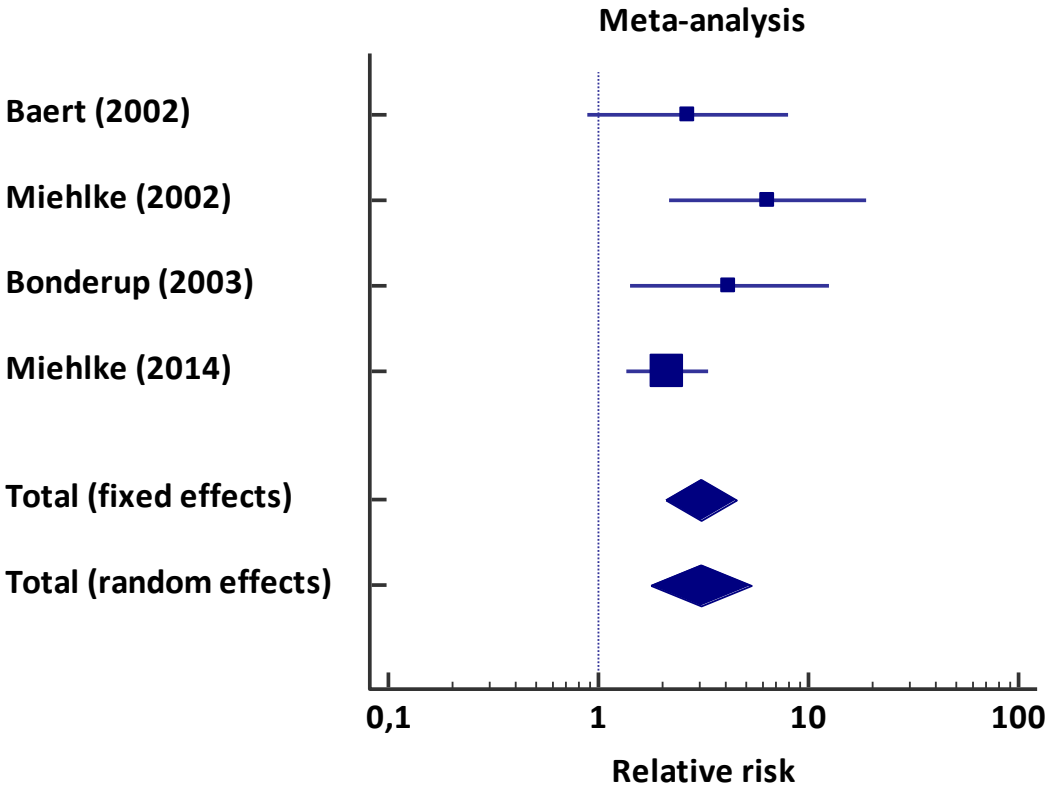

Figure 2. Meta-analysis of trials that comparing the efficacy of oral budesonide versus placebo in inducing clinical response in patients with lymphocytic colitis.