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Authors:
Zhao Xu Tian, Hong Ying Tang , Yan Ri Duan, Ang Bin Jin

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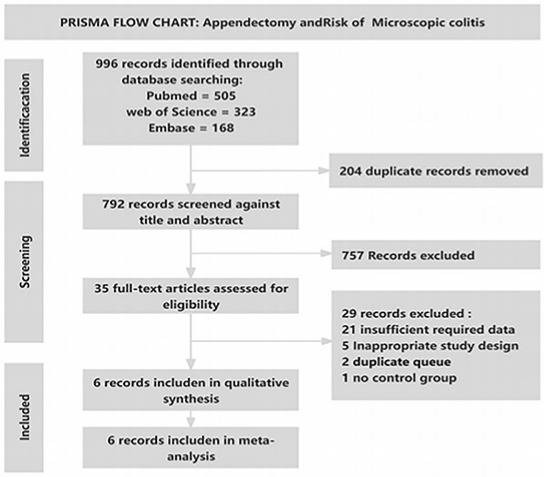

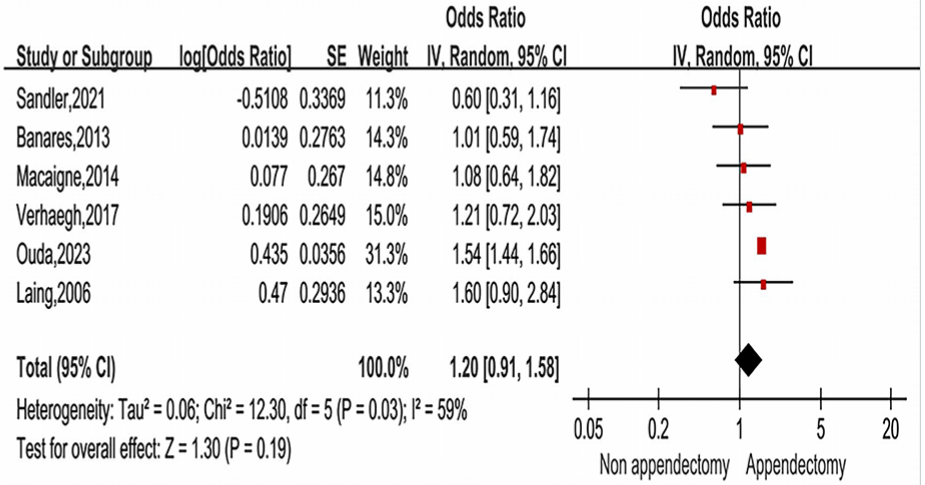

A comprehensive search was conducted in Web of Science, EMBASE, and PubMed up to January 2024, analyzing six studies (one cohort and five case–control) with 85,845 participants.

The meta-analysis showed no significant link between appendectomy and MC risk (OR: 1.20, 95% CI: 0.91–1.58), despite moderate heterogeneity (I^2 = 59%).

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Appendectomy and the risk of microscopic colitis - A systematic review and meta-analysis

Zhao Xu Tian[1], Hong Ying Tang[2], Yang Ri Duan[1], Hang Bin Jin[3*]

1. Department of Gastroenterology, Pingyao Campus of The First People's Hospital of Hangzhou, Hangzhou, 310000, China.
2. The First Clinical Medical College, Zhejiang Chinese Medical University, Zhejiang Province, Hangzhou, 310053, China.
3. Department of Gastroenterology, The First People's Hospital of Hangzhou, Hangzhou, 310000, China.

Correspondence: * kenjhb@163.com

Tian ZX and Tang HY contributed equally to this work and share first authorship.
Jin HB and Duan YR contributed equally as corresponding authors.
Tian ZX: 970747054@qq.com
Duan YR: duanyangri@outlook.com
Tang HY: HongyingTang123@outlook.com
Jin HB: kenjhb@163.com

Author Contributions: Jin HB and Duan YR conceived of and designed the study. Tang HY and Tian ZX conducted the literature search, carried out the quality assessment of the literature, and were responsible for data extraction. Tian ZX and Duan YR performed the statistical analysis and drafted the manuscript. All authors have read and approved the final version of the manuscript for publication.

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Abstract

Background: Microscopic colitis (MC), a chronic intestinal inflammatory disorder characterised by persistent watery diarrhoea, is categorised into collagenous and lymphocytic subtypes. Recent studies suggest that appendectomy influences the risk of MC, although the evidence remains inconclusive. This meta-analysis of available research was conducted to clarify the relationship between appendectomy and MC risk.

Methods: In accordance with the PRISMA guidelines, a comprehensive search was conducted in the Web of Science, EMBASE, and PubMed up to January 2024, focusing on studies that explored the association between appendectomy and MC. Quality was assessed using the Newcastle–Ottawa Scale, with data synthesis using the DerSimonian and Laird random-effects model. Heterogeneity and potential biases were evaluated; subgroup analyses were performed to investigate specific associations.

Results: Six studies were analysed, including one cohort and five case–control studies involving 85,845 participants. The combined analysis showed no significant link between appendectomy and MC risk (OR: 1.20, 95% CI: 0.91–1.58), despite moderate heterogeneity (I^2 = 59%). Subgroup analyses indicated potential associations in specific contexts. Notably, significant associations were found in subgroups based on MC subtypes (CC: OR 1.59, 95% CI: 1.20–2.10; LC: OR 1.45, 95% CI: 1.34–1.58), unadjusted ORs (OR 1.42, 95% CI: 1.17–1.73), healthy control groups (OR 1.51, 95% CI: 1.38–1.67) and studies using medical records for appendectomy history (OR 1.50, 95% CI: 1.28–1.75). Other subgroup analyses did not yield significant results.

Conclusion: This meta-analysis did not support a significant association between appendectomy and increased risk of MC. These findings highlight the need for further large-scale, prospective studies to explore this relationship in greater detail, considering the potential for nuanced interactions and the impacts of various confounding factors.

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Keywords: Microscopic colitis. Appendectomy. Systematic review. Meta-analysis.

Introduction

Microscopic colitis (MC), a chronic intestinal inflammatory disorder characterised by persistent watery diarrhoea, is subdivided into two major histological subtypes: collagenous and lymphocytic colitis.(Miehlke et al., 2019) Exploration of this disease category was initiated in 1976 when Lindström's team first described collagenous colitis, establishing a foundation for subsequent research.(Lindström, 1976) The concepts of lymphocytic colitis and MC were further elaborated in 1982 by Lazenby and colleagues, enriching the relevant body of knowledge.(Lazenby et al., 1989) Epidemiological data indicate an increasing incidence of MC in Western countries, with an overall incidence of 11.4 cases per 100,000 person-years, as well as incidence rates of 4.9 and 5.0 CASEs per 100,000 person-years for collagenous and lymphocytic colitis, respectively.(Miehlke et al., 2021) Notably, MC is prevalent among older adults, such that 25% of collagenous colitis patients are aged < 45 years; some cases in children have been reported.(Liu et al., 2013; Tong et al., 2015) Although the exact pathogenesis of MC remains unclear, it is believed to be associated with disturbances in the intestinal microenvironment and inappropriate immune responses, similar to the disturbances observed in inflammatory bowel disease (IBD), potentially due to pharmacological and lifestyle factors in genetically predisposed individuals.(Fedor et al., 2021; Zabana et al., 2022) Several studies have identified smoking(Larsson et al., 2016); alcohol consumption(Niccum et al., 2022); and the use of nonsteroidal anti-inflammatory drugs, proton pump inhibitors, and statins(Zhang et al., 2023) as potential disease triggers. Some recent studies indicated that appendectomy was a possible risk factor for MC, although the findings have been inconsistent.(Sandler et al., 2021; Maret-Ouda et al., 2023) The potential link between appendectomy and MC may involve several biological mechanisms. The appendix is rich in innate immune cells, crucial for intestinal immune response (Vitetta et al., 2019). It may contribute to intestinal disease pathogenesis, as peri-appendiceal inflammation often precedes

ulcerative colitis onset (Park et al., 2012). Additionally, the appendix serves as a reservoir for gut microbiota, maintaining microbial stability and diversity (Girard-Madoux et al., 2018). Appendectomy can disrupt this balance, reducing microbial diversity and potentially contributing to MC development (Cai et al., 2021).

Accordingly, the present study systematically reviewed existing research to define the relationship between appendectomy and MC risk.

Methods

2.1 Systematic Review Protocol

This systematic review was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.(Moher et al., 2015)

2.2 Search Strategy

Two researchers independently conducted a literature search that systematically collected relevant studies published up to January 2024 in the Web of Science, EMBASE, and PubMed databases. The search strategies included various terms related to MC and appendectomy. For example, the search strategy used in the Web of Science was (ALL= (Appendectomy OR Appendectomies OR Appendix Removal OR Appendiceal Surgery)) AND ALL= (Collagenous Colitis OR Colitis Collagenosa OR Lymphocytic Colitis OR Colitis Lymphocytica OR Microscopic Colitis OR Collagenous Colitis OR Lymphocytic Colitis OR MC). This review imposed no language restrictions; it excluded reviews, case reports, and letters. To ensure a comprehensive search, references in the included studies were manually reviewed.

2.3 Inclusion and Exclusion Criteria

The meta-analysis used stringent inclusion and exclusion criteria to ensure the research precision and accuracy. The inclusion criteria were observational studies comparing MC patients with control groups, specifically exploring the association

between appendectomy and the onset of MC. For data integrity, the studies were required to report or allow the calculation of odds ratios (ORs) with 95% confidence intervals (CIs).

Exclusion criteria were 1) incomplete data (i.e., studies that could not provide independent ORs or related data for MC patients); 2) duplicate or non-original data (i.e., studies providing non-original data or data that were republished). If multiple studies were based on the same population or database, only the study providing the most comprehensive data or analysis was included to avoid duplicate counting; and 3) inapplicable literature types, such as case reports, review articles, editorials, letters, or studies published only in abstract form. Discrepancies in study inclusion or exclusion were resolved via team discussion to ensure consistency and accuracy.

2.4 Quality Assessment and Data Extraction

The Newcastle–Ottawa Scale was used to assess study quality(Stang, 2010); it served as a standard tool for evaluating the quality of non-randomised controlled studies through emphases on selection of the study groups, comparability of the groups, and ascertainment of the exposure or outcome of interest. Studies were categorised as high quality (score ≥ 7), medium quality (score 4–6), or likely biased (score ≤ 3). Three researchers independently assessed the study quality, and any discrepancies were resolved by discussion at a meeting involving all co-authors. For thorough data extraction, the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) was used.(Moons et al., 2014) Key information and data from the included studies, such as the authors' names, locations, publication years, design types, sample details, and history of appendectomy, were systematically collected using a standardised data extraction form. The original study authors were contacted as necessary to obtain missing data, enhancing the completeness and accuracy of the research.

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2.5 Statistical Analysis

ORs and 95% CIs were extracted from all included studies. For studies that reported both pre- and post-adjustment results, the post-adjustment data were prioritised. For studies that did not report these data, ORs were calculated based on the sample sizes. To combine data from different studies appropriately and adjust for the anticipated high heterogeneity among studies, the DerSimonian and Laird random-effects model (rather than a fixed-effect model) was used. This method weights studies according to variance and considers inter-study heterogeneity to obtain an overall effect estimate, aiming to ensure accuracy and representativeness. Subgroup analyses were conducted based on factors such as study location, study type, study quality, adjusted ORs, subtypes of MC, differences in control populations, and methods of collecting appendectomy history. Heterogeneity was quantitatively assessed using the Q statistic and I^2 values. A P-value of < 0.10 for the Q statistic was considered statistically significant for heterogeneity. The I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance, with I^2 values of 0–25% indicating insignificant heterogeneity, 26–50% indicating low heterogeneity, 51–75% indicating moderate heterogeneity, and 76–100% indicating high heterogeneity. When necessary, we explored the sources of heterogeneity by excluding one study at a time or through subgroup analyses and observing changes in the level of heterogeneity to identify its sources. To assess the robustness of the results, sensitivity analyses were conducted by switching from the random-effects model to a fixed-effect model and comparing the findings. This approach helps to evaluate the stability of the results under different assumptions about the data. Publication bias was assessed using Egger's test and Begg's funnel plot when the number of included studies exceeded 10. Egger's test evaluates the symmetry of the funnel plot, where a P-value < 0.05 suggests significant publication bias. The funnel plot visually displays the relationship between study size and effect size, with asymmetry indicating potential bias. If publication bias was detected, a trim-and-fill method was applied to estimate the number of potentially missing studies and adjust the overall effect size accordingly. All statistical

analyses were conducted using Review Manager 5.3 software (Cochrane Collaboration).(Higgins, 2008)

Results

3.1 Included Studies and Patient Characteristics

Among 996 potentially relevant studies (168 from EMBASE, 323 from Web of Science, and 505 from PubMed) that were initially screened, 204 duplicates were removed; thus, 792 studies were subjected to title and abstract review. Based on pre-defined inclusion criteria, 757 articles were excluded at this stage. After full-text assessment of the remaining 35 articles, 29 were excluded for various reasons: 21 due to incomplete data, five due to study designs that did not meet inclusion criteria, two as duplicates of previously considered studies,(Maret-Ouda, Ström et al., 2023) and one due to lack of a control group.(Fumery et al., 2017) Ultimately, six studies were included in this analysis: one cohort study(Macaigne et al., 2014) and five case–control studies.(Laing et al., 2006; Fernández-Bañares et al., 2013; Verhaegh et al., 2017; Sandler, Keku et al., 2021; Maret-Ouda, Ström et al., 2023) Figure 1 outlines the process used to select and assess the included studies. Table 1 comprehensively describes these studies' characteristics and the results of quality assessment. These studies, published between 2006 and 2023, involved 15,250 patients with MC and 70,595 controls; the control groups primarily consisted of 530 patients with functional diarrhoea(Macaigne, Lahmek et al., 2014; Sandler, Keku et al., 2021) and 70,065 individuals from the general population.(Laing, Pardi et al., 2006; Fernández-Bañares, de Sousa et al., 2013; Verhaegh, Pierik et al., 2017; Maret-Ouda, Ström et al., 2023) Geographically, four studies originated from Europe(Fernández-Bañares, de Sousa et al., 2013; Macaigne, Lahmek et al., 2014; Verhaegh, Pierik et al., 2017; Maret-Ouda, Ström et al., 2023) and two studies originated from the United States.(Laing, Pardi et al., 2006; Sandler, Keku et al., 2021) All studies confirmed MC diagnoses based on symptoms and histopathological findings; appendectomy histories were obtained through patient self-administered questionnaires(Macaigne, Lahmek et al., 2014; Verhaegh, Pierik et

al., 2017; Sandler, Keku et al., 2021) or complete medical records.(Laing, Pardi et al., 2006; Fernández-Bañares, de Sousa et al., 2013; Maret-Ouda, Ström et al., 2023) Three studies also explored the relationship between appendectomy and MC subtypes.(Laing, Pardi et al., 2006; Fernández-Bañares, de Sousa et al., 2013; Maret-Ouda, Ström et al., 2023) According to the Newcastle–Ottawa Scale, three studies were categorised as high quality,(Fernández-Bañares, de Sousa et al., 2013; Macaigne, Lahmek et al., 2014; Maret-Ouda, Ström et al., 2023) and the remaining three studies were categorised as medium quality (Table 2).(Laing, Pardi et al., 2006; Verhaegh, Pierik et al., 2017; Sandler, Keku et al., 2021)

3.2 Association between Appendectomy and Risk of Microscopic Colitis

This meta-analysis integrated six studies, encompassing 85,845 participants, to explore the relationship between appendectomy and the risk of MC. There was no significant association between appendectomy and the risk of MC (OR: 1.20, 95% CI: 0.91–1.58). Heterogeneity analysis revealed an I^2 value of 59% (P = 0.19; Figure 2).

3.3 Subgroup and Sensitivity Analyses

To understand potential factors causing heterogeneity in the meta-analysis and their possible impact on the relationship between appendectomy and MC risk, a series of subgroup analyses was conducted. Notably, when subgroup analyses were based on the two pathological subtypes of MC and the methods of collecting appendectomy history, a significant reduction in heterogeneity was observed, suggesting that these factors were the primary causes of heterogeneity in the meta-analysis. Specifically, subgroup analyses focusing on locations within Europe, unadjusted ORs, MC subtypes, and healthy control groups, as well as studies confirming appendectomy history through medical records, showed an association between appendectomy and MC risk, with ORs and 95% CIs of 1.34 [1.07, 1.68], 1.42 [1.17–1.73], 1.59 [1.20–2.10] (CC), 1.45 [1.34–1.58] (LC), 1.51 [1.38–1.67], and 1.50 [1.28–1.75], respectively Figure 3, Table 3). Other subgroup analyses did not have significant combined ORs. Sensitivity analysis

using a fixed effect model, rather than a random effect model, revealed significant variation in the combined effect estimates (OR: 1.51; 95% CI: 1.41–1.61; $P < 0.00001$; Figure 4, Table 3), raising questions about the robustness of the meta-analysis results. This variation suggests that the fixed effect model, which does not account for between-study variability, may overestimate the effect size due to the assumption of homogeneity across studies. The differences observed between the fixed effect and random effects models highlight the importance of considering study heterogeneity in meta-analyses. Furthermore, the significant associations found in specific subgroups (e.g., European studies, unadjusted ORs, MC subtypes) imply that these factors may influence the relationship between appendectomy and MC risk. For example, studies conducted in Europe and those using unadjusted ORs consistently showed stronger associations, which might be due to regional differences in medical practices or variations in study designs. Considering the limited number of included studies, publication bias was not assessed. However, the potential for publication bias cannot be entirely ruled out, as smaller studies with null results may not have been published.

Discussion

Numerous studies have explored the association between appendectomy and inflammatory bowel disease (IBD); one secondary analysis of a large meta-analysis suggested a link between appendectomy and the incidence of Crohn's disease with possible protective effects against ulcerative colitis (UC).(Piovani et al., 2019) In contrast to IBD, relatively minimal research has examined the role of appendectomy in MC; the results have been inconsistent. The connection between appendectomy and inflammatory bowel conditions may involve complex pathophysiological mechanisms that are not yet fully understood. On one hand, the appendix is considered an organ rich in innate immune cells, which potentially plays a key role in the pathogenesis of intestinal immune diseases.(Vitetta et al., 2019) For instance, an analysis of appendectomy specimens from patients with UC identified histological features more consistent with UC than with acute appendicitis.(Heuthorst et al., 2021) In some cases,

the peri-appendiceal red patch preceded the onset of UC, suggesting that the pathological process originates in the appendix.(Park et al., 2012) This finding supports the hypothesis that the appendix may be an early site of inflammation in some intestinal diseases, potentially influencing the development of MC through similar pathways. On the other hand, the appendix is regarded as a "safe house" with a rich biofilm of microbiota, which may play key roles in maintaining intestinal microbial stability and diversity.(Girard-Madoux et al., 2018) There is evidence that appendectomy can lead to reduced diversity in the gut microbiome; significant decreases in the abundances of genera such as *Roseburia*, *Barnesiella*, *Butyricicoccus*, *Odoribacter*, and *Butyricimonas*(Cai et al., 2021) (important producers of short-chain fatty acids [SCFAs]) have vital roles in IBD pathogenesis.(Deleu et al., 2021) SCFAs, such as butyrate, are known for their anti-inflammatory properties and their role in maintaining the integrity of the intestinal barrier. A reduction in SCFA-producing bacteria following appendectomy could disrupt these protective mechanisms, potentially contributing to the development of MC. Additionally, appendectomy might influence systemic immune responses, altering the balance between pro-inflammatory and anti-inflammatory signals. The removal of the appendix, an organ involved in the gut-associated lymphoid tissue (GALT), could lead to changes in immune regulation and gut homeostasis. Such changes might predispose individuals to immune-mediated conditions like MC, particularly in genetically susceptible individuals. Despite these mechanistic explanations, the findings of related studies are contentious. For example, some research has not shown a significant impact of appendectomy on the composition of the gut microbiome.(Goedert et al., 2014) Conversely, experimental studies in mice have shown differences in the intestinal microbiotas of appendectomised and control groups at 4 weeks; by 8 weeks, as the number of colonic IgA secreting cells became normalised, the composition of gut microbiota was restored.(Masahata et al., 2014) These results imply that the effects of appendectomy on the gut microbiome may be transient, raising questions about the long-term impact of appendectomy on intestinal health and its potential role in the development of MC.

In summary, while the exact mechanisms linking appendectomy and MC remain unclear, the current evidence suggests a multifaceted relationship involving immune modulation, microbial alterations, and possibly transient effects on gut homeostasis. Further research is needed to elucidate these mechanisms and to determine whether specific subgroups of patients might be more susceptible to the effects of appendectomy on MC risk.

The results of this meta-analysis initially suggested that appendectomy does not significantly affect the risk of MC. However, through in-depth subgroup and sensitivity analyses, we cautiously reassessed the strength of this conclusion. Notably, in subgroup analyses focusing on unadjusted ORs, MC subtypes, and healthy control groups, as well as studies confirming appendectomy history through medical records, we found an association between appendectomy and MC risk. Significantly, subgroup analyses based on the method of collecting appendectomy history showed a substantial reduction in study heterogeneity, with results based on medical records indicating a significant association with MC risk; these findings implied that inaccuracies were present in data not obtained from reliable medical records. However, we encountered interpretative challenges with other subgroup analyses, for which we could not construct rational explanations. One possible reason is the small sample sizes and the presence of multifactorial risk factors for MC, coupled with insufficient adjustment for these potential confounders, which made it difficult to draw clear conclusions.. For instance, variations in sample sizes among the included studies might have led to inconsistent results. Smaller studies may have lacked the power to detect significant associations, while larger studies could have identified associations not apparent in smaller cohorts.The potential impact of confounding factors cannot be ignored. Factors such as smoking, use of nonsteroidal anti-inflammatory drugs (NSAIDs), and other medications have been associated with both appendectomy and MC risk. Studies that did not adequately adjust for these confounders might have produced biased estimates, contributing to the observed heterogeneity in results. Changes in the results after adjustment of the effect model in

the sensitivity analysis led to further doubt regarding the robustness of our meta-analysis findings.Although this meta-analysis explored the potential association between appendectomy and MC, we acknowledge that its conclusions were limited by several key factors. First, the sensitivity analysis revealed potential instability in the results, reflecting diversity in study design and methodology, which may introduce uncertainty concerning interpretation of the outcomes. Notably, the limited number of studies relied upon, primarily retrospective observational studies, with inherent design limitations, could introduce systematic bias and uncontrollable confounding factors. Moreover, only a few studies confirmed appendectomy history from detailed medical records, increasing the risk of recall bias, especially among individuals who underwent surgery at a younger age. The selection of control groups in some studies included patients with functional diarrhoea, potentially confounding interpretation of the relationship between appendectomy and MC risk in the general population. Furthermore, the limited number of studies in some subgroup analyses could have resulted in weak statistical power, affecting confidence in the results for these subgroups. Finally, the included studies did not consider various potential confounders, such as individual lifestyle, genetic background, and other medical conditions, leading to imprecise estimates of the relationship between appendectomy and MC risk.

While discussing these limitations in depth, we also recognise the unique value of this meta-analysis: it is the first systematic assessment of the association between appendectomy and MC risk, providing a preliminary, comprehensive evaluation of the literature through a rigorous search strategy, meticulous study inclusion, and thorough evaluation of study quality. It offers new insights into potential risk factors and establishes a foundation for future research directions. Thus, we emphasise the need for future studies using large prospective cohorts with multivariate adjustments to explore the specificity of risk for MC subtypes, examine changes in the gut microbiome after appendectomy and their impact on MC risk (including long-term follow-up and mechanistic approaches) to overcome the limitations of existing retrospective studies

and enhance the general applicability and scientific value of research findings. These studies should thoroughly consider geographic and population diversity, confounding factors (such as lifestyle and genetic background), the pathological mechanisms of MC subtypes, the role of the gut microbiome, and long-term health impacts, to provide more precise in-depth insights into the complex relationship between appendectomy and MC risk.

Conclusion

Our comprehensive meta-analysis showed no significant association between appendectomy and the risk of MC, but subgroup and sensitivity analyses revealed nuanced differences that warrant cautious interpretation. Future research, utilising large prospective studies with multifactorial adjustments and exploring the details of MC subtypes and microbiome changes post-appendectomy, is crucial for understanding the potential connections and their implications for prevention and treatment strategies.

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Conflict of Interest: The authors declare no conflicts of interest.

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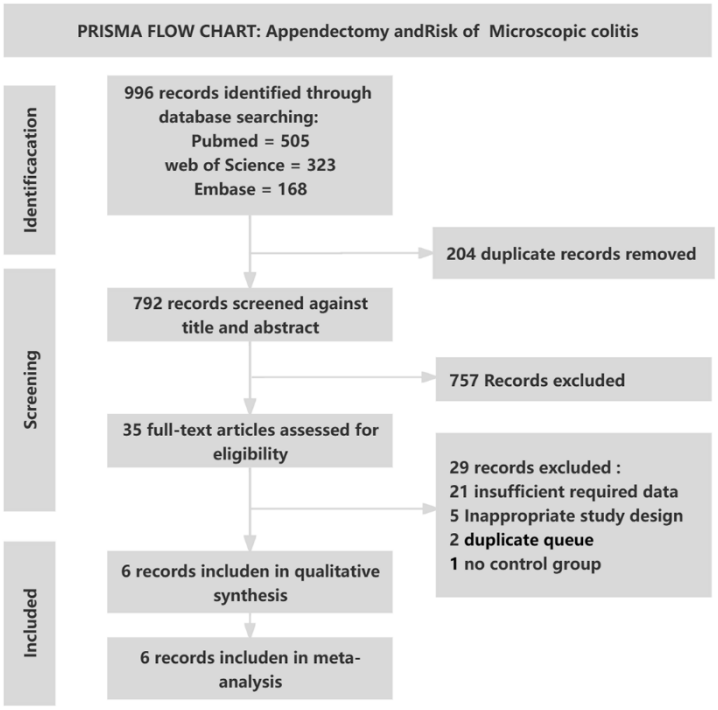

Figure 1, PRISMA FLOW CHART: Appendectomy and Risk of Microscopic Colitis.

Abbreviations: PRISMA: Preferred Reporting Items 91 for Systematic Reviews and Meta-Analyses.

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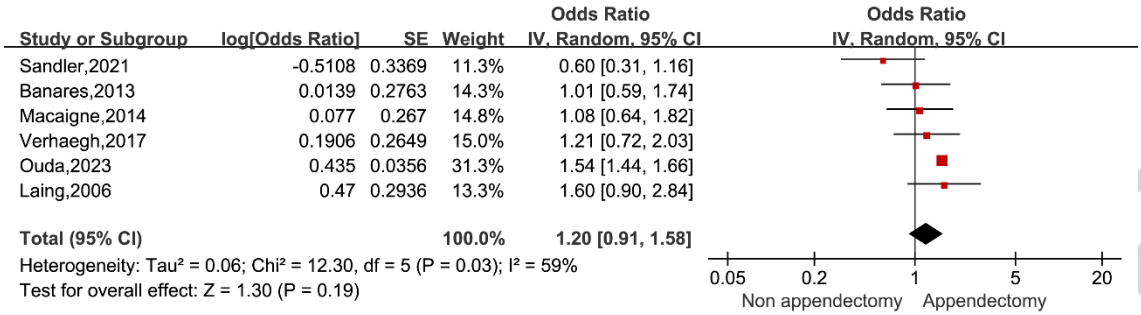

Figure 2, Meta-analysis of appendectomy and Microscopic Colitis risk.

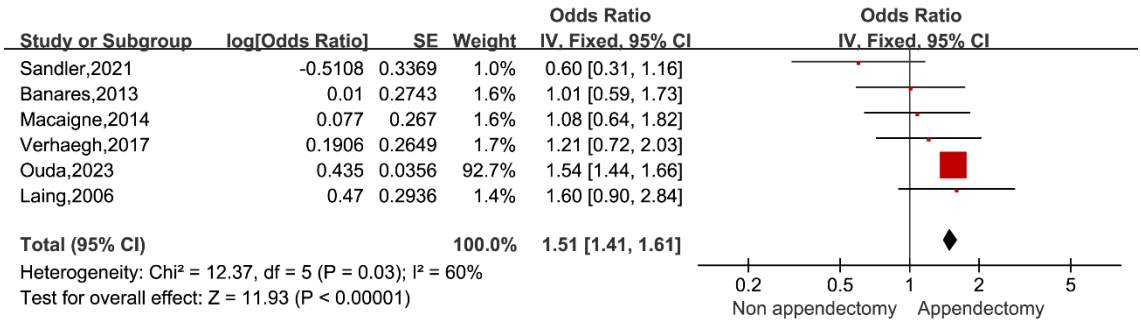

Figure 3, Subgroup Analyses Forest plot.

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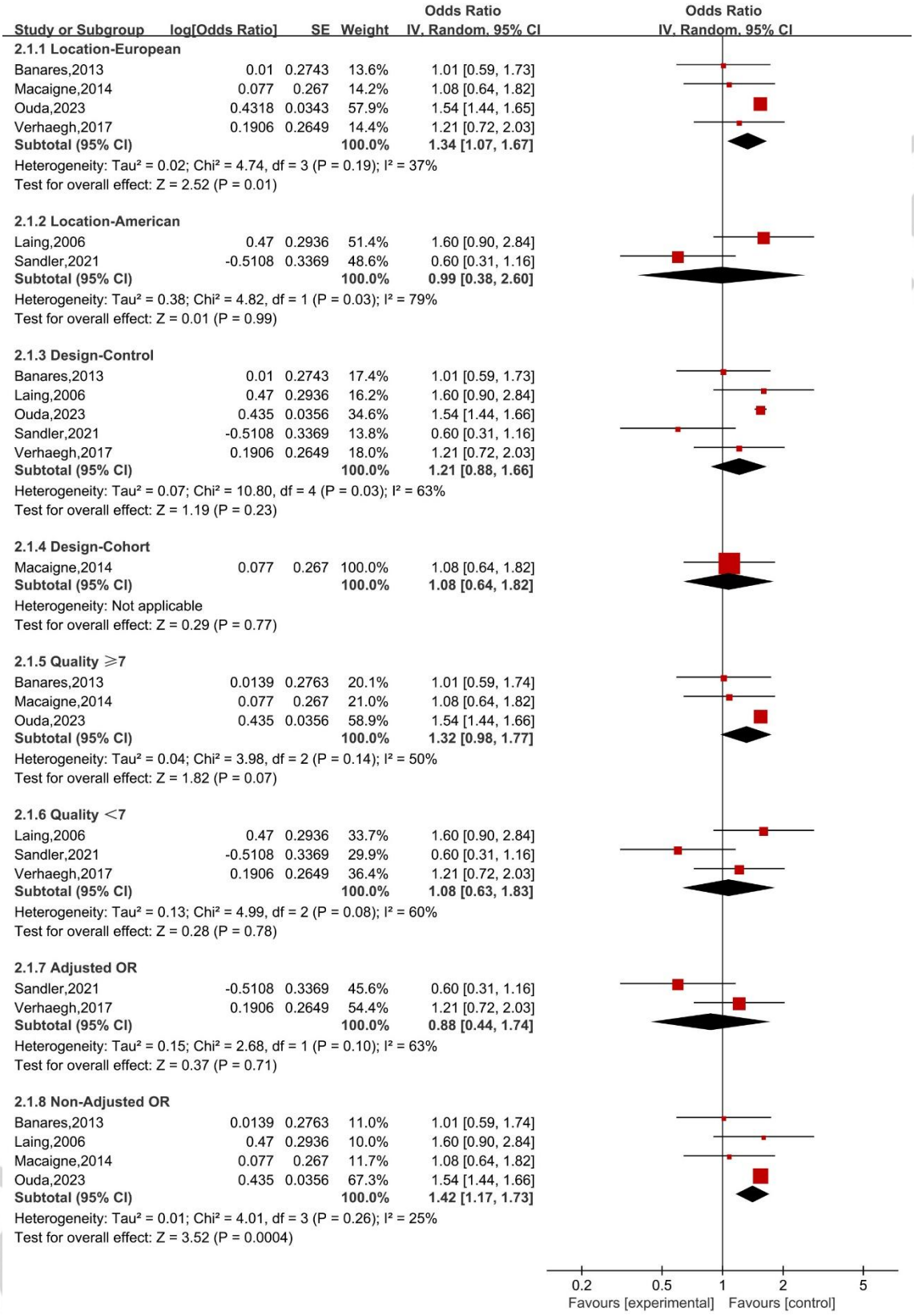

Figure 4, Sensitivity Analyses Forest plot

Table 1. Study characteristics.

First author, publication year	Country	Study design	Participants	Average	Sample size	Percentage of females	Diagnosis of microscopic colitis	Acquisition of appendectomy history	No. with appendectomy	Risk estimate (95% CI)	Adjusted Risk estimate (95% CI)	Adjusted
Ouda,2023	Sweden	case-control study	Epidemiology Strengthened by histoPathology Reports in Sweden,Each case was matched to 5 controls from the general population with no prior diagnosis of MC at date of index biopsy.	MC:<50 24.1%; 50~70 43.2%; >70 32.7%; Control:<50 24.9%; 50~70 44.1%;>70 31%	MC:14520 (CC:4684, LC 9863);Control:69491	MC:72% Control:71.8%	Epidemiology	surgical procedurecodes and the NOMESCO (Nordic Medico-Statistical Committee) system	MC:7.6% (CC:8.4%,LC:7.2%)	MC:1.545,1.441~1.658 CC:1.726,1.549~1.925 LC:1.461,1.343~1.588	NA	NA
Macaigne,2014	France	Prospective Multicenter Study	patients fulfilling the following inclusion criteria were prospectively included in 26 general hospitals in France: having at least three bowel movements daily with change in their consistency; duration of the disorder more than 4 weeks; and normal or near-normal colonoscopy.	MC:61±18.8, Control:47.2±16	MC:129 (CC:42,LC:87); Control:278	MC:74%; Control:69%	Epidemiology	Self-report	MC:20%	MC:1.08, 0.64~1.82	NA	NA

Verhaegh,2017	Netherlands	case–control Study	Case:(1) they had a PALGA registered diagnosis of MC, CC, or LC in one of the participatingclinical centers between January 2000 and December 2012, (2) they were still alive, and (3) were aged 18 years or older at the time of diagnosis; Control:Non-MC controls were retrieved from a large research cohort of more than 1650 randomly selected inhabitants (18 yr old) of South-Limburg.	MC:57.1±11.7, Control:56.1±11.3	MC:171 (CC:81,LC:73, Inco-mplete MC:17); Control:316	MC:80.7%; Control:79.1%	Epidemiology	Self-report	MC:29 (17%)	MC:1.262, 0.757~2.104	MC:1.21, 0.72~2.03	Smoking status, Excessive alcohol use, Exposure to hazardous substances at work, Educational level, Educational level, Number of comorbidities Cardiac disease, Hypertension, Asthma, Other Pulmonary disorder, Diabetes Mellitus, Gastric disorder, Renal disease, Liver disorder, Hematological disorder, Cancer, Depressive mood disorder, Arthrosis, Chronic back pain, Rheumatoid arthritis, Esophageal disorder, Thyroid disorder, Hypercholesterolemia, Colon carcinoma, Celiac disease, Allergies, Breastfeeding, Vaccinations, Frequent antibiotic use (>3x/year), Day care visit, Siblings ,Birth order, Presence of animals at home, Familial occurrence of MC, Partner with MC

Laing,2006	American	case-control study	case: the Rochester Epidemiology Project were used to identify a population-based cohort of all residents of Olmsted County (Minnesota) with an initial diagnosis of MC; control: A control group of county residents without MC was identified for comparison, matched to the 130 MC patients on gender, age (T1 year), and calendar year of visit (T1 year of the date of diagnosis of MC for the corresponding case)	Total:68 (24-94)	MC:130 (CC:46, LC:84); Control:130	Total:70%	Epidemiology	complete (inpatient and outpatient) medical records	MC:30.2% (CC:39.1%, LC:25.3%)	MC:1.6, 0.9~2.7; CC:1.8, 0.7~4.2; LC:1.4, 0.7~3.0	NA	NA
Sandler,2021	American	case-control study	patients who were referred to The University of North Carolina Hospitals for elective outpatient colonoscopy for diarrhea,The research pathologist reviewed the clinical slides and classified patients as having microscopic colitis or not.	MC:63.2±12.7, Control:54.5±11.8	MC:110; Control:252	MC:86.2%; Control:69.8%	Epidemiology	Self-report	MC:20.8%	MC:0.972, 0.577~1.769	MC: 0.6, 0.31~1.16	age, sex, education
Banares,2013	Spain	case–control study	12 teaching and community hospitals across Spain in the period March 2007 to May 2010. Cases were enrolled at the time of diagnosis and controls were assessed over the same study period.	CC: 62.4 ±1.4; LC: 62.6 ±1.9; controls: 62.4±1.4	MC:190 (CC:120,LC:70); Control:128	CC: 75%; LC: 69%; Control: 74%	Epidemiology	complete (inpatient and outpatient) medical records	MC:22% (CC:22.5%, LC:21.4%)	MC: 1.014, 0.590 ~ 1.741; CC: 1.037, 0.569 ~ 1.888; LC: 0.974, 0.480 ~ 1.978	NA	NA

Abbreviations: NA: Not Available

Table 2. NOS of Included Studies

Study	Selection	Comparability	Outcome

	Representativeness	Selection of the non-exposed cohort	Ascertainment	Outcomes of interest does not present at start	Comparability	Assessment of outcome	Follow-up duration	Adequacy follow-up	**Total score**
Ouda,2023	1	1	1	1	1	1	1	0	7
Macaigne,2014	1	1	0	1	2	1	1	0	7
Verhaegh,2017	1	1	0	1	1	1	1	0	6
Laing,2006	1	1	0	1	1	1	1	0	6
Sandler,2021	1	1	0	1	1	1	1	0	6
Banares,2013	1	1	1	1	1	1	1	0	7

Table 3. Subgroup and sensitivity analysis

Subgroup and Sensitivity analysis		No.of studies	I^2 static	Effect estimate and 95% CI	p value
Study location	American	2	79%	0.99 [0.38, 2.60]	P=0.99
	European	4	37%	1.34 [1.07, 1.68]	**P=0.01**
Study design	cohort study	1	Not applicable	1.08 [0.64, 1.82]	P=0.77
	control study	5	63%	1.21 [0.89, 1.66]	P=0.23
Study quality	≥7	3	50%	1.32 [0.98, 1.77]	P=0.07
	< 7	3	60%	1.08 [0.63, 1.83]	P=0.78
Study providing aOR	yes	2	63%	0.88 [0.44, 1.74]	P=0.71
	no	4	25%	1.42 [1.17, 1.73]	**P<0.0004**
MC type	CC	3	26%	1.59 [1.20, 2.10]	**P=0.001**
	LC	3	0%	1.45 [1.34, 1.58]	**P<0.00001**
Population of comparison	Healthy population	4	3%	1.51 [1.38, 1.67]	**P<0.00001**
	Population with diarrhea	2	47%	0.83 [0.47, 1.48]	P=0.53
Acquisition of appendectomy history	Self-report	3	31%	0.96 [0.65, 1.42]	P=0.86
	medical records	3	13%	1.50 [1.28, 1.75]	**P<0.00001**
meta-analysis obtained using a fixed-effects model for sensitivity analysis	NA	6(All)	59%	1.51 [1.41, 1.61]	**P<0.00001**