



Appendectomy Impact on Inflammatory Bowel Diseases: A Meta-Analysis

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ABSTRACT

The observed higher rate of appendectomy despite the success of the conservative (non-surgical) approach might be due to the lack of awareness. The cecal appendix is not merely rudimentary because of its role on the gut microbiota and the host immune system. This meta-analysis aimed to assess the association of appendectomy at baseline with inflammatory bowel diseases. The PubMed, Cochrane library, and Google Scholar databases were systematically searched for relevant articles. The keywords used were inflammatory bowel disease, appendicitis, appendectomy, gut lymphoid tissue, Crohn's disease, ulcerative colitis with protean "AND" or "OR". No limitation was applied to the time of publication. Out of the 622 references found, 32 full texts were screened, and only eight studies fulfilled the inclusion and exclusion criteria. There were fifteen cohorts from eight studies (five were published in Europe, two were from Asia, and one from South America with 9703 participants and 1150 events). The overall effects showed a negative impact of appendectomy on the rate of Crohn's disease, odd ratio, 0.311, 95% CI, 1.20-8.05, P-value = 0.02. In ulcerative colitis and appendectomy arm, appendectomy was protective for ulcerative colitis, odd ratio, 0.44, 95% CI, 0.35-0.55, P-value = 0.001. Significant heterogeneities were observed (95% for Crohn's disease prevalence, P-value <0.001, and Chi-square, 118.69, and 86% for ulcerative colitis arm P-value <0.001, and Chi-square, 51.54). Appendectomy was protective against ulcerative colitis, however, the impact was negative on Crohn's disease. Further studies assessing the effects of appendectomy on the prognosis of ulcerative colitis are recommended.

Keywords: Appendectomy, Inflammatory bowel disease, Crohn's disease, Ulcerative colitis

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INTRODUCTION

Inflammatory bowel disease (IBD) is a global disease in the current century, the incidence and prevalence varies widely (Srivastava *et al.*, 2019). An increasing rate is observed in Africa, Asia, and South America (newly industrialized countries), while stability or reduction was found in Europe and North America (Ng *et al.*, 2018). An increasing rate of appendectomy is observed worldwide despite the emergence of a conservative approach, a high rate of negative results were observed (15-30%) due to reliance on clinical judgement (Mundada *et al.*, 2020). In addition, the appendix together with the tonsils contains copious lymphoid tissue (MALTOmas). Furthermore, a cross-talk is thought to exist between the two lymphoid organs and the gut microbiota (Li *et al.*, 2021). The unique architecture of the caecal appendix, its diversity, and content of gut flora suggested a role as a safe house for gut biodiversity (Babakhanov *et al.*, 2021; Jabbar *et al.*, 2021) and not merely a rudimentary. IBD is a chronic immune-mediated chronic inflammatory disease with the complex interaction between environmental factors, and the gut microbiome in a genetically predisposed individual (Alshammari *et al.*, 2019; Zheng & Wen, 2021). Although the etiology of IBD remained elusive, a multifactorial (genetic predisposition and environmental factors) pathogenesis is suggested. An

interesting issue is the hygiene hypothesis, which was observed to hold. The assumption is that good hygiene during childhood with a lower infection rate predispose to autoimmune disease (Salgado *et al.*, 2020). The relationship between appendectomy and IBD is complex and controversial. Thus, this meta-analysis was conducted to assess the impact of appendectomy on IBD.

MATERIALS AND METHODS

Eligibility criteria according to PICOS (Liberati *et al.*, 2009)

Among the 622 articles screened, 502 articles remained after the removal of duplication. However, only 32 full texts were eligible and 15 cohorts from eight studies were pooled to assess the relationship of an appendectomy at baseline and inflammatory bowel disease (eight studies investigated ulcerative colitis and seven assessed the relationship between appendectomy and Crohn's disease). Because of the lack of randomized controlled trials, we included retrospective cohorts and case-control studies on humans that were published in English. Case reports, case series, experimental, and animal studies were excluded.

Intervention: Appendectomy at baseline.

Outcome measures: Inflammatory bowel disease, Crohn's disease, or ulcerative colitis at baseline. We did not investigate the temporal profile of the disease.

The search strategy

The PubMed, Cochrane library, and Google Scholar databases were systematically searched for relevant articles; the two authors independently screened the titles and abstracts. An additional search was conducted through the references of the retrieved articles. The keywords used were inflammatory bowel disease, appendicitis, appendectomy, gut lymphoid tissue, Crohn's disease, ulcerative colitis with protean "AND" or "OR". No limitation was applied to the time; all studies from the first published up to February 8, 2021 were included. Out of the 622 references found, 32 full texts were screened, and only eight studies fulfilled the inclusion and exclusion criteria. **Figure 1** shows different phases of the systematic literature search.

The quality of studies and risk of bias assessment were performed by the Ottawa Newcastle scale for non-randomized studies (Stang, 2010) **Table 1**.

Statistical analysis

The most recent RevMan version 5.4 was used for data analysis, the data were entered manually at 95% *CI*. A P-value of <0.05 was considered significant. The random effect was used due to the significant heterogeneity observed (>50%). Funnel plots assessed the sensitivity (lateralization of the included studies).

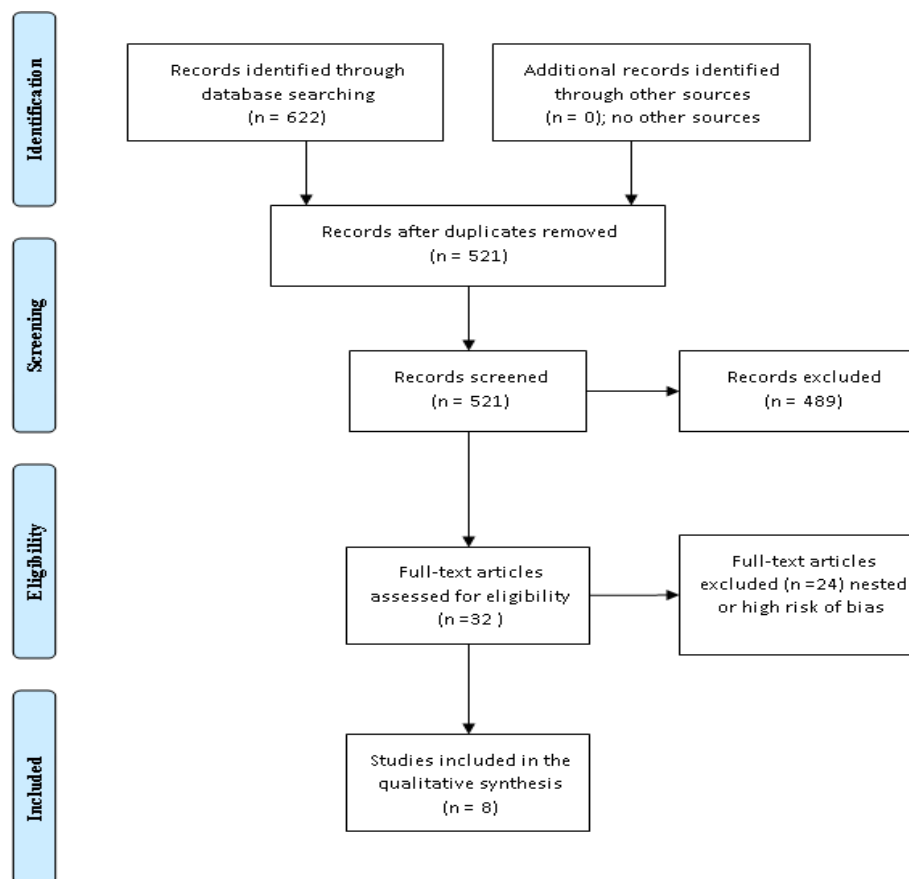


Figure 1. Appendectomy association with inflammatory bowel disease (The PRISMA Chart)

Table 1. Ottawa Newcastle assessment for the included studies

Author	Selection	Compatibility	Outcome	Score
Smithson <i>et al.</i> , 1995	3	2	4	9
Koutroubakis <i>et al.</i> , 1999	3	2	4	9
Reif <i>et al.</i> , 2001	3	2	4	9
López Ramos <i>et al.</i> 2001	3	2	4	9
Firouzi <i>et al.</i> , 2006	3	2	4	9
Castiglione <i>et al.</i> , 2012	3	2	4	9
López-Serrano <i>et al.</i> , 2010	3	2	4	9
Sakgado <i>et al.</i> , 2020	3	2	4	9

RESULTS AND DISCUSSION

In the present study, fifteen cohorts from eight studies are included (five were published in Europe, two were from Asia, and one from South America), six out of seven cohorts showed a higher rate of Crohn's disease among appendectomy patients and one reported a lower prevalence (3808 subjects included with 658 events). However, the overall effects showed a negative effect of appendectomy regarding the rate of Crohn's disease, odd ratio, 0.311, 95% CI, 1.20-8.05, P-value = 0.02. In ulcerative colitis and appendectomy arm (5895 and 492 events), one study showed lower appendectomies among the

control group (Smithson *et al.*, 1995), while the rest showed the reverse (Koutroubakis *et al.*, 1999; López-Ramos *et al.*, 2001; Reif *et al.*, 2001; Firouzi *et al.*, 2006; López-Serrano *et al.*, 2010; Salgado *et al.*, 2010; Castiglione *et al.*, 2012; AlAssad *et al.*, 2021). The results implied that appendectomy was protective for ulcerative colitis, odd ratio, 0.44, 95% CI, 0.35-0.55, P-value = 0.001. Significant heterogeneities were observed (95% for Crohn's disease prevalence, P-value <0.001, and Chi-square, 118.69, and 86% for ulcerative colitis arm P-value, <0.001, and Chi-square, 51.54.). The random effect was applied due to significant heterogeneities (Table 2, Figures 2 and 3).

Table 2. The relationship of appendectomy and inflammatory bowel disease

Author	Country	Methodology	Crohn's disease	Ulcerative colitis	Control group
Smithson <i>et al.</i> , 1995	UK	Case-control	109/ 117	39/197	24/243
Koutroubakis <i>et al.</i> , 1999	Greece	Case-control	19/76	11/ 134	18/134 U, 10/76 C
Reif <i>et al.</i> , 2001	Israel	Case-control	50/ 260	15/ 271	52/475 U, 52/475 C
López Ramos <i>et al.</i> , 2001	Spain	Case-control	16/134	11/153	41/203 U, 35/203 C
Firouzi <i>et al.</i> , 2006	Iran	Case-control	5/46	12/382	30/382 U, 4/184
Castiglione <i>et al.</i> , 2012	Italy	Retrospective	75/468	15/527	56/562
López-Serrano <i>et al.</i> , 2010	Spain	Case-control		3/146	28/278
Sakgado <i>et al.</i> , 2020	Brazil	Case-control	65/548	256/492	42/416

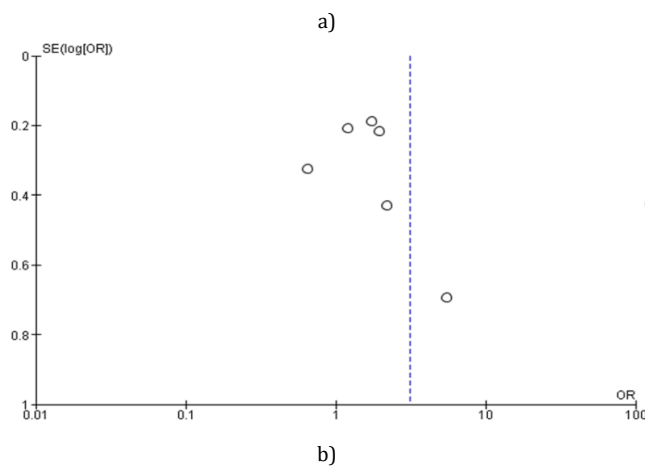
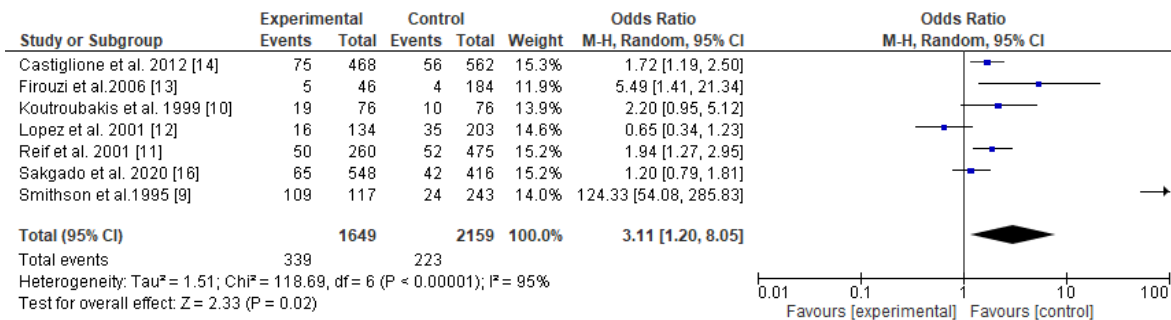


Figure 2. The effects of appendectomy on Crohn's disease

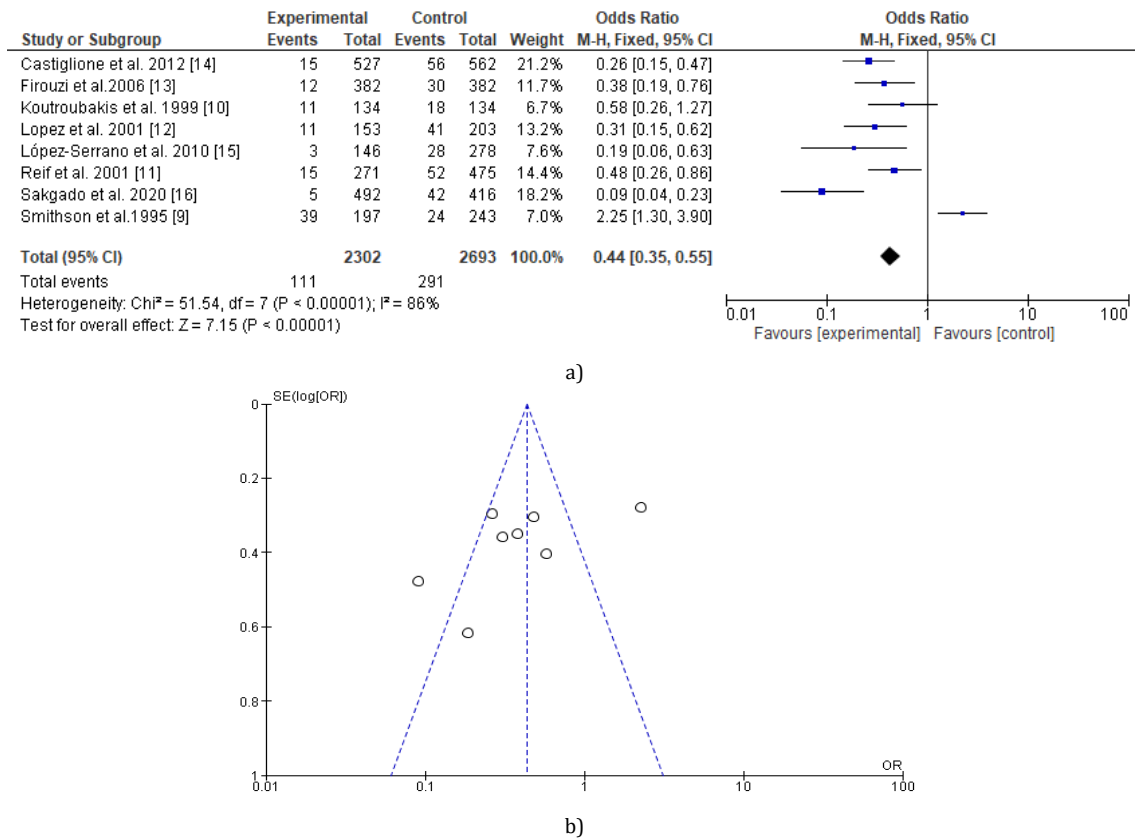


Figure 3. The impact of appendectomy on the rate of Ulcerative colitis

In the present review, appendectomy was lower among patients with ulcerative colitis in agreement with a previous study that included nineteen studies assessing both the risk of developing ulcerative colitis and the time course of the disease in addition to appendiceal orifice inflammation (Deng & Wu, 2016). The current analysis assessed both ulcerative colitis and Crohn's disease. Another study searched MEDLINE and found an increased risk of Crohn's disease in similarity to the current findings. However, the previous findings were limited by the heterogeneity observed (Kaplan *et al.*, 2008; Chanda & Aluru, 2021). A meta-analysis published more than two decades ago and limited by gathering information from articles with different methodologies (reviews, conferences, and abstracts) concluded the inverse relationship between appendectomy and ulcerative colitis (Koutroubakis & Vlachonikolis, 2000). The present study was limited by the heterogeneity, but it is among the best recent pieces of evidence to show the inverse relationship between appendectomy and ulcerative colitis and the negative impact on Crohn's disease.

Environment and inflammatory bowel disease

Recent literature found that the first-generation migrants maintained the inflammatory bowel disease risk of their naïve country and convergence to the destination on subsequent generations. Acquiring the risk of inflammatory bowel disease was stronger with the earlier age at migration suggesting a substantial influence of environmental socio-economic factors (Fiorino *et al.*, 2021). Various environmental factors are to blame in the pathogenesis of IBD, one of the crucial steps is the influence of the gut microbiota on the peroxisome proliferator-

activated receptors (PPAR γ). Impaired expression of the latter enzyme was observed among patients with ulcerative colitis (Caioni *et al.*, 2021). Other factors include antibiotic use, air pollution, infections, diets, and other lifestyles (Shouval & Rufo, 2017).

A wider look at appendectomy and ulcerative colitis

The question that needs to be addressed is the use of appendectomy as a treatment of ulcerative colitis. A meta-analysis published in the USA showed that appendectomy might increase the rate of subsequent colectomy (Parian *et al.*, 2017). These findings supported the findings from a Korean study (Lee *et al.*, 2015). Further meta-analyses found that appendectomy in the established disease was associated with a higher rate of dysplasia and colorectal cancer (Stellingwerf *et al.*, 2019). The above findings together with the observation that appendicular orifice inflammation did not influence the course of ulcerative colitis questioned the use of appendectomy as a treatment for ulcerative colitis. The study was limited by the significant heterogeneity observed, the limitation to the English language, and the unlimited period of the included studies.

CONCLUSION

Appendectomy might protect against ulcerative colitis and negatively affect Crohn's disease.

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