*ANZ Journal of Surgery*

Royal Australasian College of Surgeons

REVIEW ARTICLE OPEN ACCESS

# The Place of Appendicectomy in Inflammatory Bowel Disease—A Review

Krishanth Naidu[1,2,3] | Pearl Wong[1,3] | Pierre H. Chapuis[1,2,3] | Matthew J. F. X. Rickard[1,2,3] | Kheng-Seong Ng[1,2,3]

[1]Colorectal Surgery Unit, Concord Hospital, Concord, Australia | [2]Concord Institute of Academic Surgery, Concord Hospital, Concord, Australia | [3]Concord Clinical School, Clinical Sciences Building, Concord Hospital, University of Sydney, Concord, Australia

**Correspondence:** Kheng-Seong Ng (khengseong.ng@sydney.edu.au)

**Received:** 11 August 2024 | **Revised:** 7 April 2025 | **Accepted:** 16 April 2025

**Keywords:** appendicectomy | Crohn's disease | inflammatory bowel disease | ulcerative colitis

## ABSTRACT

The aetiology and pathophysiology of inflammatory bowel disease (IBD) are not completely understood; however, a dysregulated intestinal immune system appears key to its pathogenesis. It has been suggested that the appendix is central to nurturing the enteric mucosal system due to its production of lymphoid products and that an appendicectomy may have an immune modulating effect. The aim of this review is to explore the available evidence for the association between IBD and appendicectomy and attempt to define its impact on the incidence and risk of Crohn's disease (CD) and Ulcerative colitis (UC) onset and progression.

## 1 | Introduction

### 1.1 | The Appendix

The vermiform appendix, a true diverticulum, is positioned at the juncture of the taenia coli at the base of the caecum [1, 2]. This vestigial organ is enriched with lymphoid tissue, and the appendiceal mucosa and submucosa display distinct histological features compared to the caecum [1]. Within the appendix, the congregation of B and T lymphoid cells gives rise to a specialised lymphoid pulp. This enrichment leads to an increased synthesis of lymphoid products, notably IgA, playing an important role in the gut-associated lymphoid tissue system [1]. Additionally, the appendix serves as a sanctuary for the intestinal commensal microbiome, facilitating the re-population of the proximal large bowel and terminal ileum [3]. Alongside its microbial residents, the appendix provides a nuanced environment essential for maintaining the balance of organs with immunological and metabolic activities [3, 4]. Given these multifaceted roles, many view the appendix as central to nurturing the enteric mucosal immune system, with some theories suggesting a deep linkage to inflammatory bowel disease (IBD) [3].

### 1.2 | IBD

Crohn's disease (CD) and ulcerative colitis (UC) primarily emerged in the twentieth century, coinciding with the advent of a modern, industrialised Western society [5].

Prevailing understandings regarding IBD pathogenesis include the following concepts:

1. The default state of the intestinal immune system is one of immune tolerance. A diverse range of cell types works in a meticulously coordinated manner to uphold this immunological tolerance.
2. Gut microbial factors play a pivotal role in the atypical immune response characteristic of IBD.
3. Genetic attributes increase an individual's vulnerability to this aberrant immune response.
4. Environmental factors play a role in influencing the development of IBD and may also impact disease progression.

5. Both innate and adaptive immune responses collaboratively influence the stability of the intestinal mucosal immune system.

While the exact cause of IBD remains elusive, the dominant hypothesis involves an exaggerated immune response to intestinal microbes in genetically predisposed individuals. Genome-wide association studies (GWAS) have identified around 30 genetic loci that are shared between CD and UC [6]. Nucleotide-binding oligomerisation domain 2 (NOD2) is frequently mutated in patients with CD and is an intracellular sensor for small peptides derived from the cell wall of bacteria [3, 6, 7, 8]. NOD2 activation facilitates downstream interactions that lead to the secretion of proinflammatory cytokines and is therefore an important mediator of inflammation [9–11]. Following bacterial recognition, NOD2 also plays an important role in relation to autophagy [9]. This is a process by which ingested pathogenic bacteria and proteins arising from cellular stress responses are eliminated and hence play a role in host defence and immune response [9]. Autophagy-related (ATG) genes such as ATG16L1 are important, and polymorphisms such as the T300A variant are linked to an increased risk of CD [6]. This is due to impaired T cell responses to dietary or intestinal antigens, promoting the secretion of IgA and IgG against the natural microbiome, resulting in loss of tolerance to intestinal microbes and subsequent disruption of the mucosal barrier [6, 12].

An important overlap in the pathogenesis of both UC and CD relates to the role of the pro-inflammatory interleukin-23 cytokine and variants in the IL23R gene [13]. The latter mediates intestinal inflammation via multiple pathways. Microbial stimulation induces cytokine production by dendritic cells and macrophages. This gene also enhances the TH17 cell response and also activates innate cells to produce inflammatory cytokines that drive intestinal inflammation. It also induces the cytokine and chemokine production by endothelial cells leading to neutrophil recruitment [13, 14]. Neutrophils selectively release chemo-attractants that recruit macrophages for a second-wave inflammatory response [15]. The distinguishing factor between individuals with IBD and those without is the capacity to suppress this inflammatory state, restoring a balanced gut inflammation. In contrast, those predisposed to IBD often grapple with unrestrained inflammation with mucosal injury and increased epithelial permeability, as well as the inability to mitigate the aftermath of the commensal bacterial intrusion and recruitment of neutrophils.

As forementioned, intestinal microbiota is an important driver of an abnormal immune response in IBD patients. More than 99% of intestinal bacteria belong to four phyla—Proteobacteria, Actinobacteria, Firmicutes, and Bacteroidetes. In healthy adults, the latter two phyla dominate the intestinal microbiota [6, 16]. Dysbiosis in IBD includes a reduction in Firmicutes, short-chain fatty acid-producing bacteria, and an increase in pathogenic, mucolytic, and sulphate-reducing bacteria. This causes an aberrant response of the host's immune system, resulting in inflammation and compromise in the epithelial barrier integrity [16].

Beyond genetic and host-related factors, environmental elements have also been suggested as contributors to IBD's onset and manifestation, such as food intake, smoking, and psychological stress [17–20].

## 1.3 | IBD and Appendicectomy

### 1.3.1 | UC and Appendicectomy

In exploring the intriguing relationship between appendicectomy and UC, two contrasting theories have emerged, shedding light on the potential mechanisms underlying this connection.

Given the multifaceted role of the appendix in nurturing the enteric microbiome, the first theory speculates that the appendix may act as a reservoir for beneficial intestinal microbiota that repopulates the intestinal tract following infection or antibiotic use. Hence, the theory is based on the potential role of the appendix in ensuring gut homeostasis and maintaining an anti-inflammatory state, thereby preventing the immunopathogenesis of UC [1–5, 21]. The contrasting theory posits that the act of appendicectomy itself might offer protection against UC. From a biological perspective, the appendix—a lymphoid organ with enigmatic immunological functions—could potentially disrupt the immunological balance in the mucosa of the large intestine [22]. Such imbalances could, in theory, pave the way for UC. Hence, excising the appendix might serve a protective function.

**1.3.1.1 | Before UC Diagnosis.** Data from studies conducted in Northern Europe have demonstrated a significant reduction in the risk of developing UC in adulthood among individuals who underwent appendicectomy at a young age [19, 23]. Both Frisch et al. [19] and Andersson et al. [23] emphasize that this reduced risk is contingent on the appendicectomy being performed in response to an inflammatory condition, such as appendicitis or mesenteric adenitis.

Conversely, a British investigation comparing 3829 patients who had appendicectomies between 1986 and 2005 with an equal number of age- and sex-matched controls found no observable correlation between appendicectomy for appendicitis and IBD onset [24]. Moreover, a large cohort of 493 124 patients studied by Lin et al. [3] revealed a significantly higher UC incidence and risk in the appendicectomy group without appendicitis than in the non-appendicectomy group (13.4 vs. 2.77 per 10 000 person-years, adjusted HR 3.19, 95% CI 1.86–5.50). The latter finding remained significant even after controlling for age, sex, and comorbidities (aHR 2.23, 95% CI 1.59–3.12) [3].

**1.3.1.2 | After UC Diagnosis.** What emerges as especially compelling is the potential influence of appendicectomy on the clinical outcomes of UC. A Swedish study compared 1537 patients who underwent appendicectomies before receiving a UC diagnosis with 603 patients who had the surgery post-diagnosis [25]. The findings indicated that appendicectomy might act as a protective measure against colectomy, but only if done before a UC diagnosis and for patients who had appendicitis surgery before turning 20 [25]. Interestingly, undergoing an appendicectomy due to acute appendicitis after a UC diagnosis was associated with an increased risk of colectomy, while

surgeries conducted in the absence of inflammation showed no such correlation [25]. These findings were echoed in another study examining 111 patients with a history of appendicectomy among a total of 2980 UC patients. Here, any appendicectomy was linked to a heightened colectomy risk (OR 1.9, 95% CI 1.1–3.1), with the risk escalating further if the appendicectomy occurred post-UC diagnosis (OR 2.2, 95% CI 1.1–4.5) [7].

Conversely, in a 2009 prospective study by Bolin and colleagues, where 30 patients with active ulcerative proctitis underwent appendicectomy without detectable appendiceal inflammation, a marked decline in the median activity score was noted in 90% of these patients [8]. Impressively, 40% reached full clinical remission, subsequently halting medical treatment for several months [8]. The preliminary results published in the ACCURE trial are even more compelling that appendicectomy may decrease the rate of colitis-associated adverse events in UC patients. In this study, patients were randomised to undergo appendicectomy (intervention) or continue maintenance medical therapy (control) with the primary outcome being the 1-year UC relapse rate. This was reported as being significantly lower in the appendicectomy group compared to the control group (46.4% vs. 63.9%, $p = 0.02$) [26].

Sahami et al., conducted a prospective pilot study assessing the efficacy of appendicectomy in achieving clinical and endoscopic remission in patients with treatment-resistant UC [27]. Thirty participants were tracked and assessed at 3- and 12-months post-surgery for clinical remission. Notably, 3 months post-appendicectomy, 25 out of 30 patients witnessed a significant drop in their Mayo score ($p = 0.001$), with 12 retaining these benefits up to 12 months [27]. Unlike the Bolin study, the majority of the patients in Sahami et al.'s study had left-sided or extensive colitis (80%) [27].

Delving deeper, Sahami et al. [27] examined two additional critical facets. Firstly, they measured the inflammatory activity in both the appendix and colonic biopsies pre- and post-appendicectomy using the Geboes score. 29 of the 30 patients, 28 displayed active appendix inflammation, differing from Bolin et al.'s [8] findings. Additionally, post-surgery, 46% of colonic biopsies recorded a decrease in the Geboes score [27]. The study also identified an uptick in CD4+ T lymphocyte presence in both colonic and appendiceal samples, underscoring shared inflammatory mechanisms [27].

In summary, existing evidence suggests that appendicectomy might offer protection against UC. Additionally, certain genetic or environmental factors that heighten appendicitis risk might inversely affect UC susceptibility. This implies that appendicectomy could potentially serve as a therapeutic intervention for patients with treatment-resistant UC and even as a preventive measure for immediate family members of UC patients. However, the current body of evidence is not robust enough to recommend elective appendicectomy as a standard procedure for UC patients. There are several considerations to note. Primarily, extensive trials are necessary to conclusively prove the long-term efficacy of appendicectomy in inducing and preserving both clinical and endoscopic remission. The status of colitis at the time of surgery could play a role in determining outcomes. The few prospective studies available, which have focused exclusively on active UC cases, indicate significant clinical benefits [8, 27]. Conversely, more recent research with larger patient groups downplays the therapeutic significance of appendicectomy in established UC cases. These studies are retrospective and leave the disease activity status at the time of surgery undocumented [7, 25].

### 1.3.2 | CD and Appendicectomy

The link between CD and appendicectomy is a complex and debated topic, with current literature reporting conflicting results [20, 28–44]. The positive association between appendicectomy and CD is supported by several biological mechanisms suggesting an altered intestinal microbiome induced by appendicectomy, leading to an increased occurrence of CD [34, 38]. Another plausible explanation is that there may be possible detection bias, as patients in the early stages of CD can present with symptoms mimicking those of appendicitis. Various studies have attempted to stratify the risk of developing CD after an appendicectomy by observing the elapsed time gap between the surgical procedure and the eventual diagnosis of CD [38, 39].

In synthesising the data from a number of studies, the overall observation is a positive association of CD with appendicectomy, however significant heterogeneity is observed [38, 39]. Both Frisch et al. [20] and Kaplan et al. [32] and studied the risk of CD post appendicectomy in a Nordic region population. In both studies, there was a substantial number of CD cases diagnosed within the initial year after appendicectomy. However, over time, this association diminished and by the 5-year mark, the CD risk became negligible. Similarly, these findings were also observed in Chen et al.'s [34] case–control study in a Chinese population, where the rate of appendicectomy within 1- year before CD diagnosis was significantly higher in CD patients compared to that in controls (0.97% vs. 0%, $p = 0.031$) [34]. Furthermore, Fantodji et al.'s cohort study of 400 000 people found a strong association of CD in the first 2 years post appendicectomy, particularly occurring in early adulthood (18–29 years) [38]. These findings are consistent with Frisch et al. [28], who reported that appendicectomies performed within the ages of 21–34 years were at increased risk of CD. Interestingly, this is consistent with the peak onset of CD which is usually late in adolescence and in young adulthood [42]. Authors have commonly stated that the positive association may be reflective of a diagnostic bias, with appendicectomies being performed on persons with unrecognised CD at time of surgery, rather than a direct biological association between the two [20, 29, 32, 33]. The appendicectomy-CD link would be more compelling if effects persisted beyond CD's prodromal period, which although greatly varies among patients, averages between 2–7 years [44]. However, multiple studies examined the timing between appendicectomy and CD diagnosis and have all demonstrated that the positive association peaks between 6 months and 2 years, persists to around 5 years, and then drastically drops, reverting to baseline within 10 years [20, 38, 39].

In addition to stratifying risk estimate by time, analysis of factors such as effect on CD severity yielded inconsistent results [30, 37, 40, 41]. In patients with CD with a history of appendicectomy for perforated appendicitis, Anderson et al. demonstrated

a worse prognosis for CD with a higher rate of intestinal resections compared to control patients [30]. Similarly, Riegler et al.'s retrospective cohort study demonstrated an increased risk of bowel resections [40]. Furthermore, Cosnes et al.'s study suggested some differences in CD behaviour in patients who have had an appendicectomy [41]. Comparisons revealed that this group was more prone to formation of strictures and less to penetrating anal disease [41]. On the contrary, an Australian study demonstrated that in the same population, there was no difference in CD severity [37].

Contrary to the belief of a reduced UC risk after appendicectomy, multiple meta-analyses have noted an escalated CD risk [39]. While the meta-analysis findings do not wholly dismiss a potential biological link between appendicectomy and increased CD risk, the predominant rise in CD among appendicectomy patients seems driven by diagnostic bias. A large genome-wide association study looked at the potential causal relationship between appendicitis and IBD using Mendelian randomisation. The results indicated that IBD may have a negative causal effect on the occurrence of appendicitis, but there is no evidence to suggest that appendicitis causes IBD [45].

## 2 | Conclusion

The association of appendicectomy with the risk of developing UC remains controversial, but it may offer a protective element against the progression of UC, and this option should be explored in treatment-resistant disease. However, further studies need to be performed prior to the implementation of this recommendation. By contrast, there appears to be a positive association between appendicectomy and CD, but it remains unclear how much of this relates to diagnostic bias. However, clinicians should have a low threshold for suspicion of CD when reviewing young adults with GI symptoms after having undergone appendicectomy.

### Author Contributions

**Krishanth Naidu:** conceptualization, writing – original draft, writing – review and editing. **Pearl Wong:** project administration, writing – original draft, writing – review and editing. **Pierre H. Chapuis:** conceptualization, supervision, writing – review and editing. **Matthew Rickard:** supervision, writing – review and editing. **Kheng-Seong Ng:** conceptualization, supervision, writing – review and editing.

### Acknowledgments

Open access publishing facilitated by The University of Sydney, as part of the Wiley - The University of Sydney agreement via the Council of Australian University Librarians.

### Conflicts of Interest

The authors declare no conflicts of interest.

### References

1. B. M. Jaffe and D. H. Berger, "The Appendix," in *Schwartz's Principles of Surgery*, 8th ed., ed. S. I. B. C. Schwartz (McGraw-Hill Companies, 2005).

2. K. Buschard and A. Kjaeldgaard, "Investigation and Analysis of the Position, Fixation, Length and Embryology of the Vermiform Appendix," *Acta Chirurgica Scandinavica* 139, no. 3 (1973): 293–298.

3. W. S. Chung, S. Chung, C. Y. Hsu, and C. L. Lin, "Risk of Inflammatory Bowel Disease Following Appendectomy in Adulthood," *Frontiers in Medicine* 8 (2021): 661752.

4. C. M. Guinane, A. Tadrous, F. Fouhy, et al., "Microbial Composition of Human Appendices From Patients Following Appendectomy," *MBio* 4, no. 1 (2013): e00366-12.

5. D. J. Mulder, A. J. Noble, C. J. Justinich, and J. M. Duffin, "A Tale of Two Diseases: The History of Inflammatory Bowel Disease," *Journal of Crohn's & Colitis* 8, no. 5 (2014): 341–348.

6. Q. Guan, "A Comprehensive Review and Update on the Pathogenesis of Inflammatory Bowel Disease," *Journal of Immunology Research* 2019 (2019): 1–16, https://doi.org/10.1155/2019/7247238.

7. A. Parian, B. Limketkai, J. Koh, et al., "Appendectomy Does Not Decrease the Risk of Future Colectomy in UC: Results From a Large Cohort and Meta-Analysis," *Gut* 66, no. 8 (2017): 1390–1397.

8. T. D. Bolin, S. Wong, R. Crouch, J. L. Engelman, and S. M. Riordan, "Appendicectomy as a Therapy for Ulcerative Proctitis," *American Journal of Gastroenterology* 104, no. 10 (2009): 2476–2482.

9. W. Strober and T. Watanabe, "Nod2, an Intracellular Innate Immune Sensor Involved in Host Defense and Crohn's Disease," *Mucosal Immunology* 4, no. 5 (2011): 484–495, https://doi.org/10.1038/mi.2011.29.

10. S. Yamamoto and X. Ma, "Role of nod2 in the Development of Crohn's Disease," *Microbes and Infection* 11, no. 12 (2009): 912–918, https://doi.org/10.1016/j.micinf.2009.06.005.

11. W. Strober, A. Kitani, I. Fuss, N. Asano, and T. Watanabe, "The Molecular Basis of NOD2 Susceptibility Mutations in Crohn's Disease," *Mucosal Immunology* 1 (2008): S5–S9, https://doi.org/10.1038/mi.2008.42.

12. L. J. Cohen, J. H. Cho, D. Gevers, and H. Chu, "Genetic Factors and the Intestinal Microbiome Guide Development of Microbe-Based Therapies for Inflammatory Bowel Diseases," *Gastroenterology* 156, no. 8 (2019): 2174–2189, https://doi.org/10.1053/j.gastro.2019.03.017.

13. G. W. Sewell and A. Kaser, "Interleukin-23 in the Pathogenesis of Inflammatory Bowel Disease and Implications for Therapeutic Intervention," *Journal of Crohn's and Colitis* 16, no. S2 (2022): ii3–ii19, https://doi.org/10.1093/ecco-jcc/jjac034.

14. D. McGovern and F. Powrie, "The IL23 Axis Plays a Key Role in the Pathogenesis of IBD," *Gut* 56, no. 10 (2007): 1333–1336, https://doi.org/10.1136/gut.2006.115402.

15. B. M. Fournier and C. A. Parkos, "The Role of Neutrophils During Intestinal Inflammation," *Mucosal Immunology* 5, no. 4 (2012): 354–366, https://doi.org/10.1038/mi.2012.24.

16. A. Nishida, R. Inoue, O. Inatomi, S. Bamba, Y. Naito, and A. Andoh, "Gut Microbiota in the Pathogenesis of Inflammatory Bowel Disease," *Clinical Journal of Gastroenterology* 11, no. 1 (2017): 1–10, https://doi.org/10.1007/s12328-017-0813-5.

17. H. S. Odes, A. Fich, S. Reif, et al., "Effects of Current Cigarette Smoking on Clinical Course of Crohn's Disease and Ulcerative Colitis," *Digestive Diseases and Sciences* 46, no. 8 (2001): 1717–1721.

18. I. Bjarnason, G. Zanelli, T. Smith, et al., "Nonsteroidal Antiinflammatory Drug-Induced Intestinal Inflammation in Humans," *Gastroenterology* 93, no. 3 (1987): 480–489.

19. M. Frisch, B. V. Pedersen, and R. E. Andersson, "Appendicitis, Mesenteric Lymphadenitis, and Subsequent Risk of Ulcerative Colitis: Cohort Studies in Sweden and Denmark," *BMJ* 338 (2009): b716.

20. M. Frisch, C. Johansen, L. Mellemkjaer, et al., "Appendectomy and Subsequent Risk of Inflammatory Bowel Diseases," *Surgery* 130, no. 1 (2001): 36–43.

21. J. E. Smithson, G. Radford-Smith, and G. P. Jewell, "Appendectomy and Tonsillectomy in Patients With Inflammatory Bowel Disease," *Journal of Clinical Gastroenterology* 21, no. 4 (1995): 283–286.

22. P. Rutgeerts, G. D'Haens, M. Hiele, K. Geboes, and G. Vantrappen, "Appendectomy Protects Against Ulcerative Colitis," *Gastroenterology* 106, no. 5 (1994): 1251–1253.

23. R. E. Andersson, G. Olaison, C. Tysk, and A. Ekbom, "Appendectomy and Protection Against Ulcerative Colitis," *New England Journal of Medicine* 344, no. 11 (2001): 808–814.

24. R. Singhal, J. Taylor, M. Owoniyi, R. H. El-Khayat, S. K. Tyagi, and A. P. Corfield, "The Role of Appendicectomy in the Subsequent Development of Inflammatory Bowel Disease: A UK-Based Study," *International Journal of Colorectal Disease* 25, no. 4 (2010): 509–513.

25. P. Myrelid, K. Landerholm, C. Nordenvall, T. D. Pinkney, and R. E. Andersson, "Appendectomy and the Risk of Colectomy in Ulcerative Colitis: A National Cohort Study," *American Journal of Gastroenterology* 112, no. 8 (2017): 1311–1319.

26. E. Visser, L. Heuthorst, S. P. Pathmakanthan, et al., "P955 the Effect of Appendicectomy on the Clinical Course of Ulcerative Colitis: Preliminary Results," *Journal of Crohn's & Colitis* 18, no. S1 (2024): i1734, https://doi.org/10.1093/ecco-jcc/jjad212.1085.

27. S. Sahami, M. E. Wildenberg, L. Koens, et al., "Appendectomy for Therapy-Refractory Ulcerative Colitis Results in Pathological Improvement of Colonic Inflammation: Short-Term Results of the PASSION Study," *Journal of Crohn's & Colitis* 13, no. 2 (2019): 165–171.

28. M. Frisch and G. Gridley, "Appendectomy in Adulthood and the Risk of Inflammatory Bowel Diseases," *Scandinavian Journal of Gastroenterology* 37, no. 10 (2002): 1175–1177.

29. L. M. Kurina, M. J. Goldacre, D. Yeates, and V. Seagroatt, "Appendicectomy, Tonsillectomy, and Inflammatory Bowel Disease: A Case-Control Record Linkage Study," *Journal of Epidemiology and Community Health* 56, no. 7 (2002): 551–554.

30. R. E. Andersson, G. Olaison, C. Tysk, and A. Ekbom, "Appendectomy Is Followed by Increased Risk of Crohn's Disease," *Gastroenterology* 124, no. 1 (2003): 40–46.

31. I. E. Koutroubakis, I. G. Vlachonikolis, A. Kapsoritakis, et al., "Appendectomy, Tonsillectomy, and Risk of Inflammatory Bowel Disease: Case-Controlled Study in Crete," *Diseases of the Colon and Rectum* 42, no. 2 (1999): 225–230.

32. G. G. Kaplan, B. V. Pedersen, R. E. Andersson, B. E. Sands, J. Korzenik, and M. Frisch, "The Risk of Developing Crohn's Disease After an Appendectomy: A Population-Based Cohort Study in Sweden and Denmark," *Gut* 56, no. 10 (2007): 1387–1392.

33. Y. Chen, Y. Wang, and J. Shen, "Role of Environmental Factors in the Pathogenesis of Crohn's Disease: A Critical Review," *International Journal of Colorectal Disease* 34, no. 12 (2019): 2023–2034.

34. D. Chen, J. Ma, Q. Ben, L. Lu, and X. Wan, "Prior Appendectomy and the Onset and Course of Crohn's Disease in Chinese Patients," *Gastroenterology Research and Practice* 2019 (2019): 8463926.

35. A. D. Amarapurkar, D. N. Amarapurkar, P. Rathi, et al., "Risk Factors for Inflammatory Bowel Disease: A Prospective Multi-Center Study," *Indian Journal of Gastroenterology* 37, no. 3 (2018): 189–195.

36. A. C. C. F. Loureiro and L. E. R. Barbosa, "Appendectomy and Crohn's Disease," *Journal of Coloproctology (Rio de Janeiro)* 39, no. 4 (2019): 373–380.

37. G. L. Radford-Smith, J. E. Edwards, D. M. Purdie, et al., "Protective Role of Appendicectomy on Onset and Severity of Ulcerative Colitis and Crohn's Disease," *Gut* 51, no. 6 (2002): 808–813.

38. C. Fantodji, P. Jantchou, M. E. Parent, and M. C. Rousseau, "Appendectomy and Risk for Inflammatory Bowel Disease: Effect of Age and Time Post Appendectomy—A Cohort Study," *BMJ Open Gastroenterology* 9, no. 1 (2022): e000925.

39. L. Zhang, C. Hu, Z. Zhang, et al., "Association Between Prior Appendectomy and the Risk and Course of Crohn's Disease: A Systematic Review and Meta-Analysis," *Clinics and Research in Hepatology and Gastroenterology* 47, no. 3 (2023): 102090.

40. G. Riegler, L. Caserta, I. Esposito, et al., "Worse Clinical Course of Disease in Crohn's Patients With Previous Appendectomy," *European Journal of Gastroenterology & Hepatology* 17, no. 6 (2005): 623–627.

41. J. Cosnes, P. Seksik, I. Nion-Larmurier, L. Beaugerie, and J. P. Gendre, "Prior Appendectomy and the Phenotype and Course of Crohn's Disease," *World Journal of Gastroenterology* 12, no. 8 (2006): 1235–1242.

42. M. Gasparetto and G. Guariso, "Highlights in IBD Epidemiology and its Natural History in the Paediatric Age," *Gastroenterology Research and Practice* 2013 (2013): 829040.

43. M. G. Russel, E. Dorant, R. J. Brummer, et al., "Appendectomy and the Risk of Developing Ulcerative Colitis or Crohn's Disease: Results of a Large Case-Control Study. South Limburg Inflammatory Bowel Disease Study Group," *Gastroenterology* 113, no. 2 (1997): 377–382.

44. M. Pimentel, M. Chang, E. J. Chow, et al., "Identification of a Prodromal Period in Crohn's Disease but Not Ulcerative Colitis," *American Journal of Gastroenterology* 95, no. 12 (2000): 3458–3462.

45. Y. Zhang, L. Yang, and L. Yuan, "Investigating the Causal Relationship Between Inflammatory Bowel Disease and Simple Appendicitis Using Mendelian Randomization," *Scientific Reports* 14, no. 1 (2024): 23617, https://doi.org/10.1038/s41598-024-74572-5.