HHS Public Access

Author manuscript

Nat Rev Gastroenterol Hepatol. Author manuscript; available in PMC 2023 September 27.

Published in final edited form as:

Nat Rev Gastroenterol Hepatol. 2023 September ; 20(9): 615–624. doi:10.1038/s41575-023-00774-3.

The appendix and ulcerative colitis — an unsolved connection

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Abstract

The appendix is thought to have a role in the pathogenesis of ulcerative colitis but the nature and basis of this association remains unclear. In this Perspective, we consider the biology of the appendix with respect to its immunological function and the microbiome, and how this relates to evidence that supports the involvement of the appendix in ulcerative colitis. In experimental models, removal of the inflamed appendix prevents colitis, and in human observational studies, appendectomy is associated with protection against ulcerative colitis. Further, among people who develop ulcerative colitis, appendectomy before diagnosis might influence the course and outcomes of the disease — some evidence suggests that it protects against colectomy but could increase the risk of colorectal cancer. Appendectomy after onset of ulcerative colitis seems to have disparate consequences. Clinical trials to understand whether appendectomy has a role in the treatment of ulcerative colitis are ongoing. Major questions about the role of the appendix in the pathogenesis of ulcerative colitis remain unanswered, and further research is needed to establish whether the connection is clinically relevant.

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Author contributions

All authors contributed to all aspects of the article.

Competing interests

M.A. is supported by the National Institute of Diabetes and Digestive and Kidney Diseases (K23DK129762–02). S.M. has received research grants from Genentech and Takeda; payment for lectures from Genentech, Morphic and Taleda; and consulting fees from Arena Pharmaceuticals, Ferring, Morphic and Takeda. J.F. has received consulting fees from Vedanta Biosciences. J.-F.C. reports has received research grants from AbbVie, Janssen Pharmaceuticals and Takeda; payment for lectures from AbbVie, Amgen, Allergan. Ferring Pharmaceuticals, Shire and Takeda; has received consulting fees from AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, BMS, Celgene Corporation, Eli Lilly, Ferring Pharmaceuticals, Galmed Research, Genentech, Glaxo Smith Kline, Janssen Pharmaceuticals, Kaleido Biosciences, Imedex, Immunic, Iterative Scopes, Merck, Microbia, Novartis, PBM Capital, Pfizer, Protagonist Therapeutics, Sanofi, Takeda, TiGenix, Vifor; and holds stock options in Intestinal Biotech Development. The other authors declare no competing interests.

Introduction

The vermiform appendix is a tubular appendage extending from the caecum that is often considered to be a vestigial organ but is increasingly thought to be an immune organ and ecosystem that is relevant to mucosal immune function and colonic microbiome stability. Some evidence suggests that the appendix contributes to the pathogenesis of ulcerative colitis, an immune-mediated inflammatory disorder of the colon. The pathogenesis of ulcerative colitis is poorly understood and its aetiology has been attributed to multiple genetic and nongenetic risk factors[1]. Possible involvement of the appendix first came to light over three decades ago on the basis of reports that appendectomy modulates the risk of ulcerative colitis[2]. The association has subsequently been explored in countless mechanistic, epidemiological and interventional studies, but the data produced are ambiguous and, at times, contradictory. Consequently, the exact nature of the relationship remains unknown.

In this Perspective article, we consider the evidence that supports involvement of the appendix in ulcerative colitis and suggest hypotheses for the basis of this involvement Given that the connection between the appendix and ulcerative colitis has not been fully established, we aim to stimulate discussion and identify the research questions that need to be answered to determine the strength and nature of the connection.

Evolution and anatomy of the appendix

Evolution

The functional relevance of the appendix is long debated. In 1871, Darwin proposed that it is a vestigial remnant from plant-eating primates[3]. On the basis of phylogenetic and immunological data, others have suggested that the appendix serves a function, albeit as yet undiscovered[4,5]. In one study, a combination of anatomical comparisons of the appendix between mammals, mapping of caecal and appendiceal features onto phylogenetic analysis, and comparison of microbial biofilms between amphibians and mammals[6] indicated that the mammalian appendix has been phylogenetically conserved for >80 million years, despite that fact that it seems to have evolved independently multiple times[6,7]. Analysis of evolutionary gains and losses of the appendix in 258 mammalian species determined that the presence of the appendix was associated with increased longevity, probably owing to a reduction in extrinsic mortality associated with conditions such as fatal infectious diarrhoea[8,9]. These evolutionary studies indicate that the appendix was functional; whether it remains so is a matter of debate. One possibility is that that the appendix is no longer functional because of improvements in sanitation, but substantial evidence, discussed below, disputes this idea.

Anatomy

During human development, the appendix first appears as an outpouching at the junction between the small bowel and the colon at week 5 of intrauterine growth[10]. It grows into a tubular, closed-ended reservoir that extends up to 10 cm from the base of the caecum at the confluence of the taenia coli and has an internal diameter of 1–3 mm[6]. The appendix grows fastest in the first year of life[11]. The tubular, closed-ended anatomy of the appendix,

its narrow lumen and its location at the base of the caecum ensures it is protected from the faecal stream and pathological microorganisms, and facilitates biofilm accrual within the lumen[6,9].

The appendix as an immune organ

The appendix contains a high density of gut-associated lymphoid tissue (GALT), which develops in concert with the intestinal microbiota[12]. A rich array of immune cells has been identified in the appendix, which represents a microcosm of the intestinal immune compartment with some important differences, highlighted below.

Immune cells in the appendix include diverse populations of innate immune cells, including natural killer cells and intraepithelial $CD8^+$ T cells[13,14]. The appendix also includes immune inductive sites, such as dense, B cell-containing lymphoid follicles with constitutive germinal centres, and immune effector sites characterized by lamina-propria-resident plasma cells, which produce immunoglobulin G (IgG), IgA and macrophages[12,14,15]. Microfold (M) cells are also associated with lymphoid follicles in the appendix; these cells, which are typically found in Peyer patches, are involved in the transepithelial transport of bacterial antigens and in the targeting of antigens to antigen-presenting cells[16]. Interestingly, appendix-resident M cells seem to be morphologically distinct from those resident to Peyer patches[15,17].

Proliferation of appendiceal GALT and antibody production occurs upon exposure to intestinal bacteria in two phases: the first is B cell recruitment to emerging follicles, and the second is intrafollicular B cell proliferation in response to commensal microbes[18,19]. Bacterial translocation occurs in GALT and has a pivotal role in antigen presentation, immune response and tolerance[11]. IgG-producing and IgA-producing plasma cells are the predominant antibody-producing cells in the appendiceal GALT and are likely to play a role in B cell responses to microbial antigens[20,21]. Interestingly, the reported density of IgG-producing plasma cells in the appendix is higher than that in the colon[20], and IgG^+ plasma cells are in close proximity to lymphoid aggregates[22]. This evidence has led to the hypothesis that the IgG^+ plasma cells mature locally, whereas the IgA^+ plasma cells leave the appendix and follow conventional pathways of maturation and trafficking, possibly contributing to colonic immune surveillance[22,23]. However, this hypothesis is speculative has not been experimentally proven.

Appendiceal immune function is particularly important during early life. B cells are detectable in the appendiceal wall at gestational week 17 and increase in number throughout embryonic development[10]. Postnatally, proliferation of GALT is most pronounced in the first year of life[11]. Furthermore, electron microscopic analysis of non-inflamed appendices removed incidentally from 33 individuals aged between 1 day and 54 years demonstrated that bacterial translocation did not occur in the first 2 weeks of life (when lymphoid follicles are not yet developed), peaked between 3 and 8 weeks, decreased after 2–24 months, and remained relatively constant thereafter[11]. Age-related differences in appendiceal immune composition and function could be important for the interaction between age and nongenetic exposures in the risk of immune-mediated diseases (see The appendix and ulcerative colitis).

Some evidence suggests that the appendix is involved in immunological priming in immune-mediated disease, specifically ulcerative colitis. For example, in a cohort of 86 individuals with active or inactive ulcerative colitis, analysis of peri-appendiceal tissue, rectal tissue and the transverse colon revealed increased levels of $CD4^+$ T cells, an increased ratio of $CD4^+$ T cells to $CD8^+$ T cells, and an increase in levels of $CD4^+$CD69+ T cells in the peri-appendiceal tissue of patients with ulcerative colitis independent of disease activity[24]. These findings suggest increased immune infiltration and activity at peri-appendiceal sites in ulcerative colitis, although antigen-specific immune responses were not tested in this study. Further studies that employ high-dimensional immune profiling methodologies are needed to determine the role of the appendix in immunological priming.

The appendix and the microbiome

The appendiceal biofilm

Biofilms are colonies of intestinal microbes and other flora that reside within a matrix of glycoproteins, polysaccharides and immunoglobulins. In the gut, the dominant biofilm is a mucus-associated microbial community that has a symbiotic relationship with the host; the host gains mucosal immune tolerance and the microbial community gains metabolic and survival advantages[9,25].

The gut biofilm has been visualized in colon samples from rats, baboons and humans by use of electron microscopy, acridine orange staining of flash frozen tissues and IgA immunofluorescent microscopy[26]. This approach demonstrated that the biofilm grows in distinct layers (smaller bacteria are closer to the mucosa), the biofilm is predominant in the proximal rather than the distal colon, the structure and density of the biofilm are influenced by the faecal stream, the matrix comprises 50–90% of the biofilm, and secretory IgA is a key constituent of the biofilm[26].

In vivo work has shown that an intact innate immune system is not essential for biofilm formation, but that IgA can influence biofilm composition[27]. In this study, spatial analysis of the biofilm-like community associated with the murine colonic mucous layer demonstrated that the biofilm composition was similar in wild-type mice and Rag knockout mice that lacked T cells and B cells, whereas *Prevotellaceae* were reduced in Rag knockout mice in the absence of IgA[27]. Other work has shown that biofilm composition and integrity can also be influenced by other factors. Candida interacts with bacteria in biofilms via hyphal filaments; defective mannosylation of hyphae can impact biofilm homeostasis[28]. Nickerson et al demonstrated that maltodextrin, a starch derivative, is associated with *Escherichia* (E. coli) specific biofilm formation, including adherent-invasive E. coli (AIEC) strains[29]. Similar interactions between microbes, dietary components and immune factors are likely to influence the formation and integrity of the appendiceal biofilm.

Immune cells in the appendix interact with the biofilm and influence its stability, immune exclusion and immune inclusion (regulation of microbial entry through the epithelial barrier)[30]. Mucin and IgA, both of which are produced by immune cells, are major constituents of the biofilm and support its development[9,31]. Secretory IgA (sIgA) binds to mucus and aggregates bacteria, providing both antigen-specific and non-specific

mechanisms to influence biofilm formation[32]. sIgA also facilitates adherence of bacteria to epithelial cells[33,34]. Bacterial pili and adhesins have a role in this immune-influenced biofilm stability. For example, *Escherichia coli* growth in the biofilm is stronger when it has an intact type 1 pilus and secretory IgA is present than when either is present without the other. By contrast, mucin-mediated growth of *E. coli* in the biofilm was independent of the type 1 pilus in the presence of environmental (faecal) isolates but not in the presence of a laboratory isolate[30].

Composition of the appendiceal microbiome

The composition of the appendiceal microbiome has been studied by use of 16S ribosomal RNA (16S rRNA) gene sequencing of DNA isolated from appendiceal tissue. In the first study of the appendiceal microbial composition, published in 2013, the microbiome composition was analysed in post-surgical appendix samples from seven individuals aged 5–25 years with appendicitis[35]. The reported appendiceal microbiome was diverse, distinct from other microbiome populations in the gut in terms of the relative abundance of different taxonomic groups, and heterogeneous between individuals (as might be expected given the small sample size). However, the major phyla represented in the appendix were the same as in the colon. Specifically, *Firmicutes* was the dominant phylum, and other well-represented phyla included *Proteobacteria*, *Bacteroidetes*, *Actinobacteria* and *Fusobacteria.* In a larger analysis of appendix swabs from 85 children undergoing appendectomy for acute appendicitis, expansion and persistence of *Fusobacteria* species was observed[36].

In these studies, the appendiceal microbiome was analysed in the context of appendicitis, so the observed composition might not reflect that in the healthy appendix. One study of the appendiceal microbiome has demonstrated some such differences. In this study, tissue was obtained from 50 women who underwent appendectomy for acute, non-perforated appendicitis and 35 women who underwent incidental appendectomy of the uninflamed appendix during gynaecological surgery[37]. Individuals with gastrointestinal disease were excluded. The overall alpha diversity of the appendiceal microbiome was comparable between the two groups, although analysis of each phylum showed that the alpha diversity of *Proteobacteria* was greater in the appendicitis group. The relative abundance of the major phyla was similar between the two groups except for a slightly lower abundance of Firmicutes in the appendicitis group. However, the beta diversity of phyla *Bacteroidetes* and *Proteobacteria* differed more substantially between the two groups, and the relative abundance of families *Burkholderiaceae, Moraxellaceae* and *Campylobacteraceae* and genera *Acinetobacter* and *Campylobacter* was higher in the appendicitis group than the non-appendicitis group. Quantitative PCR analysis also demonstrated a greater abundance of *Campylobacter jejuni*, but not other *Campylobacter* species in appendicitis group than in the non-appendicitis group. Overall, these results suggest the appendiceal microbiome is largely similar to that in health, with minor alterations in a few select taxanomic groups.

The role of the microbiome in appendicitis

Some evidence suggests that alterations in the composition of the appendiceal microbiome are important in appendicitis. Comparison of the appendiceal microbiome in 70 people who had appendicitis with the microbiome in caecal biopsies and faecal samples from 400

controls (ulcerative colitis or healthy)[38] showed that Fusobacteria (primarily *Fusobacterium nucleatum* and *necrophorum)* were predominant in the mucosal appendiceal microbiome of people with appendicitis and absent in caecal biopsies of controls[38]. Further, in people with appendicitis, the abundance of Fusobacteria at the appendix epithelium correlated positively with the severity of appendicitis[38]. Microbiome analysis of samples from inflamed appendices from various international cohorts produced similar results[39], and an elevated relative abundance of Fusobacteria in the appendiceal microbiome has been observed in paediatric appendicitis[40,41]. By contrast, in people with appendicitis, appendiceal abundance of *Bacteroides, Eubacterium rectale* and *Faecalibacterium prausnitzii* was inversely related to the severity of appendicitis[38]. These data suggest that Fusobacteria have a role in acute appendicitis.

Effects of appendectomy on the microbiome

Evidence from several studies suggests that removal of the appendix can have minor influences the composition of the gut microbiome. In one such study, the microbiome composition in faecal samples collected 4–6 weeks after appendectomy from 99 people with acute appendicitis was compared with that in faecal samples from 106 healthy individuals, and appendiceal samples from 90 individuals who had undergone appendectomy for acute appendicitis were analysed[42]. The post-appendectomy gut microbiome was largely similar in composition and diversity to that of healthy volunteers, although phyla-level differences were observed; the abundance and diversity of *Firmicutes, Actinobacteria, Fusobacteria* and Verrucomicrobia were lower in people who had undergone appendectomy. These findings indicate that the gut microbiome is — at most — subtly changed after appendectomy.

In another study, bacterial and fungal diversity and composition were studied in faecal samples from 30 individuals who had undergone appendectomy >6 months earlier (indication not reported) but were otherwise healthy and 30 healthy individuals who had not undergone appendectomy. Analysis of these samples with 16S and ITS2 amplicon sequencing[43] showed that the alpha diversity was comparable between the two groups overall but was lower among those who had undergone appendectomy <2 years before study entry than among those who had undergone the procedure >2 years before. The beta diversity differed between the groups, but tended to shift over time in individuals who had undergone appendectomy toward that of individuals who had not undergone appendectomy. Taxonomic analysis identified a lower abundance of *Roseburia, Barnesiella, Butyricicoccus, Odoribacter* and *Butyricimonas* species (bacteria that produce short-chain fatty acids) and a higher abundance of *Escherichia–Shigella, Veillonella, Klebsiella, Megasphaera, Flavonifractor,* the *Ruminococcus gnavus* group and *Streptococcus* in the people who had undergone appendectomy. Gut fungal diversity was higher among people who had undergone appendectomy than among those who had not, and these alterations persisted over 5 years. Analysis of interkingdom interactions indicated that interactions between bacteria fungi were altered substantially after appendectomy.

The long-term effects of appendectomy on gut microbiome diversity have also been demonstrated in a case–control study of 40 individuals who underwent bariatric surgery, 20 of whom also underwent incidental prophylactic appendectomy[44]. Use of 16S rRNA

gene analysis of faecal samples collected over 5 years after appendectomy demonstrated that alpha diversity in the gut microbiome was lower among individuals who had undergone appendectomy than among those who had not. *Odoribacter, Bilophila, Butyricimonas* and *Faecalibacterium* were less frequently detected in samples from people who had undergone appendectomy, whereas *Lachnobacterium* was detected more frequently[44]. These results again demonstrate a potential influence of the appendix on the long-term composition of the faecal microbiome. However, generalization of these results to draw conclusions about the influence of the appendix on the gut microbiome in the broader population is more challenging owing to the underlying bariatric surgery in all patients in this study.

The appendix as a microbiome safe house

As our understanding of the biofilm and microbiome has increased, the appendix has been proposed as a so-called safe house for a stable biofilm. The anatomy of the appendix and its consequent protection from the faecal stream, makes the it an ideal biofilm repository from which the colon could be periodically reinoculated with commensal bacteria[9,12]. Though profiling of the microbiome composition has largely been limited to individuals who have undergone appendectomy, the appendiceal microbiome seems to contain the same major phyla as the colonic microbiome[35]. However, further studies are needed to determine whether this observation means that the appendiceal microbiome simply mirrors the colonic microbiome or the appendix is a reservoir that helps to maintain the colonic microbiome.

As discussed above, studies of gut microbiome composition after appendectomy indicate that removal of the appendix is associated with lower alpha diversity and some consistent differences in microbiome composition. However, these differences are subtle and do not suggest a large effect of appendectomy. Therefore, the argument that the appendix could act as a microbiome safe house that enables reseeding of the gut after disruption to the gut microbiome is logical but largely theoretical. If the safe house hypothesis is valid, its relevance in modern life in high-income countries, where serious diarrhoeal infections are infrequent, is likely to be highly context-specific. Longitudinal studies of individuals with and without an appendix would provide greater insight into strain-specific stability under homeostatic conditions and disruption of the microbiome (such as diarrhoea, antibiotics and bowel preparation for colonoscopy) and would tell us more about the magnitude of the effect of the appendix on microbiome stability. These longitudinal experiments could also identify taxa that are most susceptible to extinction from the gut in the absence of an appendix, which might explain differences in the risk of disease between individuals with and without an appendix.

The appendix and ulcerative colitis

The appendix and experimental colitis

In mice, the caecal lymphoid patch is analogous to the human appendix from an immunological perspective[6]. Removal of this structure to replicate appendectomy in various mouse models of colitis has been used to study the role of the appendix in the pathogenesis of mucosal inflammation[45–48].

The first of these models is the T cell receptor-α mutant (TCR-$\alpha^{-/-}$) mouse, in which regulation of local T cell and B cell proliferation is deficient, leading to an increase in the numbers of B cells that express IgA, IgG1 and IgG2a in appendiceal GALT. Appendectomy in TCR-$\alpha^{-/-}$ mice at 1 month of age suppressed the development of mucosal inflammation. Furthermore, B cells that produce cytoskeletal tropomyosin autoantibodies, which have been detected in individuals with ulcerative colitis but not in healthy controls[49], were detected in appendiceal GALT of TCR-$\alpha^{-/-}$ mice[45]. These data suggest that appendiceal GALT has an important role in immune cell priming and mucosal inflammation in this mouse model of colitis.

The effects of appendectomy have also been studied in IL10/Nox1^{DKO} mice, which develop histological features of colitis from 6 weeks of age and multifocal colonic high-grade dysplasia by 8 months. Appendectomy for experimental appendicitis ameliorated colitis in this model[47]. However, the risk of colorectal neoplasia seemed to increase after appendectomy when performed in the absence of induced appendicitis[47]. In the adoptive transfer model of colitis[50], the naive CD62L^{+} cells that are transferred and induce colitis preferentially migrate to the appendicular lymphoid tissues rather than the colon[48]. Furthermore, cells that were isolated from the appendix had increased expression of $\alpha_4\beta_7$ integrin and CD154[48], which indicate immune cell priming in the GALT microenvironment[22]. In this model, mice that had undergone appendectomy before the onset of inflammation had significantly lower levels of colonic inflammation than animals that underwent sham surgery[48].

Similarly, in a study of mice treated with dextran sulfate sodium (DSS) to induce colitis, appendectomy or combined appendectomy and splenectomy delayed the onset of mucosal inflammation and reduced disease activity[46]. In a different study of this model, appendectomy suppressed a potential site of T cell priming, which could reduce immune surveillance against colitis-associated cancer[51]. However, redundant surveillance pathways could mitigate the effects of appendectomy, so further research is needed to assess the risk.

Together, these data suggest that the appendiceal analogue (the caecal patch) in mice is an important site for priming of immune responses. These data also raise the possibility that in genetically predisposed conditions, abnormal antigen priming in the appendix and dysregulation of appendiceal immune pathways — possibly in response to specific microbial antigens — could have a role in the pathogenesis of ulcerative colitis (Figure 1). This hypothesis is supported by epidemiological data that suggest a protective effect of appendectomy against UC, as discussed below[52].

Appendicitis, appendectomy and the risk of ulcerative colitis

Observational studies of diverse cohorts have consistently indicated that appendectomy, which is most commonly performed as treatment for appendicitis, protects against ulcerative colitis[53–56]. However, the relationship is not straightforward, and several nuances in the evidence need to be considered.

In a nationwide case–control study conducted in Sweden between 1964 and 1995, 212,963 individuals who underwent appendectomy before the age of 50 years were matched with

controls for age, sex and residential town. Appendectomy for appendicitis or mesenteric lymphadenitis was associated with a lower risk of ulcerative colitis (incidence rate ratio (IRR) 0.73, 95% CI 0.62–0.87 for appendicitis, and IRR 0.48, 95% CI 0.27–0.83 for mesenteric lymphadenitis), but appendectomy for nonspecific abdominal pain was not (IRR 1.34, 95% CI 0.77–2.38). An interaction with age was also apparent — appendectomy at ages <20 years was associated with protection against ulcerative colitis, but appendectomy at older ages was not[57]. Analysis of combined data from Swedish and Danish population registries produced similar associations[58]. In this analysis, appendectomy without preceding inflammation was not associated with the risk of ulcerative colitis, whereas appendectomy for appendicitis or mesenteric lymphadenitis at ages <20 years was associated with a reduced risk of ulcerative colitis (IRR 0.45, 95% CI 0.39–0.53 for appendicitis and IRR 0.65, 95% CI 0.46–0.90 for mesenteric lymphadenitis). This association held among a subset of individuals who had a first-degree relative with inflammatory bowel disease and were therefore at high risk of ulcerative colitis[58]. Analyses of cohorts in Greece, Japan and Australia also produced similar results[54–56], and subsequent meta-analyses of 13 and 19 studies further corroborated these data[59,60]. These data highlight two important observations. First, the presence of inflammation before surgical removal of the appendix seems to be necessary for the protective effect. Second, the protective effect seems to be apparent among children and adolescents but not in older individuals.

In a cohort study of 7,132,317 individuals in Denmark between 1997 and 2011, the impact of a family history of appendectomy and appendicitis on the apparent protective effect was investigated[61]. This study showed that not only was a personal history of appendicitis and appendectomy at age <20 years associated with protection against ulcerative colitis, a first-degree relative with appendicitis at age <20 years without a personal history of appendicitis was also associated with a lower risk of ulcerative colitis (rate ratio (RR) 0.90, 95% CI 0.86–0.95). Appendicitis at age <20 years among more distant relatives was not associated with protection against ulcerative colitis[61]. These data raise the question of whether appendicitis itself and/or genetic and nongenetic risk factors for appendicitis modulate the risk of ulcerative colitis rather than appendectomy (Figure 2). Evidence in support of this idea comes from a population-based study conducted in Sweden, in which childhood appendicitis was associated with protection against ulcerative colitis whether it was treated with appendectomy or treated medically (adjusted HR 0.30, 95% CI 0.25–0.36 with appendectomy and adjusted HR 0.29, 95% CI 0.12–0.69 with medical treatment)[62]. However, data on medically managed appendicitis are limited owing to the primarily surgical management of appendicitis. A shift towards antibiotic therapy for uncomplicated appendicitis could help to uncouple the impact of appendicitis and appendectomy on the risk of ulcerative colitis[63].

An additional nuance in the relationship between appendectomy and the risk of ulcerative colitis is indicated by findings of a systematic review[61]. Most of the studies reviewed demonstrated a protective effect of appendectomy, yet the effect was associated with appendicitis or appendectomy before the age of 20 years in only a minority of studies. Therefore, an effect of appendectomy for indications other than appendicitis on the risk of ulcerative colitis cannot be excluded.

Periappendicular red patches

Further evidence that the appendix is involved in the pathogenesis of ulcerative colitis is the presence of periappendicular red patches (PARPs, also known as appendiceal orifice inflammation or caecal patches) in a subset of ulcerative colitis, including distal ulcerative colitis[64]. In an analysis of 140 appendectomy specimens from individuals with ulcerative colitis, histological features of the appendix were more consistent with ulcerative colitis than with acute appendicitis[65]. Furthermore, PARP precedes onset of ulcerative colitis, at least in a subset of cases, indicating that pathology starts in the appendix[66]. These data further suggest that the appendix has a role in the pathogenesis of ulcerative colitis. However, data on the impact of PARPs on the course of ulcerative colitis are conflicting, so this aspect is poorly understood and warrants further investigation[67].

The appendix and the natural history of ulcerative colitis

Some evidence suggests that, in addition to modulating the risk of ulcerative colitis, appendicitis and appendectomy influence the course of the disease and outcomes such as colectomy and colorectal cancer, but the data are unclear. The timing of appendectomy in relation to the diagnosis of ulcerative colitis seems to be key in its influence on outcomes, and a lack of clarity on this variable could account for some of the conflict in the data. We discuss the available evidence in the following sections.

Appendicitis and appendectomy before diagnosis—A cohort study of 638 patients with ulcerative colitis in France demonstrated that the proportion of patients who responded to treatment of ulcerative colitis with corticosteroids and immunosuppressive agents was comparable among patients who had undergone appendectomy before diagnosis and patients who had not (67% versus 70% for corticosteroids and 27% versus 19% for immunosuppressive agents)[68]. However, appendectomy before diagnosis was associated with a reduction in the proportion of time during the study period when the disease was active (48% versus 62%), a finding that might be related to the fact that ulcerative colitis was diagnosed at an older age in the appendectomy group. The same effect was observed in an analysis of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Inflammatory Bowel Disease Genetics Consortium cohort – patients who had undergone appendectomy before their diagnosis of ulcerative colitis were older at diagnosis than those who had not (mean 41.8 years versus 30.8 years)[69].

In the French cohort study, appendectomy before the diagnosis of ulcerative colitis was also inversely related to the risk of colectomy (adjusted HR 0.40, 95% CI 0.20–0.78)[68]. By contrast, in the NIDDK cohort, appendectomy before diagnosis of ulcerative colitis was not associated with the risk of colectomy (OR 1.52, 95% CI 0.73–3.19)[69]. A meta-analysis in the same study also indicated that appendectomy before diagnosis of ulcerative colitis was not associated with colectomy (OR 0.92, 95% CI 0.63–1.35)[69], but a subsequent meta-analysis indicated that appendectomy before diagnosis of ulcerative colitis is associated with a lower risk of colectomy (OR 0.76, 95% CI 0.65–0.89)[70]. Consequently, the association with colectomy remains unclear.

The risk of colorectal cancer after appendectomy is also unclear (Figure 2). Results of one meta-analysis indicate that appendectomy is associated with an increased risk of colorectal cancer but that this association might reflect differences in risk factors rather than a direct effect. For example, in four of seven studies, ulcerative colitis disease duration was longer in the group that had undergone appendectomy than in the group that had not, implying that the increased risk of colorectal cancer might not have been a direct effect of appendectomy but of the consequent reduction in the likelihood of colectomy[71]. In a subsequent meta-analysis, appendectomy before diagnosis of ulcerative colitis was associated with an increased risk of colorectal cancer and high-grade dysplasia (OR 2.27, 95% CI 1.11–4.66)[70]. Appendectomy was not associated with hospital admission rates, medication use or disease extent, suggesting that these factors did not confound the observed association. By contrast, in a large pooled analysis of 591,817 healthy individuals in the UK Biobank, the European Investigation into Cancer and Nutrition (EPIC), and the French E3N cohort, prior appendectomy was associated with protection against colon cancer overall (pooled HR 0.90, 95% CI 0.81–0.99) and distal colon cancer (pooled HR 0.77, 95% CI 0.65–0.90)[72]. We speculate that differential immunological or microbiome features after appendectomy in people with ulcerative colitis and healthy individuals could explain these contradictory findings, but further studies are needed to clarify the association of appendectomy before diagnosis of ulcerative colitis with the risk of colon cancer.

Appendicitis and appendectomy after diagnosis—The impact of appendectomy after diagnosis of ulcerative colitis on the risk of hospitalization (for any reason) was assessed in a case–control study of patients in Danish population-based registers. Of 11,930 individuals included in the cohort, 202 had undergone appendectomy after diagnosis of ulcerative colitis. The risk of hospitalization among these individuals was no different to that among individuals with ulcerative colitis who had not undergone appendectomy (adjusted OR 1.05, 95% CI 0.67–1.67). This risk also did not differ according to whether patients had appendicitis or not before appendectomy[73].

In a study of the effect of appendectomy on the risk of colectomy, analysis of data from the NIDDK database indicated that appendectomy is associated with an increased risk of colectomy and that this association is strongest if appendectomy occurs after diagnosis of ulcerative colitis (adjusted OR 2.2, 95% CI 1.1–4.5)[69]. However, a meta-analysis in the same study that included a total of 4,134 patients indicated no association of appendectomy with the risk of colectomy (OR 1.19, 95% CI 0.81–1.75)[69]. Another meta-analysis confirmed this lack of association, albeit with moderate heterogeneity across studies (OR 1.37, 95% CI 0.61–3.07)[70].

The risk of colorectal cancer associated with appendectomy after diagnosis of ulcerative colitis is unclear because data are limited. One meta-analysis has indicated that the risk of dysplasia and colorectal cancer is increased after appendectomy (OR, 2.71, 95% CI 1.10–6.67), but this analysis did not take into account the timing of appendectomy relative to the diagnosis of ulcerative colitis[70].

Data are emerging on the effects of elective appendectomy for treatment of ulcerative colitis. In the first study to investigate this effect, 30 individuals with active and medically

refractory ulcerative proctitis underwent appendectomy[74]. At a median follow up of 3 months (range 1–12 months), clinical improvement was observed in 27 individuals, among whom clinical remission was attained in 12 individuals. These effects were maintained at long-term follow up (median 9 months, range 6–25 months)[74]. In a subsequent prospective, multicentre cohort study (PASSION), 30 patients with medically refractory ulcerative colitis underwent elective appendectomy[75]. After 1 year of follow-up, a clinical response was seen in nine patients, of whom five were in endoscopic remission. Histological response in ulcerative colitis occurred in 85% of individuals with appendiceal inflammation, compared with 20% of individuals with no appendiceal inflammation[76]). By 1 year, seven participants had undergone colectomy and four had initiated trial medication[76], indicating failure of treatment with appendectomy. At long-term follow up (median 3.7 years), another two patients had undergone colectomy and another two had initiated trial medication[75]. Further clinical trials (ACCURE and COSTA) to explore the role of therapeutic appendectomy in refractory ulcerative colitis are ongoing and will provide greater insight (Table 1)[76–78].

Conclusions and future directions

The evidence discussed suggests that the appendix is a relevant immune organ that might contribute to intestinal microbiome and biofilm homeostasis, and supports the possibility that the appendix has a role in the pathogenesis of ulcerative colitis. However, uncertainties remain about the relationship between the appendix and ulcerative colitis (Box 1), and the mechanisms that would underlie such an association remain unknown. The apparent interaction with age indicates that appendiceal immune function in the early life period is particularly important in relation to the possible association and warrants further research. Other aspects that require further investigation and clarification include the effects of appendicitis on the biofilm, microbiome and mucosal immune function, differential effects of removing the inflamed and noninflamed appendix, and the importance of the timing of appendectomy relative to the diagnosis of ulcerative colitis. Finally, whether or not appendectomy is associated with an increased risk of colorectal cancer risk needs to be determined. Clarification of these aspects could help to understand the pathogenesis of ulcerative colitis, identify new therapeutic targets, and improve treatment paradigms.

Acknowledgements

The authors thank Jill Gregory, Certified Medical Illustrator, Icahn School of Medicine at Mount Sinai, for the original versions of the figures.

References

1. Agrawal M, Allin KH, Petralia F, Colombel JF & Jess T Multiomics to elucidate inflammatory bowel disease risk factors and pathways. Nature reviews. Gastroenterology & hepatology 19, 399–409, doi:10.1038/s41575-022-00593-y (2022). [PubMed: 35301463]
2. Gilat T, Hacohen D, Lilos P & Langman MJ Childhood factors in ulcerative colitis and Crohn's disease. An international cooperative study. Scandinavian journal of gastroenterology 22, 1009–1024, doi:10.3109/00365528708991950 (1987). [PubMed: 3685876]
3. Darwin C The Descent of Man and Selection in Relation to Sex, (John Murray, London., 1871).
4. Scott GB The primate caecum and appendix vermiformis: a comparative study. J Anat 131, 549–563 (1980). [PubMed: 7216918]

5. Spencer J, Finn T & Isaacson PG Gut associated lymphoid tissue: a morphological and immunocytochemical study of the human appendix. Gut 26, 672–679, doi:10.1136/gut.26.7.672 (1985). [PubMed: 3874811]
6. Smith HF et al. Comparative anatomy and phylogenetic distribution of the mammalian cecal appendix. J Evol Biol 22, 1984–1999, doi:10.1111/j.1420-9101.2009.01809.x (2009). [PubMed: 19678866]
7. Smith HF, Parker W, Kotzé SH & Laurin M Multiple independent appearances of the cecal appendix in mammalian evolution and an investigation of related ecological and anatomical factors. Comptes Rendus Palevol 12, 339–354, doi:10.1016/j.crpv.2012.12.001 (2013).
8. Collard MK, Bardin J, Laurin M & Ogier-Denis E The cecal appendix is correlated with greater maximal longevity in mammals. J Anat 239, 1157–1169, doi:10.1111/joa.13501 (2021). [PubMed: 34235746]
9. Randal Bollinger R, Barbas AS, Bush EL, Lin SS & Parker W Biofilms in the large bowel suggest an apparent function of the human vermiform appendix. J Theor Biol 249, 826–831, doi:10.1016/j.jtbi.2007.08.032 (2007). [PubMed: 17936308]
10. Bharath NV, Swayam jothi S & Janaki M Evolution of lymphoid tissue in the vermiform appendix in human fetuses. J. Dental. Med. Sci. 13, 16–19 (2014).
11. Gebbers JO & Laissue JA Bacterial translocation in the normal human appendix parallels the development of the local immune system. Annals of the New York Academy of Sciences 1029, 337–343, doi:10.1196/annals.1309.015 (2004). [PubMed: 15681775]
12. Vitetta L, Chen J & Clarke S The vermiform appendix: an immunological organ sustaining a microbiome inoculum. Clin Sci (Lond) 133, 1–8, doi:10.1042/CS20180956 (2019). [PubMed: 30606811]
13. Ishimoto Y et al. Age-dependent variation in the proportion and number of intestinal lymphocyte subsets, especially natural killer T cells, double-positive CD4+ CD8+ cells and B220+ T cells, in mice. Immunology 113, 371–377, doi:10.1111/j.1365-2567.2004.01961.x (2004). [PubMed: 15500624]
14. Deniz K, Sökmensüer LK, Sökmensüer C & Patiroğlu TE Significance of intraepithelial lymphocytes in appendix. Pathol Res Pract 203, 731–735, doi:10.1016/j.prp.2007.07.003 (2007). [PubMed: 17766055]
15. Kooij IA, Sahami S, Meijer SL, Buskens CJ & Te Velde AA The immunology of the vermiform appendix: a review of the literature. Clinical and experimental immunology 186, 1–9, doi:10.1111/cei.12821 (2016). [PubMed: 27271818]
16. Corr SC, Gahan CC & Hill C M-cells: origin, morphology and role in mucosal immunity and microbial pathogenesis. FEMS Immunol Med Microbiol 52, 2–12, doi:10.1111/j.1574-695X.2007.00359.x (2008). [PubMed: 18081850]
17. Clark MA, Jepson MA, Simmons NL & Hirst BH Differential surface characteristics of M cells from mouse intestinal Peyer's and caecal patches. Histochem J 26, 271–280 (1994). [PubMed: 7515869]
18. Rhee KJ, Sethupathi P, Driks A, Lanning DK & Knight KL Role of commensal bacteria in development of gut-associated lymphoid tissues and preimmune antibody repertoire. Journal of immunology (Baltimore, Md. : 1950) 172, 1118–1124, doi:10.4049/jimmunol.172.2.1118 (2004). [PubMed: 14707086]
19. Hanson NB & Lanning DK Microbial induction of B and T cell areas in rabbit appendix. Dev Comp Immunol 32, 980–991, doi:10.1016/j.dci.2008.01.013 (2008). [PubMed: 18329710]
20. Bjerke K, Brandtzaeg P & Rognum TO Distribution of immunoglobulin producing cells is different in normal human appendix and colon mucosa. Gut 27, 667–674, doi:10.1136/gut.27.6.667 (1986). [PubMed: 3721289]
21. Fujihashi K et al. Human appendix B cells naturally express receptors for and respond to interleukin 6 with selective IgA1 and IgA2 synthesis. J Clin Invest 88, 248–252, doi:10.1172/jci115284 (1991). [PubMed: 2056119]
22. Mowat AM & Viney JL The anatomical basis of intestinal immunity. Immunol Rev 156, 145–166, doi:10.1111/j.1600-065x.1997.tb00966.x (1997). [PubMed: 9176706]

23. Masahata K et al. Generation of colonic IgA-secreting cells in the caecal patch. Nature communications 5, 3704, doi:10.1038/ncomms4704 (2014).
24. Matsushita M et al. Appendix is a priming site in the development of ulcerative colitis. World J Gastroenterol 11, 4869–4874, doi:10.3748/wjg.v11.i31.4869 (2005). [PubMed: 16097061]
25. Bradshaw DJ, Homer KA, Marsh PD & Beighton D Metabolic cooperation in oral microbial communities during growth on mucin. Microbiology (Reading) 140 (Pt 12), 3407–3412, doi:10.1099/13500872-140-12-3407 (1994). [PubMed: 7881558]
26. Palestrant D et al. Microbial Biofilms in the Gut: Visualization by Electron Microscopy and by Acridine Orange Staining. Ultrastructural Pathology 28, 23–27, doi:10.1080/usp.28.1.23.27 (2009).
27. Duncan K, Carey-Ewend K & Vaishnava S Spatial analysis of gut microbiome reveals a distinct ecological niche associated with the mucus layer. Gut Microbes 13, 1874815, doi:10.1080/19490976.2021.1874815 (2021). [PubMed: 33567985]
28. Dutton LC et al. O-mannosylation in Candida albicans enables development of interkingdom biofilm communities. mBio 5, e00911, doi:10.1128/mBio.00911-14 (2014). [PubMed: 24736223]
29. Nickerson KP & McDonald C Crohn's disease-associated adherent-invasive Escherichia coli adhesion is enhanced by exposure to the ubiquitous dietary polysaccharide maltodextrin. PloS one 7, e52132, doi:10.1371/journal.pone.0052132 (2012). [PubMed: 23251695]
30. Sonnenburg JL, Angenent LT & Gordon JI Getting a grip on things: how do communities of bacterial symbionts become established in our intestine? Nat Immunol 5, 569–573, doi:10.1038/ni1079 (2004). [PubMed: 15164016]
31. Bollinger RR et al. Secretory IgA and mucin-mediated biofilm formation by environmental strains of Escherichia coli: role of type 1 pili. Mol Immunol 43, 378–387, doi:10.1016/j.molimm.2005.02.013 (2006). [PubMed: 16310051]
32. Gibbins HL, Proctor GB, Yakubov GE, Wilson S & Carpenter GH SIgA binding to mucosal surfaces is mediated by mucin-mucin interactions. PloS one 10, e0119677, doi:10.1371/journal.pone.0119677 (2015). [PubMed: 25793390]
33. Bollinger RR et al. Human secretory immunoglobulin A may contribute to biofilm formation in the gut. Immunology 109, 580–587, doi:10.1046/j.1365-2567.2003.01700.x (2003). [PubMed: 12871226]
34. Donaldson GP et al. Gut microbiota utilize immunoglobulin A for mucosal colonization. Science (New York, N.Y.) 360, 795–800, doi:10.1126/science.aaq0926 (2018). [PubMed: 29724905]
35. Guinane CM et al. Microbial composition of human appendices from patients following appendectomy. mBio 4, doi:10.1128/mBio.00366-12 (2013).
36. Rogers MB, Brower-Sinning R, Firek B, Zhong D & Morowitz MJ Acute Appendicitis in Children Is Associated With a Local Expansion of Fusobacteria. Clin Infect Dis 63, 71–78, doi:10.1093/cid/ciw208 (2016). [PubMed: 27056397]
37. Oh SJ et al. Acute appendicitis is associated with appendiceal microbiome changes including elevated Campylobacter jejuni levels. BMJ open gastroenterology 7, doi:10.1136/bmjgast-2020-000412 (2020).
38. Swidsinski A et al. Acute appendicitis is characterised by local invasion with Fusobacterium nucleatum/necrophorum. Gut 60, 34–40, doi:10.1136/gut.2009.191320 (2011). [PubMed: 19926616]
39. Swidsinski A et al. Mucosal invasion by fusobacteria is a common feature of acute appendicitis in Germany, Russia, and China. Saudi J Gastroenterol 18, 55–58, doi:10.4103/1319-3767.91734 (2012).
40. Salö M et al. Evaluation of the microbiome in children's appendicitis. Int J Colorectal Dis 32, 19–28, doi:10.1007/s00384-016-2639-x (2017). [PubMed: 27613729]
41. Jackson HT et al. Culture-independent evaluation of the appendix and rectum microbiomes in children with and without appendicitis. PloS one 9, e95414, doi:10.1371/journal.pone.0095414 (2014). [PubMed: 24759879]
42. Peeters T et al. The fecal and mucosal microbiome in acute appendicitis patients: an observational study. Future Microbiol 14, 111–127, doi:10.2217/fmb-2018-0203 (2019). [PubMed: 30663346]

43. Cai S et al. Appendectomy Is Associated With Alteration of Human Gut Bacterial and Fungal Communities. Front Microbiol 12, 724980, doi:10.3389/fmicb.2021.724980 (2021). [PubMed: 34603252]
44. Sanchez-Alcoholado L et al. Incidental Prophylactic Appendectomy Is Associated with a Profound Microbial Dysbiosis in the Long-Term. Microorganisms 8, doi:10.3390/microorganisms8040609 (2020).
45. Mizoguchi A, Mizoguchi E, Chiba C & Bhan AK Role of appendix in the development of inflammatory bowel disease in TCR-alpha mutant mice. J Exp Med 184, 707–715, doi:10.1084/jem.184.2.707 (1996). [PubMed: 8760824]
46. Krieglstein CF et al. Role of appendix and spleen in experimental colitis. J Surg Res 101, 166–175, doi:10.1006/jsre.2001.6223 (2001). [PubMed: 11735272]
47. Harnoy Y et al. Effect of appendicectomy on colonic inflammation and neoplasia in experimental ulcerative colitis. Br J Surg 103, 1530–1538, doi:10.1002/bjs.10209 (2016). [PubMed: 27500367]
48. Farkas SA et al. Preferential migration of CD62L cells into the appendix in mice with experimental chronic colitis. Eur Surg Res 37, 115–122, doi:10.1159/000084543 (2005). [PubMed: 15905618]
49. Ebert EC, Geng X, Lin J & Das KM Autoantibodies against human tropomyosin isoform 5 in ulcerative colitis destroys colonic epithelial cells through antibody and complement-mediated lysis. Cell Immunol 244, 43–49, doi:10.1016/j.cellimm.2007.02.004 (2006). [PubMed: 17416356]
50. Powrie F et al. Inhibition of Th1 responses prevents inflammatory bowel disease in scid mice reconstituted with CD45RBhi CD4+ T cells. Immunity 1, 553–562, doi:10.1016/1074-7613(94)90045-0 (1994). [PubMed: 7600284]
51. Collard MK et al. The Appendix Orchestrates T-Cell Mediated Immunosurveillance in Colitis-Associated Cancer. Cellular and molecular gastroenterology and hepatology 15, 665–687, doi:10.1016/j.jcmgh.2022.10.016 (2022). [PubMed: 36332814]
52. Roblin X, Neut C, Darfeuille-Michaud A & Colombel JF Local appendiceal dysbiosis: the missing link between the appendix and ulcerative colitis? Gut 61, 635–636, doi:10.1136/gutjnl-2011-300576 (2012).
53. Sahami S et al. The Link between the Appendix and Ulcerative Colitis: Clinical Relevance and Potential Immunological Mechanisms. The American journal of gastroenterology 111, 163–169, doi:10.1038/ajg.2015.301 (2016). [PubMed: 26416189]
54. Koutroubakis IE et al. Appendectomy, tonsillectomy, and risk of inflammatory bowel disease: case-controlled study in Crete. Diseases of the colon and rectum 42, 225–230, doi:10.1007/bf02237133 (1999). [PubMed: 10211500]
55. Naganuma M et al. Appendectomy protects against the development of ulcerative colitis and reduces its recurrence: results of a multicenter case-controlled study in Japan. The American journal of gastroenterology 96, 1123–1126, doi:10.1111/j.1572-0241.2001.03757.x (2001). [PubMed: 11316158]
56. Florin TH, Pandeya N & Radford-Smith GL Epidemiology of appendicectomy in primary sclerosing cholangitis and ulcerative colitis: its influence on the clinical behaviour of these diseases. Gut 53, 973–979, doi:10.1136/gut.2003.036483 (2004). [PubMed: 15194646]
57. Andersson RE, Olaison G, Tysk C & Ekbom A Appendectomy and protection against ulcerative colitis. The New England journal of medicine 344, 808–814, doi:10.1056/nejm200103153441104 (2001). [PubMed: 11248156]
58. Frisch M, Pedersen BV & Andersson RE Appendicitis, mesenteric lymphadenitis, and subsequent risk of ulcerative colitis: cohort studies in Sweden and Denmark. BMJ (Clinical research ed) 338, b716, doi:10.1136/bmj.b716 (2009).
59. Koutroubakis IE & Vlachonikolis IG Appendectomy and the development of ulcerative colitis: results of a metaanalysis of published case-control studies. The American journal of gastroenterology 95, 171–176, doi:10.1111/j.1572-0241.2000.01680.x (2000). [PubMed: 10638578]
60. Deng P & Wu J Meta-analysis of the association between appendiceal orifice inflammation and appendectomy and ulcerative colitis. Rev Esp Enferm Dig 108, 401–410, doi:10.17235/reed.2016.4176/2015 (2016). [PubMed: 27338627]

61. Nyboe Andersen N, Gørtz S, Frisch M & Jess T Reduced risk of UC in families affected by appendicitis: a Danish national cohort study. Gut 66, 1398–1402, doi:10.1136/gutjnl-2015-311131 (2017). [PubMed: 27196591]
62. Kiasat A, Ekstrom LD, Marsk R, Lof-Granstrom A & Gustafsson UO Childhood appendicitis and future risk of inflammatory bowel disease - A nationwide cohort study in Sweden 1973–2017. Colorectal Dis 24, 975–983, doi:10.1111/codi.16128 (2022). [PubMed: 35344255]
63. Podda M et al. Antibiotic Treatment and Appendectomy for Uncomplicated Acute Appendicitis in Adults and Children: A Systematic Review and Meta-analysis. Ann Surg 270, 1028–1040, doi:10.1097/sla.0000000000003225 (2019). [PubMed: 30720508]
64. Bakman Y, Katz J & Shepela C Clinical Significance of Isolated Peri-Appendiceal Lesions in Patients With Left Sided Ulcerative Colitis. Gastroenterology Res 4, 58–63, doi:10.4021/gr302w (2011). [PubMed: 27942315]
65. Heuthorst L et al. High prevalence of ulcerative appendicitis in patients with ulcerative colitis. United European gastroenterology journal 9, 1148–1156, doi:10.1002/ueg2.12171 (2021). [PubMed: 34750986]
66. Park SH et al. Long term follow-up of appendiceal and distal right-sided colonic inflammation. Endoscopy 44, 95–98, doi:10.1055/s-0031-1291443 (2012). [PubMed: 22198779]
67. Park SH, Loftus EV Jr. & Yang SK Appendiceal skip inflammation and ulcerative colitis. Digestive diseases and sciences 59, 2050–2057, doi:10.1007/s10620-014-3129-z (2014). [PubMed: 24705639]
68. Cosnes J et al. Effects of appendicectomy on the course of ulcerative colitis. Gut 51, 803–807, doi:10.1136/gut.51.6.803 (2002). [PubMed: 12427780]
69. Parian A et al. Appendectomy does not decrease the risk of future colectomy in UC: results from a large cohort and meta-analysis. Gut 66, 1390–1397, doi:10.1136/gutjnl-2016-311550 (2017). [PubMed: 27196594]
70. Welsh S, Sam Z, Seenan JP & Nicholson GA The Role of Appendicectomy in Ulcerative Colitis: Systematic Review and Meta-Analysis. Inflammatory bowel diseases, doi:10.1093/ibd/izac127 (2022).
71. Stellingwerf ME et al. The Risk of Colectomy and Colorectal Cancer After Appendectomy in Patients With Ulcerative Colitis: A Systematic Review and Meta-analysis. Journal of Crohn's & colitis 13, 309–318, doi:10.1093/ecco-jcc/jjy163 (2019).
72. Rothwell JA et al. Colorectal cancer risk following appendectomy: a pooled analysis of three large prospective cohort studies. Cancer Commun (Lond) 42, 486–489, doi:10.1002/cac2.12265 (2022). [PubMed: 35132829]
73. Hallas J, Gaist D, Vach W & Sorensen HT Appendicectomy has no beneficial effect on admission rates in patients with ulcerative colitis. Gut 53, 351–354, doi:10.1136/gut.2003.016915 (2004). [PubMed: 14960514]
74. Bolin TD, Wong S, Crouch R, Engelman JL & Riordan SM Appendicectomy as a therapy for ulcerative proctitis. The American journal of gastroenterology 104, 2476–2482, doi:10.1038/ajg.2009.388 (2009). [PubMed: 19584834]
75. Stellingwerf ME et al. Prospective cohort study of appendicectomy for treatment of therapy-refractory ulcerative colitis. Br J Surg 106, 1697–1704, doi:10.1002/bjs.11259 (2019). [PubMed: 31393608]
76. Sahami S 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, 165–171, doi:10.1093/ecco-jcc/jjy127 (2019).
77. Gardenbroek TJ et al. The ACCURE-trial: the effect of appendectomy on the clinical course of ulcerative colitis, a randomised international multicenter trial (NTR2883) and the ACCURE-UK trial: a randomised external pilot trial (ISRCTN56523019). BMC Surg 15, 30, doi:10.1186/s12893-015-0017-1 (2015). [PubMed: 25887789]
78. US National Library of Medicine. COlonic Salvage by Therapeutic Appendectomy. (COSTA) https://clinicaltrials.gov/ct2/show/NCT03912714 (2019).

79. Nepogodiev D et al. The ACCURE-UK trial: The effect of appendectomy on the clinical course of ulcerative colitis – A feasibility study. International Journal of Surgery 36, doi:10.1016/j.ijsu.2016.08.031 (2016).

Box 1 |

What is and is not known about the connection between the appendix and ulcerative colitis

What is known?

- The appendix is an immunologically rich and active organ with similar broad composition but distinct taxonomic proportions relative to the colonic microbiome.
- Appendectomy at a young age (<20 years) is associated with a reduced lifetime risk of ulcerative colitis.
- Appendectomy before a subsequent diagnosis of ulcerative colitis is associated with a reduced risk of colectomy compared with the risk in people with ulcerative colitis who have not undergone appendectomy.

What is not known

- The composition and role of the appendiceal biofilm
- The impact of appendicitis and appendectomy on intestinal microbial communities and immune function
- Differences in the immunological composition and function of the appendix by age
- Genetic and nongenetic risk factors for appendicitis
- Whether appendicitis itself influences the subsequent risk of ulcerative colitis independent of appendectomy
- Whether appendicitis itself influences ulcerative colitis outcomes independent of appendectomy

The appendix is thought to have a role in the pathogenesis of ulcerative colitis but the association remains unclear. In this Perspective, the authors consider the biology of the appendix with respect to its immunological function and the microbiome, and how this relates to its possible involvement in ulcerative colitis.

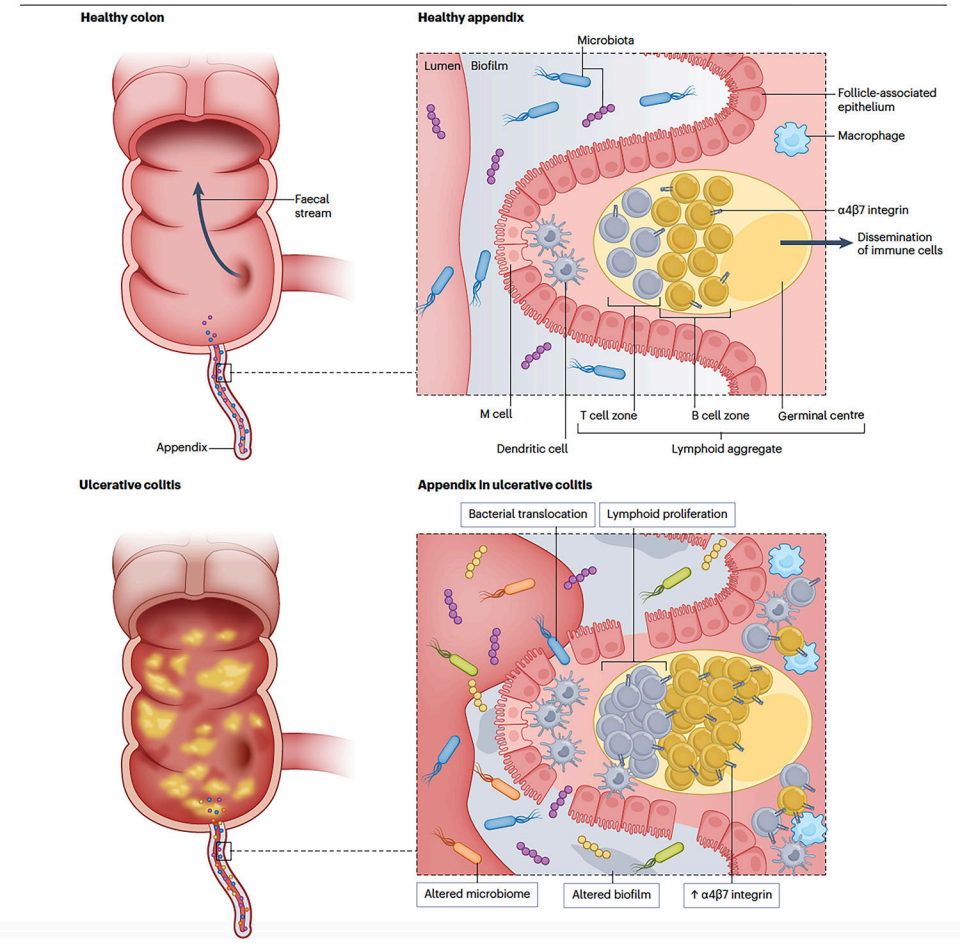

Figure 1 |. The immunological composition and function of the appendix in health and ulcerative colitis.

a, A microcosm of the mucosal immune system in the appendix. In health, lymphoid aggregates are sites of immune priming. Microfold (M) cells, which permit ingress of luminal antigens, are in close proximity to antigen-presenting cells, such as dendritic cells, in the subepithelial dome, or lymphoid aggregate. Dendritic cell-mediated, non-inflammatory immune priming is accompanied by the induction of α4β7 integrin, such that the T cells and B cells that egress from the lymphoid tissues of the appendix are imprinted to localize back to the intestines. Other immune cells, including tissue-resident macrophages, maintain homeostasis in health. Finally, luminal bacteria ‘seed’ the colon (left), especially after depletion of colonic microbial communities. b, Proposed dysregulation in the immune function of the appendix in ulcerative colitis. The appendiceal microbiota and biofilm are altered. These changes are associated with non-physiological priming of immune responses, potentially via non-M-cell-dependent pathways as a result of epithelial disruption, leading to induction of pro-inflammatory T cells and B cells. After these cells egress from the appendix to the circulation, they localize back to the colon, owing to the induction of α4β7 integrin, and contribute to inflammation. The altered appendiceal microbiome could also contribute to colonic dysbiosis (left). Illustration by Jill K. Gregory, adapted with permission of © Mount Sinai Health System.

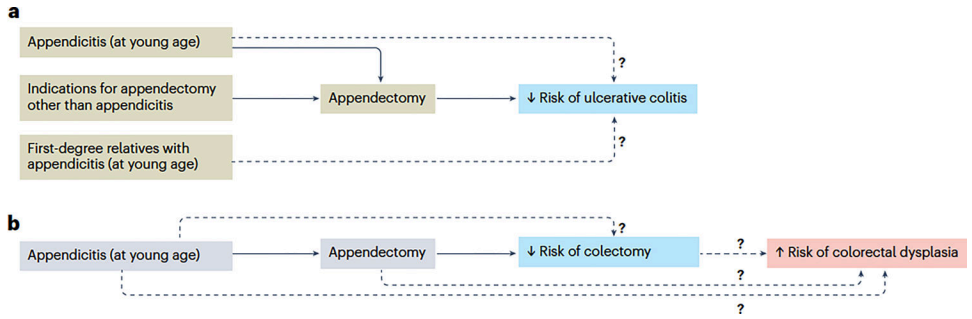

Figure 2 |. Proposed relationships between appendicitis, appendectomy and the risk of ulcerative colitis and its outcomes.

a, In healthy people, appendectomy as a result of appendicitis at a young age or of other indications for the procedure is associated with a reduced lifetime risk of ulcerative colitis relative to the risk in the general population. Whether appendicitis at a young age or appendicitis in a first-degree relative are associated with a reduced risk of ulcerative colitis independent of appendectomy is unknown, but some evidence indicates that these hypotheses should be studied further. b, In individuals with ulcerative colitis, appendectomy as a result of appendicitis at a young age is associated with a reduced risk of colectomy relative to individuals with ulcerative colitis who do not undergo appendectomy. Appendectomy in people with ulcerative colitis is also associated with an increased risk of colorectal dysplasia, although whether this association is a direct result of appendectomy or a consequence of the reduced risk of colectomy is unclear. Whether appendicitis itself is associated with the increased risk of colorectal dysplasia requires further investigation. Illustration by Jill K. Gregory, adapted with permission of © Mount Sinai Health System.

Table 1|

Ongoing clinical trials of laparoscopic appendectomy in ulcerative colitis

Trial	Study location(s)	Study design	Inclusion criteria	Interventions	Primary end point	Year of initiation	Current study status and findings
ACCURE and ACCURE-UK[77]	Netherlands and UK	Paired, phase III, randomized, muticentre	Adults with mild to moderate ulcerative colitis, relapse within 12 months of random assignment, in clinical and endoscopic remission	Laparoscopic appendectomy plus maintenance treatment with 5-ASA versus maintenance treatment only	Cumulative relapse rate (relapses defined as Mayo score ≥5 with endoscopy sub score of 2 or 3) at 12 months	2014	Recruitment completed; trial ongoing. Feasibility data (ACCURE-UK): 53 patients randomized across 6 sites. 4 patients experienced minor appendectomy complications[79]
COSTA[78]	Netherlands	Open-label, nonrandomized, parallel assignment	Adults with active ulcerative colitis refractory to standard medical treatments (appendectomy arm); adults with inactive ulcerative colitis or no ulcerative colitis (two control arms)	Laparoscopic appendectomy versus continuation of medical treatment	Endoscopic remission (defined as Mayo score of 0–1) at 12 months	2018	Recruiting