Alimentary Pharmacology & Therapeutics

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ORIGINAL ARTICLE OPEN ACCESS

Appendectomy Is Not Associated With a Milder Clinical Course of Ulcerative Colitis: A Nationwide Danish Population-Based Study

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Received: 22 February 2025 | **Revised:** 27 March 2025 | **Accepted:** 4 July 2025

Handling Editor: Sreedhar Subramanian

Funding: This work was supported by Novo Nordisk Fonden (NNF19OC0058609).

Keywords: appendectomy | clinical course | cohort study | epidemiology | surgery | ulcerative colitis

ABSTRACT

Background: Appendectomy may have a beneficial effect on the course of ulcerative colitis (UC), but the association remains debated.

Aim: To examine if appendectomy influences the clinical course of UC.

Methods: We identified all patients diagnosed with UC in Denmark from 1977 to 2017 from the Danish National Patient Registry. Patients who underwent appendectomy were matched for age, sex, calendar year and disease duration with up to 10 comparators with UC and no appendectomy. We compared UC-related admission rates, rates of initiating treatment with biologics, and colorectal resection rates between patients with UC with and without appendectomy.

Results: 22,098 patients with UC (2014 with and 20,084 without appendectomy) were followed for a median 10.3 years (interquartile range: 5.1–18.5). Hospitalisation rates were higher for those who underwent appendectomy of a normal appendix after UC (IRR = 1.11 (95% CI: 1.01–1.22)) and for those who underwent appendectomy for appendicitis before UC (IRR = 1.22 (95% CI: 1.15–1.31)). Appendectomy performed for appendicitis after UC was associated with a higher rate of colorectal resections 5–20 years after appendectomy ($aHR_{5–10\,years}$ = 2.08 (95% CI: 1.03–4.17)), $aHR_{10–20\,years}$ = 3.25 (95% CI: 1.31–8.08) and 5–10 years after appendectomy if not performed for appendicitis (aHR = 2.51 (1.01–6.23)). Rates of initiating treatment with biologics were comparable between patients with and without prior appendectomy.

Conclusion: Patients with UC who underwent appendectomy did not experience a milder clinical course compared to those without appendectomy, regardless of underlying appendicitis.

1 | Introduction

There is mounting evidence that appendectomy influences the individual's risk of developing ulcerative colitis (UC) and numerous cohort and case–control studies have consistently found a lower risk for those who undergo appendectomy [1]. The association appears most pronounced if appendectomy is performed at a young age and if performed for appendicitis [2]. This suggests a role of the innate immune system, where the removal of a pool of potentially autoreactive gut lymphocytes by

appendectomy decreases the risk of subsequent autoimmune inflammation of the large bowel, i.e., UC. Building on the hypothesis of the vermiform appendix as a potential priming site for UC, appendectomy has emerged as a potential disease modifying intervention in established UC [3, 4]. Over the past decades, observational studies of varying methodology have reached contradicting results, with some finding increased risks of disease exacerbations, including colectomy [5], while others find lower risks of colectomy following appendectomy [6–9].

Most recently, prospective trials of prophylactic appendectomy in medically-refractory UC have reported encouraging results [3], with remission rates and colectomy-free survival approaching or even surpassing medically-induced remission rates. However, sample sizes are small and long-term outcomes are currently unknown.

Observational studies on the association between appendectomy and the clinical course of UC are limited by the use of administrative data to distinguish between appendectomy of a "normal", uninflamed appendix and appendectomy performed for underlying appendicitis [5, 8, 9]. Differentiating between these two entities is important because it may eliminate some of the confounding by indication characteristic of other studies and because appendectomy performed on a healthy appendix constitutes the treatment arm of ongoing randomised trials.

The therapeutic implications of prophylactic appendectomy in UC are far-reaching, so it is important to determine if appendectomy influences favourably the clinical course of UC. The aim of this study was to examine the association between appendectomy performed for appendicitis and non-appendicitis conditions and the clinical course of UC with emphasis on appendectomy for non-appendicitis conditions after a UC diagnosis.

2 | Methods

2.1 | Setting

This cohort study was conducted using nationwide health registries that cover all medical and surgical treatments performed in public hospitals in Denmark. All healthcare contacts related to treatment with parenteral biologics, all acute and elective surgeries for IBD, and admissions for IBD in general are only performed in public hospitals in Denmark, ensuring complete capture via these registries. Data linkage between the registries was performed using the individual patient's civil registration number (CPR number), which is a unique 10-digit number provided to all Danish citizens [10]. This study was registered by Aarhus University on behalf of the Danish Data Protection Agency under file number 2624.

2.2 | Identification of Patients With UC and Appendectomy

We identified patients registered with at least two UC diagnoses in the Danish National Patient Registry (DNPR) from 1977 to 2017 and considered the date of the second diagnosis as the date of UC as this approach has a proven high validity [11]. Patients with two consecutive CD diagnoses registered before a second UC diagnosis were excluded. The DNPR was established in 1977 and holds data on all inpatient contacts since its inception in addition to outpatient contacts since 1995 [12]. All contacts registered in the DNPR contain data on main diagnosis (reason for the contact), secondary diagnoses and procedures or operations performed during the contact, all linked to the individual patient using the CPR number. Diagnoses registered in the DNPR are coded according to the International Classification of Diseases (ICD)-8 and 10 classification systems. Data in the DNPR is considered highly valid with documented high completeness [12].

From the source population of all patients diagnosed with UC, we identified those with a procedure code for appendectomy registered in the DNPR (see appendix for operation codes). The index date of patients with appendectomy prior to UC was defined as the date of UC, while the index date for those who underwent appendectomy after UC was defined as the date of appendectomy. Based on data from the Danish Pathology Registry (DPR), patients with appendectomy were subcategorized in those with and without appendicitis at appendectomy. The DPR was founded in 1999 and contains data on all pathology specimens in Denmark from 1997 onward [13]. All specimens are registered in the database according to the Danish version of the Systemized Nomenclature of Medicine (SNOMED) classification, which encompasses data on anatomical localization of the tissue, type of specimen (organ, biopsy, fluid, etc.) and cytological or histological characteristics of the tissue (inflammation, fibrosis, dysplasia, cancer, etc.). Completeness of data in the registry is high [13]. For the purpose of this study, we used SNOMED codes defining appendectomy for appendicitis as an anatomical code for vermiform appendix with a histological code for inflammation. An absence of a code for inflammation defined appendectomy performed for non-appendicitis conditions.

2.3 | Identification of Comparators With UC and no Appendectomy

For each UC patient who underwent appendectomy, up to 10 UC comparators without appendectomy were identified. These comparators were matched randomly on sex, age at UC diagnosis, calendar year (±2 years) and duration of UC, and were assigned an index date corresponding to the date of appendectomy of their matched patient. If a comparator underwent appendectomy during the observation period, the individual would transition to the appendectomy group on the date of appendectomy but simultaneously remain in the comparator group to avoid informative censoring.

2.4 | Outcomes Related to Disease Severity

We used hospitalisations (overall and emergency), treatment with biologics (inpatient and outpatient), and colorectal resections as measures of disease severity. Data on hospitalisations after the index date were enquired from the DNPR and only admissions with UC as the main discharge diagnosis were included. Treatment with biologics at hospital has been registered

in the DNPR since 2005 using specific treatment codes (see appendix), while operation codes registered in the DNPR were used to identify patients undergoing colorectal resections (see appendix) after the index date.

2.5 | Statistical Analysis

Patients with UC were followed from the index date and grouped in those with appendectomy prior to UC (and their matched comparators) and those with appendectomy after UC (and their matched comparators) and further subcategorized according to the presence or absence of underlying appendicitis. Patients were followed until a relevant outcome, death, emigration or end of follow-up, whichever came first. Because pathology data were only available for the period 1997–2017, the subgroup analysis based on appendix histology was restricted to this period. We calculated UC-specific admission rates as the number of admissions with UC as the discharge diagnosis divided by total person-years of follow-up. Admission rate ratios comparing incidence rates for UC patients with appendectomy versus no appendectomy were calculated with confidence intervals using the Wald method [14]. The cumulative incidence of initiating treatment with biologics or undergoing colorectal resections 5, 10 and 20 years after the index date was calculated using the Aalen-Johansen estimator with death as a competing risk. Because data on treatment with biologics have only been available since 2005, these analyses were performed only for patients with an index date after 31 December 2004. Patients who had received treatment with biologics or undergone colorectal resections prior to their index date were excluded from the analyses of that specific outcome.

Stratified Cox proportional hazards regression analysis was used to calculate hazard ratios (HRs) of initiating treatment with biologics and undergoing colorectal resections, comparing UC patients with and without prior appendectomy. We performed both unadjusted analyses and analyses adjusted for primary sclerosing cholangitis (PSC).

Sensitivity analyses were also performed, where admission rate ratios, cumulative incidences, and hazard ratios of the predefined outcomes were stratified in the timing of the appendectomy in before or after the 20th year of life.

3 | Results

A total of 22,098 patients with UC were identified, of whom 2014 had undergone appendectomy (Table 1). For 34 patients with appendectomy (1.7%), less than ten comparators could be matched. The mean disease duration prior to the index date was 6.9 years (SD 6.8) for UC patients and prior appendectomy and 6.2 years (SD 6.6) for UC patients without prior appendectomy. During a median follow-up of 10.1 (IQR: 4.7–17.8) years for patients with appendectomy and 10.3 (IQR: 5.1–18.5) years for patients without appendectomy, IRRs of all UC-specific admissions were comparable, regardless of timing of the appendectomy in relation to UC (appendectomy before UC: IRR = 1.00 (95% CI: 0.96–1.04), appendectomy after UC: IRR = 0.99 (0.94–1.04)). These estimates changed slightly when the analyses were restricted to emergency admissions, but only for patients who had undergone appendectomy before UC diagnosis (IRR = 1.08 (95% CI: 1.03–1.14)).

TABLE 1 | Baseline characteristics of patients diagnosed with UC in Denmark from 1977 to 2017, stratified by appendectomy status.

	UC with appendectomy	UC without appendectomy
Number of patients	2014	20,084
Male sex, *n* (%)	805 (40)	8013 (39.9)
Age at index date, mean (SD)	47.8 (17.7)	47.8 (17.6)
Follow-up in years, median (IQR)	10.1 (4.7–17.8)	10.3 (5.1–18.5)
Disease duration prior to index date, mean (SD)	6.9 (6.8)	6.2 (6.6)
Appendectomy before UC, *n* (%)	1245 (61.8)	NA

When the analyses were stratified in UC patients with appendectomy with or without underlying appendicitis, admission rates were higher for patients who had undergone appendectomy for appendicitis prior to UC (IRR = 1.22 (95% CI: 1.15–1.31)) and for those who underwent appendectomy without underlying appendicitis after UC (IRR = 1.11 (95% CI: 1.01–1.22)). Patients who underwent appendectomy for appendicitis after their UC diagnosis had a lower admission rate than those without appendectomy (IRR = 0.94 (95% CI: 0.87–1.01)), while admission rates for patients who underwent appendectomy without underlying appendicitis before UC were comparable (IRR = 1.03 (95% CI: 0.96–1.10)).

Rates of initiating treatment with biologics were comparable between UC patients with and without prior appendectomy across most strata of observation periods, regardless of timing of appendectomy in relation to UC and underlying appendicitis (Tables 2 and 3). Rates of initiating treatment with biologics were, however, higher more than 20 years after appendectomy for patients with appendectomy and no appendicitis prior to UC and during the first year and 10–20 years after appendectomy for appendicitis when performed after UC.

The rate of colorectal resections for UC patients with appendectomy before UC was comparable to the rate of colorectal resections for UC patients without appendectomy when looking at the entire historical cohort from 1977 to 2017 irrespective of underlying appendicitis (Table 2). The most common procedure performed was total colectomy (59%), followed by proctocolectomy with or without ileal pouch-anal anastomosis (IPAA) (16%), segmental colectomy (18%) and rectal resection with or without IPAA (7%). Segmental colectomies were primarily right hemicolectomies (33.5%) and sigmoid resections (25.6%), while left hemicolectomies, transverse colectomies, and unspecified colonic resections accounted for the remainder. When the analyses were restricted to total colectomies and proctocolectomies,

TABLE 2 | Rates of initiating treatment with biologics and undergoing colorectal resections comparing patients with appendectomy prior to UC to their matched comparators without appendectomy in Denmark in the period 1977–2017.

	Biologics		Colorectal resections	
	Unadjusted HR	Adjusted HR[a]	Unadjusted HR	Adjusted HR[a]
All patients with appendectomy				
0–1 years	0.67 (0.45–1.01)	0.67 (0.45–1.01)	0.80 (0.60–1.07)	0.81 (0.60–1.07)
1–5 years	0.74 (0.50–1.09)	0.75 (0.51–1.11)	1.08 (0.82–1.44)	1.09 (0.82–1.44)
5–10 years	0.99 (0.62–1.58)	1.00 (0.63–1.60)	0.95 (0.63–1.45)	0.95 (0.63–1.45)
10–20 years	0.74 (0.45–1.22)	0.74 (0.45–1.22)	0.90 (0.53–1.52)	0.90 (0.53–1.52)
20+ years	1.51 (0.73–3.09)	1.56 (0.76–3.20)	1.38 (0.45–4.26)	1.55 (0.50–4.85)
No appendicitis				
0–1 years	0.66 (0.35–1.25)	0.66 (0.35–1.26)	0.88 (0.53–1.44)	0.88 (0.53–1.45)
1–5 years	0.99 (0.56–1.77)	0.99 (0.56–1.77)	1.34 (0.83–2.16)	1.34 (0.83–2.16)
5–10 years	1.19 (0.61–2.33)	1.19 (0.61–2.33)	0.73 (0.29–1.83)	0.72 (0.29–1.81)
10–20 years	0.63 (0.23–1.75)	0.64 (0.23–1.77)	1.51 (0.57–4.01)	1.50 (0.56–4.00)
20+ years	4.14 (1.03–16.58)	5.83 (1.29–26.36)	7.00 (0.44–111.9)	6.91 (0.40–119.7)
Appendicitis				
0–1 years	0.76 (0.42–1.38)	0.76 (0.42–1.37)	0.83 (0.50–1.38)	0.83 (0.50–1.38)
1–5 years	0.92 (0.53–1.59)	0.94 (0.54–1.64)	1.34 (0.85–2.10)	1.36 (0.87–2.14)
5–10 years	1.46 (0.68–3.11)	1.47 (0.69–3.13)	1.11 (0.55–2.24)	1.15 (0.57–2.34)
10–20 years	0.80 (0.34–1.84)	0.80 (0.34–1.84)	1.32 (0.59–2.97)	1.31 (0.58–2.95)
20+ years	0.65 (0.08–5.09)	0.67 (0.09–5.29)	NA	NA

Note: The analyses stratified in histological diagnosis of the appendix are restricted to the period 1997–2017.
Abbreviations: HR, hazard ratio; NA, not applicable because of zero event.
[a]Adjusted for primary sclerosing cholangitis.

the associations were comparable with the main findings (data not shown).

Patients with UC who underwent appendectomy after UC had a higher cumulative incidence and hazard ratio of colorectal resections 0–1 year and 5–10 years after appendectomy if performed for non-appendicitis and 5–20 years after appendectomy if performed for appendicitis (Table 3 and Figure 1).

Results of the sensitivity analyses comparing outcomes between those undergoing appendectomy before or after the 20th year of life are listed in Table S1. A total of 291 patients (15.3%) underwent appendectomy before age 20 and 1612 patients (84.7%) underwent appendectomy after age 20.

For those undergoing appendectomy prior to UC, UC-specific admission rates were higher if appendectomy was performed before the 20th year of life (IRR 1.46 (95% CI: 1.31–1.62)) and lower if appendectomy was performed after the 20th year of life (IRR 0.95 (95% CI: 0.92–0.99)). For those undergoing appendectomy after UC, admission rates were lower if appendectomy was performed before the 20th year of life (IRR = 0.77 (95% CI: 0.63–0.92)) and comparable to UC patients without appendectomy if the appendectomy was performed after the 20th year of life (IRR 1.01 (95% CI: 0.95–1.06)).

There were too few outcomes related to biologics and colorectal resections to stratify exposure in appendicitis and non-appendicitis conditions.

Age at appendectomy was not associated with initiation of biologics in any follow-up period.

In the group of UC patients undergoing appendectomy before UC, there were fewer than five colorectal resections in each follow-up period for those who underwent appendectomy before their 20th birthday, impairing precision of the estimates. The association between appendectomy after UC and colorectal resection rates was only statistically significant for those who underwent appendectomy after their 20th birthday 5–10 years after appendectomy (aHR = 2.29 (95% CI: 1.42, 3.71)) and 10–20 years after appendectomy (aHR = 1.93 (95% CI: 1.01, 3.68)).

4 | Discussion

The appendix plays an important role in colonic immune homeostasis [15]. Disruptions in the appendix' normal functions, e.g., by appendicitis or appendectomy, may therefore affect the clinical course of colonic diseases associated with a dysregulated immune response [16], e.g., UC. With this study, we

TABLE 3 | Rates of initiating treatment with biologics and undergoing colorectal resections comparing patients with appendectomy after UC to their matched comparators without appendectomy in Denmark in the period 1977–2017.

	Biologics		Colorectal resections	
	Unadjusted HR	**Adjusted HR[a]**	**Unadjusted HR**	**Adjusted HR[a]**
All patients with appendectomy				
0–1 years	1.93 (0.99–3.76)	1.85 (0.94–3.62)	2.51 (1.55–4.07)	2.50 (1.54–4.04)
1–5 years	0.81 (0.46–1.43)	0.81 (0.46–1.43)	0.90 (0.55–1.49)	0.91 (0.55–1.51)
5–10 years	0.35 (0.11–1.15)	0.36 (0.11–1.18)	2.32 (1.46–3.71)	2.33 (1.46–3.72)
10–20 years	1.65 (0.90–3.03)	1.66 (0.90–3.06)	1.67 (0.90–3.13)	1.73 (0.92–3.27)
20+ years	1.78 (0.84–3.76)	1.72 (0.81–3.66)	0.43 (0.10–1.89)	0.37 (0.08–1.75)
No appendicitis				
0–1 years	0.91 (0.19–4.34)	0.91 (0.16–5.12)	7.84 (3.24–18.96)	7.89 (3.21–19.40)
1–5 years	0.47 (0.14–1.55)	0.47 (0.14–1.55)	1.11 (0.45–2.73)	1.17 (0.47–2.89)
5–10 years	0.31 (0.04–2.41)	0.24 (0.03–2.17)	2.65 (1.09–6.43)	2.51 (1.01–6.23)
10–20 years	0.70 (0.16–3.12)	0.77 (0.17–3.47)	0.56 (0.13–2.45)	0.57 (0.13–2.57)
20+ years	1.40 (0.29–6.70)	1.35 (0.28–6.51)	NA	NA
Appendicitis				
0–1 years	2.42 (1.15–5.07)	2.30 (1.10–4.84)	1.14 (0.47–2.76)	1.19 (0.49–2.88)
1–5 years	1.00 (0.53–1.90)	1.00 (0.53–1.90)	0.78 (0.37–1.65)	0.78 (0.37–1.65)
5–10 years	0.40 (0.09–1.67)	0.43 (0.10–1.81)	2.09 (1.05–4.17)	2.08 (1.03–4.17)
10–20 years	2.06 (1.00–4.24)	2.05 (0.99–4.23)	3.06 (1.27–7.36)	3.25 (1.31–8.08)
20+ years	2.14 (0.69–6.65)	2.38 (0.65–8.76)	NA	NA

Note: The analyses stratified in histological diagnosis of the appendix are restricted to the period 1997–2017.
Abbreviations: HR, hazard ratio; NA, not applicable because of zero event.
[a]Adjusted for primary sclerosing cholangitis.

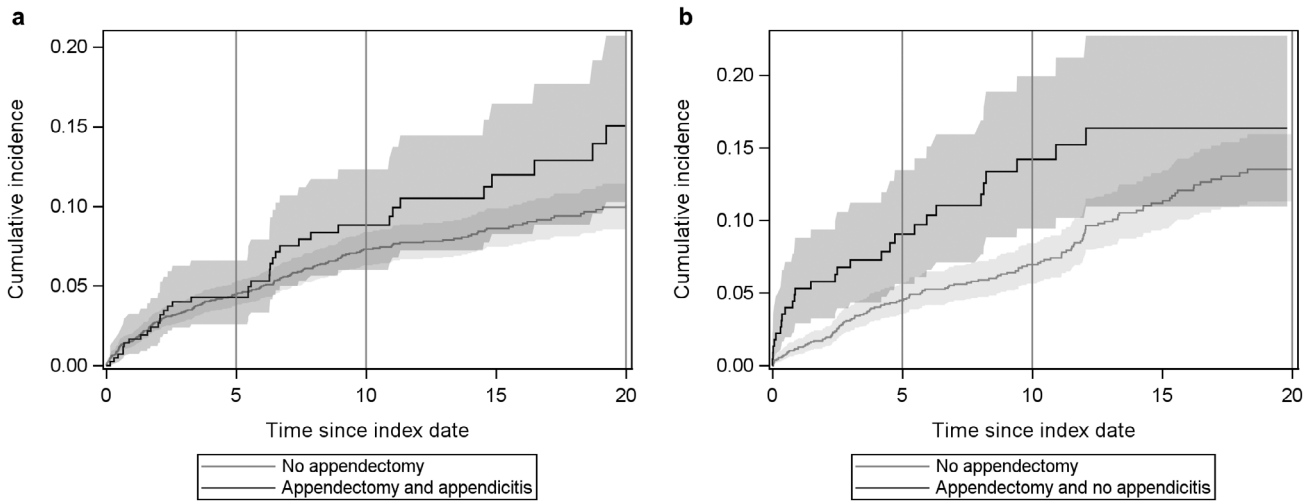

FIGURE 1 | Cumulative incidence of colorectal resections for UC patients with appendectomy after UC (black line) and without appendectomy (grey line). (a) With underlying appendicitis. (b) Without underlying appendicitis. (a) 5 years: 3.7% (2.1–6.0) versus 4.6% (3.8–5.4). 10 years: 8.4% (5.6–11.9) versus 7.4% (6.4–8.6). 20 years: 14.6% (9.8–20.3) versus 10.2% (8.8–11.8). (b) 5 years: 8.4% (5.1–12.8) versus 4.6% (3.6–5.8). 10 years: 13.6% (8.9–19.3) versus 7.1% (5.8–8.6). 20 years: 15.8% (10.4–22.1) versus 13.6% (11.4–16.1).

found that appendectomy with or without underlying appendicitis performed either before or after diagnosis of UC was not associated with a lower risk of hospitalizations, initiation of treatment with biologics or colorectal resections. In fact, appendectomy was associated with a higher risk of colorectal resections when performed in established UC. This accords

with findings from a large Swedish cohort study, where the risk of total colectomy was 56% higher among those with appendectomy for appendicitis after UC compared to those without appendectomy [9]. Patients who underwent appendectomy for appendicitis after UC in our study also experienced a lower rate of UC-related hospitalizations. Although this finding seems paradoxical in light of a parallelled higher rate of surgery, it may simply reflect that patients are cured of their UC after total colectomy.

We found no consistent associations between appendectomy and initiation of treatment with biologics. This outcome is likely the most sensitive proxy of disease severity, because UC-related hospitalizations can reflect a multitude of conditions not directly related to IBD severity, and surgery may be the culmination of a clinical course of relatively mild disease where medical options are exhausted or is associated with undesirable side effects.

Data from previous studies on the effect of appendectomy on the clinical course of UC are contradicting, with some finding lower rates of treatment with immunomodulators [6], while rates of total colectomy are higher in some studies after appendectomy [5]. However, pooled estimates from observational studies indicate comparable total colectomy rates [17], regardless of the timing of appendectomy in relation to the UC diagnosis. The most important clinical aspect of appendectomy in UC is when performed on a normal appendix in established UC as a means to either induce [3] or maintain remission [4]. In our study, appendectomy for non-appendicitis conditions after UC was associated with an increased risk of colorectal resections 0–1 year and 5–10 years after appendectomy, but not 1–5 years and 10–20 years after appendectomy. Rates of treatment with biologics were not higher in this group, but admission rates were 11% higher compared to patients without appendectomy. Whether these findings are causal is unclear, but they contrast with a prospective uncontrolled study of appendectomy performed on 30 patients with UC referred for total colectomy that found 30% of patients experienced a diminished need for treatment escalation after appendectomy [18]. Although these results are encouraging, it should be noted that placebo response rates in medical UC trials are approximately 30% [19], so in the absence of a sham-controlled comparison group, it remains unclear if appendectomy for medically refractory UC offers any real benefit. Results from our study do not suggest that appendectomy for UC is associated with a clinical benefit.

Age at appendectomy may also significantly modulate any potential effect of appendectomy on the risk of UC and on the clinical course of UC [2, 9]. When we stratified patients in those undergoing appendectomy before and after their 20th birthday, the associations remained virtually unchanged for those with appendectomy after their 20th birthday. For UC patients with appendectomy before their 20th birthday, there were too few outcomes to support meaningful analyses, so it is difficult to conclude if an effect modification by age exists.

Our study adds important knowledge to the growing body of evidence on the relationship between the appendix and UC. The large size of our study population with long follow-up and virtually complete longitudinal data capture from nationwide registries ensures robustness of estimates. Also, the use of pathology data to distinguish between appendicitis and non-appendicitis adds validity compared to other studies that have either not differentiated between these conditions [5, 8] or relied on intraoperative findings or discharge diagnoses [9].

The most important limitation to our study is that we did not have information on disease severity or the clinical setting of the appendectomy, and this may have introduced a bias. From health registry data, it is not possible to determine if appendectomy was performed for symptoms of a UC flare that was misinterpreted as appendicitis, but our use of pathology data to distinguish between appendicitis and normal appendix likely limited this potential bias. If UC flares or severe UC was more prevalent in the group undergoing appendectomy, this would likely be mirrored in a higher proportion of patients being treated with biologics after the index date, but this was not the case. The higher rate of colorectal resections for UC patients undergoing appendectomy after UC could indicate a diagnostic bias, especially in the first year after appendectomy; however, the higher rates found 5–10 years and 10–20 years after appendectomy for non-appendicitis and appendicitis, respectively, argue against this. The absence of data on the indication for colorectal resections in our study also makes it difficult to ascertain if this increased rate is due to medically refractory UC or advanced colorectal neoplasia after appendectomy, which constitutes two very different clinical scenarios. The higher colorectal resection rates from five years after appendectomy and onwards could indicate that a significant proportion of resections were performed for advanced neoplasia that was initiated by appendectomy [20].

Following right hemicolectomy or ileocecal resection, patients cannot undergo appendectomy, and it can be argued that these patients should have been censored in our study. However, because such resections are relatively rare in UC, any bias arising from this approach is likely to be minimal. Further, if the resections were performed for any indication of disease severity, excluding patients or defining them as having undergone appendectomy at these procedures could also have introduced a bias. After proctocolectomy, patients are cured of their disease, and this affects their risk of hospitalisation or treatment with biologics. This could theoretically inflate time at risk and lead to an underestimation of hospitalisation rates and rates of treatment with biologics. However, because there were no significant differences in resection rates between UC patients with and without appendectomy, any bias is likely nondifferential. Comparable outcomes in terms of both surgery, hospitalisations, and treatment with biologics for patients with and without appendectomy also indicate that lack of censoring at proctocolectomy did not introduce any significant bias. UC patients with conservatively treated appendicitis were not included in our study, primarily because the validity of an appendicitis diagnosis without concurrent appendectomy in the DNPR presumably is low, because this treatment approach to appendicitis is not generally practised or endorsed in Denmark. Our categorisation of patients undergoing appendectomy in those with or without underlying appendicitis does, however, offer an indirect measure of the association between appendicitis and the clinical course of UC; if appendicitis in itself, without appendectomy, affected the clinical course of UC, this should be reflected in an association between appendectomy performed for appendicitis, but not when performed for other indications, and we found no such pattern.

Lastly, because we included patients born before the inception of the DNPR in 1977, we may have included UC patients who had undergone appendectomy prior to this year and these patients would have been incorrectly classified as still having an appendix during follow-up. Because the associations between appendectomy and the clinical course of UC were virtually unchanged on our analyses restricted to patients with incident UC in the periods from 1997 to 2005, this potential classification bias seems negligible.

In conclusion, we found that the clinical course of patients with UC who underwent appendectomy was not milder compared to patients with UC who had not undergone appendectomy. Colorectal resection rates were higher for those who underwent appendectomy after UC, whether appendectomy was performed for appendicitis or non-appendicitis.

Author Contributions

Anders Mark-Christensen: conceptualization, investigation, writing – original draft, methodology. **Eskild Bendix Kristiansen:** conceptualization, writing – review and editing, methodology, validation, software, formal analysis, data curation, resources. **Søren Laurberg:** conceptualization, writing – review and editing, supervision, methodology. **Rune Erichsen:** conceptualization, funding acquisition, investigation, writing – review and editing, methodology, project administration, supervision.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.