Received: 24 October 2021 | Revised: 8 February 2022 | Accepted: 12 February 2022

DOI: 10.1111/codi.16128

ORIGINAL ARTICLE

Childhood appendicitis and future risk of inflammatory bowel disease – A nationwide cohort study in Sweden 1973–2017

Ali Kiasat[1] | Lucas D. Ekström[2] | Richard Marsk[1] | Anna Löf-Granström[1,3] | Ulf O. Gustafsson[1]

[1]Department of Surgery, Danderyd Hospital and Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden

[2]Department of Medicine, Solna, Clinical Epidemiology Unit, Karolinska Institutet, Stockholm, Sweden

[3]Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

Correspondence
Ali Kiasat, Consultant Surgeon, Department of Surgery, Danderyd Hospital and Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, 18288 Danderyd, Stockholm, Sweden.
Email: ali.kiasat@ki.se

Funding information
The data linkages have been supported by grants from the Stockholm Läns Landsting (grant no. FoUI-954090).

Abstract

Aim: The aim of this study was to investigate the association between juvenile appendicitis, treated conservatively or with appendectomy, and adult risk of inflammatory bowel disease (IBD), either ulcerative colitis (UC) or Crohn's disease (CD). We used nationwide population data from more than 100,000 individuals followed for over four decades.

Method: All Swedish patients discharged with a diagnosis of appendicitis before the age of 16 years between 1973 to 1996 were identified. Everyone diagnosed with appendicitis was matched to an individual in the general population without a history of juvenile appendicitis (unexposed) of similar age, sex and region of residence. The study population was retrospectively followed until 2017 for any development of UC or CD. Cox proportional-hazards models compared disease-free survival time between exposed and unexposed individuals, also analysing the impact of treatment (conservative treatment versus appendectomy).

Results: The final cohort consisted of 52,391 individuals exposed to appendicitis (1,674,629 person years) and 51,415 unexposed individuals (1,638,888 person years). Childhood appendicitis with appendectomy was associated with a significantly lower risk of adult IBD [adjusted hazard ratio (aHR) 0.48 (0.42–0.55)], UC [aHR 0.30 (0.25–0.36)] and CD [aHR 0.82 (0.68–0.97)]. Those treated conservatively had a lower risk of adult UC [aHR 0.29 (0.12–0.69)] but not CD [aHR 1.12 (0.61–2.06)] compared with unexposed individuals.

Conclusion: Juvenile appendicitis treated with appendectomy was associated with a decreased risk of adult IBD, both UC and CD. Those treated conservatively instead of with surgery had a lower risk of UC only. Our findings warrant more research on the role of the appendix and gut microbiota in the pathogenesis of IBD.

KEYWORDS
appendectomy, appendicitis, inflammatory bowel disease

INTRODUCTION

The prevalence of the inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn's disease (CD) is increasing in high-income countries [1]. IBD is a severe chronic condition, with 2.5 million patients requiring lifelong monitoring and symptomatic treatment in Europe alone [2]. Although the pathogenesis of IBD remains unknown, genetic and lifestyle factors have been suggested in relation to both UC and CD [2].

Intestinal bacteria may play a role in the causal chain of development of IBD [3]. One hypothesis suggests that both UC and CD could be caused, or at least exacerbated, by a T-cell mediated autoimmune response to a subset of commensal gut bacteria in genetically susceptible hosts [4]. Reduced biodiversity and an altered phenotypic composition of the intestinal microbiome compared with healthy subjects is frequently reported in IBD patients, where for example *Escherichia coli* strains with specific features may trigger disease in a subset of IBD patients [5].

In this context, the human vermiform appendix has been suggested to play a role associated with IBD [6–9]. The appendix is prone to inflammation, and its surgical removal has long been considered standard of care [10,11]. However, increasing evidence suggests that the appendix may function as a bacterial reservoir with the ability to reinoculate the colon with commensal gut bacteria in response to infections or treatment with antibiotics [12]. Further, the appendix has been linked to immunological functions in humans, such as shedding and regenerating high-concentration secretory immunoglobulin A (IgA) biofilm into the colon [13]. Although the appendix may play an important role in the maintenance of homeostasis of the human gut microbiota thought to protect us from disease [13], the opposite seems to apply for patients with UC [6,7]. Previous research has shown that appendectomy due to appendicitis before the age of 20 years is associated with a lower risk of UC [6,7]. The effect of appendicitis per se on UC has, however, not been explored. The aim of the current study was to investigate if juvenile appendicitis is associated with a relative risk reduction of developing IBD, UC and CD in adulthood and, if so, whether any association differs with the type of treatment, i.e. surgical removal versus conservative treatment.

What does this paper add to the literature?

This is the first study to investigate the association between treatment for childhood appendicitis and the risk of inflammatory bowel disease (IBD) in adulthood. Child appendectomy was associated with a decreased risk of adult IBD, indicating the need for more research on the role of the appendix and gut microbiota in the pathogenesis of IBD.

METHOD

Study design

This population-based retrospective cohort study included all individuals in Sweden with a discharge diagnosis of appendicitis (Table S1) before the age of 16 years during the period 1 January 1973 to 31 December 1996. For each eligible individual with appendicitis one individual without a history of juvenile appendicitis (unexposed) was matched according to age, sex and geographical region of residence at the time of exposure. The individuals with juvenile appendicitis were further stratified into subgroups based on treatment method, namely appendectomy or conservative treatment, and the whole study population was followed for ascertainment of International Classification of Diseases (ICD) diagnoses of IBD, UC and CD until 31 December 2017. Cox proportional-hazards models were used to compare disease-free survival time between subgroups and unexposed individuals for each outcome. The study was approved by the Stockholm ethical review board (2017/2411–31/1).

Data sources

Linkages of several population-based registers held by the National Board of Health and Welfare and Statistics Sweden provided diagnostic details and follow-up until 31 December 2017. All linkages were performed through the personal identification number that identifies every resident in Sweden. The Swedish National Patient Register (NPR) was used to identify all individuals with appendicitis with/without appendectomy as well as outcomes (IBD, UC and CD) (Table S1) during follow-up. The NPR contains close to 100% of medical in-patient data in Sweden since 1987, and all out-patient specialist care data since 2001. It is considered highly reliable and valid [14]. Statistics Sweden provided individuals without a history of juvenile appendicitis (unexposed) matched for sex (nominal), age (continuous) and geographical region of residence (nominal). Data from the Cause of Death Register with ICD syntax information on all deaths of Swedish residents since 1952 were used to censor patients who died before the end of follow-up.

Study population

A consort diagram detailing the construction of the analytical sample is shown in Figure 1. The study population included all individuals (n = 52,435) who were discharged from hospital with a diagnosis of juvenile appendicitis before the age of 16 years and unexposed individuals (n = 52,435) without a medical history of juvenile appendicitis. Individuals with juvenile appendicitis were further stratified by treatment method into either appendectomy or conservative treatment. Absence of appendectomy during the stay was defined as conservative treatment. Unexposed individuals were matched based on a lack of medical history of appendicitis and appendectomy between birth and time of exposure of their respective individual with

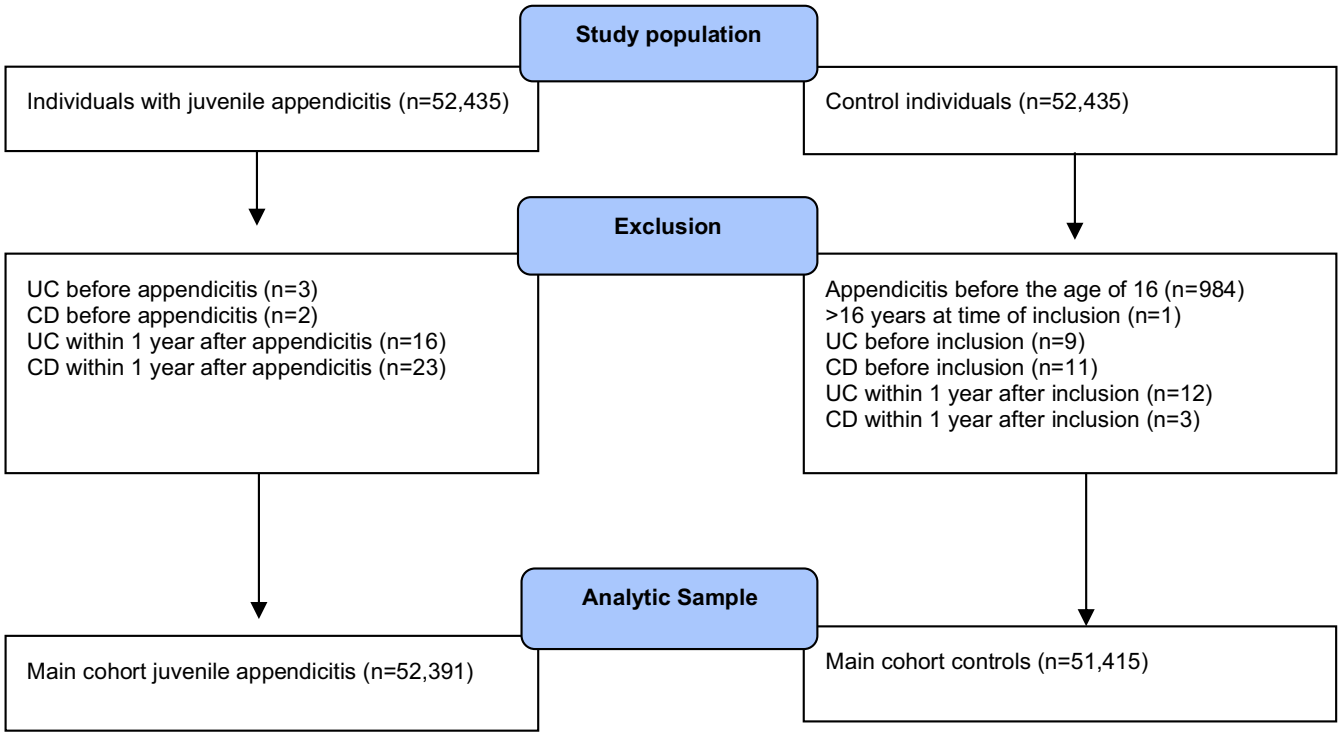

FIGURE 1 Consort diagram of the study population, excluded individuals and the analytical sample

juvenile appendicitis, but not during follow-up. However, Statistics Sweden provided us with the unexposed cohort through random selection among eligible unexposed individuals which included some individuals who had been diagnosed with appendicitis before the age 16 years (n = 984, 1.9%), i.e. the same patients who were included in the exposed group. Since such individuals cannot be considered to be unexposed they had to be excluded from the data analysis. Further exclusions among the unexposed group were also made: individuals older than 16 years at time of inclusion (n = 1, 0.002%), diagnosis of either UC or CD that preceded exposure among individuals with juvenile appendicitis (n = 5, 0.010%) and unexposed individuals (n = 20, 0.038%) and diagnosis of either UC and CD within 1 year after appendicitis in both groups, respectively n = 39 (0.074%) and n = 15 (0.029%). The final analytical sample consisted of 52,391 individuals with juvenile appendicitis (appendicitis with appendectomy N = 50,421, appendicitis without appendectomy N = 1970) and 51,415 unexposed individuals.

Exposures

The main exposure was defined as appendicitis before the age of 16 years ('juvenile appendicitis') and was ascertained from the NPR using relevant ICD codes (Table S1). Individuals with juvenile appendicitis were further stratified by treatment method into either appendectomy or conservative treatment using ICD codes for appendectomy from the NPR (Table S1). Unexposed individuals ('no juvenile appendicitis') without a history of appendicitis were matched for age, sex and geographical region of residence at the time of case patient exposure. Follow-up was delayed by 1 year after exposure in order to limit bias from pre-existing IBD.

Outcomes

The primary outcome, ascertained from the NPR, was defined as 'inflammatory bowel disease' (one or more UC or CD diagnosis), 'ulcerative colitis' (one or more UC diagnosis and UC, most recent IBD diagnosis) and 'Crohn's disease' (one or more CD diagnosis and CD, most recent IBD diagnosis) during follow-up (Table S1). Onset of disease was defined as the date of the first IBD, UC or CD diagnosis regardless of final outcome diagnosis. Since IBD in general, and UC or CD diagnoses in particular, are not always easy to determine, an increasing number of diagnostic sessions over time may strengthen the diagnosis. Therefore, to further enhance the positive predictive value of all IBD diagnoses in the NPR, we used a validated protocol [15] to create an enhanced definition of the primary outcome which used the previously outlined diagnostic requirements but raised the diagnostic threshold to two or more in all definitions ('enhanced outcome definition').

Covariates

Date of death and emigration were retrieved from Statistics Sweden and used to censor individuals who died or emigrated prior to the end of follow-up in the survival analysis. Adjusted Cox proportional-hazards regression models included a number of possible

confounding variables: sex (nominal), educational level (ordinal), individual disposable income (continuous), household disposable income (continuous) and age (continuous). The inclusion of these variables in the regression model was justified as follows: previous studies have shown an uneven distribution between men and woman in both UC and CD [16], low income has been associated with a higher prevalence of IBD [17], although overall results related to socioeconomic status have not been uniform [18], and onset of disease differs in IBD with an incidence peak at 30–40 years for UC and 20–30 years for CD [19]. Since unexposed patients were matched based on a lack of medical history of juvenile appendicitis but not appendicitis during follow-up, the final model upon which the results are based also included binary terms for appendicitis with appendectomy, appendicitis without appendectomy and appendectomy without appendicitis among unexposed patients.

Statistical analysis

The two-tailed *t*-test and Wilcoxon rank-sum test were used for crude group comparisons of continuous and categorical variables. A *p*-value <0.05 was considered statistically significant. The hazard ratio of developing each outcome in relation to exposure status was estimated by fitting Cox proportional-hazards regression models for each exposure (juvenile appendicitis, appendectomy and conservative treatment) with each outcome (IBD, UC and CD) under main and enhanced outcome definition protocols. Hazard ratios of individuals with juvenile appendicitis compared with unexposed individuals were quantified with (adjusted) and without (unadjusted) covariates, and 95% confidence limits for the ensuing hazard ratios were constructed using heteroscedasticity-consistent standard errors. Kaplan–Meier incidence plots comparing exposed and unexposed individuals for each outcome during follow-up were constructed to illustrate outcome incidence during follow-up. All tests of significance were two-sided, and analyses were performed using STATA 15.1 (Stata Corp.)

RESULTS

Population characteristics

The population characteristics of the cohort are shown in Table 1. The main cohort consisted of 52,391 individuals exposed to juvenile appendicitis and 51,415 unexposed individuals. Of the individuals exposed to juvenile appendicitis, 50,421 were treated with appendectomy and 1970 without appendectomy (Table 1). There was a predominance of men versus women in all groups ($p < 0.0001$) apart from conservative treatment where sex was equally balanced (Table 1). All other covariates were evenly balanced across all cohorts (Table 1). Among the exposed individuals who were treated conservatively, 409 (17%) later underwent appendectomy due to recurrent appendicitis. In the analysis stratified by appendicitis treatment method, these individuals were included in the appendectomy group. Of all individuals with juvenile appendicitis ($n = 52,391$), 9467 (18.1%) had a perforated appendicitis. Whether the appendix was perforated or not made no difference to the risk of developing IBD, UC or CD.

Follow up

Events during follow-up, person years at risk and unadjusted and adjusted Cox proportional-hazards ratio estimates are shown in Table 2. In the main cohort, 1148 (1.11%) patients developed IBD, 619 (0.60%) developed UC and 529 (0.51%) developed CD (Table 2). Individuals with juvenile appendicitis, irrespective of the treatment method, showed consistent reductions in relative risk for all main outcomes and enhanced outcome definitions as compared with unexposed individuals during follow-up (adjusted hazard ratios ranged from 0.18 to 0.82; $p < 0.0001$) (Table 2). Kaplan–Meier incidence plots are shown in Figure 2. The mean time from appendicitis to diagnosis of IBD among exposed individuals was 18.6 years (SD 10.0 years) while the mean time between enrolment in the cohort and IBD for unexposed individuals was 19.5 years (SD 8.8 years) ($p = 0.106$). The mean age at IBD diagnosis was 29.8 years (SD 10.1 years) for exposed individuals versus 30.1 years (SD 9.0 years) for unexposed individuals ($p = 0.1812$).

Analyses stratified by appendicitis treatment method under main outcome definitions showed similarly consistent reductions in relative risk irrespective of treatment method across outcomes, except for conservatively treated juvenile appendicitis with CD. Among 52,391 individuals with juvenile appendicitis, 371 (0.71%) developed IBD [355 (0.70%) treated with appendectomy and 16 (0.81%) conservatively treated], 145 (0.28%) developed UC [140 (0.28%) treated with appendectomy and 5 (0.25%) conservatively treated] and 226 (0.43%) developed CD [215 (0.43%) treated with appendectomy and 11 (0.56%) conservatively treated] during 1.67 million person-years at risk (Table 2). This compared with 777 (1.51%), 474 (0.92%) and 303 (0.59%), respectively, among 51,415 unexposed individuals followed for 1.64 million person-years at risk (Table 2). Adjusted Cox proportional-hazard ratio estimates for IBD under the main outcome definition was 0.48 (95% CI 0.42–0.55) for juvenile appendicitis with appendectomy versus 0.59 (95% CI 0.36–0.96) for conservatively treated juvenile appendicitis, 0.30 (95% CI 0.25–0.36) versus 0.29 (95% CI 0.12–0.69), respectively, for UC and 0.82 (95% CI 0.68–0.97) versus 1.12 (95% CI 0.61–2.06), respectively, for CD.

Under enhanced outcome definitions, the protective effect signal of juvenile appendicitis with IBD diagnoses was strengthened further and consistently across all outcomes, except for, as with the main outcome definition, conservatively treated juvenile appendicitis with CD. Among individuals with juvenile appendicitis, 236 (0.45%) developed IBD [227 (0.45%) treated with appendectomy, 9 (0.46%) conservatively treated], 74 (0.14%) developed UC [73 (0.14%) treated with appendectomy, 1 (0.05%) conservatively treated] and 162 (0.31%) developed CD [154 (0.31%) treated with appendectomy, 8 (0.41%) conservatively treated] during 1.68 million person-years at

TABLE 1 Population characteristics in the analytical sample and subsamples

Outcome and covariates	No juvenile appendicitis (unexposed) (*N* = 51,415)	Juvenile appendicitis (*N* = 52,391)	Appendectomy (*N* = 50,421)	Conservative treatment (*N* = 1970)
Inflammatory bowel disease, *n* (%)	**777 (1.51%)**	**371 (0.71%)**	**355 (0.70%)**	**16 (0.81%)**
Enhanced outcome definition, *n* (%)	*617 (1.20%)*	*236 (0.45%)*	*227 (0.45%)*	*9 (0.46%)*
Ulcerative colitis, *n* (%)	**474 (0.92%)**	**145 (0.28%)**	**140 (0.28%)**	**5 (0.25%)**
Enhanced outcome definition, *n* (%)	*397 (0.77%)*	*74 (0.14%)*	*73 (0.14%)*	*1 (0.05%)*
Crohn's disease, *n* (%)	**303 (0.59%)**	**226 (0.43%)**	**215 (0.43%)**	**11 (0.56%)**
Enhanced outcome definition, *n* (%)	*220 (0.43%)*	*162 (0.31%)*	*154 (0.31%)*	*8 (0.41%)*
Age (years) (SD)[a]	11.26 (2.86)	10.94 (2.84)	10.95 (2.81)	10.50(3.39)
Sex				
Male, *n* (%)	27,737 (53.95%)	28,255 (53.93%)	27,263 (54.07%)	992 (50.36%)
Female, *n* (%)	23,678 (46.05%)	24,136 (46.07%)	23,158 (45.93%)	978 (49.64%)
Highest educational level[b]				
Low, *n* (%)	4161 (8.10%)	4237 (8.08%)	4,084 (8.10%)	153 (7.76%)
Intermediate, *n* (%)	24,071 (46.82%)	23,944 (45.70%)	23,016 (45.65%)	928 (47.10%)
High, *n* (%)	23,183 (45.09%)	24,210 (46.21%)	23,321 (46.26%)	889 (45.13%)
Household disposable income[c]				
Mean (SEK) (median)	6105 (5391)	6029 (5391)	6037 (5391)	5834 (5391)
25th percentile (SEK)	3296	3360	3361	3293
75th percentile (SEK)	7109	7157	7169	6851
Individual disposable income[c]				
Mean (SEK) (median)	3473 (3022)	3471 (3022)	3475 (3022)	3368 (3022)
25th percentile (SEK)	2373	2382	2382	2399
75th percentile (SEK)	3761	3804	3809	3179

[a]Age at appendicitis (exposed) or age at appendicitis for corresponding exposed patient (unexposed).

[b]Highest educational level achieved during follow up. Low ≤ 9 years, intermediate 10–12 years and high ≥ 13 years of schooling.

[c]Monthly disposable income in Swedish Krona (SEK).

risk (Table 2). This compared with 617 (1.20%), 397 (0.77%) and 220 (0.43%), respectively, among control patients followed for 1.64 million person-years at risk (Table 2). Adjusted hazard ratios were consistent with main outcome definitions and ranged from 0.07 to 0.77 ($p < 0.0001$), whereas conservatively treated juvenile appendicitis with CD showed an adjusted hazard ratio of 1.05 (95% CI 0.52–2.13) as compared with unexposed individuals (Table 2).

DISCUSSION AND CONCLUSIONS

In this large population-based cohort study of 103,806 individuals followed for more than 3.3 million person years, we found an association between childhood appendicitis treated with appendectomy and a decreased risk of IBD (both UC and CD) later in life. A similar negative association was found between childhood appendicitis

TABLE 2 Association between juvenile appendicitis with inflammatory bowel disease stratified by treatment method and contributing disease outcome

Disease outcome	No. of patients	Events/person years	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio[b] (95% CI)
Inflammatory bowel disease	103,806	**1148/3,313,518**		
Enhanced outcome definition[a]		*853/3,316,876*		
No juvenile appendicitis (unexposed)	51,415	**777/1,638,888**	**1.00 (ref)**	
Enhanced outcome definition		*617/1,640,690*	*1.00 (ref)*	
Juvenile appendicitis	52,391	**371/1,674,629**	**0.47 (0.41–0.53)**	**0.49 (0.43–0.55)**
Enhanced outcome definition		*236/1,676,186*	*0.37 (0.32–0.43)*	*0.38 (0.32–0.44)*
Appendectomy	50,421	**355/1,614,849**	**0.46 (0.41–0.53)**	**0.48 (0.42–0.55)**
Enhanced outcome definition		*227/1,616,317*	*0.37 (0.32–0.43)*	*0.38 (0.32–0.44)*
Conservative treatment	1970	**16/59,781**	**0.57 (0.35–0.93)**	**0.59 (0.36–0.96)**
Enhanced outcome definition		*9/59,869*	*0.40 (0.21–0.77)*	*0.40 (0.21–0.77)*
Ulcerative colitis	103,806	**619/3,321,105**		
Enhanced outcome definition		*471/3,322,686*		
No juvenile appendicitis (unexposed)	51,415	**474/1,643,120**	**1.00 (ref)**	
Enhanced outcome definition		*397/1,643,882*	*1.00 (ref)*	
Juvenile appendicitis	52,391	**145/1,677,985**	**0.30 (0.25–0.36)**	**0.30 (0.25–0.36)**
Enhanced outcome definition		*74/1,678,804*	*0.18 (0.14–0.23)*	*0.18 (0.14–0.23)*
Appendectomy	50,421	**140/1,618,040**	**0.30 (0.25–0.36)**	**0.30 (0.25–0.36)**
Enhanced outcome definition		*73/1,618,809*	*0.19 (0.15–0.24)*	*0.18 (0.14–0.23)*
Conservative treatment	1970	**5/59,945**	**0.29 (0.12–0.71)**	**0.29 (0.12–0.69)**
Enhanced outcome definition		*1/59,995*	*0.07 (0.01–0.49)*	*0.07 (0.01–0.47)*
Crohn's disease	103,806	**529/3,321,186**		
Enhanced outcome definition		*382/3,322,963*		
No juvenile appendicitis (unexposed)	51,415	**303/1,644,677**	**1.00 (ref)**	
Enhanced outcome definition		*220/1,645,716*	*1.00 (ref)*	
Juvenile appendicitis	52,391	**226/1,676,509**	**0.73 (0.62–0.87)**	**0.82 (0.69–0.99)**
Enhanced outcome definition		*162/1,677,247*	*0.72 (0.59–0.89)*	*0.77 (0.62–0.94)*
Appendectomy	50,421	**215/1,616,662**	**0.72 (0.61–0.86)**	**0.82 (0.68–0.97)**
Enhanced outcome definition		*154/1,617,361*	*0.71 (0.58–0.88)*	*0.75 (0.61–0.93)*
Conservative treatment	1970	**11/59,847**	**1.00 (0.55–1.83)**	**1.12 (0.61–2.06)**
Enhanced outcome definition		*8/59,886*	*1.00 (0.49–2.01)*	*1.05 (0.52–2.13)*

[a]Enhanced outcome definition defined as two or more UC and/or CD diagnoses during follow-up. The most recent date of diagnosis was used as the outcome diagnosis.

[b]Adjusted models accounted for sex, age at the time of exposure, educational level, disposable income (individual and family-level) as well as for appendicitis with appendectomy, appendicitis without appendectomy and appendectomy without appendicitis among unexposed individuals.

without appendectomy (conservatively treated) and a lower risk of IBD overall. This risk was probably mainly influenced by a lower risk of UC, since there was no significant association between conservatively treated appendicitis and CD in our study.

Recent studies have shown that childhood appendectomy may increase the risk for acute myocardial infarction [20], chronic kidney disease [21], mood and anxiety disorders [22] and colorectal cancer [23], indicating that the appendix may play an important role in keeping us healthy. A possible explanatory mechanism behind this may be that the appendix has a dual function as a 'safe house' for bacteria with the ability to reinoculate the colon with commensal gut bacteria in response to infections or after treatment with antibiotics [12] and as a main producer of IgA antibodies in the gastrointestinal tract linked to important immunological functions [13]. However, if the appendix protects us against several common diseases, the opposite may also be true for some conditions. Previous population-based studies have suggested that the risk of UC declines following an appendectomy [6,7]. While this reverse association may seem inconsistent with the idea of the role of the appendix in maintaining intestinal health, histological studies of the appendiceal mucosa in patients with UC indicate a pattern consistent with the colonic mucosa [24,25], which differs from the usual changes seen in acute

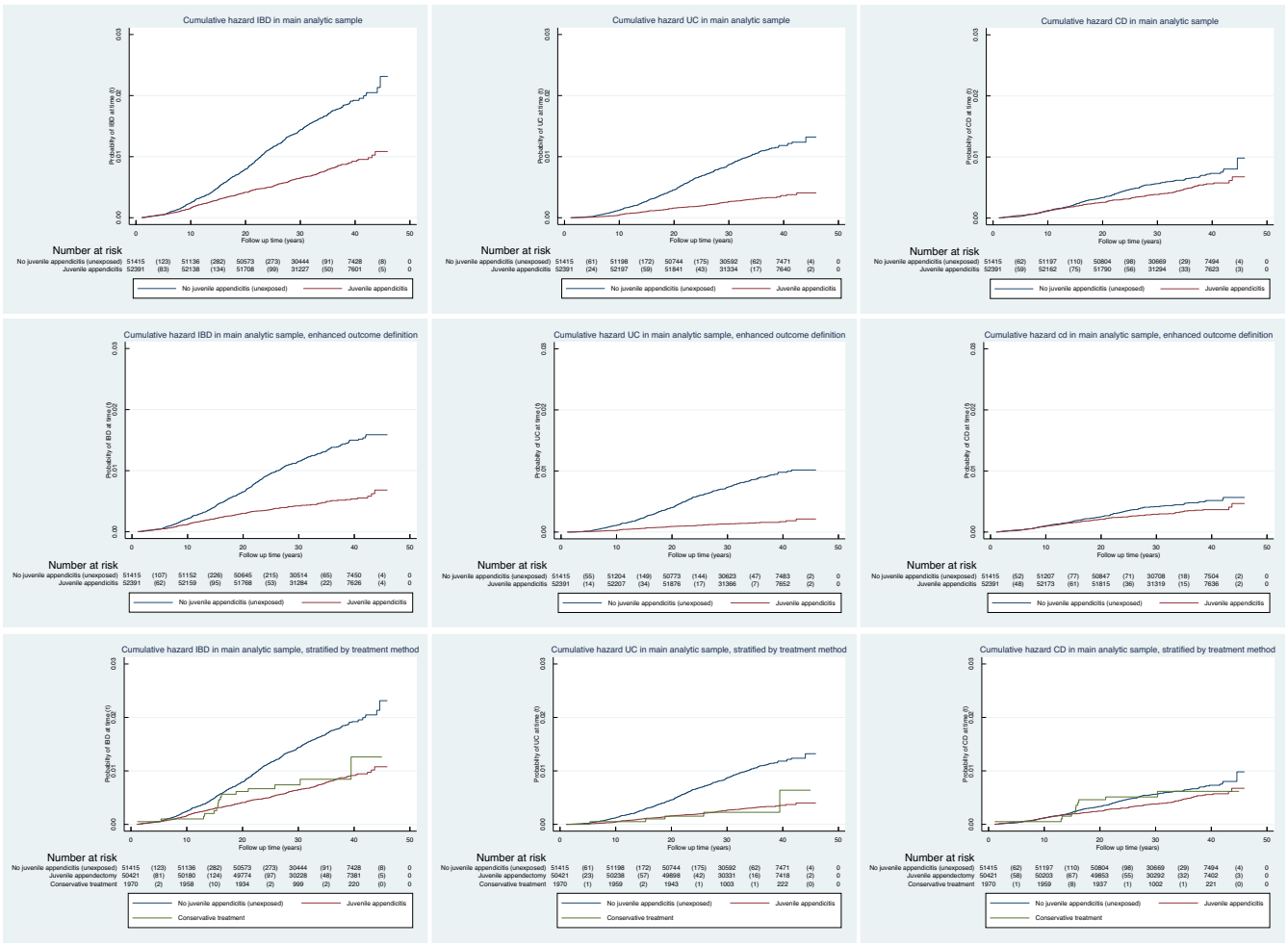

FIGURE 2 Kaplan–Meier incidence plots comparing 'no juvenile appendicitis' versus 'juvenile appendicitis' (rows 1 and 2), and 'no juvenile appendicitis' versus 'juvenile appendicitis with appendectomy' versus 'juvenile appendicitis with conservative treatment' (row 3) for each outcome (IBD left column, UC middle column, CD right column) during follow-up. Rows 1 and 3 illustrate the main outcome definition and row 2 the enhanced outcome definition

appendicitis. In the appendices of UC patients there is an excess of neutrophilic infiltration, indicating a skip lesion [26] or a priming site for UC [24]. While the appendix may serve as a 'safe house' for important commensal bacteria in the gut, it may also be reservoir for gut bacteria involved in the pathogenesis of IBD in some individuals [27]. In addition, since the appendix makes up a significant part of the gut-associated lymphatic-tissue system including a high concertation of IgA-producing B-cells and NK cells, [28] an imbalance in that system may also trigger the development of IBD. Whether this explanatory model could also be applied to the development of CD is currently not known.

Since the first report in 1987 showing that fewer UC patients had a previous history of appendectomy compared with non-UC controls [29], several studies have confirmed the negative association between appendectomy and UC [30]. However, most of these studies had small sample sizes and suffered from methodological flaws [30]. Over the last two decades two well-designed cohort studies have both reported a negative association between appendectomy due to appendicitis or lymphadenitis and subsequent development of UC [6,7], a risk reduction that was limited to patients who underwent appendectomy before the age of 20 years. The heterogeneity of the results could be due to methodological differences [31] and small sample sizes. With regard to CD, several smaller studies have shown inconsistent relationships with appendectomy, positive [32,33], negative [8] and no association [9], but two large registry-based cohort studies from Sweden and Denmark found an increased transient [31] versus long-term [34] risk of CD after appendectomy.

None of the previous studies, however, investigated if appendicitis per se, without appendectomy, is associated with later development of IBD. This is of special interest in the context of a possible bacterial origin for human disease since the appendix is linked to immunological functions [13] and may serve as a bacterial reservoir with the ability to reinoculate the colon with gut bacteria [12]. Patients with appendicitis who were not treated with appendectomy may serve as an interesting comparison group, since important appendiceal functions may be preserved and influence the development of future illness; however, this has not been studied before. Nor has juvenile appendicitis only, with or without appendectomy,

been investigated, and this may be important to prevent confounding from other concurrent risk factors for IBD in older individuals [6–9,29,31–35].

Our cohort study which investigated not only the possible impact of appendectomy on IBD but also appendicitis per se with and without appendectomy in a juvenile population corroborates previous findings [6,7] showing a negative association between appendicitis treated by appendectomy and future UC. In contrast to two previous large cohort studies [31,34] we also found a negative association between appendicitis treated by appendectomy and the future risk of CD. The significance of this finding is unclear, but it could either indicate that previous studies were biased by uncontrolled confounding through the inclusion of primarily older individuals and/or that the bacterial mechanisms behind both UC and CD are the same. On the other hand, we found an association between conservatively treated appendicitis and a decreased risk for UC but not with CD, which may either indicate that the mechanisms causing appendicitis also are protective against UC or that the function of the appendix as a reservoir for commensal or pathogenic bacteria is changed or even destroyed by inflammation. Although general treatment with antibiotics in children may not differ from treatment with antibiotics in child appendicitis, we still believe that the situation with appendicitis is unique, since a healthy appendix may protect its bacterial diversity under treatment with antibiotics while an inflamed appendix will not. Thus, it is not the effect of antibiotics per se that is interesting to compare, but the removal of an inflamed appendix or not. However, differences in outcome for conservatively treated appendicitis remain speculative since this group was rather small. Nevertheless, conservatively treated appendicitis in such a large cohort has never been studied before. In this context, 1970 conservatively treated patients may seem a small number, but in perspective it is larger than other previously published cohorts.

The strength of our population-based cohort study is the very large sample size including 105,000 individuals followed for over 3 million person-years using high-quality registries that cover all Swedish residents. According to a recent validation study [15] on IBD in the Swedish NPR, individuals with two or more UC and/or CD diagnoses had a positive predictive value of 79% for UC, 72% for CD and 93% for having any IBD. We used this enhanced outcome definition for our sensitivity analysis, which resulted in even stronger associations for IBD overall.

Our retrospective cohort study has the advantage of following a large number of initially young individuals over decades and it is substantially bigger and has more detailed information on appendicitis than previously published work; however, there are some potential weaknesses. Although the outcomes remained consistent after adjusting for possible confounding, unknown residual confounders could still affect the results. Also, we had relatively few ($N = 1970$) individuals with appendicitis treated conservatively, making it difficult to draw conclusions on the relationship with IBD. Furthermore, our findings lead us to speculate around potential bacterial explanations for later development of IBD, but observational studies cannot prove any causal links.

In conclusion, this large population-based cohort study on juvenile appendicitis confirms previous research of negative associations between early appendectomy and UC later in life. In addition, we found a similar negative association with future risk of CD. The negative association found in this study between conservatively treated appendicitis and UC is somewhat contradictory but should encourage further studies on bacterial mechanisms and the role of the appendix in future IBD.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors meet the ICMJE criteria for authorship. All authors made substantial contributions to conception and design of the study, acquisition, analysis and interpretation of data, drafting, revising and final approval of the article.

ETHICAL APPROVAL

The study was approved be the Stockholm ethical review board (2017/2411–31/1).

DATA AVAILABILITY STATEMENT

Due to Swedish legal restrictions and the current ethical approval for the study, data is not publicly available to share, but the research group can provide descriptive data in table form.

ORCID

Ali Kiasat https://orcid.org/0000-0001-5568-3265

REFERENCES

1. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142(1):46–54.e42. quiz e30.
2. Kaplan GG. The global burden of IBD: from 2015 to 2025. Nat Rev Gastroenterol Hepatol. 2015;12(12):720–7.
3. Marchesi JR, Adams DH, Fava F, Hermes GD, Hirschfield GM, Hold G, et al. The gut microbiota and host health: a new clinical frontier. Gut. 2016;65(2):330–9.
4. Sartor RB. Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. Nat Clin Pract Gastroenterol Hepatol. 2006;3(7):390–407.
5. Loh G, Blaut M. Role of commensal gut bacteria in inflammatory bowel diseases. Gut Microbes. 2012;3(6):544–55.
6. Andersson RE, Olaison G, Tysk C, Ekbom A. Appendectomy and protection against ulcerative colitis. N Engl J Med. 2001;344(11):808–14.
7. Frisch M, Pedersen BV, Andersson RE. Appendicitis, mesenteric lymphadenitis, and subsequent risk of ulcerative colitis: cohort studies in Sweden and Denmark. BMJ. 2009;338:b716.
8. Radford-Smith GL, Edwards JE, Purdie DM, Pandeya N, Watson M, Martin NG, et al. Protective role of appendicectomy on onset and severity of ulcerative colitis and Crohn's disease. Gut. 2002;51(6):808–13.

9. Russel MG, Dorant E, Brummer RJ, van de Kruijs MA, Muris JW, Bergers JM, et al. Appendectomy and the risk of developing ulcerative colitis or Crohn's disease: results of a large case-control study. South Limburg inflammatory bowel disease study group. Gastroenterology. 1997;113(2):377–82.
10. Gonzalez DO, Deans KJ, Minneci PC. Role of non-operative management in pediatric appendicitis. Semin Pediatr Surg. 2016;25(4):204–7.
11. Bhangu A, Søreide K, Di Saverio S, Assarsson JH, Drake FT. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. Lancet. 2015;386(10000):1278–87.
12. 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. 2007;249(4):826–31.
13. Kooij IA, Sahami S, Meijer SL, Buskens CJ, Te Velde AA. The immunology of the vermiform appendix: a review of the literature. Clin Exp Immunol. 2016;186(1):1–9.
14. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim J-L, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11(1):450.
15. Jakobsson GL, Sternegård E, Olén O, Myrelid P, Ljung R, Strid H, et al. Validating inflammatory bowel disease (IBD) in the Swedish National Patient Register and the Swedish quality register for IBD (SWIBREG). Scand J Gastroenterol. 2017;52(2):216–21.
16. Goodman WA, Erkkila IP, Pizarro TT. Sex matters: impact on pathogenesis, presentation and treatment of inflammatory bowel disease. Nat Rev Gastroenterol Hepatol. 2020;17(12):740–54.
17. Dahlhamer JM, Zammitti EP, Ward BW, Wheaton AG, Croft JB. Prevalence of inflammatory bowel disease among adults aged ≥18 years - United States, 2015. MMWR Morb Mortal Wkly Rep. 2016;65(42):1166–9.
18. Ng SC, Bernstein CN, Vatn MH, Lakatos PL, Loftus EV Jr, Tysk C, et al. Geographical variability and environmental risk factors in inflammatory bowel disease. Gut. 2013;62(4):630–49.
19. Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology. 2011;140(6):1785–94.
20. Janszky I, Mukamal KJ, Dalman C, Hammar N, Ahnve S. Childhood appendectomy, tonsillectomy, and risk for premature acute myocardial infarction—a nationwide population-based cohort study. Eur Heart J. 2011;32(18):2290–6.
21. Chang CH, Kor CT, Wu CL, Chiu PF, Li JR, Tsai CC, et al. Increased chronic kidney disease development and progression in diabetic patients after appendectomy: a population-based cohort study. PeerJ. 2018;6:e5019.
22. Ekström LD, Ekström H, Dal H, Kosidou K, Gustafsson UO. Childhood appendectomy and adult mental disorders: a population-based cohort study. Depress Anxiety. 2020;37(11):1108–17.
23. Wu SC, Chen WT, Muo CH, Ke TW, Fang CW, Sung FC. Association between appendectomy and subsequent colorectal cancer development: an Asian population study. PloS One. 2015;10(2):e0118411.
24. Matsushita M, Uchida K, Okazaki K. Role of the appendix in the pathogenesis of ulcerative colitis. Inflammopharmacology. 2007;15(4):154–7.
25. Scott IS, Sheaff M, Coumbe A, Feakins RM, Rampton DS. Appendiceal inflammation in ulcerative colitis. Histopathology. 1998;33(2):168–73.
26. Park SH, Loftus EV Jr, Yang SK. Appendiceal skip inflammation and ulcerative colitis. Digest Dis Sci. 2014;59(9):2050–7.
27. Rath HC, Ikeda JS, Linde HJ, Schölmerich J, Wilson KH, Sartor RB. Varying cecal bacterial loads influences colitis and gastritis in HLA-B27 transgenic rats. Gastroenterology. 1999;116(2):310–9.
28. Sahami S, Kooij IA, Meijer SL, Van den Brink GR, Buskens CJ, Te Velde AA. The link between the appendix and ulcerative colitis: clinical relevance and potential immunological mechanisms. Am J Gastroenterol. 2016;111(2):163–9.
29. Gilat T, Hacohen D, Lilos P, Langman MJ. Childhood factors in ulcerative colitis and Crohn's disease. An international cooperative study. Scand J Gastroenterol. 1987;22(8):1009–24.
30. Koutroubakis IE, Vlachonikolis IG, Kouroumalis EA. Role of appendicitis and appendectomy in the pathogenesis of ulcerative colitis: a critical review. Inflamm Bowel Dis. 2002;8(4):277–86.
31. Kaplan GG, Pedersen BV, Andersson RE, Sands BE, Korzenik J, Frisch M. The risk of developing Crohn's disease after an appendectomy: a population-based cohort study in Sweden and Denmark. Gut. 2007;56(10):1387–92.
32. Koutroubakis IE, Vlachonikolis IG, Kapsoritakis A, Spanoudakis S, Roussomoustakaki M, Mouzas IA, et al. Appendectomy, tonsillectomy, and risk of inflammatory bowel disease: case-controlled study in Crete. Dis Colon Rectum. 1999;42(2):225–30.
33. Kurina LM, Goldacre MJ, Yeates D, Seagroatt V. Appendicectomy, tonsillectomy, and inflammatory bowel disease: a case-control record linkage study. J Epidemiol Community Health. 2002;56(7):551–4.
34. Andersson RE, Olaison G, Tysk C, Ekbom A. Appendectomy is followed by increased risk of Crohn's disease. Gastroenterology. 2003;124(1):40–6.
35. Singhal R, Taylor J, Owoniyi M, El-Khayat RH, Tyagi SK, Corfield AP. The role of appendicectomy in the subsequent development of inflammatory bowel disease: a UK-based study. Int J Colorectal Dis. 2010;25(4):509–13.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Kiasat A, Ekström LD, Marsk R, Löf-Granström A, Gustafsson UO. Childhood appendicitis and future risk of inflammatory bowel disease – A nationwide cohort study in Sweden 1973–2017. Colorectal Dis. 2022;24:975–983. https://doi.org/10.1111/codi.16128