Appendicitis, mesenteric lymphadenitis, and subsequent risk of ulcerative colitis: cohort studies in Sweden and Denmark

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ABSTRACT

Objective To determine whether the repeatedly observed low risk of ulcerative colitis after appendectomy is related to the appendectomy itself or the underlying morbidity, notably appendicitis or mesenteric lymphadenitis.

Design Nationwide cohort studies.

Setting Sweden and Denmark.

Participants 709 353 Swedish (1964-2004) and Danish (1977-2004) patients who had undergone appendectomy were followed up for subsequent ulcerative colitis. The impact of appendectomy on risk was also studied in 224 483 people whose parents or siblings had inflammatory bowel disease.

Main outcome measures Standardised incidence ratios and rate ratios as measures of relative risk.

Results During 11.1 million years of follow-up in the appendectomy cohort, 1192 patients developed ulcerative colitis (10.8 per 100 000 person years). Appendectomy without underlying inflammation was not associated with reduced risk (standardised incidence ratio 1.04, 95% confidence interval 0.95 to 1.15). Before the age of 20, however, appendectomy for appendicitis (0.45, 0.39 to 0.53) or mesenteric lymphadenitis (0.65, 0.46 to 0.90) was associated with significant risk reduction. A similar pattern was seen in those with affected relatives, whose overall risk of ulcerative colitis was clearly higher than the background risk (1404 observed v 446 expected; standardised incidence ratio 3.15, 2.99 to 3.32). In this cohort, appendectomy without underlying appendicitis did not modify risk (rate ratio 1.04, 0.66 to 1.55, v no appendectomy), while risk after appendectomy for appendicitis was halved (0.49, 0.31 to 0.74).

Conclusions In individuals with or without a familial predisposition to inflammatory bowel disease, appendicitis and mesenteric lymphadenitis during childhood or adolescence are linked to a significantly reduced risk of ulcerative colitis in adulthood. Appendectomy itself does not protect against ulcerative colitis.

INTRODUCTION

Both inherited and environmental factors play important parts in the aetiology of ulcerative colitis.¹ Although numerous non-inherited factors have been proposed, however, few have been consistently associated with risk. Surgical removal of the vermiform appendix for suspected appendicitis, the single most common surgical emergency, is one such factor. Many case-control studies have linked appendectomy to a significantly reduced risk, typically with odds ratios around 0.3, suggesting a reduction of about two thirds in risk among people who have undergone appendectomy.² In two cohort studies based on national register data we previously provided support for an inverse association between appendectomy and risk,^{3,4} but relative risk estimates were much less extreme than those reported in case-control studies. To gain new insights into the repeatedly observed inverse association we expanded and combined our national cohort data to cover all recorded appendectomies in Sweden and Denmark up to 2004. Thus, with a cohort of well over 700 000 patients from two countries, we had unprecedented statistical power to address the central question⁵: is it appendectomy itself or rather the underlying morbidity (notably, appendicitis or mesenteric lymphadenitis) that is responsible for the reduced incidence of ulcerative colitis in people with a history of appendectomy?

METHODS

We used data from population based hospital discharge registries in Sweden and Denmark to identify patients who underwent appendectomy and characterise them according to underlying diagnoses, sex, and age at the time of operation.

Appendectomy cohort

Sweden—We identified 446 968 patients who underwent appendectomy during the 41 year period 1964-2004. National operation codes for appendectomy included 4510, 4511, 4517, and 0058 in 1964-96 and JEA00, JEA01, and JEA10 in 1997-2004. When initiated in 1964, the Swedish Hospital Discharge

Fig 1 | Rate ratios with 95% confidence intervals for ulcerative colitis by age at appendicectomy (10 year age intervals) adjusted for country (Sweden v Denmark), sex, attained age (10 year intervals), calendar period (<1970, 1970-9, 1980-9, 1990-9, 2000-4), and time since appendicectomy (<0.5, 0.5-1, 1-4, 5-9, 10-14, 15-19, ≥20 years). Reference rate was rate of ulcerative colitis among patients who underwent appendicectomy at age ≥50

Registry covered only six of Sweden's 26 counties, but by 1972 half of the Swedish population was covered and since 1987 the registry has had complete national coverage.⁶ We excluded 304 patients (0.07%) recorded as having both ulcerative colitis and Crohn's disease at some point in 1964-2004, 574 patients (0.13%) with ulcerative colitis and 350 patients (0.08%) with Crohn's disease before the appendicectomy, 131 patients (0.03%) with recorded ulcerative colitis and 1432 patients (0.32%) with recorded Crohn's disease during the hospital admission for appendicectomy, and 10 patients (0.002%) with recorded ulcerative colitis and 57 patients (0.01%) with recorded Crohn's disease between the date of discharge after appendicectomy and the first day of the subsequent month. Finally, we excluded 349 patients (0.08%) who died before the start of follow-up for ulcerative colitis on the first day in the month after the appendicectomy. The resulting Swedish cohort consisted of 443 761 patients (245 623 women and 198 138 men), representing 99.3% of all recorded appendicectomy patients in Sweden for 1964-2004.

Denmark—We identified 273 099 patients who underwent appendicectomy during the 28 year period 1977-2004. National operation codes for appendicectomy included 43000 and 43001 during the period 1977-95 and JEA00, JEA01, and JEA10 during the period 1996-2004. The Danish Hospital Discharge Register⁷ has had virtually complete national coverage regarding non-psychiatric hospital admissions since 1977. We excluded 2211 patients (0.81%) with non-Danish nationalities, 406 patients (0.15%) with invalid personal identifiers, and 1794 patients (0.66%) with permanent residence outside Denmark at the time of admission. We also excluded 142 patients (0.05%) recorded as having both ulcerative colitis and Crohn's disease at some point during the period 1977-2004, 355 patients (0.13%) with ulcerative colitis and 243 patients (0.09%) with Crohn's disease before the appendicectomy, 29 patients (0.01%) with recorded ulcerative colitis

and 1766 patients (0.65%) with recorded Crohn's disease during the hospital admission for appendicectomy, and 10 patients (0.004%) with recorded ulcerative colitis and 60 patients (0.02%) with recorded Crohn's disease between the date of discharge after appendicectomy and the first day of the subsequent month. Finally, we excluded 477 patients (0.17%) who died and 14 patients (0.005%) who emigrated from Denmark before the start of follow-up for ulcerative colitis on the first day in the month after the appendicectomy. The resulting Danish cohort consisted of 265 592 patients (152 256 women and 113 336 men), corresponding to 97.3% of all appendicectomy patients in Denmark for the period 1977-2004.

Coding—For each patient, the operation code for appendicectomy was accompanied by codes for relevant discharge diagnoses according to national modifications of the international classification of diseases (ICD) versions 7-10 in Sweden and versions 8 and 10 in Denmark. Using this information, we categorised cohort members according to the most likely underlying disease. Cohort members with appendicitis were categorised as appendicitis with perforation, including appendicitis with diffuse or localised peritonitis and appendicitis with periappendicular abscess, or appendicitis without perforation, including all other and unspecified cases of appendicitis. For cohort members without appendicitis, categories comprised mesenteric lymphadenitis; appendiceal disease except appendicitis, including neoplasm, mucocoele, lymphoid hyperplasia, invagination, fecalith, and fistula; unspecific abdominal pain; and other and unspecified disease.

Familial predisposition

To address the role of appendicectomy in people with a genetically increased risk of ulcerative colitis, we linked hospital admission data with family information in Statistics Sweden⁸ and the Danish Civil Registration System,⁹ continuously updated demographic databases. We identified 164 955 Swedes and 59 528 Danes for whom a mother, a father, or a sibling had a record of inflammatory bowel disease (ulcerative colitis, Crohn's disease, or both) at any time between 1964 and 2004 in Sweden or between 1977 and 2004 in Denmark.

Ulcerative colitis outcomes

As for the appendicectomies, we identified ulcerative colitis outcomes in the hospital discharge registries. In both countries, we included haemorrhagic proctitis as part of the definition of ulcerative colitis. Specifically, ulcerative colitis outcomes in Sweden were identified under national ICD-7 codes 572.20, 572.21, or 578.03 (period 1964-8), ICD-8 codes 563.10 or 569.02 (period 1969-86), ICD-9 group 556 (period 1987-96), and ICD-10 group K51 (period 1997-2004). In Denmark, ulcerative colitis outcomes were identified under national ICD-8 codes 563.19 or 569.04 (period 1977-93) and ICD-10 codes K51-K51.8B (period 1994-2004). Because associations with appendicectomy differ

considerably between ulcerative colitis and Crohn's disease,^{3,4,10} we restricted our analysis to patients with unambiguous records of ulcerative colitis. Consequently, we excluded patients with ICD codes for both ulcerative colitis and Crohn's disease from all analyses. We also excluded patients with indeterminate colitis codes only. Using these stringent definitions, we identified 31 577 first inpatient hospital contacts for ulcerative colitis in Sweden in 1964-2004 and 16 808 in Denmark in 1977-2004. Based on the distribution of sex, age, and calendar year for patients with ulcerative colitis and person time at risk in the underlying general population, we generated a set of incidence rates for ulcerative colitis for each country in strata of sex, age (five year intervals), and calendar year.

Statistical analysis

We used two measures for the relative risk of ulcerative colitis in the appendicectomy cohort and the cohort

with familial predisposition to inflammatory bowel disease. We used the standardised incidence ratio (SIR) to compare the incidence of ulcerative colitis in these cohorts with the incidence in the underlying general population (external comparison) and rate ratios to study differences in rates between cohort categories (internal comparison).

Standardised incidence ratio

This ratio was calculated as the ratio of the observed number of diagnoses of ulcerative colitis to the number expected based on background rates in the general population. For the appendicectomy cohort, each member contributed person time at risk for ulcerative colitis from the first day of the month after the appendicectomy until death or 31 December 2004, whichever came first. For the cohort with a familial predisposition, follow-up periods depended on the affected relative. For those with a parent with inflammatory bowel disease, follow-up started at birth or on the date when the relevant national (Danish relatives) or regional (Swedish relatives) hospital discharge register started, whichever came later. For those with a sibling (but no parent) with inflammatory bowel disease, follow-up started at birth or the date of diagnosis in the affected sibling, whichever came later. For all individuals with a familial predisposition, follow-up continued until death or 31 December 2004, whichever came first.

Person years at risk were summed for cohort members and tabulated in strata of sex, age (five year intervals), and calendar year. Person years for specific groups were then multiplied by the corresponding rates of ulcerative colitis for that specific group in the general population and summed over strata to yield expected numbers in the cohort. The standardised incidence ratio was the ratio of the observed to the expected number of cases in the cohort. We calculated these ratios separately in Sweden and Denmark using country specific background incidence rates and combined estimates obtained by dividing the sum of observed cases by the sum of expected cases in the two countries. We present standardised incidence ratios for the appendicectomy cohort by country, sex, age at appendicectomy, time since appendicectomy, and underlying disease. For all estimates, we calculated 95% confidence intervals, assuming a Poisson distribution of the observed cases in the cohort. We compared ratios across strata of explanatory variables using Wald tests for homogeneity as simple one factor log linear Poisson regressions on the observed cases with means proportional to the stratum specific expected numbers of cases in the cohort. This is equivalent to using the log of stratum specific numbers of expected cases as offset.

Rate ratios

For more complex comparisons of rates of ulcerative colitis in the appendicectomy cohort we performed multiple Poisson regressions with offset variables equal to the log of the expected number of cases in strata of the examined explanatory variable and the potential

Table 1 | Selected characteristics for study cohort of 709 353 appendicectomy patients, Sweden (1964-2004) and Denmark (1977-2004). Figures are numbers (percentages) of patients

	Sweden	Denmark	Both countries
Women	245 623 (55.4)	152 256 (57.3)	397 879 (56.1)
Men	198 138 (44.6)	113 336 (42.7)	311 474 (43.9)
Year of appendicectomy:			
1964-7	10 364 (2.3)	—	10 364 (1.5)
1968-70	10 605 (2.4)	—	10 605 (1.5)
1971-3	21 593 (4.9)	—	21 593 (3.0)
1974-6	34 654 (7.8)	—	34 654 (4.9)
1977-9	42 019 (9.5)	37 675 (14.2)	79 694 (11.2)
1980-2	40 479 (9.1)	37 840 (14.2)	78 319 (11.0)
1983-5	42 228 (9.5)	35 364 (13.3)	77 592 (10.9)
1986-8	44 646 (10.1)	32 158 (12.1)	76 804 (10.8)
1989-91	41 018 (9.2)	28 357 (10.7)	69 375 (9.8)
1992-4	39 599 (8.9)	24 657 (9.3)	64 256 (9.1)
1995-7	36 802 (8.3)	22 535 (8.5)	59 337 (8.4)
1998-2000	36 949 (8.3)	21 764 (8.2)	58 713 (8.3)
2001-4	42 805 (9.6)	25 242 (9.5)	68 047 (9.6)
Age (years) at appendicectomy:			
0-9	34 092 (7.7)	24 311 (9.2)	58 403 (8.2)
10-9	121 179 (27.3)	76 966 (29.0)	198 145 (27.9)
20-9	91 317 (20.6)	47 752 (18.0)	139 069 (19.6)
30-9	64 324 (14.5)	36 493 (13.7)	100 817 (14.2)
40-9	51 027 (11.5)	27 444 (10.3)	78 471 (11.1)
≥50	81 822 (18.4)	52 626 (19.8)	134 448 (19.0)
Underlying disease:			
Appendicitis:			
All	296 367 (66.8)	183 168 (69.0)	479 535 (67.6)
With perforation	54 934 (12.4)	38 300 (14.4)	93 234 (13.1)
Without perforation	241 433 (54.4)	144 868 (54.5)	386 301 (54.5)
Mesenteric lymphadenitis	24 064 (5.4)	8 119 (3.1)	32 183 (4.5)
Other disease*	123 330 (27.8)	74 305 (28.0)	197 635 (27.9)
Appendiceal disease except appendicitis	1868 (0.4)	1222 (0.5)	3090 (0.4)
Unspecific abdominal pain	28 212 (6.4)	13 433 (5.1)	41 645 (5.9)
Other/unspecified disease	93 250 (21.0)	59 650 (22.5)	152 900 (21.6)

*Other than appendicitis or mesenteric lymphadenitis.

Table 2 Standardised incidence ratios (SIR) of ulcerative colitis among 709 353 appendicectomy patients, Sweden (1964-2004) and Denmark (1977-2004)

	Person years	Observed	Expected	SIR (95% CI)	P value*
Total	11 078 855	1192	1352.3	0.88 (0.83 to 0.93)	
Sweden	7 250 881	840	958.4	0.88 (0.82 to 0.94)	0.76
Denmark	3 827 974	352	393.9	0.89 (0.80 to 0.99)	
Women	6 467 929	677	762.9	0.89 (0.82 to 0.96)	0.79
Men	4 610 926	515	589.5	0.87 (0.80 to 0.95)	
Age (years) at appendicectomy:					
<10	952 028	38	75.1	0.51 (0.37 to 0.70)	<0.001
10-9	3 358 272	205	381.4	0.54 (0.47 to 0.62)	
20-9	2 376 137	288	324.6	0.89 (0.79 to 1.00)	
30-9	1 672 986	223	211.0	1.06 (0.93 to 1.21)	
40-9	1 267 122	168	148.4	1.13 (0.97 to 1.32)	
≥50	1 452 309	270	211.9	1.27 (1.13 to 1.44)	
Years since appendicectomy:					
<0.5	351 008	76	37.2	2.04 (1.63 to 2.56)	<0.001
0.5-1	344 872	59	36.8	1.60 (1.24 to 2.07)	
1-4	2 554 495	319	285.7	1.12 (1.00 to 1.25)	
5-9	2 687 351	296	329.1	0.90 (0.80 to 1.01)	
10-4	2 129 600	191	274.1	0.70 (0.60 to 0.80)	
15-9	1 536 293	120	197.1	0.61 (0.51 to 0.73)	
≥20	1 475 237	131	192.4	0.68 (0.57 to 0.81)	
Underlying disease:					
Appendicitis:					
All	7 188 320	726	876.4	0.83 (0.77 to 0.89)	<0.001†
With perforation	1 234 469	111	149.4	0.74 (0.62 to 0.89)	
Without perforation	5 953 851	615	727.0	0.85 (0.78 to 0.92)	
Mesenteric lymphadenitis	645 698	48	74.3	0.65 (0.49 to 0.86)	
Other disease‡	3 244 837	418	401.6	1.04 (0.95 to 1.15)	
Appendiceal disease except appendicitis	43 437	6	5.5	1.09 (0.49 to 2.43)	
Unspecific abdominal pain	654 377	93	81.5	1.14 (0.93 to 1.40)	
Other/unspecified disease	2 547 023	319	314.7	1.01 (0.91 to 1.13)	

*Test for homogeneity.

†In test for homogeneity with categorisation in three (appendicitis, mesenteric lymphadenitis, other disease) or six (appendicitis with perforation, appendicitis without perforation, mesenteric lymphadenitis, appendiceal disease except appendicitis, unspecific abdominal pain, other and unspecified disease) groups of underlying disease.

‡Other than appendicitis or mesenteric lymphadenitis.

confounding variables: country, sex, attained age, calendar period, time since appendicectomy, and age at appendicectomy. Hereby we obtained rate ratios and 95% confidence intervals for comparisons between groups of appendicectomy cohort members with different profiles of explanatory variables and confounders.

We also used multiple Poisson regression to obtain rate ratios and 95% confidence intervals for the evaluation of the impact of appendicectomy and the disease underlying the appendicectomy on risk in the cohort with familial predisposition to inflammatory bowel disease. Specifically, in this cohort we modelled the observed numbers of stratum specific cases as a log linear function of attained age, calendar period, and appendicectomy status, using the log of the stratum specific person years at risk in the predisposed cohort as offset.

All computations were carried out in SAS, versions 8.2 and 9.1 (SAS Institute, Cary, NC). Poisson regression analyses and 95% confidence intervals of standardised incidence ratios and rate ratios were calculated with the GENMOD procedure. We considered confidence intervals that excluded unity and two sided P values <0.05 as significant.

RESULTS

The Swedish and Danish cohorts comprised 709 353 patients who had undergone appendicectomy (table 1). In both countries, there was a moderate predominance of females (55.4% in Sweden, 57.3% in Denmark). In recent years (2001-4) around 10 700 appendicectomies were performed each year in Sweden with its 9.0 million inhabitants (crude annual appendicectomy rate 1190/million) compared with about 6300 appendicectomies per year in Denmark with its 5.4 million

inhabitants (1170/million). Distributions of age at appendicectomy and underlying disease were largely similar in the two countries.

Standardised incidence ratios of ulcerative colitis after appendicectomy

By country and sex—The combined cohort was followed for the occurrence of ulcerative colitis for 11.1 million person years after appendicectomy (table 2), with an average follow-up of 16.3 years in Sweden and 14.4 years in Denmark. Overall, with a total of 1192 cases occurring in the two countries, the crude rate was 10.8/100 000 person years. The incidence of ulcerative colitis in people who had undergone appendicectomy was 12% lower in Sweden (standardised incidence ratio 0.88, 95% confidence interval 0.82 to 0.94) and 11% lower in Denmark (0.89, 0.80 to 0.99), with no significant difference between the two countries ($P=0.76$). As associations in the two countries were similar, we present all subsequent results for the combined cohort.

By age at appendicectomy—Appendicectomies performed in childhood or adolescence were associated with almost 50% reduction in incidence of ulcerative colitis (0.51, 0.37 to 0.70, and 0.54, 0.47 to 0.62, for appendicectomies before the age of 10 and from age 10 to 19, respectively). Standardised incidence ratios gradually increased with age at appendicectomy ($P<0.001$) with no indication of a reduced incidence of ulcerative colitis in cohort members aged 30 or more at appendicectomy. Indeed, patients who underwent appendicectomy at or after the age of 50 had a significantly higher incidence than comparable subsets of the general population (1.27, 1.13 to 1.44).

By time since appendicectomy—Standardised incidence ratios depended significantly on the time interval since the appendicectomy ($P<0.001$). The risk of ulcerative colitis was higher in the first five years after appendicectomy—notably, in the first six months after the operation (2.04, 1.63 to 2.56)—whereas it was consistently reduced in time intervals 10 or more years after appendicectomy.

By underlying disease—The incidence ratio also varied considerably according to the underlying disease leading to the appendicectomy. About 68% of cohort members who had surgery because of appendicitis had significantly reduced incidence (0.83, 0.77 to 0.89). Likewise, cohort members with a diagnosis of mesenteric lymphadenitis were at reduced risk (0.65, 0.49 to 0.86). In contrast, those who had surgery for reasons other than appendicitis or mesenteric lymphadenitis experienced no unusual risk (1.04, 0.95 to 1.15).

Rate ratios of ulcerative colitis by age <20 v $\geq$ 20 at appendicectomy

We used Poisson regression analysis to explore the association with age at appendicectomy further. Compared with people in the oldest category (≥ 50 years), rate ratios were significantly lower for patients aged 0–9 (0.30, 0.17 to 0.55) or 10–19 (0.41, 0.27 to 0.64) at appendicectomy (fig 1), after adjustment

Fig 2 Rate ratios for ulcerative colitis by time since appendicectomy in one year intervals for patients aged <20 or $\geq$ 20 at appendicectomy, adjusted as in fig 1. Reference rate was rate of ulcerative colitis five years after appendicectomy among those aged $\geq$ 20. $P<0.001$ reflects significance of effect of age at appendicectomy (<20 v $\geq$ 20) obtained in slightly reduced regression model with similar effect of time since appendicectomy in compared groups

for potential confounding by country, sex, attained age, calendar period, and time since the operation. We subsequently analysed rates of ulcerative colitis according to time since appendicectomy with cohort members dichotomised into those who underwent appendicectomy during childhood or adolescence (<20 years) or during adulthood ($\geq$ 20 years). In both groups rate ratios declined with time since appendicectomy (fig 2). In the Poisson regression model, the term for statistical interaction between age at appendicectomy (<20 v $\geq$ 20 years) and time since appendicectomy (in one year intervals) was not significant ($P=0.17$), implying that the curves for the two groups can be considered to be parallel. Thus, in the resulting reduced Poisson model, the main effect of age at appendicectomy was significant ($P<0.001$), reflecting that rates were consistently lower among people who underwent appendicectomy before the age of 20.

Standardised incidence ratios of ulcerative colitis after appendicectomy at age <20

Because the risk of ulcerative colitis was unremarkable among patients who underwent appendicectomy at or after the age of 20 (standardised incidence ratio 1.06, 0.99 to 1.13), we carried out supplementary analyses on cohort members who had undergone appendicectomy before the age of 20 (table 3). Risk after appendicectomy in childhood or adolescence was reduced for women (0.59, 0.50 to 0.70) and men (0.47, 0.39 to 0.57). As for the entire appendicectomy cohort, rates of ulcerative colitis declined with time since the operation ($P<0.001$), but incidence ratios were already lower one year after appendicectomy and remained significantly so from five years after. Rates were reduced by 71% in the long term follow-up period $\geq$ 20 years after the operation (0.29, 0.19 to 0.43). Appendicectomy for appendicitis with perforation (0.39, 0.25 to 0.61), appendicitis without perforation (0.46, 0.39 to 0.55), or mesenteric lymphadenitis (0.65, 0.46 to 0.90) were each associated with significant reduction in risk,

whereas appendicectomy for other diseases was not (0.86, 0.66 to 1.12).

Rate ratios of ulcerative colitis by age and underlying disease

Having found evidence of low risk among people who underwent appendicectomy in childhood and adolescence and among those who were operated on for appendicitis or mesenteric lymphadenitis, we used Poisson regression to evaluate the role of the underlying disease in subsets of young (<20 years) and older (≥20) patients (fig 3). Among the younger patients, risk was significantly lower in those with appendicitis or mesenteric lymphadenitis compared with those with other disease ($P<0.001$). In contrast, among older patients, there was no significant difference in rates between those with underlying appendicitis or mesenteric lymphadenitis and those without ($P=0.48$).

Role of appendicectomy in people with familial predisposition

To address the impact of appendicectomy in people with a familial predisposition to ulcerative colitis, we studied risk among 224 483 individuals whose parents (one or both) or siblings (one or more) had inflammatory bowel disease. As anticipated, the number of cases during 4.2 million person years of follow-up in this predisposed cohort clearly exceeded the expected number based on rates in the underlying general populations of Sweden and Denmark (1404 observed *v* 446 expected; standardised incidence ratio 3.15, 2.99

to 3.32). As seen in table 4, Poisson regression analysis controlled for age, calendar period, and type of relative showed no difference between rates in relatives who retained their appendix intact (reference group) and relatives who underwent appendicectomy without appendicitis (rate ratio 1.04, 0.66 to 1.55). In contrast, risk in relatives who underwent appendicectomy for appendicitis was significantly reduced (0.49, 0.31 to 0.74), a pattern seen whether the affected relative was a parent (0.43, 0.22 to 0.75) or a sibling (0.54, 0.27 to 0.96). By introducing interaction terms in the Poisson regression models between appendicectomy status on one side and country ($P=0.67$) or sex ($P=0.16$) on the other, we found that the observed risk reduction associated with appendicectomy for appendicitis (*v* no appendicectomy) was consistent for Swedish (0.45, 0.25 to 0.73) and Danish (0.63, 0.27 to 1.24) relatives and identical for female (0.49, 0.25 to 0.87) and male (0.49, 0.26 to 0.85) relatives of patients with inflammatory bowel disease.

DISCUSSION

Key findings

The inverse association between appendicectomy and risk of ulcerative colitis was first reported around 20 years ago.¹¹ The present bi-national cohort study accords with and expands previous findings in country specific analyses.^{3,4} In agreement with most published case-control studies² we observed significantly fewer subsequent diagnoses in patients who had undergone appendicectomy, the association being restricted to

Table 3 | Standardised incidence ratios (SIR) of ulcerative colitis among 357 825 patients who underwent appendicectomy before age 20 years, Sweden (1964-2004) and Denmark (1977-2004)

	Person years	Observed	Expected	SIR (95% CI)	P value*
Total	4 310 300	243	456.4	0.53 (0.47 to 0.60)	
Sweden	2 689 371	169	321.5	0.53 (0.45 to 0.61)	
Denmark	1 620 929	74	135.0	0.55 (0.44 to 0.69)	0.76
Women	2 247 490	139	234.2	0.59 (0.50 to 0.70)	
Men	2 062 810	104	222.2	0.47 (0.39 to 0.57)	0.07
Years since appendicectomy:					
<0.5	127 430	9	5.7	1.57 (0.82 to 3.02)	
0.5-1	125 978	8	6.2	1.28 (0.64 to 2.57)	
1-4	953 681	56	65.2	0.86 (0.66 to 1.12)	
5-9	1 039 320	70	106.6	0.66 (0.52 to 0.83)	
10-4	855 438	51	110.2	0.46 (0.35 to 0.61)	
15-9	626 117	27	85.6	0.32 (0.22 to 0.46)	
≥20	582 335	22	76.9	0.29 (0.19 to 0.43)	<0.001
Underlying disease:					
Appendicitis:					
All	3 234 360	154	340.1	0.45 (0.39 to 0.53)	
With perforation	507 926	19	49.0	0.39 (0.25 to 0.61)	
Without perforation	2 726 434	135	291.1	0.46 (0.39 to 0.55)	
Mesenteric lymphadenitis	486 030	34	52.7	0.65 (0.46 to 0.90)	
Other disease‡	589 910	55	63.7	0.86 (0.66 to 1.12)	
Unspecific abdominal pain	264 039	25	29.1	0.86 (0.58 to 1.27)	<0.001†

*Test for homogeneity.

†Test for homogeneity with categorisation in three groups of underlying disease (appendicitis, mesenteric lymphadenitis, other disease).

‡Other than appendicitis or mesenteric lymphadenitis.

appendicectomies for appendicitis or mesenteric lymphadenitis before the age of 20. Others have observed this age restriction,¹²⁻¹⁴ but we also showed that without appendicitis or mesenteric lymphadenitis, appendectomy has no impact on subsequent risk, even when done in childhood or adolescence. The analysis of risk in individuals with a familial predisposition to inflammatory bowel disease corroborates this view. In this genetically predisposed cohort, there was no reduction in ulcerative colitis associated with appendectomy without underlying appendicitis but, as with the general population who experienced a significant 55% reduction in risk after appendectomy for appendicitis before the age of 20 (standardised incidence ratio 0.45, 0.39 to 0.53), we observed a significant 51% reduction in risk after appendectomy for appendicitis in the cohort with a familial predisposition (rate ratio 0.49, 0.31 to 0.74). Thus, our findings consistently show that removal of the appendix itself is not responsible for the inverse association. Rather, for reasons that remain unclear, appendicitis and mesenteric lymphadenitis seem to be associated with a reduced subsequent risk of ulcerative colitis.

Despite decades of effort to understand its aetiology, the causes of ulcerative colitis remain poorly characterised. While higher rates in first degree relatives of probands with the disease strongly suggest important genetic components, the lack of affected relatives among most patients with a new diagnosis^{15,16} and concordance rates of only 7%-18% among monozygotic twins¹⁷⁻¹⁹ emphasise the role of non-inherited factors. Psychological susceptibility factors and many environmental risk factors have been proposed, including infectious agents, factors associated with urban lifestyle, high socioeconomic status, consumption of high sugar diets, soft drinks, chocolate, chewing gum, toothpaste, and oral contraceptives.²⁰ While the evidence does not support any specific environmental risk factor as genuinely associated with increased risk, two other factors, tobacco smoking and a history of appendectomy have been consistently associated with reduced risk.¹

Possible mechanisms linking appendicitis in childhood to low risk of ulcerative colitis

Theoretically, several mechanisms might explain why risk is low in people with a history of appendicitis in childhood or adolescence, and these mechanisms might apply to other childhood inflammatory conditions seen merely as unspecific inflammation of mesenteric lymph nodes. One mechanism could be that inflammatory responses elicited during the course of childhood appendicitis or mesenteric lymphadenitis somehow induce longlasting immunological changes in the colonic mucosa, which eventually protect these individuals from developing ulcerative colitis (beneficial inflammation hypothesis). Although theoretically possible, to the best of our knowledge there is no evidence to support this hypothesis.

A second mechanism could be that an, as yet, uncharacterised genetic trait that confers protection

against ulcerative colitis might be closely linked to susceptibility genes for appendicitis or, in reverse, susceptibility genes for ulcerative colitis might be closely linked to an unknown genetic trait that protects against appendicitis (linkage disequilibrium hypothesis). Future large scale family studies of the interrelations between ulcerative colitis and appendicitis might help to clarify the relevance of this hypothesis.

Thirdly, an aetiological mechanism might involve an environmental or microbial factor associated with increased risk of appendicitis and reduced risk of ulcerative colitis or the reverse, a factor associated with protection against appendicitis and increased risk (antagonistic risk factor hypothesis). However, we are aware of no empirical evidence favouring any such environmental or microbial candidate.

Finally, constitutional factors associated with a preference for immune responses orchestrated by Th1 or Th2 cells, might differ between patients developing appendicitis and those developing ulcerative colitis (constitutional immunity hypothesis). In favour of this idea, immune responses characterised by Th2 activation are generally considered to be a feature in the pathogenesis of ulcerative colitis.²¹⁻²³ In contrast,

Fig 3 | Rate ratios for ulcerative colitis by time since appendectomy in two year intervals according to underlying disease in patients aged <20 ($P<0.001$) or ≥ 20 ($P=0.48$) at appendectomy. Rate ratios adjusted for country (Sweden v Denmark), sex, attained age (10 year intervals), calendar period (<1970, 1970-9, 1980-9, 1990-9, 2000-4), and age at appendectomy. Reference rate was rate of ulcerative colitis four to five years after appendectomy among patients with other disease. P values reflect significance of effect of underlying disease (appendectomy or mesenteric lymphadenitis v other disease) obtained in slightly reduced regression models with similar effect of time since appendectomy in compared groups

Table 4 | Rate ratios* (RR) with 95% confidence intervals for ulcerative colitis according to appendectomy status in cohort of 224 483 people with familial predisposition to inflammatory bowel disease, Sweden (1964-2004) and Denmark (1977-2004). Figures are numbers of cases of ulcerative colitis per person years at risk

Relative with inflammatory bowel disease	No appendectomy		Appendectomy, no appendicitis		Appendectomy + appendicitis	
	Cases/person years	RR (95% CI)	Cases/person years	RR (95% CI)	Cases/person years	RR (95% CI)
Parent or sibling†	1361/4 047 047	1‡	22/52 608	1.04 (0.66 to 1.55)	21/102 211	0.49 (0.31 to 0.74)
Parent	854/2 803 351	1‡	12/30 195	1.01 (0.54 to 1.71)	11/61 385	0.43 (0.22 to 0.75)
Sibling	551/1 281 094	1‡	10/23 118	1.01 (0.51 to 1.79)	10/42 050	0.54 (0.27 to 0.96)

*Adjusted for age, calendar period (both in one year intervals with restricted cubic splines), and type of relative with inflammatory bowel disease (parent, sibling, or both).

†Some cases of ulcerative colitis (n=44) occurred in patients with familial predisposition to inflammatory bowel disease through both parent and sibling.

‡Reference category.

proinflammatory (Th1) cytokines seem to be upregulated in appendicitis. Tumour necrosis factor alpha has been shown to be a sensitive marker of inflammation in appendicitis,²⁴ and the tendency among individuals with a history of appendicitis to produce high concentrations of interferon γ on stimulation with tetanus toxoid more than four months after appendicitis²⁵ provides indirect support for the idea that a constitutional preference for Th1 dominated immune responses might characterise those who develop appendicitis. Obviously, dichotomisation of individuals in immunologically distinct categories based on the Th1/Th2 paradigm is highly simplistic considering the immense complexity of the immune system.²⁶ Detailed immunological data to address these speculations are needed.

Strengths of the study

The prospective nature of our historical cohort analyses eliminated potential information and selection biases and other methodological problems that are often encountered in case-control studies. Other strengths include the size of our cohort and the truly population based data sources we used to characterise cohort members and identify ulcerative colitis outcomes. Specifically, by combining data from Sweden and Denmark and extending the follow-up period to the end of 2004, our study comprised three to five times more participants, four to 11 times more observation time at risk, and four to 14 times more outcomes than the only two previously conducted national cohort studies.³⁴ The combination of Swedish and Danish data resulted in a huge dataset with sufficient statistical power to detect even minor deviations from unity as significant. Before combining data from the two countries, we first calculated all standardised incidence ratios in country specific analyses, and results were similar in the two countries in almost all strata of examined explanatory variables. The only exception was the reduced risk after appendectomy for mesenteric lymphadenitis, which was seen only in the larger Swedish cohort. Consistency between country specific standardised incidence ratios in all other analyses lends robustness and credibility to the reported associations.

In addition to presenting conventional standardised incidence ratios to compare rates of ulcerative colitis between patients undergoing appendectomy and the general population, we also compared rates between strata of the appendectomy cohort by means of Poisson regression. While the analyses of standardised incidence ratios showed significant reductions in risk with young age at appendectomy and with appendicitis or mesenteric lymphadenitis as the underlying disease, the Poisson analyses expanded these findings, showing that both factors had to be present to confer a low risk of ulcerative colitis. In other words, appendectomy in a young person without appendicitis or mesenteric lymphadenitis is not linked to low subsequent risk, just as appendicitis or mesenteric lymphadenitis leading to appendectomy in adulthood carried no risk reduction. Our finding that appendectomy is associated with reduced risk only in children and adolescents with appendicitis or mesenteric lymphadenitis, combined with the other novel observation of no risk reduction after removal of a non-inflamed appendix in people with a familial predisposition to inflammatory bowel disease, render as implausible any speculations about possible benefits of prophylactic removal of a healthy appendix in people with a predisposition to ulcerative colitis.

Limitations of the study

Our study has some limitations. We relied on routinely collected data from health and administrative registers, which are not primarily set up for research purposes. Consequently, to the extent appendectomy reports and diagnoses of appendicitis or mesenteric lymphadenitis were incorrectly recorded or entirely missing in the files of the hospital registries, the observed significant inverse associations with subsequent risk will be conservatively estimated. Swedish discharge diagnoses of appendicitis have been estimated to include about 10% false positives and 6% false negatives.²⁷ Likewise, the diagnoses of ulcerative colitis we used as outcomes in the study have a diagnostic specificity of around 90% in both countries,^{28,29} which leaves little room for non-differential misclassification. Considering the prospective nature of the study, plausible mechanisms that would lead to differential over or under-reporting of diagnoses according to

WHAT IS ALREADY KNOWN ON THIS TOPIC

Appendicectomy has been associated with low risk of ulcerative colitis, but the reason for this inverse relation remains controversial

Appendicectomy has been suggested as a possible prophylactic procedure in individuals with a predisposition to ulcerative colitis

WHAT THIS STUDY ADDS

Appendicectomy for appendicitis or mesenteric lymphadenitis in childhood or adolescence, but not after the age of 20, is linked to a reduced risk of ulcerative colitis

Appendicectomy itself does not protect against the development of ulcerative colitis

previous appendicectomy status are hard to conceive. Another possible limitation is that the hospital discharge data we used to identify patients with ulcerative colitis account only for those treated as inpatients. Theoretically, therefore, our findings might not apply to milder cases of ulcerative colitis treated only in ambulatory clinics or specialist settings. This potential limitation is not specific to our study, however, as the available literature on the subject is based almost entirely on hospital data.

Like most previous studies we were unable to adjust for smoking, the only behavioural factor that has been linked rather consistently to risk.¹ Theoretically, therefore, if smoking is also associated with appendicitis or mesenteric lymphadenitis³⁰ our estimates of rate ratios might be confounded by tobacco smoking. Major confounding, however, is unlikely because a strong inverse association between appendicectomy and risk was also observed in previous studies that took smoking into account.^{31,32} Also, in light of the considerably higher prevalence of smokers in Denmark than in Sweden (35% v 19% among men and 43% v 25% among women aged ≥ 25 years),³³ it is reassuring that we obtained almost identical results in country specific analyses.

Clinical implications

Our study has not only aetiological but also clinical implications. By dismissing appendicectomy itself as an explanation for the repeatedly observed inverse association, our findings should put an end to speculations about possible prophylactic capabilities of appendicectomy.³⁴⁻³⁷ Among members of the general population in Sweden and Denmark we found no evidence of reduced incidence in people who had had a non-inflamed appendix removed. We also found no indication that removal of a non-inflamed appendix would reduce the threefold increased risk of ulcerative colitis in genetically predisposed individuals.

Future research

Hopefully, future studies will be able to replicate and extend our findings using other high quality population based data. Our novel observation that appendicectomy in the absence of appendicitis provided no protection against ulcerative colitis in relatives of patients with inflammatory bowel disease was

consistently seen in Sweden and Denmark and in men and women. Confirmatory findings in other high risk populations would strengthen the generalisability of our findings. Also, knowledge about risk of ulcerative colitis in relatives of patients with appendicitis might improve our understanding of the underlying mechanism behind the inverse association. A better understanding of the immunological, genetic, or other mechanisms that protect young patients with appendicitis against later development of ulcerative colitis, regardless of whether they carry a familial predisposition or not, might turn out not only to be useful in attempts to understand the aetiology of ulcerative colitis. Such insight might at the same time provide clues to the aetiology of appendicitis. Of immediate clinical importance, our study should discourage doctors from considering appendicectomy as a possible measure of preventing ulcerative colitis in families affected by the disease.

Contributors: MF planned the study, raised the funding, obtained the Danish data, wrote manuscript drafts, had access to all data, and is guarantor. BVP was responsible for data management and statistical analyses. REA obtained the Swedish data. All authors interpreted the results, critically revised manuscript drafts, and read and approved the final version.

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