RESEARCH REPORT

Appendicectomy, tonsillectomy, and inflammatory bowel disease: a case-control record linkage study

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Study objective: To determine whether appendicectomy and tonsillectomy are associated with ulcerative colitis (UC) or Crohn's disease (CD); and, if so, whether the associations are related to age at operation.
Design: Nested case-control studies using a longitudinal database of linked hospital and death record abstracts.
Setting: Southern England.
Patients: Statistical records of people diagnosed with UC, CD, or a control condition admitted to hospitals in a defined area.
Main results: Appendicectomy under the age of 20 years was associated with a significantly reduced subsequent risk of UC (relative risk =0.48, 95% confidence interval 0.30 to 0.73). The association appeared strongest for appendicectomy between 10 and 14 years of age (relative risk =0.29, 95% CI 0.09 to 0.68). Appendicectomy at the age of 20 years and over was associated with an increased subsequent risk of CD (relative risk =1.92, 95% CI 1.58 to 2.32), largely confined to those people whose CD was diagnosed within a year of appendicectomy. Appendicectomy under 20 years of age, undertaken five years or more before case or control conditions, was suggestively associated with a reduced risk of CD (relative risk =0.71, 95% CI 0.47 to 1.03). Prior tonsillectomy was not associated with any increase or decrease of risk of either UC or CD.
Conclusions: Appendicectomy is associated with a reduced risk of UC; and the association is specific to young age groups when the population risk of appendicitis is itself highest. The increased risk of CD after appendicectomy, at short time intervals between the two, is probably attributable to the misdiagnosis of CD as appendicitis.

The causes of ulcerative colitis (UC) and Crohn's disease (CD) are still largely unknown. There is emerging evidence that appendicectomy is associated with a reduced risk of UC, though not of CD.[1–14] Results of a laboratory study suggested that appendicectomy itself protected against inflammatory bowel disease (IBD).[15] However, recent epidemiological evidence suggests that it may be appendicitis rather than appendicectomy that shows the inverse relation with UC.[1 13 16] The risk reduction seems most prominent in those who undergo appendicectomy under the age of 20.[1 5]

Tonsillectomy, like appendicectomy, entails the removal of gut associated lymphoid tissue. Studies have consistently shown no association between tonsillectomy and UC.[2 5 9 11 13 17 18] However, there is some evidence for a positive association between tonsillectomy and CD, particularly in some subgroups of patients.[13 14 17 18]

We have used population based data from a health region in the southern part of England to determine whether appendicectomy and tonsillectomy are associated with UC or CD in this population, and, if so, whether the associations are related to age at, and time from, operation.

METHODS

The Oxford Record Linkage Study (ORLS) database includes statistical abstracts of records of general hospital admissions (including day cases) and death certificates in a defined population in southern England.[19] The area covered had a population of about 350 000 people in 1963; it expanded to cover 1.9 million from 1975 and 2.5 million (all eight health districts in the former Oxford health region) from 1987. All diagnostic data were coded by trained coders using the International Classification of Diseases (see appendix for the codes used for the case and exposure conditions in this study). The statistical abstracts for each person have been linked together from 1 January 1963 to 31 March 1999 and anonymised (ORLS file 5v1c).

The method of analysis was a series of nested case-control studies, described in detail elsewhere.[20 21] The cases comprised all those people with UC (n=7273) or CD (n=5023) recorded on a hospital admission record or death certificate. The controls for the analyses were people who had been admitted to hospital for any one of a wide range of other medical or surgical conditions (see appendix). Approximately 750 000 persons were included as controls for each comparison. The prior "exposure" events, recorded as an operation on a hospital admission record before the first admission for the case condition, were appendicectomy (subsequently divided into appendicectomy with a diagnosis of appendicitis and appendicectomy without a diagnosis of appendicitis) and tonsillectomy. Selection procedures for dealing with multiple diagnoses per admission and multiple admissions per person were as described elsewhere.[20]

Expected numbers of exposed people among the cases were calculated as follows. We first determined the occurrence of the exposure condition in the control group, calculating rates of exposure stratified by age in five year bands, sex, district of residence, and year of occurrence. These stratified rates were then applied to the case population to generate an expected number of cases with the exposure condition. The observed number of case individuals with the exposure condition was

Abbreviations: UC, ulcerative colitis; CD, Crohn's disease; IBD, inflammatory bowel disease

Table 1 Age and sex distributions of the cases and controls

	Patients with ulcerative colitis n (%)	Patients with Crohn's disease n (%)	Controls n (%)
Total	7273 (100)	5023 (100)	749322 (100)
Sex			
Male	3533 (49)	2034 (40)	361632 (48)
Female	3740 (51)	2989 (60)	387690 (52)
Age (y)			
<20	326 (4)	445 (9)	189648 (25)
20–49	3474 (48)	2842 (57)	331198 (44)
50+	3473 (48)	1736 (34)	228476 (31)

divided by the expected number to yield an estimate of the relative risk. A Poisson distribution was assumed for the observed values, and confidence intervals for the relative risks were calculated accordingly.

RESULTS

The age and sex distributions of the cases and controls are given in table 1. A greater percentage of cases than controls were 50 years of age or older; but we stratified for age in the analyses that follow.

Ulcerative colitis

Appendicectomy in people under the age of 20 years (table 2), and particularly in those between 10 and 14 years of age (table 3), was associated with a significantly reduced risk of UC.

It seems from our data that the reduction in risk of UC may be specific to those people whose appendicectomies were associated with a diagnosis of appendicitis (table 3). However, numbers in the subgroups were small and, for people under 20 years of age at appendicectomy, the difference between those with and without appendicitis was not statistically significant.

There was no evidence that appendicectomy at older ages protected against UC (table 2). If anything, UC in older people was associated with a slightly higher appendicectomy rate than that in controls, particularly at a short time interval between case or control event and appendicectomy.

Crohn's disease

Prior appendicectomy was associated with a significantly increased risk of CD (table 2). Analysis by time interval between operation and case condition showed that the association between prior appendicectomy and CD was strongest in the year after the appendicectomy. In people who underwent appendicectomy under 20 years of age, the relative risk did not significantly exceed 1.0 at time intervals longer than one year between appendicectomy and CD. In fact, when five or more years separated the events, there was a reduction in risk (though non-significant) of CD (table 2).

Tonsillectomy before UC and CD

Prior tonsillectomy was not associated with any increase or decrease of risk of either UC or CD (table 2).

DISCUSSION

The ORLS includes hospitalised patients only and it does not follow up those who migrate outside the area. The implications of these limitations have been discussed in some detail elsewhere[20 21]; but while the *absolute values* of disease occurrence (and operation rates) are underestimated, the *relative risks* we quote should be valid measures of association.

Our prior hypotheses, generated by findings in an earlier study,[1] were that appendicectomy reduces the risk of UC; that the reduction is restricted to appendicectomy before 20 years of age; and that the risk reduction is greatest in people who undergo appendicectomy for appendicitis rather than for conditions that mimic it. Our results confirm that prior appendicectomy reduces the risk of UC and that the risk reduction is limited to people who are relatively young at the time of appendicectomy.[1 5] The strongest reduction in risk of UC was associated with appendicectomy between the ages of 10 and 14 years, which is the peak age, at least in this population, for acute appendicitis.[22] This adds some strength to the suggestion in our data, and that of others,[1 13] that the inverse association

Table 2 Prior appendicectomy or tonsillectomy in people with ulcerative colitis or Crohn's disease: observed (Obs) and expected (Exp) numbers of people with each operation and ratios of observed to expected (O/E), with their 95% confidence intervals (CI)

			Ulcerative colitis				Crohn's disease			
Operation	Age in years at operation	Years from operation	Obs	Exp	O/E	95% CI	Obs	Exp	O/E	95% CI
Appendicectomy	<20	<1	1	1.6	0.63	0 to 3.59	14	2.0	7.16	3.90 to 12.05
		1–4	4	7.9	0.51	0.13 to 1.31	12	11.2	1.07	0.55 to 1.87
		⩾5	17	36.4	0.47	0.27 to 0.75	28	39.5	0.71	0.47 to 1.03
		All	22	45.6	0.48	0.30 to 0.73	54	53.2	1.02	0.76 to 1.33
	⩾20	<1	11	6.2	1.78	0.88 to 3.20	40	5.5	7.31	5.22 to 9.96
		1–4	24	21.6	1.11	0.71 to 1.66	36	17.0	2.12	1.48 to 2.93
		⩾5	62	52.5	1.18	0.90 to 1.51	32	33.5	0.95	0.65 to 1.35
		All	97	80.5	1.21	0.98 to 1.47	108	56.2	1.92	1.58 to 2.32
	All ages	All	119	125.9	0.95	0.78 to 1.13	162	107.6	1.51	1.28 to 1.76
Tonsillectomy	<20	<1	2	1.5	1.35	0.13 to 4.96	1	1.9	0.53	0 to 3.01
		1–4	6	6.9	0.87	0.31 to 1.90	17	11.2	1.51	0.88 to 2.43
		⩾5	75	84.1	0.89	0.70 to 1.12	120	105.5	1.14	0.94 to 1.36
		All	83	92.9	0.89	0.71 to 1.11	138	119.2	1.16	0.97 to 1.37
	⩾20	<1	3	2.9	1.05	0.20 to 3.11	1	2.8	0.36	0 to 2.06
		1–4	10	9.7	1.03	0.49 to 1.90	5	9.1	0.55	0.17 to 1.29
		⩾5	19	19.2	0.99	0.59 to 1.54	15	14.7	1.02	0.57 to 1.69
		All	32	31.1	1.03	0.70 to 1.45	21	26.4	0.80	0.49 to 1.22
	All ages	All	115	124.2	0.93	0.76 to 1.11	159	144.9	1.10	0.93 to 1.28

Table 3 Appendicectomy before ulcerative colitis showing data in five year age groups at time of appendicectomy, and showing data for people who underwent appendicectomy with or without a record of appendicitis: observed (Obs) and expected (Exp) numbers of people in each subgroup, and the ratios of observed to expected (O/E) with their 95% confidence intervals (CI)

Operation	Age (y)	Obs	Exp	O/E	95% CI
All appendicectomy	<5	0	0.5	0	0 to 7.94
	5–9	4	5.8	0.69	0.18 to 1.79
	10–14	5	17.3	0.29	0.09 to 0.68
	15–19	13	22.1	0.59	0.31 to 1.01
	20–24	14	16.7	0.84	0.46 to 1.41
	25–29	15	12.9	1.17	0.65 to 1.93
	30–34	13	10.3	1.26	0.67 to 2.17
	⩾35	55	40.8	1.35	1.02 to 1.76
Appendicectomy with appendicitis	<20	15	35.3	0.43	0.24 to 0.70
	⩾20	67	58.2	1.15	0.89 to 1.46
Appendicectomy without appendicitis	<20	7	10.4	0.67	0.27 to 1.39
	⩾20	30	22.4	1.34	0.90 to 1.92

Key points

- The aetiology of inflammatory bowel disease is largely unknown and therefore any clues about aetiological factors are of interest.
- This study confirms a significantly reduced risk of ulcerative colitis in people who have undergone appendicectomy.
- The reduced risk was specific to appendicectomy in childhood and young adulthood.
- An increased risk of Crohn's disease was found after appendicectomy and was probably attributable to misdiagnosis of the former appendicitis.
- Tonsillectomy was not associated with any change of risk of ulcerative colitis or Crohn's disease.

between appendicectomy and UC may be attributable to an inverse association between *appendicitis* and UC. No association was found in our study between tonsillectomy and either IBD, giving additional weight to the specificity of the inverse relation between appendicectomy and UC.

A Danish registry study, published after the submission of our paper, found no significant reduction in risk of UC after appendicectomy.[23] The overall risk estimate for appendicectomy at all ages was 0.87 (95% CI 0.69 to 1.07). The relative risk was lower in those under 20 years of age (relative risk =0.74, 95% CI 0.47 to 1.11). Though not significant, this risk estimate is consistent with our results.

Two studies have shown a positive association between appendicectomy and CD.[7 17] The excess risk was explained as the result either of prophylactic appendicectomies done during the course of CD related laparotomies or of misdiagnosis of CD as appendicitis. It is well recognised clinically that some patients with CD "present with the clinical features of acute appendicitis".[24] Our data also show a positive association between prior appendicectomy and CD. The relative risk of CD is particularly high over very short time intervals (less than one year) after appendicectomy (table 2). The most probable explanation for these results is that, in these patients, CD is first misdiagnosed as appendicitis. In fact, our data suggest that appendicectomy rates may be low in young people at long time intervals before CD. It is conceivable that a real inverse association in young people is masked by the fact that CD sometimes mimics appendicitis.

If appendicectomy is inversely related to UC, what might the mechanism be? One hypothesis suggests that appendicitis and ulcerative colitis may be divergent responses to childhood hygiene. For example, Ekbom [16] argued that the decline in the incidence of appendicitis over the past 10 years in Sweden could be a result of the increased use of day care centres for very young children, and, presumably, the consequent increase in exposure to pathogens early in life. Citing evidence of an association between early infectious events and IBD,[27] Ekbom implied that these events might shape the immune system in such a way that the risk of appendicitis is decreased but the risk of UC increased.[16] Conversely, the steady decline in appendicitis observed in developed countries over the past few decades could be interpreted as the result of further improvements in hygiene protecting against exogenous pathogens.[25 28] The same improvements in hygiene that protect against appendicitis may predispose susceptible people to UC. For example, given that UC has an autoimmune component, reduced exposure to pathogens early in life might result in an inappropriate immune response to a triggering antigen in late adolescence or early adulthood. However, although two studies have shown a positive relation between early domestic hygiene and CD,[5 6] this relation has not been observed for UC.[5]

One of the few established risk factors for IBD is smoking. Smoking protects against UC and predisposes to CD.[2 29 30] A limitation of the ORLS dataset is the absence of information on lifestyle variables, including smoking habits. Confounding could be an important consideration if smoking is also associated with appendicitis. However, a recent case-control study showed no relation between having ever smoked and having had an appendicectomy.[5] Furthermore, there is evidence from other studies that the inverse relation between appendicectomy and UC remains after adjustment for smoking status.[4 11 12] Smoke inhalation early in life may be an important consideration; two recent cohort studies reported an increased risk of appendicectomy among the children of parents who smoke.[26 32] If these children are more likely to smoke themselves, this could, at least in part, account for the dissociation between appendicitis and UC.

In summary, we confirm that there is an inverse association between appendicectomy and UC and that it is specific to people who have appendicectomies in childhood and young adulthood. We confirm that tonsillectomy is not associated with the risk of UC or CD.

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APPENDIX

The International Classification of Diseases (ICD) diagnosis and Office of Population Censuses and Surveys (OPCS) operation codes used for the case and exposure conditions in this study were as follows:

Diagnoses	ICD 7	ICD 8	ICD 9	ICD 10
Case conditions				
Ulcerative colitis	572.2	563.1	556	K51
Crohn's disease	572.0	563.0	555.0–555.2, 555.9	K50
Exposures				
Appendicitis	550–552	540–542	540–542	K35–K37
Operations	**OPCS 1**	**OPCS 2**	**OPCS 3**	**OPCS 4**
Appendicectomy	441	441, 443, 444	441–444	H01, H02
Tonsillectomy	260–264	230–236	230–236	F34, F36

The control conditions used in this study were as follows, using the terminology of ICD9 and the OPCS Classification of Surgical Operations, Third Revision: sebaceous cyst; disorders of tooth development and eruption; diseases of hard tissues of teeth; deflected nasal septum; nasal polyps; varicose veins of lower extremities; haemorrhoids; acute respiratory infections; strabismus; cataract; inguinal hernia; diseases of nail; internal derangement of knee; bunion; contraceptive management; dilatation of cervix and curettage of uterus; head injuries; fracture of upper limb and lower limb; disloations, sprains, and strains; superficial injury and contusion; total hip replacement; total knee replacement.

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