

Prevalence and family risk of ulcerative colitis and Crohn's disease: an epidemiological study among Europeans and South Asians in Leicestershire

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Abstract

The family history of patients identified during incidence studies in Leicestershire were investigated and the prevalence and comparative risks calculated; 1254 patients aged 15 to 80 years were sent a questionnaire about their family history. All cases with a positive family history were reviewed and confirmed cases included in the study. In Europeans the standardised prevalence of Crohn's disease was 75.8/10⁵ and that of ulcerative colitis 90.8/10⁵. The prevalence of Crohn's disease among South Asians was 33.2/10⁵ and that of ulcerative colitis 135/10⁵. The prevalence of Crohn's disease in Europeans was significantly greater than that in Hindus ($\chi^2=16$, $p<0.001$), while the prevalence of ulcerative colitis was significantly lower in Europeans than Hindus ($\chi^2=27$, $p<0.001$) and Sikhs ($\chi^2=4.4$, $p<0.05$). The comparative risk of developing ulcerative colitis in first degree relatives of Europeans patients with ulcerative colitis was increased by approximately 15, but the risk of Crohn's disease was not increased. The comparative risk of developing Crohn's disease among first degree relatives of patients with Crohn's disease was increased by up to 35, the comparative risk of ulcerative colitis was approximately 3. The risk among relatives of South Asian patients with Crohn's disease was not increased, but the risk of ulcerative colitis to relatives of patients with ulcerative colitis was. This study supports the view that Crohn's disease and ulcerative colitis arise in people with a genetic predisposition and exposed to some, as yet unknown, environmental factor.

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Ulcerative colitis and Crohn's disease are chronic conditions of unknown cause. They may lead to lifelong ill health, often requiring drugs and sometimes surgery. Patients are anxious about the diagnosis and often fear they might pass the condition onto their offspring. Earlier studies¹⁻⁸ have shown that the risk of developing inflammatory bowel disease is increased in first degree relatives.

Leicestershire comprises the city and seven market towns in a large agricultural area. It is served by one health authority. The country has a population of approximately 930 000, of whom 93 000 are South Asian. 'South Asian' refers to people whose families originate from India, Pakistan, or Bangladesh.⁹⁻¹⁰ The city of Leicester has comparatively more South Asians than the rural areas, indeed 81% of South Asians in the county live within the city boundary.¹¹ Thus,

nearly 8% of the 1.2 million South Asians in Britain live in Leicestershire.¹²

The aim of this study was to investigate the comparative risk and prevalence of ulcerative colitis and Crohn's disease among relatives of patients on the community based register in Leicestershire. This would help to better advise patients about the familial risk and further assess the role of heredity as a aetiological factor in Europeans and South Asians.

Method

Both the incidence and mortality among patients with ulcerative colitis and Crohn's disease in Leicestershire have been reported.¹³⁻¹⁶ The diagnosis of Crohn's disease or ulcerative colitis had been made on the basis of internationally accepted criteria.¹⁷ Patients aged 15 to 80 years, who were resident in Leicestershire, were included in the study. Fifteen children aged less than 15 years were excluded from the calculations. Patients were sent a questionnaire about their family. The details collected included any history of ulcerative colitis or Crohn's disease among parents, siblings or offspring. The age of relatives was not collected, but the number of siblings and the birth position of the proband were recorded. The patient's total number of offspring and the number aged over 15 years were noted. Patients who did not reply were sent a second and, if necessary, third questionnaire.

Probandi were asked to give the name and address of their affected relatives. The whereabouts of unaffected relatives was not determined, although we realise that some relatives of South Asians reside overseas. Each positive family history was investigated and the diagnosis of Crohn's disease or ulcerative colitis confirmed or refuted from the relative's own case notes. The same diagnostic criteria were applied as had been used in the incidence studies.

The prevalences of ulcerative colitis and Crohn's disease in Leicestershire were found from the community based register taking into account patients who had died or moved away from the county. The prevalence was standardised to the population of Leicestershire for each ethnic group.

In the calculation of comparative risk no subject must contribute twice to the two by two table; for this reason, the prevalence of inflammatory bowel disease amongst first degree relatives was compared with that of Cardiff,¹ for Crohn's disease, and North Tees,¹⁸ for ulcerative colitis. For South Asians the prevalence reported from Bradford¹⁹ was used for comparison, even though the population is not strictly comparable

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TABLE I Standardised prevalence of inflammatory bowel disease in Leicestershire

Ethnic group	Prevalence (cases)		
	Crohn's disease	Ulcerative colitis (excluding proctitis)	Proctitis
European	75.8 (645)	90.8 (754)	37.0 (302)
South Asians	33.2 (31)	136.0 (134)	37.5 (40)
<i>South Asian subgroups</i>			
Hindus	31.9 (20)	151.5 (98)	41.5 (27)
Sikhs	30.8 (4)	138.4 (19)	69.2 (9)
Moslems	53.8 (7)	107.6 (17)	23.0 (4)

Europeans had significantly more Crohn's disease than Hindus and significantly less ulcerative colitis than either Hindus or Sikhs. Prevalence: cases/100 000.

with that of Leicester, because there was no alternative. The prevalence in each generation was compared with the 'control' population. The prevalence in each generation, however, could not be standardised because the age of the non-affected relatives was not known. The data for siblings, however, were set against the background of knowing the birth position of the proband. Confidence intervals for the prevalence values were calculated using a standard method.²⁰ Comparative risk confidence intervals were found using the method described by Katz *et al*²¹ using Confidence Interval Analysis software,²² except where the value was zero when the method described by Bailey²³ was used.

Multiple ascertainment of kindreds can confound studies of family risk. Only one subject per kindred may be attributed proband state. The decision who this should be is arbitrary and can be approached in two ways, which, in practice, have the same result; either arbitrary assignment or 'shared' assignment with each affected individual contributing. The latter was adopted; thus data from a kindred with two potentially equally valid probands (index patients sent questionnaires) were both included in the analysis in both ways, with weights of 0.5 assigned to each part of the data. Where three index patients belonged to one kindred an equivalent adjustment was made. In this way each subject did not contribute to the calculations more than once.

Results

PREVALENCE

The prevalence of Crohn's disease and ulcerative colitis on 31 December 1989 was calculated from data obtained during the incidence and mortality studies.¹³⁻¹⁶ On 1 January 1990 there were 676 patients with Crohn's disease, of whom 645 were European and 31 South Asian. Eight hundred and eighty eight people had ulcerative colitis, excluding disease limited to the rectum (proctitis); 754 were European and 134 South Asian.

In Europeans, the standardised prevalence of ulcerative colitis was 90.8/10⁵ (95% CI 84 to 97) and that of Crohn's disease 75.8/10⁵ (95% CI 70 to 83) (Table I). Among South Asians, the standardised prevalence of ulcerative colitis, excluding proctitis, was 136/10⁵ (95% CI 111 to 161) and that of Crohn's disease 33.2/10⁵ (95% CI 23 to 46). The highest prevalence for ulcerative colitis was amongst Hindus (152 cases/10⁵) while the highest value for proctitis (41.5/10⁵) was

amongst Sikhs. The prevalence of ulcerative colitis was significantly lower in Europeans than that in Hindus (95% CI of difference 34.6 to 97.8 per 10⁵, $\chi^2=27$, $p<0.001$) and Sikhs (95% CI of difference 9 to 122 per 10⁵, $\chi^2=4.4$, $p<0.05$). When other comparisons of the prevalence of ulcerative colitis were made between ethnic groups no significant difference was found. The prevalence of Crohn's disease was highest in Europeans. The prevalence of Crohn's disease in Europeans was significantly greater than that in Hindus (95% CI of difference 30 to 60.4 per 10⁵, $\chi^2=16$, $p<0.001$). Again no other comparison of prevalence was significant.

CROHN'S DISEASE PATIENTS

Four hundred and twenty four (90%) Europeans and 18 (75%) South Asian patients replied to the questionnaire. Table II summarises the results. Among Europeans, 49 patients with Crohn's disease reported 54 relatives with inflammatory bowel disease. The diagnosis was confirmed in 44, of whom four had ulcerative colitis. Of the remainder, most had irritable bowel syndrome although two had colorectal cancer. Four had died and no notes could be obtained, and one chose not to take part in the study. The prevalence of Crohn's disease of 1931/10⁵ (95% CI 1071 to 2791) among siblings. The prevalence of ulcerative colitis was 302/10⁵ (95% CI -30 to 649) among siblings. The comparative risk (CR) of developing Crohn's disease was substantially increased among first degree relatives, especially for siblings (CR=35, 95% CI 21.6 to 55.6) and offspring over 15 (CR=29.1, 95% CI 14.4 to 59). None of the patients was married to each other. The risk of developing ulcerative colitis among first degree relatives of Crohn's disease patients was increased marginally with wide confidence intervals (Table II).

Only one South Asian gave a family history of Crohn's disease, but unfortunately this could not be confirmed because of the availability of clinical notes (Table III). Less than one case, however, would be expected. The three categories of first degree relatives were combined for analysis because of the small numbers.

In Europeans, the average family size was 3.4 offspring and the mean position of the proband was 2.1. Among South Asians, the mean family size was 5.1 offspring and the mean position of the proband was 3.2. Thus, in both ethnic groups the proband was, on average, the middle born, suggesting that the prevalence is likely to be representative, although possibly the magnitude of the risk may be underestimated. In one kindred all three members had Crohn's disease.

Most of the affected relatives lived in Leicestershire. One patient's father, with Crohn's disease, however, lived in Lancashire and three patients had affected siblings who lived outside Leicestershire (one in London, one in Scotland, and one in Cornwall). For each of these patients extracts of their notes were obtained.

ULCERATIVE COLITIS RELATIVES

Among Europeans, 469 replied (response

TABLE II Prevalence and comparative risk of ulcerative colitis and Crohn's disease in first degree relatives of Europeans with inflammatory bowel disease

	Relative of patient with ulcerative colitis			Relative of patient with Crohn's disease		
	Parent	Sibling	Offspring (>15 y)	Parent	Sibling	Offspring (>15 y)
No at risk	917	1094	594	825	984	493
No of cases of ulcerative colitis	12	11	6	9	3	1
Prevalence of ulcerative colitis (cases/100)	1.31%	1.0%	1.0%	0	0.3%	0.2%
95% CI	0.6 to 2.0	0.4 to 1.6	0.2 to 1.8	0 to 0.45	0 to 0.65	0 to 0.6
Comparative risk of ulcerative colitis	19.2	14.6	14.8	0	4.5	3.0
95% CI	10.7 to 34.5	7.9 to 26.9	6.6 to 33.4	0 to 6.4	1.4 to 14.0	0.4 to 21.2
No of cases of Crohn's disease	1	1	1	8	19	8
Prevalence of Crohn's disease (cases/100)	0.1	0.09	0.17	0.9	2.0	1.6
95% CI	0 to 0.3	0.08 to 0.27	0 to 0.5	0.3 to 1.6	1.1 to 2.8	0.5 to 2.7
Comparative risk of Crohn's disease (cases/100)	2.0	1.6	3.0	17.4	34.7	29.1
95% CI	0.3 to 14.0	0.3 to 11.7	0.4 to 21.6	8.6 to 35.3	21.6 to 35.6	14.4 to 59.0

The risk of developing ulcerative colitis is considerably increased in relatives of patients with ulcerative colitis, the risk of Crohn's disease is mildly increased. The risk of developing Crohn's disease is considerably increased in relatives of patients with Crohn's disease, while the risk of ulcerative colitis is small.

rate=72%) and 57 (response rate=57%) of South Asians replied. Tables II and III show the prevalence and comparative risk among first degree family members. Among Europeans, 35 patients with ulcerative colitis reported 36 relatives with inflammatory bowel disease. The diagnosis was confirmed in 32, of whom three had Crohn's disease, giving a prevalence of ulcerative colitis of 1308/10⁵ (95% CI 573 to 2044) among parents and 1005/10⁵ (95% CI 414 to 1597) amongst siblings. The comparative risk was significantly increased in Europeans, but not to the extent found in Crohn's disease. The comparative risk was similar in parents (CR=19.2, 95% CI 10.7 to 34.5), siblings (CR=14.6, 95% CI 7.9 to 26.9), and offspring over 15 years (CR=14.8%, CI 6.6 to 33.4). The risk of first degree relatives of patients with ulcerative colitis developing Crohn's disease was not increased among 1094 siblings and 594 offspring aged over 15 years.

There was only one confirmed case among relatives of South Asian patients (Table III), although five other cases had been reported. Two were diagnosed and living overseas, one had died and his notes could not be obtained, and in the remaining two cases permission to review clinical notes and specimens was withheld. If all cases had been confirmed the prevalence of ulcerative

TABLE III Prevalence and comparative risk of ulcerative colitis and Crohn's disease in first degree relatives of South Asians with inflammatory bowel disease

	Relative of patients with ulcerative colitis	Relative of patient with Crohn's disease
No at risk	415	120
No of cases of ulcerative colitis	1	0
Prevalence of ulcerative colitis (cases/100)	0.42	0
Comparative risk of ulcerative colitis	3.5	0
95% CI	0.5 to 25.7	0 to 45.2
No of cases of Crohn's disease	0	0
Prevalence of Crohn's disease (cases/100)	0	0
Comparative risk of Crohn's disease (cases/100)	0	0
95% CI	0 to 53.8	0 to 186

Unlike European relatives the risk of inflammatory bowel disease is not obviously increased in relatives of South Asian patients.

colitis among siblings would have been 2521/10⁵ (95% CI 934 to 5400), comparable with that in siblings of European patients with ulcerative colitis. Once again the three categories of first degree relatives were combined for analysis. The comparative risk to relatives of South Asian patients was 3.5 (95% CI 0.5 to 25.7).

In Europeans, the mean family size was 3.3 offspring and the mean position of the proband was 2.1. The mean family size among South Asians was 5.2 offspring and the mean position of the proband was 3. Proposit tended to be the middle born of the family.

Most affected relatives lived in Leicestershire; four patients had affected siblings outside the country, one in Wales, one in Scotland, one in Derby and one in Kettering. One patient's affected parent lived in Nottingham.

Discussion

This study reports the prevalence of inflammatory bowel disease in Leicestershire and assesses the comparative risk to first degree relatives of patients. Its community based nature averts the inherent selection bias of hospital based series. All people with inflammatory bowel disease aged 15–80 years from a population of approximately 900 000 were approached. This design provides a wide spectrum of socioeconomic backgrounds and ethnic states.

TABLE IV Prevalence of inflammatory bowel disease in Europe

Area of study	Prevalence/10 ⁵	
	Crohn's disease	*Ulcerative colitis
United Kingdom		
Bradford ¹⁰		
South Asians	78	59
Derby ²⁷	85	
High Wycombe ²⁵		70
Leicestershire ^{13,14}		
Europeans	76	128
South Asians	33	174
North Tees ¹⁸	35	99
Nottingham ²⁹	26.5	
Oxford ³⁰	9	79.9
Denmark ²¹	34	117
Germany ^{26,†}	54.6	24.8

The prevalence of inflammatory bowel disease, among Europeans in Leicestershire was comparable with that reported in other Europeans studies. *including proctitis, †excluding proctitis.

PREVALENCE OF INFLAMMATORY BOWEL DISEASE

The prevalence of Crohn's disease and ulcerative colitis in Europeans is comparable with that in other recent European studies,^{18, 24-27} although the values have increased since studies of the 1960s and 1970s^{28, 29} (Table IV). The prevalence of Crohn's disease in South Asians was marginally lower and that of ulcerative colitis much higher than in Findlay's study¹⁹ and probably reflects the different ethnic groups – in Leicester, predominantly Gujarati Hindus, and in Bradford, mainly Pakistani Moslems. Fellows *et al* did not report the prevalence among Asians in their study.²⁷

COMPARATIVE RISK

This study has shown that the risk of developing ulcerative colitis in first degree relatives of European patients with ulcerative colitis is increased about 15-fold, but there is no increased risk of developing Crohn's disease. In contrast, relatives of European patients with Crohn's disease are at a 17- to 35-fold risk of Crohn's disease and an increased risk of ulcerative colitis. This suggests that there is no common predisposition and ulcerative colitis and Crohn's disease have a different cause. The risk of Crohn's disease among relatives of South Asian patients with Crohn's disease is not increased whereas the risk of ulcerative colitis is. This probably reflects the low prevalence of Crohn's disease in this ethnic group.

There has been interest in familial aspects of inflammatory bowel disease since the 1960s.^{5, 30-32} There are only a few studies, however, which have measured the risk to first degree relatives.^{1-3, 8} These studies suggest that the risk of developing Crohn's disease may be 30-times greater in siblings than in the general population and the overall risk to first degree relatives is 13. Such studies do not show a simple Mendelian pattern of inheritance but suggest that the genetic predisposition may be explained by another model of inheritance. Kuster *et al*⁴ have performed complex segregation analysis on the family history of 387 patients with Crohn's disease and they suggested that the condition is due to a recessive gene with incomplete penetrance which may combine with environmental factors to determine disease susceptibility.

Studies from Copenhagen⁵ and Stockholm⁶ have shown that the risk of developing ulcerative colitis among patients' relatives is increased by eight to 15-fold. The prevalence of Crohn's disease, however, is only increased 3.5 times while relatives of patients with Crohn's disease seem to be at eight to 10 times the risk of developing ulcerative colitis. Orholm *et al*⁸ showed a 10-fold increase in the risk of first degree relatives of patients with ulcerative colitis developing ulcerative colitis, after standardisation for age. Similarly, the risk of developing Crohn's disease was increased in first degree relatives of patients with Crohn's disease. Although the risk of Crohn's disease was increased in relatives of patients with ulcerative colitis, this was not statistically significant. Based on the Swedish twin registry Tysk *et al*⁷ have shown that heredity is a stronger aetiological

factor in Crohn's disease than ulcerative colitis.

In an early study, Mayberry *et al*¹ also found the risk of Crohn's disease was increased in siblings of patients and suggested the risk of ulcerative colitis may also have been increased. If the Leicestershire prevalence values are applied to the Cardiff population they studied, the comparative risk of developing Crohn's disease to siblings was 21 (95% CI 10 to 44.7). The comparative risk of developing ulcerative colitis among the first degree relatives of patients with Crohn's disease was parents 7.9 (95% CI 2 to 31.8), siblings 10.1 (95% CI 3.4 to 27), and offspring over 15 years 7.3 (95% CI 1 to 51.4). This analysis of the data supports their suggestion that the risk of developing ulcerative colitis was increased in relatives of patients with Crohn's disease. The risk, however, was less than that for Crohn's disease. These findings are not inconsistent with those we now present although the risk seems greater in the Cardiff series. There are two explanations for this, firstly, the Cardiff series was smaller than ours and, secondly, as they acknowledge, the differentiation between ulcerative colitis and Crohn's colitis may be difficult. The misclassification of one case would have a large influence on the comparative risk when dealing with so few cases.

These findings confirm that first degree relatives of European patients are at substantially increased risk of developing the same form of inflammatory bowel disease, but probably not a different variety. This suggests that Crohn's disease and ulcerative colitis are separate conditions with similar, but different, genetic predispositions. An alternate explanation, however, that the two diseases are the same but there is a familial factor determining transition to Crohn's disease, cannot be ignored. The lack of risk to relatives of South Asian patients with Crohn's disease probably reflects the low prevalence of the disease in the community and, consequently, a small study group. The smaller increased risk in relatives of South Asian patients with ulcerative colitis may reflect the fact that many relatives still live overseas, often in India, where the condition seems less common. This suggests that their colitis may be misdiagnosed as infective diarrhoea or that they are not exposed to the appropriate environmental factor. In Britain, such environmental agents may interact with the genetic predisposition to give a high prevalence among South Asians.

These findings clearly support the view that Crohn's disease and ulcerative colitis arise in people with a specific genetic predisposition and who have been exposed to an environmental factor. Studies of these diseases in migrant communities may identify the environmental factor.

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