

Mortality in Inflammatory Bowel Disease: A Population-Based Cohort Study

TIM CARD,* RICHARD HUBBARD,*[†] and RICHARD F. A. LOGAN*

*Division of Epidemiology and Public Health, Medical School, Queen's Medical Centre; and [†]Division of Medical and Surgical Sciences, Nottingham City Hospital, University of Nottingham, Nottingham, United Kingdom

See editorial on page 1881.

Background & Aims: There is no consensus regarding any increase in mortality with inflammatory bowel disease (IBD). In general, previous studies were not contemporary and were unable to correct for likely confounders. We have performed a large cohort study to examine contemporary IBD related mortality in the United Kingdom. **Methods:** We selected subjects within the General Practice Research Database with a coded diagnosis of inflammatory bowel disease and up to 5 matched controls for each. We derived the date of recorded deaths and information on smoking and a variety of medical conditions. We calculated both the absolute risk of death and the relative risk as a hazard ratio corrected for available confounders by Cox regression. **Results:** We included 16,550 IBD cases with 1047 deaths and 82,917 controls with 3758 deaths. The mortality rate was 17.1 per 1000 person-years overall for IBD cases and 12.3 for controls; this difference was greatest in the elderly. Conversion of these figures to hazard ratios by Cox regression gave hazard ratios of 1.54 (1.44–1.65) for all IBD, 1.44 (1.31–1.58) for ulcerative colitis (UC), and 1.73 (1.54–1.96) for Crohn's disease. The greatest hazard ratio for UC was among the 40–59-year age group (1.79 [1.42–2.27]) and for Crohn's disease among 20–39-year-olds (3.82 [2.17–6.75]). **Conclusions:** IBD is associated with an overall small increase in mortality rate greatest in relative terms in younger subjects but in absolute terms in the elderly.

Knowledge of the prognosis of inflammatory bowel disease (IBD) is of immense importance both to people suffering from these conditions and to their physicians. This knowledge is also used by insurance companies who have been criticized for their loading (increasing premiums to balance a perceived higher risk) of life insurance policies for IBD patients.¹ At the present time, there is considerable uncertainty as to what if any increase in mortality is associated with IBD. Current esti-

mates range from a 40% decrease to a 70% increase in mortality with ulcerative colitis (UC)^{2,3} and from no increase to doubling in mortality with Crohn's disease (CD) (Table 1).^{4,5} These inconsistencies may be caused in part by the selected nature of cases studied, a failure to control for important confounders such as smoking and weight, and differences in the time periods studied. To address these issues, statistically powerful general population-based studies of contemporary mortality risk in IBD patients are clearly required.

The aims of our study therefore were to derive measures of the relative and absolute risk of death for patients with IBD in the United Kingdom. In addition, to more closely mirror the risk assessment made by life insurers, we compared mortality risks among those with and without IBD who did not have other common chronic diseases or malignancy. To achieve these aims, we have conducted a large study of mortality in the General Practice Research Database (GPRD).

Materials and Methods

The GPRD is the world's largest longitudinal, primary care database and contains approximately 50 million patient years of data collected from computerized U.K. general practices since 1987. To ensure data quality, contributing practices received data quality training and are audited to ensure that at least 95% of prescribing and morbidity events are included. The validity of diagnoses of IBD within this data set has been specifically assessed,⁶ and 92% of diagnoses recorded found to be accurate (the diagnoses of CD [94% accurate] and UC [93% accurate] were noted to be more reliable than those for indeterminate IBD [80% accurate]). Our IBD cohort consists of all persons within GPRD with at least 1 prospectively recorded event coded as relating to IBD and a general population (control) cohort consisting of up to 5 (if available) age-, sex-,

Abbreviations used in this paper: BMI, body mass index; CD, Crohn's disease; GPRD, General Practice Research Database; HR, hazard ratio; IBD, inflammatory bowel disease; UC, ulcerative colitis.

© 2003 by the American Gastroenterological Association

0016-5085/03/\$30.00

doi:10.1053/j.gastro.2003.09.029

Table 1. Previous Large Studies of All-Cause Mortality in IBD Patients

First author, year	Area	Period	Cohort	Deaths	Standardized mortality ratio (95% confidence interval)
UC					
Langholz, 1992 ¹⁹	Copenhagen	1962–1987	1104	121	107
Farrokhyar, 2001 ⁴	3 English districts in Midlands	1978–1986	356	41	103 (79–140)
Persson, 1996 ¹²	Stockholm	1955–1984	1547	255	137 (120–154)
Ekbom, 1992 ¹⁰	Uppsala, Sweden	1965–1983	2509	505	140 (120–150)
Palli, 1998 ²	Florence	1978–1992	689	47	62 (40–80)
Davoli, 1997 ¹⁴	Rome	1970–1989	508	27	98 (64–142)
Viscido, 2001 ²⁰	Italy	1964–1989	2066	93	100 (80–120)
Gyde, 1982 ³	Birmingham	1940–1976	676	141	170
CD					
Cottone, 1996 ¹⁵	Sicily, Italy	1973–1993	531	9	97 (40–180)
Farrokhyar, 2001 ⁴	3 English districts in Midlands	1978–1986	196	23	94 (59–140)
Persson, 1996 ¹²	Stockholm	1955–1984	1251		151 (129–175)
Weterman, 1990 ⁵	Leiden, Holland	1934–1984	659	64	223 (175–285)
Ekbom, 1992 ¹⁰	Uppsala, Sweden	1963–1986	1469	179	160 (140–190)
Palli, 1998 ²	Florence	1978–1992	231	23	136 (90–200)
Jess, 2002 ¹¹	Copenhagen followed	1967–1987	374	84	130 (101–150)
Mayberry, 1980 ²¹	Cardiff, UK	1930s–1970s	219	40	216

and practice-matched controls who had no record of IBD themselves and were alive and contributing data on the date of the case's first prospective record of IBD.

IBD type was classified based on Oxmis and Read coding. Subjects were classified as having indeterminate IBD if they had codes for both UC and CD, as having UC if codes both for nonspecific IBD and UC were present, and as having CD if codes for both this and for nonspecific IBD were found. Subjects having a diagnosis of IBD first coded at least 2 years after their collection of prospective data in GPRD began were considered to be incident cases. For each subject, we used a combination of Oxmis and Read coding and the subject's registration status within GPRD to assess whether they had died, using the earliest relevant date to define the date of death. We then extracted data on smoking habits, blood pressure recording, and body mass index (BMI). Subjects' smoking status was classified based on the coding within the data set as unknown, never smoker, not current smoker, ex-smoker, or current smoker. Subjects who appeared in more than 1 of these categories at differing times were coded in the category suggesting greatest smoking experience. Height, weight, and systolic blood pressure were coded as the median recorded level for each case, and BMI was calculated only for adults.

To allow adjustment for the effect of comorbidities we used 2 approaches. Firstly, we used the Charlson index⁷ as a composite measure of comorbidity for use as a confounder in multivariate analyses. For this subjects were scored based on comorbidities coded before entry to the study. Secondly, we formed "healthy" cohorts both of IBD cases and controls by excluding subjects with ischemic heart disease, heart failure, hypertension, chronic obstructive pulmonary disease, asthma, renal disease, any malignancy, and diabetes. The presence of these conditions was assessed by using a combination of Oxmis and Read codes, with analysis again limited to disease recorded

before entry to the study. We then carried out analyses in these restricted cohorts. As well as stratifying for comorbidity, these cohorts approximately illustrate the risks of subjects unloaded for life insurance for reasons other than IBD.

Statistical Analysis

Univariate analysis of mortality using the matched cohort design was conducted by the production of crude mortality rates, survival plots, and by log rank tests. In each case, the origin of the time axis and the entry of the subject to the study were both set as the date of the first prospectively recorded IBD code (the matched case's relevant date was used for controls). Multivariate analyses were conducted by using a Cox regression model, and the validity of the assumption of proportional hazards was assessed by using Log Log plots. Because age, sex, and smoking are all known to be associated with both the risk of IBD and the risk of death, they were all included within our models on an a priori basis. Other potential confounding factors added to this base model were retained only if they resulted in a 10% or greater change in the hazard ratio. For BMI and blood pressure as for smoking, the confounding variable was included in the analysis as a categorical variable with a category representing missing data. The multivariate analyses were repeated stratifying both for disease type and age group at entry. Tests for interaction by these groups were performed. In addition, restriction analyses were performed to examine the risks among incident cases of IBD, prevalent cases, and those with a recorded date of first diagnosis at least 5 years before entry to the study (i.e., prevalent cases with at least a 5-year history). A further restriction analysis was performed after exclusion of all subjects with the chronic diseases specified previously.

To check the robustness of our results, we attempted to increase diagnostic specificity by limiting our analyses to cases with at least 2 episodes coded as IBD. To examine the reli-

Table 2. Demographic Details of Cases and Controls Subdivided by Disease Type

IBD type	All IBD		UC		CD		Indeterminate	
	Case	Control	Case	Control	Case	Control	Case	Control
Number N	16,550	82,917	8301	41,589	5960	29,843	2289	11,485
Female %	53.6	53.7	48.9	48.9	58.7	58.8	57.2	57.3
Male %	46.4	46.3	51.1	51.1	41.3	41.2	42.8	42.7
Age at entry								
Under 20%	5.4	5.4	3.2	3.2	8.2	8.2	5.9	5.9
20–39%	38.7	38.6	34.4	34.3	44.5	44.4	39.3	39.0
40–59%	32.2	32.1	35.4	35.3	28.2	28.2	30.8	30.5
60–79%	19.8	20.0	22.8	23.0	15.7	15.9	19.8	20.0
≥80%	3.9	4.0	4.1	4.3	3.3	3.4	4.3	4.6
Mean	46.16	46.3	48.59	48.74	42.8	42.89	46.07	46.31
SE	0.14	0.06	0.19	0.09	0.24	0.11	0.39	0.18
% incident	34		33		31		46	
Mean age at diagnosis	47.3		50.0		43.0		47.5	
% prevalent	66		67		69		54	
Mean age at diagnosis	39.7		41.8		36.6		41.1	

ability of death recording within GPRD and the possibility of bias within it (because of the possibility that controls may be more likely to move away without their GP knowing, and therefore more likely to die without it being recorded), we repeated the analysis excluding all subjects with no recorded medical data dated within the last year of their data. Because a diagnosis is more likely to be recorded at a time when it is causing ill health (even if it is a long-standing condition) we examined the effect of censoring data for 1 or 2 years from the date of entry to the study. Lastly, to investigate whether misclassification of ex-smokers as nonsmokers may have affected our results, we performed an analysis limited to current smokers. All analyses were conducted using Stata version 7 (Stata Corp., College Station, TX).

Results

In total, the study included 16,550 people with IBD and 82,917 appropriately matched controls. Within the IBD cohort, 5960 people had CD, 8301 had ulcerative colitis, and 2289 had indeterminate IBD. The average age at entry to the study was 46 years for both IBD cases and controls, and 46% of each cohort were men. Among the IBD cases, 5631 (34%) were incident and 10,919 (66%) were prevalent. The age at diagnosis was lower among the prevalent cases with a mean of 40 years compared to 47 years in incident cases (Table 2).

The IBD cohort had a slightly but statistically significantly lower mean systolic blood pressure (130.1 mm Hg compared with 132.6 mm Hg) and BMI (24.7 compared with 25.5) than did the controls (Table 3). They were also less likely to have a systolic blood pressure over 160 mm Hg (7.8% of the IBD cohort vs. 8.9% of the control cohort) or a BMI over 35 (1.6% vs. 2%) (Table 3). With respect to smoking, the relationship

varied between IBD types with smoking being more common among Crohn's cases than among the control cohort (28% smokers vs. 21% of their matched controls) and less common among UC cases (12% vs. 20%); indeterminate cases had intermediate levels of smoking (22% vs. 21%).

The IBD cohort contributed 61,215 years of follow-up and 1047 deaths and controls 306,183 years of follow-up and 3758 deaths. These corresponded to crude mortality rates of 17.1 per 1000 person years for cases and 12.3 per 1000 patient years for controls. A breakdown of deaths, follow-up available, and crude rates by disease and age at entry to the study are given in Table 4. These small excesses of mortality are shown graphically by Kaplan–Meier plots in Figure 1. Expressing these results as hazard ratios via a univariate Cox regression model showed hazard ratios of 1.39 (1.30–1.49) for all IBD, 1.27 (1.16–1.40) for UC, 1.62 (1.44–1.83) for CD, and 1.40 (1.17–1.66) for indeterminate IBD.

In the multivariate Cox regression analysis, we included age at entry to the study, sex, and smoking as confounders on an a priori basis. No appreciable further confounding either by Charlson index score, BMI, or systolic blood pressure was found, and hence these were not included in the final model. Overall, we found a hazard ratio for death among subjects with IBD of 1.54 (1.44–1.65) when corrected for age, sex, and smoking habits. Within this model, the hazard ratio for death associated with male sex was 1.41 (1.33–1.50) and for being a current smoker (compared with a never smoker) was 1.96 (1.57–2.45). Subdividing IBD cases by disease type showed that the hazard ratio was greater for CD at 1.73 (1.54–1.96) and that it was lower for ulcerative

Table 3. Levels of Systolic Blood Pressure, BMI, and Smoking Expressed as Percentage of Subjects Within Each Specified Group

	All IBD		UC		CD		Indeterminate	
	Case (%)	Control (%)	Case (%)	Control (%)	Case (%)	Control (%)	Case (%)	Control (%)
Systolic BP								
Under 100	1	1	1	1	2	1	1	1
100–119	20	16	16	14	24	18	22	17
120–139	30	27	31	27	28	27	30	28
140–159	18	18	21	20	14	15	17	18
Over 160	8	9	9	10	7	7	8	9
Unknown	24	30	23	29	26	32	22	28
Mean	130	133	132	134	127	130	129	132
SE	0.2	0.1	0.2	0.1	0.3	0.1	0.5	0.2
BMI								
<19	3	2	2	2	5	2	3	2
19–24	33	27	32	26	35	27	33	27
25–29	18	19	21	20	15	17	19	19
30–34	5	6	6	6	4	5	5	6
>35	2	2	2	2	2	2	1	2
Unknown	39	46	38	45	40	47	38	44
Mean	25	25	25	26	24	25	25	25
SE	0.04	0.02	0.06	0.03	0.08	0.04	0.12	0.06
Smoking								
Never smoker	3	3	3	3	2	3	3	3
Nonsmoker	42	37	48	37	35	37	41	37
Ex-smoker	5	4	7	4	4	4	5	4
Current smoker	19	21	12	20	28	21	22	21
Unknown	30	36	31	36	30	36	29	35

Table 4. Deaths, Follow-up Time (in Thousands of Years), Crude Mortality Rates, and Mortality Rate Differences Between Cases and Controls by Disease Type and Age Band Expressed as Deaths per Thousand Person Years

IBD type	Age group	Case					Control					Rate difference/ 1000 person years
		Deaths	Follow-up (/1000 years)	Mortality rate	95% Confidence interval		Deaths	Follow-up (/1000 years)	Mortality rate	95% Confidence interval		
All UC	All	1047	61.2	17.1	16.1	18.2	3758	306.2	12.3	11.9	12.7	4.8
	Under 20	0	0.9	0.0	—	—	0	4.3	0.0	—	—	0.0
	20–39	15	10.6	1.4	0.9	2.4	46	51.3	0.9	0.7	1.2	0.5
	40–59	95	12.0	7.9	6.5	9.7	297	59.1	5.0	4.5	5.6	2.9
	60–79	290	6.8	42.6	38.0	47.8	1167	35.3	33.0	31.2	35.0	9.6
	80 or over	136	0.8	161.8	136.8	191.4	586	4.8	122.6	113.1	132.9	39.2
	Total	536	31.1	17.3	15.9	18.8	2096	154.8	13.5	13.0	14.1	3.7
CD	Under 20	2	1.6	1.2	0.3	4.9	2	8.0	0.3	0.1	1.0	1.0
	20–39	22	9.4	2.3	1.5	3.6	27	46.2	0.6	0.4	0.9	1.8
	40–59	58	6.6	8.7	6.8	11.3	163	33.3	4.9	4.2	5.7	3.8
	60–79	187	3.4	55.1	47.7	63.6	591	18.6	31.8	29.3	34.5	23.3
	80 or over	82	0.5	160.0	128.8	198.6	312	3.0	104.0	93.1	116.3	55.9
	Total	351	21.6	16.3	14.6	18.0	1095	109.2	10.0	9.5	10.6	6.2
	Indeterminate	Under 20	0	0.5	0.0	—	—	1	2.5	0.4	0.1	2.8
20–39		4	3.4	1.2	0.5	3.2	16	15.9	1.0	0.6	1.6	0.2
40–59		28	2.8	10.2	7.0	14.7	59	13.8	4.3	3.3	5.5	5.9
60–79		87	1.7	51.5	41.7	63.6	316	8.6	36.7	32.8	40.9	14.9
80 or over		41	0.2	198.9	146.5	270.1	175	1.4	129.6	111.7	150.3	69.3
Total		160	8.5	18.8	16.1	21.9	567	42.2	13.5	12.4	14.6	5.3

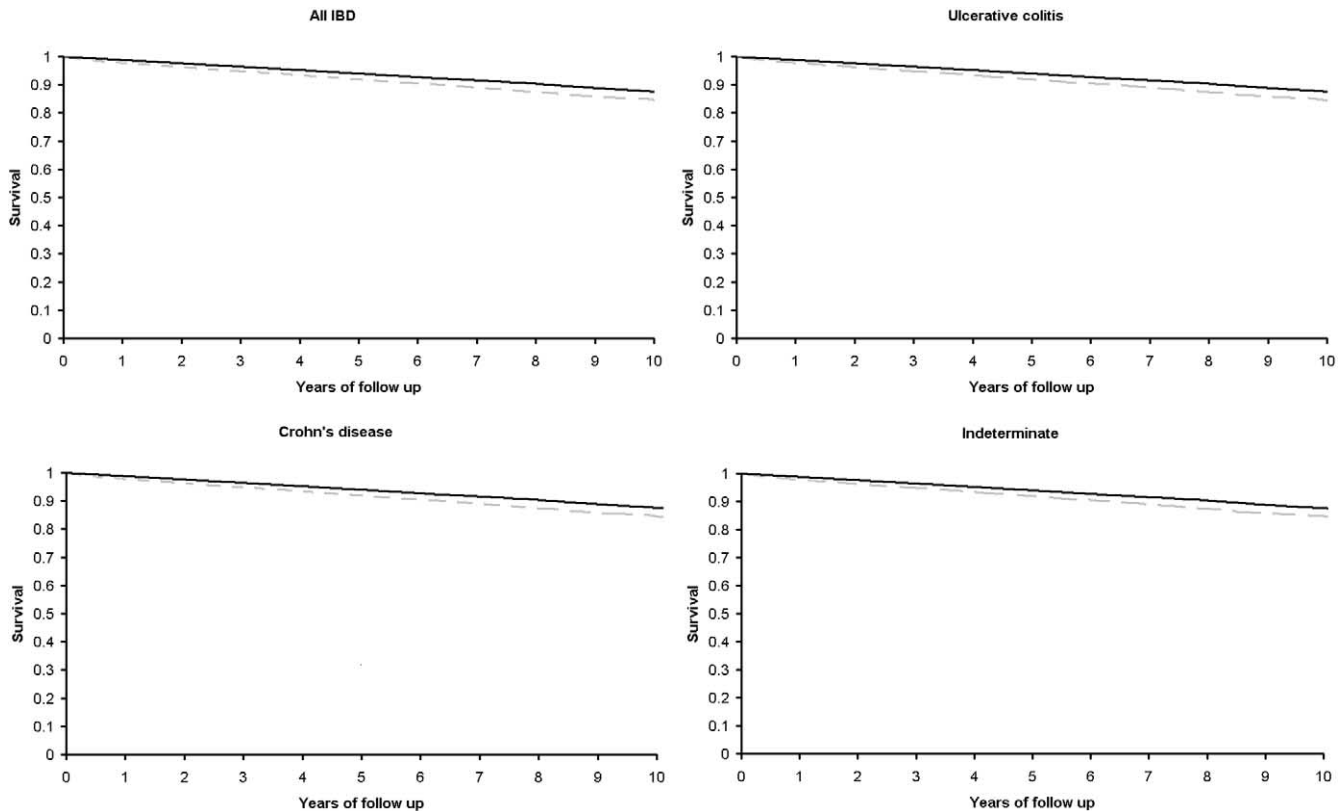


Figure 1. Kaplan-Meier survival plots of all IBD patients, UC, CD, and indeterminate IBD patients against their respective matched control populations (Cases: *dashed lines*, Controls: *solid line*).

colitis (1.44 [1.31–1.58]). There was no statistically significant evidence of interaction between the effects of sex or smoking behavior and IBD, but such interaction was detected for age group (Table 5). The hazard ratio for death associated with inflammatory bowel diseases was in general larger among younger age groups, although there were few deaths available for study in the youngest age groups.

Table 6 shows a series of analyses limited to subsets of the available data. The hazard ratios are reduced slightly if the analysis is limited to subjects with 2 or more coded episodes of IBD (hazard ratio 1.37 for UC, 1.53 for CD, and 1.31 for indeterminate disease) and are similarly reduced if subjects having no medical codes entered in the final year for which they contributed are excluded or if the first year of each subject's data after entry is censored (censoring of 2 rather than 1 year made no appreciable additional difference). The limitation of the analysis to prevalent cases diagnosed at least 5 years before entry to the study slightly reduces the hazard ratio for CD (1.58) but increases it for UC (1.49); further restricting analysis to cases diagnosed at least 5 years before entry to the study accentuates this change in UC. If only subjects without previously diagnosed heart,

Table 5. Hazard Ratios for Death by Age Group and Type of IBD Derived From Cox Regression Models Corrected for the Effects of Sex and Smoking

Age at entry (yr)	Deaths among cases	Hazard ratio	95% Confidence interval	
UC				
All ages	536	1.44	1.31	1.58
Under 20	0	1.00	—	—
20–39	15	1.68	0.94	3.02
40–59	95	1.79	1.42	2.27
60–79	290	1.37	1.20	1.56
80 or over	136	1.37	1.20	1.56
CD				
All ages	351	1.73	1.54	1.96
Under 20	2	5.30	0.74	37.87
20–39	22	3.82	2.17	6.75
40–59	58	1.80	1.33	2.43
60–79	187	1.73	1.47	2.04
80 or over	82	1.49	1.17	1.90
Indeterminate				
All ages	160	1.56	1.31	1.86
Under 20	0	0.00	—	—
20–39	4	1.31	0.44	3.94
40–59	28	2.49	1.59	3.91
60–79	87	1.46	1.15	1.86
80 or over	41	1.46	1.03	2.05

Table 6. Cox Regression Models Corrected for Age, Sex, and Smoking for Subgroups of Cases and Their Matched Controls as Specified

	UC			CD			Indeterminate		
	HR	95% Confidence interval		HR	95% Confidence interval		HR	95% Confidence interval	
All subjects	1.44	1.31	1.58	1.73	1.54	1.96	1.56	1.31	1.86
2 or more episodes of IBD coded	1.37	1.22	1.53	1.53	1.33	1.76	1.31	1.01	1.69
First year of data censored	1.37	1.22	1.53	1.58	1.37	1.82	1.21	0.97	1.52
2 or more episodes and 1 year censored	1.36	1.20	1.55	1.50	1.28	1.75	1.16	0.86	1.57
Incident cases only	1.32	1.10	1.58	2.21	1.77	2.77	1.87	1.42	2.45
Prevalent cases only	1.49	1.33	1.66	1.58	1.37	1.82	1.38	1.09	1.73
Cases > 5 years post diagnosis at entry	1.69	1.42	2.01	1.58	1.26	1.98	1.27	0.76	2.1
Subjects without specified morbidity ^a	1.83	1.54	2.17	2.33	1.89	2.88	1.97	1.43	2.72
Excluding subjects with PSC	1.41	1.28	1.55	1.74	1.54	1.96	1.54	1.29	1.84
Excluding subjects with no medical data coded in their last year	1.32	1.20	1.45	1.61	1.43	1.82	1.45	1.22	1.73

^aSpecified morbidities are any record of ischemic heart disease, heart failure, hypertension, COPD, asthma, renal disease, any malignancy, and diabetes.

lung, or renal disease; malignancy; hypertension; or diabetes are included, a rather larger increase in hazard is seen (hazard ratios 1.83 for UC and 2.33 for CD). Finally, analysis limited to current smokers slightly increases the hazard ratio for CD (1.90).

Discussion

This study of deaths in over 16,000 IBD patients is the largest of IBD mortality published to date and includes 1047 deaths among IBD cases. It has shown that in contemporary clinical practice IBD patients do have a small increase in mortality rate of about 0.5% per annum greater than an age- and sex-matched general population. This excess mortality is not removed by correction for confounding by smoking in a multivariate Cox regression nor is it limited to the initial period after diagnosis of the condition because subjects with at least 5 years of disease before entry to the study have an only slightly lower hazard than do the entire IBD cohort. Overall, the hazard associated with CD (hazard ratio [HR] 1.73) is slightly greater than is that of UC (HR 1.44).

This study is the first to compare IBD patients with both a healthy and a general population. After exclusion of subjects with a history of malignancy or of a number of common chronic diseases associated with increased mortality, we have shown a hazard ratio of around 2 for death among IBD patients. The size of this study also allows examination of the effect of age in greater detail than has previously been possible, and in this respect, it is important to note that, although the hazard ratios are greatest for these diseases among young people, the absolute risk difference is higher among older age groups.

Aside from the benefits that it derives from greater power and the correction of confounding by smoking, our study has some other advantages. First, it is likely to better represent the national (as opposed to regional or even center-based) mortality experience of IBD patients than are previous studies that have been limited to specific areas within a nation. Also because, in contrast to most other population-based studies, we have included both prevalent and incident cases, it is better able to reflect the mortality because of late complications of IBD (such as malignancy) than are previous studies. Finally, because our study is based on data purely from 1987 to 2001, it is more representative of current rather than historical levels of risk, which is of importance in view of the fall in mortality certified as caused by IBD over recent decades,⁸ despite the rise in incidence of these diseases.

There are, however, some limitations to our study. First, we were unable to individually validate the diagnoses of all the cases. Nonetheless, the diagnosis of IBD has previously been validated within the GPRD and been found to be robust.⁶ Furthermore, when we limited our analyses to cases with at least 2 coded episodes of IBD (for whom greater validity might be expected), we did not see appreciable changes in the hazard ratios calculated. Second, there may be a chance that control deaths might be underreported if controls are more likely than cases to move without informing their general practitioner (a chronic disease might well keep one in greater touch with one's doctor). Against this, when we excluded subjects with no events recorded in their last year of data, there was little change and so this potential bias is unlikely to be important. The data on confounders such as smoking are clearly incomplete. It is possible that this

has resulted in some uncorrected residual confounding, but this should be considerably less than in previous studies without data on these factors. It is also important to note that there is potential for bias with respect to which subjects have missing data (which has been shown to occur in a validation of smoking data within GPRD⁹); our analysis strategy by including a category for missing data rather than ignoring affected subjects minimized the potential influence of this. To investigate whether this was a problem specifically with respect to smoking, we performed an analysis limited to current smokers (for whom there is reason to believe the data are most valid⁹) and found that this did not greatly alter our results. As for all studies of this type, because cases present preferentially when they are most unwell, and therefore at greatest risk of death, the earliest part of the follow-up may carry a higher risk of death. In contrast to most other studies, we were able to show that this effect, although real, is not great because the censoring of the first year of follow-up only slightly reduces the hazard ratios found. Finally, the use of prevalent as well as incident cases within the study has potential to cause bias because those prevalent subjects not detected and therefore not included may differ from those who are included. Within this data set, because patients do not in general choose a general practitioner for reasons related to illness, this is most likely to occur if those susceptible to death because of IBD die early in the course of their disease (leading to a bias towards a healthier cohort) or if those with mild or quiescent disease among the prevalent cases cease to consult their general practitioner and are therefore at increased chance of being missed (leading to a bias toward a less healthy cohort). The analyses restricted to incident cases and to prevalent cases show that there is some difference between the mortality experienced by these groups with incident cases experiencing in general greater mortality for CD and lower for UC; however, the confidence intervals for these restricted analyses do not exclude the findings from the total cohort.

Our results are consistent with some other population-based studies of IBD mortality reported in the last decade that have shown standardized mortality rates from 1.3 to 1.6 for CD^{10,11} and of 1.4 for UC,^{10,12} although these studies included data from as early as the early 1960s. Other studies from Britain^{4,13} and Italy^{14,15} based on more recent data have failed to show any significant excess mortality. The studies finding no excess mortality have in general, however, been small (none of the cited examples containing more than 100 deaths) and have also been largely limited to the early years of incident disease. Among the differences between our results and those of previous studies of particular interest

is the fact that hazard ratios for death for UC are greater among those with a long disease history (at least 5 years of disease). This is in contrast to the early descriptions of UC mortality in which this was greatest in the early period¹⁶ and may well reflect improved acute disease management over the years, allowing patients to survive to experience the longer-term risks of the disease such as malignancy. It is equally notable that for CD the mortality hazard does not rise with prolonged disease as was once the case,¹⁷ perhaps suggesting improved long-term management.

In summary, our study suggests that there is a 54% excess mortality associated with a diagnosis of IBD. In relative terms this effect is most marked in the young. This excess is smaller than that associated with smoking within our study (96% excess for current versus never smokers) and is comparable to the excess associated with male sex (41%) or that reported in the United Kingdom for manual versus nonmanual occupations in the United Kingdom (48% excess).¹⁸

References

1. Travis SP. Review article: insurance risks for patients with ulcerative colitis or Crohn's disease. *Aliment Pharmacol Ther* 1997; 11:51-59.
2. Palli D, Trallori G, Saieva C, Tarantino O, Edili E, D'Albasio G, Pacini F, Masala G. General and cancer specific mortality of a population based cohort of patients with inflammatory bowel disease: the Florence Study. *Gut* 1998;42:175-179.
3. Gyde S, Prior P, Dew MJ, Saunders V, Waterhouse JA, Allan RN. Mortality in ulcerative colitis. *Gastroenterology* 1982;83:36-43.
4. Farokhyar F, Swarbrick ET, Grace RH, Hellier MD, Gent AE, Irvine EJ. Low mortality in ulcerative colitis and Crohn's disease in three regional centers in England. *Am J Gastroenterol* 2001;96:501-507.
5. Weterman IT, Biemond I, Pena AS. Mortality and causes of death in Crohn's disease. Review of 50 years' experience in Leiden University Hospital. *Gut* 1990;31:1387-1390.
6. Lewis JD, Brensinger C, Bilker WB, Strom BL. Validity and completeness of the General Practice Research Database for studies of inflammatory bowel disease. *Pharmacoepidemiol Drug Saf* 2002;11:211-218.
7. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-383.
8. Sonnenberg A. Mortality from Crohn's disease and ulcerative colitis in England-Wales and the U.S. from 1950 to 1983. *Dis Colon Rectum* 1986;29:624-629.
9. Hubbard R, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis: a population-based cohort study. *Am J Respir Crit Care Med* 2000;161:5-8.
10. Ekbohm A, Helmick CG, Zack M, Holmberg L, Adami HO. Survival and causes of death in patients with inflammatory bowel disease: a population-based study. *Gastroenterology* 1992;103: 954-960.
11. Jess T, Winther KV, Munkholm P, Langholz E, Binder V. Mortality and causes of death in Crohn's disease: follow-up of a population-based cohort in Copenhagen County, Denmark. *Gastroenterology* 2002;122:1808-1814.
12. Persson PG, Bernell O, Leijonmarck CE, Farahmand BY, Hellers G, Ahlborn A. Survival and cause-specific mortality in inflamma-

- tory bowel disease: a population-based cohort study. *Gastroenterology* 1996;110:1339–1345.
13. Probert CS, Jayanthi V, Wicks AC, Mayberry JF. Mortality from Crohn's disease in Leicestershire, 1972–1989: an epidemiological community based study. *Gut* 1992;33:1226–1228.
 14. Davoli M, Prantera C, Berto E, Scribano ML, D'Ippoliti D. Mortality among patients with ulcerative colitis: Rome 1970–1989. *Eur J Epidemiol* 1997;13:189–194.
 15. Cottone M, Magliocco A, Rosselli M, Pinzone F, Oliva L, Orlando A, Aiala MR, Cipolla C, Pagliaro L. Mortality in patients with Crohn's disease. *Scand J Gastroenterol* 1996;31:372–375.
 16. Edwards FC, Truelove SC. The course and prognosis of ulcerative colitis. *Gut* 1963;4:299–315.
 17. Truelove SC, Pena AS. Course and prognosis of Crohn's disease. *Gut* 1976;17:192–201.
 18. Harding S, Bethune A, Maxwell R, Brown J. Mortality trends using the longitudinal survey. In: Drever F, Whitehead M, eds. *Health inequalities: decennial supplement*. London: The Stationery Office, 1999:143–155.
 19. Langholz E, Munkholm P, Davidsen M, Binder V. Colorectal cancer risk and mortality in patients with ulcerative colitis. *Gastroenterology* 1992;103:1444–1451.
 20. Viscido A, Bagnardi V, Sturniolo GC, Annese V, Frieri G, D'Arienzo A, Papi C, Riegler G, Corrao G, Caprilli R. Survival and causes of death in Italian patients with ulcerative colitis: a GISC nationwide study. *Dig Liver Dis* 2001;33:686–692.
 21. Mayberry JF, Newcombe RG, Rhodes J. Mortality in Crohn's disease. *Q J Med* 1980;49:63–68.

Received April 30, 2003. Accepted September 4, 2003.

Address requests for reprints to: Tim Card, M.D., University of Nottingham, Division of Epidemiology and Public Health, Queen's Medical Centre, Nottingham, UK NG7 2UH. e-mail: tim.card@nottingham.ac.uk; fax: (44) 0115-9709316.

Supported by a project grant from the National Association for Colitis and Crohn's Disease (NACC). Dr. Card is a Wellcome Research Training Fellow in Clinical Epidemiology (number 060529).

We would like to thank both NACC and the Wellcome Trust for their financial support. We would also like to thank Janice Gillard for her help in preparing the manuscript, and Joe West for his comments.

Doppler of the Doppler Ultrasound Effect



Image courtesy of Molecular Expressions (<http://microscopyfsu.edu>).

Christian Johann Doppler (1803–1853) was born in Salzburg, Austria, the son of a stone mason. His frail physique kept him from following his father's occupation, so he enrolled in a course of mathematics at the Polytechnique Institute in Vienna. Unable to obtain a suitable job after graduation, he proposed to emigrate to the United States. He changed his mind, however, when offered a teaching position at a secondary school in Prague. Later, he succeeded his mentor Simon Stampfer as professor of mathematics and practical geometry at the Polytechnique Institute. In 1842, he presented a paper on changes in the frequency of light waves dependent on the distance from the source to the observer. His aim was to explain the perceived color of starlight; incidentally, he mentioned the same effect might apply to sound waves. His theory was not well received and was challenged by Buys Ballot, a graduate student at Utrecht. It was Ballot, not Doppler, who devised an experiment using buglers sounding a predetermined note on a fast-moving train. This confirmed the principle that the pitch of a given tone sounded higher as the train was approaching the hearer and diminished as the source receded. Thus justified, in 1850 Doppler was appointed professor of experimental physics by Emperor Franz Josef, but by this time Doppler was gravely ill with tuberculosis. He sought relief in what he thought might be the more salubrious climate of Venice, where he died at age 50. A century passed before application of the Doppler effect to the cardiovascular system was conceived by S. A. Satamura, who hypothesized that ultrasonic waves reflected by moving blood cells could provide a noninvasive means of detecting the direction and velocity of blood flow, a technique now widely employed in the diagnosis of various circulatory disorders, including those of the portal venous system.

—Contributed by WILLIAM S. HAUBRICH, M.D.
Scripps Clinic and Research Foundation, La Jolla, California