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The pattern of underlying cause of death in patients with inflammatory bowel disease in England: a record linkage study.

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Short title

Causes of death in IBD.

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Abbreviations:

IBD	Inflammatory bowel disease
UC	Ulcerative colitis
CD	Crohn's disease
CPRD	Clinical Practice Research Datalink
CI	Confidence Interval

Abstract

Background and Aims

Numerous studies have established that mortality risk in IBD patients is higher than the general population, but the causes of death have seldom been examined. We aimed to describe causes of death in IBD.

Methods

A matched cohort study using UK general practice data from Clinical Practice Research Datalink linked to death registration records. We described the distribution of causes of death among IBD patients by age at death and time since IBD diagnosis. We estimated age-specific mortality rates and hazard ratios of death in multivariable Cox proportional hazards models.

Results

20,293 IBD patients were matched to 83,261 non-IBD patients. The mortality rate was 40% higher in IBD patients (2005 deaths) than in non-IBD patients (6024 deaths) (adjusted overall hazard ratio = 1.4, 95% CI = 1.4—1.5), with greater risk of death in Crohn's disease (hazard ratio = 1.6, 1.5—1.7) than in ulcerative colitis (1.3, 1.3—1.4). Causes attributable to IBD constituted 3.7% of all deaths in ulcerative colitis and 8.3% in Crohn's disease. Among IBD patients, death was less likely to be due to circulatory, respiratory or neoplastic diseases than non-IBD patients. In both IBD and non-IBD patients all these causes became more clinically important with advancing age, with the commonest neoplastic cause of death being lung cancer, rather than gastrointestinal cancers.

Conclusion

IBD patients have an additional risk of death. Most IBD patients die of circulatory or respiratory causes, and the contribution to mortality from long-term complications of IBD are clinically less important.

Keywords. Epidemiology

Introduction

Inflammatory bowel diseases (IBD) are of increasing importance at the population level, both because of their rising incidence [1] and the increasing medical costs of managing the significant morbidity they cause [2]. They are also of importance because of their associated additional mortality.

More than a decade ago we published mortality data from the United Kingdom (UK), based on an analysis of records from 16,550 IBD patients with 1,047 deaths and 82,917 matched controls with 3,758 deaths from the Clinical Practice Research Datalink (CPRD, then known as General Practice Research Database GPRD) [3]. We found IBD to be associated with a 54% increase in mortality; and the increase was higher in Crohn's disease (CD) (hazard ratio (HR):1.73, (95% confidence interval (CI): 1.54-1.96), than in ulcerative colitis (UC) (HR:1.44; 95% CI: 1.31-1.58). Since then other studies have found lower mortality rates. A large population-based study [4] from Denmark has shown that CD patients had a 50% greater mortality and UC patients a 10% greater mortality than the general population. A recent meta-analysis[5] has shown an excess mortality of 19% and 38% in UC and CD patients respectively. It is clear from these studies taken together however that IBD is associated with a clinically important increase in mortality in many population.

Far less clear are the causes of death and how they vary over time. A recent linkage of CPRD to official records of cause of death, as well as the passage of time allow us to address both of these questions.

Methods

Data source

The CPRD is the world's largest database of anonymised, longitudinal primary care medical records. It contains over 13 million active patient records, drawn from approximately 650 primary care practices across the UK since 1987, covering 5–10% of the UK population. Within this dataset about 50% of practices have agreed that their data be linked to other national datasets, including death records from the Office for National Statistics. There is good evidence that CPRD is representative of the UK population in terms of age and sex[6], and that the levels of morbidity shown within the data are representative of those seen within the UK IBD population[7].

Subjects and data extraction

In the UK, general practitioners would not themselves diagnose and manage IBD. Patients presenting with relevant symptoms are referred by their general practitioners to gastroenterologists for further investigations and diagnosis. A diagnosis of IBD in CPRD therefore represents a communication to primary care of a diagnosis confirmed in secondary care. Patients with diagnostic codes for inflammatory bowel disease (IBD) were identified from linked CPRD practices only, using records between January 1987 and January 2011, and were individually matched by primary care practice, sex and date of birth (within one year) to up to five subjects without any records of IBD diagnosis to create a study cohort. The index date for each IBD patient, defined as the later of the date entering CPRD or the date of the earliest record of an IBD diagnosis, was constrained to fall between the dates entering and leaving CPRD in the matched non-IBD patients to ensure some overlap of observation time between the matched pairs.

From these records we extracted diagnosis of IBD classified as UC, CD (defined as patient with either CD or UC codes but not both in their history diagnosis) or unclassified (defined a

patients with both UC and CD in their history diagnosis code). We also extracted for each subject age, body mass index (based on average lifetime body mass index records) and smoking status (highest recorded level of, from the highest level to the lowest, "current", "ex-smoker", "non-smoker or "unknown").

We obtained from the Office for National Statistics linked records of deaths occurring between 1st January 1998 and 10th January 2012. From these we extracted date and cause of death. We only considered "the underlying cause of death" which is considered to be the cause which "initiated the sequence of events leading directly to death and prevention of which will result in the greatest health gain from a public health point of view"[8].

Statistical analysis

Starting follow up from the later of 1/1/98 and the index date, we estimated the age-specific mortality rate for IBD patients and their matched non-IBD patients. Estimates of HR of death among IBD patients relative to non-IBD patients were adjusted for age at diagnosis, body mass index category and tobacco use status in Cox proportional hazards models.

We examined the pattern of mortality among patients with CD or UC by classifying the underlying cause of death into one of the following groups: gastrointestinal, circulatory and respiratory, neoplastic, haematological, infective, and other specified causes. We also described the distribution of causes of death among IBD patients by age at death and time since IBD diagnosis.

Ethics approval

This project is covered under the ethical approval granted for studies in CPRD and received regulatory approval from the Independent Scientific Advisory Committee for MHRA database research (protocol number 10-147).

Results

We identified 20,293 IBD patients from CPRD consultations records, who were matched to 83,261 non-IBD patients (Table 1). Patients with CD were younger (mean age at diagnosis 42.4 years) than patients with UC (49.3 years) or non-IBD patients (45.5 years). UC patients were more likely to be male (49.0%) than CD (43.7%) and non-IBD patients (46.5%). CD patients were more likely to be underweight with 5.0% of patients having a recorded body-mass index (BMI) of under 18.5, compared to only 2.7% of UC and 2.8% of non-IBD patients. Most IBD patients were not current smokers (40.4% in CD, 49.3% in UC) reflecting the general public trend (45.9% in non-IBD). The prevalence of current smokers in the CD cohort was much higher than in the UC cohort (37.4%, versus 22.2%).

The overall mortality rate was 14.3 per 1,000 person-years among IBD patients (95% CI: 13.7-14.9) and 11.1 per 1,000 person-years in non-IBD patients (95% CI: 10.8-11.3), implying the mortality rate in IBD patients was around 40% higher than in non-IBD patients (HR: 1.4, 95% CI: 1.4-1.5) (Table 2). The age-specific mortality rates increased with age in both IBD and non-IBD patients, though this increase was steeper in IBD patients such that the absolute difference in mortality rates was greater in the elderly. For example, in CD patients aged under 20 years the absolute mortality rate was 0.8 per 1,000 person-years (compared to 0.1 per 1,000 person-years in non-IBD patients), and in UC patients of the same age the absolute mortality rate was 1.9 per 1,000 person-years (compared to 0.2 per 1,000 person-years in non-IBD patients). In contrast the mortality rate in those over 80 years of age was 190.0 per 1,000 person-years for CD patients and 182.3 per 1,000 for those with UC. Again these rates were higher than in matched non-IBD patients with rates of 133.0 and 126.3 per 1000 person years respectively. Unlike the absolute differences in mortality, the age-specific hazard ratios for mortality in IBD patients relative to non-IBD patients were large in young patients but the ratios decreased with age such that the adjusted HR for mortality rate in IBD was highest in patients diagnosed before

the age of 20 years (CD, 8.8, 95% CI: 0.8-97.5 and UC, 13.6, 95% CI: 1.4-129.9) These contrasting trends are illustrated in Table 2 and Figures 1,2 and 3.

Tables 3, 4 and 5 set out the causes of death recorded by age at death for IBD patients and controls (tables 3 and 4), and by time since diagnosis in IBD patients (table 5).

The most common causes of death in IBD patients were circulatory or respiratory diseases (41.3% in CD, 42.9% in UC), followed by neoplastic causes (23.6% in CD and 26.2% in UC) (Table 3). The commonest neoplastic cause of death in both CD and UC was lung cancer, contributing to 3.2% of deaths in CD and 5.1% in UC. In both types of IBD, lower GI malignancy was the next commonest neoplastic cause (3.9% and 4.3% respectively), followed by pancreatic and hepato-biliary tumours (1.9% and 2.7%). Inflammatory bowel diseases and their complications together accounted for 8.8% of the underlying cause of death among CD patients and 4.1% among UC patients. Infections, leukaemias and lymphomas combined accounted for a small proportion of overall deaths (3.4% in CD and 3.5% in UC).

The proportion of the underlying cause of death in CD patients accounted for by circulatory and respiratory disease increased with age from 17.7% among 20–40 year-olds to 46.1% among over 80 year-olds (Table 3). A similar pattern was also observed in UC patients. The importance of gastrointestinal diseases (other than malignancy) as a cause of death decreased from 50% among under 20 year-olds to 12% among over 80 year-olds in CD and from 50% to 8.2% in UC. The proportion of deaths attributed to a neoplastic cause fell steadily from almost 50% among 20–40 year-olds to 18.7% among over 80 year-olds in UC patients. In CD patients and non-IBD patients, no neoplastic causes of death were identified early in life but these increased to 29.1% among 60-80 years-old in CD and 42.7% among 40-60 years-old non-IBD patients, (Table 4).

The proportion of death with gastrointestinal diseases as an underlying cause similarly declined with a longer history of UC (7.8% in patients with a history of over 20 years compared to 14.8% in the first five years after diagnosis)(Table 5). The proportion of gastrointestinal deaths also declined in CD, though the decline in deaths directly due to this disease was less marked, and they remained at a higher proportion than for UC patients throughout its course (in total 4.1% of deaths in UC patients were due to IBD and its complications compared to 8.8% in CD).

In CD, the proportion of deaths attributed to neoplasia increased from 20.4% for deaths within 5 years of a diagnosis to 30.2% in patients with over 20 years of disease. This increase was predominantly driven by an increase in hepatobiliary (0.6% to 2.5%) and lung cancers (1.2% to 4.3%). Deaths due to lower gastrointestinal cancer decreased from 6.2% to 4.3% in the same time frames.

In UC, the proportion of deaths attributed to neoplasia decreased from 29.2% for deaths within 5 years of a diagnosis to 24.6% in patients with over 20 years of disease. This decline was predominantly driven by a decrease in deaths due to lung cancer (8.2% to 3.2%) within the same time frames. These were counterbalanced by an increase in deaths due to lower gastrointestinal and hepatobiliary cancers (3.1% and 1.7% with 5 years of diagnosis to 5.6% and 3.6% after 20 years of diagnosis respectively).

Discussion

We have described the pattern of 2,005 deaths in a UK cohort of 20,293 patients with IBD which, is among the largest such cohorts with linkage to data from the official records of death. We have previously published mortality data on 16,550 IBD patients using CPRD records more than a decade ago [3] providing us an excellent opportunity to witness the changes in IBD-related mortality within the UK over a period in which the use of immunosuppressive and biological therapy is increasing [9,10]. A diagnosis of IBD was associated with a roughly 40% increase in the overall risk of mortality, (60% in CD and 30% in UC) which is only marginally lower than our previously published data.

Before further examining or interpreting our results it is necessary to consider their validity. This study has provided power to examine the trends and variations in causes of death by IBD type, age and duration. Furthermore it utilises data which provide for correction of the confounding effects of BMI and smoking which are both associated with IBD, as well as being important predictors of death independent of IBD. There are some limitations to this study however. Firstly as with all studies based on electronic records there is potential for error in coding. The two gravest concerns in this regard would be for the coding of IBD and of death. Though we cannot individually validate each diagnosis of IBD, we are able to be confident as to the validity of this coding since it has previously been validated in these data [11]. This validation however confirms only that those coded as having IBD are highly likely to have it, and it remains possible that a proportion of cases prevalent when joining CPRD will remain unrecorded if quiescent throughout their record. Based upon the previous validation of duration over which prevalent cases can be expected to be recorded [12] we think it will be unlikely for this to be a major issue. Though omission of such cases may bias our estimation of the pattern of deaths associated with IBD towards that seen in more active cases this is likely to be a far smaller issue in this population based study than in many disease cohorts collected in secondary

care. With regard to death and its causes, we can be highly confident that registration of the fact of death is valid and complete given the source of such data is the official registrations of death originally from the Local Registration Service and the General Register Office. However it is well recognised that the coding of cause of death is prone to error [13]. Short of post mortem examination and full case note review (which are not available to us), the data we have used is the best possible and since it is compiled for administrative purposes rather than for this study, is unlikely to be greatly biased.

It is interesting to compare our results with those previously published. The overall pattern of our results is in agreement with our own previous findings when we reported a proportionate increase in mortality of 54% in all IBD patients [3], the magnitude of the relative risk now reported is only slightly smaller despite the quite marked changes in therapy over this period [9,10]. Other studies have identified varying increased risks of death among IBD patients [3,4,14-18] while other studies found no increase [19-23]. A recent meta-analysis of 35 studies in IBD concluded that the standardised mortality ratios in UC and CD were 1.19 (95% CI, 1.06-1.35) and 1.38 (95% CI, 1.23-1.55), respectively[5]. Our results are not too dissimilar to these.

We also are for the most part in agreement with previous studies regarding the change in relative mortality with age. Though one Scandinavian population-based study suggested a significant increased mortality in only female CD patients diagnosed in their third or fifth decade of life [15], in a subsequent larger study by the same group, the highest relative risk of death was in CD patients diagnosed before the age of 20 (adjusted HR: 1.62; 95% CI, 1.25–2.09) [4]. The same group similarly found in population-based studies of UC, [4,17] that UC-related mortality was increased 2-fold in young people diagnosed with UC before the age of 20. Our own findings that the highest relative risk of mortality was observed in patients diagnosed before the age of 20 for both UC and CD (adjusted age-specific HR of 13.6 (95% CI: 1.4-129.9) and 8.8 (95% CI: 0.8-97.5) respectively) before declining in older age groups to between

1.0 and 2.0 accords with this. A population-based study from Manitoba[16] had slightly different findings with the highest relative mortality observed in CD patients between the ages of 30-49. This study though reported this stratification only for incident cases of IBD, and did not have a separate category for those under 20. Their <30 category had the highest relative mortality in UC though the excess (HR 1.15 (95% CI: 0.66-2.01)) was not significant.

One area in which we have been able to add information not immediately comparable to previous studies is in the variations in cause of death over time. It is well recognised that patients with IBD may be at increased risk of death from a number of causes [4,14,16,20,24], and that the commonest causes of their deaths are cardiovascular disease and neoplasia just as in the general population [4,14,16]. On these points we agree. What we have been able to add is insight into how this changes with age as well as with time from diagnosis. Regarding time from diagnosis, a small number of studies have already provided some insight, showing as we do that gastrointestinal causes are prominent early in the course of IBD and decline in importance with time late [4,14]. These studies though report the declining relative risk, where we have given the proportion of deaths attributed to a particular cause. This shows that in the first 5 years after a diagnosis of CD, 11.7% of deaths in this subgroup were directly attributable to CD or its complications and all gastrointestinal causes combined (except neoplasms) were the underlying cause in 20.4% of deaths. In UC patients, 7.6% of deaths in the first five years of diagnosis were directly attributable to UC or its complications and all gastrointestinal causes (excluding neoplasms) were responsible for 14.8% of deaths. The importance of gastrointestinal diseases as the underlying cause of death declines relative to other causes such that in patients with over 20 years of IBD history, 11.1% of deaths in those with CD and 7.8% in UC were of GI cause. Overall, 15.0% of deaths in CD are due to GI causes and 8.3% directly to CD, and the comparable figures for UC are 10.0% and 3.7% respectively. We have also shown that the contribution of GI deaths declines as a proportion with age from 50% in the under 20s to about

12% in the over 80s for both diseases. Trends in other causes of death as a proportion must of course compensate for these variations, and we show that circulatory and respiratory deaths gradually rise with age from under 20% in those under age 40 to about 46% over the age of 80. Interestingly though neoplasia is classically a disease of the old, the proportion of deaths due to it in UC falls with age (though not with time since diagnosis). There were 19 deaths from lower gastrointestinal cancers in the first 5 years after the diagnosis of IBD, perhaps in keeping with the high hazard for death from this cause previously reported in the early years [4]. What may perhaps surprise gastroenterologists more is that despite the recognised high risk of developing lower gastrointestinal cancers, and the low level of smoking, UC patients remained more likely to die of lung cancer (5.1%) than of colorectal cancers (4.4%).

When comparing our current results to those from the time period we previously studied [3], the well-known changes in management of IBD have not been associated with a change in the risk of death. We are unfortunately unable to comment on changes in cause of death as we did not previously have this data. It is reassuring to note however that notwithstanding the well-recognised risks of immunosuppression and biologics and their added risk of infection [25] and haematological malignancy [26], they were not associated with an additional risk of death among IBD patients compared to non-IBD patients and remain uncommon causes of death in IBD patients.

In summary, we have shown that IBD continues to be associated with an increased risk of death in the UK, that this is at least partially explained by deaths caused by IBD itself and its complications, but that most patients with IBD will die of unrelated causes in a pattern much akin to that in the general population.

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Thomas Chu designed the study, carried out data management and statistical analysis, interpreted the findings and drafted the manuscript. Tim Card designed the study, interpreted the findings, drafted the manuscript and helped with case definition and data management. Gordon Moran searched the literature, interpreted the findings and drafted the manuscript. All authors revised the manuscript and approved the final version. No additional assistance with writing or other aspects of this work was received.

Previous publication.

This manuscript, including related data, figures and tables has not been previously published and is not under consideration elsewhere.

Declaration of interest

All authors declare that they have no conflict of interests in this work.

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Table 1: Characteristics of patients with and without inflammatory bowel disease recorded in CPRD.

		Crohn's disease		Ulcerative colitis		All IBD patients combined		Non-IBD patients	
		N = 6,599		N = 9,993		N = 20,293		N = 83,261	
		n	%	n	%	n	%	n	%
Male		2,885	43.7	4,900	49	9,465	46.6	38,708	46.5
Mean age (years)		42.4		49.3		46		45.5	
Body mass index									
	0-18.5	333	5	265	2.7	748	3.7	2,300	2.8
	18.5-25.0	2,876	43.6	3,926	39.3	8,316	41	30,632	36.8
	25.0-30.0	1,590	24.1	2,945	29.5	5,561	27.4	22,507	27
	30.0-50.0	806	12.2	1,417	14.2	2,783	13.7	12,358	14.8
	Unknown	994	15.1	1,440	14.4	2,885	14.2	15,464	18.6
Tobacco use									
	Current	2,469	37.4	2,214	22.2	5,804	28.6	26,191	31.5
	Ex-smoker	1,116	17.7	2,431	24.3	4,364	21.5	12,736	15.3
	Not current	2,669	40.4	4,931	49.3	9,270	45.7	38,254	45.9
	Unknown	295	4.5	417	4.2	855	4.2	6,080	7.3

Table 2: Mortality rates, by age at diagnosis, in patients with Crohn's disease and ulcerative colitis and their matched non-IBD patients.

	IBD patients					Matched non-IBD patients					Hazard ratio		
Age at diagnosis (years)	**Deaths**	**Follow-up (p-y)**	**Mortality rate (1,000 p-y)**	**95% CI**		**Deaths**	**Follow-up (p-y)**	**Mortality rate (1,000 p-y)**	**95% CI**		**Adjusted estimate**	**95% CI**	
Crohn's disease	**563**	**45,672.90**	**12.3**	**11.3**	**13.4**	**1,457**	**177,296.30**	**8.2**	**7.8**	**8.7**	**1.6**	**1.5**	**1.7**
0-20	2	2,393.60	0.8	0.2	3.3	1	9,403.80	0.1	0	0.8	8.8	0.8	97.5
20-40	28	22,186.20	1.3	0.9	1.8	65	83,842.00	0.8	0.6	1	1.7	1.1	2.6
40-60	113	14,354.00	7.9	6.5	9.5	256	55,346.50	4.6	4.1	5.2	1.7	1.4	2.1
60-80	262	5,907.40	44.4	39.3	50.1	695	25,395.00	27.4	25.4	29.5	1.6	1.3	1.8
over 80	158	831.6	190	162.6	222	440	3,309.00	133	121.1	146	1.3	1.1	1.6
Ulcerative colitis	**1,141**	**69,412.20**	**16.4**	**15.5**	**17.4**	**3,674**	**267,932.80**	**13.7**	**13.3**	**14.2**	**1.3**	**1.3**	**1.4**
0-20	3	1,549.40	1.9	0.6	6	1	6,103.00	0.2	0	1.2	13.6	1.4	129.9
20-40	39	23,937.70	1.6	1.2	2.2	65	89,275.40	0.7	0.6	0.9	2.4	1.6	3.6
40-60	128	25,772.30	5	4.2	5.9	459	100,184.70	4.6	4.2	5	1.2	1	1.5
60-80	523	15,695.10	33.3	30.6	36.3	1,796	61,658.60	29.1	27.8	30.5	1.2	1.1	1.3
over 80	448	2,457.80	182.3	166.2	200	1,353	10,711.10	126.3	119.8	133.2	1.4	1.3	1.6
All IBD patients	**2,005**	**140,554.5**	**14.3**	**13.7**	**14.9**	**6,024**	**544,761.70**	**11.1**	**10.8**	**11.3**	**1.4**	**1.4**	**1.5**

Table 3: Distribution of the cause of death, by age at death, in patients with a diagnosis of Crohn's disease or ulcerative colitis in CPRD.

Age at death	0-20 years		20-40 years		40-60 years		60-80 years		over 80 years		TOTAL	
Cause of death	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Crohn's disease at diagnosis												
Gastrointestinal	1	50.0	4	23.5	17	19.8	36	15.7	28	12.0	86	15.1
IBD	*1*	*50.0*	*1*	*5.9*	*8*	*9.3*	*20*	*8.7*	*17*	*7.3*	*47*	*8.3*
complications of IBD	*0*	*0.0*	*1*	*5.9*	*0*	*0.0*	*1*	*0.4*	*1*	*0.4*	*3*	*0.5*
other	*0*	*0.0*	*2*	*11.8*	*9*	*10.5*	*15*	*6.5*	*10*	*4.3*	*36*	*6.3*
Circulatory and respiratory	0	0.0	3	17.6	29	33.7	95	41.3	108	46.2	235	41.3
venous thromboembolism	*0*	*0.0*	*1*	*5.9*	*1*	*1.2*	*2*	*0.9*	*3*	*1.3*	*7*	*1.2*
stroke	*0*	*0.0*	*0*	*0.0*	*2*	*2.3*	*18*	*7.8*	*23*	*9.8*	*43*	*7.6*
other circulatory causes	*0*	*0.0*	*2*	*11.8*	*18*	*20.9*	*46*	*20.0*	*44*	*18.8*	*110*	*19.3*
all respiratory causes	*0*	*0.0*	*0*	*0.0*	*8*	*9.3*	*29*	*12.6*	*38*	*16.2*	*75*	*13.2*
Neoplastic	0	0.0	2	11.8	24	27.9	67	29.1	41	17.5	134	23.6
upper gastrointestinal	*0*	*0.0*	*1*	*5.9*	*0*	*0.0*	*5*	*2.2*	*2*	*0.9*	*8*	*1.4*
lower gastrointestinal	*0*	*0.0*	*1*	*5.9*	*4*	*4.7*	*12*	*5.2*	*5*	*2.1*	*22*	*3.9*
liver, gall bladder and pancreas	*0*	*0.0*	*0*	*0.0*	*2*	*2.3*	*6*	*2.6*	*3*	*1.3*	*11*	*1.9*
lung	*0*	*0.0*	*0*	*0.0*	*2*	*2.3*	*8*	*3.5*	*8*	*3.4*	*18*	*3.2*
skin	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*1*	*0.4*	*1*	*0.4*	*2*	*0.4*
uterine cervix	*0*	*0.0*	*0*	*0.0*	*1*	*1.2*	*0*	*0.0*	*0*	*0.0*	*1*	*0.2*
leukaemia and lymphoma	*0*	*0.0*	*0*	*0.0*	*3*	*3.5*	*6*	*2.6*	*0*	*0.0*	*9*	*1.6*
other	*0*	*0.0*	*0*	*0.0*	*12*	*14.0*	*29*	*12.6*	*22*	*9.4*	*63*	*11.1*
Haematological disorders	0	0.0	0	0.0	1	1.2	0	0.0	1	0.4	2	0.4
Infective	0	0.0	2	11.8	3	3.5	2	0.9	3	1.3	10	1.8
Other specified causes	1	50.0	6	35.3	12	14.0	30	13.0	53	22.6	102	17.9
Sub-total for Crohn's disease	***2***	***100.0***	***17***	***100.0***	***86***	***100.0***	***230***	***100.0***	***234***	***100.0***	***569***	***100.0***

Ulcerative colitis at diagnosis												
Gastrointestinal	1	50.0	1	5.6	16	13.9	46	12.0	52	8.2	116	10.1
IBD	*1*	*50.0*	*0*	*0.0*	*4*	*3.5*	*16*	*4.2*	*22*	*3.5*	*43*	*3.7*
complications of IBD	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*4*	*1.0*	*1*	*0.2*	*5*	*0.4*
other	*0*	*0.0*	*1*	*5.6*	*12*	*10.4*	*26*	*6.8*	*29*	*4.6*	*68*	*5.9*
Circulatory and respiratory	0	0.0	4	22.2	29	25.2	165	43.1	297	46.8	495	42.9
venous thromboembolism	*0*	*0.0*	*1*	*5.6*	*0*	*0.0*	*6*	*1.6*	*6*	*0.9*	*13*	*1.1*
stroke	*0*	*0.0*	*0*	*0.0*	*3*	*2.6*	*28*	*7.3*	*68*	*10.7*	*99*	*8.6*
other circulatory causes	*0*	*0.0*	*3*	*16.7*	*16*	*13.9*	*75*	*19.6*	*125*	*19.7*	*219*	*19.0*
all respiratory causes	*0*	*0.0*	*0*	*0.0*	*10*	*8.7*	*56*	*14.6*	*98*	*15.4*	*164*	*14.2*
Neoplastic	1	50.0	8	44.4	53	46.1	121	31.6	119	18.7	302	26.2
upper gastrointestinal	*0*	*0.0*	*0*	*0.0*	*2*	*1.7*	*4*	*1.0*	*7*	*1.1*	*13*	*1.1*
lower gastrointestinal	*1*	*50.0*	*1*	*5.6*	*13*	*11.3*	*19*	*5.0*	*16*	*2.5*	*50*	*4.3*
liver, gall bladder and pancreas	*0*	*0.0*	*1*	*5.6*	*6*	*5.2*	*14*	*3.7*	*10*	*1.6*	*31*	*2.7*
lung	*0*	*0.0*	*0*	*0.0*	*6*	*5.2*	*29*	*7.6*	*24*	*3.8*	*59*	*5.1*
skin	*0*	*0.0*	*0*	*0.0*	*2*	*1.7*	*1*	*0.3*	*2*	*0.3*	*5*	*0.4*
uterine cervix	*0*	*0.0*	*0*	*0.0*	*1*	*0.9*	*1*	*0.3*	*2*	*0.3*	*4*	*0.3*
leukaemia and lymphoma	*0*	*0.0*	*3*	*16.7*	*3*	*2.6*	*7*	*1.8*	*12*	*1.9*	*25*	*2.2*
other	*0*	*0.0*	*3*	*16.7*	*20*	*17.4*	*46*	*12.0*	*46*	*7.2*	*115*	*10.0*
Haematological disorders	0	0.0	0	0.0	0	0.0	2	0.5	3	0.5	5	0.4
Infective	0	0.0	0	0.0	1	0.9	5	1.3	9	1.4	15	1.3
Other specified causes	0	0.0	5	27.8	16	13.9	44	11.5	155	24.4	220	19.1
Sub-total for ulcerative colitis	***2***	***100.0***	***18***	***100.0***	***115***	***100.0***	***383***	***100.0***	***635***	***100.0***	***1,153***	***100.0***

Table 4: Distribution of the cause of death, by age at death, in patients without inflammatory bowel disease in CPRD.

Age at death	**0-20 years**		**20-40 years**		**40-60 years**		**60-80 years**		**over 80 years**		**TOTAL**	
Cause of death	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Gastrointestinal	0	0.0	6	6.2	68	11.1	108	4.5	129	3.9	311	4.9
IBD	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
complications of IBD	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*
other	*0*	*0.0*	*6*	*6.2*	*68*	*11.1*	*108*	*4.5*	*129*	*3.9*	*311*	*4.9*
Circulatory and respiratory	1	33.3	18	18.6	157	25.7	1,037	43.5	1,798	54.4	3,011	47.0
venous thromboembolism	*0*	*0.0*	*1*	*1.0*	*1*	*0.2*	*11*	*0.5*	*31*	*0.9*	*44*	*0.7*
stroke	*0*	*0.0*	*0*	*0.0*	*20*	*3.3*	*158*	*6.6*	*400*	*12.1*	*578*	*9.0*
other circulatory causes	*1*	*33.3*	*13*	*13.4*	*107*	*17.5*	*591*	*24.8*	*834*	*25.2*	*1,546*	*24.2*
all respiratory causes	*0*	*0.0*	*4*	*4.1*	*29*	*4.7*	*277*	*11.6*	*533*	*16.1*	*843*	*13.2*
Neoplastic	0	0.0	22	22.7	261	42.7	979	41.0	619	18.7	1,881	29.4
upper gastrointestinal	*0*	*0.0*	*1*	*1.0*	*18*	*2.9*	*71*	*3.0*	*47*	*1.4*	*137*	*2.1*
lower gastrointestinal	*0*	*0.0*	*2*	*2.1*	*16*	*2.6*	*99*	*4.2*	*72*	*2.2*	*189*	*3.0*
liver, gall bladder and pancreas	*0*	*0.0*	*0*	*0.0*	*22*	*3.6*	*65*	*2.7*	*43*	*1.3*	*130*	*2.0*
lung	*0*	*0.0*	*1*	*1.0*	*38*	*6.2*	*246*	*10.3*	*115*	*3.5*	*400*	*6.2*
skin	*0*	*0.0*	*3*	*3.1*	*9*	*1.5*	*13*	*0.5*	*9*	*0.3*	*34*	*0.5*
uterine cervix	*0*	*0.0*	*2*	*2.1*	*4*	*0.7*	*5*	*0.2*	*1*	*0.0*	*12*	*0.2*
leukaemia and lymphoma	*0*	*0.0*	*1*	*1.0*	*15*	*2.5*	*80*	*3.4*	*37*	*1.1*	*133*	*2.1*
other	*0*	*0.0*	*12*	*12.4*	*139*	*22.7*	*400*	*16.8*	*295*	*8.9*	*846*	*13.2*
Haematological disorders	0	0.0	0	0.0	1	0.2	1	0.0	4	0.1	6	0.1
Infective	0	0.0	0	0.0	8	1.3	17	0.7	33	1.0	58	0.9
Other specified causes	2	66.7	51	52.6	116	19.0	243	10.2	722	21.8	1,134	17.7
All causes combined	***3***	***100.0***	***97***	***100.0***	***611***	***100.0***	***2,385***	***100.0***	***3,305***	***100.0***	***6,401***	***100.0***

Table 5: Distribution of the cause of death, by time since diagnosis, in patients with a diagnosis of Crohn's disease or ulcerative colitis in CPRD.

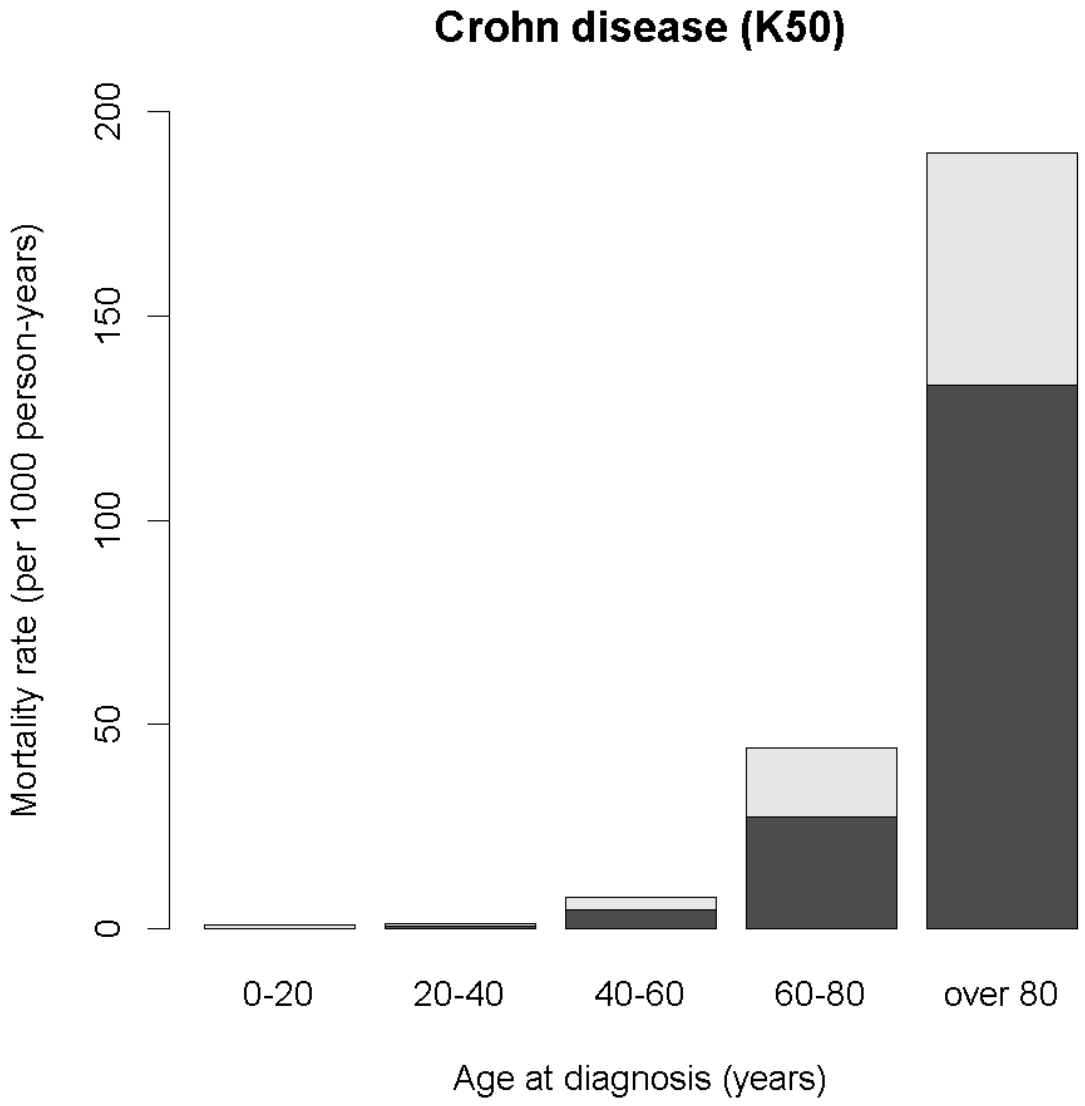
Time since IBD diagnosis	0-5 years		5-10 years		10-15 years		15-20 years		over 20 years		TOTAL	
Cause of death	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Crohn's disease at diagnosis												
Gastrointestinal	33	20.4	15	13.8	11	13.3	8	15.7	18	11.1	85	15.0
IBD	*18*	*11.1*	*8*	*7.3*	*6*	*7.2*	*5*	*9.8*	*10*	*6.2*	*47*	*8.3*
complications of IBD	*1*	*0.6*	*1*	*0.9*	*0*	*0.0*	*0*	*0.0*	*1*	*0.6*	*3*	*0.5*
other	*14*	*8.6*	*6*	*5.5*	*5*	*6.0*	*3*	*5.9*	*7*	*4.3*	*35*	*6.2*
Circulatory and respiratory	70	43.2	45	41.3	40	48.2	20	39.2	60	37.0	235	41.4
venous thromboembolism	*2*	*1.2*	*2*	*1.8*	*2*	*2.4*	*0*	*0.0*	*1*	*0.6*	*7*	*1.2*
stroke	*12*	*7.4*	*5*	*4.6*	*12*	*14.5*	*3*	*5.9*	*11*	*6.8*	*43*	*7.6*
other circulatory causes	*31*	*19.1*	*25*	*22.9*	*17*	*20.5*	*11*	*21.6*	*26*	*16.0*	*110*	*19.4*
all respiratory causes	*25*	*15.4*	*13*	*11.9*	*9*	*10.8*	*6*	*11.8*	*22*	*13.6*	*75*	*13.2*
Neoplastic	33	20.4	25	22.9	11	13.3	15	29.4	49	30.2	133	23.5
upper gastrointestinal	*1*	*0.6*	*2*	*1.8*	*2*	*2.4*	*1*	*2.0*	*2*	*1.2*	*8*	*1.4*
lower gastrointestinal	*10*	*6.2*	*4*	*3.7*	*0*	*0.0*	*1*	*2.0*	*7*	*4.3*	*22*	*3.9*
liver, gall bladder and pancreas	*1*	*0.6*	*1*	*0.9*	*2*	*2.4*	*3*	*5.9*	*4*	*2.5*	*11*	*1.9*
lung	*2*	*1.2*	*6*	*5.5*	*2*	*2.4*	*1*	*2.0*	*7*	*4.3*	*18*	*3.2*
skin	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*2*	*1.2*	*2*	*0.4*
uterine cervix	*1*	*0.6*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*0*	*0.0*	*1*	*0.2*
leukaemia and lymphoma	*3*	*1.9*	*3*	*2.8*	*0*	*0.0*	*1*	*2.0*	*2*	*1.2*	*9*	*1.6*
other	*15*	*9.3*	*9*	*8.3*	*5*	*6.0*	*8*	*15.7*	*25*	*15.4*	*62*	*10.9*
Haematological disorders	1	0.6	0	0.0	0	0.0	1	2.0	0	0.0	2	0.4
Infective	3	1.9	1	0.9	3	3.6	0	0.0	3	1.9	10	1.8
Other specified causes	22	13.6	23	21.1	18	21.7	7	13.7	32	19.8	102	18.0
Sub-total for Crohn's disease	***162***	***100.0***	***109***	***100.0***	***83***	***100.0***	***51***	***100.0***	***162***	***100.0***	***567***	***100.0***

Ulcerative colitis at diagnosis												
Gastrointestinal	43	14.8	27	14.5	7	4.3	6	6.3	32	7.8	115	10.0
IBD	*20*	*6.9*	*6*	*3.2*	*4*	*2.5*	*2*	*2.1*	*10*	*2.4*	*42*	*3.7*
complications of IBD	*2*	*0.7*	*1*	*0.5*	*0*	*0.0*	*0*	*0.0*	*2*	*0.5*	*5*	*0.4*
other	*21*	*7.2*	*20*	*10.8*	*3*	*1.8*	*4*	*4.2*	*20*	*4.9*	*68*	*5.9*
Circulatory and respiratory	119	40.9	72	38.7	86	52.8	44	45.8	172	41.8	493	43.0
venous thromboembolism	*2*	*0.7*	*1*	*0.5*	*5*	*3.1*	*0*	*0.0*	*5*	*1.2*	*13*	*1.1*
stroke	*27*	*9.3*	*12*	*6.5*	*13*	*8.0*	*9*	*9.4*	*38*	*9.2*	*99*	*8.6*
other circulatory causes	*48*	*16.5*	*35*	*18.8*	*43*	*26.4*	*21*	*21.9*	*71*	*17.3*	*218*	*19.0*
all respiratory causes	*42*	*14.4*	*24*	*12.9*	*25*	*15.3*	*14*	*14.6*	*58*	*14.1*	*163*	*14.2*
Neoplastic	85	29.2	53	28.5	40	24.5	22	22.9	101	24.6	301	26.2
upper gastrointestinal	*2*	*0.7*	*1*	*0.5*	*2*	*1.2*	*0*	*0.0*	*8*	*1.9*	*13*	*1.1*
lower gastrointestinal	*9*	*3.1*	*7*	*3.8*	*4*	*2.5*	*7*	*7.3*	*23*	*5.6*	*50*	*4.4*
liver, gall bladder and pancreas	*5*	*1.7*	*6*	*3.2*	*5*	*3.1*	*0*	*0.0*	*15*	*3.6*	*31*	*2.7*
lung	*24*	*8.2*	*9*	*4.8*	*6*	*3.7*	*6*	*6.3*	*13*	*3.2*	*58*	*5.1*
skin	*4*	*1.4*	*0*	*0.0*	*1*	*0.6*	*0*	*0.0*	*0*	*0.0*	*5*	*0.4*
uterine cervix	*1*	*0.3*	*1*	*0.5*	*0*	*0.0*	*1*	*1.0*	*1*	*0.2*	*4*	*0.3*
leukaemia and lymphoma	*5*	*1.7*	*5*	*2.7*	*7*	*4.3*	*4*	*4.2*	*4*	*1.0*	*25*	*2.2*
other	*35*	*12.0*	*24*	*12.9*	*15*	*9.2*	*4*	*4.2*	*37*	*9.0*	*115*	*10.0*
Haematological disorders	2	0.7	0	0.0	0	0.0	0	0.0	3	0.7	5	0.4
Infective	3	1.0	4	2.2	2	1.2	1	1.0	4	1.0	14	1.2
Other specified causes	39	13.4	30	16.1	28	17.2	23	24.0	99	24.1	219	19.1
Sub-total for ulcerative colitis	***291***	***100.0***	***186***	***100.0***	***163***	***100.0***	***96***	***100.0***	***411***	***100.0***	***1,147***	***100.0***

Table captions

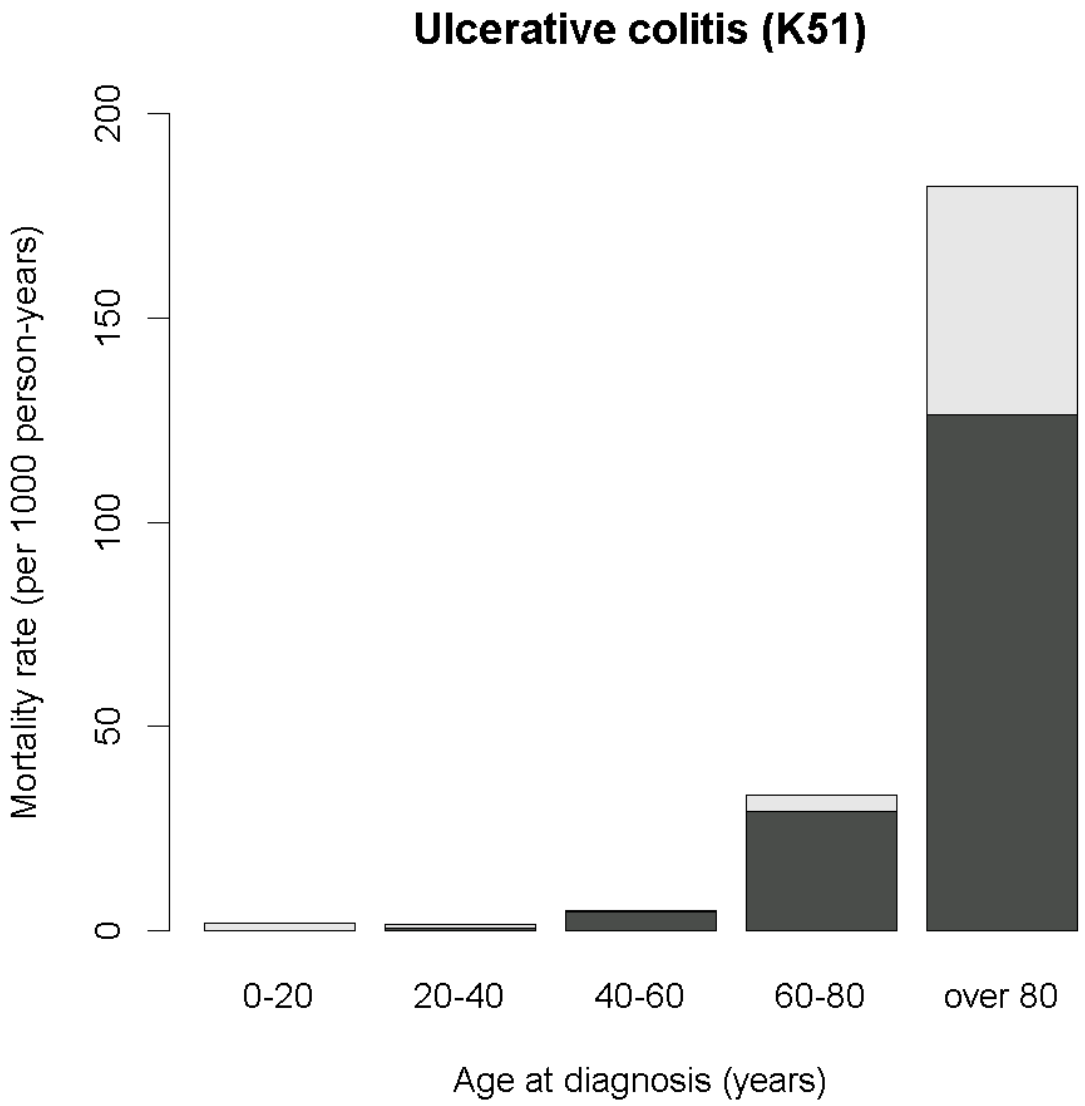
Figures

Figure 1
Mortality rates (number of deaths per 1000 person-years) in Crohn's disease patients and their matched non-IBD patients, by age at diagnosis.



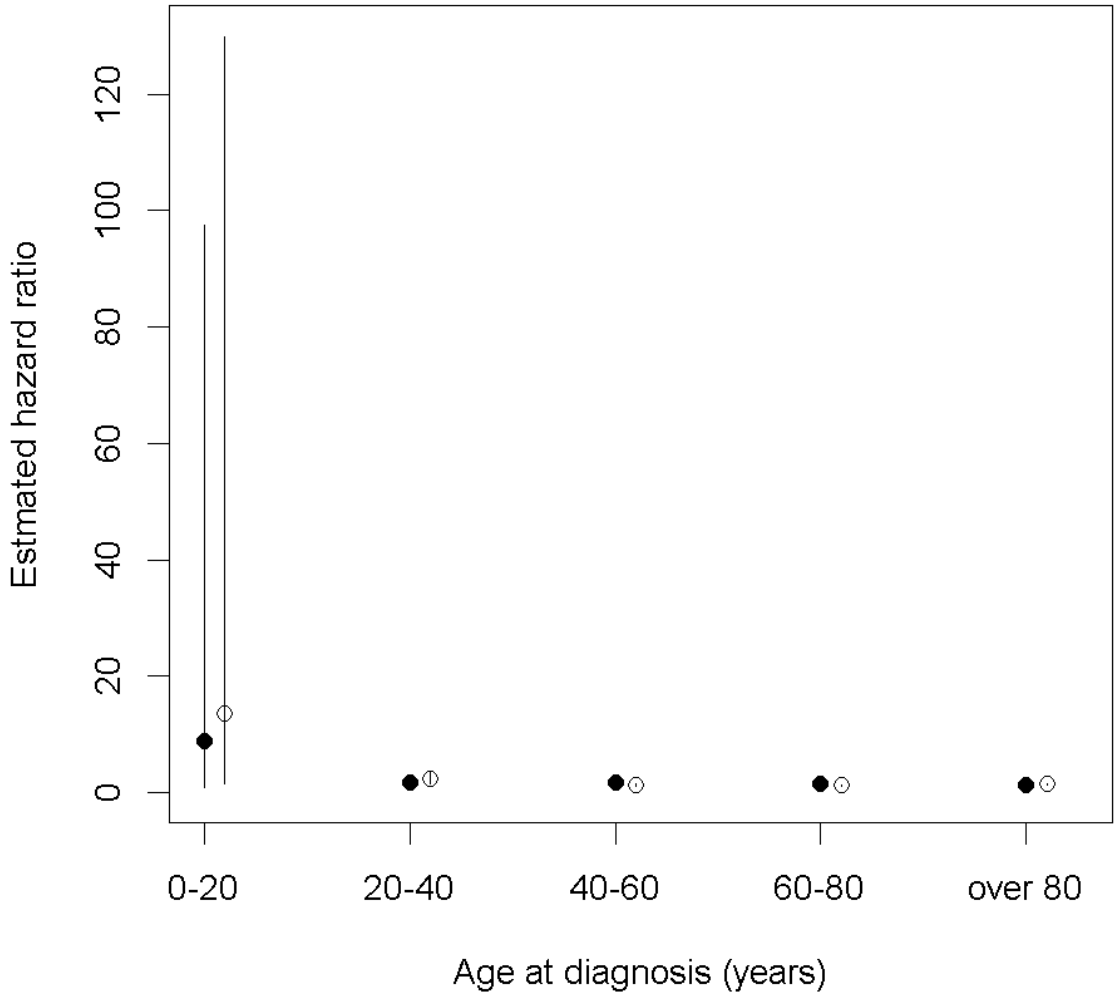
Grey bars: mortality rate in non-IBD patients, white bars: additional mortality rate in Crohn's disease patients. Total height (grey and white parts) of each bar is the mortality rate in Crohn's disease patients.

Figure 2
Mortality rates (number of deaths per 1000 person-years) in ulcerative colitis patients and their matched non-IBD patients, by age at diagnosis.



Grey bars: mortality rate in non-IBD patients, white bars: additional mortality rate in ulcerative colitis patients. Total height (grey and white parts) of each bar is the mortality rate in ulcerative colitis patients.

Figure 3
Age-related pattern in the estimated hazard ratios of death relative to matched non-IBD patients, adjusted for age at diagnosis, body mass index category and tobacco use status.



Solid circles: Hazard ratios in Crohn's disease patients, hollow circles: hazard ratios in ulcerative colitis patients. Vertical lines: 95% confidence intervals of hazard ratios.

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