INFLAMMATORY BOWEL DISEASE

Crohn's disease: increased mortality 10 years after diagnosis in a Europe-wide population based cohort

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Background: No previous correlation between phenotype at diagnosis of Crohn's disease (CD) and mortality has been performed. We assessed the predictive value of phenotype at diagnosis on overall and disease related mortality in a European cohort of CD patients.

Methods: Overall and disease related mortality were recorded 10 years after diagnosis in a prospectively assembled, uniformly diagnosed European population based inception cohort of 380 CD patients diagnosed between 1991 and 1993. Standardised mortality ratios (SMRs) were calculated for geographic and phenotypic subgroups at diagnosis.

Results: Thirty seven deaths were observed in the entire cohort whereas 21.5 deaths were expected (SMR 1.85 (95% CI 1.30–2.55)). Mortality risk was significantly increased in both females (SMR 1.93 (95% CI 1.10–3.14)) and males (SMR 1.79 (95% CI 1.11–2.73)). Patients from northern European centres had a significant overall increased mortality risk (SMR 2.04 (95% CI 1.32–3.01)) whereas a tendency towards increased overall mortality risk was also observed in the south (SMR 1.55 (95% CI 0.80–2.70)). Mortality risk was increased in patients with colonic disease location and with inflammatory disease behaviour at diagnosis. Mortality risk was also increased in the age group above 40 years at diagnosis for both total and CD related causes. Excess mortality was mainly due to gastrointestinal causes that were related to CD.

Conclusions: This European multinational population based study revealed an increased overall mortality risk in CD patients 10 years after diagnosis, and age above 40 years at diagnosis was found to be the sole factor associated with increased mortality risk.

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C rohn's disease (CD) is a chronic inflammatory condition of unknown origin that can be localised throughout the entire gastrointestinal tract. There has been debate as to whether this condition, that predominantly affects young adults, carries an increased mortality risk.[1][2] Because of the heterogeneity of the disease, specification of high risk patient groups is desirable, based on demographic and initial disease behaviour characteristics.

It seems that overall mortality in CD has decreased over the last half century[3] but based on recently published data there still remains excess mortality occurring late during the disease course.[2] Mortality rates in CD may vary in various regions of the world because of different genetic, environmental, and health care related conditions.[3] Mortality risk in CD is best evaluated in unselected patient samples acquired from randomly selected regions, prospectively incepted within a relatively short time frame, and using uniform diagnostic criteria.

The aim of this study was to evaluate whether the mortality risk in CD is different from the background population 10 years after diagnosis—using a population based prospectively and uniformly diagnosed European cohort—and to identify possible risk factors.

METHODS

Patients and centres

Between October 1991 and September 1993, the European Collaborative study group of Inflammatory Bowel Disease (EC-IBD) created a population based prospectively and uniformly diagnosed inception cohort of 2201 patients afflicted with inflammatory bowel disease (IBD) within 20 well described geographical areas in 12 European countries.[4] In this cohort, 706 patients were diagnosed with CD, 1379 with ulcerative colitis, and 116 with indeterminate colitis,[5] all according to the diagnostic criteria by Lennard-Jones and Truelove and Witts.[6]

All centres that originally participated in the EC-IBD cohort were approached to take part in the present follow up study. Thirteen of the original 20 centres distributed over nine countries participated, including 483 out of the original 706 CD patients (68.4%). Study areas and study populations of the participating centres have been described in detail previously.[5] Patients were followed up from inception, between 1 October 1991 and 30 September 1993, until data inclusion of the present study between 1 August 2002 and 31 January 2004 or any date prior to this period, indicated as being the date of death or "lost to follow up" (LTFU). Seven of the original 20 centres refrained from participation because of technical and/or logistical reasons. This did not jeopardise the population based character of the study as all participating centres had individually met the criteria for population based patient inclusion when the cohort was initially formed in the period 1991–1993. Before the start of the current data collection, an arbitrary chosen minimum response rate per centre was set at 60%.

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Ten year clinical follow up project

The EC-IBD launched a large clinical follow up study project to investigate multiple facets of disease outcome in this cohort a decade after diagnosis. The project was planned since 1998, received a grant from the European Union, and started in 2001. Details of the methods used in this follow up study project were extensively described elsewhere.[5 7] Data inclusion in this study project was supported by an electronic internet based facility.

Definitions

The vital status of each individual patient was assessed by review of the patients' hospital charts. If no satisfactory information could be obtained, patients' general practitioners or families were approached by telephone or regular mail or, in the participating Scandinavian countries, national death registries were searched. Dates of death were registered and causes of death were recorded according to the single level Clinical Classifications Software (CCS),[8] a categorisation scheme based on the International Classification of Diseases (ICD-10).[9] In the CCS, ICD-10 codes are collapsed into a smaller number of clinically meaningful categories, thus creating broad diagnosis groupings, more useful for descriptive statistics than individual ICD-10 codes. The CCS aggregates illnesses and conditions into 259 mutually exclusive categories, most of which are clinically homogeneous. Expected mortality rates were calculated using aggregate codes in each main diagnosis category, as listed in both the ICD-9 (Greece, Italy, Spain, and Portugal) and ICD-10 (Denmark, Israel, Norway, and the Netherlands) of the World Health Organisation (WHO) mortality databases[10] for the years 1995–1998.

In the original cohort, detailed information concerning disease location and presence or absence of fistula and strictures was recorded at diagnosis. In the present study, patients were retrospectively grouped regarding disease phenotype at diagnosis according to the Vienna classification[11] using the detailed information as obtained at inception.

Statistical analysis

Standardised mortality ratios (SMRs) were calculated by dividing observed mortality rates by expected mortality rates using country, age, and sex specific mortality rates from the WHO mortality database (31 January 2004 update); 95% confidence intervals (95% CI) were calculated by means of Byar's approximation.[12] The χ^2 and t test were performed to identify possible differences in terms of sex, age, disease location, and behaviour at diagnosis between patients completely followed up and those LTFU. Cox regression analysis was applied to identify risk factors for mortality using the proportional hazards assumption. The proportional hazards assumption was tested using the scaled Schoenfeld residuals.[13] The Stata statistical software package was used for the analysis.[14] Observed survival curves were calculated using the Kaplan-Meyer technique. Expected survival curves were calculated using the age specific mortality rates and age and sex specific distribution of person years of the cohort.

RESULTS

Ten of the 13 participating centres complied with the minimum 60% response threshold, giving a total of 380 CD patients to follow of whom 348 (92%) were completely followed up until at least August 2002 or death. Thirty two patients were LTFU of whom 23 were followed during varying time intervals (median follow up time 15 months (range 1–84)) and nine patients appeared to have a date of last visit equal to the date of diagnosis. These nine patients were not incorporated into the analysis. Thus a total of 371 patients participated in the present study (183 males and 188

females with a median age of 31.0 years at diagnosis (range15–83)). Patients LTFU were not different from patients with a complete follow up in terms of sex, age, disease location, or behaviour at diagnosis.

Overall mortality

Table 1 shows male, female, and total mortality rates according to age, disease phenotype at diagnosis, and residence. At the end of follow up, 311 patients were known to be alive (median follow up time 123 months (range 107–141)).Thirty seven patients had died (median time from diagnosis until death 51 months (range 3–120)) whereas 21.5 deaths were expected (SMR 1.85 (95% CI 1.30–2.55)). Mortality risk was significantly increased in both females (SMR 1.93 (95% CI 1.10–3.14)) and males (SMR 1.79 (95% CI 1.11–2.73)). Patients from northern European centres had a significantly increased mortality risk (SMR 2.04 (95% CI 1.32–3.01)) whereas a tendency towards increased overall mortality risk was observed in the south (SMR 1.55 (95% CI 0.80–2.70)). Figures 1–3 show the total, male, and female survival curves, as observed in the cohort, compared with the expected survival based on aggregate mortality statistics of all participating countries.

Phenotype at diagnosis associated mortality

Increased mortality risks were observed for both males (19 deaths observed versus 10 expected, SMR 1.90 (95% CI 1.14–2.97)) and females (14 deaths observed versus 6.58 expected, SMR 2.13 (95% CI 1.16–3.57)) older than 40 years at diagnosis. Table 1 shows that males with isolated colonic localisation at diagnosis (SMR 2.23 (95% CI 1.19–3.36)) and both males (SMR 2.12 (95% CI 1.26–3.36)) and females (SMR 2.36 (95% CI 1.13–4.34)) with inflammatory disease behaviour at diagnosis had increased mortality risks.

Cause specific mortality

Table 2 shows cause specific mortality rates for the entire cohort. The cause of death of one patient (2.7%) remained unknown. Increased mortality risks were observed in all cause specific groups but reached statistical significance only for gastrointestinal causes (SMR 9.77 (95% CI 4.20–19.2)). Male patients, patients older than 40 years at diagnosis, and patients with inflammatory disease behaviour at diagnosis were observed to have excess risks for cancer, gastrointestinal, and all causes. Female patients and patients with isolated colonic disease at diagnosis had increased mortality risks for both gastrointestinal and all causes. Increased mortality risks by gastrointestinal causes only occurred in patients younger than 40 years at diagnosis (SMR 22.6 (95% CI 2.54–81.8)), with upper gastrointestinal disease location at diagnosis (SMR (95% CI 117 13.1–422)), and those with penetrating disease behaviour at diagnosis (SMR 9.77 (95% CI 4.20–19.2)). Cause specific mortality rates for male patients only, portrayed an almost identical cause specific mortality pattern as for the entire cohort. The observed increased mortality risk by gastrointestinal causes was due to the death of two young male patients. A substantial part of the observed increased mortality risk in the male population with isolated colonic disease localisation at diagnosis was due to pulmonary causes (SMR 6.14 (95% CI 1.23–18.0)). Female patients older than 40 years at diagnosis had excess mortality risks for both gastrointestinal and all causes. The majority of deaths in female patients with inflammatory disease behaviour at diagnosis were due to cardiovascular causes (SMR 3.25 (95% CI 1.05–7.59)). When female patients with isolated colonic disease localisation at diagnosis were considered as a group, a tendency to increased mortality was observed (eight deaths observed versus 4.24 expected, SMR 1.81 (95% CI 0.78–3.57)).

Table 1 Male, female, and cohort specific mortality according to age (sex and country adjusted), disease phenotype at diagnosis (age, sex, and country adjusted), disease location at diagnosis (age, sex, and country adjusted), and residence (age and sex adjusted)

	Male				Female				Entire cohort				Groupings entire cohort			
	No	Dead	Exp	SMR (95%CI)	No	Dead	Exp	SMR (95%CI)	No	Dead	Exp	SMR (95%CI)	No	Dead	Exp	SMR (95%CI)
Total	183	21	11.8	1.79 (1.11–2.73)	188	16	8.28	1.93 (1.10–3.14)	371	37	21.5	1.85 (1.30–2.55)				
Age at diagnosis																
<40 y																
10–19	25	1	0.22	4.51 (0.06–25.1)	26	0	0.07	0 (–)	51	1	0.29	3.39 (0.04–18.9)	241	3	2.32	1.29 (0.26–3.78)
20–29	58	1	0.65	1.53 (0.02–8.51)	67	1	0.34	2.95 (0.04–16.4)	125	2	0.99	2.01 (0.23–7.27)				
30–39	28	0	0.50	0 (–)	38	0	0.41	0 (–)	66	0	0.91	0 (–)				
≥40 y																
40–49	28	1	1.28	0.78 (0.01–4.34)	21	2	0.53	3.80 (0.43–13.7)	49	3	1.81	1.66 (0.33–4.85)	117	33	16.6	1.99 (1.37–2.80)
50–59	18	2	1.94	1.03 (0.12–3.71)	15	1	0.90	1.11 (0.01–6.15)	33	3	2.85	1.05 (0.09–39.8)				
60–69	14	6	3.65	1.64 (0.60–3.58)	8	3	1.10	2.72 (0.55–7.94)	22	9	4.75	1.89 (0.86–3.59)				
70–79	11	9	3.48	2.58 (1.18–4.91)	11	7	3.36	2.08 (0.84–4.30)	22	16	6.84	2.34 (1.34–3.80)				
80–89	1	1	0.01	82.8 (1.08–461)	2	2	1.56	1.28 (0.14–4.62)	3	3	1.57	1.91 (0.38–5.57)				
Disease location at diagnosis																
Ileum	26	6	3.68	1.63 (0.60–3.55)	27	4	2.15	1.86 (0.50–4.77)	53	10	5.83	1.72 (0.82–3.16)				
Colon	73	13	5.83	2.23 (1.19–3.81)	78	8	4.41	1.81 (0.78–3.57)	151	21	10.2	2.05 (1.27–3.13)				
Ileocolon	69	1	1.67	0.60 (0.01–3.33)	65	2	0.74	2.69 (0.30–9.73)	134	3	2.41	1.24 (0.25–3.63)				
Upper GI	9	1	0.29	3.44 (0.04–19.1)	11	1	0.13	7.75 (0.10–43.1)	20	2	0.42	4.76 (0.54–17.2)				
Disease behaviour at diagnosis																
Inflammatory	132	18	8.47	2.12 (1.26–3.36)	132	10	4.24	2.36 (1.13–4.34)	264	28	12.7	2.20 (1.46–3.18)				
Stricturing	29	3	1.85	1.62 (0.33–4.74)	28	3	2.52	1.19 (0.24–3.48)	57	6	4.37	1.37 (0.50–2.99)				
Penetrating	14	0	1.12	0 (–)	16	2	0.64	3.10 (0.35–11.2)	30	2	1.77	1.13 (0.13–4.08)				
Penetrating and stricturing	2	0	0.02	0 (–)	5	0	0.03	0 (–)	7	0	0.05	0 (–)				
Country																
South																
Greece	16	4	1.51	2.65 (0.71–6.78)	5	0	0.02	0 (–)	21	4	1.53	2.61 (0.70–6.67)	130	12	7.76	1.55 (0.80–2.70)
Italy	20	2	2.05	0.98 (0.11–3.53)	22	2	1.43	1.39 (0.16–5.04)	42	4	3.48	1.15 (0.31–2.94)				
Israel	5	0	0.16	0 (–)	16	1	0.33	3.02 (0.04–16.8)	21	1	0.49	2.03 (0.03–11.3)				
Portugal	5	0	0.40	0 (–)	8	0	0.09	0 (–)	13	0	0.49	0 (–)				
Spain	25	3	1.72	1.74 (0.35–5.08)	8	0	0.04	0 (–)	33	3	1.77	1.70 (0.34–4.97)				
North																
Denmark	20	5	2.01	2.49 (0.80–5.81)	38	5	2.35	2.12 (0.68–4.96)	58	10	4.36	2.29 (1.10–4.22)	241	25	12.3	2.04 (1.32–3.01)
Norway	56	5	2.85	1.75 (0.56–4.09)	50	6	3.57	1.68 (0.61–3.65)	106	11	6.43	1.71 (0.85–3.06)				
the Netherlands	36	2	1.05	1.91 (0.21–6.91)	41	2	0.43	4.64 (0.52–16.7)	77	4	1.48	2.71 (0.73–6.94)				

Thirteen patients with no known phenotype at diagnosis, of whom one female died due to pulmonary cause, were excluded from analysis in the age (<40 years and ≥40 years), disease location, and behaviour at diagnosis categories.
No, number of patients; Exp, expected number of deaths; upper GI, upper gastrointestinal; SMR, standardised mortality ratio; 95% CI, 95% confidence interval.
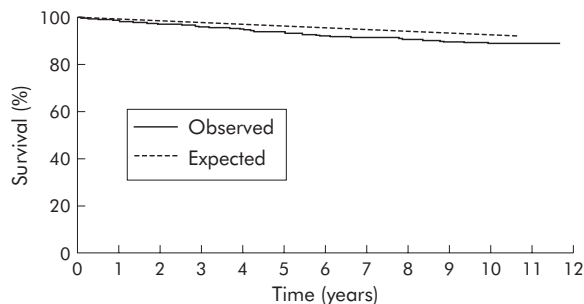
No at risk: 371 358 347 342 336 331 324 320 317 309 191 49 —

Figure 1 Total observed survival of the entire cohort versus expected survival based on aggregate mortality statistics of all participating countries. Overall expected versus observed survival rates were 99.5% versus 98.9%, 97.0% versus 94.1%, and 93.0% versus 89.6%, one, five, and 10 years after diagnosis, respectively. No, number of patients.
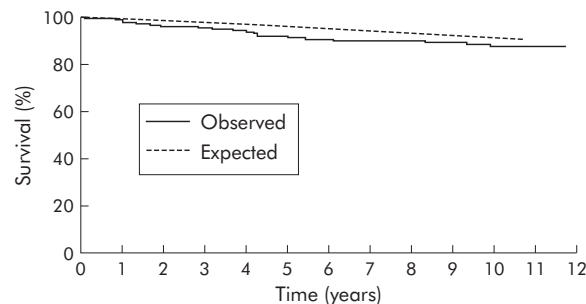
No at risk: 183 179 172 170 167 162 158 155 154 151 97 19 —

Figure 2 Male observed survival of the entire cohort versus expected survival based on aggregate mortality statistics of all participating countries. Male expected versus observed survival rates were 99.6% versus 98.9%, 96.2% versus 91.8%, and 91.2% versus 87.5%, one, five, and 10 years after diagnosis, respectively. No, number of patients.

CD related mortality

Fourteen (seven males and seven females) of the 37 observed deaths (37.8%) had a certain (6) or possible (8) CD related cause of death (table 3). Median age at diagnosis of patients with a CD related cause of death was 64 years (range 18–83). Median survival after diagnosis of this group was 39 months (range 1–112). Median age at diagnosis of patients with a cause of death not related to CD (table 4) was 71 years (range 41–81) and median survival after diagnosis of these patients was 51 months (range 6–119). All eight observed deaths due to gastrointestinal causes had a certain (4) or possible (4) causal relationship with CD. Four patients in this category died because of abdominal sepsis, one due to intestinal ischaemia, one because of intestinal haemorrhage, and one because of surgery related complications. One patient died because of gall stone mediated biliary sepsis that was interpreted as possibly CD related because of the known association of CD and biliary stones. The three deaths in patients younger than 40 years at diagnosis were certainly (2) or possibly (1) CD related. Twelve of the observed 28 deaths in the patient group with inflammatory disease behaviour at diagnosis were certainly (5) or possibly (7) CD related. Six of the observed 21 deaths in patients with isolated colonic disease location had a certain (4) or possible (2) CD related cause of death. One female patient with an unknown disease phenotype at diagnosis died because of aspiration pneumonia as a result of CD mediated bowel obstruction and ileus. Three males with isolated colonic disease location at diagnosis died due to pulmonary causes not related to CD. Two of the five female patients with inflammatory disease behaviour at diagnosis died due to cardiovascular causes that occurred in association with CD activity. None of the observed cancer associated deaths had a causal relationship with CD.

Cox regression analysis

Age and sex as well as disease location and behaviour were the factors analysed in both the uni- and multivariate analysis. Univariate analysis showed hazard ratios of 1.10 and 1.07 per year with increasing age at diagnosis for all causes of mortality (95% CI 1.08–1.12) and CD related mortality (95% CI 1.04–1.10), respectively. No other factor reached statistical significance in the univariate model. In the multivariate model, increasing age remained the only independent risk factor for both total and CD related mortality causes.

DISCUSSION

Increased overall mortality was observed 10 years after diagnosis in this European population based cohort of CD patients. Mortality risk appeared to be increased in the age group above 40 years at diagnosis. Excess mortality was mainly due to gastrointestinal causes that were either certainly or possibly related to CD.

Previous studies reporting on CD associated mortality differed in terms of patient selection, patient inception, follow up rates, and follow up duration. Referral centre based studies have mostly reported on mortality values in CD that were increased.[15–25] These studies were based on selected patient samples and must be interpreted with caution.[26] Most population based studies with good methodology, reporting on mortality in CD, had patients enrolled over decades.[2 27–30] Changes in treatment practice may have influenced mortality rates observed during the course of time. Follow up duration can influence outcome considerably: excess mortality in a Danish study was not observed after 10 years[31] but appeared after a median of 17 years of follow up in the same cohort of CD patients.[2]

The methodological strengths of the current study are threefold. Firstly, this study was based on a population based, prospectively, and uniformly diagnosed inception cohort of CD patients originating from 10 well described geographical areas in seven European countries and Israel. This multinational population based cohort is unique on the European continent and possibly also in the world. Secondly, patient inception at diagnosis took place during a short period of two
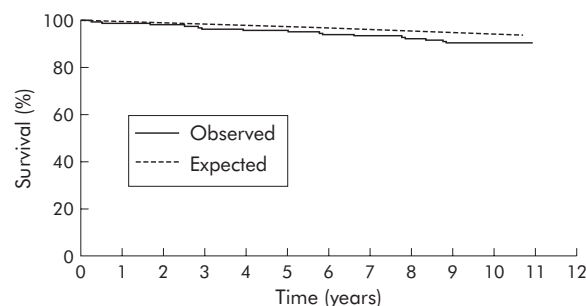
No at risk: 188 179 176 172 169 169 166 165 163 158 94 30 —

Figure 3 Female observed survival of the entire cohort versus expected survival based on aggregate mortality statistics of all participating countries. Female expected versus observed survival rates were 99.7% versus 98.9%, 97.8% versus 96.1%, and 94.6% versus 90.6%, one, five, and 10 years after diagnosis, respectively. No, number of patients.

Table 2 Overall cause specific mortality for all patients (age, sex, and country adjusted), according to sex (age and country adjusted), age (sex and country adjusted), disease location and behaviour at diagnosis (age, sex, and country adjusted), and residence (age and sex adjusted)

	No	Cancer CCS ICD-10: 011–044			Cardiovascular causes CCS ICD-10: 099–118			Pulmonary causes CCS ICD-10: 122–134			Gastrointestinal causes CCS ICD-10: 138–155			All causes CCS ICD-10: 1–259		
		Dead	Exp	SMR (95%CI)	Dead	Exp	SMR (95%CI)	Dead	Exp	SMR (95%CI)	Dead	Exp	SMR (95%CI)	Dead	Exp	SMR (95%CI)
All patients	371	11	5.60	1.96 (0.98–3.51)	11	7.39	1.49 (0.74–2.66)	4	1.50	2.66 (0.72–6.80)	8	0.82	9.77 (4.20–19.2)	37	21.5	1.85 (1.30–2.55)
Sex																
Male	183	8	3.43	2.33 (1.00–4.59)	4	4.17	0.96 (0.26–2.46)	3	0.83	3.61 (0.73–10.6)	5	0.50	10.0 (3.23–23.4)	21	11.6	1.79 (1.11–2.73)
Female	188	3	2.17	1.38 (0.28–4.04)	7	3.22	2.17 (0.87–4.48)	1	0.67	1.48 (0.02–8.25)	3	0.32	9.37 (1.88–27.4)	16	8.28	1.93 (1.10–3.14)
Age at diagnosis																
<40 y	241	0	0.54	0 (–)	1	0.31	3.18 (0.04–17.7)	0	0.05	0 (–)	2	0.09	22.6 (2.54–81.8)	3	2.32	1.29 (0.26–3.78)
≥40 y	117	11	4.83	2.28 (1.14–4.08)	10	6.60	1.51 (0.73–2.79)	3	1.35	2.22 (0.45–6.48)	6	0.68	8.78 (3.21–19.1)	33	16.6	1.99 (1.37–2.80)
Disease location at diagnosis																
Ileal	53	2	0.77	2.59 (0.29–9.34)	1	0.84	1.20 (0.02–6.66)	0	0.13	0 (–)	0	0.10	0 (–)	3	2.41	1.24 (0.25–3.63)
Colonic	151	5	2.76	1.81 (0.58–4.23)	8	4.01	2.00 (0.86–3.93)	3	0.86	3.49 (0.70–10.2)	4	0.40	9.91 (2.67–25.4)	21	10.2	2.05 (1.27–3.13)
Ileocolonic	134	4	1.71	2.35 (0.63–6.00)	2	1.96	1.02 (0.11–3.69)	0	0.40	0 (–)	2	0.26	7.84 (0.88–28.3)	10	5.83	1.72 (0.82–3.16)
Upper GI	20	0	0.13	0.00 (0.00–27.6)	0	0.11	0 (–)	0	0.02	0 (–)	2	0.02	117 (13.1–422)	2	0.42	4.76 (0.54–17.2)
Disease behaviour at diagnosis																
Inflammatory	264	10	3.68	2.71 (1.30–4.99)	8	4.64	1.73 (0.74–3.40)	2	0.91	2.21 (0.25–7.97)	6	0.50	12.0 (4.39–26.2)	28	12.7	2.20 (1.46–3.18)
Stricturing	57	1	1.11	0.90 (0.01–5.00)	3	1.73	1.74 (0.35–5.08)	1	0.34	2.91 (0.04–16.2)	0	0.18	0 (–)	6	4.37	1.37 (0.50–2.99)
Penetrating	30	0	0.56	0 (–)	0	0.55	0 (–)	0	0.15	0 (–)	2	0.09	22.5 (2.52–81.1)	2	1.77	1.13 (0.13–4.08)
Penetrating and stricturing	7	0	0.01	0 (–)	0	0.01	0 (–)	0	0.00	0 (–)	0	0.00	0 (–)	0	0.05	0 (–)
Greece																
Heraklion	15	3	0.40	7.52 (1.51–22.0)	0	0.70	0 (–)	1	0.09	11.3 (0.15–62.9)	0	0.04	0 (–)	4	1.53	2.61 (0.70–6.67)
Ioannina	6															
Italy																
Cremona	10	0	1.02	0 (–)	2	1.38	1.45 (0.16–5.25)	0	0.19	0 (–)	1	0.18	5.62 (0.07–31.3))	4	3.48	1.15 (0.31–2.94)
Reggio Emilia	32															
Israel (Beer Sheeva)	21	0	0.17	0 (–)	0	0.12	0 (–)	0	0.02	0 (–)	1	0.01	70.1 (0.92–390)	1	0.49	2.03 (0.03–11.3)
Portugal (Almada)	13	0	0.14	0 (–)	0	0.12	0 (–)	0	0.03	0 (–)	0	0.04	0 (–)	0	0.49	0 (–)
Spain (Vigo)	33	1	0.49	2.05 (0.03–11.4)	0	0.52	0 (–)	0	0.19	0 (–)	2	0.09	21.7 (2.44–78.5)	3	1.77	1.70 (0.34–4.97)
Denmark (Copenhagen)	58	5	1.29	3.88 (1.25–9.05)	3	1.52	1.98 (0.40–5.78)	1	0.39	2.56 (0.03–14.3)	1	0.20	4.89 (0.06–27.2)	10	4.36	2.29 (1.10–4.22)
Norway (Oslo)	106	1	1.53	0.65 (0.01–3.63)	5	2.64	1.89 (0.61–4.42)	2	0.55	2.63 (0.41–13.1)	1	0.20	5.09 (0.07–28.3)	11	6.43	1.71 (0.85–3.06)
the Netherlands (South Limburg)	77	1	0.56	1.79 (0.02–9.97)	1	0.39	2.56 (0.03–14.3)	0	0.05	0 (–)	2	0.05	37.8 (4.24–136)	4	1.48	2.71 (0.73–6.94)

Thirteen patients with no known phenotype at diagnosis, of whom one female died due to pulmonary cause, were excluded from analysis in the age (<40 years and ≥40 years), disease location, and disease behaviour at diagnosis categories.
Three patients died due to other causes than listed (two infectious and one unknown).
No, number of patients; Exp, expected number of deaths; upper GI: upper gastrointestinal; SMR, standardised mortality ratio; 95% CI, 95% confidence interval; CCS, clinical classifications software; ICD, International Classification of Diseases.

Table 3 Causes of death possibly or certainly related to Crohn's disease (CD)

Patient No and causality of death and CD	Centre	Sex	Disease location at diagnosis	Disease behaviour at diagnosis	Age at diagnosis (y)	Survival after diagnosis (months)	Cause of death	CCS ICD-10 code
Infections								
1 Certain	Oslo	F	Ileocolonic	Stricturing	65	34	Sepsis, steroid use for CD activity	2
2 Possible	Reggio Emilia	M	Ileocolonic	Inflammatory	67	112	Sepsis, steroid use for CD activity	2
Cardiovascular causes								
3 Possible	South Limburg	F	Ileocolonic	Inflammatory	26	94	Acute myocardial infarction during CD activity (autopsy confirmed). Steroid use	100
4 Possible	Reggio Emilia	F	Colonic	Inflammatory	80	69	Cardiac failure during CD activity. Steroid use	108
5 Certain	Copenhagen	M	Colonic	Inflammatory	78	34	Congestive heart failure after elective subtotal colectomy. Steroid use	108
Pulmonary causes								
6 Possible	Copenhagen	F	Unknown	Unknown	71	8	Aspiration pneumonia due to CD mediated bowel obstruction. Steroid use.	122
Gastrointestinal causes								
7 Certain	Reggio Emilia	M	Colonic	Inflammatory	63	44	Toxic megacolon. Steroid and cyclosporine use	144
8 Possible	Beer Sheeva	F	Upper GI	Inflammatory	60	60	Jejunal infarction. Azathioprine and steroid use.	144
9 Possible	Copenhagen	F	Colonic	Penetrating	71	4	Sepsis after elective subtotal colectomy. Topical steroid use	148
10 Certain	South Limburg	M	Ileocolonic	Inflammatory	20	23	Sepsis after acute ileocaecal resection	148
11 Certain	Vigo	M	Colonic	Inflammatory	18	50	Acute subtotal colectomy for perforation followed by sepsis. Azathioprine and steroid use	148
12 Certain	Oslo	M	Colonic	Inflammatory	83	1	Acute subtotal colectomy for perforation followed by sepsis. Steroid use.	148
13 Possible	South Limburg	F	Ileocolonic	Inflammatory	46	94	Gall bladder stones, biliary sepsis	149
14 Possible	Vigo	M	Upper GI	Inflammatory	60	16	Gastrointestinal haemorrhage	153

CCS, clinical classifications software; ICD, International Classification of Diseases.

years. All patients were followed within the same time period and had, except for those who died and were found lost to follow up, approximately identical observation times. Thirdly, no previous cohort study has been able to correlate disease phenotype at diagnosis according to the Vienna classification with mortality. Our applied prognostic model could also be tested in other contemporary and future cohorts.

There were some limitations to the study. Firstly, even though the total number of patients may seem sufficient and the 92% follow up rate must be regarded as excellent, some participating centres and clinical subgroups had low sample sizes. This has biased the actual mortality risk in certain described geographical and phenotypic patient subsets. Multivariate analysis carried out in this study did not produce a robust model as no deaths occurred in some patient subsets. Confounding may have occurred in the stratified analyses of disease phenotype at diagnosis, as these analyses were only adjusted for age, sex, and residence. In these analyses, colonic location and inflammatory disease behaviour were associated with increased mortality. It is possible that these results were not independent. Secondly, 50% of the original EC-IBD centres participated in this study, leaving 52% of the original CD patients. It is possible that centres with more of an interest in IBD and therefore with more expertise in treatment, participated, which may have been a source of bias. Thirdly, retrospective data collection concerning mortality and causes of death was used. However, for all except one patient, the exact cause of death and its relationship to CD was established. In 23 included cases the vital status remained unclear. These patients were not different in terms of baseline characteristics from those with complete follow up, and any deaths that could have occurred in this subset would probably have further upgraded the increased mortality risk observed in this cohort. Fourthly,

CD patient classification by pattern of disease behaviour at diagnosis was previously shown to yield only fair interobserver agreement.[32] In the present study, uniform definitions were used to retrospectively classify patients at diagnosis regarding disease location and disease behaviour. These findings were clearly reported in patient files. Accordingly, the risk of interpretative classification was minimised.

An increased mortality risk in CD patients was described until the mid 1970s,[3 33 34] with a subsequent decrease thereafter.[3] Seven population based studies have reported on mortality risk in CD. Most of these showed an increased SMR, but decreasing to unity during the last 40 years.[1] Although comparison was hampered by differences in follow up duration and geographical backgrounds, four of these studies showed increased mortality risks during the first 2–9 years after diagnosis,[23 27 29] a subsequent plateau phase, and thereafter an increasing risk from 14.5 to 25 years after diagnosis.[2 23] In most of these studies, early deaths occurred due to non-surgical and/or surgical complications of the disease whereas the deaths due to gastrointestinal cancer occurred late during the disease course. Findings in this study confirmed both the increased mortality risk during the first years after diagnosis and its direct relation to CD. Further follow up of this cohort in the future may reveal the impact of possible late sequelae on CD related mortality, such as intestinal cancer. Interestingly, the previously assumed geographical differences may be confirmed by findings in this study, as the northern European patient group demonstrated a slightly higher mortality risk than the southern European cohort. Apart from the relatively small sample size in the south, true differences in terms of more aggressive phenotype in the north could be responsible for this gradient. Interestingly in this context is that the use of corticosteroids

Table 4 Causes of death not related to Crohn's disease (CD)

Patient No	Centre	Sex	Disease location at diagnosis	Disease behaviour at diagnosis	Age at diagnosis (y)	Survival after diagnosis (months)	Cause of death	CCS ICD-10 code	Circumstances at death
Cancer									
15	Heraklion	M	Colonic	Inflammatory	76	12	Bronchus carcinoma	19	No immunosuppressives
16	Vigo	M	Ileocolonic	Inflammatory	70	65	Bronchus carcinoma	19	No immunosuppressives
17	South Limburg	M	Ileal	Stricturing	60	100	Bronchus carcinoma	19	No immunosuppressives
18	Oslo	F	Ileocolonic	Inflammatory	53	35	Breast cancer	24	No immunosuppressives
19	Heraklion	M	Colonic	Inflammatory	65	38	Urinary bladder cancer	32	No immunosuppressives
20	Copenhagen	M	Colonic	Inflammatory	56	21	Leukaemia	39	HIV, heart failure
21	Copenhagen	M	Ileocolonic	Inflammatory	46	119	Leukaemia	39	No immunosuppressives
22	Copenhagen	F	Colonic	Inflammatory	71	79	Multiple myeloma	40	No immunosuppressives
23	Copenhagen	M	Colonic	Inflammatory	71	48	Pancreatic cancer	41	No immunosuppressives
24	Ioannina	M	Ileocolonic	Inflammatory	77	51	Unknown primary cancer	41	Azathioprine during 3 y previously
25	Copenhagen	F	Ileal	Inflammatory	67	47	Unspecified cancer of peritoneum, probably metastasis of gynaecological or lung cancer	43	No immunosuppresives
Cardiovascular causes									
26	Oslo	M	Colonic	Inflammatory	73	10	Acute myocardial infarction	100	No CD activity
27	Oslo	M	Colonic	Inflammatory	75	73	Acute myocardial infarction	100	No CD activity
28	Oslo	F	Colonic	Stricturing	81	105	Coronary atherosclerosis	101	No CD activity
29	Oslo	F	Colonic	Inflammatory	78	30	Acute cerebrovascular disease	109	No CD activity
30	Copenhagen	M	Ileocolonic	Inflammatory	73	65	Acute cerebrovascular disease	109	No CD activity
31	Copenhagen	F	Colonic	Inflammatory	41	93	Acute cerebrovascular disease	109	No CD activity
32	Cremona	F	Ileal	Stricturing	70	100	Acute cerebrovascular disease	109	No CD activity
33	Oslo	F			79	70	Pulmonary embolism	118	No CD activity or medication use during years previously
Pulmonary causes									
34	Oslo	M	Colonic	Inflammatory	67	12	Pneumonia	122	No immunosuppressives
35	Oslo	M	Colonic	Stenotic	77	51	Pneumonia	122	No immunosuppressives
36	Heraklion	M	Colonic	Inflammatory	64	60	COPD	127	No CD activity
Unknown									
37	Oslo	F	Colonic	Inflammatory	74	6	Unknown	–	No CD activity

CCS, clinical classifications software; ICD, International Classification of Diseases.

did not differ between the northern and southern European centres but the use of azathioprine did. Of 237 patients from northern Europe, 74 (31%) had used azathioprine whereas in the south 21 of 121 patients (17%) had used the drug (p = 0.005). Median duration of azathioprine use was 24 months (range 1–114) in the north versus 36 months (range 1–87) in the south (p = 0.009). This discrepancy was caused by a relatively high number of patients from northern European centres in whom azathioprine had to be discontinued early after treatment initiation because of side affects (20/74 patients from the north used azathioprine for less than six months versus 2/21 patients from the south). The use of immunosuppressive drugs could be interpreted as a surrogate marker of disease severity and hence, given the percentages of patients in whom azathioprine was considered to be indicated, disease phenotype might be estimated as more severe in the north of Europe compared with the south.

Population based findings concerning the correlation of phenotypic characteristics at diagnosis and subsequent mortality risk in CD are scarce. In one Danish and two large Swedish cohort studies, no differences in mortality risk between the different disease location groups at diagnosis were observed.[2 28 29] A population based study from the UK reported increased mortality in patients with colonic disease location. In that study, however, it was not explicitly indicated whether disease location was recorded at diagnosis or during the course of the disease.[35] Few population based studies analysed age at diagnosis as a possible risk factor for mortality and the results were conflicting. Mayberry *et al* observed increased mortality rates in patients between the ages of 10–19 and 50–59 years at diagnosis,[23] whereas Jess *et al* observed an increased mortality risk in female patients between 20–29 and 40–49 years at diagnosis,[2] and Loftus in patients with ''older'' age at diagnosis.[30] Previous population based reports on disease behavioural characteristics at diagnosis as risk factors are lacking.

In the multivariate analysis, age above 40 years at diagnosis was the only independent risk factor. It should be noted however that the multivariate analysis was hampered by the number of patients and that deaths were few or even absent in some phenotypic subgroups. SMRs were increased in phenotypic subgroups such as upper gastrointestinal disease location and stricturing disease but differences with the background population did not reach significance, presumably because of the small patient samples. Although comorbidity was not recorded for the purpose of this study, it may have played an important role in explaining the

observed increased mortality risk in the older age group at diagnosis in this cohort. The additional effect of disease and therapy related complications may have increased the chance of death in older patients with comorbidity. Eleven of the 14 patients who had a CD related cause of death were on corticosteroid therapy at the moment of death, of whom six had a septic cause of death. Two of the patients on steroid therapy also were using azathioprine, of whom one had a septic cause of death. One patient was treated with ciclosporin in addition to corticosteroids and died because of a toxic megacolon. The use of immunosuppressive medication is a reflection of disease severity and, in addition, may have exerted a contributory effect to death in the critically ill. The availability of anti-tumour necrosis factor α (TNF-α) for severe endoluminal and perianal CD dates from 1999. The effect of treatment with anti-TNF-α and other biologicals on mortality in CD is important but could not be addressed in the context of this study. Anti-TNF-α was available only during the last three years of the observation period of the present study. Only 16 patients were treated with anti-TNF-α, of whom 14 received it for less than 10% of the entire observation period. A planned new inception cohort will address the effect of treatment with biologicals on

mortality in CD, especially in comparison with the mainly ''pre-biological'' findings of the present study. The effect of smoking could not be tested reliably because patients who died during follow up were not available for the questionnaire in this present study. Data concerning smoking behaviour, as obtained at patient inception during 1991–1993, were used as a surrogate marker but appeared rather incomplete.

A consistent finding in previously reported population based studies was an increased mortality risk from gastrointestinal causes either with[27] or without[2 28 29] CD related causes incorporated. This was confirmed in the present study. Increased mortality due to gastrointestinal causes was observed in both males and females, and in age and various disease location and behaviour groups. It may explain an important part of the excess mortality in this cohort, as all eight observed deaths due to gastrointestinal causes had a causal relationship with CD.

In conclusion, this European and Israeli multinational population based study revealed an increased overall mortality risk in CD patients 10 years after diagnosis, and age greater than 40 years at diagnosis was the sole factor associated with increased mortality risk.

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REFERENCES

1 **Wolters FL**, Russel MG, Stockbrugger RW. Systematic review: has disease outcome in Crohn's disease changed during the last four decades? *Aliment Pharmacol Ther* 2004;**20**:483–96.

2 **Jess T**, Winther KV, Munkholm P, *et al.* Mortality and causes of death in Crohn's disease: follow-up of a population-based cohort in Copenhagen County, Denmark. *Gastroenterology* 2002;**122**:1808–14.

3 **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**:624–9.

4 **Stockbrugger R**, Russel MG, van Blankenstein M, *et al.* EC-IBD: a European effort in inflammatory bowel disease. *Eur J Intern Med* 2000;**11**:187–90.

5 **Shivananda S**, Lennard Jones J, Logan R, *et al.* Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut* 1996;**39**:690–7.

6 **Lennard Jones JE**. Classification of inflammatory bowel disease. *Scand J Gastroenterol* 1989;**170**(suppl):2–6.

7 **Wolters FL**, Zeijl GV, Wessels F, *et al.* Internet-based data inclusion in a European epidemiological follow-up study of IBD patients: a description of methods used. *World J Gastroenterol* 2005;**11**:7152–8.

8 Clinical Classifications Software for ICD-10 Data. *Software and User's Guide*, January 2003. Rockville, MD, Agency for Healthcare Research and Quality (http://www.ahrq.gov/data/hcup/icd10usrgd.htm).

9 **WHO**. The tenth revision of the international statistical classification of diseases and related health problems (ICD-10). Geneva: WHO Press, 1992 (ISBN 92 4 154419).

10 Mortality Database, World Health Organization, July 2000. http://www3.who.int/whosis/mort/table1. cfm?path=mort,mort_table1&language=english (accessed 16 January 2006).

11 **Gasche C**, Scholmerich J, Brynskov J, *et al.* A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. *Inflamm Bowel Dis* 2000;**6**:8–15.

12 **Breslow MD**. Comparisons among exposure groups. In: Heseltine E (ed). *Statistical methods in cancer research, the design and analysis of cohort studies*. Lyon: Oxford University Press, 1986:48–79.

13 **Schoenfeld D**. Partial residuals for the proportional hazards regression model. *Biometrika* 1982;**69**:239–41.

14 **Cleves MAGWW**, Gutierrez RG. Cox regression models. In: *An introduction to survival analysis using Stata*. Texas: Stata Press, 2002:119–95.

15 **Prior P**, Gyde S, Cooke WT, *et al.* Mortality in Crohn's disease. *Gastroenterology* 1981;**80**:307–12.

16 **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**:1387–90.

17 **Banks BM**, Zetzel L, Richter HS. Morbidity and mortality in regional enteritis. Report of 168 cases. *Am J Dig Dis* 1969;**14**:369–79.

18 **Burton I**, Dombal FT, Goligher JC. The prognosis of Crohn's disease. *Br J Surg* 1969;**56**:692.

19 **Brill CB**, Klein SF, Kark AE. Regional enteritis and entero-colitis: a study of 74 patients over 15 years. *Ann Surg* 1969;**170**:766–74.

20 **Farmer RG**, Michener WM. Prognosis of Crohn's disease with onset in childhood or adolescence. *Dig Dis Sci* 1979;**24**:752–7.

21 **Storgaard L**, Bischoff N, Henriksen FW, *et al.* Survival rate in Crohn's disease and ulcerative colitis. *Scand J Gastroenterol* 1979;**14**:225–30.

22 **Cooke WT**, Mallas E, Prior P, *et al.* Crohn's disease: course, treatment and long term prognosis. *Q J Med* 1980;**49**:363–84.

23 **Mayberry JF**, Newcombe RG, Rhodes J. Mortality in Crohn's disease. *Q J Med* 1980;**49**:63–8.

24 **Lind E**, Fausa O, Gjone E, *et al.* Crohn's disease. Treatment and outcome. *Scand J Gastroenterol* 1985;**20**:1014–18.

25 **Andrews HA**, Lewis P, Allan RN. Mortality in Crohn's disease—a clinical analysis. *Q J Med* 1989;**71**:399–405.

26 **Truelove SC**, Pena AS. Course and prognosis of Crohn's disease. *Gut* 1976;**17**:192–201.

27 **Palli D**, Trallori G, Saieva C, *et al.* General and cancer specific mortality of a population based cohort of patients with inflammatory bowel disease: the Florence Study. *Gut* 1998;**42**:175–9.

28 **Persson PG**, Bernell O, Leijonmarck CE, *et al.* Survival and cause-specific mortality in inflammatory bowel disease: a population-based cohort study. *Gastroenterology* 1996;**110**:1339–45.

29 **Ekbom A**, Helmick CG, Zack M, *et al.* Survival and causes of death in patients with inflammatory bowel disease: a population-based study. *Gastroenterology* 1992;**103**:954–60.

30 **Loftus EV Jr**, Silverstein MD, Sandborn WJ, *et al.* Crohn's disease in Olmsted County, Minnesota, 1940–1993: incidence, prevalence, and survival. *Gastroenterology* 1998;**114**:1161–8.

31 **Munkholm P**, Langholz E, Davidsen M, *et al.* Intestinal cancer risk and mortality in patients with Crohn's disease. *Gastroenterology* 1993;**105**:1716–23.

32 **Steinhart AH**, Girgrah N, McLeod RS. Reliability of a Crohn's disease clinical classification scheme based on disease behavior. *Inflamm Bowel Dis* 1998;**4**:228–34.

33 **Newcombe RG**, Mayberry JF, Rhodes J. An international study of mortality from inflammatory bowel disease. *Digestion* 1982;**24**:73–8.

34 **Sonnenberg A**. Geographic variation in the incidence of and mortality from inflammatory bowel disease. *Dis Colon Rectum* 1986;**29**:854–61.

35 **Probert CS**, Jayanthi V, Wicks AC, *et al.* Mortality from Crohn's disease in Leicestershire, 1972–1989: an epidemiological community based study. *Gut* 1992;**33**:1226–8.