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

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Key words: Mortality, Crohn's disease, population-based, cohort

Abbreviations
CD     Crohn's disease
CI     Confidence Interval
CCS    Clinical Classifications Software
EC-IBD European Collaborative study group of Inflammatory Bowel Disease
ePpPFU electronic Physician per Patient Follow-up form
ePQ    electronic Patient Questionnaire
IBD    Inflammatory Bowel Disease
ICD-10 International Classification of Diseases
LTFU   Lost to follow-up
SMR    Standardized Mortality Ratio
WHO    World Health Organisation
Abstract

Background: No previous correlation has been performed of phenotype at diagnosis of Crohn’s disease (CD) patients and mortality. 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 ten years after diagnosis in a prospectively assembled, uniformly diagnosed European population based inception cohort of 380 CD patients diagnosed between 1991 and 1993. Standardized 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 North 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 ten years after diagnosis and age above 40 years at diagnosis to be the sole factor associated with increased mortality risk.
Introduction

Crohn’s disease (CD) is a chronic inflammatory condition of unknown origin that can be localised throughout the entire gastrointestinal tract. There has been debate 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 during the last half century (3), however, 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 ten 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 twelve 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 out 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 were previously described in detail. (5) Patients were followed up from inception between October 1st 1991 and September 30th 1993 until data inclusion of the present study between August 1st 2002 and January 31st 2004 or any date prior to this period, indicated of 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 jeopardize the population-based character of the study, since all participating centres had individually met the criteria for population-based patient inclusion when the cohort was initially formed in the period of 1991-1993. Before the start of the current data collection, an arbitrary chosen minimum response rate per centre was set at 60%.

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 by 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 categorization scheme based on the International Classification of Diseases (ICD-10). 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 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
Standardized 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 (January 31st 2004 update). 95 % Confidence Intervals (95% CI) were calculated by means of the Byar’s approximation(12). The Chi-square 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 the age- and sex-specific distribution of person-years of the cohort.

Results
Ten of the thirteen participating centres complied with the minimum 60% response threshold rendering 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 and behaviour at diagnosis.
Overall mortality

Table I shows male, female and total mortality rates according to age, disease phenotype at diagnosis and residence. At 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 North 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 I, II and III show the total, male and female survival curves as observed in the cohort compared to the expected survival based on aggregate mortality statistics of all participating countries.
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Table I: Male, female and cohort specific mortality according to age (sex and country adjusted), disease phenotype at diagnosis (age, sex and country adjusted) and residence (age and sex adjusted). Thirteen patients without 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. N: number of patients; Exp.: expected number of deaths; Upper GI: upper gastrointestinal; SMR: Standardized Mortality Ratio; CI: Confidence Interval.
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 I shows 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 to have increased mortality risks.

Cause specific mortality

Table II 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 caused by 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 caused by 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 (8 deaths observed versus 4.24 expected, SMR 1.81, 95% CI: 0.78-3.57).
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Table II: Overall cause specific mortality for all patients (age, sex and country adjusted), according to gender (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). Thirteen patients without 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. Three patients died due to other causes than listed (two infectious and one unknown). N: number of patients; Exp.: expected number of deaths; Upper GI: upper gastrointestinal; SMR: Standardized Mortality Ratio; CI: Confidence Interval; CCS: Clinical Classifications Software; ICD: International Classification of Diseases
CD related mortality
Fourteen (7 males and 7 females) of the 37 observed deaths (37.8%) had a certain (6) or possible (8) CD related cause of death (Table III). The median age at diagnosis of patients with a CD related cause of death was 64 years (range, 18-83 years). The median survival after diagnosis of this group was 39 months (range, 1-112 months). The median age at diagnosis of patients with a cause of death not related to CD (Table IV) was 71 years (range, 41-81 years) and the median survival after diagnosis of these patients was 51 months (range, 6-119 months). 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 ischemia, 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 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 because of 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.
### Table III: Causes of death possibly or certainly related to CD. CCS: Clinical Classifications Software; ICD: International Classification of Diseases

<table>
<thead>
<tr>
<th>Patient and causality of death and CD</th>
<th>Centre</th>
<th>Gender</th>
<th>Disease location at diagnosis</th>
<th>Disease behaviour at diagnosis</th>
<th>Age at diagnosis (years)</th>
<th>Survival after diagnosis (months)</th>
<th>Cause of death</th>
<th>CCS ICD-10 code</th>
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<td><strong>INFECTIONS</strong></td>
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<td>34</td>
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<td>112</td>
<td>Sepsis, steroid use for CD activity</td>
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<td>South Limburg</td>
<td>Female</td>
<td>Ileocolonic</td>
<td>Inflammatory</td>
<td>26</td>
<td>94</td>
<td>Acute myocardial infarction during CD activity (autopsy confirmed). Steroid use</td>
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<td>78</td>
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<td>Congestive heart failure after elective subtotal colectomy. Steroid use</td>
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<td>Unknown</td>
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<td>71</td>
<td>8</td>
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<td>44</td>
<td>Toxic megacolon. Steroid and cyclosporine use</td>
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<td>60</td>
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<td>47</td>
<td>Unspecified cancer of peritoneum, probably metastasis of gynecological or lung cancer</td>
<td>43</td>
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</table>

**CANCER**

| 26             | Oslo          | Male   | Colonic                       | Inflammatory                  | 73                      | 10                               | Acute myocardial infarction          | 100            | No CD activity         |
| 27             | Oslo          | Male   | Colonic                       | Inflammatory                  | 75                      | 73                               | Acute myocardial infarction          | 100            | No CD activity         |
| 28             | Oslo          | Female | Colonic                       | Stricture                     | 81                      | 105                              | Coronary atherosclerosis             | 101            | No CD activity         |
| 29             | Oslo          | Female | Colonic                       | Inflammatory                  | 78                      | 30                               | Acute cerebrovascular disease        | 109            | No CD activity         |
| 30             | Copenhagen    | Male   | Ileocolonic                   | Inflammatory                  | 73                      | 65                               | Acute cerebrovascular disease        | 109            | No CD activity         |
| 31             | Copenhagen    | Female | Colonic                       | Inflammatory                  | 41                      | 93                               | Acute cerebrovascular disease        | 109            | No CD activity         |
| 32             | Cremona       | Female | Ileal                         | Stricture                     | 70                      | 100                              | Acute cerebrovascular disease        | 109            | No CD activity         |
| 33             | Oslo          | Female | Colonic                       | Inflammatory                  | 79                      | 70                               | Pulmonary embolism                   | 118            | No CD activity nor medication use during years previously |

**CARDIOVASCULAR CAUSES**

| 34             | Oslo          | Male   | Colonic                       | Inflammatory                  | 67                      | 12                               | Pneumonia                            | 122            | No immunosuppressives  |
| 35             | Oslo          | Male   | Colonic                       | Stenotic                      | 77                      | 51                               | Pneumonia                            | 122            | No immunosuppressives  |
| 36             | Heraklion     | Male   | Colonic                       | Inflammatory                  | 64                      | 60                               | COPD                                 | 127            | No CD activity         |

**PULMONARY CAUSES**

| 37             | Oslo          | Female | Colonic                       | Inflammatory                  | 74                      | 6                                | Unknown                              | -              | No CD activity         |

**UNKNOWN**

Table IV: Causes of death not related to CD. CCS: Clinical Classifications Software; ICD: International Classification of Diseases
Cox regression analysis
Age and gender as well as disease location and behaviour were the factors analysed in both the uni- and multivariate analysis. Univariate analysis showed an Hazard Ratio 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
An increased overall mortality was observed 10 years after diagnosis in this European population based cohort of CD patients. The mortality risk appeared to be increased in the age group above 40 years at diagnosis. The 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 mostly have reported on mortality figures 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 incepted during 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 17 years median follow-up time in the same cohort of CD patients.(2)

The methodological strengths of the current study are threefold. First, this study was based on a population-based, prospectively and uniformly diagnosed inception cohort of CD patients originating from ten 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. Second, patient inception at diagnosis took place during a short period of two 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. Third, no previous cohort study had the occasion to correlate disease phenotype at diagnosis according to the Vienna classification with mortality. The herein applied prognostic model could be tested in other contemporary and future cohorts as well.

There were some limitations to this study. First, 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 represented low sample sizes. This has biased the actual mortality risks in certain described geographical and phenotypic patient subsets. The 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. Second, fifty percent of the original EC-IBD centres participated in this study, leaving 52 % of CD original patients. Possibly centres with more interest in IBD and therefore more expertise in treatment participated, which might have been a source of bias. Third, retrospective data collection concerning mortality and causes of death was used. Still, for all
except one patient the exact cause of death and its relationship to CD could be 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. Fourth, CD patient classification by pattern of disease behaviour at diagnosis was previously shown to yield only a fair inter observer 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 minimized.

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, however 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 two to nine years after diagnosis (23, 27, 29), a subsequent plateau phase, and thereafter rising 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 extension of follow-up of this cohort in the future may reveal the impact of possible late sequels 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 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). The 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 shorter than 6 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 to 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 further course of disease. (35) Few population-based studies analysed age at diagnosis as a possible
risk factor for mortality and the results were conflicting. Mayberry observed increased mortality rates in patients between ages of 10-19 and 50-59 years at diagnosis(23), whereas Jess observed 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 small patient samples. Although co-morbidity was not recorded for the purpose of this study, it may have played an important role to explain 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 co-morbidity. Eleven patients of the 14 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 cyclosporine in addition to corticosteroids and died because of a toxic megacolon. The use of immunosuppressive medication is a reflection of disease severity and, on top of that, may have exerted a contributory effect to death in the critically ill. The availability of anti-TNFα for severe endoluminal and perianal CD dates from 1999. The effect of treatment with anti-TNFα and other biologicals on mortality in CD is important but could not be addressed in the context of this study. Anti-TNFα was available only during the last three years of the observation period of the present study. Only sixteen patients were treated with anti-TNFα of whom 14 shorter 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 of 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 could be confirmed in the present study. Increased mortality due to gastrointestinal causes could be observed in both males and females, in both age and various disease location and behaviour groups. It could 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 ten years after diagnosis and age above 40 years at diagnosis to be the sole factor associated with increased mortality risk.
## Acknowledgements

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<tr>
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<th>Investigators</th>
<th>Contribution</th>
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<tr>
<td>Maastricht (project coordinator) Dept of Gastroenterology and Hepatology University Hospital Maastricht Maastricht The Netherlands</td>
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<tr>
<td>Global Vitis, Wattstraat 52, Sassenheim, The Netherlands</td>
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<td>Juan Clofent Mercedes Butron</td>
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Sponsor details
This study was granted by the European Commission as a fifth framework shared cost action (QLG4-CT-2000-01414)

Ethics approval
At all participating sites, approval for project execution was obtained from local medical ethics committees.

Statement
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Statement
The authors declare that there are no competing interests involved.
References
Figure legend

Figure I: Total observed survival of the entire cohort (-) versus the expected survival (---) based on aggregate mortality statistics of all participating countries. Overall expected versus observed mortality rates were 99.5% versus 98.9%, 97.0% versus 94.1% and 93.0% versus 89.6% 1 year, five years and ten years after diagnosis respectively. N: number of patents

Figure II: Male observed survival of the entire cohort (-) versus the expected survival (---) based on aggregate mortality statistics of all participating countries. Male expected versus observed mortality rates were 99.6% versus 98.9%, 96.2% versus 91.8% and 91.2% versus 87.5% 1 year, five years and ten years after diagnosis respectively. N: number of patents

Figure III: Female observed survival of the entire cohort (-) versus the expected survival (---) based on aggregate mortality statistics of all participating countries. Female expected versus observed mortality rates were 99.7% versus 98.9%, 97.8% versus 96.1% and 94.6% versus 90.6% 1 year, five years and ten years after diagnosis respectively. N: number of patents
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