

Meta-analysis: Mortality in Crohn's Disease

C. Canavan; K. R. Abrams; J. F. Mayberry

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Summary and Introduction

Summary

Aim: To perform a meta-analysis of published literature reporting standardized mortality ratios (SMR) for Crohn's patients from 1970 to date.

Methods: Medline search identified relevant papers. Exploding references identified additional papers. When two papers reviewed mortality of one patient group at different times, the later publication was used.

Results: Of 13 papers identified, three studies reported SMR below 1.0, two others had confidence intervals including 1.0. All other studies reported mortality higher than the general population. Meta-analysis using a random effects model shows the pooled estimate for SMR in Crohn's disease is 1.52 (95% CI: 1.32 to 1.74 [$P < 0.0001$]). Meta-regression shows the SMR for these patients has decreased slightly over the past 30 years, but this decrease is not statistically significant ($P = 0.08$).

Conclusion: Assessing evidence from original studies and conducting a meta-analysis shows age-adjusted mortality risk from Crohn's disease is over 50% greater than the general population. Whilst mortality has improved since the condition was first recognized, further evaluation of the patients studied in the cohorts included here is necessary to assess more recent changes in clinical practice.

Introduction

Incidence of Crohn's disease has been reported as becoming stable in the USA over the past 20 years,^[1] but prevalence is still higher than in previous decades.^[1-3] In Europe, however, the incidence and prevalence are still increasing.^[4-6] A recent study in the UK used data from primary care to report a prevalence of 144.8 cases per 100 000.^[7] The prevalence of Crohn's disease in North America is currently estimated as ranging from 26.0 to 198.5 cases per 100 000 persons, which equates to 400 000-600 000 patients with Crohn's disease in North America alone.^[8]

The first study into mortality in Crohn's disease was published in 1970.^[9] Since then there have been numerous reports of standardized mortality ratios (SMR) for Crohn's disease that vary from 0.72^[10] to 2.67.^[11] Standardized mortality ratios are calculated as the ratio of deaths observed in a cohort to those expected in a group of the same size from the general population in the same area and standardized for age and sex of the individuals in the study cohort. Mortality data are important because they allow patients to be aware of prognosis and make informed decisions about treatment. They also provide clinicians with an indicator of the success of their management and if this has improved over time. Current literature reporting mortality vary so much in their results^[10,11] that an accurate analysis of the SMR from this data is of importance. It will help establish whether Crohn's disease is a benign condition or if it carries a risk of increased mortality. Accurate data are also of importance to insurers when calculating risks for life policies.^[12-14] This systematic review and meta-analysis of published data aims to provide an accurate overview of the current risk of mortality in Crohn's disease and how this risk has changed over time.

Methods

Search Strategy

All published reports citing the SMR in Crohn's disease were collected by conducting a literature search on MEDLINE using the following key words, both in free text and as MESH headings: Crohn's disease, inflammatory bowel disease, mortality, outcome, prognosis. A comprehensive search of reference lists of all the review articles and original studies retrieved by this method was performed to identify additional reports. Through this approach 1195 papers that had been published between 1970 and 2004 were identified.

Inclusion and Exclusion Criteria

Only English language journal papers were included where Crohn's disease patients had been studied and mortality statistics calculated that included either SMR or reported observed and expected deaths. Studies were excluded if they only reported mortality rates with regard to surgery or as part of a randomized control trial for a drug because they focused only on a sub-group of patients with Crohn's disease. When two or more publications from one patient cohort appeared to review the same patients only the most recent study results were included. This left 13 original papers for analysis (see Figure 1).

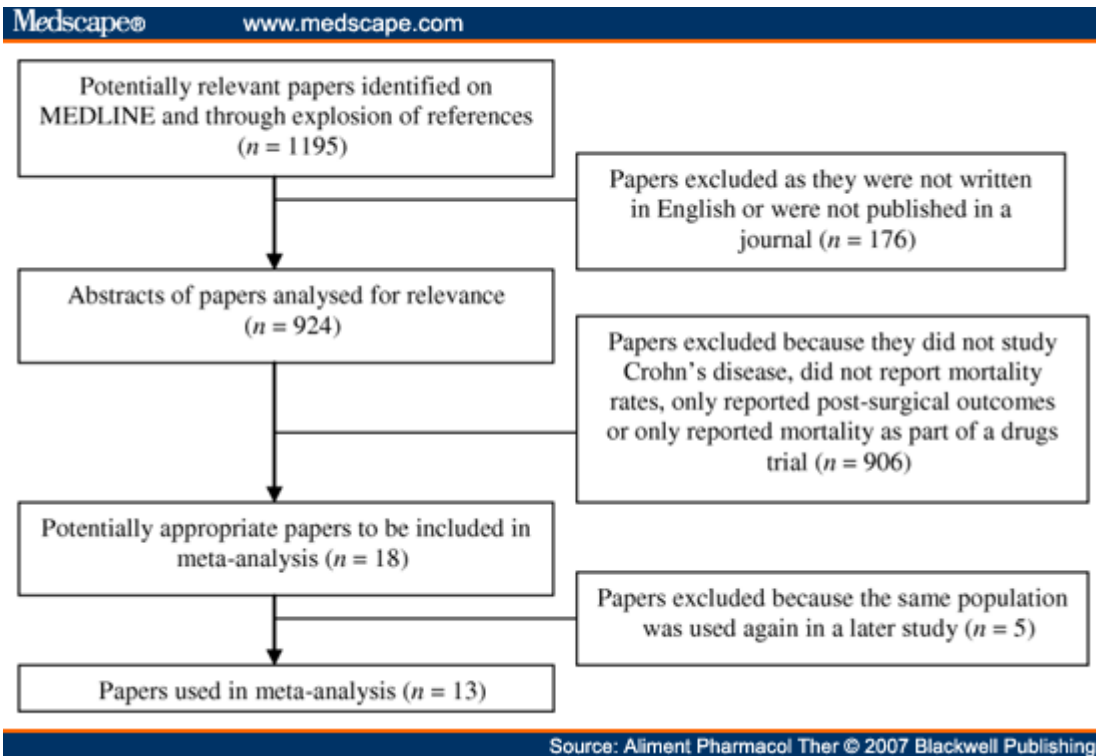


Figure 1.

QUOROM statement flow diagram¹² indicating the inclusion and exclusion criteria for papers into this meta-analysis.

Data Extraction

Each paper was critically reviewed and the following data extracted:

1. Country of origin
2. Type of centre where study was conducted
3. Period over which study was conducted
4. Number of patients in the study
5. Average follow-up of study participants (mean or median)
6. The SMR
7. The confidence interval for the SMR, and where not reported, the observed and expected numbers of deaths
8. Year of publication
9. Median year of diagnosis of the study population

Details of the studies are summarized in [Table 1](#).

Community-based studies are those in which a population of patients with Crohn's disease lived or were diagnosed in a defined geographic area, whilst hospital or specialist centre-based studies include patients referred to the institute from an undefined area. All studies are limited by bias but this can be reduced if certain criteria are met.¹³ A cohort study may be considered to be of good quality if cases are accurately established, comparable groups are assembled initially and maintained throughout the study, follow-up at least 80%, reliable and valid measurement instruments applied equally to the groups, outcome assessment is masked, interventions defined clearly, all important outcomes considered and appropriate attention to confounders in analysis. Hospital or specialist referral centers may introduce bias through the pre-selected nature of their patient cohorts. All papers included within this analysis are of good quality according to this criteria and report on a population studied for at least 15 years and all followed patients for an average of at least 6 years.

Statistical Analysis

All analyses were performed using Stata statistical software.¹¹⁶⁻¹¹⁸ The overall pooled estimate and 95% confidence interval of SMR in patients with Crohn's disease were obtained using either a fixed or random effects meta-analysis model on a log SMR scale as appropriate depending on a test for heterogeneity using a 10% significance level.¹¹⁹ Heterogeneity was explored using sub group analysis for country of origin and the type of center at which the study was conducted. Meta-regression techniques were used to assess change in log SMR with disease duration or study duration; the data used for this are included in Table 1, and results were back-transformed and presented in terms of percentage change in SMR per year. The influence of individual studied was assessed using an inference plot.

Median year of diagnosis of the study population and median year of diagnosis plus the average follow-up time were used as indicators of the period during which patients were diagnosed and treated. For example, if median year of diagnosis was 1970 and the average follow-up was 7 years, then the year used as an indication for time of diagnosis would be 1970 and the year used to indicate time during which the cohort was treated would be 1977 (1970 + 7). The weight given to the studies is inversely proportional to the variance associated with the SMR reported for each of them. For the studies where the confidence interval was not reported we calculated the standard error using the observed deaths and expected deaths reported in the papers. The data used in the meta-analysis are summarized in Table 2.

Results

Of the thirteen studies analyzed, three reported an SMR below 1.0^{110,20,21} and two had a confidence interval containing 1.0.^{22,23} All other studies report mortality for Crohn's disease as higher than for the general population. A chi-squared test for heterogeneity based on these 13 studies yielded $X^2 = 42.08$, $P < 0.001$ and therefore a random effects model was used to produce an overall pooled estimate for the SMR of 1.52 (95% confidence interval 1.32-1.74), which was highly statistically significant ($P < 0.0001$), Figure 2.

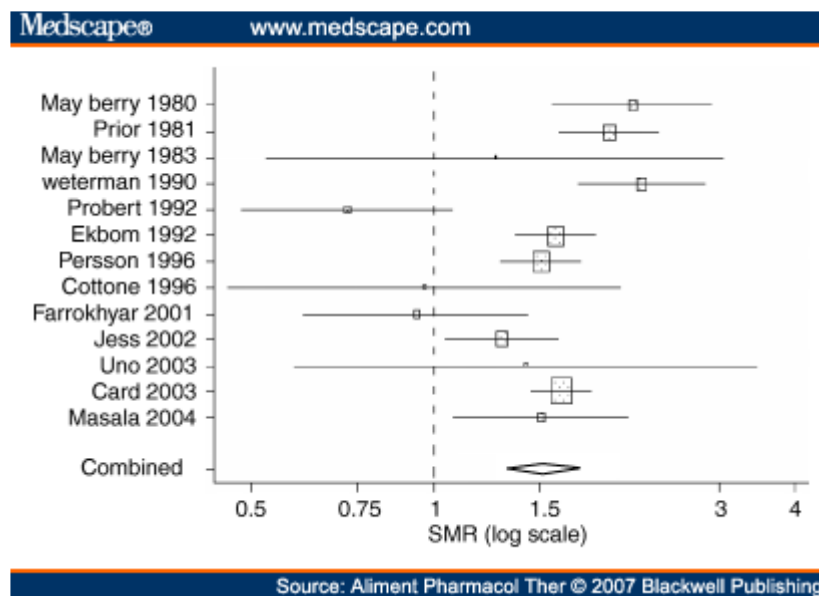


Figure 2.

Forrest plot of studies reporting SMR (log scale) for patients with Crohn's disease. The boxes represent the SMR point estimate. The size of the box represents the weight given to the study, which is inversely proportionate to the variance. The lines represent the 95% confidence interval for the point estimate in each study.

Subgroup analyses by country yielded consistent results for UK and Scandinavian-based studies, indicating a SMR statistically significantly greater than 1, with the UK^{10,21,22,24,32,41} having an SMR of 1.42 (95% CI: 1.07-1.87, $P < 0.001$) and Scandinavia^{25,26,33} 1.50 (95% CI: 1.35-1.66, $P < 0.001$), the result for Italy^{20,43} was 1.38 (95% CI: 0.98-1.96, $P = 0.07$). The combined estimate for the Italian studies was not significantly greater than 1 and so not statistically significantly different from the general population, even though it was not statistically significantly lower than either UK or Scandinavia.

Subgroup analysis of the centers at which studies were conducted showed that SMR was higher in hospitals^{21,23,41} (1.73 [95% CI: 1.45-2.47, $P < 0.001$]) and referral centres^{11,20} (2.06 [95% CI: 1.63-2.60, $P < 0.001$]) than in community-based studies^{10,22,25,26,28,33,43} (1.48 95% CI: 1.28-1.70, $P < 0.001$), but this difference was not statistically significant.

Median year of diagnosis of the study population and median year of diagnosis plus the average follow-up time were used as indicators of the period during which patients were diagnosed and treated. These data were used to assess change in SMR with time. This was performed using a mixed effects meta-regression model. There was a 2.3% decrease in SMR per year (95% CI: 0.7-3%) for median year of diagnosis, which was statistically significant ($P = 0.002$), Figure 3, and this is also true when the average follow up is included (1.6% decrease per year [95% CI: 0.1-3%]).

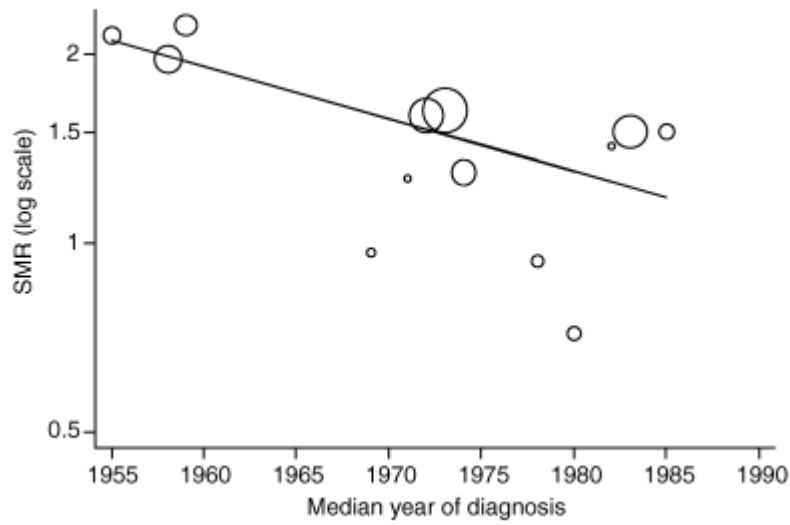


Figure 3. Meta-regression of change in SMR (log scale) with median year of diagnosis. The circles on the graph represent the studies included; the size of the circle indicates the weight given to the study, which is inversely proportionate to the study variance.

Sub-group analysis of median year of diagnosis showed a significant difference between patients diagnosed before 1970 and those diagnosed from 1970 onwards. A χ^2 -test for heterogeneity within both these sub-groups showed there was insignificant heterogeneity, so differences in SMR were because of the sampling error and a fixed meta-analysis model was used. Studies where patient cohorts have a median year of diagnosis before 1970 had a combined SMR of 1.80 (95% CI: 1.63-2.00, $P < 0.001$), whilst those with a median diagnosis in 1970 or later have a combined SMR of 1.48 (95% CI: 1.37-1.60, $P < 0.001$). Meta-regression analysis using median year of diagnosis showed no statistically significant change in SMR since 1970; 1.9% decrease per year (95% CI: 6.1% decrease to 1.7% increase, $P = 0.26$), but the subgroup for those diagnosed before 1970 does show a decrease in SMR of 2.7% per year (95% CI: 1.4%, $P = 0.003$). There was only one study with a median year of diagnosis in the 1960s, and that was 1969.⁽¹¹⁾ If the regression analysis is re-calculated placing the 1969 study with those that had patient cohorts with a median year of diagnosis from 1970 onwards and those studies with a median diagnosis year before 1960, neither of these new subgroups showed any significant change in SMR over time. Before 1960 it was 0.1% increase per year (95% CI: 9.1% decrease to 10.3% increase, $P = 0.98$) and since 1969 it was a 2.2% decrease (95% CI: 5.1% decrease to 0.7% increase, $P = 0.14$), Figure 4.

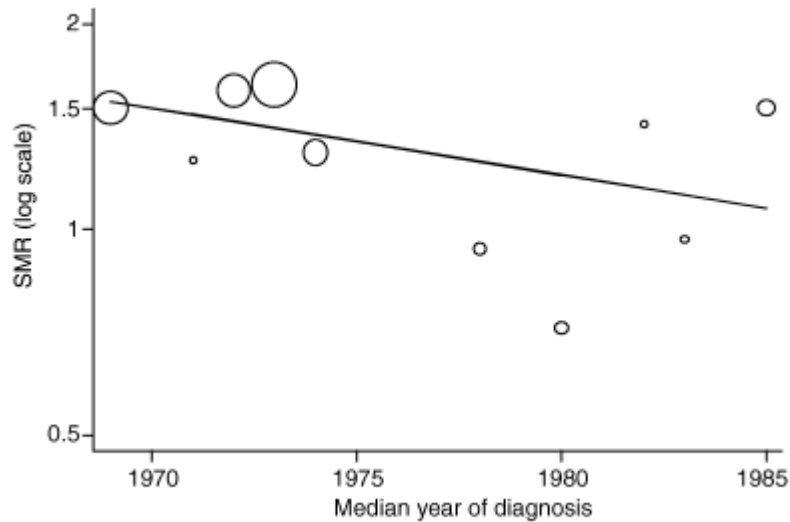


Figure 4. Meta-regression of change in SMR (log scale) with median year of diagnosis for patients diagnosed after 1969. The circles on the graph represent the studies included; the size of the circle indicates the weight given to the study, which is inversely proportionate to the study variance.

When average follow-up is added to mean year of diagnosis to give an indication of the time at which patients received treatment the results were similar. Subgroup analysis showed that studies with a median year of diagnosis plus average follow up since the 1980s have a statistically significantly lower SMR than those before 1970.

The two studies with a median year of diagnosis plus average follow-up during the 1970s are not statistically significantly different from either those in the 1960s or those since 1980

1960s combined SMR is 2.20 (95% CI: 1.82-2.66, $P < 0.001$);
 1970s combined SMR is 1.93 (95% CI: 1.60-2.33, $P < 0.001$);
 1980s combined SMR is 1.21 (95% CI: 0.91-1.61, $P = 0.19$). This includes the study by Probert *et al.*^[10] the SMR from which is an outlier and significantly reduces the SMR, as shown by an inference plot, and increases the measure of heterogeneity from 5.18 to 17.24. When this study is removed from the subgroup the combined SMR for the 1980s is 1.44 (95% CI: 1.19-1.75, $P < 0.001$);
 1990s and 2000 combined SMR is 1.50 (95% CI: 1.32-1.70, $P < 0.001$).

Meta regression of studies where the median year of diagnosis is 1970 or more recent (including the study by Probert *et al.*^[10]) including the average follow-up showed no statistically significant changes in SMR over the 30 years included in the analysis; SMR fell by 0.8% per year, which is not statistically significant (95% CI: 3.2% decrease to 1.6% increase, $P = 0.499$), Figure 5.

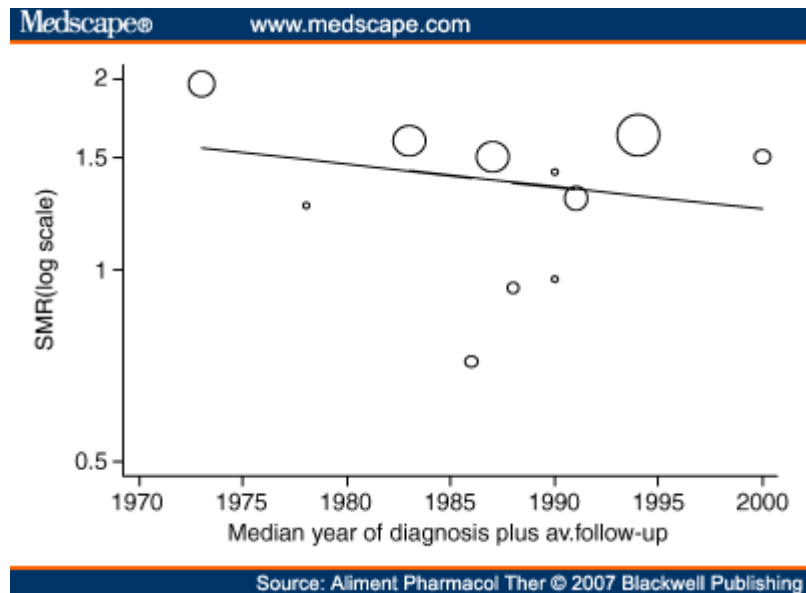


Figure 5.

Meta-regression of change in SMR (log scale) with median year of diagnosis for patients diagnosed plus average follow-up since 1970. The circles on the graph represent the studies included; the size of the circle indicates the weight given to the study, which is inversely proportionate to the study variance.

Meta regression was conducted to assess the effect that duration of follow-up had on the SMR. This showed a small non-significant increase in SMR as the duration of disease increased (1.7% increase per year [95% CI: 2.6% decrease to 6.2% increase, $P = 0.44$). Meta regression was also carried out to ascertain the effects of the duration of the study on reported SMR. The SMR was greatest in longer studies, with an increase in SMR of 2.0% per year of study duration (95% CI: 0.8-3.1%). This result was highly statistically significant ($P = 0.001$).

Sensitivity analysis was carried out and an inference plot created. This omitted individual studies and showed that no individual study significantly changes the combined SMR. The study by Probert *et al.*^[10] has the single greatest effect on combined SMR and if removed the combined SMR would increase to 1.61 (95% CI: 1.43-1.81). Three studies report SMR below 1.0.^[10,20,21] When these are excluded the combined SMR is 1.67 (95% CI: 1.51-1.86) and the meta-regression for median year of diagnosis alone or with average follow-up do not statistically significantly change. Two studies reported SMR above 2.0.^[11,22] Their removal reduces the combined SMR to 1.42 (95% CI: 1.24-1.63) and meta-regression of change in SMR with median year of diagnosis plus average follow-up is no longer statistically significant. The SMR decreases by 0.8% per year (95% CI: 3.2% to 1.6% increase, $P = 0.499$). The median diagnosis year plus average follow-up was in the 1960s for both of these studies

Discussion

Reports of age-adjusted mortality in Crohn's disease range from a 28% reduction^[10] to a risk more than twice that seen in the general population.^[11] These wide ranging results mean that recent reviews have suggested that the SMR for patients with Crohn's disease is similar to that of the general population.^[13,26-28] This meta-analysis of 13 studies reporting SMR in Crohn's disease over the past 35 years shows that this is not the case. The risk of dying for patients with Crohn's disease is over 50% higher than would be expected for someone in the general population of the same age and sex. This is reflected in a recent long-term study of prognosis for patients with Crohn's disease in Cardiff, which showed reduced life expectancy for all patients, especially those diagnosed before the age of 20.^[29] Overall life expectancy for men diagnosed with Crohn's disease in the Cardiff cohort was 77.3 years and 79.0 years for women, however, those diagnosed before the age of 20 had a median age at death of 64 years. Life expectancy of the general population over the study period was 71 for males and 77 for females.^[30]

A sensitivity analysis of the studies analysed in this paper shows that no one study changes the SMR to such an extent that omitting it would change the combined SMR sufficiently to take it outside the 95% confidence interval. The study by Probert *et al.*^[10] had the greatest single effect and if removed would increase the combined estimate of SMR in Crohn's disease to 1.61 (95% CI: 1.43-1.81). Unlike the other 12 reports, the study by Probert *et al.*^[10] included a large number of South Asian patients and this may have skewed the population as in a related study it was shown that at that time there was a difference in the disease experience between European and South East Asian patients, with South East Asians experiencing milder disease.^[31] Two studies reported mortality more than double that of the general population,^[11,32] but their removal does not significantly alter the combined SMR estimate, neither did that of the three studies reporting SMR below 1.0.^[10,20,21] Thus the overall SMR from this meta-analysis is robust. It is possible that this analysis is subject to publication bias but unlike in clinical trials the mechanism by which this exists in epidemiological studies is unknown.

Subgroup analysis of the type of centre at which the study was conducted showed specialist centers had the highest combined SMR and community-based studies the lowest. This trend reflects the fact that patients in specialist referral centers and hospitals will tend to have more severe disease than those drawn from a community. The results were not statistically significant, however, and this may reflect the small number of reports eligible for inclusion in this study. Subgroup analysis also showed no significant difference in SMR between countries, despite different management styles, with the UK maintaining patients on medication as long as possible whilst Scandinavia adopts a more active surgical approach.^[33]

Assessing change in SMR based on year of publication does not reflect the population accurately as papers tend to be published some time after completion of the study and fail to take account of when patients were diagnosed. Using the median year of diagnosis of the patient cohort is preferable as it gives a more accurate estimate of the time patients were treated. Regression analysis of change in SMR with median year of diagnosis showed a significant decrease of 1.9% per year from 1955 to 1985. Including average follow-up in the calculations reduces the decrease to 1.6% per year and includes patients treated until 2000. When studies are grouped according to the median year of diagnosis, subgroup analysis shows that SMR is significantly lower for patients diagnosed since 1970 compared with those diagnosed before 1970 (1.80 compared with 1.48). However, it has not changed significantly since 1970. This is reflected in the regression analysis that showed no significant change in SMR for patients diagnosed since 1969. There was also no statistically significant difference in SMR for patients diagnosed before 1960, although this group experienced a statistically significantly higher mortality than those diagnosed since 1969. None of the studies had a median year of diagnosis in the mid-1960s, so when using median year of diagnosis in calculations it is difficult to establish exactly when the change in SMR occurred. The use of median year of diagnosis as a marker of passage of time also only allows change in SMR to be assessed until 1985, giving little idea of how SMR may have altered subsequently.

Adding the average follow-up to median diagnosis year gives a more appropriate estimate for the period patients received treatment and allows analysis of management in the 1960s, 1970s, 1980s and the 1990s. Subgroup analysis of each decade shows no statistically significant difference from one decade to the next, but there is a significant decrease in SMR between those patients treated in the 1960s and those treated in the 1980s and 1990s. Mortality from Crohn's disease has not improved since 1970 and this is consistent with a recent systematic review that reports no change in disease outcome in 40 years.^[34] The reduction in SMR seen between patients diagnosed and treated before 1960 and those diagnosed and treated since 1970 may be because of a change in long-term treatment of Crohn's disease. In the 1960s Crohn's colitis was first recognized^[35] and steroids were introduced for treatment of Crohn's disease.^[36,37] The first mortality study of Crohn's disease in 1970^[3] recorded a higher SMR for patients treated with steroids (3.6) compared with those who had not (1.8). This has not been reported in subsequent studies and may reflect the fact that patients taking steroids have more severe disease. Azathioprine was first used in Crohn's disease in Europe in 1970.^[38] Along with corticosteroids it has been the mainstay of management and the introduction of these two drugs coincides with the reduction seen in SMR. Infliximab was first introduced for use in Crohn's disease in 1995.^[39] This study has not shown it to have a significant impact on SMR yet, but its use was not widespread until 2002.^[2,40] so it is too early to identify any changes.

Regression analysis of the data in our study also shows that there is no significant increase in mortality with duration of disease. The longest follow up of patients was 21.6 years and failed to capture a second peak in mortality, which has been suggested may occur after 20 years^[32,33,41] This would suggest that the introduction of steroids and azathioprine may have reduced deaths later in the disease course, thus eliminating this second peak of mortality, leaving surgery in more recently diagnosed patients as the main cause of mortality.^[33]

Meta-regression showed a link between duration of study and reported SMR. Studies over long periods do not necessarily have longer follow-up, thus they may have recruited more patients longer ago and so observed more deaths as treatment may have been less effective at that time.

There is a greatly increased mortality risk for patients who have been diagnosed less than 5 years,^[11,32,33,41] the majority of whom die due to surgical complications.^[33] In future this may need to be reflected in consultations with newly diagnosed patients. Patients who die later have a high incidence of gastrointestinal cancer and renal disease.^[33] Mortality is also reported to be highest in patients diagnosed under 20 years old^[32,33,41] and women diagnosed before the age of 50 years.^[33] Smoking is associated with Crohn's disease^[42] and the excess mortality seen in these studies may be partly because of this habit.^[43] In a recent study in Florence^[43] patients with Crohn's disease were shown to have a significantly raised SMR for gastrointestinal disease, all cancers and specifically lung cancer (4.49, 2.10 and 4.00 respectively); 70% of these patients were current or former smokers. Consequently, smoking is a confounding factor when analyzing mortality in Crohn's disease, however, a nationwide British study that adjusted for this characteristic still showed patients to have a higher SMR than the general population.^[24]

This analysis includes studies that were conducted within general and specialist health care settings and include results from different countries. This reduces subject bias so the results can be widely applied in Crohn's disease. There are few data about the socioeconomic class of participants, but the broad range of geographical sites at which the studies took place reduces bias from this source. Another potential source for bias is patient identification. All studies used the same criteria for diagnosis, but it is impossible to tell how rigorously these were applied, especially in the primary care setting where diagnosis was made by a third party.^[24] The study from Florence is the only study within this analysis likely to have reported the true SMR for patients with Crohn's disease in its area, as it was the only one to use a capture-recapture technique.^[44] This ensures a more comprehensive identification of cases. However, meta-analysis using aggregated patient-level co-variants (e.g. mean disease duration) has low statistical power compared with those based on individual patient data (IPD) analysis.^[25]

Almost by definition the use of meta-analysis techniques in descriptive etiological epidemiology is a blunt instrument and whilst this study casts doubt on the belief that mortality in patients with Crohn's disease is not increased, further investigation via an individual patient detail meta-analysis is required to fully elucidate the mortality experienced of patients with the condition.

In conclusion, this first meta-analysis of mortality rates in patients with Crohn's disease shows that they have an increased SMR of 1.52 and this has not changed significantly in the past 30 years. An SMR of 1.52 comparable with reports of increased mortality in rheumatoid arthritis (reports vary from 1.28^[45] to 2.644^[8]) and for smokers compared with non-smokers (1.15^[46] to 1.24^[47] for people smoking less than 15 cigarettes per day, but 2.14^[47] to 2.26^[48] for those smoking more than 15 cigarettes per day), although no meta-analyses exist and reported SMRs vary widely. It is higher than the SMR for patients with asthma (1.2^[49]), celiac disease (1.17^[50]) and the SMR attached to ulcerative colitis reported by many studies.^[21,25,51] The SMR seen in Crohn's disease is lower than that reported in diabetes, where studies report SMRs that vary from 1.73^[25] to 2.10.^[52] The concept of SMR is probably difficult for patients to grasp and information needs to be presented in terms of life expectancy, which requires further research, as does prognosis after 20 years of disease and study into the cause of the increased mortality that is seen in these patients.

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Table 1. Details of Each Study Included and Population Studied

Paper (including author and year)	Median year of diagnosis	Duration of study	Average disease duration (years)	Centre where study was conducted	Study population size
Cardiff (1980) ^[30]	1955	42 years	13.3 [median]	Community based	218
Birmingham (1981) ^[39]	1958	36 years	14.5 [mean]	Hospital based	513
Bridgend (1983) ^[22]	1971	29 years	7.6 [mean]	Community based	79

Leiden (1990) ^[11]	1959	50 years	9.9 [mean]	Specialist referral centre	659
Leicester (1992) ^[10]	1980	17 years	6.0 [median]	Community based	610
Uppsala (1992) ^[26]	1972	18 years	11.8 [mean]	Community based	1469
Stockholm (1996) ^[25]	1969	35 years	18.4 [mean]	Community based	1251
Palermo (1996) ^[20]	1983	20 years	7.8 [median]	Specialist referral centre	531
Midlands and South England (2001) ^[21]	1978	15 years	10.2 [mean]	Hospital based	196
Copenhagen (2002) ^[31]	1974	35 years 1974	17.0 [median]	Community based	374
Kyushu and Fukuoka (2003) ^[23]	1982	30 years	8.4 [median]	Hospital based	544
Nottingham (2003) ^[24]	1973	Database established 1987	21.6 [mean]	Computerised General Practice Research Database	5960
Florence (2004) ^[41]	1985	23 years	15 [median]	Community based	231

Table 2. Study Data Used in the Meta-analysis

Paper	SMR	Lower CI	Upper CI	LogSMR	SE[LogSMR]
Mayberry <i>et al.</i> ^{[30]*}	2.16	1.85	2.47	0.77	0.16
Prior <i>et al.</i> ^{[39]*}	2.00	1.80	2.19	0.68	0.10
Mayberry <i>et al.</i> ^{[22]*}	1.27	0.39	2.15	0.24	0.45
Weterman <i>et al.</i> ^[11]	2.23	1.75	2.85	0.80	0.12
Probert <i>et al.</i> ^[10]	0.72	0.49	1.10	-0.33	0.21
Ekbohm <i>et al.</i> ^[26]	1.60	1.40	1.90	0.47	0.08
Persson <i>et al.</i> ^[25]	1.51	1.29	1.75	0.41	0.08
Cottone <i>et al.</i> ^[20]	0.97	0.40	1.80	-0.03	0.38
Farrokhyar <i>et al.</i> ^[21]	0.94	0.59	1.40	-0.06	0.22
Jess <i>et al.</i> ^[31]	1.30	1.01	1.56	0.26	0.11
Uno <i>et al.</i> ^[23]	1.43	0.53	3.12	0.36	0.45
Card <i>et al.</i> ^[24]	1.63	1.43	1.80	0.49	0.06
Masala <i>et al.</i> ^[41]	1.51	1.06	2.08	0.41	0.17

*Confidence intervals calculated using observed and expected data, rather than directly extracted.

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Reprint Address

Dr C. Canavan, Digestive Diseases Centre, University Hospitals of Leicester, Leicester General Hospital, Gwendolen Road, Leicester, LE5 4PW. E-mail: cc71@le.ac.uk .

C. Canavan,* K. R. Abrams,[†] J. F. Mayberry*

*Digestive Diseases Centre, University Hospitals of Leicester, Leicester General Hospital, Leicester

[†]Centre for Biostatistics and Genetic Epidemiology, Department of Health Sciences, University of Leicester