Published by Oxford University Press on behalf of the International Epidemiological Association
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International Journal of Epidemiology 2007;**36**:890–899
doi:10.1093/ije/dym034

OTHER ORIGINAL PAPERS

Time trends of mortality from Crohn's disease and ulcerative colitis

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Accepted 12 February 2007

Aims The present study served to test whether Crohn's disease and ulcerative colitis showed similarities in the temporal variation of their mortality rates among different countries.

Methods Mortality data from 21 different countries between 1951 and 2005 were analysed, including Argentina, Australia, Austria, Belgium, Canada, Chile, Denmark, England, Finland, France, Germany, Italy, Japan, Mexico, Netherlands, Scotland, Spain, Sweden, Switzerland, Taiwan and USA. The age-specific death rates of each individual country, as well as the average age-specific rates of all countries, were plotted against the period of death.

Results Death rates from ulcerative colitis were initially 6-fold higher than those of Crohn's disease. Mortality from ulcerative colitis decreased continuously during the past 50 years. Mortality from Crohn's disease increased from 1951 to 1975 until reaching a similar level as mortality from ulcerative colitis. Since then the death rates of both diseases have followed a parallel time course. A same type of behaviour was found in the time trends of each individual age-group. The data from most countries revealed similar temporal patterns.

Conclusions The relationships between the temporal changes of mortality from Crohn's disease and ulcerative colitis might suggest the presence of one *primary* risk factor responsible for the occurrence of both diseases, and at the existence of one additional *secondary* risk factor, responsible for the expression of Crohn's disease alone.

Keywords Death rates, environmental risk factor, epidemiology, aetiology of Crohn's disease, aetiology of ulcerative colitis, inflammatory bowel disease, mortality

Introduction

In spite of numerous efforts to unravel the aetiology of Crohn's disease and ulcerative colitis, the mechanisms underlying the occurrence of inflammatory bowel disease have remained unknown. The time trends of both diseases have changed rapidly during the past five decades. The frequencies of both diseases also show marked geographic fluctuations among different countries. These temporal and geographic variations implicate the existence of environmental factors, which must influence the occurrence of inflammatory bowel disease.[1,2] The analysis of the time trends of inflammatory bowel disease represents a powerful research tool to investigate the contribution of environmental factors and gain insights about possible causative mechanisms. Ideally, one would analyse the time trends of inflammatory bowel disease following its *incidence* among different demographic strata. However, very few countries have available consistent incidence data that cover Crohn's disease and ulcerative colitis over prolonged time periods using similar and unchanging methods of data acquisition. Since both types of inflammatory bowel disease are relatively uncommon, incidence data accumulated from individual medical centres do not exceed a few hundred cases. Such low case numbers make it difficult to conduct age-specific analyses of time trends. In the present study, therefore, *mortality* is used as a surrogate morbidity parameter that is readily available for a large variety of different countries. It is hoped that mortality data can shed light on the true underlying time trends of Crohn's disease and ulcerative colitis. Peptic ulcer provides the classic epidemiologic precedent for another gastrointestinal condition with a low case fatality

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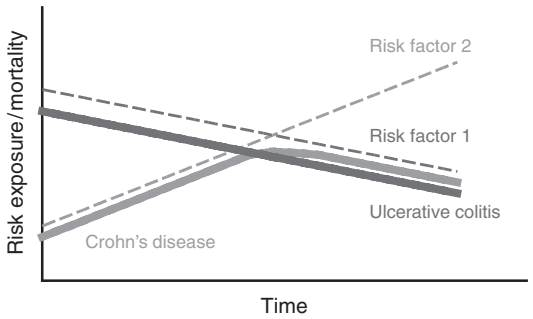

Figure 1 Hypothetical model of the interaction between the time trends of two separate risk factors for ulcerative colitis and Crohn's disease. Declining trends of the first risk factor caused a decline in mortality from ulcerative colitis and prevented a further rise in mortality from Crohn's disease. The first risk factor might be necessary for the development of either type of inflammatory bowel disease. The addition of the second risk factor might contribute to the distinction between the two diseases.

rate, where death rates proved a reliable morbidity parameter to predict long-term disease behaviour.[3]

Two previous studies revealed a characteristic relationship between the time trends of mortality from Crohn's disease and ulcerative colitis.[4,5] These previous data suggested an interaction between the time trends of ulcerative colitis and Crohn's disease that is outlined in the scheme of Figure 1. According to this model, one environmental risk factor is responsible for mortality from ulcerative colitis. The decline in this first risk factor has led to a decline in mortality from ulcerative colitis. Mortality from Crohn's disease appears to depend on the simultaneous influences of the first risk factor, as well as a second environmental risk factor specific for Crohn's disease alone. Because of this dual dependence on both risk factors, the decline of the first risk factor prevented any further rise of Crohn's disease mortality following the rising trends of the second risk factor. The present study analyses the time trends of mortality from Crohn's disease and ulcerative colitis from 21 countries between 1951 and 2005. The study extends the previous analyses by a decade including newer data and a larger variety of different countries. The inclusion of statistical data from a larger group of countries provides the opportunity to check the general validity of the relationship between the time trends of mortality from Crohn's disease and ulcerative colitis. The study also serves to test whether the most recent temporal patterns still corroborate the hypothesis of two interacting risk factors in the aetiology of inflammatory bowel disease.

Methods

Data sources

Mortality data from 21 different countries were analysed, including Argentina, Australia, Austria, Belgium, Canada, Chile, Denmark, England & Wales, Finland, France, Germany, Italy, Japan, Mexico, Netherlands, Scotland, Spain, Sweden, Switzerland, Taiwan and the United States. To be included in the study, the number of deaths from Crohn's disease or ulcerative colitis had to be broken down by 5-year age groups, individual years of death, and the vital statistics had to cover a time period of at least 20 years. Crohn's disease and ulcerative colitis became available as separate disease codes 572.0 and 572.2, respectively, since the introduction of the seventh revision of the International Classification of Diseases (ICD). The seventh revision was used from 1950 onwards in Canada, England & Wales, Italy, Netherlands and Switzerland. It was used since 1961 in Sweden and since 1962 in the United States. For the United States, previously published data by Acheson[6,7] were used to cover mortality during the period between 1950 and 1956. In the eighth revision of the ICD, Crohn's disease and ulcerative colitis were coded as 563.0 and 563.1, respectively. Australia, Austria, Belgium, Denmark, Finland, France, Germany, Japan, Scotland and Spain began listing Crohn's disease and ulcerative colitis between 1968 and 1975, concomitant with their introduction of the eighth revision of the ICD. Data from Chile, Mexico and Taiwan became available with the introduction of the ninth revision of the ICD after 1979, with Crohn's disease and ulcerative colitis being coded as 555 and 556, respectively. After 1997 most countries in the study changed from the 9th to the 10th revision of the ICD, with Crohn's disease and ulcerative colitis being coded as K50 and K51, respectively. The resident population of the 21 countries, broken down by 5-year age groups, was also supplied by the individual national offices of statistics.

Data analyses

In each country separately, age-specific death rates were calculated for consecutive 5-year periods and 10-year age groups. For instance, the total number of deaths from 1966 until 1970 among subjects aged 45–54 was divided by the corresponding number of the total resident population of the same age group and living during the same time period when the deaths occurred. The death rates were expressed per million living population. The age-specific deaths rates were then plotted against the period of death as period-age contours. In the plots, each age group was labelled by its central year, for instance, 20 indicating the age group 15–24 and 30 indicating the age group 25–34. The periods of death were labelled by the mid year of death, for instance 1953 instead of 1951–55 and 1968 instead of 1966–70. In addition to death rates of each individual country, I also calculated average age-specific death rates per 5-year time periods of all countries lumped together.

Results

Figure 2 contains the average time trends of all 21 countries analysed together. The analysis was based on 43 754 deaths from Crohn's disease and 73 557 deaths from ulcerative colitis. Between the first period of 1951–55 and the last period of 2001–05 mortality from ulcerative colitis dropped to one-fifth of its original value. In contradistinction, mortality from Crohn's disease increased almost 2-fold between 1951–51 and 1971–75 before levelling off. Similar patterns were seen in the mortality data from most individual countries. A more differentiated picture emerges, if one looks at the age-specific time trends of mortality of the two diagnoses.

The left panel of Figure 3 shows the average age-specific deaths rates from Crohn's disease. An average number of about

4843 deaths contributed to each individual curve. The time trends of mortality from Crohn's disease in the young age groups 15–24, 25–34 and 35–44 years were characterized by an initial rise between 1951 and 1960 and a subsequent fall. In the middle age groups 45–54 and 55–64, the fall did not start before 1971–75. In the oldest age groups, no fall occurred and the rise continued unabated until the most recent time periods. The middle panel of Figure 3 shows the age-specific time trends of the average death rates from ulcerative colitis in 21 countries. An average number of about 8084 deaths contributed to each individual age-specific curve. Among the three oldest age groups 66–74, 75–84 and over-85 years, mortality from ulcerative colitis rose during the initial 5–15 years between 1951 and 1965 followed by a subsequent smooth decline. Among the age groups 45–54 and 55–64 years, an initial plateau was followed by an increasingly steeper decline. The steepest and most persistent decline occurred in the youngest age groups 15–24, 25–34 and 35–44 years.

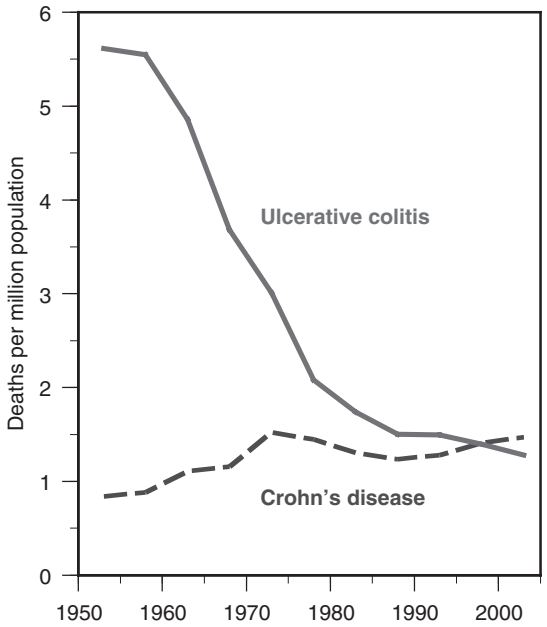

Figure 2 Time trends of death from ulcerative colitis (full line) and Crohn's disease (dashed lines). Each point represents the average death rate from 5–21 countries (depending on the period of death) and 5 consecutive years.

When the age-specific time trends of Crohn's were superimposed on those of ulcerative colitis, as in the right panel of Figure 3, it appeared as if the level of ulcerative colitis mortality presented a limit for a continued rise in mortality from Crohn's disease. In each of the young age groups, the trends of Crohn's disease started to decline upon approaching the level of mortality from ulcerative colitis. After reaching similar death rates, the trends of mortality from Crohn's disease and ulcerative colitis ran a similar downward course. In the middle age groups, the trends of Crohn's disease also levelled off after crossing mortality from ulcerative colitis, and the trends of both diseases ran a similar parallel course. Mortality from ulcerative colitis was highest in the oldest age groups with only a moderate decline during the recent time periods. Accordingly, the longest and most persistent growth in mortality from Crohn's disease was observed in the oldest age groups.

These patterns were evident in the average rates of all countries lumped together, as well as in the data from individual countries with large numbers of deaths from inflammatory bowel disease. Figures 4 and 5 contain the data

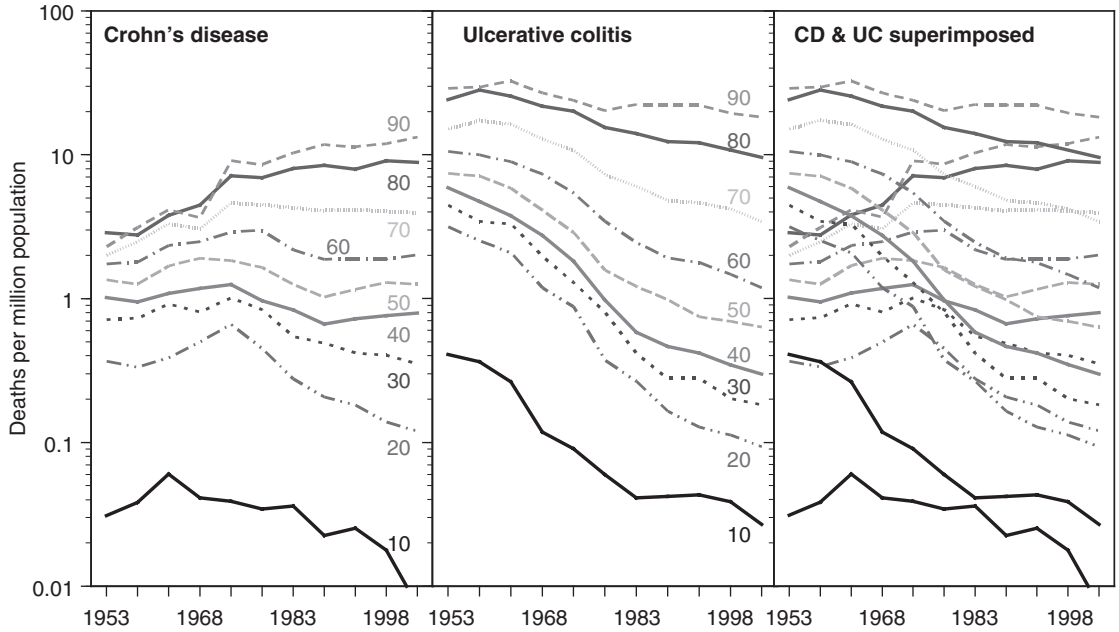

Figure 3 Average period-age contours of mortality from Crohn's disease (left panel), ulcerative colitis (middle panel) and superimposed average period-age contours of both diseases (right panel). Each point represents the average death rate from 5–21 countries (depending on the period of death) and 5 consecutive years.

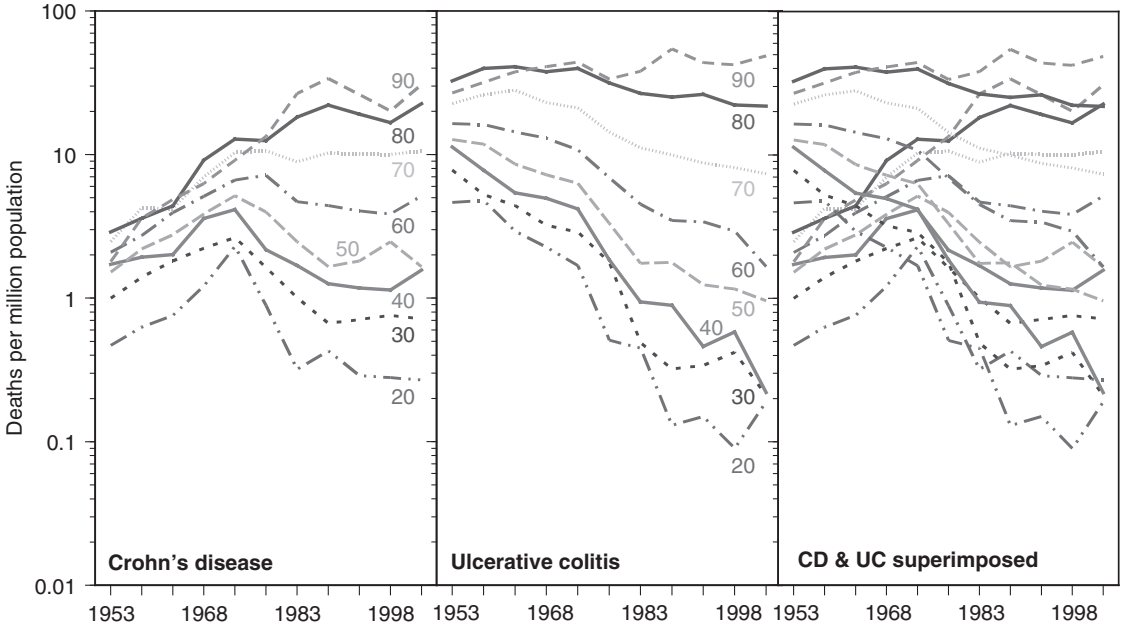

Figure 4 Period-age contours of mortality from Crohn's disease (left panel), ulcerative colitis (middle panel) and superimposed period-age contours of both diseases (right panel) in England & Wales. Each point represents the average death rate of a 5-year period.

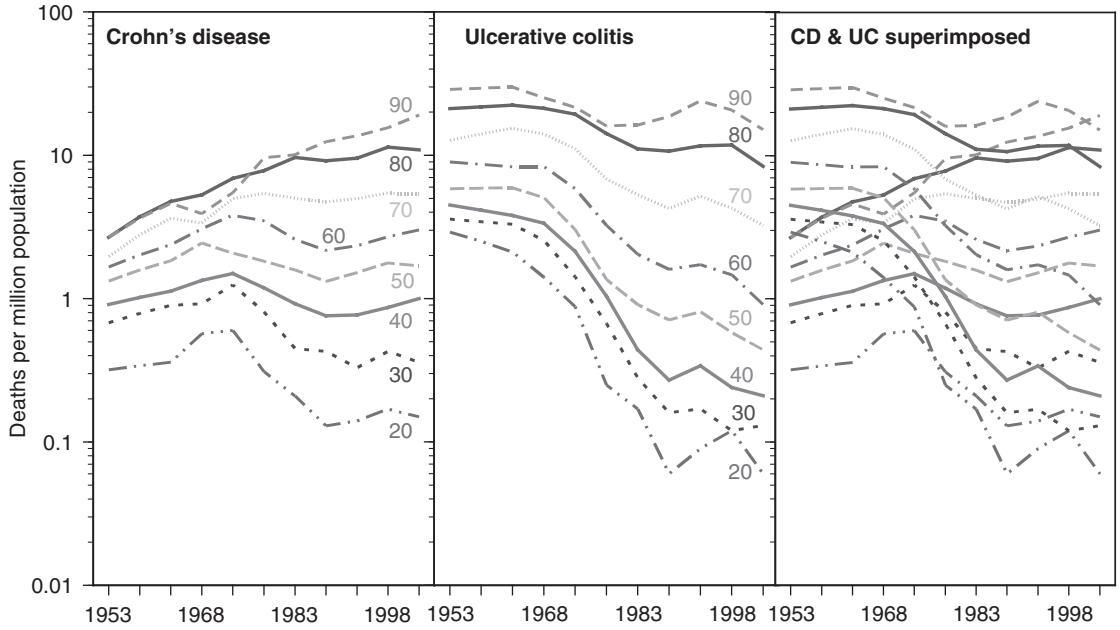

Figure 5 Period-age contours of mortality from Crohn's disease (left panel), ulcerative colitis (middle panel) and superimposed period-age contours of both diseases (right panel) in the United States. Each point represents the average death rate of a 5-year period.

from England and the United States as examples for the type of pattern seen in individual countries with a large population and high mortality from inflammatory bowel disease. As additional examples, Figures 6–9 contain the trends from Australia, Canada, Italy and The Netherlands, respectively. Because of the overall smaller number of deaths from inflammatory bowel disease among the smaller countries, the trends tended to run less smoothly and show a more jagged appearance, especially in the younger age groups. In all four countries alike, mortality from ulcerative colitis started out higher than mortality from Crohn's disease and ran a downward course, while over time mortality from Crohn's disease increased to a level similar to that of ulcerative colitis. Such patterns were also discernible in most other countries, whose individual pictures were left out for reasons of space.

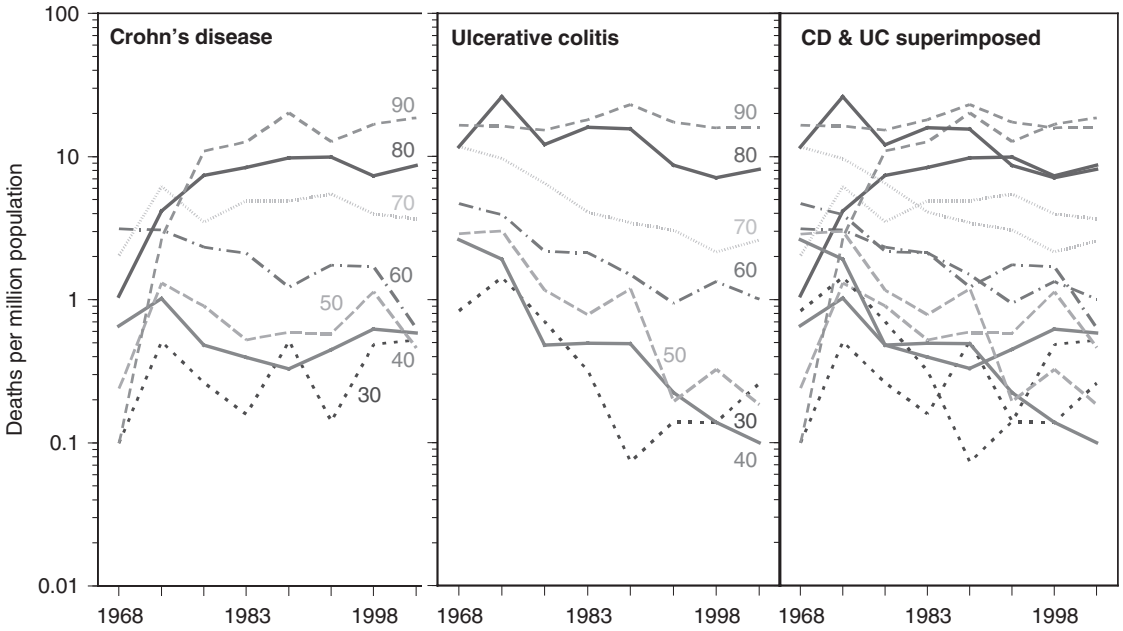

Figure 6 Period-age contours of mortality from Crohn's disease (left panel), ulcerative colitis (middle panel) and superimposed period-age contours of both diseases (right panel) in Australia.

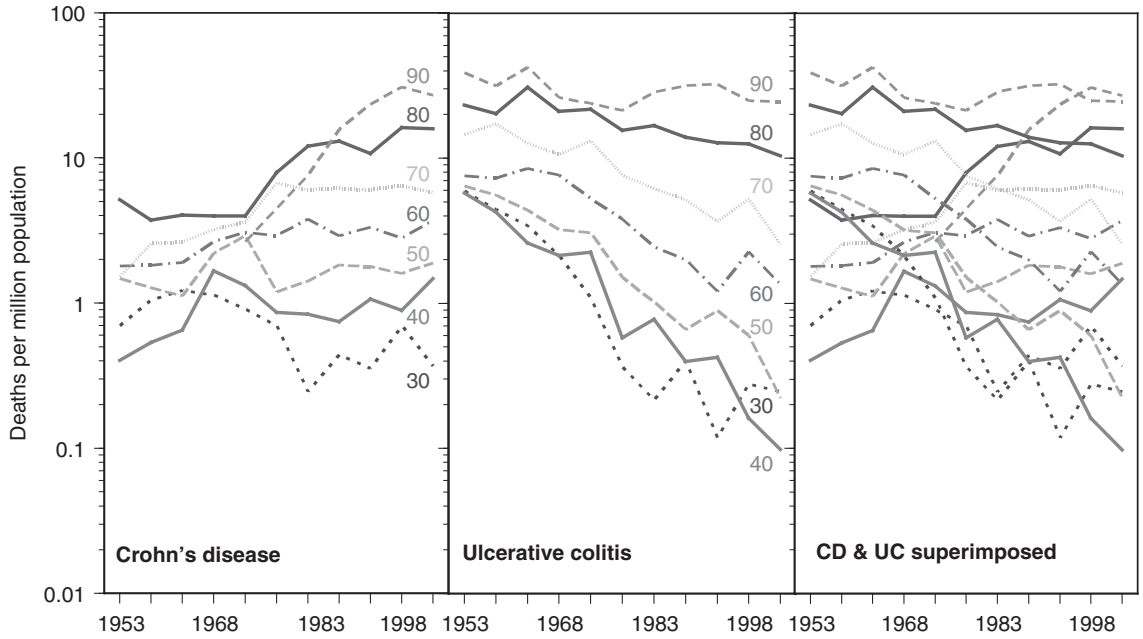

Figure 7 Period-age contours of mortality from Crohn's disease (left panel), ulcerative colitis (middle panel) and superimposed period-age contours of both diseases (right panel) in Canada.

The data from Belgium, France, Japan and Taiwan represented some minor exceptions from the overall pattern outlined earlier. The death rates from France are shown in Figure 10. After its introduction into the French mortality statistics as a separate code in 1968, the death rates from ulcerative colitis increased during the first two decades until 1981–85, before levelling off in the three oldest age groups or starting to fall in the younger age groups. Especially in the middle and younger age groups, French statistics did not show a continuous decline of ulcerative colitis as depicted characteristically in middle panels of Figures 3–5 for the majority of other countries. The French time trends of mortality from Crohn's disease showed a similar temporal pattern as ulcerative colitis. In the older age groups 65–74, 75–84 and 85+, mortality from Crohn's disease

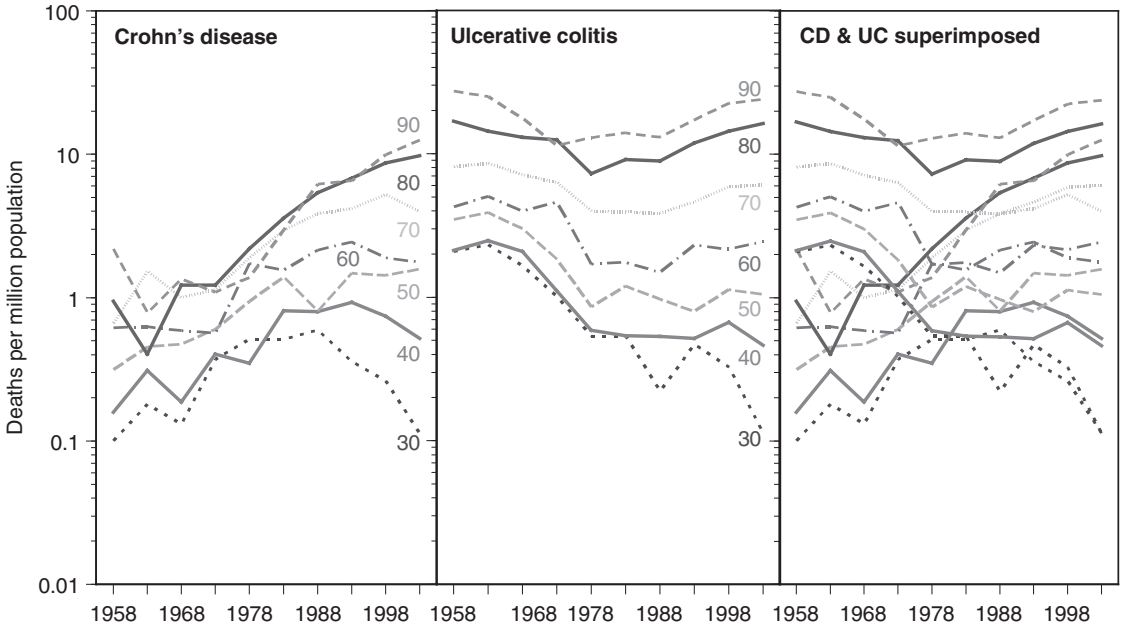

Figure 8 Period-age contours of mortality from Crohn's disease (left panel), ulcerative colitis (middle panel) and superimposed period-age contours of both diseases (right panel) in Italy.

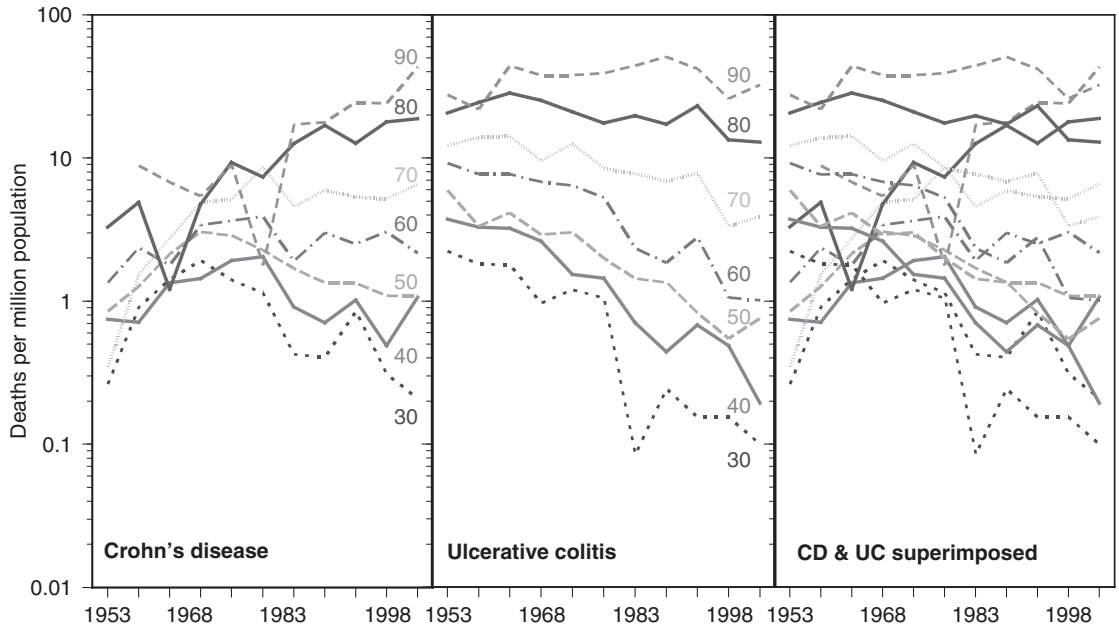

Figure 9 Period-age contours of mortality from Crohn's disease (left panel), ulcerative colitis (middle panel) and superimposed period-age contours of both diseases (right panel) in The Netherlands.

tended to stay at similar levels as mortality from ulcerative colitis. In the younger age groups, mortality from Crohn's disease started to decline gradually after 1971–75. A very similar pattern as in France was also seen in Belgium with the death rates of both inflammatory bowel diseases increasing initially after their introduction as separate ICD codes (data not shown separately).

The death rates from Japan are depicted in Figure 11. Between 1968 and 2004, the age-specific death rates from ulcerative colitis in Japan showed a similar decline as in most other countries. In contradistinction with the general trend of other countries, however, mortality from Crohn's disease failed to rise and, except for some minor statistical fluctuations, its age-specific rates remained persistently low. The death rates from Taiwan are shown in Figure 12. Similarly to the majority of other countries, death rates from ulcerative colitis in Taiwan displayed a continuous decline. Different from other countries, the death rates from Crohn's disease in Taiwan also showed

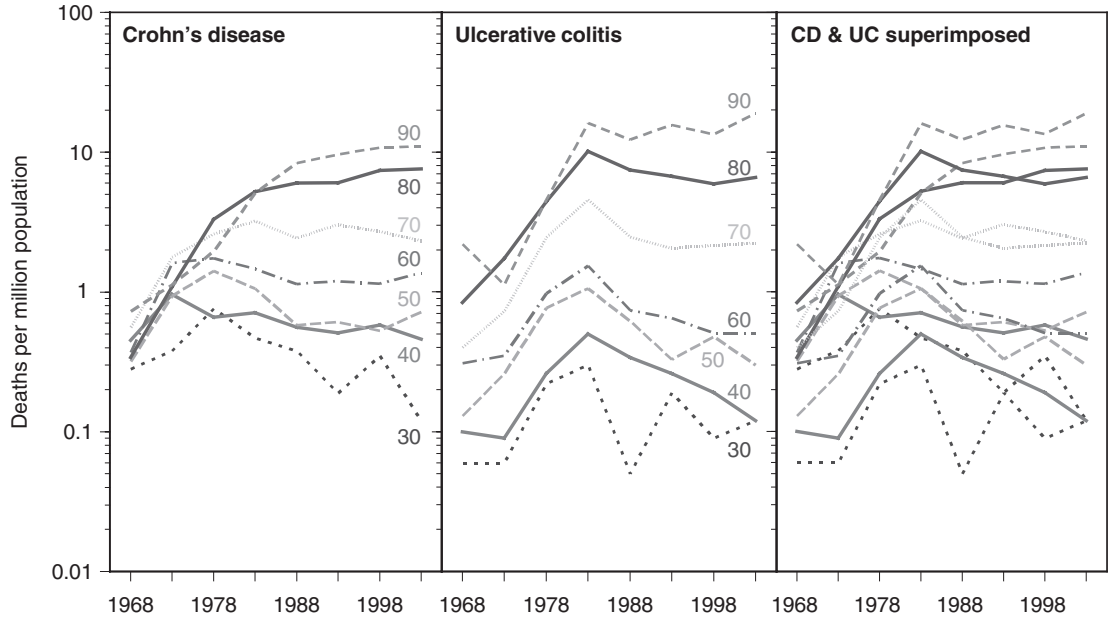

Figure 10 Period-age contours of mortality from Crohn's disease (left panel), ulcerative colitis (middle panel) and superimposed period-age contours of both diseases (right panel) in France.

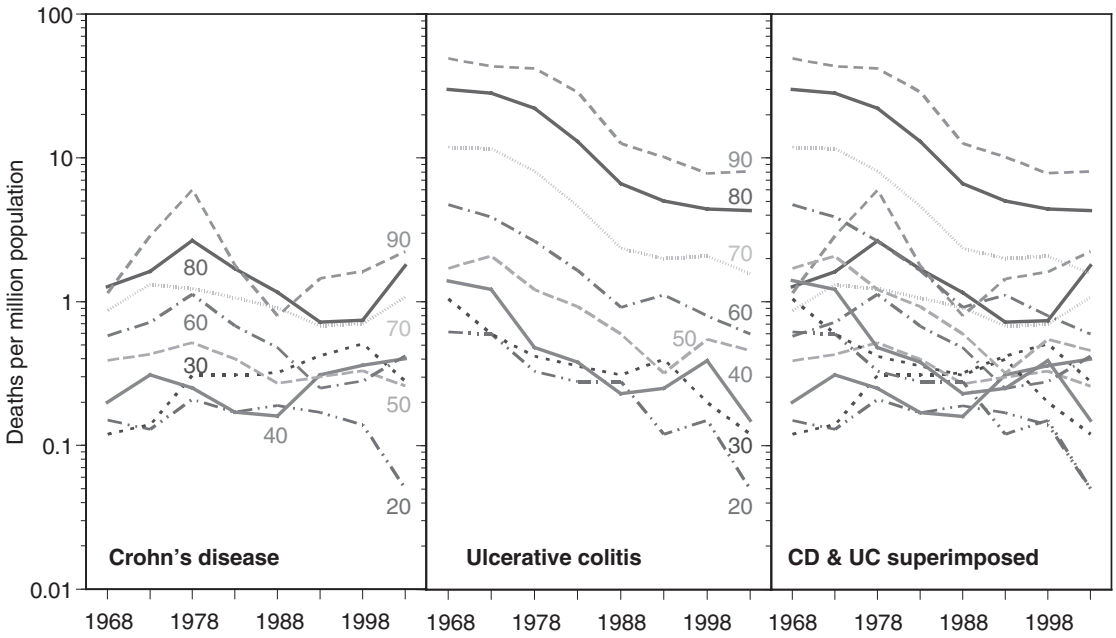

Figure 11 Period-age contours of mortality from Crohn's disease (left panel), ulcerative colitis (middle panel) and superimposed period-age contours of both diseases (right panel) in Japan.

a downward trend since its introduction to the Taiwanese mortality statistics in 1981.

Discussion

The present study analysed the time trends of mortality from ulcerative colitis and Crohn's disease among 21 different countries. On the average, mortality from ulcerative colitis was 1.7 more common than mortality from Crohn's disease. In the majority of countries, mortality from ulcerative colitis has declined steadily during the past 50 years. Mortality from Crohn's disease rose between 1951 and 1975 until reaching a similar height as mortality from ulcerative colitis. Since then the rise in mortality from Crohn's disease has levelled off and followed a similar time course as

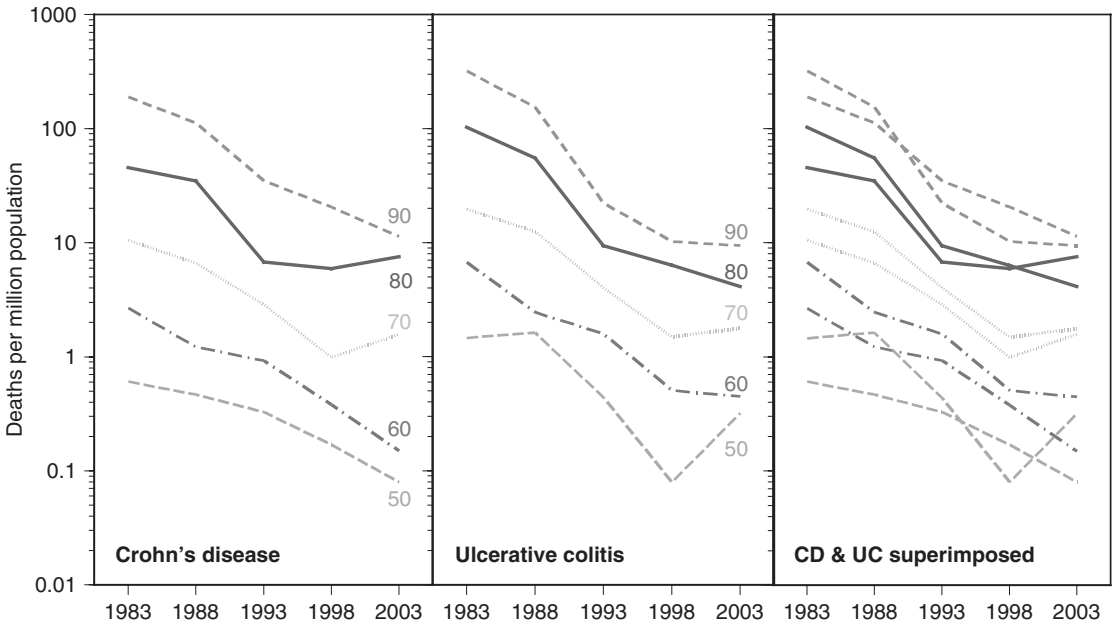

Figure 12 Period-age contours of mortality from Crohn's disease (left panel), ulcerative colitis (middle panel) and superimposed period-age contours of both diseases (right panel) in Taiwan.

ulcerative colitis. This type of relationship between the time trends of ulcerative colitis and Crohn's disease could be discerned in the time trends of each individual age group.

In addition to studying the time trends of *individual* countries, the *average* death rates from all countries were also plotted against the period of death. This approach was justified by the fact that the majority of countries showed resembling time patterns. In all countries alike, mortality from ulcerative colitis was more common than mortality from Crohn's disease. In most countries, ulcerative colitis showed a general downward trend as opposed to the upward trend of Crohn's disease. Using the entirety of countries to calculate average death rates provided the advantage of accumulating larger numbers for individual age groups and being able to plot smoother and more reliable period-age contours, especially in the younger age groups.

The average death rates from all countries, as well the death rates from countries with large populations or frequent occurrence of inflammatory bowel disease, revealed similar epidemiologic patterns. For each age-specific pair of curves of ulcerative colitis and Crohn's disease, the decline in the trends of Crohn's disease started upon reaching the level of mortality from ulcerative colitis. The point in time and the level, at which the mortality curves of ulcerative colitis and Crohn's disease met, was different for different age groups and among different countries. After reaching similar death rates in ulcerative colitis and Crohn's disease, mortality from ulcerative colitis and Crohn's disease ran a similar course. This phenomenon is remarkable, because the time trends of different age groups exhibited a rather different course, yet the same type of relationship between ulcerative colitis and Crohn's disease applied to each pair of period-age contours. It suggests that the time trends of Crohn's disease have been partly influenced by those of ulcerative colitis.

The few minor exceptions to this pattern did not appear to invalidate its general applicability. The initial decline was missing from the death rates of ulcerative colitis in Belgium and France, but otherwise their recent changes of Crohn's disease and ulcerative colitis followed a similar time course as in most other countries. In Taiwan, no initial rise occurred in the death rates of Crohn's disease, which might have been partly missed for the lack of data prior to 1981. In Japan, Crohn's disease continued to remain low and far below the levels of ulcerative colitis. This variability in the general pattern among different countries could open up the possibility to correlate variations of disease occurrence with similar variations of potential exogenous risk factors for inflammatory bowel disease. It would be interesting to investigate what environmental difference contributed to the varying disease behaviour in Belgium and France as compared with other neighbouring European countries. Similarly, the persistently low levels of Crohn's disease in Japan could provide a starting point to speculate about the nature of potential risk factors.

The genetics of inflammatory bowel disease, as well as its resulting pathophysiology and immunology, do not change within a time frame of few decades. The rise and fall in mortality from Crohn's disease and ulcerative colitis have occurred within too short a time period to be explained by anything but the action of exogenous influences. For most countries, it appears as if one primary environmental risk factor has been responsible for the general decline of ulcerative colitis. The decrease in the exposure to this unknown primary risk factor may have also prevented a further rise in Crohn's disease mortality during recent times. The exposure to this primary factor has fallen among the populations of developed countries, thereby causing an overall decline in the occurrence of both types of inflammatory bowel disease. Because Crohn's disease and ulcerative colitis are clearly

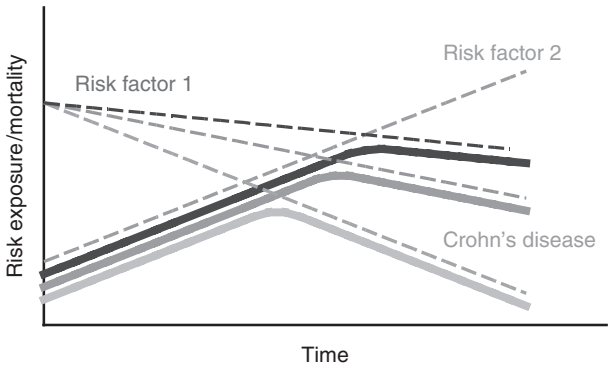

Figure 13 Modified model of the interaction between the two risk factors for ulcerative colitis and Crohn's disease to explain how an age-dependent decline of the first risk factor caused varying period-age contours of Crohn's disease.

two distinct diseases, at least one additional risk factor must underlie the occurrence of Crohn's disease. As suggested by the striking rise of Crohn's disease since 1951, the exposure to the secondary risk factor has been increasing in most developed countries. This secondary risk factor must be different from the one responsible for the decline of ulcerative colitis and the stunted growth of Crohn's disease. The joint time trends of Crohn's disease and ulcerative colitis reflect the underlying influence of the primary risk factor responsible for the overall occurrence of both diseases. A rise in exposure to the secondary factor could have caused a shift in the expression of inflammatory disease from ulcerative colitis to Crohn's disease.

In Figure 13, the original model was modified to explain how an age-dependent decline in the occurrence of the first risk factor associated with ulcerative colitis could have caused varying period-age contours of Crohn's disease. It has been shown that the time trends of mortality from ulcerative colitis, but not Crohn's disease, are governed by an underlying birth-cohort phenomenon.[8,9] The risk of dying from ulcerative colitis varies by age and period of birth. Older subjects may have been previously exposed to higher levels of factor 1 than younger subjects and harbour an increased risk for dying from both types of inflammatory bowel disease. The nature of such factor that changes the risk among consecutive birth cohorts is presently unknown, but the overall similarity with peptic ulcer and *Helicobacter pylori* might suggest an infectious aetiology. The second factor could comprise exposure to some other environmental risk associated with social habits, diet, drugs or toxins.

Mortality data provide the opportunity to study large case numbers unmatched in size or length of observation by any other type of statistics from a single hospital or a consortium of multiple medical centres. Because it was previously discussed why changes in medical coding, diagnosis, or therapy are unlikely to have caused the observed time trends of mortality, these arguments will be summarized here only briefly.[5,9,10] The decline in mortality from ulcerative colitis is far more pronounced than the rise in mortality from Crohn's disease. It is difficult to explain how changes in coding and diagnostic transfers from ulcerative colitis to Crohn's disease could be responsible for the observed time trends. Changes in coding practices and diagnostic standards should have affected all age groups similarly rather than leading to the observed age-specific variations in the time trends of both Crohn's disease and ulcerative colitis. Since similar therapeutic regimens are utilized in the management of ulcerative colitis and Crohn's disease, any new pharmaceutical and surgical therapy should have benefited both types of inflammatory bowel diseases alike, leading to similar instead of distinct time trends. If, on one hand side, mortality data were unreliable, they should have masked or obliterated rather than reveal any distinct patterns of inflammatory bowel disease epidemiology, unless the data were systematically influenced by some serious underlying bias. On the other hand, it is difficult to imagine how such bias could manifest itself similarly and simultaneously in the statistics from many different countries.

Highly significant correlations exist between the incidence and death rates of Crohn's disease, as well as ulcerative colitis, from different countries.[11] Similarly strong correlations are found between the geographic variations of mortality and hospitalization of both diseases among different US states.[12] In addition, the mortality trends reported here are corroborated by similar time trends of several incidence data.[13–17] The parallelism between the incidence and mortality rates may reflect the fact that the most severe clinical presentation and the highest mortality associated with inflammatory bowel disease tend to occur within few years from the onset of the disease.[18,19] However, other studies have reported trends that are different from those of the mortality data, suggesting a continuing rise in the incidence of Crohn's disease and ulcerative colitis.[20,21] Such discrepancies among various epidemiologic studies may stem from differences between the regional and national trends of incidence data or some general discrepancy between incidence and mortality data. Only a minority of patients with inflammatory bowel disease die from their illness. Moreover, deaths that are in fact primarily due to Crohn's disease, or ulcerative colitis might become mislabelled or associated with other secondary causes of death, such as peritonitis, colorectal cancer or thrombembolism. There are obvious limitations to the use of mortality in analysing time trends of a disease with a low case fatality rate. One would definitely need to confirm the patterns observed in the present study by the analysis of other morbidity parameters including incidence data. Even if mortality statistics were altogether unrelated to incidence data, however, their patterns described herein would still merit attention and demand an explanation.

In conclusion, the trends in mortality from inflammatory bowel disease among different countries paint a distinctive and fascinating picture. The data suggest that a reduced environmental exposure to one yet unknown primary risk factor has led to an overall decline in mortality from both types inflammatory bowel disease. The increased exposure to another secondary risk factor unique to Crohn's disease has shifted the main phenotypic expression of patients dying with inflammatory bowel disease from ulcerative colitis to Crohn's disease. These conclusions are supported by similar patterns of inflammatory bowel disease observed in many different countries alike.

KEY MESSAGES

- The time trends of mortality from Crohn's disease and ulcerative colitis show strikingly similar types of behaviour among many different countries.
- The reduced environmental exposure to one *primary* environmental risk factor common to Crohn's disease and ulcerative colitis has led to an overall decline in the mortality from both inflammatory bowel diseases.
- The increased exposure to a *secondary* risk factor unique to Crohn's disease alone has shifted the main phenotypic expression of inflammatory bowel disease from ulcerative colitis to Crohn's disease.

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