Chapter 16

Non-Hodgkin's lymphoma

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Summary

- In the UK and Ireland in the 1990s, non-Hodgkin's lymphoma accounted for 1 in 30 cases of cancer and 1 in 40 deaths from cancer.
- There was the suggestion of a north-south divide in incidence across England, with higher than average rates in London and the south, and lower incidence in the midlands and north. Incidence was also higher than average in Northern Ireland and Scotland.
- The observed pattern in mortality was similar to, but less clear-cut than that for incidence.
- There appears to be a weak (negative) link between incidence and deprivation, with slightly higher rates in more affluent areas, although there is no known causative factor for which affluence could be a marker.
- It is unlikely that any of the known risk factors for developing NHL could explain the observed geographical variations in incidence.

Introduction

Non-Hodgkin's lymphoma (NHL) is a group of conditions, all of which are malignancies of the cells on the lymphocyte developmental pathway, part of the immune system. The different histological sub-types vary widely in their clinical behaviour, progress and management, and there is some evidence that the different sub-groups of NHL have differing epidemiological features.[1] It is not known to what extent the amalgamation of these different sub-types into a single diagnostic group obscures the geographical distribution of these diseases or confuses the aetiology. NHL is the most common malignancy among the leukaemias and lymphomas. It typically arises in lymph node tissue, but in 15-20 per cent of patients the tumour develops in a site other than a node, for example, in bone, stomach or intestines, brain or breast.[2]

Incidence and mortality

In the UK and Ireland in the 1990s, there were roughly 4,500 new cases of NHL diagnosed in males each year and 4,000 in females (a male-to-female ratio of around 1.1:1). Incidence rates increased markedly with age in both sexes, but at all ages the rates in females were roughly one third lower than in males, particularly in older age groups. The overall age-standardised incidence rates were 14.2 and 9.9 per 100,000 for males and females, respectively (a male-to-female ratio of 1.4:1).

In the 1990s, around 2,400 males and 2,200 females died from NHL each year. In common with the incidence data, the male-to-female ratio of the number of deaths was 1.1:1. The overall age-standardised mortality rates were 7.3 per 100,000 for males and 4.8 for females (a ratio of 1.5:1). The overall mortality-to-incidence ratio for the UK and Ireland was around 0.50 for both sexes (Table B16.1).

Incidence and mortality trends

In England and Wales, age-standardised incidence rates increased around three fold in both sexes between 1971 and the late 1990s. There was a steady increase throughout the 1970s and 1980s, with the largest increases occurring among the elderly.[2] The cumulative risk for 30-74 year-old males from the 1915 and 1940 cohorts in three UK cancer registry areas[3] showed marked increases by cohort of 14, 24 and 50 per cent (Birmingham, Scotland and South Thames, respectively) between 1973 and 1987. There were similar increases in cumulative risk for females. The apparently marked variation in rates of change between regions indicates that geographical patterns of incidence are also likely to have changed over time.

Trends in mortality approximately followed those in incidence, with particularly large increases in the elderly. After a steep rise in the 1980s, mortality rates levelled off in the mid-1990s.[2] Increasing mortality from NHL occurred almost entirely in cohorts born before 1920. There was then little change, until a decline beginning with the cohort born in 1945-49.[4] Mortality increased by over 70 per cent in both sexes in each region between the early 1960s and early 1990s, with no obvious geographical pattern.[4]

The increased incidence of NHL around the world has been documented by numerous publications since the 1980s. It has occurred in mainly white populations in parts of western Europe, North America[5] and Australia, with annual increases in the period 1985-92 of over 4 per cent in parts of Europe.[1]

Closer examination suggests that the changes in incidence over time are not consistent for either the different histological sub-types[1] or the primary site of diagnosis of NHL, with skin lymphoma, for example, showing some of the largest increases.[6] There are some recent indications that these trends may be slowing down. The underlying basis of these trends

could be either the changing ability of laboratories to diagnose the condition more accurately, or changes in some unknown underlying biological or environmental processes (see below).

Survival

Relative survival from NHL was around 70 per cent at one year and 50 per cent at five years after diagnosis in patients diagnosed in 1996-99 in England and Wales.[7] Five-year survival was similar in Northern Ireland,[8] Ireland[9] and Scotland[10] for patients diagnosed in the 1990s. Survival rates in England and Wales were close to the European average for patients diagnosed in 1990-94.[11] In England and Wales since the 1970s, five-year survival has improved by around 14 percentage points for both men and women. Prior to the 1970s, most lymphomas were fatal, but the development of effective combination chemotherapy has resulted in the cure of many advanced tumours.[12]

Geographical patterns in incidence

Noticeably higher than average rates of NHL occurred in London, the South West of England and Northern Ireland in males (around 15 per cent above the UK and Ireland average); and in Scotland and Northern Ireland in females (17 and 27 per cent, respectively) (Figure 16.1). Rates were lower than average for both males and females in the Northern and Yorkshire; Trent; North West and West Midlands regions of England.

Within countries and regions there was some variation in incidence rates, among both males and females (Figure 16.3). Variation between the health authorities with the highest and lowest incidence within a country or region ranged from around 20 per cent in Ireland and the Eastern region of England to over 40 per cent in London and Trent (Table B16.1). Most of the rates for health authorities were, however, based on relatively small numbers of cases and it is therefore difficult to interpret this variability (Table B16.2). In both males and females the vast majority of rates at the health authority level did not differ significantly from the average. But in the Northern and Yorkshire; Trent; West Midlands; and North West regions incidence rates in most of the health authorities were below average; and in London, the South East and South West of England, Scotland and Northern Ireland the rates in many health authorities were above average. The maps (Map 16.1) dramatically reflect this pattern with virtually all of the health authorities with slightly raised incidence being in the south and south west of England, and virtually all of those with slightly lower rates being in the midlands and north of the country. The maps also emphasise the generally higher rates in Scotland and Northern Ireland, particularly for females.

Geographical patterns in mortality

Mortality rates by country and region of England broadly reflected those for incidence (Figure 16.2), although there was less variation. As for incidence, mortality rates were below average for both sexes in the Northern and Yorkshire; North West; Trent; and West Midlands regions of England. However, mortality rates were markedly higher than average only in London for males and in Scotland for females.

At the health authority level there was less variation in mortality than incidence, and the rates in most areas were not more than 10 per cent different from the average (Figure 16.4). Reflecting this, the maps for mortality (Map 16.2) show a less clear pattern than those for incidence, although again those areas in England that had slightly higher than average mortality were predominantly in the south and south west, and those areas with slightly below average mortality were in the north. The patterns of health authorities with higher incidence in Scotland and Northern Ireland were reflected, to a lesser degree, in the mortality rates, and the differences between these and the rates in the midlands and north of England were again visible, although less marked than for incidence.

Risk factors and aetiology

There are three broad lines of research linked to studies of the causation of NHL: studies of altered immunity; occupational investigations; and lifestyle studies.

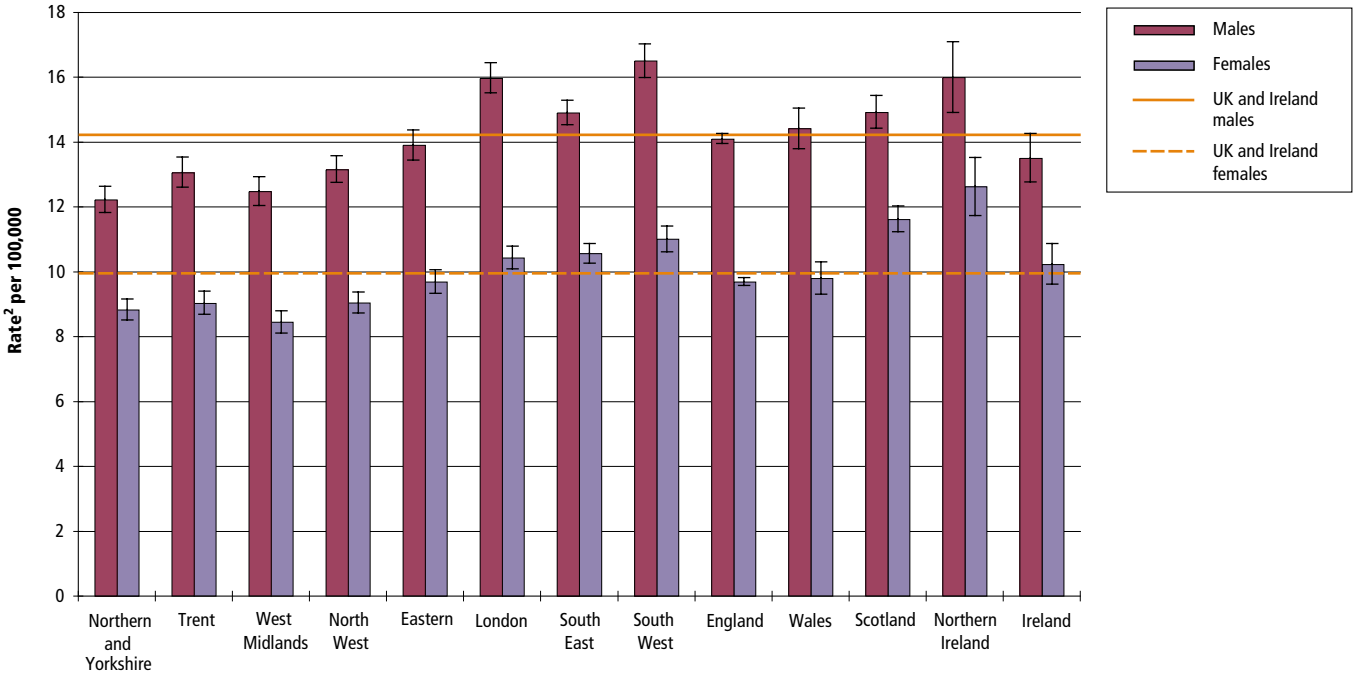
The studies of altered immunity have resulted in some convincing associations. These include an excess of NHL cases occurring in certain inherited syndromes that are characterised by failures of function within the immune system, such as ataxia telangectasia.[13] In addition, people with certain chronic illnesses (for example, those with renal disease or renal transplantation) who receive therapeutic immunosuppressant drugs, have a considerable excess risk of NHL (20 fold and more).[14] Those who suffer from viral immunosuppression also have a higher risk of NHL. These include younger people in parts of Africa with Burkitt's lymphoma, which is partly linked to Epstein-Barr virus infection in endemic malarial areas. In addition, individuals with chronic HIV infection have up to a 60-fold excess risk of developing NHL.[15,16]

Occupational associations are much weaker (2- to 3-fold risk) and are linked to chemicals that may have an adverse effect on the immune system. The most investigated area is that of certain types of agricultural exposures, in particular herbicides and other agrichemicals.[17] Despite numerous studies, no specific association has been found that is thought to be causal.

(continued on page 182)

Figure 16.1

Non-Hodgkin's lymphoma: incidence by sex, country, and region of England UK and Ireland 1991-99[1]

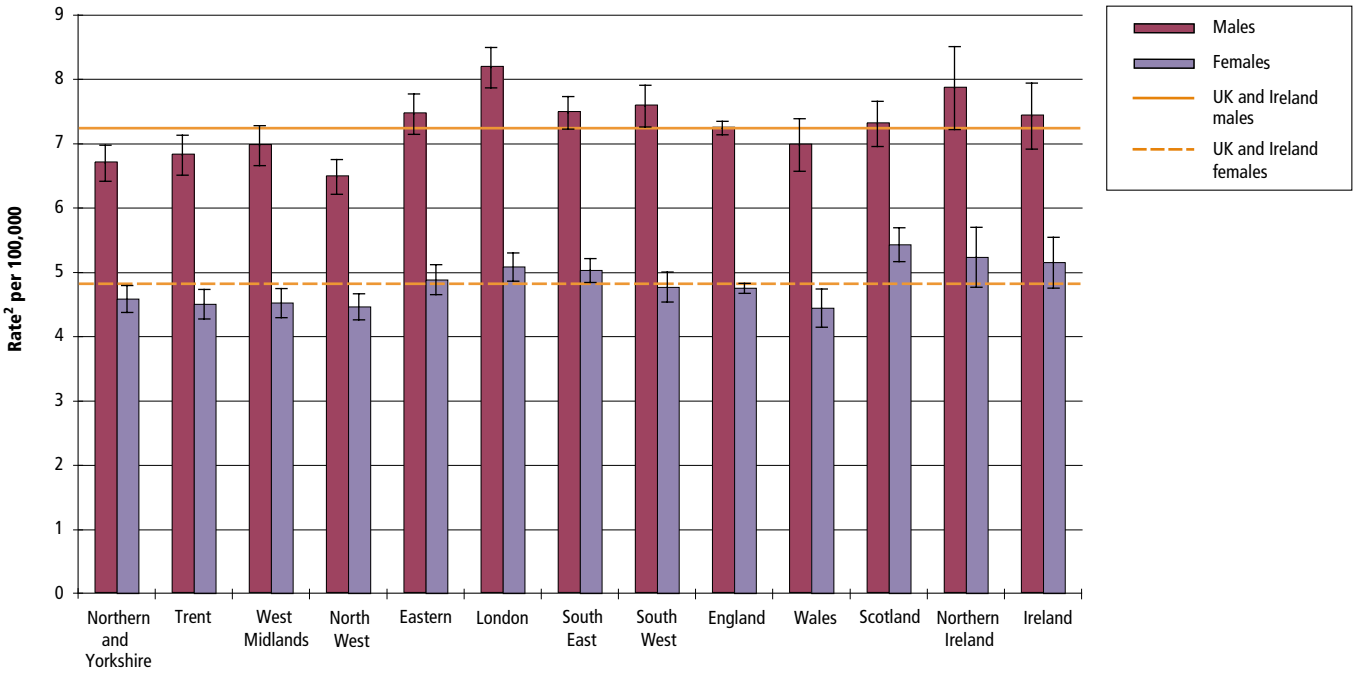


1 Northern Ireland 1993-99, Ireland 1994-99

2 Age standardised using the European standard population, with 95% confidence interval

Figure 16.2

Non-Hodgkin's lymphoma: mortality by sex, country, and region of England UK and Ireland 1991-2000[1]

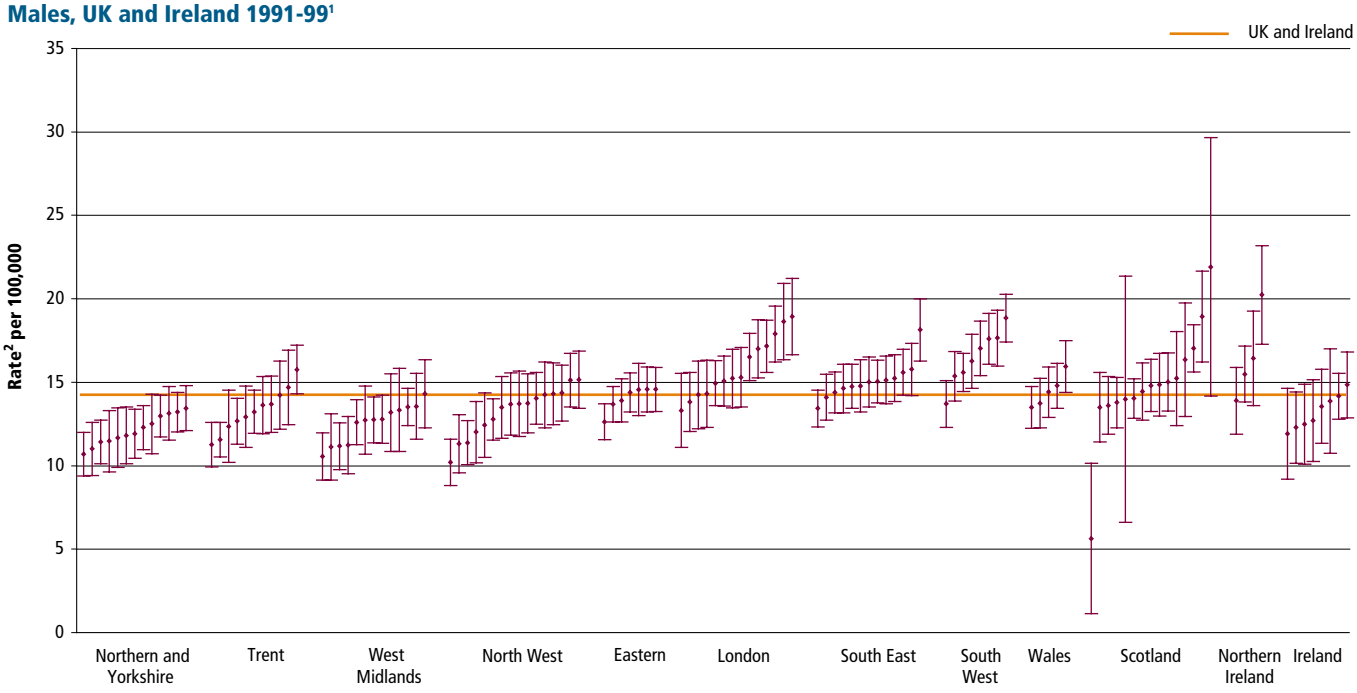


1 Scotland 1991-99, Ireland 1994-2000

2 Age standardised using the European standard population, with 95% confidence interval

Figure 16.3a

Non-Hodgkin's lymphoma: incidence by health authority within country, and region of England
Males, UK and Ireland 1991-99[1]

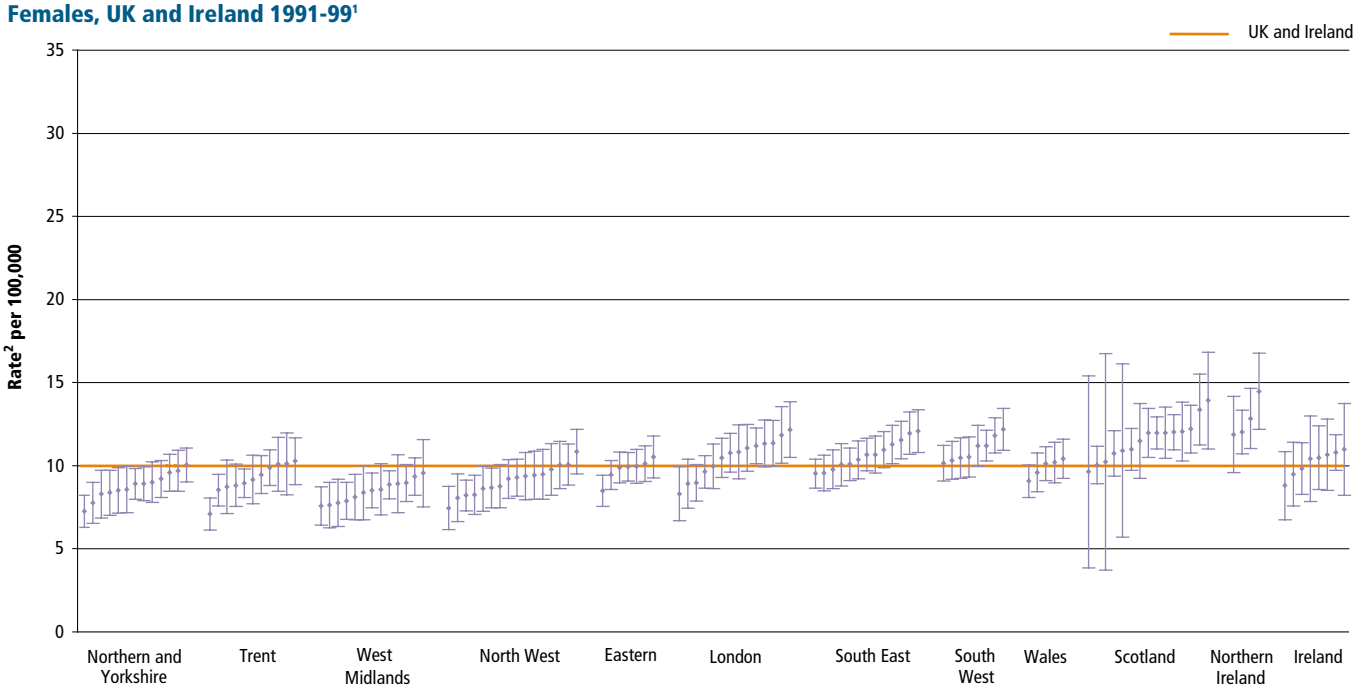


1 Northern Ireland 1993-99, Ireland 1994-99

2 Age standardised using the European standard population, with 95% confidence interval

Figure 16.3b

Non-Hodgkin's lymphoma: incidence by health authority within country, and region of England
Females, UK and Ireland 1991-99[1]

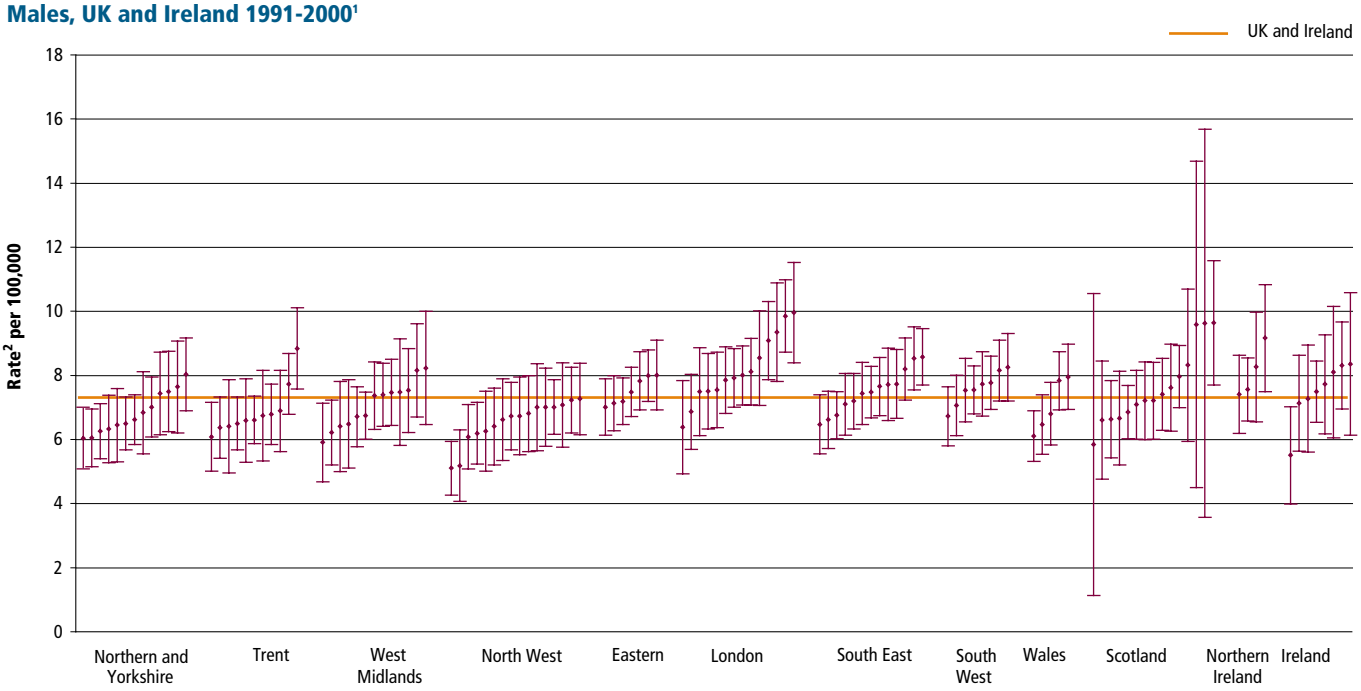


1 Northern Ireland 1993-99, Ireland 1994-99

2 Age standardised using the European standard population, with 95% confidence interval

Figure 16.4a

Non-Hodgkin's lymphoma: mortality by health authority within country, and region of England Males, UK and Ireland 1991-2000[1]

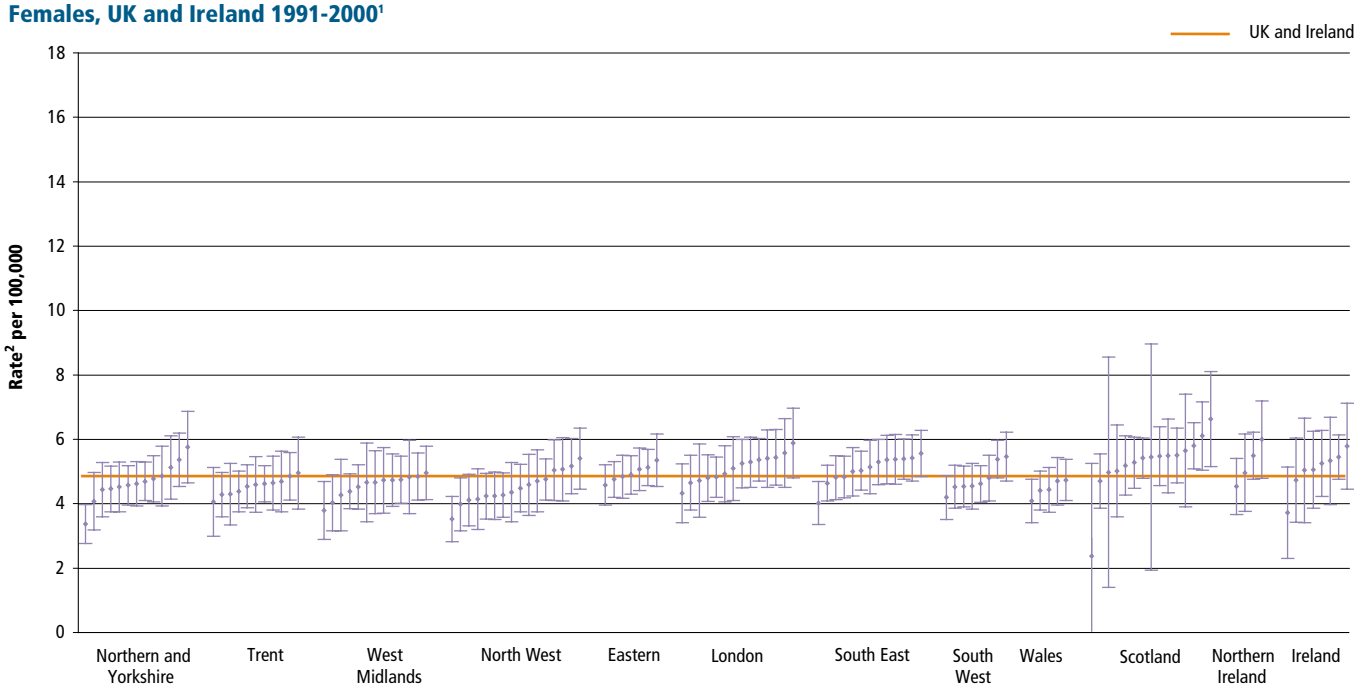


1 Scotland 1991-99, Ireland 1994-2000

2 Age standardised using the European standard population, with 95% confidence interval

Figure 16.4b

Non-Hodgkin's lymphoma: mortality by health authority within country, and region of England Females, UK and Ireland 1991-2000[1]

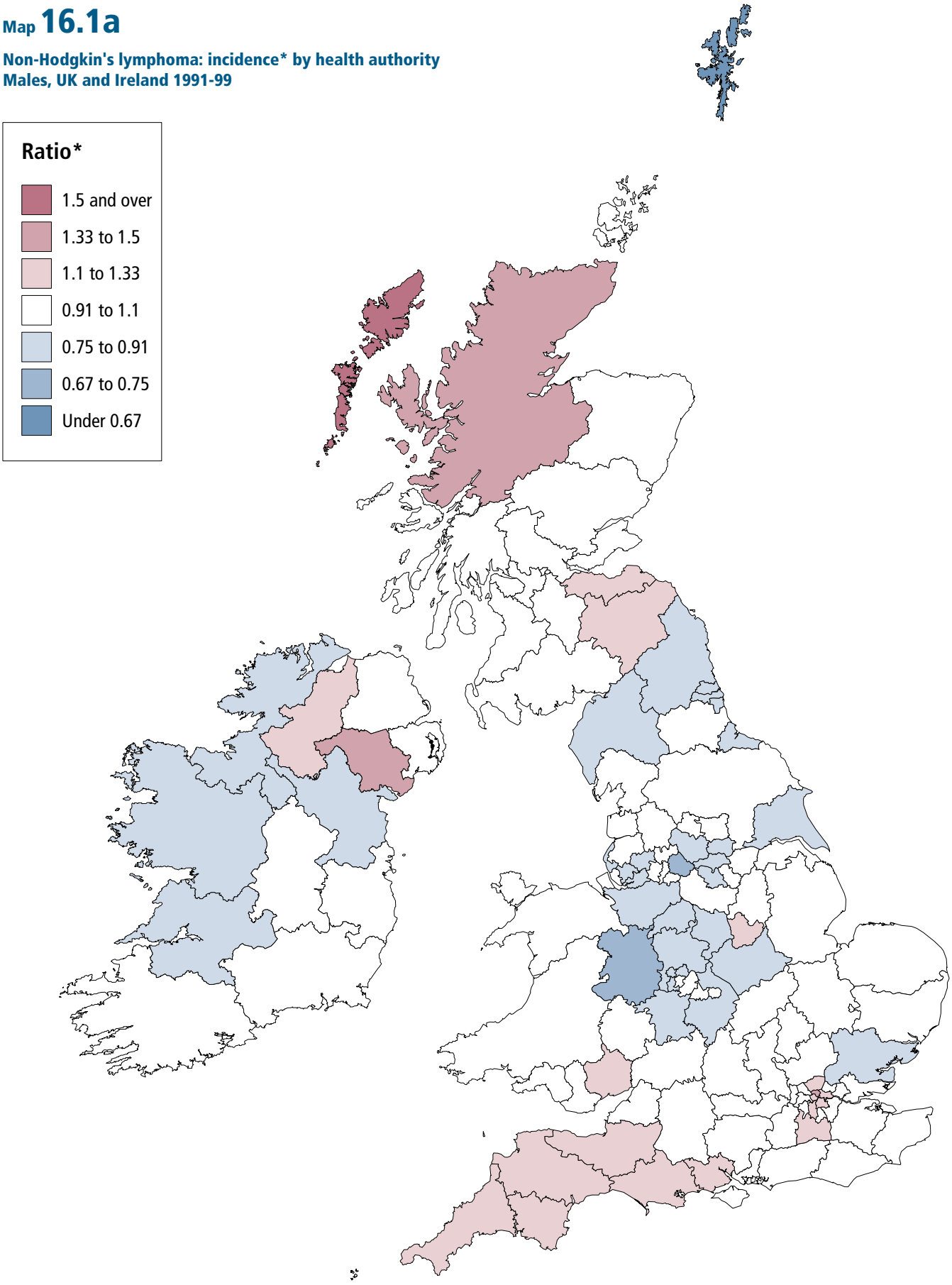


1 Scotland 1991-99, Ireland 1994-2000

2 Age standardised using the European standard population, with 95% confidence interval

Map 16.1a

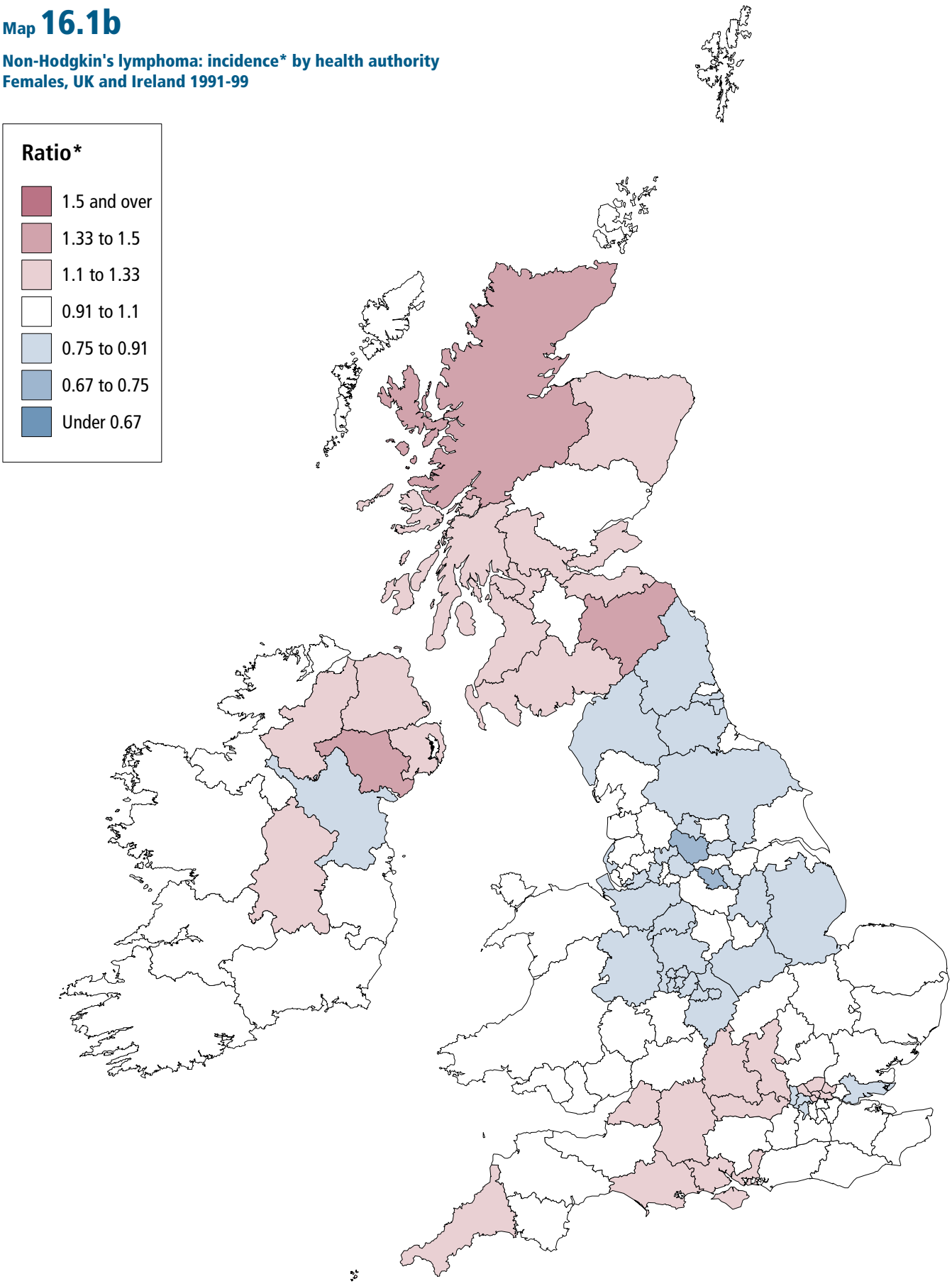
Non-Hodgkin's lymphoma: incidence* by health authority
Males, UK and Ireland 1991-99



*Ratio of directly age-standardised rate in health authority to UK and Ireland average

Map 16.1b

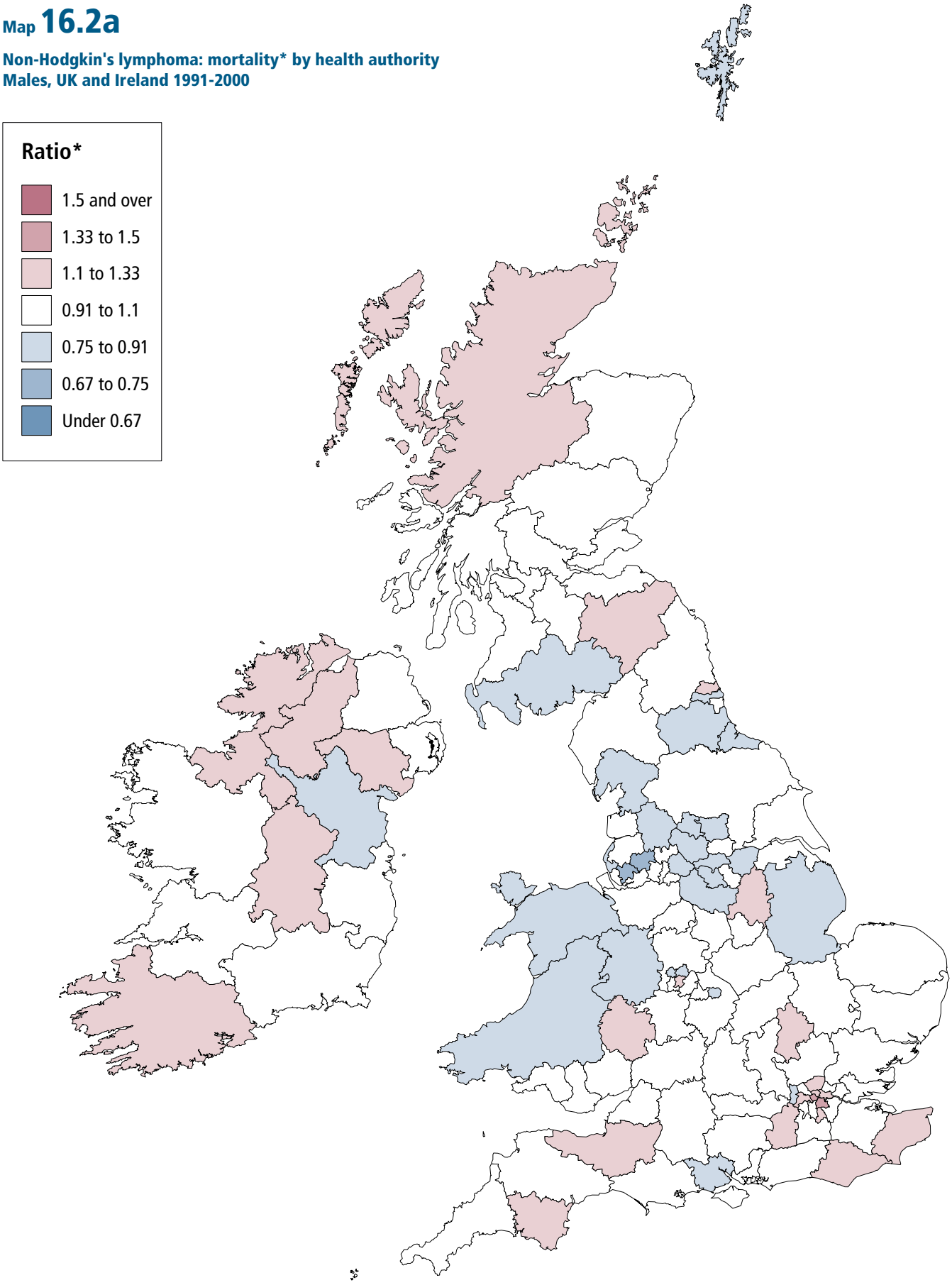
Non-Hodgkin's lymphoma: incidence* by health authority
Females, UK and Ireland 1991-99



Ratio of directly age-standardised rate in health authority to UK and Ireland average

Map 16.2a

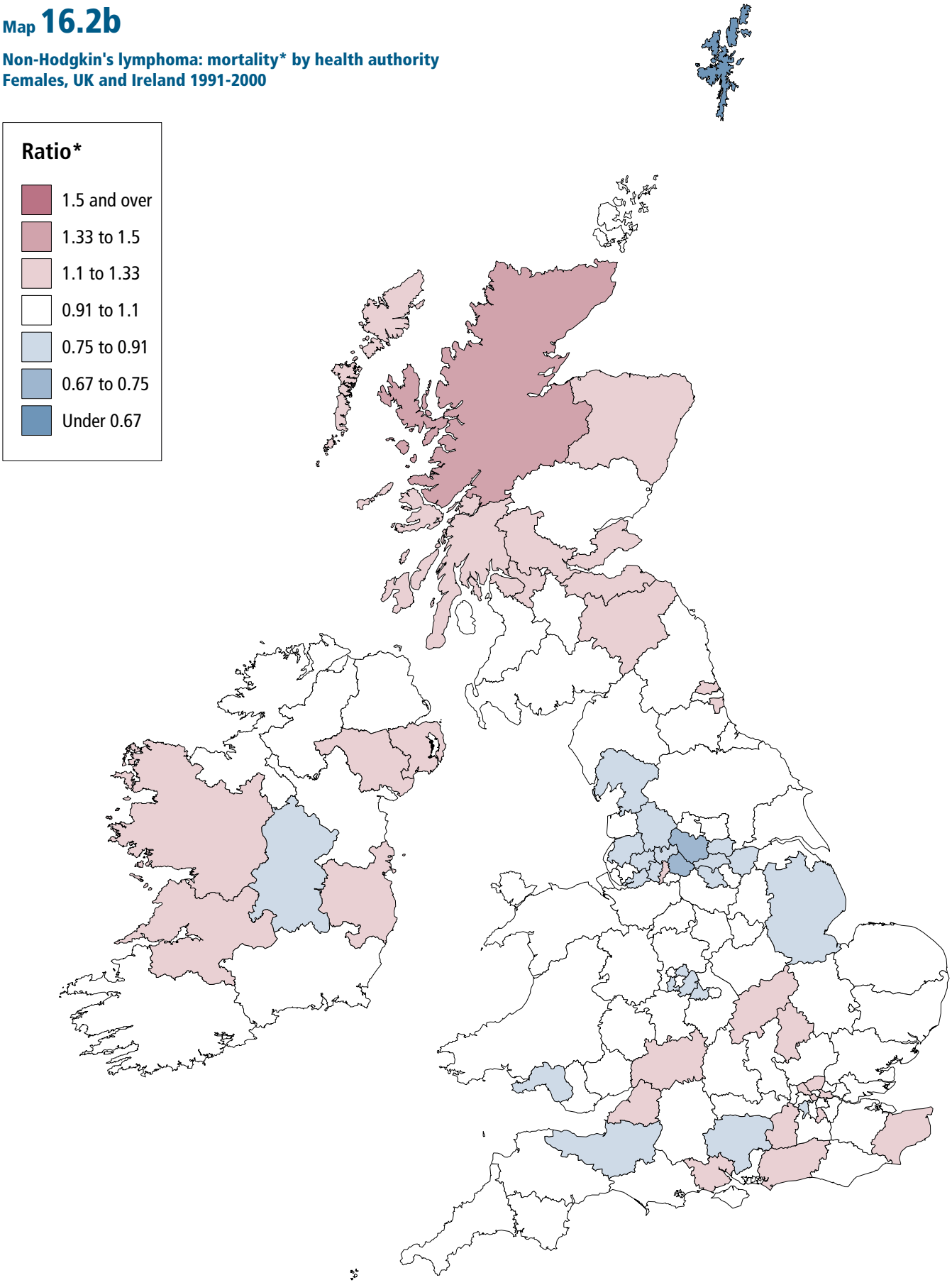
Non-Hodgkin's lymphoma: mortality* by health authority
Males, UK and Ireland 1991-2000



Ratio of directly age-standardised rate in health authority to UK and Ireland average

Map 16.2b

Non-Hodgkin's lymphoma: mortality* by health authority
Females, UK and Ireland 1991-2000



Ratio of directly age-standardised rate in health authority to UK and Ireland average

A few studies have shown a link with the petrochemical industry but the results are weaker than those for agrichemicals.[18]

Various lifestyle studies have shown little relationship between exposure to cigarette smoke or to ionising radiation and the risk of NHL. Little else has been published to suggest other possible aetiological factors in the pathogenesis of NHL, although some hypotheses have yet to be investigated. One such hypothesis, for example, is based on the possible adverse immune effects which sunlight exposure might have on lymphocytes circulating in the skin capillaries.[19] However, no strong support has emerged for this in direct studies,[20] although some indirect support is given in ecological studies and one cohort study.[21]

The strong association between immune suppression and NHL relate to a small number of people and so would not have any noticeable impact on the geographical variation in incidence. Similarly, in the UK and Ireland in the 1990s, agricultural exposures would have affected a very small proportion of the total workforce, and they are unlikely to account for the observed geographical distribution of NHL. The impact of HIV on rates of NHL in males has not been evaluated in the UK or Ireland.

Socio-economic deprivation

The incidence of NHL is only very weakly linked to deprivation, with slightly higher rates in the affluent, and there is no association between mortality from NHL and deprivation.[2] Deprivation, or any aetiological factor for which it may be a marker, would therefore not be expected to affect geographical variation to any large degree. This indicates that the dichotomy in incidence rates in England – with virtually all of the higher than average rates occurring in the south and south west, and virtually all of the lower rates occurring in both urban and rural areas in the midlands and north (Map 16.1) – suggests the involvement of factors other than those linked to deprivation. Survival from NHL has consistently been lower among deprived groups:[12] for patients diagnosed in 1996-99, there was a gap of 5-7 percentage points in five-year survival between the least and most affluent groups.[22] This partly explains why less variation was observed in mortality than incidence rates, as the lower incidence of NHL in the midlands and north of England would have been offset by worse survival, resulting in mortality rates that were closer to the average.

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