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Time trends in the registration of Hodgkin and non-Hodgkin lymphomas in Europe

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ABSTRACT

Lymphoma incidence is reported to be increasing globally. If real, these trends can only be explained by an increasing exposure to risk(s) as yet unknown. There have been numerous coding and classification changes over time and greater access to ever more sensitive diagnostic tests. It is important to understand the consequences that these changes, coupled with general improvements in cancer registration, have had on observed temporal trends. Trends in the registration rates of both non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) in Europe are presented. Age-adjusted and age-specific rates are described in men and women in 13 European countries according to both period of diagnosis and year of birth. Age, period and cohort effects are modelled. Overall, there are increases in the numbers of NHL registrations made with a corresponding decrease in HL. In recent history, however, there is a suggestion that the rate of increase is less and stable.

1. Introduction

Over the last half-century, ubiquitous global increases in the number of cancer registrations of the most common lymphomas have been interpreted as signalling a genuine increase in incidence. The incidence of non-Hodgkin lymphoma (NHL) has been reported to have risen steadily in many countries for several decades.[1,2] In the US, the rates of NHL increased by 77% in black males and by 53% in white males and by 39% and 33% among black and white females, respectively, from the early-1980s to the mid-1990s.[3] In seven European countries, the reported increase in NHL incidence was over 4% annually between 1985 and 1992, with a higher rate of increase in males than in females.[4] Increases have also been confirmed in Asia (India, Japan, and Singapore), and in South America (Brazil and Colombia).[5] Worldwide, about 287,400 new cases of NHL (about 60% in men) occurred globally in 2000,[6] constituting approximately 3% of all cancers and the most frequently diagnosed haematopoietic malignancy.[7]

The interpretation of long-term trends in the incidence of lymphoma presents a number of difficulties. As well as a dynamic and evolving classification system, improvements in disease detection and cancer registration may have contributed to the temporal trends. NHL represents an extremely diverse group of malignancies. Changes in classification over time, including classification to Hodgkin's lymphoma (HL) or

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other disease entities and *vice versa*, may account, according to one study, for about 10% of the overall increasing incidence rates.[8]

This study presents the observed trends in the registration rates of both NHL and HL in Europe. Age-adjusted and age-specific rates are described in men and women in 13 European countries according to both period of diagnosis and year of birth. The main aim is an evaluation of variations in NHL and HL registration rates in Europe, with an emphasis on determining the extent to which incidence trends are real, and to what extent the trends might be affected by changing classification.

2. Data sources

Registered incidence cases of NHL and HL (NHL: ICD-10 C82-C85, C96 HL: ICD-10 C81) and corresponding population data were obtained from the EUROCIM database[9] by European cancer registry, year of diagnosis, sex, and for 14 five-year age groups (15–19, 20–24,. . .,80–84). To ensure consistency in data quality with time, the analysis was restricted to cancer registries accepted in the last three volumes of Cancer Incidence in Five Continents.[10–12] Regional registries were combined to obtain an estimate of the national incidence. As the span of data available from these registries varied, the aggregation maximised the registration period, but ensured as many of the regional registries were involved in the national estimation as possible. Datasets for 13 countries were included in the final dataset, their spans varying from 15 to 45 years, with the former a sufficient time period for temporal analyses of quinary-quinquennial groupings.

3. Statistical methods

Observed stratum-specific rates were calculated (per 100,00 person-years at risk) by age, sex and 5-year period of diagnosis for both HL and NHL, as were truncated age-standardised rates (European standard) for the age groups 15–44, 45–64 and 65–84. Synthetic birth cohorts spanning 10-year intervals were obtained for each population by subtracting the midpoints of 5-year age groups from the corresponding 5-year periods, with each resulting cohort overlapping by exactly five years. Age, period and cohort effects were modelled using methods described by Clayton and Schifflers[13,14] and Holford.[15] The magnitude of the rates was described by a full APC model which can be fitted under the application of generalised linear model theory,[16] with birth cohort derived from period and age. The net drift,[13] the sum of the period and birth cohort slopes, was estimated as an indicator of the overall direction and magnitude of recent trends (1983–1997). Parameter estimates from the age–period–cohort model are not presented here given the difficulties attributing the linear trend to period or cohort with any degree of certainty.

Comparisons of the recent age-adjusted rates and time trends of HL and NHL are made in all 13 countries. To provide some clarity to the interpretation of the trends, the graphical presentation describes only the temporal patterns in the four Nordic countries, and in the UK. All statistical analyses were carried out using STATA version 8.[17]

4. Results

4.1. *Geographical and temporal variability across the 13 countries*

There is a twofold variation in NHL rates for both men and women (Table 1), although rates are quite similar in the UK and the Nordic countries. There are also higher rates observed in men for both HL and NHL in all 13 countries; the M:F rate ratio varies by country from around 1.2 to 1.5, and this value is consistent for both types of lymphoma.

A scatter plot comparison of the average annual rate of change in incidence 1983–1997 is presented in Fig. 1a and 1b for all 13 countries (Table 1 also shows the corresponding confidence limits); points distributed close to or on the line of equality imply that trends between sexes for a given country are of a similar magnitude. For HL, it is clear that there is a wide range of rates of change across countries, partly reflecting the random variation inherent in the data. About half the countries fall in the quadrant where the percentage changes per year is negative (Fig. 1a). There are some positive outliers, for trends observed either in women only (e.g. Slovenia), or in both sexes (Finland, Spain), but these are not significant, and may be a result of the small numbers involved (Table 1).

For NHL, all net drift values are positive (Fig. 1b), with the estimated annual change ranging from around 1% in Norway and Sweden to around 5% in Spain and Slovakia. The plot is striking in that the magnitude of the trends is similar in men and women irrespective of population. Estonia is an outlier, possibly due to an inherent random variation in underlying rates (Table 1).

4.2. *Temporal variability in Northern Europe*

4.2.1. *Rates by calendar period in three age groups in five Northern European countries*

The observed age-standardised (Europe) registration rates of NHL in 4 Nordic countries and the UK are presented in three age groups (15–44, 45–64, 65–84) by sex in Fig. 2. For NHL, the magnitude and direction of the trend is broadly similar in each of the countries for both sexes. The general trend is steep and positive from the earliest period to the late 1980s. For the latest periods under consideration (the 1990s) the curves for NHL appear to change shape, and the rate of increase diminishes. The NHL registration rates appear to level off for both sexes irrespective of age. In Denmark and Norway, the trend in the youngest age group is reversed. For all five countries there has been a doubling in NHL registration rates from the mid-1970s to the mid-1990s. For the 65–84 age group, the number of registrations has at least quadrupled since the mid to late 1950s.

For HL, the temporal variations are different. Small numbers hamper the description to some extent, but there is some consistency in the observation – as seen in the long-term data series available in Finland and Norway – that the trends appear to increase up the early to mid-1970s, and thereafter a moderate negative trend is seen in all five countries. This translates to almost a halving of the total number of HL registrations in Northern Europe since the 1970s.

Table 1 – Populations included in the analysis, rates and recent regular trend for HL and NHL by sex

Population data on incidence available				Non-Hodgkin Lymphoma			Hodgkin Lymphoma		
Area	Country	Period[a]	Person-years[b,e]	Incidence[b]	ASR[c]	Recent trend[d]	Incidence[b]	ASR[c]	Recent trend[d]
Males									
Northern	Denmark	1979–1998 (4)	2,090,792	360	16.6	2.5 (1.8–3.3)	68	3.2	−1.1 (−2.4 to 0.3)
	Estonia	1971–2000 (6)	512,228	49	10.5	4.4 (2.0–7.0)	18	3.4	−1.3 (−3.8 to 1.6)
	Finland	1955–1999 (9)	1,979,547	381	19.6	3.4 (2.6–4.3)	68	3.5	0.5 (−1.0 to 2.2)
	Norway	1953–1997 (9)	1,701,088	300	16.9	1.5 (0.7–2.3)	46	2.7	−0.4 (−2.1 to 1.4)
	Sweden	1964–1998 (7)	3,447,799	699	17.4	1.3 (0.8–1.8)	90	2.5	−2.3 (−3.4 to −1.1)
	United Kingdom[e]	1978–1997 (4)	20,919,164	3642	16.7	3.1 (2.9–3.4)	653	3.1	−1.3 (−1.8 to −0.9)
Eastern	Czech Republic	1985–1999 (3)	4,003,725	447	12.0	2.1 (1.3–2.9)	149	3.8	−1.3 (−2.3 to −0.2)
	Slovakia	1968–1997 (6)	1,981,052	163	9.6	2.3 (1.2–3.5)	51	2.6	−0.9 (−2.5 to 0.8)
Southern	Italy[f]	1983–1997 (3)	1,892,654	457	21.2	4.8 (3.9–5.7)	69	3.7	−2.8 (−4.1 to −1.4)
	Slovenia	1985–1999 (3)	776,069	83	11.4	4.9 (3.0–7.0)	19	2.4	−0.9 (−3.4 to 2.1)
	Spain[g]	1983–1997 (3)	1,292,764	180	14.0	4.8 (3.5–6.1)	47	3.6	1.1 (−0.8 to 3.3)
Western	France[h]	1979–1998 (4)	1,559,953	289	19.4	4.0 (3.0–5.0)	56	3.5	−1.4 (−2.9 to 0.2)
	Switzerland[i]	1971–2000 (6)	1,135,883	255	21.9	3.0 (2.0–4.0)	40	3.6	−1.8 (−3.5 to 0.1)
Females									
Northern	Denmark	1979–1998 (4)	2,142,832	310	12.3	2.5 (1.6–3.3)	46	2.1	0.1 (−1.7 to 2.0)
	Estonia	1971–2000 (6)	615,798	42	5.7	7.5 (4.6–10.9)	16	2.6	−2.2 (−4.7 to 0.8)
	Finland	1955–1999 (9)	2,09,9381	377	14.6	3.5 (2.7–4.3)	53	2.6	0.7 (−1.1 to 2.6)
	Norway	1953–1997 (9)	1,740,029	251	12.5	1.4 (0.5–2.3)	29	1.6	−0.9 (−2.9 to 1.4)
	Sweden	1964–1998 (7)	3,526,428	568	12.1	1.9 (1.3–2.5)	75	2.1	−1.2 (−2.5 to 0.1)
	United Kingdom[e]	1978–1997 (4)	21,753,396	3091	11.8	3.4 (3.1–3.7)	494	2.2	−0.4 (−0.9 to 0.2)
Eastern	Czech Republic	1985–1999 (3)	4,292,124	402	8.2	3.0 (2.2–3.9)	143	3.2	0.0 (−1.2 to 1.2)
	Slovakia	1968–1997 (6)	2,129,698	143	6.6	4.4 (3.0–5.8)	50	2.3	1.1 (−0.7 to 3.2)
Southern	Italy[f]	1983–1997 (3)	2,035,873	396	14.8	4.7 (3.7–5.7)	63	3.2	−2.1 (−3.6 to −0.6)
	Slovenia	1985–1999 (3)	846,247	86	8.8	5.1 (3.2–7.2)	16	1.9	2.6 (−0.8 to 6.7)
	Spain[g]	1983–1997 (3)	1,344,282	160	10.6	6.1 (4.7–7.7)	33	2.3	1.9 (−0.6 to 4.7)
Western	France[h]	1979–1998 (4)	1,639,827	230	12.5	3.5 (2.4–4.5)	42	2.5	0.4 (−1.6 to 2.5)
	Switzerland[i]	1971–2000 (6)	1,211,489	216	14.9	3.1 (2.0–4.2)	33	2.8	0.7 (−1.5 to 3.2)

a Data available according to the period of diagnosis, figure in parentheses represent number of 5-year periods available in the analysis.
b Average annual number of cases aged 15–84, and corresponding person-years 1993–1997.
c Age standardised rates (Europe) 1993–1997, ages 15–84.
d Regular trend per year based on the net drift 1983–1997, ages 15–84 (95% CI: 95% confidence interval).
e Aggregation of England, Scotland.
f Aggregation of Florence, Varese Province, Parma Province, Ragusa Province, Turin.
g Aggregation of Catalonia, Tarragona; Granada, Murcia, Navarra, Zaragoza.
h Aggregation of Bas-Rhin, Calvados, Doubs, Isere, Somme, Tarn.
i Aggregation of Basel, Geneva, Neuchatel, St.Gall-Appenzell, Vaud, Zurich.

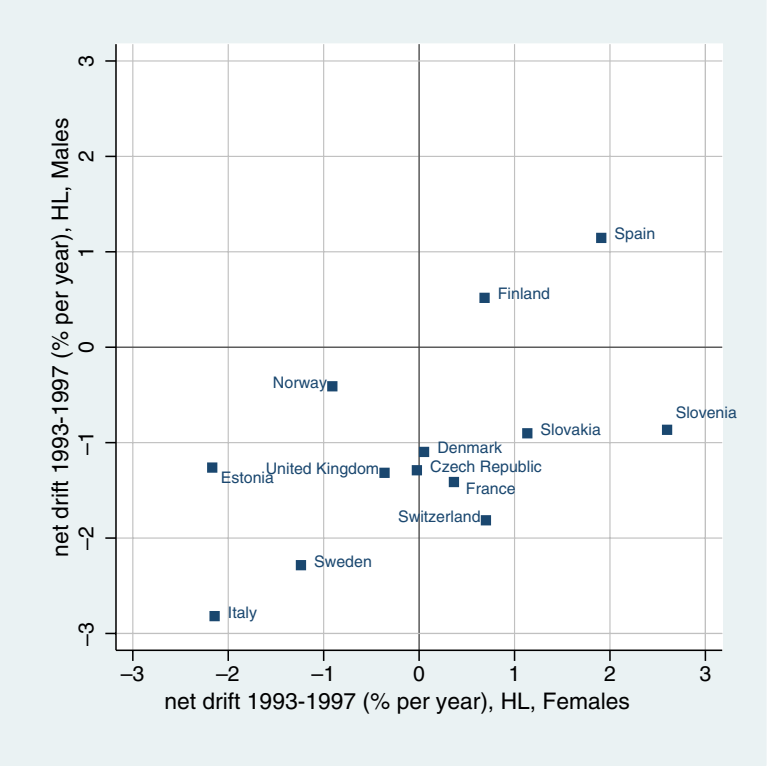

Fig. 1a – Scatterplot comparison of the mean annual rate of change in HL incidence 1983–1997 in men and women, based on the drift estimate.

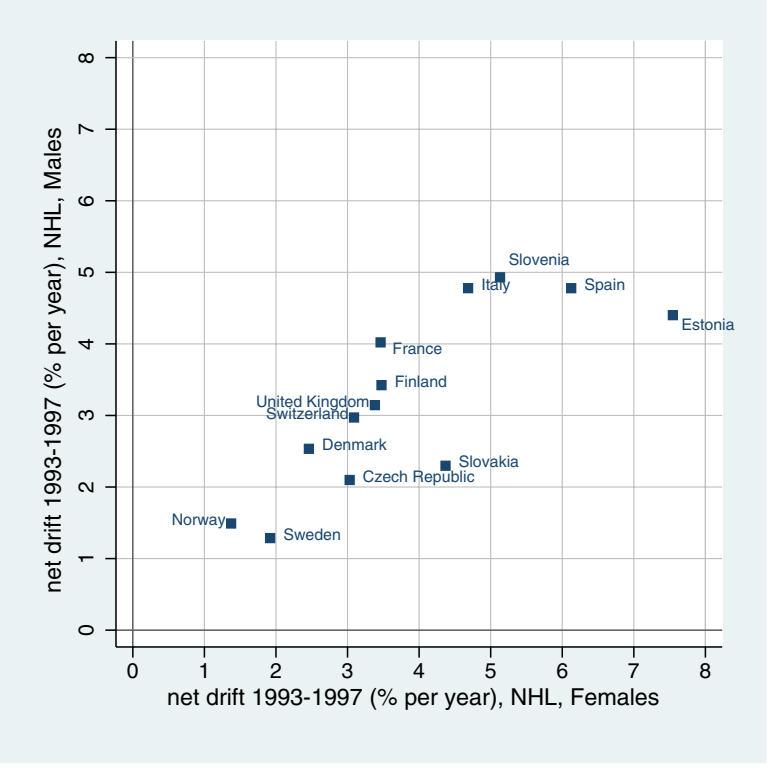

Fig. 1b – Scatterplot comparison of the mean annual rate of change in NHL incidence 1983–1997 in men and women, based on the drift estimate.

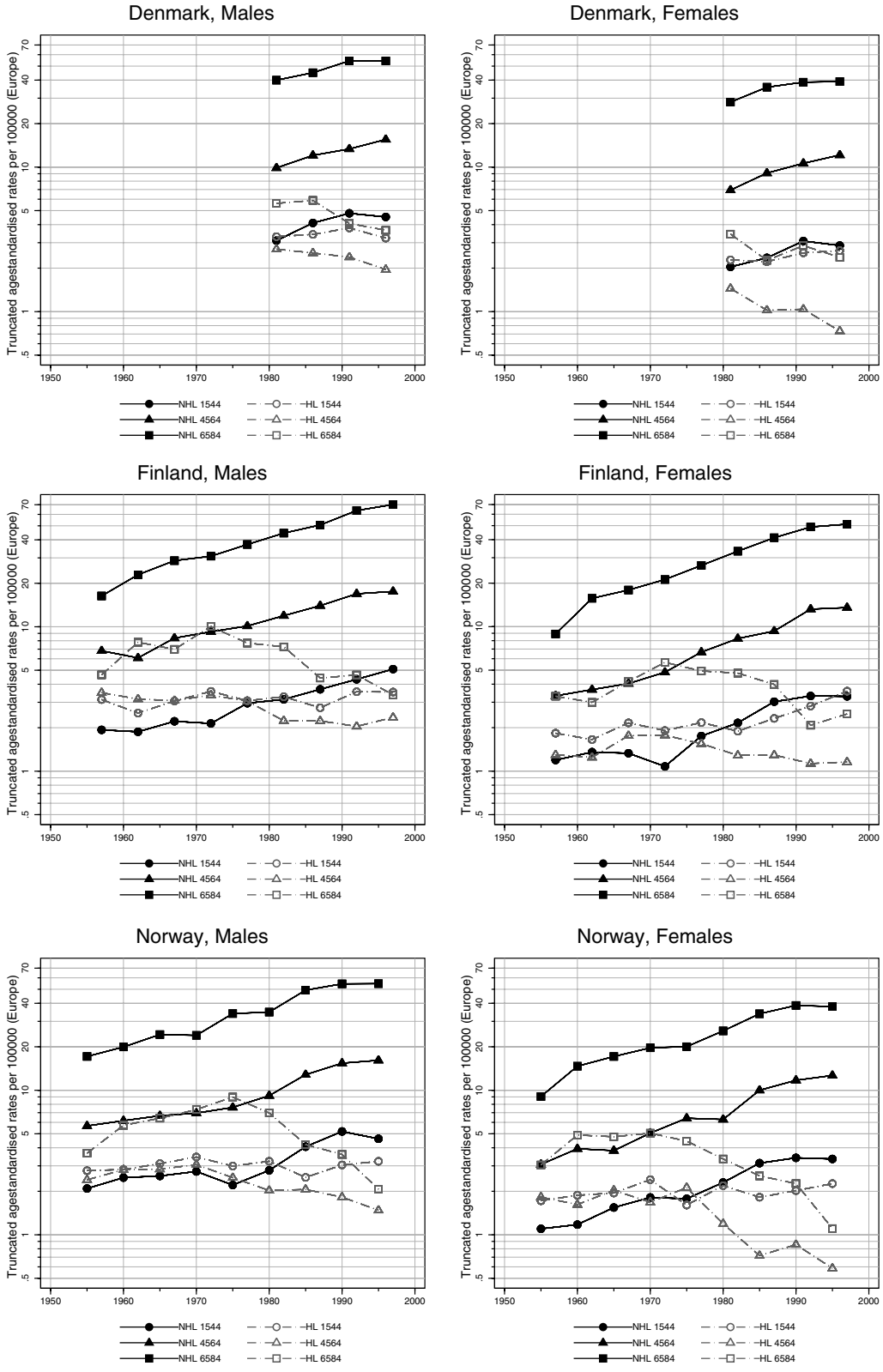

Fig. 2 – Observed truncated age-standardised incidence rates of HL and NHL (ages 15–44, 45–64 and 65–84, European standard) by calendar time in the Nordic countries and the UK, by sex.

4.2.2. Observed rates versus birth cohort and period

Trends in rates of NHL versus birth cohort and calendar time by age is difficult to interpret, but the five Northern European countries, do nevertheless have some common features. Higher incidence rates are seen in each country in successive birth cohorts and calendar periods, irrespective of age at

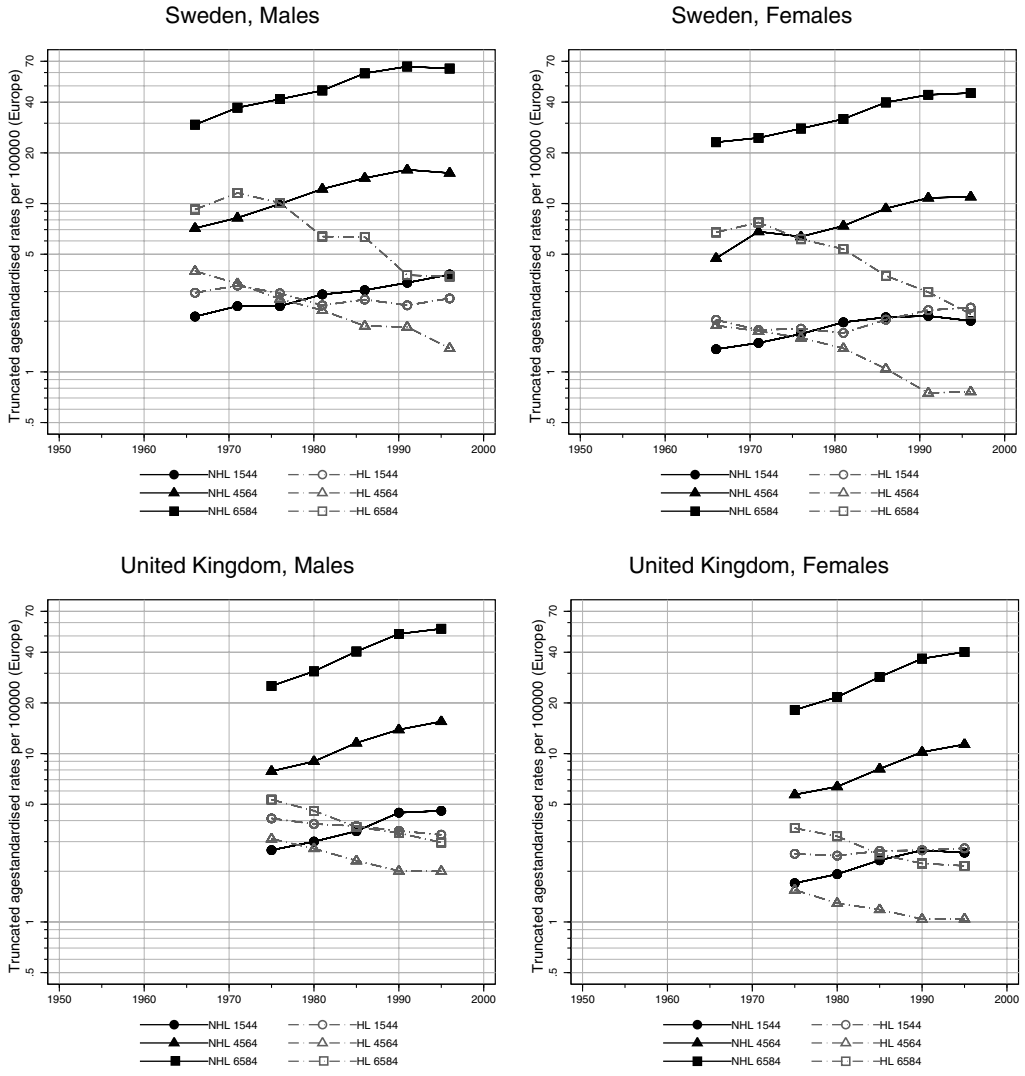

Fig. 2 – *continued*

diagnosis (Fig. 3). The trends are quite linear and parallel on the birth cohort and (therefore) period scale.

Rates of the rarer HL display substantial random variation; there is, however, a general pattern of decreasing rates in successive birth cohorts in the four Nordic countries until around 1940, and then some increases or stabilisation in consecutive birth cohorts born more recently data not shown. The UK trends appear relatively flat or even decreasing for men in cohorts born after 1940, whilst a moderate cohort-specific increase may have occurred among women (Fig. 3).

5. Discussion

We have summarised trends in incidence from HL and NHL in 13 European countries for which the registry data are considered reliable over a sufficiently extended time period. For the UK (where the numbers were large) and the Nordic countries (where long-term data were available), the observed rates versus birth cohort and calendar time were also presented. Overall, there was a consistent increase in the estimated incidence of NHL in both sexes in all countries studied, alongside a decrease in HL.

For NHL, an up to twofold variation in the rates can be seen, with clear evidence of an increase over time that varied between 1% and 5% per year in both sexes. In Northern Europe in particular, estimated incidence rates were similar in all age groups and in both genders, particularly since the 1980s. The incidence rates in the 1970s increased twofold by the mid-1990s. Of note were the trends in the over 65 age group, with the number of registrations quadrupling since the mid-1950s. In the 1990s, there was a suggestion of a less pronounced increase in the incidence in Denmark and Norway, particularly among the younger age groups. For NHL, higher rates were observed in the Northern European countries in successive birth cohorts and calendar periods irrespective of age at diagnosis.

For HL, a wider range of variation in rates was observed across countries. Where data were available long-term, the estimated incidence increased up to the 1970s and tended to decline thereafter. By the late 90s, the numbers of HL registrations in Northern Europe was half that observed in the

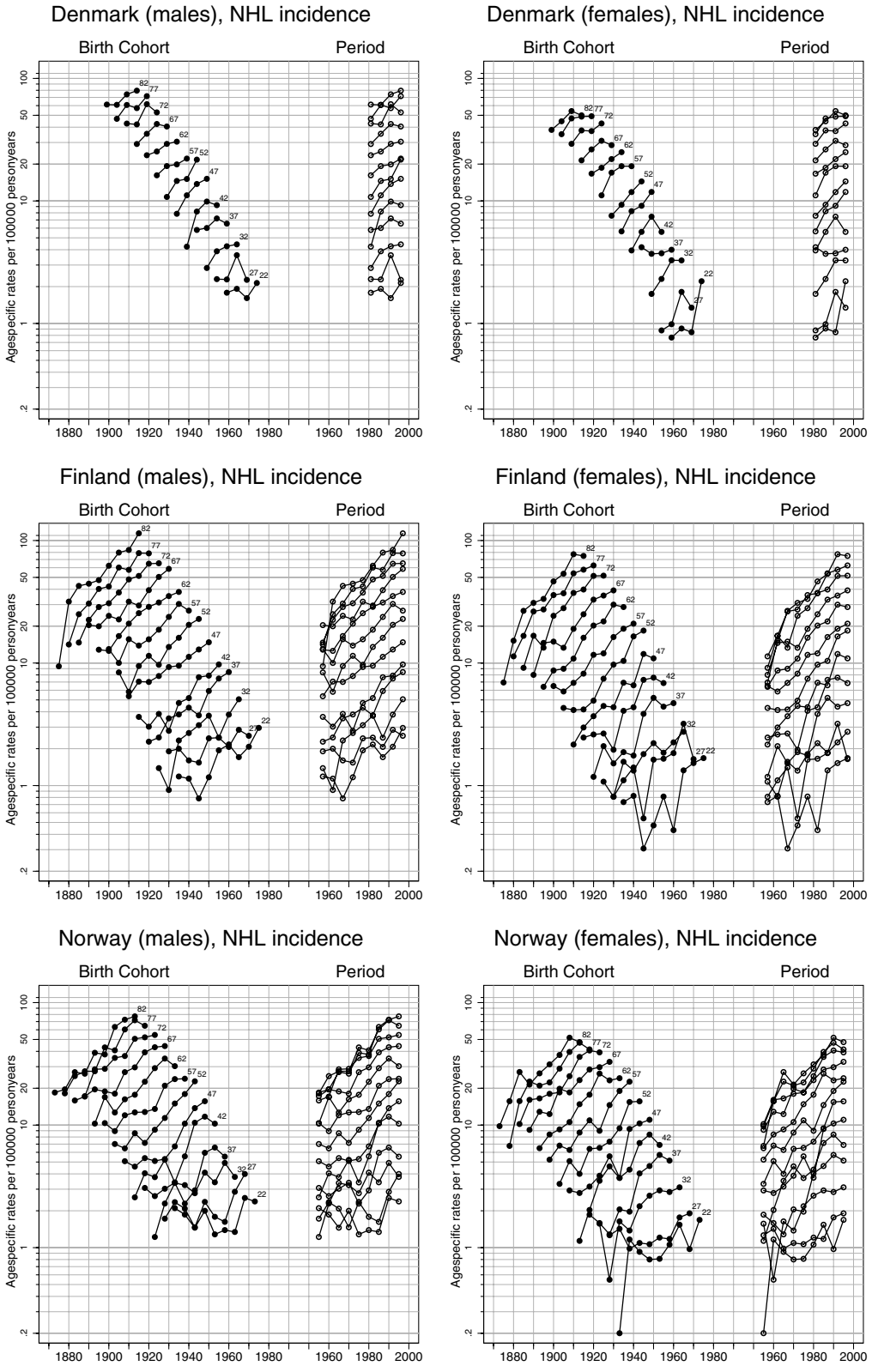

Fig. 3 – Observed age-specific incidence rates of NHL and HL by birth cohort and calendar time, by sex.

preceding 20 years. There was also a suggestion of decreasing rates of HL in successive birth cohorts in the Nordic countries until the 1940s, followed by a subsequent stabilisation thereafter.

As well as a dynamic and evolving classification system, improvements in disease detection and cancer registration may have contributed to temporal trends. Non-Hodgkin's lymphoma classified as B-cell or T/NK-cell subtypes according to

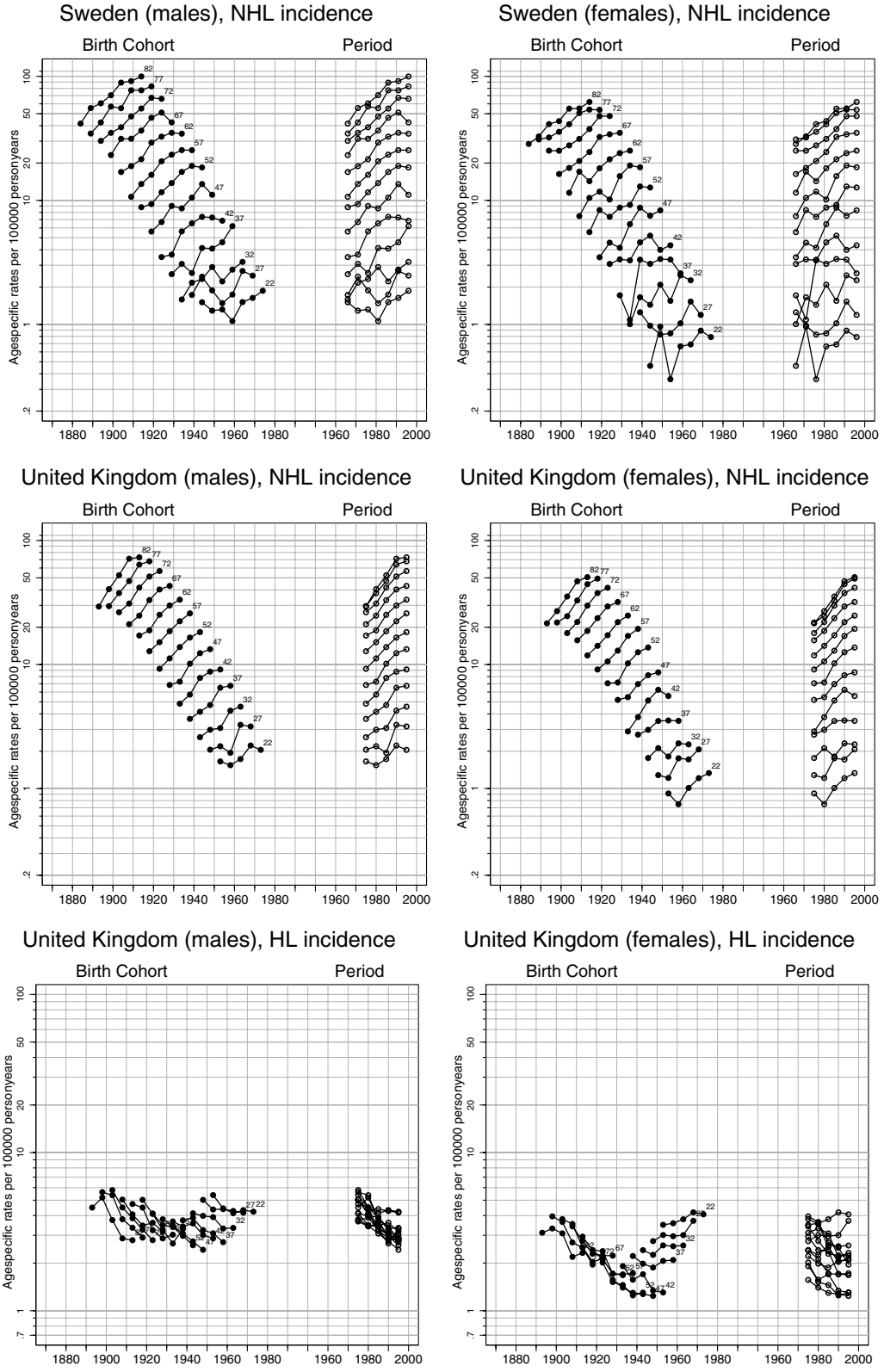

Fig. 3 – *continued*

the Revised European–American Lymphoma (REAL) classification system[18] and its successor, the WHO classification[19,20] are a heterogeneous group of malignancies.

The uniformity and extent of the increases can only be accurately quantified if we know how classifications, diagnostic and registration practice have varied over time. The

increase in NHL may relate to an increase in the number of diagnostic interventions performed. Possible, but less likely is the prospect that the numbers of registrations made in earlier time periods are equal to the totality of disease in the population – and hence increases would indicate changes in exposure and subsequent risk.

The observed incidence of NHL has been reported to be increasing in a number of Western countries, as well as in Asia and South America over the past several decades.[1,21,22] This study expanded the number of European countries analysed to 13, and indicated that although annual increases of up to 5% were observed, there was some variability according to both country of origin, and sex.

The reasons for the sharp and uniform increases in incidence rates of NHL alongside stable or decreasing incidence rates of HL across Europe are still largely unknown. The prevalence of one or more underlying aetiological factors would have been steadily changing in order to explain these trends. Potential explanations for these incidence patterns may involve risk factors that emerged during the first half of the 20th century across Europe, and that affect both sexes; although possibly not equally given NHL incidence is consistently higher in men than in women.

Little is currently known about the aetiology of both Hodgkin and non-Hodgkin lymphoma. The heterogeneous nature of these diseases and inconsistent definitions has, in the past, hindered the identification of risk factors. Although many factors are suspected, only a few inherited disorders, immunosuppressive drug therapies, high doses of ionising radiation and certain viruses and bacterial infections have been unequivocally associated with the various lymphoma subtypes. Taken together, known risk factors only account for a small proportion of disease and other possible determinants remain to be tested by further research.[23]

A problem, which is common to all comparative epidemiological studies, is the effect of changes in disease classification and coding over time.[24] For the majority of cancers this may be a minor problem, however, for the interpretation of long-term trends in the registration of lymphomas, and hence the accurate estimation of true incidence, it requires careful consideration.

Many different lymphoma classifications have been in use during the periods under study and progress with taxonomy has been dynamic and evolving. The synthesis of a system which is meaningful both clinically and epidemiologically is a recent occurrence which has yet to be implemented by all cancer registries. The taxonomic progress of the past 20 years has only been possible because of marked advances in diagnostic techniques. For example, the ever-increasing use of sensitive flow cytometric methods to examine peripheral blood samples and endoscopic biopsies of the gastro-intestinal tract mean that many more indolent lymphoproliferative disorders are coming to clinical attention now than would have done so in previous years.[25] The combined effects of improvements in lymphoma detection (lowering the threshold of detection) and the widespread use of new methods and techniques (allowing more accurate disease classification and greater access to interventions) should not be underestimated. These together with general improvements in the ascertainment of cases by cancer registries are impacting on the absolute number of registrations made.

In summary, the data presented here provide convincing evidence of uniform increases in the number of NHL registrations made over time in Europe and a decrease in the number of HL registrations made over similar periods for the same age groups. There are real difficulties in assessing long-term incidence trends given the potential changes in classification and diagnostic and registration practice that may vary with age, geography and calendar period. As yet, no study has adequately quantified the additional number of NHL registrations identified in later periods attributable to reclassifications, changes in access to diagnostic tests (particularly for the elderly) and the improvements in diagnostic accuracy resulting in more definitive diagnoses. Until such studies are undertaken, it seems sensible to be cautious in interpreting the temporal patterns of lymphoma incidence.

The reported epidemic of lymphomas is largely based on data for the period from 1950 to around 1990. Two US studies using more up-to-date data, however, reveal a decline in the rate of increase.[26–29] Incidence data for New South Wales (NSW) for the period 1973–2003 show significant increases in NHL in both sexes up to the end of 1993. Data for the period 1994–2003, however, show a marked decline in the rate of increase. Visual inspection of age-standardised incidence of NHL in NSW for the same period show a levelling off.[30] NHL incidence data for Sweden over the period 1991–2000 also indicate that the increasing incidence has levelled off. This pattern is also seen in Denmark for 1989–1998.[31]

The most recent published study into time trends in incidence for NHL details time trends in Sweden, Denmark and Finland over the period (1960–2003). It study concludes that the epidemic increase of NHL has largely subsided.[32]

This study, coupled with the Nordic study, provides good evidence for a levelling off in the number of registrations being made. One can speculate that the plateau observed in recent time periods is consistent with timely and highly effective cancer registration coupled with marked improvements in disease detection and access to diagnostic tests, particularly for the elderly - analysis of more recent data and continued surveillance may show that rates remain stable and that these reflect the totality of disease in a population.

Conflict of interest statement

None declared.

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