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Community Lifestyle Characteristics and Lymphoid Malignancies in Young People in the UK

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Data from a specialist registry of haematopoietic malignancies in England and Wales (1984–1988) have been analysed to investigate variations of incidence by age and diagnostic subtype of lymphoid malignancies in young people (aged 0–24 years). Attention has been focussed on the role of community lifestyle indicators for small areas, derived from routine sources, in an ecological analysis. The predominant conditions were acute lymphoblastic leukaemia (ALL)—42.4%, and Hodgkin's disease (HD)—37.5%. Lowest overall incidence at approximately 8 years of age corresponded to the termination of the childhood peak for ALL. Opposite trends of incidence rates with distance from urban centres (urban distance) were observed for the two age groups: odds ratios (OR) for areas >20 km from towns and cities were 1.46 (95% confidence interval 1.01–2.12) for ages 0–7 and 0.75 (95% confidence interval 0.56–0.99) for ages 8–24. For the younger group this was entirely attributable to ALL. HD, which was dominant in the older group, had highest incidence in connurbations but the gradient of risk for older onset ALL followed the overall pattern for this age group. A positive relationship with socioeconomic status was evident for both age groups but this was considerably stronger for the older cases (OR = 1.16, 95% confidence interval 1.01–1.33) than for the younger for whom it was not independent of urban distance. These results display an association between expression of lymphoid malignancies in young people and urban distance which is not attributable to socioeconomic status; for urban distances the distribution is shifted towards ALL and towards younger age at onset.
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INTRODUCTION AND BACKGROUND

THE AGE distribution of acute lymphoblastic leukaemia (ALL) and the overall incidence of disease have changed during the last half-century. The childhood incidence peak first observed in the UK [1] has emerged in other developed communities of diverse ethnic origin [2–4] and is believed to be associated with some aspects of social change [5]. Kinlen [6] found high rates in young children in areas where immigration was substantial and postulated an association with disregulated herd immunity. This would involve one or more specific agents but the Greaves hypothesis [7] suggested rather that general protection from antigenic challenge in infancy played a key role.

Similar cross-sectional [8] and secular [9] associations of the age-incidence pattern for Hodgkin's disease (HD) with socioeconomic factors have been documented. In conditions of poverty, childhood incidence was relatively high but in more affluent communities rates in children were generally lower, while a peak was found for young adults. It has been suggested [10] that this may have arisen as a result of delayed exposure to some relatively common infectious agent—the "late host response model". Considerable support for this was offered by both descriptive and analytical epidemiology [11, 12].

Although Greaves' hypothesis and the late host response model are entirely distinct, both suggest increased risk of disease for those protected from early infection. It was therefore appropriate to conduct parallel ecological analyses relating ALL

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[13] and HD [14] in young people to appropriate community lifestyle indicators.

Secular changes of incidence of lymphoid malignancies have been reported [15] in a community undergoing rapid socioeconomic development. The results of our earlier studies suggested a cross-sectional variation within the UK, dependent upon community isolation and socioeconomic status. The present study was conducted to investigate this more general issue.

METHODS

The Data Collection Survey is a specialist registry of leukaemias and lymphomas covering approximately half of England and Wales which has collected incidence data for the period 1984–1988 [16]. A fixed protocol maintains levels of ascertainment and diagnostic accuracy which are geographically unbiased. A prerequisite for registration is haematological or histopathological verification of the diagnosis. The present study applies to 1296 cases of lymphoid malignancies including lymphoid leukaemias, Hodgkin's disease and non-Hodgkin lymphoma diagnosed in people aged 0–24 years. The age range has been chosen as a compromise between those appropriate for the individual diagnostic subgroups. Results are disaggregated into age groups determined by an antimode at approximately 8 years of age. When HD results are reported separately attention is focussed on the age group 15–24 years in recognition of categories used in other reports and presumed aetiological differences between children and young adults [8]. The Kiel [17] classification of the non-Hodgkin lymphomas is used.

Administrative areal units are electoral wards with boundaries those of the 1981 census of England and Wales. Locations of population weighted centroids for these wards are provided by OPCS (Office of Population Censuses and Surveys). There are 3270 electoral wards in the area with average 0–24 population of 1465. Mid-census (1986) counts of the population at risk are estimates from CACI Ltd [16] which are constrained to agree with national statistics for larger areas. All registrations are postcoded by their address at diagnosis and the OPCS central postcode directory assigns each case by its postcode to an electoral ward.

Additional data for electoral wards provide indicators of community lifestyle [13]. For socioeconomic status, a number of measures of personal household advantage and deprivation were taken from the 1981 census of England and Wales. These included social class, car ownership, household occupancy and unemployment and were combined into a single continuous index of ward socioeconomic status using principal component analysis [18]. This index was used to split the electoral wards into two groups with approximately equal population: "higher" and "lower" status. Classification of wards by their urban rural status was taken from OPCS data [19]. In addition, we used the digitised 1:62500 Ordnance Survey map of the UK to provide segmental boundaries for each built-up area: these are shown on the printed maps as shaded areas but in general correspond to individual large towns and cities as well as connurbations made up by including urban sprawl between nearby large towns. We computed the distance from each ward centroid to the boundary of the nearest built-up area (the urban distance); wards with centroid inside a boundary formed the "inner zone" and the remainder were grouped into rings at distances <5 km, 5–20 km and >20 km from the nearest boundary. This enabled wards to be allocated to four zones [13, 14]: inner, inner intermediate, outer intermediate and outer. In Fig. 1, an additional category of isolated settlement was included; these wards were defined [13] and were primarily in the outer zone, but each contained the centroid of at least one small town or village.

Statistical methods

Since no suitable external reference rates were available, all analyses used internal standardisation [20] based on 5-year age–sex strata (population estimates for other age bands were appropriate proportions of the corresponding 5-year band). This yielded expected numbers (E) for each ward. Poisson regression modelling was applied systematically to these using GENSTAT V [21]. Observed numbers (O) as dependent variables were regressed on appropriate risk factors and covariates with log link function, offset log (E) and Poisson error [21]. Estimates of statistical significance used analysis of deviance with asymptotic χ^2 distribution for the deviance difference. In addition, 95% confidence intervals based on the asymptotic normal distribution of the regression coefficients were determined. Monte Carlo simulations were conducted to check that the use of the asymptotic distributions was appropriate for sparse data when electoral wards were analysed [18].

Table 1. Number of cases by age, diagnostic subtype and area type

	0–7 years			8–24 years			0–24		
Area	ALL	HD	NHL	ALL	HD	NHL*	ALL	HD	NHL*
Inner zones	192 (78.4%)	18 (7.3%)	35 (14.3%)	144 (24.3%)	309 (52.2%)	139 (23.5%)	336 (40.1%)	327 (39.0%)	174 (20.8%)
Outer zones	140 (84.4%)	4 (2.4%)	21 (12.7%)	71 (24.1%)	155 (52.7%)	68 (23.1%)	211 (46.0%)	159 (34.6%)	89 (19.4%)
High SES	163 (81.1%)	13 (6.5%)	25 (12.4%)	118 (26.3%)	241 (53.3%)	93 (20.3%)	281 (43.2%)	254 (38.9%)	118 (17.9%)
Low SES	169 (80.9%)	9 (4.3%)	31 (14.8%)	97 (22.4%)	223 (51.4%)	114 (26.3%)	266 (41.4%)	232 (36.0%)	145 (22.6%)
Total area	332 (81.0%)	22 (5.4%)	56 (13.7%)	215 (24.2%)	464 (52.4%)	207 (23.4%)	547 (42.2%)	486 (37.5%)	263 (20.3%)

No. (% of cases).

*Includes 12 cases of chronic lymphocytic leukaemia and 3 of multiple myeloma.

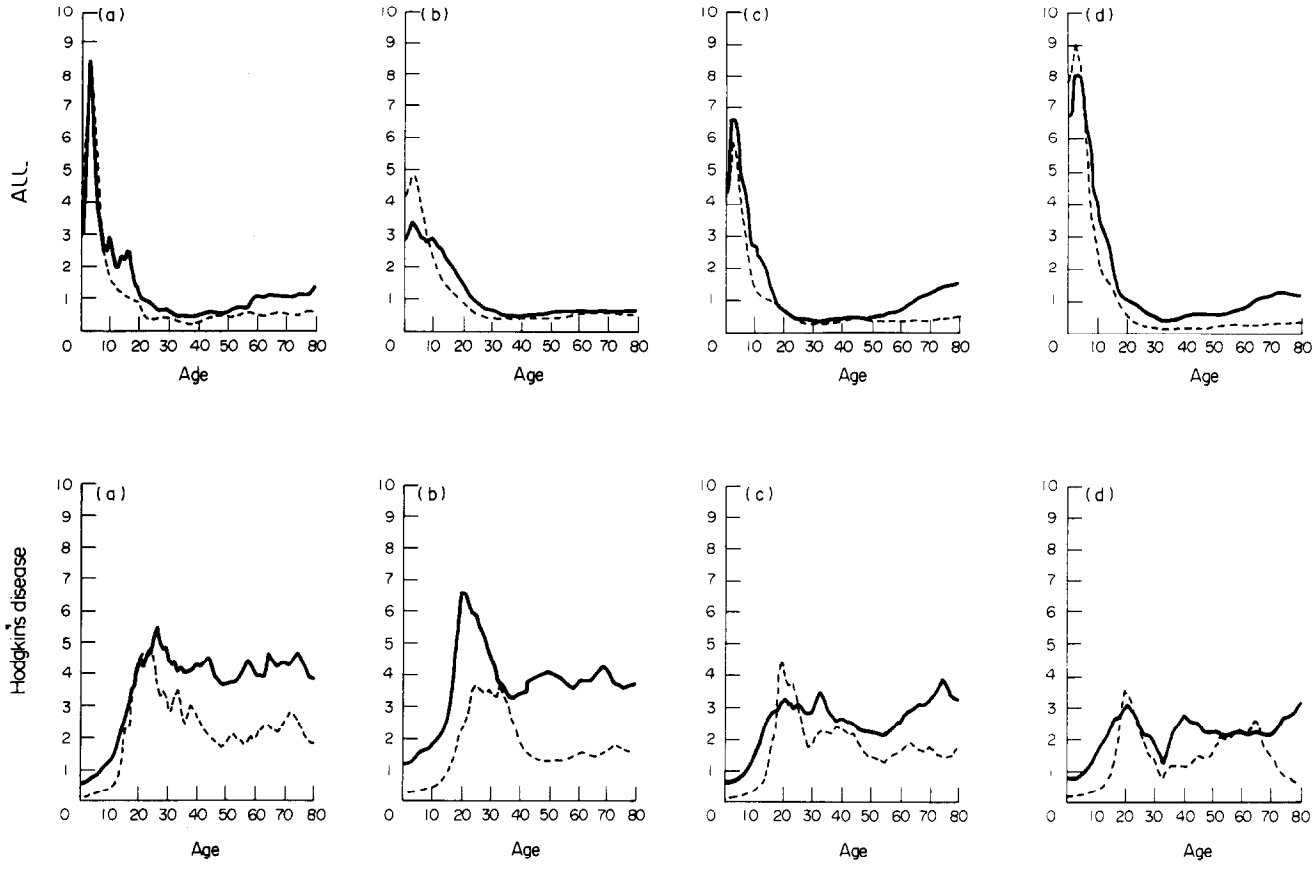

Fig. 1. Age-specific incidence rates/10 000 person-years, for (a) DCS overall, (b) built-up areas (higher socioeconomic status), (c) rural wards (predominantly higher socioeconomic status) and (d) isolated settlement wards (higher socioeconomic status). Similar patterns were evident for wards of lower socioeconomic status. —— male, --- female.

All directly standardised incidence rates used as standard a population with uniform age–sex distribution. Age and sex specific incidence rates (for those aged 0–79) were plotted using statistical smoothing methods [16]. The method is based on penalised likelihood [23] and involves relatively minor adjustments. These were applied to rates calculated for single years of age (0–34) and 2-year age bands thereafter.

RESULTS

The majority of cases in this series were ALL (42.2%) and HD (37.5%); 20.3% were non-Hodgkin lymphoma. For completeness, 12 cases of chronic lymphocytic leukaemia and 3 cases of multiple myeloma were included with the non-Hodgkin lymphomas. ALL was dominant in the younger age group and HD in the older but HD incidence below age 15 was low. Further details of the distribution, including separation by area type, are provided in Table 1. The percentage of ALL cases was increased (at ages 0–7 and over the whole age range) in the outer and outer-intermediate zones. In the inner and inner-intermediate zones the overall proportions of ALL and HD were almost identical. In areas of high socioeconomic status, non-Hodgkin lymphoma was relatively less common than ALL and HD, especially in the older age group. Incidence rates for the total series, overall and by area type (Table 2), revealed higher incidence at ages 0–7 and lower incidence at ages 8–24 in the outer zones, and higher incidence in both age groups for areas of high socioeconomic status. These results were further clarified by the Poisson regression analyses whose results are reported in Tables 3 and 4. The relationship to ward socioeconomic status was weak for the younger group and stronger in the older but in the same direction throughout. By contrast, the association with measures of urban-rural status were in different directions. These associations were weak for the OPCS urban–rural classification but strong when urban distance was taken as the indicator. Where numbers for individual diagnoses were adequate for analyses, ALL (both age groups) and HD (the older group) followed the overall trend. Indeed the trends can be attributed to these three age–diagnosis combinations. The numbers of HD cases in the younger group were extremely small but suggested an association with socioeconomic status

Table 2. Incidence of lymphoid malignancies by area type and age group (age standardised rates/10^5 per year)

	Age (years)		
	0–7	8–24	Ratio
Inner/inner intermediate	5.82	4.83	1.20
Outer/outer intermediate	6.56	4.00	1.64
High SES	6.28	4.76	1.32
Low SES	5.91	4.30	1.37
Total area	6.10	4.63	1.32

Table 3. Effects of community socioeconomic status and isolation on lymphoid malignancies in young children (0–7)

	All lymphoid malignancies	Acute lymphoblastic leukaemia
Urban–rural status		
Urban	1.00	1.00
Rural	1.10 (0.80–1.53)	1.08 (0.64–1.56)
χ^2 (1 df)	0.06 (NS)	0.17 (NS)
Socioeconomic status		
Lower	1.00	1.00
Higher	1.01 (0.81–1.23)	1.01 (0.79–1.27)
χ^2 (1 df)	<0.01 (NS)	0.00 (NS)
χ^2 for trend (1 df)*	0.24 (NS)	0.52 (NS)
Urban distance zone		
Inner	1.00	1.00
Inner-intermediate	1.09 (0.85–1.41)	1.24 (0.92–1.66)
Outer-intermediate	1.07 (0.83–1.38)	1.22 (0.90–1.65)
Outer	1.46 (1.01–2.12)	1.96 (1.30–2.95)
χ^2 (3 df)	3.81 (NS)	9.67 ($P<0.05$)
χ^2 for trend (1 df)†	2.01 (NS)	6.67 ($P<0.025$)

All analyses are adjusted for the other factors included in this table.
*Trend by continuous socioeconomic index.
†Trend across categories.

and urban distance, which was parallel to that for older ages. Results for HD reported in Table 4 are for ages 15–24 but analyses for ages 8–24 yielded similar results. Smoothed age-incidence curves for these two conditions across the entire age range 0–79 years are given in Fig. 1. These show the increasing dominance of the ALL childhood peak as isolation increased and the change in shape of the HD age–incidence curve from that typical of developed countries to the "intermediate" pattern [23] of other European rural areas. The female peak is also absent for the most isolated areas.

The non-Hodgkin lymphoma numbers were small and the diagnoses heterogeneous. The majority (over 75%) were high-grade disease, and of these there was some evidence that younger age-at-onset and the lymphoblastic subgroup were favoured in the outer zones. This applied particularly to the rare convoluted type whose mean age at onset was 8.25 years; 8 cases among young people were registered by the data collection study and of these 6 occurred in the outer zones. By contrast, the immunoblastic and centroblastic subtypes did not occur below age 8 and were rare in the outer zones.

DISCUSSION

The data collection study is a unique source of recent, high quality, population-based incidence data for the range of haematopoietic malignancies. Sociodemographic data for small areas, derived from routine sources, permit a program of ecological analyses. The limitations of such studies has been acknowledged [24, 25]. It has been suggested [26] that the relevant risk factors in this context may possibly operate at community level. In any event, ecological analyses have the capacity to suggest categories and hypotheses for analytical studies.

Our results demonstrated a clear gradient of incidence of lymphoid malignancies within the UK at the present time which was associated with increasing geographical isolation. In urban centres, older cases were more common and conditions appeared to be favourable to HD and older onset ALL. As isolation increased the age distribution shifted towards younger ages and the childhood peak of ALL became particularly prominent. Other studies have shown that the age distribution of ALL correlates with immunophenotype with common ALL (cALL) concentrated in the childhood peak and T-cell disease having

Table 4. Effects of community socioeconomic status and isolation on lymphoid malignancies in older children and young adults (aged 8–24 years): odds ratios and 95% confidence intervals

	All lymphoid malignancies	ALL	HD*
Urban–rural status			
Urban	1.00	1.00	1.00
Rural	0.94 (0.75–1.18)	0.92 (0.58–1.17)	0.97 (0.71–1.33)
χ^2 (1 df)	0.12 (NS)	0.14 (NS)	0.04 (NS)
Socioeconomic status			
Lower	1.00	1.00	1.00
Higher	1.16 (1.01–1.33)	1.42 (1.07–1.88)	1.22 (1.01–1.40)
χ^2 (1 df)	4.42‡	5.91§	4.34‡
χ^2 for trend (1 df)+	9.98‖	6.03§	9.27‖
Urban–distance zone			
Inner	1.00	1.00	1.00
Inner-intermediate	0.96 (0.82–1.13)	0.69 (0.49–0.97)	0.96 (0.76–1.20)
Outer-intermediate	0.79 (0.67–0.94)	0.63 (0.45–0.90)	0.77 (0.61–0.90)
Outer	0.75 (0.56–0.99)	0.67 (0.39–1.18)	0.72 (0.48–1.00)
χ^2 (3 df)	9.14‡	7.93†	6.23†
χ^2 for trend (1 df)⋆	8.03‖	6.08§	5.47‡

*Ages 15–24 years. +Trend by continuous socioeconomic index. ⋆Trend across categories.
$P <$ †0.10, ‡0.05, §0.025, ‖0.005.

highest incidence amongst adolescents [27]. Our results, therefore, parallel those of Gaza [15] where the dominant lymphoid malignancies in young people changed from B-cell lymphomas to T-cell ALL to cALL, as the community became "modernised".

These studies provide evidence that environmental factors are determinants of the pattern of lymphoid malignancy in young people. Numerous differences exist between connurbations and more isolated areas and between Gaza in the 1960s and subsequently; many of these could be relevant. However, it is plausible that some aspects of the community infectious and/or immune profile may be involved aetiologically. This is supported by evidence that the mean age at first exposure to certain common infections is older in rural areas of the UK [28, 29] and elsewhere [30]. These, and other possible interpretations are discussed in the earlier reports for ALL [13] and HD [14]. It seems likely that some shared environmental factors may be involved in the development of these conditions.

The non-Hodgkin lymphomas were a heterogeneous group although high-grade disease predominated in young people. No consistent pattern was evident for this subgroup. Diverse aetiologies are probable but our data gave an indication that some, at least, of the lymphoblastic subtypes had a distribution resembling that of young onset ALL.

Further investigations of these issues require analytical methods and will, we hope, include targetted serological surveys and case-control studies encompassing the full range of lymphoid malignancies arising in young people within a common protocol.

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